OXIDATION AND REARRANGEMENT IN NITROGEN HETEROCYCLIC CHEMISTRY

By

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S T A T E M E N T

The work described in this thesis was carried out by the author in the Department of Chemistry of the University of Leicester under the supervision of Professor C. W. Rees. No part of it is concurrently being submitted for any other degree.

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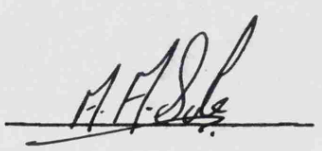
Signed 

(A. A. SALE)

T O S T E P H A N I E

A C K N O W L E D G E M E N T S

I wish to express my thanks to the following:-

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A B S T R A C T

This thesis reports a study of the preparation and oxidation of a range of heterocyclic N-amino compounds. A review of N-aminating agents is given in the Introduction.

1,2,4-Triazin-3(2H)-ones gave imidazolin-2-ones when treated with hydroxylamine-O-sulfonic acid or O-(2,4-dinitrophenyl)hydroxylamine, probably via N-amino intermediates. However, chloramine gave 1,2,3-triazoles by acting as an oxidising rather than an aminating agent. These reactions were extended to cinnolin-3(2H)-one where the 2-amino derivative could be isolated. Pyrolysis and oxidation of 2-aminocinnolin-3(2H)-one both lead to new rearrangements.

1-Aminoquinoxalin-2(1H)-one, prepared by amination of quinoxalin-2(1H)-one, gave benzo-1,2,4-triazine when oxidised by lead tetra-acetate, as well as products derived by interception of the N-nitrene intermediates.

Four 3-substituted 1-aminooxindoles were prepared by direct amination and by reduction of cinnolin-3(2H)-ones and their different oxidative decompositions determined. The oxidation of N-amino-acetanilide was investigated for comparison.

1-Amino-3-substituted benzimidazolin-2(1H)-ones were similarly studied; the corresponding tetrazenes and deaminated compounds were formed on oxidation and the N-nitrene intermediates could be intercepted with olefins or dimethyl sulfoxide. The unsubstituted 1-aminobenzimidazolin-2(1H)-one gave 1-acetylbenzotriazole, however, probably via benzo-1,2,4-triazin-3(2H)-one.

The decomposition of benzotriazole-1-carboxamide was briefly investigated.

This work illustrates the diverse reactions of amino-nitrenes; generated by dehydrogenation of 1,1-disubstituted hydrazines, which include deamination, dimerisation, intramolecular rearrangement and the formation of aziridines with olefins.

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INTRODUCTION

This Introduction is an attempt to review critically the methods of direct amination of amines to hydrazines. Four aminating agents have been used for this purpose. Chloramine and hydroxylamine-O-sulfonic acid (HOS) have been known and used extensively since 1907 and 1914 respectively, while O-mesitoylhydroxylamine and O-(2,4-dinitrophenyl)hydroxylamine are of recent introduction. No comprehensive review of chloramine has been published although reviews[1] concerning specific aspects of the chemistry of chloramine, for example, the Raschig[2] synthesis of hydrazine, have appeared. No reviews of the other aminating agents have been published, and therefore a comprehensive review of the synthetic value of this reaction is presented in this Introduction.

1. CHLORAMINE

a) Preparation and hydrolysis

Chloramine was first prepared by Raschig[2] in 1907 by the reaction of ammonia with sodium hypochlorite in dilute aqueous basic solution at 0°.

$$NH_3 + NaOCl \rightarrow NH_2Cl + NaOH$$

The process was modified slightly[1a,3,4] by using three equivalents of ammonia to one of hypochlorite when nearly quantitative yields of chloramine were obtained. The addition of ammonium chloride suppressed the formation of sodium hydroxide which decomposed the chloramine.

$$NH_4Cl + NaOCl \xrightarrow{base} NH_2Cl + NaCl + H_2O$$

Kinetic studies[5] showed that chloramine was formed by an S_N2 mechanism. The reaction was base catalysed, the pH of the solution being critical.[6] Chloramine is formed above pH 8.5, dichloramine between pH 4.4 and 8.5 and nitrogen trichloride below pH 4.4.

Aqueous solutions of chloramine (12%) free from impurities can be obtained by the vacuum distillation of dilute aqueous solutions prepared by the reaction of ammonia and hypochlorite.[7] Dehydration of the aqueous distillate with potassium carbonate gave pure anhydrous chloramine,[8] m.p.-60°, which decomposed explosively at -50°. Anhydrous ethereal chloramine solutions can be obtained by extraction of aqueous solutions and drying the organic layer with calcium chloride.[8,1c] The distribution coefficient[8] between ether and water is almost one. Anhydrous chloramine (95%) can also be prepared by the gas-phase chlorination of ammonia[9] and by the reaction of either gaseous chlorine or of a solution in carbon tetrachloride with liquid ammonia.[9a,10] Excess of ammonia was required to prevent further chlorination and the chlorine was usually diluted with nitrogen. Solid ammonium chloride was easily separated and excess of ammonia can be removed by the extraction of chloramine into a solvent. t-Butylhypochloride,[11] nitryl chloride (NO_2Cl),[12] and *N*-chlorosuccinimide[13] have also been used to prepare chloramine by reaction with ammonia. Hydrolysis of *N*,*N*'-dichlorourea[14] and potassium *N*-chloroaminosulfonate ($ClNH_2SO_3K$)[15] are also reported to yield chloramine.

Bond lengths and angles of gaseous chloramine were determined by use of infrared spectroscopy.[16] Chloramine absorbs at 243 nm, ε= 458 and this has been used for its quantitative estimation.[17] There is good agreement with results obtained by iedimetric determination except

in the presence of peroxynitrite ions, formed by the alkaline decomposition of chloramine in oxygen.[18] (See later).

Aqueous solutions of chloramine are reasonably stable when made slightly basic with ammonia but decompose rapidly in acidic solutions[6,19] via dichloramine and nitrogen trichloride to give ammonium chloride, nitrogen and hydrochloric acid which further catalyses the decomposition. Treatment with concentrated hydrochloric acid gives chlorine and ammonium chloride.[8] The decomposition of chloramine in basic media is very complex and much early work has been shown to be incorrect. A comprehensive investigation[18a] of the hydrolysis of chloramine in alkaline solutions from pH 11.55 to 12 molar MOH (M = Na or K) found large rate increases above pH 14. The products identified were N_2, N_2O, N_2H_4, $N_2O_2^-$, $O{=}NO{-}O^-$ and NH_2OH, nitrogen and nitrous oxide being the major products. No chlorate, azide, or hydrogen was detected although they had previously been reported by Raschig[2] and Marckwald.[8] Hydroxylamine was shown to be a primary product by the use of N^{15}labelled chloramine showing the original work of Riley[20] to be inaccurate. Hydroxylamine had originally been postulated by McCoy[21] in order to explain the formation of small amounts of cyclohexanone oxime when the hydrolysis was carried out in the presence of cyclohexanone. Anbar and Yagil[18a] used a similar technique with diacetylmonoxime but showed that the rate of formation of the dioxime was twenty times greater than the rate of hydrolysis under the same conditions. Thus the formation of oximes from ketones and chloramine does not imply the presence of hydroxylamine as an intermediate. The formation of peroxynitrite ions in the presence of oxygen was taken as additional supporting evidence for the formation of hydroxylamine.

No evidence for the formation of hypochlorite, as had originally been suggested[6b] could be found, and also the addition of ammonia caused an increase rather than a decrease in rate of disappearance of chloramine.

$$NH_2Cl + OH^- \not\rightleftharpoons NH_3 + OCl^-$$

The rate enhancement on adding ammonia to the solution eliminates the possible decomposition sequence:

	$OH^- + NH_2Cl$	$\rightleftharpoons$ $NHCl^- + H_2O$	(fast)
	$NHCl^-$	$\longrightarrow$ $:\ddot{N}H + Cl^-$	(slow)
	$:\ddot{N}H + H_2O$	$\longrightarrow$ NH_2OH	(fast)
and/or	$:\ddot{N}H + NH_3$	$\longrightarrow$ $NH_2.NH_2$	(fast)

as the rate of hydrazine-formation should then only depend on the rate of chloramine decomposition. No isotopic exchange between chloramine and chloride was found hence excluding the possible reaction sequence:

$$NH_2Cl \rightleftharpoons NH_2^+ + Cl^-$$
$$NH_2^+ + OH^- \longrightarrow NH_2OH$$

Proton abstraction was not involved in the rate determining stage as shown by a negligible deuterium isotope effect but a fast pre-equilibrium reaction was

$$NH_2Cl + OH^- \rightleftharpoons NHCl^- + H_2O$$

confirmed by the use of tritium labelled water.

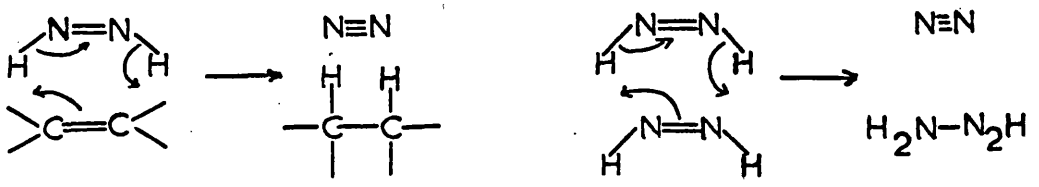
Two possible mechanisms based on the above evidence are feasible and it seems reasonable to suggest that both occur depending on the pH of the solution.

A	$OH^- + NH_2 - Cl$	$\longrightarrow HONH_2 + Cl^-$	S_N2
B	$OH^- + NH_2 - Cl$	$\rightleftharpoons NHCl + H_2O$	(fast)
	$H_2O + NHCl^-$	$\longrightarrow NH_2OH + Cl^-$	(slow)

LeNoble[22] measured the volume of activation of the hydrolysis of chloramine and the methyl chloramines in 1N sodium hydroxide and concluded that his results substantiated the bimolecular displacements proposed by Anbar and Yagil.

The formation of nitrous oxide and nitrogen was expained by the reaction of chloramine with hydroxylamine although no mechanism was suggested. Schmitz[23] has shown that chloramine and alkali in the presence of olefins produce the saturated hydrocarbon. The initial product is diimide which reacts with the olefin as shown. In the absence of an olefin, disproportionation to nitrogen and hydrazine occurred.

$$HO.NH_2 + NH_2Cl \longrightarrow NH_2\text{-}NH\text{-}OH \longrightarrow H\text{-}N{=}N\text{-}H + H_2O$$



b) Reaction with ammonia

Chloramine was first used as an aminating agent by Raschig[2] who prepared hydrazine by the reaction of aqueous chloramine and ammonia. The mechanism of this reaction was the subject of much debate, and many papers have been published providing conflicting evidence. Raschig originally proposed the initial decomposition of chloramine to form imene (NH) or nitrene, followed by attack on ammonia to give hydrazine. Audrieth et al. [11,13] suggested that the conjugate base ($NHCl^-$) either decomposed to give imene or alternatively attacked ammonia directly.

$$NHCl^- \longrightarrow :\ddot{N}H + Cl^-$$

$$:\ddot{N}H + NH_3 \longrightarrow N_2H_4$$

$$\text{or } NHCl^- + NH_3 \longrightarrow N_2H_4 + Cl^-$$

Bodenstein[24] proposed that direct substitution occurred as he found the reaction to be first order in both reactants (at pH~11). These results were confirmed by Cahn and Powell[25] who also showed that chloramine reacted much faster with hydrazine than with ammonia. Sisler[26] and Audrieth[27] showed that an added base was not essential for the formation of hydrazine and obtained high yields (80%) by passing gaseous chloramine into cold solution of aqueous ammonia. Chlorine, diluted with nitrogen, with aqueous ammonia also gave hydrazine (18%).

Anbar and Yagil[28] studied the formation of hydrazine under a variety of conditions and their results are summarised below:

(i) The reaction is first order in both chloramine and ammonia.

(ii) Maximum yields of hydrazine were obtained when low concentrations of chloramine and high concentrations of ammonia were used, and when the concentration of base was between 0.2 and 0.5 M.

(iii) Side reactions of chloramine with hydrazine are significant between pH 10.15 and 11.00 and lower the yield of hydrazine.

(iv) The reaction is independent of base between pH 11 and 14.

(v) Above pH 14 the reaction is base catalysed but the yield of hydrazine falls due to competing hydrolysis of chloramine. However, for a given pH the rate of reaction to give hydrazine was still faster than the rate of hydrolysis.

(vi) Addition of sodium chloride, gelatin or oxygen to the pure reaction mixture had negligible effects on the rate of reaction.

(vii) Rates of reaction in D_2O were slightly greater although yields of hydrazine decreased.

They therefore concluded that two mechanisms were in operation.

A base-independent path between pH 10 and 14:

$$NH_3 + NH_2Cl \longrightarrow NH_3\overset{+}{N}H_2 + Cl^- \quad \text{(slow)}$$

$$NH_3\overset{+}{N}H_2 + OH^- \longrightarrow N_2H_4 + H_2O \quad \text{(fast)}$$

and a base-catalysed path involving attack of ammonia on the chloramide ion:

$$NH_2Cl + OH^- \rightleftharpoons \overset{-}{N}HCl + H_2O \quad \text{(fast)}$$

$$NH_3 + \overset{-}{N}HCl \longrightarrow \overset{+}{N}H_3\overset{-}{N}H + Cl^- \quad \text{(slow)}$$

$$\overset{+}{N}H_3.\overset{-}{N}H \longrightarrow N_2H_4 \quad \text{(fast)}$$

The alternative mechanism:

$$NH_3 + OH^- \longrightarrow \overset{-}{N}H_2 + H_2O \quad \text{(fast)}$$

$$\overset{-}{N}H_2 + NH_2Cl \longrightarrow N_2H_4 + Cl^- \quad \text{(slow)}$$

was discounted because trimethylamine also showed a similar base-catalysed reaction with chloramine. The validity of this assumption is discussed on page 9.

The possible formation of imene as the rate determining step followed by a fast reaction with ammonia was excluded because this would render a rate expression zero order in ammonia. A fast pre-equilibrium $\overset{-}{N}HCl \rightleftharpoons :\ddot{N}H + Cl^-$ with a slow imene reaction with ammonia was excluded because no isotopic exchange between chloride ions and ammonia takes place and addition of chloride ions has no retarding effect on the rate of reaction.

Hydrazine (33%) was prepared by the amination of excess of liquid ammonia at -78° using gaseous chloramine.[9a] By varying the temperature and ratio of ammonia to chloramine yields greater than 80% were obtained.[29]

Further studies by Sisler[30] indicated that the hydrazine was formed by an S_N2 mechanism.

The low yields of hydrazine obtained when high concentrations of chloramine were used was explained by further reaction to form the triazane which then decomposed by a free radical mechanism to nitrogen and ammonia. The mechanism suggested was purely speculative however and not substantiated in any way. Sisler[31] later showed that hydrazine reacted with ammonia-free ethereal chloramine to give hydrazinium chloride, ammonium chloride and nitrogen. Reaction at -50° indicated that triazanium chloride $[H_2N.\overset{+}{N}H_2NH_2]\ Cl^-$ was initially formed and underwent subsequent decomposition on warming to room tempterature. The alternative amination mechanism whereby chloramide ions are initially formed was suggested by Jander.[10] He found that addition of potassium amide to the liquid ammonia improved the yield of hydrazine by increasing the amount of $\bar{N}HCl$ in solution. Sisler[32] and Hauser[33] however found that chloramine in liquid ammonia with potassium amide did not give any appreciable amount of hydrazine and this mechanism must be discounted. As well as water and liquid ammonia, 2-ethoxyethanol and ethanol have also been used as solvents in the preparation of hydrazine, although yields were rather lower.[26a] Ether was also tried but failed to give any hydrazine.[26a,34] (See later).

c) . N-Amination of amines.

Raschig[2c] first used chloramine as an aminating agent obtaining phenylhydrazine from aniline, and in 1915 Forster[35] isolated N-aminopiperidine as its benzaldehyde derivative by treating piperidine with aqueous chloramine. Audrieth and Diamond,[36] apparently unaware of this earlier work independently rediscovered the aminating potential

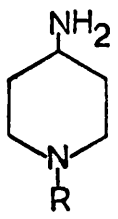
of chloramine in 1954 and extended the reaction to a wide range of primary and secondary amines. Anbar and Yagil[28] studied the kinetics of the reaction of primary, secondary and tertiary amines with aqueous chloramine and found the reaction to be first order in both amine and chloramine in a base-independent and base-catalysed reaction. The mechanisms suggested were analogous to the reaction of chloramine with aqueous ammonia.

The alternative base-catalysed mechanism:

$$OH^- + R_2NH \longrightarrow R_2N^- + H_2O \qquad \text{(fast)}$$

$$R_2N^- + NH_2Cl \longrightarrow R_2N.NH_2 + Cl^- \qquad \text{(slow)}$$

was discounted because trimethylamine gave similar kinetic results to methylamine and dimethylamine. However, although it was shown that a reaction occurred between trimethylamine and chloramine the products were never isolated and the possibility of an alternative reaction occurring other than direct amination, however unlikely, must still be considered. It is of interest to note that 1-alkyl-4-amino-piperidines (1) when treated with aqueous chloramine[37] at 0° gave the corresponding 1-alkyl-4-hydrazinopiperidine (2) rather than (3) and yet the rate of reaction of amines with aqueous chloramine was in the order $Me_3N > Me_2NH > MeNH_2 > NH_3$.



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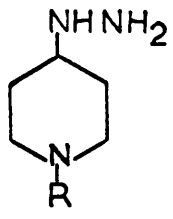
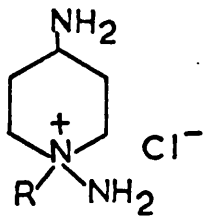


(2)



(3)

Anhydrous chloramine reacts with tertiary amines to give the 1,1,1-trialkylhydrazinium chlorides.[38] (See later).

The kinetic results by Anbar and Yagil[28] were extensions of the more empirical observations made by Audrieth and co-workers.[36,39,4] They found that primary amines gave the corresponding hydrazines in yields of 52-75%; the nature of the alkyl group had very little effect and even amines containing other functional groups such as ethanolamine, ethylenediamine, and allylamine gave good yields of hydrazines. Glycine however could not be aminated. The method has been extended to prepare a wide range of 1,1-substituted hydrazines on an industrial scale[37,40]

Anbar and Yagil[28] extended their studies to the reaction of N-alkylchloramines with ammonia. Their results showed only limited reproducibility which they attributed to competing secondary reactions and no hydrazines were ever isolated. Jander[41] demonstrated that N-methyl and N-ethylchloramine undergo preferential hydrolysis to the corresponding aldehydes even in the presence of a large excess of the amine.

$$RCH_2NH_2 + OCl^- \longrightarrow RCH_2NHCl + OH^-$$

$$OH^- + RCH_2NH\text{-}Cl \longrightarrow RCH{=}NH + H_2O + Cl^-$$

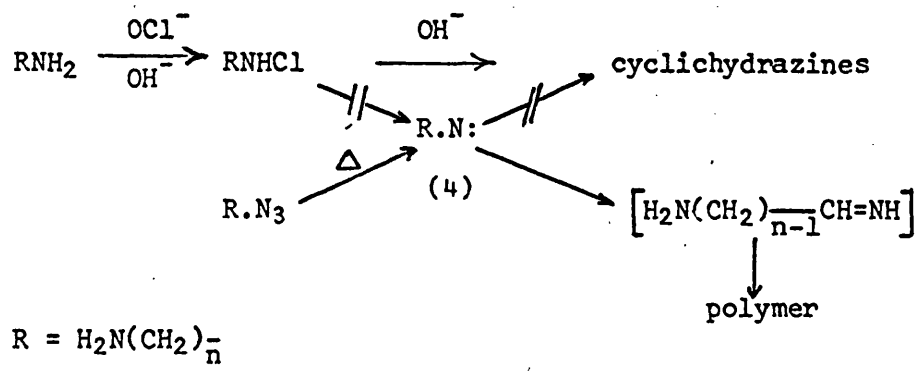
$$RCH{=}N\text{-}H + H_2O \longrightarrow RCHO + NH_3$$

$$RCH_2NHCl + RCH_2NH_2 \not\longrightarrow RCH_2NH.NHCH_2R + HCl$$

However, when 1,3-diaminopropane and 1,4-diaminobutane were treated with aqueous alkaline hypochlorite some of the corresponding 1,1'-cyclichydrazine was obtained.

$$H_2N(CH_2)_nNH_2 \xrightarrow[OH^-]{OCl^-} (CH_2)_n\begin{array}{l}NH\\|\\NH\end{array} \qquad (n=3,4)$$

It appears that the mechanism suggested by Jander is incorrect as the intermediate nitrene (4) when generated from the corresponding azide[42] gave none of the cyclichydrazine.



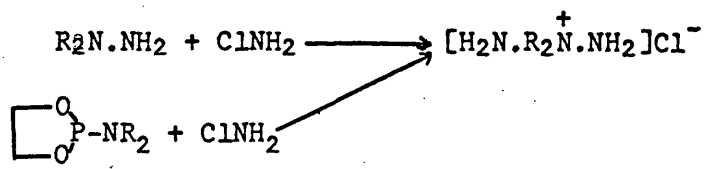
R = $H_2N(CH_2)_{\overline{n}}$

Sisler[32,43] found that primary and secondary amines formed the corresponding hydrazine when the liquid amine was treated with gaseous chloramine in excess of ammonia over a range of temperatures. Although the competing reaction of hydrazine formation occurred, better yields were obtained with ammonia present, since ammonium chloride rather than the amine hydrochloride was then precipitated. Under similar conditions pure aniline[44] gave phenylhydrazine (46%) at room temperature. Recent studies with ethereal chloramine at Leicester[45] indicated that little or no phenyl hydrazine was obtained but azobenzene was formed in good yield.

When diethylamine[32] was treated in an analogous manner none of the expected 1,1-diethylhydrazine was obtained, and the products were ethylhydrazine, ammonium chloride and diethylamine hydrochloride. Aqueous chloramine gives the expected product however.[4] No explanation for this very unusual reaction was offered.

Sisler[32] found that an increase in the initial concentration of chloramine lowered the yields of the substituted hydrazines obtained. He postulated attack of the hydrazines by chloramine in a manner analogous to that previously discussed for hydrazine itself. To test this theory he treated 1,1-disubstituted hydrazines with gaseous chloramine and chloramine-ammonia mixtures in benzene[46] or ether[31,47] and obtained the corresponding 2,2-dialkyltriazanium

chlorides (40-60%).



These interesting compounds could also be obtained by treating a benzene solution of 2-dialkylamino-1,3,2-dioxophospholane with gaseous chloramine and ammonia. In his latest paper,[48] Sisler has shown that they can be prepared directly from secondary amines by treatment with excess chloramine and ammonia. Substituted hydrazines are not attacked to any appreciable extent by excess of aqueous chloramine;[28] any unstable triazane formed would presumably be hydrolysed back to the hydrazine.

Kinetic studies were attempted by Horner[49] for the reaction of chloramine with primary and secondary amines in liquid ammonia. The reaction was complicated by the formation of hydrazine from chloramine reacting directly with the liquid ammonia and by the subsequent reaction of chloramine with hydrazine and possibly the substituted hydrazines also. It was shown, however, that at -50° the relative rates of reaction of chloramine with various amines were

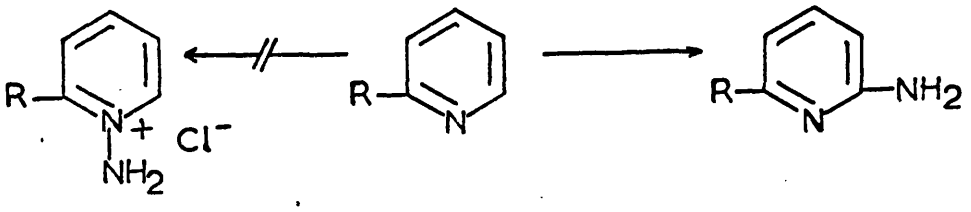
$$\underline{n}\text{-}Pr_2NH \quad (460) : \underline{n}\text{-}Pr.NH_2 \quad (140) : NH_3 \quad (1)$$

Comparison with tri-n-propylamine could not be made due to its insolubility in liquid ammonia. Substituting n-butyl for n-propyl caused only a slight decrease in the rates.

As previously mentioned trialkylamines can be aminated to 1,1,1-trisubstitutedhydrazinium chlorides using anhydrous chloramine. Sisler[38,9c] passed gaseous chloramine and ammonia mixtures through the liquid amine over a wide range of temperatures and isolated the salts in 65-99% yield based on chloramine.

$$R_3N + NH_2Cl \longrightarrow [R_3\overset{+}{N}NH_2]Cl^-$$

Mixed alkyl-aryl tertiary amines could also be used, but aromatic bases such as pyridine and 2-methylpyridine gave none of the expected product[38] (5) [R=H and Me].



(5) (6)

However, small amounts of 2-aminopyridine (6) [R=H] could be isolated from the reaction of chloramine and pyridine, and quinoline gave a mixture of 2-aminoquinoline and its hydrochloride in a combined yield of 40%. Caffeine and theobromine are also reported to react similarly and give low yields of the (8)-(?)-amino derivatives.[50]

Braude and Cogliano[51] have studied the rate of reaction of chloramine in several organic solvents. The reactions as expected were all second order and the rates of reaction increased with increasing polarity of the solvent and decreased with increase in size of the alkyl substituent. It was interesting to note that the reaction in ether was by far the slowest, as ethereal chloramine, stabilised by 0.1 M ammonia, shows only 1.2% decomposition after standing for several weeks at room temperature. This demonstrates the failure of ammonia[26a,34] and methylamine[36] to react with chloramine in dry ether.

A benzene solution of triethylenediamine reacts with gaseous chloramine at room temperature to give the monohydrazinium chloride.[44] N-Amination did not occur at both nitrogens due to precipitation of the mono-aminated product. The synthetic usefulness of this reaction has been exploited in many patents[52] and extended to include the amination of

tertiary amines containing functional groups,[52 e,h,m] alkaloids,[52j] and bridge-head nitrogen compounds[52l,i] either by reaction with the liquid amine or by reaction in a suitable solvent.

d) Miscellaneous N-aminations

Very few examples of compounds, other than amines, have been reported to undergo N-amination with chloramine. Nickon and Hill[53] attempted to aminate the tosyl derivative of 1-naphthylamine in aqueous alkali and found that at 0° no reaction occurred but on heating to reflux small amounts of naphthalene could be obtained. The N-amino compound (7) was postulated as the intermediate that underwent hydrolysis in the strongly basic solution to give naphthalene. Carpino[54] confirmed this postulate by isolating similar N-amino compounds under anhydrous conditions and showing that they decomposed in base to the hydrocarbon.

$$\text{Ar.NH.Tos} \xrightarrow{\text{ClNH}_2} [\text{Ar.}\overset{\text{NH}_2}{\underset{|}{\text{N}}}\text{—Tos}] \xrightarrow{\text{OH}^-} \text{ArH}$$

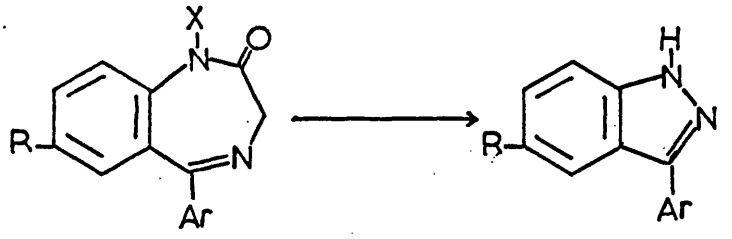
(7)

Ar = 1-naphthyl

Several amides have been N-aminated and Sisler[43] has also reported the N-amination of imines and imides as well as amides. Hoegerle[55] treated various pyridin-2-ones with a basic solution of aqueous chloramine and obtained reasonable yields of the corresponding N-amino compounds.

Quinolin-2-one gave only 7% of N-aminocarbostyril by this method however and Whitmann[56] was unable to reproduce this result. Other procedures have involved the treatment of the sodium salt of the amine derivative with ethereal chloramine in an inert solvent (see Table 1). 1,4-Benzodiazepin-2-ones[57](8) (X=H) when aminated with chloramine using

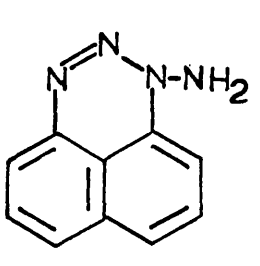
this technique gave indazoles (9) as well as the N-amino compound (8) (X=NH_2). The mechanism of this reaction as well as the mechanism of the triazinone (10) to triazole (11) rearrangement[58a] will be discussed in more detail later.



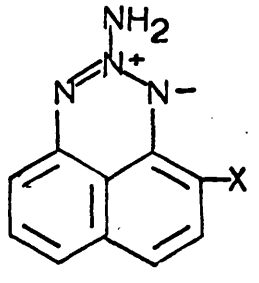
(8) (9)

(10) (11)

No satisfactory explanation has been given for the anomalous results shown by triazoles and triazines towards amination. Naphtho[1,8-de] triazine[59] when aminated with chloramine gave three N-amino compounds, (12) (43%), (13) (1.7%) , and(14)(0.8%).



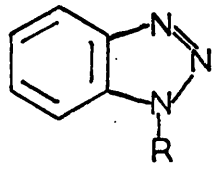
(12)

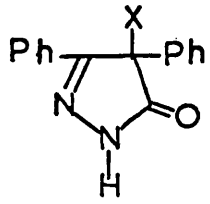


(13) X = H

(14) X = Cl

4,5-Diphenyltriazole[60] gave only 1-amino-4,5-diphenyltriazole (80%) and benzotriazole gave the ether[61] (15), which was formed from the intermediate 1-chlorobenzotriazole (16) in a radical reaction with the ether solvent.[62]





(15) R = -CH.Me.O.Et

(16) R = -Cl

(17) X = H

(18) X = Cl

Chloramine does not usually react as a chlorinating agent and besides those already mentioned only two other examples have been reported. The sodium salt of 3,4-diphenyl-2-pyrazolin-5-one (17) when treated with ethereal chloramine gave the 4-chloro derivative (18) [58a] and certain amino acids were reported to form the N-chloro derivatives[58b] although the products have only been identified spectrophotometrically.

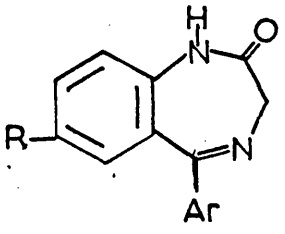
e) Reactions other than N-aminations

Schiff bases react with chloramines to give diaziridines. Schmitz[63] treated 3,4-dihydroisoquinoline with aqueous methanolic chloramine at room temperature and isolated the dimeric adduct (19). He showed that the diaziridine (20) was initially formed and when methylchloramine was used, was able to isolate the substituted diaziridine[64] (21).

Table I

Miscellaneous N-Aminations with Chloramine

Compound aminated	method	yield %	reference
$PhNHCOCH_3$	2d	60-70	57
2-Pyridone	1	25	55
	2	36	55
3-methyl	1	49	55
4-methyl	1	36	55
5-methyl	1	39	55
6-methyl	1	40	55
4,6-dimethyl	1	20	55
tetraphenyl	2a	50	58
6-methyl-3,4,5-triphenyl	2a	12	58
Carbostyril*	1	7	55
		0	56
Phenanthridone	2a	30	58
2,3-Diphenylquinolin-4-one	2a	18	58



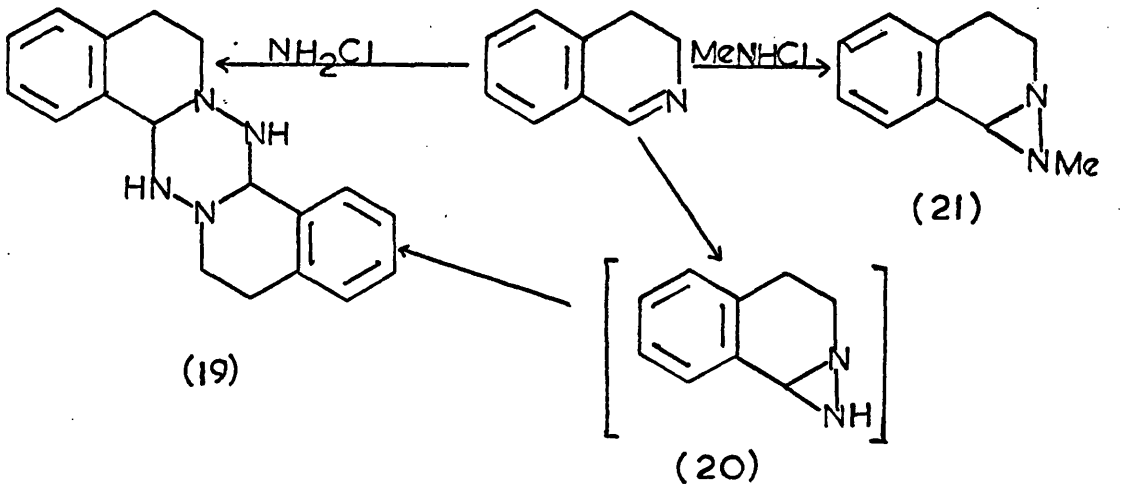
*

Ar	R			
Ph	Cl (4-N-oxide)	2d	64	57
Ph	NO_2 (4-N-oxide)	2d	20	57
o-$Cl.C_6H_4$	Cl	2c	78	57
Ph	NO_2	2c	44	57
4,5-Diphenyltriazole*		2b	80	60
Naphtho[1,8-de]triazine*		2	45[a]	62

Methods: 1 = aqueous basic chloramine; 2 = sodium salt in ether
2a= with methylene chloride added; 2b = with benzene added;
2c = with THF added; 2d = with DMF added

* - See text for further details.

a - mixture of (12), (13) and (14)



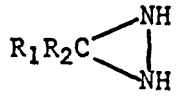
The reaction was found to be quite general and applicable to aliphatic Schiff bases derived from aldehydes, ketones and cyclic ketones.[65,66] Reaction of the Schiff base under anhydrous conditions with ethereal chloramine usually gave better yields of the diaziridines although both techniques could be used with equal results for alkyl chloramines.[65,67]

$$R_1R_2C{=}N{-}R_3 \xrightarrow[R=H,\ alkyl]{RNHCl} R_1R_2C\begin{array}{l}N{-}R\\ \\ N{-}R_3\end{array} \qquad (22)$$

Mild acid hydrolysis of the diaziridine gave the corresponding carbonyl compound and substituted hydrazine in excellent yields. This indirect method of N-amination gave better yields than direct chloramine amination and side reactions were minimised. 1,2 -Disubstituted hydrazines could readily be prepared by this method while most attempts to prepare them by direct amination with alkyl chloramines have so far proved unsuccessful.[41]

Abendroth and Henrich[68] tried to prepare hydrazine by the gas phase chlorination of ammonia and to trap any hydrazine formed with acetone. Instead of obtaining acetone hydrazone, however, they isolated the diaziridine (23). Paulsen[69] obtained the analogous compound (24) using methylethylketone and later found that better yields could be obtained by passing gaseous chloramine and ammonia mixtures (diluted with nitrogen) through the liquid ketone.[70]

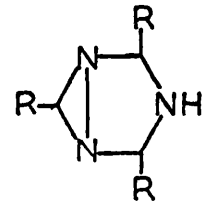
Formaldehyde was found to react with a methanolic solution of chloramine and ammonia to give the diaziridine (25),[71] although other aldehydes, including benzaldehyde, underwent further condensation to form the triazolidines (26).[72]



(23) $R_1=R_2=Me$

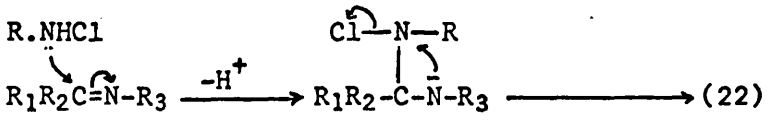
(24) $R_1=Me$, $R_2=Et$

(25) $R_1=R_2=H$

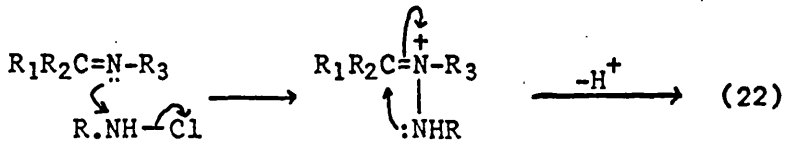


(26)

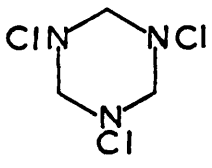
Schmitz[73] proposed the following mechanism for the formation of the diaziridines although the evidence presented was based only on



analogies with other systems and alternative mechanisms such as the one outlined below would appear to be just as feasible.



Schmitz in his mechanism postulated that chloramine and alkylchloramines reacted as nucleophiles although in most of the previous reactions mentioned chloramine can be considered as acting as an electrophile. Chloramine can act as a nucleophile, however, as Cross[74] found that formaldehyde and aqueous chloramine gave an N-chloro compound, the structure of which was shown[75] to be (27). They also found that acetaldehyde gave the monomeric product (28) although they were unable



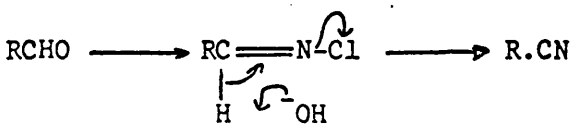
$R_1R_2C=N.Cl$

(28) $R_1=Me$, $R_2=H$

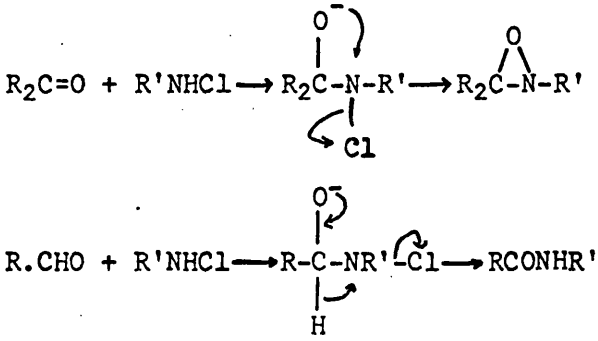
(29) $R_1=Ph$, $R_2=H$

(30) $R_1=R_2=$ alkyl

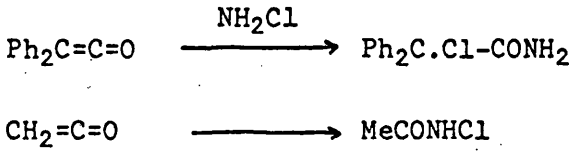
to isolate it in the pure state. Forster[35] showed that benzaldehyde gave the similar product (29) but it was Hauser[76] and co-workers who first isolated pure N-chloroaldimines by this method. Audrieth[11] used this technique to show that chloramine was formed by the action of t-butylhypochlorite on ammonia. The N-chloroaldimines were unstable to base and gave the corresponding nitriles presumably by the mechanism shown.



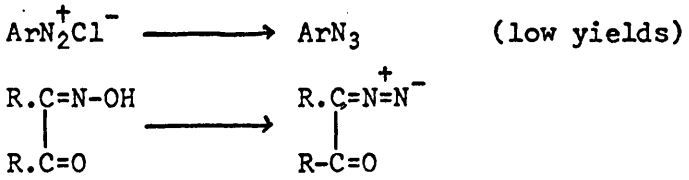
Ketones have only been treated with aqueous basic chloramine solutions[18a,21] and as previously mentioned oximes were isolated possibly via the intermediate (30). Monoalkylchloramines[77] react with aldehydes and ketones to form oxaziridines predominantly although aldehydes also give amides by a competing side reaction.



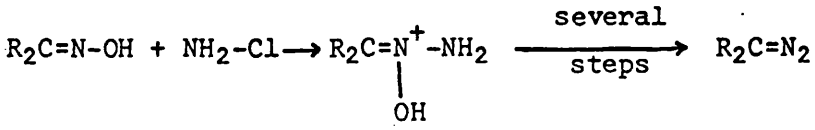
Amides are also formed when chloramine reacts with ketenes.[78] The reason for the difference in behaviour of diphenylketene and ketene is unknown.



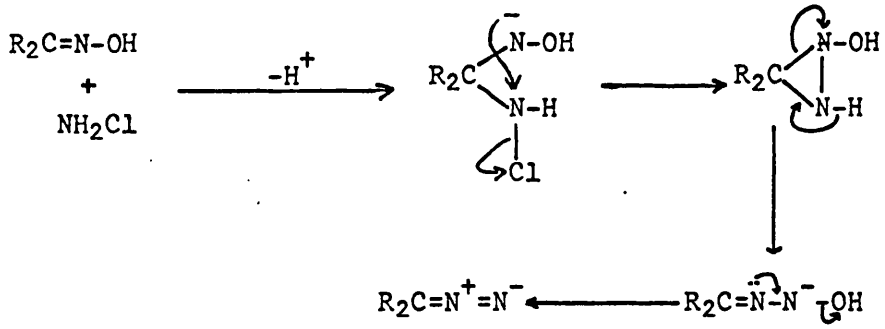
Diazonium chlorides and oximes were shown by Forster[35] to give azides and diazo compounds respectively when treated with aqueous chloramine and these may be considered as N-amination reactions. The use of the



latter reaction in synthesis has been demonstrated by several groups of workers.[79] Gassman[80] has shown that, contrary to the original findings of Carpino,[81] the presence of the α-carbonyl group was not essential and simple ketones and aldehydes gave diazo compounds when their oximes were treated with aqueous chloramine. Benzaldehyde was found to give some benzonitrile also. The mechanism postulated by Gassman is outlined below and involves initial N-amination. An alternative mechanism, not considered by



Gassman, based on similar arguments to those by Schmitz for the reaction of chloramine with Schiff bases, would give the following reaction scheme.



The synthetic use of chloramine in organo nitrogen chemistry has prompted extensive studies with the analogous phosphorus compounds. Phosphine itself gave only a polymeric phosphorus hydride, phenyl phosphine gave tetraphenyl phosphetane $(PhP)_4$ and diphenylphosphine gave tetraphenylbiphosphine $(Ph_2P\text{-}PPh_2)$.[82] This was in striking contrast to the reaction of chloramine with ammonia

and primary and secondary amines. The reaction with trisubstituted phosphines, however, produced aminophosphonium chlorides (31) or one of its condensation products, in direct comparison with tertiary amines.[83,44]

$$R_3P + NH_2Cl \rightarrow [R_3P.^{+}NH_2]Cl^{-}$$

(31)

It is of interest to note that compounds of the type (32)[84] and (33)[85] containing a secondary or tertiary amine residue only aminate on the phosphorus atom. Even when the corresponding phosphine oxides were used the nitrogen atom was still not aminated, and the compounds were recovered unchanged.

$$R_2PNHR' \longrightarrow [R_2P^{+}(NH_2).NHR']Cl^{-}$$

(32)

$$R_2PNR'_2 \longrightarrow [R_2P^{+}(NH_2).NR'_2]Cl^{-}$$

(33)

These reactions have been extended to two other members of Group V, arsenic[86] and antimony,[87] and also to silicon, germanium and tin compounds.[88] Dialkyl sulfides when treated with gaseous chloramine in ether give aminosulfonium chlorides (34)[89a] and in alcohols the sulfodiimides[89b] (35) and not (36) as was originally thought.[90]

$[R_2S^{+}NH_2]Cl$ (34) $[R_2S(NH)_2].HCl$ (35) $[R_2S\text{-}NH\text{-}NH]_2.HCl$ (36)

Mercaptans react with aqueous chloramine in basic solution to give the S-amino compounds and the success of this reaction prompted Long[92] to try to apply it to alcohols. Cold benzene solutions of the sodium salts of alcohols when treated with ethereal chloramine in general gave no reaction, except for benzyl alcohol and 2-

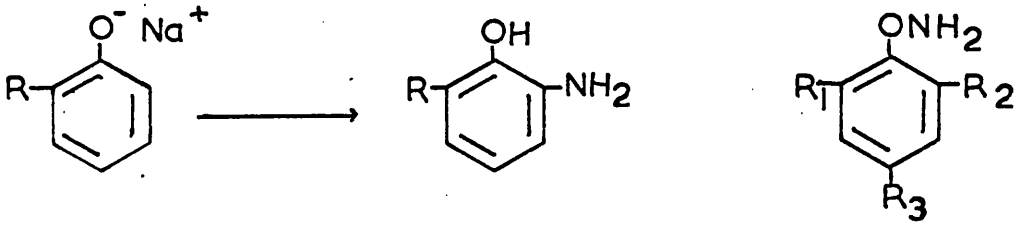
phenoxyethanol which gave the O-substituted hydroxylamine (1-5%). Theilacker[93] found that the reaction was quite general and reasonable yields of the O-hydroxylamines could be obtained when the alcohol and its sodium salt were treated with ethereal chloramine at 80°.

The reaction could not be extended to phenols, however, as phenol and O-substituted phenols gave o-aminophenols (37);

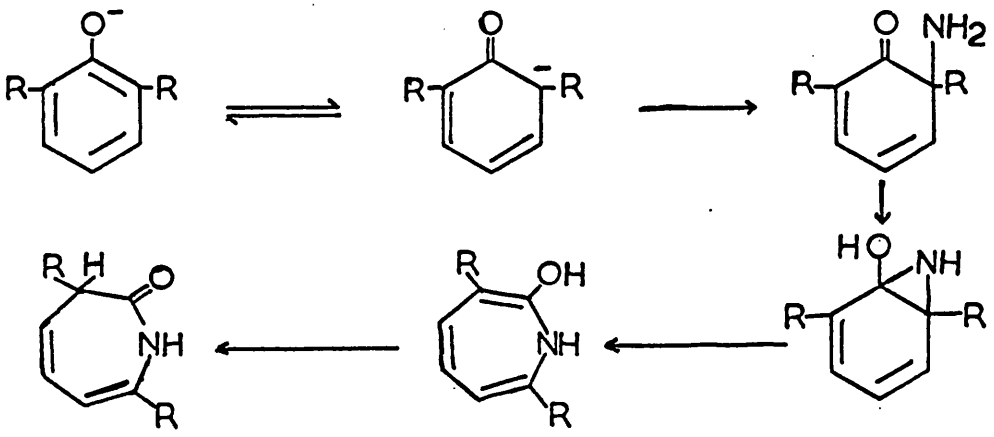
$$R.SH \xrightarrow[ClNH_2]{OH^-} RSNH_2$$

R =		
	α-pyridyl	ref. 91a
	α-piperidyl	ref. 91a
	α-benzothiazoyl	ref. 91b
	Me_2N-CS-	ref. 91c

2,6-di- and 2,4,6-tri-substituted phenols although originally reported to give the O-aryl hydroxylamine (38)[94] were found on re-examination to be 1,3-dihydro-2H-azepin-2-ones (39).[95]



(R=alkyl, H) (37) (38)



(39)

Paquette showed that the product ratio was directly related to the steric hindrance at each ortho site.[96]

If the phenol, as opposed to the sodium salt, was treated with ethereal chloramine at 120-145° then products derived by oxidative coupling were obtained. Paquette[97] postulated initial proton transfer from the phenol to the chloramine followed by an unprecedented redox reaction to give phenoxy and aminium radicals (40) and chloride ions.

$$ArOH \xrightarrow{ClNH_2} Cl^- + \underset{(40)}{\overset{+\cdot}{N}H_3} + ArO^{\cdot} \longrightarrow \text{dimers}$$

As well as the aminium radical (40), two other unusually reactive intermediates have been postulated to account for some of the reactions of chloramine. Jander[98] photolysed solid chloramine at -190° and obtained a blue compound formulated as $(NH)_n$ which decomposed at -150° to give ammonium azide. Pyrolysis of chloramine at 500° in the presence of carbon monoxide gave hydrogen cyanate and in both cases imene (ŃH) was postulated as the intermediate. Ogatawa[99] photolysed chloramine in the presence of cyclohexene and rationalised his products as arising from the intermediate amine radical ($\dot{N}H_2$), with imene also being formed in a secondary process.

Chloramine also reacts with organo boranes[100] and with Grignard reagents [101]to give the corresponding primary amines.

2 HYDROXYLAMINE-O-SULFONIC ACID (HOS)

a) Preparation and hydrolysis

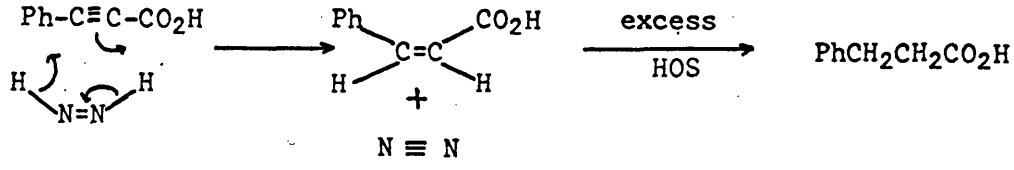
HOS was first prepared in 1914 by Sommer et al.[102] by the reaction of hydroxyammonium sulfate with chlorosulfonic acid at 100°. The method was modified slightly by the use of oleum instead of chlorosulfonic acid.[103,104] Other methods of preparation involve the reaction of sulfur trioxide with hydroxylamine[105] or nitromethane,[106] the hydrolysis of hydroxylaminetrisulfonic acid[107] and the reaction of sodium azide with fuming sulfuric acid.[108]

Numerous different names and structures have been proposed for HOS.[109] I.r.[110] and p.m.r.[111] studies suggested that in the solid state HOS is best represented as the zwitterion, $NH_3^+O\bar{S}O_3$. Diazomethane gave a trimethyl adduct identical to that prepared by the reaction between trimethylamine-N-oxide and sulfur trioxide.[109]

$$SO_3 + Me_3N^+-O^- \longrightarrow Me_3N^+-O-SO_3^- \longleftarrow CH_2N_2 + NH_3^+-O-SO_3^-$$

HOS is unstable in aqueous solution and hydrolyses to hydroxylamine and sulfate ions.[102] Sommer showed that addition of base to aqueous solutions of HOS caused rapid decomposition with formation of nitrogen and ammonia. Traces of hydrazine and hydrogen azide were also said to have been detected. The acid hydrolysis of HOS has been studied[112,108] and the conclusions reached were that two concurrent reactions were occuring; an acid independent hydrolysis of the anion of HOS and an acid catalysed hydrolysis of the free acid, both resulting in fission of the S-O bond.[112c] The mechanism of hydrolysis is unknown, however, as is the precise nature of HOS in solution.

The basic hydrolysis of HOS has not yet been studied kinetically. Empirical observations[102] showed that nitrogen and ammonia were formed and Audrieth[112b] showed that in weakly acid solutions decomposition as well as hydrolysis occurred. Chandlin[112c] showed that in basic solution N-O bond fission occurred. It was not until 1961, that Appel[113] and Schmitz[23] showed that diimide was the intermediate in the basic hydrolysis of HOS by its ability to reduce various olefins and acetylenes. Thus, phenylpropiolic acid gave cis-cinnamic acid as well as some 3-phenylpropionic acid.



