

STUDIES IN THE
ACRIDINE SERIES

by

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TO MY MOTHER

P R E F A C E

In the general form of this thesis the example of Haydn rather than Bradshaw has been followed.

The Introduction consists of a short review of polychromism and provides a background against which a particular example, discovered by Kehrmann and Matusinsky in 1912, may be seen. It was one observation made by these authors which formed the starting point for the work to be described here.

The "Main Thesis" is in four sections. The first subject of the EXPOSITION is 2-hydroxy-5-phenylacridine; the main theme is its polychromism. The transition to the second is effected by a hypothesis. The second subject is 1:1'-methylene-bis-2-hydroxyacridine.

The DEVELOPMENT section starts with a short review of hydrogen bonding, leads to the prediction of a new type of thermochromism and ends with a short general review of this subject.

In the RECAPITULATION the first and second subjects are reconsidered in the light of new features which arose in the DEVELOPMENT.

In the CODA some wider implications are considered of what has by now emerged as the main theme of the thesis. (A theme which originated in the transition paragraphs of the EXPOSITION.)

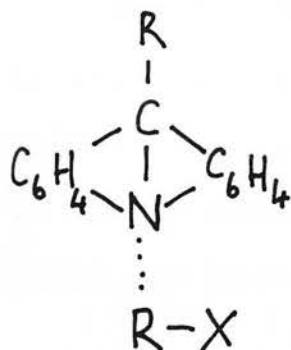
All the important experimental results are to be found in the Main Thesis, but an "Experimental" section has been added which includes details for the preparation of the compounds discussed and of some physical techniques which were used.

CONTENTS

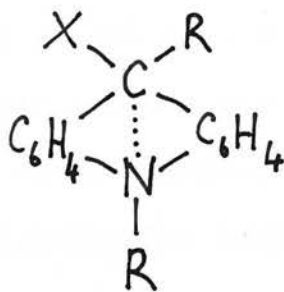
	Page
Preface	
Introduction	1
<hr/>	
<u>Section 1.</u> (Exposition)	
1st Subject	11
Transition	24
2nd Subject	26
<u>Section 2.</u> (Development)	
1. The Hydrogen Bond	37
2. Proton Transfer Thermochromism	53
3. Re-examination of 2-Hydroxy- 5-phenylacridine	57
4. The Preparation of Further Thermochromic Compounds ...	62
5. Thermochromism	72
<u>Section 3.</u> (Recapitulation)	
2nd Subject	79
Transition	84
1st Subject	86
<u>Section 4.</u> (Coda)	92
<hr/>	
Experimental Details	98
Author's Acknowledgments	116.
<hr/>	

INTRODUCTION

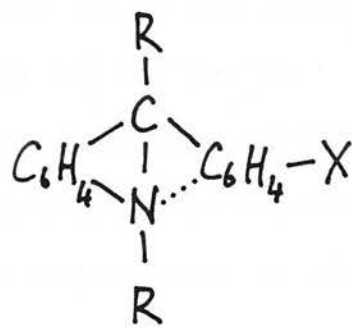
In the Annual Reports on the Progress of Chemistry for 1918 under the heading "chromoisomerism" the following passage may be found: "..... but it seems time to protest against one halfpennyworth of practice to this intolerable deal of theory, and to demand something more than assertion in proof of the constitutional formulae which are drawn up so lavishly." It is fairly clear that the reviewer is referring principally to Hantzsch who originated the term "chromoisomeric" to describe compounds which exist in two or more solid modifications with distinctly different colours. Hantzsch (1) supposed that all such cases are to be explained in terms of isomerism and he proposed many structures (for example A, B and C to explain the frequent occurrence of green, red and yellow forms in the salts of 5-phenylacridine) which on the present day theories of valency must be discarded.



A



B



C

Hantzsch, however, was right in looking for an explanation and his reviewers were wrong where they dismissed the phenomena as being "merely polymorphism" (2).

Polymorphism perhaps; but where, as in some cases, the colour change is pronounced - say from green to red - this is hardly a sufficient explanation.

In the sequel the purely descriptive term polychromism will be used, in place of Hantzsch's "chromoisomerism", to avoid the implication that isomerism is necessarily involved.

We know that electronic absorption is not exclusively a function of molecular structure; it may be affected by the polar environment of the molecule and also by more specific intermolecular forces such as hydrogen bonding or charge transfer interaction. A crystal lattice may be regarded as a structure of intermolecular interactions; to change the lattice is to change these interactions and, in so far as some of these may influence light absorption, to change the colour.

But the problem remains. If there is no difference in the structure or conformation of the molecules in different polychromic states then there must be a difference in one or other of those forms of intermolecular interaction which can have a significant effect on colour and it should

be possible to specify which of these is involved.

