A STUDY OF THE SYNTHESIS AND REACTIONS OF PHTHALAZINES

A THESIS

PRESENTED FOR THE DEGREE OF

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by

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SUMMARY

Application of existing methods of phthalazine synthesis to the preparation of derivatives substituted in the homocyclic ring was only successful for the synthesis of 6-bromophthalazine. In attempts to devise a new synthetic route, desulphurisation of phthalaz-1,4-dithione was found to give a low yield of phthalazine. A more efficient synthesis was achieved by hydrogenation of 1,4-dichlorophthalazine over palladium-on-carbon at 1 atmosphere. A new heterocyclic system, benzo[g]phthalazine, and a number of 1-substituted phthalazines were prepared by this method. 1,2,3,4-Tetrahydro derivatives were obtained when the hydrogenation was carried out at 100 atmospheres.

Dehydrazination of mono- and dihydrazinophthalazines with mercuric oxide has provided another synthetic route to phthalazine derivatives. Oxidation of 1-hydrazino- and 1,4-dihydrazinophthalazine with quinones and with bromine resulted in cleavage of the azine ring to form phthalonitrile; the use of other oxidants gave halogeno- and hydroxyphthalazines.

The oxidation of phenylhydrazine with N-bromosuccinimide has been reinvestigated but, contrary to a previous report, no hydrazobenzene was detected. Evidence was obtained for the initial formation of benzenediazonium bromide which gave rise to the observed products, bromobenzene, phenyl azide and aniline.

Phthalazine formed stable 1:1 and 1:2 addition compounds with halogens. The infrared and nuclear magnetic resonance spectra of the adducts indicated that one of the nitrogen atoms was bound, presumably

through its lone pair, to the halogen molecule. The unusually high stability of the adducts was attributed to resonance-stabilised back-coordination of the halogen to the phthalazine ring.

Phthalazine was found to react rapidly with chlorine in aqueous solution to form nitrogen and a mixture of phthalaldehyde, o-dichloromethylbenzaldehyde and N-chlorophthalazone, the ratio of products depending on the rate of addition of chlorine, the concentration of chloride ion and the pH of the medium; the same products were obtained using hypochlorous acid. The reaction of chlorine with substituted phthalazines and some related azines also resulted in oxidation and ring-fission. Mechanisms have been proposed to account for the formation of these products.

The nitration and bromination of phthalazine in 98% sulphuric acid gave 5-substituted derivatives; this orientation was predicted by reactivity indices calculated using the Hückel molecular orbital method. The rate of nitration was found to be 5.6×10^{-5} l. mole^{-1} sec.$^{-1}$ at 61.9°. Amination and hydroxylation occurred at the 1-position, as predicted.

Phthalazine reacted with keten and with maleic anhydride, forming adducts of unknown structure.

Treatment of phthalazine-2-oxide with alkaline potassium ferricyanide resulted in the formation of nitrogen and phthalaldehyde. Conversion of the 2-oxide to 2-acetylphthalazone was effected by heating with acetic anhydride. Chlorination and nitration of phthalazine-2-oxide was accomplished by the use of chlorine water and potassium

nitrate in 98% sulphuric acid respectively.

N-Substituted phthalazinium salts were found to undergo nucleophilic attack at the 1-position by hydroxide, alkoxide and cyanide ions; the products, however, resisted further degradation.

STATEMENT

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University, and to the best of my knowledge and belief contains no material previously published or written by another person, except where due reference is made in the text.

P.G. Parsons.

ACKNOWLEDGEMENTS

I am deeply indebted to Dr. H.J. Rodda for his guidance and encouragement during supervision of this work.

I wish to thank Mr. B.D. Roney for the molecular orbital calculations.

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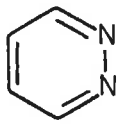
Introduction

Advances in methods of synthesis and in physico-chemical techniques during recent years have led to a vast expansion in the field of heterocyclic chemistry. In particular, those ring systems occurring in natural products and in biologically active materials have been extensively investigated. Nitrogen heterocycles are widely distributed in Nature and are commonly derived from five or six-membered aromatic rings. The latter class is structurally based on pyridine (1), which shows a degree of aromaticity comparable with benzene. However, the pyridine molecule is unsymmetrical with respect to bond lengths and charge distribution because nitrogen is more electronegative than carbon. The chemical reactivity of pyridine therefore differs from benzene; electrophilic attack, for example, is much less favourable because of the electron withdrawing effect of the nitrogen atom, while nucleophilic attack is facilitated.[1]

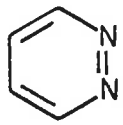
The presence of two nitrogen atoms in a six-membered aromatic nucleus would be expected to result in even greater differences and this has been found for the three isomeric diazines (2, 3 and 4). Pyridazine (2) does not undergo electrophilic substitution[2] whereas nucleophilic displacement of substituents occurs readily.[3,4,5] A further consequence of localisation of electrons on nitrogen is a reduction in the aromatic character of the diazine ring. This effect seems from valence bond calculations to be negligible in pyrimidine (3) and pyrazine (4)[6] but of appreciable magnitude in pyridazine (2) where the hetero atoms are

adjacent.[7] The Kekule structure (2a) having a single bond between

(1)



(2a)



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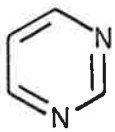

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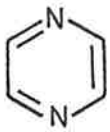

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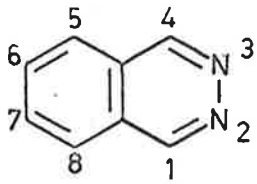


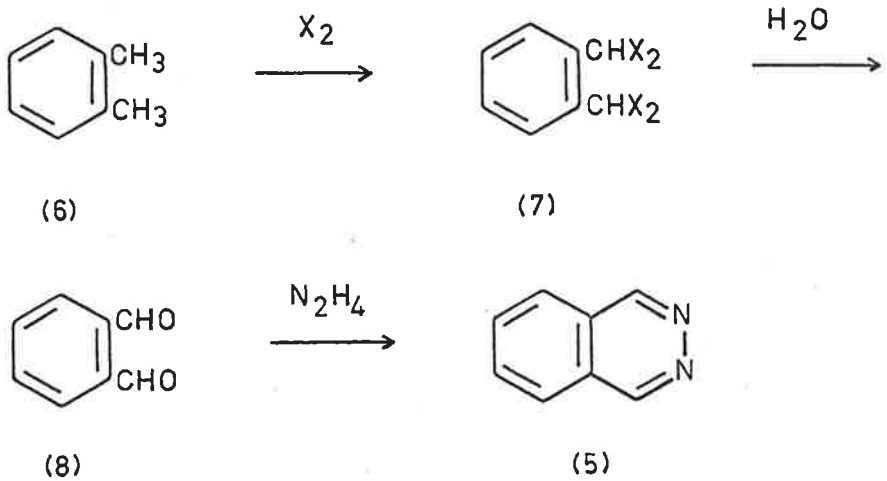
(5)

the nitrogen atoms was considered[7] to make a greater contribution to the resonance hybrid than the form (2b). The C=N bonds in pyridazine would therefore have increased double bond character and would be more susceptible to addition. This prediction was fulfilled by a recent report[8] that pyridazine undergoes addition across the C=N bond with two molecules of maleic anhydride.

Phthalazine (5), which is the diazine studied in the present work, is formally derived by fusion of a benzene ring to the d bond of pyridazine and would be expected to parallel pyridazine in chemical behaviour. The benzo ring, however, offers more favourable sites for electrophilic substitution and may modify the properties of the heterocyclic nucleus. Since the 1,2 bond in naphthalene has the greatest bond order, the double bond character of the C=N bonds in phthalazine should be enhanced compared with pyridazine.

The phthalazine ring system has not been found in Nature and has accordingly received relatively little attention; most of the recent investigations have been concerned with the preparation and properties of biologically active derivatives.[9,10,11] Reviews of phthalazine chemistry reveal considerable interest in the derivatives of phthalazones and phthalaz-1,4-diones.[12,13,14] Investigation of the deoxygenated phthalazine ring, on the other hand, has been hampered by the lack of suitable methods for its synthesis.

Gabriel and Pinkus[15] first prepared phthalazine in 1893 by condensing hydrazine (scheme 1.) with phthalaldehyde (8), the latter being obtained *in situ* from *o*-xylene (6). The tetrabromo derivative

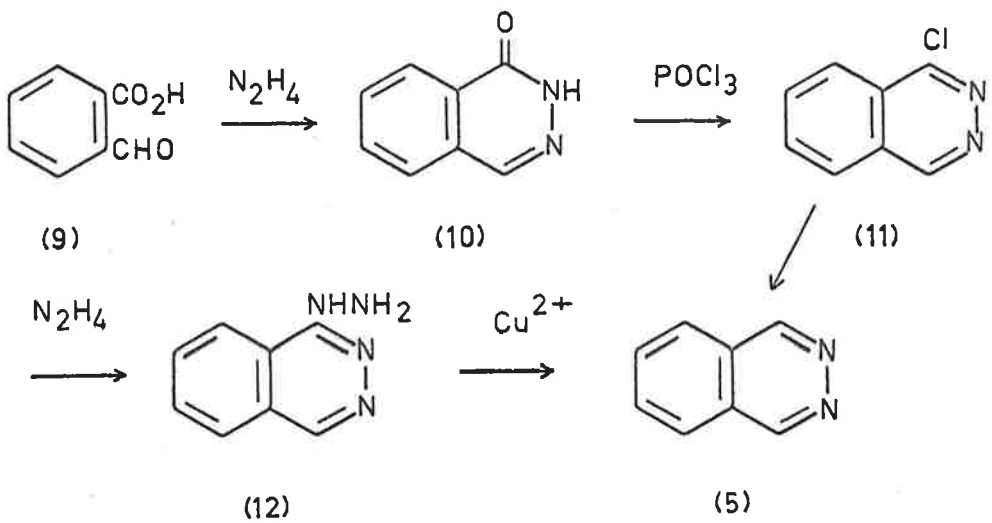


Scheme 1.

(7; X=Br) proved to be a more suitable intermediate than the chloro compound (7; X=Cl) and modification of the bromination procedure[16] has made the method one of the most satisfactory syntheses of phthalazine

on a large scale. Although phthalazine has recently been produced almost quantitatively by carrying out the condensation step at 0° in ethanol,[17] the tedious procedure required to isolate the aldehyde[18] is not warranted by the small increase in yield. The preparation of substituted phthalazines by this method is severely limited by the difficulty in obtaining substituted o-dialdehydes and o-diketones; some 1,4-disubstituted phthalazines have been synthesised from o-diketones[19,20,21] and 4-chlorophthalaldehyde has given 6-chloro-phthalazine.[22]

Condensation of hydrazine with phthalaldehydic acid (9) provides phthalazone (10) from which 1-chlorophthalazine (11) may be obtained by treatment with phosphorus oxychloride[23] (Scheme 2).

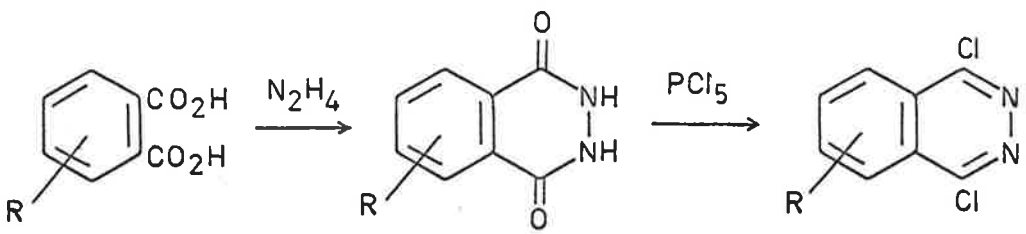


Scheme 2.

Removal of the chlorine atom by the use of red phosphorus and hydriodic acid[24] or by catalytic hydrogenation[25] has provided

phthalazine in moderate yield but the preparation of phthalazine derivatives is again restricted by the lack of suitably substituted starting materials. Nevertheless, this method remains virtually the only route to phthalazines substituted in the 1-position[26-30] and in the carbocyclic ring.[22,24] 1-Chlorophthalazine has proved a useful synthetic intermediate; the chlorine atom undergoes nucleophilic displacement with the formation of amino,[31,32] hydrazino,[33] alkoxy[34] and phenoxy[28] derivatives. Displacement by active methylene compounds can also occur.[35] 1-Hydrazinophthalazine (12) has been oxidized to phthalazine by copper sulphate[36] but the overall yield of phthalazine was less than direct dechlorination. Conversion of the chloro compound to 1-tosylhydrazinophthalazine, followed by alkaline decomposition, also gave a low yield of phthalazine.[37]

Phthalaz-1,4-diones (14), the most numerous class of phthalazine derivatives, are readily prepared from the anhydrides,[38] esters[39] or imides[40] of the corresponding phthalic acids (13) and several have been converted to 1,4-dichlorophthalazines (15) by the action of phosphorus pentachloride.[41,42] (Scheme 3.) The methods available for



(13) (14) (15)

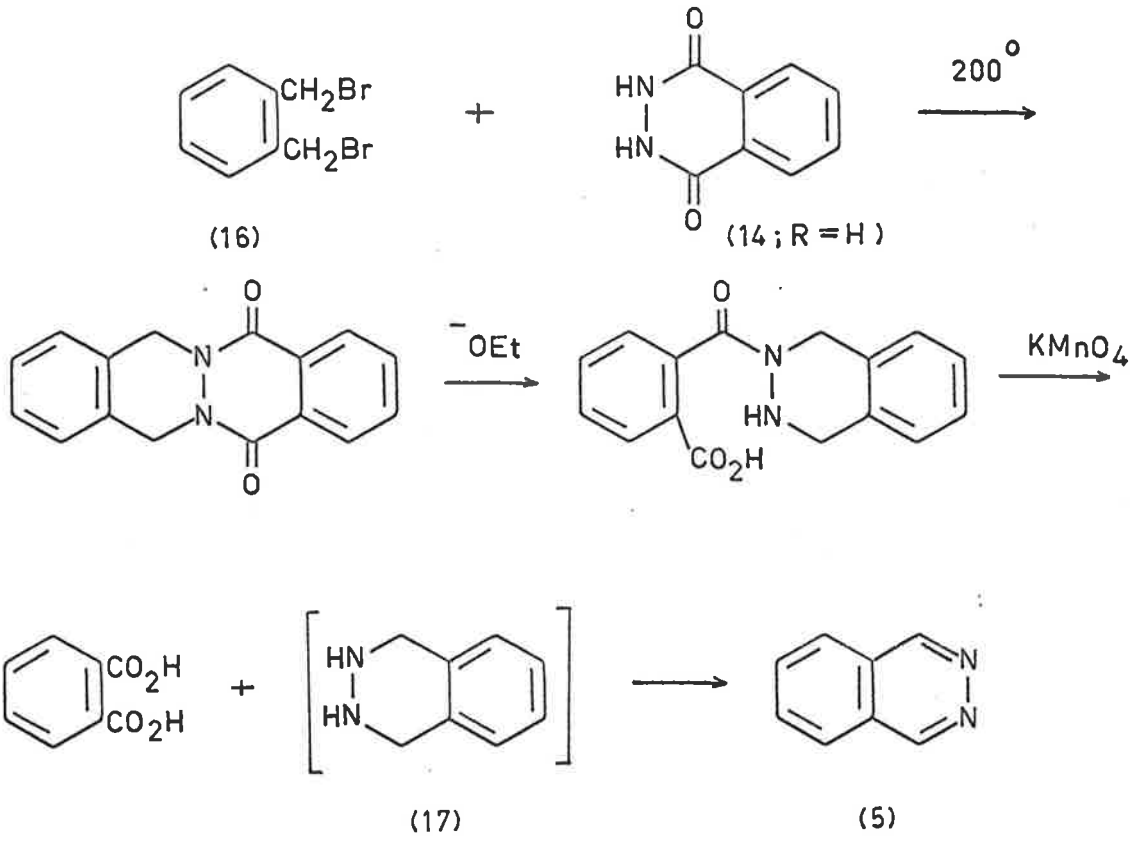
Scheme 3.

dehalogenation of nitrogen heterocycles are limited in this case by the rapid solvolysis of 1,4-dichlorophthalazines in aqueous and alcoholic solutions.[35,39] Several unsuccessful attempts have been reported,[37,43,44] although a 35% yield of phthalazine was finally achieved[37] by the action of red phosphorus and hydriodic acid on 1,4-dichlorophthalazine (15; R=H). 1,4-Dichlorophthalazine undergoes nucleophilic displacement reactions in a similar manner to the 1-chloro derivative,[31,45] more vigorous conditions being required to replace the second chlorine atom.

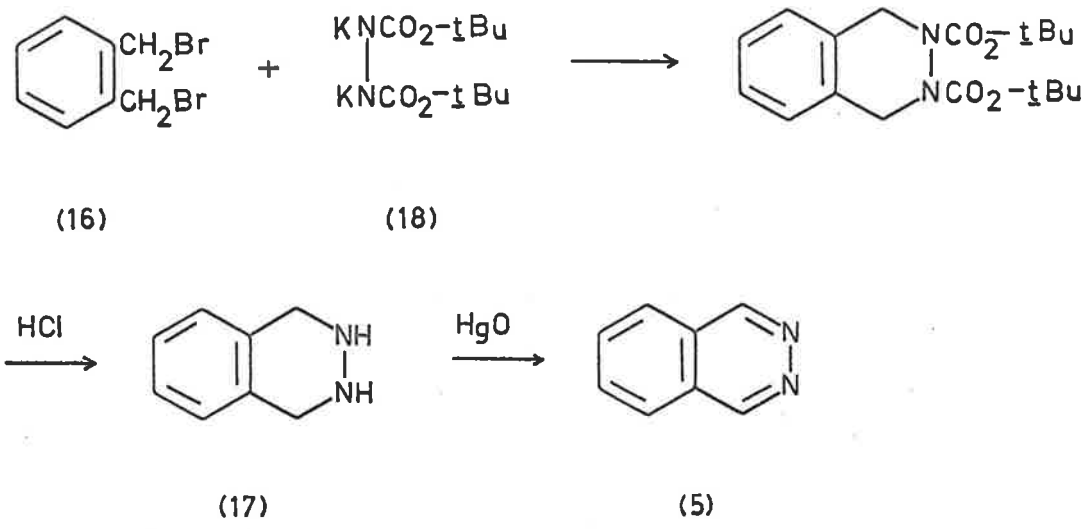
The 1,2,3,4-tetrahydrophthalazine system (17) may be formed from w,w'-dibromo-o-xylene (16) by reaction with hydrazines carrying suitable substituents. The method of Hatt and Stephenson[46] gave a poor yield of phthalazine (Scheme 4.) and is unlikely to provide substituted phthalazines because of the severe conditions required.

Carpino[47] used potassium t-butylhydrazoformate (18) and obtained a 60% overall yield of 1,2,3,4-tetrahydrophthalazine (17) from which phthalazine can be prepared by oxidation with mercuric oxide.[15] (Scheme 5.)

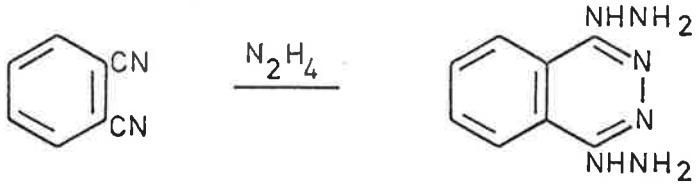
Another method for the formation of the phthalazine ring has been used in one instance; phthalonitrile (19) was found to condense with hydrazine to form 1,4-dihydrazinophthalazine (20) in excellent yield.[48] The same product was obtained from 1-amino-3-iminoisoindolenine and hydrazine.[49] The procedure has been extended to include cyclisation of o-cyanobenzaldehyde (21; R=H) but phthalazone (22; R=H) was the major product.[50] o-Cyanoacetophenone (21; R=CH_3) gave only the phthalazone[51] (22; R=CH_3).



Scheme 4.



Scheme 5.



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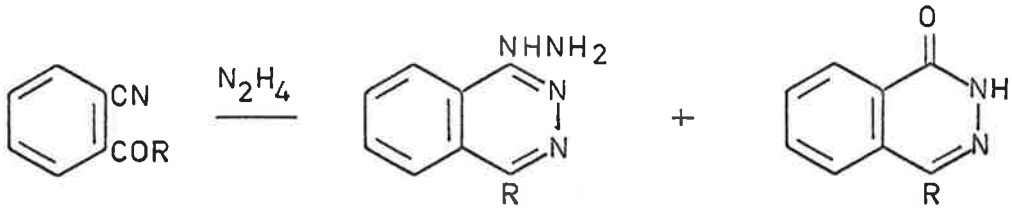
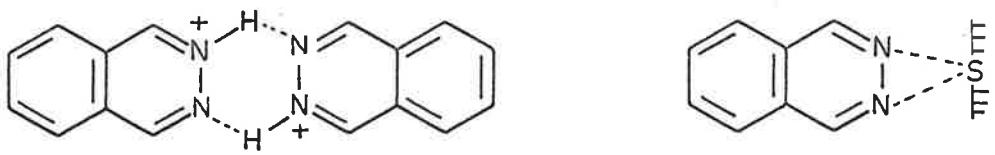


(21) (22)

Gabriel studied a few reactions of phthalazine at the end of the nineteenth century but little further work on the unsubstituted system has been reported. Phthalazine is a weak, monoacidic base, pKa 3.47,[32,52] and forms well defined salts with strong acids.[15,27] The increase in basicity from pyridazine (pKa 2.3) to phthalazine is abnormally large compared with the difference between pyridine (pKa 5.2) and isoquinoline (pKa 5.4).[53] The possibility of resonance stabilisation of a protonated dimeric species (23), similar to that proposed for pyridazine,[32] is precluded by the fact that cinnoline, which would be capable of similar stabilisation, has the same basic strength as pyridazine.



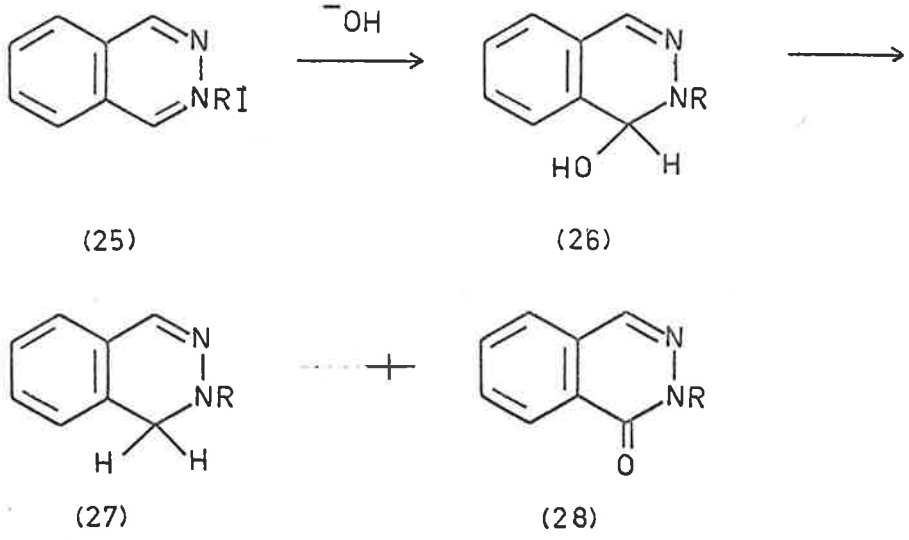
(23) (24)

In a recent chromatographic study of nitrogen heterocycles, phthalazine was found to have the highest adsorption energy of the mono and bicyclic diazines examined.[54] This was attributed to the ability of both nitrogen atoms to share one adsorption site (24). Complexes are formed by phthalazine with ammonium thiocyanate and a number of transition elements.[55]

The electronic absorption spectrum of phthalazine has been recorded and is similar to that of naphthalene.[56-61] An $n-\pi^*$ transition was observed as weak, long wavelength absorption in cyclohexane solution and lacked the sharp cut-off usually exhibited by azines. This has been explained by the fact that the lowest energy $n-\pi^*$ transition in phthalazine has forbidden symmetry but is weakly allowed by non-symmetric vibrations.[62] At shorter wavelengths an allowed $n-\pi^*$ transition of higher energy is observed. Calculations of the electronic absorption spectrum, particularly $n-\pi^*$ transitions, have been carried out using molecular orbital methods and some correlation with the observed spectrum has been obtained.[63-66] The phosphorescence,[60] nuclear magnetic resonance[67,68] and electron spin resonance spectra[69,70] of phthalazine have been recorded. The dipole moment[71] and ionisation potential[69,72,73] have also been measured and compared with theoretical values. The calculation of reactivity parameters has been limited to charge densities and will be discussed in a later chapter.

Alkyl phthalazinium iodides (25; R=CH_3, CH_2CH_3) were reported by Gabriel[74] to give a mixture of 2-alkyl-1,2-dihydrophthalazines (27)

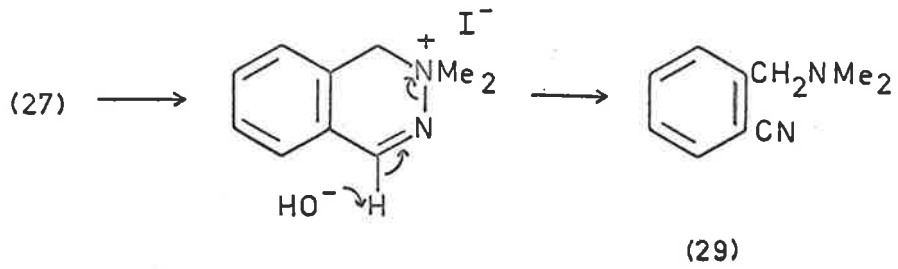
and 2-alkylphthalazones (28) on treatment with one equivalent of aqueous potassium hydroxide. It was later suggested[12] that the reaction (Scheme 6.) proceeds by disproportionation of the pseudo base (26). More



Scheme 6.

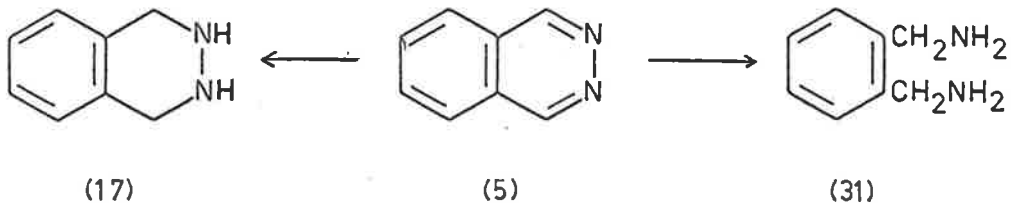
recently, Smith and Otremba[18] obtained the dihydro base (27) in high yield from the phthalazinium salt (25) by reduction with sodium borohydride. The second C=N linkage remained intact even in the presence of a large excess of reagent. Quaternisation of the dihydro base, followed by alkaline degradation, gave ∝-N,N-dimethylamino-o-tolunitrile (29), the proposed mechanism (Scheme 7.) being similar to the base-catalysed conversion of aromatic chlorimines to nitriles.[75]

The oxidation of phthalazine with potassium permanganate resulted in degradation of the carbocyclic ring and the formation of pyridazine-4,5-dicarboxylic acid.[24] Reduction with sodium amalgam gave 1,2,3,4-tetrahydrophthalazine (17)[46] while tin and hydrochloric



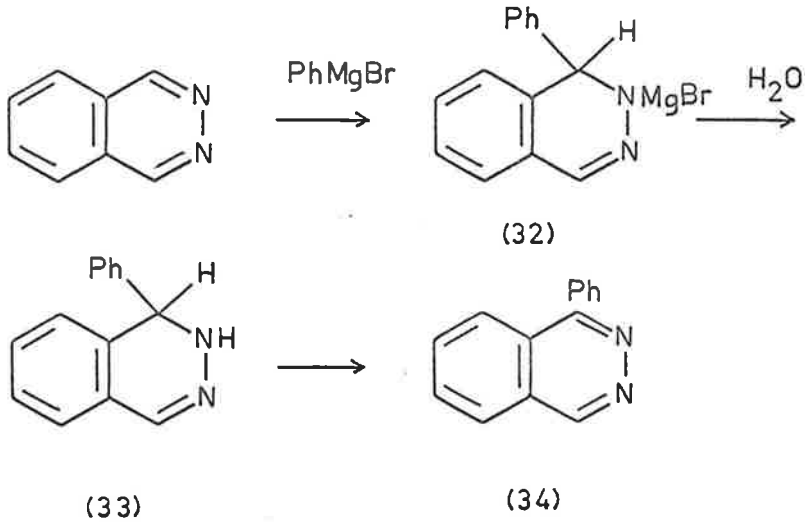
Scheme 7.

acid produced o-di(aminomethyl)benzene (31).[15] The instability of the diazine ring toward reducing agents was also observed by Stephenson,[30] who found that hydrogenation over platinum oxide released ammonia; no other products were identified.



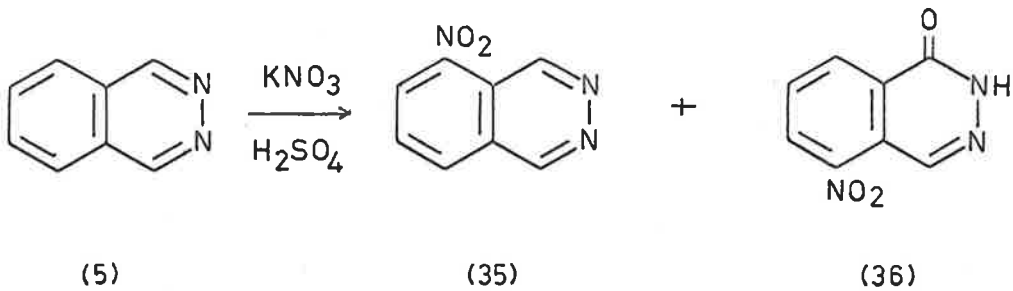
Phthalazine has been found to undergo addition across the C=N bond with phenyl magnesium bromide.[76] It was assumed that 1-phenyl-1,2-dihydrophthalazine (33), formed by hydrolysis of the complex (32), underwent autoxidation to the end-product, 1-phenylphthalazine (34), which was obtained in 45% yield (Scheme 8.). A similar reaction of alkyl and aryl lithiums with phthalazine has recently been reported;[77] some evidence was presented for the formation of a peroxide intermediate in the autoxidation step.

Few substitution reactions of phthalazine have been described. Phenylation with N-nitrosoacetanilide, presumably by a free radical



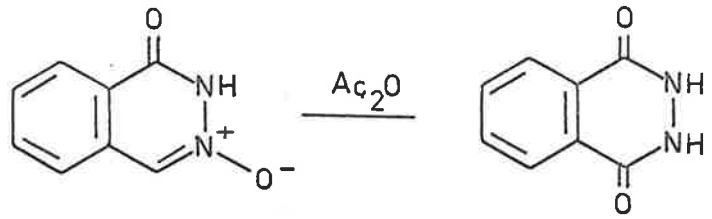
Scheme 8.

mechanism, gave an extremely low yield of 5-phenylphthalazine.[37] The nitration of phthalazine provided the 5-nitro derivative (35) as the main product,[78] together with a small amount of 5-nitrophthalazone (36). The nitration products of 1-methyl- and 1-methoxyphthalazine had similar orientations of the nitro group.[78]



Phthalazine-2-oxide has been prepared[79] by the action of monoperphthalic acid on phthalazine at 0°. 1-Alkoxyphthalazine-3-oxides were obtained under similar conditions and also by the use of peracetic acid at higher temperatures.[80] The only reaction of

phthalazine-2-oxide reported was its reduction to phthalazine by phosphorus pentachloride.[79] The action of acetic anhydride on phthalazone-3-oxide (37) afforded phthalaz-1,4-dione[80] in accord with the usual rearrangement of N-oxides in this medium.[81]



(37) (14)

Deficiencies in the present knowledge of phthalazine chemistry have already been pointed out by Vaughan[13] and by Albert.[82] Common substitution reactions, such as bromination, amination and hydroxylation, have not been attempted in the phthalazine and phthalazine-2-oxide systems. Few of the various addition reactions undergone by nitrogen heterocycles have been applied to phthalazine. The aims of the present work, therefore, were to devise an efficient synthetic route to phthalazine derivatives, to investigate more fully the chemical properties of the ring system, and to rationalise its reactivity, where possible, in terms of molecular orbital theory.

CHAPTER 1.

The Synthesis of Phthalazines.

1.1 Synthesis from phthalaldehydes.

In the preparation of phthalazine for the present work according to scheme 1, overall yields of up to 80% were obtained by using the modified bromination procedure[16] and by adding the required amount of hydrazine hydrate to the hot solution of phthalaldehyde generated *in situ* from w,w,w',w'-tetrabromo-*o*-xylene. The synthesis of nitro- and bromophthalazines by the same method, however, proved less successful.

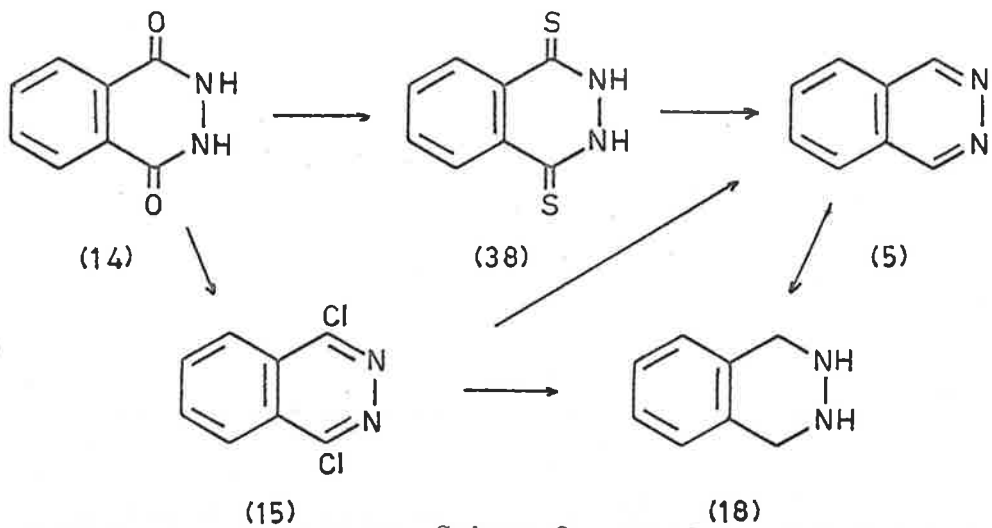
Bromination and nitration of w,w,w',w'-tetrabromo-*o*-xylene were reported[83] to give 4-substituted derivatives which yielded phthalaldehydes on hydrolysis. The aldehydes were not characterised and the experimental details available were not sufficient to allow repetition of the work. An unambiguous and more convenient route to the 4-substituted tetrabromo derivatives was achieved by the bromination of 4-bromo- and 4-nitro-*o*-xylene with elemental bromine at 180° and with *N*-bromosuccinimide in carbon tetrachloride respectively. Both products were unaffected by prolonged refluxing in water, in contrast to the 4-chloro derivative,[22] and hydrolysis was finally effected by heating with sodium acetate and aqueous ethanol at 150°. The crude products were dissolved in ethanol and treated with hydrazine. 4-Bromophthalaldehyde gave a low yield of 6-bromophthalazine but only tar was recovered after the reaction of hydrazine with 4-nitrophthalaldehyde

at temperatures ranging from -5° to 100°.