Appel[114] suggested that imene was the intermediate leading to diimide and postulated its formation as shown.

$$H_2N.O.SO_3^- \xrightarrow{OH^-} HN^-{-}OSO_3^- \longrightarrow \ddot{H}N: + SO_4^{2-}$$

$$:\ddot{N}H + HN^-{-}OSO_3^- \longrightarrow HN^-{-}NH\text{-}OSO_3^- \longrightarrow HN{=}NH + SO_4^{2-}$$

Imene cannot be formed by a reversible reaction with HOS, as radioactive sulfur is not incorporated into HOS when partially hydrolysed in a basic solution containing active sulfate.[73] If it was formed by an irreversible reaction then, assuming that the reaction with the substrate was fast, the rate of reaction would depend only on the rate of formation of imene.[73] The reaction of HOS with iodide ions,[115] for example, was faster than the rate of hydrolysis under the same conditions. Smith has shown that the reaction follows the rate law:

$$\frac{d(I_2)}{dt} = k[I^-][H_2NOSO_3H]$$

He therefore postulated the following mechanism:

$$NH_2OSO_3H + I^- \longrightarrow NH_2I + SO_4H^- \qquad \text{(slow)}$$

$$NH_2I + HI \longrightarrow NH_3 + I_2 \qquad \text{(fast)}$$

Schmitz[116] suggested a more probable mechanism to account for the formation of diimide. He postulated initial slow formation of hydroxylamine which then underwent rapid attack by more HOS to give diimide.

$$OH^- + NH_2\text{-}O\text{-}SO_3H \longrightarrow NH_2OH + HSO_4^- \qquad \text{(slow)}$$

$$HONH_2 + NH_2OSO_3H \longrightarrow HO\text{-}\overset{+}{N}H_2\text{-}NH_2 + HSO_4^-$$

$$\downarrow -H^+$$

$$\downarrow -H_2O$$

$$HN{=}NH$$

The diimide then reduced the olefin, or in the absence of olefin disproportionated to nitrogen and hydrazine. In support of his mechanism, Schmitz found that he obtained equal yields of a dihydro adduct either by using two equivalents of HOS or by using one equivalent of HOS and one equivalent of hydroxylamine. Ackermann[117] and co-workers have investigated the kinetics of the reaction of HOS with alkaline hydroxylamine solutions and found the rate law:

$$\text{rate} = k[OH^-][H_2NOH][H_2NOSO_3^-]$$

They also found that N-methylhydroxylamine reacted with HOS to give methyldiimide which they were able to isolate and characterise.

$$H_2NOSO_3^- + MeNHOH + OH^- \longrightarrow MeN{=}NH + SO_4^{2-} + H_2O$$

Bargigia et al.[118] reported that treatment of hydroxyammonium sulfate

with a basic solution of HOS at 15° gave an unspecified yield of hydrazine. This would tend to support the Schmitz theory but the usual product of HOS decomposition is ammonia and not hydrazine.[102,112]

Schmitz has suggested that hydrazine reacted with HOS in an analogous way to chloramine and formed the triazane which then decomposed to ammonia and diimide. He indicated that some triazane was formed by treating ^{15}N-labelled hydrazine with HOS and isolating some N^{15}-ammonia. Feher and Linke[119] isolated a compound ($N_3H_7SO_4$), believed to be the triazane (41), by treating a solution of anhydrous hydrazine

$$[H_2N.\overset{+}{N}H_2.NH_2]H^-SO_4 \xrightarrow{\Delta} (N_2H_4).H_2SO_4 + (NH_4)_2\ SO_4$$

(41)

in methanol with HOS under nitrogen at 0°. At room temperature it decomposed to ammonium sulfate and hydrazine sulfate The reduction of fumaric to succinic acid, even in the absence of base, would seem to indicate that diimide was formed by the reaction between HOS and hydrazine.[114]

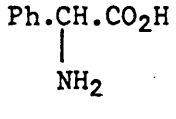
b) Reaction with ammonia

HOS, like chloramine, can be used to prepare hydrazine by reaction with ammonia.[102] Yields depend on factors very similar to those mentioned for the chloramine reaction but this method of preparation has not found widespread industrial application. Ammonium carbonate or carbamate[120] can be used in place of ammonium hydroxide to give high yields of aqueous hydrazine. Anhydrous hydrazine (98.5%) has been prepared by passing ammonia through the sulfate salt of HOS at 125°.[121]

c) N-Amination of amines

The chemistry of HOS discussed so far has been directly analogous to that of chloramine. The analogy can be extended by comparing their reactions with substituted amines. Although the reaction of HOS with ammonia has received scant attention, the reaction with amine derivatives has been widely investigated. Where appropriate any differences between HOS and chloramine will be mentioned.

Methyl-, benzyl-, and 2-aminoethylhydrazine[102] were prepared from the corresponding amines by treatment with HOS in aqueous potassium carbonate at 100°. 1-Phenylethylamine[122a] can be aminated in low yield in aqueous potassium hydroxide and Berger[122b] obtained an unspecified yield of the hydrazine (43) from the amine (42) but found that the amine (44) could not be aminated. Glycine (45) could not be aminated with HOS [104]or chloramine.[28]



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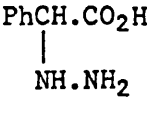

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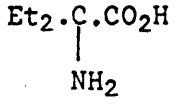
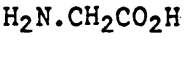


(44)



(45)

Gever[123] found that good yields of monosubstituted hydrazines could be obtained from the corresponding amine using a ratio of amine: HOS = 7:1. The presence of an additional base was not required and lower yields were obtained when a large excess of amine was used, presumably due to the HOS being hydrolysed.[123,124] Goesl[104] investigated HOS amination reactions with amines and concluded that the nature of the substituent had little effect on the yield of hydrazine obtained. For primary amines, maximum yields were obtained using a ratio similar to

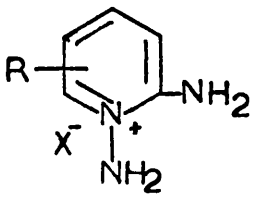
that of Gever,[123] but for secondary amines the optimum ratio was 4:1. Temperature had little effect on the yields of the hydrazines although the rate of reaction increased with increase in temperature. Addition of another base only increased the yields of hydrazines when the amine: HOS ratio was low, as HOS does not aminate in acidic solutions.

Primary aromatic amines[102,104] and recently[125] aziridines have also been N-aminated. It has been found that yields and reaction rates follow the sequence: $R_3N > ArNR_2 > R_2NH > RNH_2$, and that reaction occurs by S_N2 diplacement.

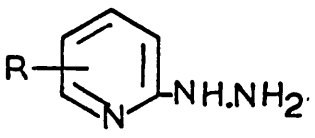
$$R_1R_2R_3N + NH_2.OSO_3H \longrightarrow R_1R_2R_3N^+.NH_2 + HSO_4^-$$

(R=H or alkyl)

Goesl[126] found that, unlike aqueous chloramine, HOS could be used to aminate trimethylamine. The method was extended to include a wide range of tertiary amines,[104,127] including those containing other functional groups. It was also found that aromatic bases such as pyridine could be N-aminated,[104,124] although all attempts using chloramine had failed. This method, with modifications, has been used by several workers.[128] 2-Aminopyridines,[129] when aminated with HOS, gave the corresponding pyridinium salt (46) and none of the hydrazines (47) were obtained. This contrasts directly with the reaction of chloramine with similar compounds (see pages 9 and 13).



(46)



(47)

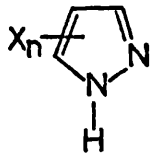
HOS, unlike chloramine, can also be used to prepare di-N-amino compounds directly,[127a,130] although the corresponding reaction with N-methylhydroxylamine-O-sulfonic acid failed. Only one example of N-amination with an N-alkyl derivative of HOS has been reported:[131]

$$PhNHMe + MeNHOSO_3H \xrightarrow{OH^-} PhN.Me\text{-}NHMe \qquad (20\%)$$

HOS has also been reported to react with 1,1-disubstituted hydrazines to give triazanes.[132]

d) Miscellaneous aminations

Pyrazoles, triazoles, triazines, tetrazoles, amides, imides, sulfonamides and inorganic X_2N-H compounds as well as amines have been aminated with HOS. Harder[133] found that addition of HOS to the substituted pyrazoles (48 a-d) in aqueous sodium hydroxide at room temperature gave low yields of the 1-amino compounds (49). None of the isomeric compound 1,3-diamino-4,5-dicyanopyrazole was reported when (48d) was aminated.



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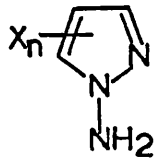
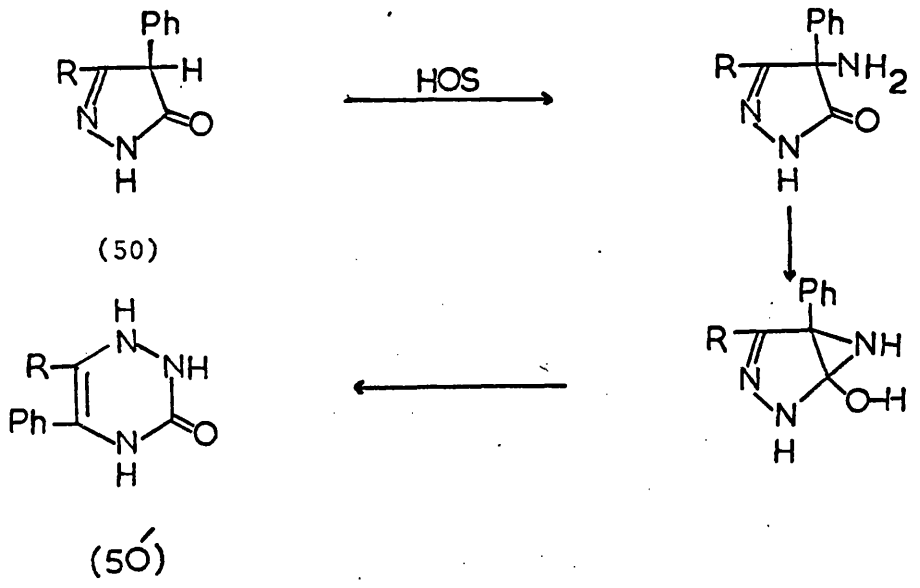


(49)

X_n = a) 4-nitro
b) 4-chloro
c) 3,4,5-tribromo
d) 5-amino-3,4-dicyano

Pyrazolin-5-ones, (50), however, did not undergo N-amination when treated with HOS in aqueous sodium carbonate,[58] but gave the ring enlarged product (50), presumably by the mechanism shown, which is similar to that suggested by Paquette[95,96] for the chloramine amination of phenols.

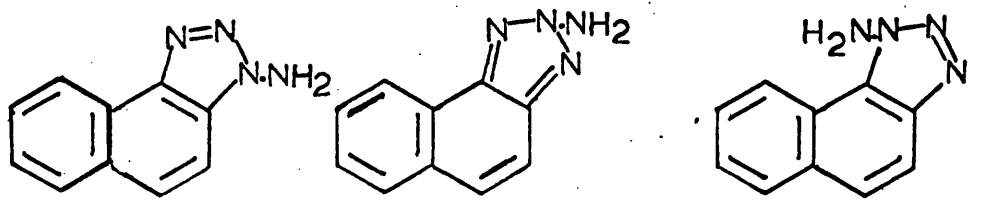


(50)

(50́)

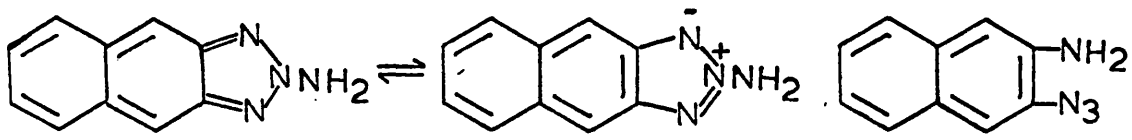
R = Ph , $PhCH_2$.

Amination of benzotriazoles[134,135] in aqueous alkali at 70° with excess of HOS gave mixtures of 1- and 2-aminobenzotriazoles in yields of up to 75%. 4,5-Diphenyltriazole gave no N-amino compounds[60] although the reverse was found with chloramine. Naphtho[1,2-d]triazole gave (51) and (52), and t.l.c. indicated the presence of a third product, presumably (53).[59]



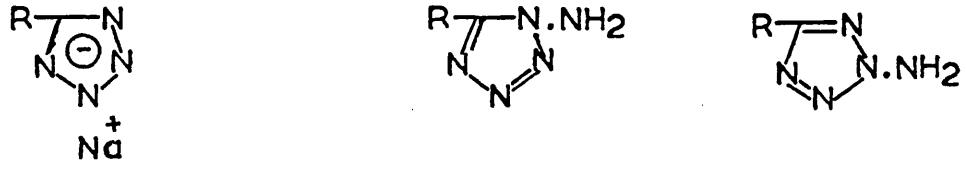
(51) (52) (53)

Amination of naphtho[2,3-d]triazole gave mainly the 1-amino compound but a small amount of 2-amino-3-azidonaphthalene was also formed, presumably by rearrangement of the expected 2-aminotriazole (54).



(54)

Naphtho[1,8-d]triazine gave the red 1-amino compound and also colourless 1-amino-8-azidonaphthalene which was shown to be formed by the alkaline rearrangement of the 2-amino compound. (The reaction of chloramine with triazoles and triazines was discussed on pages 15 and 16). Tetrazoles[136] can also be aminated to a mixture of the N-amino compounds (55) and (56) using HOS in aqueous sodium carbonate.



(55) (56)

R =	H	nPr	Ph	2-furyl	NH_2
yields %					
(55)	25	35	15	28	9
(56)	13	26	32	12	5

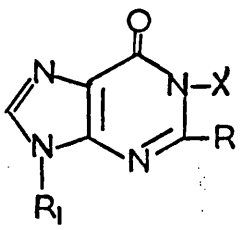
Wittman[56] obtained rather erratic results when he aminated a suspension of carbostyril in aqueous sodium hydroxide over a range of temperatures. It was later shown[137] that the sodium salt was too insoluble in aqueous base and more consistent results could be obtained with the soluble potassium salt. Metal salts of amine derivatives are often more soluble in aqueous alcohol, and although HOS has been reported to react with alcohols [102] (see later), the reaction is

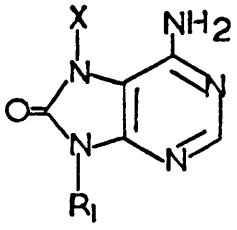
slower than N-amination and hydrolysis, and aqueous alcohol has been used effectively as an aminating solvent.[127a]

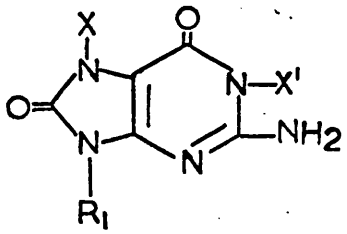
Chloramine has also been used to prepare N-aminocarbostyril although in poor yield.[55,56]

Benzoxazolin-2-one[138] gave the N-amino compound (22%) when only one equivalent of HOS was used. The yield has since been improved using excess of HOS.[139]

The purine nucleosides (57), (59) and (61) have been aminated with HOS to give (58), (60), (62) and (63). Compound (61) was found to undergo amination at both nitrogens although none of the mono-substituted product (64) was isolated.[140]





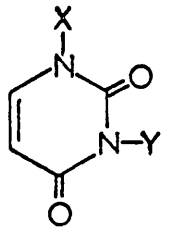


(57) X = H (59) X = H (61) X = X'= H (63) X = X'= NH_2

(58) X = NH_2 (60) X = NH_2 (62) X=H, X'=NH_2 (64) X = NH_2, X'=H

R_1 = a sugar residue

Kloetzer[141] also found that N-amination occurred at both the amide and imide nitrogens in uracil to give both mono N-amino compounds as well as 1,3-diaminouracil.

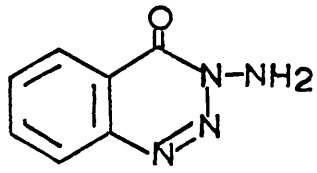


X = H, Y = NH_2

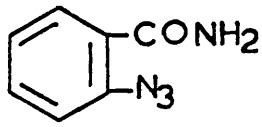
X = NH_2, Y = H

X = Y = NH_2

1,2,3-Benzotriazin-4-one[142] gave (65) when treated with HOS at 0° in aqueous sodium carbonate. Higher temperatures or a stronger base gave the azide (66).



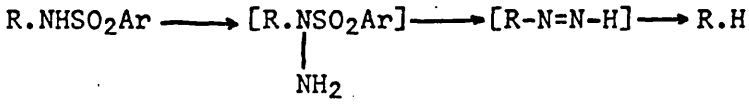
(65)



(66)

1,2,4-Triazin-4-ones, however, rearrange to imidazolin-2-ones[58] and will be discussed in more detail later.

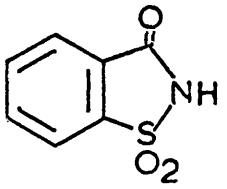
Nickon[53,143] treated a variety of sulfonamides (67) with HOS at 100° and distilled the resulting mixture to obtain the corresponding hydrocarbon (70). The N-amino compounds (68) were postulated as intermediates and were later prepared under anhydrous conditions by Carpino,[54] who showed that with base they did indeed decompose to the hydrocarbon (70). Futher investigation showed that the diimide (69) was the intermediate in the hydrolysis of (68).[144]



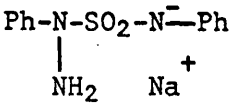
(67) (68) (69) (70)

Aqueous chloramine reacted similarly (see page 14).

Saccharin (71) has so far resisted all attempts at amination and is recovered unchanged from reaction with HOS, chloramine and O-(2,4-dinitrophenyl)hydroxylamine.[145] N,N'- Diphenylsulfamide when treated with HOS in alkali at room temperature gave (72), the only example of a compound of type (68) that has been isolated using this technique.[146]



(71)



(72)

Sulfamates (73) can be N-aminated with HOS; the yields depend on the nature of X and decrease in the order shown.

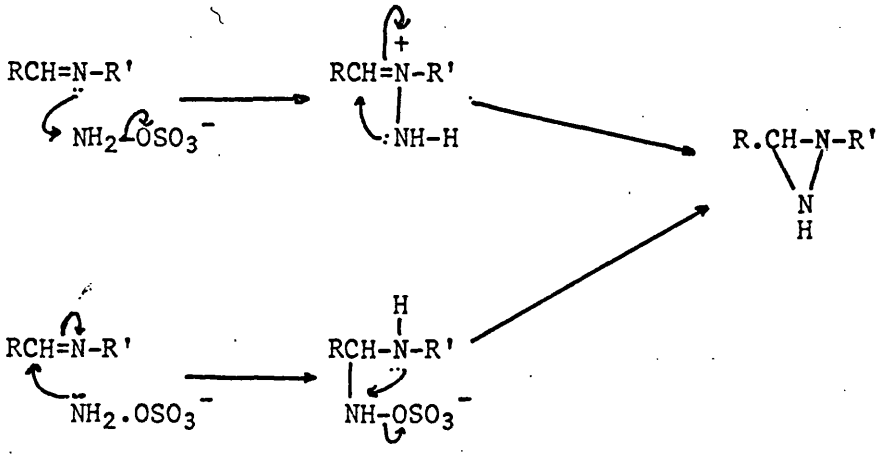
(73)

X = SO_3K > Aryl > Alkyl > H

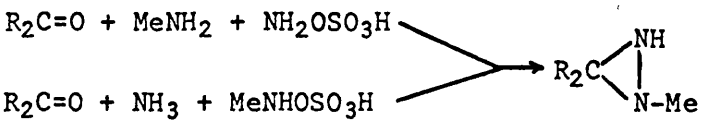
The silicon compound $(R_3Si)_2NH$ could not be aminated with HOS.[147] It would appear that HOS can be used as an aminating agent to a greater extent than chloramine. Direct comparisons, except in a few examples, cannot be made, however, as very few compounds have been aminated by both.

e) Reactions other than N-aminations

HOS was found to react with ammonia-carbonyl compound mixtures,[66,148] and Schiff bases[149] to form diaziridines; a mixture of amine and carbonyl compound can also be used in place of the Schiff base.[66,71,150] The reaction is analogous to that of chloramine and a Schiff base and probably proceeds by a similar mechanism. HOS does not incorporate radioactive sulfate by isotope exchange[73] and the rate of formation of diaziridine is much faster than the rate of hydrolysis of HOS under the same conditions. These results eliminate the reversible or irreversible formation of imene (NH) or $\overset{+}{N}H_2$ as the reactive intermediate but do not allow a distinction to be made between the two alternative mechanisms shown below.



The three membered ring structures were confirmed when identical products were obtained from the reactions shown below.[151]



Aromatic Schiff bases gave hydrazones when treated with HOS. The reaction probably proceeded via an unstable diaziridine intermediate.[152]

HOS, as well as aqueous chloramine, reacted with oximes to give diazo compounds[80] (see pages 20 and 21).

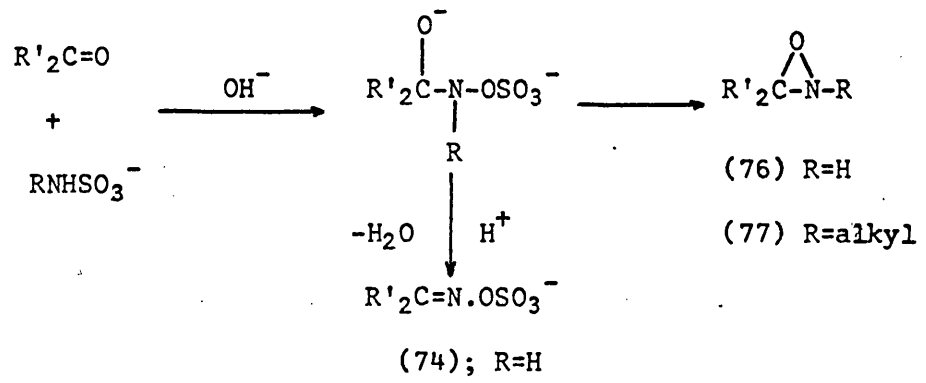
In neutral solution, HOS reacted with aldehydes and ketones to give the oxime-O-sulfonic acids (74) which were usually isolated as the potassium salt.[102] The reaction of HOS with formaldehyde gave hydrogen cyanide,[153] since the intermediate (74; R_1=R_2=H) is unstable. Higher aldehydes are only decomposed to the corresponding cyanide in acid solution.[102]

(74) (75)

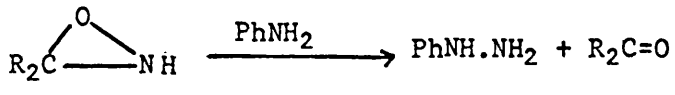
Salicylaldehyde gave a similar derivative which in the presence of base underwent intramolecular cyclisation to give benzisoxazole (75).[154] Reaction of neutral or acidic HOS with dialkyl ketone gave an oxime,

and with an alkyl aryl ketone gave an amide (ArNHCOR); diaryl ketones did not react.[155] Smith [156] later showed that the intermediates (74) were initially formed and gave either the oxime or the amide depending on the nature of the ketone. Benzaldehyde was found to form both the oxime and benzamide.[152] (For the analogous reaction with chloramine, see pages 3, 20).

In the presence of base, and at low temperatures ketones,[77,157] and benzaldehyde[73] react with HOS to give the very unstable oxaziranes (76). N-Alkyl derivatives of HOS (and of chloramine, page 20) gave similar reactions, although the substituted oxaziranes (77) were more stable.[158]



The oxaziranes (76) can be classed as a fifth aminating agent, as Schmitz[159] found that they reacted with aniline to give phenylhydrazine.



(76)

Triphenylphosphine[160] reacted with HOS in methanol to give (78) and although the reactions of chloramine with organophosphorus compounds have been studied extensively this appears to be the only reaction reported with HOS. Dialkyl[161] and diaryl sulfides[162] gave the analogous compounds (79); in the presence of sodium methoxide, however, the free base (80) was obtained.

$[Ph_3\overset{+}{P}NH_2]H\bar{S}O_4$ $[R_2\overset{+}{S}NH_2]H\bar{S}O_4$ $R_2S = NH$

(78) (79) (80)

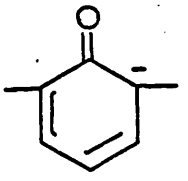
Other sulfur compounds that have been aminated are thiosulfates[163] and xanthates.[164] The latter has also been aminated with aqueous chloramine.

$$\bar{S}.SO_3K + H_2NOSO_3H \xrightarrow{0^\circ} KSO_3.S.NH_2$$

$$ROCS.S^- + H_2NOSO_3H \xrightarrow{0^\circ} RO.CS.S.NH_2 \qquad (100\%)$$

Anhydrous alcohols reacted with HOS in a similar manner to chloramine and gave the O-alkylhydroxylamines which were usually isolated as the more stable salt.[102,108,165]

$$R.OH \xrightarrow{HOS} RONH_2.HX$$



(81)

Phenols also gave O-arylhydroxylamines when treated with an aqueous basic solution of HOS.[166] Chloramine gave products arising from initial attack on the carbanion (81) (see page 23) but the conditions used were not comparable.

Carboxylic acids when heated with HOS at 170-180° until nitrogen evolution ceased gave low yields of amines.[167] The following reaction scheme was proposed.

$$RCO_2H + NH_2OSO_3H \longrightarrow [RCONHOSO_3H] + H_2O$$

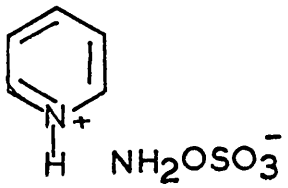
$$\downarrow$$

$$(20\text{-}25)\%.R.NH_2 \longleftarrow RNCO + H_2SO_4$$

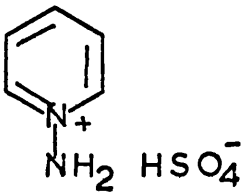
Smith[168] found that aromatic compounds could be aminated with HOS in the presence of aluminium chloride and postulated attack by either

imene or $\overset{+}{N}H_2$. Bennett[169] preferred the complex $[H_2NOSO_2OAlCl_2]AlCl_3$ as the aminating agent as two moles of aluminium chloride gave the best yields of amines.

It was also claimed that 2-(?)-aminopyridine was formed when the pyridine salt of HOS (82) was heated.[168] No experimental details were given, however, and the compound may be the N-aminopyridinium salt (83).

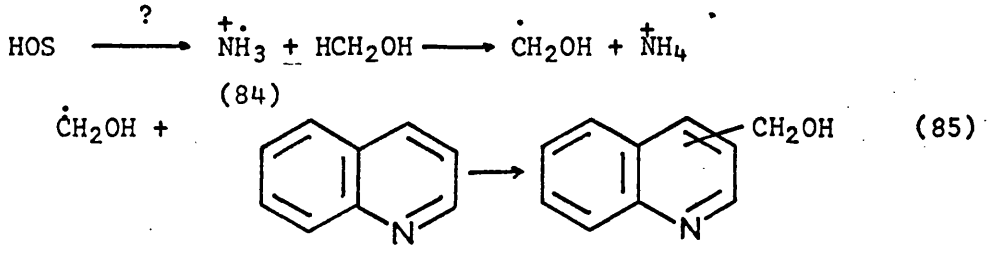


(82)



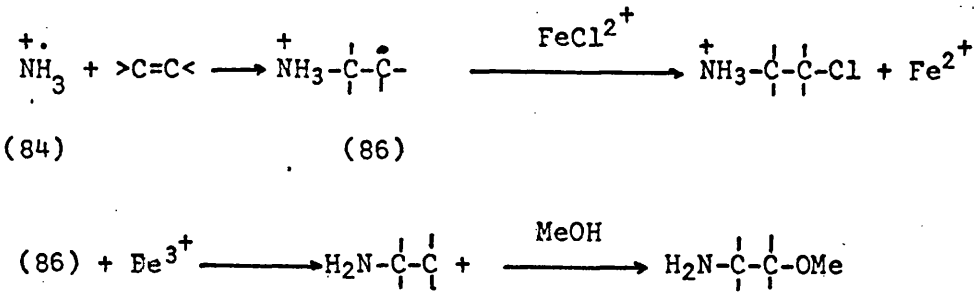
(83)

Attempted amination of substituted quinolines with HOS in methanol gave no N-amino derivatives,[170] (the mixtures used were acidic) but 2- or 4- hydroxymethyl quinolines (85) were obtained. The following scheme was proposed.



Minisci[171] also postulated the formation of the ammonium radical ion (84) for the HOS amination of aromatic hydrocarbons with either ferrous chloride or ferrous sulfate. The results in general were similar to those obtained with HOS and aluminium chloride. This radical ion has also been postulated[97] in the oxidation of phenols with chloramine.

Olefins with HOS and ferrous chloride gave the corresponding 2-chloroamine,[171,172] the following mechanism was proposed. The intermediate (86) could also be trapped with methanol to give the amino ether.



(84) (86)

HOS[173] has been reported to give a small amount of 3,4-pyrroline from butadiene in a solution of methanol and sodium methoxide and imene was proposed as the intermediate. Confirmation of this result would be of interest.

HOS reacted with organoboranes in THF[100] or diglyme[174] to give alkylamines in an analogous manner to chloramine. Several other miscellaneous reactions are shown below and HOS has also been used for polymer initiation.[175]

$H_2NOSO_3H + CN^- \longrightarrow H_2N\text{-}CN$ ref. 176

$H_2NOSO_3H + B_{10}H_{10}^{2-} \longrightarrow 2\text{-}B_{10}H_9NH_3^- + B_{10}H_8(NH_3)_2$ ref. 177

$H_2NOSO_3H + B_{12}H_{12}^{2-} \longrightarrow B_{12}H_{11}NH_3^- + B_{12}H_{10}(NH_3)_2$ ref. 177

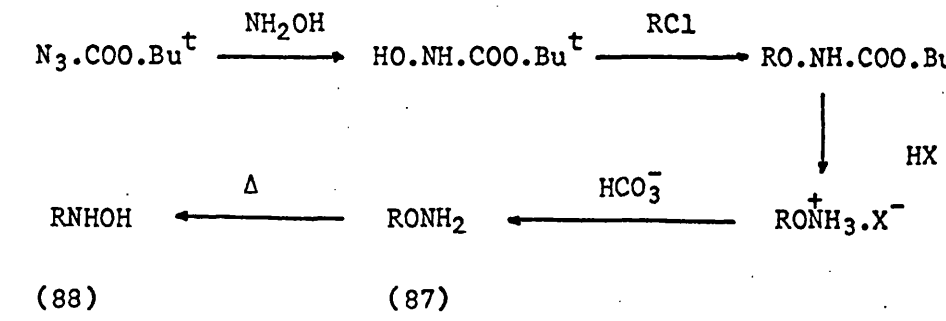
$H_2NOSO_3H + [HFe(CO)_4]^- \longrightarrow H.Fe(CO)_4.NH_2$ ref. 178

3. O-MESITOYL HYDROXYLAMINE

O-Benzoylhydroxylamine (87a) was first prepared by Jencks[179] by the reaction of neutral hydroxylamine with p-nitrophenyl benzoate. The compound was unstable and decomposed primarily to the rearrangement product, benzhydroxamic acid (88a), after standing at room temperature for 4-5 hours. The analogous compound O-acetoylhydroxylamine (87b) was even more unstable.

Carpino[81] prepared O-benzoylhydroxylamine independently as shown in Scheme I, and later[180] showed that the route had general applicability by preparing the O-arenesulfonylhydroxylamines (87 d,e) and O-mesitoyl-

hydroxylamine (87c).



(88) (87)

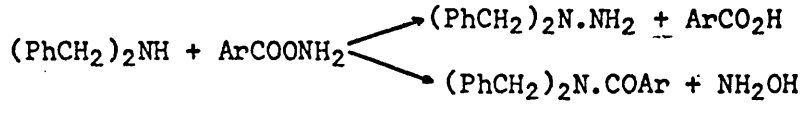
R = (a) PhCO- (d) $p\text{-}MeC_6H_4SO_2$-

(b) MeCO- (e) $2,4,6\text{-}Me_3C_6H_2SO_2$-

(c) $2,4,6\text{-}Me_3C_6H_2CO$-

Scheme 1

O-Mesitoylhydroxylamine (87c) was the most stable hydroxylamine and its o-methyl groups allowed nucleophilic displacements on nitrogen to occur without complications due to attack at the carbonyl group. For example, dibenzylamine reacted with O-benzoylhydroxylamine to give a mixture of 1,1-dibenzylhydrazine and N,N-dibenzylbenzamide. With O-mesitoylhydroxylamine, 1,1-dibenzylhydrazine (58%) was obtained and no evidence for amide formation was noted.



The reaction was carried out with an excess of dibenzylamine, the secondary amine being nucleophilic enough to displace mesitoic acid anion.

O-Mesitoylhydroxylamine has also been used to aminate amides (N-benzylbenzamide),[54] N-substituted sulfonamides [N-benzylbenzene sulfonamide[54] and N-α-menaphthyl-p-toluene sulfonamide[54] (3a)], imides (naphthalimide[54] and t-butyl iminodicarboxylate[181]) and pyrroles

(2,5-diphenylpyrrole,[182] 2,3,4,5-tetraphenylpyrrole[182] and carbazole[54]), as well as secondary amines (dibenzylamine[54] and 2,3-dihydro-1H-benz[de]isoquinoline[183]).

Except for the secondary amines, it was necessary to use the sodium salt of the amino compound in dry DMF in order to provide a nucleophile reactive enough to displace the mesitoic acid (see Table 2).

Although (2c) is more difficult to prepare than HOS it has certain advantages in some cases. Nickon and Hill[53] showed that treatment of various N-substituted sulfonamides (89) with an excess of HOS or chloramine in the presence of aqueous alkali yielded the corresponding hydrocarbon (91), presumably via the N-amino compounds (90), although the strong basic conditions did not permit their isolation. No attempt was made to isolate (90)using, for example, a dry ethereal solution of chloramine.

$$\underset{(89)}{R\bar{N}\text{-}SO_2Ar} \xrightarrow[OH^-]{HOS} \underset{\underset{NH_2}{|}}{[R.N.SO_2.Ar]} \xrightarrow{OH^-} [R\text{-}N{=}N\text{-}H] \longrightarrow \underset{(91)}{RH + N_2}$$

(90)

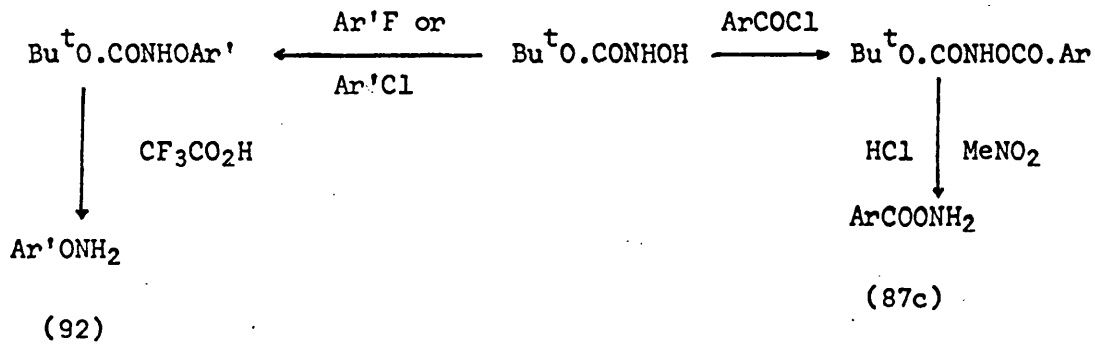
(a) R = α-$C_{10}H_7.CH_2$-

Ar = p-Me.C_6H_4-

Carpino[54] confirmed Nickon's postulate that (90) were intermediates by aminating (89a) in 43% yield using O-mesitoylhydroxylamine and showing that hydrolysis with hot aqueous ethanolic sodium hydroxide gave α-methylnaphthalene (91a) in 58% yield.

4. O-(2,4-DINITROPHENYL)HYDROXYLAMINE

Sheradsky[184] prepared O-(2,4-dinitrophenyl)hydroxylamine (92) by a similar method to that of Carpino [see Scheme 2]. This stable O-substituted hydroxylamine showed many of the properties of Carpino's compounds in that the 2,4-dinitrophenolate anion is a good leaving group when the nitrogen atom is attacked by anionic nitrogen[185] or by carbanions.[186]



Ar' = 2,4-$(NO_2)_2$ C_6H_3- Ar = 2,4,6-$Me_3C_6H_2$-

Scheme 2

The N-amino compounds were prepared by treating one equivalent of the sodium salt of the amino compound with one equivalent of (92) in dry DMF. The compounds prepared using the two aminating agents (87c) and (92) are summarised in Table 2. The analogous sulfur compound 2,4-dinitrophenylsulfonamide was found to be too stable for use as an aminating agent.[187]

Table 2

N-Aminations with O-Mesitoylhydroxylamine and O-(2,4-Dinitrophenyl)hydroxylamine

Amino Compound (A)	Aminating Agent (B)[a]	Ratio A:B	Sodium Salt	Solvent	Temp.°/Time (hr.)[b]	Yield % N-Amino Compound	Reference
$(PhCH_2)_2NH$	I	3:1	-	-	70-5° 1	58[c]	180
2-Amino-2,3-dihydro-1H-benz[de]isoquinoline	I	2:1	-	CH_2Cl_2	35-40° 1 R.T. 7	23[d]	183
$PhCH_2NHCOPh$	I	1:2	NaH	DMF	0° 1 R.T. 2	20	54
$PhCH_2NHSO_2Ph$	I[d]	3:2	NaOMe	DMF	0° 2	19	54
$PhCH_2NHSO_2Ts$	II	1:1	NaOMe	DMF	R.T. $^1/_4$	93	185
α-$C_{10}H_7$-CH_2.$NHSO_2Ts$	I	1:2	NaH	DMF	0° 1 R.T. 2	43	54
Phthalimide	II	1:1	NaOMe	DMF	R.T. $^1/_4$	88	185
1,8-Naphthdiimide	I	1:2	NaH	DMF	0° 1 R.T. 2	81	54
$(Bu^tOCO)_2NH$	I	1:1.1 1:2	NaH	DMF	55-60° 6	26 35-40	181
2,5-Diphenylpyrrole	I	1:2	?	DMF	0° 2 R.T. 10	?	182
2,3,4,5-Tetraphenyl-pyrrole	I	1:2	NaOMe	DMF	0° 2 R.T. 10	37	182

Amino Compound (A)	Aminating Agent (B) [a]	Ratio A:B	Sodium Salt	Solvent	Temp.°/Time (hr.) [b]	Yield % N-Amino Compound	Reference
Carbazole	I	1:2	NaH	DMF	0° 1 R.T. 2	60	54
2,4-Dimethyl-3,5-dicarbethoxypyrrole	II	1:1	NaOMe	DMF	R.T. 1/4	95	185

(a) Aminating agent I = O-Mesitoylhydroxylamine

II = O(2,4-dinitrophenyl)hydroxylamine

(b) R.T. = Room temperature

(c) As benzaldehyde derivative

(d) As hydrochloride

INSTRUMENTATION AND EXPERIMENTAL TECHNIQUES

1. Infrared (i.r.) spectra were recorded in the range 4000-625 $cm.^{-1}$ on a Perkin-Elmer 237 grating spectrophotometer. Solid samples were run either as nujolmulls or as potassium bromide discs and liquids as thin films, using polystyrene as reference.

2. Proton magnetic resonance (p.m.r.) spectra were recorded on a Varian A60 or a Varian T60 instrument. Carbon tetrachloride, deuteriochloroform, hexadeuterioacetone and hexadeuteriodimethylsulfoxide were used as solvents with tetramethylsilane as internal reference.

3. Ultraviolet (u.v.) spectra were recorded in the range 200-450 nm. on a Unicam SP800 spectrophotometer. Absolute ethanol was used as solvent in 1 cm. cells.

4. Mass spectra were recorded on an Associated Electrical Industries M.S.9 spectrometer and metastable peaks are indicated in the text by an asterisk.

5. Melting point (m.p.) determinatinos were carried out on a Kofler Micro Heating Stage using corrected thermometers.

6. Thin layer chromatography (t.l.c.) was used extensively as a qualitative guide to the composition of reaction mixtures and as a means of assessing the purity of compounds. Samples were run in suitable solvent mixtures on glass plates coated with a 250μ layer of Kieselgel G (E. Merck), or aluminium oxide G (Type E, pH 7.5) (E. Merck). The plates were observed under ultraviolet light or developed by spraying with iodine.

7. Preparative thin layer chromatography (prep. t.l.c.) was used to separate small amounts of reaction mixtures by a similar technique to that of t.l.c.; 20 x 20 and 100 x 20 cm. glass plates coated with a 1 mm. layer of Kieselgel PF 254 with a fluorescent indicator were used.

8. Column chromatography was carried out using silica gel MFC(B.D.H.), basic alumina (Spence type H), and deactivated alumina (prepared by deactivation of basic alumina with 6% by weight of water in a ball-mill for 12 hr.). The mixture to be chromatographed was adsorbed onto the support, from a suitable solvent, by evaporation using a rotary evaporator. Alumina columns were packed under petrol and silica gel columns were either packed by this method or packed dry, and then eluted with solvent mixtures of gradually increasing polarity. In all experiments only fractions containing significant amounts of material have been recorded.

9. Solvents were purified as follows:

Benzene and other aromatic solvents, methylene chloride, methanol, ethanol, acetonitrile, and ether were purified by refluxing over and distilling from calcium hydride. Aromatic solvents, methylene chloride, methanol, ethanol and acetonitrile were stored over molecular sieves (type 4A) and ether over sodium wine.

Dimethyl sulfoxide (DMSO) and dimethyl formamide (DMF) were dried by storage over molecular sieves (type 4A).

10. Petrol used for chromatography and for recrystallisations with ether was light petroleum, b.p. 40-60°. Petrol used for recrystallisations with benzene, chloroform or ethyl acetate was petroleum b.p. 60-80°, unless stated otherwise.

11. Lead tetraacetate (LTA) (B.D.H. or Hopkin and Williams) was freed from acetic acid by filtration and stored over concentrated sulfuric acid.

12. Hydroxylamine-O-sulfonic acid (HOS) was prepared by the method of Goesl and Meuwsen[104] and stored over concentrated sulfuric acid.

13. Chloramine was prepared in ether solution by a modification[62] of the method of Theilacker and Wegner[1a] and gave a chloramine concentration of about 0.17 M.

14. Where possible, compounds were characterised by comparison of their melting points (m.p.) and mixed melting points (m.m.p.) and i.r. spectra with those of authentic specimens. Literature m.p. and b.p. values are given with references except for well authenticated compounds for which the values quoted are those given in the Heilbron Dictionary of Organic Compounds (4th Edition).

15. Organic solvents, used to extract aqueous solutions, were dried over sodium sulfate and evaporated to dryness in a rotary evaporator under reduced pressure.

EXPERIMENTAL

1 1,2,4-TRIAZIN-3(2H)-ONES

A Reaction with HOS

(i) Benzo-1,2,4-triazin-3(2H)-one

The benzotriazinone[188] (441 mg., 3 mmoles) was dissolved in water (25 ml.) containing sodium hydroxide (720 mg., 18 mmoles). HOS (2.0 g., 18 mmoles) was added over 30 min. to the stirred solution at 60 to 70° and more sodium hydroxide was added as required to maintain an alkaline solution. The mixture was cooled to room temperature and extracted with chloroform. Evaporation under reduced pressure and crystallisation from water gave benzimidazolin-2-one (354 mg., 87%), m.p. and m.m.p. 310-311° (decomp.) (lit.[189], m.p. 310°). The compound had an i.r. spectrum identical with that of an authentic specimen prepared as follows:

1-Isopropenylbenzimidazolin-2-one[190] (5 g.) was dissolved in 1 N sulfuric acid (50 ml.) and heated under reflux for 30 min. On cooling, colourless needles separated, were filtered off, washed with water and recrystallised from water to give benzimidazolin-2-one (3.5 g., 94%), m.p. 310-311° (decomp.) (lit.[189], m.p. 310°).

(ii) Phenanthro[9,10-e][1,2,4]triazin-3(2H)-one

(a) The phenanthrotriazinone[191] (2.47 g., 0.01 mole) was dissolved in water (500 ml.) containing ethanol (50 ml.) and sodium hydroxide (4 g., 0.1 mole) at 85°. HOS (8 g., 0.07 mole) was added portionwise to the stirred solution, the temperature being kept at 85°. The solution was allowed to cool, filtered and the off-white precipitate washed well with water and recrystallised from acetic acid to give phenanthro[9,10-d]imidazolin-2-one (1.73 g., 74%), m.p.> 350° (Found: C, 76.7; H, 4.3; N, 12.2. $C_{15}H_{10}N_2O$ requires C, 76.9; H, 4.3; N, 12.0%).

m/e: 234 (P), 206, 205, 180, 117.

$\nu_{max.}$ 3150 (broad), 1700, 1685, 1644, 1014, 825, 748 and 721 $cm.^{-1}$.

The filtrate was acidified with 2N hydrochloric acid to yield starting material (0.5 g., 20%).

(b) When the reaction was carried out as a heterogeneous mixture, in the absence of ethanol, starting material (97%) was recovered.

(c) The phenanthrotriazinone (1 g.) was suspended in aqueous potassium hydroxide (10 g., in 60 ml.) and treated over 30 min. with HOS (10 g.) at 60-70°. On cooling, a yellow solid separated and was washed well with hot water and recrystallised from acetic acid to give the phenanthroimidazolinone (0.25 g., 26%), m.p.>350?

(iii) 5,6-Diphenyl-1,2,4-triazin-3(2H)-one

(a) The diphenyltriazinone[192] (2 g.) was dissolved in water (100 ml.) with sodium hydroxide (5 g.) at 0°. HOS (8 g.) was added, the temperature being maintained at 0°, and then the reaction mixture was stirred for a further 2 hr. The solid that separated was filtered and recrystallised from ethanol to give the sodium salt of 5,6-diphenyl-1,2,4-triazin-3-one (0.33 g., 15%), m.p. > 340°. (Found: C, 66.3; H, 3.9; N, 15.6. $C_{15}H_{10}N_3ONa$ requires C, 66.4; H, 3.7; N, 15.5 %).

$\nu_{max.}$ 1530, 1221, 1080, 1050, 1028, 824, 765 and 748 $cm.^{-1}$.

The filtrate, on acidification, gave unchanged diphenyltriazinone (1.1 g., 55%)

(b) The diphenyltriazinone (2.47 g.) was dissolved in water (60 ml.) containing potassium hydroxide (7.0 g.) at 40°. HOS (7.6 g.) was added, the temperature being kept between 40 and 45°. The mixture was then cooled to room temperature and neutralised with dilute hydrochloric acid to yield unchanged diphenyltriazinone (2.4 g., 97%).

(c) The diphenyltriazinone (1 g.) was suspended in water (50 ml.) at 65° and HOS (2.2 g.) added in one portion. On cooling, the precipitate was filtered and found to be unchanged diphenyltriazinone (0.94 g., 94%).

B Reaction with chloramine

(i) Benzo-1,2,4-triazin-3(2H)-one

(a) With sodium hydride

The benzotriazinone (0.5 g., 3.4 mmoles) was dissolved in dry methylene chloride (100 ml.) and dry DMF (50 ml.). Sodium hydride (1.63 g., of a 50% dispersion, 34 mmoles) was added and the mixture stirred for 30 min. Ethereal chloramine (8.5 mmoles) was then added and the mixture stirred overnight. The suspension was filtered and the filtrate evaporated to a small volume. T.l.c. indicated that benzotriazole and benzotriazinone were the only products. The precipitate was dissolved in water, neutralised with dilute hydrochloric acid and extracted with chloroform; t.l.c. indicated the same two components. The mixtures were combined and chromatographed on silica:

Ether gave benzotriazole (30 mg., 7%), m.p. and m.m.p. 98-100° (lit.[189], 100°) from ether-petrol.

Ethyl acetate gave unchanged benzotriazinone (280 mg., 56%).

(b) Without sodium hydride

The same quantities and procedure as above were used except that sodium hydride was omitted. A solid gradually precipitated and gave qualitative tests for ammonium chloride (185 mg., 100%). The filtrate was extracted with water and the organic layer was then dried. Chromatography of the filtrate on silica and elution with ether gave benzotriazole (264 mg., 65%), m.p. and m.m.p. 96-99°, from petrol (60-80°).

(ii) Phenanthro[9,10-e][1,2,4]triazin-3(2H)-one

(a) With sodium hydride

The phenanthrotriazinone (0.5 g., 2 mmoles) was dissolved in hot dry DMF (125 ml.) and treated with sodium hydride (0.96 g., of a 50% dispersion, 0.02 mole). When hydrogen evolution ceased, ethereal chloramine (5 mmoles) was added and the mixture allowed to stir at room temperature for 24 hr. The suspension was filtered and evaporated to small volume. Trituration with ether and petrol gave 9,10-phenanthrotriazole (185 mg., 43 %), m.p. and m.m.p. 322-325° (lit.[60], m.p. 325-328°). The compound had an i.r. spectrum identical to that of an authentic specimen.[60]

(b) Without sodium hydride

The phenanthrotriazinone (0.5 g., 2 mmoles) was dissolved in DMF (80 ml.) and treated with ethereal chloramine (5 mmoles). The mixture was allowed to stand at room temperature for 48 hr. and then filtered to obtain ammonium chloride (86 mg., 80%). The ether and DMF were removed by distillation under reduced pressure and the residue was recrystallised from acetic acid to give 9,10-phenanthrotriazole (400 mg., 91%), m.p. and m.m.p. 321-323° (decomp.)(lit.[60], m.p. 325-328°).

(iii) 5,6-Diphenyl-1,2,4-triazin-3(2H)-one

The diphenyltriazinone (1 g., 4 mmoles) was dissolved in dry methylene chloride (100 ml.) and ethereal chloramine (17 mmoles) added. The solution was filtered after 24 hr. to give ammonium chloride (210 mg., 100%). The filtrate was chromatographed on silica:

10% Ether-petrol gave 1-(1'-ethoxyethyl)-4,5-diphenyltriazole (44 mg., 4%); the i.r. was identical to that of an authentic specimen[58a].

50% Ether-petrol gave 4,5-diphenyltriazole (837 mg., 94%) which was recrystallised from nitromethane, m.p. and m.m.p. 136-138° (lit.[89], m.p. 138°)

C Reactions with O-(2,4-dinitrophenyl)hydroxylamine

(i) Benzo-1,2,4-triazin-3(2H)-one

The benzotriazinone (147 mg., 1 mmole) was dissolved in dry DMF (5 ml.) and sodium hydride (50 mg., of a 50% dispersion, 1 mmole) added. The solution was stirred for 10 min. until gas evolution ceased and then O-(2,4-dinitrophenyl)hydroxylamine[184] (199 mg., 1 mmole) was added. The mixture was stirred for 1.5 hr. and then the dark solution was poured into water and extracted with ether. The dried ether solution was evaporated to dryness and the residue recrystallised from water to give benzimidazolin-2-one, (20 mg., 15%), m.p. and m.m.p. 309-311° (decomp.) (lit.[189], m.p. 310°).

(ii) Phenanthro[9,10-c][1,2,4]triazin-3(2H)-one

The above method was repeated using the phenanthrotriazinone (1 mmole). When the mixture was poured into cold water a pale brown precipitate was formed. Recrystallisation from acetic acid (charcoal) gave the phenanthroimidazolinone (130 mg., 55%) m.p. >350°.

(iii) 5,6-Diphenyl-1,2,4-triazin-3(2H)-one

(a) The above method was repeated using the diphenyltriazinone (1 mmole). The mixture was poured into water, the precipitate filtered and washed with water until colourless. The solid was recrystallised from acetic acid to give 4,5-diphenylimidazolin-2-one (195 mg., 83%), m.p. and m.m.p. 310-312° (lit.[189], m.p. 320°). The i.r. spectrum was identical to that of an authentic specimen prepared by the method of Biltz.[193]

When the reaction was repeated in the absence of sodium hydride, t.l.c. indicated that no reaction had taken place after 8 hr.