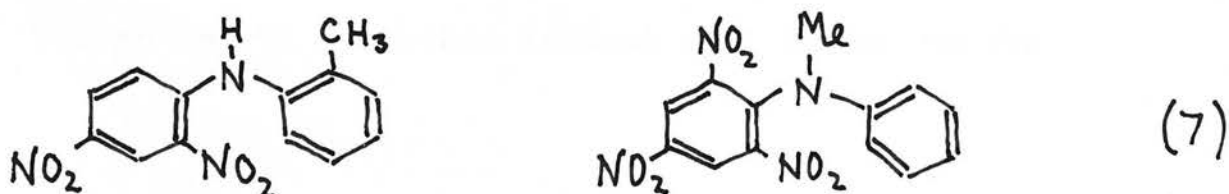
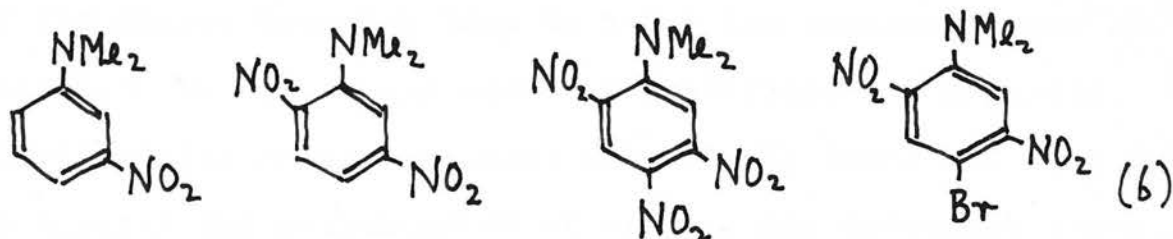
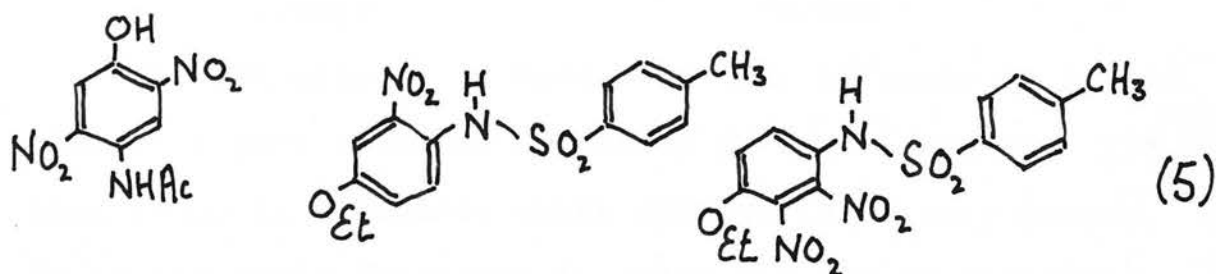
Most polychromic organic compounds for which no evident explanation in terms of isomerism exists, are either salts or aromatic nitro-compounds (usually polynitro-compounds and usually phenols or amines). The origin of polychromism in these cases has not been fully established, but it may well be that comparatively recent work on charge transfer phenomena will provide at least a partial answer. Charge transfer might be expected to occur in the solid state with both of these classes of compounds.

It is well known that aromatic polynitro-compounds can form coloured molecular compounds with aromatic hydrocarbons, amines, phenols etc. The formation of such compounds has been attributed to charge transfer interaction between the components, one of which must be a Lewis acid (e.g. a nitro-compound) and the other a Lewis base (e.g. an aromatic hydrocarbon or amine) (3 a - e).

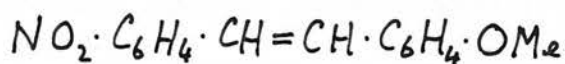
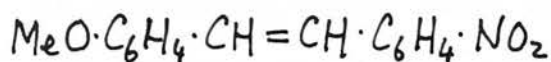
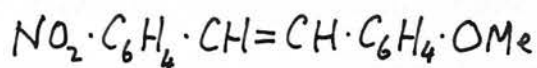
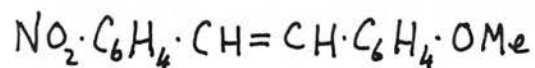
This type of interaction gives rise to a new absorption band, which has been called the charge transfer spectrum, in the visible or near ultra-violet regions. It appears to be due to the occurrence of electronic transitions between rather than within molecules. Charge transfer spectra are always broad and without fine structure. This

is probably due (3a) to the weakness of the charge transfer bonding ($\frac{1}{2}$ - 4 K.cals./mole (4)) allowing thermal vibration to provide a considerable range of displacements and orientations between the interacting groups. If the energy required for these intermolecular transitions does indeed depend upon the orientation of the interacting groups in the crystal - and this seems probable - then the colour of the solid will be a function of crystal structure. Thus where a compound, which shows charge transfer interaction in the solid, is polymorphic it will in general be polychromic.

Some examples of polychromic compounds in which the phenomenon may be due to charge transfer are given below:



This charge transfer hypothesis for polychromism must be regarded as a more modern version of a theory put forward by Pfeiffer (8) as early as 1915 in terms of residual valency. He proposed that the orange and yellow forms of nitromethoxystilbenes result from the orientations A and B respectively in the solids.



A

B

Orange

Yellow

No work appears to have been done in order to decide whether charge transfer can occur in organic salts: its occurrence in inorganic salts appears to be very common. It is too early therefore to judge whether an extension of the charge transfer idea to cover the numerous cases of polychromism in organic salts is justifiable. A purely electrostatic theory has been proposed by Lucas and Kemp (9) to explain the polychromism of organic and inorganic salts. Their general conclusion is that the electronic absorption of an ion in a crystal lattice will depend on its

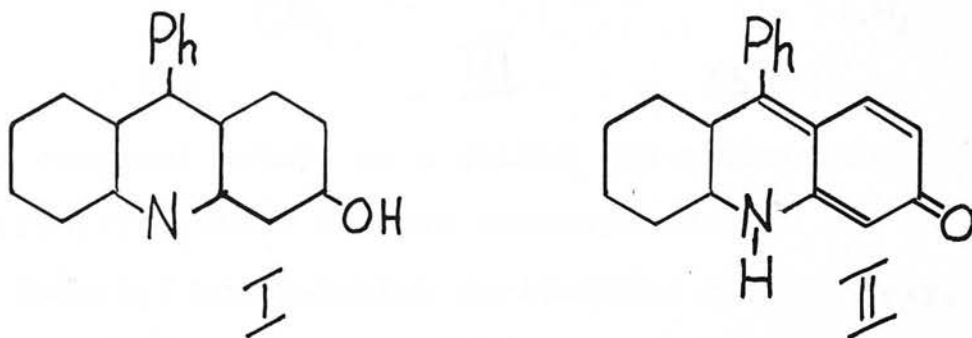
electrostatic environment, created by the surrounding ions of opposite charge, and that this will depend on the crystal structure.

