STUDIES IN THE NITROGEN HETEROCYCLIC SERIES

by

Netta W. A. Thomson, B.Sc.

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CONTENTS

GENERAL INTRODUCTION

GENERAL INTRODUCTION

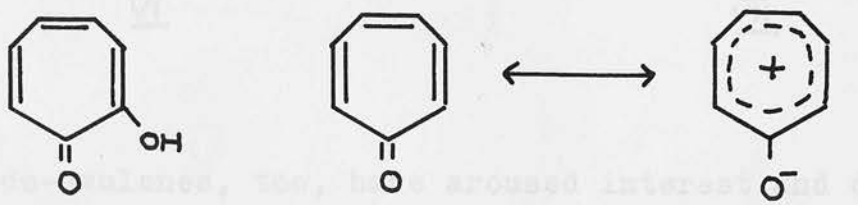
In recent years, much interest has centred on the seven-membered carbocyclic systems. Hückel[1] stated that for a carbocyclic molecule to be aromatic, it must be a planar, conjugated polyolefin with a total of $(4n + 2)\pi$ electrons. This indicates that aromatic character is not restricted to benzene and its derivatives, but will also be exhibited by systems, such as the anion of cyclopentadiene I and the cation of cycloheptatriene II, which possess the requisite arrangement of π electrons, and molecular orbital calculations[2] have confirmed that those two ions should possess aromatic character. Doering[3] has demonstrated that those ions, together with benzene, form a triad possessing aromatic resonance energy and remarkable stability.

I

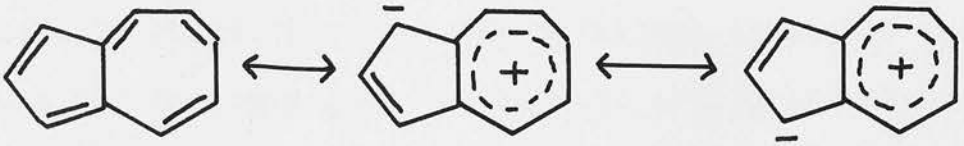
II

The presence of a seven-membered aromatic system in a molecule was not recognised until 1945, when the tropolone nucleus was found in the stipitatic acid molecule[4]. The discovery that such a system existed in certain natural products, together with the great interest in non-classical aromatic systems, led to considerable research on tropolone and its parent compound, tropone[5] IV, and on

azulene [6] V, a molecule in which the seven-membered ring is fused to a five-membered ring. The aromatic cycloheptatrienylium ion II has been isolated by Doering[3] and its predicted stability confirmed.



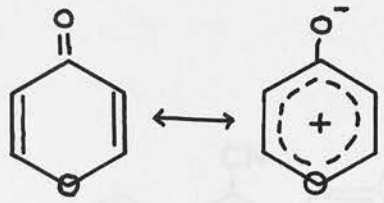
III IV



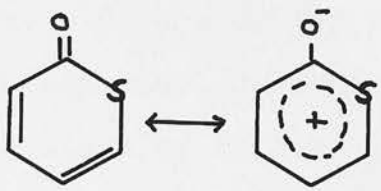
V

Inevitably, interest has arisen in the corresponding heterocyclic compounds.

The aromatic character of a system is not lost if the benzenoid - CH=CH- group is replaced by a hetero group, NR, O, S, which possesses two mobile electrons. Brown[7] predicted that the properties of tropone and of γ-pyrone VI would be similar and this has been confirmed by Dauben[8]. Mayer[9] has described the synthesis of pseudo-tropones and pseudo-tropolones, derived from α- and γ-pyrans and thia-α- and thia-γ-pyrans VII.

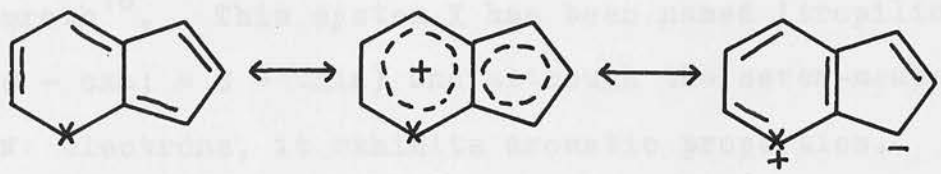


VI



VII

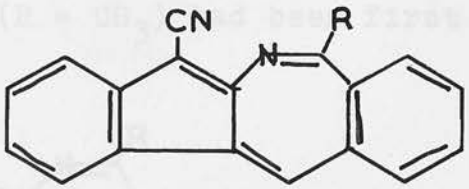
Pseudo-azulenes, too, have aroused interest and derivatives of VIII, in which X = O[10,11](oxalenes); = S[12](thialenes); = NCH_3[13,14], have been synthesised and shown to resemble azulene.



VIII

The hetero groups, N, O^+, S^+, $\overset{+}{N}R$, which possess one mobile electron, may replace a benzenoid -CH= group in a system, without any loss of aromatic character by the system. Until recently, no seven-membered aromatic systems which contained a hetero group of this type were known, but the synthesis of the 4-aza-azulene IX has been achieved by Treibs,[15] although, as yet, the properties of the system have

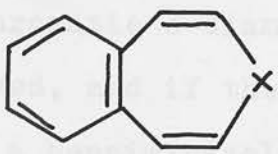
not been reported.



R = H, OH, Cl.

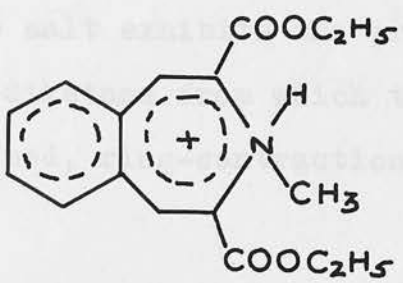
IX

Heterocyclic systems which may be regarded as derivatives of cycloheptatriene, in which the methylene group has been replaced by the hetero groups, NR, O, S, have been prepared recently by Dimroth[16]. This system X has been named 'tropilidene' (X = N - aza; = O - oxa; = S - thia) and although the seven-membered ring possesses 8 π electrons, it exhibits aromatic properties. The great stability of these tropilidenes in concentrated acids is attributed to the formation of the hetero tropylium ion, i.e. azatropylium ion, XI, which has a sextet of π electrons.



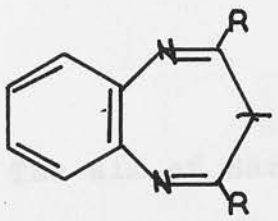
X = NCH_3
= O
= S

X



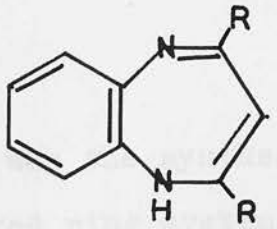
XI

Heterocyclic systems in which two hetero groups are present in a seven-membered ring, are also known. Such a system is (1,5)-benzodiazepine XII (R = H), the 2,4-dimethyl derivative of which XII (R = CH_3) had been first synthesised by Thiele, in 1907.[17]



R= H, CH_3

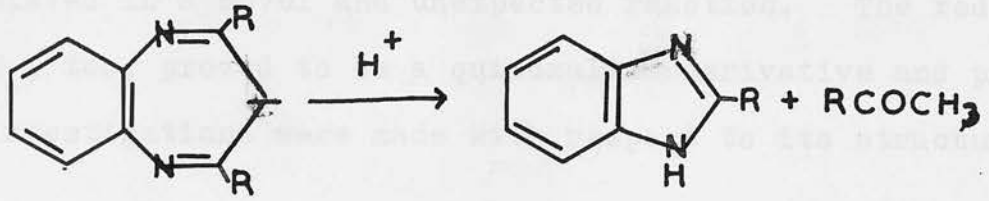
XII



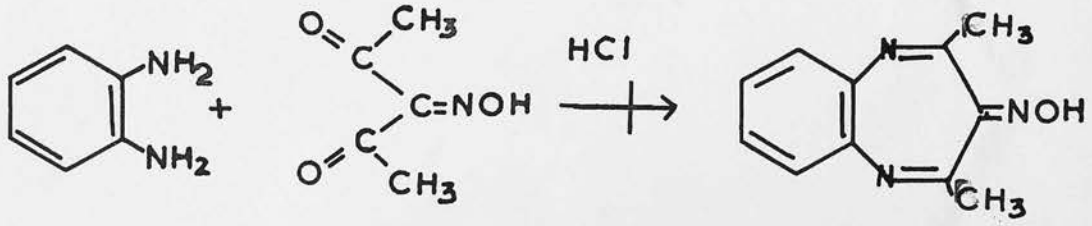
XIII

The (1,5)-benzodiazepines could exist in the form XIII, but Barltrop[18] has shown that the free bases in the solid state and in organic solution exist in the di-imino form XII.

That these diazepines, which are colourless solids and which give deep purple salts in acid, are not aromatic is easily demonstrated. Structure XII has not the requisite cyclic conjugation and structure XIII, which has cyclic conjugation, has 8π electrons associated with the seven-membered ring. Unlike the tropilidenes, the (1,5)-benzodiazepines are unstable in acid solution: the aqueous solution of a benzodiazepine salt exhibits the properties of the aromatic o-diamine and the 1,3-diketone from which the base was derived, and if the solution is warmed, ring-contraction occurs to give a benziminazole.[17]



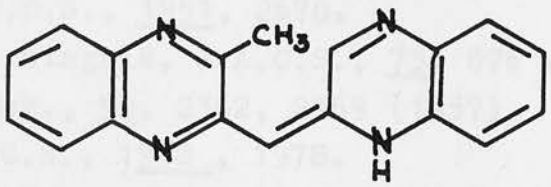
The aim of Barker's research[19] was the synthesis of fully conjugated heterocyclic seven-membered ring systems and (1,5)-benzodiazepines, which are easily accessible, were chosen for the initial investigations. During the course of this work, an attempt was made to prepare 3-hydroxyimino-2,4-dimethyl-1,5-benzodiazepine, XIV, by the condensation of o-phenylenediamine with isonitrosoacetylacetone in dilute acid; the products from this reaction were 2-methylbenziminazole, 2-acetyl-3-methylquinoxaline and its oxime, hydrogen cyanide, ammonia and a red base, $C_{20}H_{14}N_4$.



XIV

The isolation of these quinoxaline derivatives led to further investigations in the quinoxaline field and, in particular, to the isolation of an orange base, $C_{18}H_{14}N_4$, methin-(2-(3-methyl)quinoxa-

linyl)- (2'-dihydroquinoxaline) XV. The synthesis of this base was achieved in a novel and unexpected reaction. The red base, $C_{20}H_{14}N_4$, too, proved to be a quinoxaline derivative and preliminary investigations were made with respect to its structure.



XV

The nitrogen heterocyclic series which was studied in this thesis, was the quinoxaline series and two problems were tackled. Firstly, the applicability of the novel reaction, involved in the synthesis of methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline), to the synthesis of other bases was investigated, and secondly, a more extensive study of the red base, $C_{20}H_{14}N_4$, was undertaken.

B I B L I O G R A P H Y

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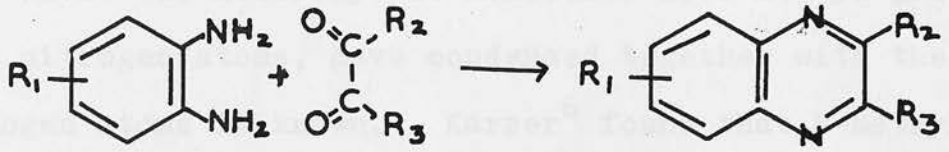
PART I.

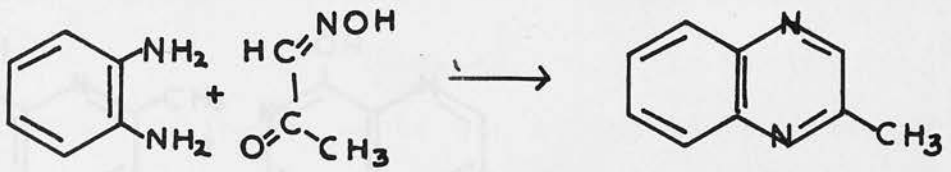
SYNTHESES IN THE QUINOXALINE SERIES.

INTRODUCTION

The simplest and most convenient way of preparing quinoxalines is by the condensation of 1,2-diketones with primary aromatic o-diamines. This reaction goes readily in ethanol or acetic acid and for this reason is used qualitatively for characterising 1,2-diketones and aromatic o-diamines.



2-Methylquinoxaline[1,2] I is readily prepared by the condensation of o-phenylenediamine and hydroxyiminoacetone in dilute acetic acid.

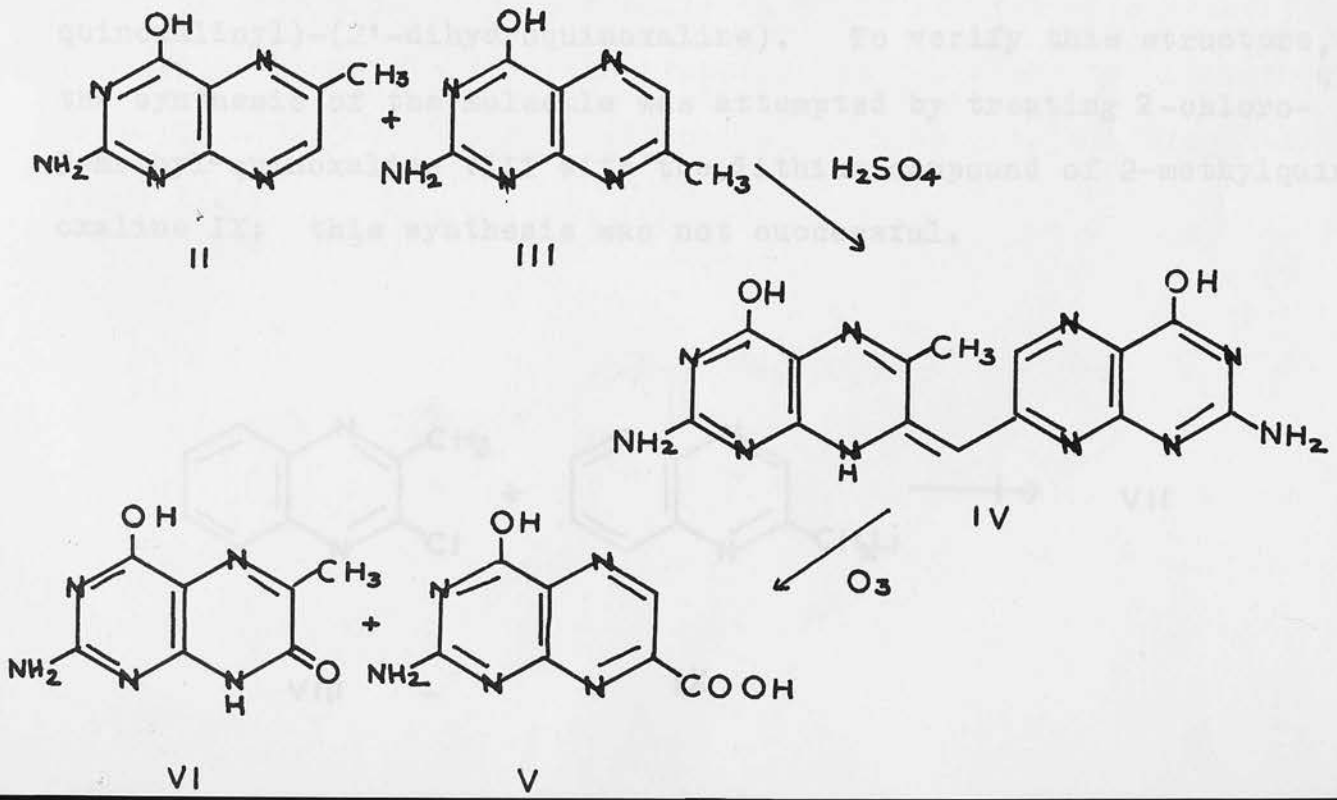


I

If, however, the reaction is carried out in dilute hydrochloric acid, not only is 2-methylquinoxaline formed, but also an orange base, $C_{18}H_{14}N_4$. Furthermore, the orange base can be obtained in greater yield when 2-methylquinoxaline itself is heated in dilute hydrochloric acid.[3,4].

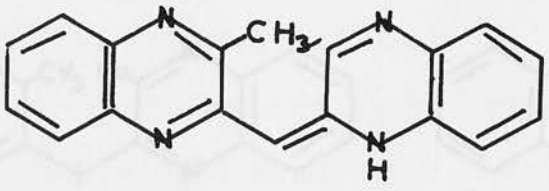
The analysis suggests that two molecules of 2-methylquinoxaline have condensed together with the loss of two atoms of hydrogen. That the compound is a true compound and not a molecular compound was confirmed by its ultraviolet and visible spectrum which differed from the spectrum of the starting material.

The methyl group in 2-methylquinoxaline is in the α position to the ring nitrogen atom and is consequently activated,[5] and another case where two heterocyclic molecules with methyl groups α to the ring nitrogen atoms, have condensed together with the loss of two hydrogen atoms is known. Karrer[6] found that 8-methyl-2-amino-6-oxy-pteridine II and 9-methyl-2-amino-6-oxy-pteridine III would react in dilute sulphuric acid to give a red pigment, $C_{14}H_{12}N_{10}O_2$, which was named 'methyl pteridine red'. A methine structure IV was suggested for this pigment and as ozonolysis of the molecule yielded 2-amino-6-pteridine-9-carboxylic acid V and methyl isoxanthopterin VI, the structure IV is justified.



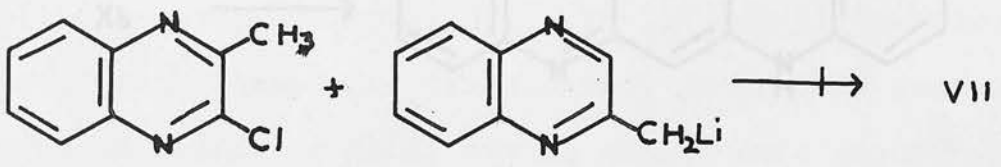
No comment on the dehydrogenation, which took place in the presence or absence of oxygen, was made, save that the sulphuric acid might be involved.

In view of this condensation, Leese and Rydon [4] proposed a similar structure VII for the orange base, which they named 'methyl quinoxaline orange.'



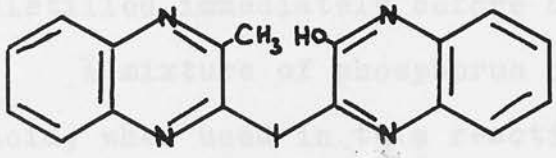
VII

Stafford and Barker[3], after consideration of several possible structures, independently put forward the same structure VII for the orange base, which they called methin-(2--(3-methyl) quinoxalinyl)-(2'-dihydroquinoxaline). To verify this structure, the synthesis of the molecule was attempted by treating 2-chloro-3-methyl-quinoxaline VIII with the lithium compound of 2-methylquinoxaline IX; this synthesis was not successful.

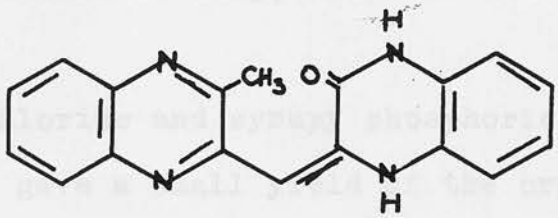


VIII IX VII

A further attempt to synthesise the orange base was made starting from the compound obtained by condensing ethyl (2-(3-methyl)quinoxalinyl)-pyruvate[2] with o-phenylenediamine; this compound had been formulated as (3-methyl-3'-hydroxy-2:2'-diquinoxalinyl)methane Xa, but a consideration of its properties suggests that the likely structure is methin-(2-(3-methyl)quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) Xb.



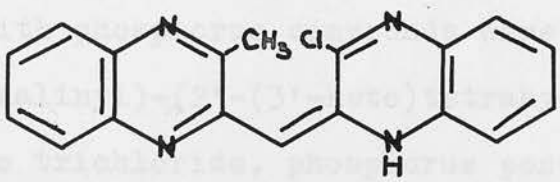
Xa



Xb

This compound Xb is extremely insoluble and since it was thought that the removal of a chlorine atom from the molecule might be accomplished more readily than the removal of a hydroxyl group, the first stage in the proposed synthesis was the formation of methin-(2-(3-methyl)quinoxalinyl)-(2'-(3'-chloro)dihydroquinoxaline) XI.

Xb ⟶



XI

Thus, compound Xb was treated with phosphorus oxychloride and from the reaction mixture was isolated, not the expected chloro-compound XI, but the orange base VII itself. This was unexpected and the experiment was repeated with a fresh sample of phosphorus oxychloride : no orange base was obtained from this second reaction.

Investigations on the first sample of phosphorus oxychloride showed that it was an old sample, and it was suspected that it might contain impurities and might also be damp, since it was not distilled immediately before use.

A mixture of phosphorus oxychloride and syrupy phosphoric acid, when used in this reaction, gave a small yield of the orange base; a mixture of phosphorus oxychloride and concentrated hydrochloric acid gave a better yield; but a solution of dry hydrogen chloride in phosphorus oxychloride gave no base at all. Addition of water to the phosphorus oxychloride gave more promising results and a series of experiments indicated the optimum conditions for the reaction - the ratio of the amounts of phosphorus oxychloride and water, and the time of heating; in this way, methin-(2-(3-methyl)quinoxalinyl)- (2'-(3'-keto)tetrahydroquinoxaline) Xb could be converted to methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) VII in 47% yield.

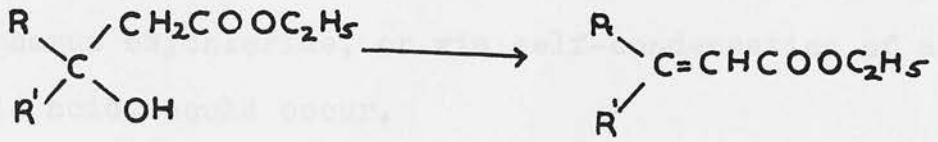
Further experiments with phosphorus compounds were carried out : methin-(2-(3-methyl)quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) was treated with phosphorus trichloride, phosphorus pentachloride and phosphorus in hydriodic acid, but no orange base was formed.

It, therefore, seemed that the reaction was not a simple reduction, involving the oxidation of trivalent phosphorus to pentavalent phosphorus, but a more complex reaction, involving both phosphorus oxychloride and water and perhaps even a splitting and recombining of the methine molecule.

DISCUSSION OF RESULTS

DISCUSSION

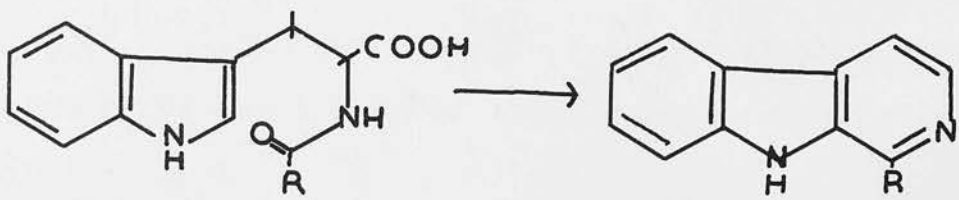
Phosphorus oxychloride is one of the most common and versatile inorganic reagents used in the preparation of organic compounds. Alone, or in a mixture with phosphorus pentachloride, it is an extremely efficient reagent for the replacement of hydroxyl groups by chlorine atoms. In a mixture with pyridine or with baryta[8], it can be used for the phosphorylation of hydroxyl groups, and a mixture of phosphorus oxychloride in pyridine has also been used for the dehydration of β-hydroxy saturated acid esters XII to αβ - unsaturated acid esters XIII[9].



XII XIII

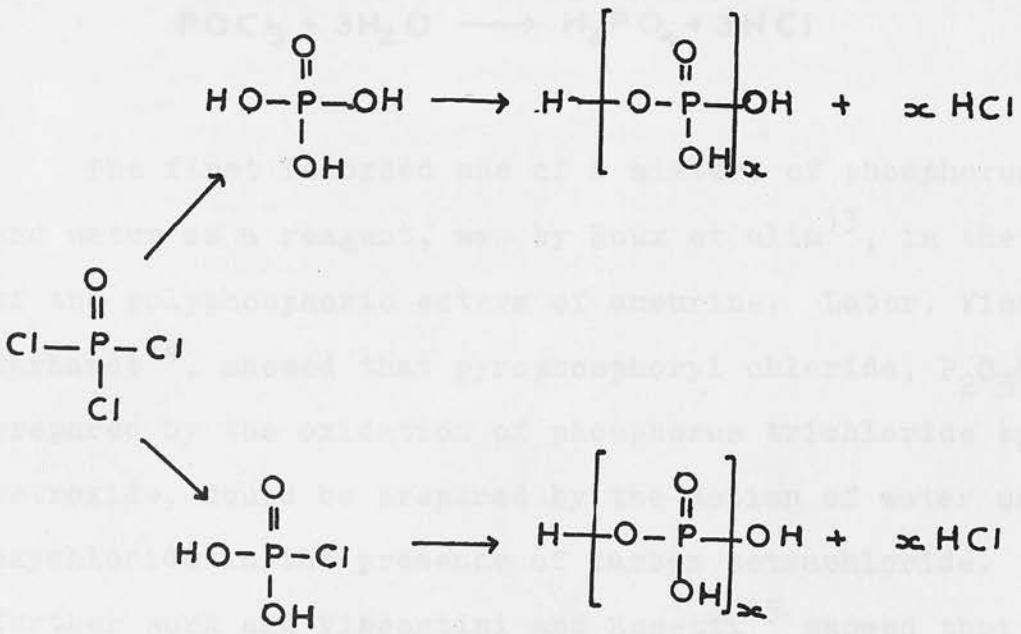
Sometimes phosphorus oxychloride can be used as a catalyst, as in the preparation of N-acylanilines[10], or a small amount can be added to another substance to produce an active reagent.[11]

An unusual reaction involving phosphorus oxychloride, was noted by Snyder and Werber[12], who observed that when an α-acylamino-β-arylpropionic acid was treated with an old sample of phosphorus oxychloride, cyclodehydration took place.

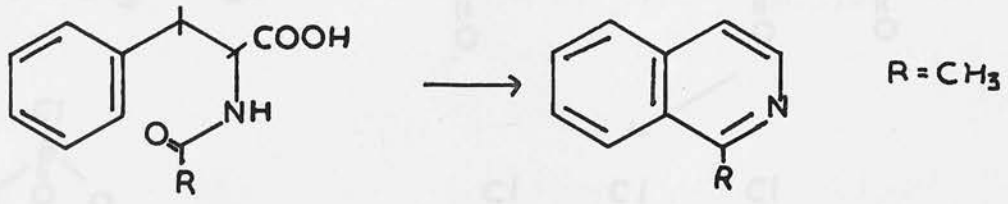


35% yield

The 'aged phosphorus oxychloride', as they termed it, had brought about elimination of water, carbon dioxide and hydrogen. When fresh phosphorus oxychloride and other dehydrating agents (phosphorus pentoxide, zinc chloride etc.) were used, only resinous products were obtained. It appeared that cyclisation was effected by a product (or a mixture of products) of the slow hydrolysis of phosphorus oxychloride and accordingly, phosphorus oxychloride and varying amounts of water, phosphorus oxychloride in phosphoric acid, and phosphoric acid were tried as reagents, but without success. The suggestion was then made that the active agent might be a polymer of phosphoric acid, which could arise from slow hydrolysis and then polymerisation, either via phosphoric acid and phosphorus oxychloride, or via self-condensation of a chloro-phosphonic acid, could occur.



Snyder found that a mixture of phosphorus oxychloride and polyphosphoric acid would give the required cyclodehydration and this method was used to prepare harman XIV.



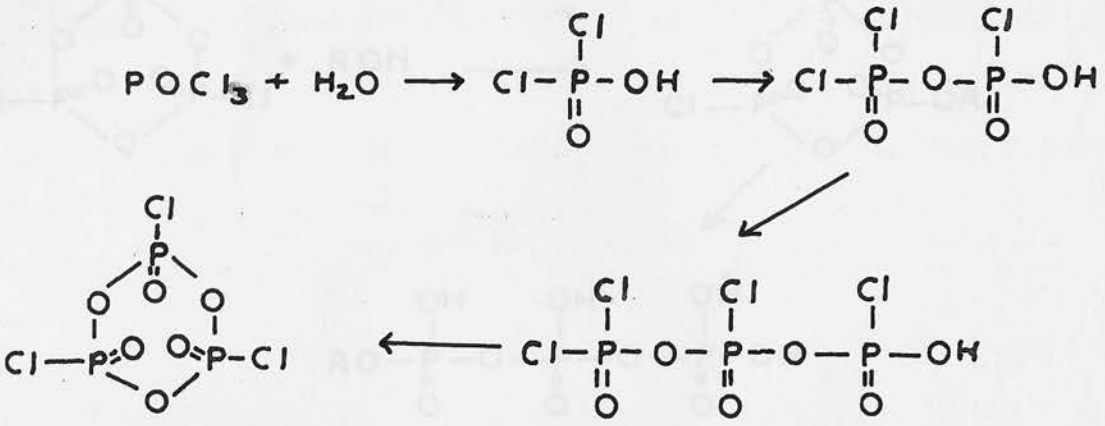
XIV

It has been known for many years that the reaction between water and phosphorus oxychloride produced phosphoric acid and hydrogen chloride, but until recently, no study of the intermediate products had been made.

$$POCl_3 + 3H_2O \longrightarrow H_3PO_4 + 3HCl$$

The first recorded use of a mixture of phosphorus oxychloride and water as a reagent, was by Roux et alia[13], in the preparation of the polyphosphoric esters of aneurine. Later, Viscontini and Ehrhardt[14], showed that pyrophosphoryl chloride, $P_2O_3Cl_4$, normally prepared by the oxidation of phosphorus trichloride by nitrogen tetroxide, could be prepared by the action of water on phosphorus oxychloride in the presence of carbon tetrachloride. This led to further work and Viscontini and Bonetti[15] showed that the main product from the interaction of 1 mole of phosphorus oxychloride and 1 mole of water was metaphosphoric acid

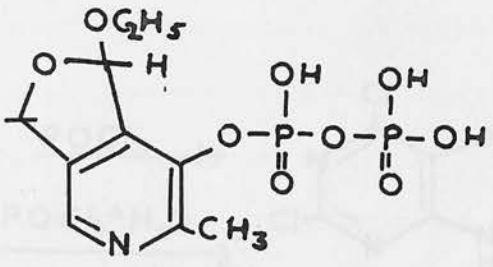
trichloride XV and suggested that it was formed in the following way.



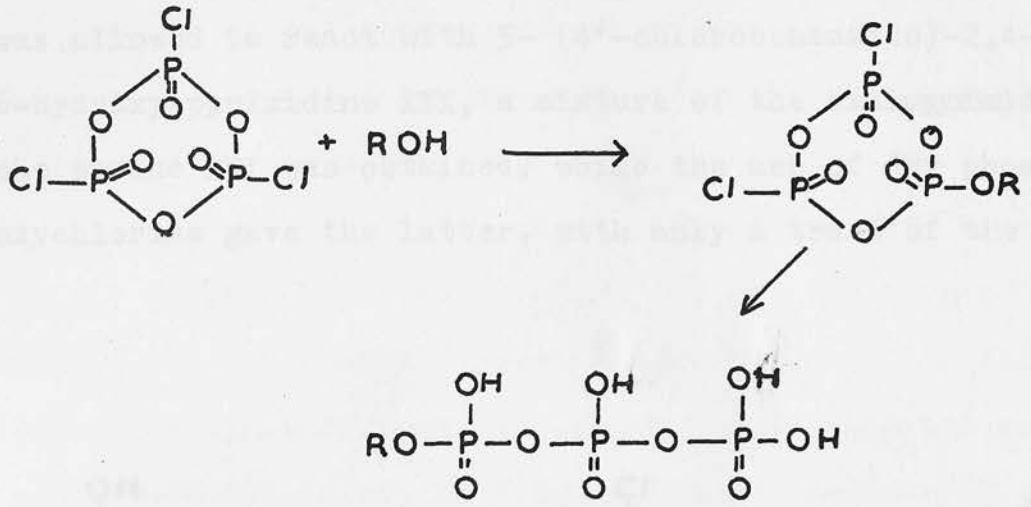
XV

Roux et alia[16] obtained evidence that there were several products, cyclic and long chain units of polyphosphoric acid chlorides, from this reaction and later[17], chromatographic methods were used to separate trimetaphosphoric acid chloride XV from the mono-, di-, and higher condensed phosphorus oxychlorides.

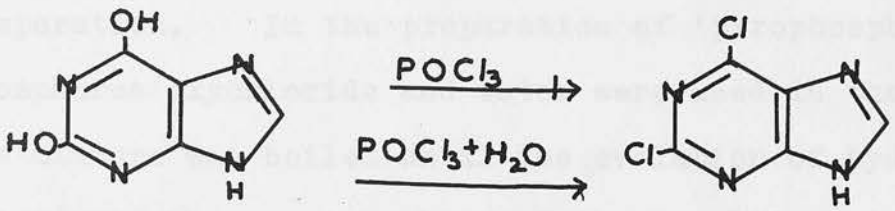
Viscontini[15], having prepared compound XV, used it to prepare pyridoxal-ethyl-acetal-3-pyrophosphoric ester XVI and suggested a possible mechanism for the reaction.



XVI

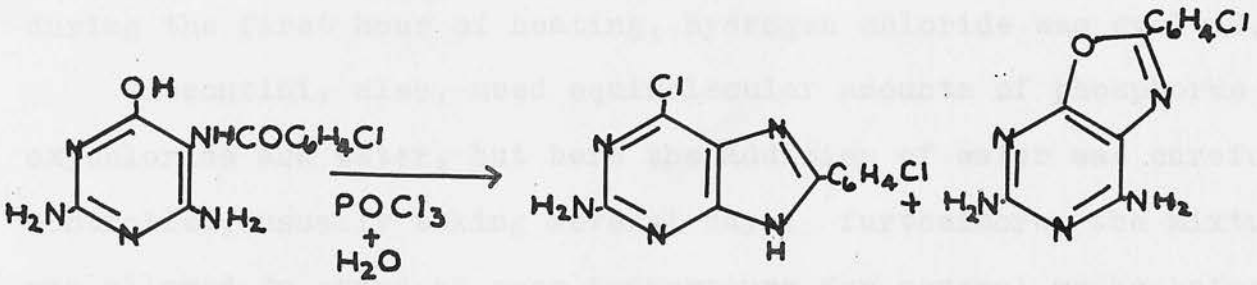


While Roux and Viscontini had used hydrated phosphorus oxychloride for the phosphorylation of hydroxy compounds, Hitchings found that a mixture of water and phosphorus oxychloride could be used for replacing hydroxyl groups by chlorine atoms.[18] He observed that, whereas pure dry phosphorus oxychloride did not react with xanthine XVII, the dichloro compound XVIII was obtained with the mixture he had named 'pyrophosphoryl chloride' (a serious misnomer, as pyrophosphoryl chloride is the known compound, $P_2O_3Cl_4$).



XVII XVIII

Furthermore, it was found that if 'pyrophosphoryl chloride' was allowed to react with 5- (4'-chlorobenzamido)-2,4-diamino-6-hydroxy-pyrimidine XIX, a mixture of the oxalopyrimidine XX and the purine XXI was obtained, while the use of dry phosphorus oxychloride gave the latter, with only a trace of the former.[19]



XIX $\xrightarrow{POCl_3}$ XXI [quantity] + XX [trace]

Thus,a mixture of phosphorus oxychloride and water has been used for the phosphorylation, chlorination and reduction of hydroxy compounds; furthermore, the compounds were all derivatives of nitrogen heterocyclic bases, where the hydroxyl group was present in the heteroaromatic ring.

It would seem that the difference in reactivity of these three phosphorus oxychloride-water reagents, is related to the method of preparation. In the preparation of 'pyrophosphoryl chloride'[18], phosphorus oxychloride and water were used in the proportion of 2:1. The mixture was boiled until the evolution of hydrogen chloride ceased and the aqueous phase of the resulting mixture was decanted

from the syrup, and used directly as the reagent.

Equimolecular amounts of phosphorus oxychloride and water were used by Stafford and Barker, and here, the water was added to the cooled phosphorus oxychloride at such a rate that the reaction never became violent - the usual time for the addition of water (3 ml) to phosphorus oxychloride (20 ml) was 15 minutes. This mixture and the reactant were then heated at 130°C for 2 hours and during the first hour of heating, hydrogen chloride was evolved.

Viscontini, also, used equimolecular amounts of phosphorus oxychloride and water, but here the addition of water was carefully controlled, usually taking several days; furthermore, the mixture was allowed to stand at room temperature for several weeks before the excess phosphorus oxychloride and water were removed and the reagent distilled.

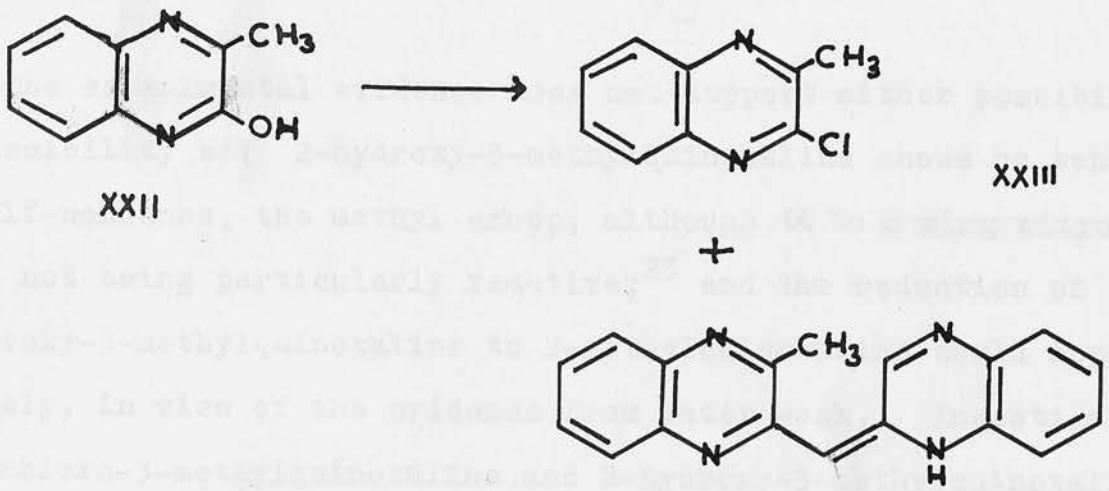
Another point is the method of use : phosphorylation was carried out with hydrated phosphorus oxychloride in pyridine at room temperature, while chlorination and reduction were effected by heating the respective reagents with the reactant in the absence of solvent.

While methin-(2-(3-methyl)quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) was not treated with Hitchings' 'pyrophosphoryl chloride', it was allowed to react in the absence of pyridine, with hydrated phosphorus oxychloride, prepared according to the method of Roux and Viscontini[17]. From the resulting mixture, starting material (80%) was recovered and methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) (50% yield), based on unrecovered starting

material) was isolated, along with a very small amount of a yellow-orange solid, M.P. 237-243°C.

Since Barker and Stafford obtained methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) from this reaction in 47% yield, it suggests that the reduction of the base and the reaction between phosphorus oxychloride and water, are intimately related.

It had been observed by Spring[20] that a red colour was obtained when 2-hydroxy-3-methylquinoxaline XXII was treated with freshly distilled phosphorus oxychloride to convert it to 2-chloro-3-methylquinoxaline XXIII. This colour was not further investigated until Barker, while repeating this work, noticed the colour and isolated from the reaction mixture an orange compound, which proved to be methin-(2-(3-methyl)quinoxalinyl)- (2'-dihydroquinoxaline) XXIV in 4% yield.



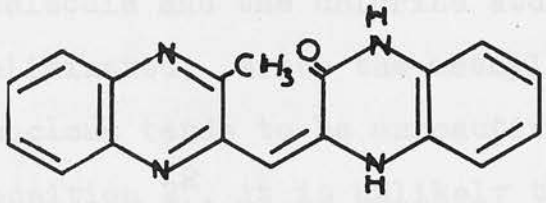
XXII

XXIII

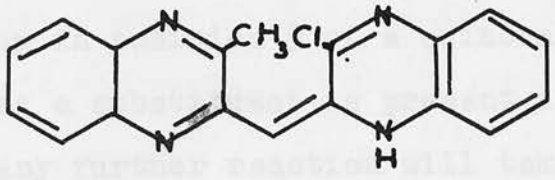
+

XXIV

The base XXIV could arise in four ways: a) Self-condensation of 2-hydroxy-3-methylquinoxaline to give methin-(2-(3-methyl)quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) XXV which would then reduce to give the required base XXIV. b) Reduction of 2-hydroxy-3-methylquinoxaline to 2-methylquinoxaline which would self-condense to give the required base. c) The compound XXV could be formed by the condensation of 2-hydroxy-3-methylquinoxaline and 2-chloro-3-methylquinoxaline and the base obtained by reduction. d) Self-condensation of 2-chloro-3-methylquinoxaline to give a molecule of type XXVI which could be reduced to the base.



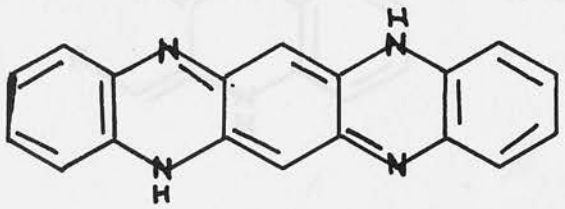
XXV



XXVI

The experimental evidence does not support either possibility a) or possibility b); 2-hydroxy-3-methylquinoxaline shows no tendency to self-condense, the methyl group, although α to a ring nitrogen atom, not being particularly reactive,[23] and the reduction of 2-hydroxy-3-methylquinoxaline to 2-methylquinoxaline would appear unlikely, in view of the evidence from later work. Investigation of 2-chloro-3-methylquinoxaline and 2-hydroxy-3-methylquinoxaline in phosphorus oxychloride was impracticable, so attention was focussed on 2-chloro-3-methylquinoxaline.

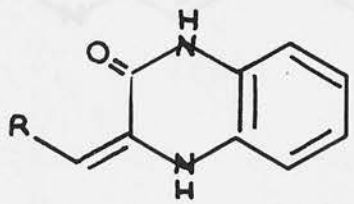
It was found that 2-chloro-3-methylquinoxaline was unaffected by freshly distilled phosphorus oxychloride, but when a mixture of water and phosphorus oxychloride was used, methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) in 12.5% yield,[22] was isolated along with unreacted starting material. This, then, would indicate that the formation of methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) from the interaction of 2-hydroxy-3-methylquinoxaline and phosphorus oxychloride takes place via 2-chloro-3-methylquinoxaline. The problem lies in the formation of the larger molecule. It has been suggested that a molecule of structure XXVI could be formed by the straightforward reaction of the methyl group of one molecule and the chlorine atom of another, hydrogen chloride being eliminated; since the methyl group in position 3 of a quinoxaline nucleus tends to be unreactive when a substituent is present in position 2[2], it is unlikely that any further reaction will take place to give homofluorindine XXVII.