(b) The reaction was repeated using dry methylene chloride as solvent instead of DMF. The mixture was stirred for 6 hr. and then filtered. The precipitate was washed with water and the insoluble portion recrystallised from acetic acid to give 4,5-diphenylimidazolin-2-one (63 mg., 27%), m.p. and m.m.p. 308-310° (lit.[193], m.p. 320°). The aqueous filtrate was acidified and then extracted with methylene chloride. The solution contained unchanged triazinone and 2,4-dinitrophenol (t.l.c.).

The organic filtrate was chromatographed on a silica gel prep.t.l.c. plate to give:

Unchanged O-(2,4-dinitrophenyl)hydroxylamine (62 mg., 31%), m.p. and m.m.p. 108-112° (lit.[184], 110-112°).

1-Amino-4,5-diphenyltriazole (4 mg.), identified by i.r. and t.l.c. comparison with an authentic specimen.

D Miscellaneous experiments

(i) Reaction of 1,2,3-triazoles with O-(2,4-dinitrophenyl)hydroxylamine

4,5-Diphenyltriazole (221 mg., 1 mmole) was dissolved in dry methylene chloride (30 ml.) and sodium hydride (50 mg., of a 50% dispersion, 1 mmole) added. The mixture was stirred for 1 hr. at room temperature and then O-(2,4-dinitrophenyl)hydroxylamine (199 mg., 1 mmole) added and stirring continued for a further 18 hr. The mixture was filtered and the filtrate chromatographed on a silica prep. t.l.c. plate with ether to give:

O-(2,4-dinitrophenyl)hydroxylamine (23 mg., 36%), m.p. and m.m.p. 108-112°.

1-Amino-4,5-diphenyltriazole (17 mg., 23%), m.p. and m.m.p. 133-135° (lit.[194], m.p. 135°), after sublimation. The compound had an i.r. spectrum identical to that of an authentic specimen prepared by the method of Stolle. [194]

None of the unknown 2-amino-4,5-diphenyltriazole was detected, although benzotriazole under the same conditions gave a mixture of 1- and 2-aminobenzotriazoles. In methylene chloride the yields of 1- and 2-aminobenzotriazoles were 35% and 36.5% but with DMF as solvent, however, lower yields of 30% and 9% respectively, were obtained.

(ii) Reaction of benzo-1,2,4-triazin-3(2H)-one with hydrazine

The benzotriazinone (735 mg., 5 mmoles) was dissolved in ethanol (100 ml.) and heated under reflux for 2 hr. with hydrazine hydrate (0.6 ml., 12 mmoles). The mixture was allowed to cool and the orange crystals which separated were filtered. Recrystallisation from ethanol gave the hydrazinium salt of benzo-1,2,4-triazin-3-one (350 mg., 39%) m.p. 124-127° (decomp.) (Found: C, 46.8; H, 5.1; N, 39.3. $C_{16}H_{15}N_3O$ requires C, 46.9; H, 5.1; N, 39.1%).

$\nu_{max.}$ 3280, 3160, 3050, 2810, 2750, 1594, 1562, 1510, 1310, 1082, 951, 745 and 730 $cm.^{-1}$.

A portion, when dissolved in hot water, gave benzo-1,2,4-triazin-3-one (51%) on extraction with chloroform.

(iii) Reaction of 5,6-diphenyl-1,2,4-triazin-3(2H)-one with hydrazine

The diphenyltriazinone (2.49 g., 10 mmoles) was dissolved in ethanol (50 ml.) and heated under reflux with hydrazine hydrate (1.2 ml., 24mmoles). Crystals separated on cooling and were recrystallised from ethanol to give the hydrazinium salt of 5,6-diphenyl-1,2,4-triazin-3-one (2.6 g., 93%), m.p. 175-180°, followed by resolidification and final melting at 220-224° (Found: C, 64.3; H, 5.5; N, 24.9. $C_{15}H_{15}N_5O$ requires C, 64.0; H, 5.4; N, 24.9%).

m/e: 249 (P-32), (no m/e = 281).

$\nu_{max.}$ 3333, 3260, 3210, 3060 (broad), 2810 (broad), 1685, 1674, 1119, 850, 758, 688 $cm.^{-1}$.

Hydrolysis in water, dilute hydrochloric acid or dilute sodium hydroxide solution gave diphenyltriazin-3-one almost quantitatively.

(iv) Reaction of benzotriazole-1-carboxamide with chloramine

Benzotriazole-1-carboxamide[195] (324 mg., 2 mmoles) was dissolved in dry methylene chloride (50 ml.) and ethereal chloramine solution (3.4 mmoles) added. The mixture was stirred for 24 hr., evaporated to dryness and the residue triturated with petrol (60-80°) to give unchanged benzotriazole-1-carboxamide (288 mg., 89%).

(v) Oxidation of 5,6-diphenyl-1,2,4-triazin-3(2H)-one with N-chlorobenzotriazole

The triazinone (249 mg., 1 mmole) was dissolved in dry benzene (50 ml.) and N-chlorobenzotriazole (153 mg., 1 mmole)[62] was added to the stirred solution. After an induction period of 2 min. the solution went cloudy but further stirring caused the precipitate to redissolve after 30 min. The mixture was stirred overnight at room temperature and then chromatographed on silica:

30% Ether-petrol gave 4,5-diphenyltriazole (220 mg., 100%). Recrystallisation from ether-petrol gave crystals m.p. and m.m.p. 136-138° (lit.[189], 138°).

60% Ether-petrol gave benzotriazole (30 mg., 25%).

10% Ethanol-ether gave a further yield of benzotriazole (45 mg., 38%), probably due to the ethanol hydrolysing benzotriazole from its hydrochloride.

(vi) Oxidation of benzo-1,2,4-triazin-3(2H)-one with LTA

The triazinone (147 mg., 1 mmole) was dissolved in benzene (50 ml.) and LTA added portionwise to the solution under reflux. The reaction was heated for a further 2 hr. and then cooled and filtered. The filtrate and methylene chloride washings were chromatographed on silica:

30% Ether-petrol gave 1-acetylbenzotriazole (139 mg., 86%), m.p. and m.m.p. 50-51° (lit.[189], m.p. 51°) from ether-petrol. An i.r. spectrum was identical to that of an authentic sample prepared as follows:

Benzotriazole (3 g., 0.026 mole) was heated in acetic anhydride (10 ml.) on a water bath for 5 min. The mixture was then cooled and poured into ice-water (150 ml.). An oil separated that gradually crystallised. Recrystallisation from aqueous ethanol (charcoal) gave 1-acetylbenzotriazole as needles, m.p. 50-51° (lit.[189], m.p. 51°).

10% Ethanol-ether gave benzotriazole (4 mg., 3.3%), m.p. and m.m.p. 93-97°.

(vii) Reaction of 5,6-diphenyl-1,2,4-triazin-3(2H)-one with sodium hypochlorite

Diphenyltriazinone (498 mg., 2 mmoles) was dissolved in glacial acetic acid (5 ml.) and treated with 1M sodium hypochlorite dropwise until no more gum separated. The aqueous solution was decanted and the gum dissolved in chloroform, dried and chromatographed on silica:

20% Ether-petrol gave unidentified oils showing several components (t.l.c.).

40% Ether-petrol gave diphenyltriazole (230 mg., 52%), m.p. and m.m.p. 136-138° (lit.[189], m.p. 138°).

2 2-AMINOCINNOLIN-3(2H)-ONE

A Reaction of cinnolin-3(2H)-one with HOS

(i) Cinnolin-3-one [196] (3.92 g., 0.027 mole) was dissolved in water (200 ml.) containing potassium hydroxide (8.4 g., 0.15 mole) at 40°. HOS (11.3 g., 0.1 mole) was added in one portion and the temperature maintained between 40 and 45° by the addition of ice. The mixture turned deep red and on cooling a brown solid separated. The precipitate was filtered off, washed with water and dried. The solid (2.45 g.) was recrystallised from a large volume of chloroform (charcoal) to give bright yellow crystals of 2-aminocinnolin-3(2H)-one (0.75 g., 17%), m.p. 128-130° (decomp.). An analysis sample, m.p. 130-131° (decomp.) was obtained after several recrystallisations from chloroform (Found: C, 59.4; H, 4.4; N, 25.8. $C_8H_7N_3O$ requires C, 59.6; H, 4.4; N, 26.0%).

m/e: 161 (P), 146, 133, 105, 104. m^*, 133-105 = 82.9.

$\nu_{max.}$ 3280, 3160, 3105, 1664, 1656, 1385, 1188, 872, 760 and 745 $cm.^{-1}$.

τ 2.6-3.3 (m, 5H); 0.00 (br.s, 2H, disappears on addition of D_2O).

Concentration of the remaining chloroform solution gave unchanged cinnolinone (1.55 g., 40%).

(ii) Cinnolinone (3.92 g., 0.027 mole) was dissolved in water (150 ml.) containing sodium hydroxide (6.2 g., 0.155 mole) at 55°. HOS (11.3 g., 0.1 mole) was added in one portion and the temperature maintained between 55 and 60° by the addition of ice. The resulting solution (pH 8) was cooled to room temperature and filtered to give a brown solid (4 g.). Recrystallisation from chloroform gave 2-aminocinnolin-3-one (0.95 g., 22%), m.p. 129-131°. The aqueous solution was extracted with chloroform to give a viscous red oil (550 mg.). The mixture was combined with the residual chloroform solution from the recrystallisation and chromatographed on silica:

Ether gave oxindole (1.06 g., 30%), m.p. and m.m.p. 125-127°, from water (lit.[189], m.p. 127°). The i.r. spectrum was identical to that of an authentic specimen.

5% Ethanol-ether gave a mixture of a solid and an oil (50 mg.), which on sublimation (100-110°, 2 mm.) gave o-azidophenylacetamide* (30 mg., 0.6%), m.p. 166-168° (decomp.) (Found: C, 53.6; H, 4.3; N, 31.4. $C_8H_8N_4O$ requires C, 54.5; H, 4.6; N, 31.8%).

m/e: 176 (P), 148, 120, 104, 77.

$\nu_{max.}$ 3370, 3170, 2125, 2100, 1690, 1670, 1621, 1410, 746 and 670 $cm.^{-1}$.

(iii) The cinnolinone (7.3 g., 0.05 mole) was dissolved in water (200 ml.) containing sodium hydroxide (15.3 g., 0.38 mole) at 60-70°. HOS (27.5 g., 0.24 mole) was added over 45 min., the temperature being maintained between 60 and 70°. The mixture was worked up as above to give 2-aminocinnolin-3(2H)-one (7%), oxindole (32%), and o-azidophenylacetamide (1%). The aqueous solution when acidified gave unchanged cinnolinone (7%).

(iv) Cinnolinone (7.3 g., 0.05 mole) was dissolved in aqueous ethanol (200 ml. of a 1:1 mixture) containing sodium hydroxide (20 g., 0.5 mole) and HOS (28.3 g., 0.25 mole) was added over 15 min. at 55-60°. On cooling, inorganic salts separated and were filtered off. The filtrate was extracted with chloroform, dried and concentrated to give 2-amino-cinnolinone (0.5 g., 6.5%). Oxindole was the main constituent of the residual chloroform solution (t.l.c.), and sublimation gave oxindole (1.0 g., 15%). The aqueous solution was acidified and extracted with chloroform to give unreacted starting material (1.85 g., 25%).

* The less likely structure, o-aminophenylacetyl azide can not be entirely eliminated on the basis of the above physical data.

B Reaction of cinnolin-3(2H)-one with chloramine

(i) Without sodium hydride

Cinnolin-3-one (0.73 g., 5 mmoles) was dissolved in dry methylene chloride (150 ml.) and ethereal chloramine (8.5 mmoles) added. The mixture was stirred overnight and then filtered to give ammonium chloride (260 mg., 95%). The filtrate was chromatographed on silica:

60% Ether-petrol gave a yellow fluorescent oil that slowly crystallised. Recrystallisation from petrol (60-80°) gave 2-(1'-ethoxyethyl)cinnolin-3(2H)-one (30 mg., 1.5%), m.p. 94-97° (decomp) (Found: C, 65.3; H, 6.6; N, 12.4. $C_{12}H_{14}N_2O_2$ requires C, 66.0; H, 6.3; N, 12.8%).

$\nu_{max.}$ 1660, 1644, 1625, 1252, 1125, 950 and 755 cm.$^{-1}$.

τ 2.35-3.00 (m, 5H); 3,4 (q, 1H, J 7 c./sec.); 8.4 (d, 3H, J 6 c./sec.); 8.85 (t, 3H, J 7 c./sec.).

70% Ether-petrol gave an oily mixture which on sublimation gave 3-chloroindazole (22 mg., 1.8%), m.p. and m.m.p. 148-148.5°, (lit.[197], m.p. 148°), from petrol (60-80°). The i.r. spectrum was identical to that of an authentic sample prepared by the method of Stephenson.[197]

5% Ethanol-ether gave a red oil, sublimation of which gave yellow needles of 4-chlorocinnolin-3(2H)-one (156 mg., 17.5%), m.p. and m.m.p. 220-223° (decomp.) (lit.[56], m.p. 220°), from ethanol (Found: C, 53.3; H, 2.8; N, 15.6. Calculated for $C_8H_5N_2OCl$ C, 53.2; H, 2.8; N, 15.5%).

m/e: 180(P), 152, 117.

An i.r. spectrum was identical to that of an authentic sample prepared by the reaction of cinnolinone with t-butylhypochlorite.[56]

10% Ethanol-ether gave a brown mixture which on sublimation gave prisms of indazole-3-carboxamide (143 mg., 18%), m.p. 279-284°. Recrystallisation from ethanol raised the m.p. to 286-288° (lit.[198],

m.p. 285-286°) (Found: C, 59.8; H, 4.5; N, 25.9. Calculated for $C_8H_7N_3O$ C, 59.6; H, 4.3; N, 26.0%).

m/e: 161 (P), 145, 118. m*, 161-145 = 130.6.

$\nu_{max.}$ 3330-2780 (m, NH), 1670, 1635, 1620, 1605, 1590, 1080, 900, 770 and 748 $cm.^{-1}$

50% Ethanol-ether gave a red polymeric substance from which unreacted cinnolinone (50 mg., 7%) could be sublimed.

(ii) With sodium hydride

Cinnolin-3(2H)-one (730 mg., 5 mmoles) was dissolved in methylene chloride (150 ml.) and sodium hydride (1.2 g., of a 50% dispersion, 25 mmoles) was added. Ethereal chloramine (8.5 mmoles) was added after 15 min. and the mixture stirred at room temperature overnight. The solution was filtered and the precipitate dissolved in water and the mixture was extracted with chloroform. The aqueous solution was then acidified and the extraction repeated.

The basic extract gave a black oil that did not show any definite compound on t.l.c. and was not investigated further. The acid extract gave unchanged cinnolinone (316 mg., 43%). The organic filtrate (above) was chromatographed on silica:

60% Ether-petrol gave 2-(1-ethoxyethyl)cinnolin-3(2H)-one (10 mg., <1%), identified by i.r. spectrum comparison and t.l.c.

Ether gave an unidentified yellow solid (40 mg.), m.p. 114-116°, from chloroform-petrol (Found: C, 55.7; H, 4.2; N, 19.5%).

$\nu_{max.}$ 3390, 3320, 2130, 2090, 1650, 1625, 1300, 750 and 670 $cm.^{-1}$.

5% Ethanol-ether gave α-azidophenylacetamide† (135 mg., 15.5%), m.p. 165-167° (decomp.) from chloroform-petrol.

10% Ethanol-ether gave indazole-3-carboxamide (32 mg., 4%), m.p. 286-288° (lit.[198], m.p. 285-286°) after sublimation and recrystallisation from ethanol.

† See page 60

C Pyrolysis of 2-aminocinnolin-3-one

(i) Alone

The N-amino compound (36 mg.) was cautiously heated to 135° and after the explosive decomposition had subsided, the residue was sublimed to give oxindole (19 mg., 64%), m.p. and m.m.p. 124-127° (lit.[189], m.p. 127°). An i.r. spectrum was identical to that of authentic oxindole.

(ii) In toluene

The N-amino compound (54 mg.) was heated under reflux in dry toluene (20 ml.) for 6 hr. and the excess of toluene then removed by distillation under reduced pressure. The residue was chromatographed on silca to give oxindole (40 mg., 90%).

(iii) With tetracyclone

A solution of the N-amino compound (322 mg., 2 mmoles) and tetraphenylcyclopentadienone (tetracyclone) in toluene (25 ml.) was heated under reflux for 16 hr. Excess of toluene was removed and the residue chromatographed on basic alumina:

Benzene gave tetracyclone (680 mg., 88%)

Ether gave oxindole (126 mg., 47%), m.p. 124-127°.

Thermolysis of cinnolinone and 2-methylcinnolin-3(2H)-one[199] in 1,2,4-trichlorobenzene under reflux for 5 hr. gave the recovered cinnolinones in 71% and 100% yields respectively.

D Oxidation of 2-aminocinnolin-3-one

(i) In cyclohexene

The N-amino compound (322 mg., 2 mmoles) was suspended in methylene chloride (60 ml.) and cyclohexene (25 ml.) and a solution of LTA (1.0 g., 2.26 mmoles) in methylene chloride (40 ml.) was added dropwise, with stirring.. Nitrogen was vigorously evolved and the mixture rapidly turned brown and then deposited a viscous black oil. The mixture was stirred for a further 30 min. and then filtered. The residue was extracted thoroughly with hot methylene chloride and the combined filtrates chromatographed on silica:

50% Ethanol-ether eluted a dark red viscous oil (100 mg.) from which cinnolin-3-one (21 mg., 7%), m.p. and m.m.p. 197-201° (decomp.) (lit.[196], m.p. 200-201°) could be obtained by sublimation.

(ii) In methyl methacrylate

LTA (1.0 g.) was added in small portions to a suspension of the N-amino compound (2 mmoles) in benzene (25 ml.) and methyl methacrylate (25 ml.). The reaction evolved nitrogen, turned bright red and deposited a black solid which was collected after 2 hr. The solid was extracted with benzene until the benzene remained colourless. The remaining black solid was treated with 6N sulfuric acid, filtered and the filtrate neutralised (pH7) with 2N sodium hydroxide solution. Extraction with chloroform yielded a trace of cinnolinone (i.r. and t.l.c.).

The organic filtrate and washings were evaporated to dryness and the residue treated in a similar manner to give cinnolinone (50 mg., 17%).

(iii) In DMSO

The reaction above was repeated with DMSO (5 ml.) as the solvent. Nitrogen was again evolved in the extremely exothermic reaction. The mixture was stirred for a further 90 min. and then poured into water, filtered and the red precipitate (210 mg.) washed well with water and dried. The i.r. spectrum wassimilar to that of oxindole, $\nu_{max.}$ 3160 (NH), 1700 (C=O), 1620 (C=C) and 740 $cm.^{-1}$. The material was polymeric and could not be crystallised or sublimed without decomposition.

The aqueous solution (above) was extracted with chloroform and chromatographed on silica:

Ether eluted an oil (22 mg.) that on sublimation gave an unidentified compound (3 mg.), m.p. 203-206°.

m/e 329 (P), 301, 226, 105, 77.

$\nu_{max.}$ 1710, 1698, 1600, 1450, 1242, 780, 704 and 650 $cm.^{-1}$.

(iv) In ethanol

The oxidation above was repeated in a similar manner in a mixture of methylene chloride (25 ml.) and dry ethanol (25 ml.). Nitrogen was evolved, and the solution went almost black; it remained homogeneous, however, and was chromatographed on silica:

70% Ether-petrol gave a red oil (60 mg.) which contained a colourless solid. The mixture was sublimed to give 3-ethoxy-oxindole (5 mg.), m.p. and m.m.p. 105-107° (lit.[200], m.p. 106-107.5°).

m/e: 177 (P), 149, 148, 133, 120, 83.

The i.r. spectrum was identical to that of an authentic specimen prepared by the method of Creger.[200]

50% Ethanol-ether gave a mixture of products (250 mg.) from which unchanged cinnolinone (20 mg., 6%) could be obtained after sublimation.

(v) With iodobenzene diacetate

The N-amino compound (161 mg., 1 mmole) was dissolved in dry methylene chloride (50 ml.) and added dropwise to a stirred solution of iodobenzene diacetate (386 mg., 1.2 mmoles)[201] in a mixture of methylene chloride (25 ml.) and cyclohexene (25 ml.). The mixture was stirred at room temperature overnight and then chromatographed on silica to give iodobenzene (161 mg., 60%) as the only product that could be identified.

E Miscellaneous experiments

(i) Attempted deamination of 2-aminocinnolin-3(2H)-one

a) The N-amino compound (80 mg., 0.5 mmole) and N-nitrosodiphenylamine (99 mg., 0.5 mmole)[202] were fused on a steam bath for 30 min., then cooled and the residue chromatographed on silica:

10% Ether-petrol gave diphenylamine (74 mg., 87%), m.p. 51-53°.

Ether gave oxindole (43 mg., 65%).

20% Ethanol-ether gave unreacted N-amino compound (26 mg., 33%).

b) The N-amino compound (80 mg., 0.5 mmole) was dissolved in glacial acetic acid (5 ml.) and an aqueous solution of sodium nitrite (35 mg., 0.5 mmoles dissolved in 5 ml. of water) added dropwise at room temperature The reaction mixture was neutralised with sodium bicarbonate and then extracted with chloroform to give cinnolinone (70 mg., 96%).

(ii) Copper chloride chelate of 2-aminocinnolin-3-one

The N-amino compound (161 mg., 1 mmole) was dissolved in hot methanol (20 ml.) and then added to a solution of copper chloride dihydrate (340 mg., 2 mmoles) in hot methanol (20 ml.). The mixture was allowed to cool and the dark green solid (146 mg., 49%) that separated was filtered off to give the copper chelate of 2-amino-

cinnolin-3(2H)-one, m.p. 184-186° (decomp.) (Found: C, 32.9; H, 2.5; Cl 25.0; N, 13.9. $C_8H_7Cl_2CuN_3O$ requires C, 32.5; H, 2.4; Cl, 24.0; N, 14.2%).

$\nu_{max.}$ 3058, 3017, 1618, 1610, 1500, 905, and 785 $cm.^{-1}$.

(iii) Amination of cinnolin-3(2H)-one with O-(2,4-dinitrophenyl)hydroxylamine

Cinnolinone (146 mg., 1 mmole) was dissolved in dry DMF and treated with sodium hydride (50 mg., of a 50% dispersion, 1 mmole). O-(2,4-Dinitrophenyl)hydroxylamine (199 mg., 1 mmole) was added when hydrogen evolution ceased and the mixture was then stirred for a further 30 min. The dark reaction mixture was diluted with water and filtered to give 2-aminocinnolin-3(2H)-one (21 mg., 13%), m.p. 127-130°. The aqueous filtrate was extracted with ether to give a yellow oil which was shown to contain 2,4-dinitrophenol, but no N-amino compound (t.l.c.).

(iv) Reaction of 2-aminocinnolin-3(2H)-one with chloramine

The N-amino compound (161 mg., 1 mmole) was dissolved in dry methylene chloride (50 ml.) and treated with ethereal chloramine (2 mmoles). The mixture was stirred for 14 hr. and then concentrated to half volume to give a brown solid (47 mg.,), m.p. 212-218°. Recrystallisation from chloroform-petrol (charcoal) gave 1- or 2-aminoindazole-3-carboxamide, m.p. 222-226° (Found: C, 54.6; H, 4.4; N, 31.2. $C_8H_8N_4O$ requires C, 54.5; H, 4.6; N, 31.8%).

m/e: 176(P), 161, 159, 145.

$\nu_{max.}$ 3390, 3338, 3260, 3170, 3050, 1665, 1638, 1605, 778, 758 and 749 $cm.^{-1}$.

The remaining solution was evaporated to dryness and triturated with ether to give unreacted N-aminocinnolinone (61 mg., 40%), m.p. 127-130° (decomp.).

(v) Attempted amination of 4-chlorocinnolin-3(2H)-one

The chlorocinnolinone was suspended in an aqueous ethanolic solution of sodium hydroxide and HOS (5 equivalents) added at 60°. Unchanged cinnolinone (16%) was the only crystalline product recovered.

3 1-AMINOQUINOXALIN-2(1H)-ONE

A Preparation from quinoxalin-2(1H)-one

3,4-Dihydroquinoxalin-2(1H)-one was prepared by the reaction of O-phenylenediamine with chloroacetic acid in ammonium hydroxide solution by the method of Perkin and Riley.[203] The dihydro compound was oxidised to the quinoxalinone either directly with potassium permanganate[204] or via the unstable 4-nitroso compound.[203]

(i) With potassium permanganate

3,4-Dihydroquinoxalin-2(1H)-one (14.8 g., 0.1 mole) was dissolved in water (200 ml.) at 90° and potassium permanganate (15.8 g., 0.1 mole) added over 1 hr. to the vigorously stirred solution at 90 to 95°. The reaction mixture was filtered while hot and on cooling, the filtrate was acidified with 2N hydrochloric acid and the yellow precipitate was collected and dried. Recrystallisation from water (charcoal) gave quinoxalin-2(1H)-one (6.1 g., 41%), m.p. 268-271° (lit.[203], m.p. 271°).

The yield of quinoxalinone remained substantially unchanged when 1.5 equivalents were used.

(ii) Via the 4-nitroso-3,4-dihydroquinoxalin-2(1H)-one

The dihydroquinoxalinone (29.6 g., 0.2 mole) was suspended in water (1 l.) which contained concentrated hydrochloric acid (60 ml.) at 5°. A 10% solution of sodium nitrite (13.8 g., 0.2 mole) in water was added dropwise to the stirred solution at 0 to 5°. The mixture was stirred for a further 30 min. at 5°, filtered and the yellow solid washed well with water, then with cold ethanol and finally with petrol (40-60°). The crude nitroso compound was, without further purification, decomposed by heating in ethanol (750 ml.) under reflux for 5 hr. Brown fumes of nitrogen dioxide were evolved after a short induction period. The mixture was allowed to cool and the solid that

had crystallised, filtered and recrystallised from water (charcoal) to give quinoxalinone (17.8 g., 60%), m.p. 270-271° (lit., m.p. 271°). Concentration of the ethanolic solution gave unchanged dihydroquinoxalinone (5.4 g., 18%).

(iii) Amination of quinoxalin-2(1H)-one

Quinoxalin-2-one (2 g., 0.014 mole) was dissolved in water (50 ml.) at 65° containing sodium hydroxide (3.3 g., 0.08 mole). HOS (4.5 g., 0.04 mole) was added over 30 min., the temperature being kept at about 65°. Needles gradually separated and on cooling were filtered off and dried (1.4 g., 64%). The solid was recrystallised from chloroform to yield 1-aminoquinoxalin-2(1H)-one, m.p. 178-179° (Found: C, 59.5; H, 4.4; N, 26.3. $C_8H_7N_3O$ requires C, 59.6; H, 4.4; N, 26.1%).

m/e: 161(P), 146, 133, 106, 105.

$\nu_{max.}$ 3298, 3185, 1652, 1625, 1605, 1588, 1472, 850, 780 and 755 $cm.^{-1}$.

τ 1.63 (s, 1H); 1.85-2.24 (m, 4H); 4.9 (br.s, 2H).

Anisylidene derivative, m.p. 170-171° from ethanol (Found: C, 68.8; H, 4.7; N, 15.0. $C_{16}H_{13}N_3O_2$ requires C, 68.8; H, 4.7; N, 15.0%).

$\nu_{max.}$ 1650, 1610, 1590, 1572, 1268, 1182, 1034, 838, and 762 $cm.^{-1}$.

τ 0.93 (s, 1H); 1.63 (s, 1H); 2.05-3.10 (m, 8H); 6.60 (s, 3H).

Chloroform extraction of the basic solution gave unchanged quinoxalin-2-one (0.7 g., 35%).

When the amination was repeated with a mole ratio of quinoxalinone: sodium hydroxide: HOS of 1:5:2.5 a slight increase in the yield of N-amino compound (67%) was obtained. When a ratio of 1:10:5 was used, the yield fell to 41-46%.

B Oxidation of 1-aminoquinoxalin-2(1H)-one

General procedure

1-Aminoquinoxalin-2(1H)-one (805 mg., 5 mmoles) was either dissolved or suspended in a mixture of solvent and the olefin and the LTA (2.7 g., 6 mmoles) was added portionwise over 10 min. The mixture was stirred for a further 1 to 2 hr., and except when DMSO was used as a trap, filtered and the filtrate and chloroform washings of the gum residue chromatographed on basic alumina.

(i) Alone

Methylene chloride (25 ml.) was used as solvent.

20% Ether-petrol gave yellow crystals of benzo-1,2,4-triazine (116 mg., 18%), m.p. 76-77° (lit.[205], m.p. 76-77°), from petrol (60-80°) (Found: C, 64.4; H, 3.9; N, 31.9. Calculated for $C_7H_5N_3$ C 64.1; H, 3.8; N, 32.0%).

m/e: 131(P), 103, 76, 58, 43.

$\nu_{max.}$ 1615, 1570, 1138, 1105, 1020, and 863 $cm.^{-1}$.

τ 0.04 (s, 1H); 1.30-1.64 (m, 1H); 1.80-2.32 (m, 3H).

(ii) In cyclohexene

Cyclohexene (20 ml.) was used together with methylene chloride (25 ml.).

20% Ether-petrol gave 2-(quinoxalin-2-on-1-yl)-7-azabicyclo-[4,1,0]-heptane, (110 mg., 9%).

Recrystallisation from chloroform petrol gave crystals, m.p. 174-176° (Found: C, 69.6; H, 6.3; N, 17.2. $C_{14}H_{15}N_3O$ requires C, 69.7; H, 6.3; N, 17.4%).

$\nu_{max.}$ 1655, 1600, 1582, 1304, 898 and 752 $cm.^{-1}$.

τ 1.83 (s, 1H); 2.08-2.83 (m, 4H); 7.07-7.27 (m, 2H); 7.40-7.98 (m, 4H); 8.40-8.80 (m, 4H).

20% Ethanol-ether gave unchanged 1-aminoquinoxalin-2-one (42 mg., 5%), m.p. 176-178°.

(iii) In methyl methacrylate

Methyl methacrylate (40 ml.) and methylene chloride (40 ml.) were used.

20% Ether-petrol gave benzo-1,2,4-triazine (67 mg., 10%), m.p. 76-77° (lit.[205], m.p. 76-77°).

70% Ether-petrol gave methyl 2-methyl-1-(quinoxalin-2-on-1-yl)-aziridine-2-carboxylate, (277 mg., 21%). Recrystallisation from petrol (60-80°) gave crystals m.p. 81-83° (Found: C, 59.9; H, 4.9; N, 16.2. $C_{13}H_{13}N_3O_3$ requires C, 60.2; H, 5.0; N, 16.2%).

$\nu_{max.}$ 1727, 1654, 1608, 1590, 1218, 1178, 928 and 767 cm.$^{-1}$.

τ 1.80 (s, 1H); 2.06-2.86 (m, 4H); 6.12, 6.60 (s, s, ratio of about 1:2.5, together 3H); 6.60, 7.03 (m,m, ratio 2.3:1, together 3H).

(iv) In DMSO

The reaction was carried out in DMSO (10 ml.). The mixture was poured into water and extracted with petrol (60-80°) to yield benzo-1,2,4-triazine (54 mg., 8.5%). Extraction of the remaining aqueous solution with chloroform gave an oily residue that on trituration with ether-petrol gave a solid (6.34 mg., 53%). Recrystallisation from chloroform petrol afforded N-(quinoxalin-2-on-1-yl)-dimethyl-sulfoximine, m.p. 187-189° (Found: C, 50.6; H, 4.4; N, 18.0; S, 13.6. $C_{10}H_{11}N_3O_2S$ requires C, 50.6; H, 4.7; N, 17.7; S, 13.5%).

$\nu_{max.}$ 3010, 2920, 1665, 1603, 1462, 1202, 955, 781 and 750 cm.$^{-1}$

τ 1.64 (s, 1H); 1.92-2.72 (m, 4H); 6.60 (s, 6H).

C Miscellaneous experiments

(i) Irradiation of N-(quinoxalin-2-on-1-yl)-dimethylsulfoximine

The DMSO adduct (237 mg., 1 mmole) was dissolved in a mixture of benzene (25 ml.) and cyclohexene (25 ml.) and heated to reflux. The mixture was irradiated with a Phillips 500 W sun lamp for 8 hr. under nitrogen at reflux temperature. The mixture was evaporated to give the cyclohexene aziridine (74 mg., 30%), m.p. 173-176°, on trituration with ether-petrol. No other crystalline products could be isolated.

(ii) Irradiation of benzo-1,2,4-triazine

Benzo-1,2,4-triazine (161 mg.) was dissolved in dry benzene (25 ml.) and irradiated under similar conditions as above. The triazine, m.p. 75-77°, was recovered unchanged (147 mg., 91%).

(iii) Pyrolysis of N-(quinoxalin-2-on-1-yl)-dimethylsulfoximine

The DMSO adduct (40 mg.) was heated at 230° for 30 min. The residue on sublimation gave the unchanged DMSO adduct (28 mg., 70%).

(iv) Amination of quinoxalin-2-one with chloramine

The quinoxalinone was dissolved in a mixture of DMF and methylene chloride and treated with sodium hydride and then chloramine by standard procedures. The mixtureswas stirred for 1 week at room temperature but no N-amino compound was formed (t.l.c.). The solution was filtered and the filtrate gave recovered starting material (4%). The precipitate was not investigated.

4 1-AMINOOXINDOLES

A 1-Aminooxindole

1-Aminooxindole was prepared by the method of Baumgarten et al.[56,196b] either by the cyclodehydration of o-hydrazinophenyl acetic acid, or by reduction of cinnolin-3-one with zinc and ethanolic sulfuric acid.

(i) Oxidation of 1-aminooxindole

a) In cyclohexene

1) 1-Aminooxindole (250 mg., 1.7 mmoles) was dissolved in a mixture of methylene chloride (15ml.) and cyclohexene (15 ml.) and LTA (1.5 g., 3.4 mmoles) added over 5 min. The mixture was evaporated to dryness after stirring for 30 min., and the residue treated with 6N sulfuric acid. The insoluble portion was washed with water and then dissolved in chloroform. The acid filtrate was neutralised with sodium acetate and extracted with chloroform. Both chloroform extracts showed cinnolin-3-one as the only product (t.l.c.) and were combined to yield cinnolin-3-one (147 mg., 60%), m.p. 198-200° (decomp.) (lit.[196], m.p. 200-201°).

2) 1-Aminooxindole (148 mg., 1 mmole) was dissolved in dry methylene chloride (20 ml.) and cyclohexene (40 ml.). Iodobenzene diacetate (386 mg., 1.2 mmoles) in methylene chloride (10 ml.) was added and the mixture stirred for 3 hr., and then chromatographed on silica:

1% Ether-petrol gave iodobenzene (132 mg., 65%) (i.r.)

50% Ethyl acetate-ether gave cinnolin-3-one (89 mg., 66%), m.p. 198-201° (decomp.).

b) In DMSO

The N-amino compound (296 mg., 2 mmoles) was dissolved in dry DMSO (10 ml.) and LTA (1.5 g., 3.4 mmoles) added portionwise to the stirred solution. The mixture was stirred for 1 hr. and then poured into water. Extraction with chloroform gave cinnolin-3-one (94 mg., 32%) as the only crystalline compound.

(ii) Attempted preparation of the triphenylphosphine imine of 1-aminooxindole

a) A solution of bromine (0.8 g., 0.27 ml.) in dry benzene (50 ml.) was added dropwise to a stirred solution of recrystallised triphenylphosphine (1.31 g., 5 mmoles) in benzene (50 ml.) at 0-5° under nitrogen. A pale yellow solid of triphenylphosphine dibromide gradually separated and pure triethylamine (2.8 ml., 10 mmoles) was then added. A solution of 1-aminooxindole (740 mg., 5 mmoles) in dry benzene (50 ml.) and dry ether (50 ml.) was added and the mixture refluxed for 1.5 hr. On cooling, the crystalline triethylamine hydrobromide (1.3 g., 72%) was filtered off and washed well with benzene. The filtrate and washings were evaporated to give an oily brown mixture which was chromatographed on basic alumina:

10% Ether-petrol gave triphenylphosphine (62 mg., 5%), m.p. and m.m.p. 80° (lit.[189], m.p. 80°).

Ether to 25% ethyl acetate-ether gave triphenylphosphine oxide (932 mg., 84%), m.p. and m.m.p. 152-153° (lit.[189], m.p. 153°).

10% Ethanol-ether gave unchanged 1-aminooxindole (282 mg., 48%), m.p. and m.m.p. 124-126° (lit.[196b], m.p. 127-128°).

b) The reaction was repeated as above. After the triethylamine hydrobromide had been filtered the solution was irradiated with a Phillips 500 W sun lamp, heated at reflux for 4 hr. No cinnolin-3-one was

detected (t.l.c.) and the mixture was then chromatographed on silica:

20% Ether-petrol gave triphenylphosphine (350 mg., 27%), m.p. 78-80°.

Ether gave 1-aminooxindole (650 mg., 92%), m.p. 123-127°.

10% Ethanol-ether gave triphenylphosphine oxide (700 mg., 50%), m.p. 151-153°.

(iii) N-(p-Toluenesulfonyl)-1-aminooxindole

This compound was prepared by the method of Whittman[56a] and Baumgarten[56b].

a) Irradiation of the sodium salt in DMSO

The tosyl derivative (604 mg., 2 mmoles) was dissolved in dry methylene chloride and sodium hydride (96 mg., of a 50% dispersion, 2 mmoles) added. The mixture was stirred for 30 min. and then evaporated to dryness. The sodium salt was dissolved in a mixture of benzene (85 ml.) and DMSO (15 ml.) and irradiated for 24 hr. in a quartz vessel with an Hanovian medium pressure lamp under nitrogen. The solvents were removed under reduced pressure and the residue dissolved in water, neutralised with dilute hydrochloric acid, and the chloroform extract chromatographed on silica:

Ether gave the unchanged tosyl derivative (14 mg., 2.3%), m.p. and m.m.p. 266°, as the only crystalline product.

Cinnolin-3-one when irradiated in benzene under similar conditions was recovered (70%).

b) Irradiation of the lithium salt in THF

The tosyl derivative (1.51 g., 5 mmoles) was suspended in dry THF (100 ml.) and lithium butyl (2 ml., of a 2.5 M solution, 5 mmoles) added. The solution gradually became homogeneous and was then irradiated under similar conditions as above for 17 hr. T.l.c. indicated that cinnolin-3-one had not been formed. The lithium tosylate was filtered and the filtrate chromatographed on silica to give the

unchanged tosyl derivative of 1-aminooxindole (244 mg., 40%) as the only crystalline product.

(iv) Attempted amination of oxindole

Oxindole (98%) and (70%) was recovered unchanged when treated with HOS under basic conditions at 25 to 30° and 35 to 40° respectively. At 60 to 70° a red polymeric material which could not be characterised was obtained. Similar procedures as already described for previous aminations with chloramine and O-(2,4-dinitrophenyl)-hydroxylamine were attempted, but only gave similar red polymeric material as was obtained above.

B 1-Amino-3-methyloxindole

(i) Preparation from 4-methylcinnolin-3-one

4-Methylcinnolin-3-one was prepared by the method of Baumgarten et al.[196a] and reduced to the N-amino compound by a method analogous to that used for 1-aminooxindole.[196b]

4-Methylcinnolin-3-one (544 mg., 3.4 mmoles) was dissolved in 95% ethanol (20 ml.) and zinc dust (0.75 g.) was added. The mixture was heated under reflux and 6N sulfuric acid (8.6 ml.) added over 5 min. After a further 30 min. at reflux the solution was filtered while hot and the excess of zinc washed thoroughly with hot ethanol. The ethanol was removed under reduced pressure and the residue diluted with water (20 ml.) and then made alkaline with concentrated aqueous ammonia. The solution was extracted with chloroform and the extract chromatographed on silica:

Ether gave a colourless oil that gradually crystallised (493 mg., 90%). Recrystallisation from ether-petrol gave needles of 1-amino-3-methylindolin-2-one, m.p. 78-80°. (Found: C, 66.9; H, 6.2; N, 17.3. $C_9H_{10}N_2O$ requires C, 66.7; H, 6.2; N, 17.3%).

$\nu_{max.}$ 3325, 3198, 1704, 1640, 1620, 1246, 1011, 768 and 704 $cm.^{-1}$

τ 2.70-3.32 (m, 4H); 5.25 (br.s, 2H); 6.18 (q, 1H; J 7 c./sec.); 8.71 (d, 3H, J 7 c./sec.).

Anisylidene derivative, m.p. 126-128°, from aqueous ethanol, (Found: C, 73.2; H, 6.0; N, 9.7. $C_{17}H_{16}N_2O_2$ requires C, 72.8; H, 5.8; N, 10.0%).

$\nu_{max.}$ 1704, 1618, 1605, 1255, 1172, 838 and 752 cm.$^{-1}$.

τ 0.08 (s, 1H); 2.15-3.14 (m, 8H); 6.14 (s, 3H); 6.43 (q, 1H, J 7 c./sec); 8.50 (d, 3H, J7 c./sec.).

(ii) Deamination of 1-amino-3-methyloxindole

The N-aminooxindole (76 mg., 0.47 mmole) and N-nitrosodiphenylamine (93 mg., 0.47 mmole) were fused on a steam bath for 30 min. and on cooling the mixture was chromatographed on silica:

5% Ether-petrol gave diphenylamine (52 mg., 66%), m.p. and m.m.p. 51-53° (lit.[189], m.p. 53°)

5% Ether-petrol gave recovered N-nitrosodiphenylamine (8 mg., 8.5 %), m.p. and m.m.p. 67-68° (lit.[189], m.p. 68°).

Ether gave 3-methyloxindole (41 mg., 60%), m.p. and m.m.p. 120-122° (lit., m.p. 122-123°). An i.r. spectrum was identical to that of an authentic specimen.

(iii) Attempted preparation from 3-methyloxindole

3-Methyloxindole was prepared by the cyclisation of β-propionylphenylhydrazine according to the method of Endler and Becker.[206]

a) Amination with HOS

3-Methyloxindole (1.0 g., 6.8 mmoles) was dissolved in water (40 ml.) containing sodium hydroxide (1.6 g., 40 mmoles) at 60°. HOS (2.9 g., 25 mmoles) was added at a temperature between 60 and 65°. On cooling, the solution was extracted with chloroform and the extract chromatographed on silica:

80% Ether-petrol gave unchanged 3-methyloxindole (350 mg., 35%), m.p. and m.m.p. 119-122° (lit.[206], m.p. 122-123°).

50% Methanol-ether gave an oil (435 mg.) that showed two overlapping spots on t.l.c. A partial separation was obtained using prep.t.l.c. and the compound of highest Rf. value was found to be 3-amino-3-methyloxindole, m.p. 182-183° (lit., [207] m.p. 182-183°), from chloroform-petrol (Found: C, 66.7; H, 6.1; N, 17.5. Calculated for $C_9H_{10}N_2O$ C, 66.7; H, 6.2; N, 17.3%)

$\nu_{max.}$ 3358, 3280, 3140, 2975, 2880, 2825, 1710, 1680, 1622, 750, 740 720 and 658 $cm.^{-1}$.

τ 1.40-1.72 (br.s, 1H, disappears on addition of D_2O); 2.50-3.20 (m, 4H); 8.00-8.40 (br.s, 2H, disappears on addition of D_2O); 8.52 (s, 3H).

The remaining oil could not be separated entirely from the compound above. The crude product was found to be 1,3-diamino-3-methylindolin-2-one (b.p. 140-150°/0.3 mm.) (Found: C, 63.5; H, 5.4; N, 23.7. $C_9H_{11}N_3O$ requires C, 61.0; H, 6.3; N, 23.7%).

m/e: 176 (P), 161, 149, 134, 133, 132. m^*_1, 177-149 = 125.5; m^*_2, 149-133 = 118.9; m^*_3, 149$\rightarrow$132 = 116.9.

$\nu_{max.}$ 3310, 3190, 2965, 1715, 1620, 1485, 1468, 1198, and 750 $cm.^{-1}$.

τ 2.54-3.17 (m, 4H); 7.80 (s, 2H); 8.12 (s, 2H); 8.63 (s, 3H).

Di-anisylidene derivative, m.p. 169-170°, from ethanol (Found: C, 72.3; H, 5.8; N, 10.1. $C_{25}H_{23}N_3O_3$ requires C, 72.6; H, 5.6; N, 10.1%).

$\nu_{max.}$ 1712, 1630, 1617, 1609, 1260, 840 and 760 $cm.^{-1}$.

τ 0.41 (s, 1H); 1.72 (s, 1H); 2.07-3.28 (m, 12H); 6.24 (s, 3H); 6.26 (s, 3H); 8.28 (s, 3H).

b) Amination with chloramine

3-Methyloxindole (4.4 g., 0.03 mole) was dissolved in dry methylene chloride and treated with sodium hydride (2.9 g., of a 50% dispersion, 0.06 mole). When hydrogen evolution ceased, ethereal chloramine (0.075 mole) was added and the mixture stirred overnight. The mixture was filtered and the filtrate chromatographed on silica:

Ether gave unchanged 3-methyloxindole (204 mg., 4.5%), m.p. and m.m.p. 121-123° (lit.[207], 122-123°).

50% Ethanol-ether gave an oil (3.72 g.) that contained a similar mixture of mono and di-aminooxindoles as in the HOS amination. A partial separation could be obtained by the method previously described.

(iv) Oxidation of 1-amino-3-methyloxindole

a) In cyclohexene

The N-amino compound (162 mg., 1 mmole) was dissolved in methylene chloride (10 ml.) and cyclohexene (10 ml.) added. LTA (665 mg., 1.5 mmoles) was added portionwise and the mixture turned bright yellow. Stirring was continued for a further 30 min. and then filtered to give lead diacetate (450 mg., 93%). The filtrate was chromatographed on silica and 4-methylcinnolin-3-one (89 mg., 56%), m.p. and m.m.p. 230-234° (decomp.), was the only crystalline product obtained.

b) Alone

The reaction was repeated under similar conditions using a mixture of methylene chloride (10 ml.) and benzene (10 ml.). 4-Methylcinnolin-3-one (60%) was the only product obtained.

c) In DMSO

The reaction was repeated in DMSO (1 ml.). The mixture was diluted with water, extracted with ether, dried and chromatographed as above to give the cinnolinone (35%).

C 1-Amino-3,3-dimethyloxindole

(i) 3,3-Dimethyloxindole

Phenylhydrazine (50 ml.) and 2-methylpropionic acid (50 ml.) were treated with stirring for 3.5 hr. at 150°. The mixture was cooled and recrystallised from water (charcoal) to give 2-methylpropionylphenylhydrazide (38 g.), m.p. 140-143° (lit.[189], 142-143°).

The hydrazide (32.2 g., 0.2 mole) and finely powdered calcium hydride (14 g., 0.33 mole) were heated cautiously to 170°. At this temperature the mixture violently decomposed. When the reaction had subsided, heating was continued at 250° for 3 hr. Methanol (50 ml.) and water (50 ml.) were cautiously added to the cooled reaction mixture, followed by concentrated hydrochloric acid (60 ml.) and water (50 ml.) and the mixture heated under reflux for 1 hr. The crude black solid was filtered and then distilled under reduced pressure. The fraction, b.p. 136-142° /2 mm., was collected and crystallised from aqueous ethanol (charcoal) to give 3,3-dimethyloxindole (6.14 g., 19%), m.p. 152-153° (lit.[189], m.p. 152-153°).

(ii) 1-Amino-3,3-dimethyloxindole

3,3-Dimethyloxindole (1.61 g., 0.01 mole) was dissolved in a mixture of water (50 ml.) and ethanol (10 ml.) containing sodium hydroxide (4 g., 0.1 mole) at 65°. HOS (5.65 g., 0.05 mole) was added over 15 min. at such a rate that the temperature was maintained between 60 and 65°. An oil gradually separated and on cooling was extracted into ether to give 1-amino-3,3-dimethylindolin-2-one (1.72 g., 98%) as an oil which

quickly solidified. Repeated recrystallisations from petrol (60-80°) gave fine needles m.p. 109-110° (Found: C, 68.0; H, 7.0; N, 16.1. $C_{10}H_{12}N_2O$ requires C, 68.2; H, 6.9; N, 15.9%).

$\nu_{max.}$ 3303, 3210, 1708, 1688, 1650, 1632, 1612, 768, 756, 750 and 700 $cm.^{-1}$.

τ 2.67-3.12 (m, 4H); 5.68 (br.s, 2H); 8.70 (s, 6H).

(iii) Oxidation of 1-amino-3,3-dimethyloxindole

a) In cyclohexene

The N-amino compound (880 mg., 5 mmoles) was dissolved in methylene chloride (10 ml.) and cyclohexene (20 ml.) and LTA (2.66 g., 6 mmoles) was then added. The mixture became dark red and a gas was evolved. The mixture was stirred for 1 hr. and then filtered free of the lead diacetate (1.6 g., 83%). The filtrate and methylene chloride washings were chromatographed on basic alumina:

30% Ether-petrol gave 3,3-dimethylindazole (132 mg., 18%) as a colourless oil, b.p. 77-80°/2 mm. (Found: C, 73.9; H, 7.0; N, 18.8. $C_9H_{10}N_2$ requires C, 73.9; H, 6.9; N, 19.2%).

$\nu_{max.}$ 2965, 2917, 1595, 1482, 1458, 912, 773 and 757 $cm.^{-1}$.

τ 1.80-2.13 (m, 1H); 2.50-2.73 (m, 3H); 8.51 (s, 6H).

$\lambda_{max.}$ 209 (inflexion), 219 (log ε 3.68), 263 nm (3.58).

40% Ether-petrol gave a crystalline compound. Recrystallisation from chloroform-petrol (charcoal) gave the tetrazene, 1.2-di-(3,3-dimethylindazolin-2-on-1-yl)-diimide (8 mg., 0.9%), m.p. 221-222° (decomp.) (Found, C, 68.8; H, 5.9; N, 16.0. $C_{20}H_{20}N_4O_2$ requires C, 68.9; H, 5.8; N, 16.1%).

m/e: 348 (P), 320, 161, 146, m*, 348-320 = 294.6.

$\nu_{max.}$ 1740, 1605, 1260, 1184, 982, 761, 750 and 662 $cm.^{-1}$.

τ 2.50-2.88 (m, 8H); 8.43 (s, 12H).

20% Ethyl acetate-ether gave 3,3-dimethyloxindole (200 mg., 26%), m.p. and m.m.p. 150-153° (lit.[189], m.p. 152-153°) after sublimation.

b) With tetracyclone present

The N-aminooxindole (880 mg., 5 mmoles) was dissolved in methylene chloride (75 ml.) containing tetracyclone (1.92 g., 5 mmoles). Powdered LTA (2.66 g., 6 mmoles) was added, gas evolution took place and the mixture stirred for a further 90 min. The mixture was filtered and the lead diacetate (1.6 g., 82%), washed with methylene chloride. The combined filtrate and washings were chromatographed as above:

Benzene gave unchanged tetracyclone (1.84 g., 96%), m.p. and m.m.p. 216-219° (lit.[189], m.p. 220°).

20% Ether-petrol gave 3,3-dimethylindazole (146 mg., 20%).

