THE SYNTHESIS AND STRUCTURES OF SOME AROMATIC HETEROCYCLIC COMPOUNDS

A THESIS

PRESENTED FOR THE DEGREE OF

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by

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CONTENTS

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I am deeply grateful to Professor G.M. Badger and Dr. K.T. Potts for their stimulating supervision of this work. I am also indebted to other members of the staff, particularly Professor J.W. Clark-Lewis, for their many helpful suggestions.

Nuclear magnetic resonance spectra were determined and interpreted by Dr. T.M. Spotswood of this department, and Dr. T.H. Crawford of the University of Louisville, Kentucky. I should like to thank Dr. R.A. Jones for infrared measurements and for determination of absorption spectra. I am also grateful to Dr. G.E. Lewis for determining a number of absorption spectra.

Pharmacological testing of compounds was carried out at the Cancer Chemotherapy National Service Centre, Maryland, U.S.A.

SUMMARY

The synthesis and structures of a number of polycyclic azahydrocarbons containing the -N=C-C=N- system were investigated. The dihydro-derivative of quinoxalino[2,3-b]quinoxaline was shown to be 5,12-dihydroquinoxalino[2,3-b]quinoxaline and not the 5,11-isomer as claimed by several workers. The above structure was assigned on the basis of the similarity of the absorption spectra of 5,12-dimethylquinoxalino[2,3-b]quinoxaline and the dihydro-compound. Attempts to prepare 5,12-dimethylquinoxalino[2,3-b]-quinoxaline from 2,3-dihydroxyquinoxaline and N,N'-dimethyl-o-phenylenediamine resulted in the loss of a methyl group, and 5H-12-methylquinoxalino[2,3-b]quinoxaline was obtained. The same compound was isolated following attempts to prepare 5,11-dimethylquinoxalino-[2,3-b]quinoxaline; the latter compound has not been obtained.

The methods available for the synthesis of indolo[3,2-b]-indole were evaluated and it was proposed to prepare this ring system by dehydrogenation of 5,10-dihydroindolo[3,2-b]indole. The preparation of the latter compound by pyrolytic ring closure of 3-azido-2-phenylindole was investigated but this work was terminated when the synthesis of indolo[3,2-b]indole was published by Treibs.

Indolo[2,3-b]quinoxaline was shown to exist predominantly in the 6H-form, but on methylation it gives a mixture of 5- and 6-methylindoloquinoxalines. 11-Methylindolo[2,3-b]quinoxaline was not detected among the methylation products. 5-Methylindolo[2,3-b]-

quinoxaline is protonated and methylated at the 11-position, and the 6-methyl isomer is protonated and methylated at the 5-position. These assignments were made on the basis of U.V. spectral and N.M.R. data.

Derivatives of the *s*-triazolo[4,3-*a*]pyrazine and *s*-triazolo[2,3-*a*]pyrazine ring systems were prepared. The most efficient method of synthesis of *s*-triazolo[4,3-*a*]pyrazines was found to be ring closure of 2-hydrazinopyrazines with ortho esters. This procedure was superior to that using acidic cyclodehydration agents. The structures of several interesting by-products obtained in these reactions are also discussed. 2-Phenyl-*s*-triazolo[2,3-*a*]-pyrazines were obtained from the corresponding *N*-2-pyrazinylphenyl-amidines by dehydrogenation with lead tetra-acetate. The above amidines were prepared by the reaction of 2-aminopyrazines and benzonitrile in the presence of aluminium chloride. This reaction was not successful when aliphatic nitriles were used in place of benzonitrile.

The absorption spectra of the *s*-triazolo[4,3-*a*]pyrazine and *s*-triazolo[2,3-*a*]pyrazine derivatives were compared with those of their pyridine and pyrimidine analogues. The similarity of the curves was taken as further support for the structures of these compounds.

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, it contains no material previously published or written by another person, except where due reference has been made in the text.

(P.J. Nelson)

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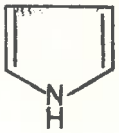
INTRODUCTION

The study of heterocyclic compounds forms one of the largest and most important fields in organic chemistry. The importance of these compounds is due to the presence of heterocyclic ring systems in dyestuffs, pharmaceuticals, antibiotics, vitamins, and a large variety of natural products. The nucleic acids, which control the fundamental processes of life, are derivatives of heterocycles.

Despite the fact that enormous advances have been made in the chemistry of this class of compound over the past fifty years, there are many gaps in this knowledge. These may be attributed to the large number of heterocyclic ring systems theoretically possible. Any atom capable of forming two covalent bonds may take part in a ring system and the number of annular atoms may be any number greater than two. Thus it is clear that the number of heterocyclic systems possible is of astronomical proportions.

A large number of heterocyclic ring systems may be regarded as being aromatic. According to Badger,[1] an aromatic compound is defined as a cyclic compound with a large resonance energy in which all the annular atoms take part in a single conjugated system. A convenient method of classifying heterocyclic aromatic compounds is to regard them as being derived from the corresponding hydrocarbons by replacement of one or more of the carbon atoms with a hetero-atom. In the case of the benzene analogues, the

atom introduced into the ring is required to contribute one π-electron to the aromatic sextet. Of the three most common hetero-atoms, nitrogen, sulphur and oxygen, only nitrogen can take part in an uncharged six-membered aromatic system. However, with the cyclopentadiene analogues, the atom replacing the $-CH_2-$ is required to contribute two π-electrons to complete the aromatic sextet. All three atoms previously mentioned are capable of this, and give rise to pyrrole (I), thiophen (II), and furan (III), respectively.



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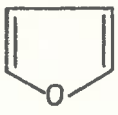
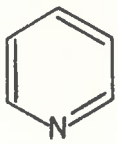
(II)



(III)

The replacement of carbon atoms by hetero-atoms in these five- and six-membered ring systems results in aromatic heterocycles whose properties are very similar to those of the parent hydrocarbons, though modified by the presence of the hetero-atoms. Of particular interest is the change in properties when carbon atoms are replaced by nitrogen atoms. The introduction of a nitrogen atom into a six-membered ring gives pyridine (IV). The nitrogen atom is in

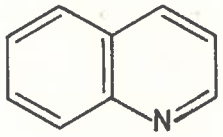


(IV)

a trigonal state of hybridization, with two of the sp^2 orbitals forming σ-bonds with the corresponding orbitals of the two adjacent carbon atoms, and the lone pair of electrons occupying the third orbital. The remaining 2p orbital overlaps with the 2p orbitals of the two adjacent carbon atoms so that there is a π-electron cloud above and below the plane of the ring as in benzene. As nitrogen is more electronegative than carbon, the electron cloud will be more dense at the nitrogen atom than at the carbon atoms in the ring. The differences in chemical behaviour of pyridine and benzene may be attributed to the deactivating effect of the nitrogen atom on the ring, and the presence of the lone pair of electrons on the nitrogen atom.

As pyridine contains an electron-attracting nitrogen atom it is not surprising that nucleophilic substitution is more facile than electrophilic substitution. The latter takes place with difficulty, and vigorous conditions are required. This is in contrast to benzene, which is very susceptible to attack by electrophilic reagents, but requires the presence of an electron-attracting substituent for nucleophilic attack. Consequently, the reactivity of pyridine has often been compared to that of nitrobenzene.[2,3] As oxidising agents may be regarded as electron acceptors, the carbon atoms of the pyridine ring, with their low electron densities, would be expected to be comparatively resistant to oxidation. Alkyl groups and benzene rings joined to a pyridine

nucleus are oxidised to the corresponding pyridine carboxylic acids by a variety of reagents.[4] Pyridine-2,3-dicarboxylic acid (VI) is formed when quinoline (V) is oxidised with a mixture of hydrogen peroxide, sulphuric acid and copper sulphate.[5] Oxidation



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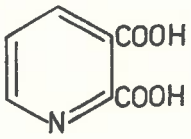
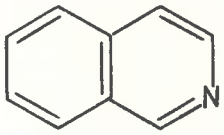


(VI)

of isoquinoline (VII) with ozone gives pyridine-3,4-dicarboxylic acid



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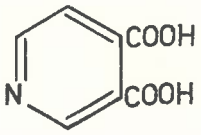
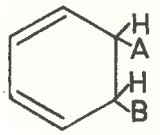


(VIII)

(VIII).[4] Reduction of pyridine occurs more readily than benzene and may be achieved by catalytic hydrogenation or by chemical means. Piperidine is formed when platinum[6] and nickel[7] are used as catalysts for the hydrogenation and also when reduction is effected by sodium and alcohol.[8] The use of sodium hydrosulphite[9] and sodium amalgam[10] results in partial reduction of the ring.

The presence of a lone pair of electrons on the annular nitrogen atom gives pyridine a number of properties which have no analogies among benzene derivatives. Among these is the ability to form salts, quaternary compounds and N-oxides. Addition to a C=N

bond in pyridine occurs more readily than addition to a C=C bond in benzene, and it has been suggested that this is due to the smaller loss in π-electron energy when pyridine undergoes addition.[11] If a reagent AB adds to the double bond of benzene the product (IX) has four π-electrons distributed over four atoms. With pyridine the resulting unsaturated system (X) has six



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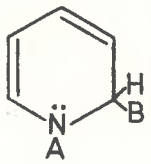
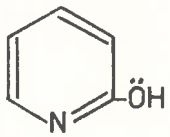


(X)

π-electrons distributed over five atoms and therefore the change in π-electron energy is much less than in the case of benzene. Both ketene[12] and dimethyl acetylenedicarboxylate[13] have been reported to form addition compounds with pyridine whereas benzene does not undergo these reactions.

The keto-enol tautomerism of 2- and 4-hydroxypyridines is due to the availability of the lone pair of electrons on the nitrogen atom for bond formation with a proton. With 2-hydroxypyridine (XI) for example, the pyridone structure (XII) would be expected to be stable as the unsaturated systems of the two tautomeric forms remain



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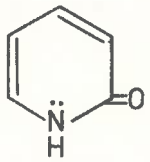
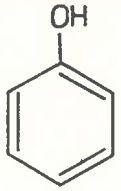


(XII)

almost unchanged with eight π-electrons distributed over seven atoms. It has been shown that in neutral solution the pyridone structure predominates whereas in alkaline solution the lactim form is more important.[14] In contrast to this, phenol (XIII) shows no tendency to undergo tautomerism as the keto form (XIV) would have considerably less resonance energy than the hydroxy



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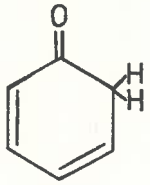
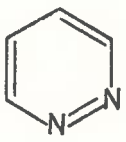


(XIV)

compound. 1-Alkylpyridones show considerable aromatic character as they undergo nitration and other electrophilic substitutions. Elvidge and Jackman[15] have shown by means of nuclear magnetic resonance spectroscopy that 1-methyl-2-pyridone has approximately 35% of the aromaticity of benzene, as defined by the ability to sustain an induced ring current.

The replacement of a carbon atom in a pyridine ring with a nitrogen atom gives rise to three isomeric diazines, pyridazine (XV), pyrimidine (XVI) and pyrazine (XVII). The carbon atoms in these



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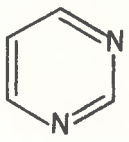
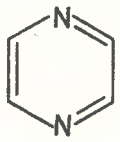
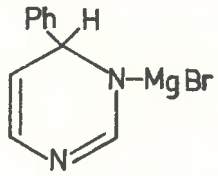


(XVI)



(XVII)

ring systems are even more deficient in electrons than those in pyridine, and consequently electrophilic substitutions are very difficult to achieve and nucleophilic substitutions take place with more ease than pyridine. The polarization of the carbon-nitrogen bonds in these compounds is so pronounced that addition reactions can occur, especially when these ring systems form part of fused polynuclear heterocycles. For example, treatment of pyrimidine with phenylmagnesium bromide at room temperature results in addition to the 3,4-bond, and hydrolysis of the product (XVIII) gives 3,4-dihydro-4-phenylpyrimidine (XIX).[16] When quinoxaline (XX)



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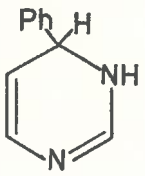
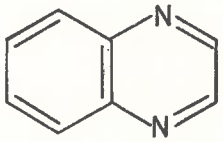
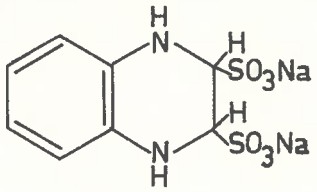


(XIX)

is treated with aqueous sodium bisulphite the addition compound (XXI) is readily formed and analogous reactions also occur when hydrogen cyanide or Grignard reagents are used.[17] There is considerable



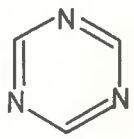
(XX)



(XXI)

interaction between the annular nitrogen atoms of the diazines as shown by their base strengths when compared to that of pyridine. This effect is most noticeable in the case of the 1,4-diazines; pyrazine, for example, has a pK_a value of 0.6 compared to 5.2 for pyridine.[18]

The six-membered ring systems containing three nitrogen atoms are known as triazines and of the three possible isomers only 1,3,5-triazine (XXII) has been prepared in an unsubstituted form.



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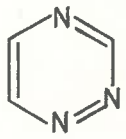

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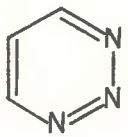
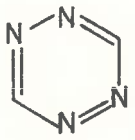


(XXIV)

Substitution reactions are difficult to achieve with this compound as ring cleavage occurs with considerable ease. The latter property may be attributed to the highly polarized nature of the carbon-nitrogen bonds. A solution of 1,3,5-triazine in distilled water is completely hydrolysed after standing for 10 mins. at 25°.[19] Derivatives of 1,2,4-triazine (XXIII) and 1,2,3-triazine (XXIV) are known, but the parent compounds have resisted all attempts at synthesis.

Three classes of tetrazines are theoretically possible. 1,2,4,5-Tetrazine (XXV) is known, but it is very susceptible to hydrolysis and can be reduced to the dihydro-compound. Only dihydro-derivatives of



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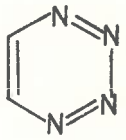

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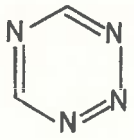
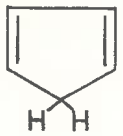


(XXVII)

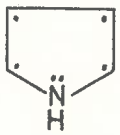
1,2,3,4-tetrazine (XXVI) have been prepared and no compounds containing the 1,2,3,5-tetrazine ring (XXVII) are known.

Dihydro-derivatives of pentazine are known but the fully aromatic compound has not been prepared.

Cyclopentadiene (XXVIII) is not aromatic as the four π-electrons cannot form a conjugated system which would incorporate all the annular carbon atoms. If the methylene group is replaced by an imido group the aromatic compound pyrrole (XXIX) is obtained. The nitrogen atom



(XXVIII)



(XXIX)

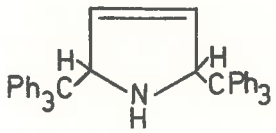
is in an $\underline{sp}^2$ state of hybridisation, with two of the hybrid orbitals forming σ-bonds with orbitals from the adjacent carbon atoms, and the third overlapping with the $\underline{1s}$ orbital of a hydrogen atom to form the N-H bond. The lone pair of electrons is in a $\underline{p}$ orbital which is perpendicular to the plane of the ring. The aromatic sextet is made up of four π-electrons from the carbon atoms and two from the nitrogen. As the pyrrole nucleus has six π-electrons distributed

over five atoms, its reactions will be those of an activated ring system. Its π-electron density is higher than that of benzene and is comparable to that of a benzene ring substituted with an electron donating group. The reactivity of pyrrole has been compared to that of phenol.[20] The two π-electrons of the nitrogen atom are spread over the whole ring and consequently the nitrogen atom is electron-deficient. This is illustrated by the acidic nature of the imido group. Pyrrole reacts with potassium liberating hydrogen and forming a potassium salt.

Electrophilic substitution of pyrrole takes place with great ease and generally involves the 2-position if this is available and in fact there are very few examples known where the attacking species enters a β-position when an α-position is free. If the 2- and 5-positions are substituted then reaction occurs in the 3- or 4-position. Nucleophilic attack on the pyrrole nucleus is unknown and this is undoubtedly due to its high π-electron density. The ease of oxidation of pyrrole and its simple derivatives can also be attributed to this fact.

In contrast to pyridine, the nitrogen atom in pyrrole does not have a lone pair of electrons available for salt formation. If the lone pair is utilised in bond formation the pyrrole nucleus loses its aromatic character. Consequently, it is a very weak base with a pK_a value of approximately 0.4[18] and undergoes resinification in the presence of strong acids.

Pyrrole takes part in very few addition reactions and Diels-Alder type adducts are formed in all known cases. In this respect it resembles cyclopentadiene. The product (XXX) is formed when pyrrole is treated with triphenylmethyl radicals.[21] The intermediate (XXXI) has been postulated in the reaction between 1-methylpyrrole and dimethyl acetylenedicarboxylate.[22]



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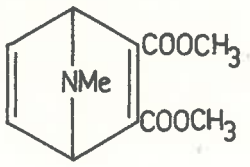
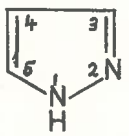
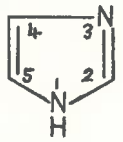


(XXXI)

The isomeric diazoles, pyrazole (XXXII) and imidazole (XXXIII), may be regarded as pyrrole nuclei in which the carbon atoms in the 2- and 3-positions respectively, have been replaced by nitrogen atoms. The amphoteric properties of these ring systems may be



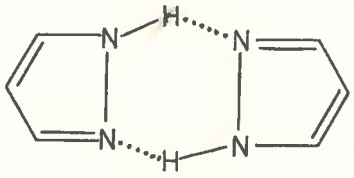
(XXXII)



(XXXIII)

attributed to the presence of both an acidic imido group and a basic nitrogen atom. Pyrazole and imidazole are stronger acids than pyrrole as the tertiary nitrogen atom is electron attracting and thus increases the tendency of the imido hydrogen to separate as

a proton. The diazoles would be expected to be stronger bases than pyridine (pK_a 5.2) as the basic nitrogen atom is in a ring of high π-electron density. This is true in the case of imidazole (pK_a 7.16[23]) but does not explain the low basicity of pyrazole (pK_a 2.53[23]). It has been suggested that the low value for the latter compound is due to the formation of a hydrogen bonded dimer (XXXIV), but this explanation has been rejected in view of the weak basic properties of 1-methylpyrazole (pK_a 2.09[23]).[24]

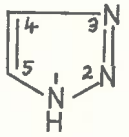


(XXXIV)

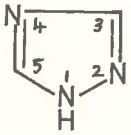
The tertiary nitrogen atom has a deactivating effect on these ring systems and the π-electron densities at the carbon atoms are not as high as at those in pyrrole. Consequently, the ease of electrophilic substitution of these nuclei is intermediate between that of pyrrole and benzene, and their resistance to oxidation is greater than pyrrole.

Imidazole and pyrazole are tautomeric compounds and the imido hydrogen may be attached to either of the nitrogen atoms. The 4- and 5-positions in imidazole are equivalent and it is not possible to distinguish between 4- and 5-monosubstituted derivatives. Similarly, 3- and 5-monosubstituted pyrazoles are identical.

Five-membered rings containing three nitrogen atoms are known as triazoles. Two isomers are possible, 1,2,3-triazole or v-triazole (XXXV), and 1,2,4-triazole or s-triazole (XXXVI). The



(XXXV)



(XXXVI)

tertiary nitrogen atoms in these ring systems are electron-attracting and electrophilic substitution at the carbon atoms takes place with difficulty. The chemical properties of the triazoles suggest that the carbon atoms in these nuclei have lower π-electron densities than those in a benzene ring and theoretical calculations are in agreement with this postulate.[25]

Electrophilic attack on the 1,2,3-triazole nucleus occurs only under neutral conditions. 4,5-Dibromo-1,2,3-triazole is formed when the parent compound is treated with bromine.[26] 4-Methyl-1,2,3-triazole is converted to the corresponding 5-halo-4-methyl-1,2,3-triazole by the action of chlorine, bromine or iodine, in chloroform.[27] When acid conditions are used in the halogenation of 2-phenyl-1,2,3-triazole, substitution occurs in the p-position of the phenyl group rather than in the triazole nucleus.[28]

Sulphonation, halogenation and Friedel-Crafts alkylation and acylation of the 1,2,4-triazole nucleus are unknown. The formation

of 3-hydroxymethyl-1,2,4-triazole from formaldehyde and 1,2,4-triazole is one of the few examples known of electrophilic attack on the carbon atoms of the triazole ring.[29]

As the carbon atoms in the triazoles have lower π-electron densities than those in benzene, it would not be unreasonable to expect them to be susceptible to attack by nucleophilic reagents. Reactions of this type are, however, unknown. This is undoubtedly due to the removal of the imido hydrogen by the nucleophiles and formation of the anions which have higher π-electron densities.

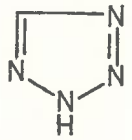
1,2,4-Triazole and 1,2,3-triazole are weak bases, and the cations formed with mineral acids are usually completely dissociated in aqueous solution. The basic pK_a for 1,2,4-triazole is 2.55,[23] but the value for 1,2,3-triazole has not been determined. These compounds are stronger acids than the diazoles and form salts with a number of metal ions.[30,31] 1,2,4-Triazole has an acid pK_a 10.1[32] and the benzo-derivative of 1,2,3-triazole has a value of 8.57.[18]

Triazoles are tautomeric and it is possible to write three structures in which the hydrogen atom is attached to each of three nitrogen atoms. In the case of 1,2,3-triazole it has been suggested that the structure with the hydrogen in the 2-position offers the most accurate description of the molecule.[33] This argument is based on the observation that the value of the dipole moment of 1,2,3-triazole (1.77 D) is closer to that of pyrazole (1.57 D) than that of imidazole (3.84 D). However, methylation with dimethyl sulphate

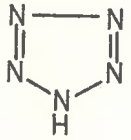
and alkali yields predominantly the 1-isomer[27] and quaternary salt formation with 1-alkyl derivatives takes place at the 3-position.[34] The 4- and 5-positions of the 1,2,3-triazole ring are equivalent and 4- and 5-monosubstituted derivatives are indistinguishable.

Alkylation of 1,2,4-triazole with a diazoalkane, or an alkyl halide and the sodium salt of the triazole, gives mainly the 1-alkyltriazole.[35] Recently, it has been shown by means of nuclear magnetic resonance studies that the acetyl group in N-acetyl-1,2,4-triazole is attached to the nitrogen in the 1-position.[36] Theoretical calculations[25,37] predict that quaternary salt formation will take place at the 4-position of the 1,2,4-triazole ring and this has been verified experimentally in the case of 1,3,5-trimethyltriazole.[38] The equivalence of the 3- and 5-positions in the 1,2,4-triazole nucleus is due to the tautomeric nature of this compound.

Tetrazole (XXXVII) is a strong acid (pK_a 4.89[39]) and its strength is comparable to that of many organic carboxylic acids.



(XXXVII)



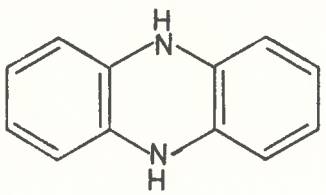
(XXXVIII)

The tendency for the imido hydrogen atom to separate as a proton is increased by the electron-attracting properties of the three tertiary nitrogen atoms. The weak basic properties and resistance to oxidation

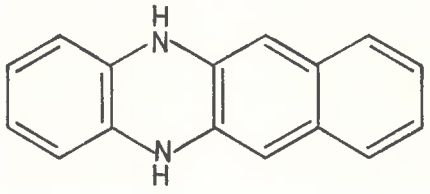
of the tetrazole ring system are further indications of its low π-electron density. Compounds containing a high percentage of nitrogen are often thermally unstable and it is not surprising that many tetrazoles exhibit explosive properties. The parent compound decomposes violently when heated above its melting point.

Derivatives of pentazole (XXXVIII) are very unstable and are known only in solution. Phenylpentazole has been postulated as an intermediate in the reaction between the azide ion and phenyldiazonium salts.[40] The evidence for its formation is based on kinetic studies of this reaction.

Many of the properties of polynuclear azahydrocarbons closely resemble those of the corresponding hydrocarbons. In the series benzene, naphthalene, anthracene, naphthacene, pentacene and hexacene, the reactivity and tendency to form dihydro-derivatives increases as the series is ascended. The related azahydrocarbons show a similar tendency to form dihydro-compounds and the higher members of the series are very reactive. Dihydrophenazine (XXXIX) is not particularly stable as it undergoes oxidation in air to form phenazhydrin, a 1:1 molecular complex of phenazine and dihydrophenazine.[41] Benzo/b/phenazine has been reduced to the corresponding dihydride (XL) which was found to be stable in air,

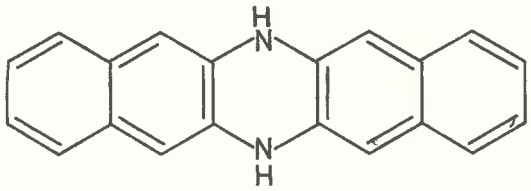


(XXXIX)



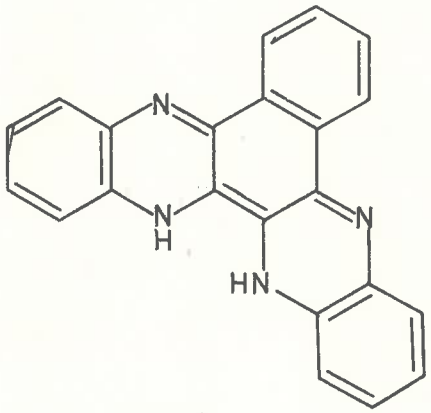
(XL)

but could be oxidised to the aromatic compound with dichromate.[42] Dihydrodibenzo[b,i]phenazine (XLI) is so stable that all attempts to oxidise it to the aromatic compound have been unsuccessful.[42]

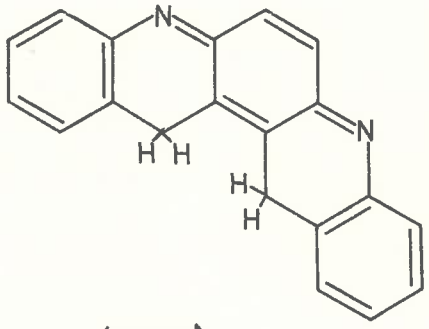


(XLI)

The presence of the nitrogen atoms in these heterocyclic systems imparts a number of properties which have no parallels in the hydrocarbons. The most interesting of these is the ability to form p-quinonoid-type structures which are of varying stability. The dihydro-derivative (XLII) of benzo[a]quinoxalino[2,3-c]-phenazine is unstable[43] whereas 13,14-dihydrodibenzo[b,j][4,7]-phenanthroline (XLIII) is sufficiently stable for it to be isolated.[44]

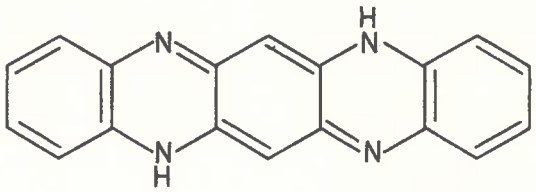


(XLII)



(XLIII)

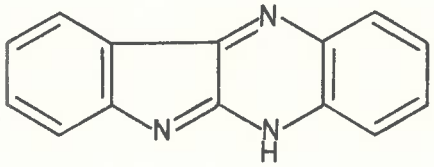
The quinonoid structure of 5,12-dihydroquinoxalino[2,3-b]-phenazine (XLIV) is particularly resistant to oxidation as all



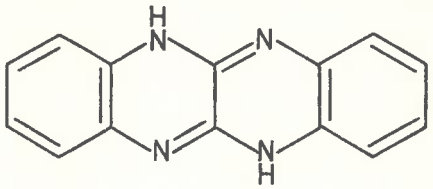
(XLIV)

attempts to convert it to the aromatic compound have been unsuccessful.[45] It can be seen from the above examples that the stability of the conjugated system, -N=C-C=C-C=N-, varies greatly and depends on the structure of the fused heterocycle. It seemed of interest to determine whether the related system, -N=C-C=N-, showed a similar tendency.