XXVII

Again, experimental evidence suggests that the reduction of the relatively stable 2-chloro-3-methylquinoxaline to 2-methylquinoxaline with subsequent self-condensation, is unlikely. It must be concluded that although methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) is obtained, albeit in low yield, by the reaction of phosphorus oxychloride on 2-hydroxy-3-methylquinoxaline, and by the reaction of phosphorus oxychloride and water on both 2-hydroxy-3-methylquinoxaline and 2-chloro-3-methylquinoxaline, its mode of formation is not yet understood.

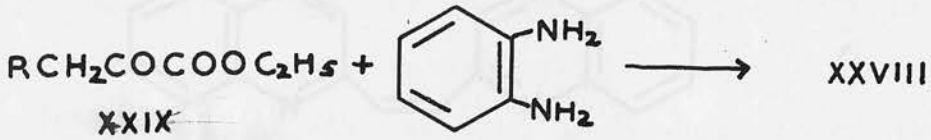
It was of interest to examine the effect of phosphorus oxychloride and water on other α-hydroxy nitrogen heterocyclic bases, and the first compounds studied were of the same form as methin-(2-(3-methyl)quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) XXVIII.



R is an α-substituted base

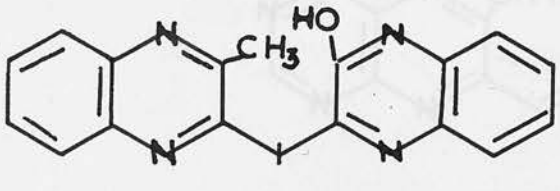
XXVIII

Compounds of this type were first synthesised by Borsche and Doeller,[2] by the condensation of the appropriately substituted pyruvic ester XXIX with o-phenylenediamine.

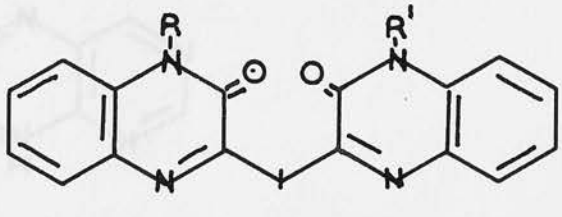


XXIX XXVIII

Borsche formulated his compound from ethyl 2-(3-methyl)quinoxalinyl-pyruvate and o-phenylenediamine as (3-methyl-3'-hydroxy-2,2'-diquinoxalinyl-)methane XXX, and his example was followed by Cook and Naylor,[23] who synthesised molecules of type XXXI.



XXX

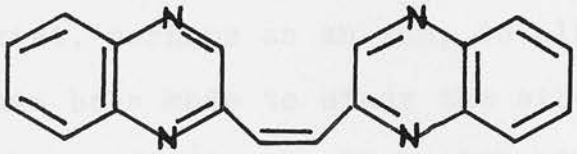


R = H, CH_3, C_6H_5
R' = CH_3, C_6H_5

XXXI

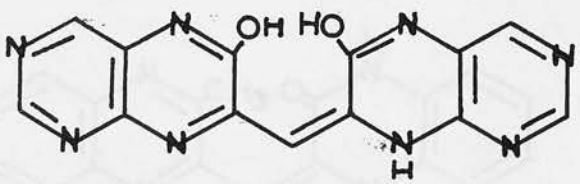
Since these compounds are highly coloured (usually orange or red) and insoluble in most organic solvents, except nitrobenzene and pyridine, the methylene structure seems unlikely; by analogy with diquinoxalinyl-ethylene XXXII, a molecule in which two quinoxaline nuclei are linked by a hydrocarbon chain in which

tautomerism is unlikely, a methylene derivative would be a colourless compound.



XXXII

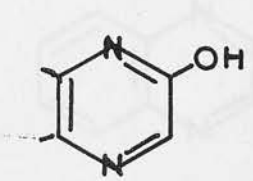
Methine derivaties, for example pterorhodin[24], XXXIII, are highly coloured compounds and the hydroxy derivatives tend to be insoluble in most organic solvents and to be high melting.



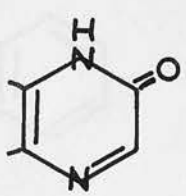
XXXIII

It would appear that the methine structure is more probable than the methylene structure for these compounds XXVIII.

Borsche, furthermore, assumed that the lactim structure XXXIVa was present, although the possibility of the lactam structure XXXIVb did exist.



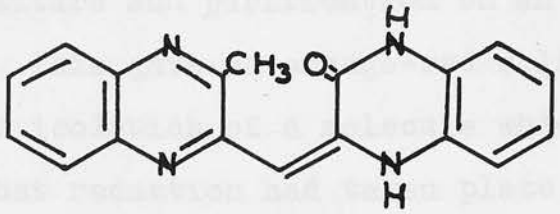
XXXIVa



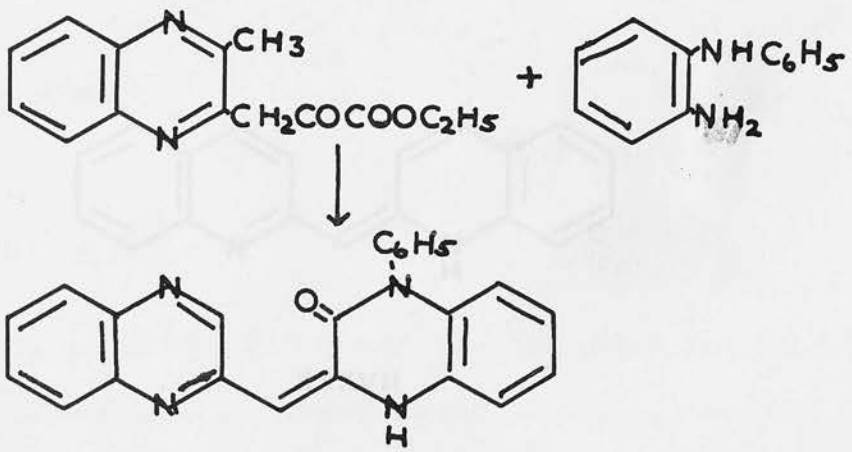
XXXIVb

Studies by Cheeseman[25] and Bodforss[26] on 2-hydroxyquinoxalines and their N-methyl and O-methyl derivatives, have indicated that in solution, the compounds exist in the lactam form, XXXIVb, and not in the lactim form, XXXIVa; Bodforss has shown that the lactim form does exist, perhaps as an ion, in alkaline solution. As yet, no attempt has been made to study the structure of solid hydroxyquinoxalines, but if the parallel with other α-hydroxy nitrogen heterocyclic bases holds, then the 2-hydroxyquinoxalines will exist in the amide form in the solid state.[27]

It, therefore, seems likely that the methine compounds will exist in the lactam form XXXV and this supposition is borne out by the similarity between the compounds XXXV and XXXVI prepared by Cook[23] - compound XXXVI must have the lactam structure.

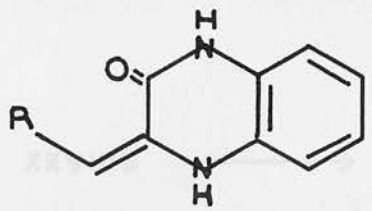


XXXV



XXXVI

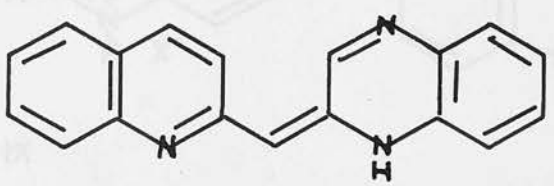
Several compounds of structure XXVIII were prepared: the pyruvic esters by a modification of the procedure of Wislicenus[28] and the methin-(2'-(3'-keto)tetrahydroquinoxaline) derivatives by the method of Borsche.[2]



XXVIII

R = 2-quinolinyl- XXVIIIa
= 2-pyrazinyl- " b
= 2-quinoxalinyl- " c

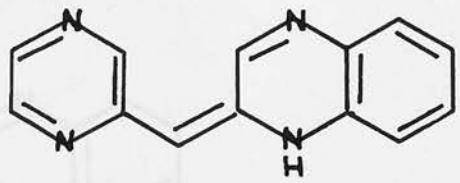
Methin-(2-quinolinyl)-(2'-(3'-keto)tetrahydroquinoxaline) XXVIIIa reacted smoothly with the phosphorus oxychloride-water mixture, and after extraction of the basic substances from the resulting mixture and purification on an alumina column, one band separated. This gave an orange-red solid, $C_{18}H_{13}N_3$, in 87.5% yield. The isolation of a molecule which did not contain oxygen, indicated that reduction had taken place and the proposed structure for this compound is methin-(2-quinolinyl)-(2'-dihydroquinoxaline) XXXVII.



XXXVII

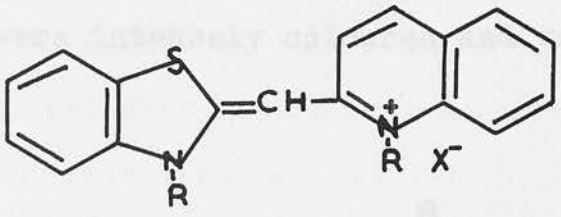
Similarly, a dark red base, $C_{13}H_{10}N_4$, was isolated in 32% yield from the reaction of the phosphorus oxychloride-water mixture with methin-(2-pyrazinyl)-(2'-(3'keto)tetrahydroquinoxaline) XXVIIIb. The structure suggested for this product is methin-(2-pyrazinyl)-(2'-dihydroquinoxaline) XXXVIII.

XXVIIIb ⟶

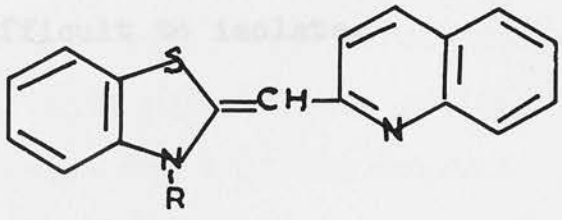


XXXVIII

The structures XXXVII and XXXVIII are similar to those of the monomethincyanines,[29] e.g. thia-2'-cyanine XXXIX. Cyanines, of course, by definition, possess both a tertiary and a quaternary nitrogen atom, but several of the bases of which cyanine dyes are quaternary derivatives, have been prepared,[30] e.g. 2-methyl-thio-ψ-cyanine XL, the base of the compound XXXIX, has been prepared.



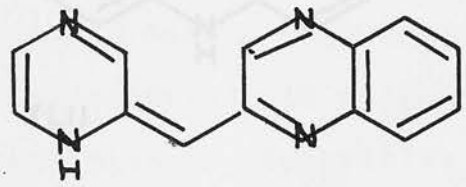
XXXIX



XL

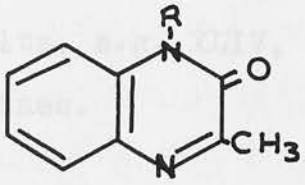
One point of interest concerning the base XL, is that the alkyldihydro structure is never found on the quinoline nucleus

(unless by synthesis from the N-substituted quinoline[31]) and so, by analogy, the molecule of methin-(2-quinolinyl)-(2'-dihydroquinoxaline) XXXVII will always have the dihydro structure in the quinoxaline nucleus. With methin-(2-pyrazinyl)-(2'-dihydroquinoxaline) XXXVIII, on the other hand, it is equally likely that the dihydro structure can be found on the pyrazine nucleus XXXVIIIa.



XXXVIIIa

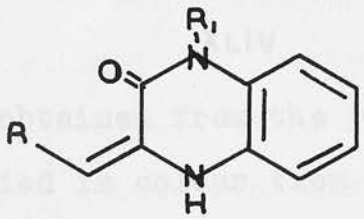
Quinoxaline cyanines have not been as thoroughly studied as the cyanines of other bases. The first reference to the use of quinoxalines in cyanine dye syntheses is in a patent[32] and the only study has been made by Cook.[33] He showed that the methyl group in 2-methylquinoxaline and one of the methyl groups in 2,3-dimethylquinoxaline participate in cyanine dye formation, as do compounds of type XLI. The dyes obtained from these compounds were intensely coloured and very difficult to isolate.



R = CH_3, C_2H_5, C_6H_5

XLI

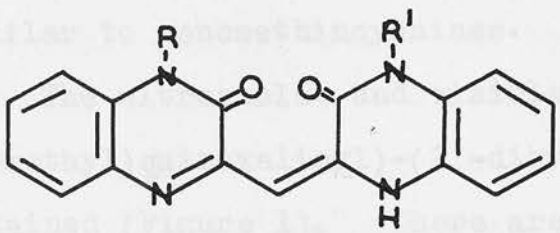
In an extension of the work, compounds of types XLII and XLIII were prepared and unsuccessful attempts were made to quaternise the compounds of type XLIII, although brilliantly coloured solutions were obtained.



XLII

R_1 = H, CH_3

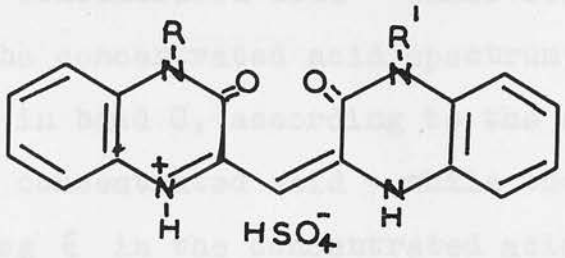
R = 2-quinolinyl, etc.



XLIII

R and R^1 - combinations of CH_3, H, C_6H_5

It was found that compounds of these two types gave intensely coloured solutions in concentrated sulphuric acid, the colours of solutions of substances in which both heterocyclic nuclei were quinoxaline derivatives, being particularly brilliant and also stable. It was therefore suggested that the colours were due to salts, e.g. XLIV, which may be compared to monomethincyanines.



XLIV

The bases obtained from the phosphorus oxychloride-water reductions, varied in colour from orange to dark red, and gave intensely coloured solutions in sulphuric acid - deep green in concentrated acid, blue or blue-violet in dilute acid and red in very dilute acid - and it is probable that they are forming salts similar to monomethincyanines.

The ultraviolet and visible absorption spectrum of methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) in ethanol has been obtained (Figure 1). There are three main absorption bands, designated A, B and C with the possibility of yet another band in the far ultraviolet region. (Simple 2- and 2,3-substituted quinoxalines normally possess two-banded spectra.[34]) The absorption spectra in dilute and in concentrated sulphuric acid were also obtained (Figure 2) and the three-banded spectra found to persist: the position of band A remained unchanged, although the value of log ϵ fell according to the solvent - ethanol > dilute acid > concentrated acid; the double peak in band B disappeared in acid solution and there was a bathochromic shift of the maxima without significant change in log ϵ , according to the solvent - ethanol <

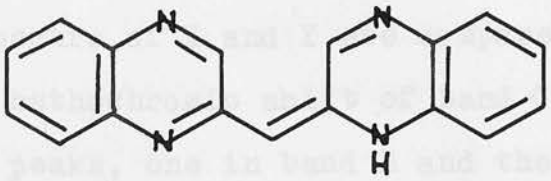
dilute acid < concentrated acid - while some fine structure appeared in the concentrated acid spectrum; there was a bathochromic shift in band C, according to the solvent - ethanol < dilute acid < concentrated acid - while there was also a slight increase in log ϵ in the concentrated acid spectrum.

The ultraviolet and visible spectra of methin-(2-quinolinyl)-(2'-dihydroquinoxaline) and methin-(2-pyrazinyl)-(2'-dihydroquinoxaline) in ethanol were obtained (Figures 3 and 4), and the resemblance to the spectrum of methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) is most marked - three-banded spectra with a double peak in band B. Slight differences are found: the pyrazine base has a narrower band B than the other two, the difference between the maxima being 11 mμ while for the others, it is 18 mμ and 19 mμ ; the quinoline base has quite an amount of fine structure in band A, which is not found in the spectra of the bases which have two nitrogen atoms in this nucleus, and this is in agreement with Badger's conclusion that the replacement of a methine group by a nitrogen atom in an aromatic system, causes a loss in fine structure without marked change in the maxima.[35]

This similarity in the spectra of these three bases, indicates a similarity in structure and confirms that the quinoline and pyrazine bases have the heterocyclic nuclei linked by a methine group.

The next compound to be treated with phosphorus oxychloride and water was methin-(2-quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) XXVIIIc.

It was expected that it would react similarly to the above compounds XXVIIIa and XXVIIIb, and give methin-(2-quinoxalinyl)-(2'-dihydroquinoxaline) XLV.



XLV

The basic materials were extracted from the reaction mixture and purified on an alumina column. Two bands separated: a red band, which showed no fluorescence in ultraviolet light, was eluted with benzene-ether (9:1) and a dark red band, which showed orange fluorescence in ultraviolet light, was eluted with benzene-ether (1:3). From the first eluate was obtained a red solid, $C_{17}H_{10}N_4$, which crystallised from benzene as rose-red needles, M.P. 308-311°C. (Compound X). From the second eluate was obtained a dark solid, $C_{17}H_{11}N_4$, which crystallised from benzene as fine red-orange needles, M.P. 247-248°C. (Compound Y). Both compounds were stable.

The isolation of two bases from this reaction mixture was unexpected. The hydrogen analyses were not good; X gave an analysis for 10 hydrogen atoms and Y for 11 hydrogen atoms, whereas methin-(2-quinoxalinyl)-(2'-dihydroquinoxaline) requires 12 hydrogen atoms.

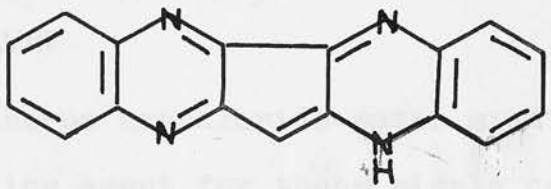
The ultraviolet and visible spectra of X and Y in dioxan are shown in Figures 5 and 6. The three-banded spectra are again found: band B in these spectra is not so well defined and although the double peak is still found, other maxima appear, particularly in the spectrum of Y.

When the spectra of X and Y are compared, it is observed that there is a bathochromic shift of band C in the spectrum of Y, and two main peaks, one in band B and the other in band A, have emerged which are only hinted at in the spectrum of X. The differences in the spectra are such as to suggest that X and Y are not isomers.

Both bases gave green solutions in concentrated sulphuric acid and blue solutions in dilute acid. The absorption spectra of X and Y in concentrated sulphuric acid are shown in Figures 7 and 8. Although both spectra have three bands, there is little resemblance between them, bands B being quite different. If, however, the spectrum of Y in sulphuric acid is compared with that of methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) in sulphuric acid (Figure 2), it is seen that they are very similar. If the spectra of the salts are similar, it is reasonable to suppose that the structures are similar and therefore, that the bases have the same type of structure, i.e. compound Y is methin-(2-quinoxalinyl)-(2'-dihydroquinoxaline), $C_{17}H_{12}N_4$. It is not usually possible to predict a melting-point with any certainty, but it had been observed that the melting-points of the various methine

bases were considerably lower than those of their methin-(2'-(3'-keto)tetrahydroquinoxaline) derivatives, and as the melting-point of Y is 70°C lower than that of methin-(2-quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline), it follows the others in this respect. The melting-point of X, 308-311°C, is only 10°C below that of methin-(2-quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline).

The number of possible structures for X is limited, since the methine structure has been assigned to Y, and cyclisation to give a five-membered ring XLVI has been suggested. This molecule has the formula, $C_{17}H_{10}N_4$, and this is in agreement with the analysis of X. Confirmation of this structure by synthesis is however required.

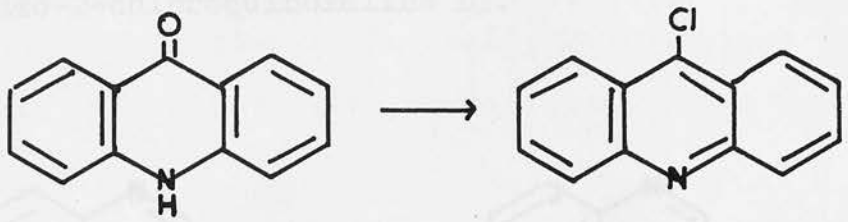


XLVI

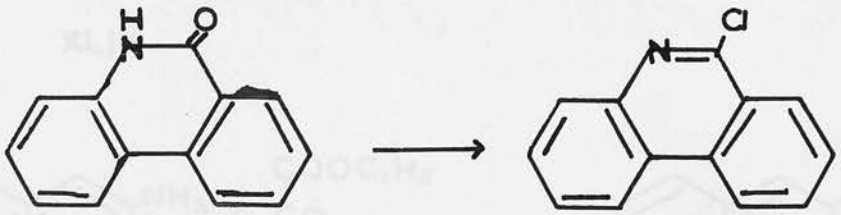
Once it had been shown that reduction of the molecule will take place in these methine systems, attention was turned to the simpler systems.

Acridone XLVII, after treatment with phosphorus oxychloride and water, gave 9-chloroacridine in 15% yield as well as a 50% recovery of the starting material. No acridine was isolated. Similarly, phenanthridone XLVIII, when treated with the reagent

gave 9-chlorophenanthridine in 10% yield and a 50% recovery of the starting material. No phenanthridine was detected.



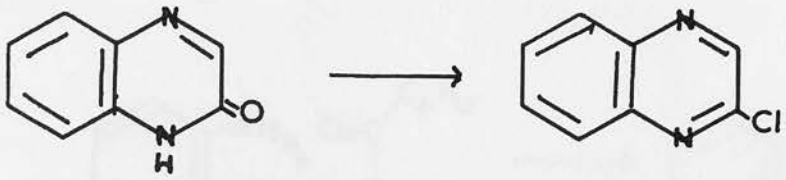
XLVII



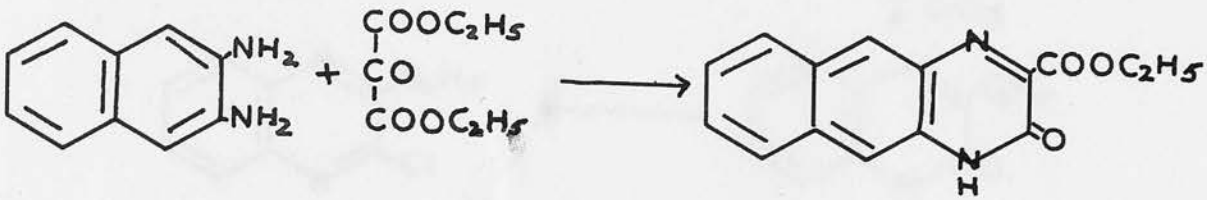
XLVIII

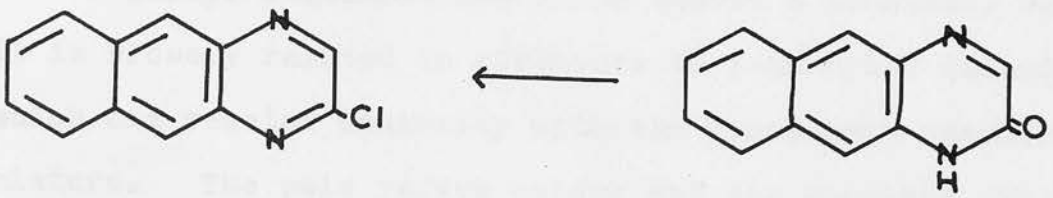
The phosphorus oxychloride-water mixture, therefore, did not act as a reducing agent for these simple compounds, but acted as an inefficient chlorinating agent - the yields of the chloro compounds being much smaller than those obtained when freshly distilled phosphorus oxychloride was used. This reduction in yield, when 'contaminated' phosphorus oxychloride was used as the chlorinating agent, had already been observed when 3-methyl-2-quinoxalone was treated with the reagent, the yield of the product being reduced from 67% with the dry reagent to 35% with the moist reagent.

2-quinoxalone XLIX, when treated with the reagent, gave only 2-chloroquinoxaline, and 6,7-benzo-2-quinoxalone L, prepared from 2,3-diaminonaphthalene and ethyl ketomalonate, gave only 6,7-benzo-2-chloroquinoxaline LI.



XLIX

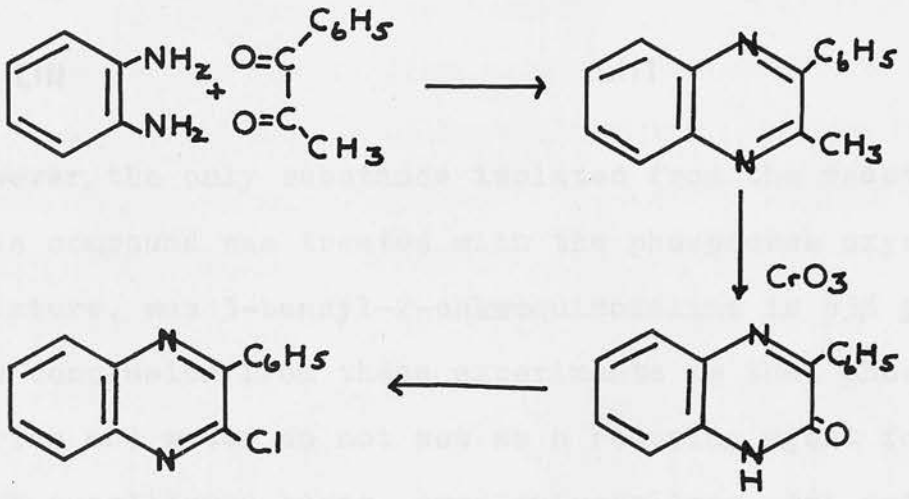




LI L

Since unsubstituted 2-quinoxalones were not reduced, several 3-substituted compounds were prepared.

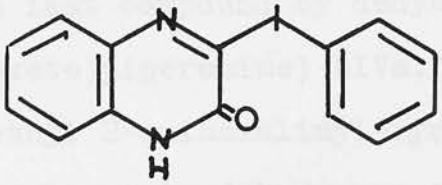
2-Methyl-3-phenylquinoxaline was prepared and oxidised to 3-phenyl-2-quinoxalone LII, according to the method of Blatt[36]. Only 2-chloro-3-phenylquinoxaline was obtained when this compound LII was treated with phosphorus oxychloride and water.



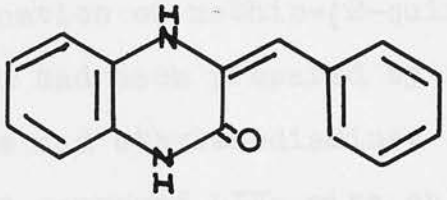
LII

3-Benzyl-2-quinoxalone LIIIa seemed a promising substance as it is closely related in structure to 3-methyl-2-quinoxalone, which had reacted unusually with the phosphorus oxychloride-water mixture. The pale yellow colour and the spectrum (Figure 9), so markedly different from that of methin-(2-pyrazinyl)-(2'-(3'-keto) tetrahydroquinoxaline (Figure 10), indicate that this molecule exists in the methylene form, although it is theoretically possible that it could exist in the methine form LIIIb. This

molecule LIIIb will possess the methin-(2'-(3'-keto)tetrahydroquinoxaline) structure found in the molecules which have been reduced by the phosphorus oxychloride-water mixture.



LIII

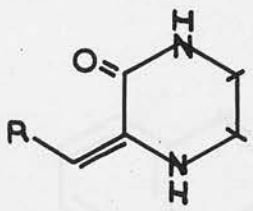


LIII

However, the only substance isolated from the reaction mixture when this compound was treated with the phosphorus oxychloride-water mixture, was 3-benzyl-2-chloroquinoxaline in 53% yield.

The conclusion from these experiments is that phosphorus oxychloride and water do not act as a reducing agent for simple α-hydroxy substituted bases, even quinoxalines, but act rather as an inefficient chlorinating agent, as compared with freshly distilled phosphorus oxychloride.

The derivatives of methin-(2'-(3'-keto)piperazine) LIV comprised the third group of compounds which were treated with phosphorus oxychloride and water.

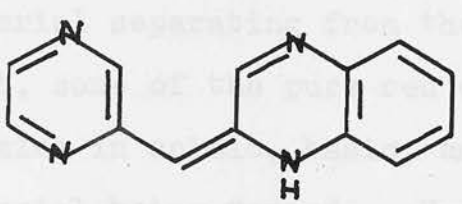


LIV

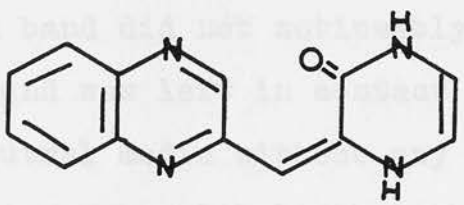
R = 2-quinoxalinyl - LIVa

= 2-pyrazinyl - LIVb

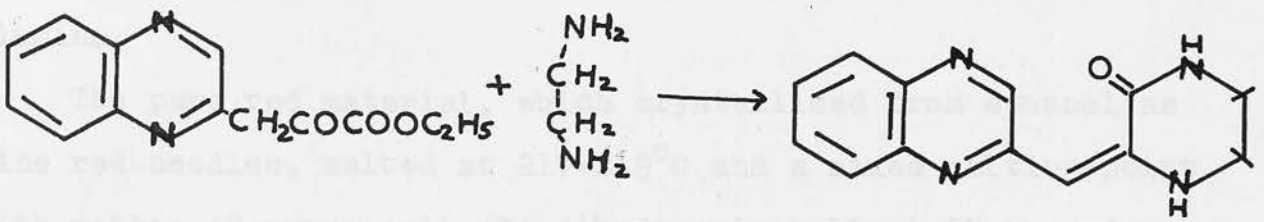
Interest in these compounds derived from the fact that the structure of methin-(2-pyrazinyl)-(2'-dihydroquinoxaline) LV could be confirmed if it were synthesised from methin-(2-quinoxalinyl)-(2'-(3'-keto)tetrahydropyrazine) LVI. It was proposed to synthesise this last compound by dehydrogenation of methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine) LIVa, which had been prepared by the condensation of ethyl 2-quinoxalinyl-pyruvate and ethylenediamine. Unfortunately, the attempt to dehydrogenate the compound LIVa with chloranil was not successful, and so it was decided to treat the compound with the phosphorus oxychloride-water mixture first and, if the reduction were successful, to dehydrogenate the base ~~LVII~~ to give methin-(2-pyrazinyl)-(2'-dihydroquinoxaline).



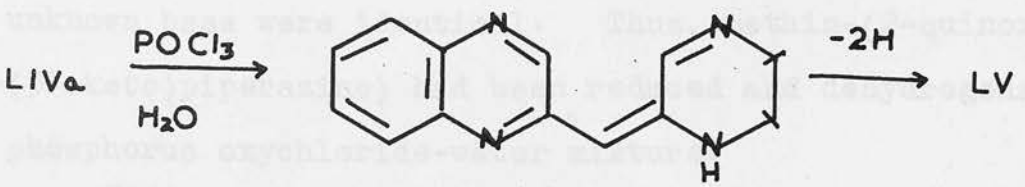
LV



LVI



LIVa

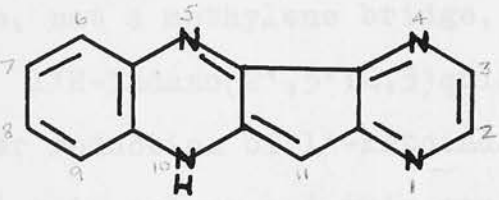


Therefore, methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine) was treated with phosphorus oxychloride and water and the basic products extracted and purified on an alumina column in the usual manner. One band separated and proved to consist of two parts: a) a brilliant yellow band, and b) a dark red band. Unfortunately, complete separation of these two bands was not achieved, even when a carefully graded series of eluants was used, but by means of several chromatographic separations, the bulk of the red material was separated from the bulk of the yellow material. This failure of the band to separate completely led to the idea that the red material was decomposing to the yellow material on the column; accordingly, some of the mixed red-yellow band was allowed to remain on the alumina for several days, but the amount of yellow material separating from the red band did not noticeably increase. Also, some of the pure red compound was left in contact with alumina in acidic, basic, and neutral media without any yellow material being formed. Hence it seems unlikely that the yellow material is formed by decomposition of the red material on the alumina.

The pure red material, which crystallised from ethanol as fine red needles, melted at 217-219°C and a mixed melting-point with methin-(2-pyrazinyl)-(2'-dihydroquinoxaline) LV showed no depression. The absorption spectra of the latter compound and of the unknown base were identical. Thus, methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine) had been reduced and dehydrogenated by the phosphorus oxychloride-water mixture.

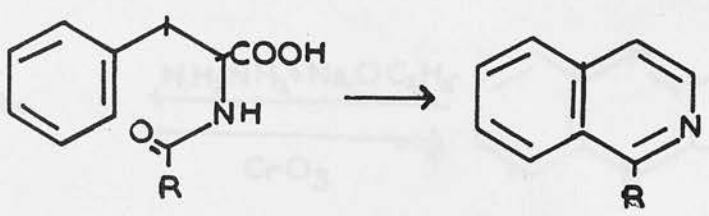
The most noticeable property of the yellow compound obtained from the above reaction is its fluorescence in solution : its solutions in organic solvents have an intense yellow-green fluorescence, even in visible light. The solid itself in ultraviolet light shows yellow fluorescence. This compound, which crystallises from ethanol as yellow cubic prisms, M.P. 202-203°C, has the formula $C_{13}H_8N_4$. It dissolves in both dilute and concentrated sulphuric acid to give pale red solutions, unlike the methine bases which give deep blue and green solutions respectively with these solvents; its spectrum in ethanol (Figure 11), however, is of the same form as those of the methine bases - three-banded, with a double peak in band B. The molecule proved to be resistant to oxidation by chromium trioxide in acetic acid. The isolation of these two bases from the action of phosphorus oxychloride and water on methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine), have aroused interest in the action of freshly distilled phosphorus oxychloride on this compound. In this case, the extracted bases gave a red-yellow band on the alumina column, but the yellow compound comprised the bulk of the band, only a very small amount of red compound being isolated. The qualitative spectrum of this last compound in ethanol is given in Figure 12, and it will be noted that, although bands A and B are the same as in the spectrum of methin-(2-pyrazinyl)-(2'-dihydroquinoxaline) (Figure 4), there is a hypsochromic shift of band C in the spectrum of the unknown compound.

The formation of a molecule of formula, $C_{13}H_8N_4$, by the action of phosphorus oxychloride, either by itself or with water, on methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine), $C_{13}H_{12}N_4O$, means that reduction and dehydrogenation have taken place. The suggested structure for this compound is 10H-pyrazino(2',3':3,4)cyclopenta(b)quinoxaline, LVII.



LVII

That phosphorus oxychloride could be involved in cyclisation reactions, has been shown by Snyder and Werber[12], who found that an 'aged' sample of phosphorus oxychloride would cyclise an α-acylamino-β-arylpropionic acid LVIII, and that phosphorus oxychloride in polyphosphoric acid was equally effective. They, however, found that freshly distilled phosphorus oxychloride, and mixtures of water and phosphorus oxychloride gave only tars and resins.

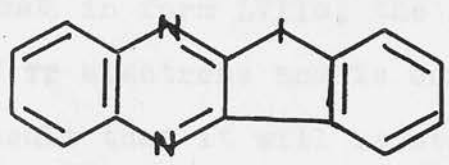


LVIII

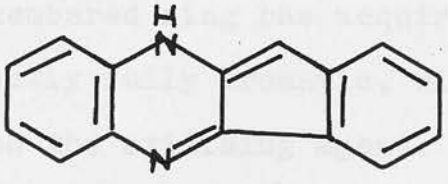
This reaction, involving dehydration and dehydrogenation, is basically similar to the above reaction and to the reduction and dehydrogenation which takes place, giving methin-(2-pyrazinyl)-(2'-dihydroquinoxaline).

The suggested structure LVII, having a five-membered ring, gives a planar molecule which will in all probability fluoresce, and fluorescence is one of the most marked properties of this compound.

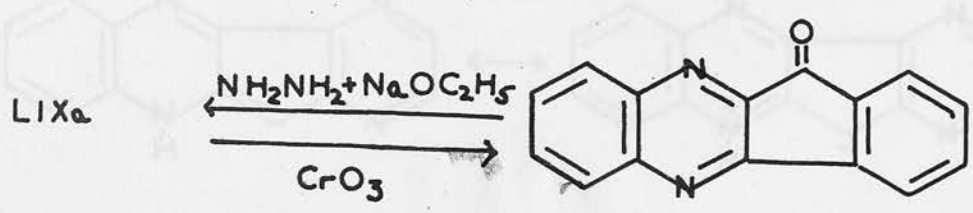
The bright yellow colour of the compound suggests that there is a methine bridge, not a methylene bridge, between the two heterocyclic nuclei. 1'H-Indano(2',3':2,3)quinoxaline LIXa, prepared by the Wolff-Kishner reduction of 1'-ketoindano(2',3':2,3)quinoxaline LX, is pale yellow in colour and this would indicate a methylene bridge between the quinoxaline and benzene units, although theoretically this molecule could tautomerise to give the methine structure LIXb. The difference, then, between the yellow compound and 1'H-indano(2',3':2,3)quinoxaline is exactly the same as the difference between methin-(2-pyrazinyl)-(2'-(3'-keto)tetrahydroquinoxaline) and 3-benzyl-2-quinoxalone.



LIXa

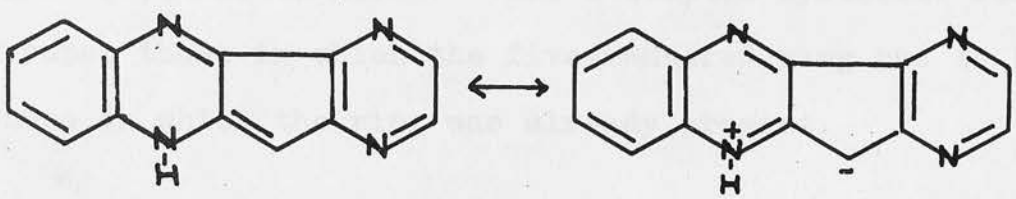


LIXb



LX

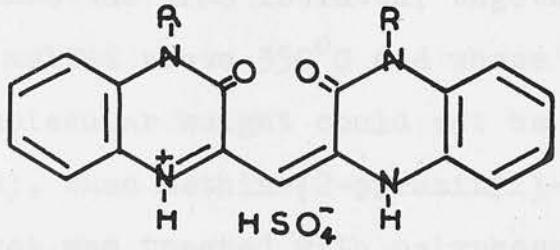
There is also the question of oxidation by chromium trioxide in acetic acid. The methylene group of 1'H-indano(2',3':2,3)quinoxaline is readily oxidised to the ketone. On the other hand, the yellow compound is resistant to oxidation, while qualitative experiments with the methine bases have shown that oxidation occurs with this reagent, although the products have not been identified. The oxidation of the methine bases may be regarded as the simple oxidation of a carbon-carbon link, while the oxidation of 1'H-indano(2',3':2,3)quinoxaline is the normal oxidation of the methylene group of a cyclopentadiene molecule. This resistance to oxidation by the yellow compound confirms that there is not a methylene group present in the molecule, and also that the nuclei are not just linked by a methine bridge. The structure proposed for the yellow compound LVII shows an unsaturated five-membered ring, with the hydrogen atom located on the nitrogen atom in position 10 (it could of course be found on the nitrogen atom in position 1). If the contributing forms to the resonance hybrid of this structure are considered, it will be noted that in form LVIIa, the five-membered ring has acquired a sextet of π electrons and is consequently fully aromatic, with the result that it will be stable to the oxidising agent.



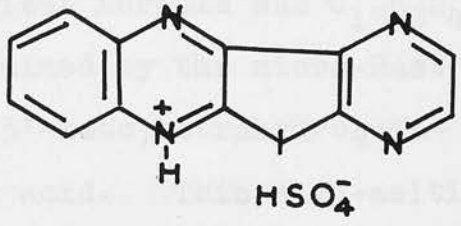
LVII LVIIa

The absorption spectrum of this compound would be expected to be somewhat similar to those of the methine bases, because although a more rigid molecule, there are two heterocyclic nuclei linked by a methine group.

The colour of its solution in concentrated sulphuric acid is pale red, unlike the dark green solutions of the methine bases. This difference can be accounted for if the probable structures of the resulting salts are considered. Cook[23] proposed that the dark green colour was due to the formation of a quaternary derivative of type LXI. If, however, a proton is added to the molecule of the yellow compound, it will add on at the point of high electron density, i.e. position 11, thereby giving a molecule which has a methylene group, and which will therefore not possess an intense colour, LXII.



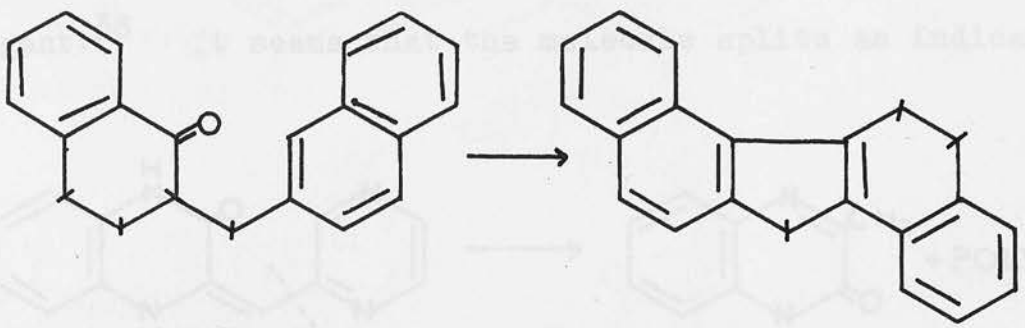
LXI



LXII

The next step was to try to synthesise 10H-pyrazino(2',3':3,4) cyclopenta(b)quinoxaline. The attempted syntheses fell into two groups, those in which the five-membered ring had to be formed, and those in which the ring was already present.

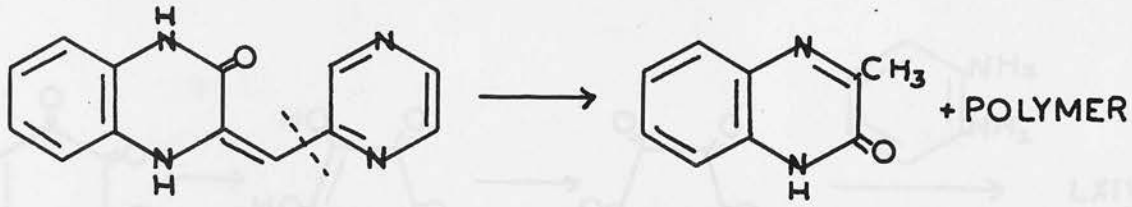
The first synthesis attempted was based on the method of Bergmann and Szmuszkovicz,[37] who cyclised compounds of type LXIII with polyphosphoric acid.