20% Ethanol-ether gave 3,3-dimethyloxindole (211 mg., 26%).

c) In DMSO

(1) The reaction was repeated using the same quantities of N-amino compound and oxidant in DMSO (10 ml.) and methylene chloride (5 ml.). The mixture was stirred for 30 min. and then the excess of solvents removed under reduced pressure. The residue was extracted with chloroform; the insoluble fraction was lead diacetate (1.45 g., 76%). The filtrate was chromatographed on silica:

20% Ether-petrol gave a red oil (60 mg.). T.l.c. indicated the presence of 3,3-dimethylindazole, but this could not be isolated.

50% Ether-petrol gave an oily product that on trituration with ether gave the tetrazene (16 mg., 1.8%), m.p. 220-223° (decomp.).

Ether gave a red oily mixture (150 mg.) from which 3,3-dimethyloxindole (55 mg., 7%) could be sublimed.

(2) The reaction was repeated on one-fifth scale. The reaction mixture was poured into cold water and extracted with chloroform. The dried extract was chromatographed on basic alumina to give 3,3-dimethyloxindole (42 mg., 26%) as the only crystalline product.

d) With iodobenzene diacetate and cyclohexene

1-Amino-3,3-dimethyloxindole (528 mg., 3 mmoles) was dissolved in a mixture of methylene chloride (25 ml.) and cyclohexene (25 ml.). Iodobenzene diacetate (1.2 g., 3.5 mmoles) was added and the mixture stirred for 3 hr. and then chromatographed on silica:

Petrol gave iodobenzene (430 mg., 55%),(i.r.).

40% Ether-petrol gave the tetrazene (79 mg., 7.5%), m.p. 222-223° (decomp.) which could be separated from the accompanying oils (200 mg.) by trituration with ether.

Ether gave 3,3-dimethyloxindole (275 mg., 57%).

(iv) Pyrolysis of the tetrazene

The tetrazene (43 mg.) was cautiously heated to 225-230° for 15 min. On cooling, the residue was sublimed to give 3,3-dimethyloxindole (24 mg., 60%), m.p. and m.m.p. 150-153° (lit.[189], m.p. 152-153°).

(v) Attempted preparation of 3,3-dimethylindazole

1-Aminobenzotriazole was prepared by HOS amination of benzotriazole according to the method of Rees and Campbell[134b]. Acetone hydrazone was prepared by the method of Staudinger and Gaule.[208]

Acetone hydrazone (288 mg., 4 mmoles) was dissolved in methylene chloride (25 ml.) at 0°. LTA (2.2 g., 5 mmoles) was then added followed by 1-aminobenzotriazole (536 mg., 4 mmoles). A further

portion of LTA (2.2 g.) was added and the mixture stirred for 6 hr. before being filtered. The filtrate was chromatographed on silica:

Petrol gave biphenylene (110 mg., 38%), m.p. and m.m.p. 109-110° (lit.[189], m.p. 110°).

10% Ether-petrol gave phenyl acetate (57 mg., 11%), (i.r. and p.m.r.).

D 1-Amino-3,3-diphenyloxindole

(i) 3,3-Diphenyloxindole

The method of preparation was adapted from that of Wegmann et al.[209]

Isatin (18 g.) was dissolved in benzene (1200 ml.) and powdered aluminium chloride (33 g.) added. The mixture was stirred under reflux for 90 min., cooled and treated cautiously with water and then neutralised with 2N sodium hydroxide solution. The benzene layer was separated, dried and evaporated to half volume. 3,3-Diphenyloxindole (24 g., 69%) crystallised to fluffy needles, m.p. 225-226° (lit.[209], m.p. 225-226°).

(ii) 1-Amino-3,3-diphenyloxindole

(a) Amination of 3,3-diphenyloxindole with HOS

The oxindole (1.425 g., 5 mmoles) was dissolved in a mixture of water (25 ml.) and ethanol (20 ml.) containing sodium hydroxide (2 g., 0.05 mole) at 60°. HOS (2.9 g., 0.025 mole) was added over 10 min., the temperature being maintained between 60 and 70°. On cooling a crystalline compound separated and was collected. The filtrate, when extracted with ether, gave a further (0.6 g.) of 1-amino-3,3-diphenyloxindole (97.5%), m.p. 150-152° (lit.[210], m.p. 151-152°) from aqueous ethanol. An i.r. spectrum was identical to that of an authentic sample prepared by the method of Bird.[210]

When the reaction was carried out in the absence of ethanol with

either sodium or potassium hydroxide as the base, a quantitative recovery of the unchanged oxindole was obtained.

(b) Amination of 3,3-diphenyloxindole with chloramine

The diphenyloxindole (9.75 g., 0.034 mole) was dissolved in dry methylene chloride (200 ml.) and sodium hydride (3.3 g., of a 50% dispersion, 0.066 mole) added. When hydrogen evolution ceased, ethereal chloramine (0.068 mole) was added and the mixture stirred overnight. The reaction mixture was filtered and the filtrate evaporated to dryness. Recrystallisation from chloroform-petrol (charcoal) gave 1-amino-3,3-diphenyloxindole (9.0 g., 88%), m.p. 150-152°.

When the chloramine to oxindole ratio was 1.5:1, 2.5:1 and 3.0:1, the yields of the N-aminooxindole were 80, 80 and 57% respectively.

(iii) Oxidation of 1-amino-3,3-diphenyloxindole

The following general procedure was used except when DMSO and methyl phenyl sulfoxide were used. The N-aminooxindole (900 mg., 3 mmoles) was dissolved in the solvent and LTA (2.0 g., 4.5 mmoles) was added portionwise over 10 min. The mixture was stirred for a further 1 hr. and then filtered. The filtrate and chloroform washings were combined and chromatographed on a suitable support.

a) Alone

(1). Ether (50 ml.) was used as solvent and the mixture was chromatographed on deactivated basic alumina:

10% Ether-petrol gave an oil (147 mg., 18%) that rapidly solidified to give 3,3-diphenylindazole, m.p. 87-89°, from petrol (60-80°) (Found: C, 84.9; H, 5.2; N, 10.1. $C_{19}H_{14}N_2$ requires C, 84.5; H, 5.2; N, 10.4%).

m/e: no parent (270), 242, 165, 121.

$\nu_{max.}$ 3055, 1595, 1490, 1461, 992, 762, 749, 698 and 655 cm.$^{-1}$.

50% Ethylacetate-ether gave a yellow solid. Recrystallisation from chloroform-petrol gave the tetrazene 1,2-di-(3,3-diphenyl-indolin-2-on-1-yl)-diimide (290 mg., 32%) as fine yellow needles, m.p. 284-288 (decomp.) (Found: C, 80.8; H, 4.6; N, 9.1. $C_{40}H_{28}N_4O_2$ requires C, 80.5; H, 4.7; N, 9.4%).

m/e: 596 (P), 568, 554, 526, 312, 300, 285, 256, 240.

m_1*, 596-568 = 541.5; m_2*, 596-554 = 514.9; m_3*, 554-526 = 499.4.

$\nu_{max.}$ 1734, 1685, 1615, 1250, 1211, 756 and 705 cm.$^{-1}$.

(2) Benzene (50 ml.) was used as solvent and similar work up gave the indazole (30%) and the yellow tetrazene (18%).

(3) Methylene chloride was used as solvent and with similar workup as above:

10% Ether-petrol gave the indazole (30%), m.p. 87-89°.

10% Ether-petrol also eluted a crystalline compound m.p. 224-226° (decomp.) from chloroform-petrol. Physical data suggested an isomeric tetrazene (23 mg., 2.5%) (Found: C, 80.5; H, 4.7; N, 9.2. $C_{40}H_{28}N_4O_2$ requires C, 80.5; H, 4.7; N, 9.4%).

m/e: 596 (small P), 582, 568 (large), 540, 463, 285, 256.

m_1*, 568-540 = 514; m*, 540-463 = 397.

$\nu_{max.}$ 1750, 1602, 1465, 1320, 1264, 757 and 707 cm.$^{-1}$.

Pyrolysis at 230° followed by sublimation of the residue gave 3,3-diphenyloxindole, identified by i.r. spectral comparison.

50% Ethyl acetate-ether gave the yellow tetrazene (368 mg., 47%).

b) In cyclohexene

Methylene chloride (25 ml.) and cyclohexene (25 ml.) were used. The filtrate was chromatographed on basic alumina:

20% Ether-petrol gave a mixture of the indazole and the aziridine adduct which could not be separated by chromatographic techniques. Fractional recrystallisation afforded the aziridine (120 mg., 10.5%) and repeated recrystallisation from chloroform-petrol gave pure 2-(3,3-diphenylindolin-2-on-1-yl)-7-azabicyclo-[4,10]-heptane, m.p. 190-192° (Found: C, 81.9; H, 6.4; N, 7.4. $C_{26}H_{24}N_2O$ requires C, 82.1; H, 6.4; N, 7.4%).

m/e: 376 (P), 300, 285, 256, 241, 240, 239, 165.

$\nu_{max.}$ 2955, 1710, 1611, 1470, 768 and 703 cm^{-1}.

τ 2.74-3.00 (m, 14H); 7.15-7.30 (m, 2H); 7.67-8.24 (m, 4H); 8.46-8.84 (m, 4H).

The residual oil showed characteristic peaks due to both the indazole and the aziridine.

Ethyl acetate gave the yellow tetrazene (221 mg., 25%).

c) In cyclooctene

Methylene chloride (20 ml.) and cyclooctene (20 ml.) were used and the mixture was chromatographed on basic alumina:

20% Ether-petrol gave the indazole (162 mg., 20%) m.p. 87-89°.

25% Ether-petrol gave 2-(3,3-diphenylindolin-2-on-1-yl)-9-azabicyclo-[6,1,0]-nonane (390 mg., 32%), m.p. 133-135° from petrol (60-80°) (Found: C, 81.9; H, 7.0; N, 7.1. $C_{28}H_{28}N_2O$ requires C, 82.3; H, 6.9; N, 6.9%).

$\nu_{max,}$ 2920, 1715, 1614, 1466, 754 and 703 cm.$^{-1}$.

τ 2.70-3.12 (m, 14H); 7.32-7.88 (m, 4H); 8.23-8.90 (m, 10H).

d) In methyl methacrylate

Methylene chloride (15 ml.) and methyl methacrylate (15 ml.) were used and the mixture was chromatographed on basic alumina:

20% Ether-petrol gave 3,3-diphenylindazole (60 mg., 7.5%)

25% Ether-petrol gave the colourless tetrazene (6 mg., 0.7%) m.p. 222-226° (decomp.).

60% Ether-petrol gave the aziridine adduct (230 mg., 16%) as a viscous oil. Trituration with ether-petrol and recrystallisation of the solid from petrol (60-80°) gave methyl 2-methyl-1-(3,3-diphenylindolin-2-on-1-yl)aziridine 2- carboxylate, m.p. 112-114° (Found: C, 75.1; H, 5.6; N, 7.4. $C_{25}H_{22}N_2O_3$ requires C, 75.4; H, 5.6; N, 7.0%).

$\nu_{max.}$ 1727, 1709, 1611, 1340, 1206, 749 and 706 $cm.^{-1}$.

τ 2.60-3.25 (m, 14H); 6.24, 6.93 (s,s, together 3H); 7.07 (d, 1H, J 2.5 c./sec.); 7.49 (d, 1H, J 2.5 c./sec.); 8.38, 8.73 (s,s, ratio 1:1.5, together 3H).

Distillation of the aziridine resulted in decomposition with formation of 3,3-diphenyloxindole, m.p. and m.m.p. 224-226°. The reaction was repeated in methyl methacrylate (10 ml.) alone. The indazole (3%) and the aziridine (46%) were obtained.

e) In methyl phenyl sulfoxide

1-Amino-3,3-diphenyloxindole (900 mg., 3 mmoles) was dissolved in methyl phenyl sulfoxide (5 ml.) and LTA (2.0 g., 4.5 mmoles) added. The mixture was stirred for 2 hr. and then poured into water and filtered. Recrystallisation from chloroform-petrol (charcoal) gave N-(3,3-diphenylindolin-2-on-1-yl)-methyl phenyl sulfoximine (758 mg., 58%), m.p. 169-171° (decomp.) (Found: C, 73.6; H, 5.1; N, 6.6; S, 7.8. $C_{27}H_{22}N_2O_2S$ requires C, 74.0; H, 5.1; N, 6.4; S, 7.3%).

$\nu_{max.}$ 1718, 1616, 1210, 1097, 750 and 702 $cm..^{-1}$.

τ 1.68-1.90 (m, 2H); 2.40-3.24 (m, 17H); 6.74 (s, 3H).

f) In DMSO

Reaction (e) above, was repeated in dry DMSO (10 ml.). The crude precipitate, obtained after the reaction mixture was poured into water, was dissolved in hot acetone (charcoal) and then dried (Na_2SO_4). The acetone was removed under reduced pressure to give an oil that rapidly turned red on standing. Trituration with ether gave the sulfoximine (824 mg., 73%). Recrystallisation from chloroform-petrol under nitrogen gave N-(3,3-diphenylindolin-2-on-1-yl)-dimethyl sulfoximine, m.p. 185-186° (decomp.) (Found: C, 70.3; H, 5.5; N, 7.4; S, 8.4. $C_{22}H_{20}N_2O_2S$ requires C, 70.2; H, 5.4; N, 7.4; S, 8.5%).
m/e: 376 (P), 333, 300, 285, 256, 249, 240, 239, 165.
$\nu_{max.}$ 1710, 1611, 1462, 1229, 1210, 764, 750 and 703 $cm.^{-1}$.
τ 2.64-2.83 (m, 14H); 6.88 (s, 6H).
$\lambda_{max.}$ 217 (log ϵ 3.33); 264 nm (log ϵ 2.79).

Attempted purification by sublimation under reduced pressure resulted in decomposition of the sulfoximine with formation of 3,3-diphenyloxindole (i.r. and t.l.c.).

(iv) Miscellaneous experiments

a) Photolysis of 3,3-diphenylindazole

The indazole (74 mg.) was dissolved in dry benzene (100 ml.) and irradiated for 4 hr. under nitrogen with an Hanovian 100 W medium pressure lamp with quartz windows. The mixture was chromatographed on silica:

1% Ether-petrol gave 9-phenylfluorene (27 mg., 41%), m.p. 147-148° (lit.[189], m.p. 147-148°) from petrol (60-80°) (Found: C, 94.0; H, 6.0. Calculated for $C_{19}H_{14}$ C, 94.2; H, 5.8%).

b) Attempted pyrolysis of 3,3-diphenylindazole

The indazole was heated for 10 min. at 200°, cooled and the

residue sublimed to give the unchanged indazole (66%), m.p. 86-89°.

c) Photolysis of the sulfoximine of 1-amino-3,3-diphenyloxindole

The sulfoximine (376 mg., 1 mmole) was dissolved in a mixture of dry benzene (50 ml.) and cyclohexene (50 ml.) and irradiated as in (iv)a) above for 17 hr. under nitrogen. Chromatography on basic alumina gave 9-phenylfluorene (132 mg., 55%), m.p. 146-148°.

Under similar conditions the aziridine formed from cyclohexene also gave 9-phenylfluorene (59%).

d) 3,3-Diphenylindazole

Benzophenone hydrazone[211] (681 mg., 3.5 mmoles) was dissolved in methylene chloride (25 ml.) at 0°, and LTA (1.95 g., 4.4 mmoles) added. There was a vigorous evolution of gas and the mixture turned dark red. 1-Aminobenzotriazole (0.49 g., 3.66 mmoles) was added followed by more LTA (1.95 g.). The mixture was stirred for 5 min. and then filtered. Evaporation under reduced pressure and extraction of the residue with petrol (60-80°) gave 3,3-diphenylindazole (0.27 g., 29%), m.p. and m.m.p. 87-89°. An i.r. spectrum was identical to that of a specimen prepared by LTA oxidation of 1-amino-3,3-diphenyloxindole.

E 1,4-Dihydrocinnolin-3(2H)-one

(i) Reduction of 4-chlorocinnolin-3(2H)-one

4-Chlorocinnolin-3-one[56] (180 mg., 1 mmole) was dissolved in a mixture of ethanol (10 ml.) and water (5 ml.). Ammonium chloride (160 mg., 3 mmoles) and zinc dust (260 mg.) were added and the mixture heated under reflux for 30 min. The solution faded to a very pale yellow and the excess of zinc was removed by filtration and washed with hot ethanol (10 ml.). The filtrate and washings were extracted with chloroform to give a pale yellow solid (130 mg., 88%).

Recrystallisation from carbontetrachloride-petrol gave 1,4-dihydrocinnolin-3(2H)-one, m.p. 161-164° (lit.[212], m.p. 160-164°) (Found: C, 64.9; H, 5.4; N, 18.6. Calculated for $C_8H_8N_2O$ C, 64.8; H, 5.4; N, 18.9%).

m/e: 148 (P), 147, 146, 121, 120, 119, 58.

$\nu_{max.}$ 3335, 3180, 3055, 1645, 1392, and 739 $cm.^{-1}$.

τ 2.65-2.90 (m, 4H); 3.20-3.60 (br.s, 2H); 6.44 (s, 2H).

Cinnolin-3-one when reduced with zinc in similar conditions to those above gave the dihydrocinnolin-3-one (100%), m.p. 160-164°.

(ii) Oxidation of 1,4-dihydrocinnolin-3(2H)-one

The dihydrocinnolinone (48 mg.) was dissolved in methylene chloride (25 ml.) and LTA (222 mg., 0.5 mmole) added. The mixture was filtered and the filtrate evaporated to give cinnolin-3-one (40 mg., 84%), m.p. and m.m.p. 199-201° (decomp.).

5 N-AMINOACETANILIDE

(i) Preparation from acetanilide

N-Aminoacetanilide was prepared by a modification of the method of Sternbach et al.[57]

(a) Acetanilide (5.4 g., 0.04 mmole) was dissolved in methylene chloride (100 ml.) and treated with sodium hydride (3.8 g., of a 50% dispersion, 0.08 mole). When hydrogen evolution ceased, the mixture was stirred overnight with ethereal chloramine (0.06 mole). The solution was filtered and the filtrate evaporated under reduced pressure to give N-aminoacetanilide (4.15 g., 70%), from chloroform-petrol (charcoal), m.p. 124-125° (lit.[57], m.p. 125°).

(b) Attempted amination of acetanilide in aqueous ethanolic sodium hydroxide solutions gave quantitative recovery of acetanilide.

(ii) Oxidation of N-aminoacetanilide

The N-amino compound was dissolved in methylene chloride and cyclohexene. LTA was added and a vigorous evolution of gas occurred. The mixture was filtered and the filtrate chromagographed to give acetanilide (22%) as the only crystalline product.

When the reaction was repeated in methyl methacrylate, the yield of acetanilide fell to 3%. Methyl methacrylate polymers were also obtained.

The reaction was also carried out in DMSO. The mixture was poured into water and the ether extract chromatographed on silica to give acetanilide (6.5%).

(iii) 1-Acetyl-2-phenyldiimide

1-Acetyl-2-phenylhydrazine[213] (1.48 g., 10 mmoles) was dissolved in methylene chloride (50 ml.) and treated portionwise with LTA (5.35 g., 12 mmoles). The mixture was stirred for 30 min. and then

filtered. The bright red filtrate was extracted with sodium bicarbonate solution and then washed with water. The organic layer was dried, evaporated and extracted with petrol (60-80°) to give 1-acetyl-2-phenyldiimide (1.04 g., 69%) as a bright red oil. The i.r. spectrum was identical to that of an authentic specimen prepared by the oxidation of 1-acetyl-2-phenylhydrazine with N-bromosuccinimide by the method of Book et al.[214]

6 1-AMINOBENZIMIDAZOLIN-2-ONES

A 1-Amino-3-isopropenylbenzimidazolin-2-one

3-Isopropenylbenzimidazolin-2-one was prepared by the method of Davoll[190] by the cyclisation of ethyl o-aminoanilinocrotonate with sodium 2-ethoxyethoxide.

a) The benzimidazolinone (10.44 g., 0.06 mole) was dissolved in water (100 ml.) containing sodium hydroxide (14 g., 0.35 mole) at 60°. HOS (21 g., 0.18 mole) was added over 1 hr. the temperature being maintained between 60 and 70°. Crystals gradually separated and on cooling were filtered to yield 1-amino-3-isopropenylbenzimidazolin-2-one (10.2 g., 90%), m.p. 111-112.5°, from petrol (60-80°)
(Found: C, 63.7; H, 6.0; N, 22.3. $C_{10}H_{11}N_3O$ requires C, 63.6; H, 5.8; N, 22.2%).
m/e: 189 (P), 174, 173, 171, 149, 148, 133, 132, 118. m*, 189-144 = 109.7.
$\nu_{max.}$ 3345, 3275, 3235, 1703, 1657, 1605, 1201, 748, 742 and 715 $cm.^{-1}$.
τ 2.65-2.97 (m, 4H); 4.67 (d, 1H); 4.80 (d, 1H); 5.55 (br.s, 2H); 7.82 (s, 3H).
$\lambda_{max.}$ 215 (log ϵ 4.20); 283 nm (3178).

b) The benzimidazolin-2-one (3.5 g., 0.02 mole) was suspended in ether (100 ml.) and sodium hydride (1.5 g., of a 50% dispersion, 0.03 mole) added. Ethereal chloramine (0.022 mole) was added when hydrogen evolution ceased and the mixture was stirred overnight. The mixture was filtered and the solvent removed under reduced pressure to give an oil which gradually crystallised. The brown solid was extracted with petrol (60-80°), charcoaled and evaporated to a small volume. The N-amino compound (320 mg., 8.5%), m.p. 110-112°, crystallised.

(ii) Oxidation of 1-amino-3-isopropenylbenzimidazolin-2-one

a) Alone

The N-amino compound (500 mg., 2.64 mmoles) was dissolved in methylene chloride (20 ml.) and LTA (2.34 g., 5.3 mmoles) in methylene chloride (20 ml.) added dropwise. The mixture was stirred for 1 hr. and the filtrate chromatographed on basic alumina:

Ether eluted a crystalline compound contaminated by a red oil. Recrystallisation from chloroform-petrol gave the tetrazene, 1,2-di-(3-isopropenylbenzimidazolin-2-on-1-yl)-diimide (160 mg., 32%) m.p. 205-206° (decomp.) (Found: C, 63.9; H, 4.7; N, 22.3. $C_{20}H_{18}N_6O_2$ requires C, 64.2; H, 4.8; N, 22.5%).

m/e: 374 (P), 346, 187, 174, 173, 159.

$\nu_{max.}$ 1730, 1655, 1598, 901, and 736 cm.$^{-1}$.

τ 2.60-2.83 (m, 4H); 4.49 (d, 1H, J 1.5 c./sec.); 4.64 (d, 1H, J 1.5 c./sec.); 7.72 (s, 3H).

Attempted purification by sublimation caused the tetrazene to decompose to 1-isopropenylbenzimidazolin-2-one and irradiation with a Phillips 500 W sun lamp for 72 hr. in ethyl acetate also gave the benzimidazolinone (88%), m.p. and m.m.p. 120-121° (lit.[190], m.p. 120-121°).

b) In cyclohexene

A solution of LTA (3.3 g., 7.5 mmoles) in methylene chloride (25 ml.) was added dropwise to a solution of the N-amino compound (945 mg., 6 mmoles) in methylene chloride (25 ml.) and cyclohexene (25 ml.). The mixture was stirred for 2 hr. and then two drops of glycerol added. The mixture was filtered and evaporated to dryness. Trituration with ether gave the tetrazene (320 mg., 34%) m-p. 203-205° (decomp.). The ether soluble fraction was chromatographed on basic alumina to give the aziridine (200 mg., 14%) as the only crystalline compound. Recrystallisation from petrol (60-80°) gave 2-(3-isopropenylbenzimidazolin-2-on-1-yl)-7-azabicyclo-

[4,1,0]-heptane, m.p. 81.5-83.5° (Found: C, 71.4; H, 7.2; N, 15.8. $C_{16}H_{19}N_3O$ requires C, 71.3; H, 7.1; N, 15.6%).

m/e: 269 (P), 174, 173, 96.

$\nu_{max.}$ 1702, 1654, 1608 and 743 $cm.^{-1}$.

τ 2.87-3.12 (m, 4H); 4.80 (d, 1H, J 1.5 c./sec.); 4.91 (d, 1H, J 1.5 c./sec.); 6.92-7.10 (m, 2H); 7.70-8.85 (m, 11H, s at 7.82).

c) In DMSO

LTA (5.5 g., 12.5 mmoles) was added to a solution of the N-amino compound (2 g., 10.5 mmoles) in DMSO (10 ml.). The mixture was stirred for 30 min. and the excess of DMSO removed under reduced pressure. The residue was extracted with acetone and chromatographed on silica:

Ether gave the tetrazene (10 mg.), m.p. 203-206° (decomp.) and 3-isopropenylbenzimidazolin-2-one (84 mg., 4.5%) The mixture could be separated by trituration with a small amount of cold ether, the tetrazene being almost insoluble.

5% Methanol-ether gave a colourless glass that could not be crystallised (950 mg., 34%). The compound readily decomposed on standing and all attempts to purify by distillation failed due to decomposition with formation of DMSO and 3-isopropenylbenzimidazolin-2-one. A middle fraction of N-(3-isopropenylbenzimidazolin-2-on-1-yl)-dimethyl sulfoximine obtained from rechromatography was analysed (Found: C, 47.4; H, 5.2; N, 15.9; S, 12.6. (sample decomposing) . $C_{12}H_{15}N_3O_2S$ requires C, 54.3; H, 5.7; N, 15.8; S, 12.1%).

m/e: 265 (P), 225, 189, 174, 134.

$\nu_{max.}$ 3025, 2938, 1725, 1658, 1619, 1220, 1175, 1050, 1025 and 746 $cm.^{-1}$

τ 2.74-3.16 (m, 4H); 4.73-4.92 (m, 2H); 6.80(s, 6H); 7.82 (s, 3H).

(iii) Photolysis of the DMSO adduct

The adduct (146 mg.) was dissolved in a mixture of ethyl acetate (70 ml.) and cyclohexene (10 ml.) and the mixture irradiated under reflux with a Phillips 500 W sun lamp for 44 hr. under nitrogen. The resulting solution was chromatographed on deactivated basic alumina:

10% Ether-petrol gave the aziridine adduct (22 mg., 15%), m.p. and m.m.p. 80-83°.

Ether gave the isopropenylbenzimidazolinone (22 mg., 25%), m.p. and m.m.p. 117-120°, after sublimation.

10% Methanol-ether gave the unchanged DMSO adduct (16 mg., 11%), with i.r. spectrum identical to that of an authentic specimen.

(iv) Oxidation of 3-isopropenylbenzimidazolin-2-one

LTA (1.5 g.) was added to the benzimidazolinone (250 mg.) in methylene chloride. The mixture was stirred for 30 min. and then filtered; the filtrate was chromatographed on silica to give the unchanged benzimidazolinone (30 mg., 12%), m.p. and m.m.p. 118-121°, as the only crystalline compound.

B 1-Amino-3-isopropylbenzimidazolin-2-one

(i) Preparation from 3-isopropylbenzimidazolin-2-one

3-Isopropylbenzimidazolin-2-one, m.p. 127-128°, was prepared by reduction of the isopropenyl compound according to the method of Davoll.[190]

The isopropyl compound (9 g., 0.05 mole) was dissolved in water (90 ml.) containing sodium hydroxide (12 g., 0.3 mole) at 60°. HOS (18 g., 0.16 mole) was added over 30 min., the temperature being maintained at 60 to 70°. An oil gradually separated which was extracted into chloroform and dried. Evaporation gave an oil that gradually crystallised to give 1-amino-3-isopropylbenzimidazolin-2-one (9.2 g., 95%), m.p. 86-87°, from petrol (40-60°) (Found: C, 62.7; H, 6.9; N, 21.8. $C_{10}H_{13}N_3O$

requires C, 62.8; H, 6.9; N, 22.0%).

m/e: 191 (P), 176, 159, 149, 148, 132, 106.

$\nu_{max.}$ 3240, 3330, 1710, 1690, 1648, 1603, 1135, 759, 730 and 716 $cm.^{-1}$.

τ 2.67-3.00 (m, 4H); 5.12-5.58 (m, 3H); 8.57 (d, 6H, J 6.5 c./sec.).

(ii) Preparation from 1-amino-3-isopropenylbenzimidazolin-2-one

The isopropenyl compound (3.2 g., 0.017 mole) was dissolved in ethyl acetate (100 ml.) and hydrogenated at room temperature with 10% palladium on charcoal catalyst (0.4 g.). A quantitative uptake of hydrogen (0.017 mole) was recorded. The mixture was filtered and the residues washed with hot ethyl acetate and then evaporated to give an oil that solidified on scratching. Recrystallisation from petrol (60-80°) gave needles of 1-amino-3-isopropylbenzimidazolin-2-one (2.4 g., 73%), m.p. and m.m.p. 85-87°.

(iii) Oxidation of 1-amino-3-isopropylbenzimidazolin-2-one

a) Alone

(i) The N-amino compound (654 mg., 3.4 mmoles) was dissolved in dry ether (60 ml.) and powdered LTA (2.2 g., 5 mmoles) added. The mixture was stirred overnight and filtered. The filtrate and ether washings were chromatographed on deactivated basic alumina:

60-80% Ether-petrol gave the tetrazene, 1,2-di-(3-isopropylbenzimidazolin-2-on-1-yl)-diimide (170 mg., 26%), m.p. 213-215° (decomp.), from chloroform-petrol (Found: C, 63.5; H, 6.0; N, 22.1. $C_{20}H_{22}N_6O_2$ requires C, 63.5; H, 5.9; N, 22.2%).

m/e: 378 (P), 350, 335, 308, 176, 175, 134, 106 m_1* 378-350 = 324.1; m_2*, 350-308 = 271.0; m_3*, 176-134 = 102.0; m_4*, 134-106 = 83.8.

$\nu_{max.}$ 1727, 1605, 1340, 1296, 1103, and 745 $cm.^{-1}$

τ 2.67-2,92 (m, 4H); 5.30 (q, 1H, J 6.5 c./sec.); 2.39 (d, 6H, J 6.5 c./sec.).

30% Methanol-ether gave 3-isopropylbenzimidazolin-2-one (250 mg., 41%), m.p. and m.m.p. 125-128° (lit.[190], m.p. 127-128°).

(ii) The reaction was repeated using methylene chloride as solvent. The tetrazene (83%) contaminated with a small amount of polymeric material was obtained. Recrystallisation from chloroform-petrol gave the pure tetrazene, m.p. 212-215°.

b) In cyclohexene

The N-amino compound (510 mg., 2.7 mmoles) was dissolved in cyclohexene (30 ml.) and LTA (1.8 g., 4 mmoles) added. The mixture was stirred overnight and then filtered. The filtrate and ether washings were chromatographed on deactivated basic alumina:

10% Ether-petrol gave a colourless oil that gradually crystallised (318mg., 44%). Recrystallisation from petrol (40-60°) gave 2-(3-isopropylbenzimidazolin-2-on-1-yl)-7-azabicyclo-[4,1,0]-heptane, m.p. 94-95° (Found: C, 70.6; H, 7.8; N, 15.5. $C_{16}H_{21}N_3O$ requires C, 70.8; H, 7.8; N, 15.5%).

$\nu_{max.}$ 1700, 1615, 1490, 1380, 745, 725 and 710 cm.$^{-1}$.

τ 2.93-7.17 (m, 4H); 5.52 (q, 4H, J 6.5 c./sec.); 6.90-7.10 (m, 2H); 7.73-8.90 (m, 14H, including d, 2.56, J 6.5 c./sec.).

50% Ether-petrol gave the tetrazene (35 mg., 7%), m.p. 211-214° (decomp.), from chloroform-petrol.

10% Methanol-ether gave 3-isopropylbenzimidazolin-2-one (142 mg., 30%), m.p. and m.m.p. 125-128° (lit.[190], m.p. 127-128°).

c) In DMSO

The N-aminobenzimidazolinone (2 g., 10.5 mmoles) was dissolved in DMSO (5 ml.) and LTA (6 g., 13.5 mmoles) added. The solution was stirred for 30 min., and then the excess of DMSO removed under reduced pressure. The residue was extracted with acetone and the

soluble fraction chromatographed on deactivated basic alumina:

60% Ether-petrol gave the tetrazene (30 mg., 1.5%), m.p. 211-215°(decomp.), from chloroform-petrol.

Ether gave crystals of isopropylbenzimidazolinone (168 mg., 9%), m.p. 125-128°, after sublimation.

5% Methanol-ether gave an oil that solidified on trituration with ether. Recrystallisation from chloroform-petrol gave N-(3-isopropylbenzimidazolin-2-on-1-yl)-dimethyl sulfoximine (1.63 g., 60%), m.p. 140-141° (with decomp. from 134°) (Found: C, 53.6; H, 6.5; N, 15.8; S, 12.0. $C_{12}H_{17}N_3O_2S$ requires C, 53.9; H, 6.4; N, 15.7; S, 12.1%).

m/e: 267 (P), 191, 176, 161, 149, 134, 78.

$\nu_{max.}$ 1700, 1615, 1600, 1145, 1125, 760 and 710 $cm.^{-1}$.

τ 2.66-2.98 (m, 4H); 5.35, (q, 1H, J 6.5 c./sec.); 6.74 (s, 6H); 8.48 (d, 2H, J 6.5 c./sec.).

(iv) Photolysis of the DMSO adduct

a) The DMSO adduct (128 mg.) was dissolved in cyclohexene (20 ml.) and ethyl acetate (30 ml.), and irradiated with a Phillips 500W sun lamp for 94 hr. under nitrogen. The mixture was chromatographed on deactivated basic alumina:

20% Ether-petrol gave the aziridine adduct (12 mg., 9%), m.p. and m.m.p. 92-94°, from petrol (40-60°).

10% Methanol-ether gave 3-isopropylbenzimidazolin-2-one (71 mg., 84%), m.p. and m.m.p. 124-127° (lit.[190], m.p. 127-128°), from petrol (60-80°).

b) The reaction was repeated under similar conditions with the DMSO adduct (175 mg.) in cyclohexene (50 ml.) for 17 hr. Chromatography as above gave the aziridine (27 mg., 15%), 3-isopropylbenzimidazolin-2-one (25 mg., 20%) and unchanged DMSO adduct (65 mg., 37%).

C 1-Amino-3-methylbenzimidazolin-2-one

(i) Preparation from 1-methylbenzimidazolin-2-one.

1-Methylbenzimidazolin-2-one, m.p. 190-192°, was prepared by methylation of 1-isopropenylbenzimidazolin-2-one followed by hydrolysis according to the method of Davoll.[190]

a) 1-Methylbenzimidazolin-2-one (8 g., 0.054 mole) was dissolved in water (150 ml.) containing sodium hydroxide (14 g., 0.35 mole) at 60°. HOS (12 g., 0.105 mole) was added over 45 min. and then stirred for a further 90 min. at 60-70°. On cooling the off-white crystals were collected (5.0 g., 57%) and recrystallised from methylene chloride-petrol to give plates of 1-amino-3-methylbenzimidazolin-2-one, m.p. 135-137° (Found: C, 59.3; H, 5.6; N, 26.0. $C_8H_9N_3O$ requires C, 59.0; H, 5.5; N, 25.8%).

m/e: 163 (P), 148, 147, 134, 133, 119, 92. m_1*, 163-147 = 132.6; m_2*, 147-119 = 96.3; m_3*, 163-119 = 86.9; m_4*, 119-92 = 71.1

$\nu_{max.}$ 3300, 3215, 3063, 1764 (sh.), 1725, 1664, 1618, 748 and 726 cm.$^{-1}$.

τ 2.75-3.30 (m, 4H); 5.55 (s, 2H); 6.77 (s, 3H).

$\lambda_{max.}$ 212 (log ε 4.38); 233 (3.71); 282 nm. (2.79).

Hydrochloride, m.p. 150-151° (decomp.) from ethanol (Found: C, 48.2; H, 4.8; N, 21.1; Cl, 18.0. $C_8H_{10}N_3OCl$ requires C, 48.0; H, 5.0; N, 21.0; Cl, 17.8%).

$\nu_{max.}$ 3390, 3315, 2730, 1705, 1550, 758 and 724 cm.$^{-1}$.

Extraction of the basic solution gave a mixture of the N-amino compound and the starting material. A partial separation could be obtained by chromatography on basic alumina, but in general, the mixture was re-cycled.

When sodium carbonate was used as the base, unchanged starting material (82%) was recovered.

b) The benzimidazolinone (1.48 g., 10 mmoles) was dissolved in methylene chloride (40 ml.) and sodium hydride (500 mg., of a 50% dispersion, 10 mmoles) added. Ethereal chloramine (18 mmoles) was added when hydrogen evolution ceased, and the mixture stirred overnight. The solution was filtered and the filtrate chromatographed on silica:

1% Methanol-ether gave a mixture of the N-amino compound and unchanged starting material (350 mg.) (t.l.c.). The i.r. spectrum of the mixture indicated that less than 10% of the N-amino compound was present.

(ii) Oxidation of 1-amino-3-methylbenzimidazolin-2-one

a) In 1,3-butadiene

1,3-Butadiene (5 g.) was dissolved in methylene chloride (70 ml.) at -80° and then the N-amino compound (1.0 g., 6.1 mmoles) added. The mixture was allowed to warm to -5° with stirring and then a solution of LTA (5.0 g., 11 mmoles) in methylene chloride (30 ml.) added dropwise, the temperature being maintained at -5°. The mixture was stirred for 1 hr. and then allowed to warm to room temperature and filtered. The solid was washed with methylene chloride and the filtrate and washings chromatographed on basic alumina:

60% Ether-petrol gave needles of an unidentified compound (3 mg.) $\nu_{max.}$ 1687, 1618, 1492, 1187, 917, and 750 $cm.^{-1}$.

70% Ether-petrol gave the tetrazene, 1,2-di-(3-methylbenzimidazolin-2-on-1-yl)-diimide (240 mg., 24%), m.p. 235-236° (decomp.), from chloroform-petrol (Found: C, 59.5; H, 4.7; N, 25.8. $C_{16}H_{14}N_6O_2$ requires C, 59.6; H, 4.4; N, 26.1%).

m/e: 322 (P), 294, 161, 147, 119, 92. m_1^*, 322-294 = 268.4; m_2^*, 147-119 = 96.3; m_3^*, 119-92 = 71.1.

$\nu_{max.}$ 3080, 1725, 1618, 1200, 1031, 1001, 748, 715 and 689 cm.$^{-1}$.

5% Methanol-ether gave 1-methylbenzimidazolin-2-one (150 mg., 16%), m.p. and m.m.p. 189-192°, after sublimation.

b) In cyclohexene

The N-amino compound (978 mg., 6 mmoles) was dissolved in methylene chloride (25 ml.) and cyclohexene (25 ml.) and LTA (3.54 g., 9 mmoles) added in small portions over 10 min. The mixture was stirred for 1.5 hr. and then filtered. The filtrate was chromatographed on basic alumina:

50% Ether-petrol gave 2-(3-methylbenzimidazolin-2-on-1-yl)-7-azabicyclo-[4,1,0]-heptane (526 mg., 36%) m.p. 123-124° (Found: C, 69.1; H, 6.8; N, 17.6. $C_{14}H_{17}N_3O$ requires C, 69.1; H, 7.0; N, 17.3%).

$\nu_{max.}$ 3065, 2940, 1700, 1622, 1500, 1018, 752 and 748 cm.$^{-1}$.

τ 2.70-3.23 (m, 4H); 6.65 (s, 3H); 6.93-7.04 (m, 2H); 7.80-8.18 (m, 4H); 8.43-8.89 (m, 4H).

Ether gave the tetrazene (33 mg., 3.5%), m.p. 232-236°, from chloroform-petrol.

20% Ethanol-ether gave 1-methylbenzimidazolin-2-one (100 mg., 11%), m.p. 189-192°, after sublimation.

c) In DMSO

The N-amino compound (489 mg., 3 mmoles) was dissolved in DMSO (5 ml.) and LTA (1.77 g., 4.5 mmoles) added over 5 min. The mixture was stirred at room temperature for 30 min. and then poured into

cold water. The solution was extracted with chloroform and the chloroform extract washed with warm water, dried, and evaporated to give a red oil that gradually crystallised to a buff solid (316 mg., 46%). The compound decomposed quickly in air, especially when in solution. Recrystallisation from chloroform-petrol gave crystals of N-(3-methylbenzimidazolin-2-on-1-yl)-dimethyl sulfoximine, m.p. 176-178° (decomp.) (Found: C, 50.0; H, 5.4; N, 17.8; S, 13.4. $C_{10}H_{13}N_3O_2S$ requires C, 50.2; H, 5.5; N, 17.6; S, 13.4%).

$\nu_{max.}$ 3030, 3000, 2925, 1700, 1625, 1614, 1500, 1218, 1204, 762 and 738 $cm.^{-1}$.

τ 2.63-3.20 (m, 4H); 6.40 (s, 3H); 6.75 (s, 6H).

D 1-Aminobenzimidazolin-2-one

(i) Preparation of 1-aminobenzimidazolin-2-one

a) 1-Amino-3-isopropenylbenzimidazolin-2-one (1 g.) was suspended in 1N sulfuric acid (15 ml.) and then heated under reflux for 30 min. The mixture gradually became homogeneous, and on cooling, an off-white solid (0.6 g.) separated. The mixture was filtered and the filtrate extracted with chloroform to give more of the solid (0.1 g.). The crude 1-aminobenzimidazolin-2-one (0.7 g., 91%) was recrystallised from ethyl acetate to yield prisms (0.4 g., 52%), m.p. 238-241° (decomp.) (Found: C, 56.5; H, 4.7; N, 27.8. $C_7H_7N_3O$ requires C, 56.4; H, 4.7; N, 28.2%).

m/e: 149 (P), 134, 133, 132, 119, 106. m_1^*, 149-132 = 116.9; m_2^*, 149-106 = 75.4

$\nu_{max.}$ 3340, 3200 (br.), 3070, 1730, 1672, 1645, 1616, 1210 and 742 $cm.^{-1}$

τ 2.83-3.06 (m, 4H); 7.30 (s, 2H).

$\lambda_{max.}$ 213 (log ε 4.06); 228 (3.78); 282 nm (3.86).

Copper chelate (44%), m.p. 225-230° (decomp.) from methanol (Found: C, 29.3; H, 2.5; N, 15.0. $C_7H_7CuCl_2N_3O$ requires C, 29.6; H, 2.5; N, 14.8%).

$\nu_{max.}$ 3330, 3200, 3090, 1675, 1620, 1610, 1595, 1112, 1088 and 768 $cm.^{-1}$.

b) Benzimidazolin-2-one (1.34 g., 0.01 mole) was suspended in water (30 ml.) containing sodium hydroxide (4 g., 0.1 mole) at 60°. HOS (7 g., 0.06 mole) was added over 30 min. at 60-65°. The solution gradually became homogeneous, and then a precipitate appeared when most of the HOS had been added. On cooling, the precipitate was filtered off and found to be unchanged benzimidazolin-2-one (0.85 g., 62%) m.p. 308-310° (lit.[189], 310°). The aqueous solution was extracted with chloroform and then acidified with 2N hydrochloric acid and extracted again with chloroform. The basic extract (0.2 g.) and the acidic extract (0.25 g.) were both mixtures of benzimidazolin-2-one and the mono N-amino compound (i.r.). The mixture could not be separated by chromatography, sublimation or fractional recrystallisation.

(ii) Deamination of 1-aminobenzimidazolin-2-one

The N-amino compound (75 mg., 0.5 mmoles) was dissolved in glacial acetic acid (3 ml.) and a solution of sodium nitrite (40 mg., 0.6 mmole) in water (2 ml.) added dropwise at room temperature. Crystals gradually separated and were filtered off and dried to give benzimidazolin-2-one (22 mg., 33%), m.p. and m.m.p. 310-311° (decomp.) (lit.[189], 310°).

(iii) Oxidation of 1-aminobenzimidazolin-2-one

a) In methyl methacrylate

1-Aminobenzimidazolin-2-one (894 mg., 6 mmoles) was suspended in a mixture of benzene (65 ml.) and methyl methacrylate (25 ml.).

The mixture was heated to reflux and LTA (3.54 g., 9 mmoles) added portionwise to the stirred solution. The mixture was heated with stirring for a further 2 hr., cooled and then filtered. The filtrate was chromatographed on silica:

30% Ether-petrol gave 1-acetylbenzotriazole (430 mg., 45%), m.p. and m.m.p. 50-51° (lit.[189] 51°). The i.r. and p.m.r. spectra were identical to those of an authentic sample.

Ether gave benzotriazole (71 mg., 10%), m.p. and m.m.p. 96-99° (lit.[189], m.p. 100°).

b) Alone

(i) The N-amino compound (270 mg., 2 mmoles) was suspended in benzene (50 ml.) and LTA (886 mg., 2 mmoles) added to the mixture under reflux. The mixture was heated under reflux for 2 hr. and then worked up as above.

30% Ether-petrol gave 1-acetylbenzotriazole (119 mg., 37%).

Ether gave unchanged 1-aminobenzimidazolin-2-one (71 mg., 26%).

(ii) The reaction was repeated using LTA (4 mmoles) to give 1-acetylbenzotriazole (61%) as the only product.

(iii) The reaction gave 1-acetylbenzotriazole (93%) when LTA (8 mmoles) was used.

E 1,3-Diaminobenzimidazolin-2-one

1-Aminobenzimidazolin-2-one (750 mg., 5 mmoles) was dissolved in a solution of sodium hydroxide (2 g., 50 mmoles) in water (50 ml.) at 40°. HOS (2.8 g., 25 mmoles) was added in one portion, and after a short induction period, the temperature rose to 45°. The solution was extracted with chloroform on cooling to give a crystalline solid

(500 mg., 61%). Recrystallisation from ethanol gave 1,3-diamino-benzimidazolin-2-one, m.p. 197-199° (Found: C, 50.9; H, 4.7; N, 33.7. $C_7H_8N_4O$ requires C, 51.2; H, 4.9; N, 34.1%).

$\nu_{max.}$ 3345, 3330, 3250, 3205, 1725, 1690, 1640, 1200 and 738 cm.$^{-1}$.

τ 2.70-2.54 (m, 4H); 5.64 (br.s, 4H).

Di-anisylidene derivative, m.p. 183-184°, from aqueous ethanol (Found: C, 68.8; H, 5.2; N, 14.1. $C_{23}H_{20}N_4O_3$ requires C, 69.0; H, 5.0; N, 14.0%).

$\nu_{max.}$ 1705, 1694, 1610, 1258, 1162, 827 and 734 cm.$^{-1}$

τ 0.60 (s, 2H); 2.10-3.10 (m, 12H); 6.18 (s, 6H).

The aqueous solution was acidified and extracted with chloroform as above to give a mixture of the mono- and di- N-amino compounds (90 mg.), (i.r.) that could not be separated.

(ii) Oxidation of 1,3-diaminobenzimidazolin-2-one

The diamino compound was oxidised by LTA in the presence of cyclohexene and also tetracyclone. T.l.c. showed that no biphenylene, tetraphenylnaphthalene or aziridine adducts had been formed.

7 BENZOTRIAZOLE AND BENZOTRIAZOLE-1-CARBOXAMIDE

Benzotriazole-1-carboxamide was prepared from benzotriazole and potassium cyanate in acetic acid.[195]

A Oxidations of benzotriazole-1-carboxamide with LTA

a) With t-butylamine

Benzotriazole carboxamide (810 mg., 5 mmoles) was dissolved in dry DMF (25 ml.) and LTA (2.21 g., 5 mmoles) added in small portions over 10 min. The mixture turned bright red and was stirred for 1 hr. t-Butylamine (2 ml.) was then added, and the colour faded. The mixture was poured into water, but only inorganic compounds were precipitated.

b) With DMSO

The carboxamide (1.62 g., 10 mmoles) was dissolved in DMSO (5 ml.) and LTA (4.8 g., 11 mmoles) added. The mixture was stirred for 90 min. and then two drops of glycerol added. Dilution of the reaction with water produced a buff-coloured solid. The solid was extracted with methylene chloride and evaporated to give the unchanged carboxamide (600 mg., 36%).

c) With cyclohexene

(i) The carboxamide (1.62 g., 10 mmoles) was dissolved in DMF (25 ml.) and cyclohexene (5 ml.), and LTA (4.6 g., 10.5 mmoles) was added in small portions. The mixture was stirred for 5 hr. and then divided into two equal portions. From one, the DMF was removed under reduced pressure, and the residue extracted with ether. The other portion was poured into water and extracted with ether.

Both ether extracts showed similar composition of products (t.l.c.) and were combined and chromatographed on silica:

20% Ether-petrol gave 1-cyclohexylbenzotriazole (300 mg., 15%), m.p. 103-104° (lit.[215], m.p. 104°), from aqueous ethanol (Found: C, 71.6; H, 7.6; N, 21.1. Calculated for $C_{12}H_{15}N_3$ C, 71.6; H, 7.5; N, 20.9%).

$\nu_{max.}$ 1268, 1232, 1055, 782 and 754 $cm.^{-1}$.

τ 1.85-2.75 (m, 4H); 5.16-5.67 (m, 1H); 7.60-8.90 (m, 10H).

60% Ether-petrol gave benzotriazole (200 mg., 17%), m.p. 96-99° (lit.[189], m.p. 100°).

(ii) Benzotriazole carboxamide (1.62 g.) was suspended in a mixture of dry acetonitrile (25 ml.) and cyclohexene (10 ml.). LTA (5 g.) in methylene chloride (50 ml.) was added dropwise to the stirred solution over 1 hr. and then stirred for a further 3 hr. Chromatography as above gave 1-cyclohexylbenzotriazole (28 mg., 1.5 %), and benzotriazole (98 mg., 8.5%).

B Oxidation of benzotriazole with LTA

a) In cyclohexene

Benzotriazole (500mg., 4.2 mmoles) was dissolved in a mixture of cyclohexene (5 ml.) and methylene chloride (25 ml.) and LTA (3 g., 6.8 mmole) added in small portions. The mixture was stirred for 24 hr., filtered and the filtrate chromatographed on silica:

20% Ether-petrol gave 1-cyclohexylbenzotriazole (356 mg., 42%), m.p. 103-104°.

70% Ether-petrol gave benzotriazole (90 mg., 18%), m.p. 96-99° after sublimation.

The reaction also gave other products which eluted from the column over a wide range of solvent mixtures, and could not be identified. The i.r. and p.m.r. spectra of various fractions indicated that they were a mixture of 1- and 2-substituted

benzotriazoles incorporating an acetoxy group and also cyclohexyl residues.

b) In cyclooctene

Benzotriazole (1.19 g., 10 mmoles) was dissolved in methylene chloride (20 ml.) and cyclooctene (20 ml.). LTA (4.5 g., 10 mmoles) was added over 5 min. and the mixture stirred for 3 hr. The mixture was filtered and the filtrate chromatographed on silica:

20%-60% Ether-petrol gave a series of oils (598 mg.) that showed very similar i.r. and p.m.r. spectra. Distillation (140-150°/ 1.5 mm.) gave a mixture of isomers of 1- and 2-(acetoxy-cyclooctyl)-benzotriazoles (Found: C, 67.4; H, 7.7; N, 14.6. $C_{16}H_{21}N_3O_2$ requires C, 66.9; H, 7.4; N, 14.6%).

m/e: 287 (P), 244, 227, 199, 186, 170, 156, 143.

$\nu_{max.}$ 3010, 2925, 2855, 1734, 1567, 1244 and 748 $cm.^{-1}$.

τ 2.00-2.40 (m, 2H); 2.60-2.85 (m, 2H); 4.05-4.52 (m, 2H); 7.50-8.85 (m, 15H).