The bromination of 3-nitro-, 3-bromo- and 4,5-dibromo-o-xylene yielded only di- and tribrominated products. Chromic acid oxidation of o-xylene has given phthalaldehyde in poor yield;[84] application of the method to 4-nitro- and 4-bromo-o-xylene gave no useful products. Phthalaldehyde has also been prepared by the reduction of N,N-dimethylphthalamide with lithium aluminium hydride[85] but the procedure, being unsuitable for large scale syntheses and for derivatives containing reducible groups, was not further considered in the present work.

1.2 Synthesis from phthalic acids.

A more convenient starting point for phthalazine synthesis was considered to be the phthalaz-1,4-dione system (14) which is readily obtainable from phthalic acid and may be converted to phthalaz-1,4-dithione (38)[86] and 1,4-dichlorophthalazine (15).[41] Removal of the thio or



Scheme 9.

chlorine groups would then provide synthetic routes to phthalazine derivatives with substituents in the benzo ring. (Scheme 9).

The removal of mercapto groups from aromatic nuclei by reductive desulphurisation has provided on efficient synthetic route to many heterocyclic derivatives, including diazine and triazine systems.[87,88] The dithione (38), however, was found to undergo ring fission with evolution of ammonia in the presence of various grades of Raney nickel. Nitrogen-nitrogen single bonds are known to suffer catalytic cleavage[80,90,91] and the bond in this case appeared to be particularly labile, as ammonia was formed by the action of alkali alone. Phthalazine was eventually obtained in 12% yield using W7 Raney nickel in pyridine at 100°. Attempted thiations of the mononitro- and monoaminophthalaz-1,4-diones (14; R = NO_2, NH_2) were unsuccessful.

Atkinson and Sharpe[37] treated 1,4-dichlorophthalazine (15) with p-toluenesulphonhydrazine by the method of Albert[92] but alkaline decomposition of the resulting hydrazide produced no phthalazine. Reduction of the dichloro compound with phosphorus and hydriodic acid gave phthalazine in 35% yield.[37] Similar results were obtained on repetition of this work and, in addition, the use of zinc dust proved unsuccessful in removing the chlorine groups. The major product was 4-chlorophthalazone, confirming the ease of hydrolysis of the chlorine group reported by previous workers.[37,41] A ditosylhydrazide adduct could not be obtained by treating 1,4-dihydrazinophthalazine with tosyl chloride. Catalytic hydrogenation of 1,4-dichlorophthalazine under the same conditions as were used for 3,6-dichloropyridazines[93] gave ammonia

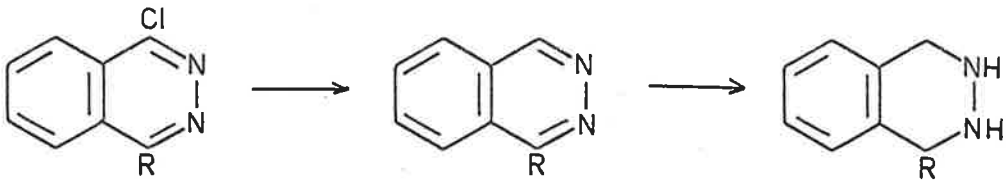
and intractable material.

Efficient removal of the chloro groups was finally achieved in the present work by hydrogenation at atmospheric pressure over palladium-on-carbon in a mixture of dioxan and ammonia. No reaction occurred in the absence of ammonia, and the use of an inert solvent was necessary since in methanol 4-chloro-1-methoxyphthalazine was formed as well as phthalazine. When the hydrogenation was carried out at 100 atmospheres, rapid conversion to 1,2,3,4-tetrahydrophthalazine (17) was observed; the same product was obtained by hydrogenation of phthalazine under identical conditions.

To extend the scope of this method, a number of substituted 1,4-dichlorophthalazines were required. A general method was used, involving heating the corresponding phthalaz-1,4-dione with two equivalents of phosphorus pentachloride in phosphorus oxychloride until a solution was obtained. Prolonged heating gave dark solutions from which very little product could be isolated. Excess phosphorus oxychloride was removed <u>in vacuo</u> and the anhydrous product purified by recrystallisation or sublimation. 6,7-Dimethyl-1,4-dichlorophthalazine could be obtained by refluxing the dione in phosphorus oxychloride alone and proved remarkably resistant to hydrolysis and hydrogenolysis. During attempts to chlorinate the amino- and acetamidophthalaz-1,4-diones evolution of hydrogen chloride occurred but only dark gums were isolated. When hydrogenated under the same conditions as 1,4-dichlorophthalazine, 5-nitro, 6-nitro-and 6-chloro-1,4-dichlorophthalazine each absorbed hydrogen but no products could be obtained other than the starting

materials and hydrolysed derivatives. In the first two instances, water formed by reduction of the nitro group may permit hydrolysis of the chlorine groups before hydrogenolysis can occur.

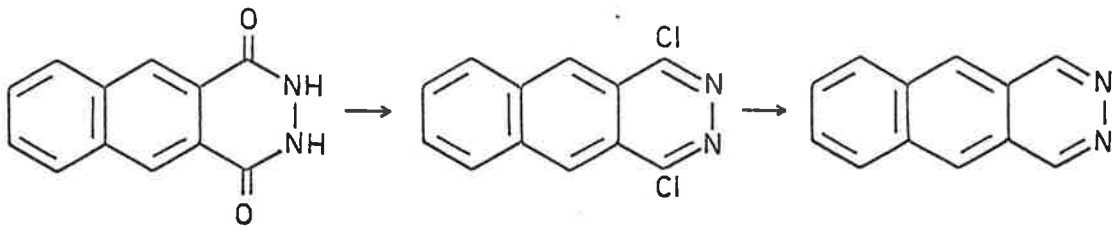
Several monochlorophthalazines (39; R = H,CH_3) have been dechlorinated by Stephenson[25,30] using palladium and sodium hydroxide in ethanol. Ammonia was found to be a more suitable base for these reductions and the method was also used for the preparation of 1-phenylphthalazine (40; R = Ph) and phthalazone (40; R = OH).



(39) (40) (41)

Dehalogenation of 4-chlorophthalazone (39; R = OH) required hydrogenation at 100 atmospheres and 100°, and was more readily effected by refluxing the compound with palladium and hydrazine in ethanol after the method of Mosby.[94] 1-Chloro- and 1-chloro-4-methylphthalazine formed 1,2,3,4-tetrahydro derivatives (41; R = H,CH_3) when hydrogenated at 100 atmospheres.

A new diaza-anthracene, benzo[g]phthalazine (44) was prepared from 1,4-dichlorobenzo[g]phthalazine by the same method as phthalazine (Scheme 10). If the volume of hydrogen absorbed was allowed to reach



(42) (43) (44)

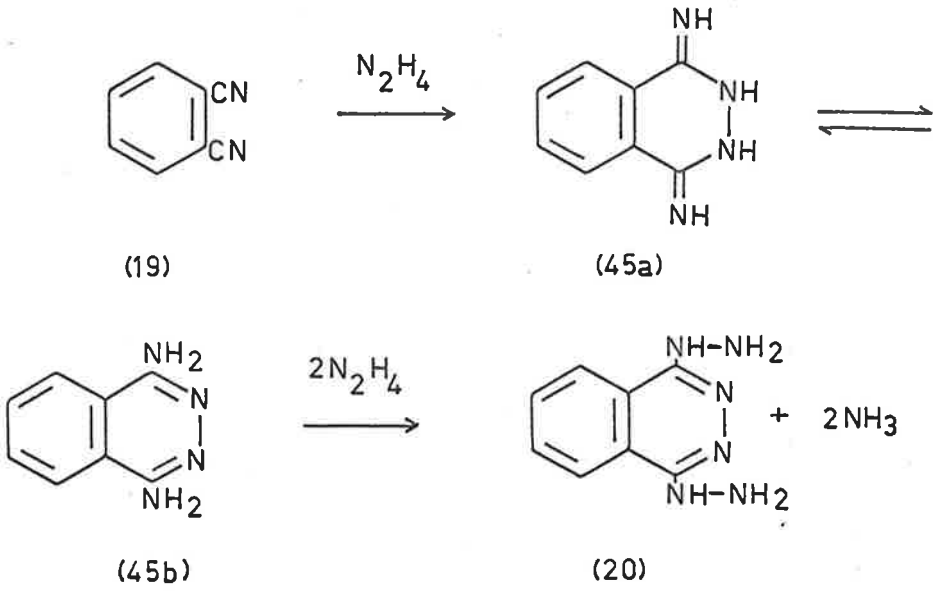
Scheme 10.

three moles, a white precipitate was obtained which, being insoluble in all solvents tried, could not be freed from the catalyst. When the mixture was sublimed or boiled in acetic acid benzo[g]phthalazine was recovered as the sole product, indicating that the substance may be a readily dehydrogenated dihydro derivative. Benzo[g]phthalazine was found to be a relatively strong base (pKa3.5) forming salts which exhibited a green fluorescence in solution. The base itself did not fluoresce under ultraviolet light and its electronic absorption spectrum was more similar to that of naphthalene-2,3-dialdehyde than anthracene. Pyrolysis of benzo[g]phthalazine in air at temperatures over 300° gave a decomposition product which showed a nitrile absorption peak in the infra-red spectrum. It would seem, therefore, that π-electron localisation at the C=N bonds in benzo[g]phthalazine is sufficient to cause the N-N bond to become susceptible to pyrolytic fission.

Although the dechlorination procedure described above has not yet provided substituted phthalazines, it has subsequently been successfully applied to the synthesis of azaphthalazines.[95]

1.3 Synthesis from phthalonitriles.

Earlier it was stated that 1,4-dihydrazinophthalazine (20) is produced by the action of hydrazine on phthalonitrile in the presence of acetic acid.[48] The mechanism proposed for this reaction (scheme 11) requires cyclisation with one mole of hydrazine to form 1,4-diaminophthalazine (45), followed by nucleophilic displacement of the amino groups with hydrazine. To verify this route, 1,4-diaminophthalazine was synthesised by cleavage of the N-N bonds in 1,4-dihydrazinophthalazine with Raney nickel. This appears to be the first example of degradation of a dihydrazino derivative, although several monohydrazides and hydrazines yielded amides and amines[91] when treated with Raney nickel. The heterocyclic N-N bond in 1,4-diaminophthalazine was unaffected by the



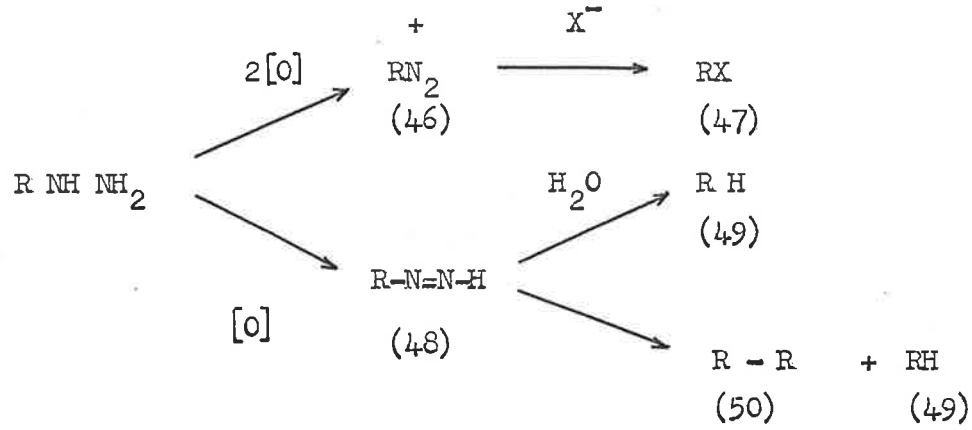
Scheme 11.

catalyst, in contrast to benzo[c]cinnoline[89] and phthalazine, which in the present work was found to evolve ammonia under these conditions.

When 1,4-diaminophthalazine was allowed to react with hydrazine under the same conditions as phthalonitrile, a high yield of 1,4-dihydrazinophthalazine was rapidly obtained. Moreover, the ultraviolet spectrum of a reaction mixture using phthalonitrile showed, after seven minutes reaction time, a maximum at 335 mμ identical with that of the diamino derivative ; a small amount of the latter could be isolated from the mixture at this stage. The use of one mole of hydrazine gave a mixture of the starting material and 1,4-dihydrazinophthalazine, suggesting that the diamino derivative, once formed, is rapidly converted to the dihydrazino compound. Phenylhydrazine failed to react with phthalonitrile and with 1,4-diaminophthalazine. In attempts to prepare 1,4-dihydrazinophthalazines with substituents in the homocyclic ring, 3-nitro- and 4-nitrophthalonitrile were treated with hydrazine but mixtures of the starting material and nitro- and aminophthalimides were obtained. 4-Chlorophthalonitrile formed a considerable quantity of polymeric material as well as the dihydrazino derivative. The reaction of hydrazine with 3-methylphthalonitrile only proceeded when trifluoroacetic acid was used as the catalyst. The product showed complex N-H bands in the infra-red spectrum but, being inert toward mercuric oxide, contained no primary hydrazine groups.

Generally, the course of oxidation of primary aromatic hydrazines is dependent upon the nature of the oxidising agent, the solvent, and the pH of the medium. Two equivalents of oxidant produce the

diazonium ion (46) which may undergo decomposition to hydroxy and halogeno derivatives (47; X = OH, halogen).

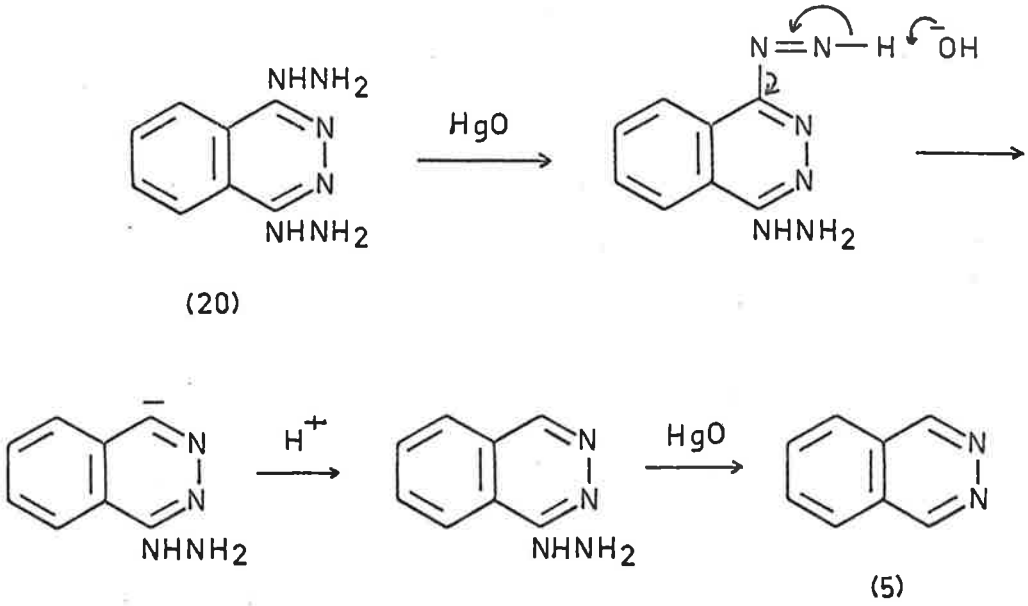


Scheme 12.

Some oxidants, however, are only capable of forming the diimine (48) which decomposes in water to the hydrocarbon (49). Homolytic decomposition of the diimine species may occur in aprotic solvents with the formation of dimers (50). Oxidation *via* a diimine intermediate is pertinent to the present investigation because a method was required for replacing the hydrazino groups in 1,4-dihydrazinophthalazine with hydrogen.

Chattaway[96,97] studied the reaction of metallic oxides, permanganates and chromates with several primary aromatic hydrazines and reported the formation of hydrocarbons together with small quantities of phenols, diphenyls, azo compounds and tar. Of these oxidants, mercuric oxide was found to be the most satisfactory for the conversion of 1,4-dihydrazinophthalazine to phthalazine (reaction 1, Table 1.)

When the reaction was conducted in water at room temperature rapid oxidation and evolution of nitrogen was observed, the yield being unaffected by increases in reaction time (reaction 2) or temperature (reactions 3 and 4). The crude product was relatively pure and free from hydroxyphthalazines. No azo dye was produced when the reaction was carried out in alkaline 2-naphthol, indicating the absence of a diazonium ion intermediate. Since the existence of diimines is well established,[98] the following mechanism is proposed. (Scheme 13.)



Scheme 13.

The hydrazine groups may be oxidised consecutively as shown or concurrently; in either case, base-catalysed decomposition of the diimino group followed by protonation of the resulting carbanion would lead to the formation of phthalazine. This mechanism is analogous to the latter stages of the Wolff-Kishner reduction[99] and to the McFadyen-Stevens synthesis of aldehydes[100] where loss of nitrogen is thought to

TABLE 1.

Oxidation products of 1,4-Dihydrazinophthalazine.

Reaction	Oxidant	Solvent	time (hr)	temp.	Product	% Yield
1	HgO	H_2O	3	20°	phthalazine	73
2	"	"	24	20	"	75
3	"	"	3	100	"	73
4	"	"	3	0	"	72
5	"	benzene	24	20	"	49
6	$Hg(OAc)_2$	H_2O	3	25	"	40
7	$HgO/HgCl_2$	"	3	20	"	23
8	Ag_2O	"	24	20	"	21
9	"	ether	24	20	"	20
10	"	HOAc/cyclohexane	24	20	"	24
11	$NaOH/O_2$	H_2O	12	100	phthalaz-1,4-dione	81
12	$CuSO_4/O_2$	1N HCl	84	100	phthalazine	7
13	chloranil	H_2O	14	40	"	45
					phthalonitrile	52

TABLE 1 (Contd.)

Oxidation products of 1,4-Dihydrazinophthalazine.

Reaction	Oxidant	Solvent	time (hr)	temp.	Product	% Yield
14	benzoquinone	H_2O	14	20°	phthalonitrile	39
15	bromine	"	3	20	"	23
16	nitrobenzene	nitrobenzene	0.2	180	phthalazine	63
17	azobenzene	azobenzene	0.5	165	"	19
18	sodium hypochlorite	4$\underline{N}$ HCl	2	20	4-chlorophthalazone	89
19	"	1.4$\underline{N}$ HCl	0.2	-15	"	76
20	sodium periodate	2$\underline{N}$ H_2SO_4	0.2	70	phthalaz-1,4-dione	95
21	"	4$\underline{N}$ HCl	0.3	70	4-chlorophthalazone	62
22	$\underline{N}$-bromosuccinimide	$CHCl_3$	0.5	60	4-bromophthalazone	42

give an intermediary carbanion. Additional evidence for the ionic

$$R_1R_2\,CH\text{-}N = NH \longrightarrow R_1R_2\,\overset{-}{C}H \longrightarrow R_1R_2CH_2$$

$$R\,CO\,N = NH \longrightarrow \overset{-}{R}CO \longrightarrow RCHO$$

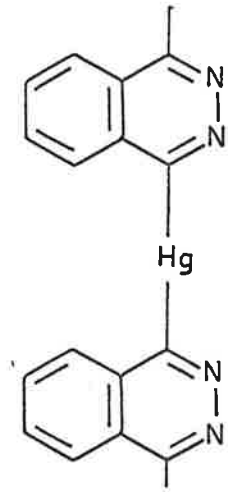
mechanism is the partial retention of configuration observed[101] during the base-catalysed decomposition of alkyl diimines. The complete

$$\overset{*}{R}\text{-}NH\text{-}NH_2 \longrightarrow \overset{*}{R}\text{-}N = NH \longrightarrow$$

$$\overset{*}{R}^{-} \;\ldots\ldots\; HB \longrightarrow \overset{*}{R}H \;+\; B^{-}$$

racemisation which occurred in the absence of base was explained on the basis of homolytic decomposition. The lower yields of phthalazine obtained in non-polar solvents can thus be attributed to slow, homolytic degradation of the diimino groups (reactions 5, 8, and 9).

Infra-red spectra and ignition tests of residues from the oxidation of 1,4-dihydrazinophthalazine revealed the presence of organic material but none could be extracted using a variety of solvents. Earlier workers reported the formation of mercury compounds from the oxidation of primary hydrazines with mercuric oxide.[102] Presumably nucleophilic displacement of nitrogen by the metal occurred, as in the replacement of sulphinyl and labile carboxyl functions by mercury and mercuric ions.[103-105] A similar transformation in the phthalazine system would conceivably give rise to a mercury polymer (51). The formation of such



(51)

a derivative would be favoured by a high concentration of mercuric ion, and is consistent with the 40% yield of phthalazine obtained from an oxidation using excess mercuric acetate (reaction 6); the starting material was completely consumed. The use of a mixture of mercuric oxide and mercuric chloride gave phthalazine in even lower yield (reaction 7).

Mercury aryls generally react with sodium at room temperature with displacement of mercury[106] but the above residue was unaffected even after reflux in toluene. A small quantity of tarry material was liberated by treating the residue with bromine but attempts at further purification were unsuccessful.

The synthesis of substituted phthalazines by the mercuric oxide method appears to be limited by the difficulty in preparing the appropriate dihydrazino derivatives; 6-chlorophthalazine was prepared, however, and a number of azaphthalazines have been subsequently obtained[95] by this route.

Oxidation of 1,4-dihydrazinophthalazine with silver oxide was attempted in several solvents (reactions 8, 9, and 10) but the yields of phthalazine were inferior to those obtained using mercuric oxide. Alkaline decomposition of primary hydrazines offers an alternative route to diimines.[98] It was hoped that 1,4-dihydrazinophthalazine

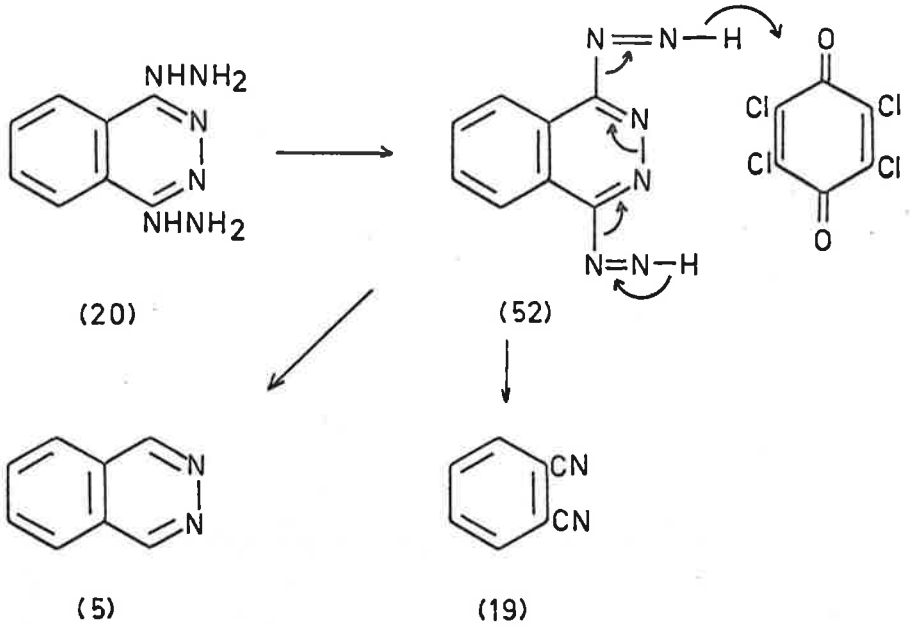
$$NH_2NHTs \xrightarrow{^-OH} NH = NH + p\text{-}CH_3C_6H_4SO_2H$$

would decompose to phthalazine in a similar fashion but nucleophilic displacement of the hydrazino groups by hydroxide ion gave phthalaz-1,4-dione as the only product (reaction 11). The methods employed by Corey,[98] involving oxidation in the presence of cupric ion, were also ineffective. 1,4-Dihydrazinophthalazine formed a copper complex which provided a very low yield of phthalazine on prolonged reflux in aqueous acid (reaction 12).

Another approach to the diimine system was made using quinones. These have proved useful for dehydrogenation between carbon atoms and between a carbon and a nitrogen atom[107] but little synthetic use has been made of the ability of quinones to oxidise hydrazine groups. Benzene is obtained from phenylhydrazine,[108] whereas 2-nitro and 2,4-dinitrophenylhydrazines give condensation products identical with those obtained by coupling 2-nitro-and 2,4-dinitrobenzenediazonium salts with phenol.[109] Dehydrogenation of the hydrazine groups in 1,4-dihydrazino-phthalazine to the diimine functions would lead to the formation of phthalazine by the same route as oxidation with mercuric oxide. The

possibility of a side reaction was evident from blank experiments which showed that although phthalazine was unaffected by chloranil, it formed a complex quantitatively with the reduction product, tetrachloroquinol; the phthalazine could be recovered by alkaline decomposition of the complex.

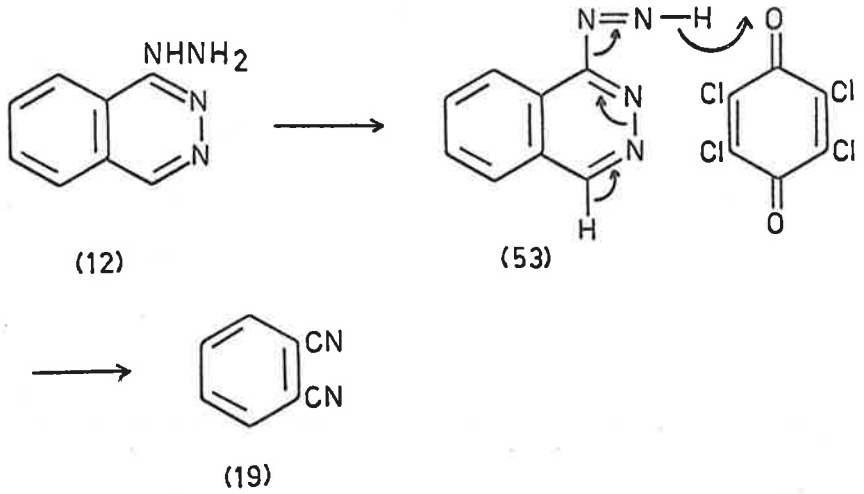
Brisk evolution of nitrogen occurred when 1,4-dihydrazinophthalazine was warmed with an aqueous suspension of chloranil and the reaction was complete after the addition of 2.5 moles of oxidant. The dark brown solid was filtered, washed with hot water and digested in alkali. The filtrate and washings yielded phthalonitrile and phthalazine was obtained by extraction of the alkaline solution (reaction 13, Table 1). This result is consistent with the formation of 1,4-bis-diiminophthalazine (52) which may decompose directly to phthalazine or undergo further oxidation and subsequent decomposition to phthalonitrile (19) (Scheme 14). Although a concerted electron movement is illustrated for the



Scheme 14.

latter step a stepwise process involving the 4-diiminophthalazine-1-diazonium salt is equally possible. The isolation of equal quantities of phthalazine and phthalonitrile accounts for the consumption of 2.5 moles of oxidant. Reactions carried out in organic solvents gave low yields of the same ratio of products due to the low solubility of 1,4-dihydrazinophthalazine. The ability of benzoquinone to react at room temperature is attributed to its greater solubility in water than chloranil., (reaction 14); only phthalonitrile was obtained.

The controlling factors in the oxidation of hydrazine groups with quinones are not clear. Attempts in the present work to change the product ratios by varying the temperature and by the addition of bases were unsuccessful. Bromine water was also found to effect ring cleavage in 1,4-dihydrazinophthalazine, forming phthalonitrile and a large amount of intractable material (reaction 15). The reaction of two moles of chloranil with 1-hydrazinophthalazine (12) yielded phthalonitrile; hydride ion abstraction from the diimine nitrogen (53) is considered more likely than from the electron-deficient 4-position (Scheme 15).

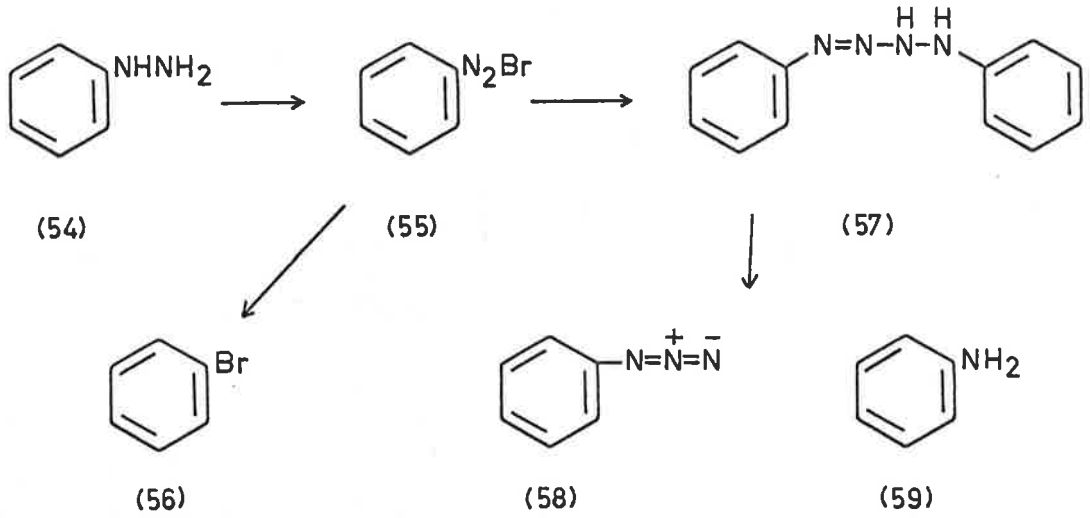


Scheme 15.

Azobenzene and nitrobenzene reacted with 1,4-dihydrazinophthalazine at high temperatures to give variable yields of phthalazine (reactions 16 and 17), formed presumably *via* the diimine intermediate. A number of red, high melting point solids were obtained which have not been identified.

Recent investigations[110] into the oxidation of monohydrazinopyridazines with hypohalous acids have established the existence of short-lived diazonium salts which rapidly decomposed under the reaction conditions to hydroxy and halogeno derivatives. On treating an acidic solution of 1,4-dihydrazinophthalazine with sodium hypochlorite (reaction 18), nitrogen was vigorously evolved and a high yield of 4-chlorophthalazone was obtained. Evidently this reaction also proceeds *via* a diazonium salt intermediate, which may form the product directly by attack of chloride ion and water. Alternatively, replacement of both diazo groups by chloride ion would give 1,4-dichlorophthalazine which undergoes rapid hydrolysis to 4-chlorophthalazone in acid solution.[41] An attempt to isolate 1,4-dichlorophthalazine from the reaction mixture by reducing the time, temperature and acid concentration was unsuccessful (reaction 19). Oxidation of 1,4-dihydrazinophthalazine with sodium periodate yielded phthalaz-1,4-dione in sulphuric acid solution (reaction 20) and 4-chlorophthalazone in the presence of chloride ion (reaction 21). To confirm the presence of a diazonium salt intermediate, 1,4-diaminophthalazine was diazotised in both hydrochloric and sulphuric acid solutions and the same products were obtained as from the oxidation of 1,4-dihydrazinophthalazine in these media.

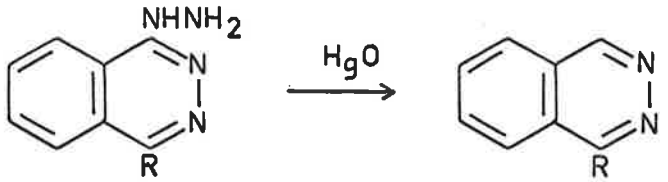
The mechanism of the oxidation of 1,4-dihydrazinophthalazine with N-bromosuccinimide (reaction 22) is not clear; decomposition of a diazonium salt or homolytic displacement of diimine groups by bromine atoms would both lead to the formation of 1,4-dibromophthalazine and finally its hydrolysis product, 4-bromophthalazone. The oxidation of phenylhydrazine with one mole of N-bromosuccinimide in carbon tetrachloride was reported by Barakat and coworkers[111] to give hydrazobenzene in 87% yield. On repetition of this experiment during the present work, no hydrazobenzene could be isolated but instead a mixture of bromobenzene, phenylazide and aniline was obtained. The first step in the reaction is considered to be oxidation of phenylhydrazine (54) to benzenediazonium bromide (55) which may decompose to bromobenzene (56) and nitrogen or combine with excess phenylhydrazine to form the tetrazine (57) (Scheme 16). Disproportionation of the latter to phenyl azide (58) and aniline (59) is a well-known process.[112]



Scheme 16.

When anhydrous benzenediazonium bromide was prepared by the method of Chattaway,[113] involving the reaction of bromine with phenylhydrazine in ethanol, a similar transient purple colouration was observed as in the above reaction. Furthermore, the salt yielded bromobenzene when refluxed in carbon tetrachloride. Since the formation of benzenediazonium bromide from phenylhydrazine requires two moles of N-bromosuccinimide, half the starting material was recovered. However, when the reaction was carried out using two moles of oxidant some phenylhydrazine still failed to react because of the formation of the insoluble hydrogen bromide salt. In cold, aqueous solution, phenylhydrazine and N-bromosuccinimide produced phenyl azide and aniline but no bromobenzene; formation of the diazonium salt was demonstrated by coupling with 2-naphthol. By working up under aqueous conditions a reaction carried out in carbon tetrachloride, a small quantity of 2,4,6-tribromophenol was isolated. The same product was obtained by Chattaway[113] on treating benzenediazonium bromide with water. It appears, therefore, that the oxidation of phenylhydrazine with N-bromosuccinimide proceeds *via* the diazonium salt under both anhydrous and aqueous conditions. At no stage was hydrazobenzene detected, contrary to the report of Barakat and coworkers who based their structure assignment on the melting point alone.

Several monohydrazinophthalazines (60; R = H, OH, CH_3, Ph) were successfully oxidised to 1-substituted derivatives (61) by mercuric oxide, the method having synthetic value where the chloro compounds from which the hydrazines are prepared cannot be reduced directly.



(60) (61)

Attempts to obtain satisfactory yields of hydrazines from the o-keto-nitriles (21; R = H, CH_3) mentioned earlier (p.6) were unsuccessful.

Pyridazine was obtained from 3,6-dihydrazinopyridazine in 57% yield on treatment with mercuric oxide, while 3-chloro-6-hydrazino-pyridazine provided 3-chloropyridazine which had previously been prepared[22] by a more tedious procedure.

CHAPTER 2.