LXIII

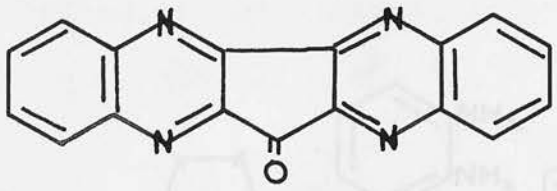
These compounds LXIII are somewhat similar in structure to the methin-(2'-(3'-keto)tetrahydroquinoxaline) derivatives. When methin-(2-(3-methyl)quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) was treated with polyphosphoric acid, the only product isolated from the reaction mixture was 3-methyl-2-quinoxalone, $C_9H_8N_2O$. This substance was also isolated, together with a tan-coloured compound, which melted above 350°C and whose empirical formula was $C_{13}H_8N_4O$ (the molecular weight could not be determined by the micro-Rast method), when methin-(2-pyrazinyl)-(2'-(3'-keto)tetrahydroquinoxaline) was treated with polyphosphoric acid. This high-melting compound was thought to be a polymer of the starting material or of part of that molecule, since the isolation of 3-methyl-2-quinoxalone implies that the methin-(2-pyrazinyl)-(2'-(3'-keto)tetrahydroquinoxaline) molecule has been split. Similarly, high-melting substances (but no 3-methyl-2-quinoxalone) were obtained when methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine) was treated with

the reagent. The failure of the molecule to cyclise was less unexpected (Snyder[12] had reported that polyphosphoric acid did not cyclise α-acylamino-β-arylpropionic acids) than the fission of the molecule, since polyphosphoric acid is regarded as a 'mild' reagent.[38] It seems that the molecule splits as indicated:-

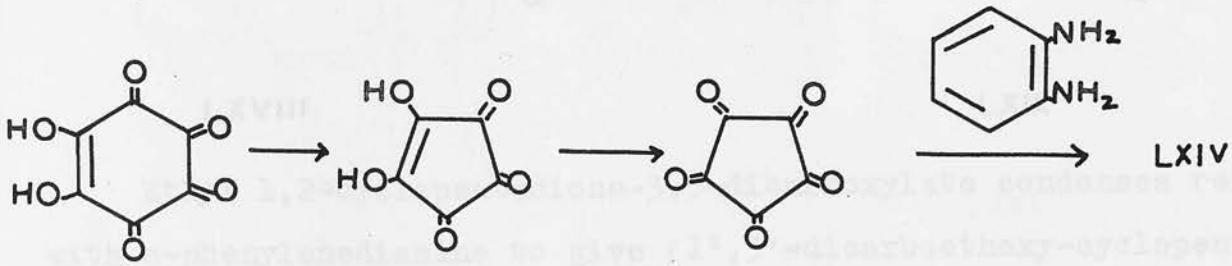


This method was therefore abandoned.

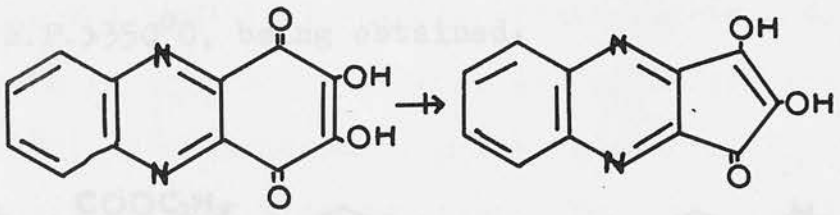
The second synthesis attempted involved repeating work which had been carried out by Nietzki.[39] The compound LXIV had been synthesised and if it could be reduced, would form the benz-analogue of the required compound. Unfortunately, the experimental methods were not given and several attempts to convert rhodizonic acid LXV to krokonic acid LXVI were unsuccessful, as was the attempted benzilic acid rearrangement of 1,4-diketo-2,3-dihydroxy-1,4-dihydrophenazine LXVII. This synthesis was abandoned in favour of a starting material in which the five-membered ring was already present.



LXIV



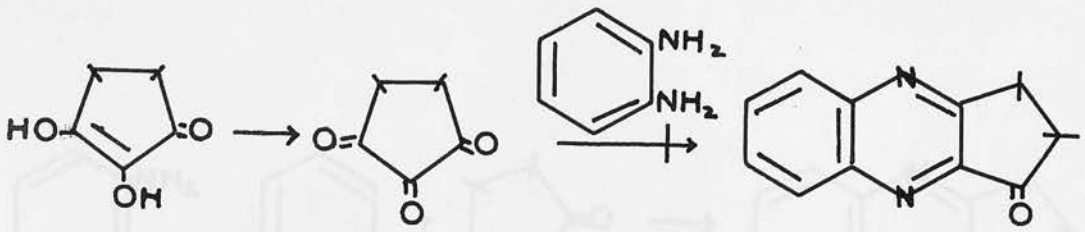
LXV LXVI LXIV



LXVII

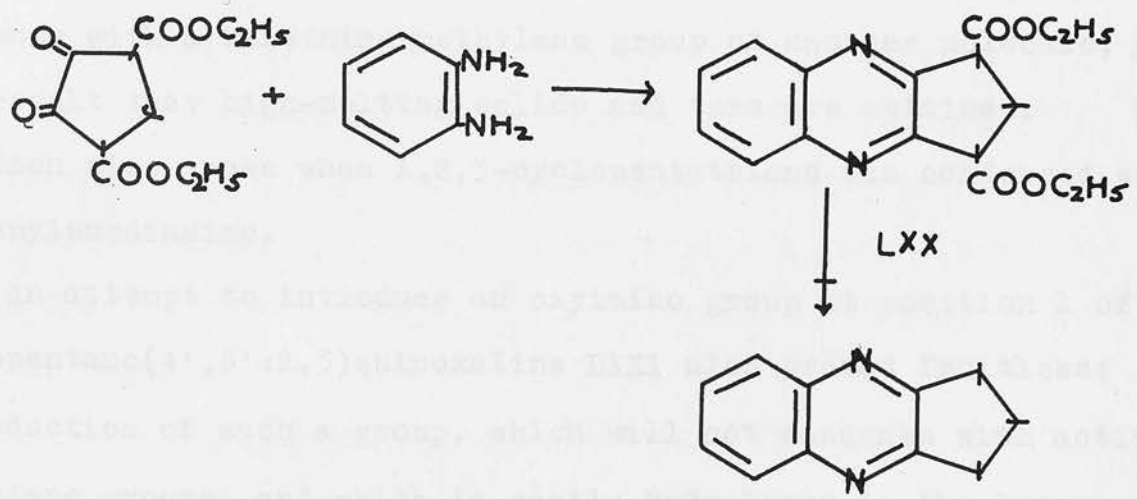
1,2,3-Cyclopentatrione had been obtained by the oxidation of reductic acid LXVIII, by Reichstein and Oppenauer[40] and so an attempt to prepare 1'-keto-cyclopentano(4',5':2,3)quinoxaline LXIX was made by treating 1,2,3-cyclopentatrione with o-phenylenediamine. Unfortunately, the product from this reaction was a black solid,

M.P.>350°C, which was probably a polymer, formed by the condensation of the ketonic groups with active methylene groups.



LXVIII LXIX

Ethyl 1,2-cyclopentadione-3,5-dicarboxylate condenses readily with o-phenylenediamine to give (1',3'-dicarboethoxy-cyclopentano-(4',5':2,3)quinoxaline[41] LXX. However, attempts to hydrolyse and decarboxylate this compound, using acid or alkali, failed to give the required cyclopentano(4',5':2,3)quinoxaline LXXI, only black solids, M.P.>350°C, being obtained.



LXXI

Landquist[42] reported that cyclopentano(4',5' : 2,3)quinoxaline could be obtained by reacting o-aminoazobenzene and cyclopentanone and using this method, a 50% yield of the compound LXXI was obtained.

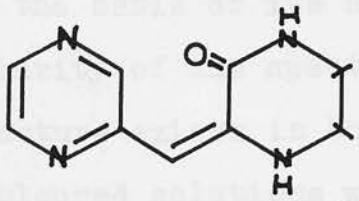
LXXI

Since the fusion of a five-membered ring and a heterocyclic ring in the above manner results in the activation of the methylene groups in positions 1' and 3' of the five-membered ring, the introduction of ketonic groups to these positions is not difficult. There is, however, a very great tendency for the ketonic group of one molecule to condense with a remaining methylene group of another molecule, with the result that high-melting solids and tars are obtained. This position also arose when 1,2,3-cyclopentatrione was condensed with o-phenylenediamine.

An attempt to introduce an oxyimino group at position 1 of cyclopentano(4',5':2,3)quinoxaline LXXI also proved fruitless; the introduction of such a group, which will not condense with active methylene groups, and which is easily hydrolysed to the ketone,

should be possible if the experimental conditions are rigidly controlled.[21]

The action of phosphorus oxychloride and water on methin-(2-pyrazinyl)-(2'-(3'-keto)piperazine) LXXII was also studied.

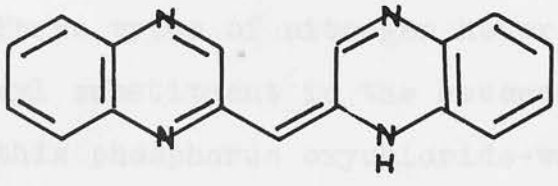


LXXII

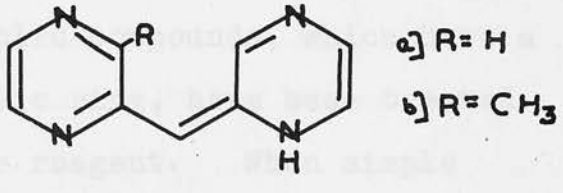
As in the case of methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine), two bases were isolated from the reaction mixture, and were purified on an alumina column. The first base separated as a dark yellow band, which did not fluoresce in ultraviolet light, and was eluted with benzene-ether (4:1), giving fine golden-yellow needles, M.P. 174-176°C. (Compound P). The yield of this base was poor and it was not analysed. The absorption spectrum is shown in Figure 19. The second base separated as a yellow band, which fluoresced yellow in ultraviolet light, and was eluted with benzene-ether (1:1), giving a yellow solid, $C_9H_6N_4$, which crystallised from ethanol as yellow rods, M.P. 162-163.5°C. (Compound Q). The spectrum of Q is shown in Figure 20.

When methin-(2-pyrazinyl)-(2'-(3'-keto)piperazine) was treated with freshly distilled phosphorus oxychloride, Q was the only base isolated.

When methin-(2-quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) is treated with the phosphorus oxychloride-water mixture, two bases, X and Y, whose spectra are shown in Figures 5 and 6, are obtained. It is noticeable that the spectrum of P resembles that of Y, and that the spectrum of Q resembles that of X. The structure LXXIII was assigned to Y on the basis of its spectrum in concentrated sulphuric acid. The similarity of the spectra of P and Y suggests that the same methine structure exists in both compounds; the methine bases give intensely coloured solutions with concentrated sulphuric acid, and P gives an intense red-purple solution in this solvent. It must, however, be stressed that there are no analytical results for P and the structure LXXIVa, methin-(2-pyrazinyl)-(2'-dihydropyrazine), is merely suggested. It had been hoped to prepare methin-(2-(3-methyl)pyrazinyl)-(2'-dihydropyrazine) LXXIVb for comparison with P, but 2-methylpyrazine shows no tendency towards self-condensation in acid, cf. 2-methylquinoxaline.



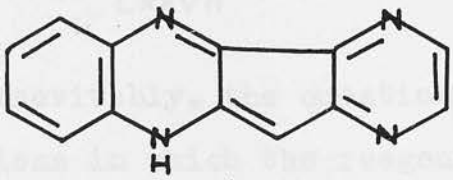
LXXIII



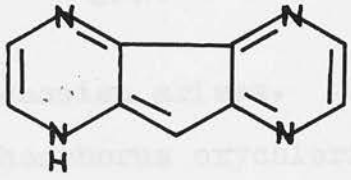
LXXIV

Since the structure of X is not known, the structure of Q could not be deduced by analogy, but it was observed that Q gave a pale red solution in concentrated sulphuric acid. The yellow base,

$C_{13}H_8N_4$, obtained by treating methin-(2-quinoxalinyl)-(2'-(3'-keto) piperazine) with phosphorus oxychloride, gives a similar solution in this solvent. The structure assigned to this yellow base, but not yet confirmed, is 10H-pyrazino(2',3':3,4)cyclopenta(b)quinoxaline LXXV. The analysis of Q indicates that the structure, 8H-pyrazino(2',3':3,4)cyclopenta(b)pyrazine LXXVI, is possible and the spectra of Q and of the yellow base are similar although not identical.



LXXV

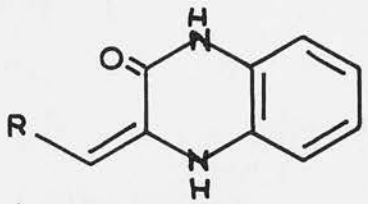


LXXVI

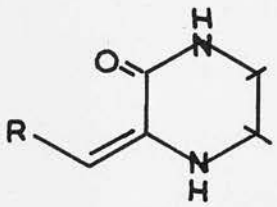
Although the structures of P and Q are not definitely known, the fact that these bases no longer contain oxygen is important. These methin-(2'-(3'-keto)piperazine) derivatives have been reduced, cyclised and aromatised by the phosphorus oxychloride-water mixture.

Three types of nitrogen heterocyclic compounds, which have a hydroxyl substituent in the heterocyclic ring, have been treated with this phosphorus oxychloride-water reagent. When simple systems, such as acridone, and 3-phenyl-2-quinoxalone, were treated with this reagent, chlorination occurred, and the mixture proved to be a less efficient chlorinating agent than phosphorus oxychloride itself. The mixture acted as a reducing agent for derivatives of methin-(2'-(3'-keto)tetrahydroquinoxaline) LXXVII, the unsubstituted

bases being obtained in good yield. For the derivatives of methin-(2'-(3'-keto)piperazine) LXXVIII, the reagent was not only a reducing agent but also an aromatising agent, and a cyclising agent.



LXXVII



LXXVIII

Inevitably, the question of mechanism arises. Chlorination reactions in which the reagent is phosphorus oxychloride, have not been extensively studied, but individual cases, such as 1-phenyl-methylcarbinol,[88] and β-n-octyl alcohol,[89] have been investigated and Ingold[90] has suggested mechanisms for those reactions in which inversion of configuration takes place, while Gerrard[91] has studied the phosphorylation and chlorination of the above-named alcohols and suggested possible mechanisms. Viscontini[15] has suggested a mechanism for the phosphorylation of pyridoxal-acetal-3-pyrophosphate by 'hydrated phosphorus oxychloride', but the mechanism has not been studied.

Since the active agent in the phosphorus oxychloride-water mixture has not been identified, it is not possible to speculate about the reaction mechanisms involved in the reductions, aromatisations, and cyclisations.

ABSORPTION SPECTRA

FIGURE 1. Methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) in ethanol.

Maxima	275 mu	log E	4.68
	368 mu		4.18
	386 mu		4.22
	470 mu		3.77

FIGURE 2. Methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) in sulphuric acid.

In 1.8N H_2SO_4	Maxima	274 mu	log E	4.64
		409 mu		4.24
		537 mu		3.74
In 36N H_2SO_4		274 mu		4.53
		378 mu		4.02
		424 mu		4.24
		571 mu		3.81
		615 mu		3.80

FIGURE 3. Methin-(2-quinolinyl)-(2'-dihydroquinoxaline) in ethanol.

Maxima	211 mu	log E	4.67
	237 mu		4.38
	274 mu		4.57
	298 mu		4.57
	362 mu		4.11
	381 mu		4.38
	487 mu		3.92

FIGURE 4. Methin - (2-pyrazinyl)-(2'-dihydroquinoxaline) in ethanol.

Maxima -	271 mu	log E	4.71
	366 mu		4.00
	377 mu		4.07
	500 mu		3.58

FIGURE 5. Compound X in dioxan.

Maxima	286 mu	log E	4.60
	335 mu) 336 mu)		4.08
	358 mu		4.05
	375 mu		4.12
	393 mu		4.12
	493 mu		3.58

FIGURE 6. Compound Y in dioxan.

Maxima	258 mu	log E	4.46
	288 mu) 289 mu)		4.55
	343 mu		4.22
	377 mu		4.15
	396 mu		4.08
	509 mu) 510 mu)		3.57

FIGURE 7. Compound X in sulphuric acid.

Maxima	229 mu	log E	4.30
	256 mu		4.43
	281 mu) 282 mu)		4.46
	409 mu		4.29
	625 mu		3.58
	672.5 mu		3.56

FIGURE 8. Compound Y in sulphuric acid.

Maxima	222 mu	log E	4.46
	274 mu		4.59
	340 mu		3.82
	384 mu		3.96
	435 mu) 436 mu)		4.26
	459 mu) 460 mu)		4.25
	589 mu) 590 mu)		3.80
	635 mu		3.79

FIGURE 9. 3-Benzyl-2-quinoxalone in ethanol.

Maxima	229 mu	log E	4.28
	280 mu		3.78
	343 mu		3.85

FIGURE IO. Methin-(2-pyrazinyl)-(2'-(3'-keto)tetrahydroquinoxaline) in chloroform.

Maxima	274 mu	log E	3.94
	301 mu		3.90
	417 mu		4.33
	438 mu		4.33

FIGURE II. Yellow base, $C_{13}H_8N_4$, in ethanol.

Maxima	262 mu	log E	4.43
	343 mu		3.99
	357 mu		4.06
	417 mu		3.80

FIGURE 12. Red base from the reaction of phosphorus oxychloride and water on methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine), in ethanol. (Qualitative).

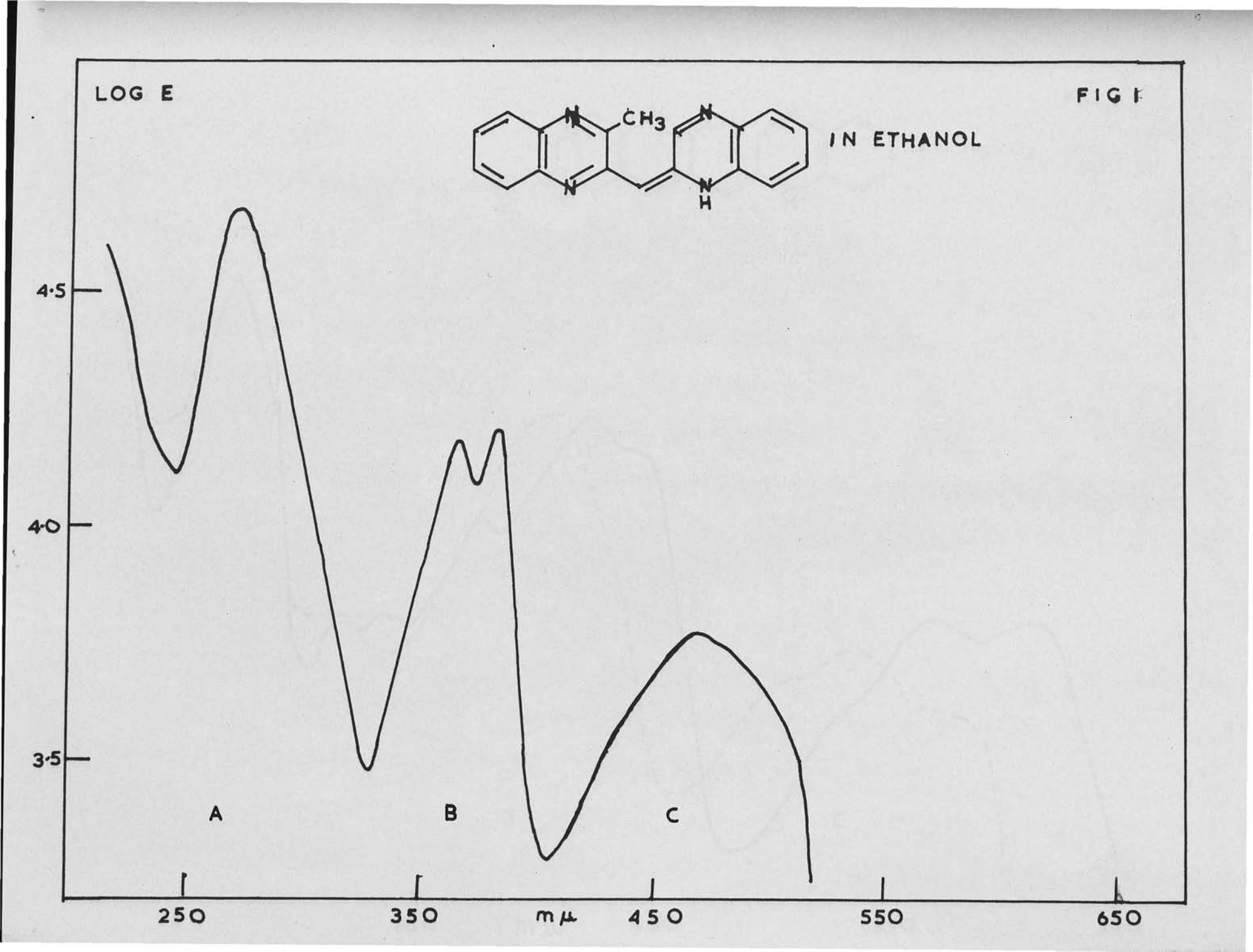
Maxima	270 mu	log T.D.	1.10
	368 mu		0.40
	379 mu		0.48
	480 mu		$\bar{1}$.85
	508 mu		$\bar{1}$.83

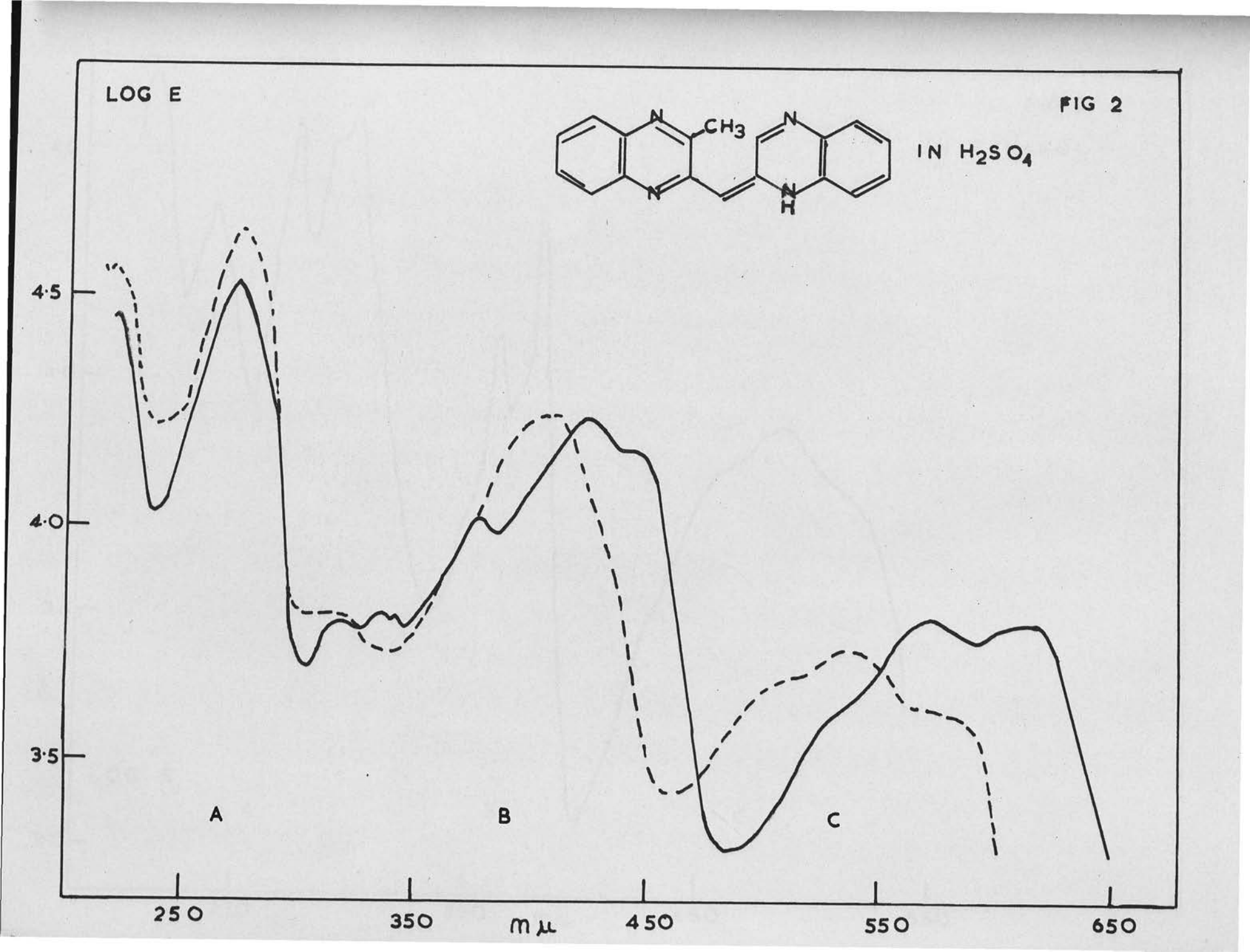
FIGURE 19. Compound P in ethanol.

Maxima	230 mu	log E_1	1.73
	262 mu		2.20
	294 mu		1.50
	321 mu		1.41
	335 mu		1.36
	449 mu		1.22

FIGURE 20. Compound Q in ethanol.

Maxima	258 mu	log E	4.43
	332 mu		3.76
	345 mu		3.64
	427 mu		3.53
	450 mu		3.46


LOG E
FIG I
CH3
N
N
N
H
IN ETHANOL
4·5
4·0
3·5
A
B
C
250
350
mμ
450
550
650


LOG E
FIG 2
IN H_2SO_4
4·5
4·0
3·5
A
B
C
250
350
mμ
450
550
650

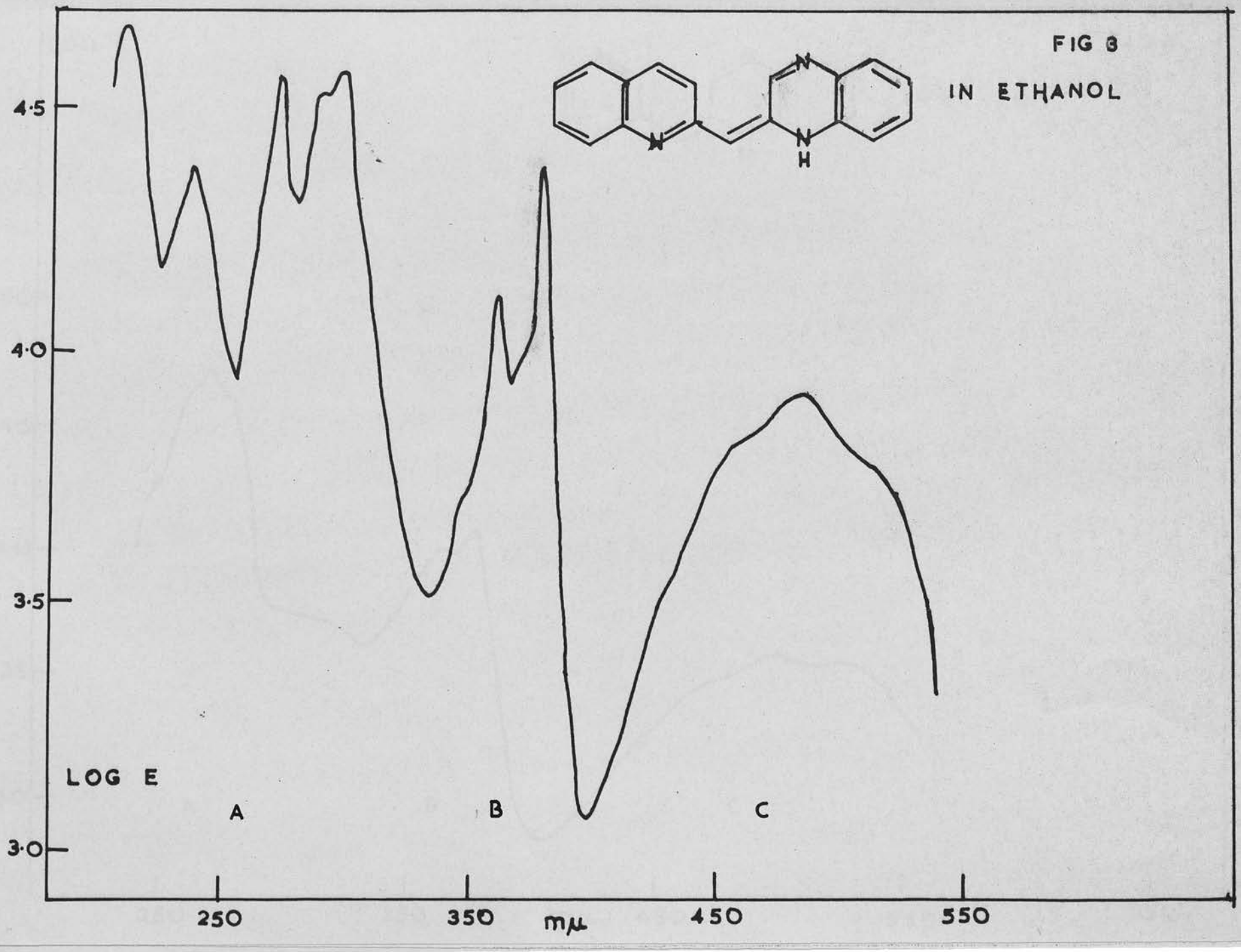


FIG 3
IN ETHANOL
4·5
4·0
3·5
3·0
LOG E
A
B
C
250
350
mμ
450
550
N
N
H

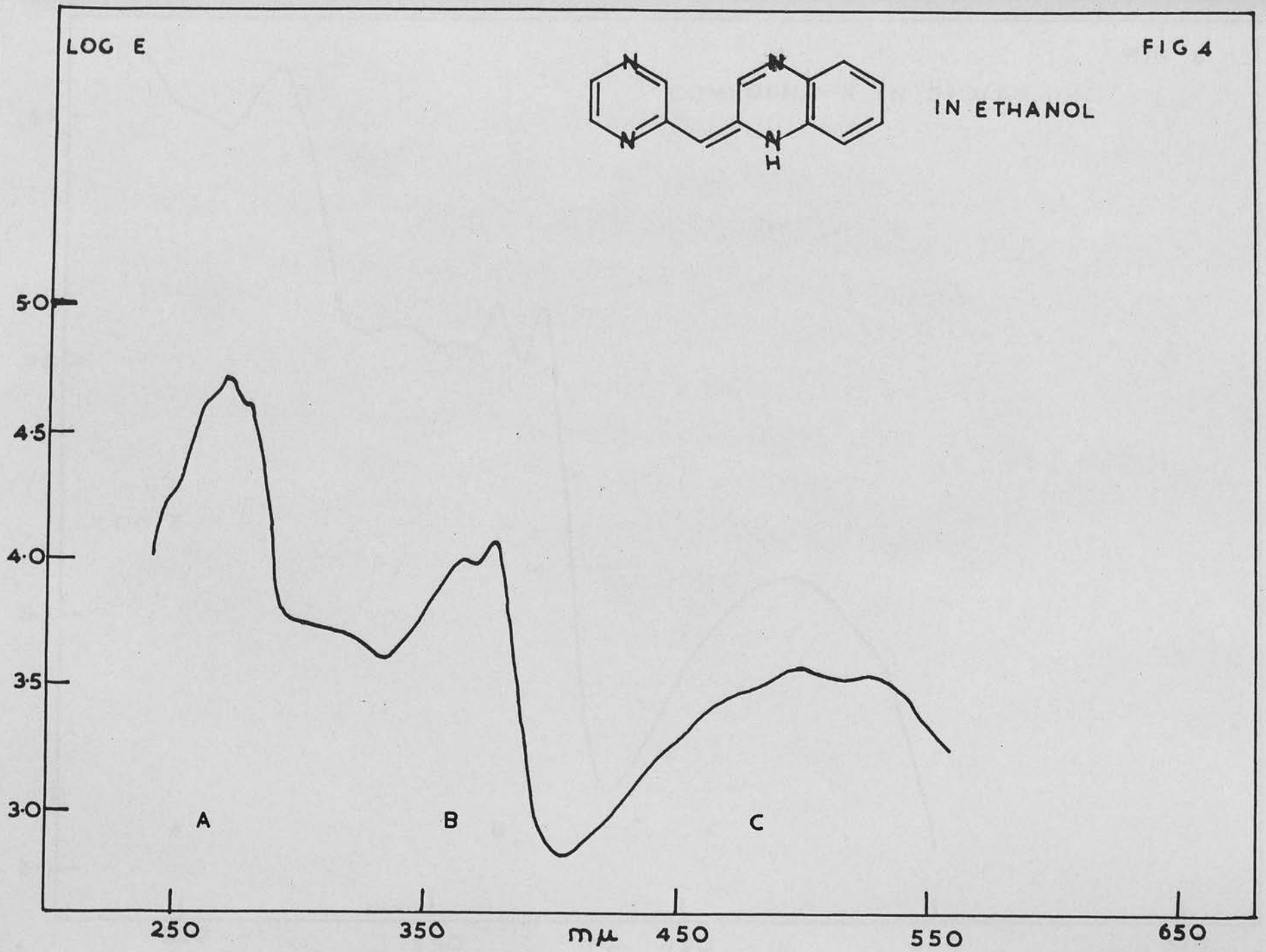
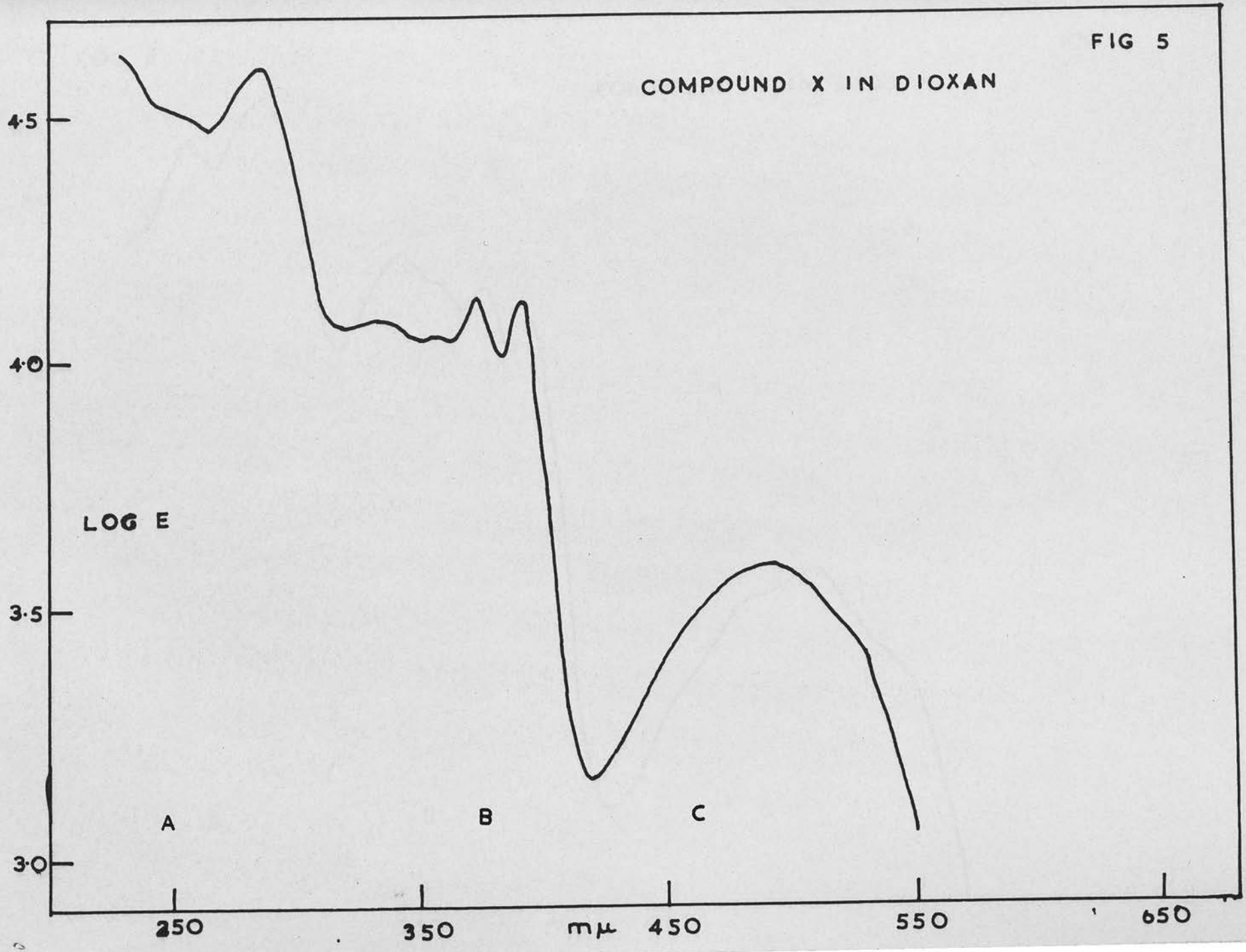
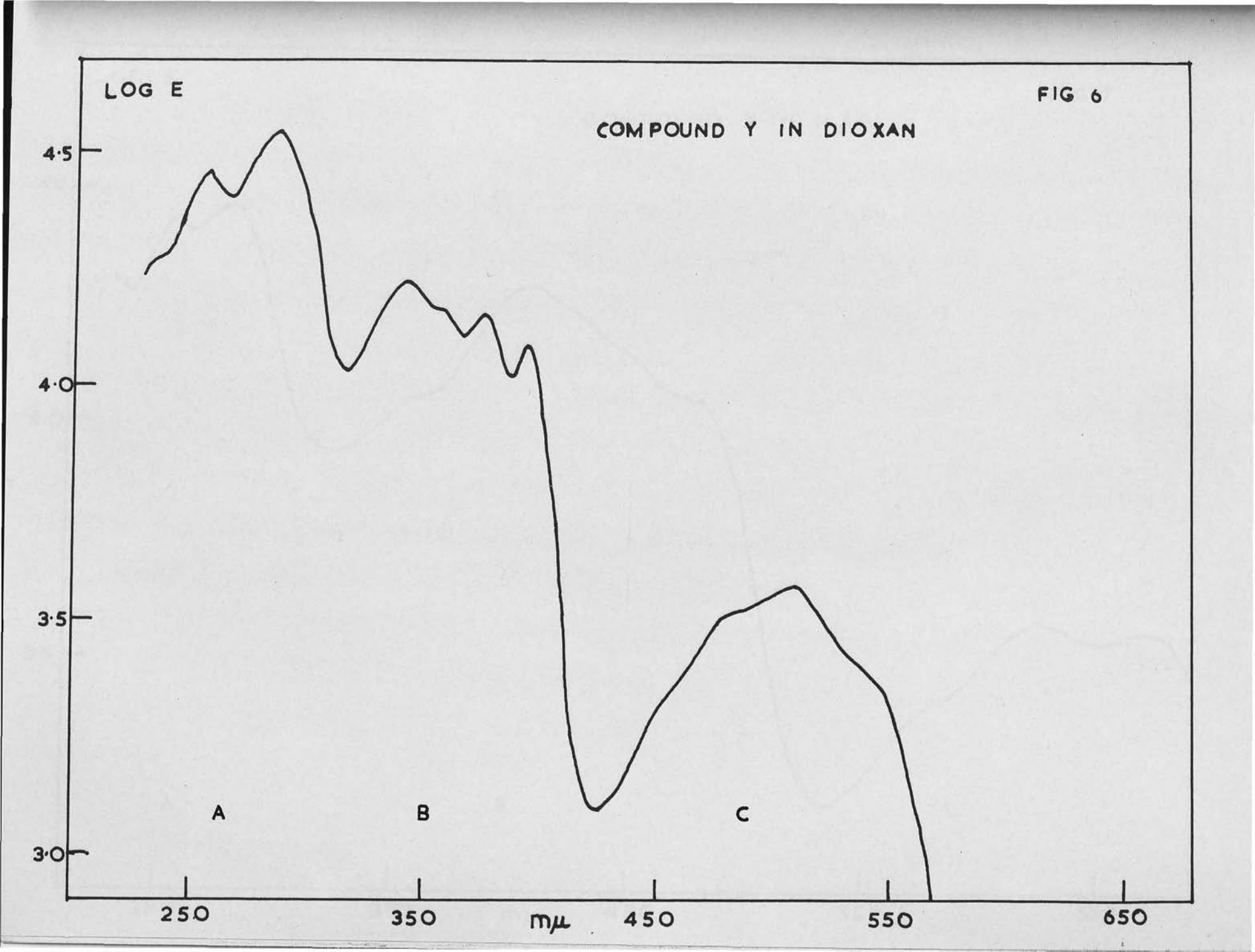
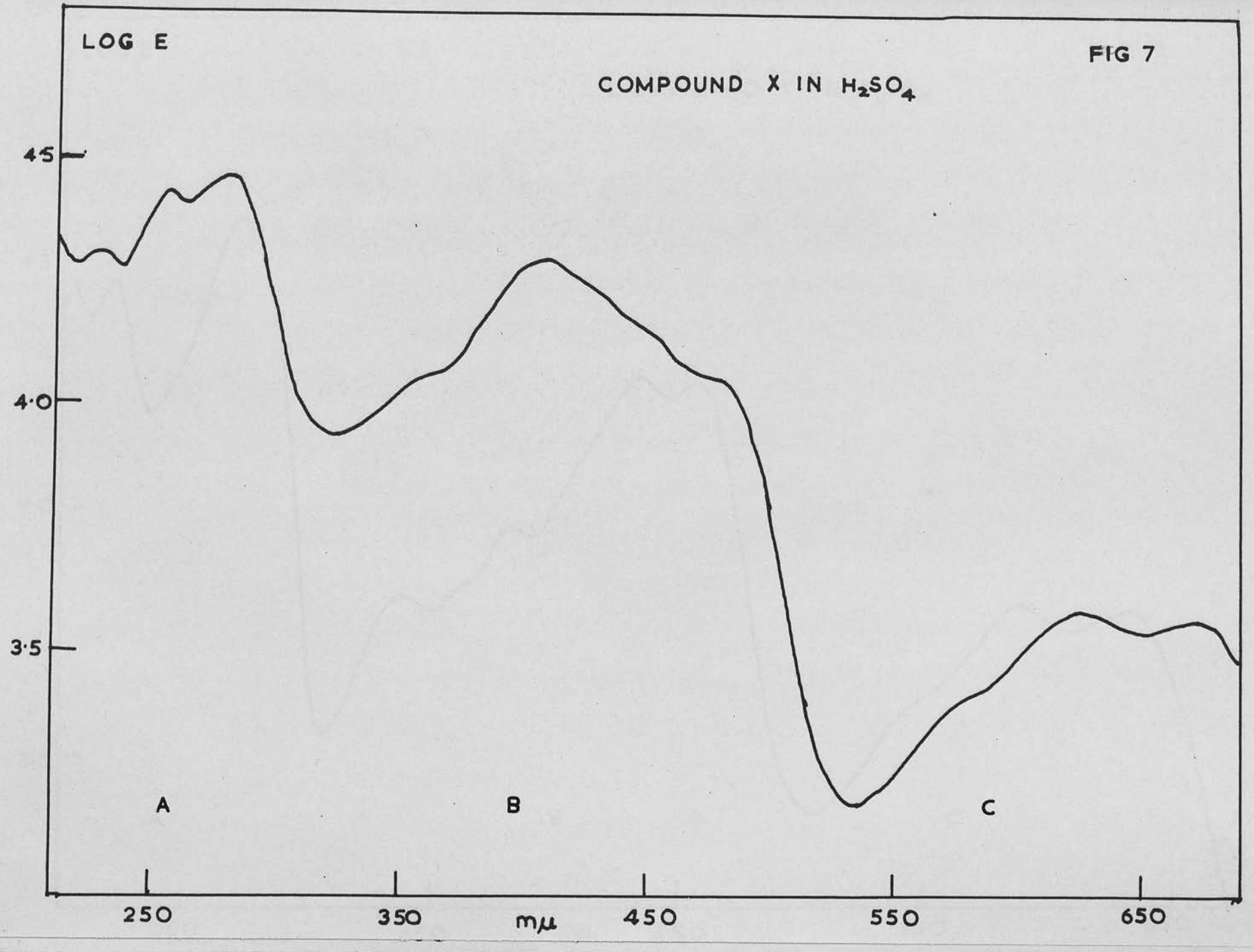
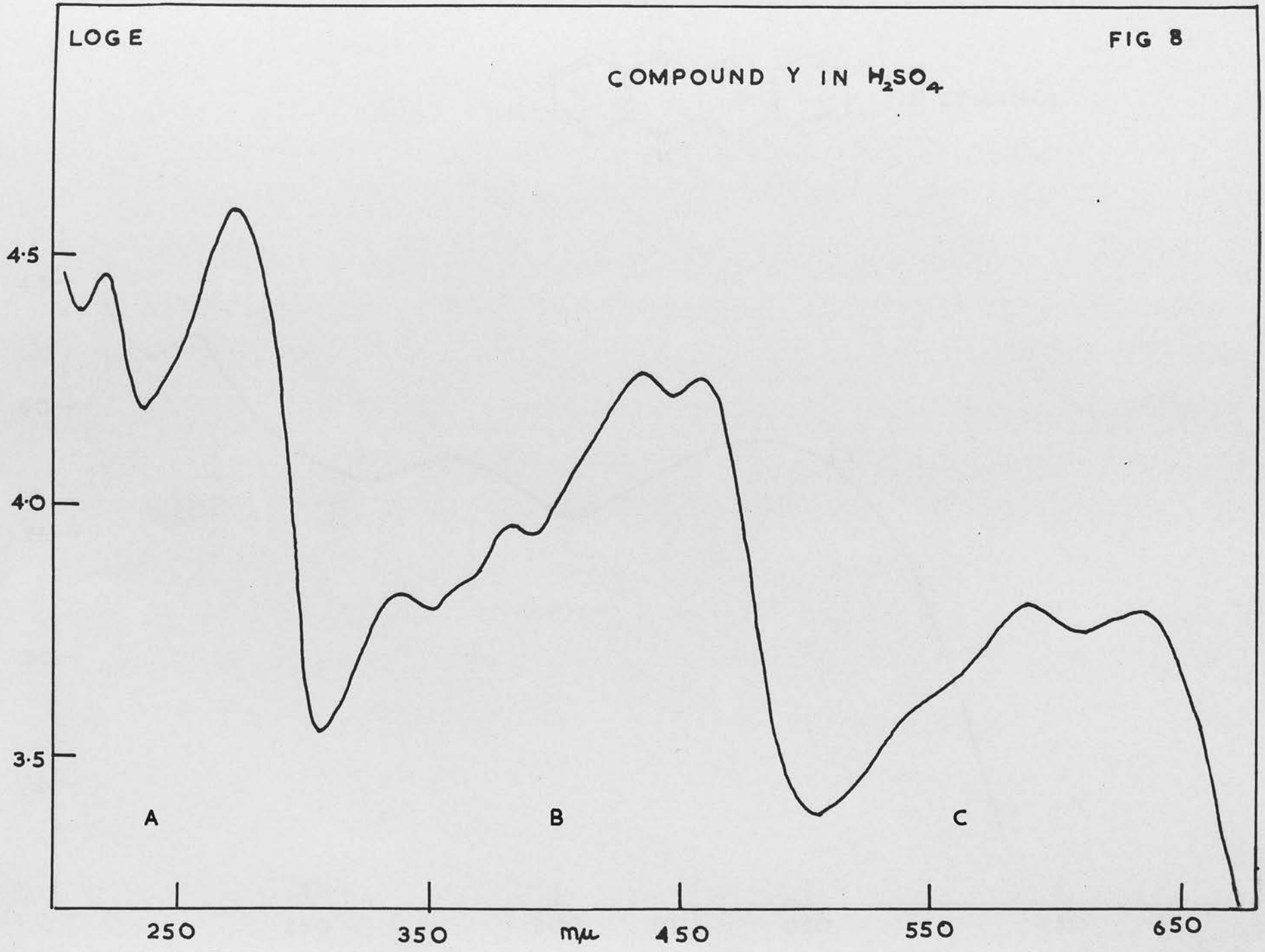