Ether gave unchanged benzotriazole (300 mg., 25%), m.p. 96-99°.

c) In benzene

Benzotriazole (1.19 g., 0.01 mole) was dissolved in dry benzene (50 ml.) and the mixture heated to reflux with LTA (6.7 g., 0.015 mole). The mixture was heated under reflux for a further 2 hr., cooled, filtered and the filtrate chromatographed on silica:

30% Ether-petrol gave 1-acetylbenzotriazole (32 mg., 2%), crystals from petrol (40-60°), m.p. and m.m.p. 50-51° (lit.[189], m.p. 51°).

30% Ether-petrol gave 1-phenylbenzotriazole (90 mg., 4.5%), as crystals from ether-petrol, m.p. and m.m.p. 89-90° (lit.[61], 89-90°). An i.r. spectrum was identical to that of an authentic sample prepared by the method of Campbell.[61]

Ether gave unchanged benzotriazole (780 mg., 65%).

Benzotriazole, when heated under reflux in a mixture of benzene and acetic acid for 2.5 hr., gave no 1-acetylbenzotriazole (t.l.c.).

d) With other oxidants

When the reactions were carried out in the presence of cyclohexene, potassium permanganate only gave a small yield of recovered benzotriazole (2.3%) and mercuric oxide gave a trace of the 1-cyclohexylbenzotriazole (t.l.c.) although benzotriazole (1.7%) was the only product isolated.

e) Indoline-1-carboxamide

Indoline (6 g., 0.05 mole) was dissolved in glacial acetic acid (40 ml.) and concentrated hydrochloric acid (1 ml.). A solution of potassium cyanate (6 g., 0.075 mole) in water (15 ml.) was added dropwise to the solution. After a short induction period a solid began to separate and, after stirring for 1 hr., was filtered off to give a pale pink solid (5.9 g., 73%). Recrystallisation from chloroform gave indolin-1-carboxamide, m.p. 184-186° as prisms (Found: C, 77.0; H, 5.9; N, 17.0. $C_9H_{10}N_2O$ requires C, 66.7; H, 6.2; N, 17.3%).

$\nu_{max.}$ 3390, 3200, 1660, 1630, 1608, 1600, 1162, 755 and 748 $cm.^{-1}$.

τ 2.05-2.25 (m, 1H); 2.70-3.00 (m, 3H); 5.15 (br.s, 2H); 5.85-6.25 (m, 2H); 6.65-7.04 (m, 2H).

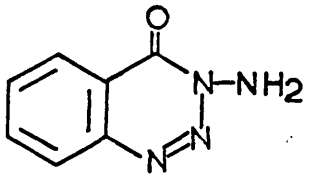
The carboxamide (500 mg.) was suspended in a solution of sodium hydroxide (8 g.) in water (80 ml.) at 70-80° for 30 min. On cooling, the solution was filtered to give the unchanged carboxamide (500 mg., 100%). Benzotriazole-1-carboxamide, when dissolved in 5% sodium hydroxide at room temperature for 30 min., gave the unchanged carboxamide (70%) on acidification. Ether extraction of the acidic solution gave benzotriazole.

Indoline-1-carboxamide did not undergo the Hofmann rearrangement with sodium hypochlorite in sodium hydroxide and oxidation with LTA in the presence of t-butylamine failed to give any urea derivative.

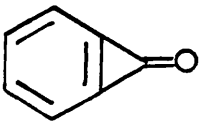
1 1,2,4-TRIAZIN-3(2H)-ONES

A Rearrangement to imidazolin-2-ones

Oxidation of the N-aminobenzotriazinone (I) by lead tetraacetate (LTA) gave benzocyclopropenone (2) and indazolone (3).[216] An attempt was therefore made to synthesise the isomeric N-aminobenzo-1,2,4-triazinones (4) and (5) in order to investigate the oxidation reactions of these compounds.



(1)



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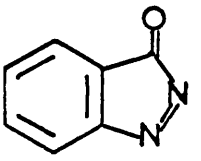

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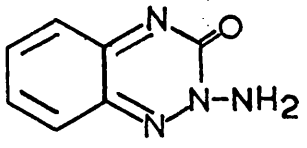

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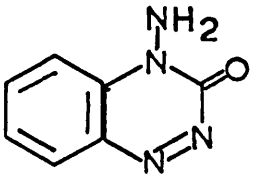
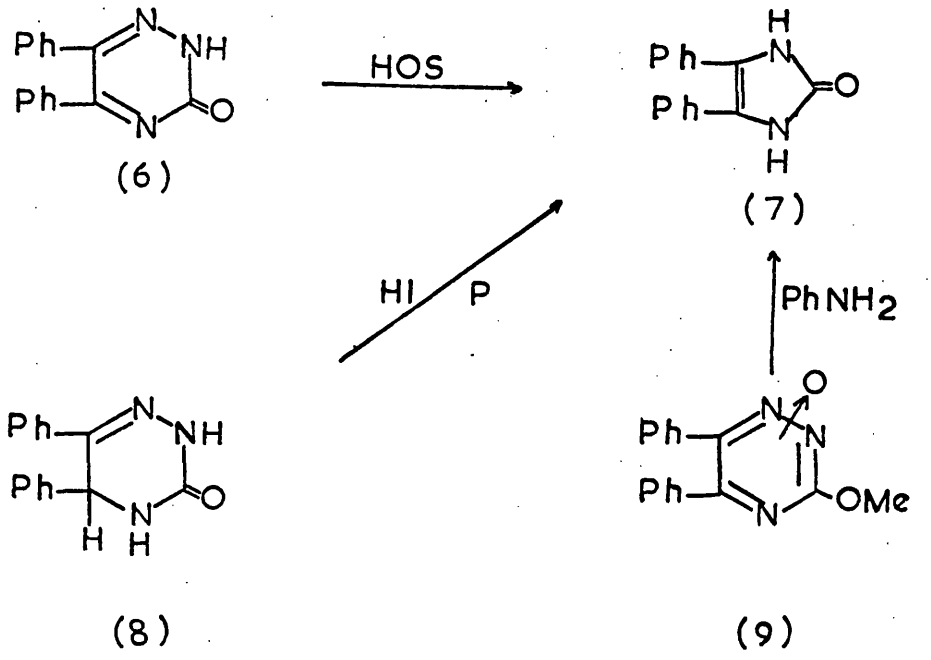


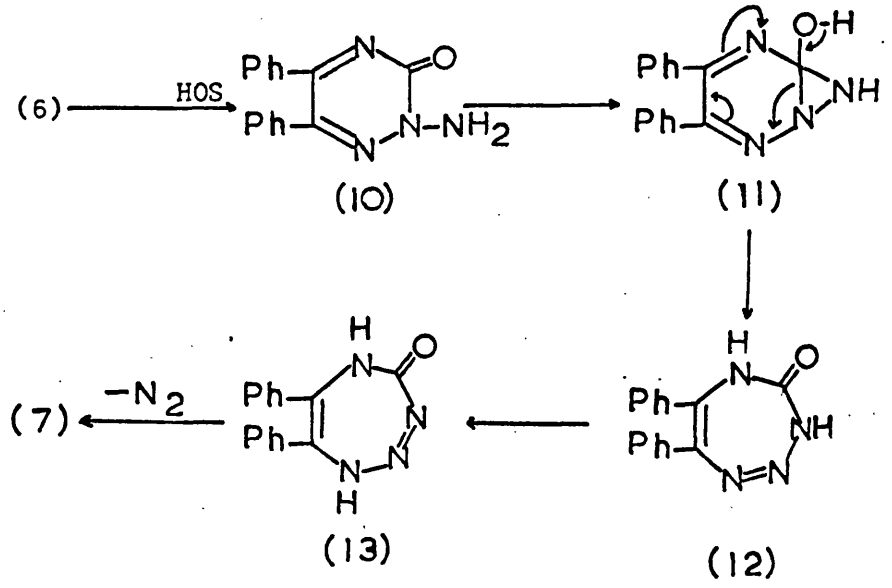
(5)

When 5,6-diphenyl-1,2,4-triazin-3-one (6) was aminated with hydroxylamine-O-sulfonic acid (HOS) in aqueous alkali, a novel ring contraction occurred to give 4,5-diphenylimidazolin-2-one (7) (68%) and none of the possible N-amino compounds were obtained.[58a]

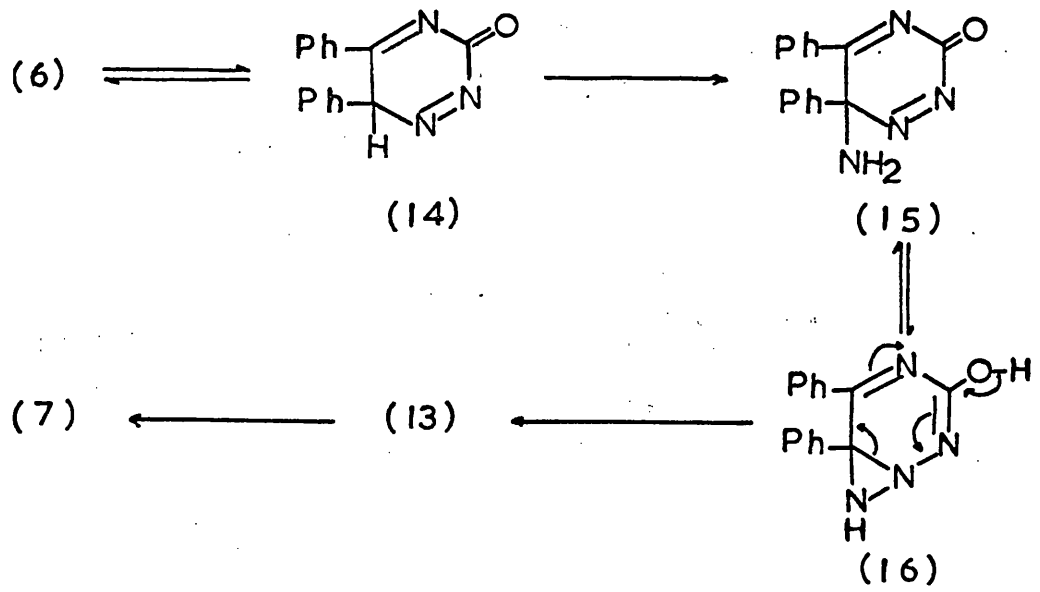
A related ring contraction has been reported by Biltz.[217] The dihydrotriazinone (8) prepared by zinc and acetic acid reduction of (6), when treated with red phosphorus and hydriodic acid for 5 hr. at 180° also gave (7) (85%). A further example of a triazinone to imidazolinone rearrangement was reported by Sasaki and Minamoto.[218] The 3-methoxy-triazinone-N-oxide (9) when reacted with aniline at 150° for 5 hr. also gave (7) (15%).



Although HOS has been used successfully as a reducing agent,[116] the mild conditions under which it was used here suggested that a different mechanism was involved and the mechanism below was postulated (Scheme I).[58a]

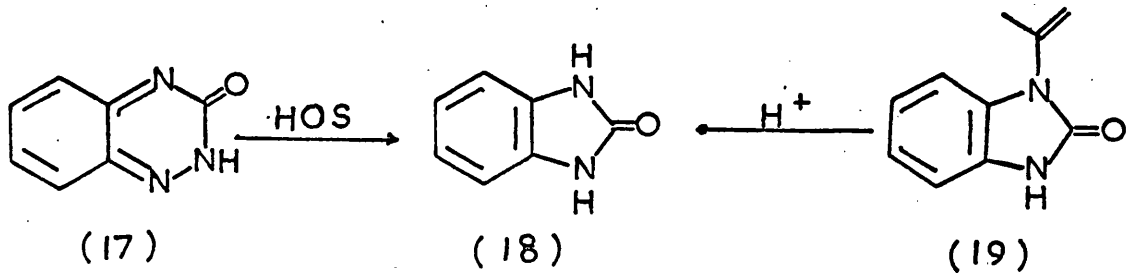


Scheme (1)

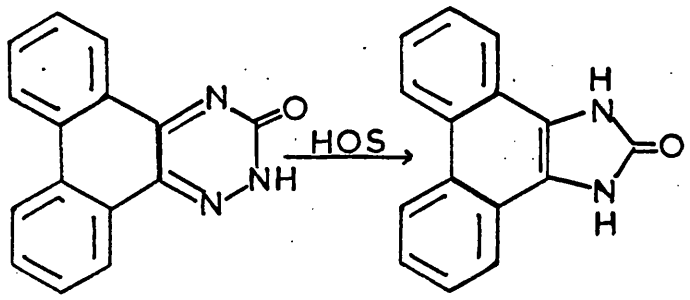


Scheme (2)

The alternative mechanism postulated in Scheme 2 was also suggested.[58a] In the present work, the benzotriazinone (17)[188] and the phenanthrotriazinone (20)[191] were synthesised by standard literature methods and treated with HOS in aqueous alkali. The benzotriazinone (17) gave benzimidazolin-2-one (18) (87%) identical in all respects to an authentic specimen prepared by the hydrolysis of 1-isopropenyl-benzimidazolin-2-one (19).[190] The phenanthrotriazinone (20), however, was recovered unchanged when treated with HOS under similar conditions. This was found to be due to the insolubility of the triazinone in aqueous sodium hydroxide. When potassium hydroxide or aqueous ethanolic sodium hydroxide was used, the phenanthroimidazolin-2-one (21) was obtained in yields of 26% and 74% respectively. Physical and spectral data were in accord with the proposed structure.



(17) (18) (19)



(20) (21)

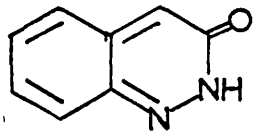
The reaction of fused triazinones with HOS to give the imidazolinones would tend to eliminate the possible alternative mechanism proposed by Yelland (Scheme 2).[58a]

In order to examine the validity of the mechanism postulated in Scheme 1, an attempt was made to isolate the intermediate N-amino compound (10). When the diphenyltriazinone (6) was reacted with HOS at 0° in sodium hydroxide, the sodium salt of (6) (15%) and unreacted triazinone (55%) were recovered. At 40°, the triazinone was recovered in 97% yield. Although the N-amino compounds were not obtained, N-amination still presumably occurred as the first stage of the reaction since only unchanged triazinone was obtained when the reaction was carried out in the absence of alkali.

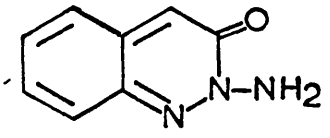
Carpino[54] has shown that N-amino compounds that are unstable to the basic conditions used in reaction with HOS can be isolated when aminated under anhydrous conditions using O-(2,4-dinitrophenyl)hydroxylamine (see Introduction).

However, when the sodium salts of the benzo, phenanthro and diphenyltriazinones were treated with O-(2,4-dinitrophenyl)hydroxylamine in DMF at room temperature, no N-amino compounds were isolated and ring contraction again occurred to give the imidazolinones in yields of 15%, 55% and 83% respectively. When methylene chloride was used as solvent, the diphenyltriazinone (6) gave the imidazolinone (7) (27%), and unreacted aminating agent (31%). 1-Amino-4,5-diphenyltriazole was also isolated in a trace amount. The significance of this reaction is discussed fully in Section 1B.

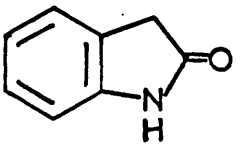
In the mechanism proposed (Scheme 1), the nitrogen in position 4 of the triazinone ring system only acts as a proton acceptor, and therefore substitution of =N- by =CH-should give a similar ring contraction. Thus cinnolin-3(2H)-one (22) should give oxindole (24) via the N-amino compound (23).



(22)



(23)

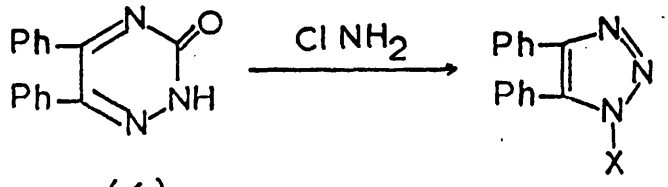


(24)

Cinnolinone, when aminated with HOS in aqueous alkali at 60°, did indeed give a mixture of the N-amino compound (23) and oxindole. Furthermore, it was found that the N-amino compound (23) on heating to its melting point decomposed explosively to give oxindole. This strongly suggests that N-amino compounds are intermediates in the reaction of triazinones with HOS, but are unstable under the basic conditions employed (see Section 2). The mechanism proposed by Yelland[58a] (Scheme 1) would therefore appear to be substantially correct.

B Rearrangement to 1,2,3-triazoles

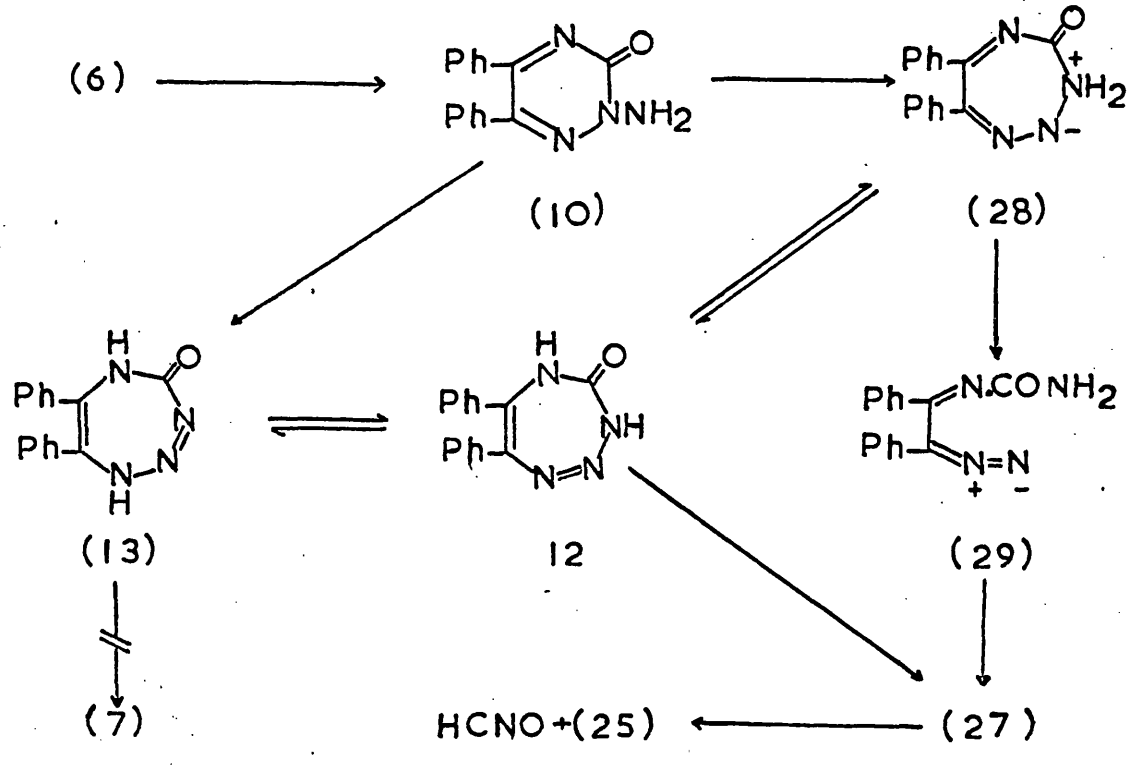
Yelland[58a] found that diphenyltriazinone (6) failed to give any N-aminotriazinones when aminated with chloramine. Instead a different ring contraction occurred to give 4,5-diphenyltriazole (25) and the 1-etherate (26).



(6)

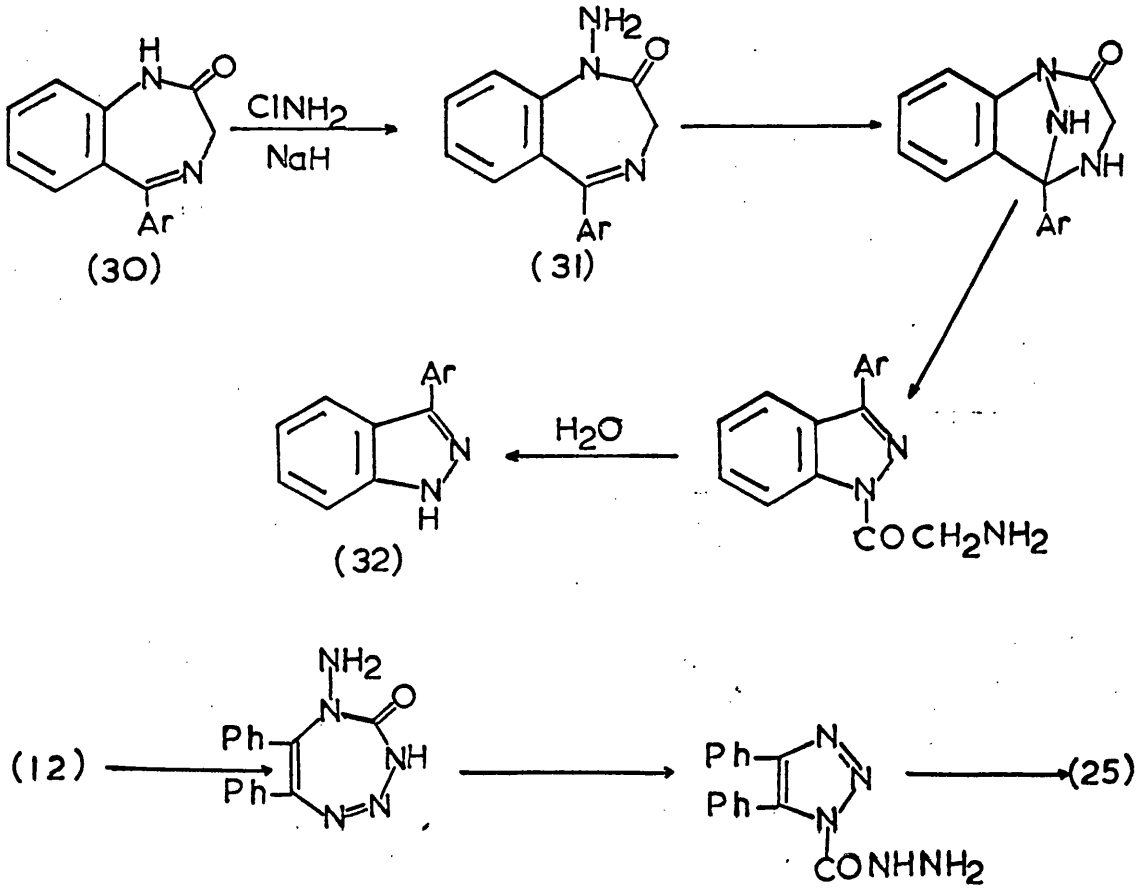
X = H (25)
CH(Me)OEt (26)
$CONH_2$ (27)

The two alternative mechanisms postulated by Yelland[58a] both involved initial formation of the 2-aminotriazinone (10) followed by subsequent rearrangement to the carboxamide (27) which hydrolysed under the reaction conditions to the triazole and cyanuric acid (Scheme 3).



Scheme 3

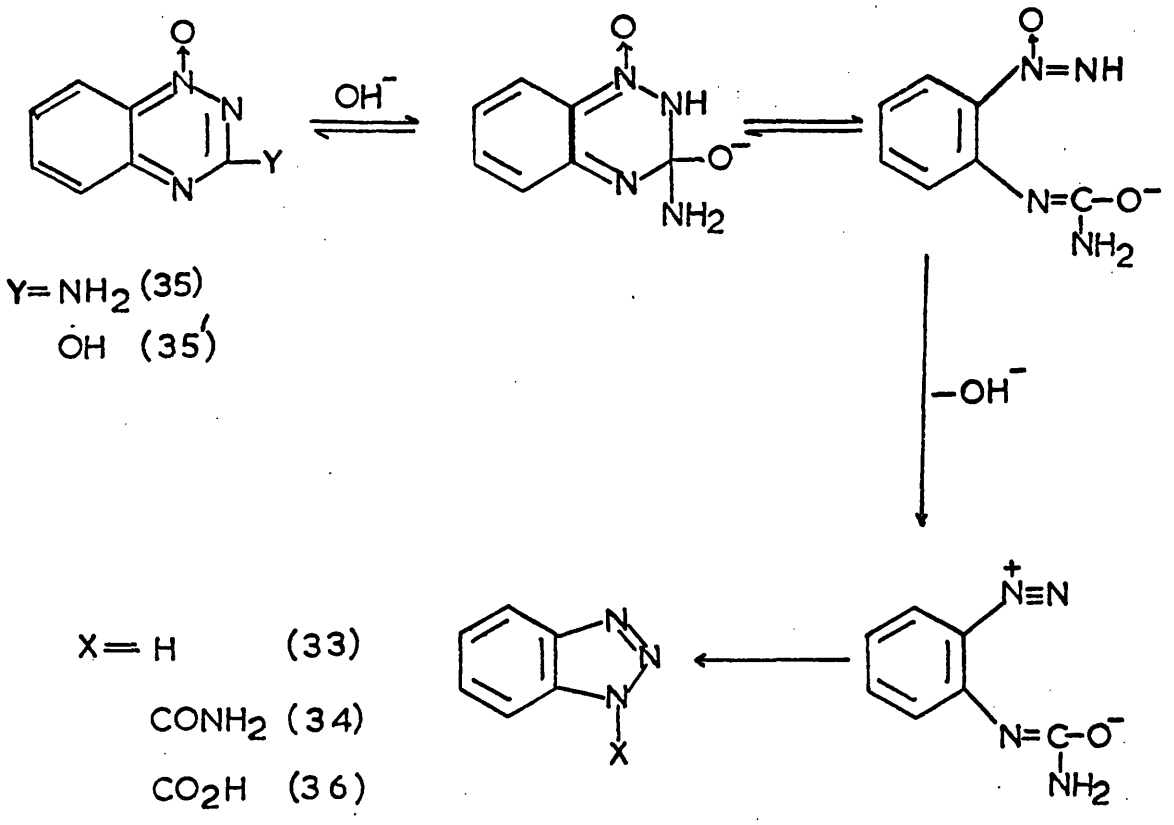
The structures (12), (13) and (28) are tautomeric and the different modes of decomposition with HOS and chloramine were attributed to the polarity of the solvent. A related seven to five numbered ring contraction was reported by Sternbach et al.[57] The sodium salt of 1,4-benzodiazepin-2-ones (30) when treated with chloramine in DMF gave the indazoles (32) as well as the N-amino compounds (31) which were shown to be intermediates. As excess of chloramine was used, a similar mechanism could have been operative in the triazinone to triazole ring contraction as shown below (Scheme 4).



Scheme 4

The mechanism preferred by Yelland (Scheme 3a) was based on a related ring contraction reported by Carbon.[195] Treatment of 3-amino-1,2,4-benzotriazine 1-oxide (35), or the isomeric 2-oxide, with hot aqueous sodium hydroxide gave benzotriazole-1-carboxamide (34) and

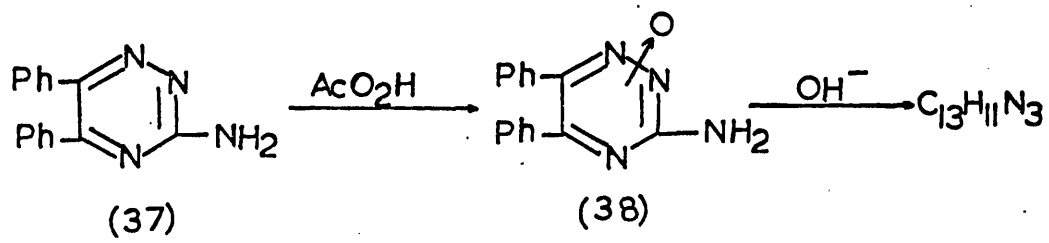
benzotriazole (33). The closely related compound, benzo-1,2,4-triazin-3(2H)-one 1-oxide (35′) was rather more stable in alkali, although prolonged heating under reflux gave benzotriazole. The presumed intermediate, benzotriazole-1-carboxylic acid (36) could not be isolated because of its very ready decarboxylation.



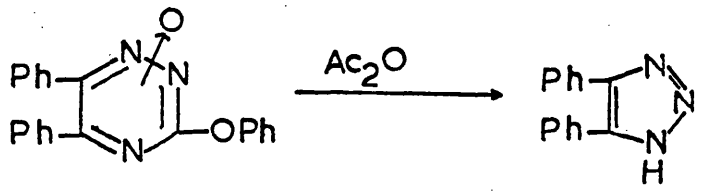
It is interesting to note that Sasaki and Minamoto[219] obtained 3-amino-5,6-diphenyl-1,2,4-triazine 1- or 2-oxide (38) by oxidation of the triazine (37) with peracetic acid and found that hydrolysis of (38) with 30% aqueous potassium hydroxide gave an unknown compound, m.p. 142-143°, which analysed for $C_{13}H_{11}N_3$. 4,5-Diphenyltriazole ($C_{14}H_{11}N_3$) (lit., m.p.[189] 138-139°) is the expected product by analogy with Carbon's work.

In a later paper[218] Sasaki and Minamoto found that the 3-phenoxytriazine N-oxide (39) when heated in acetic anhydride for

17.5 hr. gave diphenyltriazole (25) (18%). No mechanism was suggested.



(37) (38)



(39) (25)

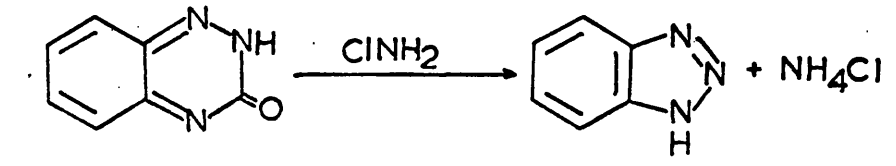
In both the benzo and diphenyltriazinone series, the N-oxide function was found to be necessary for the ring contraction to occur. The reactions have been extended to include triazine N-oxides fused to heterocyclic systems.[195b]

Yelland had found that the presence of sodium hydride in the reaction of the triazinone (6) with chloramine was not required and that the diphenyltriazole (25) (75%) was obtained together with cyanuric acid (100%).

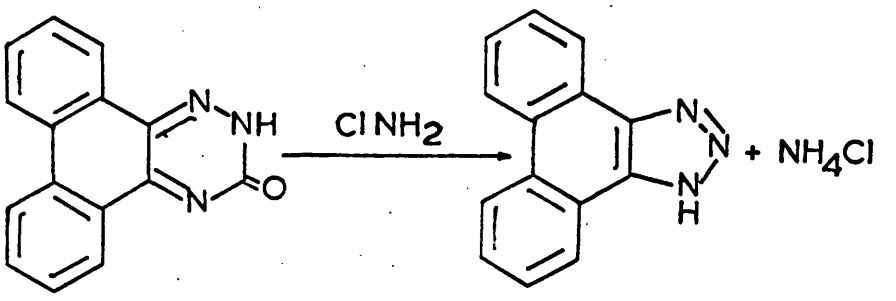
The chloramine reaction has now been extended to include both benzotriazinone (17) and phenanthrotriazinone (20). In the presence of sodium hydride, (17) gave benzotriazole (33) (7%) and recovered triazinone (56%) and (20) gave phenthrotriazole (40) (43%), identical in all respects to that of an authentic specimen.[60] No N-amino compounds were detected.

Under similar conditions, but without sodium hydride present, the

triazoles (33) and (40) were obtained in yields of 65% and 91% respectively. During the reactions, however, a crystalline solid separated and this was found to be ammonium chloride. The reaction of the diphenyltriazinone was also repeated in the absence of sodium hydride and found to give the triazole (25) (94%) and the l-etherate (26) (4%) together with ammonium chloride. Cyanuric acid, for which the ammonium chloride had presumably been mistaken, was not detected.



(17) (33)

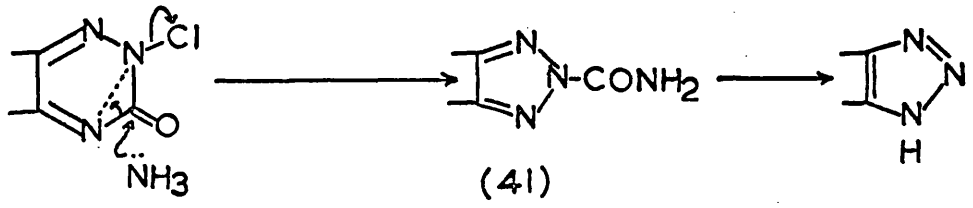


(20) (40)

The mechanism postulated by Yelland[58a] (Scheme 3) can now be discounted for several reasons. Nucleophilic attack by an amide nitrogen on chloramine to give an N-amino compound is extremely unlikely. When the sodium salt was used, the yields of triazoles fell markedly and yet one would expect the nucleophilic character of the anionic nitrogen to be increased. It was also shown that benzotriazole-1-carboxamide (34) could be recovered almost quantitatively when treated with chloramine under similar conditions and was therefore unlikely to be an intermediate in the ring contraction. The formation of ammonium chloride, and not cyanuric acid, indicated that the chloramine had been reduced during the course of the reaction and was therefore acting as an oxidising rather than an aminating agent.

An alternative mechanism could therefore involve initial formation of an N-chlorotriazinone and other N-chlorinating agents should also give a similar reaction. It was found that the diphenyltriazinone (6) did indeed give diphenyltriazole (25) (52%), on treatment with sodium hypochlorite, although a preliminary report[58a] indicated that the triazinone (80%) was recovered unchanged from this reaction. N-Chlorobenzotriazole[62] could also be used, and gave 4,5-diphenyltriazole (25) quantitatively; benzotriazole (33) (63%) was also obtained.

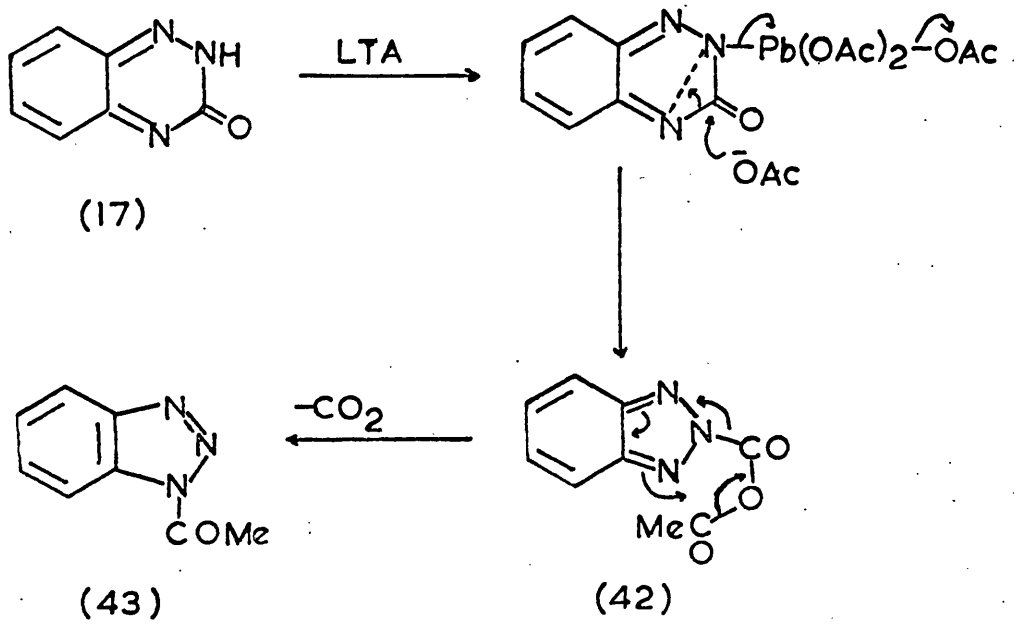
The alternative mechanism tentatively given below presupposes initial N-chlorination of the triazinone followed by a Favorskii type rearrangement[220] to give the triazole-2-carboxamide (41), for example when chloramine was used. Only triazole-1-carboxamides have been prepared, and not the 2-carboxamides, possibly due to the inherent instability of the 2-isomers which would hydrolyse to the corresponding triazole.



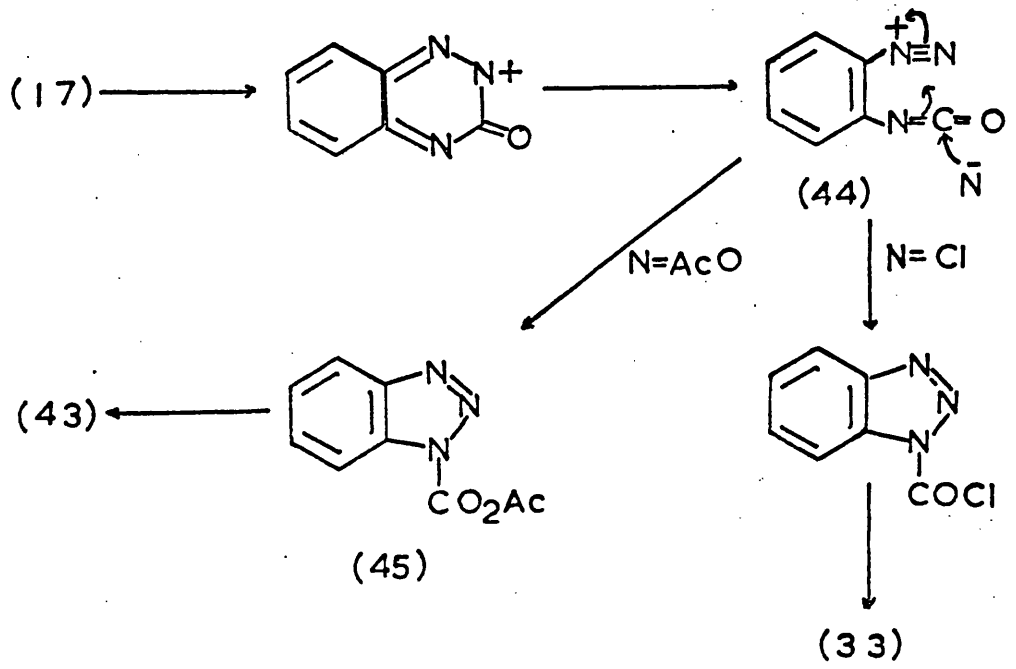
(41)

It was of interest to see if other oxidising agents would cause a similar ring contraction. Benzo-1,2,4-triazin-3(2H)-one (17) when oxidised with lead tetraacetate gave 1-acetylbenzotriazole (43) (86%) and benzotriazole (3%). The primary product must have been 1-acetylbenzotriazole, since benzotriazole, when oxidised with LTA under similar conditions gave only a low yield of the N-acetyl derivative (43) (2%). The benzotriazole presumably arose by hydrolysis of the N-acetyl compound (43) on chromatographic work up, since acetic acid, the

only other possible acylating agent present did not react with benzotriazole under these conditions. Furthermore, 1-acetylbenzotriazole slowly hydrolyses to benzotriazole on storage. A similar mechanism can be postulated as above (Scheme 5) although the alternative, less likely, mechanism shown (Scheme 6) cannot be entirely eliminated at the present time.



Scheme 5



Scheme 6

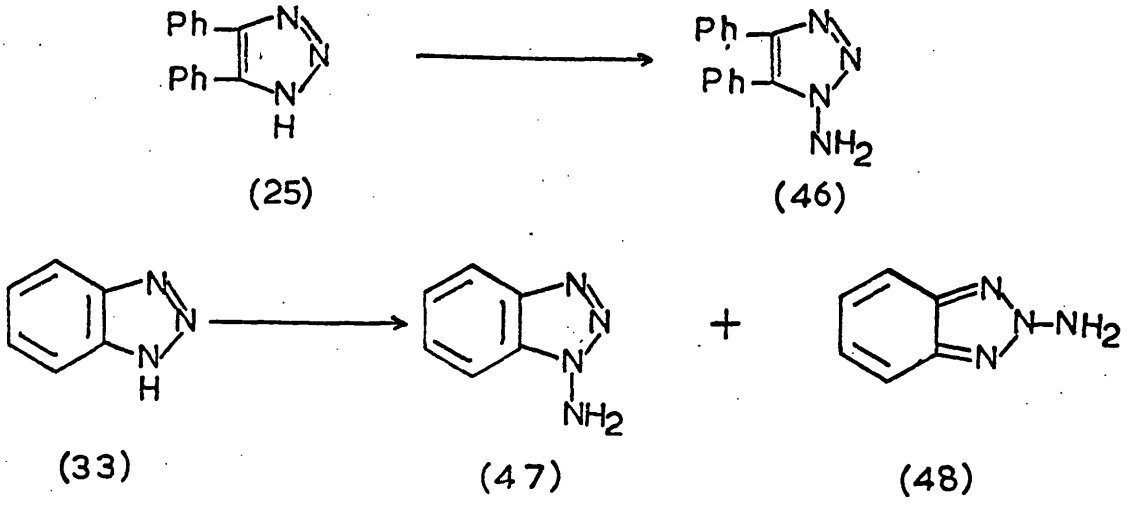
In the presence of LTA, the diazonium isocyanate (44) would be readily attacked by acetic acid to give the mixed anhydride (45). Loss of carbon dioxide from such compounds occurs readily[221] to give the corresponding amide. The 1-substituted anhydride (45) would lose the carbon dioxide via a four membered cyclic transition state, if intramolecular, whereas the 2-substituted isomer (42) would decompose via the more favourable five membered transition state shown in Scheme 5.

It is still not clearly understood why, of the triazinones that have been reacted with chloramine, only diphenyltriazinone (6) gave the corresponding triazole-1-etherate (26). A previous report[62] indicated that benzotriazole reacted with chloramine via 1-chlorobenzotriazole to give the corresponding 1-etherate and no N-amino compounds. 4,5-Diphenyltriazole, however, gave none of the corresponding etherate and only 1-amino-4,5-diphenyltriazole (46).[60]

The significance of the trace of the 1-amino compound (46) obtained in the reaction of the diphenyltriazinone (6) with O-(2,4-dinitrophenyl)hydroxylamine can now be explained. The hydroxylamine usually reacts as an aminating agent, and indeed most of the triazinone (6) is converted to the imidazolinone (7). However, it must also react to a very small extent as an oxidising agent, converting the triazinone to diphenyltriazole (25) which is then aminated to the 1-amino compound (46).

Under similar conditions, the triazole (25) was indeed found to be aminated to the 1-amino compound (46) (23%). Unreacted hydroxylamine (36%) was also recovered. None of the unknown 2-amino-4,5-diphenyltriazole was obtained although benzotriazole was found to give a mixture of both isomers (47) and (48). When methylene chloride was used as the solvent, the yields of the 1- and 2-isomers were 35% and 36% respectively, but when DMF was used the respective yields fell

to 30% and 9%.

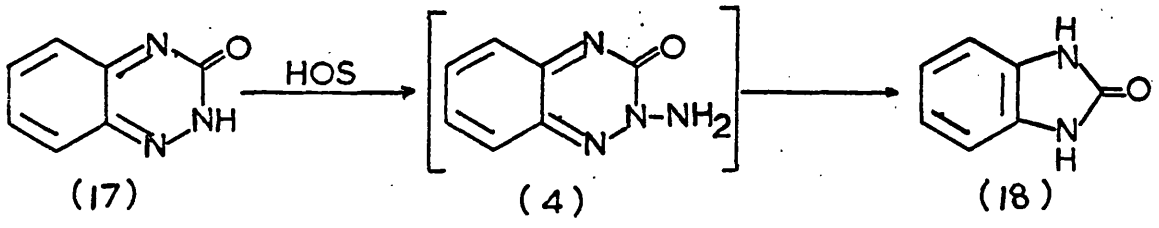


Finally, although phthalimide can be converted into N-amino-phthalimide with hydrazine, the same reaction could not be applied to the triazinones (6) and (17); instead the corresponding hydrazinium salts were obtained.

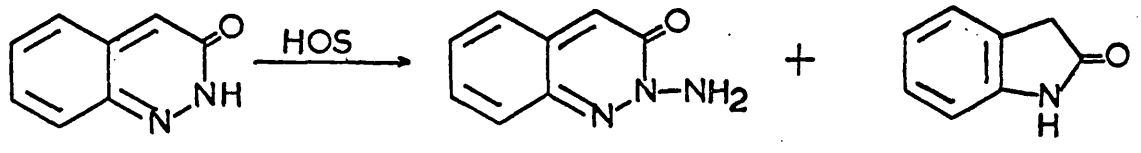
2 2-AMINOCINNOLIN-3(2H)-ONE

A Reaction of cinnolin-3(2H)-one with HOS

In Section 1A, the ring contraction that 1,2,4-triazin-3(2H)-ones undergo on treatment with HOS was discussed. The structural similiarity between cinnolin-3(2H)-one (22) and benzotriazinone (17) suggested that a similar reaction should occur. Indeed when cinnolinone was treated with HOS in aqueous alkali the ring contracted product, oxindole (24), was isolated together with 2-aminocinnolin-3(2H)-one (23).



(17) (4) (18)

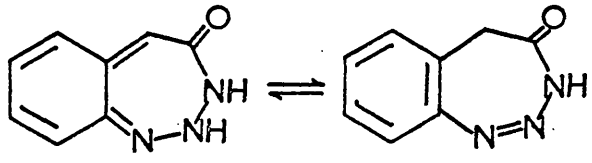


(22) (23) (24)

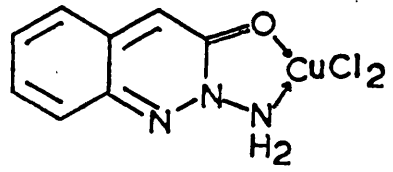
When the reaction was carried out with HOS in aqueous sodium hydroxide at 60 to 70°, the N-aminocinnolinone (23) (7%) was isolated. Analytical and spectral data were in agreement with the assigned structure (23) although the alternative less likely ring inserted structure (49) could not be entirely discounted.

N-Nitrosodiphenylamine has been used successfully to deaminate N-amino compounds,[61,137] but when fused with 2-aminocinnolin-3(2H)-one (23) at 100° the N-aminocinnolinone (23) (33%) was recovered. Oxindole (24) (65%) and diphenylamine (87%) were also isolated. Deamination with sodium nitrite was more successful, however, and cinnolinone (22)

was obtained almost quantitatively (96%). Further proof of the assigned structure was obtained by the formation of the green copper chelate (50) in which ν_{CO} has shifted characteristically from 1664 $cm.^{-1}$ to 1618 $cm.^{-1}$. Cinnolinone itself did not form a complex. El-Kholy and Rafla[223] have recently shown that N-aminopyridones form copper chelates as highly crystalline compounds when treated with a methanolic solution of copper chloride dihydrate.



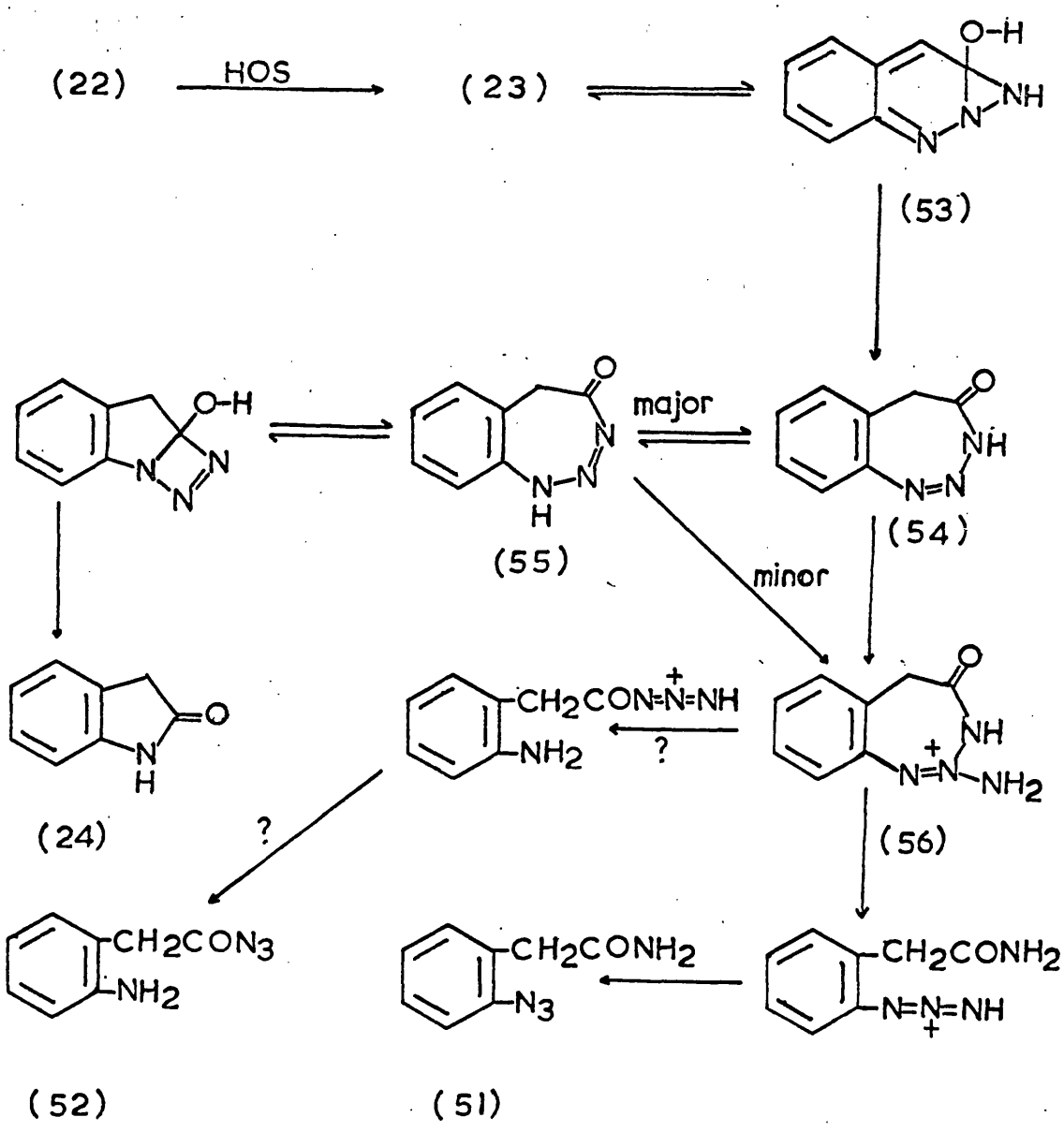
(49)



(50)

As well as the 2-aminocinnolinone (23), other products isolated in the amination of cinnolinone were oxindole (24), (32%), the azide (51) (1%) and recovered cinnolinone (22) (7%). When the reaction was carried out at a slightly lower temperature the yield of N-amino compound (23) rose to 22%; oxindole (30%) and the azide (51) (0.6 %) were also isolated. At 40 to 45°, the yield of N-amino compound (23) fell slightly to 17% and more cinnolinone (40%) was recovered. Addition of ethanol to the reaction mixture did not increase the yield of N amino compound (23) (7%), however, and oxindole (15%) and cinnolinone (25%) were still obtained.

These results suggest that N-amination occurs as the initial step, and that as the temperature is raised, the rate of decomposition of the N-amino compound (23) to oxindole (24) increases. The following mechanism (Scheme 7) based on the reaction of triazinones with HOS would account for the experimental observations.