Although at present it is not possible to decide which, if any, of these theories is true, one thing is clear: where a compound exists in more than one differently coloured solid form it is not possible to conclude directly from this that different molecular structures must be assigned to these forms. On the other hand a knowledge of the general classes of compounds which show polychromism and an appreciation of the factors which may influence light absorption in a crystal will help in deciding, in specific cases, whether it is worth looking for an explanation in terms of isomerism. For example if the compound in question is a salt or a polynitro-compound, or indeed if it is a betaine or contains both Lewis acid and Lewis base functions, any "isomeric" theory will be somewhat unconvincing. But the converse also is true.

According to Kehrman and Matusinsky (10) 2-hydroxy-5-phenylacridine crystallises from hot benzene as fine yellow needles with a melting point of 264°C . On crystallising slowly from cold benzene red prisms are obtained which may be converted to the yellow form by heating at 135°C . The red modification is formed from the yellow slowly on

standing and rapidly by crushing and powdering. From these observations it was concluded that the yellow is the form stable at higher temperatures and the red the lower temperature stable form.

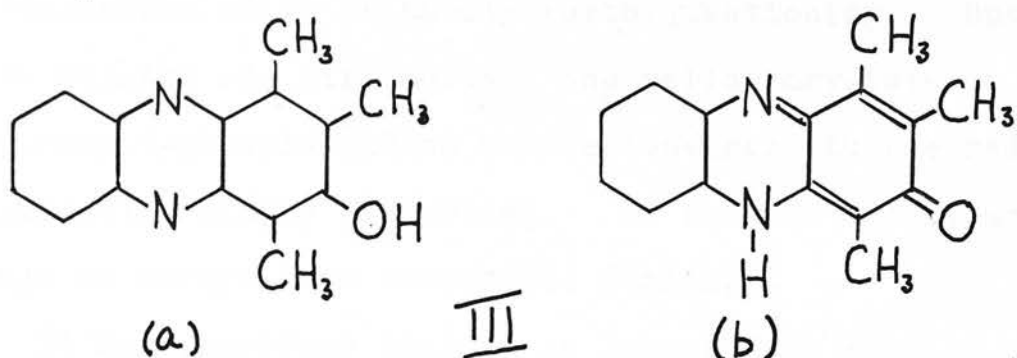
In view of the difference of more than 100°C between the melting points of the two forms and in view of their strong difference in colour, Kehrmann suggested that this was a case of tautomerism between the structures (I) and (II).



Neither argument is very convincing and the great ease with which the red modification can be formed from the yellow would seem to weigh heavily in favour of an explanation in terms of polymorphism. But if this example is considered in the context of polychromism in general and in the light of work carried out more recently by John (11) and by Albert and Short (12) on the tautomerism of analogous compounds, Kehrmann's theory becomes distinctly more probable.

In the first place 2-hydroxy-5-phenylacridine does not fall into any of the general classes of polychromic compounds:

this appears to be the only published example of a polychromic free acridine (although polychromism in acridine salts is very common). On the other hand John has studied a group of 2-hydroxy-phenazine derivatives of which (III a or b) is an example.



This compound exists in a yellow and a deep violet modification, these colours corresponding to the colours of the O-Methyl and N-Methyl derivatives respectively. In solution 1:3:4 trimethyl-2-hydroxyphenazine is present as an equilibrium mixture of the structures (IIIa) and (IIIb). John concluded that the yellow and violet modifications were to be identified with (IIIa) and (IIIb) respectively. In this case however interconversion between the solids can only be brought about by recrystallising from solution or by heating to 135°C at which temperature sublimation can be seen to occur.

Albert and Short (12) have shown that 2-hydroxyacridine also is tautomeric (although not polychromic) existing in

solution as an equilibrium mixture of lactim and lactam structures analogous to (I) and (II). Here the lactim structure is yellow and the lactam structure red.

Kehrmann and Matusinsky's theory might now seem to be so reasonable as to be hardly worth questioning. But there remains one difficulty: the yellow crystals of 2-hydroxy-5-phenylacridine can be converted to the red modification simply by rubbing. If this is a tautomeric change it occurs with remarkable facility.

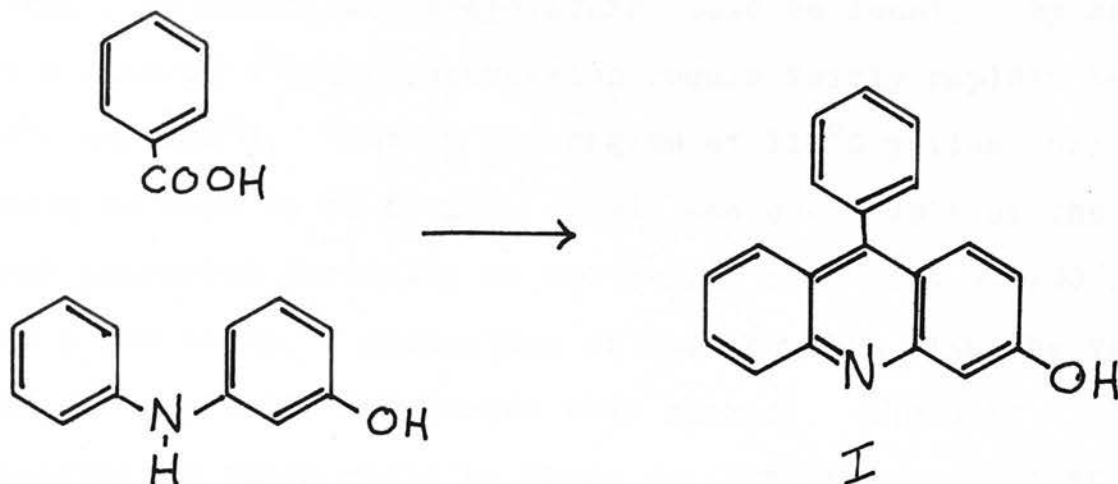
It was therefore decided to investigate more thoroughly the colour changes of 2-hydroxy-5-phenylacridine.