Reactions of phthalazine with Halogens.

2.1 Addition compounds.

In 1858 the action of bromine on pyridine in water was reported by Anderson[113] to give an adduct. A considerable number of complexes between halogens and nitrogen heterocycles are now known but in many cases the structures have not been established. Even the constitution of some of these substances has been a subject of disagreement in the literature. The terms "complex", "adduct", and "perhalide" are commonly used in the nomenclature of these systems; in the present work, individual complexes will be named as perhalides or halogen halides.

Anderson obtained from pyridine a red crystalline substance to which he assigned the formula $C_5H_5N.Br_2$. The same formula was suggested by Hofmann[114] for an orange adduct prepared from bromine and pyridine hydrochloride and which was found to decompose at 200° to a bromopyridine. Grimaux[115] recrystallised a similar adduct from chloroform, obtaining red plates from which pyridine was recovered by alkaline decomposition. Analysis indicated the formula $(C_5H_5Br_2)_2HBr$. In a detailed study of the reaction of halogens with pyridine, Trowbridge and Diehl[116] prepared a substance by the action of bromine on pyridine hydrobromide in water and assigned to it the formula $(C_5H_5N.HBr)_2Br_3$. A lower molecular weight derivative, $C_5H_5N.HBr.Br$, was also isolated. The addition of excess bromine to pyridine in chloroform gave a dark red 1:2 adduct, $C_5H_5N.Br_4$, which lost bromine on standing and formed a yellow 1:1 complex. In carrying out halogen analyses of the above

compounds, Trowbridge and Prescott[117,118] differentiated between "active" or reducible halogen and halogen present as halide ion.

The usefulness of carbon tetrachloride as the solvent in the preparation of halogen complexes was noted by Williams[119] in 1931. Equimolar quantities of bromine and pyridine in this medium gave a red 1:1 adduct of lower melting point than those previously described. Addition of bromine to pyridine hydrobromide in acetic acid[120] gave a substance which had an active bromine content corresponding to the formula $C_5H_5N.HBr.Br_2$.

Most of the complexes described above appear from their melting points to be different even where the analyses are similar. Such inconsistencies in the literature may be accounted for by the formation of non-integral ratios of heterocycle to halogen according to the concentrations of the reactants. Furthermore, mixtures of adducts may be isolated which would confuse the analysis results. Similar discrepancies have been observed in the reaction of pyridine with chlorine and iodine;[113,116,121] two molecules of iodine were detected in the adduct with pyridine[118] but only one molecule of chlorine.[121,122] Pyridine also forms adducts with fluorine[123] and a variety of mixed halogens.[116, 124, 125, 126]

Conflicting reports concerning quinoline perbromides[127,128,129] were critically examined by Eisch[130,131] who concluded that the methods of preparation may have resulted in decomposition of the initial product. Eisch obtained a 1:1 adduct by mixing equimolecular quantities of bromine and quinoline in carbon tetrachloride at room temperature in the absence

of light. Acridine has been found to add chlorine, bromine and iodine, ratios of approximately 1:1 and 1:2 being observed.[132,133,134]

Halogen adducts with nitrogen heterocycles generally lose the halogen slowly on standing and are readily decomposed to the parent bases by alkali or sodium thiosulphate. Decomposition by iodide ion, followed by titration of the liberated iodine with sodium thiosulphate has proved a useful method for the determination of active halogen in these adducts.[130] Pyridine perbromide has been used as a brominating agent[135] and is thought to act as a source of bromine cations.[133] In fact, pyridine perbromide undergoes rearrangement on heating to form 3-bromopyridine and nuclear-brominated products are also obtained by heating the quinoline and acridine perbromides.[130,134]

No halogen complexes of ring systems with more than one nitrogen appear to have been reported. The aim of the present investigation, therefore, was to prepare a series of complexes between halogens and phthalazine for comparison with those from the monoaza-aromatic series.

Phthalazine was treated with excess liquid chlorine at -60° and the yellow slurry then allowed to reach room temperature. A yellow, free-flowing powder was obtained which evolved chlorine too rapidly for satisfactory analyses or physical data to be obtained. The increase in weight, however, based on the phthalazine used, corresponded to a 1:2 complex with the formula $C_8H_6N_2.Cl_4$. Decomposition of the adduct in air and water will be discussed in section 2 of this chapter.

The addition of bromine to a solution of phthalazine in either

water or carbon tetrachloride gave an immediate yellow, microcrystalline precipitate which was recrystallised from chloroform without decomposition. Iodometric and microanalyses indicated the formula $C_8H_6N_2 \cdot Br_2$. The substance was stable to light, air and moisture, although prolonged exposure to the atmosphere resulted in some loss of bromine and the sample assumed a reddish tinge. Phthalazine was recovered after iodometric analysis of the complex and after alkaline decomposition. Nearly quantitative yields of the perbromide were achieved by adding a large excess of bromine to phthalazine in carbon tetrachloride and the product after drying in vacuo gave the same bromine analysis.

A number of halogen complexes were similarly prepared by mixing solutions of phthalazine and the halogen in carbon tetrachloride. Some physical properties and the analytical figures of these complexes are shown in Table 2. The halogen analyses were performed iodometrically on freshly-prepared samples and, with the exception of the iodine trichloride complex, were in good agreement with the calculated values. Analysis for carbon, hydrogen and nitrogen could only be carried out several days after preparation but excellent agreement was again obtained. Iodine monochloride and iodine bromide formed 1:1 and 1:2 adducts with phthalazine, depending on the amount of halogen used; only 1:1 ratios were detected using excess bromine, iodine or iodine trichloride. Nearly quantitative yields could be obtained in each case if the solutions were sufficiently concentrated. Phthalazine iodine trichloride hydrogenperiodate was prepared by adding phthalazine to a solution obtained by treating aqueous potassium iodide with chlorine. A solution of iodine in aqueous potassium

TABLE 2.

Halogen complexes of phthalazine.

Complex	Colour	m.p. °C	Solubility in $CHCl_3$	Found %				Calc. %			
				C	H	N	Halogen	C	H	N	Halogen
$R.Br_2$	yellow	116	slight	32.85	2.14	9.28	55.0	33.13	2.09	9.97	55.1
$R.I_2$	brown	137	moderate	24.79	1.63	7.08	66.6	25.02	1.58	7.30	66.2
R.ICl	pale yellow	189-190	v.slight	32.68	2.14	9.47	55.5	32.85	2.07	9.58	55.4
$R.(ICl)_2$	yellow	167-169	v.slight	21.82	1.48	6.32	71.1	21.12	1.33	6.16	71.4
R.IBr	yellow	172-173	slight	28.70	1.90	8.19	61.6	28.51	1.80	8.31	61.4
$R.(IBr)_2$	orange	124-126	slight	17.60	1.35	5.04	75.9	17.66	1.11	5.15	76.1
$R.ICl_3$	pale yellow	130-132	insol.				64.23				61.2

footnote: R = phthalazine.

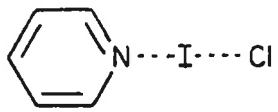
iodide gave phthalazine hydrogen triodide, from phthalazine hydrochloride.

The 1:1 complexes containing mixed and therefore more polarised halogens (ICl, ICl_3 and IBr) appeared to be more stable than phthalazine perbromide and periodide with regard to loss of halogen to the atmosphere. The 1:2 iodine bromide complex liberated some halogen over a period of several weeks, as did the perbromide and periodide. All of the complexes appeared to be unaffected by light in contrast to the instability of quinoline perbromide reported by Eisch.[131]

Phthalazine was recoverable from the complexes after iodometric analysis or decomposition in sodium hydroxide. When phthalazine perbromide was heated in ethanol, the bromine was reduced to hydrogen bromide which yielded phthalazine hydrobromide. On boiling an aqueous suspension of the perbromide, bromine was evolved and phthalazine was recovered but the addition of excess bromine to the boiling solution over a long period gave a low yield of phthalic acid. Phthalazine hydrogen tribromide was obtained using acetic acid as the solvent while chloroform gave a mixture of phthalazine-bromine complexes of unknown constitution. Phthalazine perbromide decomposed to a black tar on heating in carbon tetrachloride and phthalazine was the only discrete product which could be isolated. The absence of brominated phthalazines in these reactions is not surprising in view of the fact that the pyridine and quinoline perbromides give almost exclusively β-substituted derivatives; a position of similar environment is not present in the phthalazine ring.

The structures of the perhalides of heterocycles have been a subject of considerable speculation in the literature. X-ray analysis

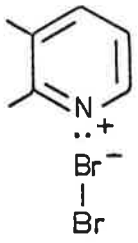
of the complexes formed between pyridine and iodine monochloride[136] and γ-picoline and iodine[137] indicated a linear arrangement of heterocycle and halogen by bonding through the nitrogen (62). The addition compounds



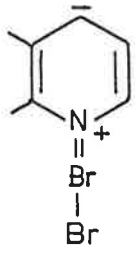
(62)

of halogens and tertiary amines had similar structures.[138] Such definitive data, however, is not available for the majority of the known halogen complexes and the relative merits of at least three possible structures need consideration. One possibility[131] is "dicoordinate complexation" of the type $(R_3N)_2Br^+Br_3^-$. Analogous structures have been proposed for the perchlorates of the diquinoline- and diisoquinoline-bromine cation[139a] and for iododipyridinium salts.[139b] Charge-transfer bonding involving the π-electrons of the heterocycle is another possibility.[140] The third proposed structure is that indicated by the X-ray studies; the nitrogen lone pair is assumed to take part in Lewis-base bonding to form an n-donor complex of the type $R_3N \rightarrow Br\text{-}Br$.

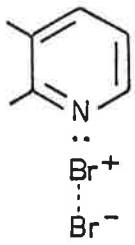
Detailed studies of the quinoline and acridine systems by Eisch[131] and by Chandler[134] have led these workers to believe that the perhalides exist as n-donor complexes. The electronic structure of the addition compounds was represented as a resonance hybrid of three contributing structures (63a-c). The infrared and ultraviolet absorption



(63a)



(63b)



(63c)

spectra of the complexes closely resembled those of the heterocyclic cations and, more significantly, the stability of the quinoline complex was similar to that of an n-donor type and much greater than the stability of π-donor complexes. The dicoordinate structure was excluded by the lack of tribromide ion absorption in the ultraviolet spectrum.

In attempting to deduce the structures of the phthalazine-halogen complexes, their infrared spectra in Nujol were compared with the infrared spectra of phthalazine, phthalazine hydrochloride and phthalazine methiodide (Table 3.). The spectra of the 1:1 adducts closely resemble that of phthalazine hydrochloride, particularly in the 900-1000 cm^{-1} range where three bands appear close to 920, 940 and 970 cm^{-1}. Phthalazine and phthalazine methiodide showed less similarity. All of the compounds gave an intense band near 760 cm^{-1} with the exception of phthalazine methiodide which exhibited a pair of bands at 765 and 770 cm^{-1}. A striking similarity was observed between the iodine monochloride and iodine bromide 1:2 complexes both in band intensity and positions (650, 760, 930, 965, and 1165 cm^{-1}.). The bands in these complexes, although fewer than in the 1:1 adducts, occurred quite close to the corresponding absorptions of the latter. It can therefore be concluded that the infrared spectra evince some similarity in structure

TABLE 3

Infrared maxima of phthalazine derivatives in Nujol

R	R.HCl	R.MeI	$R.Br_2$	$R.I_2$	R.ICl	$R.(ICl)_2$	R.IBr	$R.(IBr)_2$
1620w	1600m	1590m	1610w	1610w	1610m	1605w	1605m	1605w
1580w	1590w	1580m	–	–	–	–	1565w	–
1485w	1485w	1475s	1485w	1480w	1485w	–	1480w	1480w
1375m	–	1350m	1310w	1310m	1310m	1315m	1310m	1305w
1305m	–	1315m	1300w	–	–	–	–	–
1275m	1285w	1280m	1275m	1270m	1270m	–	1270m	1270w
1245m	1265m	–	–	1240w	1235w	1225w	1235w	–
1210m	1210m	1230m	1210w	1210m	1210m	–	1210s	1205w
1150w	–	1160m	1160w	1155w	–	1165m	–	1195m
1130w	–	1120w	1130w	–	–	–	–	–
1010w	1050w	–	–	–	–	–	–	–
970m	980w	990m	990m	–	–	–	–	–
960w	970m	970w	970w	965m	975m	965s	970m	965w
950w	950s	940m	940m	935m	930m	930m	930s	955s
915s	920m	–	920s	920s	920m	–	920s	920m
–	905w	910m	910w	–	–	–	–	–
–	–	880m	–	–	–	–	–	–
810w	810s	–	–	–	–	–	820w	–
–	–	770s	–	–	–	–	790w	790w
765s	765s	765s	760s	755s	755s	760s	755s	750s
640m	–	–	645m	645m	645m	650m	645m	640m

Footnotes: (a) R = phthalazine

(b) Intensities are shown as weak (w), medium (m) or strong (s).

between the phthalazine-halogen complexes and the phthalazinium system.

Determination of the ultraviolet spectra of these compounds was hampered by their low solubility in carbon tetrachloride. In each case a broad maximum at 290-296 mμ was observed, in agreement with the absorption of quinoline perbromide at 290 mμ.[131] This contrasts with the absorption at 346 mμ of the π-complex between bromine and naphthalene.[141] Eisch[131] was able to measure the stability constant of quinoline perbromide by spectroscopic methods and obtained a value of 115 , compared with 0.23 for naphthalene. Although similar measurements could not be made in the phthalazine system, the perbromide appeared from its slow rate of loss of bromine to be more stable than the quinoline adduct and would therefore possess the n-donor structure.

Nuclear magnetic resonance (n.m.r.) spectra of halogen complexes have not previously been reported. The spectra of some of the phthalazine-halogen complexes in deuterochloroform are shown in Table 4. With the exception of phthalazine periodide, the spectra consisted of one signal which was evidently produced by the four carbocyclic ring protons. Since the complexes were only slightly soluble in deuterochloroform the less intense absorption of the two heterocyclic ring protons, which occurs in phthalazine at τ 0.44, was not observed. The more soluble iodine complex gave peaks at τ 0.50 and τ 1.97 in the ratio 1:2. The A_2B_2 system in the benzo ring of phthalazine is spread over about 30 c.p.s. ; the main absorption band occurs at τ 2.18 and has a width of 11 c.p.s. In the complexes, however, only one band 5 cycles wide was observed. This data may be explained by extending

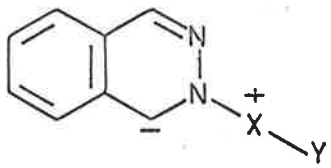
TABLE 4

The n.m.r. spectra of phthalazine-halogen complexes.

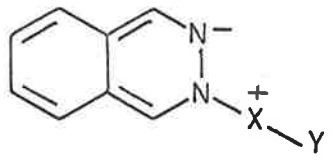
Complex	τ
$R.Br_2$	1.97
$R.I_2$	1.97, 0.50
R.ICl	1.89
$R.(ICl)_2$	1.93
R.IBr	1.91
$R.(IBr)_2$	1.89

footnote: R = phthalazine

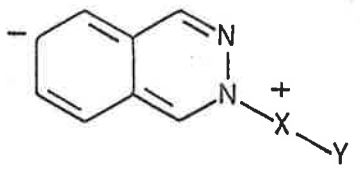
the back-coordination concept mentioned by Eisch.[131] It is now suggested that structures of the type (5a-c) may be better representations of back-donation of electrons to the ring than (63b) which



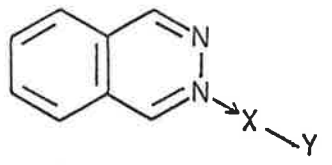
(5a)



(5b)



(5c)



(5d)

contains a triply-bound bromine. Delocalisation of the negative charge over the diazine ring is favoured by the electronegative heteroatoms

(5b) and the increased electron density at the 1- and 4- positions (5a) would cause these protons to shift upfield in the n.m.r. spectrum, as observed in phthalazine periodide. Delocalisation into the carbocyclic ring (5c) would increase the electron density at the 6- and 7- positions, which in the parent system are more electron-deficient than the 5- and 8- positions. Apparently the delocalisation is sufficient to nearly equate the electronic environments of all four protons so that one relatively narrow signal is obtained. The down-field shift of this peak relative to phthalazine results from donation of the nitrogen lone pair electrons to bromine (5d). The spectrum of phthalazine methiodide also showed a down-field shift (τ 1.45). If back-coordination plays a significant part in bonding, the more electropositive halogen should be attached to the nitrogen when mixed halogens are used. This has already been demonstrated by the x-ray studies.[136] In the present work, the chemical shifts of the 1:1 iodine monochloride and iodine bromide complexes were almost identical, perhaps indicating that the iodine atom in each case is attached to nitrogen. Furthermore, iodine monochloride forms the most stable complexes both in the phthalazine and pyridine series. This may be explained on the basis that iodine monochloride, being the most polar mixed halogen, would be most susceptible to n-donation from nitrogen.

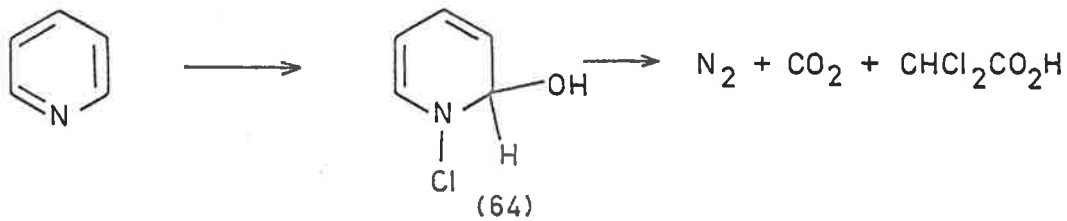
Previous investigations into the halogen complexes of heterocycles have not attempted to correlate their stability with the basicity of the parent system. The existence of such a relationship was evident in the present work when it was found that quinoxaline (pKa 0.7)[53] and

bromine formed an unstable adduct which rapidly decomposed to the constituents. It has been stated in the literature[142] that the formation of perhalide hydrogen halide complexes of the type $R_3N.Br_2.HBr$ demonstrates the ability of protonated nitrogen to form halogen complexes, whereas the theory outlined earlier requires donation of electrons from a basic nitrogen. These "anomalous" adducts, however, can be assigned the salt structure, $R_3\overset{+}{N}H.\overset{-}{X}_3$, in which the halogen is bound to the halide to form a trihalide ion. In the present work, attempts to prepare such complexes from phthalazine hydrochloride and hydrobromide gave only phthalazine perbromide. No bromine complex could be obtained from phthalazine-2-oxide where one nitrogen lone pair is bound to oxygen and the second nitrogen is weakly basic.

In summary, it appears that phthalazine and a variety of halogens form addition compounds which are more stable than those of mono-azines. They are considered to be n-donor complexes where increased stability is achieved by back-coordination of electrons from the halogen to the ring.

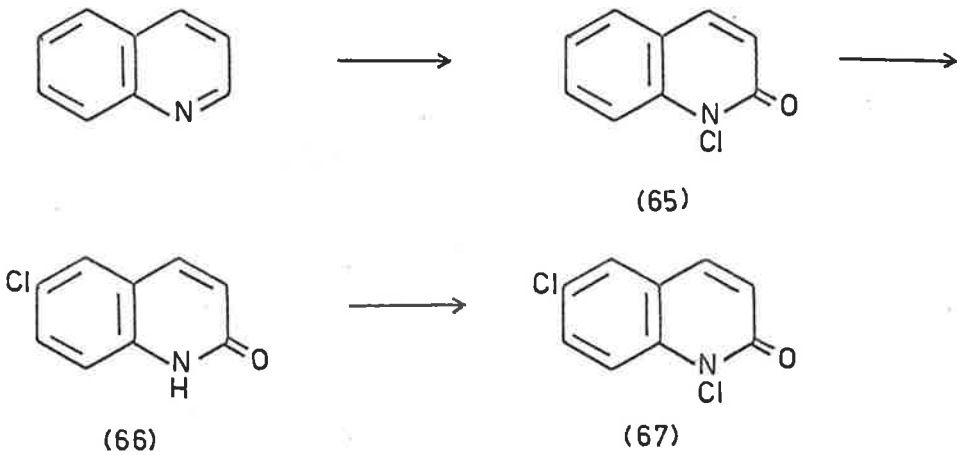
2.2 Reactions with chlorine and chlorinating agents.

The passage of chlorine into aqueous pyridine was reported in 1887 to give nitrogen, carbon dioxide and dichloroacetic acid.[121,143] Kaiser[121] postulated the formation of N-chloro-2-hydroxy-1,2-dihydropyridine (64) as an intermediate (Scheme 17) and isolated an unstable compound with a similar formula but offered no proof for its structure other than analytical figures. A detailed investigation of the action



SCHEME 17.

of hypochlorous acid on quinoline was carried out by Einhorn and Lauch.[144] The primary product was considered to be N-chloroquinolone (65) which underwent rearrangement (Scheme 18) to 6-chloroquinolone (66) in a manner analogous to the rearrangement of N-chloroacetanilide. Further chlorination provided the N-chloro derivative (67). No rearrangement occurred when the 6-position was blocked by a methyl group.

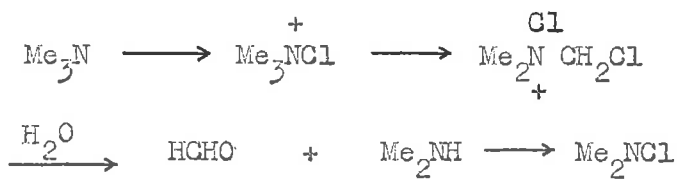


SCHEME 18.

The oxidation of acridine and phenanthridine with calcium hypochlorite in the presence of cobalt was reported[145] to give low yields of acridone and phenanthridone. Exhaustive chlorination of barbituric acid in alkaline solution yielded dichloroacetylurea[146]

whereas addition of hypochlorous acid to the 4,5 C=C bond occurred in some uracil derivatives.[147] Other reports of the action of aqueous chlorine on nitrogen heterocycles appear to be confined to the formation of azo compounds[148-151] and N-chloro derivatives[149] from primary amines. Schiff bases form 1:1 adducts with chlorine and bromine which on decomposition in water give aldehydes and p-halogenoanilines.[152,153]

Triethylamine yielded formaldehyde and N-chlorodimethylamine on treatment with aqueous chlorine.[154] The mechanism was considered to involve C-chlorination of the N-chlorotrimethylammonium ion followed by hydrolysis (Scheme 19), the overall process resulting in oxidation whereas the Schiff bases suffered only hydrolysis.



SCHEME 19.

The reaction of aqueous chlorine with nitrogenous bases may therefore yield several products; an amide, an N-chloroamide or products resulting from fission between the nitrogen and an adjacent carbon atom.

The 1:2 complex between phthalazine and chlorine described in the previous section was allowed to stand in the atmosphere at room temperature. Chlorine was rapidly liberated at first and after several days o-dichloromethylbenzaldehyde was obtained, together with phthalazine hydrochloride. The structure of the former was deduced

from its analytical figures, n.m.r. spectrum and by hydrolysis to phthalaldehyde. The dichloroaldehyde was also obtained by passing chlorine into a solution of phthalazine in carbon tetrachloride. When the freshly prepared complex was treated with water, nitrogen was vigorously evolved and a mixture of phthalaldehyde and o-dichloromethylbenzaldehyde was produced. The passage of chlorine into an aqueous solution of phthalazine gave a similar ratio of the same products and a series of reactions were then carried out using solutions of phthalazine over a range of pH. The results are summarised in Table 5. Before attempting to formulate a mechanism for these reactions, some environmental factors will be discussed.

Since nitrogen is evolved from the reactions described in Table 5, part of the chlorine must undergo reduction to hydrogen chloride which will lower the pH of the solution. The pH of chlorine water, calculated from the dissociation constant given by Hagisawa,[155] is 3.68; thus the chlorinations carried out in water alone would commence at a pH close to 3.7 which would rapidly decrease as the reaction proceeds. In fact, the final pH was found to be less than 2, while in the buffered solutions the pH reached approximately 4 after exhaustive chlorination. Phthalazine is completely stable at room temperature in both aqueous alkali and acid at all concentrations. The amount of chlorine gas used in these reactions affected the total product yield but not the product ratios, except in reactions 9 and 10 (Table 5.). The measurement of chlorine gas added was therefore not attempted.

It is evident from Table 5 that phthalaldehyde was formed

TABLE 5.

Products from the reaction of chlorine with phthalazine

Reaction	Medium	Time of Addition (Min.)	Time of Reaction (Min.)	% PRODUCTS				
				Phthalazine	Phthalaldehyde	o-dichloromethylbenzaldehyde	N-chlorophthalazone	Others
1	H_2O	15	15		84	10		
2	Buffer pH 3.4	15	15		87	11		
3	Buffer pH 4.5-7	15	15		35	6	40	
4	Buffer pH 6	30*	30	26	44	5	19	
5	Buffer pH 6	0.5*	2	23	64	8		
6	NaOH pH 8.5	15*	15	31	15		27	A; 23
7	NaOH pH 10	10*	120	65	trace		trace	A; 26
8	2N NaOH	10	16 hr.	90				B; 7
9	20% NaCl	15	15	12	40	40		
10	20% NaCl	0.5*	2	45	31	17		
11	HCl, 1 equiv.	15	15	84		12		

Footnotes: * not exhaustive chlorination A = phthalaldehydic acid B = phthalide

over the whole pH range. Under alkaline conditions nitrogen was evolved very slowly and the phthalaldehyde produced was oxidized to phthalaldehydic acid (reactions 6 and 7). In strong base (reaction 8) phthalide was formed, in agreement with previous reports[196] of the internal Cannizzaro reaction of phthalaldehyde in this medium. Both of these artifacts were obtained in good yield by treating phthalaldehyde with chlorine under the same conditions.

o-Dichloromethylbenzaldehyde was formed in a nearly constant ratio to phthalaldehyde in reactions carried out below pH 7. The amount of the former was markedly increased, however, by the presence of added chloride ion (reactions 9 and 10) and, in the case of phthalazine hydrochloride, (reaction 11), was the sole product.

The formation of N-chlorophthalazone was only observed in the pH range 4-8.5. The maximum yield was obtained at pH 7, decreasing slightly at pH 4 and more markedly at pH 8.5 (reactions 3 and 6). Slow addition of chlorine water to phthalazine at pH 6 gave 19% of the N-chloroamide (reaction 4) whereas extremely rapid addition (reaction 5) produced aldehydes alone. To test the scope of the reaction of chlorine with heterocycles, the chlorination procedure was applied to a number of azines (Table 6.).

The equilibria in chlorine water permit the formation of hypochlorous acid, hypochlorite ion, hypochlorous hydronium ion and chlorine monoxide as shown in equations 1-5.

TABLE 6.

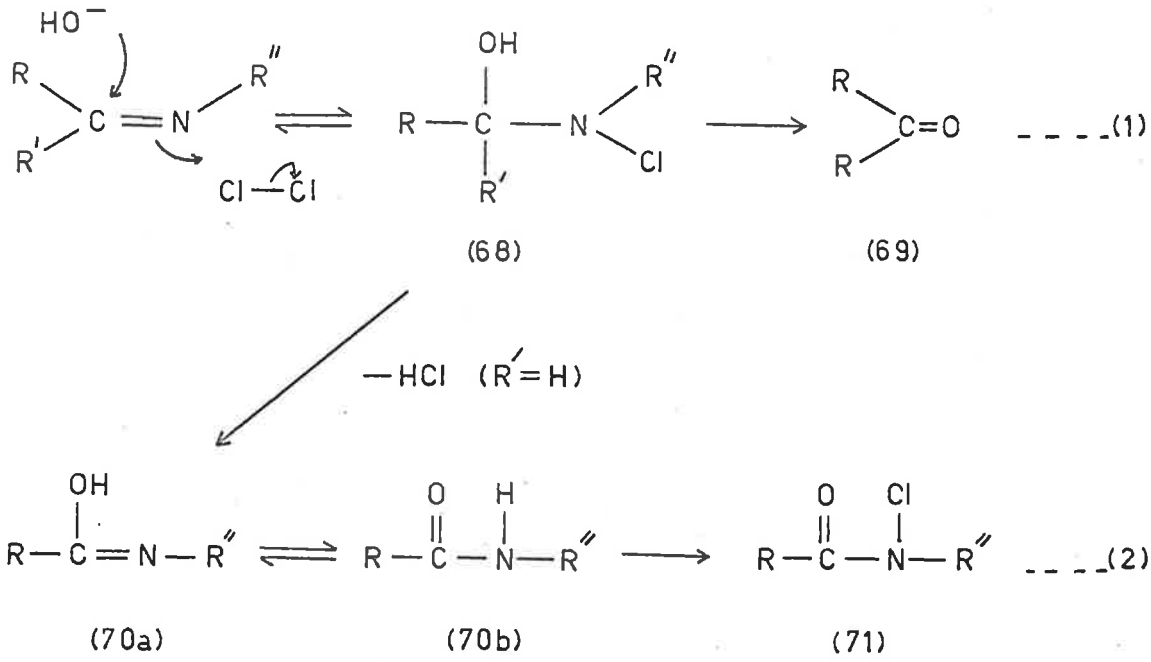
Products from the reaction of chlorine with azines

Reaction	Substrate	Product	Yield %
1	benzylideneazine	benzaldehyde	92
2	1-methylphthalazine	o-acetylbenzaldehyde	61
3	1,4-diethoxyphthalazine	diethylphthalate	54
4	benzo[g]phthalazine	naphthalene-2,3-dialdehyde	88
5	1-aminophthalazine	o-cyanobenzaldehyde	94
6	1,4-diaminophthalazine	1,4-di(N-chloroimino)-1,4-dihydrophthalazine	91
7	phthalaz-1,4-dione	phthalic anhydride	88
8	1-phenylphthalazine	2-chloro-4-phenylphthalazone	56
9	1-chlorophthalazine	2,4-dichlorophthalazone	79
10	5,8-dibromophthalazine	3,6-dibromophthalaldehyde	35
11	quinoxaline	2,3-dihydroxyquinoxaline	81
12	2,3-diphenylquinoxaline	benzil	25

$Cl_2 + H_2O$	$HOCl + HCl$	(1)
$2Cl_2 + H_2O$	$Cl_2O + 2HCl$	(2)
$HOCl$	$ClO^- + H^+$	(3)
$HOCl + H^+$	$ClOH_2^+$	(4)
$2HOCl$	$Cl_2O + H_2O$	(5)

Kinetic studies of the chlorination of olefins and aromatic systems in aqueous media have shown that, of the above species, chlorine is by far the most powerful chlorinating agent,[157,158] followed by chlorine monoxide and hypochlorous acid. The rate of chlorination with the latter was found to be markedly increased by traces of chlorine.[159]

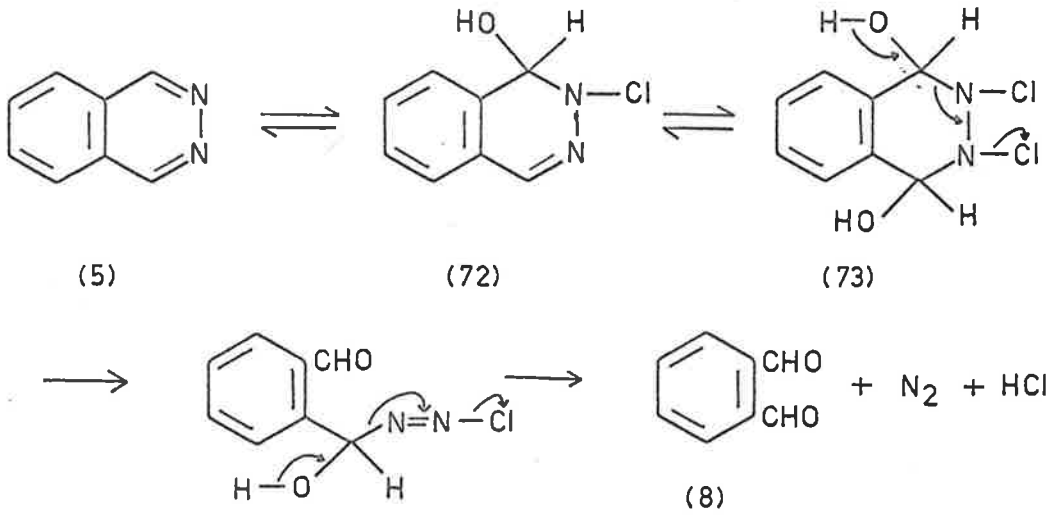
The mechanism of the reaction of chlorine with azines may therefore be formulated as an electrophilic attack by chlorine on the nitrogen lone pair, followed by, or concommittant with, the addition of hydroxide ion to the adjacent carbon atom (Scheme 20). The α-hydroxy-N-chloroamine (68) thus formed appears to be unstable and could not be isolated in the present work at any stage; the "adduct" reported by Kaiser (p. 47) was more probably N-chloropyridone. Schiff bases, however, are known[160] to form stable adducts of similar structure to the carbinolamine (68) on reaction with t-amylhypochlorite. Most of the products in Tables 5 and 6 can be considered to arise by decomposition of the intermediate (68) by pathways (1) or (2) in Scheme 20. Hydrolysis (pathway 1) would give an aldehyde or ketone (69). If



Scheme 20.

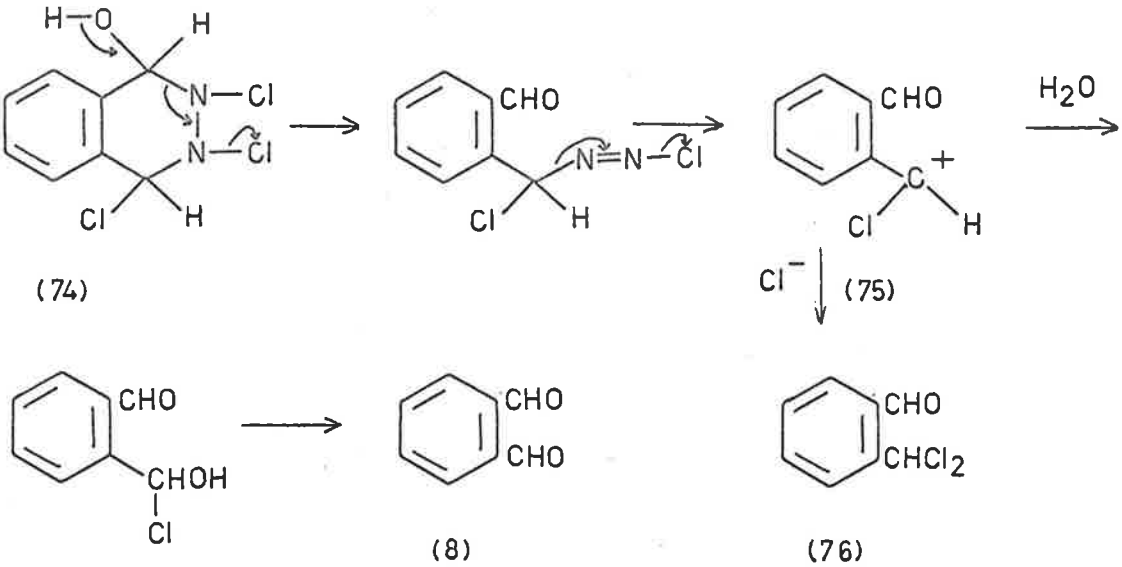
R' = H, elimination of HCl from (68) would form the imidol (70a) which may react in the tautomeric form (70b) with excess chlorine to yield an N-chloroamide (71) as shown in pathway (2). The overall process represents oxidation.