LOG E
FIG 4
IN ETHANOL
N
N
N
H
5·0
4·5
4·0
3·5
3·0
A
B
C
250
350
mμ
450
550
650

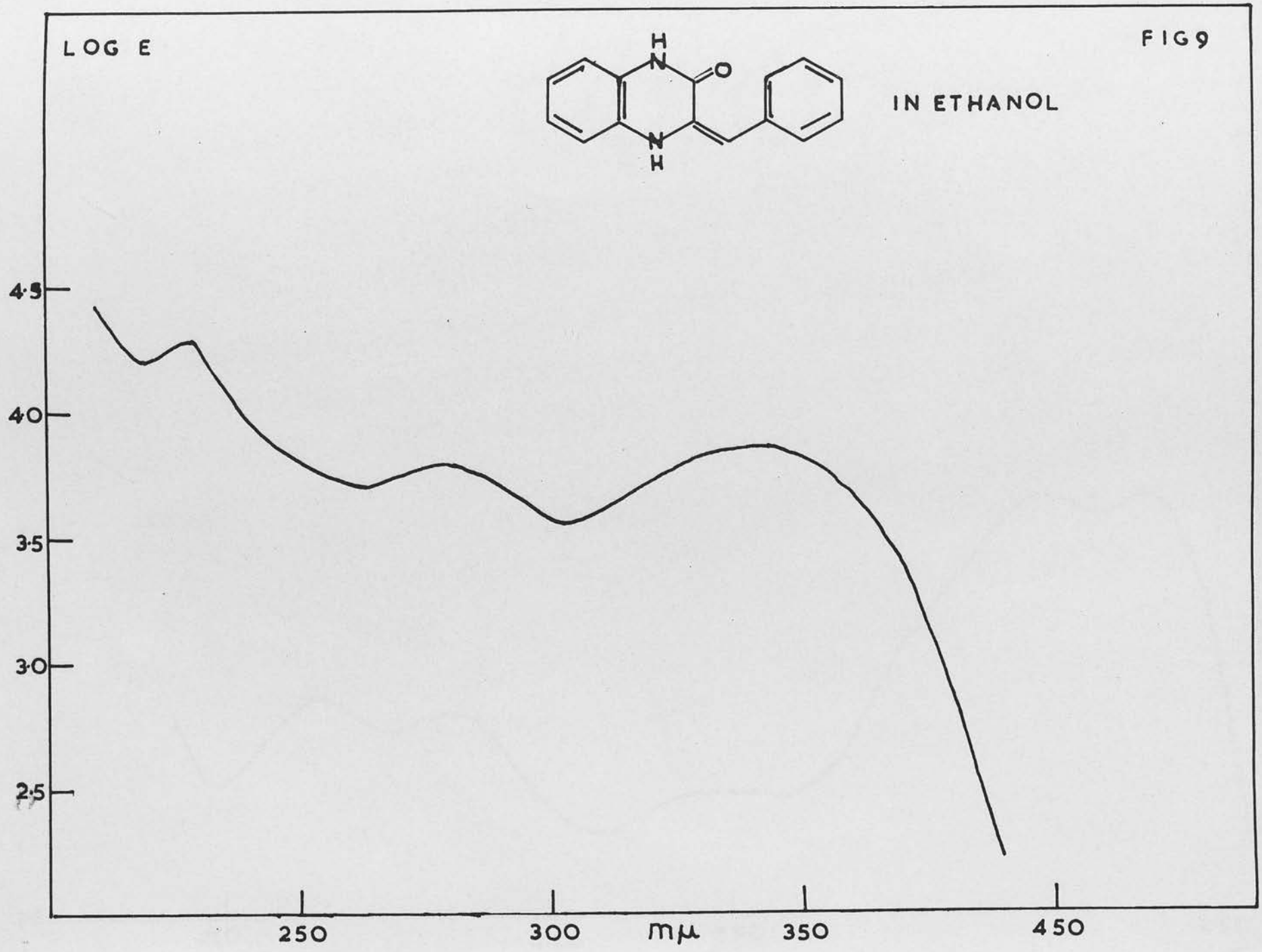
FIG 5

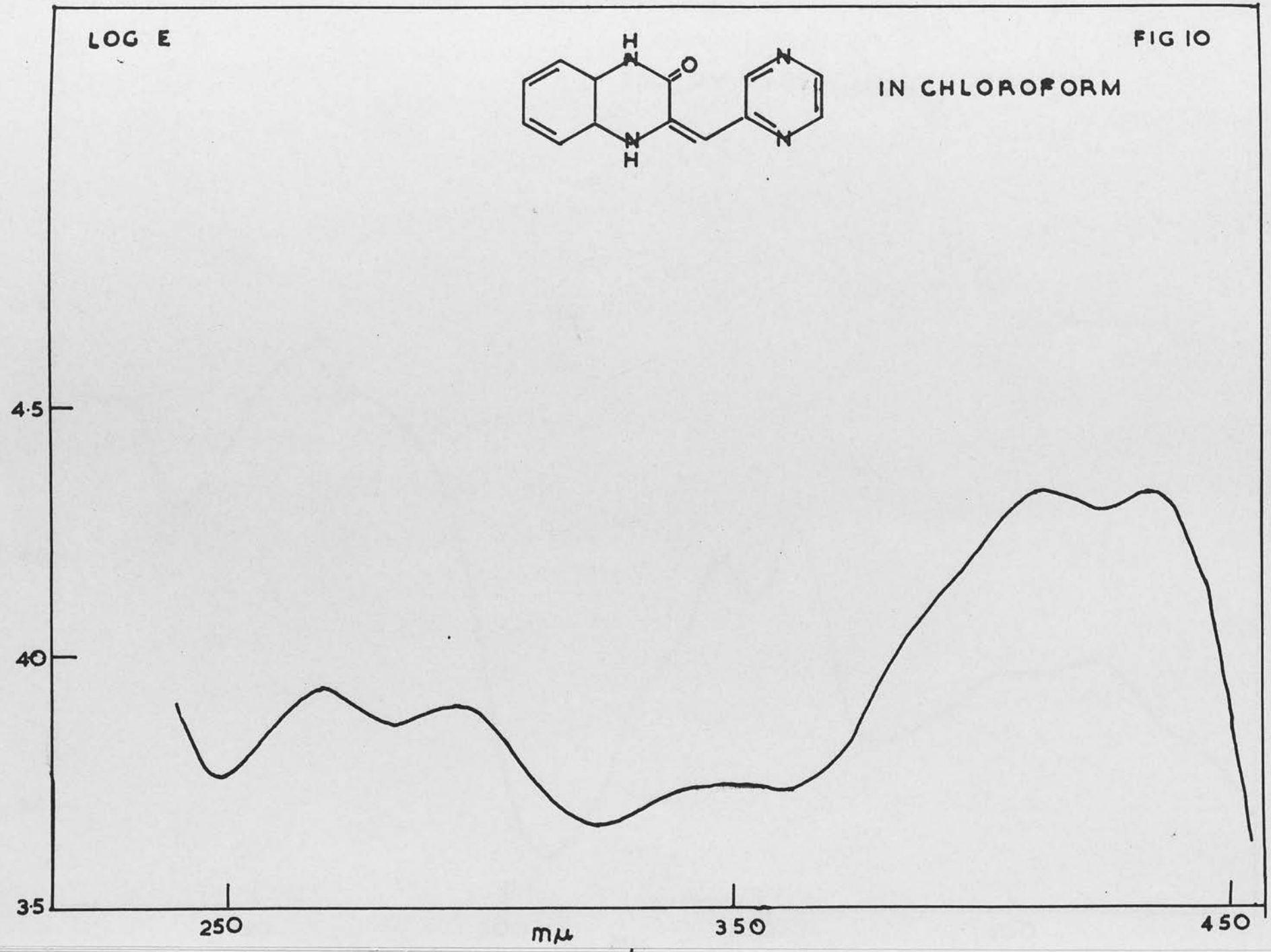


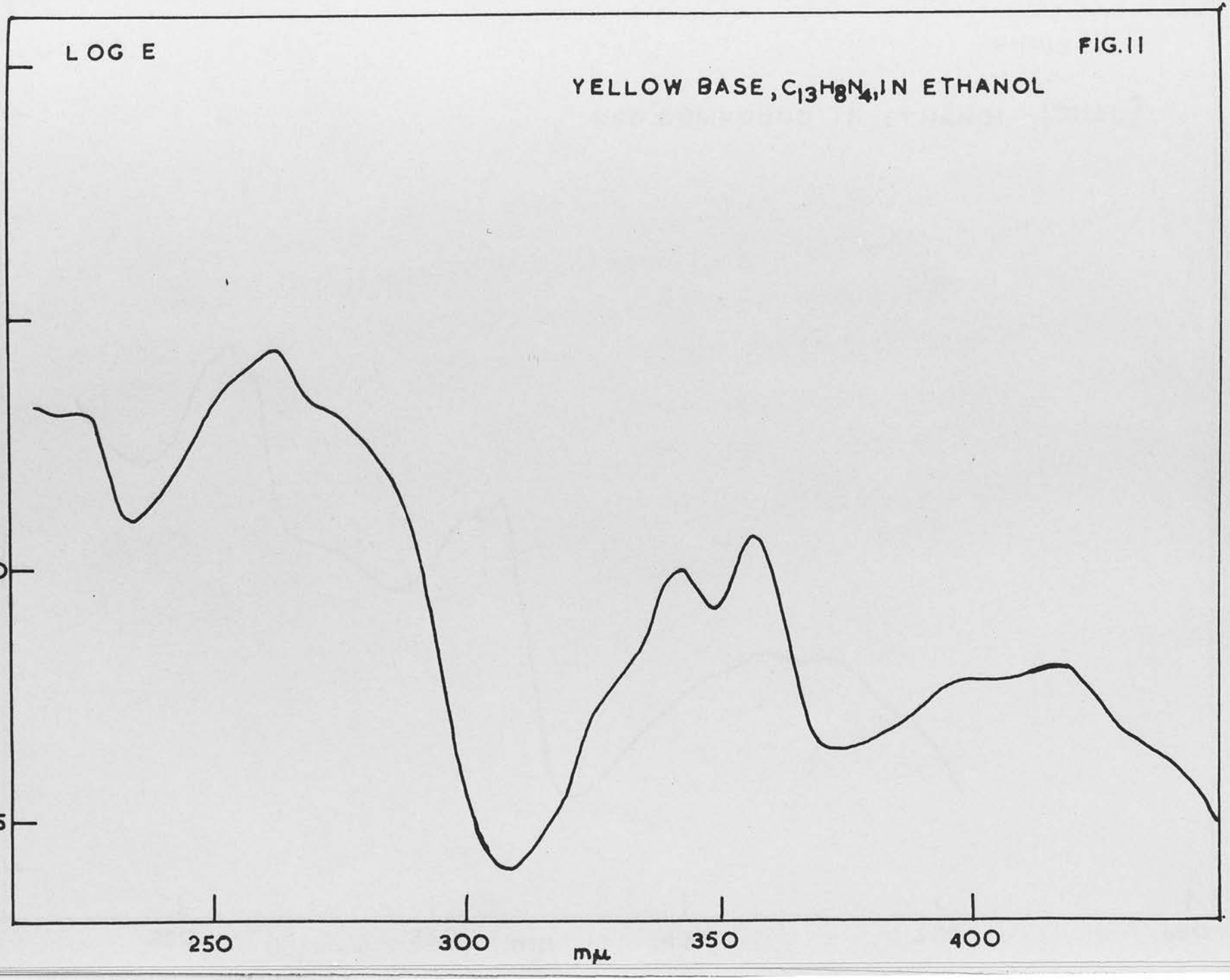

LOG E
FIG 6
COMPOUND Y IN DIOXAN
4·5
4·0
3·5
3·0
A
B
C
250
350
mμ
450
550
650

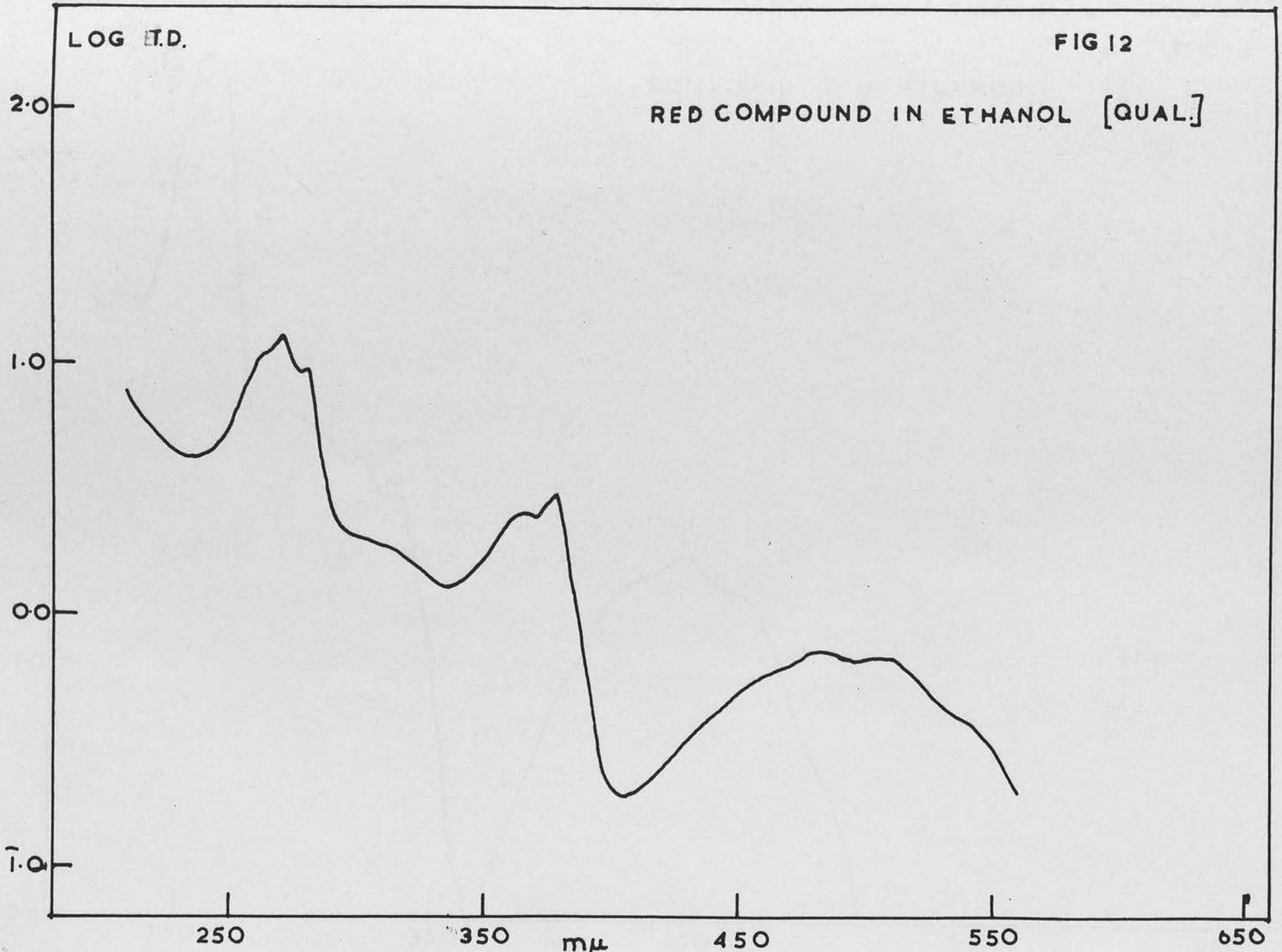

LOG E
FIG 7
COMPOUND X IN H_2SO_4
4·5
4·0
3·5
A
B
C
250
350
mμ
450
550
650

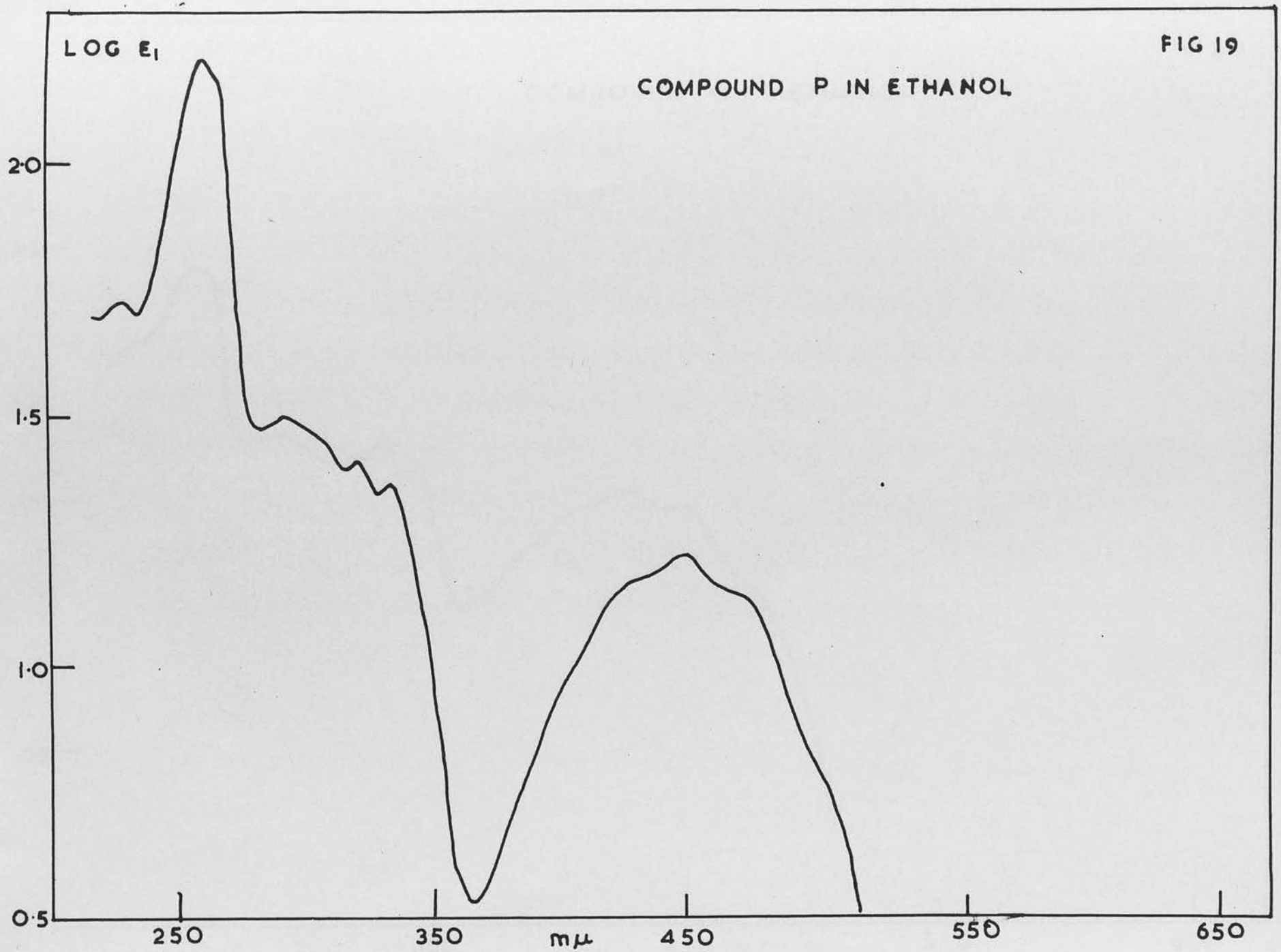

LOG E
FIG 8
COMPOUND Y IN H_2SO_4
4·5
4·0
3·5
A
B
C
250
350
mμ
450
550
650

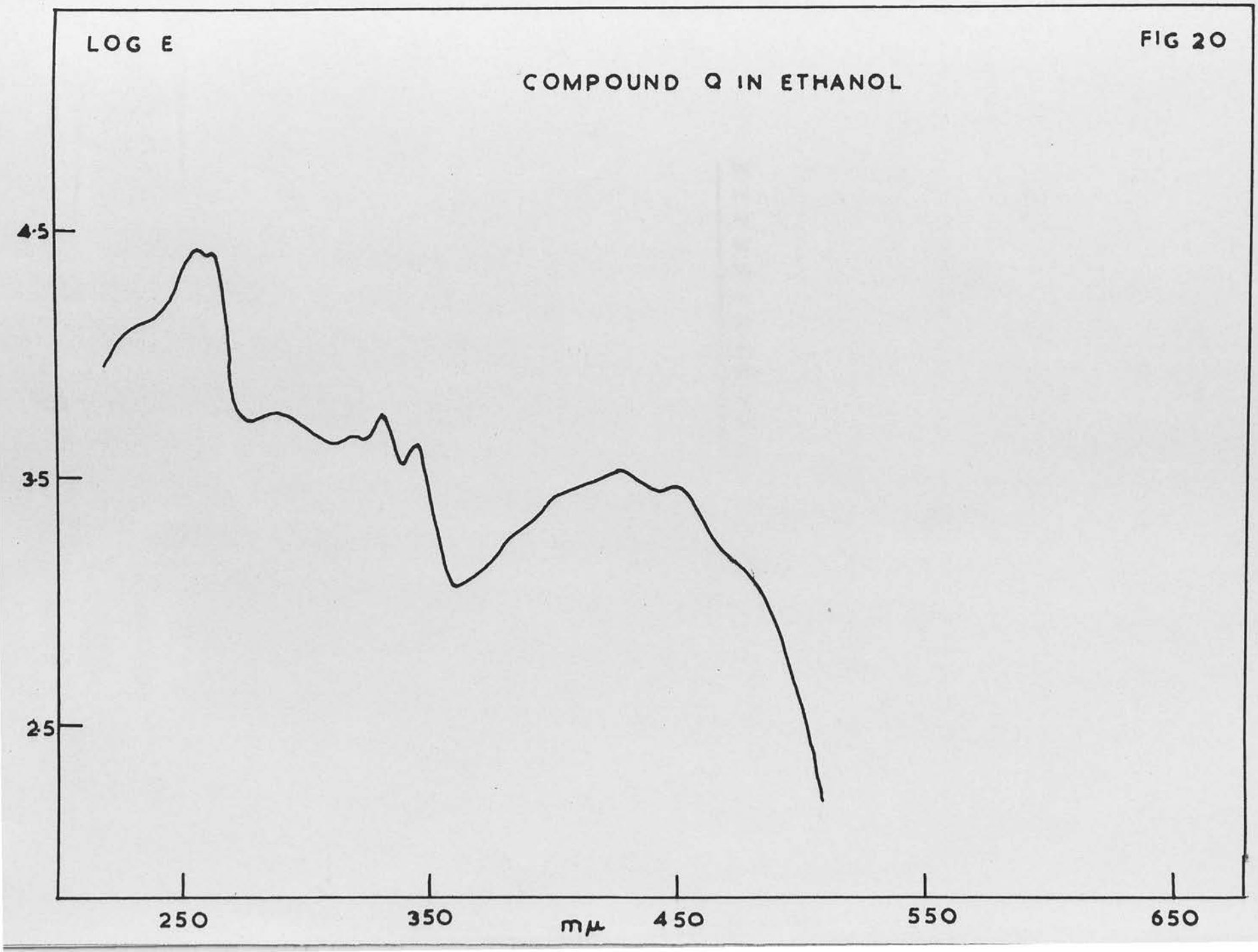

LOG E
FIG 9
IN ETHANOL
H
N
O
N
H
4·5
4·0
3·5
3·0
2·5
250
300
mμ
350
450


LOG E
FIG 10
IN CHLOROFORM
4·5
4·0
3·5
250
mμ
350
450


LOG E
FIG. 11
YELLOW BASE, $C_{13}H_8N_4$, IN ETHANOL
4·5
4·0
3·5
250
300
350
400
mμ


LOG E.T.D.
FIG 12
RED COMPOUND IN ETHANOL [QUAL.]
2·0
1·0
0·0
1·0
250
350
mμ
450
550
650


LOG E1
FIG 19
COMPOUND P IN ETHANOL
2·0
1·5
1·0
0·5
250
350
mμ
450
550
650


LOG E
FIG 20
COMPOUND Q IN ETHANOL
4·5
3·5
2·5
250
350
mμ
450
550
650

EXPERIMENTAL

EXPERIMENTAL

All melting-points were determined by means of a Kofler micro-melting point apparatus.

Chromatographic separations were carried out on Activated Alumina Type 'H'.

Spectral determinations were made using a Unicam SP 500 spectrophotometer.

Unless otherwise stated, solutions were dried over anhydrous calcium sulphate.

Analyses were by Drs. Weiler and Strauss, Oxford.

Preparation of hydrated phosphorus oxychloride.

cf. Roux, Thilo, Grunze & Viscontini, Helv. Chim. Acta, 38, 15 (1955).

Water (4 ml) was added dropwise over a period of 5 days, to freshly distilled phosphorus oxychloride (34 g). The mixture was allowed to stand at room temperature for 8 days, and the excess water and phosphorus oxychloride were removed by distillation at 60°C and 12 mm. pressure.

Reaction of hydrated phosphorus oxychloride and methin-(2-(3-methyl) quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline).

Methin-(2-(3-methyl)quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) (1.4 g) was added to the above hydrated phosphorus oxychloride and the mixture heated at 170°C for 2 hours. Water was added to the cooled mixture and potassium hydroxide was added until the mixture was alkaline. A reddish-brown precipitate was filtered off, dried, and extracted in a Soxhlet thimble with benzene for 18 hours. The hot benzene extract was filtered.

1. The residue, ca. 100 mg, decomposed at 336°C.

Mixed melting-point with starting material 335-345°C.

2. The filtrate was purified on an alumina column: two bands separated.

a) A pink band was eluted with benzene, giving an orange solution which had a yellow fluorescence in U.V. light. Removal of the eluant gave a very small amount of red solid, which was not further investigated.

b) An orange band, which fluoresced yellow in U.V. light, was

eluted with benzene-ether (9:1), giving a golden-yellow solution. Removal of the eluant gave an orange solid.

Yield 150 mg.

M.P. 253-4°C.

Mixed melting-point with methin-(2-(3-methyl)quinoxalinyl) (2'-dihydroquinoxaline) 252-254°C.

Residue in the Soxhlet thimble (1 g).

The brown solid was recrystallised from nitrobenzene as dark orange needles, which sublimed at 290°C to orange needles and small pale yellow prisms. The prisms disappeared at 305°C and the needles decomposed at 332°C. The mixture was then extracted with chloroform. The residue from the extraction was fine orange needles, M.P. 348-350°C and a mixed melting-point with starting material showed no depression. A yellow-orange solid, in very small amount, was isolated from the chloroform extract. M.P. 237-243°C.

Preparation of ethyl 2-quinoxalinyl-pyruvate.

cf. Borsche and Doeller, Ann., 537, 39 (1939).

To a solution of potassium (3.2 g) in absolute ethanol (14 ml) and anhydrous ether (30 ml), were added freshly distilled ethyl oxalate (5.8 g), and after cooling for 1 hour, freshly distilled 2-methylquinoxaline (5.8 g). After allowing the mixture to stand for 2 hours, more ether was added (20 ml) and hydrochloric acid (2N, 100 ml). The ether layer was separated and the aqueous layer re-extracted several times with ether. The combined extracts were dried over calcium sulphate, the solvent removed and the yellow solid obtained. The solid crystallised from ethanol as golden yellow needles.

Yield 7.75 g.

M.P. 161-163°C.

Preparation of methin-(2-quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline).

cf. Borsche and Doeller, loc. sit.

Ethyl 2-quinoxalinyl-pyruvate (3 g) and o-phenylenediamine (2 g) were dissolved in glacial acetic acid (50 ml). After a few minutes warming, an orange solid separated. More acid was added and the precipitate digested for 10 minutes. The solid was filtered, washed with hot ethanol and with ether. It recrystallised from nitrobenzene as orange needles.

Yield 2.8 g.

M.P. 319-321°C.

Analysis. Found : C, 71.0; H, 4.0; N, 18.6; O, 6.4%

$C_{17}H_{12}N_4O$ requires C, 70.8; H, 4.2; N, 19.4; O, 5.6%

Reaction of phosphorus oxychloride and water on methin-(2-quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline).

cf. Barker, Thesis, p. 106.

Methin-(2-quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) (1.5 g) was added to phosphorus oxychloride (20 ml) and water (3 ml) and the mixture was boiled under reflux for 2 hours. The excess phosphorus oxychloride was distilled off and the residual mixture made alkaline with potassium hydroxide. The black precipitate was filtered off, dried and extracted in a Soxhlet

thimble with benzene for 16 hours. The orange-red extract was concentrated and chromatographed on an alumina column. Three bands separated.

a) An orange band, which fluoresced yellow in U.V. light, was eluted with benzene. Removal of the eluant gave a very small amount of yellow solid, which was not further investigated.

b) A red band, which did not fluoresce in U.V. light, was eluted with benzene-ether (9:1), giving an orange-red solution. Removal of the eluant gave a red solid, which crystallised from benzene as rose-red needles.

Yield 0.3 g.

M.P. 308-311°C.

Analysis. Found : C, 74.1; H, 3.6; N, 20.2%

$C_{17}H_{10}N_4$ requires C, 75.6; H, 3.7; N, 20.7%

Conc. H_2SO_4 - green.

Dil. H_2SO_4 - blue.

c) A dark red band, which fluoresced orange in U.V. light, was eluted with benzene-ether (1:3), giving an orange-red solution. Removal of the eluant gave a dark red solid, which crystallised from benzene as orange-red needles, which sublimed ca. 220°C, and melted 247-248°C.

Yield 0.3 g.

Analysis. Found : C, 76.2; H, 3.8; N. 20.2%

$C_{17}H_{11}N_4$ requires C, 75.3; H, 4.1; N, 20.6%

Conc. H_2SO_4 - green.

Dil. H_2SO_4 - blue.

Preparation of ethyl 2-quinolinyl-pyruvate.

cf. Borsche and Manteuffel, Ann., 526, 22 (1936).

Leonard & Boyer, J.A.C.S., 72, 2980 (1950).

To a solution of potassium (4.3 g) in ethanol (20 ml) and ether (50 ml), was added freshly distilled ethyl oxalate (8.5 g) and after cooling to 0°C, freshly distilled quinaldine (8 g) in ether (20 ml). The mixture was allowed to stand at room temperature for 14 days. Ether (50 ml) and hydrochloric acid (2N, 100 ml) were added and the ether layer separated. The aqueous layer was re-extracted and the combined ether extracts dried over calcium sulphate, and then the ether removed to give a yellow solid. This crystallised from ethanol as yellow needles.

Yield 8 g.

M.P. 131-132°C.

Preparation of methin-(2-quinolinyl)-(2'-(3'-keto)tetrahydro-quinoxaline).

Ethyl 2-quinolinyl-pyruvate (2.5 g) and o-phenylenediamine (1.1 g) were dissolved in ethanol (100 ml) containing hydrochloric acid (10N, 4 ml) and the solution warmed on a waterbath for 30 minutes. A red precipitate was formed, filtered off and re-crystallised from pyridine, after treatment with charcoal. Orange-red needles were obtained, which between 280-285°C changed form, giving dark red rods, M.P. 295-296°C.

Yield 2.5 g.

Analysis. Found : C, 75.6; H, 4.9; N, 14.3; O, 5.2%

$C_{18}H_{13}N_3O$ requires C, 75.3; H, 4.5; N, 14.6; O, 5.6%

Reaction between phosphorus oxychloride and water and methin-(2-quinolinyl-2'-(3'-keto)tetrahydroquinoxaline).

Methin-(2-quinolinyl)-(2'-(3'-keto)tetrahydroquinoxaline) (1.1 g) was added to phosphorus oxychloride (20 ml) and water (3 ml) and the mixture heated at 130°C for 2 hours. A purple solution was obtained and after removal of the excess phosphorus oxychloride, the mixture was made alkaline with potassium hydroxide. A red solid was precipitated and after drying, this was extracted in a Soxhlet thimble with benzene for 18 hours. The orange-red extract, with intense green fluorescence, was purified on an alumina column. An orange-red band separated and was eluted with benzene-ether (4:1), giving an orange solution with a green fluorescence. The removal of the solvent gave an orange-red solid, which crystallised from benzene as plates.

Yield 0.91 g.

M.P. 218-219°C.

Analysis. Found: C, 79.4; H, 4.1; N, 15.1%

$C_{18}H_{13}N_3$ requires C, 79.7; H, 4.8; N, 15.5%

Conc. H_2SO_4 - green.

Dil. H_2SO_4 - blue-violet.

Very dil. H_2SO_4 - red.

Preparation of ethyl 2-pyrazinyl-pyruvate.

cf. Stock, Donahue and Amstutz, J. Org. Chem., 23, 1840 (1958).

To a solution of potassium (9 g) in ethanol (15 ml) and anhydrous ether (40 ml), were added freshly distilled ethyl oxalate (16 g) and after cooling for 1 hour, freshly distilled 2-methylpyrazine (11 g) in ether (20 ml). The mixture was allowed to stand at room temperature for 13 days. The yellow solid was filtered off, treated with hydrochloric acid (5N, 30 ml), and the ester was extracted into ether. From the ether extract was obtained a yellow solid, which crystallised from ether as yellow rods.

Yield 10 g.

M.P. 69-70°C. (Stock reports M.P. 74-75°C.)

Analysis. Found : C, 55.7; H, 5.1; N, 14.5%

$C_9H_{10}N_2O_3$ requires C, 55.7; H, 5.2; N, 14.4%

Preparation of methin-(2-pyrazinyl)-(2'-(3'-keto)tetrahydro-quinoxaline).

Ethyl 2-pyrazinyl-pyruvate (6 g) and o-phenylenediamine (6 g) were dissolved in glacial acetic acid (40 ml) and the mixture boiled under reflux for 2 hours. On cooling, a yellow solid precipitated and this crystallised from pyridine as clusters of small yellow needles.

Yield 6 g.

M.P. 269-270°C.

Analysis. Found : C, 65.8; H, 4.3; N, 24.2%

$C_{13}H_{10}N_4O$ requires C,65.5; H, 4.2; N, 23.5%

Reaction between phosphorus oxychloride and water and methin - (2-pyrazinyl)-(2'-(3'-keto)tetrahydroquinoxaline).

Methin-(2-pyrazinyl)-(2'-(3'-keto)tetrahydroquinoxaline) (1.35 g) was dissolved in phosphorus oxychloride (20 ml) and water (3 ml). The dark blue solution was heated at 130°C for 2 hours and after the excess phosphorous oxychloride had been removed, the mixture was made alkaline with potassium hydroxide. The black solid was filtered off, dried, and extracted in a Soxhlet thimble with benzene for 14 hours. The deep red extract was chromatographed on an alumina column. A deep red band slowly separated, was cut from the extruded column, and extracted with ethanol for 14 hours. The extract was concentrated and dark red crystals separated. These recrystallised from ethyl acetate as fine dark red needles.

Yield 0.4 g

M.P. 219-220°C.

Analysis. Found : C, 70.8; H, 4.2; N, 24.9%

$C_{13}H_{10}N_4$ requires C, 70.3; H, 4.5; N, 25.2%

Conc. H_2SO_4 - green.

Dil. H_2SO_4 - blue.

NaOH - red.

Condensation of ethyl 2-quinoxalinyl-pyruvate and ethylenediamine.

cf. Mason, Ber., 20, 267 (1887).

Mason & Dryfoos, J.C.S., 1893, 1310.

Ethyl 2-quinoxalinyl-pyruvate (5 g) and ethylenediamine (1.75 g) were dissolved in ethanol (40 ml) and the solution boiled under reflux for 2 hours. On cooling, a yellow solid was precipitated. This crystallised from xylene, after treatment with charcoal, as yellow rods.

Yield 3.5 g.

M.P. 248°C.

Analysis. Found : C, 64.8; H, 5.0; N, 23.4%

$C_{13}H_{12}N_4O$ requires C, 65.0; H, 5.0; N, 23.3%

Condensation of ethyl 2-pyrazinyl-pyruvate with ethylenediamine.

cf. Mason, loc. cit.

Ethyl 2-pyrazinyl-pyruvate (5.5 g) and ethylenediamine (2 g) in ethanol (100 ml) were boiled under reflux for 18 hours. Ethanol (70 ml) was distilled off and on cooling, a yellow solid precipitated. This was recrystallised from a large volume of benzene, as yellow needles.

Yield 6 g.

M.P. 174-174.5°C.

Analysis. Found : C, 56.6; H, 5.3; N, 29.3%

$C_9H_{10}N_4O$ requires C, 56.8; H, 5.3; N, 29.5%

Reaction of phosphorus oxychloride and water with acridone.

A mixture of acridone (2 g), phosphorus oxychloride (40 ml) and water (6 ml) was heated at 130°C for 2 hours. The excess phosphorus oxychloride was distilled off and the remaining 'glue' was made alkaline with potassium hydroxide (2N, 100 ml). The yellow solid was filtered off.

The solid was in the form of pale yellow crystals.

Yield 1 g.

M.P. 350-352°C.

Mixed M.P. with acridone 350-352°C.

The filtrate was extracted with chloroform. After concentrating the extract to 30 ml, an equal volume of benzene was added and the solution purified on an alumina column. A yellow band separated and was eluted with benzene. Removal of the eluant gave yellow crystals, which recrystallised from light petroleum (40/60) as pale yellow needles.

Yield 0.3 g.

M.P. 115-117°C.

Analysis. Found : C, 73.1; H, 3.7; N, 7.2; Cl, 15.8%

$C_{13}H_8ClN$ requires C, 73.1; H, 3.7; N, 6.6; Cl, 16.6%

Preparation of phenanthridone.

a) Fluorenone oxime.

Spiegler, Monatsh., 5, 195 (1884).

Fluorenone (8.5 g) and hydroxylamine hydrochloride (6.6 g) in ethanol (70%, 80 ml) were boiled under reflux for 3 hours. The

ethanol was distilled off and water (25 ml) added. The crystals were filtered off and washed until the filtrate did not reduce Fehling's solution. The solid was recrystallised from ethanol as pale yellow needles.

Yield 6 g.

M.P. 191-192°C.

b) Phenanthridone.

Horning, Stromberg and Lloyd, J.A.C.S., 74, 5153 (1952).