References:

- (1) Hantzsch Ber. 1911 44 1783, Ber. 1916 49 2169
- (2) Ann. Reports 1911 8 57
- (3) (a) Quart. Rev. 1954 8 437-9
(b) Robertson Organic Crystals and Molecules (1953) 249
(c) Mulliken J.Amer.Chem.Soc. 1950 72 600,
ibid. 1952 74 811,
J. Phys. Chem. 1952 56 801.
(d) Weiss J. 1942 245.
(e) Woodward J.Amer.Chem.Soc. 1942 64 3058
- (4) (a) Briegleb Z. phys. Chem. 1936 B 31 58.
(b) Briegleb and Kambeitz ibid. 1936 B 32 305.
- (5) Reverdin and Roethlisberger H.C.A. 1922 5 300-14.
- (6) Forster and W. Coulson J. 1922 121 1988-97.
- (7) H. Kaufmann (1920) Beziehungen Zwischen Physikalischen Eigenschaften und Chemischer Konstitution. P 300.
- (8) Pfeiffer Ber. 1915 48 1777.
- (9) Lucas and Kemp J.Amer.Chem.Soc. 1921 43 1654.
- (10) Kehrman and Matuzinsky Ber. 1912 45 3498.
- (11) John Angew. Chem. 1947 59 188.
- (12) Albert and Short J. 1945 760.

SECTION I (EXPOSITION) 1st SUBJECT.

A sample of 2-hydroxy-5-phenylacridine was prepared using Bernthsen's reaction (1).



It was confirmed that 2-hydroxy-5-phenylacridine exists in a yellow and a red form; that the yellow form may be obtained by recrystallisation from benzene; that this on rubbing is converted to a red powder, and that the red powder reverts to the yellow form on heating.

The other observations made by Kehrmann and Matusinsky on this subject are more doubtful. Thus while a distinct reddening was observed in one sample of the yellow form left standing in the light over a period of months, no such change occurred in another sample kept in the dark for a similar time. The red prisms which were reported to crystallise from cold benzene could not be obtained.

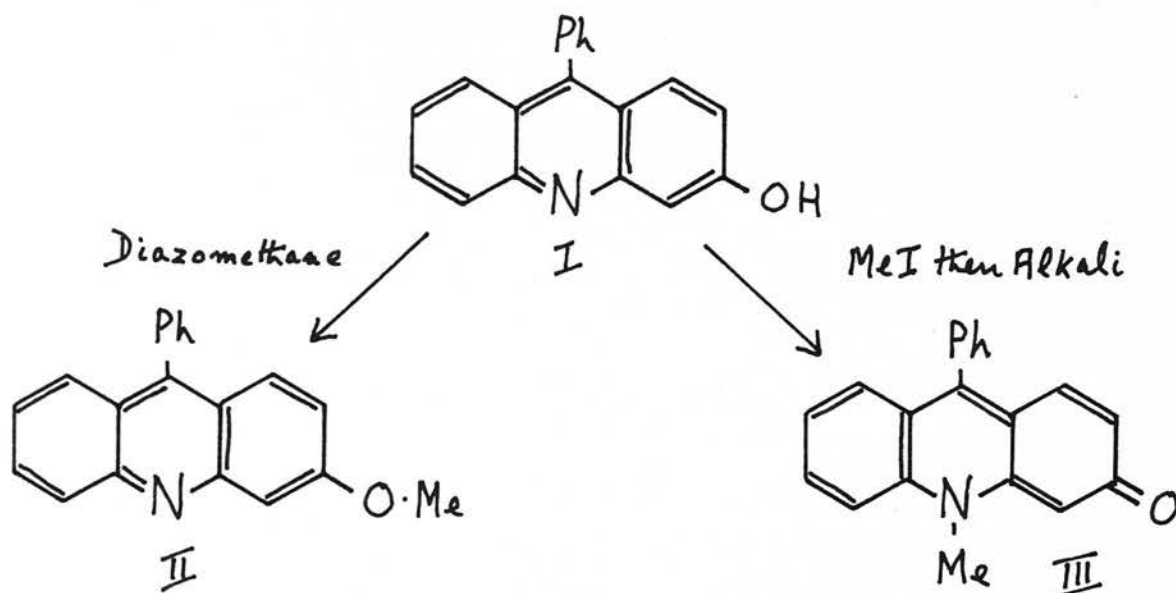
The red \rightarrow yellow change, which takes place on heating,

was examined under a hot-stage microscope in an attempt to find the transition temperature. This must exist if Kehrman's conclusion is correct, that the red is the lower temperature and the yellow the higher temperature stable form. No transition temperature could be found. By heating at a rate of $4^{\circ}\text{C}/\text{min}$. conversion occurs fairly rapidly between 130°C and 140°C . But in the region of 110°C yellow needles could be seen to be forming slowly and one sample of the red form converted partially to the yellow when left at 100°C for a few weeks. Nucleation of the red form with the yellow did not appear to accelerate this change. The only conclusions which could be drawn at this stage were that the transition temperature between the yellow and red modifications of 2-hydroxy-5-phenylacridine - if it exists - lies between room temperature and 100°C and that the temperature of 135°C , quoted by Kehrman and Matusinsky, is of no particular significance.