Phthalazine may undergo addition at both C = N bonds with the formation of a di-N-chloro intermediate (73) which may break down by a number of possible mechanisms, one of which is illustrated (Scheme 21). Loss of two molecules of HCl is shown in two concerted steps although phthalaldehyde (8) could also result from fission of the C-N bond to give a carbonium ion followed by attack of hydroxide ion or water. The formation of o-dichloromethylbenzaldehyde (76) suggests the existence of another intermediate (74) where addition of chlorine as such has



Scheme 21.

occurred across at least one of the C=N bonds (Scheme 22.). Breakdown similar to Scheme 21 would give a carbonium ion (75) from which the



Scheme 22.

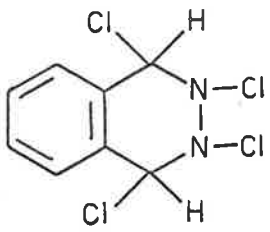
required products may be derived by attack of chloride or hydroxide ion.

The reason for the sole formation of o-dichloromethylbenzaldehyde from phthalazine hydrochloride (reaction 11, Table 5) is not clear; the increased chloride ion concentration cannot be the only factor since in 20% sodium chloride solution equal quantities of the two aldehydes were obtained (reaction 9). This effect is also apparent in reaction 10 where partial chlorination in sodium chloride solution showed that phthalaldehyde was formed initially in greater yield. As the reaction proceeds the concentration of HCl increases and on exhaustive treatment equal amounts of the two aldehydes were obtained (reaction 9).

The above observations can be explained by considering the relative concentrations of the nucleophilic species present. At low pH the concentration of hydroxide ion would be insignificant compared with that of chloride ion, thus leading to the exclusive formation of o-dichloromethylbenzaldehyde from the carbonium ion (75). The formation of the precursor (74) to the carbonium ion could conceivably be enhanced if envisaged as proceeding by attack of chloride ion on an N-chlorophthalazinium species instead of formal addition of Cl_2 across the C=N bond. Rather than invoke the presence of hydroxide ions in acidic solutions, hydroxylation of the carbonium ion may alternatively be achieved by attack of water, the effective concentration of which would be decreased in acid by protonation. The difference in nucleophilic character between chloride ion and water is not significant because

the rate of substitution involving a carbonium ion is independent of the nucleophile.[161] This is exemplified by the identical specific rates of substitution of t-butyl bromide with chloride ion, bromide ion, pyridine and water.[162,163] All attempts to obtain a fluorinated aldehyde by carrying out the chlorination in the presence of fluoride ion were unsuccessful. Concentrated sodium fluoride solutions appeared to act as buffers, phthalaldehyde and N-chlorophthalazone being the major products.

Formation of a tetrachloro adduct (77) by addition of two moles of chlorine would be expected to yield some w,w,w',w'-tetrachloro-o-xylene (7; X=Cl) on decomposition. This compound was not detected and was unlikely to be the precursor of the aldehydes since its hydrolysis is known to require prolonged reflux in water.[15] A 1,4-addition of

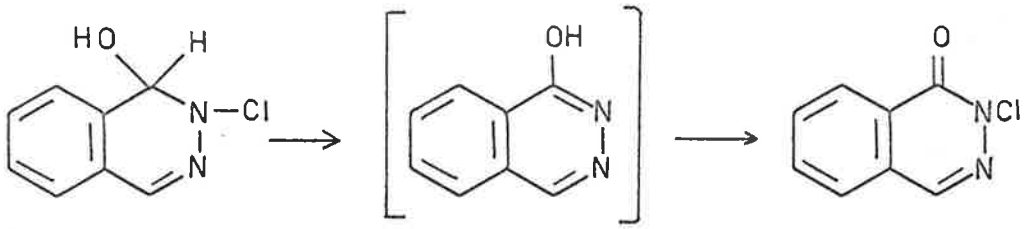


(77)

(78)

chlorine would give the azo derivative (78) which, by analogy with 1,4-dihydrophthalazine,[47] would lose nitrogen rapidly and give dimeric products resulting from a diradical. Although the intermediate (74) accounts for the formation of both aldehydes, the dichloro-dihydroxy adduct (73) may also be generated and appears to be the only intermediate formed at pH greater than 7.

The formation of N-chlorophthalazone (79) during the chlorination of phthalazine in buffer solutions (reactions 3,4, 6 and 7, Table 5.) is attributed to oxidation (pathway 2, Scheme 20) of the intermediate (72) formed by addition across one C=N bond. In equation 1 (p.54)



(72) (79)

removal of hydrochloric acid favours the conversion of chlorine to hypochlorous acid, so that in the buffer solutions the chlorine concentration will be considerably reduced. The adduct (72) may then form by addition of hypochlorous acid to one C=N bond in phthalazine and the rate of addition to the second C=N bond by hypochlorous acid or chlorine may be sufficiently reduced to allow the slower oxidation step to occur. This effect was demonstrated by varying the rate of addition of chlorine gas to reaction mixtures at pH 6. (reactions 5 and 6). Rapid addition (reaction 6) resulted in the formation of aldehydes alone because the presence of high local concentrations of chlorine would favour addition to both C=N bonds. Chlorination in a buffer solution at pH 3.4, just less than the pH of chlorine water, gave the usual ratio of aldehydes regardless of the rate of addition (reaction 2).

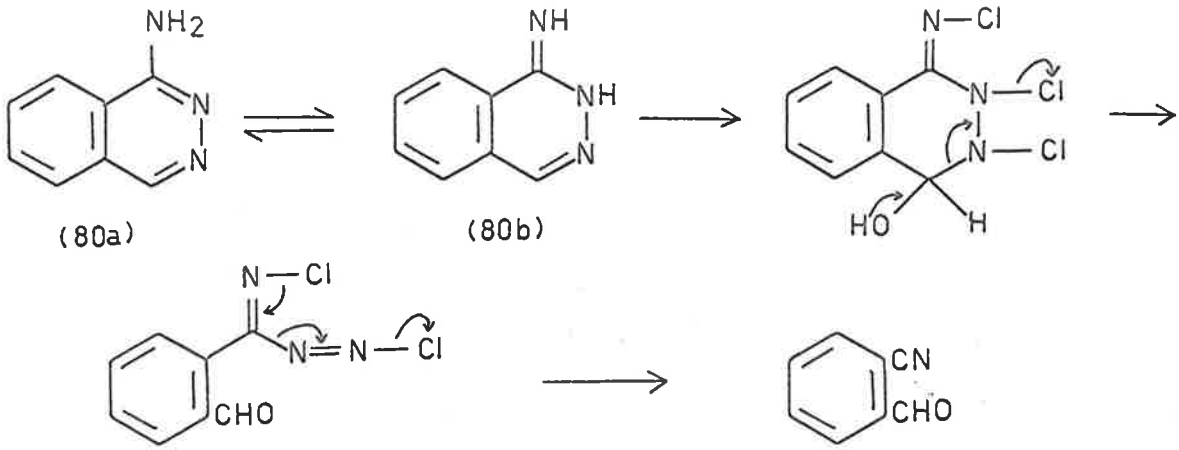
A further consequence of the use of buffer solutions was the

effect on the rate of elimination of HCl from the intermediate (72). Kinetic studies[75] of the elimination of HCl from N-chloroimines to form nitriles indicated a base-catalysed E_2 mechanism, and a large number of β -eliminations in aliphatic systems are known to follow a similar course.[151] The increase in yield of N-chlorophthalazone (79) from pH 4 to pH 7 may thus be ascribed to bimolecular, base-catalysed elimination of HCl from the intermediate (72). Maximum yield was obtained at the pH of hypochlorous acid. The lower yield of N-chlorophthalazone produced at pH 8.5 (reaction 6) would result from a reduction in the concentration of hypochlorous acid by conversion to sodium hypochlorite. At higher pH, phthalaldehyde is formed exclusively by the action of chlorine which is present in a small equilibrium concentration.

Attempts to isolate the intermediate (72) by the addition of small volumes of chlorine water were unsuccessful. After an induction period of about 15 seconds, bubbles of nitrogen appeared in the solution and the same product ratios were obtained as before. The ultraviolet spectrum of 10^{-3} M phthalazine in a buffer solution at pH 7 showed, after the addition of dilute chlorine water, weak absorption at 395 mμ which rapidly decreased in intensity and finally disappeared after 10 minutes.

Products from the reaction of chlorine water with azines (Table 6) can be accommodated by the mechanism shown in Scheme 20. No buffer solutions were used and the occurrence of pathways (1) and

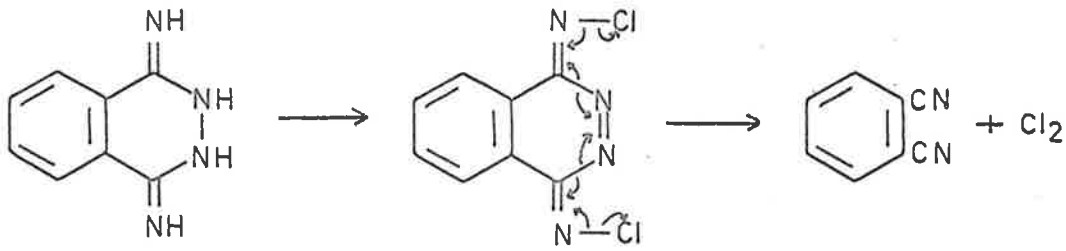
(2) in the same reaction was not observed; no dichloromethyl derivatives were isolated. Benzylideneazine was rapidly decomposed by chlorine to nitrogen and benzaldehyde (reaction 1, Table 6) but was completely stable in acid alone at pH 3.5. Phthalazine derivatives bearing electron-donating groups in the heterocyclic ring (reaction 2-4) gave similar products. The formation of o-cyanobenzaldehyde (21) from 1-aminophthalazine (80; reaction 5) is attributable to the ability of the amine (80a) to react in the tautomeric form (80b) as shown in Scheme 23. The electron shifts proposed are analogous to those in Scheme 21;



Scheme 23.

in the second step an N-Cl system is involved instead of O-H. Chlorination of the imino nitrogen is not essential since the intermediate corresponding to (81) could lose a proton to give the same product. An N-chloro derivative was suggested, however, by analogy with the product obtained from 1,4-diaminophthalazine (45; reaction 6). This compound also appears to react in the tautomeric form (45a), giving a bright

green solid which is formulated as 1,4-di(N-chloroimino)-1,4-dihydrophthalazine (82). The compound was stable toward oxidising agents but



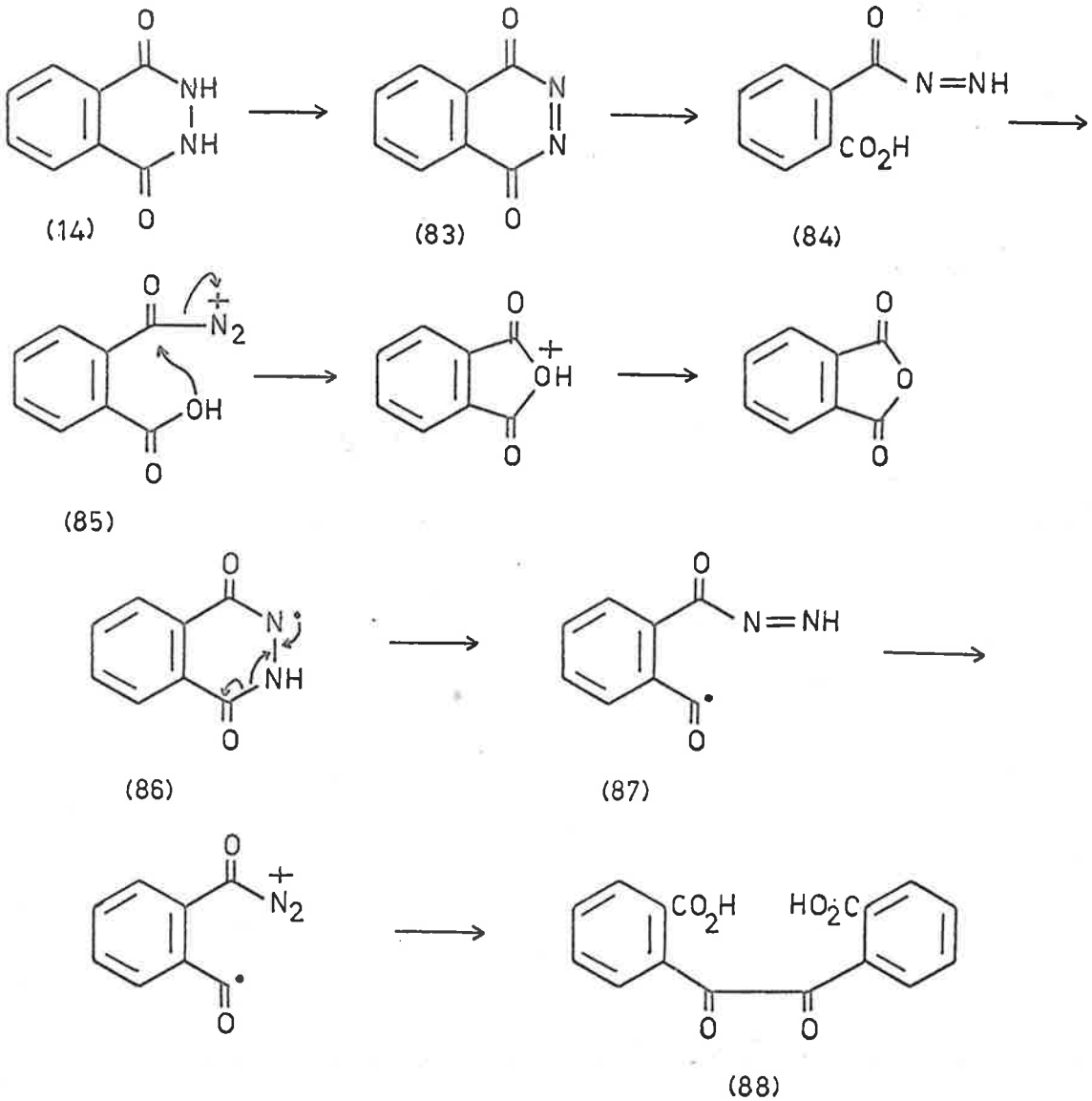
(45a) (82) (19)

Scheme 24.

could be reduced by tin and hydrochloric acid to the starting material. Recrystallisation was achieved from acetic acid but on prolonged heating in this solvent the green colour disappeared and a mixture of phthalimide and phthalonitrile was obtained. Pyrolysis at 130° provided phthalonitrile in 73% yield, chlorine being evolved. This product may result from homolytic fission of the 1,2 and 3,4 bonds as shown in Scheme 24.

Previous workers[164,165] found that the reaction of sodium hypochlorite with phthalaz-1,4-dione in 0.33N sodium hydroxide afforded benzil-2,2'-dicarboxylic acid but no mechanism was suggested. In the present work, phthalic anhydride was obtained in 88% yield using chlorine as the oxidant (reaction 7) while in 3.7N sodium hydroxide the major product was phthalic acid, a small amount of benzil-2,2'-dicarboxylic acid being also obtained. It is proposed that 1,4-phthalazinedione

(88), formed by oxidation of the hydrazide linkage in phthalaz-1,4-dione (14), undergoes hydrolysis to the diimine species (84) which on further oxidation would provide a diazonium salt (85). Displacement of the diazonium group by the neighbouring hydroxyl group would then give the observed product (Scheme 25.). In the reaction conducted in alkaline



Scheme 25.

solution, phthalic acid would be formed by replacement of the diazo group with hydroxide ion. The production of benzil-2,2'-dicarboxylic acid (88) is attributed to the dimerisation of a radical (87) formed after homolytic C-N bond fission in a species (86) generated by abstraction of one hydrogen atom from phthalaz-1,4-dione. (Scheme 25).

Oxidation of the sodium salt of phthalaz-1,4-dione with t-butyl hypochlorite was reported by Kealy[166] to give 1,4-phthalazinedione (83) which decomposed in the presence of water to phthalic anhydride (8%) and polymeric derivatives of phthalaz-1,4-dione. The diazaquinone (83) was isolated at low temperatures and was bright green in colour, characteristic of the 1,4-naphthoquinone system. In the present work, a transient green colouration was observed during chlorination of phthalaz-1,4-dione in water, but none of the products described by Kealy were isolated, with the exception of phthalic anhydride.

The introduction of electron-withdrawing groups into the carboxylic ring of phthalazine does not change the course of the reaction with chlorine; thus 5,8-dibromophthalazine gave 3,6-dibromophthalaldehyde (reaction 10, Table 6). Such substituents in the 1- or 1,4- positions, however, appear to prevent attack by positive chlorine on the adjacent nitrogen atom. When only one position was substituted, addition of HOCl at the 3,4 bond was followed by oxidation to phthalazones which were isolated as N-chloro-phthalazones (reactions 8 and 9). 1,4-Diphenyl- and 1,4-dichlorophthalazine were recovered unchanged after

treatment with chlorine.

Quinoxaline was rapidly oxidized by chlorine to 2,3-dihydroxyquinoxaline (reaction 11) in good yield. The same product has been obtained using ammonium persulphate[167] as the oxidant. 2,3-Diphenylquinoxaline underwent hydrolysis because oxidation is prevented by the substitution pattern (reaction 12). The low yield of benzil may indicate that the addition of HOCl to C-N bonds is reversible, and that only an irreversible step, such oxidation of the adduct or, in the case of phthalazine, loss of nitrogen, can take the reaction to completion. The action of chlorine on aqueous quinoline provided a substance different from those obtained by Einhorn and Lauch.[144] The infrared spectrum indicated the presence of an amide group and was similar to the spectrum of a substance produced by the action of chlorine on carbostyril. Isoquinoline also gave an amide derivative of unknown structure. A high-melting product was obtained from acridine and chlorine, and appeared from analytical figures to contain far less nitrogen than any possible acridine derivative. All attempts to purify the substance were unsuccessful. Pyridazine evolved nitrogen on treatment with aqueous chlorine but no discrete product could be isolated.

In attempts to isolate the intermediates (72) and (73), phthalazine was treated with chlorine-free hypochlorous acid under a variety of conditions. The results are summarised in Table 7. The course of the reactions closely followed that exhibited by chlorine. After a short induction period, nitrogen was evolved with the formation

of phthalaldehyde, o-dichloromethylbenzaldehyde and N-chlorophthalazone. It is clear that hypochlorous acid can add as such to the C=N bonds to form the intermediates (72) and (73) which break down as before to organic products, nitrogen and hydrogen chloride. The latter, once formed, immediately converts hypochlorous acid to chlorine,[168] according to equation 1. Displacement of the equilibrium towards chlorine was confirmed in the present work by adding dilute hydrochloric acid to a solution of hypochlorous acid at 0°. Yellow crystals of chlorine hydrate were immediately formed. In these reactions, therefore, initial attack of hypochlorous acid occurs but the products arise, in the main, from attack by chlorine.

Since hypochlorous acid has pH 7.4,[169] the pH of the reaction would favour the formation of N-chlorophthalazone for the same reason as described earlier, when the passage of chlorine into buffer solutions was considered. The higher yield of aldehydes obtained by rapid addition of hypochlorous acid (reaction 2) is attributed to conversion of the temporary excess of reagent to chlorine which then attacks both C=N bonds. The same effect was observed on inverse addition (reaction 3.). An additional product, 3-chlorophthalide, was isolated when a reaction time of 2 hours was employed (reaction 3.). A blank experiment showed that this product could be obtained by treating phthalaldehyde with hypochlorous acid under conditions identical to those used in reaction 3. Hypochlorites are known to convert aldehydes to acid chlorides,[170,171] the product in the present case, 3-chlorophthalide, being

TABLE 7.

Products from the reaction of hypochlorous acid with phthalazine.

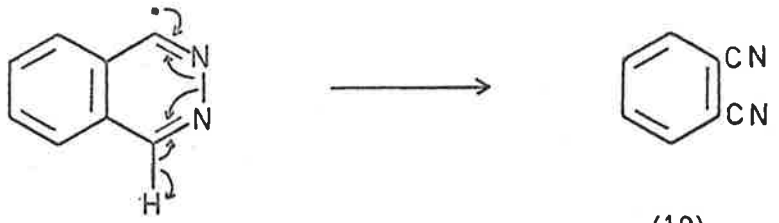
Reaction	Medium	Mode of Addition	Reaction time (min.)	% Products			
				Phthalaldehyde	o-dichloromethylbenzaldehyde	N-chlorophthalazone	3-chlorophthalide
1	H_2O	normal	20	28	4	31	
2	H_2O	normal	0.5	42	6	20	
3	H_2O	inverse	120	35	8	5	31
4	20% NaCl	normal	2	36	30	trace	
5	20% NaCl	normal	20	28	18	25	
6	HCl, 1 equiv.	normal	2	11	1.4		

the cyclic form of phthalaldehydic acid chloride. The reaction of hypochlorous acid with phthalazine in sodium chloride solution gave increased yields of o-dichloromethylbenzaldehyde (reactions 4 and 5). Hypochlorous acid was evidently converted to chlorine by phthalazine hydrochloride (reaction 6) which provided the same ratio of aldehydes as phthalazine and chlorine.

It has been proposed above that the formation of o-dichloromethylbenzaldehyde from the intermediate (74) is due to the presence of chloride ion; to test this hypothesis, some reactions were conducted in media capable of removing chloride ion as soon as it was formed. Previous workers[158] have used mixtures of silver perchlorate and perchloric acid for this purpose in studying the addition of hypochlorous acid to olefins, but aqueous silver nitrate was found to be more convenient in the present work. Although phthalazine formed an insoluble complex with silver nitrate, evolution of nitrogen occurred when chlorine water or hypochlorous acid was added to a suspension of the complex in a solution containing excess silver nitrate. In another approach, chlorine was passed into a mixture of phthalazine, silver sulphate and 92% sulphuric acid. In each case phthalaldehyde was the only product isolated, thus verifying that chloride ion is necessary for the formation of the dichloro-aldehyde. In the reaction using hypochlorous acid, the formation of phthalaldehyde can only be attributed to addition of HOCl across both C=N bonds.

Phthalazine appeared to be unaffected by t-butyl hypochlorite in the absence of air and moisture. On heating a carbon tetrachloride

solution of the reagents in contact with air, phthalazine hydrochloride (81%), o-dichloromethylbenzaldehyde (1.7%), phthalonitrile (0.61%) and a small quantity of viscous solid were obtained. The first two compounds were also produced on decomposition of the phthalazine tetrachloride complex, and can be accounted for by attack of positive chlorine on the phthalazine ring in the presence of a limited amount of water to give the intermediate (74). The formation of phthalonitrile (19) is attributed to fragmentation of the azine ring after hydrogen abstraction from the 1-position (Scheme 26.). When the reaction mixture was



(19)

Scheme 26.

stirred in air at room temperature prior to reflux, the yield of the viscous solid was greatly increased. The infrared spectrum of this material indicated the presence of a polymeric, phthalazone-type system. When an aqueous solution of phthalazine was treated with t-butyl hypochlorite, nitrogen was evolved after several minutes and the same ratio of aldehydes was isolated as obtained using chlorine water (reaction 1, Table 5.). Evidently the t-butyl hypochlorite is hydrolysed slowly at first to chlorine which then reacts with phthalazine

in the usual way. The ability of the hydrochloric acid produced to catalyse the hydrolysis of t-butyl hypochlorite was confirmed in a blank experiment.

The present work, then, has shown that the reaction of chlorine and hypochlorous acid with the phthalazine system can lead to oxidation or ring fission, depending on the conditions used and on the substitution pattern. Some evidence has been collected for the addition of HOCl and Cl_2 across the C=N bonds but the isolation of such adducts has not been achieved. To understand more clearly the reaction of chlorine with nitrogen heterocycles, the products obtained from quinoline, isoquinoline, acridine and pyridazine should be further investigated. Research could also be carried out in the phthalazine series using other sources of chlorine, such as calcium hypochlorite, N-chlorosuccinimide and chloramine T. The use of organic hypohalites may prove to be a more successful approach to the isolation of an intermediate from these reactions.

CHAPTER 3

Substitution and Addition Reactions of Phthalazine.

3.1 Theoretical principles.

Predictions of the mode of substitution in heteroaromatic nuclei are often based on the simplifying assumption that reactivity depends solely on the distribution and polarisability of the π-electron system.[172,173] This can be described in terms of a wave function derived by linear combination of the atomic π-orbitals of the atoms in the system. Evaluation of the wave equation for complex molecules requires the use of certain approximations; calculations carried out in the present work will be based on the Hückel molecular orbital (HMO) method.[174]

In this approach it is assumed that π-electrons can be treated independently of the σ-bond framework and that the π-orbitals can be described by the use of several empirically derived parameters. Coulomb integrals (α) and resonance integrals (β) are the most significant parameters; both have the dimensions of energy. Coulomb integrals approximately represent the energy of an electron in an atomic 2p-orbital. Resonance integrals represent the energy of interaction between two atomic orbitals and are considered to be zero if the atoms are non-bonded. In aromatic hydrocarbons all the carbon atoms have the same Coulomb integral and all C-C bonds the same resonance integral; calculation of π-electron distribution is therefore

considerably simplified.

Application of the HMO method to heteroaromatic molecules requires the use of additional parameters to modify the values of α and β. The Coulomb integrals for nitrogen (α_N) and carbon (α_C) may be expressed as

$$\alpha_N = \alpha_o + h\beta_o$$

$$\alpha_c = \alpha_o + h' \beta_o$$

Variation of α is considered as a differential charge in units of β relative to a standard β_o, usually that of benzene, and is determined by the arbitrary parameter, h. The most commonly used values of h are 1.5, 0.5 and 2.0 for secondary, tertiary and quaternary nitrogen respectively.[172] Since the inductive effect of the heteroatom on adjacent carbon atoms can be transmitted through σ-bonds, variation of the coulomb integrals of these atoms is obtained by use of an auxiliary inductive parameter, h'. Values of h' in the literature[172,175,176] range from $\frac{1}{8}$ to $\frac{1}{3}$. The resonance integrals of bonds between carbon and a heteroatom are defined by a dimensionless number, k, which depends

$$\beta_{CN} = k_{CN} \beta_o$$

largely on the bond length. Most calculations in nitrogen heterocycles assume that k=1, although a value of 0.8 has been suggested.[172]

The use of these parameters enables a symmetric matrix to be set up in which the elements represent atomic π-orbitals defined in terms of α and β. Solution of the matrix provides a series of

molecular π-orbitals which are described by sets of coefficients (eigenvectors) and energies (eigenvalues). This data can then be used to calculate a number of reactivity indices, some of which will now be briefly discussed.

Aromatic substitution reactions are generally classified as electrophilic, homolytic or nucleophilic, depending on the electronic structure of the attacking species. Early attempts to predict the orientation and rate of substitution were based on the assumption that electrophilic agents are attracted to sites of highest electron density[177,178] whereas nucleophiles attack electron-deficient positions. The calculation of π-electron densities in nitrogen heterocycles was first carried out using valence-bond[6] and perturbation[176] methods, which are now considered less accurate than molecular orbital techniques. In the HMO method, the π-electron density (q) at atom r is given by the formula

$$q_r = \sum_j n_j C_{jr}^2$$

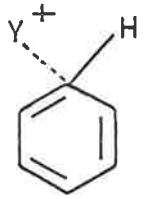
where C_{jr} is the coefficient of atom r in the j^{th} molecular orbital, occupied by n_j electrons. The π-electron densities thus obtained predict the observed electrophilic and nucleophilic substitution pattern in some heterocylic systems;[179-182] refinements have been introduced by considering only the highest-bound π-electrons, as in frontier electron density[183] or superdelocalisability[184,185] calculations.

Homolytic substitution has been rationalized[186] in terms of the free valence number, Fr, which is a measure of residual π-bonding power at atom r and is given by the relation

$$F_r = \sqrt{3} - \sum_s p_{rs}$$

where p_{rs} is the bond order of the bond between atoms r and s.

Sufficient anomalies exist, however, to challenge the validity of these isolated molecule approximations; that is, the assumption that the π-electron system of the transition state (89) is similar to that of the substrate is not always applicable. A more useful concept, the localisation approximation,[187] involves a transition state (90) where the attacking species is covalently bound to a carbon atom in the ring.



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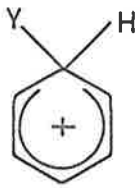


(90)

The substitution pattern of the product will thus be determined by the energy required to isolate the position from the conjugated system. The reactivity index is termed the localisation energy,[173] which is the energy required to localise two, one or zero electrons from the π-system depending on whether the attacking species is electrophilic, free-radical or nucleophilic respectively. Good correlation of localisation energy with reactivity has been found in aromatic hydrocarbons,[188] particularly if the approximation method of Dewar[189] is used.

Application to heterocyclic systems has been successful in predicting the site of substitution in a particular molecule[179,190,191] but not the relative reactivity of various systems. Electrophilic substitution in the quinolinium ion, for example, should by localisation energy calculations occur at a faster rate than naphthalene.[192] Most electrophilic substitution reactions are carried out under strongly acidic conditions where the protonated heterocycle rather than the free base acts as the substrate. Dewar and Maitlis[179] and Brown[193] have suggested that the extremely slow rates of these reactions are due to mutual repulsion between the positively charged electrophile and the quaternary nitrogen of the substrate. The magnitude of this effect will depend not only on the nature of the reactants and the medium but also on the distance between the quaternary nitrogen and the point of attack. It is apparent, therefore, that predictions of reactivity in nitrogen heterocycles cannot rely on molecular orbital considerations alone.

3.2 HMO calculations for phthalazine.

To determine the π-electron densities in phthalazine, a 10 x 10 matrix was set up using the following parameters

$$h = 0.58, \quad h' = \frac{1}{8}$$

$$\beta_{CC} = \beta_{CN} = \beta_0, \quad \beta_{NN} = 0.67\beta_0 \quad (k_{NN} = 0.67)$$

Calculation[194] of the value of β_{NN} was based on the difference in C-C and N-N bond lengths; a value of $k_{NN} = 0.70$ was used[197] in a HMO treatment of the pyridazine ring. The charge densities obtained are given

in Table 8, together with those calculated by previous workers. The perturbation[176] and valence bond[6] methods placed more emphasis on the

TABLE 8.

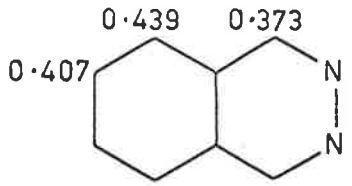
Net atom charges in phthalazine

Reference	Position				
	1	2	5	6	9
176	0.183	-0.308	0.028	0.040	
6	0.154	-0.330	0.067	0.062	
71	0.0797	-0.1198	0.0107	0.0131	
195	0.134	-0.150	0.010	0.011	
196	0.101	-0.151	0.014	0.017	0.020
This work	0.1319	-0.2060	0.0239	0.0252	0.0251

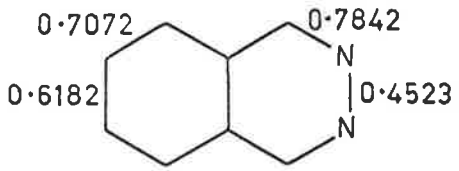
electronegativity of nitrogen than the molecular orbital approaches.[71,195,196] Electron densities derived in the present work were lower than the perturbation and valence bond values but greater than those obtained by previous molecular orbital calculations. The latter methods took $\beta_{NN} = \beta_o$ whereas in this case a lower and more realistic value of β_{NN} was used. The calculation of electron densities from chemical shifts in the n.m.r. spectrum of phthalazine was only partially successful.[195] All except the valence bond method[6] predict electrophilic substitution at the 5-position.

The free valence numbers and bond orders were calculated for

phthalazine and are shown in diagrams (5e) and (5f) respectively. The



(5e)



(5f)

5-position has the highest free valence number, in agreement with the observed formation of 5-phenylphthalazine in homolytic phenylation studies.[37] The bond orders show that the C=N bonds have considerably greater double bond character than the 1,2-bonds in naphthalene, quinoline and isoquinoline,[198] (Table 9.), and, conversely, the 2,3-bond has greater singe-bond character. This effect can be attributed, as in pyridazine, to the lower stability of the azo linkage.

Bond distances in phthalazine (5g) were calculated using the relation proposed by Coulson.[199] The values obtained can be adjusted

$$\text{bond distance} = S - \frac{s-d}{1 + 0.765(1-b)/b}$$

where b = bond order

s = single bond distance (1.542Å)

d = double bond distance (1.340Å)

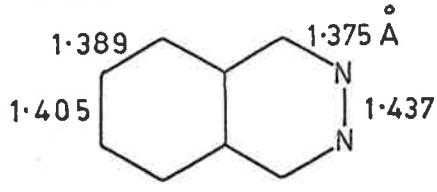
to give the experimental mean, if known, by subtracting a constant increment from each calculated distance.[200] As no X-ray determination

TABLE 9.

Bond orders

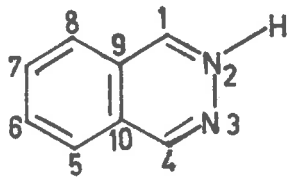
Bond	naphthalene	quinoline	isoquinoline	phthalazine
1,2	0.747	0.743	0.742	0.784
2,3	0.582	0.578	0.586	0.452
3,4		0.749	0.741	
4,6		0.534	0.536	0.511
5,6		0.748	0.748	0.707
6,7		0.580	0.581	0.618
7,8		0.749	0.748	
8,9		0.527	0.532	0.576
9,10	0.554	0.551	.554	
9,1	0.532	0.537	.530	
10,5		0.531	.531	

of phthalazine has been carried out, the calculated bond lengths are only useful for comparison within the system.



(5g)

Since electrophilic substitution reactions of phthalazine were conducted in strongly acidic media π-electron densities for the cation (91 and 92) were calculated. The same parameters were used as for phthalazine, with the protonated nitrogen, h = 2.0.



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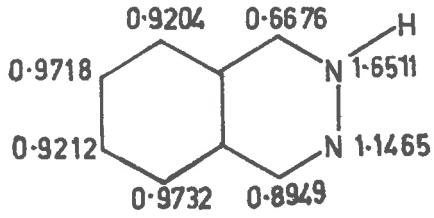


(92)

Electrophilic substitution is predicted at the 5 position predominately.