As one of the possible tautomeric forms of indolo[2,3-b]quinoxaline (XLV) contains the latter conjugated system, a study of the tautomerism and reactions of this compound was undertaken. The structure of the azahydrocarbon fluoflavin has not been established beyond doubt and one group of workers has regarded it as 5,11-dihydroquinoxalino-[2,3-b]quinoxaline (XLVI).[46] An investigation of the structure of fluoflavin was desirable as this would yield information concerning

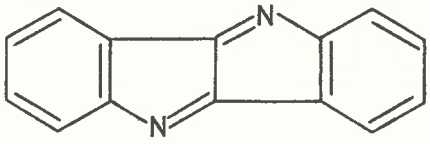


(XLV)



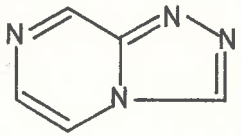
(XLVI)

the stability of the -N=C-C=N- system. This linkage is also present in indolo[3,2-b]indole (XLVII), and as this ring system is unknown its synthesis was also attempted.

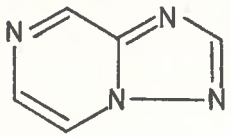


(XLVII)

The fusion of a 1,2,4-triazole nucleus and a pyrazine nucleus can theoretically give rise to two isomers, s-triazolo[4,3-a]-pyrazine (XLVIII) and s-triazolo[2,3-a]pyrazine (XLIX). Only one



(XLVIII)



(XLIX)

of these is known and was prepared in the form of its benzo-derivative, s-triazolo[4,3-a]quinoxaline.[47] As part of a long term research programme into the chemistry of fused 1,2,4-triazole systems, the methods available for the synthesis of the above structures were investigated.

The corresponding pyridazine and pyrimidine derivatives have interesting pharmacological properties, especially in relation to cancer[48] and nucleic acid metabolism.[49] A number of derivatives of

polynuclear 1,2,4-triazole systems have been utilized in photography.[50,51] A pharmacological evaluation of the s-triazolopyrazines prepared in this study is also to be carried out.

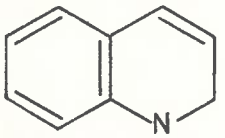
In the preceding section it has been shown that while the properties of nitrogen-containing aromatic compounds are very similar to those of their carbocyclic analogues, they are modified to some extent by the presence of the hetero-atoms. The absorption spectra of nitrogen heterocycles also resemble those of the corresponding hydrocarbons. The intense ultraviolet and visible absorption of aromatic compounds is due to electronic transitions from bonding to non-bonding π-orbitals ($\pi \rightarrow \pi^*$ transitions). As the azahydrocarbons contain the same number of π-electrons as the corresponding hydrocarbons it is not surprising that their absorption spectra are similar even though there are small differences in electronic energy levels and molecular dimensions.

The aromatic hydrocarbons generally exhibit three main regions of absorption in the ultraviolet and visible region and these bands are referred to as group I, II and III bands, respectively.[52] The group III bands are due to transitions which are forbidden by the symmetry of the molecules and thus are usually much less intense than the shorter wavelength bands. Benzene has an intense region (group I) of absorption at 179 mμ[53] a second region (group II) of relatively intense absorption around 200 mμ[54] and a third region (group III) around 230-260 mμ.[54] The absorption maxima of naphthalene occur at

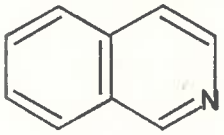
longer wavelengths and are more intense than those in benzene. The bands in the spectrum are at 220 mμ(group I), 275 mμ(group II) and 310 mμ(group III).[55] The linear condensed ring compounds anthracene, naphthacene, pentacene, and hexacene, show only two regions of absorption (groups I and II) as the group III bands are hidden under the group II bands. This effect is not observed with the angular compounds as all three regions of absorption can be distinguished.

The absorption spectrum of pyridine is very similar to that of benzene, with maxima at 170 mμ,[53] 200 mμ and 250 mμ.[56,57] The main difference is that the intensity of the long wavelength band is about ten times as great as that in benzene. The transition associated with this band is not forbidden by symmetry and thus gives rise to an absorption band of greater intensity. The higher members of the azine series also possess spectra similar to that of benzene. Maccoll[58] compared the group III absorption bands of benzene, pyridine, pyrimidine, pyridazine, and s-tetrazine and concluded that the absorption is shifted progressively to longer wavelengths with each additional nitrogen atom, and that the effect is most marked when the nitrogen atoms are adjacent.

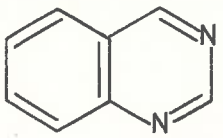
The absorption curves for quinoline (L), isoquinoline (LI), and quinazoline (LII), all show the same three main regions of absorption as naphthalene.[59,60] In every case the intensity of absorption in the group III region is greater for the azahydrocarbon than for naphthalene.



(L)

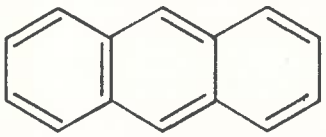


(LI)

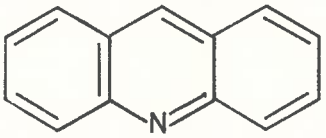


(LII)

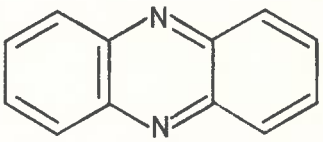
The nitrogen heterocycles corresponding to anthracene exhibit two main regions of absorption, the group III region being hidden under the group II bands as in the parent hydrocarbon. The spectra of anthracene (LIII), acridine (LIV) and phenazine (LV) are very similar (Fig. 1) although there is much less fine structure in the case of the heterocycles.[61]



(LIII)



(LIV)



(LV)

Badger and co-workers[61] have examined the spectra of a large number of azahydrocarbons and have concluded that the spectra of these compounds closely resemble those of their carbocyclic analogues although there are some differences. The chief differences are: (1) the group III absorption bands are much more intense than those of the hydrocarbons; (2) in anthracene analogues the group II bands are sometimes more intense than those of the hydrocarbon;

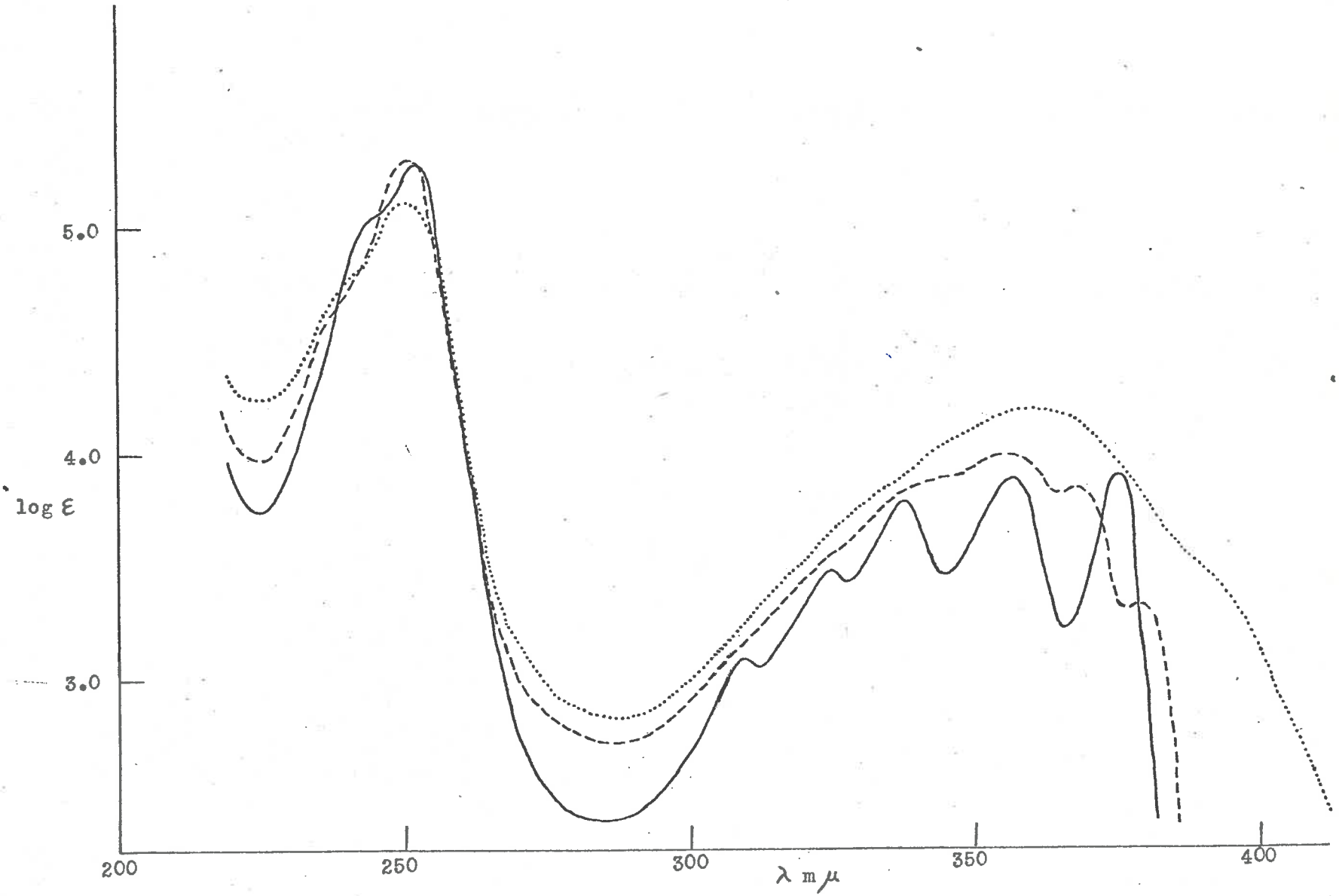


Fig. 1. Absorption spectra of anthracene (———), of acridine (– – – –) and of phenazine (••••••), in 95% ethanol.[61]

(3) there is considerable loss of fine structure in replacing a methine group by an annular nitrogen atom, but as far as can be ascertained the various maxima are not shifted to any marked extent; and (4) the absorption spectra generally extend to longer wavelengths than those of the corresponding hydrocarbons.

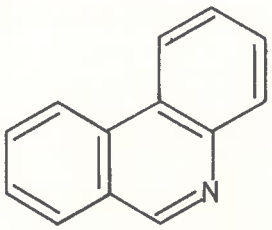
A considerable solvent effect is observed when the spectra of azahydrocarbons are determined in polar and non-polar solvents.[62] In cyclohexane solution many compounds exhibit an additional absorption band which is not present when the spectra are determined in ethanolic or aqueous solution. These long wavelength bands have been assigned to transitions involving the excitation of an electron from a non-bonding orbital of a nitrogen atom (n-electron) to an unoccupied π-orbital ($n \rightarrow \pi^*$ transition).[62-66] In polar solvents such as ethanol and water the n-electrons of the nitrogen atoms are involved in hydrogen bonding and the absorption resulting from $n \rightarrow \pi^*$ transitions is shifted to shorter wavelengths, and in many cases, hidden under the group III bands.[67]

In cyclohexane solution the $n \rightarrow \pi^*$ transition in pyridine appears as a series of shoulders on the long wavelength side of the group III bands.[67] The diazines, pyridazine, pyrimidine, and pyrazine, show well-defined bands at longer wavelengths. For example, a solution of pyridazine in cyclohexane gives a distinct $n \rightarrow \pi^*$ absorption band at 345 mμ whereas the group III absorption has a

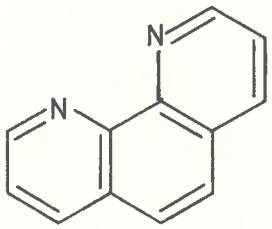
maximum at 250 mμ.[68] When water is used as the solvent the $\underline{n}\rightarrow\pi^*$ absorption is shifted to shorter wavelengths, the maximum being at 300 mμ.[68]

Badger and Walker[67] have examined the spectra of a large number of azahydrocarbons and in many cases have established the presence of $\underline{n}\rightarrow\pi^*$ absorption bands.

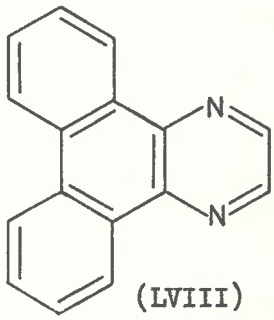
A number of nitrogen-containing ring systems do not exhibit $\underline{n}\rightarrow\pi^*$ bands in their spectra as the absorption due to this transition is of very low intensity and is hidden under the group III bands. This has been found to be the case with phenanthridine (LVI), 1,10-phenanthroline (LVII) and dibenzo[f,h]quinoxaline (LVIII).[67]



(LVI)



(LVII)



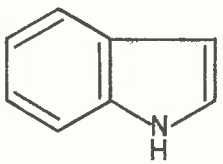
(LVIII)

Pyrrole is isoelectronic with benzene and may be considered to be derived from it by the replacement of one of the -CH=CH- groups with a -NH- group. The spectrum of pyrrole has absorption bands at 172, 183 and 211 mμ,[69-71] but does not show absorption at wavelengths corresponding to the group III region of benzene (230-260 mμ). The

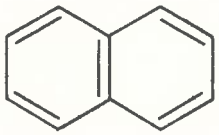
dissimilarity of the spectra of pyrrole and benzene has been ascribed to the effect of the electronegative nitrogen atom in restricting the delocalization of its lone pair of electrons.[72] 1-Methylpyrrole shows absorption in the 230-260 mμ region and this is thought to be due to a reduction in the electronegativity of the nitrogen atom by methyl substitution.[73] It has been pointed out that the resemblance of the spectra of furan, pyrrole, and thiophen, to that of benzene increases as the electronegativity of the heteroatom decreases.[72]

The spectra of pyrazole,[74] imidazole,[74] 1,2,3-triazole,[75] and 1,2,4-triazole[76] have been determined and in all cases there is an absorption band with a maximum at about 210 mμ. Imidazole has an additional band of low intensity at 250 mμ and this has been assigned to the $\underline{n} \rightarrow \pi^*$ transition of the -C=N- group.[77]

Indole (LIX) contains the same number of π-electrons as naphthalene (LX) and the absorption spectra of the two ring systems



(LIX)



(LX)

have been found to be very similar (Fig. 2).[79] The principal differences are in the long wavelength region where the group III absorption of indole is at a shorter wavelength than that for

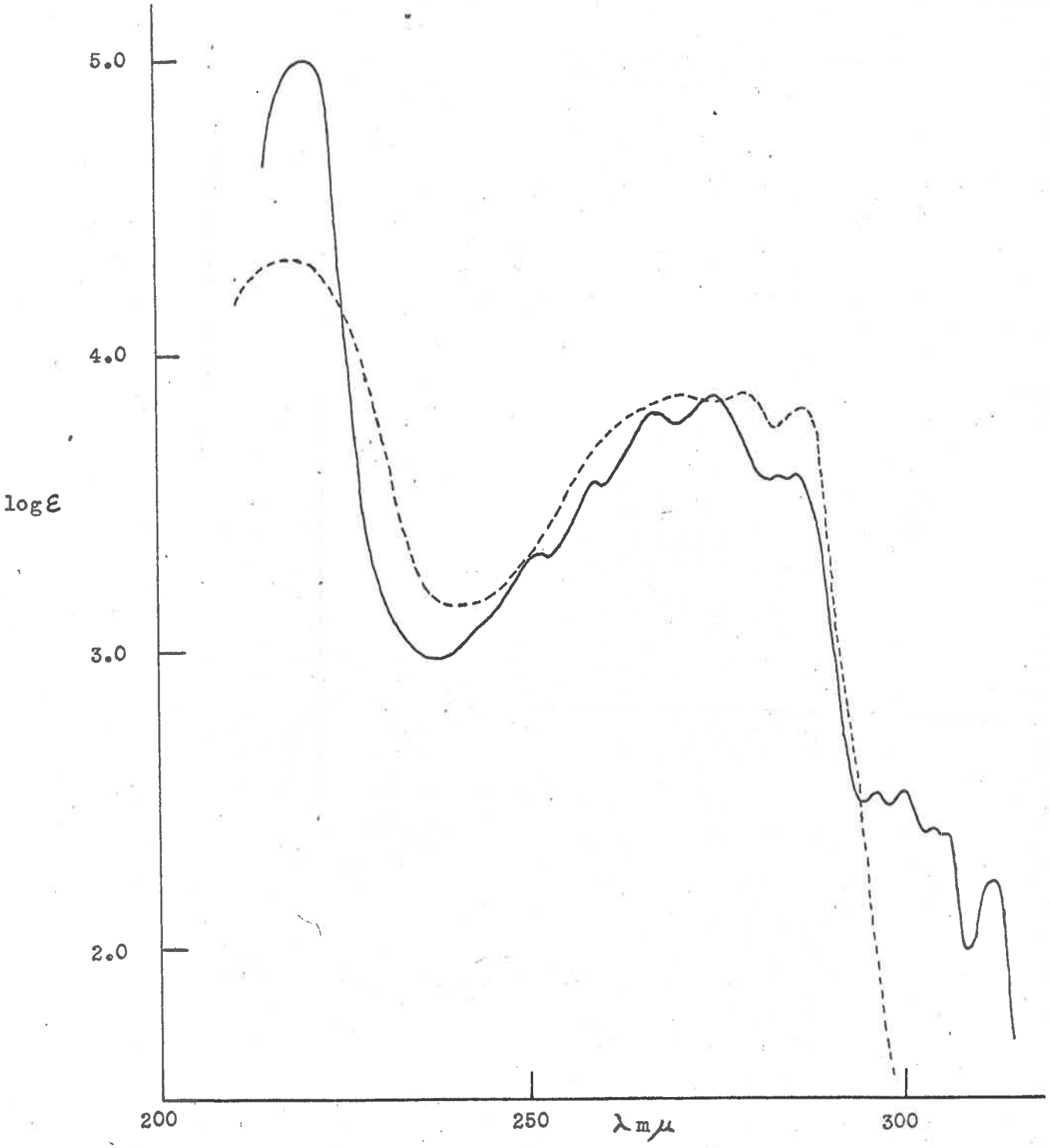
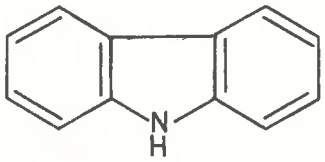


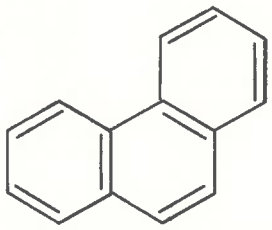
Fig. 2. Absorption spectra of naphthalene[78] (———) and of indole[79] (– – – –), in 95% ethanol.

naphthalene. As a result the group II band of indole cannot be clearly distinguished.

The spectrum of carbazole (LXI) has been compared with that of phenanthrene (LXII) and the similarity was found to be greater than in the case of indole and naphthalene.[79] Both compounds exhibit



(LXI)



(LXII)

three regions of absorption, but the group I band in carbazole is at a shorter wavelength than the corresponding band in the hydrocarbon. There is an additional difference in the group III region where the intensity of the absorption of carbazole is greater than that of phenanthrene.

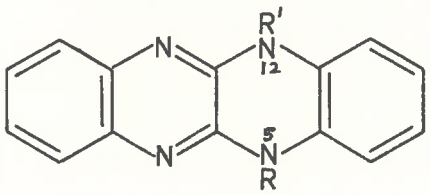
Badger and Christie[79] examined the absorption spectra of a large number of polycyclic compounds containing five-membered heterocyclic rings and found that they are fundamentally similar to the spectra of the related benzenoid hydrocarbons. These workers concluded that three main regions of absorption corresponding to the group I, II and III bands of the aromatic hydrocarbons can generally be resolved and

that the main differences are: (1) the absorption (particularly the group I bands) is shifted to shorter wavelengths; and (2) the group III bands have much higher extinction coefficients than those of the hydrocarbons.

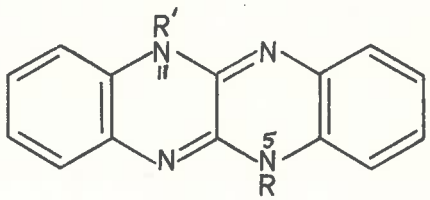
DISCUSSION

A. DIHYDROQUINOXALINO[2,3-b]QUINOXALINES.

In the literature there is no agreement as to the structure of the polynuclear azahydrocarbon, fluoflavin. This compound was first prepared by Hinsberg and Pollak[80] who assigned it the structure 5,12-dihydroquinoxalino[2,3-b]quinoxaline (LXIII; R=R'=H). More recently, Bagans and Krüger[46] reported a novel synthesis of fluoflavin and regarded it as 5,11-dihydroquinoxalino[2,3-b]quinoxaline (LXIV;



(LXIII)

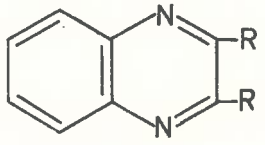


(LXIV)

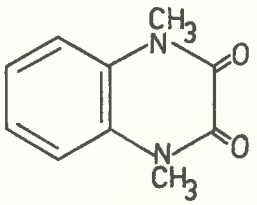
R=R'=H). Two chloro-derivatives have also been reported and these were considered to be derivatives of 5,11-dihydroquinoxalino[2,3-b]-quinoxaline.[81]

As the structure (LXIV) contains the conjugated system under discussion, an investigation of the structure of fluoflavin was desirable. It was thought that a comparison of the absorption spectra of fluoflavin and the two dimethyl derivatives (LXIII and LXIV; $R=R'=CH_3$) would solve this question, and the synthesis of the latter compounds was attempted.

Previous syntheses of fluoflavin have been achieved by the condensation of o-phenylenediamine and dichloro- or dihydroxyquinoxaline (LXV; R=Cl or OH).[80] These methods involved fusion reactions and were unsatisfactory because of the low yields and formation of troublesome by-products. The alternative method,[46] involving the reaction of o-phenylenediamine and 1,1,2,2-tetrachloro-1,2-dibutoxyethane, gave a good yield of fluoflavin but has little practical value due to



(LXV)

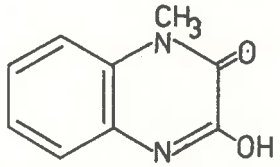


(LXVI)

the difficulty of obtaining the ethane derivative. It has been found that fluoflavin may be obtained in good yield by heating o-phenylenediamine and 2,3-dihydroxyquinoxaline (LXV; R=OH) in polyphosphoric acid.

The most satisfactory method for the preparation of 5,12-dimethylquinoxalino[2,3-b]quinoxaline (LXIII; $R=R'=CH_3$) was found to be by the condensation of 2,3-dichloroquinoxaline (LXV; R=Cl) and N,N'-dimethyl-o-phenylenediamine using sodium chloride as diluent. The same compound was obtained in very poor yield when o-phenylenediamine and 1,2,3,4-tetrahydro-1,4-dimethyl-2,3-dioxoquinoxaline (LXVI) were heated together in polyphosphoric acid.

The same product (LXIII; R=R'=CH_3) was also expected from the reaction of 2,3-dihydroxyquinoxaline (LXV; R=OH) and N,N'-dimethyl-o-phenylenediamine in polyphosphoric acid. However, the product isolated was shown to be 5H-12-methylquinoxalino[2,3-b]-quinoxaline (LXIII; R=H, R'=CH_3). It was identified by comparison with an authentic sample prepared by the condensation of o-phenylenediamine and 1,2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (LXVII) in polyphosphoric acid. The presence of the NH group was satisfactorily confirmed by the ready formation of an acetyl derivative and an N-methyl determination showed that only one N-CH_3 group was present.



(LXVII)

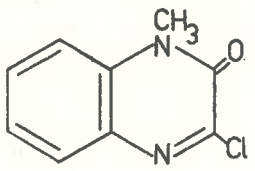
The loss of a methyl group in this latter condensation was of some interest. 5,12-Dimethylquinoxalino[2,3-b]quinoxaline (LXIII; R=R'=CH_3) was recovered unchanged after heating in polyphosphoric acid for two hours. This proved that the final product was stable under the reaction conditions and that demethylation must have taken place at some previous stage. The acidic nature of polyphosphoric acid would result in protonation of the N,N'-dimethyl-o-phenylene-diamine and the conditions would therefore be very similar to those

required for the Hofmann rearrangement of the salts of alkylanilines.[82] A nuclear magnetic resonance spectrum of the crude reaction product showed a band (τ, 7.73) which was assigned to an aromatic C-CH_3 group. As this band was of low intensity, it seemed likely that the methyl groups were eliminated predominantly as carbonium ions which then reacted with phosphate anions to form methyl esters. This would be analogous to the formation of alkyl halides in the Hofmann rearrangement.[82]

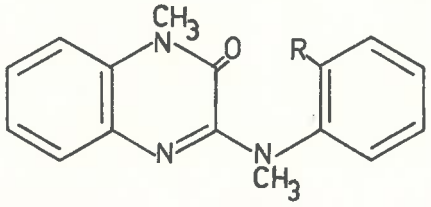
In an attempt to prepare 5,11-dimethylquinoxalino[2,3-b]-quinoxaline (LXIV; $R=R'=CH_3$), N-methyl-o-phenylenediamine and 1,2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (LXVII) were heated together in polyphosphoric acid. The product isolated from the reaction was identified as 5H-12-methylquinoxalino[2,3-b]quinoxaline (LXIII; $R=H$, $R'=CH_3$). Lower reaction temperatures were used in an attempt to prevent the loss of the methyl substituent, but it was found that below 200° there was no reaction and above this temperature the demethylated product was formed. The use of glacial acetic acid and of polyphosphoric acid of higher phosphorus pentoxide content, as reaction media, was also unsuccessful.

A more satisfactory synthetic route to 5,11-dimethyl-quinoxalino[2,3-b]quinoxaline would be one in which ring closure was effected by two separate reactions. In an attempt to achieve this, N-methyl-o-nitroaniline was treated with 3-chloro-1,2-dihydro-1-methyl-2-oxoquinoxaline (LXVIII). The yield of the

product (LXIX; R=NO_2) was so low that the projected further steps (reduction of the nitro group, and cyclization) were not attempted.



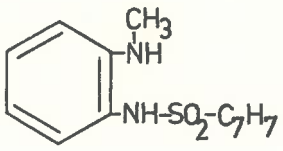
(LXVIII)



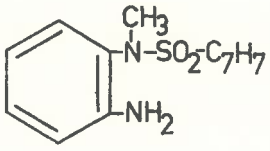
(LXIX)

As the poor yield was probably due to the low basicity of N-methyl-o-nitroaniline, a more basic amine was employed. N-(o-Methylamino-phenyl)toluene-p-sulphonamide (LXX) was used in place of N-methyl-o-nitroaniline, but the desired compound (LXIX; R=$C_7H_7SO_2NH$) could not be obtained.

N-(o-Methylaminophenyl)toluene-p-sulphonamide (LXX) was prepared from N-methyl-o-phenylenediamine and toluene-p-sulphonyl chloride. A comparison of a sample of this compound with an authentic sample of the isomer,[83] N-(o-aminophenyl)-N-methyltoluene-p-sulphonamide (LXXI), showed that reaction had occurred at the primary amino group.