2-hydroxy-5-phenylacridine shows marked differences in colour in different solvents. Dilute solutions in cyclohexane ether or acetone, for example, are yellow with a blue fluorescence. In alcohol or chloroform the colour is deep orange. This behaviour is similar to that of 2-hydroxyacridine where it has been shown (2) that the colour changes are due to the existence of a tautomeric equilibrium between lactim

and lactam structures the position of which depends on the solvent.

The O-methyl (II) and N-methyl (III) derivatives of 2-hydroxy-5-phenylacridine were prepared as shown below, thus fixing the lactim and lactam structures of the molecule.



The ultra-violet spectra of these were determined both in cyclohexane and absolute alcohol. They are shown in Figs. 1 and 2.

The ultra-violet spectrum of 2-hydroxy-5-phenylacridine was determined in three different solvents: cyclohexane, absolute alcohol and 20% aq. alcohol. These are shown in Fig. 3.

It will be seen that the change of solvent has little effect on the visible absorption of the methylated compounds. The absorption of the parent compound is altered considerably

Fig. 1

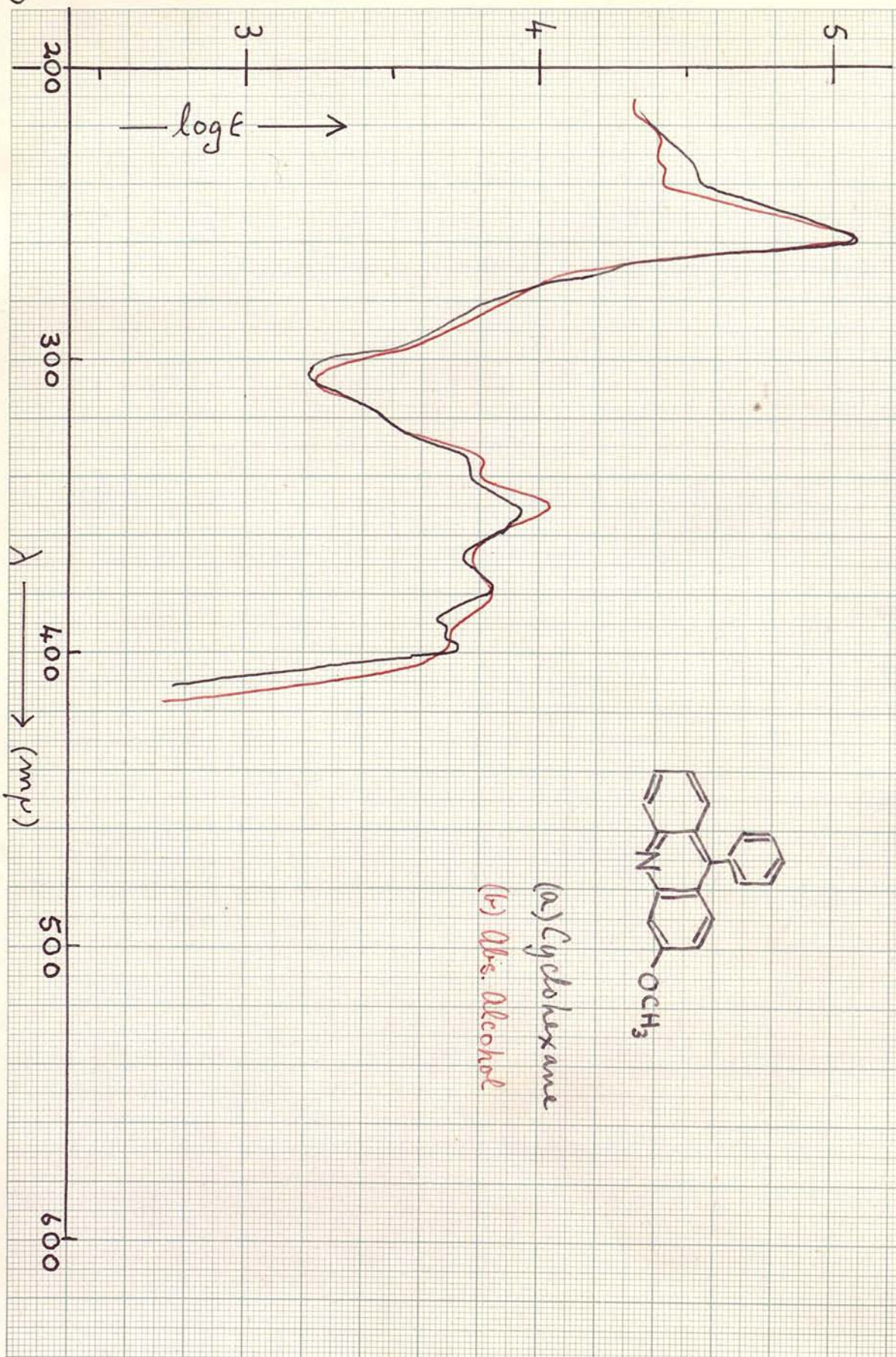


Fig. 2

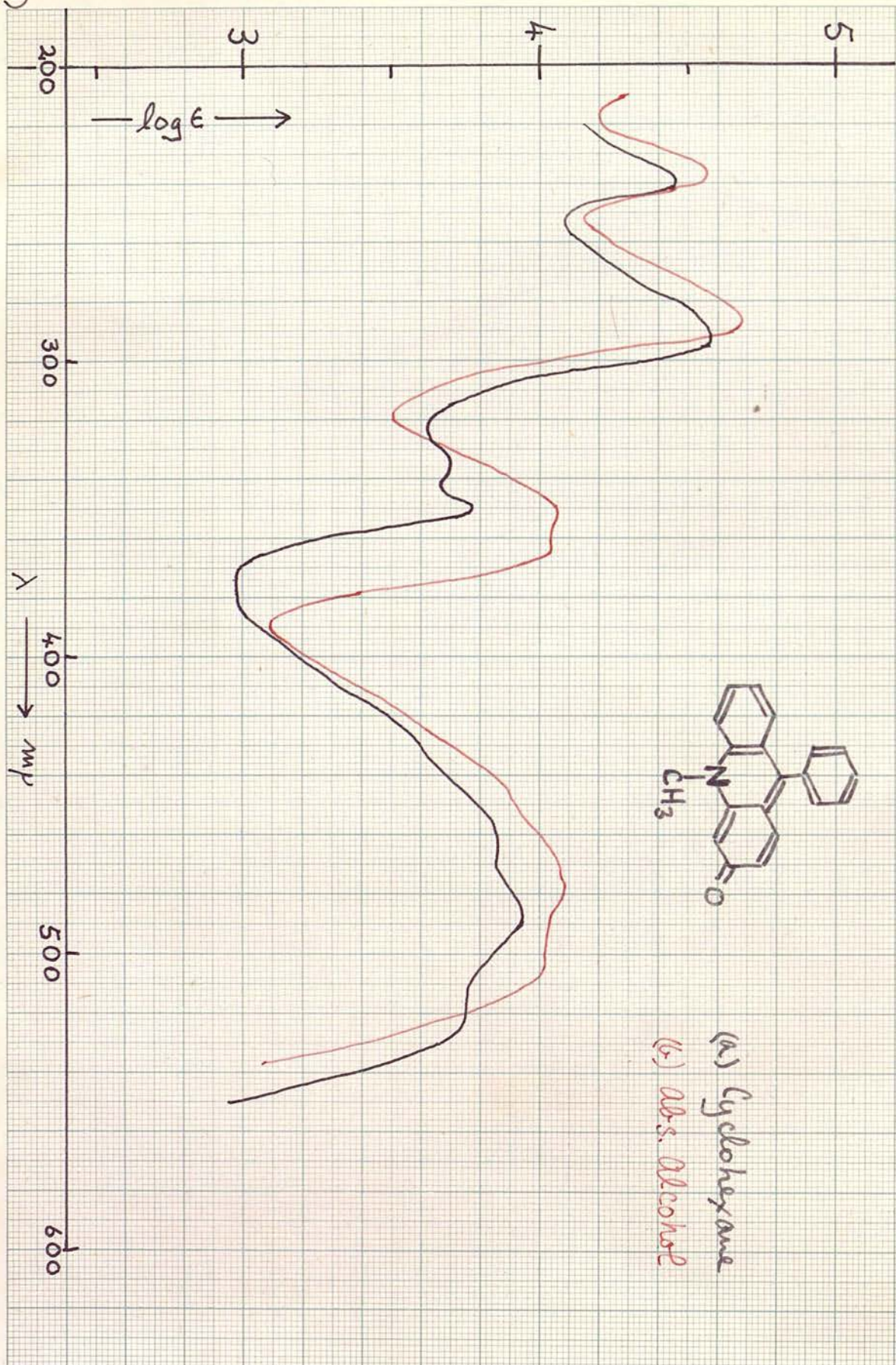
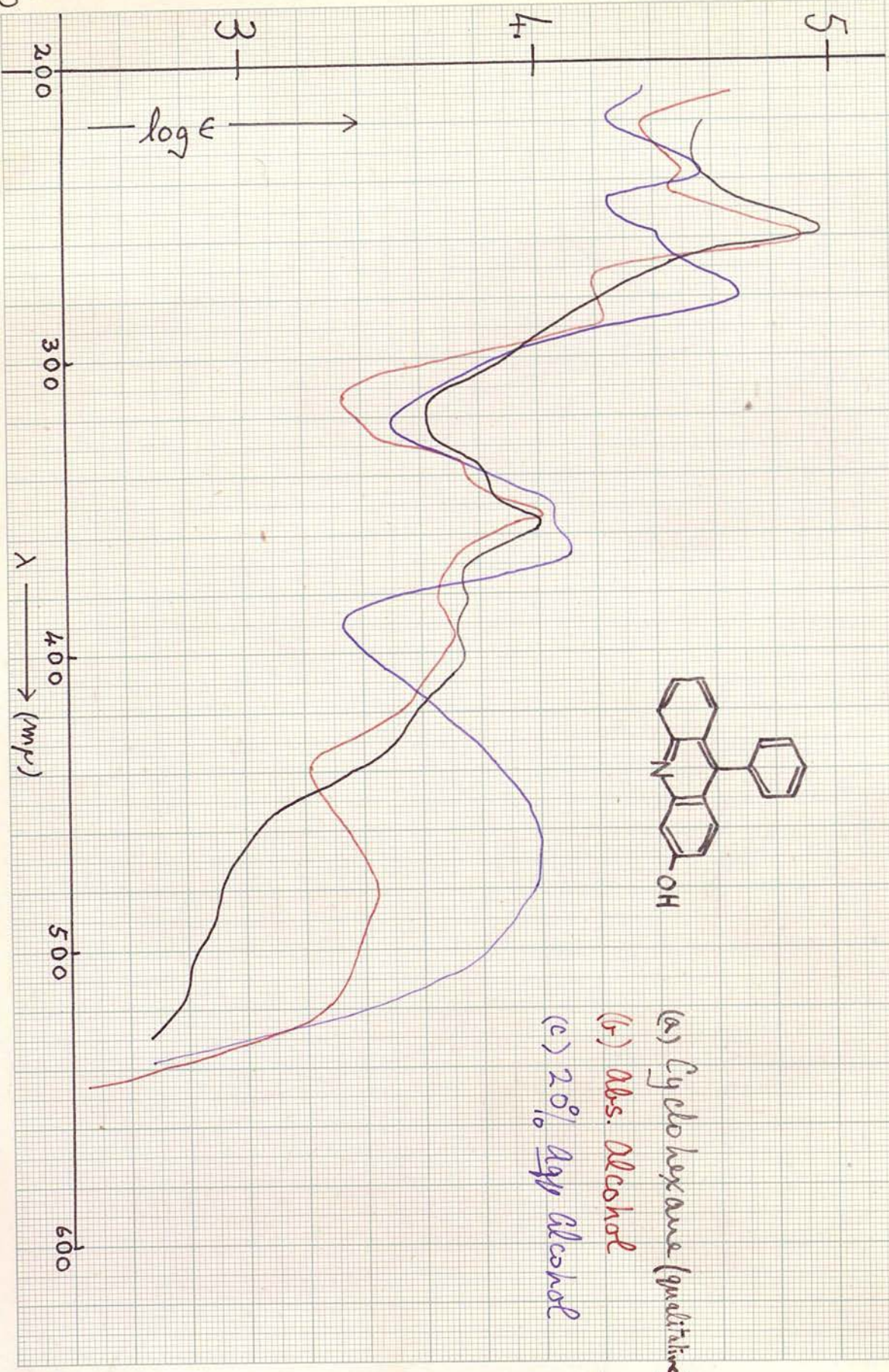