To obtain the localisation energies, the energies of the π-system of the cation and of the transition state were calculated by summing the energies of all the occupied molecular orbitals. Application of this method to transition states bearing electrophiles at the 1-, 5-, 6- and 8-positions gave localisation energies of -1.1505β, -1.0413β, -2.0962β and -1.9868β respectively. On this basis electrophilic substitution should therefore occur in the order $5 > 1 > 8 > 6$.

3.3 Electrophilic substitution.

At the commencement of this work no electrophilic substitution reactions of phthalazine had been reported although the nitration of cinnoline,[201] quinoxaline[202] and quinazoline[203,204] had been found to give mononitro derivatives substituted in the benzo ring. The reactions were generally carried out at 0° using mixtures of concentrated sulphuric and fuming nitric acids. Application of this method to phthalazine was unsuccessful; no reaction occurred at 0° and elevation of the temperature resulted in oxidation of the heterocycle to phthalic acid. The same product could be obtained using fuming nitric acid alone. Nitration was finally achieved without oxidation by the use of potassium nitrate in 98% sulphuric acid, although the rate of nitration under such conditions is known to be retarded.[192,202,205,206] Examination of the basic product by thin-layer chromatography showed that 5-nitrophthalazine was the only nitration product, even on prolonged treatment with excess reagent. While this work was being completed, Kanahara[78] reported that the nitration of phthalazine under similar conditions gave the 5-substituted isomer.

The observed orientation is identical with that predicted by the calculated π-electron densities of phthalazine and the phthalazinium ion. Although the 1-position in the phthalazinium ion has the lowest localisation energy, electrostatic repulsion between the electrophile and the adjacent quaternary nitrogen would strongly inhibit attack at this position. Of the remaining possibilities, the 8-position has

the lower localisation energy and undergoes substitution as predicted. To distinguish between the 5- and 8- positions it would be necessary to nitrate a quaternary derivative such as the N-methylphthalazinium ion. Earlier it was stated that localisation energies were unsuitable for the comparison of reaction rates and this was found to be so in the present work. The localisation energy of the 8-position in the phthalazinium ion was calculated to be $-1,99\beta$ compared with $-2,33\beta$ ($h = 2$, $h' = 0.1$) for the 8-position of quinoline,[191] whereas the latter is far more susceptible to nitration than phthalazine.

The mechanism of nitration in sulphuric acid is currently considered to involve attack by the nitronium ion or a related species on the heterocyclic base or its cation.[193,206,207] Kinetic studies of the nitration of quinoline systems have shown that the reaction proceeds *via* the quinolinium ion.[192,206] Attempts were made in the present work, therefore, to determine the rate of nitration of phthalazine over a range of acid concentrations to decide whether the free base or its cation underwent nitration. In 98% sulphuric acid and a large excess of potassium nitrate a temperature of 62° was required to give a measurable rate, which was determined spectroscopically by using aliquot parts of the reaction mixture after dilution with water. The reaction exhibited pseudo first order kinetics and had a rate constant 5.6×10^{-5} l. mole^{-1} sec.$^{-1}$ at 61.9°. Attempts to measure the rate coefficient at lower acidities were unsuccessful because the formation of oxidation

products prevented spectroscopic analysis.

Austen and coworkers[192,206] calculated the concentration of quinoline in 98% sulphuric acid from its basicity (pK_a 4.94) and estimated the corresponding second order rate coefficient to be 10^{-6} l. $mole^{-1}$ $sec.^{-1}$ for nitration at 25°. The actual rate constant was found to be 9.44×10^{-3} l. $mole^{-1}$ $sec.^{-1}$, suggesting that the quinoline molecule does not undergo nitration as such. Phthalazine, however, is a weaker base (pK_a 3.47) than quinoline and, being present in greater concentration, the free base could have a theoretical rate coefficient comparable to the observed value. The data available, therefore, does not distinguish between the possibilities of phthalazine or the phthalazinium ion acting as the substrate in nitration.

In order to compare the rates of nitration of quinoline and phthalazine, the three rate coefficients given by Austen and Ridd at temperatures up to 45° were plotted and extrapolated to 61.9°. This procedure gave a rate coefficient of 7.4×10^{-2} l. $mole^{-1}$ $sec.^{-1}$, indicating that the reaction rates of quinolinium ion and phthalazine differ by a factor of 1.3×10^{3}. Indirect comparison by Austen and Ridd of the rate coefficients of benzene and quinoline showed a ratio of 4×10^{7}; the reactivity of benzene towards nitration therefore differs from phthalazine by a factor of about 5×10^{10}.

Bromination of the diazanaphthalenes does not appear to have been reported but the action of bromine on quinoline has been extensively

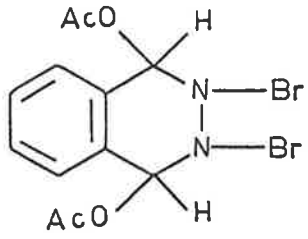
investigated using a variety of conditions. Substitution into the heterocyclic ring was obtained by bromination in the vapour phase[208] and by the rearrangement of quinoline perbromide.[130] The use of silver sulphate and concentrated sulphuric acid gave 5-, 8- and 5,8-dibromoquinoline[209,210] while silver acetate and acetic acid or acetic anhydride provided a mixture of 3-, 3,6- and 3,6,8-substituted derivatives.[209,193] The bromination of isoquinoline in silver sulphate and sulphuric acid led to the formation of the 5-isomer exclusively[211] while in the vapour phase 1-bromoisoquinoline was obtained.[208]

In the present work, phthalazine was treated with one mole of bromine in a mixture of silver acetate and acetic acid at room temperature. The bromine was rapidly consumed but only phthalazine (8%) and phthalaldehyde (10%) could be isolated. A monobromo derivative (3.3%) and a dibromo derivative (6.9%) were obtained by bromination of phthalazine in a mixture of silver sulphate and 98% sulphuric acid using one mole of bromine. The n.m.r. spectrum of the monobromo derivative showed that substitution had occurred in the homocyclic ring and since the compound was not identical to 6-bromophthalazine it was formulated as 5-bromophthalazine. The n.m.r. spectrum of the dibromo derivative exhibited two peaks of equal intensity which indicated either of the symmetrical 5,8- and 6,7- structures. Assignment of the former substitution pattern was based upon the fact that the derivative could be obtained by bromination of 5-bromophthalazine.

Where considerably less than one mole of bromine was used, most of the starting material was recovered, together with some 5-bromophthalazine (5.7%). de la Mare and coworkers[210] observed a similar tendency in the bromination of quinoline and found that variation of the acidity of the medium had little effect on the degree of polybromination. This fact refutes the suggestion by Brown[209] that the monobromoquinolinium ion, being a stronger acid, would undergo further bromination as the free base at a faster rate than monobromination of the quinolinium ion. Attempts to brominate phthalazine over a range of sulphuric acid concentrations were unsuccessful; no reaction occurred in fuming sulphuric acid while in 92% acid half the starting material was consumed and some phthalic acid was isolated. A series of blank experiments showed that the loss of phthalazine was not due to attack by one of the reagents alone.

The formation of phthalaldehyde and phthalic acid indicates that the brominating species generated by silver salts[212,213,214] causes rupture of the azine ring as well as leading to brominated products. The nature of this species is not fully understood; Arotsky and coworkers[214,215] have obtained considerable evidence in favour of an $AgBr_2^+$ complex, rather than the bromonium ion or protonated hypobromous acid (H_2OBr^+) previously suggested.[212] A source of positive bromine would permit the formation of an N-bromophthalazinium intermediate which could undergo nucleophilic attack at the α-carbon by acetate ion or water, depending on whether the reaction was conducted

in acetic acid or 92% sulphuric acid. Decomposition of the resulting adduct (94 or 95) in a similar fashion to that proposed for the reaction



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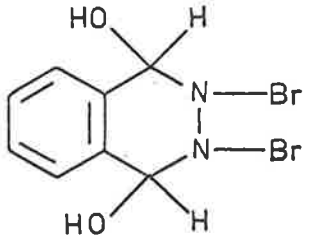


(95)

of phthalazine with chlorine (p.56) would then provide phthalaldehyde from which phthalic acid may be formed by oxidation.

The bromination of pyridines in the presence of excess aluminium trichloride was reported[216] to give 3-bromo derivatives, but no substitution products were obtained from phthalazine under the same conditions. Attempts to iodinate phthalazine in a mixture of iodine, silver sulphate and sulphuric acid at temperatures up to 130° were unsuccessful. High concentrations of the iodine cation are generated under these conditions.[215,217,218]

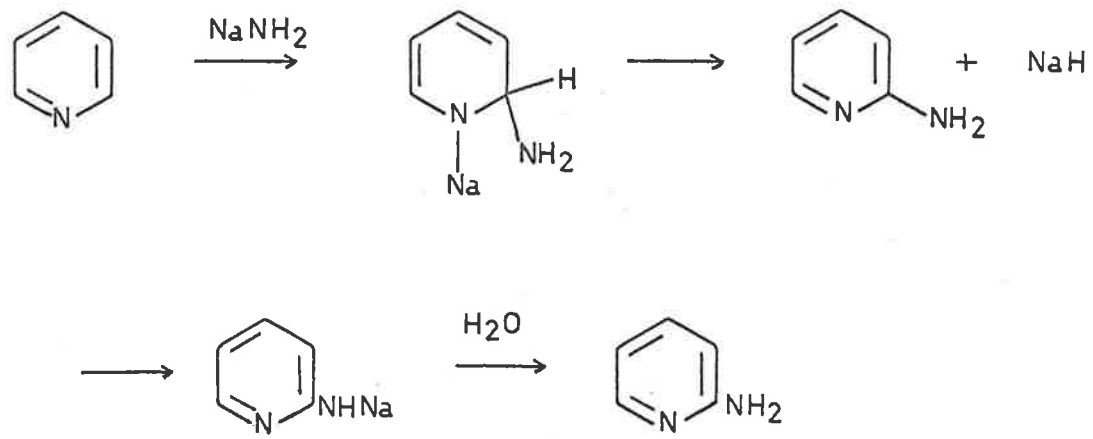
Treatment of benzo[g]phthalazine nitrate with 98% sulphuric acid gave a compound which was formulated as 9-nitrobenzo[g]phthalazine; a completely satisfactory analysis and n.m.r. spectrum has not yet been obtained.

3.4 Nucleophilic substitution.

According to the definition of Bunnett and Zahler,[219] nucleophilic aromatic substitution involves the formation of a bond in which

both electrons are supplied by the attacking species. For such a reaction to occur with any facility, the group displaced must generally be reasonably stable as an anion and the point of attack must be activated by an electron-withdrawing substituent or heteroatom.[219,220] Earlier in this work (p.5) the nucleophilic displacement of 1- and 4-substituents from the phthalazine system was described; in this section, only nucleophilic substitution involving replacement of hydrogen will be discussed.

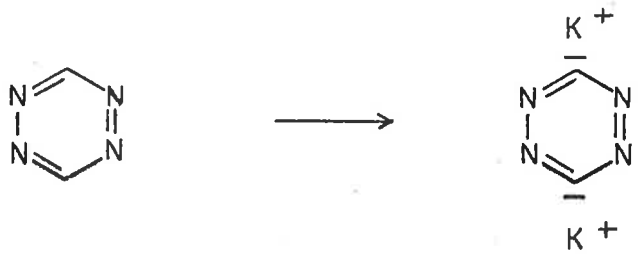
The replacement of hydrogen with nucleophiles in heterocyclic systems was first reported in 1914 by Chichibabin[221] who converted pyridine to 2-aminopyridine by the action of sodamide. The reaction has since found general application in 6-membered monoazines and has been extensively investigated, notably by Bergstrom.[222,223,224] The following mechanism has been proposed.[225] (Scheme 89)



Scheme 89.

Addition of the metal amide across the C=N bond in the first step is formally similar to the reaction of Grignard reagents and organolithiums with nitrogen heterocycles.[225] The second step, involving loss of a hydride ion, is slow[226] because of the low stability of the leaving group. To overcome this difficulty, temperatures above 100° are frequently employed but reactions may be carried at lower temperatures in the presence of an oxidizing agent such as potassium nitrate.[227]

Quinoline[228,229] and isoquinoline[224] gave high yields of 2- and 1-amino derivatives respectively at moderate temperatures. Application of the reaction to diazines has been reported in only one system; 2,5-dimethylpyrazine furnished the 3-amino derivative[230] but no product could be isolated from the reaction of potassium amide with pyrazine.[231] Tetrazine (96) gave a red, unstable dipotassium salt for which the following structure (97) was proposed.[232]

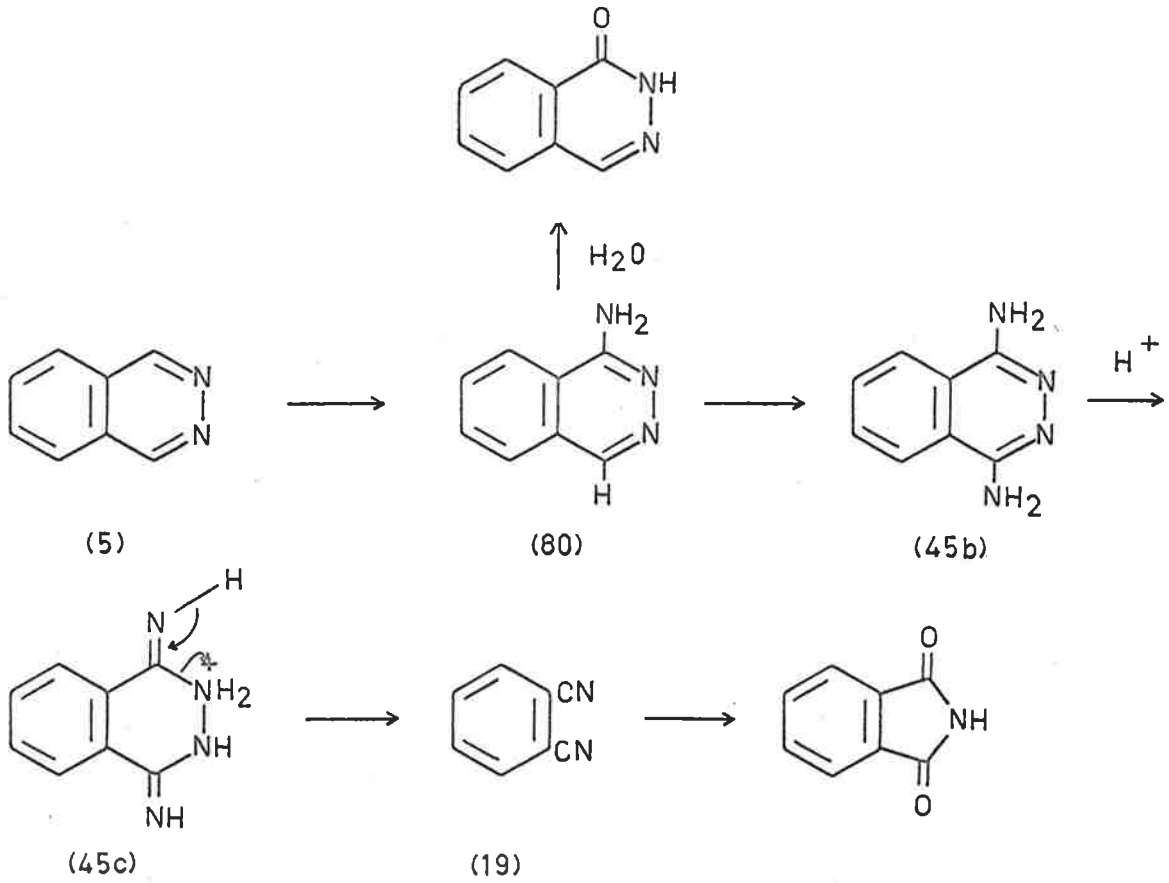


(96) (97)

In the present work, phthalazine was treated with sodamide in dimethylaniline at 130°. A considerable amount of tar was obtained and no compound other than phthalazine (13%) could be isolated. The addition of powdered phthalazine to two moles of sodamide in liquid

ammonia gave a dark red solution which became greenish black in colour after one hour. The excess ammonia was allowed to evaporate and decomposition of the residue with sodium hydroxide produced green, tarry material from which phthalazine (26%) was isolated. Traces of phthalimide, phthalonitrile and phthalazone were obtained on acidification of the aqueous solution. When the decomposition of the residue was carried out using ice-water, some tarry material formed which dissolved on addition of acid. Basification gave a dark green precipitate and phthalazine was removed by extraction with chloroform. The addition of picric acid to the neutralised solution gave 1-aminophthalazine picrate (20%). No increase in yield was achieved by the use of potassium nitrate, although the aqueous solution obtained on hydrolysis was much less contaminated with tar.

These products may be attributed to the initial formation of 1-aminophthalazine (80), some of which reacts further with sodamide to give 1,4-diaminophthalazine (45b; Scheme 27). The latter compound could not be isolated from the reaction mixture as it was found to undergo hydrolysis to phthalonitrile and finally phthalimide under the acid conditions used in the work-up procedure. The mode of hydrolysis is considered to be the reverse of its formation from phthalonitrile (p.20), namely, acid catalysed decomposition of the imino form (45c) in two steps. The red colouration observed on addition of phthalazine to sodamide in liquid ammonia suggests that the sodium salt of a carbanion may be formed, analogous to the red tetrazine salt reported



Scheme 27.

by Bergstrom[232] but removal of the ammonia at this stage gave only the starting material.

The hydroxylation of pyridine and quinoline by fusion with potassium hydroxide represents a similar type of nucleophilic substitution and was also discovered by Chichibabin.[233-235] The reaction has received less attention than amination because the α-hydroxy derivatives produced are more readily prepared by alternative methods. Phthalazine was found to undergo rapid decomposition when heated with

potassium hydroxide at 220°. Hydrazine and ammonia were evolved with the formation of tarry material; a trace of phthalazone was isolated. The same products were obtained when the reaction was carried out at 100°. The melt assumed a deep purple colour which turned black after several hours heating.

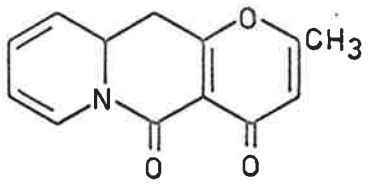
The observed nucleophilic substitution at the 1-position in phthalazine is in agreement with that predicted by the electron density and localisation energy calculations. The high calculated bond order of the C=N bonds raises the possibility of phthalazine acting as a Schiff base in the presence of strong alkali. Any aldehyde thus formed would polymerise under the reaction conditions, thereby accounting for the low recovery of phthalazine and the formation of tarry material in the above reactions.

3.5 Addition reactions.

In this work the possibility of addition of inorganic reagents across the C=N bonds in phthalazine has been suggested in order to account for ring fission and the formation of substitution products. However, no stable adducts resulting from the interaction of phthalazine with an organic moiety appear to have been reported.

Nitrogen heterocycles have long been known to form adducts with keten.[236] The pyridine adduct was recently shown[237] to have the structure (98), derived by fusion of four molecules of keten to the C=N

bond. Two molecules of dimethylketene participated in the addition to quinoline[238,239] giving the lactone (99). The reaction of dimethylketen



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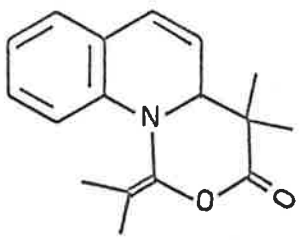

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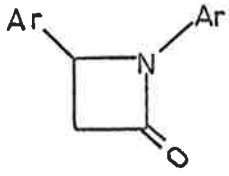
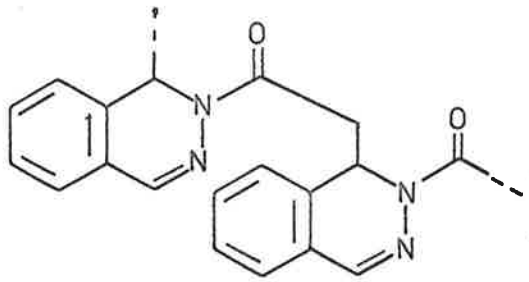


(100)

with isoquinoline,[239] phenanthridine[239] and 9-methylacridine[240] yielded products with similar structures, 1,4-addition occurring in the latter case. Schiff bases, on the other hand, form β-lactam rings (100) with one molecule of keten.[241]

The passage of keten gas into a benzene solution of phthalazine at room temperature afforded a colourless precipitate which gave carbon and hydrogen analyses corresponding to a 1:1 ratio of phthalazine and keten. Nitrogen analyses were consistently high by 1%. The substance slowly decomposed to phthalazine on standing, and more rapidly on heating or treatment with sodium hydroxide. The ultraviolet absorption spectrum of the adduct was identical with the spectrum of benzaldehyde N,N-dimethylhydrazone, suggesting that addition of keten had occurred at one C=N bond. A β-lactam structure was excluded by the infrared spectrum, which showed a carbonyl absorption at 1670 cm^{-1}. The n.m.r. spectrum consisted of poorly resolved bands typical of a polymer. The structure of the substance was therefore formulated as a polymer (101)

where phthalazine units are linked between carbon and nitrogen by keten.



(101)

Benzo[g]phthalazine and 5-nitrophthalazine also reacted with keten giving substances with a 1:1 ratio of keten to heterocycle and which had the same carbonyl absorption frequency in the infrared spectrum as the phthalazine adduct.

When phthalazine was treated with maleic anhydride under the same conditions as were used by Cookson[8] for preparing the pyridazine adduct a brown solid was obtained which appeared to be a mixture but attempts at purification were unsuccessful.

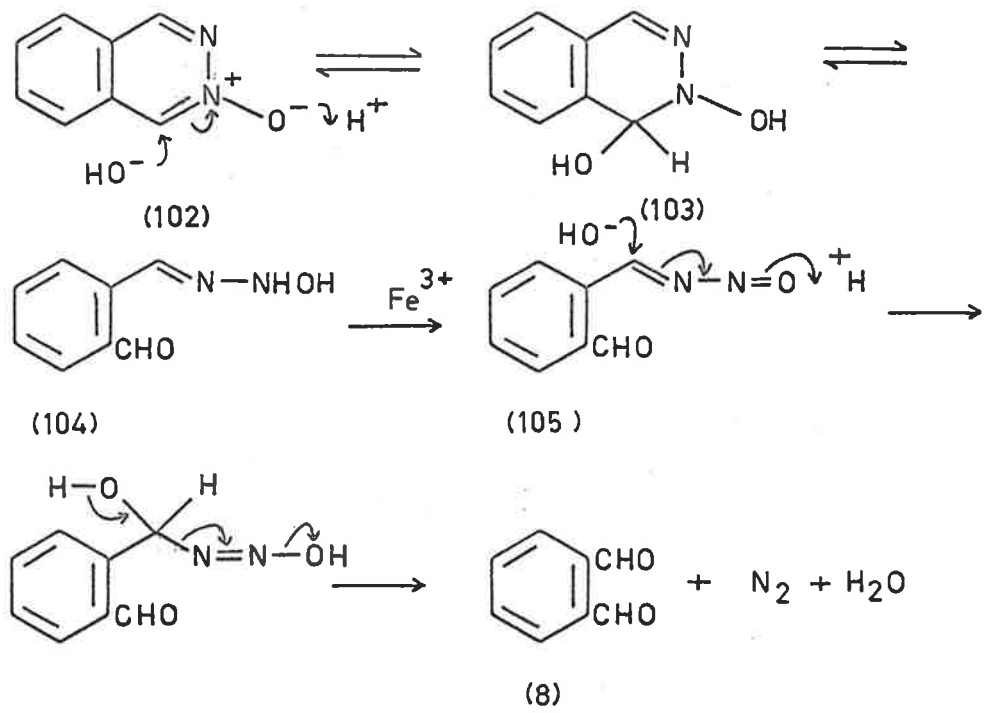
CHAPTER 4

N-Substituted Phthalazine Derivatives.

4.1 Phthalazine-2-oxide.

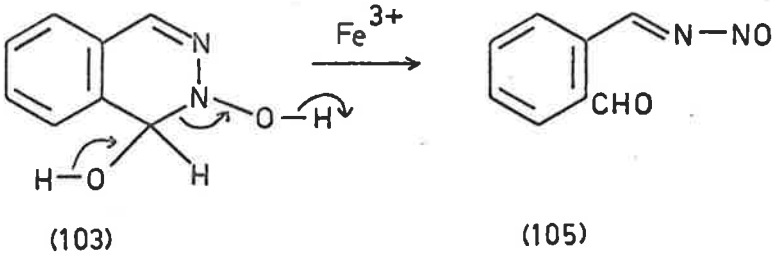
The preparation of phthalazine-2-oxide reported in the literature[79] involves the oxidation of phthalazine by perbenzoic acid at 0°. In the present work, the use of peracetic acid at 100° was found to be more satisfactory. The product was isolated as the hydrate which lost water on sublimation but reverted to the hydrate on exposure to air.

When phthalazine-2-oxide was treated with alkaline potassium ferricyanide, nitrogen was evolved and a high yield of phthalaldehyde was obtained; no reaction occurred in the absence of alkali or oxidizing agent. The mechanism (Scheme 28) may involve attack by hydroxide ion at the 1-position forming the hydrated species (103) which may undergo hydrolytic ring cleavage to give an aldehyde (104). Since the ultraviolet spectra of phthalazine-2-oxide in neutral and alkaline solution are identical, it appears that the species (103) and (104) can only be present in very low equilibrium concentrations. In the presence of potassium ferricyanide, however, irreversible oxidation of the hydroxylamine (104) to the nitrosimine (105) may occur and hydrolysis of the latter would give phthalaldehyde (8) and nitrogen. A number of oxidants, including ferric salts, are capable of oxidising hydroxylamines;[242a] the use of alkaline hydrogen peroxide gave the same products.



Scheme 28.

An alternative mechanism (Scheme 29) for the formation of the nitrosimine (105) is based upon that suggested by Baumgarten and coworkers[242b] for the oxidation of N-acyl-N-arylhydroxylamines to nitroso compounds with lead tetraacetate. Oxidation of the hydration



Scheme 29.

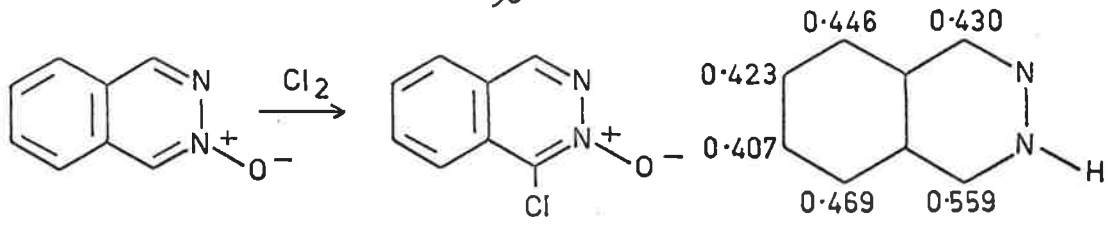
product (103) would thus give the nitroso compound (105) directly. The former possibility could be confirmed by isolation of the aldehyde(104) or a derivative of the aldehyde from an alkaline solution of phthalazine-2-oxide.

The action of acetic anhydride on phthalazine-2-oxide gave a low yield of 2-acetylphthalazone in accord with the usual rearrangement of N-oxides in this medium.[81]

Phthalazine-2-oxide was found to react slowly with chlorine water, yielding a monochloro derivative and a complex mixture of carbonyl compounds. The n.m.r. spectrum of the chloro derivative indicated that substitution had occurred in the heterocyclic ring and the chemical shift of the remaining proton in this ring (τ 0.95) was close to that of the 4-proton in phthalazine-2-oxide (τ 0.92). The derivative was therefore formulated as 1-chloro-phthalazine-2-oxide (106); this appears to be the first example of direct substitution into an N-oxide system by chlorine.

Homolytic chlorination of phthalazine-2-oxide would be expected to occur at the position of highest free valence. The calculation of this parameter was carried out on the phthalazinium ion (91) which is isoelectronic with the aromatic system of phthalazine-2-oxide (102). The 1-position was found to have the highest free-valance number, in agreement with the suggested orientation.

Nitration of phthalazine-2-oxide with potassium nitrate and



(102) (106) (91)

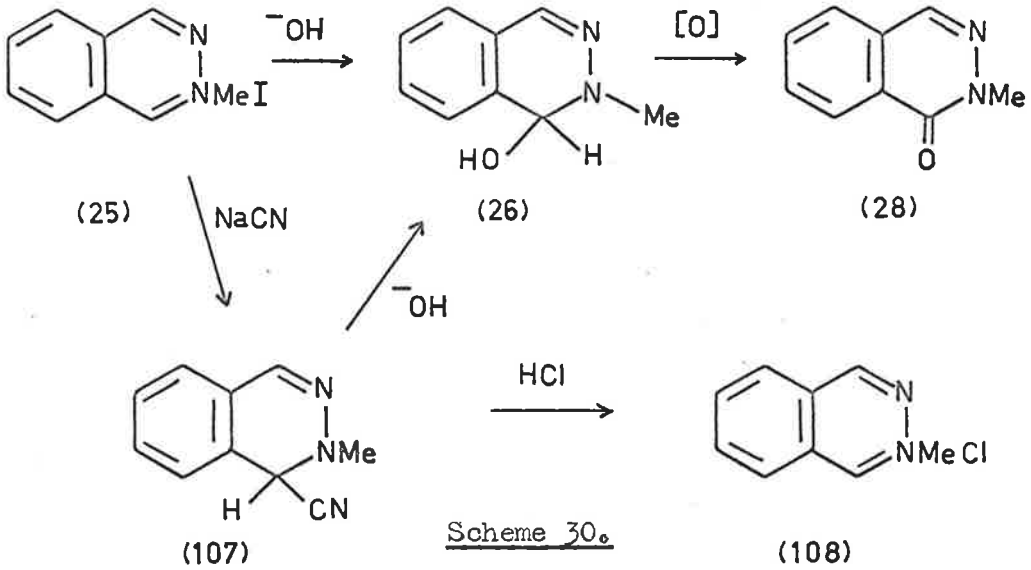
98% sulphuric acid gave a mixture of products from which 8-nitrophthalazine-2-oxide was isolated. The structure of this derivative was deduced by a correlation of the change in chemical shifts of the heterocyclic ring protons with that for phthalazine on introducing a nitro group into the 8-position. The 1- and 4- protons shifted downfield by 14 and 47 c.p.s. respectively, the corresponding shifts in the 2-oxide system being 18 and 56 c.p.s. Localisation energy calculations for the phthalazinium ion (p 79,80) predicted electrophilic substitution to occur at the 8-position.

4.2 Phthalazinium salts.

Several alkylphthalazinium salts are known and have been subjected to reduction and alkaline degradation[18,74,243] but the synthesis of phthalazinium salts having electron-withdrawing N-substituents and the behaviour of both classes toward nucleophiles other than hydroxide ion does not appear to have been reported.

When phthalazine methiodide (25) was treated with aqueous alkali a small quantity of what was presumed to be the pseudo base (26) was isolated; it could not be adequately characterised because it was rapidly oxidised in air to 2-methylphthalazone (28). The latter product could be obtained quantitatively by oxidation of an aqueous

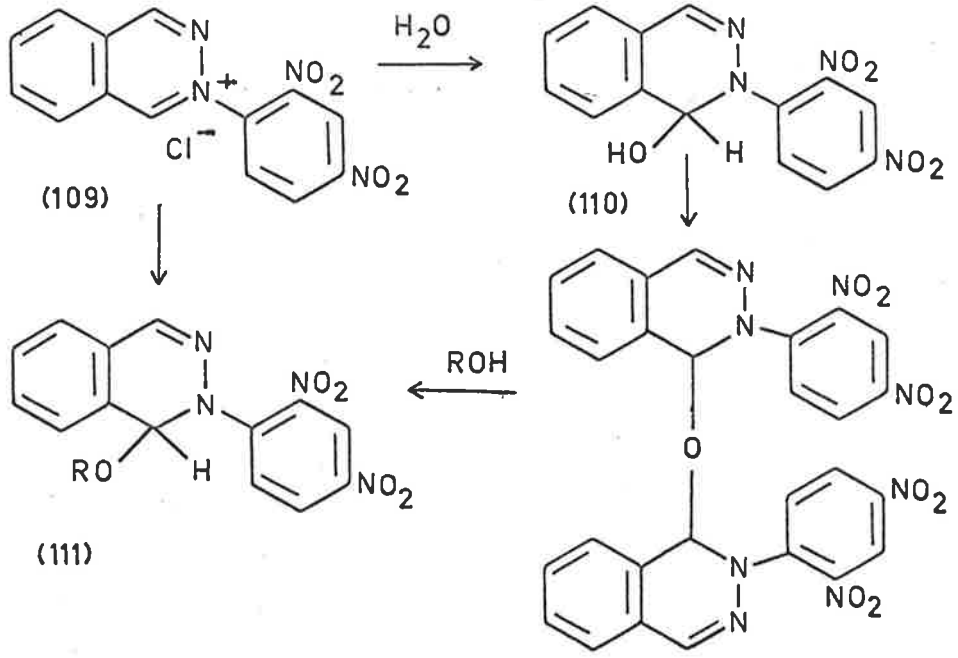
solution of the methiodide with alkaline potassium ferricyanide. (Scheme 30).



Scheme 30.

On the addition of sodium cyanide to an aqueous solution of phthalazine methiodide a crystalline adduct separated. This was assigned the 1,2-dihydro structure (107) on the basis of its analysis and n.m.r. spectrum; one proton gave a signal at τ 4.90, characteristic of a benzylic position. The absence of nitrile absorption in the infrared spectrum does not exclude the proposed structure since the intensity of the nitrile peak may be greatly reduced by adjacent polar groups.[244] The addition of cyanide ion to the 2- and 4- positions of pyridinium salts has given products of similar structure.[245] Attempts to hydrolyse compound (107) to a carboxylic acid were unsuccessful; hydrogen cyanide was liberated on treatment with hydrochloric acid, thus reforming the phthalazinium system (108), while the action of alkali resulted in replacement of the cyano group by hydroxide ion. (Scheme 30).

Only black, intractable material was obtained in attempts to quaternise phthalazine with 2,4-dinitrochlorobenzene by refluxing the components in benzene, toluene or xylene. Heating the compounds in the absence of solvent or in chloroform afforded a yellow solid which appeared to be a mixture of phthalazine hydrochloride and the required salt (109). This reacted rapidly with water, giving an orange solid which was formulated as the pseudo base (110). The compound was



Scheme 31.

difficult to purify and satisfactory analytical figures have not yet been obtained. It was also prepared by heating phthalazine and 2,4-dinitrochlorobenzene in water.

By treatment of the salt (109) with ethanol or methanol it was converted to the alkyl ethers (111; R=CH_3, CH_2CH_3); however, these

were better prepared by heating a mixture of phthalazine, 2,4-dinitrochlorobenzene and the respective alcohol under reflux. The structures of the alkyl ethers were deduced from their analyses and n.m.r. spectra. No distinct products were obtained using higher alcohols.