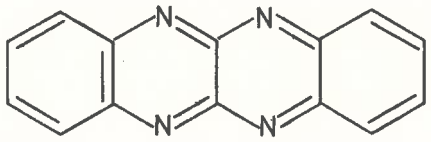
(LXX)



(LXXI)

The absorption spectrum of fluoflavin was found to be very similar to that of 5,12-dimethylquinoxalino[2,3-b]quinoxaline (Fig. 3) and it seems certain therefore that in 95% ethanol it has the structure (LXIII; R=R'=H). 5H-12-Methylquinoxalino-[2,3-b]quinoxaline also has a similar absorption spectrum (Fig. 3) and this establishes its structure as the 5,12-derivative.

Fluoflavin was dehydrogenated to the aromatic compound, quinoxalino[2,3-b]quinoxaline (LXXII), by treatment with lead tetra-acetate. A dilute solution of this compound in ethanol was



(LXXII)

reduced photochemically to fluoflavin. In this respect it resembles phenazine which has been transformed to dihydrophenazine in a similar manner.[84] It has been postulated that the ethanol is oxidised to acetaldehyde in this reaction.[84] Hinsberg and Pollak[80] have reported that quinoxalino[2,3-b]quinoxaline may be reduced to fluoflavin using hydrogen sulphide, stannous chloride or hydroquinone.

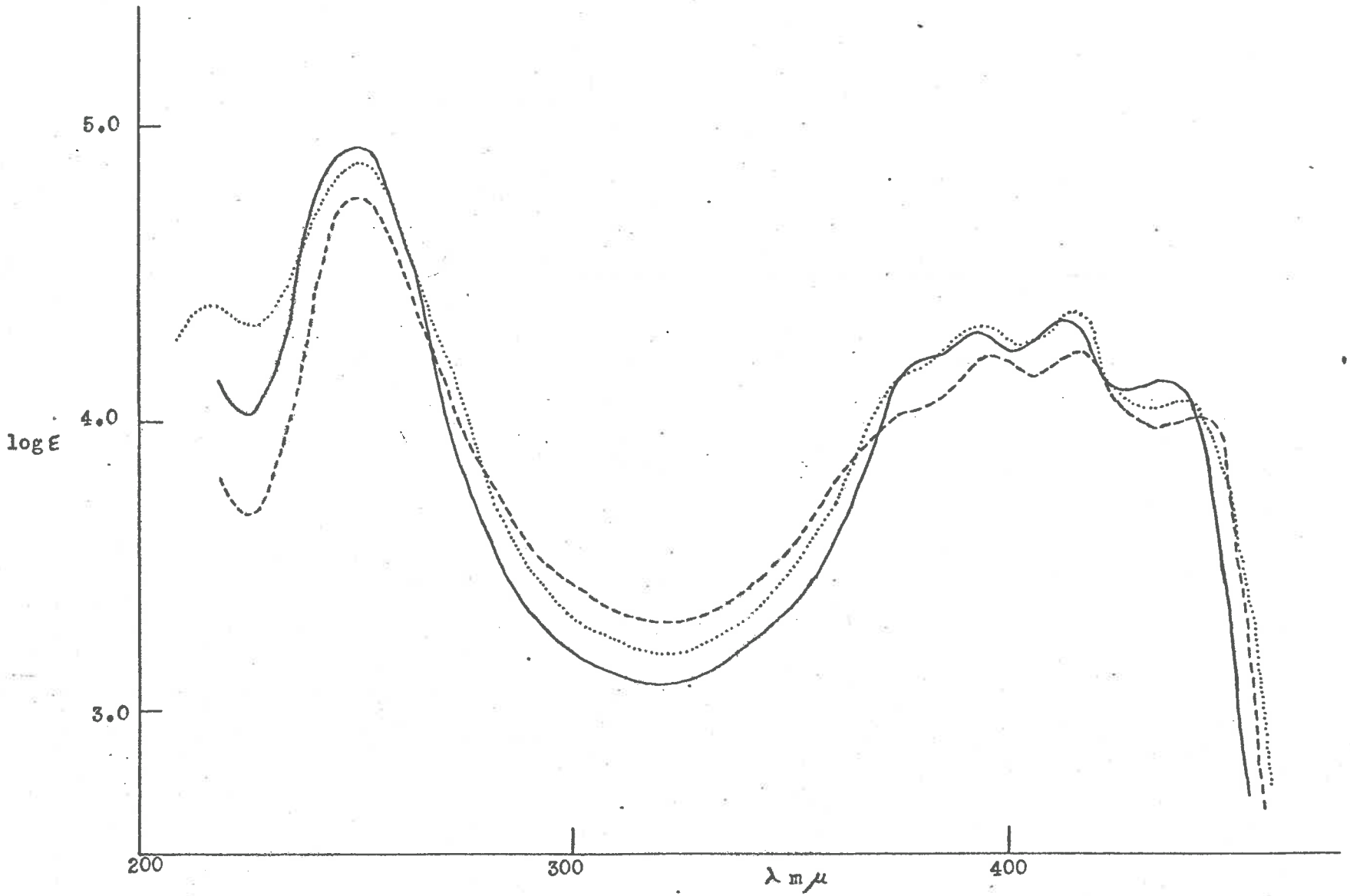
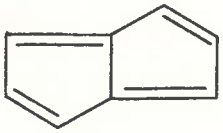


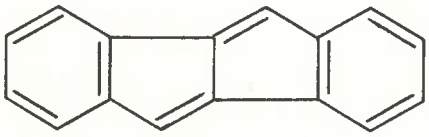
Fig. 3. The absorption spectra of 5,12-dimethylquinoxalino[2,3-b]quinoxaline (LXIII; R = R' = CH_3, ———), of 5H-12-methylquinoxalino[2,3-b]quinoxaline (LXIII; R = H, R' = CH_3, ·····), and of 5,12-dihydroquinoxalino[2,3-b]quinoxaline (LXIII; R = R' = H, – – –), all in 95% ethanol.

B. INDOLO[3,2-b]INDOLE.

In 1922, Robinson[85] suggested pentalene (LXXIII) as a possible aromatic compound. In the following years there were many attempts



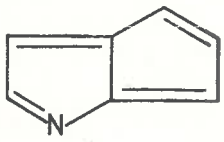
(LXXIII)



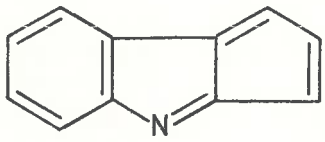
(LXXIV)

to prepare this ring system, but all were unsuccessful. Although theoretical calculations have shown that this structure would have a resonance energy of about 40 kcals./mole,[86,87] there is a wide difference of opinion regarding its stability.[86,88] A number of derivatives of pentalene are known and among these is indeno[2,1-a]-indene (LXXIV). This compound was found to behave as a conjugated diene and had no aromatic stability.[89]

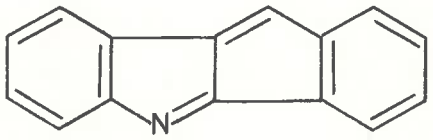
The replacement of a methine group in an aromatic hydrocarbon with a tertiary nitrogen atom results in an aromatic heterocycle whose properties resemble those of the hydrocarbon to a certain extent. This fact has prompted a number of workers to prepare derivatives of azapentalene (LXXV) with the object of examining their chemical properties. The synthesis of the benzo-, dibenzo-, and benzonaphtho-derivatives (LXXVI, LXXVII, and LXXVIII, respectively) was achieved by Treibs,[90] and derivatives of (LXXVII) have been prepared by Kempster and co-workers.[91] In each instance the mode of synthesis was



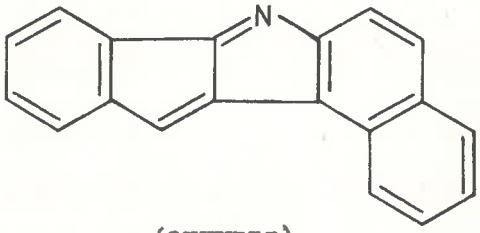
(LXXV)



(LXXVI)



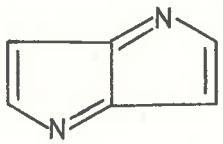
(LXXVII)



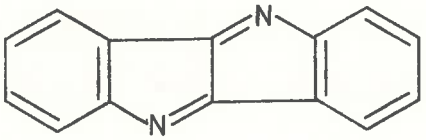
(LXXVIII)

via the dihydro-compound which was prepared from the corresponding hydrazine and ketone by the Fischer indole synthesis. Dehydrogenation gave the required azapentalene.

Several attempts have been made to prepare derivatives of diazapentalene (LXXIX). Kato and Ohta[92] attempted the synthesis of the dibenzo-derivative, indolo[3,2-b]indole (LXXX), by the intramolecular condensation of 2-(o-aminophenyl)-3-oxoindolenine (LXXXI). Many dehydrating agents were tried, but the desired product was not obtained. Dehydrogenation of 5,10-dihydroindolo[3,2-b]indole (LXXXII) with chloranil was also unsuccessful.[92]



(LXXIX)



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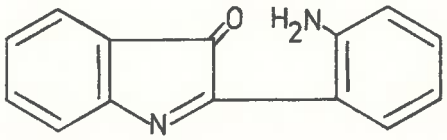
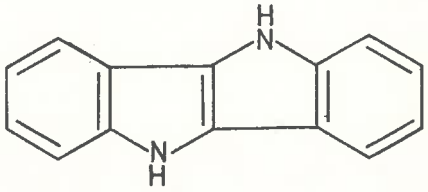


(LXXXI)

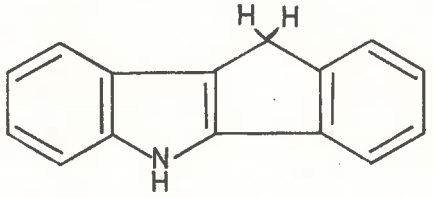


(LXXXII)

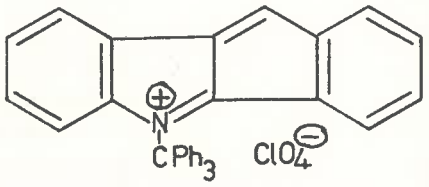
It has been pointed out previously that many compounds containing quinonoid-type structures are very stable and that in some cases their stability is greater than that of the corresponding aromatic compounds, for example, 5,12-dihydroquinoxalino[2,3-b]phenazine (XLIV). Indolo-[3,2-b]indole (LXXX) contains an analogous conjugated system and thus it is possible that this structure may be more stable than its carbocyclic analogue, indeno[2,1-a]indene (LXXIV). As a study of its properties would yield information concerning the stability of the —N=C— C=N— linkage, the synthesis of this compound was undertaken. A further point of interest was that on theoretical grounds both indolo[3,2-b]indole and its dihydro-derivative would

be expected to be aromatic.

Triphenylmethyl perchlorate has been used to dehydrogenate dihydro-derivatives of aromatic systems.[93] For example, 5,10-dihydroindeno[1,2-b]indole (LXXXIII) is readily converted to 5-triphenylmethylindeno[1,2-b]indolium perchlorate (LXXXIV) using this reagent.[93] It was proposed to attempt the preparation of



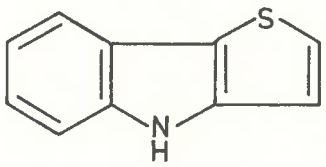
(LXXXIII)



(LXXXIV)

indolo[3,2-b]indole by dehydrogenation of the 5,10-dihydro-compound with triphenylmethyl perchlorate.

The methods available for the synthesis of 5,10-dihydroindolo-[3,2-b]indole are unsatisfactory in that a number of steps are involved and the overall yields are low.[94-96] A general procedure for the formation of the indole component of fused ring systems is by the pyrolysis of azides of the o-azidodiaryl type. Thieno[3,2-b]-indole[97] (LXXXV) and carbazole[98] (LXI) have been prepared from 2-(o-azidophenyl)thiophen (LXXXVI) and o-azidodiphenyl (LXXXVII), respectively, using this method. It was considered that an



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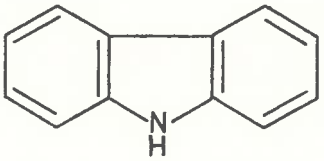
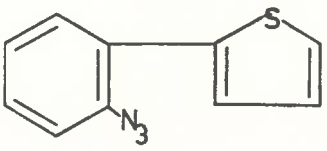
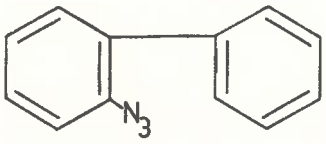


(LXI)

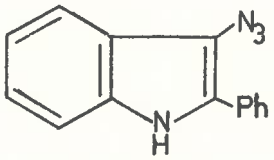


(LXXXVI)



(LXXXVII)

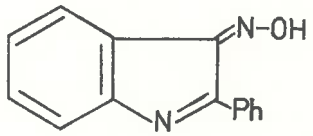
investigation of a synthesis involving the pyrolytic ring closure of 3-azido-2-phenylindole (LXXXVIII) might result in a more convenient route to 5,10-dihydroindoloindole.



(LXXXVIII)

The general procedure for the introduction of an azido group into a molecule is by displacement of the diazo substituent in the corresponding diazonium salt. The preparation of the diazonium salt

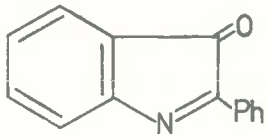
necessitated the synthesis of the amine, and this was achieved by reduction of the corresponding isonitrosoindole with sodium hydrosulphite and alkali.[99] 3-Isonitroso-2-phenylindole (LXXXIX) has been prepared from 2-phenylindole by treatment with nitrous



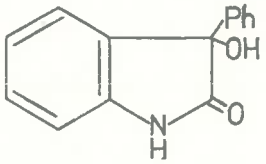
(LXXXIX)

acid,[100] or with amyl nitrite in ether.[101] As 3-isonitrosoindole is readily formed by treatment of indole with amyl nitrite and sodium ethoxide,[102] the analogous reaction using 2-phenylindole was carried out. The product was obtained in greater yield than with the other methods of preparation.

In the first attempt to prepare 5,10-dihydroindolo[3,2-b]-indole, 3-amino-2-phenylindole was treated with sodium nitrite and then with sodium azide. The resulting solid was heated in boiling decalin, but it was not possible to isolate any compounds in a pure state from the reaction mixture. One of the products formed red needles, m.p. 97-99°, and its infrared spectrum showed two bands in the carbonyl region. Recrystallization and chromatography on alumina failed to effect complete purification of this material. It is thought that this product was impure 3-oxo-2-phenylindolenine (XC); Kalb and Bayer[99] have reported that this compound forms red



(XC)



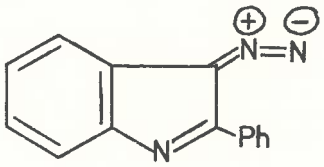
(XCI)

needles, m.p. 102°. The intermediate formed in the reaction of the diazotised amine and sodium azide was isolated by pouring the reaction mixture into water and collecting the precipitated solid. The mixture was allowed to stand for one day, and the filtrate deposited colourless crystals which were identified as 3-hydroxy-2-oxo-3-phenylindoline (XCI). The assignment of this structure was based on analytical and infrared spectral data. Kalb and Bayer[99] prepared this compound by treating 3-oxo-2-phenylindolenine (XC) with alkali. They postulated that the first step was addition of water to the C=N bond followed by a benzilic acid type rearrangement to give the product.

As the initial experiment indicated that extensive oxidation had occurred in the 3-position of the indole nucleus, all further reactions were carried out in an atmosphere of nitrogen. Treatment of 3-amino-2-phenylindole with nitrous acid afforded the diazo-compound which was sufficiently stable to be isolated. A solution of this compound in glacial acetic acid was treated with sodium azide. The required azide was not formed and the infrared spectrum of the crude product had a band in the carbonyl region showing that some oxidation

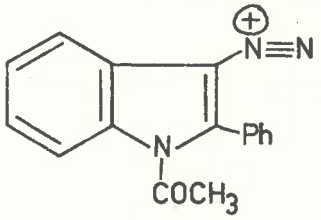
had taken place. The only pure material isolated from this reaction was a violet compound whose structure was not determined.

3-Diazo-2-phenylindole (XCII) cannot be regarded as a diazonium salt which was the species treated with sodium azide



(XCII)

in previous applications of this method. The failure to obtain the azide was attributed to the unusual stability of the diazo-compound; Castellana and d'Angelo[103] have reported that it is stable in boiling dilute mineral acids. Acetylation of 3-diazo-2-phenylindole would result in the formation of the compound (XCIII) which would have properties similar to those of a diazonium salt. In an attempt to



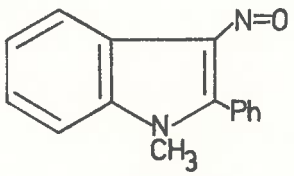
(XCIII)

prepare 3-azido-2-phenylindole, the diazo-compound was treated with acetyl chloride and then with sodium azide. Hydrolysis with alkali gave a product which was not the desired azide as its infrared

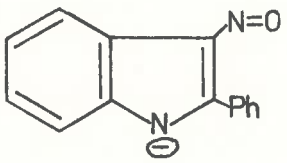
spectrum did not show absorption in the region characteristic of the azido group (4.70μ [104]).

Work on this project was terminated when Treibs[105] announced that he had prepared indolo[3,2-b]indole by dehydrogenating 5,10-dihydroindolo[3,2-b]indole (LXXXII) with chloramine.

3-Isonitroso-2-phenylindole (LXXXIX) is a potentially tautomeric compound and this property was investigated. Campbell and Hooper[106] have shown that it exists almost entirely in the oximino-form in ethanol. To determine whether the equilibrium between the oximino- and nitroso-forms was dependent on the dielectric constant of the solvent, the absorption spectrum in 1:1 ethanol-water was compared with that in ethanol (Fig. 4). The similarity of the two curves showed that the equilibrium was not appreciably affected by a change in the polarity of the solvent. The spectrum of 3-isonitroso-2-phenylindole in 0.1 N-alcoholic sodium hydroxide was found to be similar to that of 1-methyl-3-nitroso-2-phenylindole (XCIV) in ethanol (Fig. 4), and this suggested that the anion (XCV)



(XCIV)



(XCV)

must have a large proportion of the charge located at the 1-position.

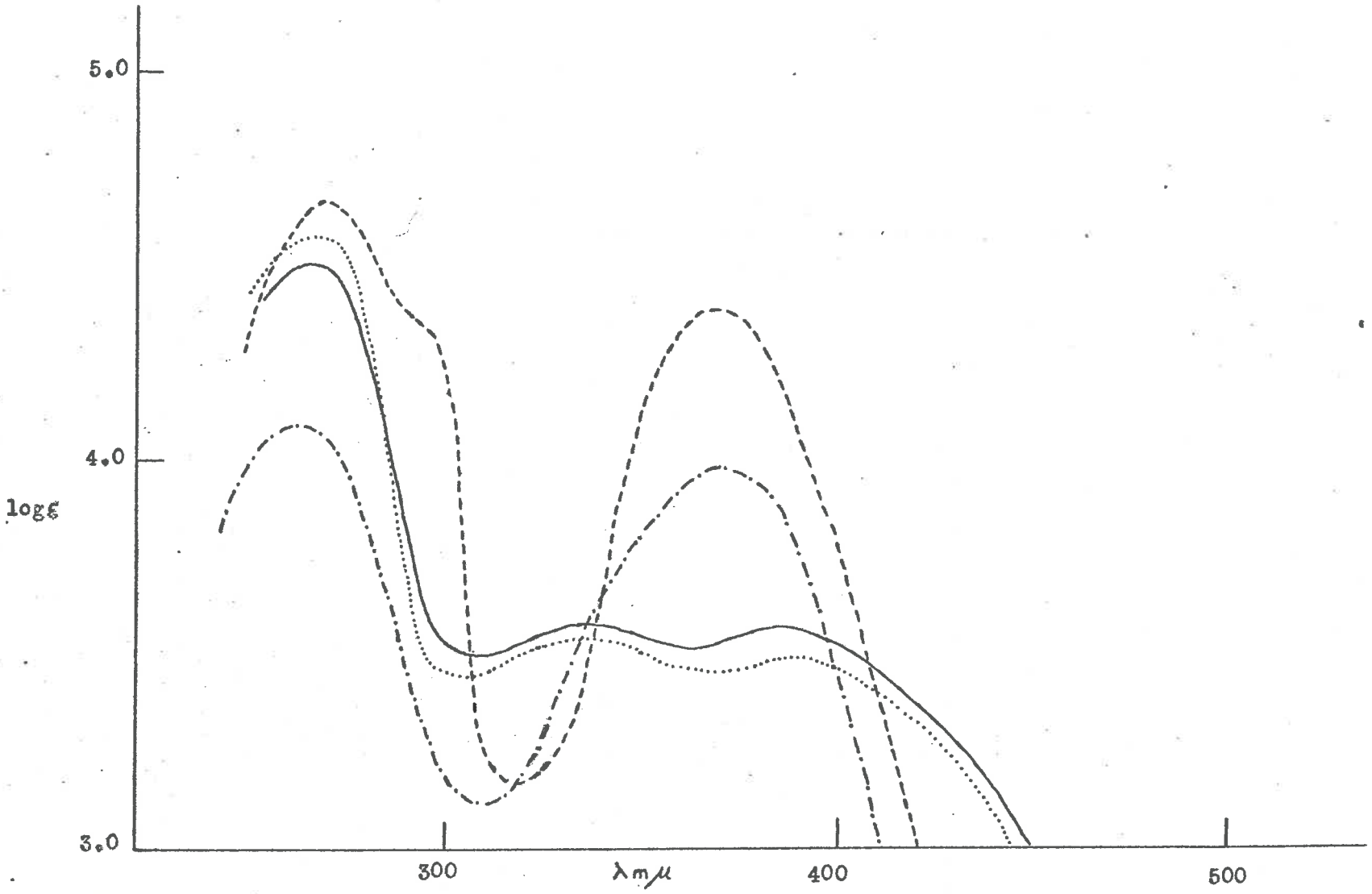
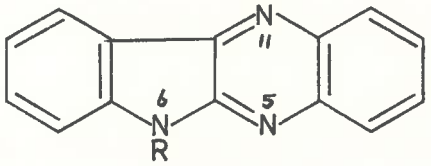


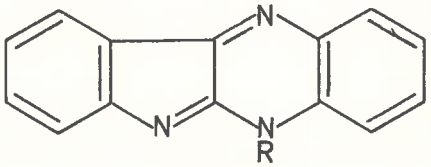
Fig. 4. Absorption spectra of 3-isonitroso-2-phenylindole (LXXXIX) in ethanol (••••••), in 1:1 ethanol-water (————), and in 0.1N-alcoholic sodium hydroxide, and of 1-methyl-3-nitroso-2-phenylindole (XCIV) (106) in ethanol (—•—•—•—)

C. INDOLO[2,3-b]QUINOXALINES.

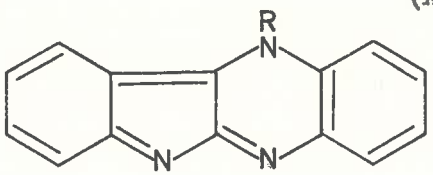
Indolo[2,3-b]quinoxaline has three possible tautomeric forms as the hydrogen atom may be attached to any one of the three nitrogen atoms. The first(XCVI; R=H) is generally regarded as being the most important, and the second (XCVII; R=H) contains the conjugated system, —N=C—C=N—, of interest. The third



(XCVI)



(XCVII)

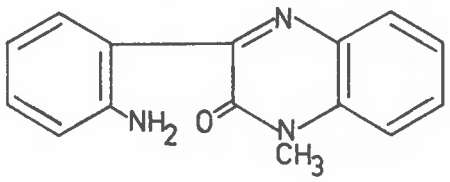


(XCVIII)

(XCVIII; R=H) must be unimportant owing to its smaller resonance stabilisation. A study of the tautomeric behaviour of indoloquinoxaline was commenced with the object of assessing the contribution of the structure (XCVII; R=H).

Indolo[2,3-b]quinoxaline was readily prepared from isatin and o-phenylenediamine.[107] 6-Methylindoloquinoxaline (XCVI; R=CH_3) was obtained from N-methylisatin and o-phenylenediamine.[108] 5-Methylindoloquinoxaline (XCVII; R=CH_3) was formed from the reaction of isatin and N-methyl-o-phenylenediamine.[108] The

synthesis of 5-methylindoloquinoxaline by this method is ambiguous as the isomer, 11-methylindoloquinoxaline (XCVIII; R=CH_3) is a possible product. The ring closure of 3-o-amino-phenyl-1,2-dihydro-1-methyl-2-oxoquinoxaline (XCIX) in polyphosphoric acid gave a compound which was identical in all respects with that



(XCIX)

obtained using the method of Buraczewski and Marchlewski.[108] 5-Ethylindoloquinoxaline (XCVII; R=C_2H_5) was prepared from isatin and N-ethyl-o-phenylenediamine.

The absorption spectrum of indoloquinoxaline in ethanol was found to be very similar to that of 6-methylindoloquinoxaline (XCVI; R=CH_3), whereas the spectrum of 5-methylindoloquinoxaline (XCVII; R=CH_3) was found to have a number of important differences, particularly at long wavelengths (Fig. 5). Even in solvents of greater dielectric constant (1:1 ethanol-water, or formamide), which might be expected to favour the structure (XCVII; R=H), the curves closely followed that for the 6-methyl derivative. On the basis of this evidence it may therefore be concluded that indolo[2,3-b]-quinoxaline exists predominantly in the 6H-form (XCVI; R=H).