Fig. 3



on changing from cyclohexane to absolute alcohol: in 20% aq. alcohol the spectrum has changed almost completely. In cyclohexane the spectrum is closely similar to that of the O-methyl compound, showing that here the lactim structure is almost exclusively present. In 20% aq. alcohol the spectrum approximates to that of the N-methyl derivative: here the molecules must be almost entirely in the lactam form. In absolute alcohol both those maxima characteristic of the lactim and those characteristic of the lactam structures are clearly visible: in this case there is evidently a substantial amount of both forms present in the equilibrium mixture.

By comparing the spectra of 2-hydroxy-5-phenylacridine with those of 2-hydroxyacridine (2) it can be seen that the 5-phenyl group has little effect. This is almost certainly due to the steric interference of the hydrogen atoms at positions 4 and 6 of the acridine nucleus with those at the ortho positions of the phenyl substituent forcing the phenyl group out of the plane of the acridine nucleus and so causing both to absorb independently. The absorption maxima for benzene alone (at 240 - 260 $m\mu$) are weak and co-incide with a region of strong absorption in 2-hydroxyacridine. The effect of such steric interference on absorption spectra has been noted elsewhere, for example in the diphenyl series (3).

The closely similar stabilities and the colours of the

lactim and lactam structures, indicated by the absorption spectra in Fig. 3, lend some support to Kehrman's theory. But there is also the further point that the visible absorptions of the methylated compounds are not greatly affected by the change of solvent. This weighs against any theory which attempts to explain the polychromism of the parent compound as being due to a difference in the electrostatic environment of the same structure (lactim or lactam) in two different lattices.

The ultra-violet absorption of 2-hydroxy-5-phenylacridine in solution depends only on the solvent and not on which solid form is used to prepare the solution. If the solids are tautomers then tautomerisation must occur rapidly on solution. This would be expected in any case since the colour of a solution changes immediately on adding excess of another suitable solvent and, as we have seen, such colour changes in solution are due to tautomerism. This means that any final answer to the problem of the polychromism of 2-hydroxy-5-phenylacridine requires a direct study of the solid forms. Attempts were therefore made to obtain ultra-violet spectra from solid films of this compound.

At a fairly high temperature, and under reduced pressure, 2-hydroxy-5-phenylacridine sublimes. The sublimate may be

obtained in the form of a hard red crust. This effect was used to prepare solid samples for examination. A small quantity of the material was heated under high vacuum to a temperature of 180°C close to a clean silica plate maintained at a much lower temperature. In this way a thin film of the red form could be obtained in which the particle size was too small to be visible under the microscope. By heating the plate for one minute at 140°C the red film could be converted to a corresponding yellow film and, provided the change occurred rapidly enough, the crystal size was still below the limits of a low powered microscope. From these films satisfactory qualitative spectra were obtained in which the absorption maxima could be distinguished clearly. A pair of such curves is shown in fig. 4(a) and (b). Curve (a) was obtained from the film before and curve (b) after heating at 140°C . We may note the following points:

(1) After the transition from the red to the yellow form an absorption maximum at $480\text{ m}\mu$ has disappeared: this is evidently responsible for the change in colour. The position of this maximum is close to the typical "lactam" peak which can be seen in the spectra of the N-methyl derivative at $490\text{ m}\mu$ (cyclohexane) and $478\text{ m}\mu$ (absolute alcohol).