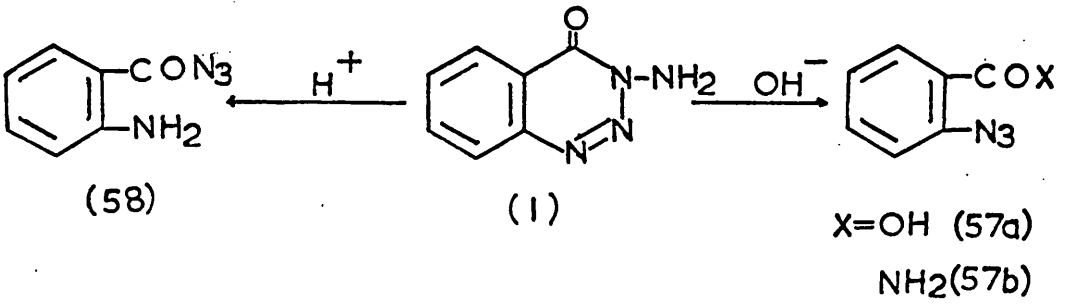


Scheme 7

Initial N-amination to give (23) followed by ring expansion via diaziridine (53) would give the seven membered ring intermediate (54). The major reaction path would then be a rapid 1-3 proton migration to give (55) followed by loss of nitrogen to give oxindole (24). The intermediates (54) and (55) must be relatively long-lived, however, for nucleophilic attack on the excess of HOS to occur. The minor reaction path shows N-amination on the middle nitrogen to give (56). Similar mechanisms, although rather more complicated, can be postulated for N_1 or N_3 amination leading to the o-azidophenylacetamide (51).

The i.r. spectrum of o- azidophenylacetamide (51) showed $\nu_{max.}$ 3370, 3170 (NH_2); 2125, 2100 (N_3) and 1690, 1670 ($CONH_2$). The alternative isomeric structure (52), although less likely, cannot be entirely discounted, as it could have been formed by fission of the N_1-N_2 bond in intermediate (56).

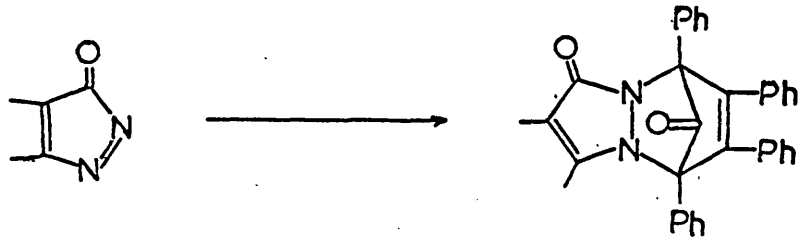
A related rearrangement has been reported by Gibson and Green.[224] 3-Aminobenzotriazinone (1) when heated in alkali gave o-azidobenzoic acid (57a). Treatment with acid, however, gave the isomeric anthranilazide (58). Forster[142] later showed that o-azidobenzamide (57b) could be isolated when milder basic conditions were used.



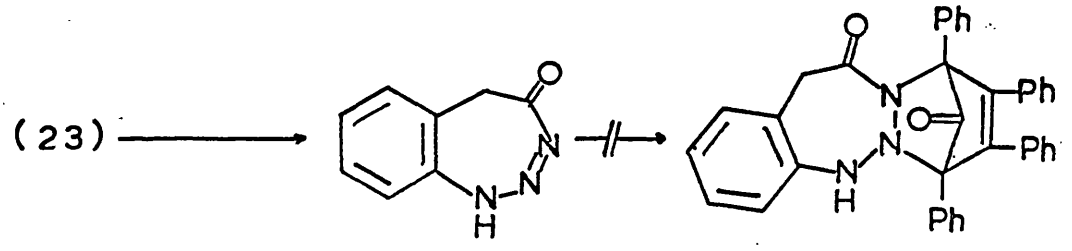
(58) (1)

On heating to its melting point, 2-aminocinnolin-3(2H)-one (23) undergoes an explosive decomposition with formation of oxindole (64%). This strongly suggests that the N-amino compound (23) is an intermediate in the conversion of cinnolinone (22) into oxindole by HOS, and that it is unstable under the alkaline reaction conditions (see Scheme 7). Decomposition can also occur at temperatures below its melting point. Oxindole (90%) was obtained when the N-amino compound (23) was heated to reflux in toluene. No rearrangement occurred when cinnolinone and 2-methylcinnolinone[199] were heated in trichlorobenzene at over 200°. Unchanged reactants were recovered in yields of 70% and 100% respectively.

Yelland[58a] and Adamson[60] have used tetraphenylcyclopentadienone (tetracyclone) to intercept pyrazole-3-ones and indazolin-3-ones as the Diels-Alder adducts (59). It was hoped that pyrolysis of the N-aminocinnolinone (23) in the presence of tetracyclone would give the corresponding Diels-Alder adduct (60). None of the adduct (60) was isolated, however, and oxindole (47%) and recovered tetracyclone (88%) were obtained. Presumably the α-azo carbonyl group in this seven membered ring is not reactive enough towards cycloaddition for reaction with tetracyclone to compete with intramolecular rearrangement.

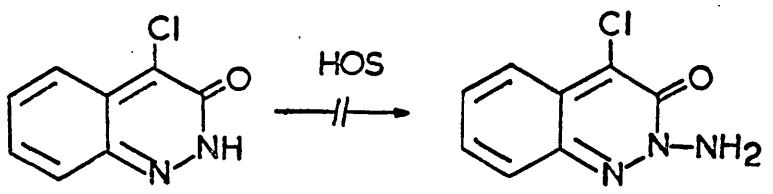


(59)



(55) (60)

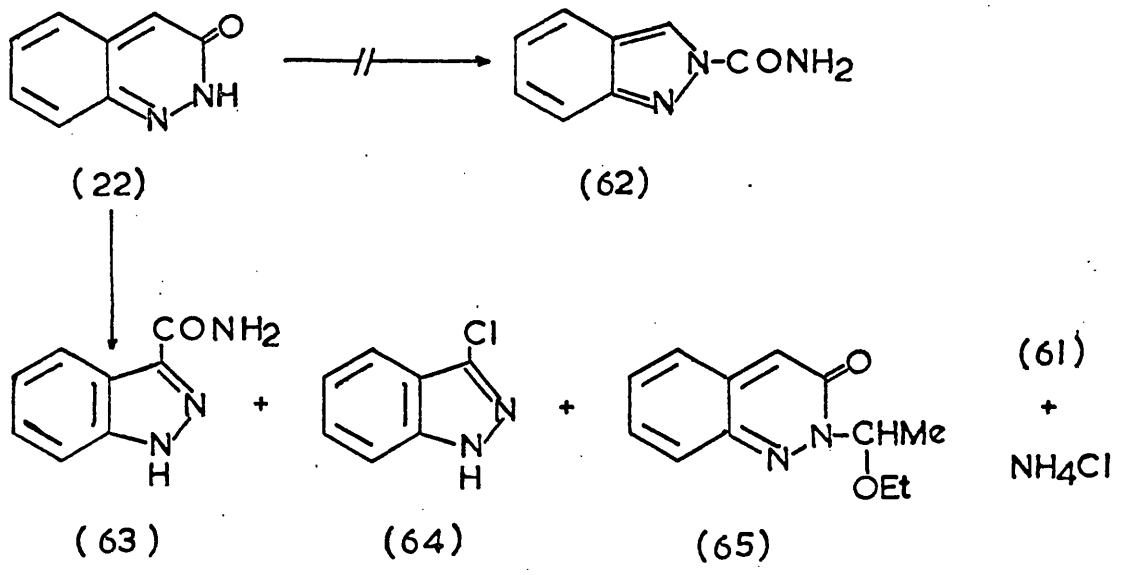
2-Aminocinnolin-3(2H)-one (13%) can also be prepared by the amination of cinnolinone (22) with O-(2,4-dinitrophenyl)hydroxylamine. Although no side products were detected, there appeared to be little experimental advantage in using this aminating agent. The reaction could not be extended to 4-chlorocinnolin-3(2H)-one (61)[56] since when aminated with HOS the unchanged cinnolinone (61) was recovered. This was possibly due to the insolubility of the chloro compound (61) even in aqueous ethanolic alkali.



(61)

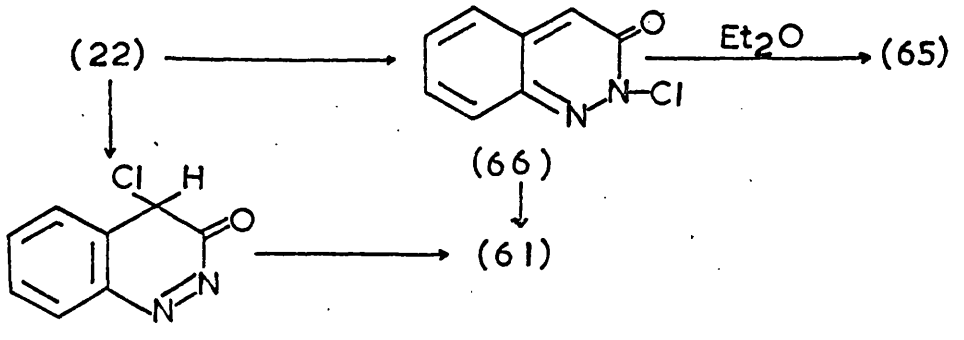
B Reaction of cinnolin-3(2H)-one with chloramine

By analogy with the reaction of triazinones with chloramine one would expect cinnolin-3(2H)-one to give indazole-2-carboxamide (62). However, none was isolated and instead the 3-isomer (63) (18%)[198] was obtained together with ammonium chloride (95%), 4-Chlorocinnolin-3(2H)-one (61) (18%)[56a], the etherate (65) (1.7%) and 3-chloroindazole (64) (1.8%).[197] Unchanged cinnolinone (7%) was also recovered.

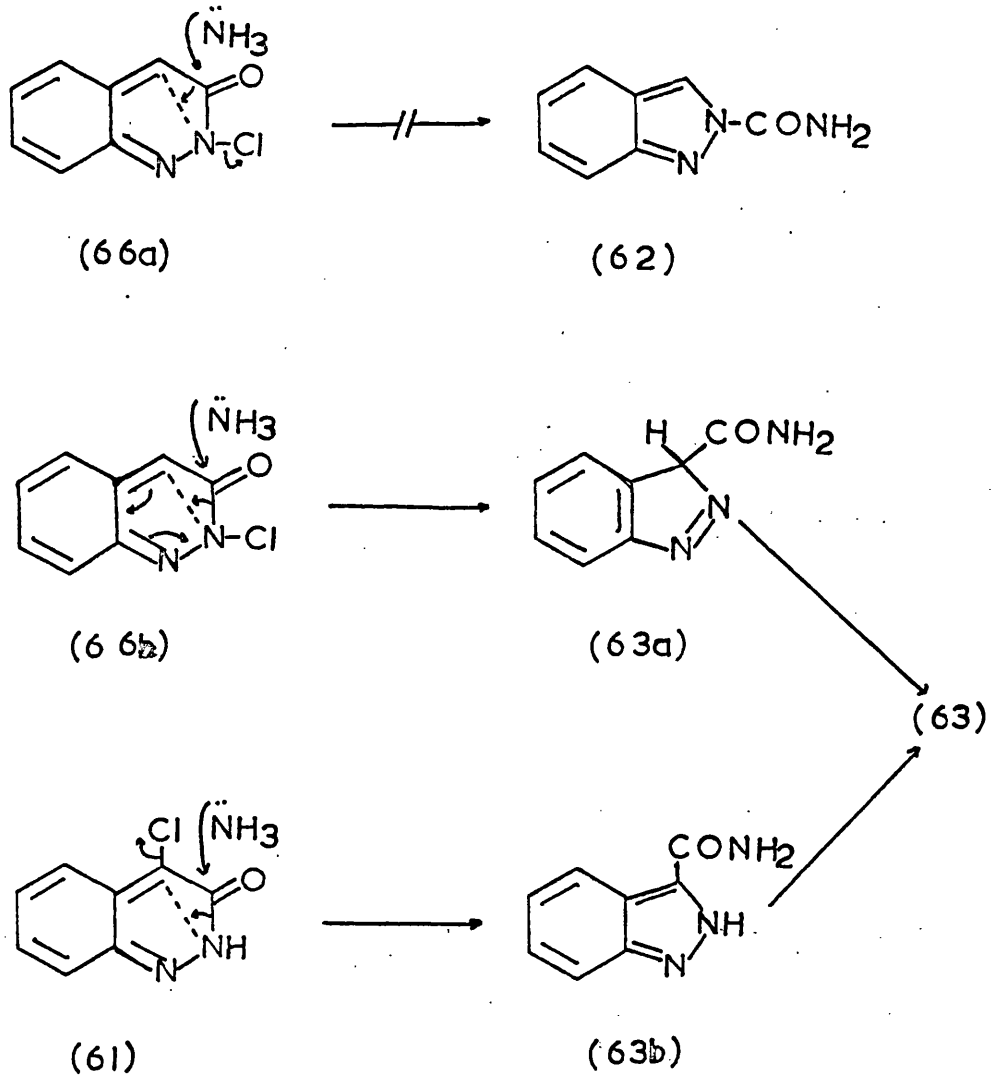


It is apparent that the reaction is complex and it is interesting to note that if Yelland's[58a] mechanism for the reaction of triazinones with chloramine is applied to cinnolinone, the carboxamide (63) is the expected product.

The etherate (65) was presumably formed by reaction via the intermediate N-chlorocinnolinone (66). The formation of analogous compounds in the reaction of benzotriazole[62] and diphenyltriazole[60] has already been discussed (see Section 1B). An Orton type rearrangement of the N-chloro compound (66) would explain the formation of the 4-chlorocinnolinone (61), although direct chlorination is equally possible. Cinnolinone (22) can be directly chlorinated in the 4-position with t-butyl hypochlorite[56] and probably involves a similar mechanism.

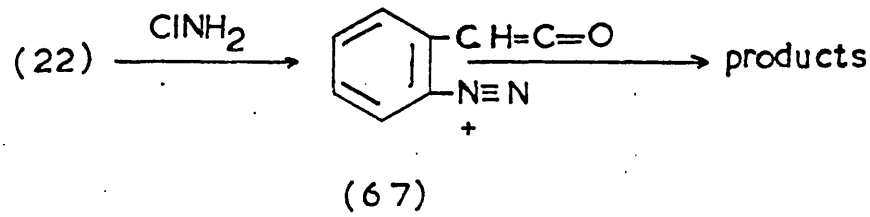


If the N-chloro intermediate (66) is the precursor to the indazole-3-carboxamide (63), then the mechanism for the triazinone to triazole ring contraction has to be amended slightly in the cinnolinone reaction with chloramine (scheme 8). The above type of Favorskii rearrangement (arrows in 66a) is modified to an extended type (arrows in 66b) where additional driving force is provided by aromatisation of the o-quinonoid system. It is also possible that it is the 4-chlorocinnolinone (61) that undergoes the Favorskii type reaction, and clearly further work is required in order to differentiate between the various tentative postulates shown below.

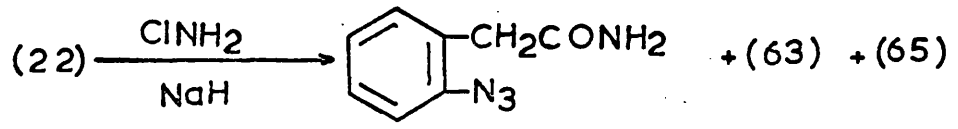


Scheme 8

Various routes to the minor product 3-chloroindazole can be envisaged. These include for example further reaction of the carboxamide (63) or its isomer (62) with chloramine, the initial formation of 2,4-dichlorocinnolin-3-one followed by a ring contraction similar to those above, and formation of the o-diazoniumketene intermediate (67) analogous to the diazonium isocyanate (44) of Section 1. Obviously further work is required to distinguish between these.

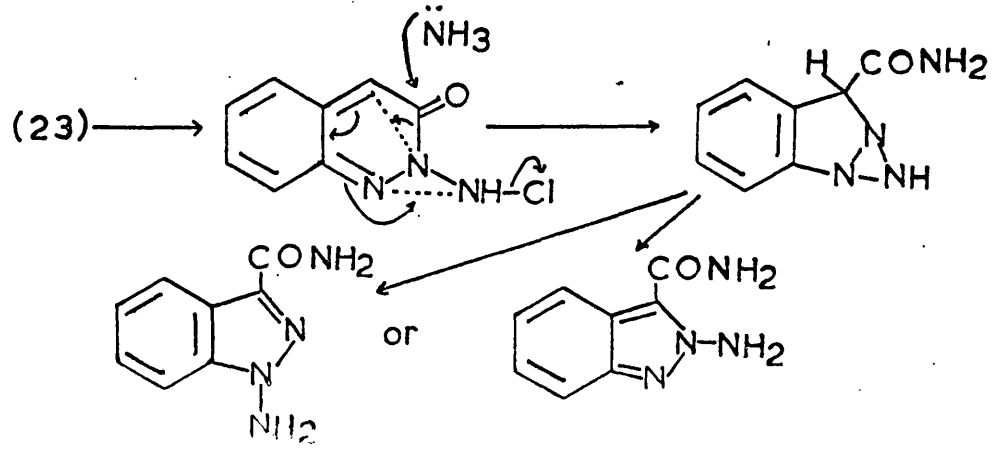


When the reaction of cinnolinone with chloramine was repeated in the presence of sodium hydride the carboxamide (63) (4%) and the etherate (65) (<1%) together with recovered cinnolinone (43%) were isolated. o-Azidophenylacetamide (51) (15%) was also obtained.



(51)

Presumably the N-amino compound (23) had initially been formed and had then reacted further as shown in Scheme 7. The yield of carboxamide (63) had fallen considerably which indicated that the N-amino compound (23) was not an intermediate in the ring contraction reaction. Further proof was obtained when it was found that the N-aminocinnolinone did not react with chloramine to give indazole-3-carboxamide. Instead, a compound which analysed for $C_8H_8N_4O$, m/e: 176(P), was obtained. The i.r. spectrum showed complex NH (3390-3050) and amide carbonyl (1665, 1638 $cm.^{-1}$) absorption. The mass spectral decomposition pattern was similar to that of indazole-3-carboxamide and the compound is probably either 1- or 2-aminoindazole-3-carboxamide. The mechanism shown below is tentatively suggested for its formation.



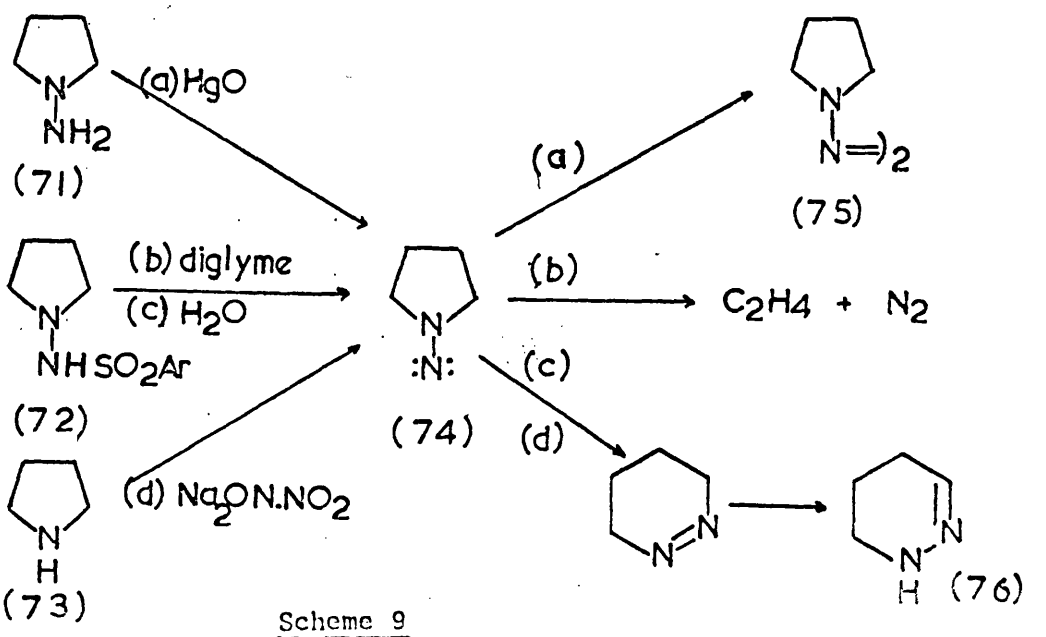
C. Oxidation of N-aminoamides

Before attempting to describe the oxidation of N-aminocinnolin-3-one it is instructive to mention the reactions that other N-amino amides undergo in similar conditions (see Table 1). Where relevant, other examples of the reactions of N-nitrenes (70) will be taken from the abundant literature.

$R_2N\text{-}NH_2$ (69) $\qquad R_2N\text{-}\ddot{N}: \leftrightarrow R_2\overset{+}{N}=\overset{-}{N}$ (70)

The usual reactions of the hydrazines (69) on oxidation include fragmentation with and without recombination of the substituents R, deamination, and tetrazene formation. Only one report has appeared whereby ring expansion occurs in the hydrazines (69) (R=alkyl or aryl).

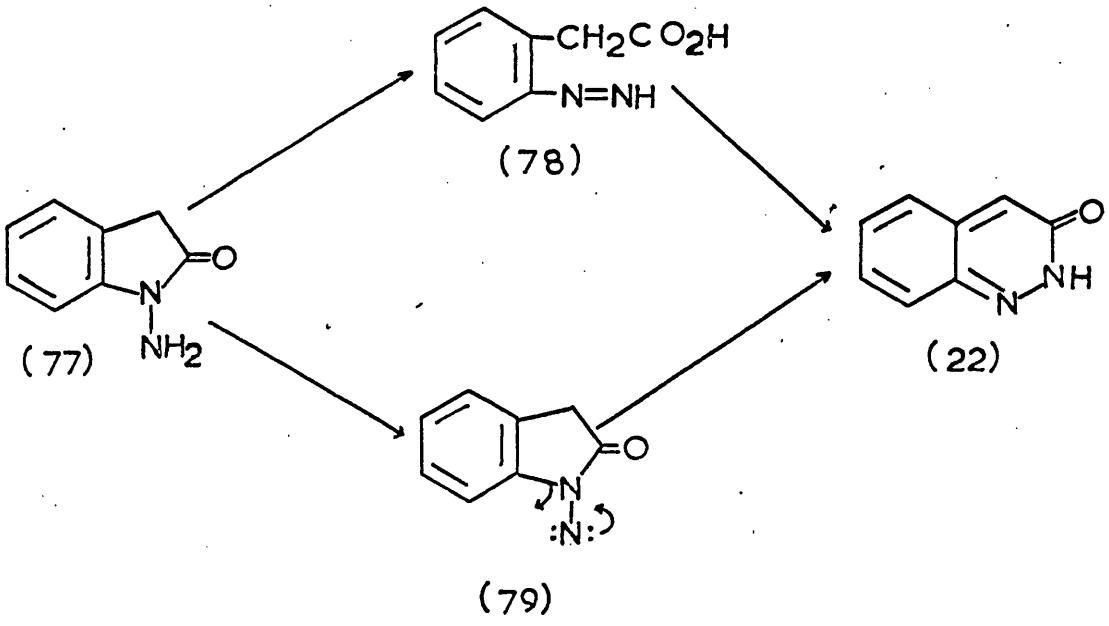
Lemal[225] decomposed the arylsulfonamide (72) in aqueous solution and obtained the tetrahydropyridazine (76) (56%). He also obtained the same compound when pyrrolidine (73) was treated with nitrohydroxylamine (introduced as Angeli's salt, $Na_2ON.NO_2$)[226] in acid solution. Thermolysis of the sulfonamide (72) in diglyme at 175° gave high combined yields of nitrogen and ethylene, and oxidation of the N-amino compound (71) with mercuric oxide gave the tetrazene (75).

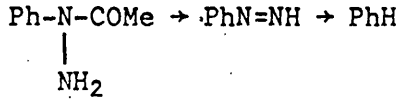


Scheme 9

The three different products were presumed to have been derived from the common N-nitrene intermediate (74) and the subsequent reaction paths were controlled by the different nature of the environment (Scheme 9).

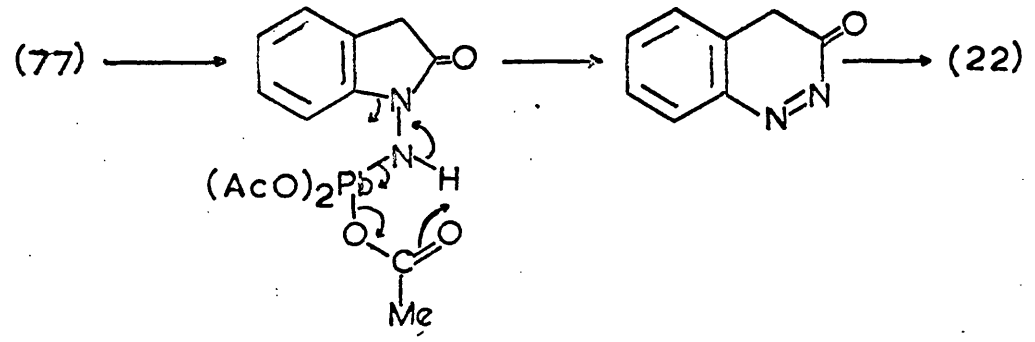
The first N-amino amides to be oxidised were N-aminooxindole (77) and N-aminoacetanilide (81). Baumgarten[196b] postulated two mechanisms to explain the products, cinnolin-3-one (22) and benzene respectively.





(81) (82)

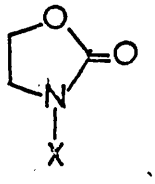
The mechanism via the diimides (78) and (82) was later withdrawn in favour of the concerted process via (79) which was later modified slightly, as shown below, to incorporate the "nitrenoid" intermediate (80).



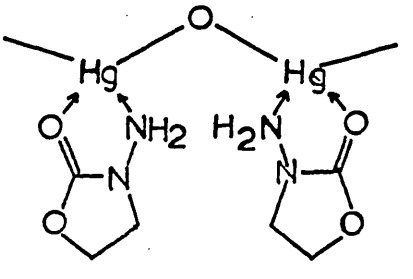
(80)

(For a more detailed discussion see Sections 4a and 5).

3-Aminooxazolidin-2-one (83)[227] when oxidised in homogeneous mixtures gave the trans-tetrazene (84) in high yield. When oxidised with mercuric oxide, the cis-tetrazene (84) (50%) was obtained together with some of the trans-isomer (84) (10%). The surface chelate complex (85) was postulated as an intermediate to explain the formation of the cis-isomer in an orientated arrangement of the oxazolidinone molecules.



X = NH_2 (83)
N=)$_2$ (84)



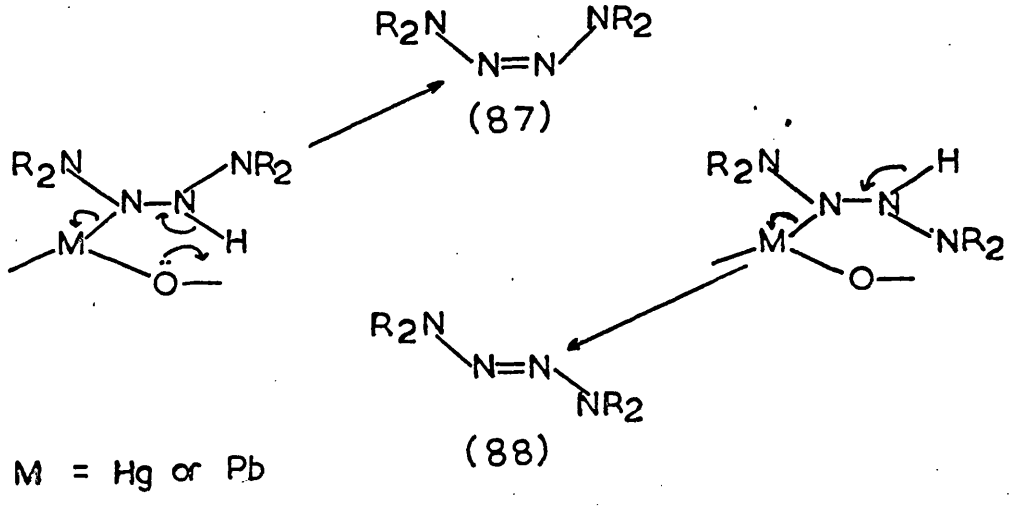
(85)

The structurally similar 3-aminobenzoxazolin-2-one (86)[138] when oxidised with LTA in solution also gave a mixture of cis and trans-tetrazenes.[139] (See Table 1). The similarity of these reactions indicates that a common mechanism is operative, although with N-amino-benzoxazolinone (89) deamination also occurred.

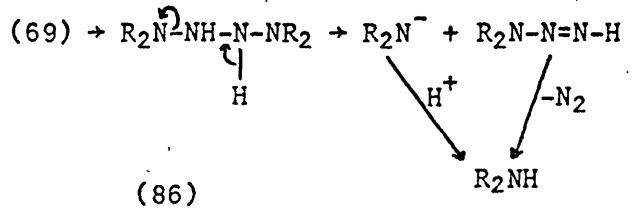
The dimerisation of two, kinetically-free, highly reactive intermediates is extremely unlikely and a more probable mechanism for the formation of tetrazenes is shown below. Concerted oxidation of the initially formed tetrazane (86) via the five membered transition state would then give the thermodynamically less stable cis tetrazene (87). The more usual trans elimination would give the alternative isomer (88).

$$R_2\ddot{N}\text{-}\ddot{N}\text{:} + R_2N.NH_2 \rightarrow R_2N\text{-}\overset{-}{N}\text{—}\overset{+}{N}H_2\text{-}NR_2 \rightarrow R_2N\text{-}NH\text{-}NH\text{-}NR_2$$

(70) (86)



At present, the most satisfactory mechanism that can be written for deamination of the hydrazines (69) under oxidative conditions is shown below.



The benzoxazolinone (89) when oxidised in the presence of olefins and dienes gave aziridines by 1,2-addition of the intermediate

N-nitrene. Oxidation of the oxazolidinone (83) in similar conditions has not been reported (see Table 1).

N-Aminophthalimide (90) and recently N-aminonaphthalimide[139] (91) were also found to give aziridines when oxidised in the presence of olefins. N-Aminophthalimide also underwent deamination and formed a tetrazene.

No adequate reason has been suggested as to why, of the five-membered heterocyclic N-amino amides studied, only N-aminooxindole ring expands on oxidation in preference to reacting with olefins and dienes.

The behaviour of six membered heterocyclic N-amino amides towards oxidation appears to be as complex as the five membered. The nitrene from N-aminopyridin-2-one (92) can be intercepted with olefins[229] and although some of the N-aminopyridones shown in Table 1 have not beenoxidised in these conditions, the indications are that they would react similarly.

The substituted N-aminopyridin-2-ones (93), (94) and (95) also gave pyridazines by ring expansion to the α-azo-carbonyl compound (108) followed by loss of carbon monoxide. The N-aminotetraphenylpyridone (95) also gave a low yield of tetracyclone (110) (1%). The general reaction scheme is given below.

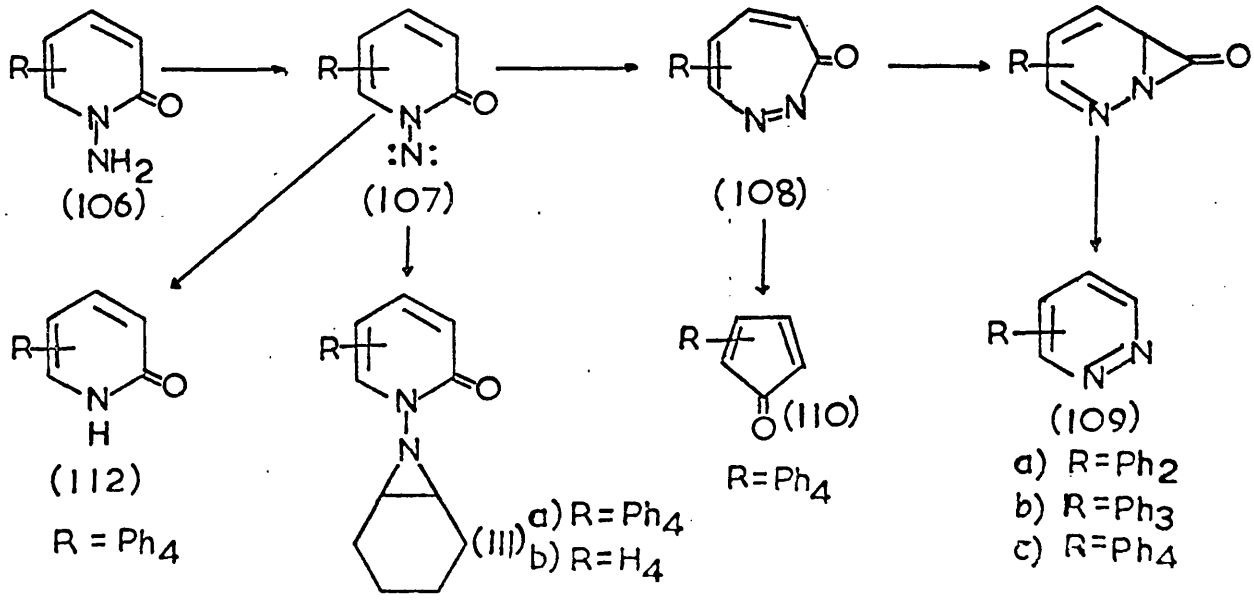
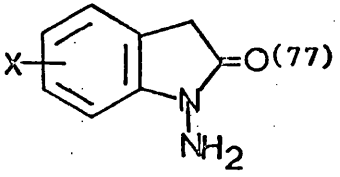
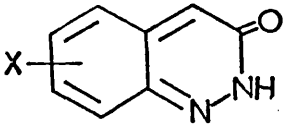
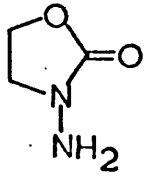
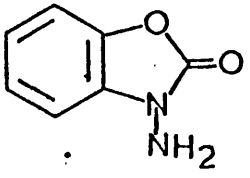
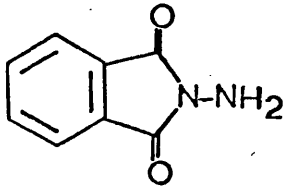
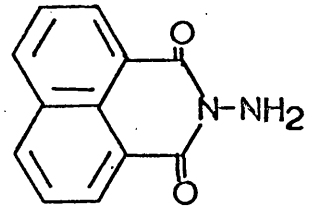
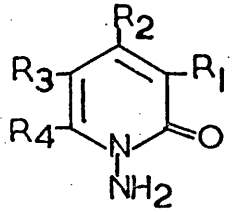
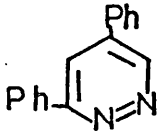
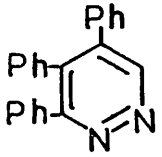
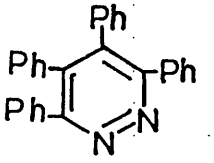
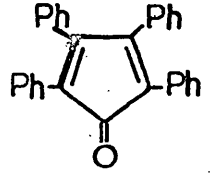
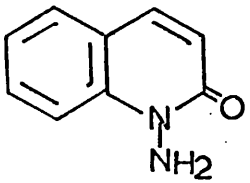
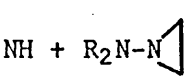
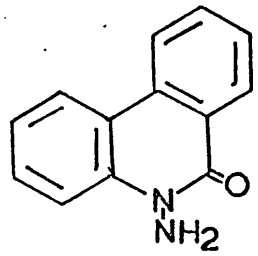
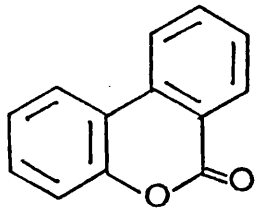
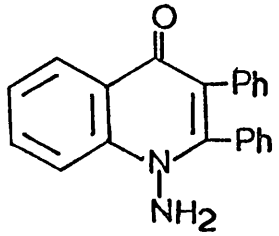
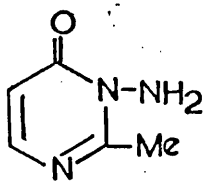
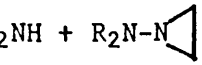


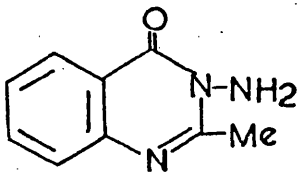
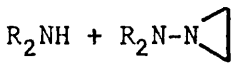
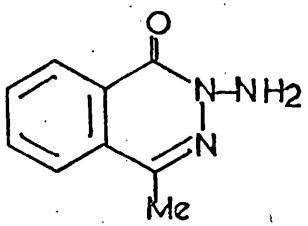
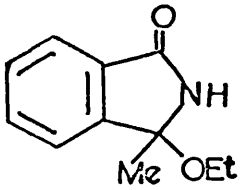
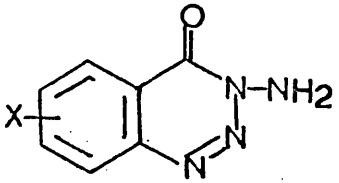
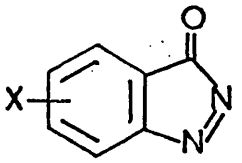
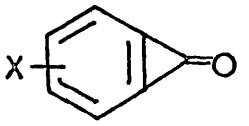
Table 1

Oxidation of N-Aminoamides

N-Amino Compound	Products[1]	Reference
Ph-N(NH$_2$)-COMe (81)	PhH [2]	196b
 (77)		56b 138 196b
 (83)	$R_2N-N=N-NR_2$ [2][3][4]	227
 (89)	$R_2NH + R_2N-N=N-NR_2 + R_2N-N$ [3][5][6]	138 139
 (90)	$R_2NH + R_2N-N=N-NR_2 + R_2N-N$ [6]	139 228

N-Amino Compound	Products (1)	Reference
 (91)	R_2NH + R_2N-N	139
	(6)	
$R_1=R_2=R_3=R_4=H$ (92)	R_2NH + R_2N-N	229
$R_1=R_3=H$; $R_2=R_4=Ph$ (93)	 (2)	58a
$R_1=H$; $R_2=R_3=R_4=Ph$ (94)	R_2NH +  (2)	58a
$R_1=R_2=R_3=R_4=Ph$ (95)	R_2NH + R_2N-N +  + 	58a 230
$R_1=R_2=R_3=Ph$; $R_4=Me$ (96)	R_2NH (2)	58a

N-Amino Compound		Products (1)	References
	(97)	R_2NH +  (6)	56 229
	(98)	R_2NH + 	58a 230
	(99)	$R_2NH + R_2N\text{-}NR_2$ (2)	58a
	(100)	R_2NH +  (6)	229

N-Amino Compound	Products[1]	References
 (101)	$R_2NH + R_2N\text{-}N$  (6)	229
 (102)		229
 (103)	 + 	216

NOTES TO TABLE 1

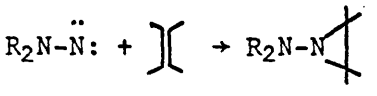
1) Not all of the products shown may have been isolated in the same reaction. For example, an oxidation in the presence of an olefin may have given an aziridine to the exclusion of the formation of the deaminated material.

2) Oxidations have not been carried out in the presence of an olefin.

3) Cis and trans tetrazenes were isolated.

4) R_2N- denotes the heterocyclic residue throughout the Table.

5) The addition of N-nitrenes to olefins to give aziridines was discovered in these Laboratories as a method of "trapping" the N-nitrene and is now used as a standard technique.



6) The N-nitrenes derived from these N-amino compounds have also been intercepted with DMSO to give the sulfoximines (104) in exceptionally high yields.

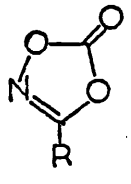
$$R_2N\text{-}\ddot{N}\text{:} + Me_2SO \longrightarrow R_2N\text{-}N{=}SOMe_2$$

(104)

DMSO had been shown to react with sulfonyl nitrenes generated by thermolysis or photolysis of arylsulfonyl azides.

$$Me_2SO + ArSO_2N_3 \xrightarrow[\Delta]{h\nu} ArSO_2N{=}SOMe_2 + N_2$$

C-Nitrenes have also been trapped in a similar manner when generated by the pyrolysis of dioxazolin-5-ones (105), and in this instance the ambiguity as to whether the actual nitrene or the azide was reacting with the DMSO was removed.

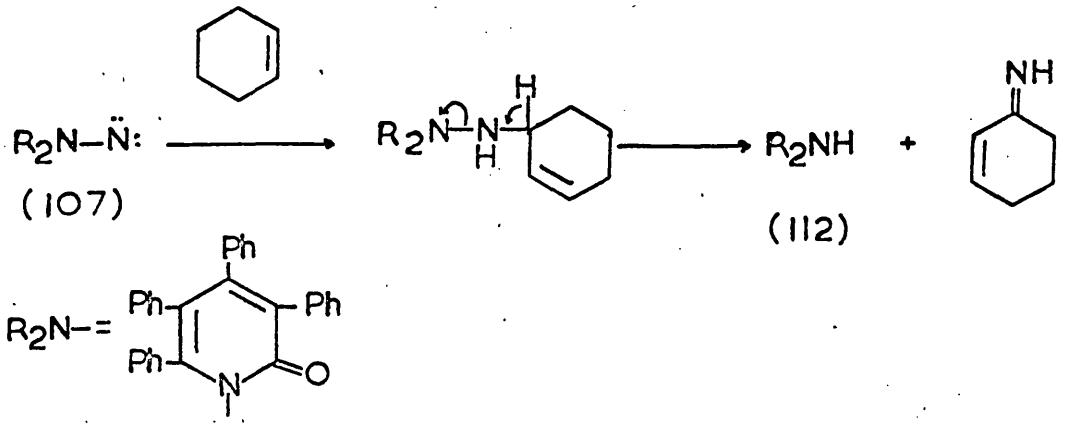


$$\xrightarrow{150^\circ} RCO\ddot{N}\text{:} \xrightarrow{DMSO} RCON{=}SOMe_2 + CO_2$$

(105)

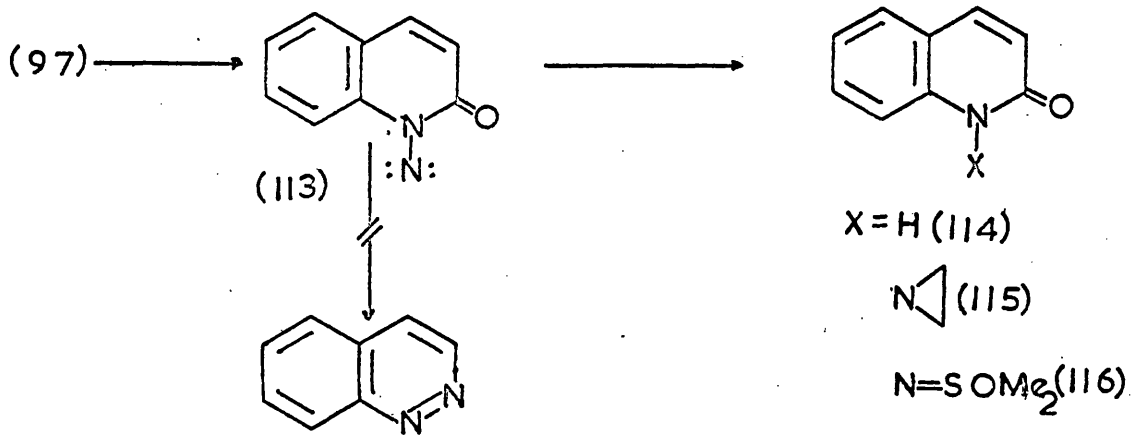
When the N-aminotetraphenylpyridone (95) was oxidised in cyclohexene the aziridine (111a) was isolated in moderate yield and the yield of pyridazine (109c) fell markedly. The yield of deaminated pyridone (112) rose significantly.

The reaction of the N-nitrene (107) with cyclohexene was thus effectively competing with the intramolecular rearrangement. The possibility of the nitrene (107) inserting into the allylic -CH- of cyclohexene can also be considered and the reaction scheme below would then account for the increased yield of (112). The low molecular weight cyclohexene residues were not isolated.



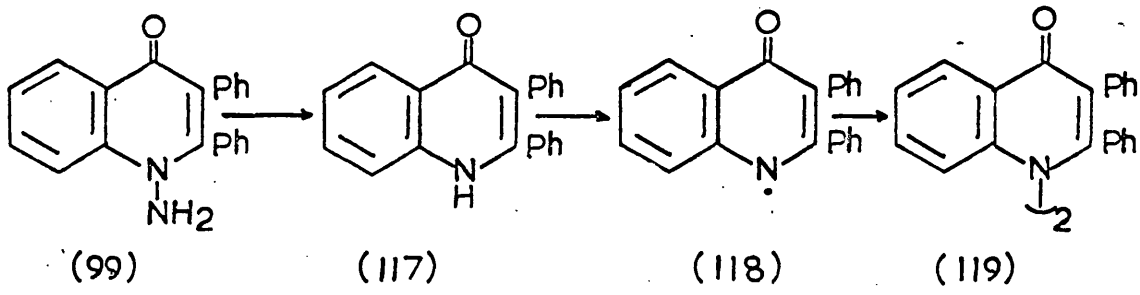
N-Aminopyridin-2-one (92) itself and the triphenylmethyl derivative (96) did not form the expected pyridazines.

The similar fused compound, N-aminoquinolin-2-one (97) gave no cinnoline (22) and was originally shown to deaminate to quinolin-2-one (114).[56] The intermediate nitrene (113) has since been intercepted with olefins and DMSO to give the adducts, (115) and (116) respectively.[229]



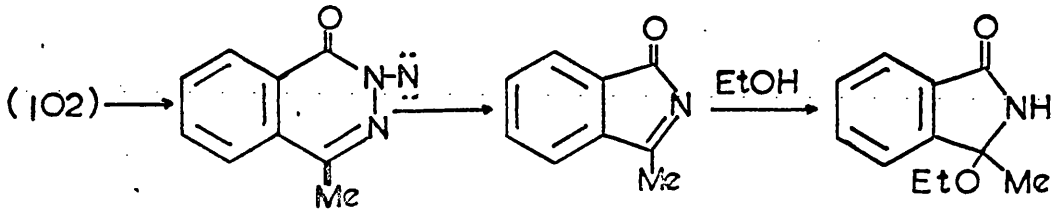
The addition of a further fused benzene ring to give N-amino-phenanthridone (98)[230] caused an entirely different reaction to take place. Benzocoumarin and phenanthridone were isolated and no benzo[c]cinnoline was detected. The mechanism of formation of the benzocoumarin is uncertain but possibly proceeds via the N-nitrosophenanthridone.

1-Amino-2,3-diphenylquinolin-4-one (99)[58a] when oxidised with LTA gave the dimer (119), probably by initial deamination followed by oxidation to the radical (118), which then dimerised. A small amount of (117) was also isolated.



The N-aminoquinazolinone (101) and pyrimidone (100) do not show unusual behaviour on oxidation; both deaminate and both give aziridines in the presence of olefins. No rearrangement products have been detected.[229]

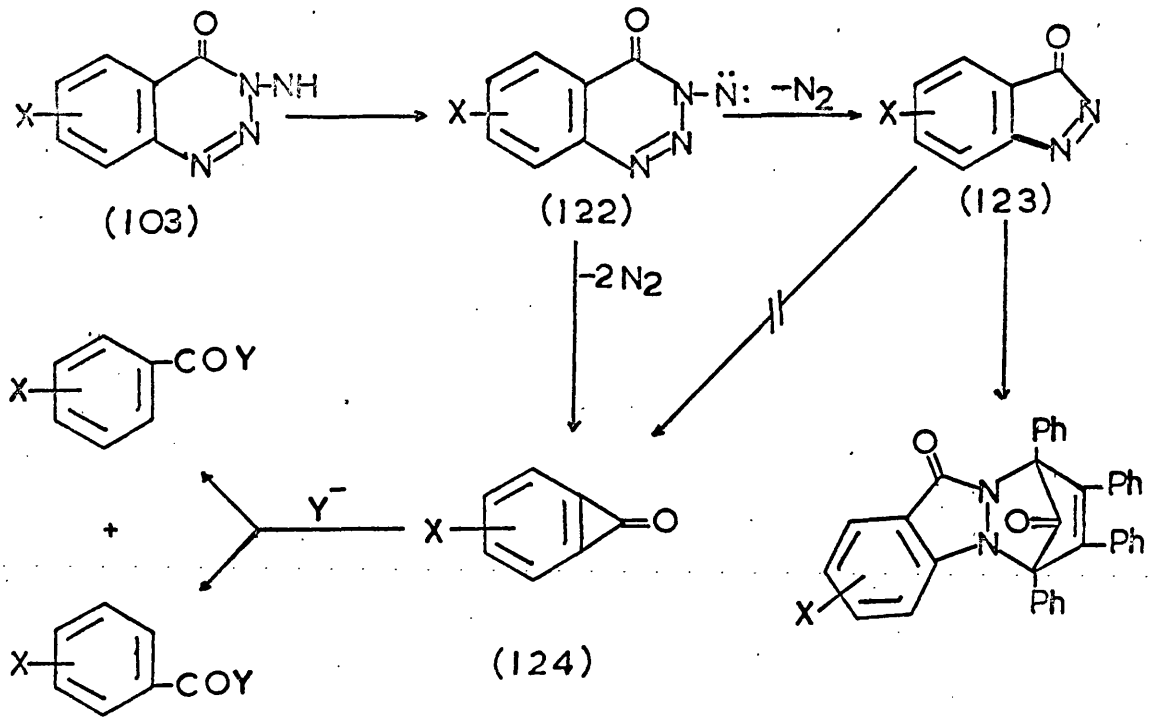
3-Amino-1-methylphthalazin-4-one (102) shows unusual behaviour on oxidation. The intermediate nitrene (120) cannot be trapped with olefins or DMSO and no products due to ring expansion of the nitrene are obtained. Instead, when oxidised in the presence of ethanol , the ethoxyphthalimidine (121) can be isolated in good yield. The following mechanism was proposed.[229]



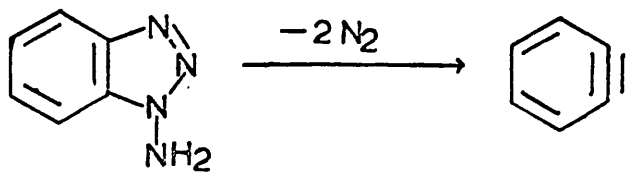
(120) (121)

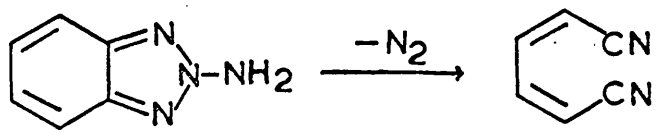
There are therefore two classes of N-amino amides. Those which lose nitrogen on oxidation and those which do not. A requirement of the former is that the N-amino function should be adjacent to a nitrogen atom. A further example of this class of N-amino compounds can be found with the 3-aminobenzo-1,2,3-triazin-4-ones (103).

Oxidation with LTA gives the N-nitrenes (122) which then either lose one molecule of nitrogen to give indazolone (123) or lose two molecules of nitrogen to give benzocyclopropenones (124). The cyclopropenones were formed by a concerted loss of the two molecules of nitrogen, as the indazolone were not intermediates. Tetracyclone (TC) could be used to detect the indazolone and addition of a nucleophile gave a mixture of benzoic acid derivatives indicating the presence of the unsymmetrical benzocyclopropenones (124).[216]

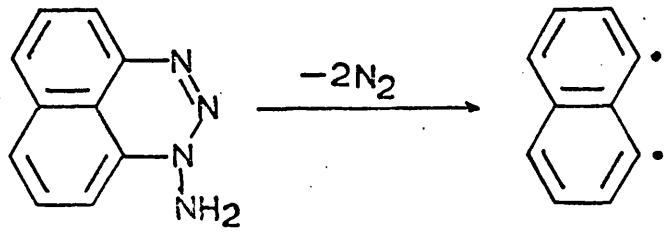


The best example of loss of nitrogen from a heterocyclic N-amino compound was reported by Campbell and Rees.[134b] Oxidation of 1- and 2-aminobenzotriazoles gave benzyne and cis,cis-muconononitrile respectively.