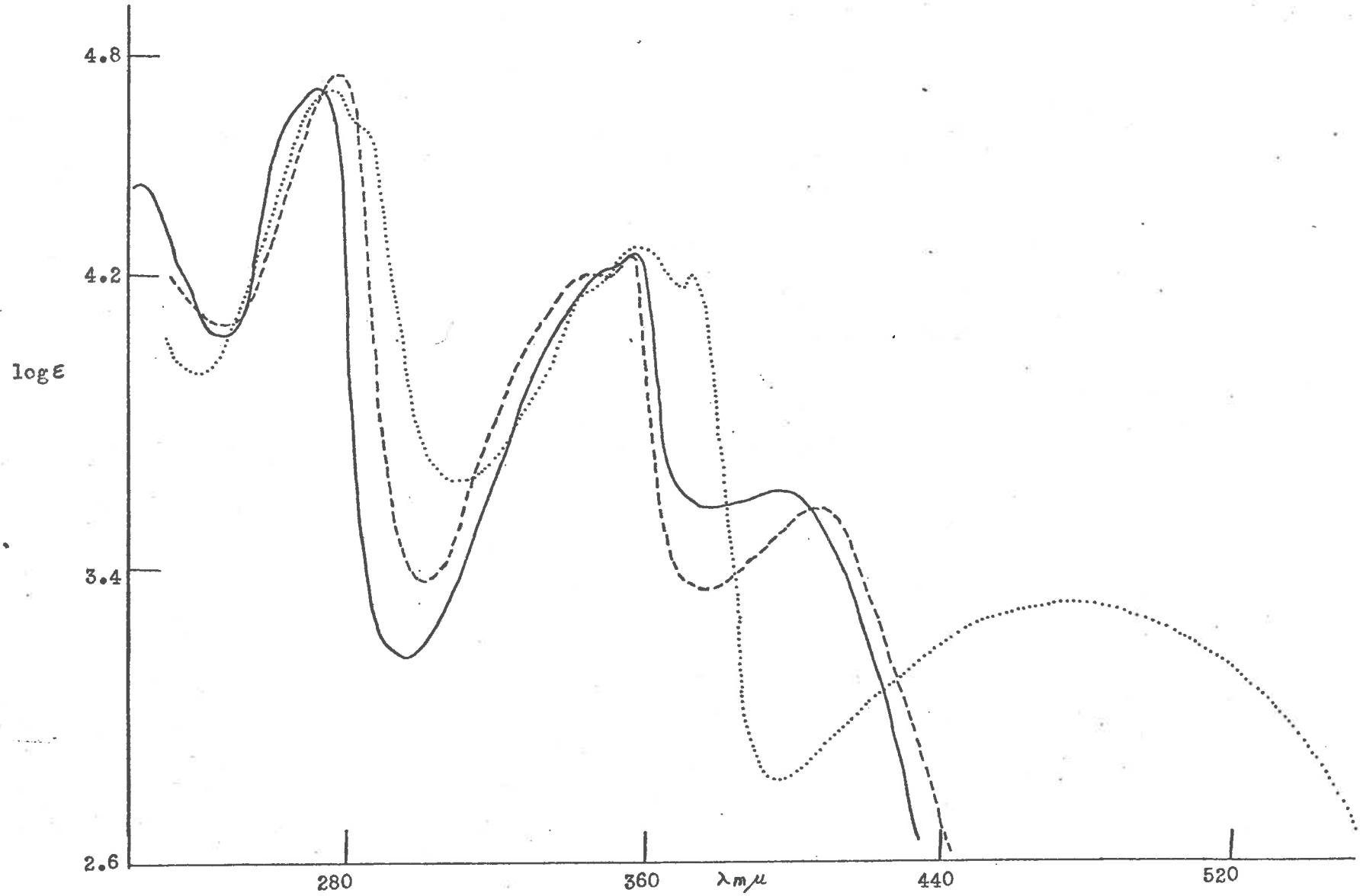


Fig. 5. Absorption spectra of indolo[2,3-b]quinoxaline (———), of 6-methylindoloquinoxaline, (– – – –) and of 5-methylindoloquinoxaline (••••••), all in 95% ethanol.

On the other hand, the absorption spectrum of indoloquinoxaline in sodium hydroxide solution was found to be very similar to that of its 5-methyl derivative (XCVII; $R=CH_3$), and the indoloquinoxaline anion must therefore have a large proportion of the charge located at the 5-nitrogen atom (Fig. 6).

The acid and base pK_a values for indoloquinoxaline were determined at 20° in 1:1 ethanol-water. The base pK_a value was found to be approximately 0.3 and the value for the acid pK_a was 13.6.

Buraczewski and Marchlewski[108] treated indoloquinoxaline with a mixture of methyl iodide and sodium hydroxide, and isolated only one product, 6-methylindoloquinoxaline (XCVI; $R=CH_3$). A special procedure for purification was employed and this suggested that other methylated products were present. As the anion derived from indoloquinoxaline has a significant proportion of the charge at the 5-position, it seemed likely that 5-methylindoloquinoxaline would also be formed in this reaction.

The methylation of indoloquinoxaline was studied using a variety of alkylating agents and 5-methylindoloquinoxaline was invariably among the products. Table I shows the yields of 5- and 6-methylindoloquinoxalines obtained when methyl iodide and alkali, dimethyl sulphate and alkali, and when diazomethane were used as methylating agents. 11-Methylindoloquinoxaline was not isolated from any of these reactions.

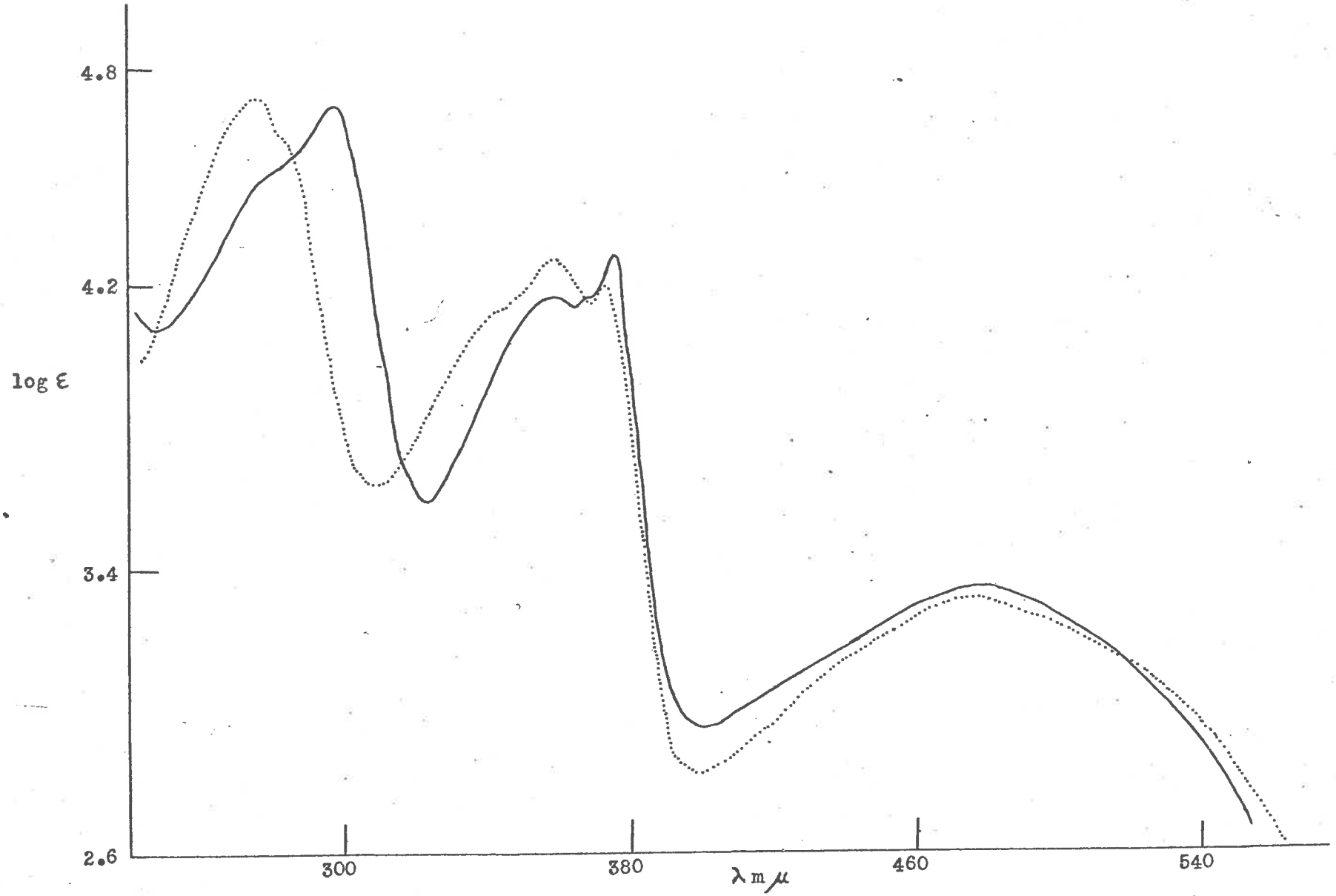


Fig. 6. Absorption spectra of indolo[2,3-b]quinoxaline in 2N-sodium hydroxide (———) and of 5-methylindoloquinoxaline in 95% ethanol (••••••).

TABLE I

Methylating Agent	% Yield of 6-isomer	% Yield of 5-isomer
Methyl iodide and alkali	40	12
Dimethyl sulphate and alkali	70	15
Diazomethane	19*	16

* Approximate yield.

An interesting by-product was obtained when a suspension of indoloquinoxaline in acetone was treated with diazomethane. This product could not be separated from 6-methylindoloquinoxaline and its structure was not elucidated. The unsuccessful attempts at purification included chromatography on alumina, acetylated cellulose, and silica gel.

The methylation and protonation of indoloquinoxaline and 5- and 6-methylindoloquinoxalines have also been examined. 6-Methyl-indoloquinoxaline was methylated with methyl toluene-p-sulphonate and the resulting salt treated with perchloric acid. The absorption spectrum of this dark red perchlorate showed a band in the visible region at 480 mμ (Fig. 7), and this suggested that it contained a conjugated system similar to that in 5-methylindoloquinoxaline (Fig. 5). Methylation at the 6- or the 11-position would give compounds (C and CI, respectively) which would have absorption

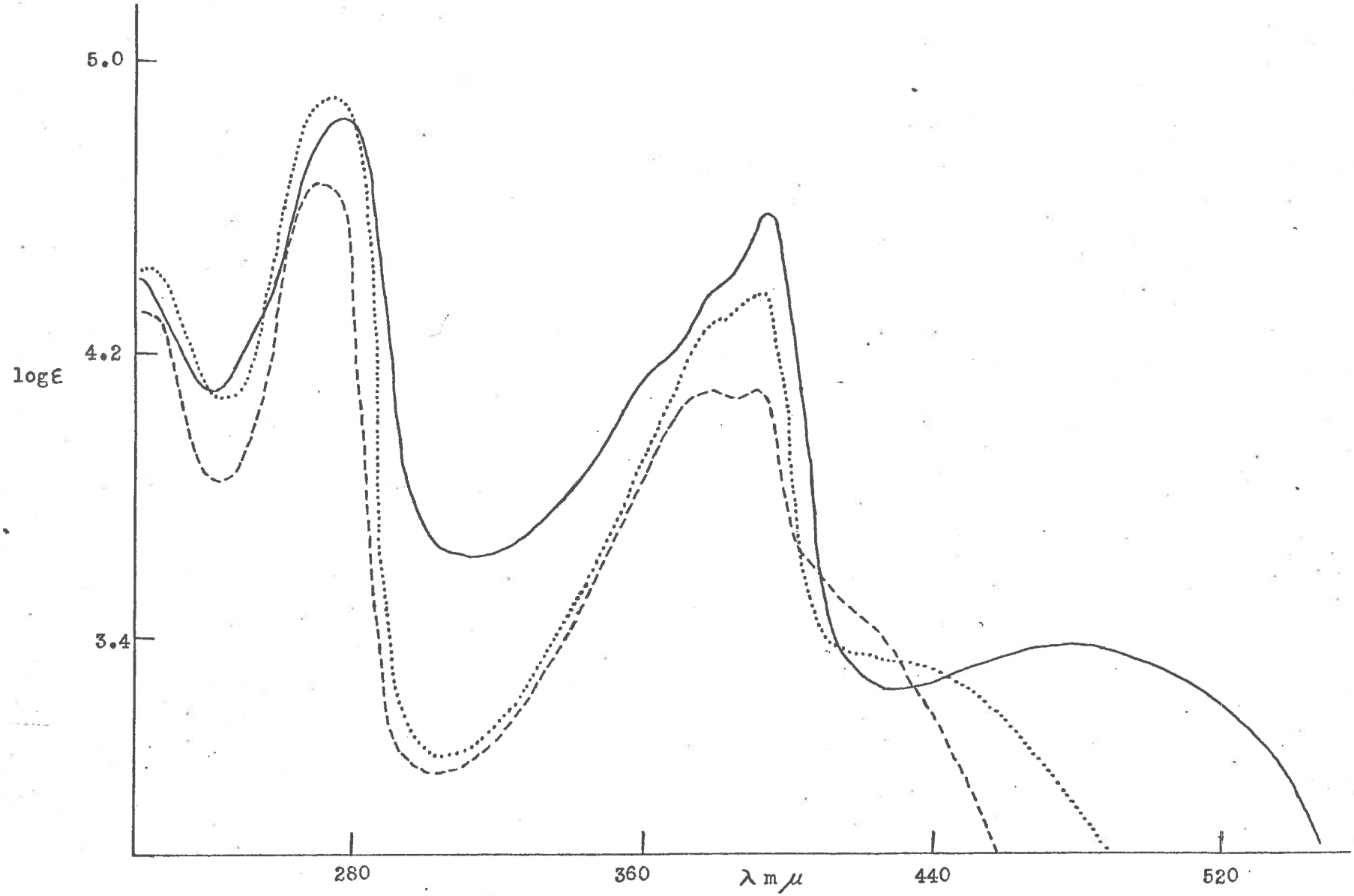
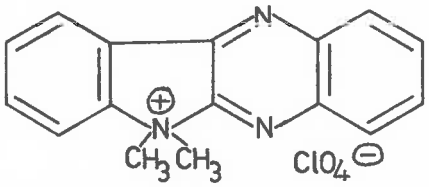
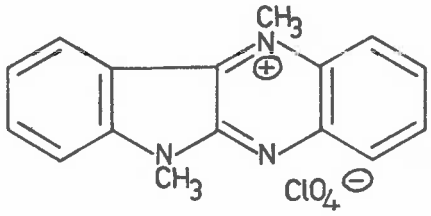


Fig. 7. Absorption spectra of 5,6-dimethylindolo[2,3-b]quinoxalinium perchlorate (CII; $R = R' = CH_3$) in 95% ethanol, of 6-methylindoloquinoxaline in 5N-sulphuric acid (cf. CII; $R = CH_3, R' = H$) (·····), and of indoloquinoxaline in 5N-sulphuric acid (— — —).

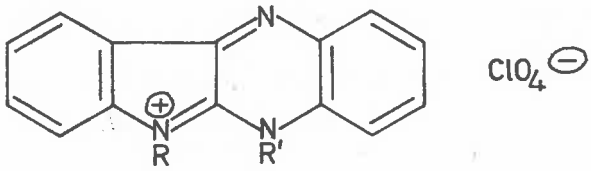


(C)



(CI)

spectra similar to that of quinoxaline. It seems certain therefore that the salt obtained from the methylation of 6-methylindoloquinoxaline is 5,6-dimethylindoloquinoxalinium perchlorate (CII; $R=R'=CH_3$). The absorption spectrum of this compound was similar

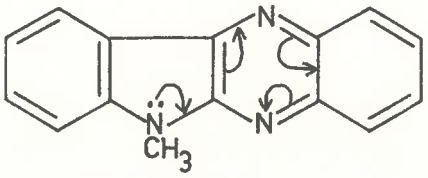


(CII)

to that of a solution of 6-methylindoloquinoxaline in 5N-sulphuric acid (Fig. 7). Thus protonation of 6-methylindoloquinoxaline must also have occurred at the 5-position and the cation formed in acid solution must have the structure as in (CII; $R=CH_3$, $R'=H$).

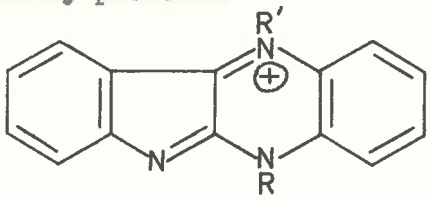
It is not surprising that protonation and methylation of 6-methylindoloquinoxaline occurs in the 5-position. It has recently been shown that indole protonates in the 3-position.[109,110] If this is extended to 6-methylindoloquinoxaline, protonation would

be expected to take place either at the 5- or the 11-nitrogen atoms. The electron density in the 5-position would be expected to be higher than that in the 11-position because an electron shift as shown in (CIII) is possible.



(CIII)

The absorption spectrum of indoloquinoxaline in 5N-sulphuric acid was found to be similar to that given by 6-methylindoloquinoxaline in 5N-sulphuric acid (Fig. 7), and it may therefore be concluded that this compound is also protonated at the 5-position. This salt is tautomeric, however, and both possible forms (CII and CIV; R=R'=H) are probably present.



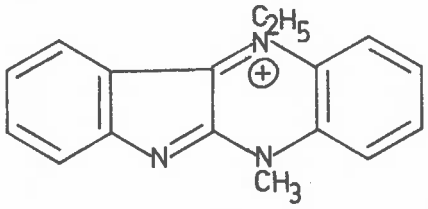
(CIV)

Methylation of indoloquinoxaline with methyl toluene-p-sulphonate gave 11H-5-methylindolo[2,3-b]quinoxalinium toluene-p-sulphonate (cf. CIV; R=CH_3; R'=H), the position of the methyl group being established by isolation of 5-methylindoloquinoxaline following treatment of the salt with water. The same salt was

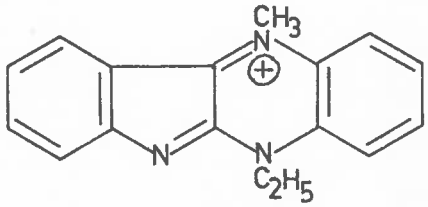
obtained from 5-methylindoloquinoxaline by treatment with toluene-p-sulphonic acid. The presence of the toluene-p-sulphonate ion in this salt was demonstrated by determination of its infrared spectrum. Weisenborn and Burn[111] have shown that in chloroform the toluene-p-sulphonate ion has four characteristic bands at 8.56, 8.96, 9.71 and 9.94 μ. The infrared spectrum of a solution of this salt in chloroform had absorption bands at 8.66, 8.93, 9.71 and 9.92 μ. Treatment of indoloquinoxaline with methyl iodide gave 11H-5-methylindoloquinoxalinium iodide (cf. CIV; $R=CH_3, R'=H$) which was identical with the salt obtained by treatment of 5-methylindoloquinoxaline with hydriodic acid.

The location of hydrogen atoms in the above toluene-p-sulphonate and iodide was inferred by comparison with the product obtained from the methylation of 5-methylindoloquinoxaline. The latter compound was methylated with methyl toluene-p-sulphonate and the anion replaced by perchlorate. The resulting salt was not identical with 5,6-dimethylindoloquinoxalinium perchlorate (CII; $R=R'=CH_3$) prepared as described above. Thus it must be either the 5,11-dimethyl derivative or the 5,5-dimethyl derivative. The nuclear magnetic resonance spectrum of this compound showed two absorption peaks for methyl protons (at 5.06 and 5.52 τ) in trifluoroacetic acid solution. On the basis of this evidence it must be concluded that it has the structure 5,11-dimethylindoloquinoxalinium perchlorate (CIV; $R=R'=CH_3$).

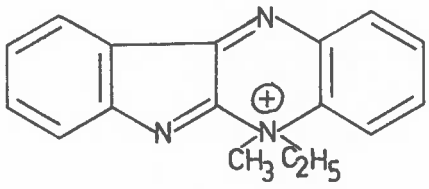
In an attempt to confirm this conclusion by chemical means, 5-methylindoloquinoxaline was treated with ethyl iodide, and 5-ethylindoloquinoxaline was treated with methyl iodide. If alkylation occurred at the 11-position, two isomeric compounds (CV and CVI, respectively) would be formed. On the other hand, alkylation at the 5-position would result in the formation of the same compound (CVII) in both cases. This method was found to be unsatisfactory as the product isolated from the reaction of ethyl iodide and 5-methylindoloquinoxaline was identified as 11H-5-methylindoloquinoxalinium iodide (cf. CIV; $R=CH_3, R'=H$). With 5-ethylindoloquinoxaline and methyl iodide, the product of the



(CV)



(CVI)



(CVII)

reaction was found to be a mixture of 11H-5-ethylindoloquinoxalinium iodide (cf. CIV; $R=C_2H_5, R'=H$) and an unidentified quaternary compound.

The above difficulties were overcome by the use of methyl and ethyl toluene-p-sulphonates as alkylating agents. Treatment of the resulting salts with perchloric acid gave the corresponding perchlorates which were shown to be non-identical. On the basis of this evidence it was concluded that alkylation had occurred at the 11-position.

The absorption spectrum of 5,11-dimethylindoloquinoxalinium perchlorate (Fig. 8) was similar to that of 5-methylindoloquinoxaline (Fig. 5) except that the maximum at 480 mμ has been reduced to a shoulder at somewhat shorter wavelengths. The absorption spectrum of 5-methylindoloquinoxaline in 5N-sulphuric acid (Fig. 8) was similar to that of the above salt and is strong evidence that protonation occurs at the 11-position to give the 11H-5-methylindoloquinoxalinium cation (CIV; $R=CH_3, R'=H$).

In 1925, Armit and Robinson[112] investigated the reaction of 2,3-dimethoxyindoloquinoxaline and dimethyl sulphate. They postulated that methylation occurred at the 11-position to give the 2,3-dimethoxy-11-methylindoloquinoxalinium salt (CVIII). Treatment of this quaternary salt with potassium hydroxide in aqueous ethanol gave a compound which was regarded as the anhydronium base (CIX). This

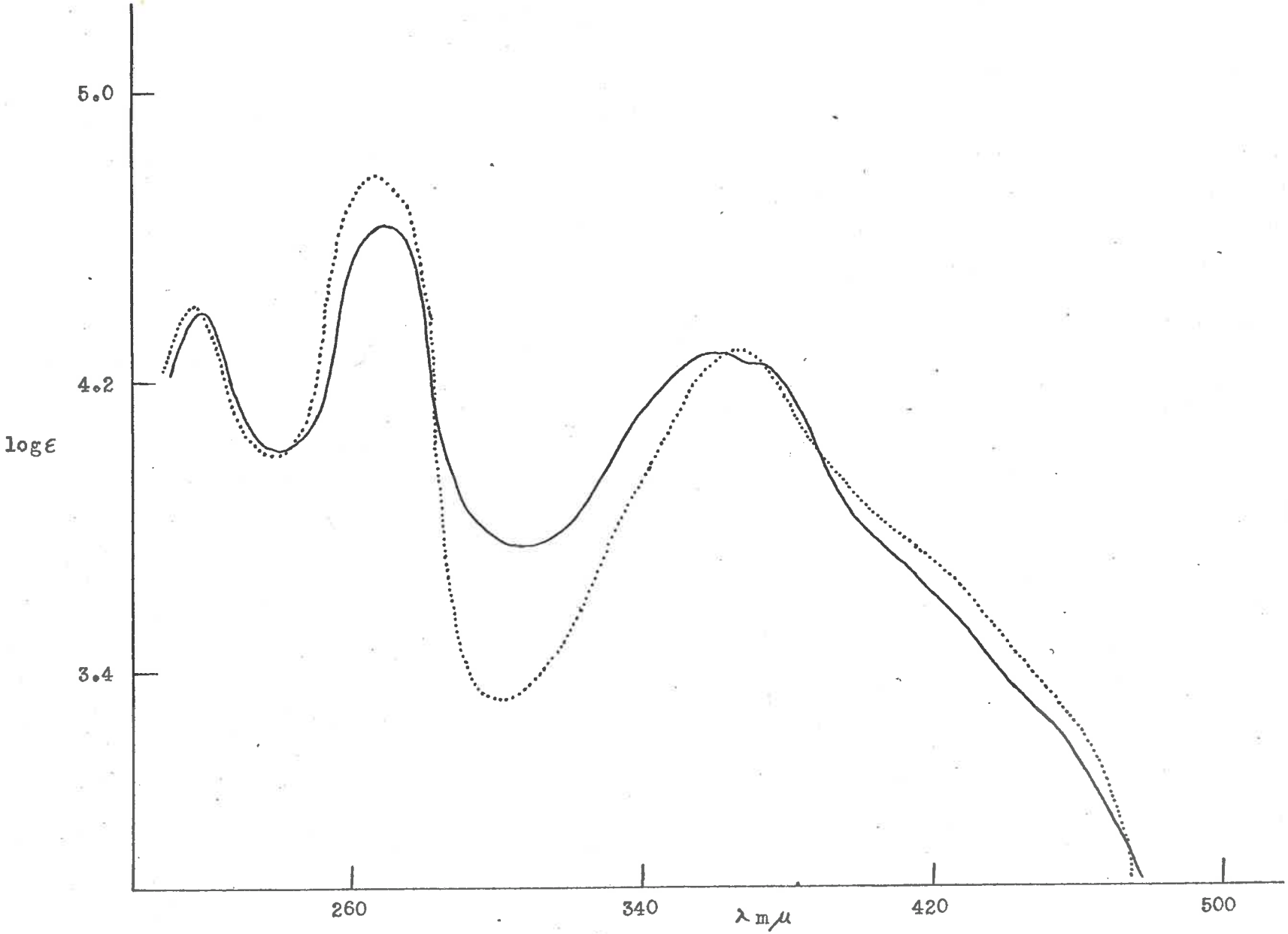
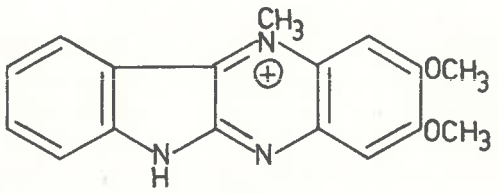
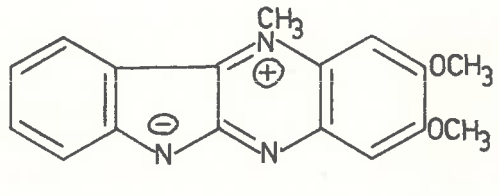


Fig. 8. Absorption spectra of 5,11-dimethylindoloquinoxalinium perchlorate (CIV; $R = R' = CH_3$) in 95% ethanol (_____), and of 5-methylindoloquinoxaline in 5N-sulphuric acid(•••••••) (cf. CIV; $R = CH_3, R' = H$).

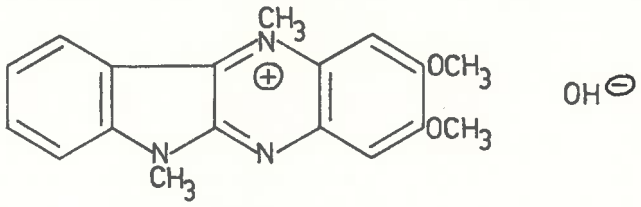


(CVIII)



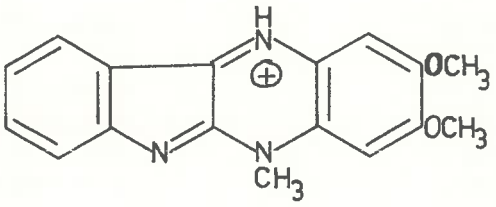
(CIX)

product was isolated as scarlet needles, and it was observed that addition of acid to a dilute aqueous solution resulted in a colour change from orange to yellow. Methylation of the supposed anhydronium base with dimethyl sulphate and subsequent treatment with aqueous potassium hydroxide gave a salt which was considered to be (CX).

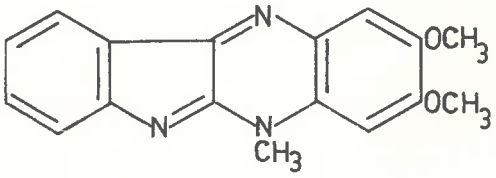


(CX)

The structures assigned to the compounds obtained from these reactions were supported only by analytical data. In view of the work carried out on indoloquinoxaline, the structures proposed by Armit and Robinson may now be revised. The assumption has to be made that the two methoxyl groups do not affect the positions of methylation. Quaternisation of 2,3-dimethoxyindoloquinoxaline with dimethyl sulphate would be expected to give the salt (CXI) which would be readily converted to 2,3-dimethoxy-5-methylindoloquinoxaline (CXII) on treatment with aqueous potassium hydroxide. The properties

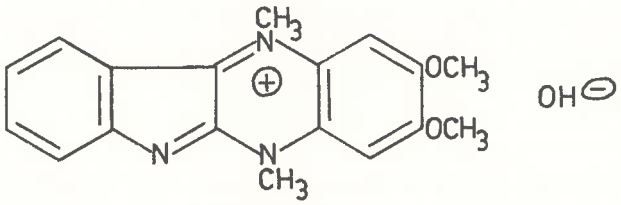


(CXI)



(CXII)

of this compound are, in fact, very similar to those of 5-methylindoloquinoxaline. Methylation of this base with dimethyl sulphate followed by treatment with alkali would give 2,3-dimethoxy-5,11-dimethylindoloquinoxalinium hydroxide (CXIII) which was obtained as orange-yellow needles. It is significant that 5,11-dimethyl-

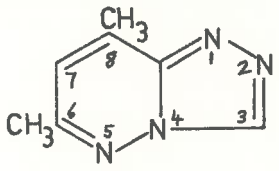


(CXIII)

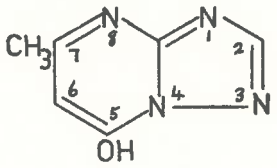
indoloquinoxalinium perchlorate (CIV; $R=R^1=CH_3$) was also obtained as orange-yellow needles.