Fluorenone oxime (4 g) and polyphosphoric acid (120 g) were heated with stirring to 175-180°C and the temperature kept in this range for 10 minutes. After cooling, the mixture was poured into water (600 ml) and a white solid precipitated. The solid was boiled under reflux with ethanol (500 ml) and the solution hot-filtered. White crystals were obtained from the filtrate. The residue from the filtration was dissolved in hot glacial acetic acid and then a drop of water was added, causing precipitation of white crystals.

Yield 3.6 g.

M.P. 287-288°C.

Reaction between phosphorus oxychloride and water and phenanthridone.

Phenanthridone (1 g) was boiled under reflux with phosphorus oxychloride (20 ml) and water (3 ml) for 3.5 hours. The mixture was made alkaline with potassium hydroxide (10N, 50 ml). A white

solid precipitated and was filtered off. The solid was extracted with benzene (5 x 20 ml) and the residue was a white crystalline substance.

Yield 0.5 g.

M.P. 285-287°C.

Mixed M.P. with phenanthridone 285-288°C.

The filtrate was extracted with benzene and this solution was combined with the above extracts and purified on an alumina column. Two bands separated.

a) A colourless band, which fluoresced blue in U.V. light, was eluted with benzene, giving a yellow solution. Removal of the eluant gave white crystals.

Yield 100 mg.

M.P. 113-115°C.

Mixed M.P. with phenanthridine 95-100°C.

M.P. of 9-chlorophenanthridine 116.5°C.

b) A colourless band, which fluoresced white in U.V. light, was eluted with benzene-ether (1:1). Removal of the eluant gave a small amount of 9-chlorophenanthridine.

Preparation of 2-quinoxalone.

cf. Gowenlock, Newbold & Spring, J.C.S., 1945, 622.

Sodium mesoxalate (15 g) was dissolved in ethanol (100 ml) and dry hydrogen chloride passed into the solution. After the sodium chloride had been filtered off, the solution was boiled under reflux for 3 hours and then allowed to stand at room temperature

for 12 hours. o-Phenylenediamine (8 g) was added to the solution and the mixture boiled under reflux for 1 hour. On cooling, some brown solid precipitated and was filtered off (3 g). An equal volume of water was added to the filtrate which was then extracted continuously with ether for 20 hours. Removal of the ether gave orange crystals, which were recrystallised from ethanol as yellow prisms.

Yield 6 g.

M.P. 175°C.

The ester was hydrolysed with sodium hydroxide (10%, 30 ml), by heating on a steam-bath for 45 minutes. The solution was made acid to Congo Red, with hydrochloric acid (5N) and a yellow solid precipitated.

Yield 5 g.

The acid was decarboxylated at 280°C and sublimed at 200°C and 10 mm. pressure to give 2-quinoxalone.

Yield 2.8 g.

M.P. 267.5-268°C.

M.P. of 2-quinoxalone (Spring) 266°C.

Reaction of phosphorus oxychloride and water with 2-quinoxalone.

2-Quinoxalone (1 g) was boiled under reflux for 2 hours with phosphorus oxychloride (20 ml) and water (3 ml). The excess phosphorus oxychloride was distilled off and water added to the residue, giving brown needles (0.5 g) which were filtered off, dissolved in ether and purified on an alumina column. Three bands separated.

a) A band which fluoresced green in U.V. light, was eluted with ether. Removal of the ether gave white crystals.

Yield 0.4 g.

M.P. 44.5-45.5°C.

Mixed M.P. with 2-chloroquinoxaline 45-47°C.

b) A band was eluted with ethanol and gave a white solid on removal of the solvent.

c) A band was eluted with ethanol, giving a brown solution which yielded a brown solid.

The products from bands b) and c) were in very small amounts and were not further investigated.

The filtrate from the reaction mixture was thoroughly extracted with ether and removal of the solvent gave a whitish-yellow solid, which was washed with ether.

M.P. 224-230°C.

The ether washings were purified on an alumina column, and a band separated and was eluted with ether. Removal of the eluant gave white crystals.

Yield 50 mg.

M.P. 43-45°C.

Mixed M.P. with 2-chloroquinoxaline 43-47°C.

No quinoxaline was isolated from this reaction mixture.

Total yield of 2-chloroquinoxaline = 0.45 g (40%).

Yield of 2-chloroquinoxaline from this reaction when freshly distilled phosphorus oxychloride is used = 85% (Spring et alia, J.C.S., 1945, 622).

Preparation of 2-chloroquinoxaline.

Gowenlock, Newbold and Spring, J.C.S., 1945, 622.

2-Quinoxalone (1.5 g) gave 2-chloroquinoxaline (1.3 g).

M.P. 45-47°C.

Preparation of 6,7-benzo-2-quinoxalone.

Ethyl ketomalonate was prepared from sodio-ketomalonic ester (15 g) by boiling under reflux for 3 hours with ethanolic hydrogen chloride. 2,3-diaminonaphthalene (8 g) was added to the solution and, immediately, a solid was precipitated from solution. This precipitate was allowed to digest in the hot mother liquor for 30 minutes, after which it was filtered and washed with ether. This was the hydrochloride of the base.

Yield 16.5 g.

The hydrochloride (11 g) in sodium hydroxide (10%, 100 ml) was heated on a steam-bath for 30 minutes and then filtered hot, leaving a brown residue (2.5 g), which was not further investigated. The cooled filtrate was made acid to Congo Red with hydrochloric acid (5N) and orange-red crystals were precipitated.

Yield 4.5 g.

A little of this precipitate was recrystallised from nitrobenzene as orange-brown needles, which sublimed to plates ca. 200°C and lost carbon dioxide between 276-280°C, forming yellow rods which decomposed at 312-315°C.

Analysis. Found : C, 73.7; H, 4.2; N, 13.9%

$C_{12}H_8N_2O$ requires C, 73.4; H, 4.1; N, 14.3%

The rest of the precipitate was decarboxylated and sublimed at 240°C. The yellow crystals were purified by sublimation at 200°C and 0.2 mm. pressure, giving yellow granules, which sublimed to yellow plates ca. 190-200°C, and decomposed at 310°C.

Yield 2.25 g.

Analysis. Found : C, 73.3; H, 3.9; N, 14.5%

$C_{12}H_8N_2O$ requires : C, 73.4; H, 4.1; N, 14.3%

Reaction of phosphorus oxychloride and water with 6,7-benzo-2-quinoxalone.

6,7-Benzo-2-quinoxalone (1 g) was boiled under reflux for 2 hours with phosphorus oxychloride (20 ml) and water (3 ml), giving a red solution. The excess phosphorus oxychloride was distilled off and the mixture made alkaline with potassium hydroxide (10%, 100 ml). The black precipitate was filtered off, dried and extracted in a Soxhlet thimble with benzene, for 14 hours. The benzene extract was filtered to remove some solid (50 mg) which came out of solution, and then combined with the benzene extract of the alkaline filtrate. The combined extract was dried and concentrated to 50 ml. before purification on an alumina column. Two bands separated.

a) A yellow band, which fluoresced green in U.V. light, was eluted with benzene. Removal of the eluant gave a yellow solid, which was purified by sublimation, giving lemon yellow plates.

Yield 0.2 g.

M.P. 137-138°C.

Analysis. Found : C, 67.4; H, 3.9; N, 12.7; Cl, 16.2%
$C_{12}H_7ClN_2$ requires C, 67.1; H, 3.3; N, 13.1; Cl, 16.5%

b) A brown band was eluted with ether. Removal of the solvent gave a very small amount of orange material.

M.P. 263-268°C (decomposition).

No 6,7-benzoquinoxaline (M.P. 125-126°C - Landquist, J.C.S., 1953, 2816) was isolated.

Preparation of 2-methyl-3-phenylquinoxaline.

cf. v. Auwers, Ber., 50, 1177 (1917).

Acetylbenzoyl (5 g) and o-phenylenediamine (3.7 g) in ethanol (100 ml) containing hydrochloric acid (5N, 10 ml), were boiled under reflux for 1 hour. After cooling, the solution was poured into water (200 ml) and this mixture was extracted with ether. The extract was neutralised with sodium bicarbonate, washed with water and dried over anhydrous calcium sulphate. A white solid was obtained on removal of the ether and recrystallised from light petroleum (40/60) as white needles.

Yield 4 g.

M.P. 56-57°C (v. Auwers reported 57-58°C).

Preparation of 3-phenyl-2-quinoxalone.

cf. Blatt, J.A.C.S., 57, 1103 (1935).

2-Methyl-3-phenylquinoxaline (2 g) was dissolved in glacial acetic acid (90 ml) and to the solution was added chromium trioxide (AnalaR) (3 g) in glacial acetic acid (5 ml) and water (5 ml), the

addition being controlled so that the temperature of the mixture did not rise above 40°C. The mixture was then boiled under reflux for 30 minutes, cooled and diluted with water (200 ml), and finally extracted with ether.

The ether extract was itself extracted with sodium carbonate (5%), to remove acidic material, and then with sodium hydroxide (10%). This last extract was taken to pH 6 and the precipitate filtered off and purified by sublimation at 210°C, giving pale yellow needles.

Yield 1 g.

M.P. 250°C.

Analysis. Found : C, 75.3; H, 4.9; N, 12.4%

$C_{14}H_{10}N_2O$ requires C, 75.7; H, 4.5; N, 12.6%

Preparation of 2-chloro-3-phenylquinoxaline.

3-Phenyl-2-quinoxalone (80 mg) was boiled under reflux for 20 minutes with freshly distilled phosphorus oxychloride (10 ml). Water (20 ml) was added and the mixture made alkaline with potassium hydroxide (25%, 75 ml). The white solid was filtered off and boiled with light petroleum (60/80) (3 x 15 ml). The white residue was 3-phenyl-2-quinoxalone (20 mg).

M.P. 247-249°C.

Mixed M.P. with 3-phenyl-2-quinoxalone 247-250°C.

The extract was purified on an alumina column. One band was eluted with benzene and removal of the eluant gave pale yellow needles, which recrystallised from light petroleum (40/60).

Yield 50 mg.

M.P. 127-128°C.

Analysis. Found : C, 70.2; H, 4.1; N, 11.0; Cl, 13.4%

$C_{14}H_9ClN_2$ requires C, 69.9; H, 3.8; H, 11.6; Cl, 14.7%

Reaction of phosphorus oxychloride and water with 3-phenyl-2-quinoxalone.

3-Phenyl-2-quinoxalone (0.5 g) in phosphorus oxychloride (20 ml) and water (3 ml), was boiled under reflux for 2 hours. The solution was poured into ice-water (100 ml), giving a white precipitate, which was filtered off and extracted into benzene, leaving a small, insoluble brown residue. The benzene solution was purified on an alumina column and three bands separated.

a) A yellow band, which fluoresced green in U.V. light, was eluted with ether. Removal of the eluant gave a pale yellow solid, which crystallised from light petroleum (40/60) as whitish-yellow needles.

Yield 380 mg.

M.P. 126-127°C.

Mixed M.P. with 2-chloro-3-phenylquinoxaline 126-128°C.

b) A yellow-brown band, which fluoresced yellow in U.V. light, was eluted with ether. Removal of the solvent gave a very small residue, which was not investigated further.

c) A pale yellow band, which fluoresced blue in U.V. light, was eluted with ethanol. Removal of the eluant gave pale yellow material.

Yield 30 mg.

M.P. 250°C.

Mixed M.P. with 3-phenyl-2-quinoxalone 248-250°C.

No 2-phenylquinoxaline (M.P. 78°C. - Hinsberg, Ann., 292, 245 (1896)) was isolated.

Preparation of phenylpyruvic acid.

a) Acetylglycine.

Organic Syntheses, 19, 4.

Glycine (30 g) gave acetylglycine (30 g).

M.P. 206-207°C.

b) α-Acetaminocinnamic acid.

Organic Syntheses, 19, 1.

Acetylglycine (25 g) gave α-acetaminocinnamic acid (14 g).

M.P. 191-192.5°C.

c) Phenylpyruvic acid.

Organic Syntheses, 19, 77.

α-Acetaminocinnamic acid (10 g) gave phenylpyruvic acid (6 g).

M.P. 154°C.

Preparation of 3-benzyl-2-quinoxalone.

Cook and Perry, J.C.S., 1943, 394.

Phenylpyruvic acid (3 g) in ethanol (25 ml) was mixed with o-phenylenediamine (1.8 g) in ethanol (25 ml). A solid precipitated from solution almost immediately and the mass was allowed to

stand at room temperature for 1 hour. The solid crystallised from ethanol as white needles.

Yield 3 g.

M.P. 195.5-196.5°C.

Analysis. Found : C, 76.7; H, 5.0; N, 11.6%

$C_{15}H_{12}N_2O$ requires C, 76.2; H, 5.1; N, 11.9%

Reaction of phosphorus oxychloride and water with 3-benzyl-2-quinoxalone.

3-Benzyl-2-quinoxalone (2 g) in phosphorus oxychloride (20 ml) and water (3 ml) was boiled under reflux for 2 hours; the yellow solution became blue on heating. After cooling, the solution was poured into ice-water (150 ml), giving 1) a whitish precipitate containing green particles, and 2) a blue solution.

1) The precipitate was warmed with benzene, giving a deep red solution and a green oil. The benzene was decanted off and the oil dissolved in sodium hydroxide (10%, 20 ml) and this solution was extracted with benzene.

2) The filtrate was made alkaline with sodium hydroxide (10%, 50 ml), the colour changing from blue through purple to pink, and was then extracted with benzene.

The combined benzene extracts were dried, concentrated to 30 ml. and purified on an alumina column. Three bands separated.

a) A colourless band, which fluoresced orange in U.V. light, was eluted with benzene, giving an orange solution. Removal of the benzene gave pink crystals, which recrystallised from light

petroleum (40/60), after treatment with charcoal, as white prisms.

Yield 1.14 g.

M.P. 83-84°C.

Analysis. Found : C, 70.4; H, 4.4; N, 11.1; Cl, 13.7%

$C_{15}H_{11}N_2Cl$ requires C, 70.7; H, 4.4; N, 11.0; Cl, 13.9%

b) A pale red band, which fluoresced blue in U.V. light, was eluted with benzene, giving a yellow solution, which proved to contain a small amount of slightly impure 2-benzyl-3-chloroquinoxaline.

c) A yellow band, which fluoresced green in U.V. light, was eluted with ether-ethanol (1:1), giving a yellow solution. Removal of the eluant gave a very small amount of solid.

No 2-benzylquinoxaline (a brown oil; picrate M.P. 117°C. - Bennett and Willis, J.C.S., 1928, 1960) was isolated.

Reaction between phosphorus oxychloride and 2-chloro-3-methylquinoxaline.

cf. Barker, Thesis, p. 108.

2-Chloro-3-methylquinoxaline (0.3 g) was boiled under reflux with freshly distilled phosphorus oxychloride (20 ml) for 30 minutes. On cooling, the red solution was poured into ice-water (200 ml) and made alkaline with sodium hydroxide (20%, 100 ml). The solution was extracted with benzene, giving a very pale orange solution, which was purified on an alumina column. Two bands were eluted.

a) A colourless band was eluted with benzene and removal of this solvent gave 2-chloro-3-methylquinoxaline.

Yield 0.2 g.

M.P. 82-83°C.

b) A very faint orange band, which fluoresced orange in U.V. light, was eluted with ether. No solid was visible on removal of the solvent, but a green colour was obtained when concentrated sulphuric acid was added to the flask.

Reaction of phosphorus oxychloride and water on 3-methyl-2-quinoxalone.

cf. Barker, Thesis, p. 99.

3-Methyl-2-quinoxalone (0.8 g) in phosphorus oxychloride (20 ml) and water (3 ml) was boiled under reflux for 2 hours. The excess phosphorus oxychloride was distilled off and the mixture made alkaline with potassium hydroxide (10%, 30 ml). The red precipitate was filtered off and extracted in a Soxhlet thimble with benzene for 14 hours. The red solution with intense green fluorescence, was purified on an alumina column. Two bands separated.

a) A colourless band, which had a faint blue fluorescence in U.V. light, was eluted with benzene. Removal of the eluant gave a white solid, which crystallised as white prisms from light petroleum (60/80).

Yield 350 mg.

M.P. 80-82°C.

Mixed M.P. with 2-chloro-3-methylquinoxaline 80-83°C.

b) An orange band, which fluoresced orange in U.V. light, was eluted with benzene-ether (9:1), giving an orange solution. Removal

of the eluant gave an orange solid, which crystallised as bright orange needles from carbon tetrachloride.

Yield 30 mg.

M.P. 253-255°C.

Mixed M.P. with methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) 253-257°C.

Reaction of phosphorus oxychloride and water on methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine).

Methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine) (1.4 g) was boiled under reflux for 2 hours with phosphorus oxychloride (20 ml) and water (3 ml). The excess phosphorus oxychloride was distilled off and the black residue made alkaline with potassium hydroxide (10%, 50 ml). The red solution, containing a small amount of black solid, was extracted continuously with benzene for 20 hours, giving a dark red solution with an intense green fluorescence. After concentrating the solution to 30 ml, the extract was purified on an alumina column. One band separated and appeared to consist of two bands: a) a yellow band, and b) a red band. These bands did not separate with mixtures of benzene and light petroleum, or with benzene itself, so the pure yellow fraction was collected, and the rest of the band (red and yellow) was collected, concentrated to small volume, and chromatographed again. A pure yellow fraction and a mixed fraction were eluted. The chromatography of the mixed fraction was repeated four more times, with the same result. Since the yellow band was produced every time, the mixed fraction was

allowed to remain on the column for 2 days, but there was no noticeable increase in the amount of yellow material separating from the red.

a) The pure yellow band, which fluoresced yellow in U.V. light, was eluted with benzene, giving a yellow solution with a green fluorescence in visible light. Removal of the solvent gave a yellow solid, which crystallised from ethanol as yellow cubic prisms.

Yield 100 mg.

M.P. 202°C.

Analysis. Found : C, 70.9; H, 3.4; N, 25.4%

C, 70.9; H, 3.8; N, 25.2%

$C_{13}H_8N_4$ requires C, 70.9; H, 3.7; N, 25.4%

Conc. H_2SO_4 - pale red.

Dil. H_2SO_4 - pale red.

Dil. NaOH - orange.

b) The final red-yellow fraction from the chromatographic separations, gave a deep red solution. Removal of the benzene gave a mixture of red and yellow solids, which were dissolved in ethanol. After standing for 2 days, red crystals came out of solution and were recrystallised as deep red needles, from ethanol.

Yield 100 mg.

M.P. 217-219°C.

Mixed M.P. with methin-(2-pyrazinyl)-(2'-dihydro-quinoxaline) 217-219°C.

Reaction of phosphorus oxychloride on methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine).

Methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine) (1.4 g) and freshly distilled phosphorus oxychloride (30 ml) were boiled under reflux for 3 hours. The solution was concentrated to 10 ml. and this was poured into ice-water (200 ml). This suspension was made alkaline with potassium hydroxide and a small black precipitate was obtained. The black precipitate was extracted in a Soxhlet thimble with benzene for 40 hours and the filtrate was extracted continuously with the same solvent for 45 hours. The extracts were combined, concentrated to small volume and purified on an alumina column. Several bands separated.

a) A colourless band, which fluoresced green in U.V. light, was eluted with benzene. Removal of the solvent gave a very small amount of material.

b) A yellow band, which fluoresced yellow in U.V. light and which did not separate completely from the band following it, was eluted with benzene, giving a yellow solution with an intense green fluorescence in visible light. Removal of the eluant gave a yellow solid, which crystallised from ethanol as yellow cubic prisms.

Yield 170 mg.

M.P. 202.5-203°C.

Mixed M.P. with the yellow compound obtained in the preceding experiment 202-204°C.

c) A red band, without fluorescence in U.V. light, which did not separate completely from band b), was eluted with benzene.

The orange-red eluate yielded a very small amount of red material, which was dissolved in ethanol and a qualitative spectrum obtained.

Maxima (mu)	Unknown	$C_{13}H_{10}N_4$
	508	528
	480	500
	379) 368)	377) 368)
	270	271

The other bands were not investigated.

Attempted oxidation of the yellow compound, $C_{13}H_8N_4$.

The yellow base (100 mg) was dissolved in glacial acetic acid (4 ml) and to the solution was added chromium trioxide (AnalaR) (75 mg) in acetic acid (4 ml) and water (0.5 ml). This mixture was allowed to stand overnight, at room temperature, before being boiled under reflux for 1 hour. No reduction of the chromium trioxide occurred, so a mixture of sulphuric acid (5 drops) and acetic acid (1 ml) was added and the boiling continued for 30 minutes. On cooling, the solution was poured into water (50 ml), neutralised with sodium bicarbonate and then extracted with ether. Removal of the ether gave a yellow solid, M.P. 186-192°C, which was dissolved in benzene and purified on an alumina column. One band separated and was eluted with benzene. Removal of the eluant gave a yellow solid.

Yield 70 mg.

M.P. 200-202°C.

Mixed M.P. with the base, $C_{13}H_8N_4$, 200-202.5°C.

Reduction of 1'-keto-indano(2',3':2,3)quinoxaline.

1'-Keto-indano(2',3':2,3)quinoxaline (0.45g) was added to a mixture of potassium hydroxide (0.6g), trimethylene glycol (8ml) and hydrazine hydrate (90%, 1.5ml) which was then boiled under reflux for 1.3 hours. The condenser was removed and the temperature of the oil-bath slowly raised to 200°C. The temperature was kept there for 6 hours and then the mixture was allowed to cool. The mixture was thoroughly extracted with ether, giving a yellow solution. Removal of the ether gave a yellow solid, which crystallised from methanol after treatment with charcoal, as very pale yellow cubic prisms.

Yield 200mg.

M.P. 157.5 - 158.5°C.

Analysis, Found : C, 81.7; H, 4.6; N, 13.3%

$C_{15}H_{10}N_2$ requires C, 82.6; H, 4.6; N, 12.8%

Oxidation of 1'H-indano(2',3':2,3)quinoxaline.

1'H-Indano(2',3':2,3)quinoxaline (50mg) was dissolved in glacial acetic acid (7ml) and to the solution was added chromium trioxide (AnalaR) (30mg) in acetic acid) (5ml) and water (1ml). This was boiled under reflux for 30 minutes. On cooling, the mixture was poured into water (25ml), neutralised with sodium bicarbonate, and extracted with ether. From the extract was obtained a yellow solid, which crystallised from methanol as large bright yellow prismatic rods.

Yield 30 mg.

M.P. 211-213°C.

Mixed M.P. with 1'-keto-indano(2',3':2,3)quinoxaline 210-213°C.

Oxidation of methine bases.

The bases were dissolved in glacial acetic acid and chromium trioxide in dilute acetic acid was added. The oxidation was followed by colour changes. Only a few milligrammes of base were used and no products were isolated.

1. Methin-(2-pyrazinyl)-(2'-dihydroquinoxaline).

In the cold, the colour changed from red to purple, with precipitation of a solid. On gently warming the mixture, the colour rapidly changed to brown.

2. Methin-(2-quinolinyl)-(2'-dihydroquinoxaline).

In the cold, the red solution became purple and on warming the mixture, the colour became brown and a solid precipitated.

Reaction of phosphorus oxychloride and water on methin-(2-pyrazinyl)-(2'-(3'-keto)piperazine).

Methin-(2-pyrazinyl)-(2'-(3'-keto)piperazine) (2 g) in phosphorus oxychloride (30 ml) and water (4.5 ml) was boiled under reflux for 2 hours. The excess phosphorus oxychloride was distilled off and the residue made alkaline with potassium hydroxide (10%, (50 ml). The solution was extracted continuously with benzene for 20 hours and then the dark red extract was purified on an alumina column. Three bands separated.

a) A pale yellow band was eluted with benzene-ether (9:1), but removal of the solvent gave only a very small amount of material.

b) A dark yellow band, which appeared orange in U.V. light, was eluted with benzene-ether (4:1), giving a yellow solution which did not fluoresce in U.V. light. Removal of the eluant gave a deep yellow solid, which crystallised from light petroleum (60/80) as fine golden yellow needles.

Yield 20mg.

M.P. 174-176°C.

Conc. H_2SO_4 - deep red.

c) A dark yellow band, which fluoresced yellow in U.V. light, was eluted with benzene-ether (1:1), giving a yellow solution, which fluoresced yellow in U.V. light. Removal of the solvent gave a yellow solid, which crystallised from ethanol as yellow needles.

Yield 150 mg.

M.P. 160-161.5°C.

Conc. H_2SO_4 - pale red.

Analysis. Found : C, 63.5; H, 3.8; N, 32.6%

$C_9H_6N_4$ requires C, 63.5; H, 3.6; N, 32.9%

Reaction of phosphorus oxychloride on methin-(2-pyrazinyl)-(2'-(3'-keto)piperazine).

Methin-(2-pyrazinyl)-(2'-(3'-keto)piperazine) (2 g) dissolved in freshly distilled phosphorus oxychloride (40 ml), giving an orange solution which was boiled under reflux for 2 hours. The excess phosphorus oxychloride was distilled off and the black residue was made alkaline with potassium hydroxide (40%, 20 ml). The black solid was filtered off and extracted in a Soxhlet thimble with benzene for 16 hours, while the filtrate was extracted continuously with benzene for the same period. The two extracts were combined and concentrated to 20 ml, and purified on an alumina column. A yellow band, which fluoresced yellow in U.V. light, separated and was eluted with benzene-ether (1:4). Removal of the solvent gave a yellow solid, which crystallised from methanol as yellow needles.

Yield 100 mg.

M.P. 162-163°C.

Mixed M.P. with the yellow base, $C_9H_6N_4$, 160-163°C.

Attempted cyclisation of methin-(2-quinoxalinyl)-(2'-(3'-keto) tetrahydroquinoxaline) using polyphosphoric acid.

cf. Bergmann & Szmuszkovicz, Bull. soc. chim. France, 1953, 566.

Polyphosphoric acid was prepared from phosphorus pentoxide (92 g) and syrupy phosphoric acid (75 ml).

I. Methin-(2-quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) (0.5 g) in polyphosphoric acid (10 ml) was heated on a boiling

water-bath for 3 hours. The colour of the solution changed from deep green to blue-green. After cooling, the solution was poured into ice-water (50 ml) and a brown precipitate was formed. This precipitate was extracted in a Soxhlet thimble with benzene for 40 hours. Orange material was obtained from the extract.

M.P. 314-316°C.

Mixed M.P. with starting material 315-317°C.

The acid filtrate was also extracted continuously with benzene for 40 hours, giving an orange solution, which yielded a very small amount of orange material.

II. Methin-(2-quinoxalinyl)-(2'-(3'-keto)tetrahydroquinoxaline) (0.75 g) in polyphosphoric acid (10 g) was heated at 150°C for 3 hours. The deep green solution changed through purple to dark red in colour, during the heating. The cooled solution was added to ice-water (100 ml) and a brown precipitate was obtained. This precipitate was filtered off, dried and extracted continuously with ether for 8 hours; it was found that although the extract was coloured yellow, only a small amount of solid had been extracted and the brown material was relatively unaffected. The ether extract was added to the extract of the filtrate, a yellow solution with a green fluorescence in U.V. light, and removal of the solvent gave an orange solid, which crystallised from benzene, after treatment with charcoal, as pale yellow needles.

Yield 200 mg.

M.P. 247-248°C.

Mixed M.P. with 3-methyl-2-quinoxalone 245-247.5°C.

Analysis. Found : C, 67.3; H, 4.7; N, 17.9%

$C_9H_8N_2O$ requires C, 67.5; H, 5.0; N, 17.5%

The brown solid, after the extraction was completed, was suspended in sodium hydroxide (10%) and this was extracted continuously with ether for 60 hours. Removal of the solvent gave a very small amount of material.

Attempted cyclisation of methin-(2-pyrazinyl)-(2'-(3'-keto)tetrahydroquinoxaline.

Methin-(2-pyrazinyl)-(2'-(3'-keto)tetrahydroquinoxaline) (1 g) in polyphosphoric acid (11 g) was heated at 150°C for 4 hours. The colour of the solution changed from green to deep red. After cooling, the solution was poured into water (100 ml) and a brown precipitate was obtained (0.6 g). The brown solid crystallised from nitrobenzene as tan needles.

M.P. > 350°C.

Analysis. Found : C, 66.0; H, 3.5; N, 23.8%

$C_{13}H_8N_4O$ requires C, 66.1; H, 3.4; N, 23.7%

The aqueous filtrate was extracted with benzene and from this extract was obtained a yellow solid. This crystallised from benzene, after treatment with charcoal, as white needles.

Yield 150 mg.

M.P. 241-242°C.

Mixed M.P. with 3-methyl-2-quinoxalone 242.5-243.5°C.

Analysis, Found: C,67.5; H, 4.8; N, 17.7%

$C_9H_8N_2O$ requires C,67.5; H, 5.0; N, 17.5%

Attempted cyclisation of methin-(2-quinoxalinyl)-(2'-(3'-keto) piperazine) with polyphosphoric acid.

Methin-(2-quinoxalinyl)-(2'-(3'-keto)piperazine) (1g) in polyphosphoric acid (10g) was heated at 150°C for 30 minutes, the initial magenta colour changing to deep red. After cooling, the solution was poured into water (100ml) and the solid filtered off (325mg). This solid recrystallised from nitrobenzene as small yellow prisms.

M.P. > 350°C.

Molecular weight could not be determined by the micro-Rast method.

Analysis, Found : C, 65.1; H, 3.9; N, 23.8%

$(C_{13}H_9N_4O)_x$ requires C,65.8;H, 3.8; N, 23.6%

The aqueous filtrate was extracted continuously with ether for 18 hours, giving a yellow solution. The yellow solid, obtained from this extract, was crystallised from chlorobenzene as yellow needles.

M.P. > 350°C.

Molecular weight could not be determined by the micro-Rast method.

Analysis. Found : C, 65.3; H, 4.2; N, 23.8%

$(C_{13}H_9N_4O)_x$ requires C, 65.8; H, 3.8; N, 23.6%

Attempted self-condensation of 2-methylpyrazine in dilute hydrochloric acid.

Freshly distilled 2-methylpyrazine (10 g) in hydrochloric acid (5N, 100 ml) was boiled under reflux for 2 hours. The dark brown solution was cooled and made alkaline with potassium hydroxide (5N, 130 ml), and the solution was extracted continuously with benzene for 8 hours. The extract was dried over calcium sulphate and the solvent removed, giving a colourless liquid. The picrate of this liquid was prepared and crystallised from ethanol as yellow prisms.

M.P. of picrate 131-132°C.

Mixed M.P. with 2-methylpyrazine picrate 131-133°C.

Yield of recovered 2-methylpyrazine 7.5 g.

Attempted preparation of 1'-keto-cyclopentano(4',5':2,3)quinoxaline.

cf. Reichstein and Oppenauer, Helv. Chim. Acta, 17, 390 (1934).

I. Reductic acid (1 g) was dissolved in water (10 ml) and iodine (2.5 g) in ethanol (50 ml) was slowly added to the solution. Water (100 ml) was added to decolorise the solution and more iodine solution was added, until there was an excess present (tested with starch paper). Silver chloride (10 g) was prepared and added to the solution, which was then shaken for 20 minutes. The solid was filtered off and

washed with ethanol. o-Phenylenediamine dihydrochloride (1.6g) was added to the filtrate and after being well shaken, the mixture was boiled under reflux for 1 hour. The volume of the solution was reduced to 80ml. and after making alkaline with potassium hydroxide (2N), the mixture was steam-distilled until about 300ml. of distillate had collected. This solution was extracted continuously with ether for 2 hours and gave an extract which had a blue fluorescence in U.V. light. Removal of the solvent, however, gave no appreciable amount of solid.

The residue from the steam-distillation was extracted continuously with ether for 18 hours. Removal of the solvent from this extract yielded a small amount of yellow oil, which did not crystallise.

II. Reductic acid (1g) was oxidised with iodine, as described above. After shaking the solution with silver chloride, freshly prepared silver carbonate (1g) was added to the filtered solution, which was then shaken for a further 10 minutes. The solution was filtered and distilled in vacuo at 30°C; a deep yellow syrup remained in the flask. To the syrup was added o-phenylenediamine (1g) in absolute ethanol (10ml) and the mixture was boiled under reflux for 30 minutes. During the heating, a black solid came out of solution, and was filtered off. Removal of the solvent from the filtrate yielded more black solid.

M.P. > 350°C.

III. Reductic acid (0.5g) and o-phenylenediamine (0.5g) were dissolved in ethanol (15ml) and glacial acetic acid (3 drops). The mixture was boiled under reflux for 90 minutes and on cooling, a black solid, separated from solution.

M.P. > 350°C.

Preparation of 1,4-dioxo-2,3-dihydroxy-1,4-dihydrophenazine.

Nietzki & Schmidt, Ber.,21, 1227 (1888).

Sodium rhodizonate (2g) was dissolved in hydrochloric acid (2N, 15ml) and o-phenylenediamine dihydrochloride (2g) added. A brown solid precipitated from solution almost immediately. After allowing the mixture to stand at room temperature for 30 minutes, the solid was filtered off and washed with water and ether.

Yield 2g.

The glistening brown needles, on heating to 175-180°C, changed to orange needles, which melted, with decomposition, at 308-311°C.

Analysis. Found : C, 59.3; H, 2.9; N, 11.6%

$C_{12}H_6N_2O_4$ requires C, 59.5; H, 2.5; N, 11.6%

The brown solid (100mg) was heated at 190°C for 3 hours. The orange solid was obtained and was allowed to stand at room temperature for 2 days. There was no reversion to the brown solid. The orange solid crystallised from nitrobenzene as orange needles.

M.P. 308-311°C

Analysis. Found : C, 59.7; H, 2.4; N, 11.3%

$C_{12}H_6N_2O_4$ requires C, 59.5; H, 2.5; N, 11.6%

Attempted Benzilic acid rearrangement of 1,4-dioxo-2,3-dihydroxy-1,4-dihydrophenazine.

1,4-Dioxo-2,3-dihydroxy-1,4-dihydrophenazine (0.5 g) in a mixture of potassium hydroxide (5 g), ethanol (10 ml) and water (10 ml), was boiled under reflux for 4 hours. The mixture was allowed to stand at room temperature overnight, before filtering to give a blue-black solid. This solid gave a deep violet colour when added to water, and addition of hydrochloric acid (5N) caused precipitation of a yellow solid. This was crystallised from nitrobenzene as yellow-orange needles.

Yield 0.3 g.

M.P. 303-305°C (with decomposition).

Mixed M.P. with starting material 300-312°C.

Analysis. Found : C, 59.8; H, 2.6; N, 12.6%

$C_{12}H_6N_2O_4$ requires C, 59.5; H, 2.5; N, 11.6%

Preparation of o-aminoazobenzene.

a) Nitrosobenzene.

Org. Syn., 25, 80.

Nitrobenzene (40 g) gave nitrosobenzene (23 g).

M.P. 67°C.

b) N-Benzoyl-o-nitroaniline.

Witt, Ber., 45, 2380 (1912).

o-Nitroaniline (50g) was dissolved in pyridine (75ml) and benzoyl chloride (50g) was added. The mixture was warmed until the precipitated solid had dissolved and was allowed to stand at room temperature for 1 hour. Water (50ml) was added, and the solid was filtered off and washed with hydrochloric acid (N), and with water. The solid crystallised from ethanol as yellow needles.

Yield 72g.

M.P. 97-98°C.

c) N-Benzoyl-o-phenylenediamine.

Witt, loc.cit.

Skraup, Ber.,49, 2142 (1916).

N-Benzoyl-o-nitroaniline (60g) was added to a strongly stirred mixture of iron powder (150g) and acetic acid (50%,150ml), which was then heated on a steam-bath for 1 hour. The mixture was made alkaline with sodium hydroxide and the aqueous solution was decanted from the brown residue, which was extracted with hot ethanol. From the extract, N-benzoyl-o-phenylenediamine crystallised as white needles.

Yield 23g.

M.P. 141-143°C.

d) o-(Benzoyl-amino)-azobenzene.

Witt, loc. cit.

N-Benzoyl-o-phenylenediamine (18 g) was dissolved in acetic acid (90 ml) and ethanol (36 ml). Nitrosobenzene (9 g) was added and the mixture was shaken until all the solid had dissolved. The colour changed from green, through deep green, to red-brown. Solid separated from solution and the mixture was allowed to stand at room temperature for 24 hours before being filtered. The brown solid crystallised from acetic acid as orange prisms.

Yield 13 g.

M.P. 121.5-122°C.

e) o-Aminoazobenzene.

o-(Benzoyl-amino)-azobenzene (11 g) was added to a solution of sodium ethoxide (sodium (2 g) in ethanol (250 ml)) and the mixture was boiled under reflux for 17 hours. Water (100 ml) was added and heating was continued for a further 60 minutes. The solution was extracted continuously with light petroleum (40/60) for 18 hours. The extract was concentrated and large orange-red prisms separated.

Yield 6.5 g.

M.P. 57-59°C.

Preparation of cyclopenta(4',5':2,3)quinoxaline.

Landquist, J.C.S., 1956, 2551.

o-Aminoazobenzene (6 g), cyclopentanone (50 ml) and hydrochloric acid (10N, 0.3 ml), were boiled under reflux for 2 hours. The

mixture was then distilled until the temperature was 180°C. The residue was dissolved as far as possible in ether and this solution was extracted with hydrochloric acid (N). The acid extract was basified with sodium hydroxide and the solution was extracted continuously with ether for 10 hours. The extract was distilled to small volume and fractionally distilled at 0.1 mm. pressure. The fraction boiling between 70-90°C was collected. The oil crystallised as pale yellow rods.

Yield 2 g.

M.P. 98-100°C.

Attempted nitrosation of cyclopenta(4',5':2,3)quinoxaline.

I. Cyclopenta(4',5':2,3)quinoxaline (0.2 g) was dissolved in anhydrous ether (15 ml) and butyl nitrite (0.1 ml) was added. Anhydrous hydrogen chloride was passed through the cooled solution for 15 minutes; a green precipitate was obtained. The mixture was allowed to stand at room temperature for 24 hours. A black precipitate was formed. Water (20 ml) was added and the mixture extracted continuously with ether for 4 hours. Removal of ether from the brown extract gave a black solid, M.P. > 360°C.

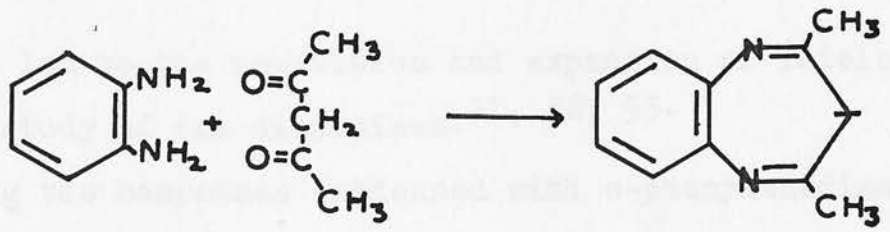
II. The experiment was repeated. The black precipitate was treated with sodium hydroxide solution (10%) and the alkaline extract was acidified and extracted with ether. From the ether extract was obtained a black solid, M.P. > 350°C.

PART II.

STUDIES ON CERTAIN QUINOXALINE DERIVATIVES

INTRODUCTION

The formation of the quinoxaline nucleus by the condensation of an aromatic o-diamine with a 1,2-diketone, has been known for many years. The reaction was first reported in 1884 by Hinsberg[43] and by Körner[44]. The reaction between an aromatic o-diamine and a 1,3-diketone was first recorded in 1907 by Thiele[45], who condensed o-phenylenediamine and acetylacetone in dilute acid and obtained a substance, which he suggested had a seven-membered ring, I.

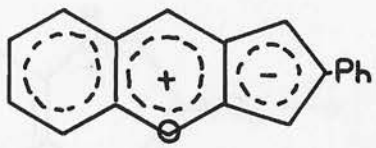


I

This particular seven-membered ring system in which two nitrogen atoms are present, is named 'diazepine', and so substance I is 2,4-dimethyl-1,5- benzodiazepine.

The formation of these molecules with seven-membered ring systems aroused no interest for more than thirty years, although Schwarzenbach[46] and Vaisman[47] prepared more compounds of this type. In 1945, however, Dewar suggested that a seven-membered aromatic ring was present in the stipitatic acid molecule, and thus inaugurated a period of intensive research on this ring

system, tropolones and azulenes, synthetic compounds and natural products. Eventually, interest turned to pseudo-seven-membered ring systems, e.g. 2-phenylbenzocyclopentapyran II[49], and to seven-membered ring systems containing hetero-atoms, e.g. 4,5-benzo-oxa-tropilidene-2,7-dicarboxylic acid III[50].



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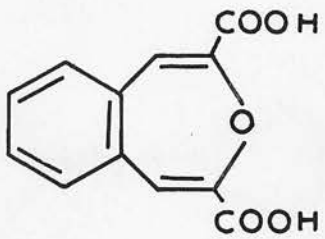
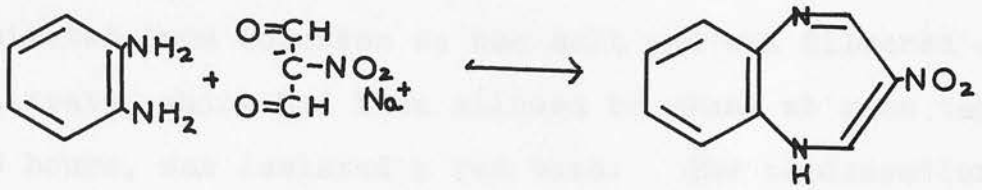


III

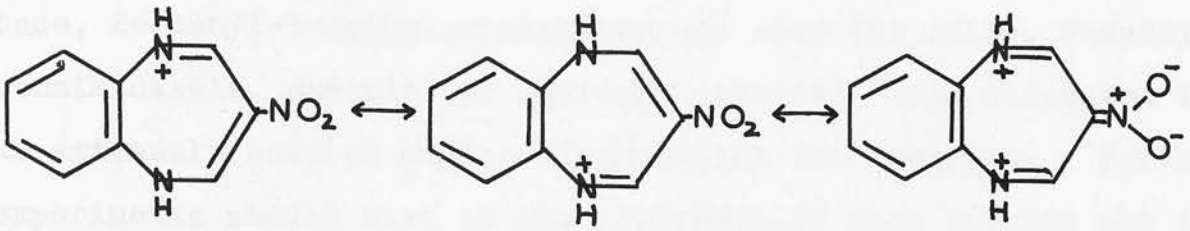
This led to the repetition and expansion of Thiele's work, and to a study of the diazepines.[51, 52, 53]

Among the compounds condensed with o-phenylenediamine during attempts to prepare new (1,5)-benzodiazepines was sodionitro-malondialdehyde.[54] The properties of the product, $C_9H_7N_3O_2$, obtained from this condensation differed from those of previously prepared (1,5)-benzodiazepines. The salts of (1,5)-benzodi-azepines in aqueous solution give reactions characteristic of o-phenylenediamine and the β-diketones from which they are derived, whereas the above compound, $C_9H_7N_3O_2$, proved to be stable even in concentrated sulphuric acid. Nevertheless, the diazepine structure IV was proposed for this compound and the stability of the molecule in sulphuric acid was explained in terms of resonance.