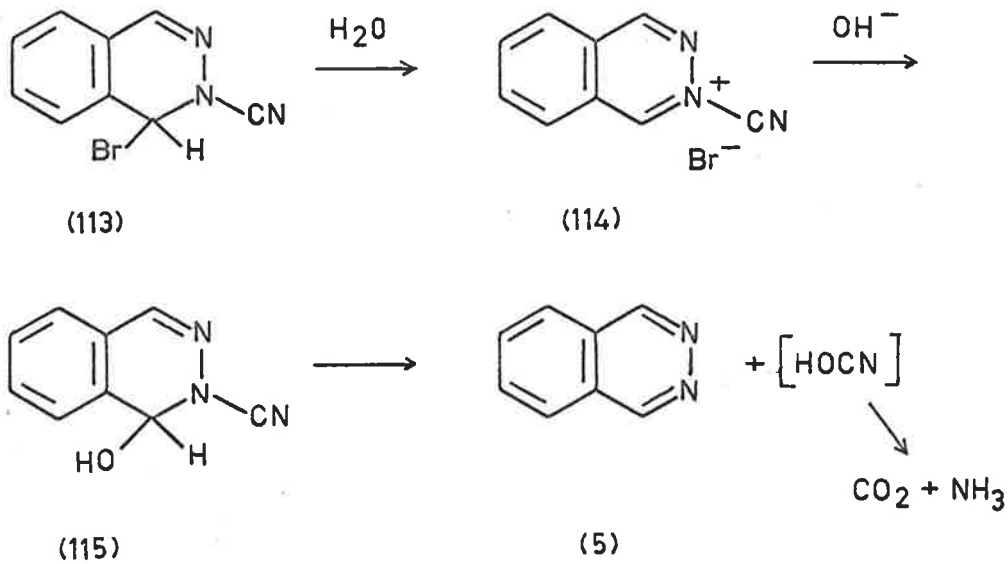
The structure proposed for the pseudo base (110) must be considered as tentative; several other possibilities exist, including a quaternary hydroxide salt or the open-chain tautomer. Methods for distinguishing between these structures in solution have been recently reviewed by Beke,[246] but were limited in the present case by the low solubility of the compound. The infrared spectrum in Nujol showed no carbonyl absorption but had a narrow O-H absorption band, suggesting that the compound has the pseudo base structure (110) in the solid state.

The pseudo base (110) was hydrolysed with sodium hydroxide in dimethyl sulphoxide to phthalazine and 2,4-dinitrophenol. All attempts to oxidize the hydroxyl group in (110) were unsuccessful. The evolution of carbon dioxide observed during potassium permanganate oxidation indicated extensive degradation of the system, while the use of alkaline potassium ferricyanide resulted in hydrolysis as above.

Concentrated nitric acid rapidly converted the pseudo base to a compound which was found by analysis to contain less oxygen than the starting material. The n.m.r. spectrum indicated the presence of the 1,2-dihydrophthalazine system and the infrared spectrum was strikingly similar to that of the ethyl ether (111; R=CH_2CH_3). The bimolecular ether structure (112) is therefore proposed for this compound (Scheme 31).

Variable yields were obtained in its preparation and the controlling factors are not yet clear.

A preliminary study was made of the reaction of phthalazine with cyanogen bromide in chloroform. The crystalline solid thus obtained appeared to be an adduct (113) which rearranged to the salt (114) on treatment with water or ethanol (Scheme 32). The salt (114)



Scheme 32.

formed what appeared to be the pseudo base (115) in the presence of cold alkali. The latter compound was rapidly decomposed by hot alkali to phthalazine, ammonia and carbon dioxide. Cyanic acid (HOCN) is known[247] to undergo hydrolysis to ammonia and carbon dioxide and would thus give rise to these products if formed in the above reaction.

It appears, therefore, that phthalazinium salts are readily attacked at the 1-position by nucleophiles but the resulting C-N

linkage is stable toward hydrolysis in contrast to the ring-opening reactions of pyridine and quinoline quaternary salts.[248] Products analogous to those obtained from the reaction of phthalazinium salts with water and alcohols were prepared by Rowe[249] from 3-aryl-1-keto-phthalazines; and 1-chlorophthalazine was considered[250] to couple with itself to form a quaternary salt which was then substituted at the 1-position by water.

EXPERIMENTAL

General.

Melting points were determined in capillaries in a Gallenkamp apparatus and are uncorrected.

The petroleum ether used had b.p. 60-80°. All organic extracts were dried over calcium chloride.

Iodometric analyses were carried out by treating the compound (ca. 150 mg) with potassium iodide in aqueous acetic acid and titrating the liberated iodine against 0.1N sodium thiosulphate. All other analyses were performed by the Australian Microanalytical Service, Melbourne.

Infrared and ultraviolet spectra were recorded on Perkin-Elmer model 137 spectrophotometers. The n.m.r. spectra were recorded by Dr. T.M. Spotswood and Mr. L. Paltridge with a Varian DP60 spectrometer, operated at 60 Mc/s using tetramethyl silane as internal reference.

The molecular orbital calculations were carried out by Mr. B.D. Roney on a C.D.C. 3200 computer using programmes written in Fortran IV.

Chapter 1

w,w,w',w'-Tetrabromo-o-xylene - This compound was prepared by bromination of o-xylene under ultraviolet light as described by Bill and Tarbell.[16] The product was decolourised with charcoal, the solvent removed and the crude oil used in the following step.

Phthalazine - The crude tetrabromo derivative (250 g) was stirred with water (4 l) under reflux until the oil had dissolved (36 hr). Hydrazine hydrate (50 ml) in water (500 ml) was added dropwise to the hot, stirred solution and water (2.5 l) was removed by distillation. The cooled solution was extracted with chloroform (2 x 250 ml) to remove traces of phthalazone and tar. Basification followed by chloroform extraction (3 x 400 ml) gave phthalazine (65 g, 84%) which was obtained as a white solid after sublimation (0.1 mm/100°), m.p. 91° (lit.[15] m.p. 92°).

4-Bromo-o-xylene - was prepared by the iron-catalysed bromination of o-xylene according to the method of Wisansky and Ansbacher,[251] except that the temperature was allowed to reach 10° during the reaction and the steam distillation procedure was omitted. Fractional distillation of the crude product gave 4-bromo-o-xylene (72%), b.p. 86-88°/10 mm (lit.[251] b.p. 92-94°/14-15 mm), and 4,5-dibromo-o-xylene (16%), b.p. 132-134°/10 mm.

w,w,w',w',4-Pentabromo-o-xylene - was synthesised by the dropwise addition of bromine (75 g) to 4-bromo-o-xylene (20 g) at 180° during irradiation with ultraviolet light. The solid was dissolved in hot chloroform, treated with charcoal and allowed to crystallise. Several recrystallisations from ethanol gave the product as colourless needles (31 g, 57%), m.p. 117-118° (lit.[83] m.p. 114°). The n.m.r. spectrum ($CDCl_3$) showed two protons at τ 2.46 and one each at τ 3.03 and τ 2.97.

6-Bromophthalazine - The pentabromo-o-xylene (9.0 g) was heated with ethanol (500 ml), water (200 ml) and sodium acetate (6.0 g) at 150° (48 hr). Removal of the solvent gave a yellow oil which was refluxed with hydrazine (20 ml) in ethanol (70 ml), for 2 hr. The red oil obtained on evaporation of the solvent was dissolved in chloroform and washed with 2N hydrochloric acid (2 x 100 ml). The washings were rendered alkaline and extracted with chloroform. The extract yielded a yellow solid which was sublimed (0.05 mm/140°) and recrystallised from ethanol-water. 6-Bromophthalazine (1.1 g, 2%) was obtained as colourless needles, m.p. 145°. (Found: N, 12.8. $C_8H_5BrN_2$ requires : N, 13.4%.) The picrate had m.p. 200-201° (ethanol-water). (Found: N, 15.59. $C_{14}H_8BrN_5O_7$ requires : N, 15.98%.)

3-Nitro- and 4-nitro-o-xylene - Nitration of o-xylene by the method of Emerson and Smith[252] gave a mixture which on fractionation yielded 3-nitro-o-xylene, b.p. 125-127°/17 mm (lit.[252] b.p. 127-130°/18 mm), 4-nitro-o-xylene, b.p. 138-140°/17mm.(lit.[253] b.p. 143°/21 mm), and

a mixture of dinitro- derivatives.

4-Nitro-w,w,w',w'-tetrabromo-o-xylene - A mixture of 4-nitro-o-xylene (5.0 g), N-bromosuccinimide (26 g) and benzoyl peroxide (1.5 g) was refluxed in carbon tetrachloride (200 ml) for 24 hr. The solution, after filtration, was washed with aqueous sodium hydroxide and water and the solvent removed. A red oil was obtained which crystallised on standing. Recrystallisation from ethanol gave the tetrabromide (13.5 g, 87%) as small, yellow prisms, m.p. 123°. (Found: N, 3.03%. Calc. for $C_8H_5Br_4NO_2$: N, 2.99%). The n.m.r. spectrum ($CDCl_3$) showed one proton each at τ 2.89, τ 2.85, τ 2.08 (doublet, J = 8.8 c.p.s.), τ 1.76 (quartet, J = 2.4 and 8.8 c.p.s.) and τ 1.45 (doublet, J = 2.4 c.p.s.).

3-Bromo-o-xylene - was prepared from 3-amino-o-xylene by the same procedure as used for p-bromotoluene[254] and was obtained as a colourless liquid, b.p. 213-214° (lit.[255] b.p. 213°).

Phthalaz-1,4-dione - was best prepared by heating phthalic anhydride with excess hydrazine hydrate in ethanol under reflux (2 hr). The white precipitate (95%) was washed with ethanol and water and dried at 100°. The compound had m.p. 332-335° (lit.[41] m.p. 334-336°).

Phthalaz-1,4-dithione - The literature method,[86] involving the reaction of phthalaz-1,4-dione with phosphorus pentasulphide at 200°, was modified as follows. The dione (5.0 g) was intimately mixed with phosphorus

pentasulphide (20 g) and dry pyridine (200 ml) added, whereupon an exothermic reaction occurred. After 6 hours reflux the pyridine was removed, the residue digested in water (150 ml) on the steam bath (30 min) and the solution filtered. Acidification of the filtrate with hydrochloric acid gave phthalaz-1,4-dithione (5.0 g, 82%) as a yellow solid, m.p. 262-264° (lit.[86] m.p. 262-265°).

Desulphurisation of phthalaz-1,4-dithione - The thione (3.0 g) and Raney nickel (1.0 g, W7) were refluxed in pyridine (150 ml) for 1 hr. After removal of the catalyst and solvent, water (100 ml) was added to the residue and evaporated to dryness under reduced pressure, the procedure being repeated to remove traces of pyridine. The solid was then dissolved in sodium hydroxide solution (100 ml, 10%) and extracted with chloroform. Phthalazine (0.26 g, 13%) was obtained from the extract as colourless needles after sublimation (0.05 mm/90°) and crystallisation from cyclohexane, m.p. and mixed m.p. 92°.

1,4-Dichlorophthalazine - This compound was prepared by refluxing phthalaz-1,4-dione with phosphorus pentachloride (2 moles) in phosphorus oxychloride (1 hr). Concentration of the solution and cooling afforded a crystalline solid which was filtered, washed with benzene and dried in vacuo over potassium hydroxide. Recrystallisation from benzene gave the product as colourless needles (89%), m.p. 163° (lit.[41] m.p. 162-164°).

Reaction of 1,4-dichlorophthalazine with zinc dust - 1,4-Dichlorophthalazine (5.0 g) was heated under reflux with zinc dust (10 g) in water (150 ml) for 14 hr. The metal was removed by filtration and the filtrate basified with sodium hydroxide. Extraction of the basic solution with chloroform yielded phthalazine (0.16 g, 5%).

When acetic acid was used as the solvent, 4-chlorophthalazone (4.4 g, 95%) was obtained after evaporating the solution to dryness under reduced pressure. The compound had m.p. 273-274° after crystallisation from ethanol (lit.[41] m.p. 274°).

Hydrogenation of 1,4-dichlorophthalazine -

(1) 1,4-dichlorophthalazine (1.98 g, 0.01 mole) in dioxan (150 ml) and ammonia (1.5 ml, d 0.880) was hydrogenated over palladium-on-carbon (0.5 g, 5%) at 1 atm. until the theoretical volume (450 ml) had been absorbed (45 min). The catalyst was filtered and the solvent removed. The residue was dissolved in chloroform (150 ml), filtered and evaporated to dryness. Sublimation of the residue (0.05 mm/100°) gave phthalazine (1.05 g, 81%).

An identical experiment was carried out using half the required volume of hydrogen. The crude product was treated with dilute hydrochloric acid (50 ml) and the residue removed by filtration. Recrystallisation of the latter from ethanol yielded 4-chlorophthalazone (0.95 g, 53%), m.p. 273-274°. Extraction of the basified filtrate with chloroform provided phthalazine (0.58 g, 40%).

(2) A solution of the dichloro derivative (0.85 g, 0.0043 mole) and ammonia gas (0.4 g) in cold methanol (150 ml) was hydrogenated over palladium-on-carbon (0.5 g, 5%) at 1 atm. until the theoretical volume (200 ml) had been absorbed. Removal of the catalyst and solvent gave a residue which was dissolved in water, filtered and treated with aqueous picric acid. A yellow precipitate was collected and identified as phthalazine picrate (0.71 g, 72%) by its m.p. and mixed m.p. 208-209°, (lit.[15] m.p. 209-210°).

(3) The dichloro derivative was dissolved in boiling methanol (150 ml) and hydrogenated as in (2) above. The residue obtained after removal of the catalyst and solvent was stirred with sodium hydroxide solution (50 ml, 10%) and filtered. The insoluble material was recrystallised from petroleum ether (b.p. 60-80°) and identified as 4-methoxy-1-chlorophthalazine (0.31 g, 31%) by its m.p. 108° (lit.[45] m.p. 108°). Extraction of the filtrate with chloroform gave phthalazine (0.35 g, 54%).

(4) A solution of 1,4-dichlorophthalazine (3.51 g) in dioxan (300 ml) and ammonia (3.0 ml, d 0.880) was hydrogenated over palladium-on-carbon (1.0 g, 5%) at 100 atm. (1 hr). The catalyst and solvent were removed and the residue was distilled. 1,2,3,4-Tetrahydrophthalazine (1.81 g, 77%) was obtained as a colourless liquid, b.p. 90°/0.75 mm, which crystallised on standing. The picrate had m.p. 157° (lit.[46] m.p. 159-160°).

Hydrogenation of phthalazine under the same conditions gave the tetrahydro derivative in 81% yield.

1-Chlorophthalazine - was obtained by heating phthalazone with excess phosphorus oxychloride on the water-bath until evolution of hydrogen chloride ceased. The mixture was poured into aqueous sodium hydroxide (10%) and ice and the precipitate filtered and dried *in vacuo*. Recrystallisation from ether afforded colourless needles of 1-chlorophthalazine (75%), m.p. 113° (lit.[23] m.p. 113°).

1-Chloro-4-methyl- and 1-chloro-4-phenylphthalazine - were prepared by the same procedure as 1-chlorophthalazine, and after recrystallisation from ethanol had m.p. 130° (lit.[30] m.p. 129-130°) and m.p. 160° (lit.[256] m.p. 160-161°) respectively.

Hydrogenation of 1-chlorophthalazine -

(1) A solution of 1-chlorophthalazine (6.10 g, 0.037 mole) in ethanol (150 ml) and ammonia (5 ml, d 0.88) was hydrogenated over palladium-on-carbon (2.5 g, 5%) at 1 atm. until the theoretical volume had been absorbed (830 ml). The catalyst was filtered and the solvent removed under reduced pressure. The residue was dissolved in dilute ammonia and extracted with chloroform. Phthalazine (3.1 g, 56%) was obtained from the extract as a yellow liquid, b.p. 100°/0.2 mm, which solidified on standing.

(2) When the hydrogenation was carried out at 100 atm. for 1 hr, 1,2,3,4-tetrahydrophthalazine was obtained in 53% yield.

Hydrogenation of 1-chloro-4-methylphthalazine -

(1) The procedure of Stephenson[30] was followed for hydrogenation at 1 atm., 1-methylphthalazine (75%) being isolated by distillation of the crude product.

(2) A solution of 1-chloro-4-methylphthalazine (10.5 g, 0.059 mole) in ethanol (300 ml) and ammonia (6 ml, d 0.880) was hydrogenated over palladium-on-carbon (3.0 g, 5%) at 100 atm. (1 hr). After removal of the catalyst and solvent the residue was dissolved in dilute ammonia and extracted with chloroform. Distillation of the extract gave 4-methyl-1,2,3,4-tetrahydrophthalazine (6.50 g, 76%) as a colourless liquid, b.p. 93°/0.8 mm, which became pink on standing. (Found: C, 73.14; H, 7.93; N, 18.22. $C_9H_{12}N_2$: requires C, 72.94; H, 8.16; N, 18.90%). The picrate had m.p. 145° (lit.[26] m.p. 146°).

1-Phenylphthalazine - A solution of 1-chloro-4-phenylphthalazine (4.3 g, 0.018 mole) in ethanol (150 ml) and ammonia (3 ml, d 0.880) was hydrogenated over palladium-on-carbon (1.7 g, 5%) at 100 atm. (1 hr). Removal of the catalyst and solvent gave a residue which was stirred with hot chloroform and filtered. Evaporation of the filtrate provided 1-phenylphthalazine (2.60 g, 71%) as yellow prisms (ethanol), m.p. 141-142° (lit.[257] m.p. 142-143°).

4-Chlorophthalazone - was prepared by stirring a suspension of 1,4-dichlorophthalazine (5.0 g) in dilute hydrochloric acid (100 ml) for 15 hr. The solid was filtered, washed with water and recrystallised from ethanol, giving 4-chlorophthalazone (4.1 g, 91%) as colourless needles, m.p. 273-274° (lit.[41] m.p. 274°).

Phthalazone -

(1) 4-Chlorophthalazone (5.0 g) in ethanolic dioxan (300 ml, 50%) and ammonia (10 ml, d 0.880) was hydrogenated over palladium-on-carbon (2.0 g, 5%) at 150° and 100 atm. for 2 hr. Removal of the catalyst and solvent left a grey solid which on crystallisation from ethanol-water gave phthalazone (3.1 g, 77%), m.p. and mixed m.p. 184°, (lit.[23] m.p. 184-185°).

(2) The chloro derivative (2.0 g) was refluxed with palladium-on-carbon (0.5 g, 5%) and hydrazine hydrate (10 ml) in ethanol (150 ml) for 10 hr. After removal of the solvent the residue was dissolved in ethanol (100 ml) and filtered. Water (50 ml) was added to the filtrate and evaporation of the ethanol gave 4-chlorophthalazone (0.25 g). Further concentration of the aqueous solution yielded phthalazone (1.38 g, 86%).

5-Nitro- and 6-nitrophthalaz-1,4-dione - These compounds were prepared by the action of hydrazine on the corresponding phthalic anhydrides as described by Drew and Pearman.[40]

1,4-Dichloro-5-nitrophthalazine - 5-Nitrophthalaz-1,4-dione (5.0 g) was refluxed with phosphorus pentachloride (10.0 g) in phosphorus oxychloride (20 ml) until a clear solution was obtained (30 min). After removal of excess phosphorus oxychloride under reduced pressure, benzene (2 x 20 ml) was added to the residue and evaporated to dryness. The solid was dried over potassium hydroxide in vacuo and recrystallised from benzene.

1,4-Dichloro-5-nitrophthalazine (4.9 g, 83%) was obtained as yellow prisms, m.p. 188°. (Found: C, 39.41; H, 1.93; N, 17.12%. $C_8H_3Cl_2N_3O_2$ requires C, 39.38; H, 1.53; N, 17.20%.)

1,4-Dichloro-6-nitrophthalazine - was similarly prepared from 6-nitrophthalaz-1,4-dione (72%) and purified by sublimation and crystallisation from benzene. The dichloro-derivative had m.p. 203-204°. (Found: N, 17.44. $C_8H_3Cl_2N_3O_2$ requires N, 17.20%.)

6-Chlorophthalaz-1,4-dione - 4-Chlorophthalic anhydride (6.0 g) in ethanol (250 ml) was refluxed with hydrazine hydrate (5 ml) for 2 hr. The flocculent white precipitate was filtered, washed with water and dried in vacuo (6.1 g, 95%), m.p. 347-349° (lit.[46] m.p. 348-350°).

1,4,6-Trichlorophthalazine - An intimate mixture of 6-chlorophthalaz-1,4-dione (9.0 g) and phosphorus pentachloride (19.0 g) was treated with

phosphorus oxychloride (10 ml) and refluxed with exclusion of moisture until evolution of hydrogen chloride ceased (1 hr). Excess phosphorus oxychloride was removed under reduced pressure, the residue dissolved in benzene (200 ml), washed with cold sodium hydroxide solution (250 ml, 5%) and water (100 ml) and dried. After removal of the benzene the residue was sublimed (0.05 mm/150°), giving 1,4,6-trichlorophthalazine hydrate (9.3 g, 68%) as a white solid, m.p. 110-111°. (Found: C, 38.41; N, 11.01. $C_8H_5Cl_3N_2O$ requires C, 38.20; N, 11.14%.)

4,5-Dimethylphthalic anhydride - Dehydrogenation of 4,5-dimethyl-Δ^4-tetrahydrophthalic anhydride using nitrobenzene or chlorine[258] was found to be less convenient than the action of sulphur[259] at 200°. The anhydride was obtained by the latter method as a white solid, m.p. 204° (lit.[259] m.p. 206°).

6,7-Dimethylphthalaz-1,4-dione - A solution of 4,5-dimethylphthalic anhydride (4.5 g) and hydrazine hydrate (2.0 ml) in ethanol (100 ml) was refluxed for 3 hr. Removal of the solvent gave a brown solid which was purified by precipitation from alkaline solution with acetic acid. 6,7-Dimethylphthalaz-1,4-dione (4.45 g, 92%) was obtained as a white powder, m.p. > 360°. (Found: C, 62.91; H, 5.34; N, 14.73. $C_{10}H_{10}N_2O_2$ requires C, 63.15; H, 5.30; N, 14.73%.)

1,4-Dichloro-6,7-dimethylphthalazine - A mixture of 6,7-dimethylphthalaz-1,4-dione (5.3 g) and phosphorus oxychloride (100 ml) was

heated under reflux until a clear solution was obtained. The excess phosphorus oxychloride was removed and the residue poured into a mixture of aqueous sodium hydroxide (250 ml, 10%) and ice. The precipitate was collected, dried in vacuo and sublimed (0.05 mm/200°). 1,4-Dichloro-6,7-dimethylphthalazine was obtained as a white solid (5.1 g, 81%), m.p. 217°. (Found: C, 53.21; H, 3.53; N, 12.33. $C_{10}H_8Cl_2N_2$ requires C, 52.88; H, 3.57; N, 12.33%.)

Benzo[g]phthalaz-1,4-dione - was prepared by the method of Drew and Garwood[38] from naphthalene-2,3-dicarboxylic acid.[260]

1,4-Dichlorobenzo[g]phthalazine - A mixture of benzo[g]phthalaz-1,4-dione (5.0 g), phosphorus pentachloride (10.0g) and phosphorus oxychloride (50 ml) was heated under reflux until the solid had dissolved. 1,4-Dichlorobenzo[g]phthalazine (1.7 g, 30%) separated on cooling and was recrystallised from dioxan as fine, yellow needles, m.p. 237°. (Found: C, 58.01; H, 2.68; N, 11.25. $C_{12}H_6Cl_2N_2$ requires C, 57.81; H, 2.43; N, 11.32%.) Concentration of the reaction mixture provided a second crop (2.5 g, 43%).

4-Chlorobenzo[g]phthalazone - A suspension of 1,4-dichlorobenzo[g]-phthalazine (0.26 g) in water (10 ml) was heated at 100° (3 hr). The solid was collected and recrystallised from dioxane/water giving 4-chlorobenzo[g]phthalazone (0.23 g, 95%) as colourless plates, m.p. 309-310°. (Found: C, 62.11; H, 3.14; N, 11.58. $C_{12}H_7ClN_2O$ requires

C, 62.47; H, 3.06; N, 12.15%.)

2,3-Bis(dibromomethyl)naphthalene - For the preparation of this compound, treatment of 2,3-dimethylnaphthalene with N-bromosuccinimide (4 mole) in one step using a reaction time of 15 hr was found to be more convenient than the two stage synthesis described by Reid and Bodem.[261] The tetrabromo derivative was obtained as yellow plates (59%) from chloroform, m.p. 161° (lit.[261] m.p. 161°).

Naphthalene-2,3-dialdehyde - was prepared by hydrolysis of 2,3-bis(dibromomethyl)naphthalene according to the method of Reid and Bodem.[261] The compound was isolated as yellow needles (76%) from ethanol, m.p. 131° (lit.[261] m.p. 131°).

Benzo[g]phthalazine -

(1) A solution of 1,4-dichlorobenzo[g]phthalazine (1.0 g, 0.004 mole) in ammonia (1.0 ml, d 0.880) and dioxan (150 ml) was hydrogenated over palladium-on-carbon (1.0 g, 5%) at 1 atm. until 2 moles of hydrogen had been absorbed. After removal of the catalyst and solvent, the residue was dissolved in chloroform, filtered and the filtrate evaporated to dryness. Several recrystallisations of the residue from ethanol (charcoal) gave benzo[g]phthalazine (0.51 g, 70%) as yellow prisms, m.p. 213°. (Found: C, 79.76; H, 4.45; N, 15.38. $C_{12}H_8N_2$ requires C, 79.98; H, 4.48; N, 15.55%.) The picrate was obtained as

yellow needles from ethanol, m.p. 259-260° dec. (Found: N, 17.11. $C_{18}H_{11}N_NO_7$ requires N, 16.95%.)

A solution of benzo[g]phthalazine (0.10 g) in dilute nitric acid (5 ml) was evaporated to dryness on the water-bath. The residue (0.12 g) crystallised from ethanol as yellow needles of benzo[g]-phthalazine nitrate, m.p. 170° d. (Found: C, 58.6; H, 3.91; N, 16.70. $C_{12}H_9N_3O_3$ requires C, 59.2; H, 3.74; N, 17.28%.)

Addition of a solution of benzo[g]phthalazine in ethanol to maleic acid in water afforded benzo[g]phthalazine maleate as silky, yellow needles (ethanol), m.p. 140° d. (Found: C, 64.92; H, 4.31; N, 9.59; O, 21.3. $C_{16}H_{12}N_2O_4$ requires C, 64.86; H, 4.08; N, 9.46; O, 21.6%.)

(2) Naphthalene-2,3-dialdehyde (5.1 g) was refluxed with hydrazine hydrate (5.0 ml) in ethanol (100 ml) for 10 hr. After removal of the solvent the residue was recrystallised from ethanol (charcoal), giving benzo[g]phthalazine (4.63 g, 93%) as yellow prisms, m.p. and mixed m.p. 213°.

1,4-Dihydrazinophthalazine - was obtained as orange plates (water), m.p. 190°, by the reaction of phthalonitrile with hydrazine[48] (lit.[48] m.p. 190°). The yield was slightly increased by stirring the reaction mixture.

1,4-Diaminophthalazine hydrate -

(1) A mixture of 1,4-dihydrazinophthalazine (2.0 g), Raney nickel (12 g, W7) and water (100 ml) was heated under reflux until evolution of ammonia ceased. The hot solution was filtered and the product obtained on cooling was recrystallised from water, giving 1,4-diaminophthalazine monohydrate (1.12 g, 57%) as colourless needles, m.p. 253-254°. (Found: C, 53.69; H, 5.41; N, 31.10. $C_8H_{10}N_4O$ requires C, 53.92; H, 5.66; N, 31.45%.) The hydrate was soluble in dioxan but insoluble in ethanol and chloroform; prolonged reflux with benzaldehyde in aqueous ethanol (50%) and a trace of acetic acid gave the starting materials. The picrate crystallised from water as silky, yellow needles, m.p. 308-310°d. (Found: N, 24.98. $C_{14}H_{11}N_7O_7$ requires N, 25.19%.)

(2) Phthalonitrile (12.5 g) was heated on the water-bath with a mixture of hydrazine hydrate (25 ml), acetic acid (3 ml) and dioxan (50 ml). After 7 min the yellow solution became red and was immediately poured into water (200 ml). The mixture was cooled in ice and the precipitate of phthalonitrile (11.5 g) filtered. The volume of the filtrate was reduced to 30 ml and the cream solid which separated was collected and washed successively with chloroform, ethanol and ether. Two recrystallisations from water (charcoal) yielded 1,4-diaminophthalazine monohydrate (0.24 g, 1.5%) as colourless needles, m.p. and mixed m.p. 253-254°.

A reaction time of 23 min afforded phthalonitrile (90%) and

1,4-dihydrazinophthalazine (9.5%). No amine derivative was isolated from reactions using benzene, n-butanol or acetic acid as the solvent.

Reaction of 1,4-diaminophthalazine with hydrazine - A solution of 1,4-diaminophthalazine (0.18 g) in dioxan (0.8 ml) was treated with hydrazine hydrate (0.4 ml) and acetic acid (0.05 ml) and the mixture heated on the water-bath (3 hr). The solid material was removed and recrystallised from water, giving 1,4-dihydrazinophthalazine (0.175 g, 92%) as cream plates, m.p. and mixed m.p. 190°.

Oxidation of 1,4-dihydrazinophthalazine with mercuric oxide - In reactions 1-4 (Table 1), an aqueous solution of the hydrazino compound (2.0 g in 150 ml) was added dropwise to a stirred suspension of yellow mercuric oxide (10 g) in water (200 ml) at the given temperature. The residue was removed by centrifugation and washed with hot water (3 x 75 ml) by decantation. Extraction of the combined aqueous solutions with chloroform gave phthalazine, m.p. and mixed m.p. 92° after sublimation (0.5 mm/100°). The addition of a few drops of octan-2-ol prevented excessive foaming in reactions carried out on a preparative scale.

For reaction 5, powdered 1,4-dihydrazinophthalazine was added portionwise to a stirred suspension of mercuric oxide (10 g) in benzene (300 ml). The residue was filtered, washed with benzene (3 x 100 ml) and the combined solutions evaporated to dryness. The

product was purified as above.

Reactions 6 and 7 were conducted in the same way as reaction 1, using mercuric acetate (10 g) and a mixture of mercuric oxide (10 g) and mercuric chloride (10 g) respectively. In each case the reaction mixture was basified with sodium hydroxide before centrifugation.

Attempted decomposition of the mercury residues -

(1) The residue from reaction 5 was refluxed with sodium (1.1 g) in toluene (50 ml) for 10 hr. After dilution with benzene (50 ml) the mixture was treated with water (50 ml) and the organic layer removed. No product was obtained from the latter or by chloroform extraction of the aqueous phase.

(2) The residue from reaction 2 was treated with bromine (30 ml), whereupon an exothermic reaction occurred. Distillation of excess bromine over a period of 2 hr afforded a white residue which was dissolved in ethanol. Dilution with water gave a white precipitate from which mercuric bromide was removed by sublimation (0.5 mm/100°). The dark, organic residue (0.3 g) was insoluble in all solvents tried.

Oxidation of 1,4-dihydrazinophthalazine with silver oxide - Reactions 8 and 9 were carried out by adding the powdered hydrazino compound (2.0 g) to a stirred suspension of silver oxide (15 g) in the appropriate solvent (200 ml). The residues were collected and extracted

with chloroform (Soxhlet). The filtrate was also extracted with chloroform (2 x 100 ml) and the combined extract evaporated to dryness and the product sublimed.

In reaction 10, using a mixture of cyclohexane (200 ml) and acetic acid (100 ml), the residue was separated by centrifugation and washed with water (2 x 100 ml). The washings were combined with the cyclohexane mixture and the solvents were removed. The residue, after chromatography in chloroform on alumina, was recrystallised from cyclohexane and identified as phthalazine.

Aerial oxidation (reaction 11) -

1,4-Dihydrazinophthalazine (3.5 g) was heated under reflux in an aerated solution of sodium hydroxide (150 ml, 10%) for 12 hr. The sodium salt of phthalaz-1,4-dione (2.8 g, 81%) separated on cooling and was converted to phthalaz-1,4-dione by treatment with dilute hydrochloric acid. Acidification of the basic solution gave an additional crop of phthalaz-1,4-dione (0.35 g, 12%), m.p. 333-335° (lit.[41] 334-336°).

1,4-Dihydrazinophthalazine and copper sulphate (reaction 12) -

A solution of 1,4-dihydrazinophthalazine (3.9 g) and copper sulphate (7.5 g) in hydrochloric acid (165 ml, 1N) was refluxed for 84 hr. The insoluble copper complex was removed, the filtrate basified and again filtered (Celite). Extraction with chloroform gave phthalazine (0.20 g).

Tetrachloroquinol - Excess hydrazine hydrate (2 ml) was added dropwise to a suspension of chloranil (0.50 g) in water (20 ml) with shaking. After 15 min the mixture was acidified with dilute hydrochloric acid and the precipitate of tetrachloroquinol (0.46 g, 92%) was filtered. It had m.p. 231° after recrystallisation from acetic acid/ethanol (lit.[262] m.p. 230-231°).

Phthalazine tetrachloroquinolate - A suspension of tetrachloroquinol (0.10 g) in water (15 ml) was treated with an aqueous solution of phthalazine (0.07 g in 5 ml) and the mixture shaken vigorously (10 min). Recrystallisation of the precipitate from ethanol/water gave phthalazine tetrachloroquinolate (0.15 g, 91%) as buff needles, m.p. 160-161°. (Found: C, 44.15; H, 2.27; N, 7.09. $C_{14}H_8Cl_4N_2O_2$ requires C, 44.46; H, 2.41; N, 7.41%.) Decomposition of the complex was accomplished by warming a sample with sodium hydroxide solution; extraction with chloroform provided phthalazine (96%).

Dehydrogenation of 1,4-dihydrazinophthalazine with quinones.

In reaction 13, an aqueous solution of 1,4-dihydrazinophthalazine (2.0 g in 150 ml) was added dropwise to a stirred suspension of chloranil (10 g) in water (200 ml) at 40°. The residue was filtered and washed with hot water (5 x 100 ml). Removal of the solvent from the filtrate and washings gave phthalonitrile (0.70 g), m.p. and mixed m.p. 139-140° after crystallisation from benzene (lit.[263] m.p. 140°).

The infrared spectrum was identical with an authentic sample. Excess quinone in the residue was destroyed by treatment with hydrazine hydrate (10 ml) and the mixture was digested with sodium hydroxide solution (100 ml, 10%) on the water-bath (2 hr). Extraction of the filtered solution with chloroform yielded phthalazine (0.61 g).