D. *s*-TRIAZOLOPYRAZINES

The methods described in the literature for the synthesis of *s*-triazolopyrimidines and *s*-triazolopyridazines may be divided into two classes. Firstly, there are those methods that utilize amino-1,2,4-triazoles in a condensation with compounds having two reactive β-positions. An example of this reaction is that between 4-amino-1,2,4-triazole and acetylacetone to give 6,8-dimethyl-*s*-triazolo[4,3-*b*]pyridazine (CXIV).[113] Similarly, 5-hydroxy-7-methyl-*s*-triazolo[2,3-*a*]pyrimidine (CXV) is formed from the condensation of 3-amino-1,2,4-triazole and ethyl acetoacetate.[114-116] The second



(CXIV)

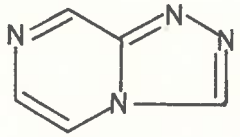


(CXV)

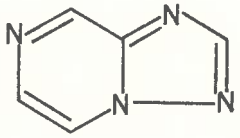
class represents the ring closure of hydrazinopyrimidines and hydrazinopyridazines with various cyclization agents. The nature of the reagent used determines the substituent introduced into the 3-position of the fused triazole system. Treatment of the hydrazine with formic acid,[117] triethyl orthoformate,[115] or dimethylformamide,[115] effects ring closure with a hydrogen atom in the 3-position. The 3-methyl derivatives have been prepared by the use of acetic anhydride [118] or triethyl orthoacetate.[119] Acyl derivatives of 4-hydrazinopyrimidine have been prepared by treatment of the hydrazine with

either the acid, acid chloride or ester, and subsequently cyclized to the fused s-triazolopyrimidines by the action of phosphorus oxychloride.[120]

With s-triazolo[4,3-a]pyrazine (XLVIII) and s-triazolo-[2,3-a]pyrazine (XLIX), it is impracticable to begin with the

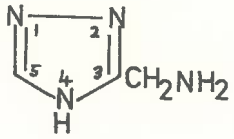


(XLVIII)



(XLIX)

1,2,4-triazole nucleus and build up the pyrazine ring. This would involve the cyclization of a compound such as 3-aminomethyl-1,2,4-triazole (CXVI) to the 4- and 2-positions, respectively, by a reagent which would form a two carbon atom bridge.



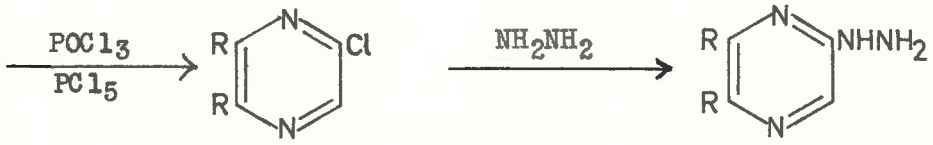
(CXVI)

The most convenient route to the s-triazolo[4,3-a]pyrazine ring system (XLVIII) would seem to be the cyclization of the corresponding 2-hydrazinopyrazines. The latter compounds have not been reported in the literature, and a convenient method of synthesis was established at the outset of this work. 2-Chloropyrazine is readily converted to 2-aminopyrazine by treatment with ammonia,[121,122] and would be expected

to undergo an analogous reaction with hydrazine. The required hydrazinopyrazines were prepared in good yield from the reaction of the corresponding 2-chloropyrazines with anhydrous hydrazine. They were characterised as their picrates, which very strongly held half a mole of benzene of recrystallization.

The 2-chloropyrazines were obtained by the method of Karmas and Spoerri.[123] The condensation of aminoacetamide with glyoxal, diacetyl, and benzil, afforded the 2-hydroxypyrazines (CXVII; R=H, CH_3 and Ph, respectively). With 2-hydroxypyrazine (CXVII; R=H) and

(CXVII)

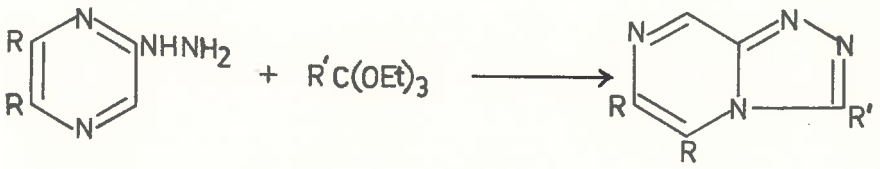


(CXVIII) (CXIX)

2,3-dimethyl-6-hydroxypyrazine (CXVII; R=CH_3), the original procedure was modified slightly to give a method which was less time consuming and more economical. Chlorination of the 2-hydroxypyrazines with phosphorus pentachloride and phosphorus oxychloride gave the 2-chloropyrazines (CXVIII), which were used to prepare the 2-hydrazinopyrazines (CXIX). A satisfactory yield of 6-chloro-2,3-diphenylpyrazine (CXVIII; R=Ph) was obtained only by using a longer

reaction time and a 1:2 molar mixture of phosphorus pentachloride and phosphorus oxychloride.

The most successful method of effecting the ring closure of the 2-hydrazinopyrazines was their reaction with orthoesters. The use of triethyl orthoformate, triethyl orthoacetate, and triethyl orthopropionate gave _s_-triazolo[4,3-_a_]pyrazines (CXX) with a hydrogen atom, a methyl group, and an ethyl group, respectively, in the 3-position. The derivatives prepared by this method are



(CXX)

shown in Table II. All the _s_-triazolo[4,3-_a_]pyrazines were characterised as their picrates (Table III).

As triethyl orthoformate was the only orthoester available commercially, the remainder were synthesized by the method of McElvain and Nelson.[124] Iminoester hydrochlorides, prepared from aliphatic nitriles, were treated with ethanol to yield the corresponding orthoesters.

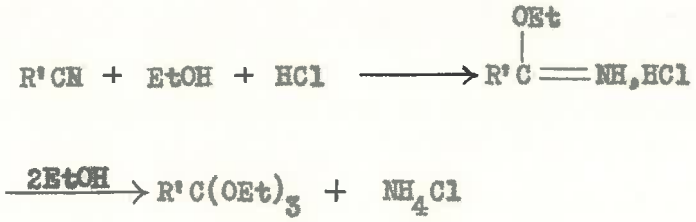
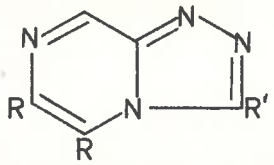


TABLE II



3,5,6-Trisubstituted s-Triazolo[4,3-a]pyrazines

Compound No.	R	R'	M.Pt. °C	Yield %	Solvent	Formulae	Analyses Found C	Found H	Found N	Calculated C	Calculated H	Calculated N
1.	H	H	194-5	75	a	$C_5H_4N_4.0.5H_2O$	46.6	4.1	43.0	46.5	3.9	43.4
2.	CH_3	H	190	55	d	$C_7H_8N_4$	56.6	5.3	37.4	56.7	5.4	37.8
3.	C_6H_5	H	187-8	72	d	$C_{17}H_{12}N_4$	74.8	4.5	20.7	75.0	4.4	20.6
4.	H	CH_3	239	78	a	$C_6H_6N_4$	53.7	4.4	41.7	53.7	4.5	41.8
5.	CH_3	CH_3	126-7	55	c	$C_8H_{10}N_4.H_2O$	53.6	6.7	31.2	53.3	6.7	31.1
6.	C_6H_5	CH_3	200-1	43	d	$C_{18}H_{14}N_4$	75.4	5.0	19.3	75.5	4.9	19.6
7.	H	C_2H_5	158	70	b	$C_7H_8N_4$	57.1	5.4	37.5	56.7	5.4	37.8
8.	CH_3	C_2H_5	93-4	52	d	$C_9H_{12}N_4$	61.1	6.9	31.8	61.3	6.9	31.8
9.	C_6H_5	C_2H_5	234-5	50	d	$C_{19}H_{16}N_4$	75.7	5.5	18.6	76.0	5.4	18.7

All crystallized as white needles except (2) which separated as rectangular plates.

a = methanol; b = benzene; c = petrol; d = benzene/petrol.

TABLE III

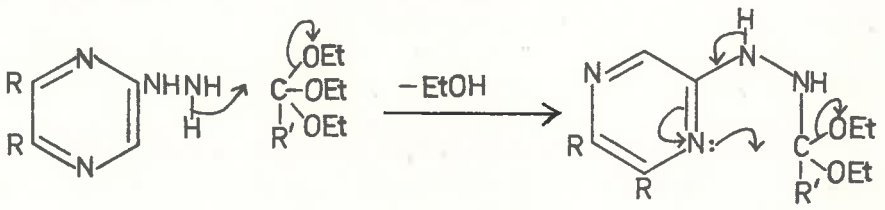
Picrate Derivatives of 3,5,6-Trisubstituted s-Triazolo[4,3-a]pyrazines

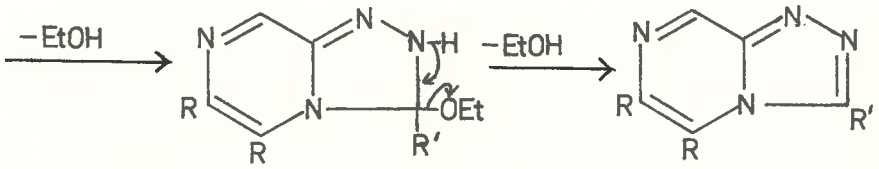
Compound No.	M.Pt. °C	Solvent	Formulae	Analyses Found C	Found H	Found N	Calculated C	Calculated H	Calculated N
1.	177 (decomp.)	a	$C_{11}H_7N_7O_7$	38.1	2.3	28.0	37.8	2.2	28.0
2.	136-7	b	$C_{13}H_{11}N_7O_7$	41.7	3.1	25.7	41.4	2.9	26.0
3.	145-6	c	$C_{23}H_{15}N_7O_7$	55.6	3.1	19.4	55.2	2.8	19.6
4.	156-7	b	$C_{12}H_9N_7O_7$	39.9	2.8	26.7	39.7	2.5	27.0
5.	134-5	c	$C_{14}H_{13}N_7O_7 \cdot 0.5C_6H_6$	47.2	3.8	23.3	47.4	3.8	22.8
6.	158-9	c	$C_{24}H_{17}N_7O_7 \cdot 0.5C_6H_6$	58.7	3.9	17.3	58.5	3.6	17.7
7.	100-1	c	$C_{13}H_{11}N_7O_7$	41.9	3.2	26.0	41.4	2.9	26.0
8.	127-8	c	$C_{15}H_{15}N_7O_7$	44.7	4.1	23.8	44.4	3.7	24.2
9.	132-3	c	$C_{25}H_{19}N_7O_7 \cdot 0.5C_6H_6$	59.6	3.9	16.9	59.2	3.9	17.3

All crystallized as yellow needles except (2) and (3) which formed orange rhombs and orange rosettes, respectively.

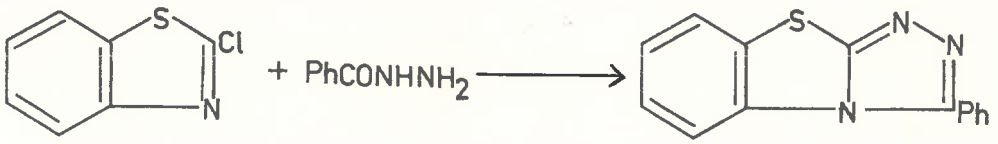
a = chloroform; b = benzene; c = benzene/petrol.

A possible mechanism for the ring closure with orthoesters is shown below. A similar scheme has been postulated for the ring closure of 2-hydrazinopyrimidines.[115]





Although s-triazolo[4,3-a]pyrazines were readily available by the orthoester ring closure, other methods of synthesis were investigated. Fused s-triazole systems have been prepared by the reaction of benzhydrazide and a heterocyclic system containing a reactive chlorine atom. An example of this procedure is the formation of 3-phenyl-s-triazolo[3,4-b]benzothiazole (CXXII) from 2-chlorobenzothiazole (CXXI) and benzhydrazide.[125] 2-Chloropyrazines react readily with hydrazine to form 2-hydrazinopyrazines and it seemed reasonable to expect them to undergo a similar reaction with benzhydrazide. Subsequent ring closure would yield the fused

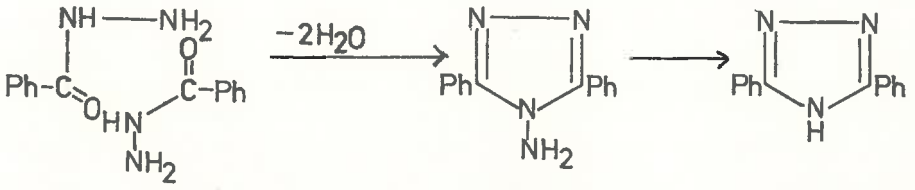


(CXXI) (CXXII)

s-triazole containing a phenyl group in the 3-position. Application of this method to 2-chloropyrazines did not give the expected s-triazolopyrazines, but instead self-condensation products of benzhydrazide. 3,5-Diphenyl-1,2,4-triazole (CXXIV) was the major product isolated from the reaction of benzhydrazide and 6-chloro-2,3-diphenylpyrazine in boiling phenol containing a trace of sodium phenoxide. A small quantity of a second product, probably 2,3-diphenyl-6-phenoxypyrazine, was obtained. This could arise from the chloropyrazine and the small amount of sodium phenoxide added as a catalyst. 2,5-Diphenyl-1,3,4-oxadiazole (CXXVI) was obtained from the reaction of 2,3-dimethyl-6-chloropyrazine under the same conditions. A similar reaction between 2-chloropyrazine and benzhydrazide yielded dibenzoylhydrazine (CXXV). Benzhydrazide is a weaker nucleophile than hydrazine, and its ability to replace the chlorine atom at a faster rate than it undergoes self-condensation, may be attributed to this fact. There are a number of examples in the literature of the self-condensation of benzhydrazide at elevated temperatures.[126,127] It has been reported that s-triazolo[4,3-a]-

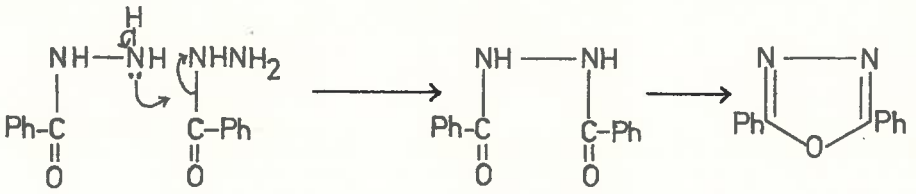
quinoxalines are formed in very low yields by the above procedure.[47]

A possible mechanism for the formation of 3,5-diphenyl-1,2,4-triazole (CXXIV) would be the condensation of two moles of benzhydrazide to give 4-amino-3,5-diphenyl-1,2,4-triazole (CXXIII),



(CXXIII) (CXXIV)

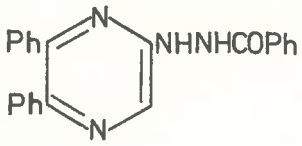
followed by deamination. The amino group could be eliminated as hydroxylamine after the attack of a water molecule. The formation of 3,5-diphenyl-1,2,4-triazole from benzhydrazide has been previously reported in the literature.[128] 2,5-Diphenyl-1,3,4-oxadiazole (CXXVI) can be regarded as being formed by an alternative condensation of two moles of benzhydrazide. A molecule of the hydrazide could attack another, eliminating hydrazine to form dibenzoylhydrazine (CXXV). Elimination of water from dibenzoyl-



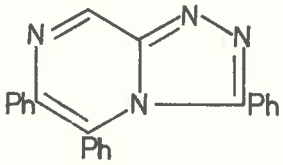
(CXXV) (CXXVI)

hydrazine would give 2,5-diphenyl-1,3,4-oxadiazole (CXXVI). It has been reported that this compound is formed by pyrolysis of benzhydrazide.[129]

The ring closure of 2-hydrazinopyrazines with acidic reagents was found to have limited application. Complete decomposition occurred when 2-hydrazinopyrazine was heated in boiling formic acid. 2,3-Diphenyl-6-hydrazinopyrazine formed the corresponding 5,6-diphenyl-s-triazolo[4,3-a]pyrazine (compound 3) in only 10% yield using this reagent, and the accompanying red and yellow compounds made purification difficult. Dimethylformamide was also unsatisfactory as this triazole was again formed in very low yield. Attempted cyclization with an acetic acid-acetic anhydride mixture did not give the 3-methyl derivative (compound 6), but gave a complex acetylated product the structure of which is discussed later. The ring closure of N-benzoyl-2,3-diphenyl-6-hydrazinopyrazine (CXXVII)



(CXXVII)

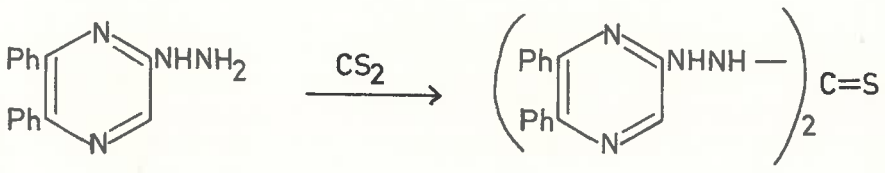


(CXXVIII)

was also investigated. Cyclization was not effected by heating in phenol, and the use of phosphorus oxychloride gave a very small yield of the product. However, the desired 3,5,6-triphenyl-s-triazolo[4,3-a]pyrazine (CXXVIII) was formed in good yield when

the benzoyl derivative was heated in polyphosphoric acid at 150° for 3 hr.

Treatment of 2-hydrazinopyrimidines with carbon disulphide gives the corresponding s-triazolopyrimidines with a mercapto group in the 3-position.[117,130] However, 2-hydrazinopyrazines were not cyclized under these conditions, but gave a product derived from the condensation of two moles of the hydrazine with one of carbon disulphide. The reaction of 2,3-diphenyl-6-hydrazinopyrazine with carbon disulphide gave 1,3-di(2,3-diphenyl-6-pyrazinylamino)thiourea (CXXIX). The formation of this product is analogous to the formation of substituted thioureas (CXXX) from aromatic amines and carbon disulphide.[131]



(CXXIX)

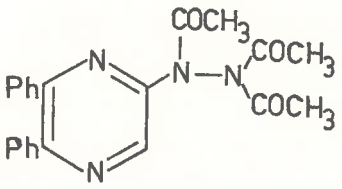
$$2ArNH_2 + CS_2 \longrightarrow ArNHC(=S)NHAr$$

(CXXX)

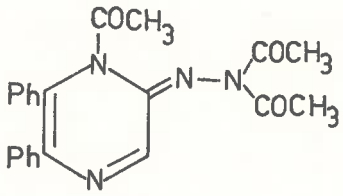
Phenyl isothiocyanate was also used in an attempt to prepare these s-triazolopyrazines with a mercapto group in the 3-position.

In a reaction with 2,3-diphenyl-6-hydrazinopyrazine, the only product isolated was 5,6-diphenyl-*s*-triazolo[4,3-*a*]pyrazine (compound 3). This compound was obtained in very low yield and was probably formed by removal of the mercapto group from 5,6-diphenyl-3-mercapto-*s*-triazolo[4,3-*a*]pyrazine (CXX; R=Ph, R'=SH) under the conditions of the reaction. In the *s*-triazole series , a mercapto group is easily removed by oxidising agents and Raney nickel.[115,117,130]

The product obtained by treatment of 2,3-diphenyl-6-hydrazinopyrazine with boiling acetic acid-acetic anhydride was found to be a triacetyl derivative of the hydrazine. Two structures (CXXXI and CXXXII) are possible for this compound, but the latter was excluded on the basis of spectral data shown in



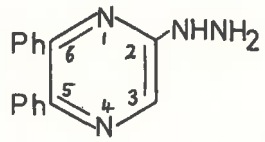
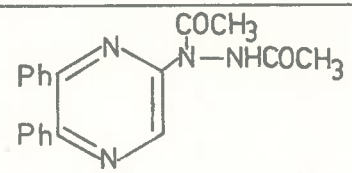
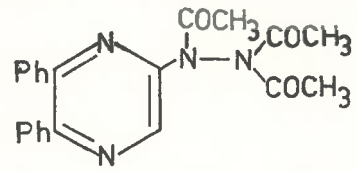
(CXXXI)



(CXXXII)

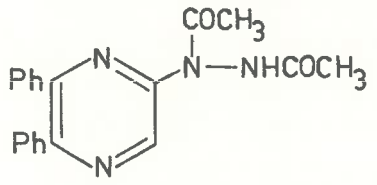
Table IV. This triacetyl derivative was readily converted into the diacetyl compound, which was also obtained from the hydrazine and acetyl chloride in pyridine. Treatment of the hydrazine with the theoretical amount of acetyl chloride for monoacetylation always

TABLE IV

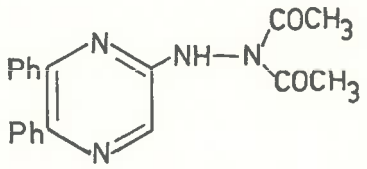
	Absorption Maxima (in ethanol)		Infrared Data[a] ν cm^{-1}				N.M.R. Data[b] τ Values for protons		
	λ	Log ε	NH	Bonded NH	ØO	Amide II	CH_3	Phenyl	C_3
	228	4.11	3390	3279	---	---		2.78(10)[c]	1.87(1)[c]
	293	4.20							
	350	3.85							
	229.5	4.40	3333	3252	1709	1471	7.72(3)[c]	2.72(10)[c]	0.78(1)[c]
	285	4.12					7.92(3)[c]		
	326	4.15							
	228	4.38			1733[d]		7.55(6)[c]	2.76(10)[c]	0.78(1)[c]
	283	4.08			1712(sh)		7.71(3)[c]		
	324	4.08							

[a] Determined in chloroform solution. [b] Determination in acetonitrile solution. [c] No. of protons.

[d] Broad absorption band.



(CXXXIII)



(CXXXIV)

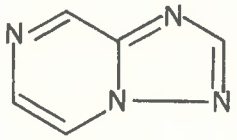
gave the diacetyl product. The structure (CXXXIII) was assigned to this compound as its nuclear magnetic resonance spectrum showed two bands for methyl protons (Table IV). The alternative structure (CXXXIV) would be expected to show only one absorption peak for methyl protons. The formation of 1,2-diacetyl-1-phenylhydrazine from 2-acetyl-1-phenylhydrazine and acetic anhydride[132,133] was taken as further support for the above assignment. It has been reported that 2-hydrazinoquinoxaline did not cyclize to the corresponding _s_-triazolo[4,3-_a_]quinoxaline with acetic anhydride, but formed a diacetyl derivative.[47] On the basis of the above evidence this product is probably 1,2-diacetyl-1-(2-quinoxalinyl)-hydrazine.

Many of the methods applied to the synthesis of _s_-triazolo-[4,3-_a_]pyrazine derivatives are standard methods for the preparation of _s_-triazolopyrimidines and _s_-triazolopyridazines. The interesting question arises why the majority of these procedures were unsuccessful

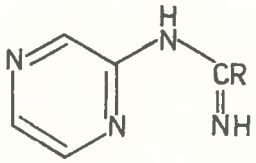
in the pyrazine series. The ring closure with acids, and also with orthoesters, can be regarded as occurring through the attack of an intermediate carbonium ion on the nitrogen atom of the pyrazine ring. The ease of cyclization should thus be related to the basic strength. As pyrazine has a pK_a of 0.6 compared to pyrimidine 1.3, and pyridazine 2.3,[18] it is not surprising that 2-hydrazinopyrazines are more difficult to cyclize than the corresponding pyrimidine or pyridazine derivatives. Protonation of one of the nitrogen atoms in the pyrazine ring would lower the availability of the lone pair of electrons on the second nitrogen atom, and thus retard cyclization. With pyrazine, the interaction between the two nitrogen atoms is greater than in the other diazines and this probably explains why ring closure with acids occurs more readily with pyrimidine and pyridazine derivatives. Cyclization with orthoesters takes place under neutral conditions and the unprotonated pyrazine nucleus is sufficiently basic for this reaction to take place. The failure of carbon disulphide to effect ring closure may also be attributed to the low basicity of the pyrazine nucleus. However, *s*-triazolo[4,3-*a*]quinoxaline derivatives have been prepared in good yields by the action of acids on the appropriate 2-hydrazino compounds.[47] As the pK_a of quinoxaline is also about 0.6,[18] it is difficult to reconcile this ease of cyclization with the basicity of the nucleus. The carbon-nitrogen double bonds of quinoxaline are particularly susceptible to attack

by nucleophilic agents such as sodium bisulphite, hydrogen cyanide, and Grignard reagents.[17] This behaviour can be attributed to the electronic influences of the benzene ring as pyrazine does not undergo these addition reactions. The presence of the benzene ring also enables the second nitrogen to act as though it is not deprived of electrons in the above acidic cyclodehydrations, so that cyclization occurs with ease.

The most convenient method of preparing derivatives of the _s_-triazolo[2,3-_a_]pyrazine ring system (XLIX) would be by ring closure

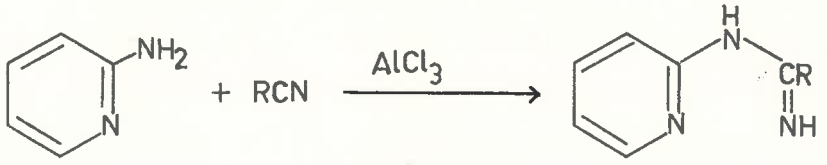


(XLIX)



(CXXXV)

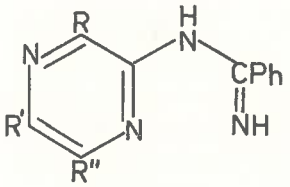
of the corresponding _N_-2-pyrazinylamidines (CXXXV). These compounds have not been reported in the literature, and the methods available for their synthesis were investigated. _N_-2-Pyridylamidines (CXXXVI) are formed by reaction of 2-aminopyridines with nitriles in the



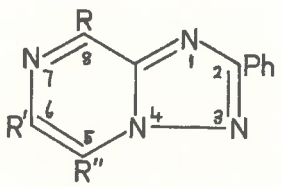
(CXXXVI)

presence of aluminium chloride.[134] It was thought that 2-aminopyrazines should behave in a similar manner and it was proposed to synthesise the required amidines in this way. The 2-aminopyrazines were prepared by ammonolysis of the corresponding 2-chloropyrazines.[122] 2-Chloro-3,6-dimethylpyrazine was available commercially and thus 2-amino-3,6-dimethylpyrazine could be prepared in large quantities.