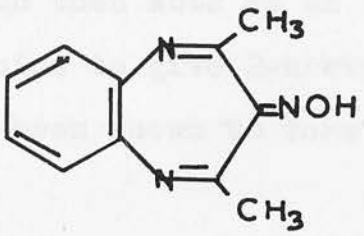


IV

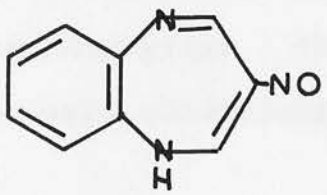
IN ACID:



The condensation of o-phenylenediamine and isonitroso-acetylacetone would be expected to give 3-hydroxyimino-2,4-dimethyl-1,5-benzodiazepine V, but this compound could exist as the nitroso derivative VI, in which case, the properties should show some resemblance to those of the above nitro compound IV.



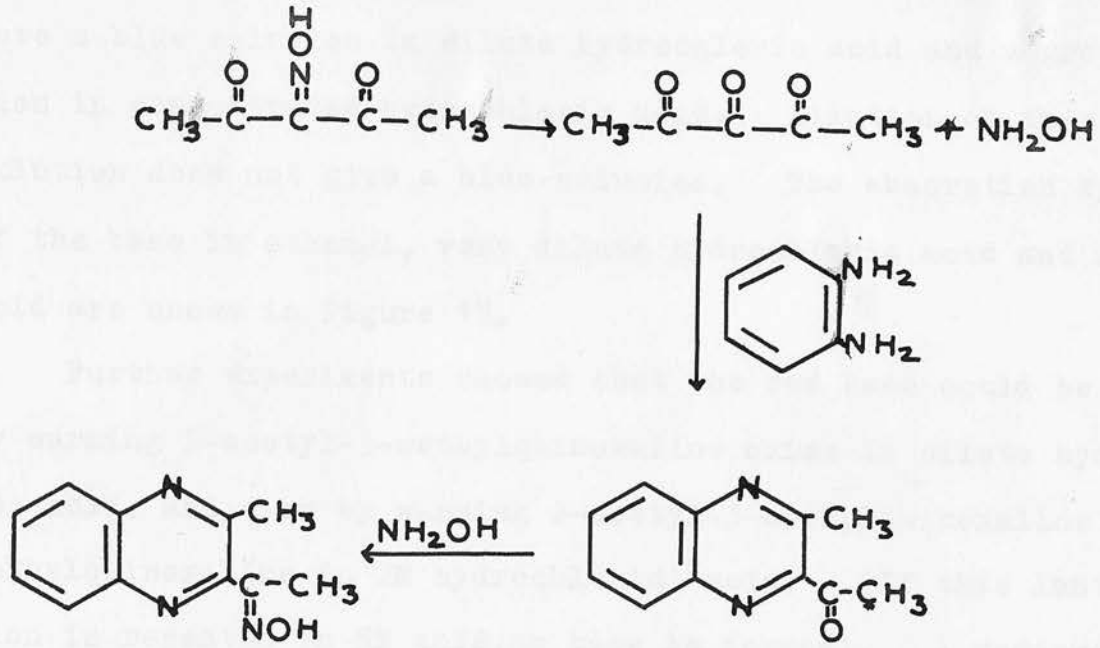
V



VI

When isonitrosoacetylacetone and o-phenylenediamine were allowed to react under Thiele's conditions, most of the diamine precipitated from solution as the salt and was filtered off; from the filtrate, which had been allowed to stand at room temperature for 20 hours, was isolated a red base. The condensation of the same reactants was repeated in more concentrated hydrochloric acid and the following products were isolated in small yield, the red base, 2-acetyl-3-methylquinoxaline and also its oxime, 2-methylbenziminazole, ammonia and hydrogen cyanide; this indicated that an extremely complex series of reactions had occurred. Further experiments showed that if the condensation were carried out in 2N hydrochloric acid at room temperature, 2-acetyl-3-methylquinoxaline oxime was formed in 87.5% yield.

The condensation of o-phenylenediamine with 1,2-diketones in aqueous solutions at room temperature has been studied by Haley and Maitland[55] and they have shown that o-phenylenediamine will condense with acetylacetone at pH 5.8, giving 2,4-dimethyl-1,5-benzodiazepine in 56% yield. Both Barker[56] and Barltrop[52] have suggested that the first stage in the condensation of o-phenylenediamine with isonitrosoacetylacetone in dilute acid solution, is the hydrolysis of isonitrosoacetylacetone to 2,3,4-pentanetrione, which then acts as an α-diketone and condenses with o-phenylenediamine to give 2-acetyl-3-methylquinoxaline. This last compound has been shown to form an oxime in acid conditions.



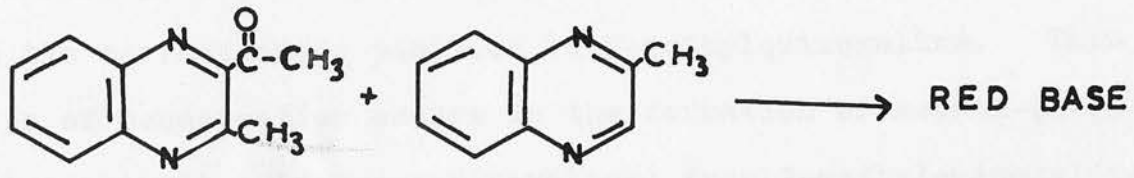
During this condensation in dilute hydrochloric acid, hydrogen cyanide is evolved by a reaction not yet understood.

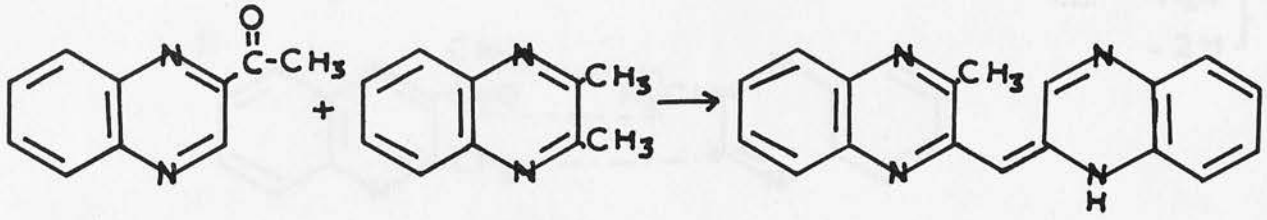
The formation of 3-hydroxyimino-2,4-dimethyl-1,5-benzodiazepine V has been reported by Barltrop,[52] who carried out the condensation of o-phenylenediamine and isonitrosoacetylacetone in benzene. The properties of this compound were those of a typical (1,5)-benzodiazepine, and bore no resemblance to those of the nitro compound IV.

The red base, which had been isolated in the above reactions, was then examined. This compound of empirical formula C_5H_4N crystallised from ethanol as red plates with a green glance. X-Ray measurements gave a molecular weight of 308 and hence the formula of the base was $C_{20}H_{16}N_4$. Further analysis showed the presence of one C-methyl group and of one active hydrogen atom.

The base, which was easily soluble in the common organic solvents, gave a blue solution in dilute hydrochloric acid and a green solution in concentrated hydrochloric acid. Dilution of this green solution does not give a blue solution. The absorption spectra of the base in ethanol, very dilute hydrochloric acid and in dilute acid are shown in Figure 13.

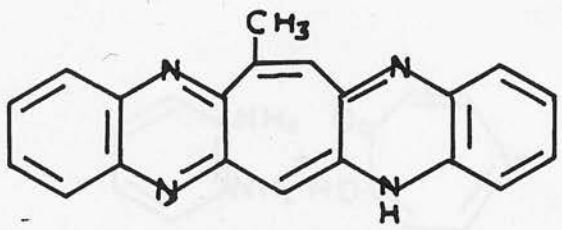
Further experiments showed that the red base could be obtained by warming 2-acetyl-3-methylquinoxaline oxime in dilute hydrochloric acid, and also by warming 2-acetyl-3-methylquinoxaline and 2-methylquinoxaline in 2N hydrochloric acid. (If this last reaction is repeated in 5N acid,no base is formed). A reciprocal synthesis of the base, starting with 2-acetylquinoxaline and 2,3-dimethylquinoxaline, failed - a small yield of methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) VII was obtained.



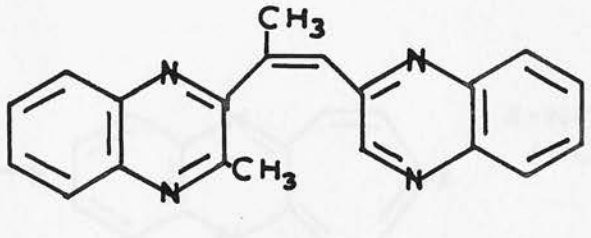


VII

It was at first suggested that an ethylenic molecule VIII had been formed, but the properties of the base were not compatible with those of a molecule of this structure and therefore it was suggested that a seven-membered ring had been formed, giving the structure IX, a molecule of formula $C_{20}H_{14}N_4$.

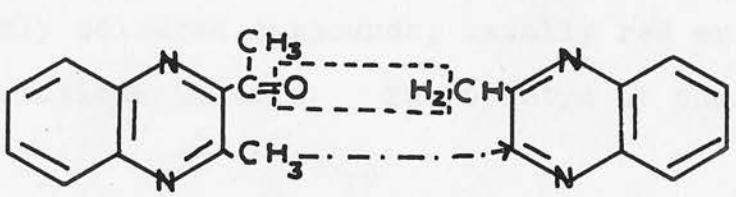


IX

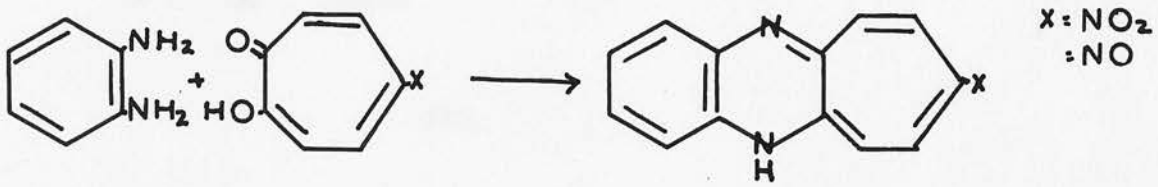


VIII

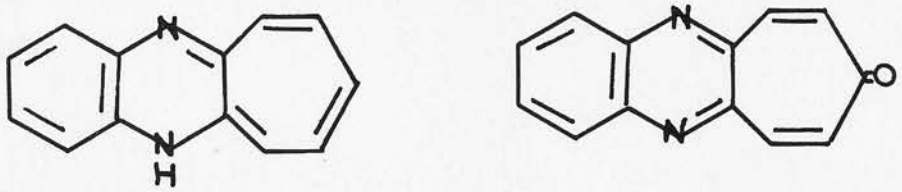
It was suggested that the seven-membered ring was formed by the condensation of the carbonyl group of 2-acetyl-3-methylquinoxaline with the (active) methyl group of 2-methylquinoxaline, preceded by or followed by the interaction of the methyl group in position 3 of 2-acetyl-3-methylquinoxaline with the hydrogen atom in the corresponding position in 2-methylquinoxaline. This latter type of condensation occurs in the formation of methin-(2-(3-methyl) quinoxalinyl)-(2'-dihydroquinoxaline) from 2-methylquinoxaline.



Molecules in which a seven-membered ring is fused to a quinoxaline nucleus, have been prepared by Nozoe[57,58]. It was found that, whereas tropolone would not condense with o-phenylenediamine, its 5-nitro and 5-nitroso derivatives would react to give quinoxaline derivatives X.



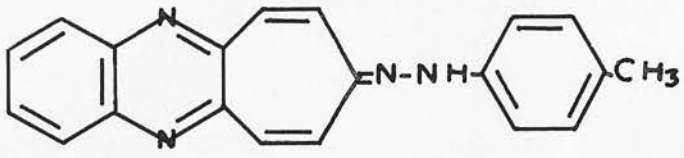
X



XI XII

Quinoxalo(d)tropone XII and several of its derivatives have been prepared and the base XI, benzo(b)tropazine, has been synthesised. The arylhydrazones and arylazo derivatives of the tropone XII are highly coloured compounds, usually red or violet, which give blue solutions in acid. The spectra of these coloured

derivatives are somewhat similar to that of the red base. (The spectra of the red base and quinoxalotropone p-tolylhydrazone XIII are very similar.)



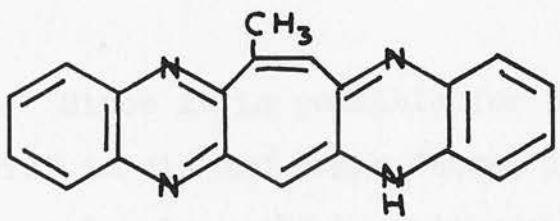
XIII

The structure suggested for the red base, quinoxalo(2',3':8,9) benzo(2,3)-7-methyltropazine IX, a molecule in which a seven-membered ring is fused between two quinoxaline nuclei, therefore seemed likely.

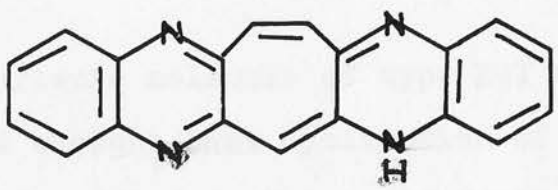
DISCUSSION OF RESULTS

DISCUSSION

The object of this research was to confirm the suggestion that the structure of the red base, obtained from the reaction of 2-acetyl-3-methylquinoxaline with 2-methylquinoxaline, was quinoxalo(2',3' : 8,9)benzo(2,3)-7-methyltropazine XIV. It was proposed to synthesise quinoxalo(2',3':8,9)benzo(2,3)tropazine XV and to remove the methyl group from the red base, thereby giving the substance XV.



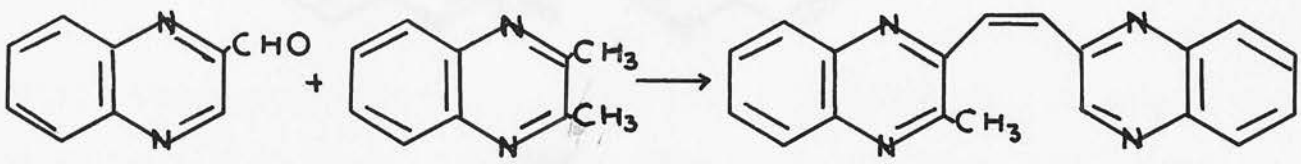
XIV



XV

The obvious synthesis of quinoxalo(2',3':8,9)benzo(2,3)tropazine is to condense 3-methylquinoxaline-2-aldehyde with 2-methylquinoxaline, but 3-methylquinoxaline-2-aldehyde is not known. However, the ethylenic compound XVI was obtained by condensing quinoxaline-2-aldehyde with 2,3-dimethylquinoxaline in acetic anhydride[59], and an attempt to cyclise the molecule to give a seven-membered ring was made using 2N hydrochloric acid. From the largely insoluble black residue was obtained a very small amount of an orange compound, whose qualitative spectrum in ethanol is shown in Figure 15.

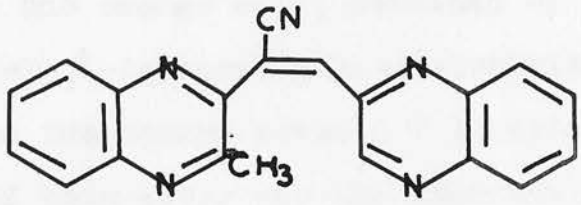
The spectrum of this orange compound is quite different from that of quinoxalo(2',3':8,9)benzo(2,3)-7-methyltropazine XIV, Figure 13, and also from that of the ethylenic compound XVI, Figure 14.



XVI

Since it is possible for an ethylenic molecule of type XVI to exist in cis and trans forms, it was thought that cyclisation of the molecule would be unlikely, if it existed in the trans form. Chromatographic purification failed to separate any isomers, and irradiation with ultraviolet light caused no change in the spectrum of the compound. Nevertheless, it was still thought that the configuration of the ethylenic molecule was important and so it was proposed to synthesise α-(3-methylquinoxalinyl-2-)-β-(quinoxalinyl-2'-)acrylonitrile XVII. If the first stage in the synthesis of the red base is the formation of an ethylenic bond, the methyl group may influence the configuration of the molecule and hence the cyclisation, in the same way as the corresponding substituent acts in the Pschorr synthesis. The nitrile group was chosen as the substituent because it could be readily removed. Unfortunately, the proposed condensation

between 3-methylquinoxaline-2-acetonitrile and quinoxaline-2-aldehyde would not take place.



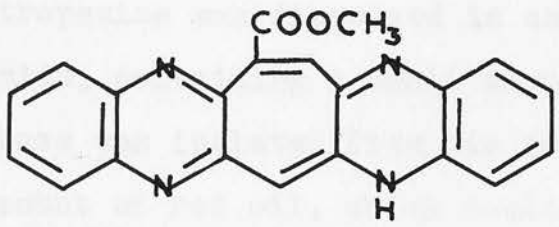
XVII

It was decided to abandon this synthesis of quinoxalo(2',3';8,9)benzo(2,3)tropazine and to concentrate on the degradation of the red base. The methyl group in quinoxalo(2',3':8,9)benzo(2,3)-7-methyltropazine should be active and should therefore be oxidised by selenium dioxide. 2-Methylquinoxaline may be oxidised to quinoxaline-2-carboxylic acid, by oxidising firstly to the aldehyde with selenium dioxide, [2,60] and then to the acid with alkaline hydrogen peroxide[61].

The oxidation of the red base with selenium dioxide, and then with alkaline hydrogen peroxide, did not appear to proceed readily; indeed, the common feature of the many attempts was the recovery of unreacted red base. Acidic material, which was methylated with diazomethane before isolation, was extracted from the reaction mixtures in very low yields. When the reaction was carried out in dioxan containing a little water, an orange solid, whose spectrum is shown in Figure 16, was obtained, and when the reaction was

carried out in dry xylene, a red-brown oil, which could not be crystallised, was isolated.

It will be noted that there is little resemblance between the spectra of the orange base, obtained by heating α-(3-methyl-quinoxalinyl-2-)-β-(quinoxalinyl-2'-)ethylene XVI in acid, (Figure 14) and the orange ester (?), obtained from this oxidation. If this ester was the expected carbomethoxy compound XVIII, the spectrum should not show such a marked change from that of quinoxalo(2',3':8,9)benzo(2,3)-7-methyltropazine, nor indeed should the colour of the compound change from deep red to orange.



XVIII

It was decided to brominate the C-methyl group and by hydrolysis, the alcohol would be obtained.

$$A\text{-}CH_3 \longrightarrow A\text{-}CH_2Br \longrightarrow A\text{-}CH_2OH$$

Direct bromination of 2-methylquinoxaline gives ααα-tri-bromomethylquinoxaline,[59] i.e. bromination occurs only in the side-chain. Accordingly, bromination of quinoxalo(2',3':8,9)benzo(2,3)-7-methyltropazine was attempted with bromine in chloroform and in

carbon tetrachloride, but in neither case, could a pure product be isolated. When bromination was carried out in a sodium acetate-acetic acid mixture, 2-methylquinoxaline gave ααα-tribromomethylquinoxaline,[62] while 3-methyl-2-quinoxalone gave 3-monobromomethyl-2-quinoxalone.[4] The product from the bromination of the red base in sodium acetate-acetic acid was a black tar.

N-Bromosuccinimide is a reagent which reacts with active methylene groups and although it has not as yet been used to brominate 2-methylquinoxaline, Buu-Hoi[63] showed that quinaldine brominated only in the side-chain, when this reagent was used, and Hasegawa[64] has separated the various bromo-derivatives. Quinoxalo(2',3':8,9)benzo(2,3)-7-methyltropazine was dissolved in chloroform and treated with N-bromosuccinimide, containing a small amount of benzoyl peroxide;[65] unreacted red base was isolated from the reaction mixture, along with a small amount of red oil, which could not be crystallised. When carbon tetrachloride was used as solvent, although unreacted red base was recovered, succinimide was isolated, which indicated that bromination had occurred. A small amount of red oil, which could not be crystallised and which did not form a picrate, was also isolated from the reaction mixture, and if this oil was warmed with ethanol, a small amount of insoluble black solid, M.P. $> 350^{\circ}C$, was formed. Repetition of this treatment of the re-extracted oil with ethanol yielded more black solid. An insoluble black solid, M.P. $> 350^{\circ}C$, was formed when the base was heated with N-bromosuccinimide and it was observed that more solid was formed when carbon tetrachloride was the solvent than when chloroform was used.

Since, in spite of using an excess of N-bromosuccinimide, and in spite of allowing the reaction to continue until all the reagent had been used and succinimide could be isolated, unreacted red base was always recovered and the only products of the reaction were a black insoluble solid and a red oil, which could not be crystallised, it appeared that bromination of the C-methyl group was not the answer to the problem.

Since the attempts to attack the C-methyl group with these reagents, which react only with active methylene groups, had failed, it was concluded that the methyl group in the red base molecule was not reactive and it was decided to study the oxidation of the whole molecule.

Alkaline hydrogen peroxide was the first oxidising agent used. This reagent readily oxidises tropolones[66], but it does not attack azulene[69] and so it was hoped that oxidation with this reagent would give a product, in which the seven-membered ring was still intact.

With this reagent, it was found that experimental results were not reproducible; unreacted red base was always recovered and a red oil, which could not be crystallised, was always obtained, while from several experiments was isolated a very small amount of an orange acid. The qualitative spectrum of this acid is shown in Figure 17. It will be noted that this spectrum closely resembles that of the ester (?), obtained by oxidising the red base with selenium dioxide, and then with hydrogen peroxide (Figure 16). This suggests that the ester (or rather its acid) arose from the hydrogen peroxide oxidation

of the red base and not by oxidation with selenium dioxide, followed by a second oxidation with alkaline hydrogen peroxide. The yields of orange ester and of orange acid are both very small.

Osmium tetroxide will oxidise a double bond to the corresponding glycol[68] and it was hoped that the double bond between the two heterocyclic nuclei of the red base would be attacked.

The red base readily formed a complex with osmium tetroxide, which decomposed to give a black solid, M.P. > 350°C, and a red solid. When this solid was warmed with ethyl acetate, the ethyl acetate distilled and the residue treated with benzene, the solid dissolved, leaving a black residue. If the solid was again treated with ethyl acetate and then with benzene, more black solid, M.P. > 350°C, was obtained (cf. the effect of ethanol on the oil obtained in the bromination experiments). From the benzene extract was obtained a red solid, M.P. 44-100°C, which could not be further purified.

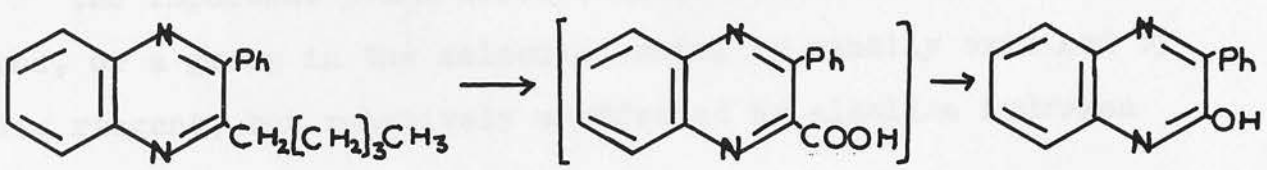
Another specific double bond reagent is ozone and it was hoped that ozonolysis, followed by hydrolysis, would provide some information about the structure of the red base. It is known that this reagent will break a methine linkage between two heterocyclic nuclei[7], and also that the seven-membered ring in azulene is completely disrupted[67].

The ozonolysis of a solution of quinoxalo(2',3':8,9)benzo(2,3)-7-methyltropazine in ethyl acetate appeared to go in stages : the colour of the solution changed from orange-red, to dark red and then to pale orange, and finally solid was precipitated from solution. When the reaction was allowed to proceed until the colour of the solution was

pale orange and the ozonide was decomposed with Raney nickel and water, the product was a yellow-brown solid, M.P. 164-169°C, which was converted to a black solid, M.P. > 350°C, by boiling with benzene. If the reaction was stopped when the dark red colour had just disappeared, the amount of yellow-brown solid obtained was smaller and a very small amount of a yellow solid, M.P. 145-150°C, was isolated. If the reaction was stopped when the initial orange-red colour had just disappeared, from the reaction mixture were obtained in small yields, acidic material, the yellow-brown solid, the yellow solid, an orange solid, M.P. 104-108°C, and a red-brown oil, which could not be crystallised. These results would indicate that oxidation was taking place with subsequent decomposition or reaction of the products.

Since so little is known about the red base, it was decided to leave this oxidation until more information had been gathered about the structure of this compound.

The fourth oxidising agent to be used was chromium trioxide in acetic acid, a reagent which does not attack the quinoxaline nucleus. An unusual oxidation, however, does occur with alkyl substituents in positions 2 and 3 in the quinoxaline nucleus; the alkyl side-chain is oxidised to the carboxylic acid, which is then further oxidised to the hydroxyl compound.



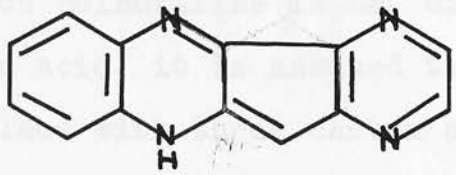
This was first demonstrated by Blatt[36] and this method was used to establish the structures of various alkyl substituted quinoxalines.[70, 71, 72, 73.]

When quinoxalo(2',3':8,9)benzo(2,3)-7-methyltropazine was treated with this reagent, oxidation took place in the cold, giving a straw-coloured solid, M.P. 165.5-166.5°C, $C_{11}H_8$ or $_9N_2O$. This substance is neutral to litmus and gives a buff precipitate with neutral ferric chloride. When warmed with sodium hydroxide, a purple mixture is obtained from which no organic material could be extracted. The compound dissolves in ethanol, giving a yellow solution which quickly becomes red-purple; the colour of the solution reverts to yellow if the solution is left at room temperature for several days. An attempt to purify this product by chromatography on alumina, resulted in the retention of the substance at the top of the column; the substance was recovered after extraction of the alumina with boiling ethanol. The compound, $C_{11}H_8$ or $_9N_2O$, did not restore the colour to Schiff's reagent, but it readily formed a 2,4-dinitrophenylhydrazone, M.P. 249.5-250°C, which did not however analyse as the expected derivative of the carbonyl compound. The infra-red spectrum showed a very intense peak at 1700 cm^{-1}, which suggests that there is a carbonyl group conjugated to an aromatic ring; there is no indication either of a hydroxyl group or of an imino group. Attempts to nitrosate this oxidation product failed.

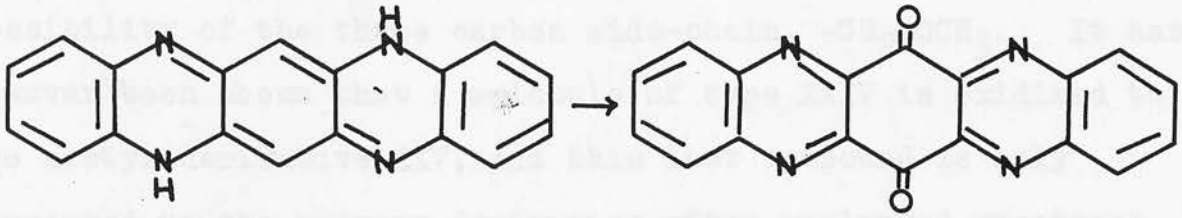
The important point about this oxidation is that there is a bond, or a group in the molecule, which is readily oxidised by this reagent, but relatively unaffected by alkaline hydrogen

peroxide, selenium dioxide, etc. Since the quinoxaline nucleus is not susceptible to attack, the oxidation must have occurred either at a side-chain, or at a carbocyclic ring.

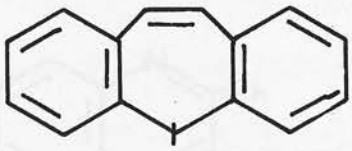
A compound has been prepared in which it is thought that a five-membered ring is fused between a quinoxaline and a pyrazine nucleus, XIX: this substance is resistant to oxidation by chromium trioxide in acetic acid. Homofluorindine, XX, a molecule in which a six-membered ring is fused between two quinoxaline nuclei, is oxidised by chromium trioxide in concentrated sulphuric acid to 6,13-dihydroquinoxalo(2,3-b)phenazine-6,13-dione, XXI.[74] As yet, (2,3:6,7)-dibenzocycloheptatriene XXII has not been treated with chromium trioxide in acetic acid, so it is not possible to predict with certainty the effect of this reagent on an unsaturated seven-membered ring, fused between two quinoxaline nuclei; but it does seem unlikely that oxidation of the ring would occur immediately, and in the cold, particularly as the seven-membered ring in the azulene molecule is unaffected by this reagent.[75] It has been shown, however, that the methine linkage between two heterocyclic nuclei, as in XXIII, is readily oxidised by chromium trioxide in acetic acid.



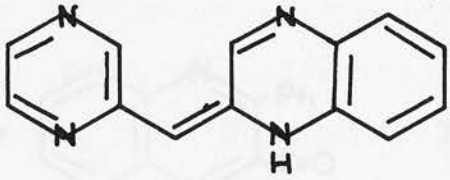
XIX



XX XXI



XXII

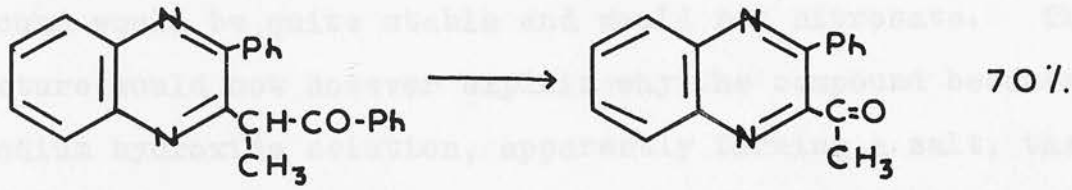


XXIII

The isolation of the compound, $C_{11}H_8$ or $_9N_2O$, from the oxidation of the red base, $C_{20}H_{14}N_4$, indicates that fission of the molecule rather than oxidation of an alkyl side-chain, has taken place, and the presence of only one carbonyl group indicates that the fragment is the result of one oxidation, i.e. the link between the fragment and the rest of the

molecule has been broken, while the fragment itself has remained unattacked. Since quinoxaline is not oxidised by chromium trioxide in acetic acid, it is assumed that the fragment contains a quinoxaline nucleus with three carbon atoms attached, one of which carries the ketonic oxygen atom.

Alkyl groups in positions 2 and 3 of the quinoxaline nucleus are readily attacked by this reagent thus eliminating the possibility of the three carbon side-chain, $-CH_2COCH_3$. It has however been shown that a molecule of type XXIV is oxidised to the acetyl derivative XXV, and this last compound is only converted to the hydroxy derivative after prolonged treatment with the oxidising agent.[73]

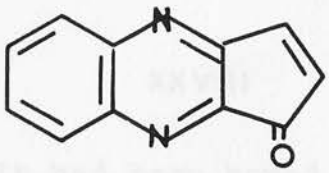


XXIV XXV

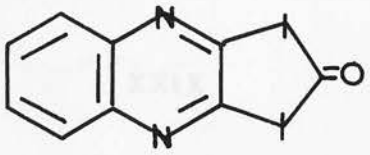
There is therefore a possibility that the side-chain attached at position 2 of the quinoxaline nucleus is $-COCH_2CH_3$, but as neither of the reactants, 2-methylquinoxaline and 2-acetyl-3-methylquinoxaline, used in the preparation of the red base, possesses a three carbon side-chain, it is unlikely that such a unit would exist in the oxidation product.

The three carbon atoms may form part of a carbocyclic ring

and may therefore be unaffected by oxidation: either an unsaturated ring XXVI, or a saturated ring XXVII (or isomer) might be present.



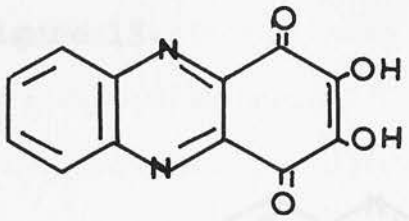
XXVI



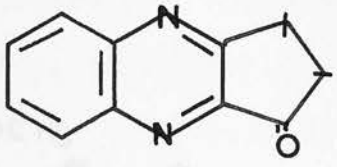
XXVII

Since the oxidation product is stable towards acid and alkali and is relatively unreactive, structure XXVII can be rejected.

This then leaves structure XXVI, 1'-ketocyclopenteno(4',5':2,3) quinoxaline. Since there are no active methylene groups, this compound would be quite stable and would not nitrosate. This structure would not however explain why the compound becomes purple in sodium hydroxide solution, apparently forming a salt, the existence of which is indicated by the failure to extract anything from the alkaline solution by means of an organic solvent, and by the recovery of the original compound by acidifying the alkaline solution. Another compound which behaves in this way is 1,4-dioxo-2,3-dihydroxy-1,4-dihydrophenazine XXVIII, which can of course form a sodium salt, but the compound, $C_{11}H_8$ or $_9N_2O$, does not possess either a hydroxyl group, or an imino group in the solid state, and in solution gives no colour reaction with neutral ferric chloride, which suggests that enolisation of the carbonyl group does not occur.



XXVIII

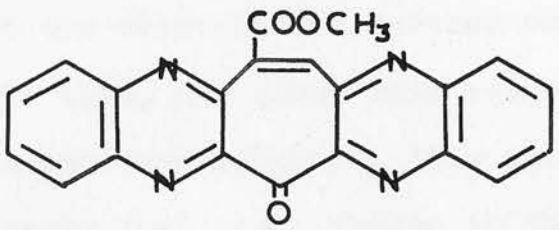


XXIX

It had been hoped that the synthesis of 1'-ketocyclopenta(4',5':8,9)quinoxaline XXIX would be the first stage in the synthesis of 1'-ketocyclopenteno(4',5':2,3)quinoxaline XXVI, but the first synthesis has not yet been achieved. The structure XXVI suggested for the oxidation product is therefore based on indirect evidence, is quite tentative and is not wholly satisfactory.

The oxidation of quinoxalo (2',3':8,9)benzo(2,3)-7-methyltropazine by potassium permanganate was carried out by Barker.[76] Since aqueous potassium permanganate oxidises quinoxaline to pyrazine-2,3-dicarboxylic acid,[77] and also breaks up the azulene molecule, acetone was used as solvent; potassium permanganate in acetone does not attack the seven-membered ring in azulene[75] and it was hoped that the reagent would not cause the complete disruption of the red base. However, during the oxidation a white acid was formed and was isolated as the potassium salt and as the methyl ester. The interpretation of the analytical results proved difficult: the empirical formula was $C_{21}H_{19}N_4O_3$ and the molecular weight was about 300. It was suggested that the structure of this ester might be XXX and since the ester showed no carbonyl activity, it was pointed out that tropones do not

behave as carbonyl compounds. The spectrum of the ester is shown in Figure 18.



XXX

It must be emphasised that the above structure XXX was only very tentatively advanced and several observations must be made. Firstly, the colour of the ester is white. Generally, a quinoxaline nucleus fused to a five- or six-membered ring, saturated or unsaturated, substituted or unsubstituted, gives a coloured compound, although benzo(b)tropazine has been reported to be a colourless compound.[58] A seven-membered ring fused between two quinoxaline nuclei would be expected to give a coloured compound; in the structure XXX, the two nuclei are linked through an ethylenic bond and the $\alpha\beta$-diquinoxalinyl-ethylenes are coloured compounds. Secondly, the spectrum of the ester (Figure 18) resembles those of the simple quinoxalines, cf. 2-d-arabotetrahydroxybutylquinoxaline[78] and 2-acetylquinoxaline,[79] rather than those of more complex quinoxalines, cf. α-(3-methylquinoxalinyl-2)-β-(quinoxalinyl-2')-ethylene and homofluorindine,[74] the former a molecule in which two quinoxaline nuclei are linked through an ethylenic bond, and the latter a molecule in which a six-membered

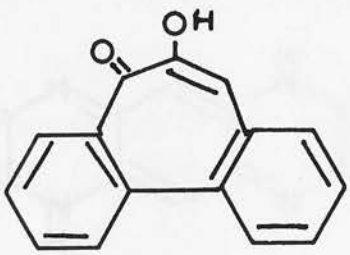
ring is fused between two quinoxaline nuclei. There is, however, some similarity between the spectrum of the ester and that of quinoxalo(d)tropone.[57] Thirdly, qualitative experiments have indicated that the ester is not further oxidised by chromium trioxide in acetic acid, and since this reagent appears to cause fission of the red base molecule, this lack of reaction shown by the ester suggests that the linkages in the red base molecule, which are oxidised by this reagent, have been already oxidised by potassium permanganate in acetone, or have become resistant to oxidation. Lastly, the analytical results must be considered. The ester was analysed twice giving : C,67.5, 67.1; H,5.0,4.9; N,15.0, 14.6%, in good agreement with the formula, $C_{21}H_{19}N_4O_3$, which requires : C,67.2; H,5.1; N,14.9%. This formula, however, requires a molecular weight of 375 for the ester, whereas two micro-Rast determinations gave 292 and 300. In view of the good agreement of these results, the marked discrepancy between the required molecular weight and the observed value requires explanation.

It would appear that more work must be done on this oxidation product in order to determine its structure, as it seems unreasonable to postulate a structure, XXX, merely on the basis of analytical results, which although consistent, may not be entirely reliable.

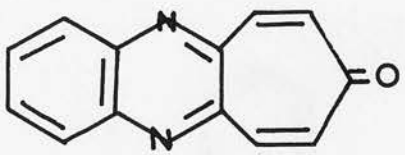
A study ofthe results from the above brominations and oxidations, prompts the thought that this base is an unusual

substance : certain experiments which might be expected to succeed, have given only very low yields of crystalline products, red oils commonly being formed, while in many cases, the unreacted red base has been recovered from the reaction mixtures. The two successful oxidations with chromium trioxide in acetic acid and with potassium permanganate in acetone, gave products which were difficult to identify, and suggested structures for these compounds cannot be related confidently to quinoxalo(2',3':8,9)benzo(2,3)-7-methyltropazine. These confusing results led to the idea that the structure suggested for the red base might be incorrect.

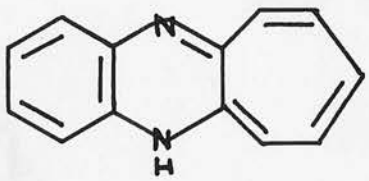
Dibenzo(a,c)(1,3)cycloheptadien-6-one XXXI has been reported to form a quinoxaline[80], but so far only Nozoe[57,58] has studied compounds in which a seven-membered ring is fused to a quinoxaline nucleus, e.g. quinoxalo(d)tropone, XXXII, and benzo(b)tropazine, XXXIII.



XXXI



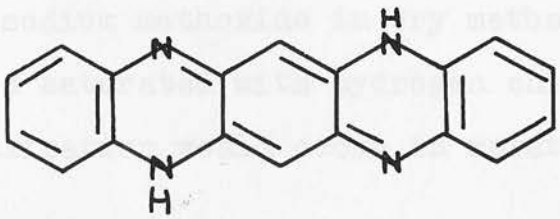
XXXII



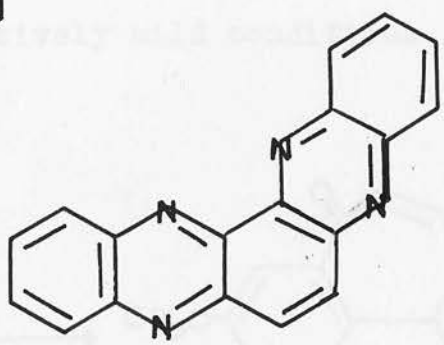
XXXIII

Benzo(b)tropazine XXXIII the parent compound of quinoxalo-(2',3':8,9)benzo(2,3)-7-methyltropazine is a colourless compound, M.P. 216°C, which is sparingly soluble in hot benzene and hot pyridine, but almost insoluble in other organic solvents, and is stable to, but insoluble in alkali and is very labile towards acid. The red base, M.P. 185-186°C, is soluble in ethanol and other organic solvents, and is stable in acid and in alkali.

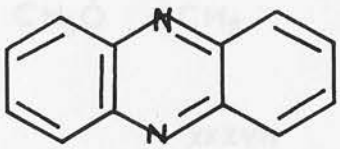
Generally, the fusion of an aromatic or heterocyclic ring with a phenazine ring tends to increase the melting-point of the compound and to reduce its solubility in the common organic solvents. 5,12-Dihydroquinoxalo(2,3-b)phenazine XXXIV, a deep purple powder, which does not melt and which is sparingly soluble in organic solvents, and quinoxalo(2,3-a)phenazine XXXV, a yellow crystalline solid, M.P. 304°C, may be compared with phenazine XXXVI, a yellow crystalline solid, M.P. 171°C, which is soluble in ethanol.



XXXIV



XXXV

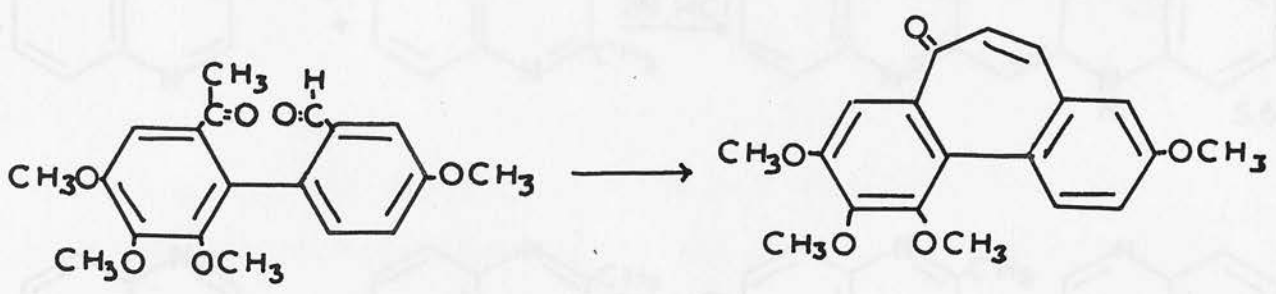


XXXVI

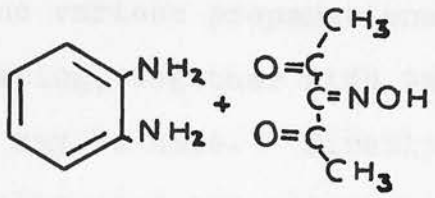
An analogy between benzo(b)tropazine and phenazine, and their respective quinoxalo derivatives, may not of course be valid; but nevertheless, it is surprising that the melting-point of the red base should be lower than that of benzo(b)tropazine and that the solubility of the former in the common organic solvents should be so much greater than that of the parent compound.