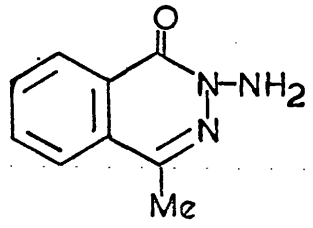


The reaction was later extended to other N-amino triazoles[59,60,62] and also to N-aminonaphtho[1,8-de]triazine.[59]

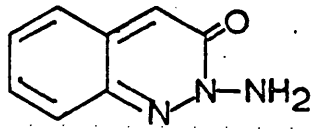


D Oxidation of 2-Aminocinnolin-3-one

Of the N-amino amides discussed above, the structural features of N-aminocinnolinone (23) most closely resemble those of 3-amino-1-methylphthalazin-4-one (102).



(102)



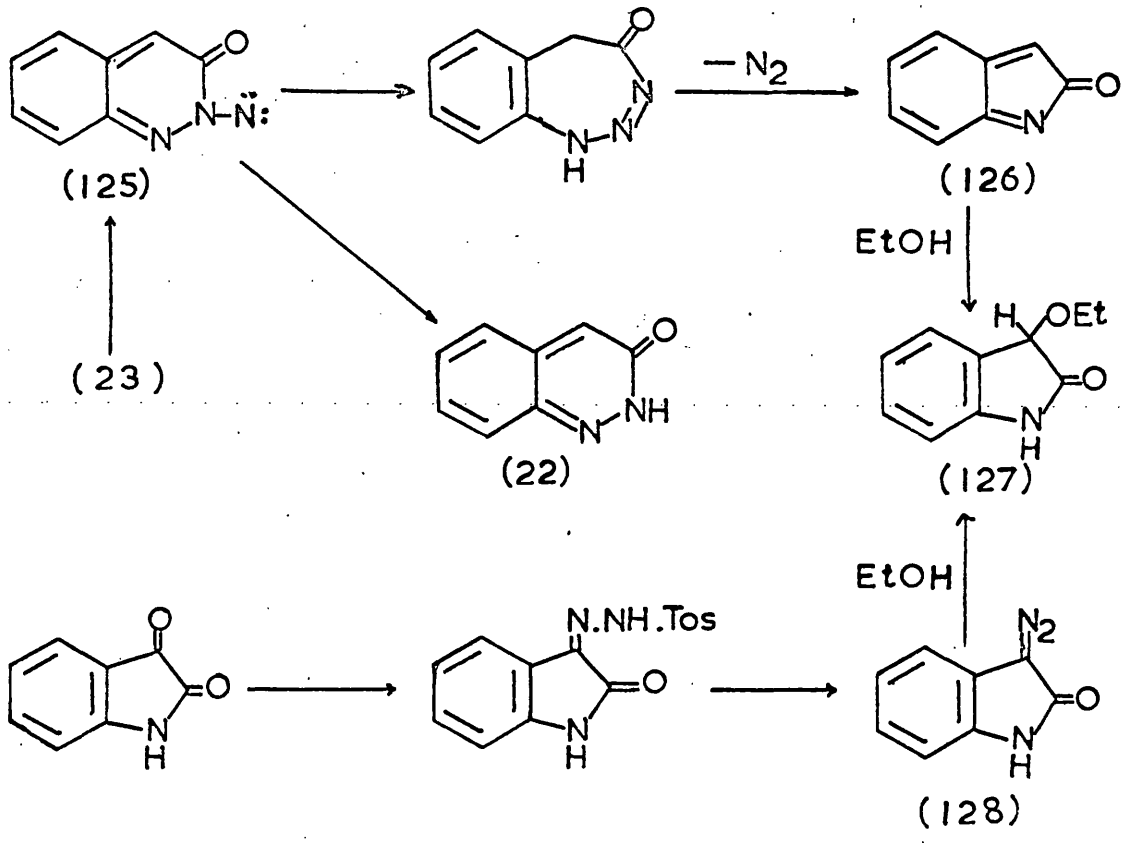
(23)

Both contain a carbonyl group and a ring nitrogen atom adjacent to the N-amino function. As mentioned above, the phthalazinone (102) when oxidised with LTA in the presence of 1,3-butadiene and DMSO did not give aziridine or sulfoximine adducts, but in the presence of ethanol the ethoxyphthalimidine (121) (65%) was formed.[229]

In the present work N-aminocinnolinone (23) was oxidised with LTA in methylene chloride. Nitrogen was evolved and black polymeric material depositied; the filtrate gave cinnolin-3-one (22) (7%). Cinnolinone (17%) was again the only product isolated when the reaction was carried out in the presence of methyl methacrylate. In DMSO a small amount of an unidentified compound (<1%), m.p. 203-206°, m/e: 329 (P) which showed a carbonyl absorption at ν_{max}. 1710 and 1698 $cm.^{-1}$. was obtained, although no cinnolinone (22) could be isolated.

When the oxidation was carried out in a mixture of ethanol and methylene chloride, 3-ethoxyoxindole (127) (1.5%) was obtained as well as cinnolinone (6%). The oxindole (127) was identical in all respects with a sample prepared by reacting 3-diazooxindole

(128) with ethanol according to the method of Creger.[200]

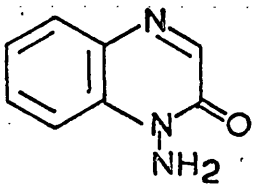


The low yield of the oxindole (127) compared to that of the analogous ethoxyphthalimidine (121) was presumably due to the highly reactive nature of the o-quinonoid intermediate (126) which would polymerise very easily. The phthalimidine (121) also showed some tendency to polymerise.

The aminocinnolinone (23) was also oxidised with the milder oxidant, iodobenzene diacetate in the presence of cyclohexene. No aziridine adduct of the N-nitrene (125) could be obtained and iodobenzene (60%) was the only product isolated.

3 1-AMINOQUINOXALIN-2(1H)-ONE

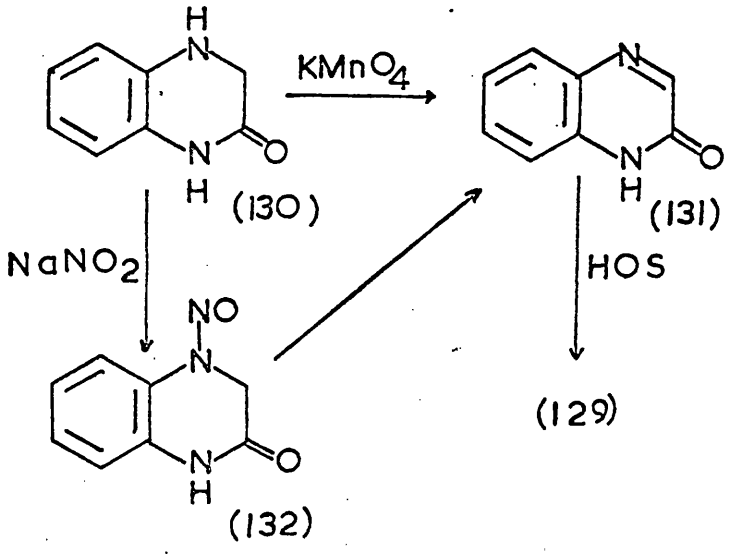
The previous six membered heterocyclic N-amino amides that contained two nitrogen atoms in the same heterocyclic ring (Table 1), either had the nitrogen atoms adjacent to each other or in the 1:3 positions. 1-Aminoquinoxalin-2(1H)-one was therefore of special interest, being the first example in which the nitrogen atoms were in the 1:4 positions.



(129)

A Preparation from quinoxalin-2(1H)-one

Quinoxalin-2-one (131) was prepared by the reaction of o-phenylenediamine with chloroacetic acid in aqueous ammonia, followed by oxidation of the dihydro compound (130) that is formed, either directly with potassium permanganate[204] or via the 4-nitroso compound (132).[203]



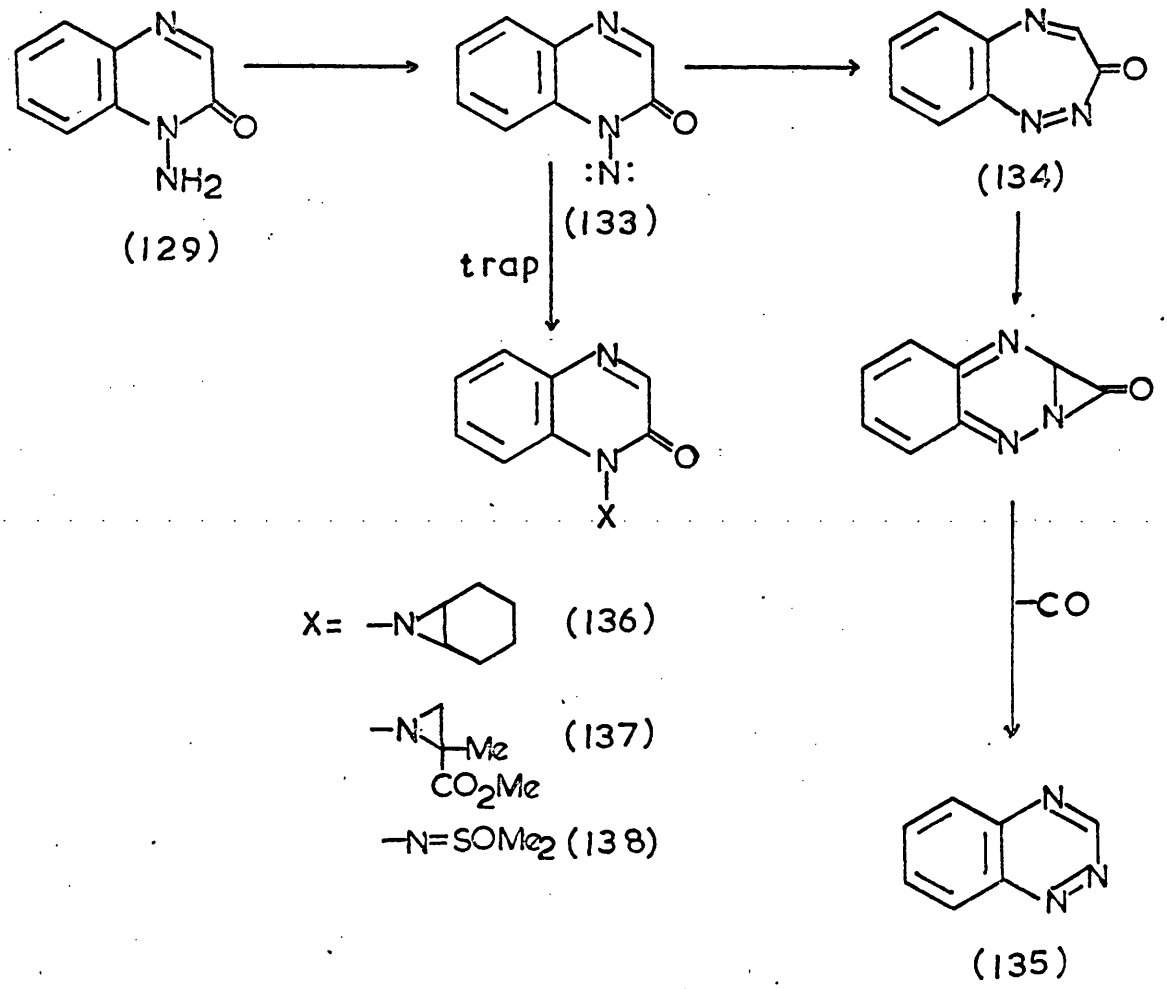
The quinoxalinone (131) could be converted into the N-amino compound (129) (67%) with HOS in aqueous alkali, and unreacted quinoxalinone was also recovered. An increase in concentration of both the HOS and the sodium hydroxide used caused a decrease in the yield of N-amino compound. The sodium salt of the quinoxalinone (131) could not be aminated with ethereal chloramine and the quinoxalinone was recovered unchanged. The N-amino compound (129) and its anisaldehyde derivative were characterised by their analytical and spectral data.

B Oxidation of 1-aminoquinoxalin-2(1H)-one

The structural features of 1-aminoquinoxalin-2-one (129) closely resemble those of 1-aminoquinolin-2-one (97). By analogy, one would expect the N-amino compound to give aziridines when oxidised in the presence of olefins and to deaminate when oxidised alone.[56,229]

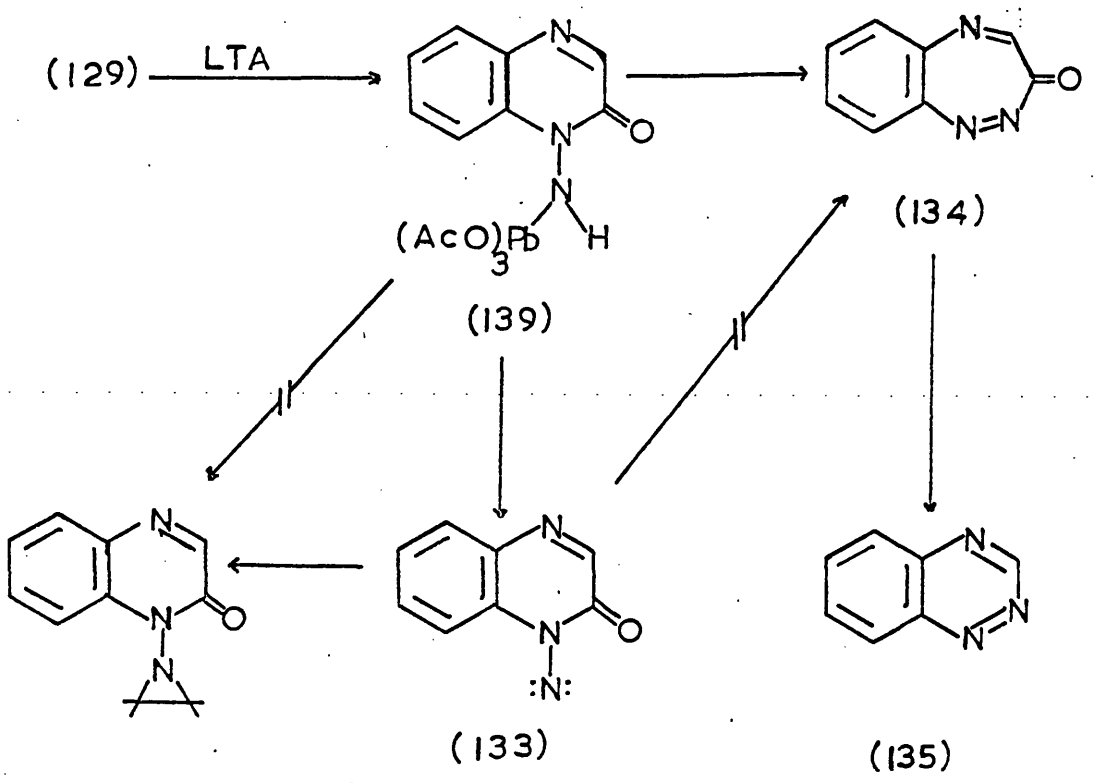
When N-aminoquinoxalinone (129) was oxidised in methylene chloride, the only product that could be isolated was benzo-1,2,4-triazine (135) (18%).[205] In the presence of cyclohexene, oxidation of the N-amino compound (129) gave the aziridine (136) (9%) together with benzo-1,2,4-triazine (13%). The unchanged N-amino compound (129) (5%) was also recovered although excess of LTA was used. This resulted from the formation of a polymeric gum which coated some of the undissolved N-amino compound thereby preventing its oxidation.

An oxidation in methyl methacrylate gave the aziridine (137) (21%) and benzotriazine (10%) and in DMSO gave the sulfoximine (138) (53%) and benzotriazine (9%). No deaminated material could be detected and the following scheme would account for the observed products.



The N-nitrene that is initially formed either reacts intermolecularly with the olefins and DMSO or undergoes an intramolecular rearrangement to give the α-azo-carbonyl intermediate (134) which then undergoes a Cope-type rearrangement followed by extrusion of carbon monoxide to give benzotriazine.

In the limited series of experiments above, the yield of the intermolecular N-nitrene adducts increased with increase in efficiency of the external reagent (9%-53%). However, the yield of benzotriazine (9-18%) remained substantially unchanged. The alternative mechanism shown below is an attempt to rationalise the relatively insensitive variation in the yield of the benzotriazine with change in the external environment.



The "nitrenoid" intermediate (139) would not be trapped with olefins or DMSO and could decompose by two alternative pathways independent of the external environment. The first, a concerted elimination of acetic acid and lead diacetate to give the highly reactive N-nitrene (133) of short, but finite, lifetime. This nitrene could be trapped to some extent by olefins and DMSO, but would not rearrange to the α-azo-carbonyl intermediate (134). The second path would be a concerted elimination and insertion reaction to give the intermediate (134).

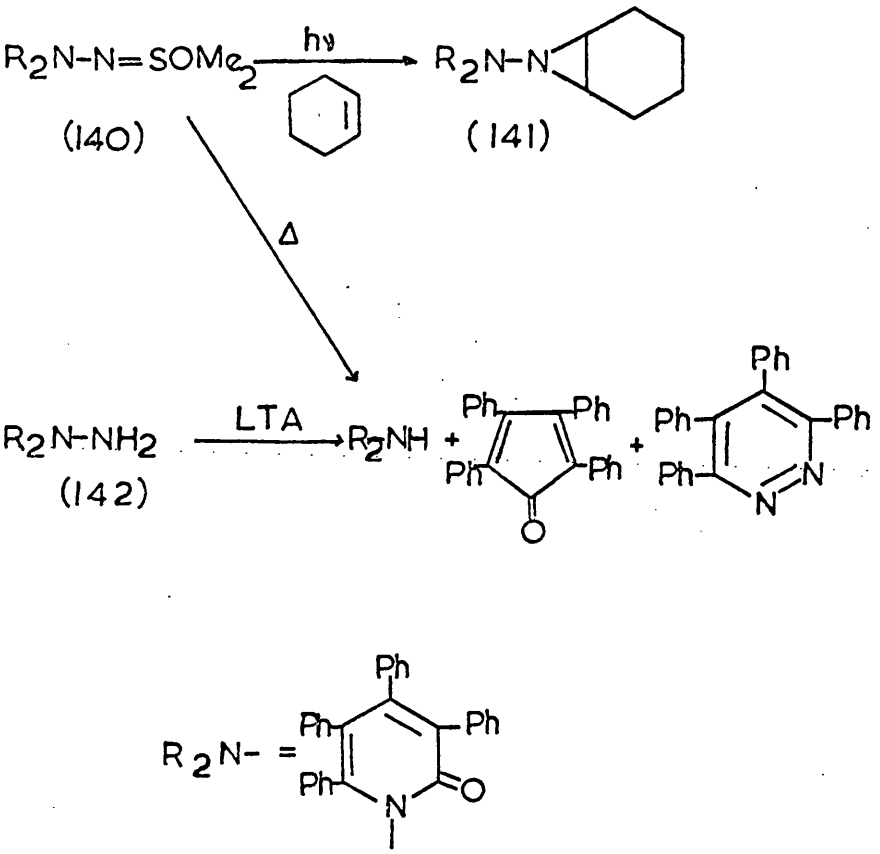
This alternative mechanism was supported to some degree when it was found that the sulfoximine (138) gave the aziridine (136) (30%) when irradiated in cyclohexene. No benzotriazine (135) was detected, however, even though it could be readily recovered in

similar conditions (91%). The sulfoxime (138) was found to be stable at 230° for 30 min. and was largely recovered (70%).

If irradiation of the sulfoximine (138) gave the N-nitrene (133), then in the presence of excess of cyclohexene, the aziridine (136) would be obtained. In the above mechanism it is the nitrenoid (139) and not the N-nitrene (133) that undergoes the ring expansion reaction and therefore benzotriazine should not be obtained.

An objection to this postulate is that the N-nitrene (133) is generated under entirely different conditions. LTA oxidation of the N-aminoquinoxalinone (129) would almost certainly give the singlet nitrene, whereas irradiation of the sulfoximine (138) may generate the triplet diradical nitrene which may well not undergo the ring expansion.

Alternatively, a discreet nitrene may not be formed when the sulfoximine is irradiated, but instead reaction between an excited state of the DMSO adduct (138) and cyclohexene may occur. This postulate was originally suggested by Yelland[58a] to explain why the sulfoximine (140), on irradiation in cyclohexene gave the cyclohexyl aziridine (141) as the only product and in the absence of cyclohexene could be recovered unchanged after 48 hr. Thermolysis of the sulfoximine (140), however, gave the same products as when the N-amino compound (142) was oxidised with LTA.



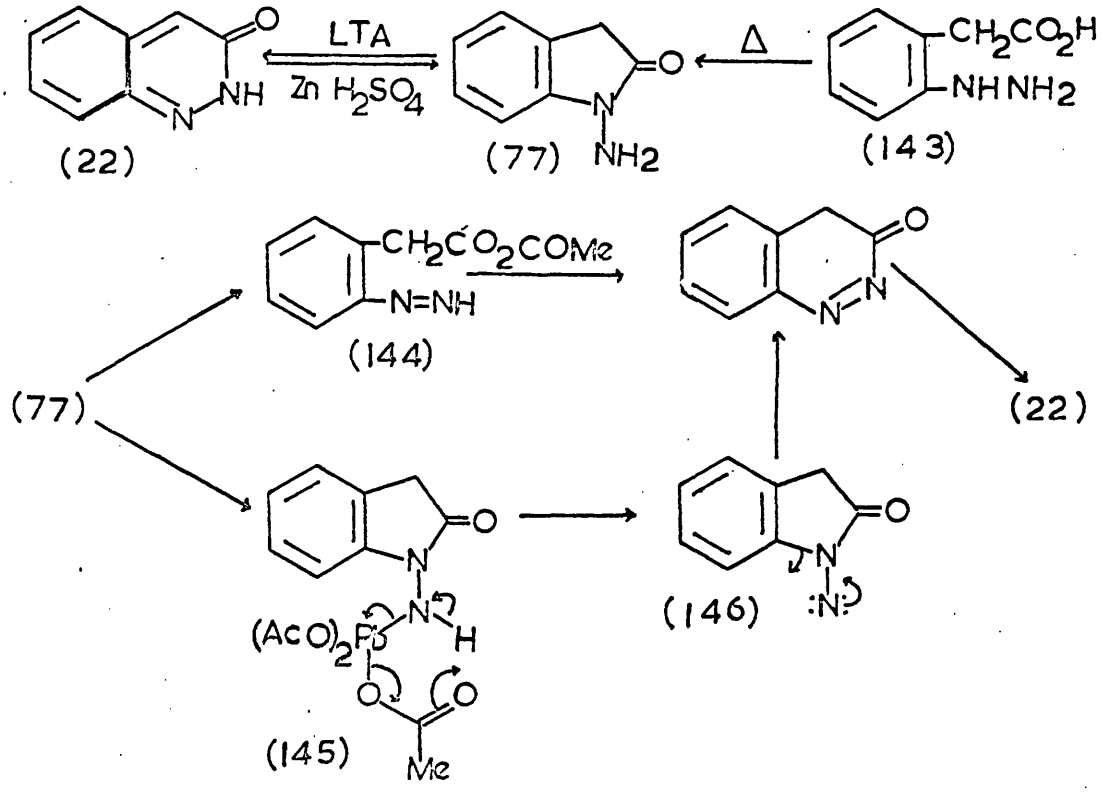
Clearly, further work is required to elucidate this mechanistic problem which is basically a question of whether the lead acetate residue leaves the "nitrenoid" intermediate at the same time or immediately prior to the ring expansion reaction. The main problem still to be solved is the influence of structural factors upon the nature of the reactive intermediate and on its subsequent reactions.

4 N-AMINOOXINDOLES

A 1-Aminooxindole

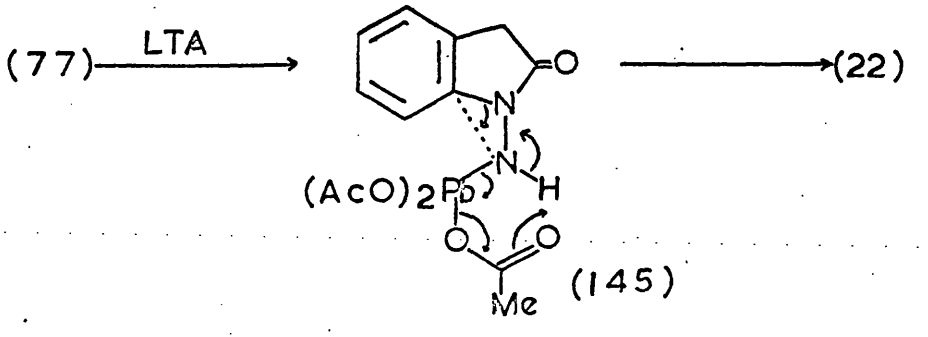
Baumgarten et al.[196b] prepared 1-aminooxindole (77) by zinc and sulfuric acid reduction of cinnolin-3-one (22) and showed that it was identical to the compound prepared by cyclodehydration of o-hydrazinophenylacetic acid (143).

N-Aminooxindole (77) on oxidation with LTA gave cinnolin-3-one.[56,196b] Two mechanisms were originally proposed to explain the ring expansion that occurred. The first involved initial formation of the diimide (144), but in a later paper[56] this was withdrawn because acylation of diimides had never been observed; their more usual reaction was loss of nitrogen to give an arene. The alternative mechanism involved the N-nitrene (146) which ring expanded as shown.



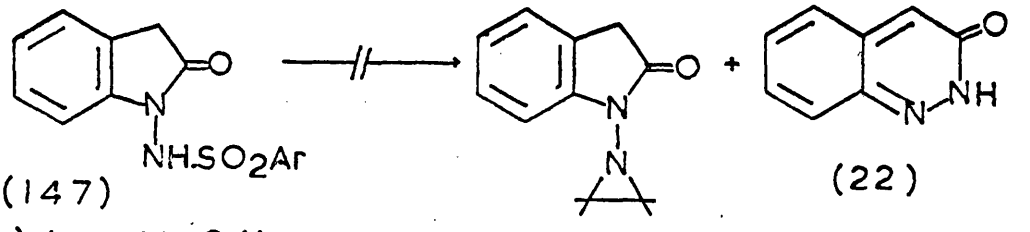
The failure to trap the N-nitrene (146) with 1,3-butadiene or tetracyclone to give the respective aziridines[138] prompted Baumgarten, in a later paper,[56] to suggest that it was perhaps premature to conclude that a nitrene was the intermediate in the oxidation of 1-aminooxindole.

He suggested that the nitrenoid intermediate (145) was the actual intermediate that underwent the ring expansion with more or less simultaneous loss of $Pb(OAc)_3$.



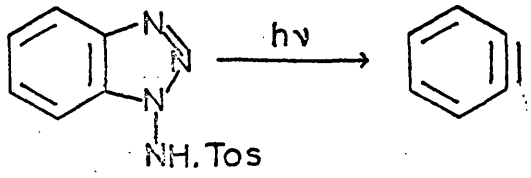
In support of this theory he reported that the arene sulfonamides (147), when subjected to base-catalysed or photochemical treatment of the type used to generate certain acyl nitrenes,[231] failed to give any cinnolin-3-one, and failed to give aziridines in the presence of olefins.

No experimental conditions were given, although it was reported that the conditions were similar to those used by Schlosser[232] in his unsuccessful attempt to generate benzyne from the tosyl derivative of 1-aminobenzotriazole. Graveling[233] has recently shown that irradiation of the sodium or, better, lithium salts of the tosyl derivative (149) do give benzyne, however.



(a) Ar = p-Me.C_6H_4.

(b) Ar = p-NO_2.C_6H_4.

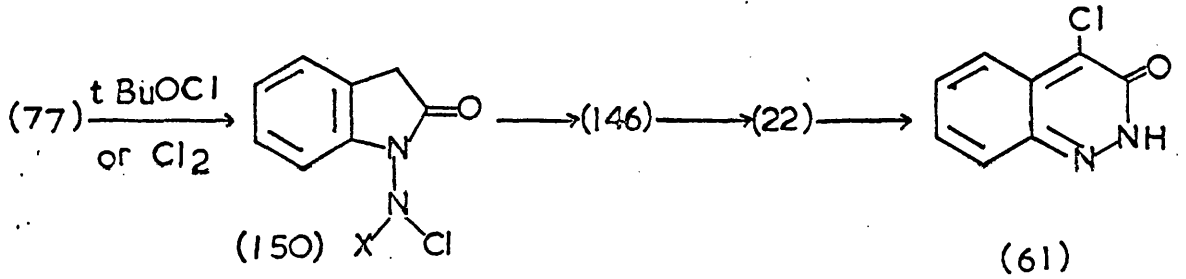


(149)

In the present work we have also used similar conditions to those used successfully by Graveling. The sodium and potassium salts of the tosyl derivative (147a), on irradiation, gave none of the aziridine (148) when the reactions were carried out in the presence of an olefin, and no cinnolin-3-one was detected.

t-Butyl hypochlorite and chlorine were also found to oxidise 1-aminooxindole to cinnolin-3-one, although excess of t-butyl hypochlorite was found to react further to give 4-chlorocinnolin-3-one (61).[56] Mercuric oxide, potassium bromate, bromine and iodosobenzene diacetate (see below) gave either little or no cinnolin-3-one.[56b]

A similar ambiguity existed in the mechanism of the t-butyl hypochlorite and chlorine oxidations. The N-chloramine (150a) and the N,N-dichloramine (150b) are both possible intermediates and could lose hydrogen chloride or chlorine respectively to give the N-nitrene (146) or alternatively they could both act as nitrenoid intermediates.



(150) X = H, Cl

(a) X = H

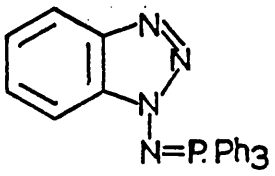
(b) X = Cl

Whittman also prepared the 4-chloro and 6-chloro derivatives of 1-aminooxindole and showed that oxidation with LTA gave the corresponding chlorinated cinnolin-3-ones.

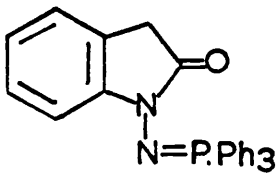
In the present work, the more efficient N-nitrene 'traps', cyclohexene and DMSO were used in an unsuccessful attempt to intercept the N-nitrene of oxindole (146). Cinnolin-3-one was the only product isolated in 60% and 32% yield respectively.

Iodosobenzene diacetate was also used as oxidant in the presence of cyclohexene. No aziridine was formed and iodobenzene (65%) and cinnolin-3-one (66%) were obtained. This is contrary to the report of Baumgarten[56] that little or no cinnolin-3-one is obtained in the complex reaction of 1-aminooxindole with iodosobenzene diacetate.

Graveling[233] has recently found that irradiation of the triphenylphosphineimine (151) in benzene gave benzyne.



(151)



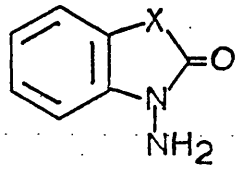
(152)

All attempts to prepare the analogous phosphineimine of 1-aminooxindole (152) failed. Treatment of 1-aminooxindole with triphenylphosphine dibromide gave the unchanged N-amino compound (77) and a mixture of triphenylphosphine and triphenylphosphine oxide. It is possible that the phosphineimine (152) was formed but decomposed on attempted isolation. The preparation was therefore repeated and the reaction mixture was irradiated directly. No cinnolin-3-one was detected, however, and the same three products were again obtained.

N-Aminooxindole could not be prepared by direct amination of oxindole. With HOS at low temperatures oxindole was recovered but as the temperature increased, a red polymeric material was obtained. Chloramine and O-(2,4-dinitrophenyl)hydroxylamine gave the same polymeric material.

B 1-Amino-3-methyloxindole

The results of Atkinson and Rees[138] and those of Baumgarten et al.[56,196b] showed clearly how the nature of X- in the compounds (153)determined the properties of the respective N-amino amides towards oxidation.



(153)

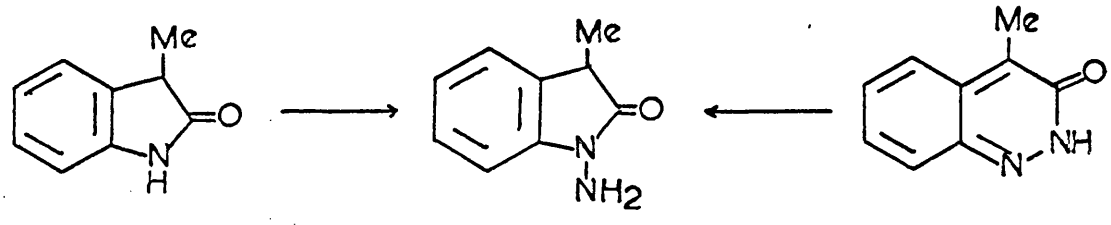
(77) X = CH_2

(78) X = O

Although Whittman[56] had made the 4-chloro and 6-chloro-1-aminoxindoles and showed that their behaviour on oxidation was similar to N-aminooxindole itself, it was thought that a more instructive approach in determining those factors which caused rearrangement could be made with 1-aminooxindoles substituted in the 3-position.

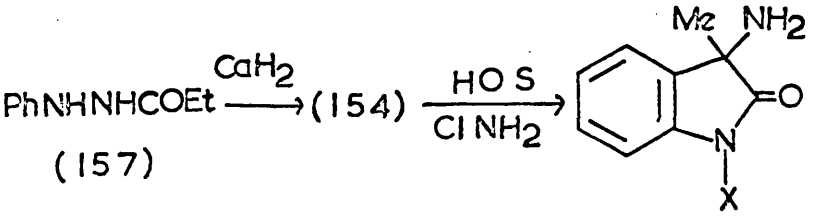
(i) Preparation of 1-amino-3-methyloxindole

Two possible routes to 1-amino-3-methyloxindole (155) appeared feasible. The first was by amination of 3-methyloxindole (154)[206] and the second was by reduction of 4-methylcinnolin-3-one (156).[196a]



(154) (155) (156)

3-Methyloxindole (154) was prepared by the cyclisation of 1-phenyl-2-propionylhydrazine (157) by the method of Endler and Becker. Amination with HOS gave a mixture of two amino compounds that could only be partially separated by column chromatography. One of the compounds was found to be the previously reported 3-amino-3-methyloxindole (158)[207] and was obtained pure. The second, however, could not be entirely freed of the first but analytical and spectral data of the impure compound indicated that it was 1,3-diamino-3-methyloxindole (159) and this was confirmed by preparing the di-anisylidene derivative which could be obtained pure. No 1-amino-3-methyloxindole was isolated although the oxindole (154)(35%) was recovered.



(158) X = H

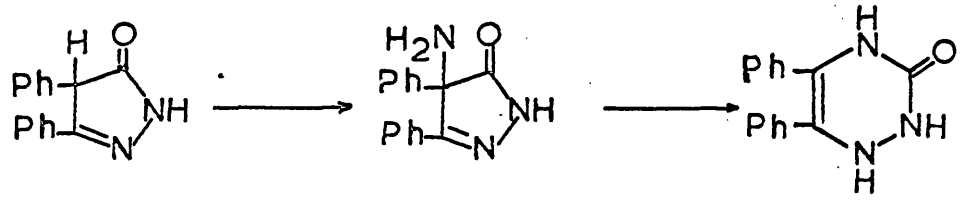
(159) X = NH_2

Chloramine was also found to give the same mixture of amino-oxindoles in high combined yield and the oxindole (154) was recovered in only 5% yield. It is therefore reasonable to expect that oxindole itself would behave in an analogous manner and the failure to obtain any 1-aminooxindole is therefore not surprising.

The amination on carbon, rather than on nitrogen as expected, may be related to the stability of the required benzylic anion. Very few examples of HOS amination of carbanions have been reported. Bargigia and Cambi[176] found that cyanide ions were aminated with HOS to give cyanamide (80%) and Yelland[58a] has postulated C-amination in the ring expansion of the pyrazoline(160) into the dihydrotriazinone

(162) (see Introduction), although the intermediate (161) was not isolated.

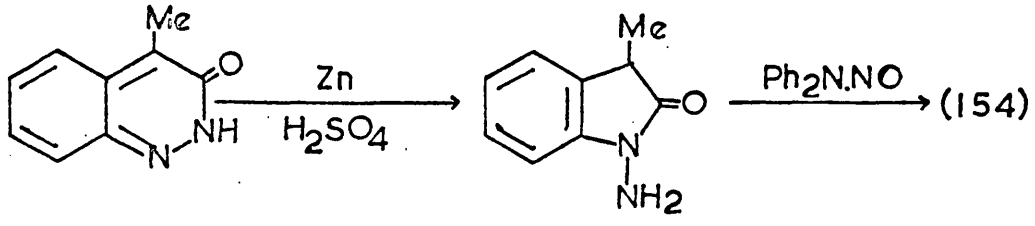
$$NH_2OSO_3H + CN^- \longrightarrow H_2N\text{-}CN$$



(160) (161) (162)

Chloramine, however, has been used more extensively in the amination of carbanions,[50,94,95,96] and recently Sheradsky and Nir[186] have also used O-(2,4-dinitrophenyl)hydroxylamine for the same purpose (see Introduction).

4-Methylcinnolin-3(2H)-one (156) was prepared by the method of Baumgarten et al.[196a] and reduction with zinc and sulfuric acid, using similar conditions as those for the reduction of cinnolin-3-one to 1-aminooxindole,[56] gave 1-amino-3-methyloxindole (155) (90%).



(156) (155)

Analytical and spectral data were consistent with the proposed structure (155) and also of its anisylidene derivative. Further proof of the structure was obtained when it was found that N-nitrosodiphenylamine gave the deaminated 3-methyloxindole (154) (60%).

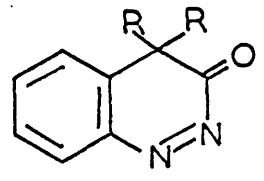
(ii) Oxidation of 1-amino-3-methyloxindole

1-Amino-3-methyloxindole (155) was oxidised with LTA in methylene chloride, alone and in the presence of cyclohexene and DMSO. The only product that could be isolated from these oxidations was 4-methylcinnolin-3(2H)-one (156) in yields of 56%, 60% and 35% respectively.

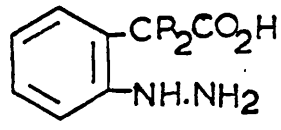
It is apparent that 1-amino-3-methyloxindole behaves in an entirely analogous way to 1-aminooxindole itself and the addition of a mono alkyl substituent in the 3-position does not modify the properties on oxidation.

C 1-Amino-3,3-dimethyloxindole

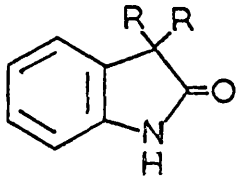
4,4-Disubstituted cinnolin-3-ones (163) have not been reported presumably due to the inherent instability of the α-azo-carbonyl system. An alternative route to 1-amino-3,3-disubstituted oxindoles via the cyclo-dehydration of o-hydrazino-2,2-disubstituted phenylacetic acids (164) appeared equally uninviting. However, 3,3-disubstituted oxindoles (165) do not contain a proton α to the amide carbonyl group and therefore can only be aminated at the nitrogen atom to give the derivatives (166).



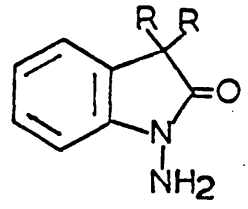
(163)



(164)



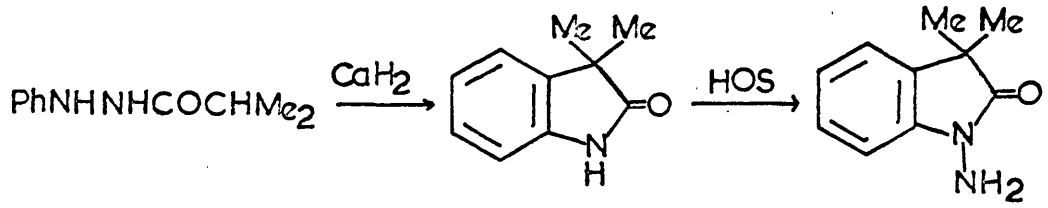
(165)



(166)

(i) Preparation of 1-amino-3,3-dimethyloxindole

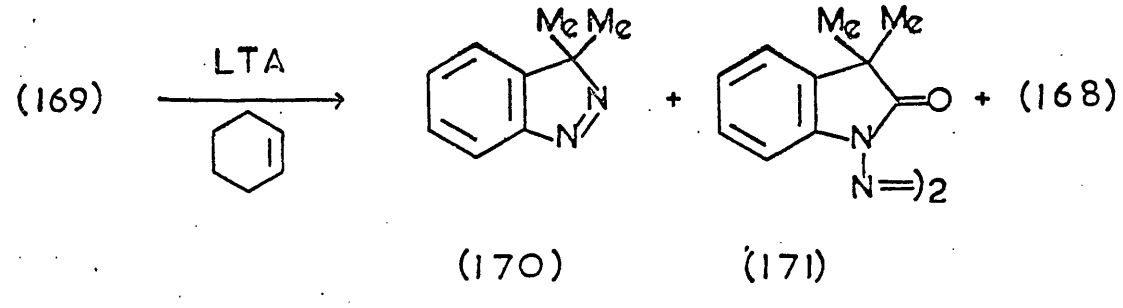
3,3-Dimethyloxindole (168) was prepared by the cyclisation of 2-methylpropionylphenylhydrazide (167) by a modification of the method of Brunner.[234] The dimethyloxindole was insoluble in aqueous alkali but could be aminated to the N-amino compound (169) (98%) with HOS in the presence of ethanol. Analytical and spectral data were in accord with the assigned structure.



(167) (168) (169)

(ii) Oxidation of 1-amino-3,3-dimethyloxindole

1-Amino-3,3-dimethyloxindole (169) gave three products when oxidised with LTA in the presence of cyclohexene; 3,3-dimethylindazole (170) (18%), the tetrazene (171) (1%) and 3,3-dimethyloxindole (168) (26%). The indazole (170) and the tetrazene (171) were characterised by their analytical and spectral data. The tetrazene, on heating to its melting point lost nitrogen to give 3,3-dimethyloxindole (60%).



(170) (171)

The indazole (170) presumably arose by initial ring expansion of the N-nitrene (172) or nitrenoid intermediate to give the 4,4-dimethylcinnolin-3-one (173). The α-azo-carbonyl compounds usually formed undergo a proton migration to give the cinnolin-3-one. This method of stabilisation is not available to 4,4-dimethylcinnolin-3-one (173) and consequently extrusion of carbon monoxide occurs to give the indazole (170).

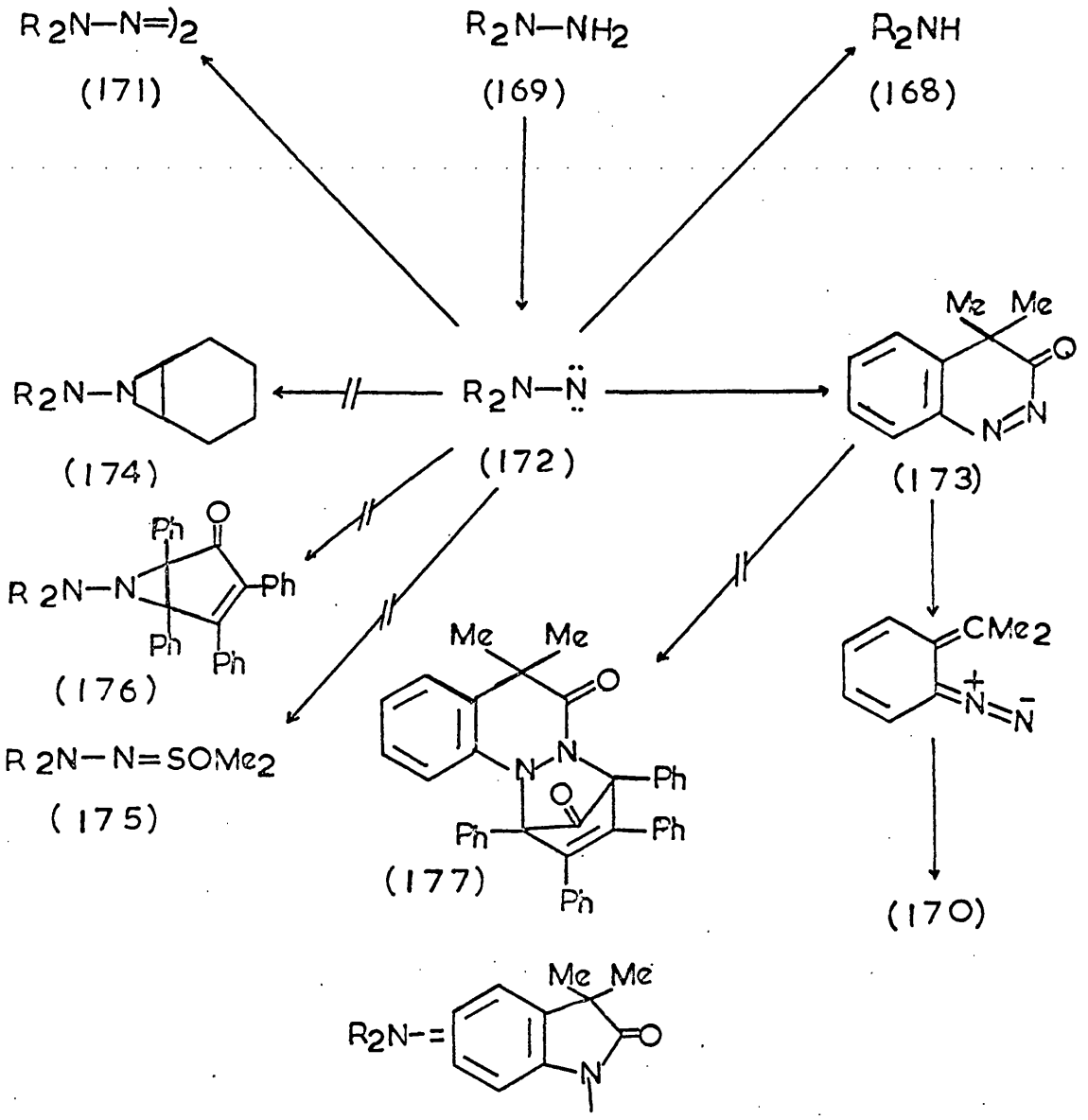
The formation of the tetrazene (171) and the oxindole (168) was unexpected in view of the previous behaviour of N-aminooxindoles (77) and (155). It is also unusual in that previously all N-amino-amides, that had formed a tetrazene or had deaminated on oxidation, also gave aziridine adducts when oxidised in the presence of olefins.

When oxidised in the presence of tetracyclone the indazole (170) (20%) and the oxindole (168) (26%) were obtained together with unchanged tetracyclone (96%). None of the aziridine (176) was obtained and the tetracyclone also failed to intercept the intermediate α-azo carbonyl compound (173).

DMSO has been found to be the most efficient 'trap' for N-nitrenes in our Laboratories. Oxidation of the oxindole (169) in DMSO gave none of the sulfoximine (175), however, and the tetrazene (171) (1.8%) and 3,3-dimethyloxindole (7%) together with a trace of the indazole (170) (t.l.c.) were obtained. When the method of work up was changed from removing the excess of DMSO under reduced pressure to pouring the reaction mixture into water, the only product that could be isolated was 3,3-dimethyloxindole (26%).

An oxidation using iodoso benzene diacetate in the presence of cyclohexene gave a cleaner reaction with only a small amount of tar formed. Although none of the aziridine (174) or the indazole (170) was isolated, increased yields of the tetrazene (171) (7.5%) and 3,3-dimethyloxindole (57%) were obtained together with iodobenzene

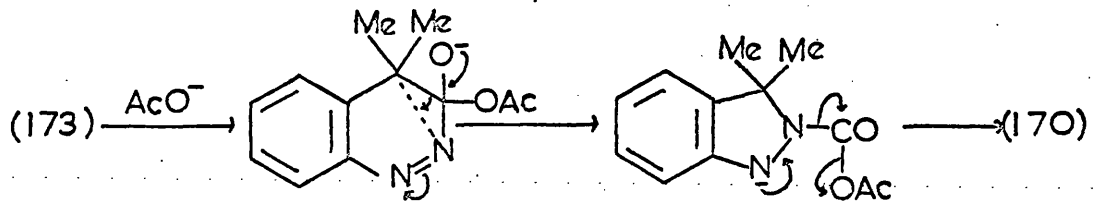
(55%). A summary of the oxidation reactions is given below (Scheme 10).



Scheme 10

The failure of olefins and DMSO to intercept the N-nitrene (172) is rather surprising in view of the fact that a tetrazene was formed and deamination occurred on oxidation. However, it is possible that a nitrenoid intermediate leads to these products and not a nitrene as

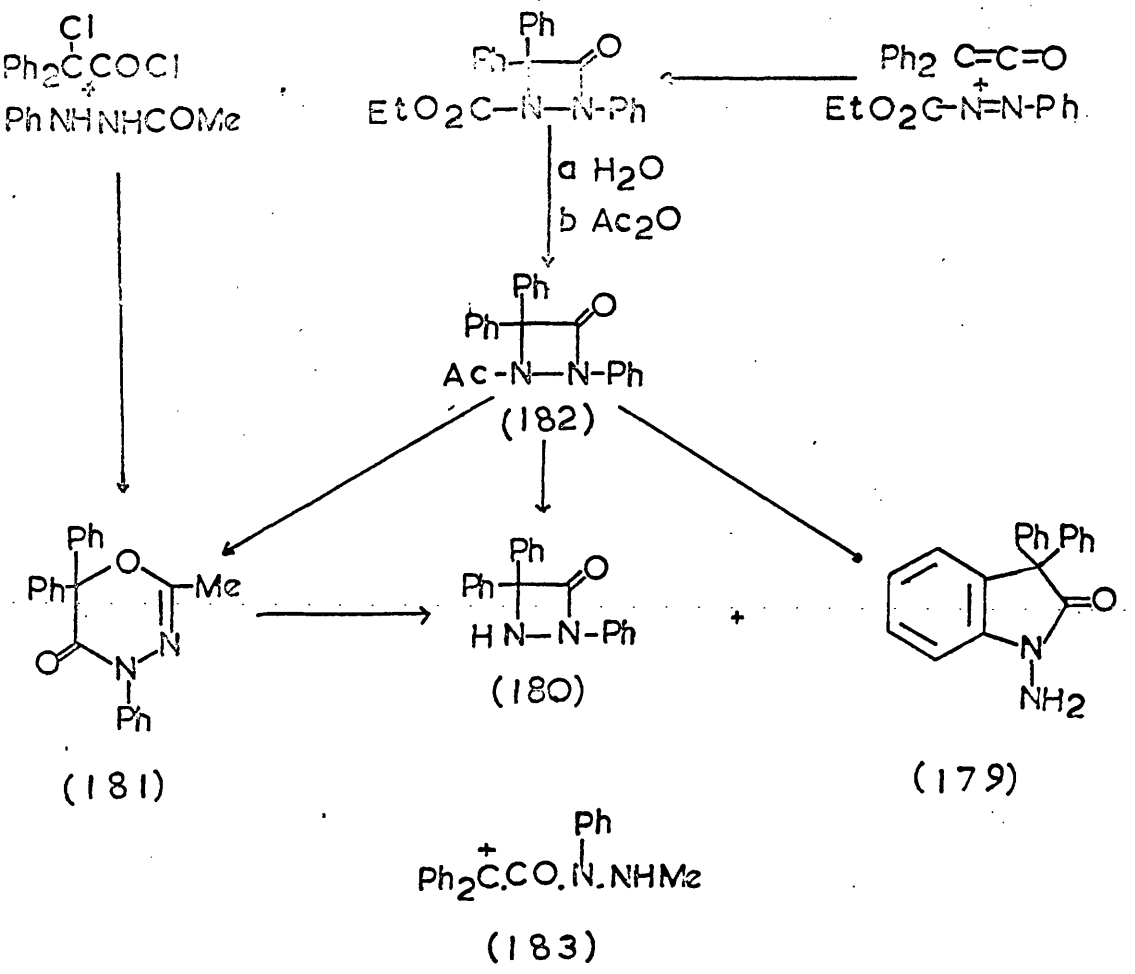
has originally been supposed. That the cinnolinone (173) was not intercepted by tetracyclone to give the Diels-Alder adduct (177) is somewhat puzzling, and may be due to its very rapid reaction with acetate ions:



An attempt was made to add benzyne to dimethyldiazomethane in order to synthesise the 3,3-dimethylindazole independently. 1-Aminobenzotriazole was oxidised in the presence of acetone hydrazone but this gave biphenylene (38%) and phenyl acetate (11%) and none of the required indazole.