The substituted 2-aminopyrazines were treated with nitriles in the presence of aluminium chloride. The use of benzonitrile gave N-2-pyrazinylphenylamidines (CXXXVII) which were cyclized to the 2-phenyl-s-triazolo[2,3-a]pyrazines (CXXXVIII) with lead tetraacetate. This reagent has been used to effect the oxidative ring



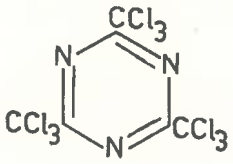
(CXXXVII)



(CXXXVIII)

closure of pyridine[134,135] and pyrimidine[130] derivatives. Three derivatives of the required ring system were prepared by this method, 5,8-dimethyl-2-phenyl-s-triazolo[2,3-a]pyrazine (CXXXVIII; $R = R'' = CH_3$, $R' = H$), 5,6-dimethyl-2-phenyl-s-triazolo[2,3-a]pyrazine (CXXXVIII; $R = H$, $R' = R'' = CH_3$), and 2,5,6-triphenyl-s-triazolo[2,3-a]pyrazine (CXXXVIII; $R = H$; $R' = R'' = Ph$).

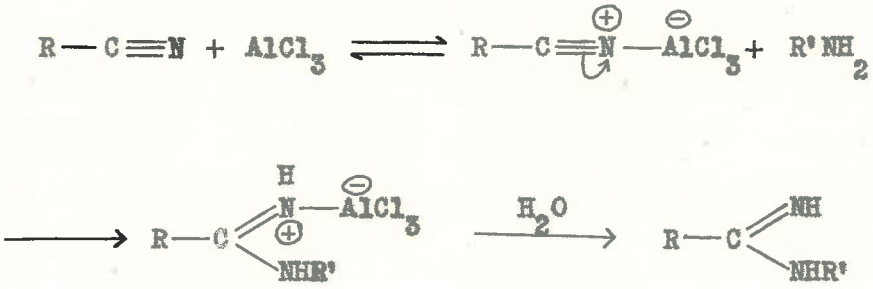
A study of the absorption spectrum of the s-triazolo-[2,3-a]pyrazine ring system was planned, and for this purpose it was desirable to prepare alkyl derivatives. However, the use of acetonitrile and propionitrile did not yield the corresponding amidines. High reaction temperatures resulted in complete decomposition of the amine; at lower temperatures the amine was recovered unchanged. With trichloroacetonitrile, the only product isolated was 2,4,6-tris(trichloromethyl)-1,3,5-triazine (CXXXIX).



(CXXXIX)

It has been reported that this compound is readily formed from trichloroacetonitrile and aluminium chloride.[136] The tendency for polymerisation may be attributed to the strong electron-attracting properties of the trichloromethyl group. Chloroacetonitrile was used in an attempt to reduce the formation of polymeric material, but the desired amidine was not obtained. The use of acrylonitrile and phenylacetonitrile in this reaction was also unsuccessful.

The mechanism proposed by Oxley, Partridge and Short[137] for the formation of amidines by this method is shown below.



On this basis it is clear that when R is an electron-attracting substituent the reaction would be expected to proceed more readily than when it is electron-donating. The basic strength of the amine would also determine the ease of the reaction. The failure of 2-amino-3,6-dimethylpyrazine to react with aliphatic nitriles may therefore be attributed to its low basicity, and it may be noted that 2-aminopyridine (pK_a 6.86[18]) and aniline (pK_a 4.58) react with acetonitrile to give N-2-pyridylacetamidine[134] and N-phenylacetamidine,[137] respectively. The reaction of trichloroacetonitrile and ethylenediamine takes place with great ease, and a catalyst such as aluminium chloride is not necessary.[138] As many of the aliphatic nitriles used in this work form amidines with more basic amines, it seems that derivatives of 2-aminopyrazine (pK_a 3.14[18]) are not sufficiently basic to take part in analogous addition reactions.

Amidine formation with benzonitrile is difficult to explain in view of the lack of success with aliphatic nitriles. It cannot be attributed to the weak -I effect of the phenyl group as aliphatic nitriles containing more strongly electron-attracting substituents

were unreactive. It would appear that conjugation with the benzene ring makes the cyano group more susceptible to addition reactions of this type. The greater tendency for aromatic nitriles to undergo addition reactions of this nature has been reported in the literature. The synthesis of 3,5-disubstituted-1,2,4-triazoles from nitriles and acid hydrazide benzenesulphonates was found to be limited to aromatic nitriles.[126] The use of aliphatic nitriles gave products formed by self-condensation of the acid hydrazide benzenesulphonates.

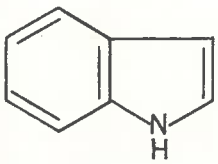
A well known method for the synthesis of amidines is by treatment of iminoester hydrochlorides with amines.[139-141] This procedure was

not successful when applied to the synthesis of N-2-pyrazinylamidines. 2-Amino-3,6-dimethylpyrazine was heated with ethyl acetimidate hydrochloride[124] under a variety of conditions, but the amine was always recovered unchanged. The failure of this method is undoubtedly due to the inability of the weakly basic amine to displace the ethoxy group.

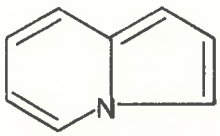
Several compounds prepared in this investigation were subjected to tests for anticancer activity. 2,3-Diphenyl-6-hydrazinopyrazine (CXIX; R = Ph), s-triazolo[4,3-a]pyrazine (CXX; R = R' = H) and 5,6-diphenyl-s-triazolo[4,3-a]pyrazine (CXX; R = Ph, R' = H) were tested against sarcoma 180, leukemia, Solid Friend Virus leukemia, and in cell culture. All three compounds were found to be non-toxic and inactive.

E. ABSORPTION SPECTRA OF s-TRIAZOLOPYRAZINES

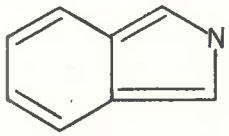
The replacement of a -CH=CH- group in naphthalene with a tertiary nitrogen atom gives either indole (LIX), pyrrocoline (CXL) or isoindole (CXLI), depending on the position of introduction of



(LIX)



(CXL)

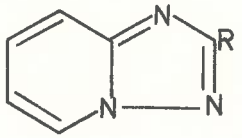


(CXLI)

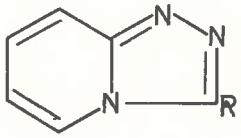
the hetero-atom. All three compounds contain the same number of π-electrons as naphthalene, and their absorption spectra would be expected to resemble that of the hydrocarbon. The similarity of the spectra of indole and naphthalene (Fig. 2) has already been discussed. The spectrum of pyrrocoline is also similar and has three main regions of absorption with maxima at 238, 280 and 347 mμ.[142] These bands are at longer wavelengths than those of naphthalene and the group III band is considerably more intense.

Bower[142] studied the spectra of nitrogen heterocycles derived from pyrrocoline and concluded that there was a relationship between the spectra and the number and positions of the nitrogen atoms. Replacement of the -CH= group in the 2-position by nitrogen results in a slight hypsochromic shift of the three bands, whereas introduction

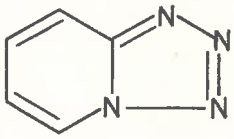
of a nitrogen atom into the 1- or 3-position has a much greater effect, especially on the group III band. In the spectrum of s-triazolo[2,3-a]pyridine (CXLII; R=H) this band occurs at much shorter wavelengths than that in s-triazolo[4,3-a]pyridine (CXLIII; R=H). The above effect is cumulative with the introduction of



(CXLII)



(CXLIII)



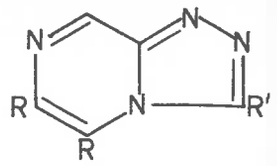
(CXLIV)

further nitrogen atoms and results in the merging of the group II and III bands in the spectrum of tetrazolopyridine (CXLIV).

The absorption spectra of derivatives of the s-triazolo-[4,3-a]pyrazine and s-triazolo[2,3-a]pyrazine ring systems were examined and evidence was obtained to support the structures assigned to these compounds. Table V lists the spectral data of compounds containing the s-triazolo[4,3-a]pyrazine ring system. The majority of these measurements were made in cyclohexane solution, but a number were done in ethanol because of the low solubility of some derivatives in non-polar solvents.

TABLE V

Absorption spectra of s-triazolo[4,3-a]pyrazine derivatives.



R	R'	Solvent[a]	Absorption maxima (mμ) and log ε values (in parentheses)									
H	H	E	206 (4.46)		253(sh) (3.31)	262(sh) (3.37)	269(sh) (3.40)		292 (3.57)			
H	CH_3	C[b]	214 (4.11)	231(sh) (3.08)		257 (3.14)	270(sh) (3.05)	298 (3.10)	308 (3.09)	322 (2.98)	338 (2.64)	
		E	211.5 (4.38)		255(sh) (3.24)	262 (3.27)	270 (3.26)		299.5 (3.48)			
H	C_2H_5	C	212 (4.47)	219(sh) (4.41)		260 (3.41)	268(sh) (3.35)	290(sh) (3.39)	299 (3.42)	308 (3.42)	322 (3.30)	339 (2.94)
CH_3	H	C	213 (4.50)	218(sh) (4.42)	231(sh) (3.36)	261(sh) (3.45)	278(sh) (3.51)	292(sh) (3.59)	299 (3.61)	307.5(sh) (3.57)	321(sh) (3.28)	
CH_3	CH_3	C	217 (4.49)	223(sh) (4.39)	263(sh) (3.35)	269(sh) (3.38)	280 (3.39)	302(sh) (3.53)	309 (3.56)	319(sh) (3.50)	333(sh) (3.23)	
CH_3	C_2H_5	C	217.5 (4.53)	224 (4.46)	260(sh) (3.37)	272(sh) (3.41)	280.5 (3.43)	304(sh) (3.56)	310 (3.58)	318(sh) (3.53)	333(sh) (3.22)	
Ph	H	C	205 (4.56)	229(sh) (3.58)		253 (4.33)			321 (3.71)			

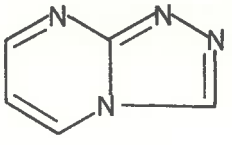
TABLE V - continued

Ph	CH_3	C	205 (4.59)			251 (4.39)	315.5 (3.63)	325(sh) (3.61)	336(sh) (3.37)
Ph	C_2H_5	C	205		250.5 (4.33)		316 (3.59)	324(sh) (3.58)	340.5(sh) (3.37)
Ph	Ph	E	207.5 (4.83)	223(sh) (4.35)	254 (4.31)		318(sh) (3.71)		

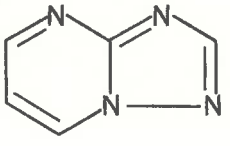
[a] E = 95% ethanol; C = cyclohexane

[b] This compound was not sufficiently soluble in cyclohexane for accurate determination of log ε values.

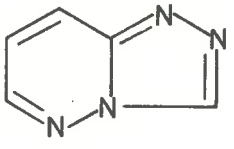
The parent compound exhibited three main absorption bands in its spectrum (Fig. 9) and these probably correspond to the group I, II and III bands in the spectrum of naphthalene. The group II absorption appears as a series of shoulders on the long wavelength band. Examination of the spectra of a number of fused s-triazole systems (Table VI) confirmed the assignment of the s-triazolo[4,3-a]pyrazine structure to this compound. Its spectrum was found to be very similar to that of 3-methyl-s-triazolo[4,3-a]-pyridine (CXLIII; $R=CH_3$) and s-triazolo[4,3-a]pyrimidine (CXLV) (Fig. 9), whereas the spectra of 2-methyl-s-triazolo[2,3-a]pyridine (CXLII; $R=CH_3$) and s-triazolo[2,3-a]pyrimidine (CXLVI) showed important differences. The s-triazolo[4,3-b]pyridazine ring system



(CXLV)



(CXLVI)



(CXLVII)

(CXLVII) has absorption maxima at 240 and 307 mμ.[143] From the spectra of the above compounds it can be seen that replacement of a -CH= group in the pyridine ring of s-triazolo[4,3-a]pyridine

TABLE VI

Absorption spectra of fused s-triazole systems

	Solvent[a]	Absorption maxima (mμ) and log ε values (in parentheses)							
3-methyl-s-triazolo[4,3-a]-pyridine (CXLII; R = CH_3)	E	209 (4.38)	244(sh) (3.14)	249(sh) (3.26)	252(sh) (3.30)	258 (3.39)	262 (3.41)	268 (3.47)	288 (3.47)
2-methyl-s-triazolo[2,3-a]-pyridine (CXLI; R = CH_3)[142]	C	217.5 (4.58)					273 (3.57)	281(i) (3.52)	294(i) (3.20)
s-triazolo[4,3-a]pyrimidine (CXLIV)	E	209 (4.04)	213(sh) (3.98)				250 (3.20)	266(sh) (3.08)	298 (3.31)
s-triazolo[2,3-a]pyrimidine (CXLV)	E	208 (4.50)							273 (3.56)
s-triazolo[4,3-b]pyridazine[143] (CXLVI)	b			240 (4.22)					305 (3.81)
3-phenyl-s-triazolo[4,3-a]-pyridine (CXLII; R = Ph)[142]	C		221 (4.23)	243 (4.16)				287.5 (3.97)	
2-phenyl-s-triazolo[2,3-a]-pyridine (CXLI; R = Ph)[142]	C		244.5 (4.56)	252.5 (4.56)			281(i) (3.88)	292.5(i) (3.73)	306 (3.58)

[a] E = 95% ethanol; C = cyclohexane.

[b] Solvent not given.

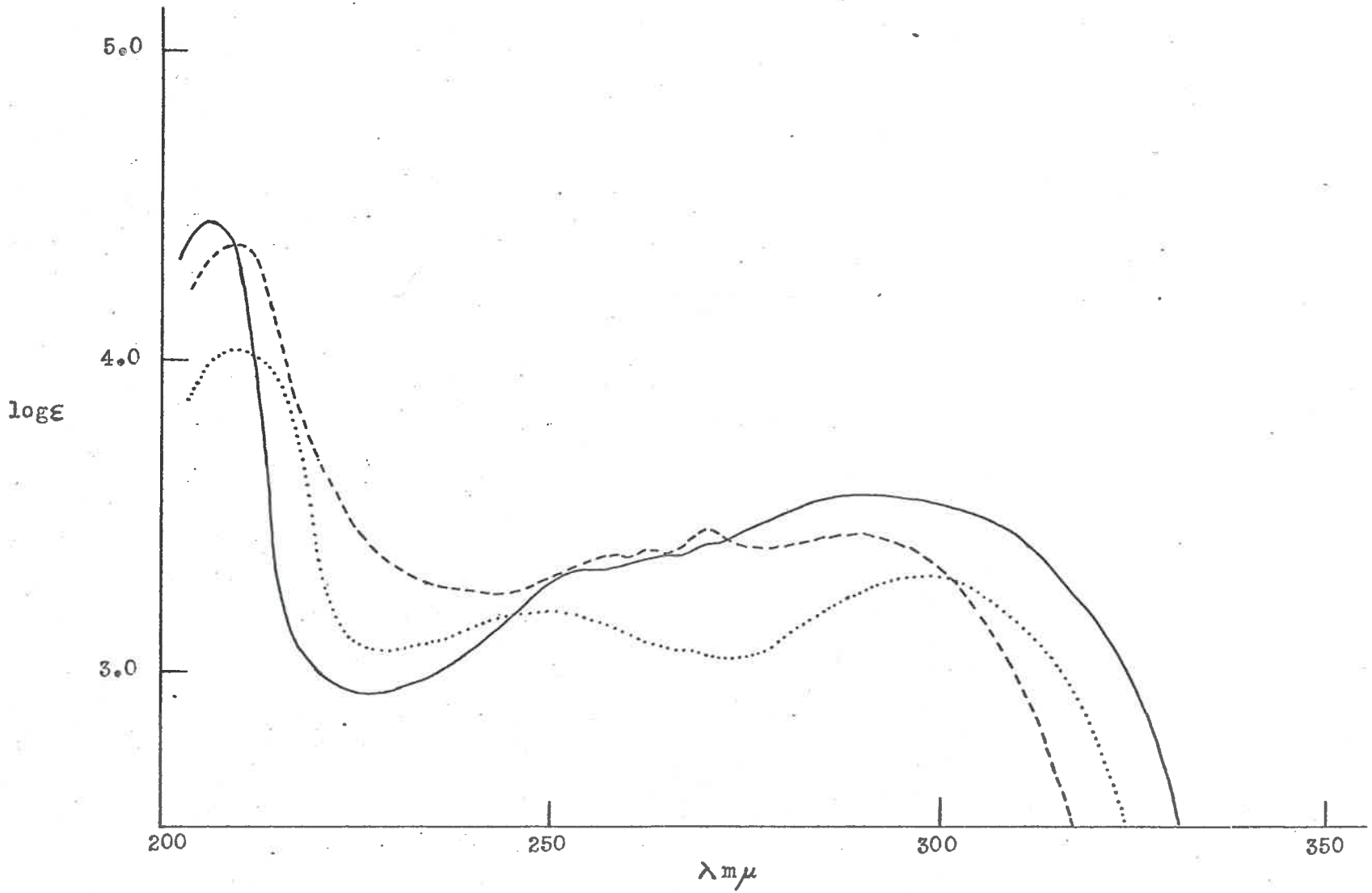


Fig. 9. Absorption spectra of s-triazolo[4,3-a]pyrazine (———), of s-triazolo[4,3-a]-pyrimidine (••••••), and of 3-methyl-s-triazolo[4,3-a]pyridine (— — — —), all in 95% ethanol.

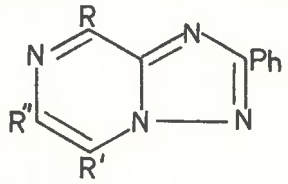
with a nitrogen atom results in a shift of the group III band to longer wavelengths. In addition to this, the group II band moves to slightly shorter wavelengths. Both these effects are most noticeable when the two nitrogen atoms are in adjacent positions, as in s-triazolo[4,3-b]pyridazine.

The s-triazolo[4,3-a]pyrazine nucleus contains three nitrogen atoms which possess lone pairs of electrons and thus a band due to a $n \rightarrow \pi^*$ transition should be observed when the spectrum is determined in non-polar solvents. Some evidence was obtained for an absorption band of this nature when the spectrum of 3-methyl-s-triazolo[4,3-a]-pyrazine was determined in cyclohexane and in ethanol (Fig. 10). In cyclohexane the long wavelength band extended to slightly longer wavelengths than in ethanol and this could be due to the presence of an $n \rightarrow \pi^*$ absorption band of low intensity. In ethanol the transition associated with this band would require greater energy because of hydrogen bonding of the lone pair of electrons with the solvent and thus the absorption peak would occur at shorter wavelengths and probably be hidden under the group III band.

The absorption spectra of derivatives of 2-phenyl-s-triazolo-[2,3-a]pyrazine were determined and the data is shown in Table VII. The spectrum of 5,6-dimethyl-2-phenyl-s-triazolo[2,3-a]pyrazine was compared with that of 2-phenyl-s-triazolo[2,3-a]pyridine (CXLII; R=Ph) (Fig. 11) and the close similarity of the curves was taken as further support for the structure of the s-triazolo[2,3-a]pyrazine derivative.

TABLE VII

Absorption spectra of s-triazolo[2,3-a]pyrazine derivatives.



R	R'	R''	Absorption maxima (mμ) and log ε values (in parentheses)						
H	CH_3	CH_3	205	249	258	281(sh)	294	301(sh)	315
				(4.65)	(4.62)	(3.91)	(3.82)	(3.78)	(3.55)
CH_3	CH_3	H	205	247	255(sh)	278(sh)	286(sh)	303(sh)	
				(4.61)	(4.59)	(4.01)	(3.91)	(3.54)	
H	Ph	Ph	204	220(sh)			268.5	292	
			(4.66)	(4.31)			(4.69)	(4.16)	

All spectra were determined in cyclohexane solution.

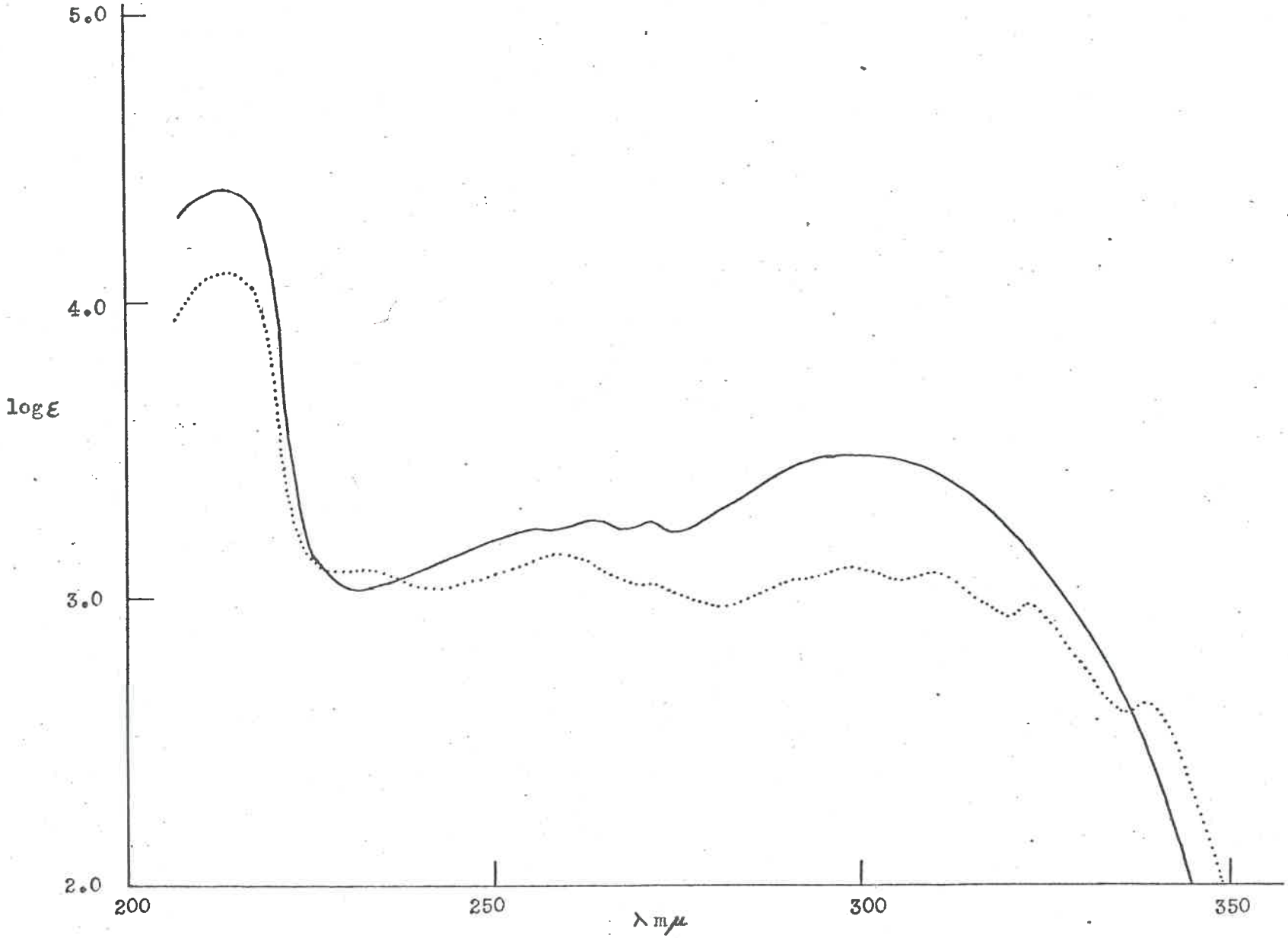


Fig. 10. Absorption spectra of 3-methyl-s-triazolo[4,3-a]pyrazine in ethanol (———) and in cyclohexane (••••••).

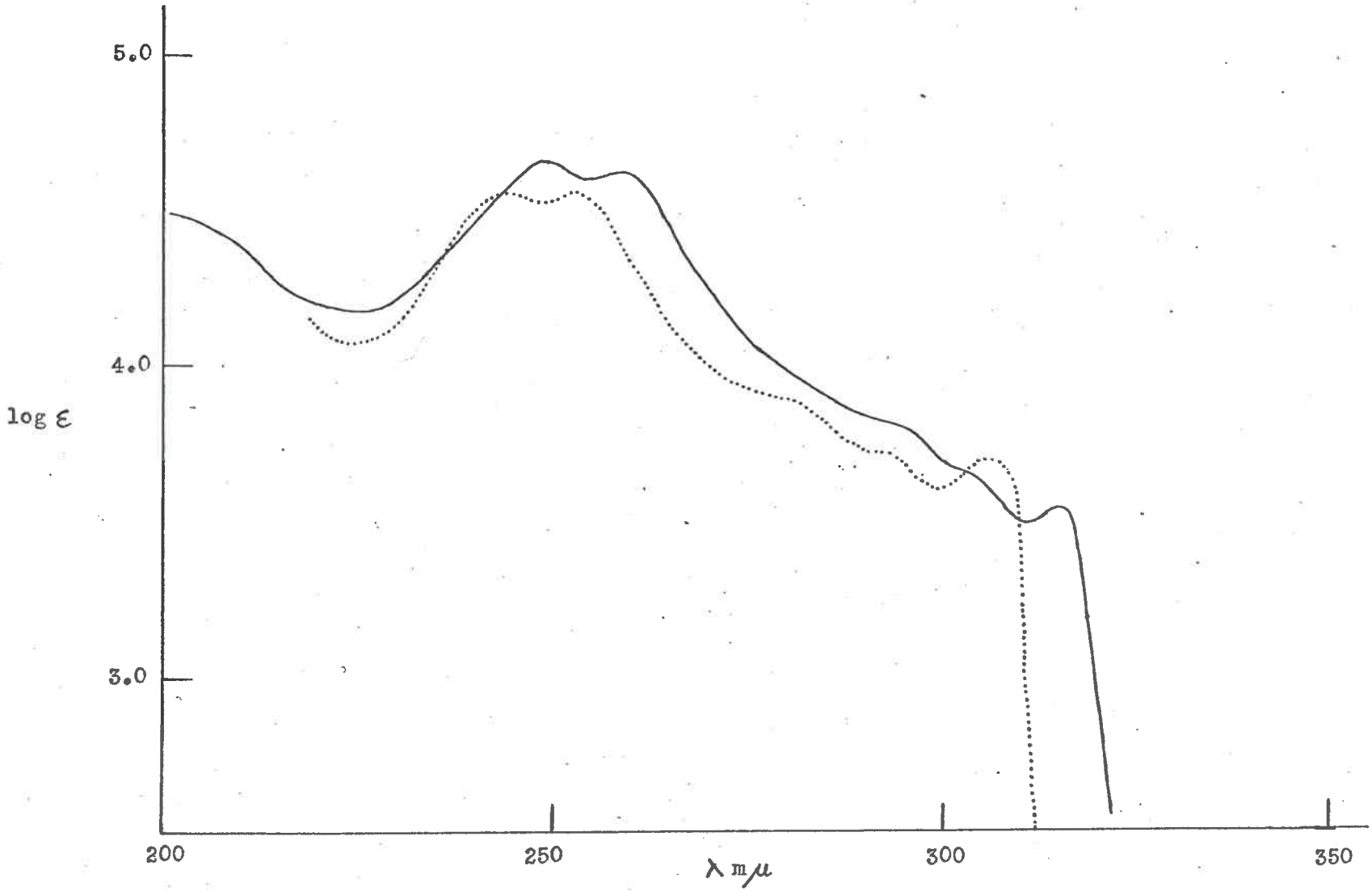


Fig. 11. Absorption spectra of 5,6-dimethyl-2-phenyl-s-triazolo[2,3-a]pyrazine (———) and of 2-phenyl-s-triazolo[2,3-a]pyridine (•••••), (142) in cyclohexane.