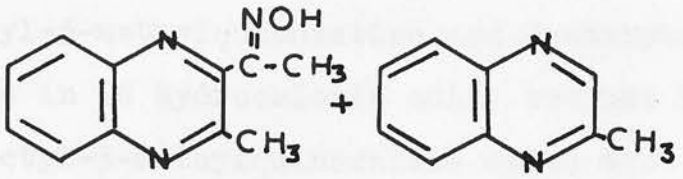
A reconsideration of the formation of the red base seemed essential.

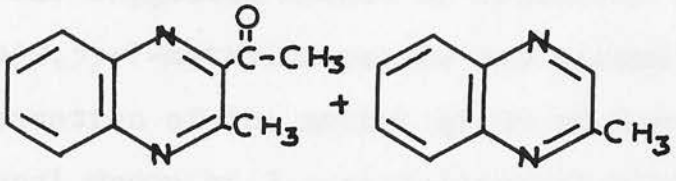
There are two main methods for the synthesis of condensed molecules containing seven-membered rings: a) the seven-membered ring is already present, as in the synthesis of benzo(b)tropazine,[58] and b)the seven-membered ring is formed by the ring-enlargement of a six-membered ring.[81] Several cases in which the seven-membered ring is formed by ring-closure are known.[82] Cook[83] was able to cyclise the keto-aldehyde XXXVII to the tropone XXXVIII, using a) sodium hydroxide in aqueous methanol at room temperature, b) sodium methoxide in dry methanol at 0°C, and c) glacial acetic acid saturated with hydrogen chloride at room temperature - cyclisation would occur in relatively mild conditions.

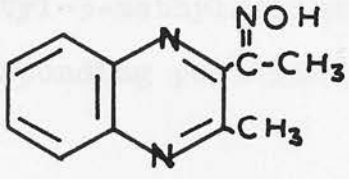


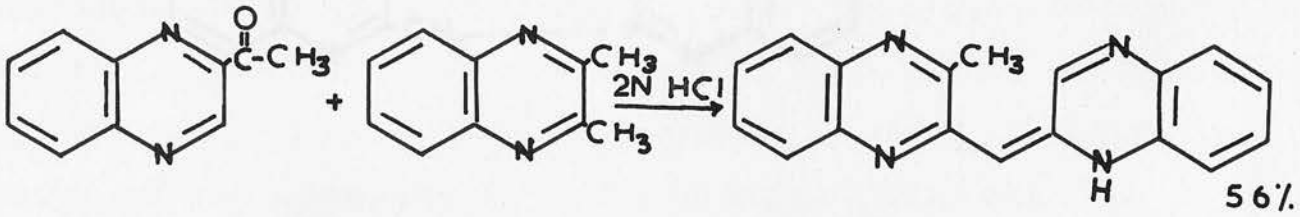
XXXVII XXXVIII

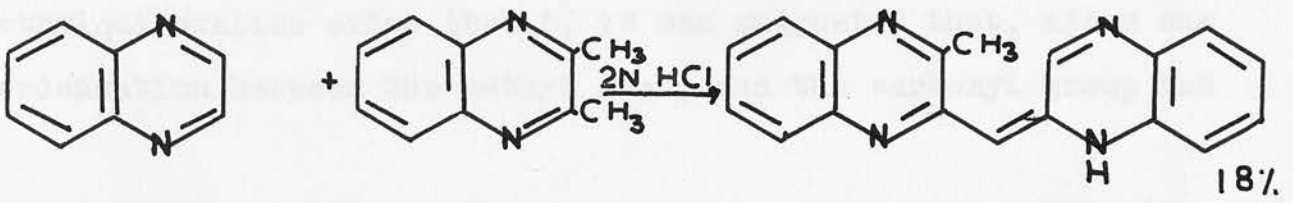
1. 
HOAc HCl
EtOH
HCl EtOH
RED BASE

2. 
2N HCl
RED BASE
55%.

3. 
2N HCl
5N HCl
RED BASE
68%.

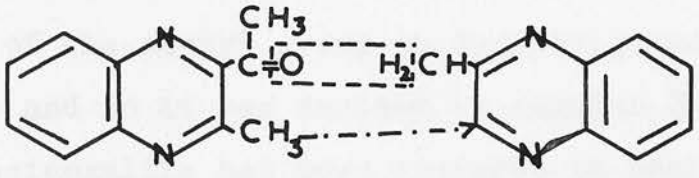
4. 
2N HCl
RED BASE
8%.

5. 
2N HCl
56%.

6. 
2N HCl
18%.

The various preparations of the red base are given on the page facing, together with two relevant syntheses, and several points may be made. Firstly, it appears that 2-acetyl-3-methylquinoxaline (or its oxime) is an essential reactant in the preparation of the red base. Secondly, condensation of 2-acetyl-3-methylquinoxaline and 2-methylquinoxaline will take place in 2N hydrochloric acid, but not in 5N acid. Thirdly, 2-acetyl-3-methylquinoxaline oxime will self-condense with the elimination of a two-carbon fragment, to give the red base.

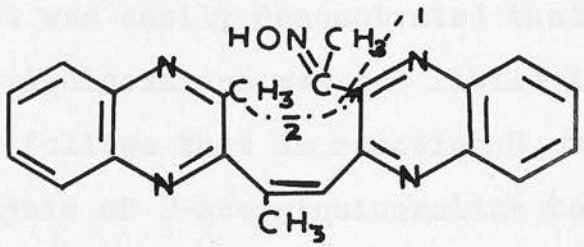
The suggested method of formation of quinoxalo(2',3':8,9) benzo(2,3)-7-methyltropazine has already been given - the condensation of the methyl group of 2-methylquinoxaline with the carbonyl group of 2-acetyl-3-methylquinoxaline, preceded by or followed by the interaction of the methyl group in position 3 of 2-acetyl-3-methylquinoxaline with the hydrogen atom in the corresponding position of 2-methylquinoxaline.



I.E. $-H_2O$, $-2H$

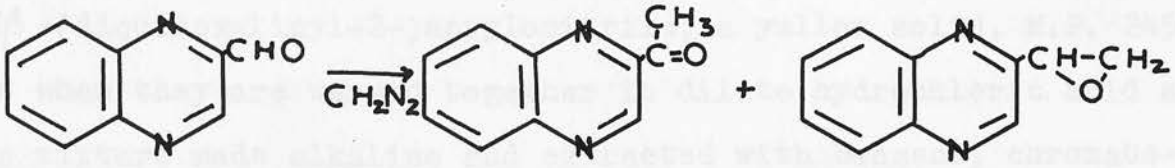
To explain the formation of the red base from 2-acetyl-3-methylquinoxaline oxime itself, it was suggested that, after the condensation between the methyl group and the carbonyl group had

occurred, the remaining acetyl group (or its oxime) became labile and was hydrolysed, leaving the position free for interaction with the other methyl group. The idea that the acetyl group in position 2 of a quinoxaline nucleus might be acid labile, gained in favour when reaction 5, the reciprocal of reaction 3, gave methin-(2-(3-methyl)quinoxalinyl)-(2'-dihydroquinoxaline) instead of the red base. Since it had been observed that quinoxaline and 2,3-dimethylquinoxaline reacted to give this last compound, it seemed likely that 2-acetylquinoxaline might hydrolyse to quinoxaline, which would then react.



No mention could be found in the literature about the lability of the acetyl group in 2-acetylquinoline or in 2-acetylpyrazine, and so it was decided to examine 2-acetylquinoxaline. 2-Acetylquinoxaline had been prepared in small yield[84] by treating quinoxaline-2-aldehyde with diazomethane; a larger yield of a white substance, thought to be the epoxide, XXXIX, was also obtained. Henseke,[85] using a similar method, reported a quantitative yield of the acetyl compound, but repetition of his method gave 2-acetylquinoxaline along with the same white

substance that Barker had obtained. A better preparation of the acetyl compound was from ethyl quinoxaline-2-carboxylate.[86]



XXXIX

$$R\text{-}COOC_2H_5 \longrightarrow R\text{-}COCH_2COOC_2H_5 \longrightarrow R\text{-}COCH_3$$

It was easily demonstrated that the acetyl group of 2-acetylquinoxaline was not labile in dilute hydrochloric acid, and it follows that in reaction 5, the first stage is not the hydrolysis of 2-acetylquinoxaline to quinoxaline. The acetyl group must become labile after one of the methyl groups of 2,3-dimethylquinoxaline has reacted with the hydrogen in position 3 of 2-acetylquinoxaline.

The condensation of ketones with the active methylene groups in positions 2 and 3 of substituted quinoxalines has been investigated by several workers. Bennett and Willis[59] carried out the condensations in acetic anhydride, Ried[87] used xylene containing a little piperidine, Bodforss[26] used an ethanol-acetic acid mixture, while Borsche[2] found ethanol containing piperidine, a satisfactory medium. It was therefore decided to study the reaction in 2N

hydrochloric acid, between two quinoxalines, one carrying an active methylene group and the other a carbonyl group.

Quinoxaline-2-acetonitrile and quinoxaline-2-aldehyde condense together in ethanol, containing piperidine,[2] to give αβ-(diquinoxalinyl-2-)acrylonitrile, a yellow solid, M.P. 245°C, but when they are warmed together in dilute hydrochloric acid and the mixture made alkaline and extracted with benzene, chromatography of the extract indicates that several substances have been formed, the main product being an orange solid, M.P. 280-285°C. Some reaction therefore occurs, but not the required condensation. In the same way, quinoxaline-2-acetonitrile and 2-acetyl-3-methylquinoxaline oxime were warmed together in dilute acid and from the reaction mixture both reactants were recovered unchanged. The failure to react of these two compounds is interesting: the methylene group of quinoxaline-2-acetonitrile is active[2] and therefore, if the first stage in the formation of the red base is the condensation of the carbonyl group of 2-acetyl-3-methylquinoxaline with the methyl group (active) of 2-methylquinoxaline, it would be expected that condensation would take place when 2-methylquinoxaline was replaced by quinoxaline-2-acetonitrile. Similarly, if the first stage in the formation of the red base is the interaction of the methyl group in position 3 of 2-acetyl-3-methylquinoxaline with the hydrogen atom in the corresponding position of 2-methylquinoxaline, the replacement of a hydrogen atom in the methyl substituent of the latter compound by a cyano group, should not affect this interaction.

The activity of the 3-methyl substituent in 2-acetyl-3-methylquinoxaline must also be considered. While both methyl groups of 2,3-dimethylquinoxaline form styryl derivatives,[59] only one reacts with ethyl oxalate[2] and it has been shown that the 3-methyl group of ethyl 3-methylquinoxaline-2-pyruvate does not possess the properties expected of a methyl group ∝ to the ring nitrogen atom. Similarly, the methyl group of 3-methylquinoxaline-2-acetonitrile is completely unreactive,[2] although the methylene group reacts normally. The methyl groups of several other 2-substituted-3-methylquinoxalines are also unreactive. It is significant that when ∝-(3-methylquinoxalinyl-2)-β-(quinoxalinyl-2')-ethylene was heated with dilute hydrochloric acid, only the merest trace of a base was isolated; it was assumed that cyclisation failed because the molecule possessed a trans configuration, but the methyl group in this molecule may be completely unreactive and so cyclisation could not occur. It is therefore to be expected that the 3-methyl group of 2-acetyl-3-methylquinoxaline is unreactive and unlikely to interact with the hydrogen atom at position 3 of 2-methylquinoxaline either before or after a condensation has taken place between the carbonyl group of 2-acetyl-3-methylquinoxaline and the methyl group of 2-methylquinoxaline. That this condensation takes place at all in 2N hydrochloric acid seems doubtful.

These experiments have invalidated the suggested method of formation of the red base, both from 2-acetyl-3-methylquinoxaline and 2-methylquinoxaline, and from 2-acetyl-3-methylquinoxaline oxime

itself, without giving any information about the actual reactions that do occur. These results, together with the inconclusive bromination and oxidation experiments and with the present inability to identify the oxidation products, indicated that the synthesis of the base must be further studied.

The red base was first isolated from the reaction of isonitrosoacetylacetone with o-phenylenediamine in dilute hydrochloric acid; this reaction has been shown to give 2-acetyl-3-methylquinoxaline oxime and it was noted that this compound (or its ketone) was essential for the formation of the red base. Barker had found that isonitrosoacetylacetone would condense with tolylene-3,4-diamine and with 4-bromo-o-phenylenediamine under similar conditions, giving in each case a red 'glass', which could not be crystallised, but which gave the same colour reactions with hydrochloric acid as the first red base isolated. In each of these experiments, the 2-acetyl-3-methyl derivative and its oxime were also formed.

The condensation between isonitrosoacetylacetone and 4-bromo-o-phenylenediamine was repeated, and purification of the basic extract on an alumina column gave two red compounds, neither of which crystallised well and both of which melted below 100°C; the red glass, obtained in the earlier experiment, was therefore a mixture of bases.

If a compound similar to the red base were synthesised, in which one of the benzene rings had a bromo substituent, this

substituent might act as a marker in oxidation experiments. Isonitrosoacetylacetone was allowed to condense with 4-bromo-o-phenylenediamine in 2N hydrochloric acid at room temperature, and a small yield of 6- or 7-bromo-2-acetyl-3-methylquinoxaline oxime (or perhaps a mixture of the isomers) was obtained. This compound was warmed with 2-methylquinoxaline in dilute hydrochloric acid and from the reaction mixture was isolated one red base, a semi-solid mass which would not crystallise; when warmed the crystalline structure disappeared between 80° and 89°C. The analysis of the picrate of this base showed that one bromine atom was present in the molecule.

This approach seems promising and experiments starting from 4,5-dibromo-o-phenylenediamine, which will give an oxime of unambiguous structure, should give more information about this condensation and its product, which might be degraded by oxidation to known substituted quinoxalines.

Another suggested approach is the determination of whether or not the methyl group of the acetyl substituent is involved in the formation of the red base. This methyl group, being adjacent to a carbonyl group, will be active, but it has always been assumed that this group forms the C-methyl group of the red base, although there is no experimental evidence to justify this assumption.

ABSORPTION SPECTRA

FIGURE 13. Red base, $C_{20}H_{14}N_4$, in ethanol.

	Maxima	232 mu	log 4.57
		311 mu	4.32
		502 mu	4.40
In 0.4N HCl		229 mu	4.57
		322 mu	4.21
		358 mu	4.14
		544 mu	4.39
		586 mu	4.46
In 2N HCl		240 mu	4.45
		298 mu	4.18
		386 mu	4.56
		615 mu	3.59

FIGURE 14. α-(2-(3-methyl)quinoxalinyl)-β-(2'-quinoxalinyl)-ethylene in chloroform.

Maxima	280 mu	log 4.56
	381 mu	4.52

FIGURE 15. The orange base isolated from the attempted cyclisation of α-(2-(3-methyl)quinoxalinyl)-β-(2'-quinoxalinyl)-ethylene in ethanol. (Qualitative).

Maxima	277 mu	log T.D. 3.21
	368 mu	2.68
	384 mu	2.71
	471 mu	2.24

In 2N HCl (Qualitative)	Maxima	244 mu	log T.D.	2.25
		278 mu		2.08
		330 mu		1.91
		410 mu		1.63
		530 mu		1.14

FIGURE 16. The orange ester obtained by SeO_2 and H_2O_2 oxidation of the red base, $C_{20}H_{14}N_4$, in ethanol (Qualitative).

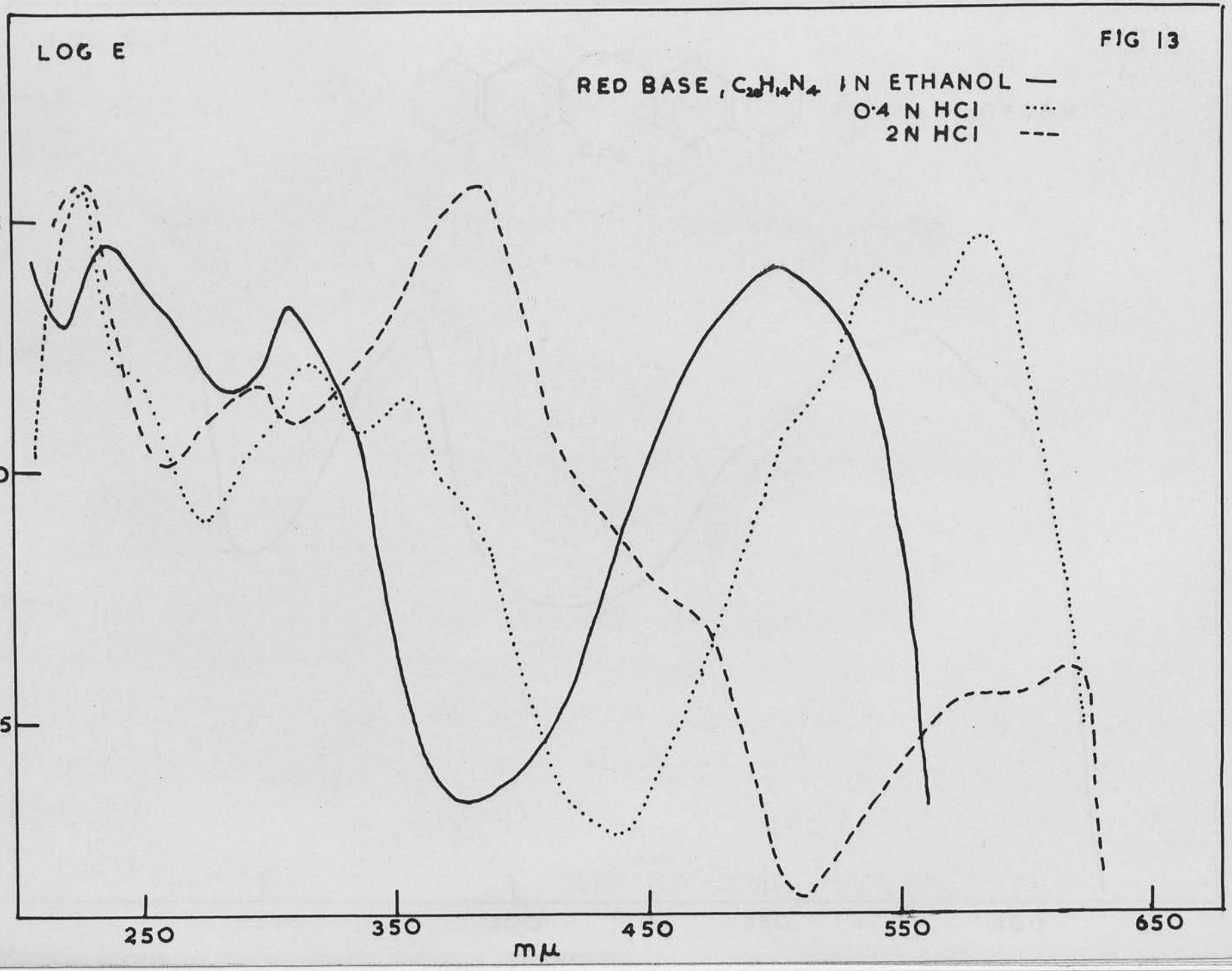
Maxima	235 mu	log T.D.	1.09
	279 mu		0.71
	321 mu		0.46
	470 mu		$\bar{1}$.59

FIGURE 17. The orange acid obtained by H_2O_2 oxidation of the red base, $C_{20}H_{14}N_4$, in ethanol (Qualitative).

Maxima	238 mu	log T.D.	1.46
	319 mu		0.99
	452 mu		$\bar{1}$.57
	481 mu		$\bar{1}$.56

FIGURE 18. The ester obtained by $KMnO_4$ oxidation of the red base, $C_{20}H_{14}N_4$, in ethanol.

Maxima	239 mu	log ϵ	4.64
	280 mu		3.98
	324 mu		4.05


LOG E
FIG 13
RED BASE, $C_{28}H_{14}N_4$ IN ETHANOL
0·4 N HCl
2N HCl
4·5
4·0
3·5
250
350
450
550
650
mμ

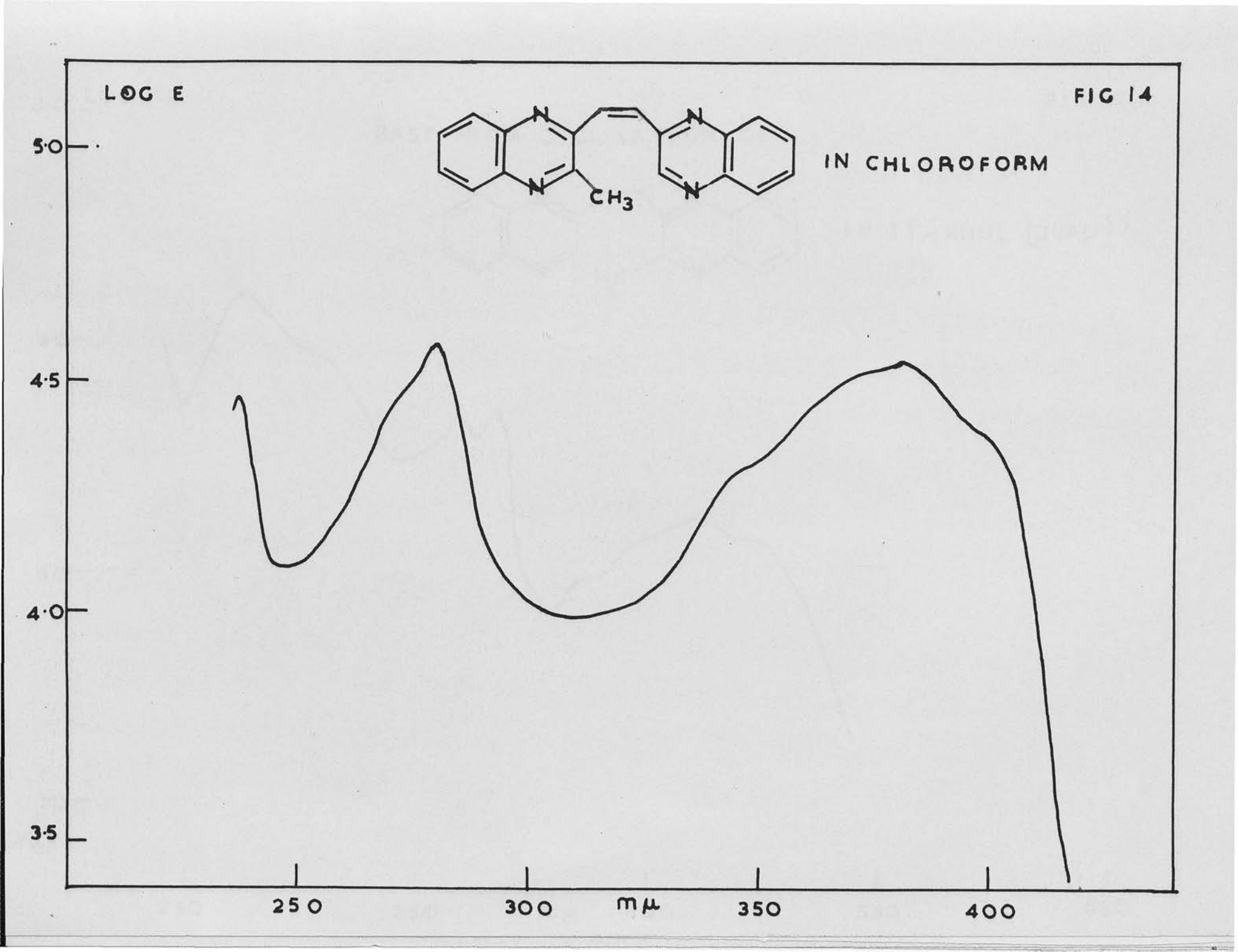
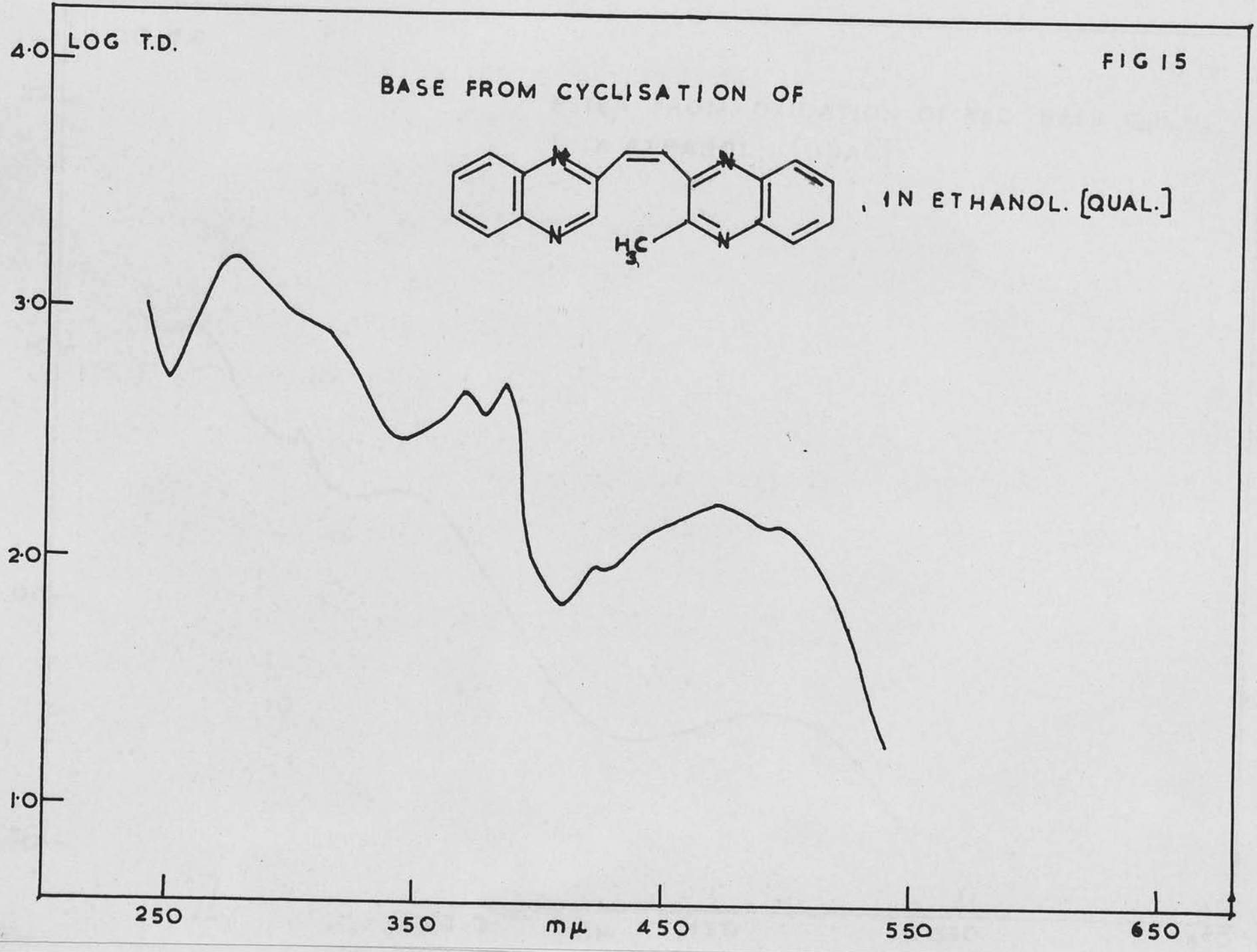
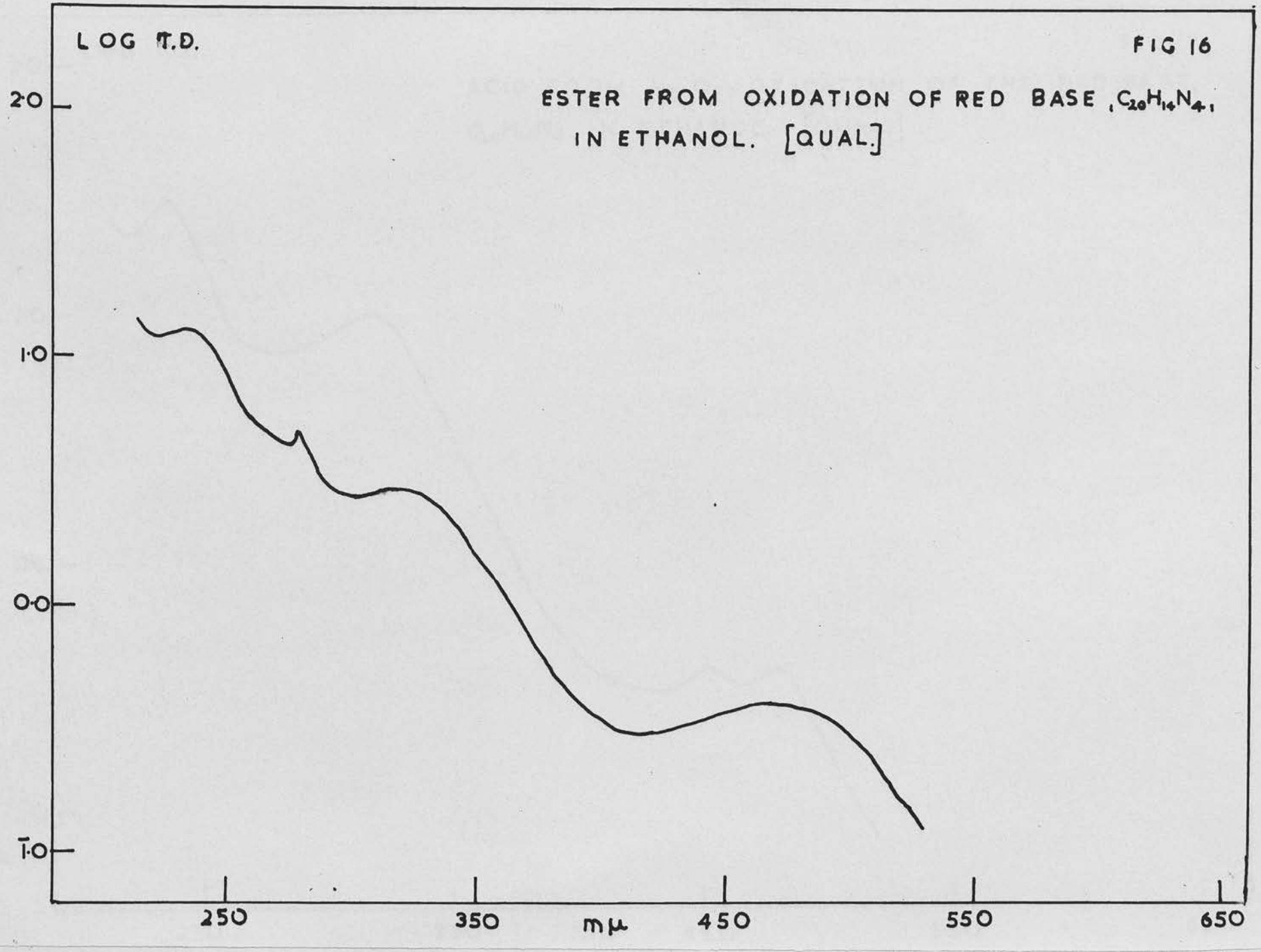

LOG E
FIG 14
5·0
4·5
4·0
3·5
IN CHLOROFORM
N
N
N
N
CH3
250
300
mμ
350
400

FIG 15



BASE FROM CYCLISATION OF

, IN ETHANOL. [QUAL.]


LOG T.D.
FIG 16
ESTER FROM OXIDATION OF RED BASE ,$C_{20}H_{14}N_4$,
IN ETHANOL. [QUAL.]
2·0
1·0
0·0
1̄·0
250
350
mμ
450
550
650

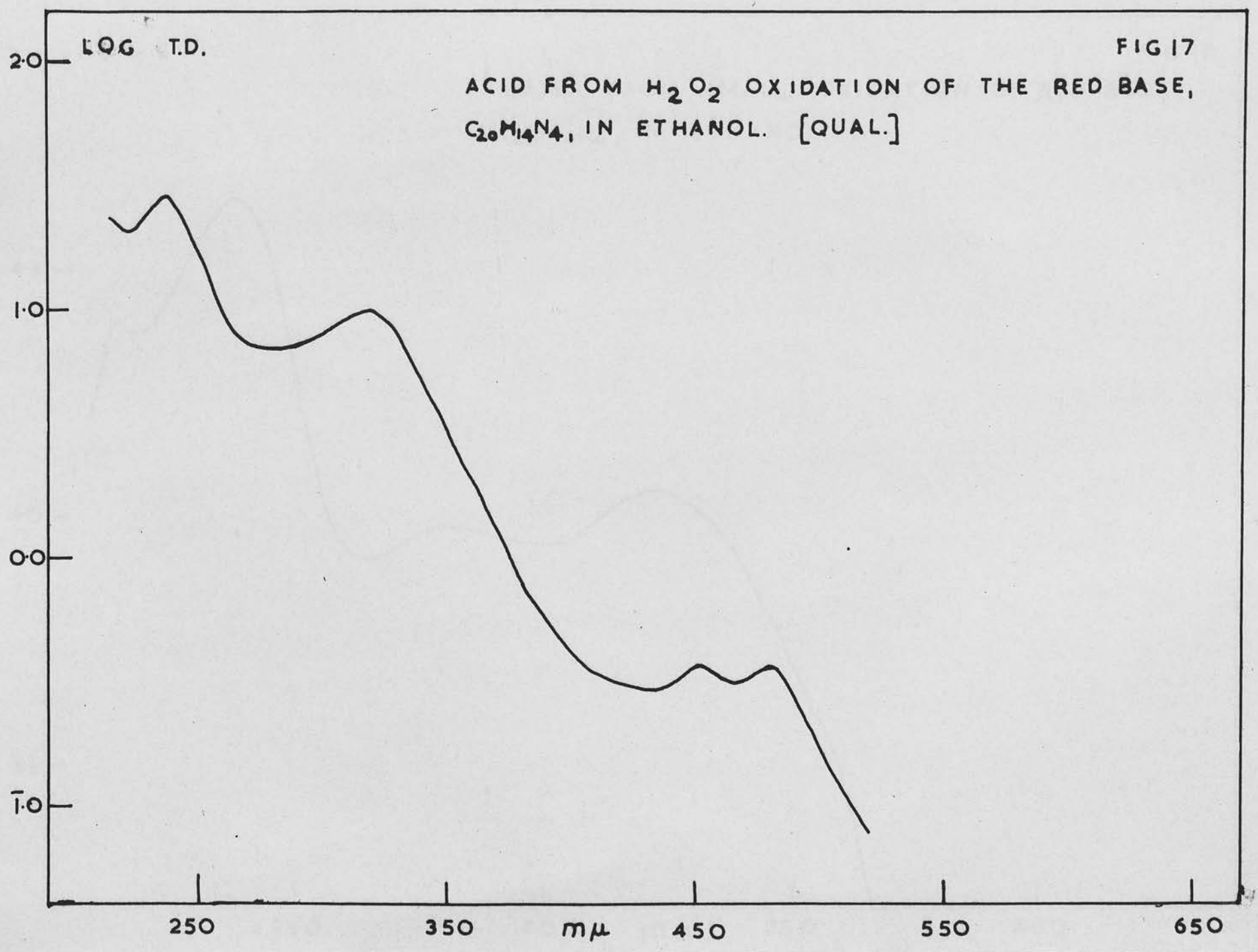
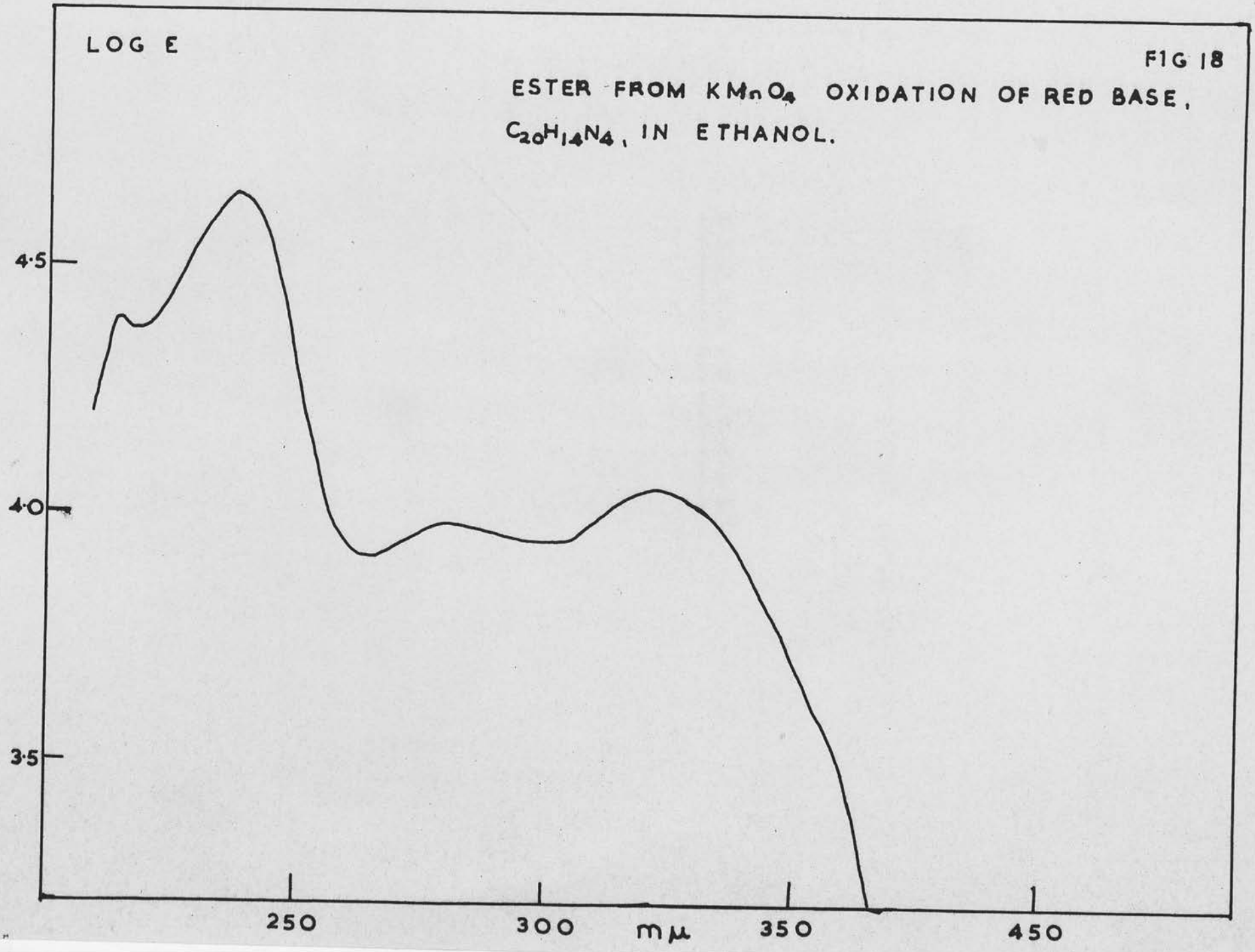


FIG 17

ACID FROM H_2O_2 OXIDATION OF THE RED BASE, $C_{20}H_{14}N_4$, IN ETHANOL. [QUAL.]


LOG E
FIG 18
ESTER FROM $KMnO_4$ OXIDATION OF RED BASE, $C_{20}H_{14}N_4$, IN ETHANOL.
4·5
4·0
3·5
250
300
mμ
350
450

EXPERIMENTAL

Preparation of isonitrosoacetylacetone.

Wolff, Ann., 325, 139 (1902).

Freshly distilled acetylacetone (44 g) gave isonitrosoacetylacetone (30 g).

Preparation of 2-acetyl-3-methylquinoxaline oxime.

cf. Barker, Thesis, p. 89.

A solution of o-phenylenediamine (38 g) and isonitrosoacetylacetone (45 g) in hydrochloric acid (2N, 700 ml), was allowed to stand at room temperature for 7 days. The brown precipitate was filtered off, dried and extracted in a Soxhlet thimble with benzene for 50 hours. From the extract was obtained a white solid, which crystallised from ethanol as white needles.

Yield 38 g.

M.P. 195-196°C.

Preparation of the Red base, $C_{20}H_{14}N_4$.

Barker, Thesis, p. 114.

Freshly distilled 2-methylquinoxaline (6 g) and 2-acetyl-3-methylquinoxaline oxime (9.5 g) in water (100 ml), ethanol (100 ml), and hydrochloric acid (10N, 50 ml), were boiled under reflux for 1 hour. A dark green precipitate came out of solution during the heating and was filtered off. The precipitate was suspended in ethanol (100 ml), and potassium hydroxide (10%, 100 ml) was added. The mixture was extracted continuously with benzene for 30 hours.

The dark red extract with green fluorescence, was distilled to dryness and the residue dissolved in benzene. This solution was purified on an alumina column; a bright red band separated and was eluted with benzene-ether (3:1). Removal of the solvent gave a red oil with a green lustre, which crystallised from ethanol as dark red plates, with a green glance.

Yield 7.7 g.

M.P. 182-184°C.

The picrate of the base was prepared in ethanol. It precipitated from solution as red plates, with a yellow glance.

M.P. > 350°C.

Analysis. Found : N, 18.3%

$C_{26}H_{17}N_7O_7$ requires N, 18.2%

Preparation of 4-bromo-o-phenylenediamine.

a) p-Bromoacetanilide.

p-Bromoaniline (12.5 g) was dissolved in acetic acid (25 ml) and water (25 ml) and the solution was cooled to 0°C. Acetic anhydride (12 ml) was added in one portion and the mixture stirred. A white solid precipitated from solution. The mixture was heated on a water-bath at 80°C, for 15 minutes, and was then allowed to stand at room temperature for 2 hours. The precipitate was filtered, washed with sodium carbonate (10%, 25 ml) and water, and crystallised from ethanol as colourless prisms.

Yield 14 g.

M.P. 163.5°C.

b) 4-Bromo-2-nitroacetanilide.

Hübner, Ann., 209, 359 (1881).

p-Bromoacetanilide (10 g) was mixed with nitric acid (dens. 1.52, 13.5 ml) and the mixture kept at 0°C for 8 minutes, before being poured into water (100 ml). The mixture was allowed to stand at room temperature for 1.5 hours, before the yellow solid was filtered off and washed with water, until free of acid. The solid crystallised from ethanol as yellow plates.

Yield 7.5 g.

M.P. 103.5-104°C.

c) 4-Bromo-2-nitroaniline.

cf. Organic Syntheses, 25, 79.

4-Bromo-2-nitroacetanilide (7.5 g) was dissolved in Claisen's alkali (potassium hydroxide (8.8 g) in water (6.3 ml) and diluted to 25 ml with methanol) and then heated on a boiling water-bath for 15 minutes. Water (25 ml) was added and the heating continued for a further 15 minutes. The mixture was allowed to stand at 0°C for 10 hours, before filtering off the orange solid, which crystallised from ethanol as orange needles.

Yield 5.5 g.

M.P. 109-110.5°C.

d) 4-Bromo-o-phenylenediamine.

cf. Hübner, loc. cit.

4-Bromo-2-nitroaniline (5.5 g) and granulated tin (6 g) in hydrochloric acid (10N, 30 ml), were heated on a steam-bath for 45 minutes. On cooling, a solid separated from the dark red solution and was filtered off. The solid was suspended in potassium hydroxide (10N, 15 ml) and this was extracted with ether. The filtrate was made alkaline with potassium hydroxide (10N, 45 ml) and extracted with ether. From the combined extracts was obtained a fawn solid, which crystallised from ethanol as cream plates.