D 1-Amino-3,3-diphenyloxindole

1-Amino-3,3-diphenyloxindole was originally prepared by Bird.[210] Acid treatment of the oxadiazinone (181) gave a mixture of the N-aminooxindole (179) and the diazetidinone (180) as well as unreacted oxadiazinone (181). The mixture could also be obtained by acid treatment of the acetyl diazetidinone (182). The products were rationalised as being obtained from the carbonium ion (183).



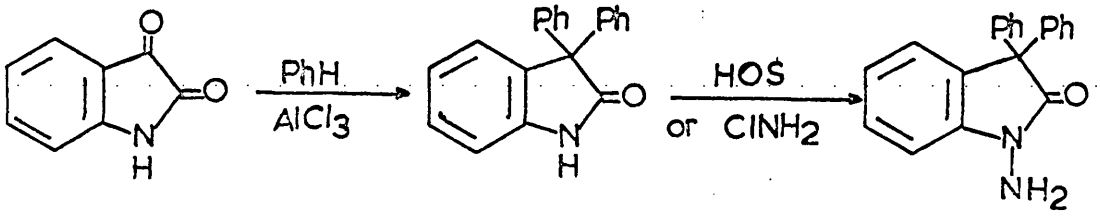
The N-aminooxindole (179) was characterised by its analytical and spectral data and also as its benzylidene derivative. Final proof of the structure (179) was supplied by the conversion into 3,3-diphenyloxindole (184) on treatment with nitrous acid. The overall yield of the N-amino compound (179) was very low and the following alternative route by direct amination of the oxindole (184) was now found to give excellent yields of the N-amino compound (179).

(i) Preparation of 1-amino-3,3-diphenyloxindole

3,3-Diphenyloxindole (184) was prepared by the Friedel-Crafts reaction of isatin (185) with benzene in the presence of aluminium chloride.[209] Amination of (184) with HOS in aqueous ethanolic sodium hydroxide gave the N-amino compound (179) (97%). The ethanol was required in order to make the reaction mixture homogeneous, and its omission resulted in quantitative recovery of the oxindole (184).

The N-amino oxindole (179) obtained by this method was identical in all respects with a sample prepared by the method of Bird.[210]

The sodium salt of the oxindole could also be aminated with ethereal chloramine. Optimum yields of the N-amino compound (179) (87%) were obtained when the ratio of oxindole (184):chloramine was 1:2.



(185) (184) (179)

(ii) Oxidation of 1-amino-3,3-diphenyloxindole

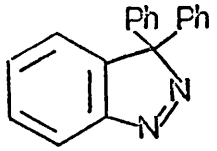
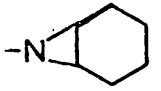
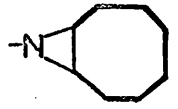
The products obtained when 1-amino-3,3-diphenyloxindole was oxidised under a variety of conditions are shown in Table 2.

1-Amino-3,3-diphenyloxindole (179) showed similar behaviour to the dimethyl compound (169) in that they both formed indazoles and gave rather erratic amounts of colourless tetrazenes. The colourless tetrazene (186) was also found to lose nitrogen at its melting point to give the oxindole (184).

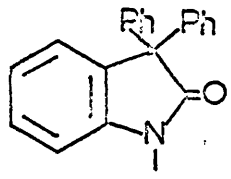
There the comparison ends, however. No oxindole (184) due to the deamination of (179) was ever detected and instead, a yellow isomeric tetrazene (186) (in erratic, but high yields whenever it was isolated), and products due to the interception of the N-nitrene (188) with olefins and sulfoxides were obtained. The analytical and spectral data were satisfactory for all the new compounds reported in Table 2.

Table 2

OXIDATION OF 1-AMINO-3,3-DIPHENYLOXINDOLE

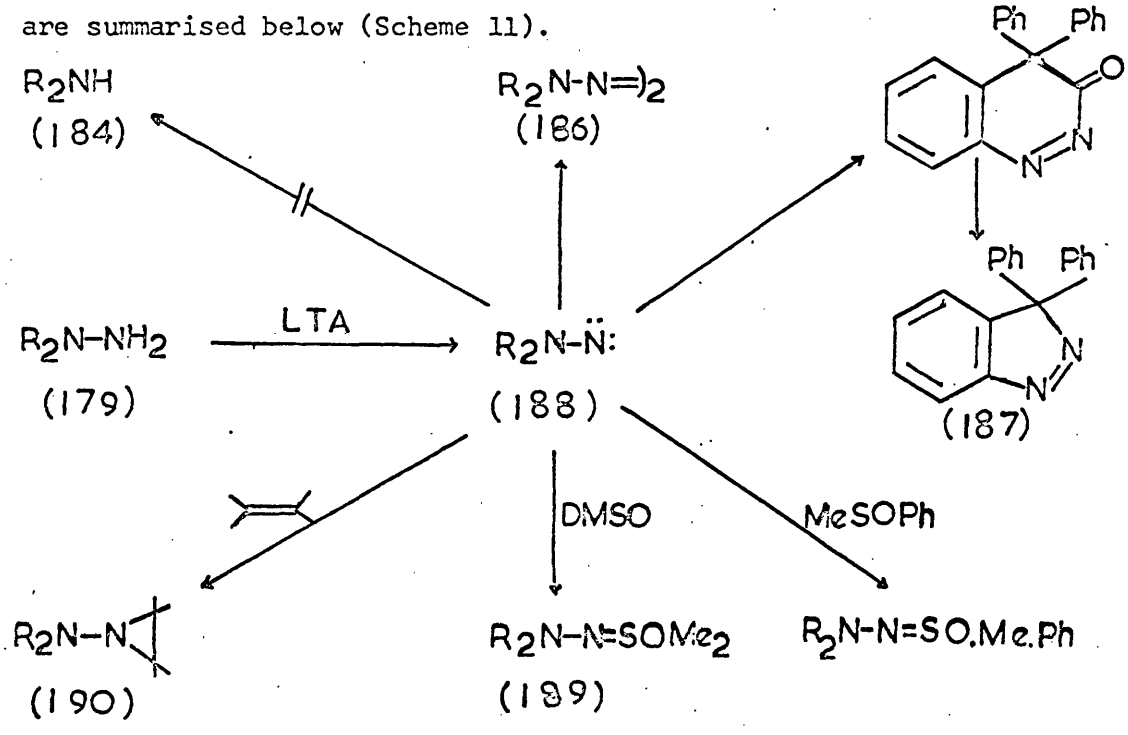
Solvent	Trap		Yield of Products (%) $R_2N-N=N-NR_2$ (1)		Nitrene adducts R_2N-
			Yellow	Colourless	
1) Et_2O	-	18	32	-	-
2) PhH	-	30	18	-	-
3) CH_2Cl_2	- -	30	47	2.5	-
4) CH_2Cl_2	cyclohexene	(?) (2)	25	-	 (?) (2)
5) CH_2Cl_2	cyclooctene	20	-	-	 (32)
6) CH_2Cl_2	$CH_2=C(Me)CO_2Me$	7.5	-	0.7	 (16)
7) -	$CH_2=C(Me)CO_2Me$	3	-	-	(46)
8) -	MePhSO	-	-	-	-N=SOMePh (58)
9) -	DMSO	-	-	-	$-N=SOMe_2$ (73)

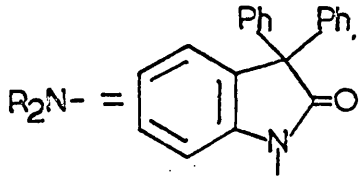
Notes to Table 2

1. R_2N- represents 

2. A mixture was obtained that could be partially separated by fractional crystallisation.

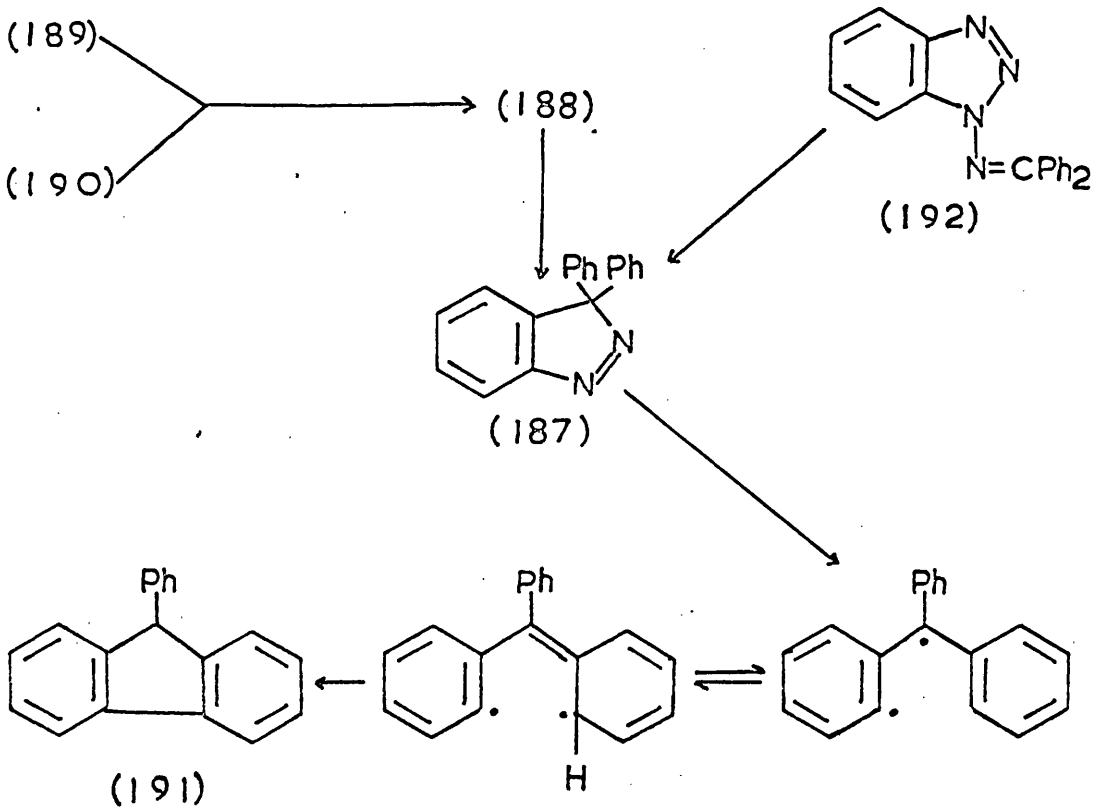
It can be seen from Table 2, that to a reasonable approximation, the yield of 'nitrene adducts' increases with an increase in efficiency of the trapping reagent and that there is also a corresponding drop in the yields of the indazole (187). It seems reasonable to suggest, therefore, that the same intermediate gives rise to both sets of products, and that the intramolecular reactions of the N-nitrene (188) competes effectively with the intermolecular formation of the indazole (187). The reactions of the oxindole (179) on oxidation are summarised below (Scheme 11).





Scheme 11

In order to test this theory, the dimethylsulfoximine (189) wasirradiated in the presence of cyclohexene. If the N-nitrene (188) was a common intermediate then both the aziridine (190) and the indazole (187) should have been obtained. The only product that could be isolated, however, was 9-phenylfluorene (191) (55%). Under similar conditions it was found that both the aziridine (190) and the indazole (187) gave 9-phenylfluorene in yields of 59% and 41% respectively. It would appear that both the DMSO adduct (189) and the cyclohexyl aziridine (190) on irradiation undergo fission to the N-nitrene (188), which then forms the indazole (187), before losing nitrogen to give 9-phenylfluorene as indicated below (Scheme 12).



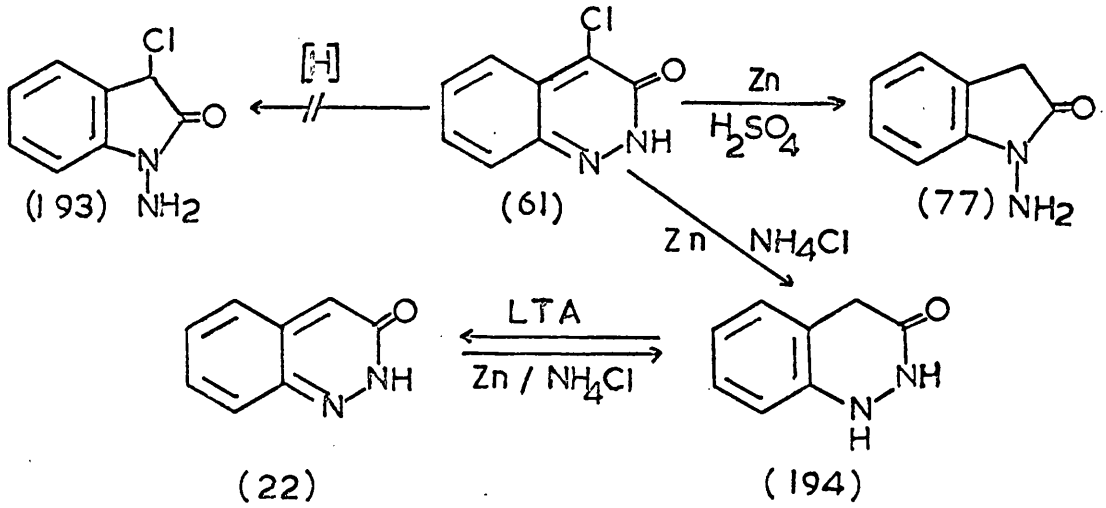
Scheme 12

Burgess et al.[235] also obtained 9-phenylfluorene (191) when the triazole (192) was irradiated in acetonitrile. The indazole (187) was postulated as the intermediate.

Ried[236] has added benzyne to several substituted diazomethanes and obtained the corresponding indazoles. We have found that addition of benzyne to diphenyldiazomethane gave the 3,3-diphenyl-indazole (187) identical in all respects to a specimen prepared by oxidation of the oxindole (179).

E 1,4-Dihydrocinnolin-3(2H)-one

In an attempt to prepare 1-amino-3-chlorooxindole (193), Whittman[56] reduced 4-chlorocinnolin-3-one (61). The zinc and sulfuric acid conditions that were used were too vigorous however and fission of the C-Cl bond also occurred to give 1-aminooxindole (77).



It was hoped that use of a milder reducing agent would prevent C-Cl bond fission and give the chlorooxindole (193). Zinc and aqueous ethanolic ammonium chloride[237] gave a compound (88%) that contained no chlorine and had a m.p. higher than that reported for N-aminooxindole. Oxidation with LTA gave cinnolin-3-one (22) (84%) and spectroscopic and analytical data suggested that the compound was

an isomer of N-aminooxindole, the dihydrocinnolin-3-one (194). Confirmation was obtained when it was found that cinnolin-3-one gave the same compound (194) (100%) under similar reduction conditions.

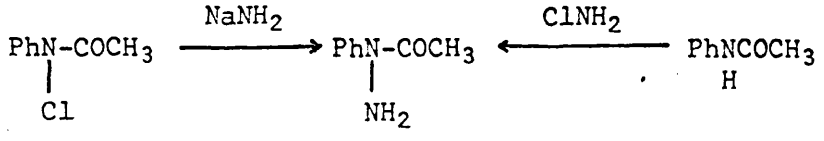
Cinnolin-3-one can also be reduced to the dihydrocompound (194) under electrolytic conditions. Lund[212] reported the compound (194) as an unstable solid that was readily oxidised back to cinnolinone on standing; he gave no analytical figures.

When pure, the dihydrocinnolinone (194) is stable for several days at room temperature, and can be kept unchanged for weeks when stored under dry nitrogen.

5 N-AMINOACETANILIDE

N-Aminoacetanilide (81) is the acyclic equivalent of 1-amino-oxindole and it was therefore of interest to compare their respective properties on oxidation.

N-Aminoacetanilide (81) was originally prepared by the reaction of N-chloroacetanilide with sodamide.[238] Sternbach later[57] used chloramine in dry DMF to aminate acetanilide directly. In the present work, methylene chloride was found to be just as effective a solvent and had the added advantage of an easier method of work up. Somewhat surprisingly, attempts to aminate acetanilide using HOS, over a wide range of conditions, failed and the acetanilide was always recovered quantitatively.



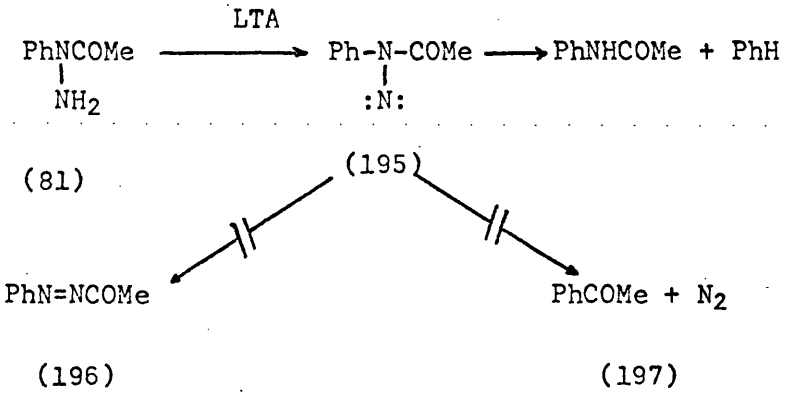
(81)

Baumgarten[196b] originally oxidised N-aminoacetanilide with LTA and reported that rather erratic yields of benzene were obtained. No other products were detected and the reaction was thought to proceed via phenyldiimide (199) which then lost nitrogen to give benzene. No mechanism for the formation of phenyldiimide was suggested.

In the present work it was decided to reinvestigate the reaction of N-aminoacetanilide with a view to try to intercept the intermediate N-nitrene (195). No attempt was made to estimate the amount of benzene produced.

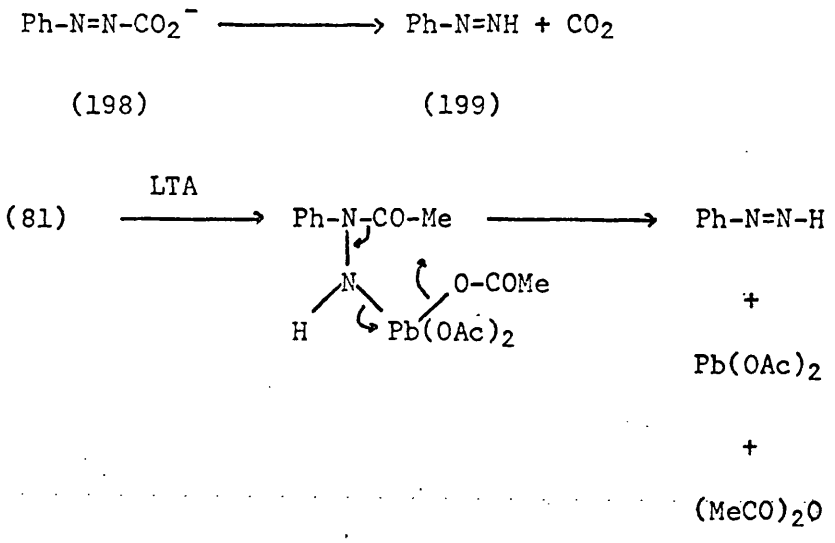
N-Aminoacetanilide, when oxidised in the presence of cyclo-hexene, methyl methacrylate or DMSO, gave acetanilide as the only

product that could be isolated, in yields of 22%, 3% and 6.5% respectively. In all reactions, a vigorous evolution of nitrogen was observed and no acetophenone (197) was detected. The concerted elimination of nitrogen with recombination of the two fragments was therefore eliminated.



1-Acetyl-2-phenylhydrazine[213] when oxidised with excess of LTA gave the diimide (196) which was identical in all respects with a sample prepared by the method of Book et al.[214] The diimide (196) was found to be stable towards excess of LTA and was not detected when N-aminoacetanilide was oxidised, therefore eliminating an analogous reaction to that which occurs when 1-aminooxindole is oxidised.

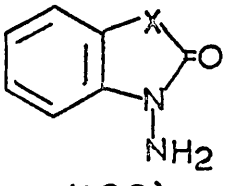
The original mechanism proposed by Baumgarten, via phenyldiimide (199), would appear to be correct. In support of his mechanism Kosower has shown that phenyldiimide when generated by decarboxylation of the phenyldiazene carboxylate anion (198) decomposes to benzene in variable yield. The diimide can be detected in acetonitrile solution spectroscopically and in the presence of oxygen it rapidly decomposes. A possible mechanism for formation of phenyldiimide is shown below.



Although (81) is structurally similar to 1-aminooxindole, there appears to be little similarity in their properties towards oxidation. It would be of interest, however, to see if modification of the methyl group in (81) caused any variation in the oxidation reactions of these acyclic N-aminoamides.

6 1-AMINOBENZIMIDAZOLIN-2-ONES

No reasonable explanation has been given for the difference in behaviour of N-aminobenzoxazolinone (89) and the various 3-substituted N-aminooxindoles (Section 4) towards oxidation under similar conditions. It was therefore of interest to extend the range of N-amino compounds, differing in structure in the nature of X (200), to include 1-amino-3-substituted benzimidazolin-2-ones (201) and study their reactions on oxidation.



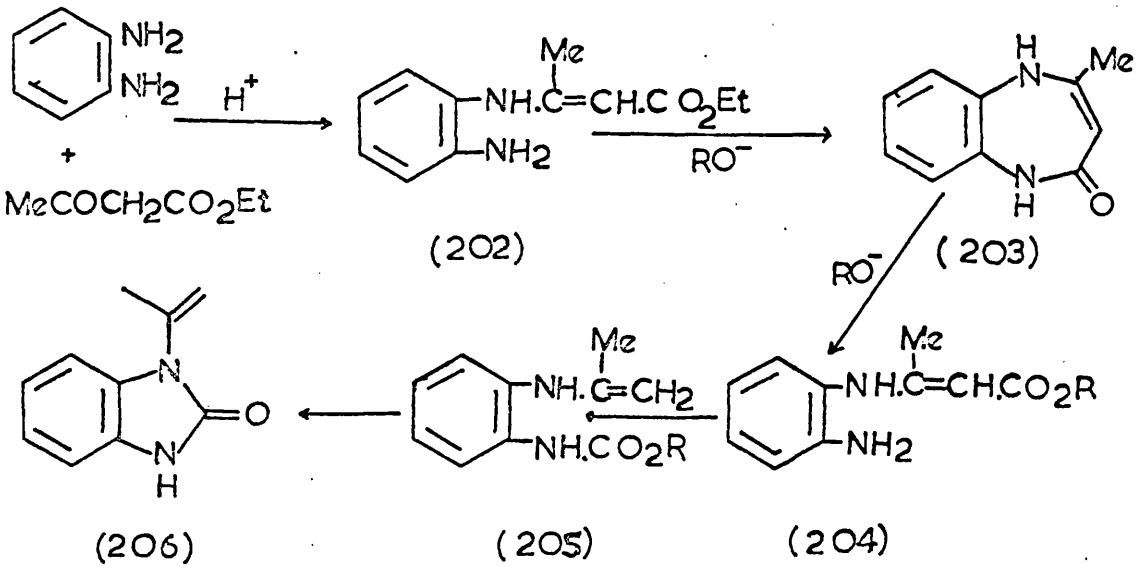
(200)

X =		
	O	(89)
	CH_2	(77)
	CHMe	(155)
	CMe_2	(169)
	CPh_2	(179)
	NR	(201)

A 1-Amino-3-isopropenylbenzimidazolin-2-one

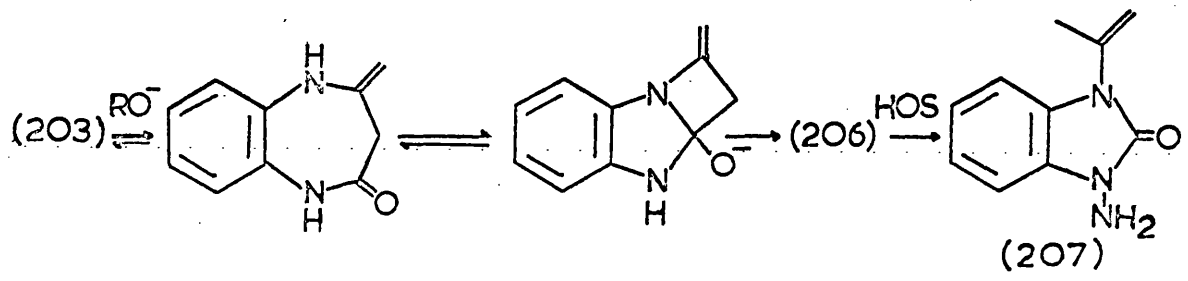
(i) Preparation from 1-isopropenylbenzimidazolin-2-one

1-Isopropenylbenzimidazolin-2-one (206) was prepared by cyclisation of the crotonate (202) with sodium 2-ethoxyethoxide in 2-ethoxyethanol. Davoll[190] proposed the following reaction scheme.



(202) (203) (204) (205) (206)

No mechanism was suggested for the conversion of the intermediates (204) into (205) and a more plausible reaction scheme from the diazepine (203) to the isopropenylbenzimidazolinone (206) is shown below.

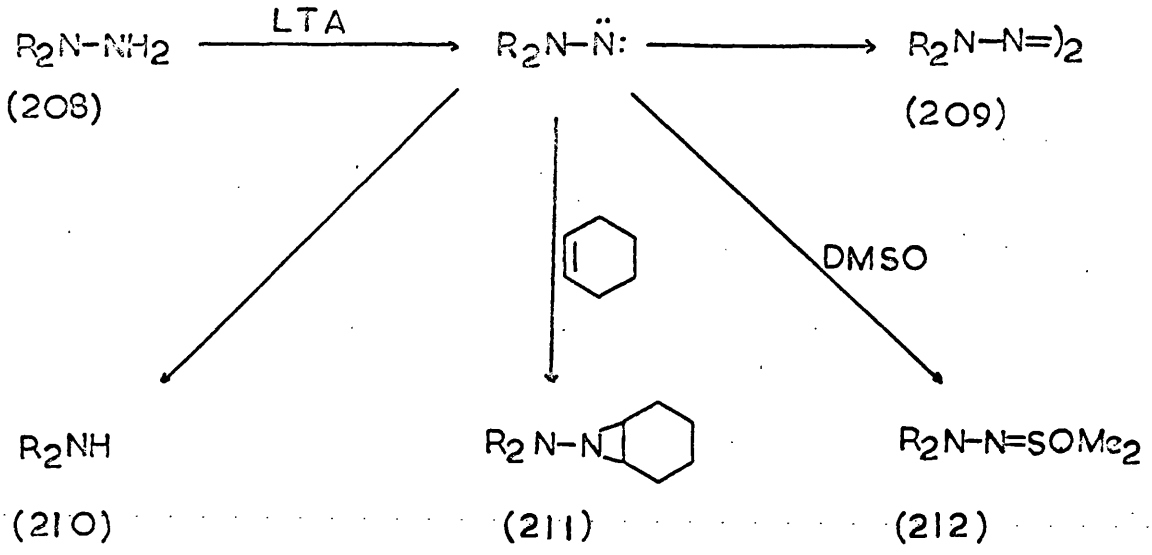


[R = $EtOCH_2CH_2$ - in both schemes]

The benzimidazolinone (203) was aminated with HOS in aqueous sodium hydroxide to give the N-amino compound (207) (90%). 1-Amino-3-isopropenylbenzimidazolin-2-one could also be obtained, although in poor yield, by the amination of the sodium salt of (206) with ethereal chloramine. Analytical and spectral data were in agreement with the assigned structure.

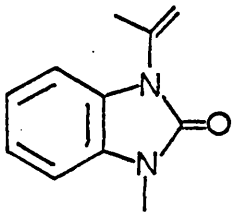
(ii) Oxidation of 1-amino-3-isopropenylbenzimidazolin-2-one

Oxidation of 1-amino-3-isopropenylbenzimidazolin-2-one (208A) with LTA in methylene chloride gave the tetrazene (209A) (32%). In the presence of cyclohexene, the tetrazene (34%) was obtained together with the aziridine (211A) (14%). When the reaction was carried out in DMSO, the tetrazene was obtained only in trace yield together with the benzimidazolinone (210A) (4.5%) and the unstable sulfoximine (212A) (34%). The results are summarised below in Scheme 13 .



Scheme 13

A. R_2N- =



It is apparent that the results are basically similar to those obtained when N-aminobenzoxazolinone (89) was oxidised. Surprisingly however, a relatively high yield of the tetrazene (209A) was obtained even in the presence of cyclohexene. The tetrazene was found to decompose at its melting point to give the benzimidazolinone (210A) and irradiation in ethyl acetate also gave the benzimidazolinone (210A) (88%).

The sulfoximine (212A) was obtained as an unstable oil that readily polymerised on standing. The compound was found to be stable under dry nitrogen, however, and when irradiated for 44 hr. in the presence of cyclohexene the aziridine (211A) (15%) and the benzimidazolinone (210A) (25%) were obtained together with recovered sulfoximine (212A) (11%). The substantial yield of the benzimidazolinone is possibly due to initial formation of the tetrazene (209A) which then underwent subsequent decomposition.

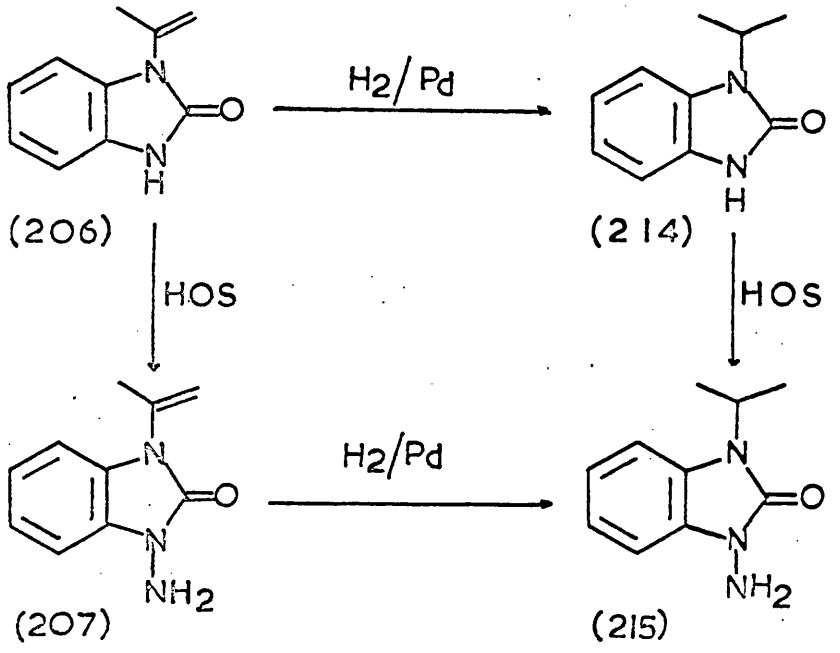
The failure to obtain the benzimidazolinone from the oxidations, except in the presence of DMSO, was probably due to the formation of lead salts of the benzimidazolinone. Indeed, when 1-isopropenylbenzimidazolinone was oxidised under similar conditions only 12% could be recovered.

The reactions were also accompanied by large amounts of polymeric material. It was thought that the reactivity of the enamine residue could well have been responsible and consequently other members of the 1-amino-3-substituted benzimidazolin-2-one series, not containing other functional groups, were prepared.

B 1-Amino-3-isopropylbenzimidazolin-2-one

(i) Preparation of 1-amino-3-isopropylbenzimidazolin-2-one

The N-amino compound could easily be prepared either from the N-amino compound (207) (73%) by catalytic reduction, or by direct amination of 1-isopropylbenzimidazolin-2-one (214) (95%) as indicated below. Initial amination followed by reduction was found to give the cleaner product.

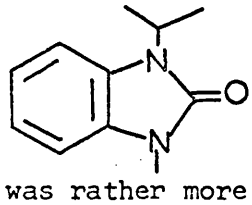


(ii) Oxidation of 1-amino-3-isopropylbenzimidazolin-2-one

The oxidations attempted were very similar to those described in the preceding Section, and the products obtained were basically the same. When the N-amino compound (208B) was oxidised in ether, the tetrazene (209B) (26%) and the benzimidazolinone (210B) (41%) were obtained. When methylene chloride was used, however, the tetrazene was isolated in 83% yield.

Oxidation of (208B) in the presence of cyclohexene gave the tetrazene (209B) (7%), together with the benzimidazolinone (210B) (30%) and the aziridine (211B) (44%). When DMSO was used, the sulfoximine (212B) (60%) was the major product although deamination to the benzimidazolinone (210B) (9%) also occurred and a trace of the tetrazene (209B) was isolated.

The reactions are summarised in Scheme 13 .

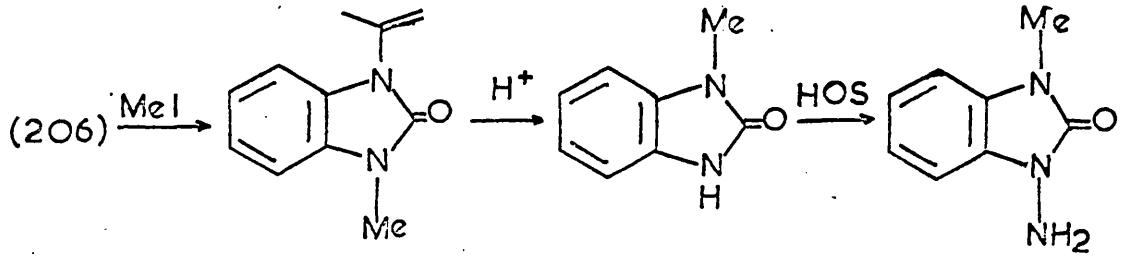
B. $R_2N-=$ 

The sulfoximine (212B) was rather more stable than its counterpart (212A) and showed similar behaviour when irradiated in the presence of cyclohexene. After a reaction time of 94 hr. the benzimidazolinone (210B) (84%) and the aziridine adduct (211B) (9%) were obtained. When the reaction time was reduced to 17 hr., however, the yield of aziridine (211B) increased to 15%. The benzimidazolinone (210B) (20%) and unchanged sulfoximine (212B) (37%) were also isolated. It would appear that the aziridine (211B) on prolonged irradiation also decomposes to the benzimidazolinone.

C 1-Amino-3-methylbenzimidazolin-2-one

(i) Preparation from 1-methylbenzimidazolin-2-one

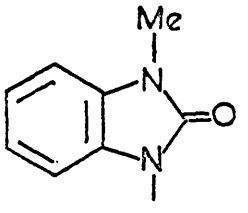
1-Methylbenzimidazolin-2-one (217) was prepared by methylation of the isopropenyl compound (206) followed by hydrolysis of the intermediate (216) according to the method of Davoll.[190] HOS amination of (217) gave the corresponding 1-amino-3-methylbenzimidazolin-2-one (218) (57%). Sodium hydroxide was found to be necessary for the amination to occur; it failed when sodium carbonate was used as the base. Chloramine also gave the N-amino compound (218) in low yield.



(216) (217) (218)

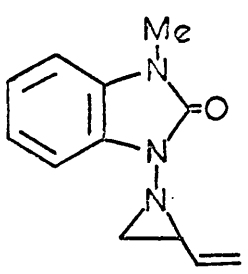
(ii) Oxidation of 1-amino-3-methylbenzimidazolin-2-one

The products obtained on oxidation of 1-amino-3-methylbenzimidazolin-2-one (208C) are directly analogous to those obtained from the corresponding isopropenyl and isopropyl compound and are summarised in Scheme 13 .

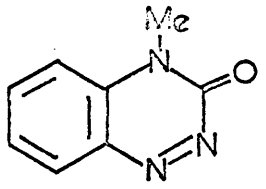
C. $R_2N-=$ 

1,3-Butadiene failed to intercept the N-nitrene, however, and none of the expected aziridine (219) was formed. The tetrazene (209C) (24%) together with the benzimidazolinone (210C) (16%) were obtained. Cyclohexene, however, gave the aziridine (211C) (36%) as well as 3-methylbenzimidazolin-2-one (11%) and the tetrazene (3%). When the oxidation was carried out in DMSO, however, the only

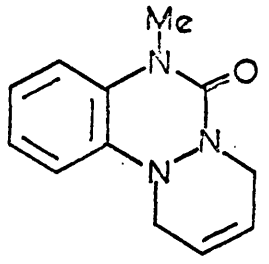
product that was isolated was the sulfoximine (212C) (46%).



(219)



(220)



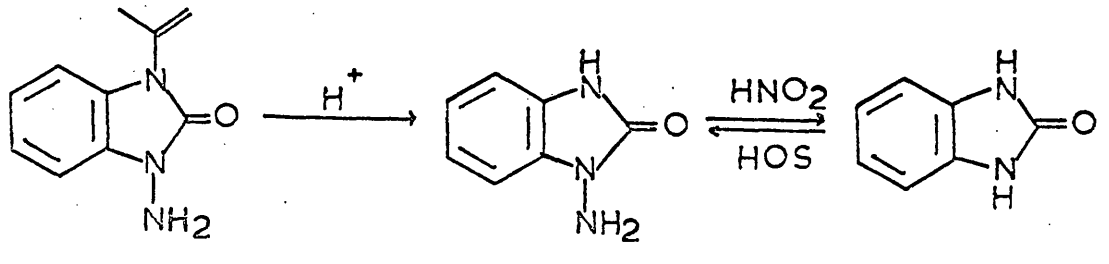
(221)

Although the reactions show the same characteristics as those of the previous N-amino compounds mentioned in this Section, the total yield (40-50%) of products were reasonably consistent. It is possible that ring expansion had also occurred to give the triazinone (220) initially, with subsequent decomposition. In the presence of 1,3-butadiene, however, none of the Diels-Alder adduct (221) was obtained and 1-methylbenzotriazole, obtained by extrusion of carbon monoxide from (220), was not detected.

D 1-Aminobenzimidazolin-2-one

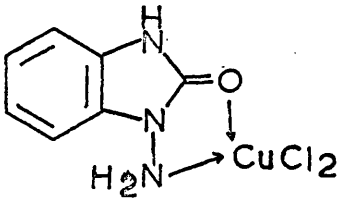
(i) Preparation from 1-amino-3-isopropenylbenzimidazolin-2-one

The N-amino compound (207) was hydrolysed to 1-aminobenzimidazolin-2-one (219) (91%) by heating with 1N sulfuric acid. It could also be obtained by HOS amination of benzimidazolin-2-one (18), although separation of the N-amino compound (219) from its precursor (18) was extremely difficult.



(207) (219) (18)

Analytical and spectroscopic data were in accord with the assigned structure. The compound also formed the copper chelate (220) and could be deaminated to benzimidazolinone (18) with nitrous acid.



(220)

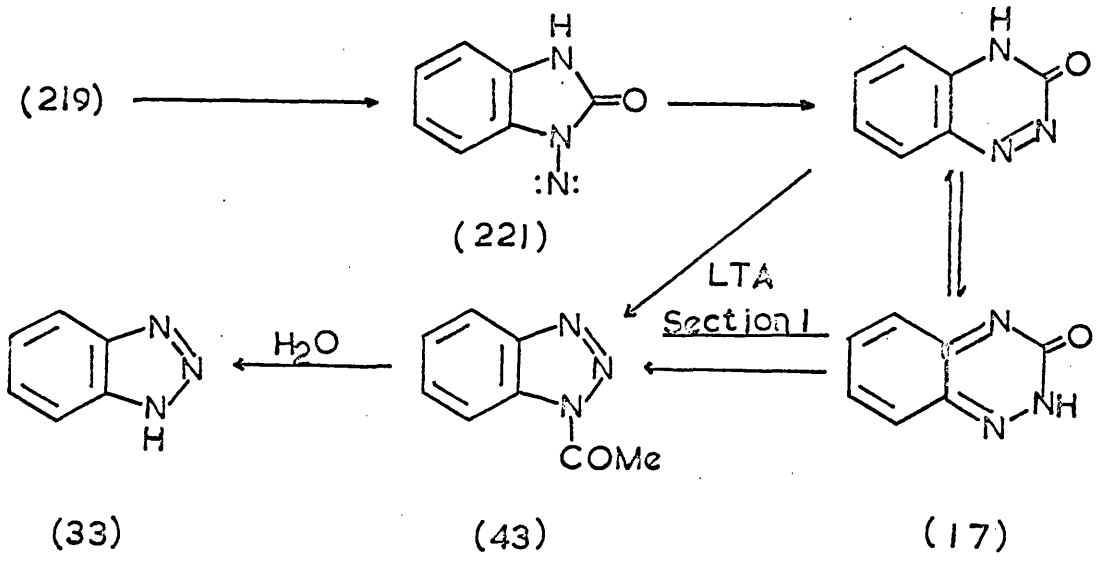
(ii) Oxidation of 1-aminobenzimidazolin-2-one

When a suspension of the N-amino compound (219) in either cyclohexene or DMSO was oxidised at room temperature, no products were obtained. It was thought that the insolubility of the N-amino compound may have prevented the N-nitrene (221) being generated.

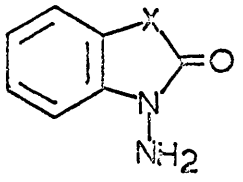
The reaction was therefore carried out in a mixture of benzene and methyl methacrylate heated to reflux, in which most of the N-amino compound (219) dissolved; 1.5 equivalents of LTA was used. No aziridine resulting from interception of the nitrene was obtained and instead benzotriazole (33) (10%) and 1-acetylbenzotriazole (43) (45%) were obtained.

The mechanism proposed is initial ring insertion of the intermediate N-nitrene (221), or nitrenoid, to give the triazinone (17) which is then further oxidised by excess of LTA to give 1-acetylbenzotriazole. Benzo-1,2,4-triazin-3(2H)-one has previously been shown to give 1-acetylbenzotriazole when oxidised with LTA in similar conditions (Section 1). The benzotriazole probably arose by hydrolysis of the N-acetyl derivative (43) on chromatographic work up, for in all subsequent experiments the mixtures were rapidly chromatographed and no benzotriazole was isolated.

In an attempt to isolate the triazinone (17), the N-amino compound (219) was oxidised with one equivalent of LTA. No triazinone was obtained, however, and 1-acetylbenzotriazole (37%) together with unchanged 1-aminobenzimidazolinone (26%) were isolated. Obviously, oxidation of the triazinone (17) is much faster than oxidation of the N-amino compound. When two equivalents of LTA were used, the yield of 1-acetylbenzotriazole rose to 61% and with four equivalents a 93% yield was obtained.

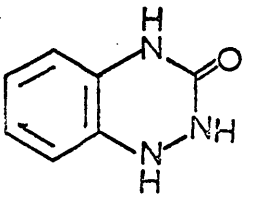


There appears to be no simple explanation of why the unsubstituted 1-aminobenzimidazolin-2-one behaves in a totally different way to the 3-alkyl derivatives. The unsubstituted compound is directly analogous to 1-aminooxindole and the 3-substituted N-aminobenzimidazolin-2-ones react in a similar manner to N-aminobenzoxazolinone. The significant structural difference is that 1-aminooxindole (77) and the unsubstituted benzimidazolinone (219) both contain a proton at position X in (200). However, the difference in behaviour cannot be explained satisfactorily in this way because the disubstituted oxindoles also appear to undergo an initial ring insertion reaction, and seem to have properties intermediate between the two extremes mentioned above.



X= CH_2(77)
NH (219)

(200)



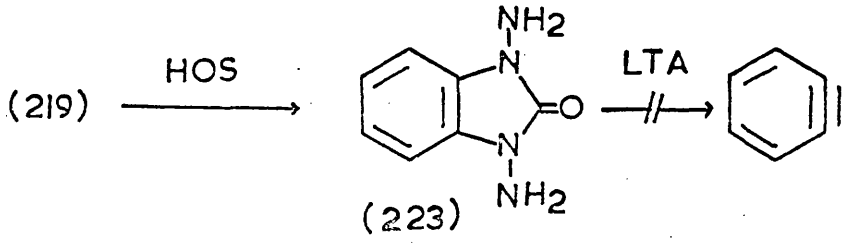
(222)

It is unlikely that 1-aminobenzoxazolinone rearranged to the isomeric compound (222) when prepared by acid hydrolysis of 1-amino-3-isopropenylbenzimidazolin-2-one (207). The N-amino compound (219) formed a copper chelate (220) (unlike the parent benzimidazolin-2-one) and could also be deaminated to benzimidazolin-2-one (220) with nitrous acid. Gaha and Ray[239] have also reported the dihydrotriazin-one (222) as having a melting point 70° higher than the N-amino compound (219).

E 1,3-Diaminobenzimidazolin-2-one

The diamino compound (223) was prepared by HOS amination of 1-aminobenzoxazolinone (219). It was characterised by analytical and spectral data of both itself and its di-anisylidene derivative.

This interesting compound appeared at the outset of this work as a potential benzyne precursor by the loss of two moecules of nitrogen and a molecule of carbon monoxide on oxidation. However, in the limited number of oxidations tried, no biphenylene or tetraphenyl-naphthalene (in the presence of tetracyclone) was detected, and only polymeric material appeared to be formed.

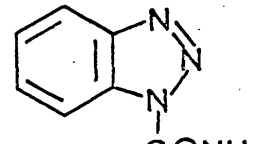


(223)

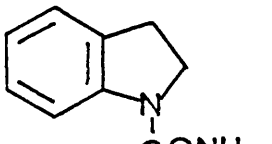
7 BENZOTRIAZOLE AND BENZOTRIAZOLE-1-CARBOXAMIDE

The preparation of 1-aminobenzotriazole[134b] involves either a multi-stage synthesis or a tedious separation from the isomeric 2-amino compound. Therefore a possible alternative route via a Hofmann rearrangement on the easily prepared benzotriazole-1-carboxamide (34)[195] was considered.

However, it was found that the carboxamide was very readily hydrolysed by base to benzotriazole and the normal conditions of the Hofmann rearrangement would certainly have caused preferential hydrolysis. Indoline carboxamide(224) although stable to base did not undergo the Hofmann reaction.



(34)

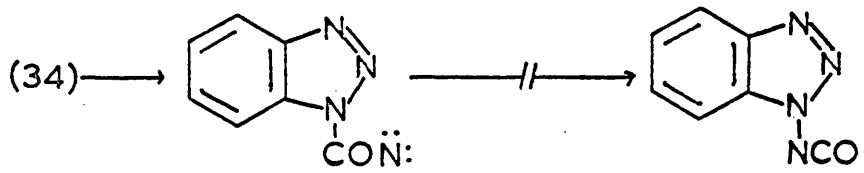


(224)

Beckwith et al.[240] reported that alkyl amides reacted with LTA to give isocyanates that can be trapped with amines, for example, to give the corresponding urea. Vigorous hydrolysis of the urea gave the amines.

$$RCONH_2 \xrightarrow{LTA} RNCO \xrightarrow{R'NH_2} RNHCONHR' \longrightarrow RNH_2 + R'NH_2$$

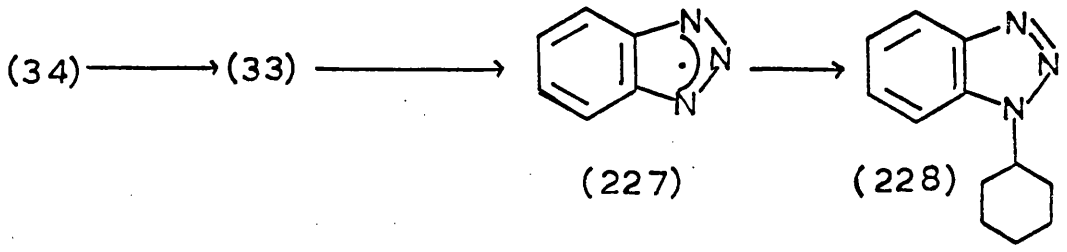
When benzotriazole-1-carboxamide was oxidised with LTA and t-butylamine added, no urea from interception of the isocyanate (226) was obtained. It was possible, that the LTA oxidised the carboxamide to the acyl nitrene (225) which belonged to the class of rigid nitrenes[241] that do not rearrange to the isocyanates.



(225) (226)

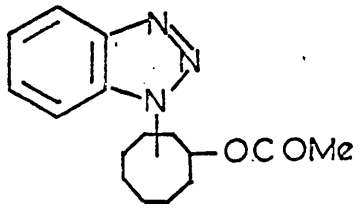
In order to try to intercept the intermediate nitrene (225) the carboxamide was oxidised in the presence of DMSO and of cyclohexene. With DMSO, the carboxamide (36%) was recovered unchanged, but in a mixture of DMF and cyclohexene, benzotriazole (17%) and 1-cyclohexylbenzotriazole (228) (15%) were obtained. When the carboxamide was oxidised in a mixture of acetonitrile and cyclohexene the yields fell to (8.5%) and (1.5%) respectively.

It was apparent that the carboxamide was undergoing initial decomposition to benzotriazole and then being oxidised to the radical (227) which was intercepted by the cyclohexene. As expected, it was found that when benzotriazole was oxidised in cyclohexene, the cyclohexyl derivative (228) (42%) was obtained together with unchanged benzotriazole (18%).

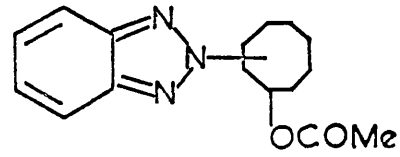


(227) (228)

The reaction does not seem generally applicable to other olefins, however. Cyclooctene gave no 1-cyclooctylbenzotriazole, but only various mixtures of oils, the spectral data of which indicated that they were the acetoxycyclooctyl derivatives of benzotriazole (229) and (230).

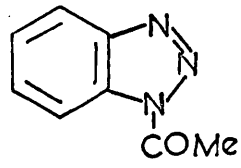


(229)

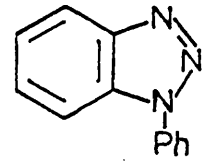


(230)

When oxidised with LTA in benzene, benzotriazole gave 1-acetylbenzotriazole (43) (2%) and 1-phenylbenzotriazole (231) (4.5%), and 60% was recovered.



(43)



(231)

Potassium permanganate and mercuric oxide were also used as oxidants, in the presence of cyclohexene, but none of the derivative (228) could be isolated. Indeed, only small yields of benzotriazole could be recovered, presumably due to the formation of metal salts of benzotriazole.

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e) U.S., 2 945 884 f) U.S., 2 933 500
g) U.S., 2 929 847 h) U.S., 2 909 567
i) U.S., 2 891 060 j) Brit., 880 589
k) Brit., 858 488 l) Brit., 823 332
m) Ger., 1 087 134

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