EXPERIMENTAL

Melting points were determined in capillaries and are uncorrected. Light petroleum refers to the fraction, b.p. 60-80°. Unless stated otherwise, absorption spectra were measured with an Optica CF-4 recording spectrophotometer. Infrared spectra were examined with a Perkin-Elmer Infracord spectrophotometer, Model 137, or with a Grubb-Parsons DB1 spectrophotometer. Analyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

A. DIHYDROQUINOXALINO[2,3-b]QUINOXALINES.

2,3-Dihydroxyquinoxaline.- This was prepared from o-phenylenediamine and diethyl oxalate by the method of Newbold and Spring.[144]

2,3-Dichloroquinoxaline.- 2,3-Dihydroxyquinoxaline was treated with phosphorus pentachloride under the conditions used by Hinsberg and Pollak.[80]

1,2,3,4-Tetrahydro-1,4-dimethyl-2,3-dioxoquinoxaline.- This compound was prepared from N,N'-dimethyl-o-phenylenediamine and diethyl oxalate.[145]

1,2-Dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline.- N-methyl-o-phenylenediamine was treated with diethyl oxalate according to Cheeseman.[145]

3-Chloro-1,2-dihydro-1-methyl-2-oxoquinoxaline.- Chlorination of 1,2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline was carried out using phosphorus oxychloride.[145]

Polyphosphoric Acid.- The polyphosphoric acid used in this work was equivalent to 80% phosphorus pentoxide in water.

5,12-Dihydroquinoxalino[2,3-b]quinoxaline.- A mixture of o-phenylenediamine (1.1 g., 0.01 mole), 2,3-dihydroxyquinoxaline (1.6 g., 0.01 mole), and polyphosphoric acid (25 g.) was heated at 250° for 2 hr. The cooled reaction mixture was treated with excess water and then made alkaline with 10% sodium hydroxide solution. The precipitated solid was collected, sublimed at 280°/0.1 mm., and recrystallized from glacial acetic acid. 5,12-Dihydroquinoxalino-[2,3-b]quinoxaline (1.8 g., 77%) separated as golden yellow needles, m.p. 487° (vacuo) (lit.,[80] > 360°).

Quinoxalino[2,3-b]quinoxaline.- The following method was found to be superior to that using dichromate.[80] Lead tetra-acetate (1.2 g., 0.0027 mole) was added to a suspension of 5,12-dihydro-quinoxalino[2,3-b]quinoxaline (0.5 g., 0.0022 mole) in glacial acetic acid (50 ml.) and the mixture warmed for 5 min. and then poured into water. The precipitated solid was collected and recrystallized from ethanol. Quinoxalino[2,3-b]quinoxaline (0.32 g., 65%) formed red needles, m.p. > 520° (vacuo) (lit.,[80] > 360°).

A solution of quinoxalino[2,3-b]quinoxaline (2 mg.) in ethanol (100 ml.), in a stoppered flask, was allowed to stand in sunlight. After ½ hr. the colour of the solution had changed from orange-red to yellow with an intense green fluorescence. Its absorption spectrum was identical with that of an ethanolic solution of 5,12-dihydroquinoxalino[2,3-b]quinoxaline.

5,12-Dimethylquinoxalino[2,3-b]quinoxaline.- (i) 2,3-Dichloroquinoxaline (1.0 g.), N,N'-dimethyl-o-phenylenediamine (0.68 g.), and sodium chloride (10 g.) were heated together at 160° for 2 hr. Water was then added, and the mixture made alkaline with 10% sodium hydroxide solution. The resulting solid, in benzene, was chromatographed on alumina (70 g.) and the first fraction evaporated and the residue recrystallised from light petroleum. 5,12-Dimethylquinoxalino-[2,3-b]quinoxaline (0.3 g., 23%) was obtained as yellow needles, m.p. 218-219° (Found: C, 73.5; H, 5.3; N, 21.2. $C_{16}H_{14}N_4$ requires C, 73.3; H, 5.4; N, 21.4%). The picrate separated from benzene-light petroleum as orange needles m.p. 218-219° (decomp.) (Found: C, 56.3; H, 4.0; N, 18.6. $C_{22}H_{17}N_7O_7$, 0.5 C_6H_6 requires C, 56.6; H, 3.8; N, 18.5%).

(ii) A mixture of o-phenylenediamine (0.41 g.), 1,2,3,4-tetrahydro-1,4-dimethyl-2,3-dioxoquinoxaline (0.72 g.), and polyphosphoric acid (15 g.) was heated at 220° for 2 hr. The cooled reaction mixture was treated with excess water and then basified with

10% sodium hydroxide solution. The precipitated solid was collected and chromatographed on alumina using benzene as eluant. The first fraction gave 5,12-dimethylquinoxalino[2,3-b]quinoxaline. After recrystallization from light petroleum it formed yellow needles (0.06 g., 6%), m.p. and mixed m.p. 218-219°.

Treatment of 5,12-Dimethylquinoxalino[2,3-b]quinoxaline with Polyphosphoric Acid.- 5,12-Dimethylquinoxalino[2,3-b]quinoxaline (100 mg.) and polyphosphoric acid (10 g.) were heated together at 220° for 2 hr. The reaction mixture was treated with excess water and then basified with 10% sodium hydroxide solution. The resulting solid was recrystallized from light petroleum and formed yellow needles, (80 mg.), m.p. 218-219°. These were identified as unchanged starting material by mixed m.p. and comparison of infrared spectra.

5H-12-Methylquinoxalino[2,3-b]quinoxaline.- (i) A mixture of 2,3-dihydroxyquinoxaline (1.6 g., 0.01 mole), N,N-dimethyl-o-phenylenediamine (1.4 g., 0.01 mole) and polyphosphoric acid (25 g.) was heated at 250° for 2 hr. The cooled reaction mixture was treated with excess water, and the precipitate collected and recrystallized from aqueous tetrahydrofurfuryl alcohol. Further purification was effected by sublimation at 250°/0.1 mm., followed by recrystallization from acetic acid-ethanol. 5H-12-Methyl-quinoxalino[2,3-b]quinoxaline (1.6 g., 62%) separated as yellow

needles, m.p. 317-318° (vacuo) (Found: C, 72.7; H, 5.2; N, 22.3; N-CH_3, 11.4. $C_{15}H_{12}N_4$ requires C, 72.6; H, 4.9; N, 22.6; N-CH_3, 11.8%). The m.p. was not depressed by admixture with an authentic sample prepared as in (ii), and the infrared spectra of the two samples were identical.

A portion of the above compound was heated with excess acetic anhydride for 2 hr. The reaction mixture was poured into water and made neutral to litmus with aqueous sodium hydroxide. The precipitated solid was collected and recrystallized from light petroleum. 5-Acetyl-12-methylquinoxalino[2,3-b]quinoxaline was obtained as fine yellow needles, m.p. 190-191° (Found: C, 70.7; H, 5.1; N, 19.3. $C_{17}H_{14}N_4O$ requires C, 70.3; H, 4.9; N, 19.3%).

(ii) A mixture of o-phenylenediamine (1.08 g., 0.01 mole), 1,2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (1.76 g., 0.01 mole) and polyphosphoric acid (25 g.) was heated at 220° for 2 hr. The reaction mixture was decomposed with water and made alkaline with aqueous sodium hydroxide. The resulting solid was collected and recrystallized from acetic acid-ethanol. 5H-12-Methylquinoxalino-[2,3-b]quinoxaline (1.1 g., 44%) separated as yellow needles, m.p. 317-318° (vacuo).

Attempted Preparation of 5,11-Dimethylquinoxalino[2,3-b]-quinoxaline.- (i) A mixture of N-methyl-o-phenylenediamine (1.3 g., 0.01 mole), 1,2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (1.7 g.,

0.01 mole) and polyphosphoric acid (25 g.) was heated at 250° for 2 hr. The reaction mixture was treated with excess water and the resulting precipitate collected and recrystallized from aqueous tetrahydrofurfuryl alcohol. The solid that separated was sublimed at 250°/ 0.1 mm., and then recrystallized from acetic acid-ethanol. The resulting 5H-12-methylquinoxalino[2,3-b]quinoxaline (1.6 g., 62%) formed yellow needles, m.p. 317-318° (vacuo). A mixed m.p. with an authentic sample showed no depression and the infrared spectra of the two compounds were identical.

(ii) N-Methyl-o-phenylenediamine (0.7 g., 0.006 mole) and 1,2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (0.9 g., 0.005 mole) were heated together in glacial acetic acid (50 ml.) for 5 hr. The reaction mixture was poured into water and made alkaline with 10% sodium hydroxide solution. It was not possible to isolate any compounds other than the starting materials.

(iii) Polyphosphoric acid equivalent to 84% phosphorus pentoxide in water was prepared by the method of Badger and Sasse.[146] N-Methyl-o-phenylenediamine and 1,2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline were heated together in this medium at temperatures in the range 150-200°, but no reaction occurred. At temperatures above 200°, 5H-12-methylquinoxalino[2,3-b]quinoxaline was obtained.

(iv) A mixture of N-methyl-o-nitroaniline (0.4 g., 0.026 mole) and 3-chloro-1,2-dihydro-1-methyl-2-oxoquinoxaline (0.5 g., 0.026 mole) was heated in a Teflon bomb at 160° for 24 hr. The resulting solid

was chromatographed, in benzene, on alumina (70 g.). The first fraction gave unchanged N-methyl-o-nitroaniline. Evaporation of the second fraction and recrystallization of the residue from methanol gave 1,2-dihydro-1-methyl-3-(o-nitro-N-methylanilino)-2-oxoquinoxaline (0.02 g., 3%) as orange rhombs, m.p. 205-206° (Found: C, 61.8; H, 4.7; N, 18.3. $C_{16}H_{14}N_4O_3$ requires C, 61.9; H, 4.6; N, 18.1%). The yield of product from this reaction could not be increased and the intention to use this compound as an intermediate in the preparation of 5,11-dimethylquinoxalino[2,3-b]-quinoxaline was therefore abandoned.

(v) A solution of toluene-p-sulphonyl chloride (19.0 g., 0.1 mole) in anhydrous pyridine (25 ml.) was added dropwise to a solution of N-methyl-o-phenylenediamine (12.0 g., 0.1 mole) in anhydrous pyridine (25 ml.). The mixture was allowed to stand at room temperature for 20 hr. and then poured into an excess of dilute hydrochloric acid. The solid was collected and chromatographed, in benzene, on alumina. Further purification was effected by recrystallization from benzene-light petroleum. N-(o-Methylamino-phenyl)toluene-p-sulphonamide (11.1 g., 41%) was obtained as colourless needles, m.p. 119-120° (Found: C, 60.8; H, 6.0; N, 10.0. $C_{14}H_{16}N_2O_2S$ requires C, 60.9; H, 5.8; N, 10.1%). Its m.p. was depressed to (85-90°) by admixture with an authentic sample of the isomeric compound, N-(o-aminophenyl)-N-methyltoluene-p-sulphonamide.[83] (This sample was kindly presented by Professor J.W. Clark-Lewis).

Equimolar quantities of 3-chloro-1,2-dihydro-1-methyl-2-oxoquinoxaline and *N*-(*o*-methylaminophenyl)toluene-*p*-sulphonamide were heated together in boiling benzene for 24 hr. The solvent was removed by evaporation under reduced pressure and the residue was found to be a mixture of starting materials.

The procedure was repeated using xylene as a solvent but reaction did not take place.

Equimolar quantities of the two compounds were fused together at 150° for 15 min. The resulting solid was chromatographed, in benzene, on alumina, but no pure compounds could be isolated.

B. INDOLO[3,2-b]INDOLE.

3-Isonitroso-2-phenylindole.- 2-Phenylindole (9.7 g., 0.05 mole) was dissolved in a mixture of sodium ethoxide (3.9 g., 0.06 mole) and ethanol (150 ml). After the addition of amyl nitrite (3.9 g., 0.06 mole), the solution was allowed to stand at room temperature for 18 hr. The reaction mixture was acidified with acetic acid and then diluted with water (250 ml.). The precipitated yellow solid was collected by filtration and purified by recrystallization from a large volume of ethanol. 3-Isonitroso-2-phenylindole was obtained in quantitative yield and formed orange-yellow needles, m.p. 272° (decomp.) [lit.,[101] 272-273° (decomp.)].

3-Amino-2-phenylindole.- Sodium hydrosulphite (8.0 g.) was added to a solution of 3-isonitroso-2-phenylindole (4.0 g.) in ethanol (10 ml.) and 10% sodium hydroxide (20 ml.). The reaction mixture was heated on a water-bath until colourless and then diluted with an equal volume of water. The precipitated solid was collected and purified by recrystallization from benzene. 3-Amino-2-phenylindole (2.3 g., 62%) separated as light brown plates, m.p. 178-179° (lit.,[147] 180°).

3-Diazo-2-phenylindole.- A solution of 3-amino-2-phenylindole (1.0 g.) in acetic acid (10 ml.) was cooled in an ice-bath while a solution of sodium nitrite (0.4 g.) in water (4 ml.) was added dropwise. The reaction mixture was poured into water and then made

alkaline with 10% aqueous sodium hydroxide. The yellow solid was collected by filtration and recrystallized from light petroleum. 3-Diazo-2-phenylindole (0.6 g., 55%) separated as orange-yellow needles, m.p. 115° (decomp.) [lit.,[103] 115° (decomp.)]. The infrared spectrum (Nujol mull) of this compound showed a band at 4.81 μ.

Attempted Synthesis of 5,12-Dihydroindolo[3,2-b]indole.- An aqueous solution of sodium nitrite (1.7 g., 0.02 mole) was added dropwise to a mixture of 3-amino-2-phenylindole (4.0 g., 0.019 mole), acetic acid (30 ml.), and 50% hydrochloric acid (4 ml.). The temperature was maintained at 0° throughout the addition. A saturated aqueous solution of sodium azide (1.6 g., 0.024 mole) was then added and the reaction mixture allowed to stand at room temperature for 3 hr. Addition of water (1 litre) followed by neutralization with aqueous sodium hydroxide (litmus) resulted in the precipitation of a solid A (2.7 g.). This was collected by filtration and not further purified. After standing at room temperature for 24 hr., the filtrate deposited colourless crystals (1.0 g.) which were collected and purified by recrystallization from ethyl acetate. This material separated as colourless rhombs, m.p. 212-213°, and was identified as 3-hydroxy-2-oxo-3-phenylindolenine (lit.,[99] m.p. 213°) (Found: C, 74.4; H, 5.1; N, 6.2. Calc. for $C_{14}H_{11}NO_2$: C, 74.7; H, 4.9; N, 6.2%).

A portion (2.0 g.) of the solid A was heated in boiling decalin (100 ml.) for 2 hr. The solvent was removed by evaporation under reduced pressure and the residue recrystallized from benzene-light petroleum and then sublimed. Red needles (0.6 g.), m.p. 97-99°, were obtained and chromatography on alumina using a 1:4-chloroform-benzene mixture as eluant did not yield a purer product.

Attempted Preparation of 3-Azido-2-phenylindole.- (i) 3-Diazo-2-phenylindole (1.0 g., 0.005 mole) was dissolved in acetic acid (15 ml.), and the solution saturated with nitrogen. Powdered sodium azide (0.4 g., 0.006 mole) was added while a stream of dry nitrogen was bubbled through the reaction mixture. The acetic acid was removed by evaporation under reduced pressure and the solid residue extracted with light petroleum to remove starting material. The infrared spectrum of the crude product showed a broad band at 5.9 μ. Sublimation at 280°/0.01 mm. gave a small quantity of violet material, m.p. 306-307°, the structure of which was not established (Found: C, 84.2; H, 5.0; N, 10.7%). A molecular weight determination using Rast's method was impossible due to the dark colour of the camphor solution.

(ii) Acetyl chloride (0.4 ml., 0.005 mole) was added dropwise to a solution of 3-diazo-2-phenylindole (0.9 g., 0.004 mole) in glacial acetic acid (10 ml.) while the temperature of the mixture was kept at 0°. After the addition of powdered sodium azide (0.3 g.,

0.005 mole) the reaction mixture was allowed to stand at room temperature overnight. The solution was then made alkaline with 5% aqueous sodium hydroxide and the precipitated solid collected. The infrared spectrum of this violet material (0.9 g.), m.p. 130-135°, showed a band in the N-H region and another at 6.0μ in the carbonyl region.

C. INDOLO[2,3-b]QUINOXALINES.

Indolo[2,3-b]quinoxaline.- The method used was that of Schunck and Marchlewski.[107] It was purified by recrystallization from ethanol and formed yellow needles, m.p. 295-296° (lit.,[148] 295-297°).

6-Methylindolo[2,3-b]quinoxaline.- o-Phenylenediamine (2.0 g., 0.019 mole) in 1:1 aqueous acetic acid (20 ml.) was added to a hot solution of N-methylisatin (2.0 g., 0.012 mole) in 1:1 aqueous acetic acid (20 ml.) and the mixture was heated for 30 min. The cooled reaction mixture was poured into water and the yellow precipitate collected by filtration. The crude product was purified by chromatography on alumina in light petroleum. 6-Methylindoloquinoxaline (1.6 g., 56%) separated from light petroleum as fine yellow needles, m.p. 148-149° (lit.,[108] 149°).

5-Methylindolo[2,3-b]quinoxaline.- (i) The condensation of isatin and N-methyl-o-phenylenediamine was carried out in aqueous acetic acid using the method of Buraczewski and Marchlewski.[108] After recrystallization from aqueous ethanol it formed red needles, m.p. 177-178° (lit.,[108] 175-176°).

(ii) A mixture of 3-o-aminophenyl-1,2-dihydro-1-methyl-2-oxoquinoxaline[149] (50 mg.)[x] and polyphosphoric acid (1 g.) was

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[x] A sample of this compound was kindly presented by Professor J.W. Clark-Lewis.

heated at 150° for 2 hr. Water was added dropwise to the cooled reaction mixture and the solution basified with 10% aqueous sodium hydroxide. The precipitate was collected and purified by recrystallization from aqueous ethanol. 5-Methylindoloquinoxaline (41 mg., 88%) separated as red needles, m.p. 177-178°. A mixed m.p. with a sample from the previous experiment showed no depression.

5-Ethylindolo[2,3-b]quinoxaline.- Isatin (5.2 g., 0.036 mole) and N-ethyl-o-phenylenediamine (2.0 g., 0.044 mole) were dissolved in 1:1 aqueous acetic acid (150 ml.) and the solution heated for 1 hr. The cooled reaction mixture was made alkaline by the addition of aqueous sodium hydroxide and the precipitated solid collected by filtration. Purification was effected by chromatography in light petroleum on alumina, followed by recrystallization from light petroleum. 5-Ethylindoloquinoxaline (4.0 g., 50%) separated as red needles, m.p. 174-175° (Found: C, 77.8; H, 5.3; N, 17.5. $C_{16}H_{13}N_3$ requires C, 77.7; N, 5.3; N, 17.0%).

Determination of Acid and Base Strengths of Indoloquinoxaline.- (i) Acid strength. pH Determinations were carried out on a Pye Universal pH meter which was standardised at pH 9.18 using a 0.05M-sodium borate solution at 20°. A Hilger Uvispek was used for optical density measurements of 2 x 10^{-5}M-solutions of indoloquinoxaline in 1:1 ethanol-water at 295 mμ. The solutions had pH values in the range 12.8-13.3. The pK_a values were calculated using the equation:-

$$pK_a = pH - \frac{E_{sol.} - E_{acid}}{E_{c.\ base} - E_{sol.}}$$

where $E_{sol.}$ is the optical density of the solution.

E_{acid} is the optical density of a 2×10^{-5}M-solution of indoloquinoxaline in 1:1 ethanol-water.

$E_{c.\ base}$ is the optical density of a 2×10^{-5}M-solution of indoloquinoxaline in 0.1N-sodium hydroxide in 1:1 ethanol-water.

The acid pK_a value for indoloquinoxaline was found to be 13.6 $\pm$ 0.1.

(ii) Base strength. The method was similar to that used for the determination of the acid pK_a. The pH meter was standardised at pH 3.97 using a 0.05M-potassium hydrogen phthalate solution at 20°. Optical density values were determined at wavelengths 381 and 272 mμ using 2×10^{-5}M-solutions in 1:1 ethanol-water. The solutions had pH values in the range 0.6-1.44. The pK_a values were calculated using the equation:-

$$pK_a = pH - \frac{E_{sol.} - E_{c.\ acid}}{E_{base} - E_{sol.}}$$

where $E_{sol.}$ is the optical density of the solution.

$E_{c.\ acid}$ is the optical density of a 2×10^{-5}M-solution of indoloquinoxaline in 0.2N-sulphuric acid in 1:1

ethanol-water.

E_{base} is the optical density of a 2 x 10^{-5}M-solution of indoloquinoxaline in 1:1 ethanol-water.

The base pK_a value for indoloquinoxaline was found to be approximately 0.3.

Methylation of Indoloquinoxaline.- (i) A mixture of indoloquinoxaline (2.2 g., 0.01 mole), sodium hydroxide (0.4 g., 0.01 mole), methyl iodide (1.5 g., 0.01 mole), and absolute ethanol (100 ml.) was heated under reflux for 24 hr. and then poured into water. The precipitated solid was collected, recrystallized from aqueous ethanol, and extracted with boiling hexane. The insoluble residue (0.70 g.) was indoloquinoxaline. The soluble fraction was chromatographed on alumina (100 g.). Elution with hexane gave 6-methylindoloquinoxaline (0.92 g., 40%), m.p. 146-147°, followed by 5-methylindoloquinoxaline (0.27 g., 12%), m.p. 176-177°.

(ii) Indoloquinoxaline (2.5 g., 0.012 mole) was dissolved in a mixture of ethanol (100 ml.) and 5% aqueous sodium hydroxide (100ml.). The solution was heated on a steam bath and dimethyl sulphate (6 ml., 0.06 mole) was added dropwise. The reaction mixture was allowed to stand overnight and the precipitated solid (2.4 g.) collected and chromatographed, in hexane, on alumina (100 g.). The first fraction yielded 6-methylindoloquinoxaline (1.9 g., 70%), m.p. 146-147°, and the second gave 5-methylindoloquinoxaline (0.4 g., 15%), m.p. 176-177°.

(iii) An ethereal solution of diazomethane (ca. 4 g.) was added to a suspension of indoloquinoxaline (2.2 g.) in acetone (250 ml.) at 0°. After 2 hr. at this temperature, the reaction mixture was left at room temperature overnight. The solvent was removed by evaporation and the residue extracted with boiling hexane. The insoluble material (0.32 g.) was indoloquinoxaline. The soluble fraction was chromatographed on alumina (60 g.)using hexane as eluant. The first fraction gave an unknown colourless compound (0.59 g.) which could not be purified by recrystallization or by chromatography on alumina, acetylated cellulose or silica gel. After repeated recrystallization from ethanol it formed colourless needles, m.p. 202-203° after sintering. Analysis indicated that it contained oxygen (Found: C, 69.3; H, 4.4; O, 7.6%). The second fraction contained an inseparable mixture (0.46 g.) of 6-methylindoloquinoxaline and the colourless substance. The third fraction consisted of essentially pure 6-methylindoloquinoxaline (0.43 g., 19%), m.p. 146-148°, and further elution gave 5-methylindoloquinoxaline (0.36 g., 16%) as red needles, m.p. 176-177°.

11H-5-Methylindolo[2,3-b]quinoxalinium Toluene-p-sulphonate.- (i) Indoloquinoxaline (2 g., 0.008 mole), methyl toluene-p-sulphonate (2 g., 0.012 mole), and ethanol (5 ml), were heated together at 120° for 2 hr. The resulting solid was extracted with chloroform (20 ml.) to give the product as a residue (1 g.), m.p. 244-245°, and a further

yield (0.4 g.) was obtained by concentration of the extract. After recrystallization from ethanol, 11H-5-methylindoloquinoxalinium toluene-p-sulphonate (1.4 g., 39%) formed yellow needles, m.p. 247-248° (decomp.) (Found: C, 65.0; H, 4.8; N, 10.4. $C_{22}H_{19}N_3O_3S$ requires C, 65.2; H, 4.7; N, 10.4%). λ_{max} (in ethanol) 220 (log ε 4.41), 274 (4.65), shoulder 340 (4.10), 355 (4.23), 371 (4.18), and 417 mμ (3.33); ν_{max} (in chloroform) 8.66, 8.93, 9.71 and 9.92μ.

A solution of this salt (100 mg.) in ethanol (30 ml.) was poured into excess water. The resulting precipitate was collected and recrystallized from aqueous ethanol. 5-Methylindoloquinoxaline was obtained in quantitative yield as red needles, m.p. and mixed m.p. 177-178°.

(ii) A solution of toluene-p-sulphonic acid in acetone was added dropwise to 5-methylindoloquinoxaline in acetone until the mixture became yellow. The addition of ether followed by cooling resulted in the formation of yellow crystals which were collected and recrystallized from ether-acetone. 11H-5-Methylindoloquinoxalinium toluene-p-sulphonate separated as yellow needles, m.p. 247-248° (decomp.) alone or admixed with a specimen prepared as above. The infrared spectrum was also identical with that of the above compound.

11H-5-methylindolo[2,3-b]quinoxalinium Iodide.- (i) A mixture of indoloquinoxaline (1 g.), methyl iodide (10 ml.), and

ethanol (10 ml.) was heated under reflux for 60 hr. The resulting precipitate was collected by filtration and recrystallized from ethanol. 11H-5-Methylindoloquinoxalinium iodide (0.75 g., 47%) separated as orange-yellow needles, m.p. 255-256° (decomp.) (Found: C, 49.7; H, 3.7; N, 11.5. $C_{15}H_{12}IN_3$ requires C, 49.9; H, 3.4; N, 11.6%). λ_{max} (in ethanol) 219 (logε 4.56), 273 (4.83), shoulder 340 (4.16), 355 (4.30), 371 (4.23), and 417 mμ (3.38).

(ii) 5-Methylindoloquinoxaline was dissolved in acetone and hydriodic acid added dropwise until the solution became permanently yellow. Ether was added, the solution cooled, and the resulting solid recrystallized from ether-acetone. The iodide formed orange-yellow needles, m.p. and mixed m.p. 255-256° (decomp.).

5,6-Dimethylindolo[2,3-b]quinoxalinium Perchlorate.- A mixture of 6-methylindoloquinoxaline (1 g., 0.004 mole), methyl toluene-p-sulphonate (1.1 g., 0.006 mole), and ethanol (3 ml.) was heated at 120° for 1 hr. An ethanolic solution of the resulting solid was acidified with perchloric acid and then poured into water. The precipitate was collected and purified by recrystallization from ethanol. 5,6-Dimethylindoloquinoxalinium perchlorate (1.4 g., 93%) formed red needles, m.p. 273-274° (decomp.) (Found: C, 55.3; H, 4.2; N, 12.0. $C_{16}H_{14}ClN_3O_4$ requires C, 55.3; H, 4.1; N, 12.1%).

5,11-Dimethylindolo[2,3-b]quinoxalinium Perchlorate.- Methylation of 5-methylindoloquinoxaline was carried out in the same manner as for

the 6-methyl derivative. 5,11-Dimethylindoloquinoxalinium perchlorate (0.61 g., 41%) crystallized from ethanol as orange-yellow needles, m.p. 308-309° (decomp.) (Found: C, 55.0; H, 4.2; N, 12.2%).