Yield 3.35 g.

M.P. 62-63°C.

Condensation of 4-bromo-o-phenylenediamine and isonitrosoacetylacetone.

a) In the cold.

4-Bromo-o-phenylenediamine (8 g) and isonitrosoacetylacetone (5.25 g) were dissolved in hydrochloric acid (2N, 100 ml), and the solution was allowed to stand at room temperature for 8 days. The mixture was filtered, giving a whitish solid contaminated by a black tar, which was extracted in a Soxhlet thimble with

benzene for 5 hours. The benzene solution was concentrated to small volume and a white solid came out of solution. This crystallised from ethanol, after treatment with charcoal, as white needles.

Yield 3.5 g.

M.P. 227-229°C.

M.P. of Bromo-2-acetyl-3-methylquinoxaline oxime 234-235°C (Barker, Thesis, p. 93).

b) With heating.

cf. Barker, Thesis, p. 92.

4-Bromo-o-phenylenediamine (3 g) and isonitrosoacetylacetone (2.1 g) were dissolved in hydrochloric acid (10N, 10 ml), ethanol (20 ml) and water (20 ml), giving a red-brown solution. The solution was boiled under reflux until the evolution of hydrogen cyanide (detected with copper acetate and benzidine acetate) had ceased (7.5 hours). The black precipitate was filtered off and suspended in ethanol (30 ml). Potassium hydroxide (5N, 10 ml) was added and the mixture was extracted continuously with benzene for 16 hours. The deep red extract was purified on an alumina column. Two bands separated.

1) A bright red band, which fluoresced orange in U.V. light, was eluted with benzene, giving an orange-red solution. Removal of the solvent gave a red oil with a green lustre. This was dissolved in methanol and slow evaporation of the solvent gave a red semi-solid mass, which 'melts' between 90°C and 110°C.

2) A red band, which fluoresced orange in U.V. light, was eluted with benzene-ether (1:1), giving a red solution. Removal of the eluant gave red material, which was dissolved in methanol. Slow evaporation of the solvent gave red plates with a green lustre, slightly contaminated by a red oil. This solid 'melted' between 85°C. and 110°C.

Condensation of 2-methylquinoxaline and bromo-2-acetyl-3-methylquinoxaline oxime.

Freshly distilled 2-methylquinoxaline (1.75g) and bromo-2-acetyl-3-methylquinoxaline oxime (2.5g) were dissolved in hydrochloric acid (10N, 7.5ml), ethanol (15ml) and water (15ml), and the solution boiled under reflux for 1 hour. A dark green precipitate came out of solution and was filtered off. This was suspended in ethanol (25ml) and potassium hydroxide (40%, 25ml) was added. The mixture was extracted continuously with benzene for 17 hours. The extract was distilled to dryness and the residue was dissolved in benzene. The solution was purified on an alumina column. Two bands separated.

1) A red band was eluted with benzene, giving a red solution which fluoresced orange in U.V. light. Removal of the solvent gave a red oil with a green lustre, which was dissolved in methanol. A red solid contaminated with red oil came out of solution. The melting-point of this material was 80-89°C. The picrate of the base was prepared - a black crystalline substance.

M.P. > 350°C.

Analysis. Found : C, 51.3; H, 3.3; N, 16.1; Br, 11.3%

$C_{26}H_{16}BrN_7O_7$ requires C, 50.5; H, 2.6; N, 15.9; Br, 12.9%

The picrate was decomposed by adding to sodium hydroxide (5N, 20 ml) and the base was extracted with benzene. The benzene extract was purified by passing through a short alumina column. Removal of the eluant gave a red oil which did not crystallise.

2) A deep red band was eluted with benzene-ether (1:1), giving a red solution which fluoresced green in U.V. light. Removal of the eluant gave a small amount of red oil with a green lustre, which did not crystallise.

Attempted oxidation of the Red base, $C_{20}H_{14}N_4$, by selenium dioxide.

cf. Borsche and Doeller, Ann., 537, 39 (1939).

Müller and Varga, Ber., 72, 1993 (1939).

I. The red base (1.5 g) was dissolved in dioxan (purified by freezing) (50 ml) and the solution was added to a solution of selenium dioxide (purified by sublimation) (0.7 g) in dioxan (50 ml) and water (3 ml). The mixture was boiled under reflux for 17 hours and then filtered to remove selenium. The filtrate was distilled to small volume (20 ml) under reduced pressure. Ether (100 ml) was added and a solid precipitated from solution. This was filtered off and extracted in a Soxhlet thimble with ether for 2 hours. This extract was combined with the ether filtrate and distilled to dryness (the last traces of water were removed

azeotropically with benzene). A red oil was obtained and was dissolved in water (15 ml), ethanol (15 ml), sodium hydroxide (2N, 5 ml) and hydrogen peroxide (33%, 2 ml). The solution was allowed to stand at room temperature for 2 hours, before being heated on steam-bath for 1.5 hours. After cooling, the solution was extracted with methylene chloride, which was in turn extracted with sodium carbonate solution (5%).

The sodium carbonate extract was neutralised with hydrochloric acid (2N) and then extracted with ether, giving a yellow solution with a green fluorescence in U.V. light. The extract was distilled until the volume was 25 ml and an ethereal solution of diazomethane (from N-methyl-N-nitrosotoluene-p-sulphonamide (2.4 g)) was slowly added. This was allowed to stand at room temperature overnight. The excess diazomethane was destroyed by adding a few drops of very dilute formic acid and the ethereal solution was distilled to dryness. A small amount of orange-yellow material was obtained. This was dissolved in ethanol and a qualitative spectrum obtained (Figure 16).

The methylene chloride solution was evaporated to dryness and the red oil dissolved in benzene and purified by passing through a short alumina column. Removal of the benzene-ether (4:1) eluant gave a red oil, which crystallised from ethyl acetate as red plates with a green glance.

M.P. 182-184°C.

Mixed M.P. with starting material 181-184°C.

II. The red base (1.2 g) was dissolved in sulphur-free xylene (50 ml) and selenium dioxide (purified by sublimation) (0.5 g) was added in small amounts over 1 hour. The mixture was boiled under reflux for 8 hours and then filtered. The residue was boiled with ethanol (25 ml) to remove organic material. The xylene filtrate was distilled under reduced pressure and a red oil with a green lustre was obtained. This oil was dissolved in ethanol (75 ml) and after combination with the above extract, water (100 ml), potassium hydroxide (10 g) and hydrogen peroxide (33%, 10 ml) were added. The mixture was allowed to stand at room temperature overnight, before being boiled under reflux for 3 hours. The solution was distilled until the volume was 100 ml and then acidified with hydrochloric acid (2N). This solution was extracted with methylene chloride, which was in turn extracted with sodium carbonate solution (10%). This last extract was acidified with hydrochloric acid (2N) and extracted with ether. The ether extract was distilled until the volume was 25 ml, and an ethereal solution of diazomethane (from nitroso-N-methylurea (2 g)) was slowly added. The solution was allowed to stand at room temperature overnight. The excess diazomethane was destroyed by adding a few drops of very dilute formic acid. Removal of the ether gave a small amount of red-brown oil, which had a pleasant smell and which did not crystallise.

The methylene chloride solution yielded starting material as in the above reaction.

III. The red base (2 g) was dissolved in dioxan (purified by freezing) (50 ml) and the solution was added to a suspension of selenium dioxide (purified by sublimation) (1 g) in dioxan (25 ml). The mixture was boiled under reflux for 20 hours. The mixture was filtered and the dioxan removed under reduced pressure, giving a red solid with a green lustre. This was dissolved in ethanol (150 ml) as far as possible and the small black residue was filtered off. The ethanol solution was distilled to dryness, giving a red oil which would not crystallise.

Attempted oxidation of the Red base, $C_{20}H_{14}N_4$, with alkaline hydrogen peroxide.

cf. Nozoe, Satô, Itô, Matsui & Ôzeki, Science Rep. of Tôhoku Univ., Series I, 38, 190 (1954).

I. The red base (1.5 g) was allowed to stand overnight at room temperature in a solution of sodium hydroxide (10%, 25 ml), ethanol (25 ml) and hydrogen peroxide (33%, 7 ml), before being boiled under reflux for 3 hours. The solution was extracted continuously with benzene for 8 hours (Extract A), and was then acidified with hydrochloric acid (2N) and the extraction with benzene continued for a further 8 hours (Extract B).

Extract A was distilled to dryness, giving a red oil with a green lustre, which was dissolved in benzene and the solution purified on an alumina column. A red band was eluted with benzene-ether (4:1) and removal of the eluant gave a red oil, which crystallised from ethanol as red plates with a green glance.

Yield 0.45g.

M.P. 184-186°C.

Mixed M.P. with starting material 184-186°C.

Extract B was thoroughly extracted with sodium carbonate solution (10%). After acidification with hydrochloric acid (10N), this solution was extracted continuously with ether for 4 hours. Removal of the ether from the extract gave some yellow material, which was dissolved in ethanol and a qualitative spectrum obtained. (Figure 17).

After removal of the acidic material from Extract B, the benzene was distilled off, leaving a red oil which would not crystallise.

II. The red base (2g) in a solution of ethanol (40ml), sodium hydroxide (50%, 10ml) and hydrogen peroxide (33%, 15ml) was allowed to stand at room temperature for 3 days. During this period, a solid separated from solution. The mixture was boiled under reflux for 3 hours and extracted continuously with benzene for 8 hours.(Extract A). The solution was acidified with hydrochloric acid (10N) and then extracted with benzene for a further 16 hours. (Extract B).

From extract A, as in the same extract in the above experiment, was obtained starting material.

Yield 1g.

M.P. 183-185°C.

Extract B was thoroughly extracted with sodium carbonate solution (10%), which was then acidified with hydrochloric acid (10N)

and extracted continuously with ether for 16 hours. Removal of the ether from this extract gave a red-brown semi-solid mass which could not be crystallised.

After removal of the acidic material, the benzene was distilled from extract B and a very small residue of brown solid was obtained. This was not further investigated.

Attempted oxidation of the Red base, $C_{20}H_{14}N_4$, with osmium tetroxide.

The red base (200mg) was dissolved in dry thiophene-free benzene (20ml) and anhydrous pyridine (0.75ml) and to the solution was added osmium tetroxide (200mg) in benzene (5ml). This mixture was allowed to stand at room temperature for 20 hours. The brown crystalline precipitate (450mg) was filtered off and added to a suspension of mannitol (20g) and potassium hydroxide (0.2g) in water (20ml). This mixture was shaken for 20 hours. The colour of the solution became purple-red as the complex decomposed. Water (25ml) was added and the mixture filtered.

The residue was extracted continuously with chloroform for 3 hours, giving a deep green solution.

The filtrate was boiled under reflux with chloroform for 3 hours; the chloroform layer was dark green.

The two extracts were combined and dried over anhydrous calcium sulphate, whereupon the colour became blue. Removal of the solvent gave a black solid. Ethanol (20 ml) and charcoal (0.05g)

were added, and the mixture was boiled and then filtered, giving a red solution. Removal of the solvent gave a dark residue which would not dissolve in ethyl acetate. The solid was extracted with boiling benzene (4 x 10 ml), giving a dark red solution and a small black residue. This solution was distilled to dryness, giving a red solid, which was boiled with ethyl acetate. The ethyl acetate was distilled off and benzene was added to the mixture. The material would not dissolve completely; a black residue, M.P. > 350°C, was again obtained. From this benzene extract was obtained dark red material, which did not appear to be homogeneous, M.P. 44-100°C.

Attempted ozonolysis of the Red base, $C_{20}H_{14}N_4$.

I. The red base (1 g) in anhydrous ethyl acetate (75 ml) was cooled to 0°C and ozone was passed through the solution for 1 hour. The colour changed from deep red, through orange, to yellow, and some solid was deposited. Raney nickel suspension (10 ml) and water (5 ml) were then added cautiously and the mixture was allowed to stand at room temperature for 24 hours, before being heated at 80°C for 1 hour. The mixture was filtered and the organic layer separated. The aqueous layer was extracted with ethyl acetate and this extract was added to the brown organic layer. Removal of the ethyl acetate gave a yellow-brown solid.

Yield 0.97 g.

M.P. 164-169°C.

The solid was boiled with benzene but would not dissolve.

Distillation of the benzene left a black solid.

M.P. > 350°C.

II. The red base (1 g) in anhydrous ethyl acetate (75 ml) was cooled to 0°C and ozone was passed through the solution until the colour just became orange (ca. 30 minutes). (There appears to be three stages of colour change - orange-red, to very dark red, to orange.) Raney nickel (10 mg) and water (50 ml) were added to decompose the ozonide. The mixture was heated at 80°C for 15 minutes. The colour of the organic layer changed from orange to red-brown. The organic layer was separated and the aqueous layer was extracted with ethyl acetate, this extract being added to the organic layer. Distillation of the ethyl acetate left a brown oil, which was immediately dissolved in benzene. A few drops of light petroleum were added to the benzene solution and a pale brown solid precipitated from solution.

Yield 500 mg.

M.P. 165-170°C.

To the filtrate was added an equal volume of light petroleum (40/60) and a yellow-orange solid was precipitated from solution.

Yield 200 mg.

M.P. 125-128°C.

Repeated purifications of the solid with benzene-light petroleum (40/60) improved the melting-point to 145-150°C (decomposition).

III. The red base (1 g) in anhydrous ethyl acetate (75 ml) was cooled to 0°C and ozone was bubbled through the solution until it lost its orange-red colour. The ozonide was decomposed by adding Raney nickel (50 mg) and water (50 ml), and boiling the mixture under reflux for 15 minutes. The organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined ethyl acetate extracts were extracted with sodium carbonate solution (10%).

The sodium carbonate extract was acidified with hydrochloric acid (10N) and extracted with ether. From the ether extract was obtained a very small amount of orange solid, M.P. 170-180°C (with decarboxylation).

The ethyl acetate extract was distilled to dryness and the red oil immediately dissolved in benzene. Light petroleum (40/60) was added.

a) A few drops. A very small amount of brown solid was obtained.

b) An equal volume. A yellow solid (0.22 g) was precipitated, M.P. 133-138°C. Crystallisation from benzene-light petroleum (60/80) improved the melting-point to 140-144°C.

c) 1.5 x volume. A small amount of orange solid was obtained (0.05 g).

M.P. 104-108°C.

Mixed M.P. with quinoxaline-2-aldehyde 70-90°C.

The solution was distilled to dryness and gave a red oil, which would not crystallise.

Oxidation of the Red base, $C_{20}H_{14}N_4$, with chromium trioxide.

A solution of chromium trioxide (AnalaR) (2 g) in glacial acetic acid (10 ml) and water (10 ml), was added dropwise to a solution of the red base (2 g) in acetic acid (20 ml). The mixture was allowed to stand at room temperature for 12 hours and was then boiled under reflux for 30 minutes. The cooled solution was poured into ice-water (100 ml). The brown precipitate was filtered off and extracted in a Soxhlet thimble with benzene for 6 hours. The benzene extract of the filtrate was added to the first extract, and the combined solution was extracted with sodium carbonate solution (10%). The sodium carbonate extract was acidified with hydrochloric acid and then extracted with ether. From this solution was obtained a very small amount of yellow material, which was not further investigated.

$M.P._{crude}$ 173-177°C.

The acid-free benzene extract was distilled and a brown residue obtained. This crystallised from benzene-light petroleum (1:3) as straw-coloured prisms.

Yield 575 mg.

M.P. 165.5-166.5°C.

Analysis. Found : C, 71.5; H, 4.6; N, 15.6%

C, 71.2; H, 3.8; N, 15.5%

$C_{11}H_9N_2O$ requires C, 71.3; H, 4.9; N, 15.1%

$C_{11}H_8N_2O$ requires C, 71.7; H, 4.4; N, 15.2%

This compound formed a dinitrophenylhydrazone which

crystallised from pyridine or xylene as small yellow prisms.

M.P. 249.5-250.5°C.

Analysis. Found : C, 59.4; H, 3.5; N, 19.4%

C, 59.9; H, 3.6; N, 19.4%

Attempted nitrosation of the oxidation product.

I. The oxidation product (50 mg) was dissolved in sulphuric acid (18N, 6 ml) and cooled to 0°C. A solution of sodium nitrite (25 mg) in water (3 ml) was added dropwise over 15 minutes, and then water (20 ml) was added. A buff precipitate was obtained and was extracted into ether. A yellow solid was obtained from the ether extract and was crystallised from methanol.

M.P. 163-166°C.

Mixed M.P. with starting material 164.5-166°C.

Yield of recovered starting material 35 mg.

II. The oxidation product (50 mg) was dissolved in anhydrous ether (20 ml) and cooled to 0°C. Butyl nitrite (50 mg) was added and anhydrous hydrogen chloride was passed through the mixture for 15 minutes. After the addition of benzene (30 ml), the mixture was allowed to stand at room temperature for 16 hours. The mixture was filtered and distillation of the ether left a small amount of greenish-black material. The residue from the filtration was suspended in water and the mixture thoroughly extracted with ether. Distillation of the ether from this extract gave a brown oil, which crystallised from methanol as straw-coloured prisms.

M.P. 164.5-165.5°C.

Mixed M.P. with starting material 164.5-166°C.

Yield of starting material recovered 20 mg.

Attempted bromination of the Red base, $C_{20}H_{14}N_4$.

A. Direct bromination.

1. In chloroform.

The red base (0.2 g) was dissolved in chloroform (10 ml) and a solution of bromine (0.25 ml) in chloroform (10 ml) was slowly added. The colour of the solution changed from orange-red, through dark red, then blue, to green; a solid separated from solution. The solution was warmed at 80°C for a few minutes and then allowed to stand at room temperature for 15 minutes. The mixture was filtered, giving a dark red tarry solid which was dissolved in ethanol. The solution was made alkaline with sodium hydroxide solution (2N) and extracted with benzene. Meanwhile, the chloroform filtrate had been distilled to dryness, the red residue dissolved in sodium hydroxide (2N) and this solution extracted with chloroform. The chloroform and benzene extracts were combined and distilled to dryness and the residue was dissolved in benzene and purified on an alumina column. A red band separated and was eluted with benzene. The dark red eluate yielded a red tar, which could not be crystallised.

2. In carbon tetrachloride.

The red base (1 g) was dissolved in carbon tetrachloride

(50 ml) and a solution of bromine (3 ml) in carbon tetrachloride (25 ml) was added. A dark green precipitate was obtained. This was filtered off and suspended in sodium hydroxide (2N) and the suspension extracted with benzene. The extract was purified on an alumina column. A large number of bands separated, but the main band was not eluted with ether. The separation was abandoned.

3. In acetic acid.

cf. Leese and Rydon, J.C.S., 1955, 303.

The red base (0.5 g) and anhydrous sodium acetate (0.25 g) were dissolved in warm glacial acetic acid (20 ml). Bromine (0.5 g) in acetic acid (2 ml) was added slowly to the solution. Solid precipitated from solution and the colour changed to green. The mixture was warmed for 10 minutes on a steam-bath. On cooling, a black solid (0.9 g) was filtered off and extracted continuously in a Soxhlet thimble with benzene for 18 hours. Removal of the benzene from the red solution gave a black tar.

B. Bromination with N-bromosuccinimide.

4. In chloroform.

To the red base (0.4 g) in dry chloroform (25 ml) were added N-bromosuccinimide (0.3 g) and benzoyl peroxide (50 mg), and the mixture was boiled under reflux for 90 minutes. The mixture was filtered and the filtrate distilled to dryness. The residue was dissolved as far as possible in benzene. Some black solid (100 mg), which melted above 350°C, did not dissolve. The benzene solution

was purified on an alumina column. Two bands separated.

a) A red band was eluted with benzene. Removal of the eluant gave a red oil which would not crystallise.

b) A red band, which fluoresced orange in U.V. light, was eluted with benzene-ether (9:1). Removal of the eluant gave a red oil which crystallised from ethanol as red plates.

Yield 50 mg.

M.P. 182-185°C.

Mixed M.P. with starting material 182-185°C.

5. In carbon tetrachloride.

N-Bromosuccinimide (0.5 g) and benzoyl peroxide (25 mg) were added to a solution of the red base (0.5 g) in freshly distilled carbon tetrachloride (20 ml).

The mixture was boiled under reflux for 25 hours and then filtered. The black crystalline residue (675 mg) was washed with carbon tetrachloride (50 ml).

M.P. > 350°C.

The filtrate was concentrated to 20 ml and light petroleum (40/60) was added. A red solid (275 mg) was obtained.

M.P. 80-90°C.

This solid was extracted continuously with ether for 6 hours, leaving a residue (45 mg).

M.P. 117-121°C.

Mixed M.P. with succinimide 117-119°C.

The ether extract was distilled to dryness and gave a red oil

which would not crystallise from ethanol. The solvent was removed and the oil boiled with benzene; a black residue, M.P. > 350°C, did not go into solution. The extract was distilled to dryness and the oil dissolved in methanol. Since crystallisation did not occur, the methanol was distilled and the oil again boiled with benzene. Solution, however, was incomplete, a black residue, M.P. > 350°C, again remaining. The benzene extract was purified on an alumina column; two bands separated.

a) A red band was eluted with benzene and removal of the solvent gave a small amount of red oil, which would not crystallise.

b) A red band, which fluoresced orange in U.V. light, was eluted with benzene-ether (9:1). Removal of the eluant gave a red oil which crystallised from methanol as red plates.

Yield 35 mg.

M.P. 183-184°C.

Mixed M.P. with starting material 184-185°C.

6. <u>In carbon tetrachloride</u>.

To a solution of the red base (0.5 g) in freshly distilled carbon tetrachloride (20 ml) were added N-bromosuccinimide (0.5 g) and benzoyl peroxide (50 mg). The mixture was boiled under reflux for 19 hours. The solution was filtered.

The black residue (600 mg) was extracted constantly with ether for 2.5 hours and a red solution was obtained. Removal of the solvent gave pale blue crystals, which were recrystallised from benzene as colourless cubic prisms.

Yield 150 mg.

M.P. 119-121°C.

Mixed M.P. with succinimide 117-120°C.

A black solid remained from the extraction.

Yield 250 mg.

M.P. > 350°C.

The carbon tetrachloride filtrate was distilled to dryness and a red solid was obtained.

Yield 330 mg.

M.P. 90-100°C.

This was dissolved in benzene and purified on an alumina column. Two bands separated.

a) A red band was eluted with benzene. Removal of the eluant gave a red oil which could not be crystallised. This oil would not form a picrate.

b) A red band, which fluoresced orange in U.V. light, was eluted with benzene-ether (3:1). Removal of the eluant gave a red oil which crystallised from ethanol as red plates.

Yield 80 mg.

M.P. 184-185°C.

Mixed M.P. with starting material 183-186°C.

Preparation of 2,3-dimethylquinoxaline.

cf. Bost and Towell, J.A.C.S., 70, 903 (1948).

o-Phenylenediamine dihydrochloride (42 g) was dissolved in acetic acid (10%, 100 ml) and to the solution was added dropwise,

diacetyl (19.5 g) in acetic acid (10%, 50 ml). The mixture was heated on a boiling water-bath for 45 minutes. On cooling, solid separated from the solution and crystallised from aqueous ethanol as colourless needles.

Yield 25 g.

M.P. 106°C.

Preparation of p-tolyl-d-isoglucosamine.

Weygand, Ber., 73, 1259 (1940).

d-Glucose (500 g) and p-toluidine (400 g) gave p-tolyl-d-isoglucosamine (564 g).

M.P. 150-152°C.

Preparation of (d-arabo-tetrahydroxybutyl)-quinoxaline.

Weygand and Bergmann, Ber., 80, 255 (1947).

p-Tolyl-d-isoglucosamine (100 g) gave (d-arabo-tetrahydroxybutyl)-quinoxaline (47 g).

M.P. 183-184°C.

Preparation of lead tetra-acetate.

C.J.M. Stirling, Ph.D. Thesis, University of London, 1955, p. 36. cf. Bailer, Inorganic Syntheses, 1, 47 (1939).

Red lead (100 g) was slowly added, with vigorous stirring, to a mixture of glacial acetic acid (AnalaR) (180 ml) and acetic anhydride (AnalaR) (60 ml), in a 1-litre flask, fitted with a thermometer side-arm. Stirring was continued for 2 hours at

35°C, for 2 hours at 70°C, and finally for 2 hours at 95°C. The clear colourless solution was cooled and the white crystals of lead tetra-acetate were filtered off. The product was dried in vacuo over potassium hydroxide.

Yield 44 g.

M.P. 180-185°C.

Preparation of quinoxaline-2-aldehyde.

I. cf. Müller & Varga, Ber., 72, 1993 (1939).

(d-arabo-Tetrahydroxybutyl)-quinoxaline (40 g) was suspended in dry benzene (900 ml) and glacial acetic acid (450 ml). Lead tetra-acetate (75 g) was added in small quantities and when the addition was complete, the mixture was allowed to stand at room temperature for 2 hours. After filtration, the filtrate was washed with water, dried over anhydrous calcium sulphate, and then distilled in vacuo. The residue crystallised from light petroleum (60/80) as straw-coloured needles.

Yield 6 g.

M.P. 106-108°C.

II. cf. Leese and Rydon, J.C.S., 1955, 303.

(d-arabo-Tetrahydroxybutyl)-quinoxaline (20 g) and sodium metaperiodate (52 g) were suspended in water (1.2 l) and acetic acid (40 ml). The mixture was allowed to stand at 17°C for 20 hours. The mixture was filtered, giving unreacted (d-arabo-tetrahydroxybutyl)-quinoxaline (2.25 g). The filtrate was

extracted continuously with ether for 10 hours. The ether extract was distilled to dryness in vacuo and the residue dissolved as far as possible in light petroleum (40/60). (Insoluble residue - 2 g.) The light petroleum solution was concentrated and the aldehyde crystallised as white needles.

Yield 5 g.

M.P. 105-107°C.

Condensation of quinoxaline-2-aldehyde and 2,3-dimethylquinoxaline.

cf. Bennett and Willis, J.C.S., 1928, 1960.

Quinoxaline-2-aldehyde (5 g) and 2,3-dimethylquinoxaline (5 g) in acetic anhydride (AnalaR) (250 ml), were boiled under reflux for 2 hours. The volume of the solution was reduced to 125 ml and on standing, a yellow solid (4.5 g) separated from solution. This solid was dissolved in benzene and purified on an alumina column. Two bands separated.

a) A pale yellow band, which fluoresced pale green in U.V. light, was eluted with benzene. Removal of the eluant gave a pale yellow solid, which crystallised from benzene in pale yellow clusters of small needles, which fluoresced bright yellow in U.V. light.

Yield 3.75 g.

M.P. 211-212°C.

Analysis. Found : C, 75.6; H, 4.8; N, 19.4%

$C_{19}H_{14}N_4$ requires C, 76.5; H, 4.7; N, 18.8%

b) An orange band, which was not further investigated, was eluted with ether.

Attempted cyclisation of α-(2-(3-methyl)quinoxalinyl)-β-(2'-quinoxalinyl)-ethylene.

α-(2-(3-methyl)quinoxalinyl)-β-(2'-quinoxalinyl)-ethylene (0.5 g) in hydrochloric acid (10N, 5 ml), ethanol (10 ml) and water (10 ml), was boiled under reflux for 3 hours. The solution showed the following colour changes within 15 minutes of heating: yellow, through green, to brown-red, with precipitation of solid material. The mixture was made alkaline with potassium hydroxide and extracted continuously with benzene for 6 hours. The extract was distilled to dryness and the residue dissolved in benzene. This solution was purified on an alumina column. Three bands separated.

a) An orange band was eluted with benzene-ether (3:1), giving a yellow solution, which had a green fluorescence in U.V. light. Removal of the eluant gave an orange solid (< 20 mg). This was dissolved in ethanol and a qualitative spectrum obtained (Figure 15).

b) A green band was eluted with benzene-ether (1:3). Removal of the eluant gave a very small amount of yellow material.

c) A deep pink band, which decolorised on exposure to visible light, was not further investigated.

A dark brown solution was obtained when ethanol was used as eluant, and removal of the solvent gave a black tar.

Preparation of quinoxaline-2-carboxylic acid.

cf. Maurer & Boettger, Ber., 71, 1383 (1938).

(d-arabo-Tetrahydroxybutyl)-quinoxaline (20 g) was suspended

in hydrogen peroxide (6%, 1.2 l) and gradually sodium hydroxide (48 g) was added. The mixture was allowed to stand at room temperature for 48 hours, until the evolution of oxygen had ceased and was then warmed on a water-bath for 2 hours. The hot solution was acidified with hydrochloric acid (10N) and the acid crystallised from solution. The acid recrystallised from ethanol as colourless needles.

Yield 9 g.

M.P. 212-213°C.

Preparation of quinoxaline-2-carboxylic acid chloride.

Maurer & Boettger, Ber., 71, 1383 (1938).

Quinoxaline-2-carboxylic acid (9 g) gave quinoxaline-2-carboxylic acid chloride (8 g).

M.P. 114-115°C.

Preparation of ethyl quinoxaline-2-carboxylate.

cf. Maurer & Boettger, Ber., 71, 1383 (1938).

Quinoxaline-2-carboxylic acid chloride (8 g) was dissolved slowly in anhydrous ethanol (30 ml). The mixture was allowed to stand at room temperature overnight before the precipitate was filtered. The ester crystallised from ethanol as colourless needles.

Yield 6.1 g.

M.P. 84-86°C.

Preparation of ethyl (3-methyl)quinoxalinyl-2-pyruvate.

Borsche & Doeller, Ann., 537, 39 (1939).

2,3-Dimethylquinoxaline (15.8 g) and diethyl oxalate (14.6 g) gave ethyl (3-methyl)quinoxalinyl-2-pyruvate (17 g).

M.P. 127-128°C.

Preparation of the oxime of ethyl (3-methyl)quinoxalinyl-2-pyruvate.

Borsche & Doeller, loc. cit.

Ethyl (3-methyl)quinoxalinyl-2-pyruvate (17 g) gave the oxime (14 g).

M.P. 180°C.

Preparation of 3-methylquinoxalinyl-2-acetonitrile.

Borsche & Doeller, loc. cit.

Ethyl (3-methyl)quinoxalinyl-2-pyruvate oxime (14 g) gave 3-methylquinoxalinyl-2-acetonitrile (4.5 g).

M.P. 127-130°C.

Attempted condensation of 3-methylquinoxalinyl-2-acetonitrile and quinoxaline-2-aldehyde.

Quinoxaline-2-aldehyde (4 g) and 3-methylquinoxalinyl-2-acetonitrile (4 g) in acetic anhydride (250 ml), were boiled under reflux for 5 hours. The solution was distilled to dryness, the last traces of acetic anhydride being removed azeotropically with benzene, and the dark brown viscous tar dissolved in benzene. An attempt to purify the solution on an alumina column was unsuccessful,

as was the attempt to extract material from the tar. The synthesis was therefore abandoned.

Preparation of ethyl quinoxalinyl-2-pyruvate oxime.

Borsche & Doeller, loc. cit.

Ethyl quinoxalinyl-2-pyruvate (2.8 g) gave the oxime (2.8 g).

M.P. 146-147°C.

Preparation of quinoxalinyl-2-acetonitrile.

cf. Borsche and Doeller, loc. cit.

Ethyl quinoxalinyl-2-pyruvate oxime (2.7 g) was boiled under reflux in methanol (20 ml) and sodium hydroxide (2N, 40 ml) for 1 hour. The acid crystallised from solution as white needles, which decarboxylate at 154-160°C, giving yellow clusters of needles which melt 189-190°C.

Yield 2.5 g.

The acid (245 mg) in acetic anhydride (50 ml), was warmed at 45°C for 1 hour. The acetic anhydride was distilled off and the residue was extracted thoroughly with light petroleum (100/120). The acetonitrile crystallised from the concentrated extract as yellow needles.

Yield 1.15 g.

M.P. 115-117°C.

Attempted condensation of quinoxalinyl-2-acetonitrile and 2-acetyl-3-methylquinoxaline oxime.

Quinoxalinyl-2-acetonitrile (0.1 g) and 2-acetyl-3-methylquinoxaline oxime (0.125 g) in hydrochloric acid (10N, 5 ml), ethanol (10 ml), and water (10 ml), were boiled under reflux for 1 hour; the solution became brown, but no precipitate was observed. The solution was made alkaline with potassium hydroxide (40%) and then extracted continuously with benzene for 6 hours, giving an orange solution, which had a green fluorescence in visible light. Removal of the solvent gave an orange solid, M.P. 130-150°C. Most of this solid dissolved in cold benzene, leaving white material (20 mg).

M.P. 193-195°C.

Mixed M.P. with 2-acetyl-3-methylquinoxaline oxime 193-195°C.

The solution was purified on an alumina column; three bands separated.

a) A yellow band was eluted with benzene. Removal of the eluant gave a very small quantity of solid.

b) An orange band, which fluoresced orange in U.V. light, was eluted with benzene-ether (9:1). Removal of the eluant gave an orange solid (prisms).

Yield 50 mg.

M.P. 102-104°C.

Mixed M.P. with quinoxalinyl-2-acetonitrile 101-104°C.

c) A red band was eluted with benzene-ether (2:3). Removal of the eluant gave white needles.

Yield 70 mg.

M.P. 193-195°C.

Mixed M.P. with 2-acetyl-3-methylquinoxaline oxime 193-196°C.

Attempted condensation of quinoxalinyl-2-acetonitrile and quinoxaline-2-aldehyde.

cf. Borsche and Doeller, loc. cit.

Quinoxalinyl-2-acetonitrile (0.1 g) and quinoxaline-2-aldehyde (0.1 g) in hydrochloric acid (10N, 5 ml), water (10 ml) and ethanol (10 ml), were boiled under reflux for 1 hour; the solution became red-brown, but no precipitate appeared. The solution was made alkaline with potassium hydroxide (40%) and then extracted continuously with benzene for 14 hours. The extract was distilled to dryness and the residue dissolved in benzene. This solution was purified on an alumina column. Four bands separated.

1) A very pale yellow band, which fluoresced yellow in U.V. light, was eluted with benzene-ether (4:1). Removal of the eluant gave a very small amount of yellow solid.

2) A pale yellow band, which fluoresced blue in U.V. light, was eluted with benzene-ether (3:2). Removal of the eluant gave a very small amount of yellow material.

3) An orange band was eluted with benzene-ether (3:7), giving a deep yellow solution. Removal of the solvent gave a very small amount of orange material.

4) An orange band was eluted with ether-ethanol (1:1), giving a red solution. Removal of the eluant gave a red solid, which

crystallised from ethanol as red granules. This solid sublimes as orange needles, M.P. 280-285°C (decomposition).

The substance prepared by Borsche from these reactants melted at 245°C.

Preparation of 2-acetylquinoxaline.

cf. Barker, Thesis, p. 127.

I. cf. Henseke & Bähner, Ber., 91, 1605 (1958).

Quinoxaline-2-aldehyde (2.5 g) was dissolved in anhydrous chloroform (15 ml) and the solution was cooled to 0°C. To the solution was added an ethereal solution (200 ml) of diazomethane (from nitroso-N-methylurea (12 g)). The solution was allowed to stand at room temperature for 2 days. A yellow solid separated from solution. The excess diazomethane was destroyed with very dilute formic acid. The mixture was filtered.

Yield of solid 0.55 g.

$M.P._{crude}$ 169.5-172°C (decomposition).

M.P. of the compound, $C_{10}H_7N_2O$, obtained by Barker 173-175°C.

The filtrate was distilled to dryness, giving a red-brown oil, which crystallised from a mixture of benzene-light petroleum (40/60) (1:1) as colourless needles.

Yield 0.275 g.

M.P. 74-77°C (with decomposition).

II. cf. Campbell and Kerwin, J.A.C.S., 68, 1837 (1946).

A. Preparation of ethyl 2-quinoxaloyl acetate.

To a mixture of sodium ethoxide (2.7 g) in dry toluene (20 ml) were added anhydrous ethyl acetate (3.4 g) and ethyl quinoxaline-2-carboxylate (4.65 g). The mixture was heated with constant stirring, at 120°C for 6 hours. After cooling, the mixture was poured into water (100 ml) and a yellow solid separated. The solid was filtered off and the toluene was separated from the aqueous layer of the filtrate. The yellow solid was suspended in this aqueous solution, which was then acidified to Congo Red with hydrochloric acid, and extracted continuously with ether for 18 hours. From the ether extract was obtained a brown oil, which crystallised from methanol, after treatment with charcoal, as yellow rods.

Yield 4.3 g.

M.P. 63-65°C.

Analysis. Found : C, 63.5; H, 4.6; N, 11.7%

$C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 5.0; N, 11.5%

B. Preparation of 2-acetylquinoxaline.

Ethyl 2-quinoxaloyl acetate (3 g) in sulphuric acid (4 ml) and water (100 ml), was heated on a steam-bath for 7 hours. The acid solution was decanted from a small amount of brown oil, and basified with potassium hydroxide (40%). The solution was extracted continuously with ether for 4 hours. From the extract was obtained a cream solid, which crystallised from light petroleum

(60/80), after treatment with charcoal, as white needles.

Yield 625 mg.

M.P. 74-75°C.

Investigation of the action of dilute hydrochloric acid on 2-acetylquinoxaline.

2-Acetylquinoxaline (0.5 g) in hydrochloric acid (10N, 5 ml), ethanol (10 ml) and water (10 ml), was boiled under reflux for 6 hours. The solution was made alkaline with potassium hydroxide (40%) and extracted continuously with ether for 16 hours. Removal of the ether gave pale yellow crystals, M.P. 67-71°C, which were dissolved in benzene and the solution was purified on an alumina column. Three bands separated.

1) A colourless band, which fluoresced blue in U.V. light, was eluted with benzene. Removal of the solvent gave a very small amount of material.

2) A yellow band, without fluorescence in U.V. light, was eluted with benzene. Removal of the eluant gave colourless rods.

M.P. 73-74°C.

Mixed M.P. with starting material 73-75°C.

Yield of 2-acetylquinoxaline 200 mg.

3) A yellow band, which fluoresced green in U.V. light, was eluted with benzene-ether (4:1). Removal of the eluant gave a yellow solid which crystallised from light petroleum, as colourless rods.

M.P. 73-75°C.

Mixed M.P. with starting material 73-75°C.

Yield of 2-acetylquinoxaline 100 mg.

Total recovery of 2-acetylquinoxaline is 300 mg.

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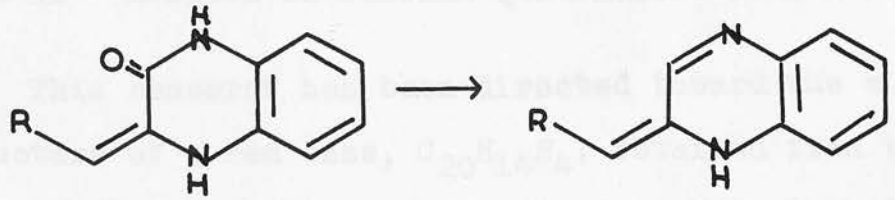
SUMMARY

Part I Syntheses in the Quinoxaline Series.

Several α-hydroxy nitrogen heterocyclic bases have been treated with an equimolecular mixture of phosphorus oxychloride and water.

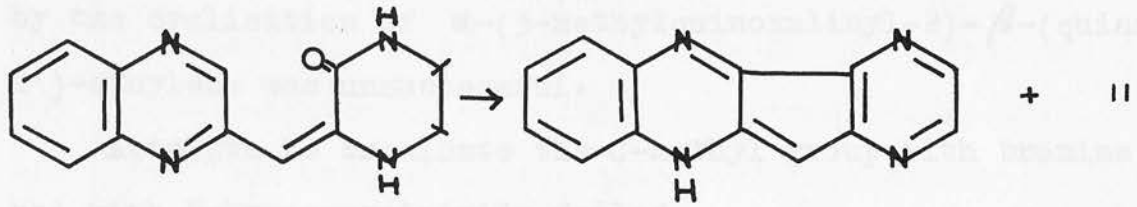
Simple α-hydroxyquinoxalines, acridone, and phenanthridone are converted to the corresponding chloro derivatives by this mixture. The mixture is a less efficient chlorinating agent than phosphorus oxychloride itself.

Derivatives of methin-(2'-(3'-keto)tetrahydroquinoxaline) I are converted to the corresponding methin-(2'-dihydroquinoxaline) bases II in good yield by this mixture.



I II

Methin-(2-pyrazinyl)-(2'-dihydroquinoxaline) (II - R = 2-pyrazinyl) and a yellow base, $C_{13}H_8N_4$, for which the structure 10H-pyrazino(2',3':3,4)cyclopenta(b)quinoxaline III has been suggested, are obtained when methin-(2-quinoxalinyl)-(2'-(3'-keto) piperazine) IV is treated with the mixture.



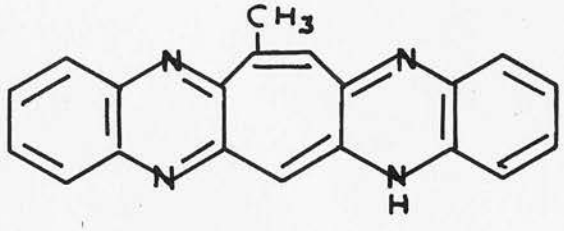
IV III

Two bases are also obtained when methin-(2-pyrazinyl)-(2'-(3'-keto)piperazine) is treated with the mixture. Structures have been proposed for these bases.

Attempts to synthesise 1'-ketocyclopenta(4',5':2,3)quinoxaline, the starting material for a proposed synthesis of 10H-pyrazino (2',3':3,4)cyclopenta(b)quinoxaline III, have been made.

Part II Studies on Certain Quinoxaline Derivatives.

This research has been directed toward the elucidation of the structure of a red base, $C_{20}H_{14}N_4$, obtained from the reaction of 2-acetyl-3-methylquinoxaline with 2-methylquinoxaline in dilute acid. A structure, quinoxalo(2',3':8,9)benzo(2,3)-7-methyl-tropazine V, had been proposed for this base.



V

An attempt to prepare quinoxalo(2',3':8,9)benzo(2,3)tropazine by the cyclisation of α-(3-methylquinoxalinyl-2)-β-(quinoxalinyl-2')-ethylene was unsuccessful.

Attempts to brominate the C-methyl group with bromine directly and with N-bromosuccinimide failed.

Attempted oxidations of the C-methyl group with selenium dioxide, and of the base with hydrogen peroxide, ozone and osmium tetroxide failed to give identifiable products. Chromic acid oxidation, however, gave a ketone, $C_{11}H_8$ or $_9N_2O$, for which a structure has been tentatively advanced.

Investigations into the method of formation of the base have ruled out the previously proposed method of formation.

Doubt has been cast on the proposed structure of the base and preliminary investigations of a similar bromo-substituted red base have been made.

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Figures 1, 13, and 18 are taken from Dr. P.W. Barker's thesis (University of London, 1956).

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N.W.A.T.