In reaction 14, an aqueous solution of the dihydrazino compound (2.0 g in 100 ml) was added dropwise to a stirred suspension of benzoquinone (3.1 g) in water (150 ml). The residue was removed and the filtrate and washings gave phthalonitrile (0.62 g) as before.

1-Hydrazinophthalazine - was prepared by the action of hydrazine on 1-chlorophthalazine as described by Druey and Hartmann.[264] The compound had m.p. 172-174° (lit.[264] m.p. 172-173°).

Reaction of 1-hydrazinophthalazine with chloranil - A solution of the hydrazino compound in water (1.05 g in 50 ml) was added dropwise to a stirred suspension of chloranil (3.5 g) in water (50 ml). After 6 hr the residue was filtered and washed with water (5 x 100 ml). The filtrate and washings yielded phthalonitrile (0.40 g, 41%) on extraction with chloroform.

Reaction of 1,4-dihydrazinophthalazine with bromine (reaction 15) - Bromine water (150 ml) was added dropwise to a stirred solution of 1,4-dihydrazinophthalazine (1.25 g) in water (150 ml) over 2 hr. An orange

precipitate was filtered and washed with water (5 x 40 ml). Extraction of the combined filtrate and washings with chloroform gave phthalonitrile (0.27 g), identified as before.

1,4-Dihydrazinophthalazine and nitrobenzene (reaction 16) - The hydrazine derivative (2.0 g) was refluxed in nitrobenzene (50 ml) for 10 min. The solution was cooled, diluted with ether (100 ml) and a red precipitate removed by filtration. The passage of dry hydrogen chloride into the filtrate afforded phthalazine hydrochloride (0.96 g), m.p. 231° after crystallisation from ethanol (lit.[15] m.p. 231°).

1,4-Dihydrazinophthalazine and azobenzene (reaction 17) - A mixture of azobenzene (3.0 g) and 1,4-dihydrazinophthalazine (1.0 g) was heated at 160-170° until effervescence ceased (30 min). The product was digested with water (100 ml) at 100° for 2 hr, cooled and filtered. Acidification of the filtrate to pH 4 followed by extraction with chloroform gave phthalazine (0.13 g), m.p. 92° after sublimation.

Oxidation of 1,4-dihydrazino phthalazine with sodium hypochlorite - In reaction 18, a stirred solution of 1,4-dihydrazinophthalazine (1.0 g) in hydrochloric acid (50 ml, 4N) was treated with sodium hypochlorite solution (20 ml, 12.5% available chlorine). A dry ice bath was used in reaction 19 to maintain the temperature at -15°. The precipitate was collected and a further quantity of solid was obtained by chloroform extraction of the filtrate. The combined product was recrystallised

from ethanol and identified as 4-chlorophthalazone by its m.p. and mixed m.p. 275° (lit.[41] m.p. 274°).

Oxidation of 1,4-dihydrazinophthalazine with sodium periodate - In reaction 20, a solution of the dihydrazino compound (5.0 g) in sulphuric acid (100 ml, 2N) was added dropwise to a solution of sodium metaperiodate (20 g) in sulphuric acid (100 ml, 2N) at 70° during 15 min. On cooling, the white precipitate (4.25 g) was removed and identified as phthalaz-1,4-dione by its m.p. and mixed m.p. 333-335°.

Diazotisation of 1,4-diaminophthalazine -

(1) A solution of 1,4-diaminophthalazine (0.045 g) in hydrochloric acid (5 ml, 2N) was treated at room temperature with aqueous sodium nitrate (10 ml, 20%). The precipitate of 4-chlorophthalazone (0.040 g, 89%) was recrystallised from ethanol, m.p. and mixed m.p. 275°.

(2) A similar experiment using the amine (0.036 g) in sulphuric acid (7 ml, 2N) gave phthalaz-1,4-dione (0.030 g, 91%), m.p. and mixed m.p. 334-335°.

Oxidation of 1,4-dihydrazinophthalazine with N-bromosuccinimide (reaction 22) - Powdered 1,4-dihydrazinophthalazine (1.0 g) was added in portions to a stirred mixture of N-bromosuccinimide (4.3 g) and chloro-

form (100 ml). An exothermic reaction occurred, with evolution of nitrogen. A red solid was filtered and identified as 1,4-dihydrazinophthalazine (0.55 g, 55%) by m.p. and mixed m.p. 190°. The solvent was removed from the filtrate and the residue (3.53 g) was boiled with water (50 ml) for 15 min and filtered. Recrystallisation of the remaining solid from pyridine/water (charcoal) gave 4-bromophthalazone (0.50 g, 42%) as yellow needles, m.p. 284-285° after sintering (lit.[265] m.p. 273°).

Oxidation of phenylhydrazine with N-bromosuccinimide -

(1) Phenylhydrazine (2.16 g, 0.02 mole) was treated with N-bromosuccinimide (3.6 g, 0.02 mole) in carbon tetrachloride (120 ml) according to the method of Barakat and coworkers.[111] After 5 hrs reflux the solution was filtered and the residue stirred with aqueous sodium hydroxide (100 ml, 5%) for 2 hr. Extraction of the alkaline solution with chloroform yielded phenylhydrazine (0.43 g, 20%), identified by its b.p. 118-120°/12mm and infrared spectrum. The chloroform filtrate was concentrated and a small quantity of succinimide was removed by filtration. Chloroform (75 ml) was added to the mother liquor, which was then washed with dilute hydrochloric acid and distilled under reduced pressure, giving bromobenzene (0.79 g, 23%) which was identified by its b.p. 156° and infrared spectrum. The residue, phenyl azide (0.48 g, 21%), was identified by comparison of its infrared spectrum with that of an authentic sample. The acid washings were basified and extracted with chloroform. Removal of the solvent from the

extract provided aniline (0.43 g, 23%) which was identified by its infrared spectrum and by conversion to benzanilide, m.p. 162°.

(2) An aqueous solution of phenylhydrazine (1.0 g in 10 ml) was added to a stirred suspension of N-bromosuccinimide (4.5 g) in water (75 ml). After 15 min the solution was extracted with ether (3 x 100 ml) and the extract washed with sodium hydroxide, water and dried over magnesium sulphate. Removal of the solvent gave phenyl azide (0.27 g, 24%). The aqueous phase from the reaction mixture was treated with alkaline 2-naphthol, yielding 1-benzeneazo- 2 -naphthol (1.10 g, 43%), m.p. and mixed m.p. 133-134° (ethanol). In an identical oxidation, the aqueous phase was rendered alkaline and extracted with ether, giving aniline (0.22 g, 25%).

Phenyl azide - was prepared by treating phenylhydrazine with sodium nitrite as described by Lindsay and Allen.[266]

Benzenediazonium bromide - The method of Chattaway,[113] involving the reaction of phenylhydrazine with bromine in ethanol, was employed.

Oxidation of 1-hydrazinophthalazine - The hydrazino compound (1.1 g) was stirred with mercuric oxide (7.5 g) in water (100 ml) for 7 hr; nitrogen was evolved vigorously and the solution became black. After removal of the residue by centrifugation the supernatant was acidified

with dilute hydrochloric acid and the solvent removed under reduced pressure, leaving a residue of phthalazine hydrochloride (1.0 g, 91%), m.p. and mixed m.p. 231°.

1-Methylphthalazine hydrochloride - A solution of 1-hydrazino-4-methylphthalazine hydrochloride[264] (3.0 g) in water (300 ml) was stirred with mercuric oxide (15 g) for 24 hr. The residue was removed and the filtrate acidified with dilute hydrochloric acid. Removal of the solvent gave 1-methylphthalazine hydrochloride (1.6 g, 65%), m.p. and mixed m.p. 221° (lit.[30] m.p. 222-223°).

1-Phenylphthalazine - Finely powdered 1-hydrazino-4-phenylphthalazine[264] (2.1 g) was added in portions to a stirred suspension of mercuric oxide (10 g) in water (200 ml) and ethanol (30 ml). After 3 hr the mixture was filtered and the solvent removed, leaving a residue of 1-phenylphthalazine (0.70 g) which crystallised from ethanol as colourless prisms, m.p. and mixed m.p. 161° (lit.[256] m.p. 162°). A further quantity was obtained by chloroform extraction of the mercury residue (Soxhlet). A total yield of 1.4 g (79%) was obtained.

4-Hydrazinophthalazone - was prepared by refluxing an aqueous solution of 1,4-dihydrazinophthalazine (2.7 g in 100 ml) for 30 hr. Concentration of the solution yielded 4-hydrazinophthalazone (1.8 g, 72%), m.p. 243-245° (lit.[267] m.p. 214°).

Phthalazone - A mixture of 4-hydrazinophthalazone (0.55 g), mercuric oxide (2.5 g) and water (150 ml) was heated under reflux (3 hr). The hot solution was treated with ammonia (20 ml, d 0.880) and filtered. Evaporation of the filtrate gave phthalazone (0.37 g, 81%) which crystallised from ethanol/water as fine needles, m.p. and mixed m.p. 181°.

Pyridazine - A suspension of 3,6-dihydrazinopyridazine[268] (2.50 g) was stirred with mercuric oxide (10 g) for 3 hr. After removal of the residue the solution was concentrated, basified and extracted with chloroform. Distillation of the extract under reduced pressure afforded pyridazine (0.81 g, 57%), b.p. 88-90°/16 mm (lit.[269] b.p. 86-87°/14 mm).

3-Chloropyridazine - A solution of 3-chloro-6-hydrazinopyridazine[270] (1.40 g) was stirred with mercuric oxide (4.3 g) in water (200 ml) for 3 hr, after which the mixture was filtered and extracted with chloroform. The passage of hydrogen chloride into the dried extract yielded a white precipitate of 3-chloropyridazine hydrochloride (0.85 g, 56%), m.p. 120-122° (lit.[271] m.p. 122°).

Chapter 2.

Phthalazine tetrachloride complex - Finely powdered phthalazine (2.00 g) was treated with chlorinegas in a dry-ice cooled flask until a yellow slurry of liquid was obtained (1 hr). The mixture was allowed to reach room temperature with exclusion of moisture over a period of 30 min, after which a yellow, free-flowing powder (4.16 g, 99.3%) of the tetrachloride complex remained. Chlorine was rapidly evolved by the substance at room temperature and on heating; melting began at 60° and was complete at 230°, which is the m.p. of phthalazine hydrochloride.

Phthalazine-halogen complexes (Table 2) -

For the preparation of 1:1 adducts, a solution of phthalazine (0.20 g, 0.00154 mole) in carbon tetrachloride (10 ml) was treated with a solution of the halogen (0.0016 mole) in carbon tetrachloride (10 ml). The precipitate was filtered and recrystallised from chloroform. The iodine monochloride complex was more readily crystallised from water, while the iodine trichloride complex was insoluble in both solvents.

Adducts with a 1:2 ratio of phthalazine to halogen were obtained by the addition of excess halogen (0.004 mole) to phthalazine (0.20 g, 0.00154 mole) in carbon tetrachloride. The iodine bromide complex was recrystallised from chloroform. An analytical sample of the insoluble iodine monochloride complex was prepared by mixing filtered solutions of the reagents.

Phthalazine iodine trichloride hydrogen periodate - An aqueous solution of potassium iodide (5.0 g in 50 ml) was treated with chlorine until a clear, yellow-brown solution was obtained. Phthalazine (0.20 g) in water (5 ml) was added to the hot solution which immediately deposited a yellow precipitate. The solid was filtered and dried *in vacuo* (0.35 g). Iodometric analysis showed 42.4% ICl_3. ($C_8H_7Cl_3I_2O_4$ requires ICl_3, 42.0%.)

Reaction of phthalazine with trihalide ions -

(1) Phthalazine (0.20 g) in water (10 ml) was mixed with a solution of bromine (0.2 ml) in aqueous sodium bromide (2.0 g in 15 ml). A precipitate of phthalazine perbromide (0.32 g, 72%) was obtained which was identified by its m.p., mixed m.p. and infrared spectrum and by iodometric analysis. (Found: Br, 55.7%.)

(2) Phthalazine (0.20 g) in water (10 ml) was treated with a solution of iodine (0.50 g) in aqueous potassium iodide (2.0 g in 15 ml). Phthalazine periodide (0.44 g, 74%) was obtained as a golden-brown microcrystalline solid which was washed with water and dried *in vacuo*. The compound was identified by its m.p., mixed m.p. and infrared spectrum. (Found: I, 66.2%.)

Decomposition of phthalazine perbromide -

(1) The perbromide (1.30 g) was heated in ethanol (25 ml) under reflux until the red colour disappeared (15 min). On concentration and cooling, phthalazine hydrobromide (0.90 g, 95%) was deposited as colourless needles, m.p. 250-251°. (Found: C, 44.71; H, 3.64; N, 13.0. $C_8H_7N_2Br$ requires C, 45.5%; H, 3.35; N, 13.27%.)

(2) A suspension of the perbromide (2.0 g) in water (200 ml) was refluxed for 1 hr, during which bromine was evolved. The colourless solution was concentrated, basified and extracted with chloroform (2 x 75 ml), giving phthalazine (0.76 g, 85%). No material was obtained on acidification of the basic solution and extraction with chloroform. When excess bromine (10 ml) was added dropwise during reflux (10 hr) some phthalic acid (27%) was isolated after concentration of the solution.

(3) The perbromide (0.81 g) was heated in acetic acid (15 ml) on the water-bath (6 hr). Some bromine was evolved and the solution became deep red in colour. On cooling, large orange prisms of phthalazine hydrogen tribromide (0.54 g, 53%) were deposited, m.p. 120-121°. (Found: C, 26.28; H, 2.01; N, 7.63; active Br (iodometric), 42.7. $C_8H_7Br_3N_2$ requires C, 25.90; H, 1.91; N, 7.55; Br, 43.1%.)

The mother liquor was diluted with water (50 ml), basified and phthalazine (0.15 g, 41%) recovered from the solution by extraction

with chloroform.

(4) A solution of phthalazine perbromide (2.0 g) in chloroform (200 ml) was refluxed for 12 hr, during which time a mixture of yellow and orange crystals separated. The solution was concentrated and filtered while hot (filtrate A). The residue (1.81 g) was ground to a fine powder, then stirred with water (20 ml) at room temperature (15 min) and filtered (filtrate B.). Basification of filtrate B followed by chloroform extraction gave phthalazine (0.16 g, 18%). The residue (1.55 g) was dried in vacuo and melted in the range 100-110° with decomposition. (Found: active Br, 41.2%.)

Filtrate A deposited yellow prisms on cooling which turned dark red immediately the solvent was removed but retained their crystalline structure. On redissolving the material in chloroform a yellow solution was obtained from which the same yellow substance could be deposited by concentration. The complex infrared spectrum and wide melting point range, 95-125°, of the red material indicated that it was a mixture.

All of the above substances yielded phthalazine when treated with aqueous sodium hydroxide and extracted with chloroform.

(5) Phthalazine perbromide (2.0 g) was refluxed in carbon tetrachloride (200 ml) for 15 hr, during which the bromine colour disappeared and a viscous, black solid deposited on the sides of the flask. The solution was decanted and the solvent removed, giving phthalazine

(0.15 g, 17%). The black solid was triturated with hot water (150 ml) for 30 min and the solution decanted and extracted with chloroform. No material was obtained from the extract or from the basified solution. The tarry residue which remained was insoluble in all solvents tried.

Reaction of phthalazine hydrochloride with halogens -

(1) A solution of phthalazine hydrochloride (0.20 g) in water (10 ml) was treated with bromine water (50 ml). The yellow precipitate was filtered, dried *in vacuo* and identified as phthalazine perbromide by its m.p., mixed m.p. and infrared spectrum. (Found: Br (iodometric) 55.5%.)

(2) Addition of an aqueous solution of iodine (2.0 g) and potassium iodide (2.0 g in 20 ml) to phthalazine hydrochloride in water (10 ml) afforded a brown precipitate which became black after several minutes. The solid (0.41 g) was filtered, dried *in vacuo* and titrated with 0.1$\underline{N}$ sodium thiosulphate. The compound was formulated as phthalazine hydrogen triiodide, m.p. 100 dec. (Found: active I, 49.2. $C_8H_7N_2I_3$ requires active I, 49.6%.)

Reaction of phthalazine hydrobromide with halogens -

(1) Phthalazine hydrobromide (0.61 g) in water (10 ml) was shaken vigorously with bromine (0.5 ml) for 15 min. The yellow precipitate (0.59 g) was removed, dried *in vacuo* and identified as phthalazine perbromide as before. (Found : Br, 55.1%.)

(2) An aqueous solution of potassium iodide (2 g in 20 ml) and iodine (2.0 g) was added to phthalazine hydrobromide (0.50 g) in water (10 ml). The black precipitate was washed with water and chloroform and dried. The compound was identified as phthalazine hydrogen tri-iodide as before.

Decomposition of phthalazine tetrachloride -

(1) Phthalazine (1.0 g) was treated with chlorine gas at -60° until a slurry was obtained. The mixture was allowed to reach room temperature and the yellow powder left exposed to the atmosphere (2 days). The infrared spectrum of the product exhibited bands corresponding to phthalazine hydrochloride and also a carbonyl absorption at 1690 cm^{-1} (Nujol). The product was treated with 1N hydrochloric acid (50 ml) and extracted with chloroform (2 x 50 ml). Evaporation of the extract gave o-dichloromethylbenzaldehyde (0.16 g, 11%) as colourless needles from ether, m.p. 60°. (Found: C, 50.58; H, 3.52, Cl, 36.9. $C_8H_6Cl_2O$ requires C, 50.85; H, 3.21; Cl 37.5%.) The infrared spectrum ($CHCl_3$) had bands at 2865, 2775 (CH), 1690 (CO), 870, 785, 740 and 690 cm^{-1}. The n.m.r. spectrum (CCl_4) had τ 2.15 (multiplet, 5 protons) and τ -0.28 (singlet, 1 proton).

Phthalazine (0.71 g, 71%) was recovered from the aqueous solution on basification and extraction with chloroform (2 x 50 ml).

(2) A sample of the complex, freshly prepared from phthalazine

(0.50 g), was treated with water (50 ml) at room temperature. Evolution of nitrogen was observed and a mixture of phthalaldehyde (0.20 g, 39%) and o-dichloromethylbenzaldehyde (0.08 g, 12%) was obtained by extraction of the solution with chloroform (2 x 50 ml). The aldehydes were separated by chromatography on neutral alumina using benzene as the eluent. Phthalaldehyde was identified by its m.p. and mixed m.p. 53° (lit. m.p. 53°) after crystallisation from petroleum ether (b.p. 60-80°) and by its infrared absorption bands at 2850, 2750 (CH), 1690 (CO), 860, 810, 765 and 710 cm^{-1}.

Phthalazine (0.23 g, 46%) was recovered from the aqueous phase as before.

Hydrolysis of o-dichloromethylbenzaldehyde - A suspension of o-dichloromethylbenzaldehyde (0.24 g) in water (25 ml) was heated under reflux (2 hr). Removal of the solvent gave a yellow oil which after being chromatographed in benzene on neutral alumina was found to be a mixture of the starting material (0.15 g, 62%) and phthalaldehyde (0.06 g, 35%).

Reaction of phthalazine with chlorine in carbon tetrachloride -

(1) The passage of chlorine gas into a solution of phthalazine (1.0 g) in carbon tetrachloride (50 ml) at room temperature afforded a yellow precipitate which became white on standing. Filtration was

carried out in a dry-box. No material could be recovered from the filtrate and the residue was shown to be phthalazine hydrochloride (1.24 g, 99.7%) by its infrared spectrum.

(2) A slow stream of chlorine was passed into a solution of phthalazine (1.0 g) in carbon tetrachloride (50 ml) under reflux (18 hr). A precipitate of phthalazine hydrochloride (0.86 g, 68%) was filtered and the filtrate washed with water and evaporated to dryness, giving o-dichloromethylbenzaldehyde (0.20 g, 14%) as a yellow oil.

Phthalaldehydic acid - A suspension of phthalaldehyde (0.20 g) in alkaline sodium hypochlorite (50 ml, pH 8.5, 1.2% available chlorine) was shaken at room temperature (30 min). The solution was extracted with chloroform to remove the starting material and then acidified. Phthalaldehydic acid (0.11 g, 49%) was obtained on chloroform extraction as a white solid, m.p. and mixed m.p. 98-99°. The infrared spectrum was identical with that of an authentic sample.

Phthalide - A suspension of phthalaldehyde (0.20 g) in alkaline sodium hypochlorite (50 ml, 2N, 1.2% available chlorine) was shaken vigorously for 2 hr. Acidification and chloroform extraction of the solution yielded phthalide (0.03 g, 15%) which was identified by its m.p. and mixed m.p. 72-73° (water) and infrared spectrum.

N-Chlorophthalazone - A mixture of phthalazone (0.25 g), chloroform

(15 ml) and water (20 ml) was treated with chlorine gas for 30 min with vigorous shaking. The chloroform layer was removed, dried and evaporated, leaving N-chlorophthalazone (0.21 g, 69%) as a colourless solid, m.p. 147°. The chlorine was estimated iodometrically. (Found: Cl, 19.1. $C_8H_5ClN_2O$ requires Cl, 19.5%.)

A sample (0.15 g) was dissolved in chloroform (50 ml) and treated first with potassium iodide and then with sodium thiosulphate solution. Phthalazone (0.12 g, 99%) was obtained from the chloroform layer and identified by its m.p. and mixed m.p. 183° and infrared spectrum. Conversion to phthalazone was also achieved by heating the N-chloro derivative in ethanol.

Reactions of phthalazine with chlorine in aqueous media (Table 5)-

Reaction 1 - was carried out by passing a stream of chlorine into a vigorously agitated solution of phthalazine (0.50 g) in water (50 ml) at room temperature. After 15 min the solution was extracted with chloroform (2 x 50 ml) and the solvent was removed from the extract. The residual oil was chromatographed in benzene on neutral alumina and the aldehydes identified as before.

The relative yields were independent of temperature over the range 0-95°. The ratio of the two aldehydes was conveniently estimated by comparing the relative intensities of the strong bands near 860 cm^{-1} in the infrared spectrum ($CHCl_3$) of the mixture with those of mixtures containing known ratios of the aldehydes.

Reaction 2 - was performed similarly to reaction 1, except that a buffer solution, obtained by mixing appropriate volumes of 2M sodium monohydrogen phosphate and 1M citric acid, was used.

Reactions 3-5 - were conducted using buffer solutions prepared from 1N sodium hydroxide and 1M potassium dihydrogen phosphate mixtures. The residue obtained by chloroform extraction was redissolved in the same solvent and evaporated, the process being repeated to remove traces of chlorine. Repeated extraction of the solid with ether provided a residue which was identified as N-chlorophthalazone by its m.p., mixed m.p. and infrared spectrum.

To estimate the yield of N-chlorophthalazone, the crude solid was treated with aqueous potassium iodide (2 g in 5 ml) and acetic acid (5 ml) and the liberated iodine titrated against 0.1N sodium thiosulphate. The solution was then basified and immediately extracted with chloroform (2 x 50 ml). The mixture of aldehydes obtained from the extract was separated by chromatography as before.

In reaction 3, the yields were measured at pH 4.5, 5, 6, and 7. Chlorine water was used in reaction 4 to allow slow addition of chlorine.

Reactions 6 and 7 - were carried out by adding excess sodium hypochlorite solution (45 ml, 1.2% available chlorine) at the required pH to a solution of phthalazine (0.20 g) in water (15 ml), also at the required pH. The precipitate of N-chlorophthalazone was collected and

the filtrate acidified and extracted with chloroform (2 x 30 ml). Phthalazine was recovered from the aqueous phase after basification and chloroform extraction. The first chloroform extract was washed with sodium hydroxide (10%) and the solvent removed to give phthalaldehyde. The alkaline washings were acidified and yielded phthalaldehydic acid on extraction with chloroform. All of the above products were identified by their m.p., mixed m.p. and infrared spectra.

Reaction 8 - A solution of phthalazine (0.30 g) in 2N sodium hydroxide (50 ml) and sodium hypochlorite solution (1 ml, 12.5% available chlorine) was allowed to stand at room temperature (16 hr). Extraction with chloroform gave phthalazine (0.27 g, 90%). The aqueous phase was acidified and extracted with chloroform. Phthalide (0.02 g, 7%) was isolated from the extract as colourless plates after recrystallisation from water, m.p. and mixed m.p. 72-73°. The infrared spectrum was identical with that of an authentic sample.

Reaction 9 - Phthalazine (0.20 g) in aqueous sodium chloride (15 ml, 20%) was treated with chlorine gas for 15 min. Extraction of the solution with chloroform gave a mixture of aldehydes which were separated as before. The aqueous layer was basified and extracted with chloroform to recover the starting material.

Reaction 10 - was conducted similarly to reaction 9, except that chlorine water (10 ml) was rapidly added to the solution instead of chlorine gas; work-up was commenced after 2 min.

Reaction 11 - Phthalazine hydrochloride (1.0 g) in water (20 ml) was treated with chlorine gas at 5-10° (15 min). A colourless solid was filtered and identified as o-dichloromethylbenzaldehyde (0.14 g, 12%) by its m.p., mixed m.p. and infrared spectrum. Phthalazine was recovered from the filtrate by basification and extraction with chloroform.

When the reaction was carried out at 65-70°, phthalaldehyde (15%) and o-dichloromethylbenzaldehyde (17%) were obtained.

Reactions of azines with chlorine in aqueous media (Table 6) -

Reactions 1-5, 10 - were carried out by passing chlorine gas into a vigorously agitated mixture of the azine (0.50 g), chloroform (25 ml) and water (25 ml) at room temperature. After 15 min the chloroform layer was removed and the aqueous phase further extracted with chloroform (2 x 50 ml). The combined extracts were dried and the solvent removed. Benzaldehyde (reaction 1) and diethylphthalate (reaction 3) were identified by their boiling points (179° and 298°) and infrared spectra. Naphthalene-2,3-dialdehyde (reaction 4) and o-cyanobenzaldehyde (reaction 5) were identified by their m.p., mixed m.p. (131° and 103-104°) and infrared spectra after recrystallisation from ethanol and water respectively.

The structures of o-acetylbenzaldehyde (reaction 2) and 3,6-dibromophthalaldehyde (reaction 9), m.p. 135-136° (ethanol/water), were deduced from their infrared spectra and by conversion to the starting materials by condensation with hydrazine hydrate in ethanol.

Reaction 6 - Chlorine was passed into a solution of 1,4-diaminophthalazine monohydrate (0.30 g) in water (40 ml) at room temperature. A bright green precipitate formed immediately and after 15 min the solid was filtered and recrystallised from acetic acid. 1,4-Di(N-chloroimino)-1,4-dihydrophthalazine (0.35 g, 91%) was obtained as deep green plates, m.p. 155° d. (Found: N, 24.32; Cl, 30.1. $C_8H_4Cl_2N_4$ requires N, 24.46; Cl, 31.2%.) When a solution of the compound in acetic acid was treated with tin and dilute hydrochloric acid, the green colour disappeared and the addition of concentrated sodium hydroxide gave a precipitate of 1,4-diaminophthalazine.

The compound (12 mg) was added in small portions to a test-tube in an oil-bath at 125-130°. After 10 min the residue was dissolved in chloroform, filtered, and the filtrate evaporated to dryness. The residue was identified as phthalonitrile (6 mg, 88%) by its m.p., mixed m.p. (140°) and infrared spectrum.

Reaction 7 - A vigorously shaken suspension of phthalaz-1,4-dione (1.0 g) in water (25 ml) and chloroform was treated with chlorine gas (5 min). The mixture assumed a bright lime-green colouration which disappeared after several minutes; nitrogen was evolved rapidly. The chloroform layer was removed, the aqueous phase extracted with chloroform and the combined extracts on evaporation to dryness yielded phthalic anhydride (0.80 g, 88%), which was identified by its m.p. and mixed m.p. 132° and infrared spectrum. When phthalic anhydride in chloroform was shaken with chlorine water (30 min) nearly quantitative

conversion to phthalic acid was achieved.

The passage of chlorine gas into a solution of phthalaz-1,4-dione (1.0 g) in 3.7N sodium hydroxide (50 ml) resulted in rapid evolution of nitrogen and the reaction was complete after 1 min. Acidification of the solution gave a colourless precipitate which was collected and heated with water (50 ml) on the water-bath (15 min). A white powder of benzil-2,2'-dicarboxylic acid (0.11 g, 6%) was filtered and after drying in vacuo had m.p. 277° (lit.[164] m.p. 277°). The filtrate was combined with the acidic solution and concentrated under reduced pressure. Phthalic acid (0.81 g, 80%) was obtained as white crystals, m.p. 208-210°, and identified by its mixed m.p., infrared spectrum and conversion to phthalic anhydride.

Reactions 8 and 9 - were conducted by treating the heterocycle (0.50 g) in a mixture of chloroform (25 ml) and water (25 ml) with chlorine gas (15 min). After separation of the organic layer the solution was extracted with chloroform and the combined extracts evaporated to dryness, 2-chloro-4-phenylphthalazone was obtained from reaction 8 as a colourless solid, m.p. 176°. (Found: Cl, 13.5. $C_{14}H_9ClN_2O$ requires Cl, 13.8%.) The compound was converted to 1-phenylphthalazone, m.p. and mixed m.p. 236° (lit.[256] m.p. 236°), by heating with ethanol.

2,4-Dichlorophthalazone was isolated from reaction 9 as light green crystals, m.p. 157-159°. The compound had a strong odour of chlorine and iodometric analysis gave figures 1-2% below the theoretical. Conversion to 4-chlorophthalazone was effected by boiling ethanol.

Reaction 11 - Chlorine gas was bubbled into a solution of quinoxaline (1.0 g) in water (25 ml) for 30 min. A dark, tarry material initially formed which changed to a yellow solid on standing. The compound was identified as 2,3-dihydroxyquinoxaline (1.01 g, 81%) by comparison of its infrared spectrum with that of an authentic sample prepared by the method of Phillips.[272] It had m.p. > 350°.

Reaction 12 - was performed by passing chlorine into a shaken mixture of 2,3-diphenylquinoxaline (2.0 g), chloroform (25 ml) and water (25 ml). After 15 min the chloroform layer was separated and washed with sodium carbonate solution and dilute hydrochloric acid. Removal of the solvent gave benzil (0.24 g, 25%) which was recrystallised from ethanol and identified by its m.p. and mixed m.p. 94-95° and infrared spectrum.

2-Chloro-4-phenylphthalazone - was prepared by treating 4-phenylphthalazone (0.50 g) with chlorine in a mixture of chloroform (25 ml) and water (25 ml). Evaporation of the chloroform layer afforded 2-chloro-4-phenylphthalazone (0.52 g, 91%) as a colourless solid, m.p. 176°. Chlorination of the phthalazone in chloroform alone was ineffective.

2,4-Dichlorophthalazone - was prepared similarly to the above compound and was obtained as a light green solid (79%), m.p. 157-159°.

2-Chloro-4-methylphthalazone - A mixture of 4-methylphthalazone (0.25 g), chloroform (25 ml) and water (25 ml) was chlorinated for 15 min with vigorous agitation. Evaporation of the chloroform phase gave 2-chloro-4-methylphthalazone (0.28 g, 92%) as a colourless solid, m.p. 173-174°. The chlorine was estimated iodometrically. (Found: Cl, 17.8. $C_9H_7ClN_2O$ requires Cl, 18.2%.)

Conversion to the starting material was accomplished by heating the compound in ethanol (30 min).

Action of chlorine on quinoline - Chlorine was passed into a shaken mixture of quinoline (5.0 g) chloroform (100 ml) and water (75 ml) for 1 hr. Quinoline (2.7 g, 54%) was recovered from the aqueous phase by basification and extraction with chloroform. The chloroform layer yielded a dark gum (2.3 g), the infrared spectrum of which showed an amide-type CO frequency. The material was dissolved in ethanol and decolourised with charcoal. A small quantity of yellow solid, m.p. 190-200° d, separated from the solution on concentration but attempts at further purification were unsuccessful. A substance with a similar infrared spectrum was obtained by chlorination of carbostyril under the same conditions.

Action of chlorine on isoquinoline - This reaction was conducted using the same method as for the chlorination of quinoline. Some isoquinoline (62%) was recovered. The yellow oil obtained from the chloroform layer

spontaneously decomposed with evolution of hydrogen chloride to an orange solid, m.p. 85-95° d, which showed an amide-type CO absorption in the infrared spectrum.

Action of chlorine on acridine - A solution of acridine (1.0 g) in chloroform (25 ml) and water (25 ml) was treated with chlorine gas (15 min). A yellow solid separated from the aqueous phase and the mixture became a semi-solid paste on continued shaking. The product (0.71 g) was filtered at the pump and dried at 100°, m.p. > 350°. (Found: C, 42.11; H, 3.09; N, 2.92%.) The substance was insoluble in all solvents tried.

Hypochlorous acid - was prepared by passing chlorine into a suspension of mercuric oxide (40 g) in water (200 ml) as previously described.[158] Distillation of the filtered solution in vacuo gave a colourless, aqueous solution of hypochlorous acid which could be kept at 0° for up to 5 days without becoming contaminated by chlorine.

Hypochlorous acid (0.5-1.0N) was more conveniently prepared by treating a saturated solution of sodium carbonate with chlorine until evolution of carbon dioxide commenced and then distilling the mixture under reduced pressure over mercuric oxide.

Reactions of phthalazine with hypochlorous acid (Table 7) -

Reactions 1 and 2- were performed by adding hypochlorous

acid solution (50 ml) to a solution of phthalazine (0.20 g) in water (50 ml). The mixture was extracted with chloroform (2 x 50 ml) and the material obtained from the extract was treated with aqueous potassium iodide (5 ml, 10%). The iodine liberated was titrated against 0.1N sodium thiosulphate to measure the yield of N-chlorophthalazone. The aldehydes were separated as before.

Reaction 3 - was carried out by adding the phthalazine solution (2.0 g in 50 ml) to excess hypochlorous acid at 0-5°. After 2 hr the solid was removed by filtration and found to be a mixture of o-dichloromethylbenzaldehyde (0.22 g, 8%) and N-chlorophthalazone (0.14 g, 5%) which were separated as above. Extraction of the filtrate with chloroform gave a mixture, the infrared spectrum of which indicated the presence of phthalaldehyde and 3-chlorophthalide. The mixture was dissolved in chloroform and treated with sodium hydroxide solution (50 ml, 2%). Phthalaldehyde (0.71 g, 35%) was isolated from the chloroform phase; acidification and chloroform extraction of the aqueous phase yielded phthalaldehydic acid (0.72 g, 31%) formed by hydrolysis of 3-chlorophthalide.

Reactions 4 and 5 - were conducted as for reaction 1, except that sodium chloride solution (20%) was used as the medium.

Reaction 6 - A solution of phthalazine hydrochloride (0.35 g) in water (25 ml) was treated with excess hypochlorous acid at 0-5°. Extraction of the solution with chloroform gave a mixture of phthalaldehyde (11%) and o-dichloromethylbenzaldehyde (1.4%).