Attempted Ethylation of 5-Methylindoloquinoxaline.- A mixture of 5-methylindoloquinoxaline (0.5 g.), ethyl iodide (10 ml.), and ethanol (10 ml.), was heated under reflux for 8 hr. The precipitated solid was collected and recrystallized from ethanol. 11H-5-Methylindoloquinoxalinium iodide (0.5 g., 64%) separated as orange-yellow needles, m.p. 255-256° (decomp.). The infrared spectrum of this material was identical to that of an authentic sample and a mixed m.p. showed no depression.

An ethanolic solution of this material was poured into water and the resulting precipitate collected and recrystallized from aqueous ethanol. 5-Methylindoloquinoxaline separated as red needles, m.p. 177-178°, alone or admixed with an authentic sample.

Attempted Methylation of 5-Ethylindoloquinoxaline.- A mixture of 6-ethylindoloquinoxaline (1.0 g.), methyl iodide (10 ml.), and ethanol (20 ml.) was heated under reflux for 30 hr. The reaction mixture was concentrated and the resulting solid collected and recrystallized from ethanol. Repeated recrystallization did not yield a pure product and an infrared spectrum of this material indicated that it was an impure sample of 11H-5-ethylindoloquinoxalinium iodide.

The above mixture was separated by descending chromatography on Whatman No. 1 paper using a solvent which was prepared in the following manner. Acetic acid (10 ml.), n-butanol (50 ml.), and water (35 ml.) were shaken together and the two phases allowed to separate. A portion (55 ml.) of the upper layer was shaken with benzene (15 ml.) and the two layers separated. The upper phase was removed and used as the solvent. Chromatography of the mixture yielded a yellow fraction (R_F 0.71) and a red fraction (R_F 0.84). The latter was shown to be 5-ethylindoloquinoxaline which was formed by decomposition of 11H-5-ethylindoloquinoxaline. Authentic samples of 5-ethylindoloquinoxaline and its hydriodide gave red spots (R_F values 0.84).

11H-5-Ethylindolo[2,3-b]quinoxalinium Iodide.- The method of preparation was similar to that used for 11H-5-methylindoloquinoxalinium iodide. After recrystallization from ether-acetone the 11H-5-ethylindoloquinoxalinium iodide formed orange-yellow needles, m.p. 275-8° (decomp.) (Found: C, 51.3; H, 4.0; N, 11.4. $C_{16}H_{14}N_3I$ requires C, 51.2; H, 3.8; N, 11.2%).

11-Ethyl-5-methylindolo[2,3-b]quinoxalinium Perchlorate.- A mixture of 5-methylindoloquinoxaline (0.5 g., 0.002 mole), ethyl toluene-p-sulphonate (0.6 g., 0.003 mole), and ethanol (1 ml.) was heated at 120° for 1 hr. The resulting solid was dissolved in ethanol, and the solution acidified with perchloric acid and then

poured into water. The precipitated solid was collected and purified by recrystallization from ethanol. 11-Ethyl-5-methylindoloquinoxalinium perchlorate (0.35 g., 77%) formed orange-yellow needles, m.p. 291-292° (decomp.) (Found: C, 56.3; H, 4.4; N, 11.4. $C_{18}H_{16}ClN_3O_4$ requires C, 56.4; H, 4.5; N, 11.6%).

5-Ethyl-11-methylindolo[2,3-b]quinoxalinium Perchlorate.- Methylation of 5-ethylindoloquinoxaline was carried out using methyl toluene-p-sulphonate. The precedure was similar to that of the previous experiment. 5-Ethyl-11-methylindoloquinoxalinium perchlorate (0.35 g., 77%) crystallized from ethanol as orange-yellow needles, m.p. 279-280° (decomp.) (Found: C, 56.3; H, 4.4; N, 11.8%). The infrared spectrum of this compound was not identical with that of the above isomer. A sample containing an equal quantity of the two isomers melted at 280-281° (decomp.).

D. s-TRIAZOLOPYRAZINES

Modified Preparation of 2-Hydroxypyrazine.- A solution of glyoxal monohydrate (46 g., 0.6 mole) in methanol was added slowly to a solution of aminoacetamide hydrochloride (55 g., 0.5 mole) in methanol (1 litre) at -30°. The mixture was vigorously stirred at -30° while 12.5N-sodium hydroxide (100 ml.) was added dropwise over a period of 20 mins. Stirring was continued for a further 30 mins. The reaction mixture was allowed to stand at room temperature overnight and then made neutral to litmus by the dropwise addition of 12N-hydrochloric acid. The reaction mixtures from five runs were combined and concentrated to a volume of 1 litre in a cyclone evaporator. The precipitated 2-hydroxypyrazine was collected and purified by extraction with chloroform in a Soxhlet apparatus. The mother-liquor from the reaction was evaporated to dryness in a film evaporator and the residue dried in a vacuum-desiccator over phosphorus pentoxide. The dry solid was ground to a powder and extracted with chloroform in a Soxhlet apparatus. 2-Hydroxypyrazine (100 g., 40%) crystallized from chloroform as light brown needles, m.p. 181-185° (lit.,[123] 188-189°), and was not further purified before use.

2,3-Dimethyl-6-hydroxypyrazine.- The following procedure was found to be superior to the original method.[123] Aminoacetamide hydrochloride (55 g., 0.5 mole) and diacetyl (60 ml., 0.5 mole)

were dissolved in water (500 ml.) and the solution treated with 12.5N-sodium hydroxide (100 ml.) while the temperature was kept below 5°. The reaction mixture was allowed to stand at room temperature for 18 hr., neutralized with 10N-hydrochloric acid (litmus), and then extracted with chloroform in a continuous extractor. Evaporation of the chloroform extract gave a dark brown residue which was recrystallized from ethyl acetate (charcoal). 2,3-Dimethyl-6-hydroxypyrazine (23 g., 37%) separated as clusters of colourless needles, m.p. 198-199° (lit.,[123] 201-202°).

6-Chloro-2,3-diphenylpyrazine.- This compound was only obtained in satisfactory yield by the following precedure. A mixture of 2,3-diphenyl-6-hydroxypyrazine (75 g.), phosphorus oxychloride (275 ml.), phosphorus pentachloride (75 g.), and several drops of concentrated sulphuric acid was refluxed for 20 days. Evaporation of the phosphorus oxychloride, followed by addition of methanol, gave a yellow solid which was collected by filtration. The crude chloro-compound (75 g., 93%), m.p. 122-124°, was purified by recrystallization from methanol, and formed pale yellow plates, m.p. 126-127° (lit.,[123] 126-127°).

2-Hydrazinopyrazines. General Method of Preparation.- A mixture of the crude 2-chloropyrazine (0.1 mole), 98% hydrazine (16 ml., 0.5 mole) and absolute ethanol (50 ml.) was refluxed for

4 hr. The ethanol was removed by evaporation under reduced pressure, and the resulting solid recrystallized from benzene. 2-Hydrazinopyrazine (6.6 g., 60%) separated as cream needles, m.p. 112-113° (Found: C, 43.7; H, 5.4; N, 50.6. $C_4H_6N_4$ requires C, 43.6; H, 5.5; N, 50.9%). The picrate crystallized from acetone-light petroleum as yellow plates, m.p. 155-156° (decomp.) (Found: C, 41.3; H, 3.2; N, 26.0. $C_{10}H_9N_7O_7.0.5C_6H_6$ requires C, 41.1; H, 3.5; N, 25.7%). After two recrystallizations from benzene, 2,3-dimethyl-6-hydrazinopyrazine (7.6 g., 54%) formed pale yellow needles, m.p. 119-120° (Found: C, 52.0; H, 7.2. $C_6H_{10}N_4$ requires C, 52.2; H, 7.3%). The picrate crystallized from ethanol as yellow needles, m.p. 169-170° (decomp.) (Found: C, 44.0; H, 4.2; N, 23.9. $C_{12}H_{13}N_7O_7.0.5C_6H_6$ requires C, 44.4; H, 4.0; N, 24.1%). After recrystallization from benzene, 2,3-diphenyl-6-hydrazinopyrazine (17.2 g., 69%) formed cream needles, m.p. 154-155°. (Found: C, 73.4; H, 5.4; N, 21.2. $C_{16}H_{14}N_4$ requires C, 73.3; H, 5.4; N, 21.4%). The picrate separated from benzene as orange rhombs, m.p. 157° (decomp.) (Found: C, 56.2; H, 3.9; N, 18.7. $C_{22}H_{17}N_7O_7.0.5C_6H_6$ requires C, 56.6; H, 3.8; N, 18.5%).

3,5,6-Trisubstituted-s-triazolo[4,3-a]pyrazines. General Method of Preparation.- A mixture of the 2-hydrazinopyrazine (1 g.), the orthoester (3 ml.), and xylene (10 ml.) was refluxed for 4 hr.

The solvent was removed by evaporation under reduced pressure, and the resulting solid recrystallized from the appropriate solvent (see Table II). The picrates were prepared by mixing a solution of the s-triazolo[4,3-a]pyrazine in benzene with an equal volume of a saturated solution of picric acid in benzene. It was sometimes necessary to heat the mixture for a considerable time before the picrate separated (compounds 5, 6, 9). The picrates were recrystallized from the solvents shown in Table III.

Attempted Reaction of Benzhydrazide with 6-Chloropyrazines.- (i) Using 2,3-diphenyl-6-chloropyrazine. A mixture of benzhydrazide (2.0 g.), 2,3-diphenyl-6-chloropyrazine (1.0 g.) and phenol (4.0 g.) containing a trace of sodium phenoxide, was heated under reflux for 10 days. The phenol was removed by steam-distillation and the remaining water evaporated under reduced pressure. The solid residue (0.76 g.), m.p. 175-183°, was chromatographed on alumina (15 g.) using benzene as eluant. The resulting solid was recrystallized five times from benzene, and separated as colourless needles, m.p. 187-189°. This compound was identified as 3,5-diphenyl-1,2,4-triazole (lit.[150] 190°) by mixed m.p. determination, and comparison of its infrared spectrum with that of an authentic sample. (Found: C, 76.2; H, 5.1; N, 18.6. Calc. for $C_{14}H_{11}N_3$: C, 76.0; H, 5.0; N, 19.0%).

In another experiment, carried out on a smaller scale, chromatography on alumina in benzene, gave a product, probably

2,3-diphenyl-6-phenoxypyrazine, which separated from light petroleum as small colourless irregular prisms (0.15 g.), m.p. 94-95° (Found: C, 81.7; H, 4.9. $C_{22}H_{16}N_2O$ requires C, 81.5; H, 5.0%).

(ii) Using 2,3-dimethyl-6-chloropyrazine. A mixture of benzhydrazide (0.85 g.), 2,3-dimethyl-6-chloropyrazine (1.0 g.) and phenol (3.0 g.) containing a trace of sodium phenoxide was heated under reflux for 40 hr. The phenol was removed by steam-distillation and the residue remaining after evaporation of the water was chromatographed on alumina (20 g.) using benzene as eluant. The resulting product crystallized from light petroleum as colourless needles, m.p. 135-136°, and was identified as 2,5-diphenyl-1,3,4-oxadiazole (lit.[151] 138°) (Found: C, 75.5; H, 4.6. Calc. for $C_{14}H_{10}N_2O$: C, 75.7; H, 4.5%). The infrared spectrum was identical with that of an authentic specimen, which did not depress the melting point of the product.

(iii) Using 2-chloropyrazine. The reaction of benzhydrazide (1.2 g.) with 2-chloropyrazine (1.0 g.) was carried out as above, and the residue remaining after removal of the phenol by steam-distillation was identified as dibenzoylhydrazine (0.45 g., 51%), m.p. 234-235°. Recrystallization from benzene-ethanol gave colourless needles, m.p. 240-241° (lit.,[152] 240-241°) (Found: C, 70.0; H, 5.1; N, 12.0. Calc. for $C_{14}H_{12}N_2O_2$: C, 70.0; H, 5.0; N, 11.7%). The

m.p. was not depressed by admixture with an authentic sample, and the infrared spectra were identical.

N-Benzoyl-2,3-diphenyl-6-hydrazinopyrazine.- 2,3-Diphenyl-6-hydrazinopyrazine (2.0 g., 0.008 mole) was dissolved in pyridine (6 ml.) and the solution cooled in an ice-bath while benzoyl chloride (1.2 ml., 0.008 mole) was added dropwise. After vigorous shaking the mixture was allowed to stand overnight and then poured onto crushed ice. The resulting oil was scratched and cooled until it solidified and it was then recrystallized from benzene-light petroleum. N-Benzoyl-2,3-diphenyl-6-hydrazinopyrazine (2.5 g., 89%) separated as colourless needles, m.p. 189-190°. (Found: C, 75.6; H, 5.0; N, 15.2. $C_{23}H_{18}N_4O$ requires C, 75.4; H, 5.0; N, 15.3%).

Ring Closure of N-Benzoyl-2,3-diphenyl-6-hydrazinopyrazine.- (i) Using phenol. A mixture of the benzoyl compound (0.4 g.) and phenol (1.0 g.) was refluxed for 20 hr. The phenol was removed by steam-distillation, and the residue (0.12 g.) recrystallized from benzene-light petroleum. The resulting colourless needles, m.p. 186-187°, were identified as unreacted N-benzoyl-2,3-diphenyl-6-hydrazinopyrazine.

(ii) Using phosphorus oxychloride.- The benzoyl compound (0.5 g.) and phosphorus oxychloride (5 ml.) were heated together under reflux for 2 hr. The reaction mixture was poured into ice-

water and the insoluble solid collected. This material was identified as the unchanged benzoyl compound. The filtrate was neutralized with aqueous sodium hydroxide, and the precipitate collected. Recrystallization from benzene-light petroleum gave a product (0.007 g.), m.p. 238-239°, whose infrared spectral characteristics indicated that it was most likely 3,5,6-triphenyl-s-triazolo[4,3-a]pyrazine.

(iii) Using polyphosphoric acid. Phosphorus pentoxide (35 g.) and orthophosphoric acid (17 ml.) were heated together on a water-bath for 3 hr. N-Benzoyl-2,3-diphenyl-6-hydrazinopyrazine (3.8 g.), was added and the reaction mixture heated at 150° for 3 hr. After cooling, water was added and the solid material collected and recrystallized from ethanol. 3,5,6-Triphenyl-s-triazolo[4,3-a]-pyrazine (3.0 g., 83%) separated as colourless needles, m.p. 240-241° (Found: C, 79.0; H, 4.6; N, 16.2. $C_{25}H_{16}N_4$ requires C, 79.3; H, 4.6; N, 16.1%).

It was not possible to prepare a picrate derivative of this compound.

Attempted Preparation of s-Triazolo[4,3-a]pyrazine Using Formic Acid.- A mixture of 2-hydrazinopyrazine (0.5 g.) and 98% formic acid (5 ml.) was heated under reflux for 2 hr. Removal of the formic acid by evaporation under reduced pressure gave a carbonaceous residue from which it was not possible to isolate any pure material.

Extensive decomposition also occurred when the reactants were heated at 70°.

5,6-Diphenyl-s-triazolo[4,3-a]pyrazine.- (i) Using 98% formic acid. A mixture of 2,3-diphenyl-6-hydrazinopyrazine (1.0 g.) and 98% formic acid (15 ml.) was heated under reflux for 3 hr. The formic acid was evaporated under reduced pressure, and the residue recrystallised from benzene-light petroleum. The product separated as a yellow microcrystalline powder (0.1 g., 10%), m.p. 181-183°. Repeated recrystallization did not raise the m.p., but the infrared spectrum was identical with that of 5,6-diphenyl-s-triazolo[4,3-a]-pyrazine prepared by the orthoester reaction.

(ii) Using dimethylformamide. 2,3-Diphenyl-6-hydrazinopyrazine (0.5 g.) and dimethylformamide (20 ml.) were heated together under reflux for 18 hr. The dimethylformamide was evaporated and the residue recrystallised from benzene-light petroleum. The pure product (0.01 g., 0.5%), m.p. 187-188°, was identical in all respects with the product from the ethyl orthoformate ring closure.

Acetylation of 2,3-Diphenyl-6-hydrazinopyrazine.- (i) Formation of 1,1,2-triacetyl-2-(2,3-diphenyl-6-pyrazinyl)hydrazine. A mixture of the hydrazinopyrazine (1.0 g.), acetic anhydride (2 ml.), and acetic acid (2 ml.) was heated under reflux for 2.5 hr. The acetylation mixture was removed by evaporation under reduced pressure, and the residue recrystallised from methanol (charcoal). The

triacetyl derivative formed colourless rhombs, m.p. 178-179° (Found: C, 68.2; H, 5.3; N, 14.6%, M, 400. $C_{22}H_{20}N_4O_3$ requires C, 68.0; H, 5.2; N, 14.4%; M, 388).

(ii) Formation of 1,1-diacetyl-2-(2,3-diphenyl-6-pyrazinyl)-hydrazine. The hydrazinopyrazine (1.0 g., 0.004 mole) was dissolved in pyridine (6 ml.) and acetyl chloride (0.4 ml., 0.004 mole) added dropwise. The mixture was allowed to stand at room temperature for 1 hr. and then poured into ice-water. The crude product (0.85 g., 71%) was collected and recrystallized from benzene-light petroleum. After repeated recrystallization the diacetyl derivative separated as small, colourless needles, m.p. 167-168° (Found: C, 69.1; H, 5.2; N, 16.2. $C_{20}H_{18}N_4O_2$ requires C, 69.4; H, 5.2; N, 16.2%).

The same product was obtained from the above triacetyl compound by evaporating a solution in methanol to dryness on a water-bath. The resulting diacetyl derivative was first recrystallized from methanol, and then from benzene-light petroleum.

Attempted Synthesis of 3-Mercapto-5,6-diphenyl-s-triazolo-[4,3-a]pyrazine.- (i) Using carbon disulphide. A mixture of 2,3-diphenyl-6-hydrazinopyrazine (1.0 g., 0.004 mole), carbon disulphide (2 ml., 0.025 mole), and pyridine (10 ml.) was heated under reflux until hydrogen sulphide evolution ceased (7 hr.). The solvent was removed by evaporation under reduced pressure and the residue recrystallized from a tetrahydrofuran-ethanol mixture. 1,3-Di-(2,3-diphenyl-6-pyrazinylamino)thiourea was obtained in poor

yield as a pale yellow, microcrystalline solid, m.p. 239-240° (Found: C, 68.4; H, 4.5; N, 19.3; S, 5.9. $C_{33}H_{26}N_8S.0.5H_2O$ requires C, 68.8; H, 4.7; N, 19.6; S, 5.6%).

(ii) Using phenyl isothiocyanate. A mixture of 2,3-diphenyl-6-hydrazinopyrazine (1.0 g., 0.004 mole), phenyl isothiocyanate (0.7 g., 0.005 mole), and trichlorobenzene (5 ml.) was refluxed for 5 hr. The solvent was evaporated under reduced pressure (0.05 mm.) and the residue sublimed at 150°/0.001 mm. The sublimate crystallized from benzene-light petroleum as colourless needles, m.p. 187-188°, and was identified as 5,6-diphenyl-*s*-triazolo[4,3-*a*]pyrazine by mixed m.p. determination, and by comparison of its infrared spectrum with that of an authentic sample.

General Method of Preparation of N-2-Pyrazinylphenylamidines.- Equimolar quantities of the 2-aminopyrazine, aluminium chloride, and benzonitrile were heated together at 180° for 2 hr. in a reaction flask fitted with a calcium chloride tube. Water was added to the cooled reaction mixture, and the resulting solution basified with aqueous sodium hydroxide. The precipitated solid was collected and recrystallized from light petroleum. Extraction of the filtrate with ether did not give a further yield of the product. N-(2,5-Dimethyl-6-pyrazinyl)phenylamidine (18%) separated as colourless needles, m.p. 145-146° (Found: C, 68.7; H, 6.1; N, 24.7. $C_{13}H_{14}N_4$ requires C, 69.0; H, 6.2; N, 24.8%). The picrate crystallized

from chloroform-light petroleum as yellow needles, m.p. 153-154° (Found: C, 50.3; H, 3.9; N, 21.2. $C_{19}H_{17}N_7O_7$ requires C, 50.1; H, 3.8; N, 21.5%). N-(2,3-Dimethyl-6-pyrazinyl)phenylamidine (37%) formed colourless needles, m.p. 165-166° (Found: C, 68.6; H, 6.2; N, 24.8. $C_{13}H_{14}N_4$ requires C, 69.0; H, 6.2; N, 24.8%). N-(2,3-Diphenyl-6-pyrazinyl)phenylamidine (56%) formed colourless needles, m.p. 187-188° (Found: C, 78.7; H, 5.2; N, 16.1. $C_{25}H_{18}N_4$ requires C, 78.8; H, 5.2; N, 16.0%). The picrate crystallized from aqueous ethanol in fine yellow needles, m.p. 259-260° (decomp.) (Found: C, 60.3; H, 3.9; N, 16.5. $C_{29}H_{21}N_7O_7$ requires C, 60.1; H, 3.7; N, 16.9%).

Dehydrogenation of N-pyrazinylphenylamidines.- A mixture of the amidine (0.005 mole), lead tetra-acetate (3.5 g., 0.008 mole), and benzene (50 ml.) was heated under reflux for 30 min. The precipitated lead acetate was removed by filtration and the filtrate shaken with 30% sodium hydroxide solution (100 ml.). The benzene solution was dried (anhydrous sodium sulphate) and then evaporated to dryness. The residue was recrystallized from the solvent specified below. 5,8-Dimethyl-2-phenyl-s-triazolo[2,3-a]pyrazine (0.63 g., 56%) crystallized from light petroleum as colourless needles, m.p. 103-104° (Found: C, 69.5; H, 5.5; N, 24.8. $C_{13}H_{12}N_4$ requires C, 69.6; H, 5.4; N, 25.0%). The picrate separated from benzene-light petroleum as yellow needles, m.p. 216-217° (Found: C, 50.0; H, 3.2; N, 21.3. $C_{19}H_{15}N_7O_7$ requires C, 50.3; H, 3.3; N, 21.6%). 5,6-Dimethyl-2-phenyl-s-triazolo-

/2,3-a/pyrazine (0.57 g., 51%) crystallized from light petroleum as colourless needles, m.p. 133-134° (Found: C, 69.3; H, 5.3; N, 24.8. $C_{13}H_{12}N_4$ requires C, 69.6; H, 5.4; N, 25.0%). The picrate separated from benzene-light petroleum as yellow needles, m.p. 192-193° (Found: C, 50.5; H, 3.7; N, 21.4. $C_{19}H_{15}N_7O_7$ requires C, 50.3; H, 3.3; N, 21.6%). 2,5,6-Triphenyl-s-triazolo-/2,3-a/pyrazine (1.22 g., 70%) crystallized from ethanol as colourless needles, m.p. 238-239°. (Found: C, 78.9; H, 4.8; N, 15.9. $C_{25}H_{16}N_4$ requires C, 79.3; H, 4.6; N, 16.1%). All attempts to prepare picrate or methiodide derivatives of this compound were unsuccessful.

Treatment of 2-Amino-3,6-dimethylpyrazine with Aliphatic Nitriles.- (i) Acetonitrile. (a) A mixture of the amine (0.62 g., 0.005 mole), aluminium chloride (0.8 g., 0.006 mole), and acetonitrile (2 ml.) was heated in a sealed tube at 160° for 2 hr. The reaction mixture was dissolved in water, basified with sodium hydroxide, and extracted with ether. Evaporation of the ether gave a residue (0.42 g.) which was found to be unchanged amine.

(b) The same quantities were heated together in a sealed tube at 175° for 9 hr. Extensive decomposition occurred and it was not possible to isolate any pure compound.

(ii) Propionitrile. A mixture of the amine (0.62 g., 0.005 mole), aluminium chloride (1.0 g., 0.008 mole), and propionitrile

(2 ml.) was heated in a sealed tube at 180° for 4 hr. The only material isolated was the unchanged amine (0.15 g.).

(iii) Trichloroacetonitrile. (a) A mixture of the amine (0.62 g., 0.005 mole), aluminium chloride (0.8 g., 0.006 mole), and trichloroacetonitrile (3 ml.) was heated in a sealed tube at 180° for 5 hr. The resulting solid was extracted with ethanol, and evaporation of this extract gave a colourless solid (0.91 g.) which was recrystallized from aqueous ethanol. This material separated as colourless needles, m.p. 91-92°, and was identified as 2,4,6-tris(trichloromethyl)-1,3,5-triazine (lit.,[153] m.p. 91-92°) (Found: C, 16.8; N, 9.4. Calc. for $C_6N_3Cl_9$: C, 16.6; N, 9.7%). It was not possible to isolate any other compounds from this reaction.

(b) In a second run, the reactants were heated together in a sealed tube at 120° for 2 hr. The reaction mixture was extracted with water and the aqueous solution basified with sodium hydroxide and then extracted with ether. No pure compounds could be isolated from this ether extract. It was not possible to obtain any products from the water-insoluble material.

(iv) Chloroacetonitrile. The amine (0.62 g., 0.005 mole), aluminium chloride (0.7 g., 0.005 mole), and chloroacetonitrile (3 ml.) were heated together at 150° for 2 hr. in a flask fitted with a calcium chloride tube. The reaction mixture was dissolved in water and the resulting solution basified with sodium hydroxide. Extraction with ether yielded only the unchanged amine (0.25 g.).

(v) Acrylonitrile. A mixture of the amine (0.62 g., 0.005 mole), aluminium chloride (0.7 g., 0.005 mole), and acrylonitrile (2.5 ml.) was heated in a sealed tube at 120° for 5 hr. The usual work-up did not give any material in a pure state.

(vi) Phenylacetonitrile. The amine (0.62 g., 0.005 mole), aluminium chloride (0.8 g., 0.006 mole), and phenylacetonitrile (3 ml.) were heated together at 200° for 2 hr. in a flask fitted with a calcium chloride tube. The reaction mixture was dissolved in water, basified with sodium hydroxide, and extracted with ether. The only material isolated was unchanged amine (0.2 g.).

Attempted Reaction of 2-Amino-3,6-dimethylpyrazine with Ethyl Acetimidate Hydrochloride.- (i) A mixture of the amine (0.6 g., 0.005 mole), ethyl acetimidate hydrochloride[124] (0.6 g., 0.005 mole), and ether was heated under reflux for 10 hr. The insoluble material was collected by filtration, and the filtrate evaporated to dryness. The residue (0.45 g.) consisted of unchanged amine. The insoluble material was dissolved in water and the solution basified with aqueous sodium hydroxide. No further compounds were obtained by extracting this solution with ether.

(ii) The amine (0.45 g., 0.003 mole), ethyl acetimidate hydrochloride[124] (0.5 g., 0.004 mole), and dioxan (50 ml.), were heated together under reflux for 2.5 hr. The only material isolated from the reaction was unchanged amine (0.4 g.).

(iii) A mixture of the amine (0.5 g., 0.004 mole), ethyl acetimidate hydrochloride[124] (0.5 g., 0.004 mole), and acetonitrile (50 ml.) was heated under reflux for 3 hr. The insoluble solid was removed by filtration and the solvent evaporated to dryness. Extraction of the residue with light petroleum gave only unchanged amine (0.3 g.). It was not possible to isolate any pure compound from the solid precipitated from the reaction mixture.

E. ABSORPTION SPECTRA OF *s*-TRIAZOLOPYRAZINES.

All measurements were made with a Unicam SP700 recording spectrophotometer in cyclohexane and in 95% ethanol.

Samples of 3-methyl-*s*-triazolo[4,3-*a*]pyridine, *s*-triazolo-[4,3-*a*]pyrimidine, and *s*-triazolo[2,3-*a*]pyrimidine were kindly presented by Dr. K.T. Potts, University of Louisville, Kentucky.

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