Reaction of hypochlorous acid with phthalaldehyde - A mixture of phthalaldehyde (0.25 g), chloroform (10 ml) and water (10 ml) was treated with hypochlorous acid solution at room temperature with vigorous shaking (15 min). The chloroform layer afforded a mixture of phthalaldehyde (0.15 g, 60%) and 3-chlorophthalide (0.11 g, 34%) which were separated as above. For comparison of infrared spectra, an authentic sample of 3-chlorophthalide was prepared by the action of thionyl chloride on phthalaldehydic acid as described by Gabriel.[273]

t-Butylhypochlorite - was prepared by the method of Teeter and Bell.[274] Distillation of the product at atmospheric pressure removed all traces of chlorine.

Reactions of phthalazine with t-butylhypochlorite -

(1) A solution of phthalazine (0.20 g) in dry carbon tetrachloride (50 ml) was flushed with dry nitrogen and then treated with t-butyl-hypochlorite (0.5 ml). After standing at room temperature for 2 days the solution was evaporated to dryness under reduced pressure, giving phthalazine (0.18g); a trace of phthalazine hydrochloride was observed in the infrared spectrum.

(2) A mixture of phthalazine (2.0 g), t-butyl hypochlorite (4 ml) and carbon tetrachloride (150 ml) was heated under reflux (5 hr). The solvent was removed and the residue treated with 1N HCl (50 ml).

Extraction of the solution with chloroform gave a yellow oil (0.42 g). Phthalazine (1.61 g, 81%) was recovered from the acid solution by basification and extraction with chloroform.

The oil was chromatographed on silica gel using benzene as the eluent. The first fraction consisted of o-dichloromethylbenzaldehyde (50 mg, 1.7%), followed by phthalonitrile (12 mg, 0.61%) which was identified by its m.p., mixed m.p. and infrared spectrum. Elution with 50% benzene-chloroform and then pure chloroform gave traces of a carbonyl compound with a high frequency (1895 cm^{-1}) in the infrared spectrum.

Elution with ethanol afforded a reddish-coloured gum, the infrared spectrum of which exhibited a phthalazone-type carbonyl frequency at 1665 cm^{-1}. Attempts to purify the material by recrystallisation, chromatography on alumina, sublimation or distillation were unsuccessful.

(3) The procedure given in (2) was repeated, except that the mixture was allowed to stand at 0-5° for 4 days before being heated. Phthalazine hydrochloride (10%) was deposited during the former period and the quantity of gum obtained was greatly increased.

(4) A solution of phthalazine (2.0 g) and t-butyl hypochlorite (4 ml) in carbon tetrachloride (200 ml) was allowed to stand at 0° for 24 hr and then stirred while exposed to the air at room temperature (15 hr). More t-butyl hypochlorite was added (4 ml) and the solution was refluxed (3 hr). After removal of the solvent the residue was

dissolved in chloroform (100 ml) and washed with 1N hydrochloric acid (50 ml). No material was obtained from the acid solution by basification and extraction with chloroform. The first chloroform solution was evaporated to dryness and the residue chromatographed in benzene on silica gel. The first fraction (250 ml) gave o-dichloromethylbenzaldehyde (0.51 g, 17%). The next fractions consisted of mixtures of a high-frequency carbonyl compound and o-dichloromethylbenzoic acid (0.11 g, 55%) which was obtained as colourless needles from carbon tetrachloride, m.p. 156°. (Found: C, 47.32; H, 3.45. $C_8H_6Cl_2O_2$ requires C, 46.87; H, 3.0%.)

Elution with ethanol again gave a red gum.

(5) t-Butyl hypochlorite (2.0 ml) was added dropwise to a stirred solution of phthalazine (0.50 g) in water (15 ml). After about 30 seconds nitrogen began to evolve and ceased after 15 min. The mixture was then extracted with chloroform (2 x 25 ml) and the solvent was removed. Chromatography of the residue on neutral alumina in benzene gave phthalaldehyde (0.41 g, 83%) and o-dichloromethylbenzaldehyde (0.04 g, 5.5%).

Reaction of chlorine with phthalazine in the presence of silver salts -

(1) A solution of phthalazine (0.20 g) and silver nitrate (2.0 g) in water (20 ml) was treated with chlorine water (50 ml). The mixture was shaken with chloroform (100 ml) for 30 min and then filtered (Celite). The chloroform layer was washed with dilute hydrochloric acid to remove

phthalazine and on evaporation to dryness gave phthalaldehyde (0.068 g, 34%), the purity of which was indicated by its infrared spectrum.

(2) A mixture of phthalazine (0.35 g), silver sulphate (3.8 g) and sulphuric acid (8 ml, 92%) was treated with a slow stream of dry chlorine gas for 2 hr at room temperature. The solution was poured into ice-water (50 ml), sodium chloride solution (20 ml, 20%) added, and the mixture shaken with chloroform (30 min). After filtration (Celite) the chloroform layer was evaporated, giving phthalaldehyde (0.17 g, 49%) as the only product.

Reaction of hypochlorous acid with phthalazine in the presence of silver nitrate - Hypochlorous acid solution (50 ml) was mixed with a solution of silver nitrate (2.0 g) in water (10 ml) and immediately added to phthalazine (0.20 g) in water (15 ml). Nitrogen was vigorously evolved. The mixture was shaken with chloroform (100 ml) for 30 min and filtered (Celite). The chloroform layer was washed with dilute hydrochloric acid (50 ml) and on evaporation gave phthalaldehyde (0.13 g, 65%). The absence of o-dichloromethylbenzaldehyde was again confirmed by the infrared spectrum.

Chapter 3.

Oxidation of phthalazine - Finely powdered phthalazine (1.0 g) was rapidly added to fuming nitric acid (10 ml, d 1.5) at room temperature. The solution became hot and nitrogen dioxide was evolved vigorously. The solution was diluted with water (30 ml) and evaporated to dryness on the water-bath, giving phthalic acid (1.05 g, 82%), which was converted to phthalic anhydride by sublimation and identified by its m.p., mixed m.p. and infrared spectrum.

Phthalazine nitrate - A solution of phthalazine (0.50 g) in concentrated nitric acid (5 ml) was evaporated to dryness on the water-bath. The residue on crystallisation from methanol yielded phthalazine nitrate as yellow needles (0.65 g, 88%), m.p. 162°. (Found: C, 49.74; H, 3.69; N, 21.2. $C_8H_7N_3O_3$ requires C, 49.74; H, 3.65; N, 21.76%.)

5-Nitrophthalazine -

(1) A solution of phthalazine nitrate (1.0 g) in sulphuric acid (15 ml, 98%) was heated at 65° with exclusion of moisture (50 hr). Basification of the diluted solution, followed by extraction with chloroform gave a red solid which was recrystallised from ethanol (charcoal). 5-Nitrophthalazine was obtained as orange plates (0.23 g, 17%), m.p. 185°. (Found: C, 55.02; H, 2.95; N, 23.94; O, 18.40. Calc. for $C_8H_5N_2O_2$: C, 54.88; H, 2.88; N, 23.99; O, 18.27%.) (lit.[78] m.p. 187-188°.)

(2) A mixture of phthalazine (2.50 g), potassium nitrate (5.0 g) and sulphuric acid (15 ml, 98%) was heated at 100° for 80 hr. After dilution with water (100 ml) the solution was neutralised with sodium carbonate and extracted with chloroform (3 x 50 ml). 5-Nitrophthalazine (2.66 g, 79%) was obtained from the extract. Thin-layer chromatography of the crude product on silica gel (chloroform) gave only one spot (R_F 0.67), corresponding to pure 5-nitrophthalazine; n.m.r. spectrum ($CDCl_3$) : τ 1.88 (triplet, 1 proton, J = 8 c.p.s.), τ 1.62 (quartet, 1 proton J = 2,8 c.p.s.), τ 1.25 (quartet, 1 proton, J = 2,7 c.p.s.), τ 0.21 (singlet, 1 proton), τ -0.66 (1 proton).

Kinetic measurements - Weighed quantities of phthalazine (approx. 15 mg) and A.R. potassium nitrate (1.00 g) were added to sulphuric acid (10 ml, 98%) in a long-necked flask at 0°. The stoppered mixture was then placed in a thermostat bath at 61.9°. At 30 min intervals the flask was removed and the contents rapidly cooled to room temperature; 1 ml samples were withdrawn with a pipette and diluted to 100ml with water. The ultraviolet absorption spectrum of the diluted solution was determined using the same concentrations of sulphuric acid and potassium nitrate in the reference cell. After several hours, samples were taken at hourly intervals, allowing the reaction to be followed over 7 hrs. The increase in concentration of 5-nitrophthalazine was measured from the increase in optical density (O.D.) at 290 mu. A plot of log O.D. versus time gave a straight line from which the rate coefficient k_1 was

calculated to be 5.7×10^{-5} l.mole^{-1} sec^{-1}. A series of identical runs showed a variation in k_1 of $\pm 0.1 \times 10^{-5}$ l.mole^{-1} sec^{-1}.

Bromination of phthalazine in acetic acid - A stirred mixture of phthalazine (2.0 g), silver acetate (4.8 g) and acetic acid (150 ml) was treated dropwise with a solution of bromine (2.5 g) in acetic acid (40 ml) during 15 min and the stirring continued at room temperature for 30 min. After this time a sample removed from the solution gave a negative iodine test with potassium iodide. The solution was treated with aqueous sodium bromide (50 ml, 10%) to remove excess silver ion and the precipitate was filtered (Celite). The solvent was removed from the filtrate under reduced pressure and water (50 ml) added to the residue. A yellow solid was filtered (filtrate A), dissolved in chloroform and the solution dried. Evaporation of the solvent gave phthalaldehyde (0.21 g, 10%), identified by its infrared spectrum. Filtrate A was basified and extracted with chloroform, giving phthalazine (0.16 g, 8%).

Bromination of phthalazine in sulphuric acid -

(1) Bromine (2.5 g) was added dropwise to a mixture of phthalazine (2.0 g), silver sulphate (2.1 g) and sulphuric acid (10 ml, 98%) with vigorous shaking. After 3 hr the solution was poured into water (100 ml), filtered, basified with sodium hydroxide solution (10%) and cooled to 0°. Recrystallisation of the precipitate from ethanol gave 5,8-dibromophthalazine (0.31 g, 6.9%) as colourless needles, m.p. 224-225° d. (Found: C, 33.42; H, 1.52; N, 9.60. $C_8H_4Br_2N_2$ requires C, 33.36;

H, 1.40; N, 9.97% .) The n.m.r. spectrum had τ 2.02 (singlet, 2 protons) and τ 0.21 (singlet, 2 protons).

The aqueous solution was extracted with chloroform (3 x 50 ml), giving a mixture of phthalazine and 5-bromophthalazine which was dissolved in a minimum of hot water. After several days the crystals deposited were removed by filtration (filtrate B) and recrystallised from ethanol and carbon tetrachloride. 5-Bromophthalazine (0.105 g, 3.3%) was obtained as colourless needles, m.p. 116°. (Found: C, 46.26; H, 2.85; N, 13.59. $C_8H_5BrN_2$ requires C, 45.95; H, 2.42; N, 13.40%.) The n.m.r. spectrum ($CDCl_3$) had τ 2.02 (multiplet, 3 protons), τ 0.55 (doublet, 1 proton, J = 1.5 c.p.s.) and τ 0.21 (doublet, 1 proton, J = 1.5 c.p.s.).

Phthalazine (0.24 g, 10%) was recovered from filtrate B by basification and extraction with chloroform. The bromo derivatives were separated from phthalazine by thin-layer chromatography on silica gel using ethanol as the solvent. The observed spots, which were developed with iodine, had the following R_F values : phthalazine, 0.65; 5-bromophthalazine, 0.69; 5,8-dibromophthalazine, 0.79.

(2) A vigorously shaken mixture of phthalazine (1.0 g), silver sulphate (1.0 g) and sulphuric acid (5 ml, 98%) was heated to 65° and treated with bromine (0.5 g) in two portions (2 min). The solution was cooled, poured into ice-water (100 ml) and treated with aqueous sodium bromide (30 ml, 10%). After the addition of sodium sulphite (2 g) to remove excess bromine, the solution was filtered (Celite),

basified with sodium hydroxide and extracted with chloroform (2 x 50 ml). The mixture of phthalazine (0.56 g, 56%) and 5-bromophthalazine (91 mg, 5.7%) was separated as before.

(3) The addition of bromine (1.2 g) to phthalazine (1.0 g) and silver sulphate (1.5 g) in sulphuric acid (5 ml, 98%) at 120-130° gave 5,8-dibromophthalazine (0.43 g, 19%) and phthalazine (0.65 g, 65%); the same work-up procedure was used as in (2).

Similar experiments were carried out using 92% sulphuric acid and fuming sulphuric acid (d 1.90); the only compound isolated was phthalazine in 49% and 85% yields respectively. In the former experiment, the residue obtained by filtering the acid solution was extracted with boiling water (5 x 50 ml), giving phthalic acid (12%).

5,8-Dibromophthalazine - A mixture of 5-bromophthalazine (0.23 g), silver sulphate (0.24 g) and sulphuric acid (2.5 ml, 98%) was treated with bromine (0.5 g) and shaken at room temperature (2 hr). The solution was diluted with water (20 ml), sodium bromide (0.5 g) and sodium sulphite (1.5 g) added and the mixture filtered (Celite). Basification of the filtrate provided a precipitate which was extracted into chloroform (2 x 30 ml). The extract yielded 5,8-dibromophthalazine (0.22 g, 70%), m.p. and mixed m.p. 244-245° (ethanol).

9-Nitrobenzo[g]phthalazine - was prepared by allowing a solution of benzo[g]phthalazine nitrate (0.10 g) in sulphuric acid (5 ml, 98%) to

stand at room temperature (24 hr). Dilution with water and basification gave a yellow solid which on sublimation (0.05 mm/200°) yielded 9-nitrobenzo[g]phthalazine (45 mg, 42%) as a light yellow powder, m.p. 270°. (Found: C, 63.1; H, 3.30. $C_{12}H_7N_3O_2$ requires C, 63.9; H, 3.14%.) The n.m.r. spectrum (CF_3CO_2H) had τ 1.27 (triplet, 1 proton, J = 8.6 c.p.s.), τ 0.70 (triplet, 3 protons, J = 8.6 c.p.s.), τ 0.13 (singlet, 1 proton), τ -0.82 (singlet, 1 proton) and τ -0.90 (singlet, 1 proton).

Reaction of phthalazine with sodamide -

(1) A solution of phthalazine (1.0 g) in dimethylaniline (20 ml) was heated at 130° with sodamide, freshly prepared from sodium (0.65 g) and liquid ammonia by the method of Leffler.[225] After 3 hr the mixture was cooled, treated with water (100 ml) and evaporated to dryness under reduced pressure. The black residue was extracted with chloroform (3 x 100 ml) and the extract after treatment with charcoal yielded phthalazine (0.13 g, 13%).

(2) Finely powdered phthalazine (2.0 g) was added portionwise to a stirred suspension of potassium nitrate (2.0 g) and sodamide (prepared from 1.0 g sodium) in liquid ammonia (40 ml). The reaction mixture, which was initially deep red in colour, was stirred under reflux with exclusion of moisture for 2 hr, during which time the solution became dark green. The ammonia was allowed to distill off over 2 hr and the residue treated with water (100 ml). The dark, tarry material formed was extracted from the basified solution with chloroform (2 x 50 ml)

and phthalazine (0.52 g, 28%) was recovered from the extract after treatment with charcoal.

The alkaline solution was acidified with dilute hydrochloric acid and extracted with chloroform (3 x 50 ml). The extract afforded a small quantity of material (50 mg), the infrared spectrum of which indicated the presence of phthalonitrile, phthalimide and phthalazone. After standing for several days the acid solution deposited crystals of phthalimide (25 mg), m.p. and mixed m.p. 233-234°. The infrared spectrum was identical with that of an authentic specimen.

(3) Finely powdered phthalazine (1.0 g) was added to a stirred suspension of sodamide (from 0.5 g sodium) and potassium nitrate (1.0 g) in liquid ammonia (30 ml). After 2 hr the ammonia was removed and the residue treated slowly with ice-water (150 ml). The tarry material dissolved on acidification with hydrochloric acid and the solution was then basified and extracted with chloroform (2 x 100 ml) to recover phthalazine (0.27 g, 27%). Addition of saturated aqueous picric acid (20 ml) to the neutralised solution (pH 7) afforded a precipitate of 1-aminophthalazine picrate (0.57 g, 20%) which crystallised from water as silky yellow needles, m.p. 308° (lit.[275] m.p. 301°). (Found: C, 44.52; H, 2.61; N, 21.90. Calc. for $C_{14}H_{10}N_6O_7$: C, 44.92; H, 2.70; N, 22.46%.)

An authentic specimen was obtained by adding picric acid to an aqueous solution of 1-aminophthalazine, prepared from 1-chlorophthalazine by the method of Rodda.[275]

Hydrolysis of 1,4-diaminophthalazine - was carried out by warming a solution of the compound in dilute hydrochloric acid. On cooling, a mixture of phthalimide and the amine hydrochloride was deposited.

Reaction of phthalazine with potassium hydroxide - An intimate mixture of phthalazine (0.50 g) and potassium hydroxide (0.70 g) was heated at 220° (30 min). A basic gas was evolved which was identified as hydrazine by its decolourising action on potassium permanganate solution. The residue was dissolved in water and extracted with chloroform to remove phthalazine (0.11 g, 22%). Acidification of the aqueous solution, followed by extraction with chloroform provided phthalazone (21 mg, 4%), m.p. and mixed m.p. 183°.

A reaction carried out at 100° gave phthalazine (75%) and phthalazone (6%).

Reaction of keten with phthalazine - Keten was generated by the pyrolysis of acetone in a simplified apparatus described recently by Blau.[276] A slow stream of nitrogen carried the gas through two dry ice-acetone traps and then into a solution of phthalazine (1.9 g) in benzene (40 ml). After 45 min the colourless powder was collected (2.51 g) and after drying in vacuo had m.p. 158-159° on rapid heating. (Found: C, 69.84; H, 4.91; N, 17.04, 17.12. $C_{10}H_8N_2O$ requires C, 69.75; H, 4.68; N, 16.27%.) The substance had $\lambda_{max.}$ 306 mμ and $\nu_{max.}$ 1670 cm^{-1}.

A sample of the substance (0.35 g) was stirred with sodium

hydroxide solution (50 ml, 10%) at room temperature (12 hr). Extraction of the solution with chloroform (2 x 50 ml) gave phthalazine (0.21 g, 79%).

Reaction of 5-nitrophthalazine with keten - A solution of 5-nitrophthalazine (0.27 g) in benzene (40 ml) was treated with keten (30 min). The orange precipitate (0.29 g) had m.p. 195° d. (Found: C, 55.43; N, 3.71. $C_{10}H_7N_3O_3$ requires C, 55.30; H, 3.25%.) The substance had $\nu_{max.}$ 1670 cm^{-1}.

Reaction of benzo[g]phthalazine with keten - A solution of benzo[g]-phthalazine (0.11 g) in benzene (75 ml) was treated with keten (30 min). The yellow precipitate (0.10 g) had m.p. 215° d. (Found: C, 75.76; H, 4.69. $C_{14}H_{10}N_2O$ requires C, 75.65; H, 4.54%.) The substance had $\nu_{max.}$ 1665 cm^{-1}.

Reaction of maleic anhydride with phthalazine.- Solutions of maleic anhydride (0.80 g) and phthalazine (0.50 g) in chloroform (15 ml) were mixed at -5° and kept at -10° in the refrigerator for 12 hr. The solution was then allowed to stand at room temperature (24 hr) and the solvent removed under reduced pressure. The red oil thus obtained solidified on standing (30 hr). The solid was extracted with boiling chloroform (2 x 50 ml) and the resulting yellow powder (1.17 g) was collected. Recrystallisation from chloroform gave a pale yellow solid, m.p. ca. 105° d. (Found: C, 51.19; 51.21; H, 4.30, 4.32; N, 7.26, 7.49;

O, 25.6, 25.6%).

When solutions of the starting materials were mixed at 25-30°, a black tar separated over several days. No reaction was observed between maleic anhydride and 1,4-diphenylphthalazine or quinoxaline.

The n.m.r. spectrum (K_2CO_3-D_2O) of the phthalazine adduct had τ 3.93 (doublet, 1 proton, J = 14 c.p.s.), τ 2.87 (multiplet, 4 protons), τ 2.67 (singlet, 2 protons), τ 2.30 (singlet, 2 protons), τ 1.73 (singlet, 1 proton) and τ 0.93 (singlet, 1 proton). In addition a broad, complex multiplet (ca. 5 protons) was observed at τ 6.38.

Chapter 4.

Phthalazine-2-oxide - A mixture of phthalazine (4.0 g), hydrogen peroxide (5.5 ml, 30%) and acetic acid (50 ml) was heated on the water-bath (10 hr). The solvent was removed under reduced pressure. The residue was treated with water (50 ml) and evaporated under reduced pressure, the process being repeated to remove traces of peracetic acid. The product was then dissolved in sodium hydroxide solution (50 ml, 10%) and extracted with chloroform. Phthalazine-2-oxide hydrate (4.8 g, 95%) was obtained from the extract as a white solid, m.p. 92-93°. The analytical figures indicated that slightly more than one mole of water was present. (Found: C, 56.38; H, 5.16; N, 16.28; O, 23.1. $C_8H_6N_2O$ 1.4 H_2O requires: C, 56.09; H, 5.18; N, 16.36; O, 22.4%.)

Sublimation of the hydrate (0.05 mm/140°) gave phthalazine-

2-oxide as a white solid, m.p. 144-145°, (lit.[79] m.p. 143°). (Found: C, 66.37; H, 4.27; O, 11.7. Calc. for $C_8H_6N_2O$: C, 65.75; H, 4.14; O, 11.0%.) $\lambda_{max.}$ 217 (ε 1470), 252 (ε 2440), 292 (ε 855) and 302 mμ (ε 784).

Oxidation of phthalazine-2-oxide - A solution of phthalazine-2-oxide (0.32 g) in water (10 ml) was treated dropwise with potassium ferricyanide (2.25 g) in aqueous sodium hydroxide (20 ml, 10%). After several minutes, nitrogen was evolved and a small quantity of solid separated from the solution. The mixture was acidified with hydrochloric acid and extracted with chloroform (3 x 50 ml). Evaporation of the extract gave phthalaldehyde (0.27 g, 92%) which was identified by its infrared spectrum and mixed m.p. after recrystallisation from petroleum ether.

An identical experiment was carried out using hydrogen peroxide (5 ml, 30%) instead of potassium ferricyanide. Nitrogen and phthalaldehyde (77%) were again produced.

Reaction of phthalazine-2-oxide with acetic anhydride - A solution of phthalazine-2-oxide (0.50 g) in acetic anhydride (15 ml) was heated on the water-bath (3 hr). Removal of the solvent under reduced pressure gave a red oil from which 2-acetylphthalazone (55 mg, 9%) was obtained by sublimation (0.5 mm/100°). The feathery, colourless crystals had m.p. and mixed m.p. 133° (lit.[34] m.p. 133°). The infrared spectrum was

identical with that of an authentic sample.

1-Chlorophthalazine-2-oxide - A solution of phthalazine-2-oxide (0.25 g) in water (75 ml) was treated with a slow stream of chlorine gas for 10 hr at room temperature. Some nitrogen appeared to evolve. The solution was extracted with chloroform (3 x 500 ml) and evaporation of the extract gave a yellow residue, the infrared spectrum of which exhibited complex carbonyl bands. The residue was dissolved in chloroform (100 ml), washed with dilute hydrochloric acid and again evaporated. Recrystallisation of the residue from ethanol gave light yellow plates which were sublimed (0.05 mm/140°.) 1-Chlorophthalazine-2-oxide (50 mg, 16%) was obtained as a white solid, m.p. 187-188°. A further quantity (45 mg, 15%) was obtained from the acid washings on basification and extraction with chloroform. The n.m.r. spectrum ($CDCl_3$) had τ 2.05 (multiplet, 4 protons) and τ 0.95 (singlet, 1 proton).

Nitration of phthalazine-2-oxide - was carried out by allowing a mixture of phthalazine-2-oxide (2.0 g), potassium nitrate (2.0 g) and sulphuric acid (20 ml, 98%) to stand at room temperature (48 hr). The solution was poured into water (200 ml) and the yellow precipitate collected. Sublimation (0.05 mm/140°) gave 8-nitro-phthalazine-2-oxide as a yellow solid (0.73 g, 28%), m.p. 243-244°. The n.m.r. spectrum ($CDCl_3$) had τ 1.45 (multiplet, 2 protons), τ 1.20 (quartet, 1 proton, J = 0.6 and 7.5 c.p.s.), τ 0.61 (multiplet, 1 proton) and τ 0.48 (multiplet, 1 proton).

N-Methylphthalazinium iodide - was prepared by heating phthalazine (2.0 g) with methyl iodide (3 ml) in chloroform (10 ml). After cooling to 0° the yellow prisms (3.57 g, 85%) were collected and dried in vacuo, m.p. 237-240° (lit.[74] m.p. 235-240°). The n.m.r. spectrum (D_2O) had τ 1.45 (multiplet, 4 protons), τ 0.12 (singlet, 1 proton) and τ-0.50 (singlet, 1 proton).

1-Hydroxy-2-methyl-1,2-dihydrophthalazine - Aqueous solutions of N-methylphthalazinium iodide (0.50 g in 15 ml) and sodium hydroxide (1.5 g in 15 ml) were flushed with nitrogen, cooled to 0° and then mixed. The mixture was immediately extracted with chloroform (2 x 30 ml) and evaporation of the extract gave a colourless oil which solidified on standing. Recrystallisation from a mixture of petroleum ether (b.p. 60-80°) and ether yielded 1-hydroxy-2-methyl-1,2-dihydrophthalazine (0.02 g, 7%) as colourless prisms, m.p. 84°. The infrared spectrum had bands at 3400 (OH), 1620, 1610, 1590, 1520, 1350 (CO), 1020, 930 and 850 cm^{-1}.

2-Methylphthalazone -

(1) A solution of potassium ferricyanide (1.0 g) in sodium hydroxide solution (20 ml, 10%) was added to N-methylphthalazinium iodide (0.21 g) in water (10 ml). After 5 min stirring the solution was extracted with chloroform (2 x 25 ml). 2-Methylphthalazone (0.11 g, 88%) was obtained

from the extract as a white solid, m.p. 113-114° after crystallisation from benzene (lit.[74] m.p. 112-114°).

(2) Phthalazone (0.67 g) was shaken with dimethyl sulphate (0.8 g) in sodium hydroxide solution (3 ml, 10%) for 30 min. The solid was collected and recrystallised from benzene, yielding 2-methylphthalazone (0.59, 81%), m.p. and mixed m.p. 112-114°.

1-Cyano-2-methyl-1,2-dihydrophthalazine - An aqueous solution of sodium cyanide (3.5 g in 25 ml) was added to N-methylphthalazinium iodide (1.00 g) in water (25 ml) and the white, cloudy precipitate removed by extraction with chloroform (3 x 50 ml). The solid obtained from the extract was recrystallised from a mixture of ether and petroleum ether (b.p. 60-80°), giving 1-cyano-2-methyl-1,2-dihydrophthalazine (0.61 g, 97%) as colourless rods, m.p. 70°. (Found: C, 69.76; H, 5.40; N, 24.84. $C_{10}H_9N_3$ requires C, 70.15; H, 5.31; N, 24.55%.) The n.m.r. spectrum (CCl_4) had τ 6.87 (singlet, 3 protons), τ 4.90 (singlet, 1 proton), τ 2.63 (multiplet, 4 protons) and τ 2.37 (singlet, 1 proton).

N-Methylphthalazinium chloride -

(1) A solution of 1-cyano-2-methyl-1,2-dihydrophthalazine (0.12 g) in 2N hydrochloric acid (10 ml) was evaporated to dryness on the water-bath; hydrogen cyanide was evolved. The residue was dissolved in ethanol (2 ml) and precipitated by addition of ether. N-Methylphthalazinium chloride monohydrate (0.11 g, 79%) was isolated as a colourless powder,

m.p. 268-269°. (Found: C, 54.43; H, 5.68; N, 13.83. $C_9H_9ClN_2.H_2O$ requires C, 54.50; H, 5.59; N, 14.10%.)

(2) A solution of N-methylphthalazinium iodide (0.21 g) in 2N hydrochloric acid (10 ml) was evaporated to dryness on the steam-bath. Precipitation of the residue from ethanol with ether gave N-methylphthalazinium chloride monohydrate (0.15 g, 92%), m.p. and mixed m.p. 268-269°.

Alkaline hydrolysis of 1-cyano-2-methyl-1,2-dihydrophthalazine - A mixture of the cyano compound (0.23 g) and sodium hydroxide solution (5 ml, 10%) was heated on the water-bath (10 hr). The solid obtained by chloroform extraction of the solution was recrystallised from benzene and identified as 2-methylphthalazone (0.15 g, 70%) by its m.p., mixed m.p. and infrared spectrum.

Reactions of phthalazine with 2,4-dinitrochlorobenzene -

(1) An intimate mixture of phthalazine (0.50 g) and 2,4-dinitrochlorobenzene (1.0 g) was heated on the water-bath with exclusion of moisture (4 hr). The glassy solid obtained on cooling was crushed to a powder and digested in water (30 ml) at 100° for 3 hr. The insoluble material was collected and recrystallised from dimethyl sulphoxide, giving 1-hydroxy-2-(2',4'-dinitrophenyl)-1,2-dihydrophthalazine (0.59 g, 49%) as orange leaflets, m.p. 194-195° d. (Found: C, 53.92; H, 3.64; N, 16.87. $C_{14}H_{10}N_4O_5$ requires C, 53.5; H, 3.19; N, 17.83% .)

(2) A solution of phthalazine (0.50 g) and 2,4-dinitrochlorobenzene (0.97 g) in chloroform (15 ml) was heated under reflux (4 hr). The yellow crystals (0.27 g) deposited on cooling were collected and had m.p. 184-185° d. (Found: C, 50.06; H, 3.25; N, 16.83%.) The product was treated with water as in (1), giving the pseudo base (0.18 g, 15%).

(3) A solution of phthalazine (0.50 g) and 2,4-dinitrochlorobenzene (1.01 g) in ethanol was refluxed for 10 hr, during which time silky yellow needles separated. The solution was cooled, and the product collected and recrystallised from ethanol. 1-Ethoxy-2-(2',4'-dinitrophenyl)-1,2-dihydrophthalazine (0.57 g, 43%) was obtained as yellow needles, m.p. 183-184° d on rapid heating. (Found: C, 55.71; H, 4.12; N, 16.42. $C_{16}H_{14}N_4O_5$ requires C, 56.14; H, 4.13; N, 16.37%.) The n.m.r. spectrum ($CDCl_3$) had τ 8.98 (triplet, 3 protons, J = 6.9 c.p.s.), τ 6.93 (multiplet, 2 protons), τ 3.45 (singlet, 1 proton) and τ 2.17 (multiplet, 8 protons).

(4) A solution of phthalazine (0.50 g) and 2,4-dinitrochlorobenzene (1.0 g) in methanol was heated under reflux (5 hr). The solution was cooled and the product collected and recrystallised from methanol, giving 1-methoxy-2-(2',4'-dinitrophenyl)-1,2-dihydrophthalazine (0.56 g, 44%) as fine, yellow needles, m.p. 194° d. (Found: C, 54.65; H, 3.45; N, 17.03. $C_{15}H_{12}N_4O_5$ requires C, 54.92; H, 3.69; N, 17.08%.) The n.m.r. spectrum (D.M.S.O.) had τ 3.27 (singlet, 1 proton) and τ 1.97 (multiplet, 8 protons).

(5) A mixture of 2,4-dinitrochlorobenzene (1.85 g) and phthalazine (1.0 g) in water (250 ml) was heated under reflux with mechanical stirring (24 hr); magnetic stirring was ineffective. The lumps of dark solid were removed and recrystallised from dimethyl sulphoxide. The pseudo base was obtained as orange plates (1.17 g, 49%), m.p. and mixed m.p. 194-195° d.

Hydrolysis of the pseudo base - A solution of the compound (0.20 g) in dimethyl sulphoxide (20 ml) was shaken with sodium hydroxide (0.15 g) for 16 hr. The dark red solution was poured into water (50 ml) and extracted with chloroform (2 x 50 ml). Evaporation of the extract gave a residue which was diluted with water (30 ml) and treated with saturated aqueous picric acid (15 ml). The precipitate of phthalazine picrate (0.16 g, 76%) was removed, dried and identified by its m.p., mixed m.p. and infrared spectrum.

The aqueous layer was acidified with 2N hydrochloric acid and extracted with chloroform (2 x 50 ml). 2,4-Dinitrophenol (0.10 g, 99%) was recovered from the extract and identified by its infrared spectrum.

Reaction of the pseudo base with nitric acid - The compound (0.30 g) was heated with concentrated nitric acid (5 ml) at 100° for 5 min, by which time all of the solid had dissolved giving a yellow solution. Dilution with water gave no precipitate, although the starting material was insoluble in dilute nitric acid. Sodium hydroxide solution was added dropwise until a yellow precipitate formed. Extraction of the

solution with chloroform gave the bimolecular ether (0.21 g, 70%) as a yellow glass, m.p. 172-174° d. (Found: O, 23.8. $C_{28}H_{18}N_8O_9$ requires O, 23.77%.) The n.m.r. spectrum (D.M.S.O./$CDCl_3$) had τ 3.37 (singlet, x protons) and τ 2.17 (multiplet, 8x protons).

Reaction of phthalazine with cyanogen bromide - Phthalazine (3.0 g) was refluxed with cyanogen bromide (5.5 g) in chloroform (50 ml) for 24 hr. After cooling, reddish-brown crystals (2.15 g), m.p. 153-155° d, were filtered from the dark solution. The product was dissolved in water (25 ml), filtered, basified with sodium hydroxide and the dense, white precipitate collected and dried in vacuo. 1-Hydroxy-2-cyano-1,2-dihydrophthalazine (0.83 g, 21%) was obtained as a colourless powder, m.p. 106-107°d. The n.m.r. spectrum ($CDCl_3$) had τ 3.33 (singlet, 1 proton), τ 2.27 (multiplet, 4 protons) and τ 1.98 (singlet, 1 proton).

The brown crystals were soluble in ethanol but after several minutes reflux in this solvent a light brown powder was deposited. This gave the hydroxy compound on treatment with sodium hydroxide solution.

Hydrolysis of 1-hydroxy-2-cyano-1,2-dihydrophthalazine - The compound (0.23 g) was heated with 2N hydrochloric acid (10 ml) on the water-bath (30 min); a gas was evolved which clouded a solution of lime-water. Chloroform extraction of the acidic solution gave no product. Ammonia was evolved when the solution was basified and extraction with chloroform provided phthalazine (0.16 g, 92%).

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