(2) In both curves there is a maximum at $410\text{ m}\mu$: the intensity of this increases on changing from the red to the

Fig. 4.



yellow form. This absorption is near the first absorption maxima of the O-methyl derivative (380 - 400 $m\mu$ (cyclohexane and absolute alcohol)). The absorption of the N-methyl derivative is low in this region.

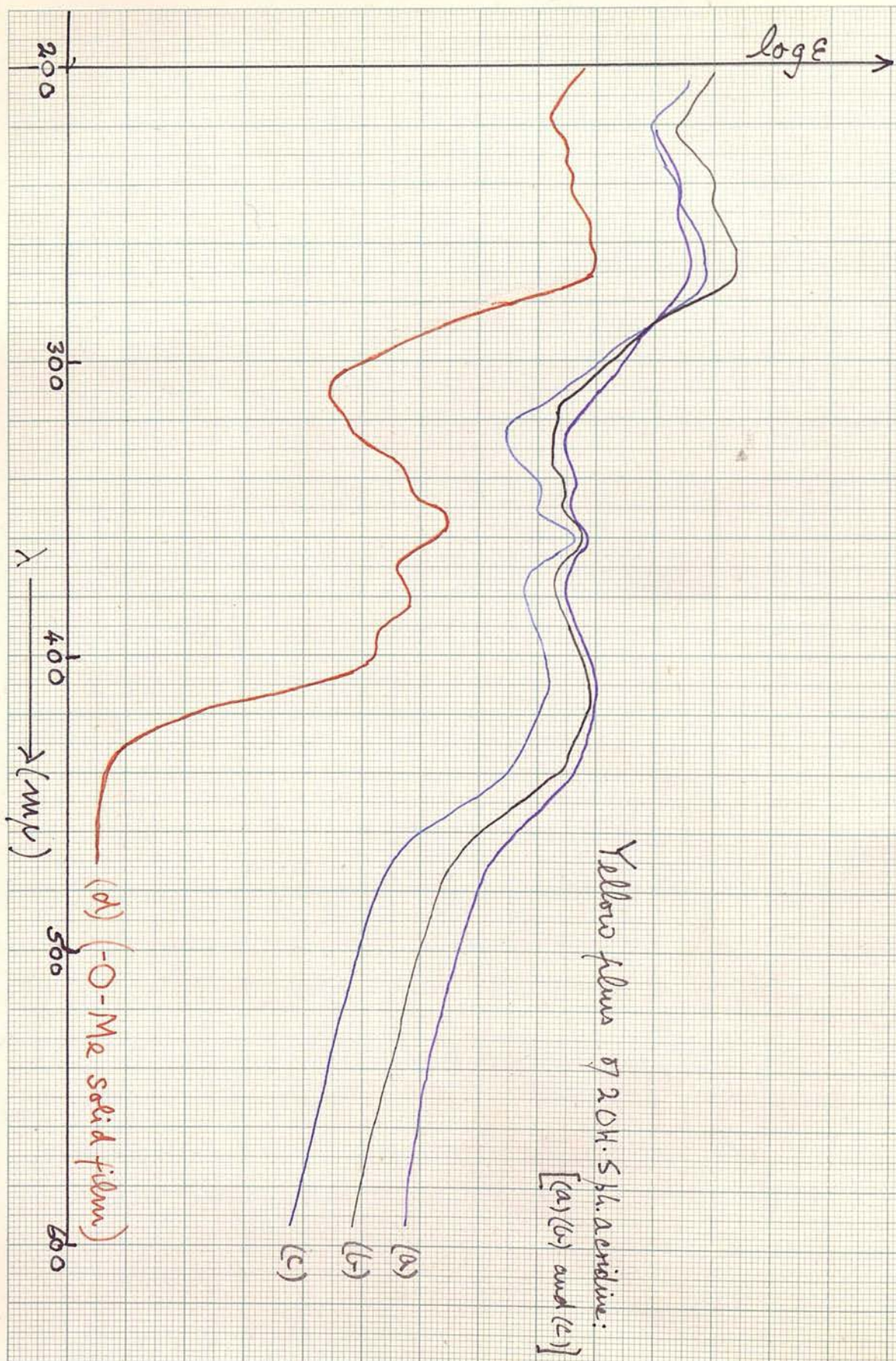
(3) Both the yellow and the red forms show a maximum in their spectra between 358 and 360 $m\mu$ together with a shoulder or smaller maximum at 345 $m\mu$. A feature of this type appears to be common to the lactim and lactam absorptions (see figs. (1) and (2)).

(4) At about 300 $m\mu$ there is a slight inflexion in the absorption curve of the yellow film: this probably corresponds to the similar feature occurring at about 290 $m\mu$ in the spectra of the O-methyl compound. In absolute alcohol this comes at about the same height as the "shoulder" at 335 $m\mu$. The spectrum of the parent compound in cyclohexane shows a similar inflexion.

(5) At 290 $m\mu$ there is a shoulder in the absorption curve obtained from the red film which has disappeared after the transition to the yellow form. This shoulder is in the region of the distinctive "lactam" peak which can be seen in the spectra of the N-methyl derivative at 288 $m\mu$ (absolute alcohol) and 294 $m\mu$ (cyclohexane).

An absorption curve obtained from a thinner film of the red form is shown in fig. 4(c). Two further features can be

Fig. 5



seen here. There is a strong maximum at 268 $m\mu$ near the position of the most intense "lactim" absorption (see fig.(1) and another at 240 which corresponds closely to the position of a typical "lactam" absorption maximum (cf. maximum in "N-methyl" spectra: 240 $m\mu$ in cyclohexane and 238 $m\mu$ in absolute alcohol).

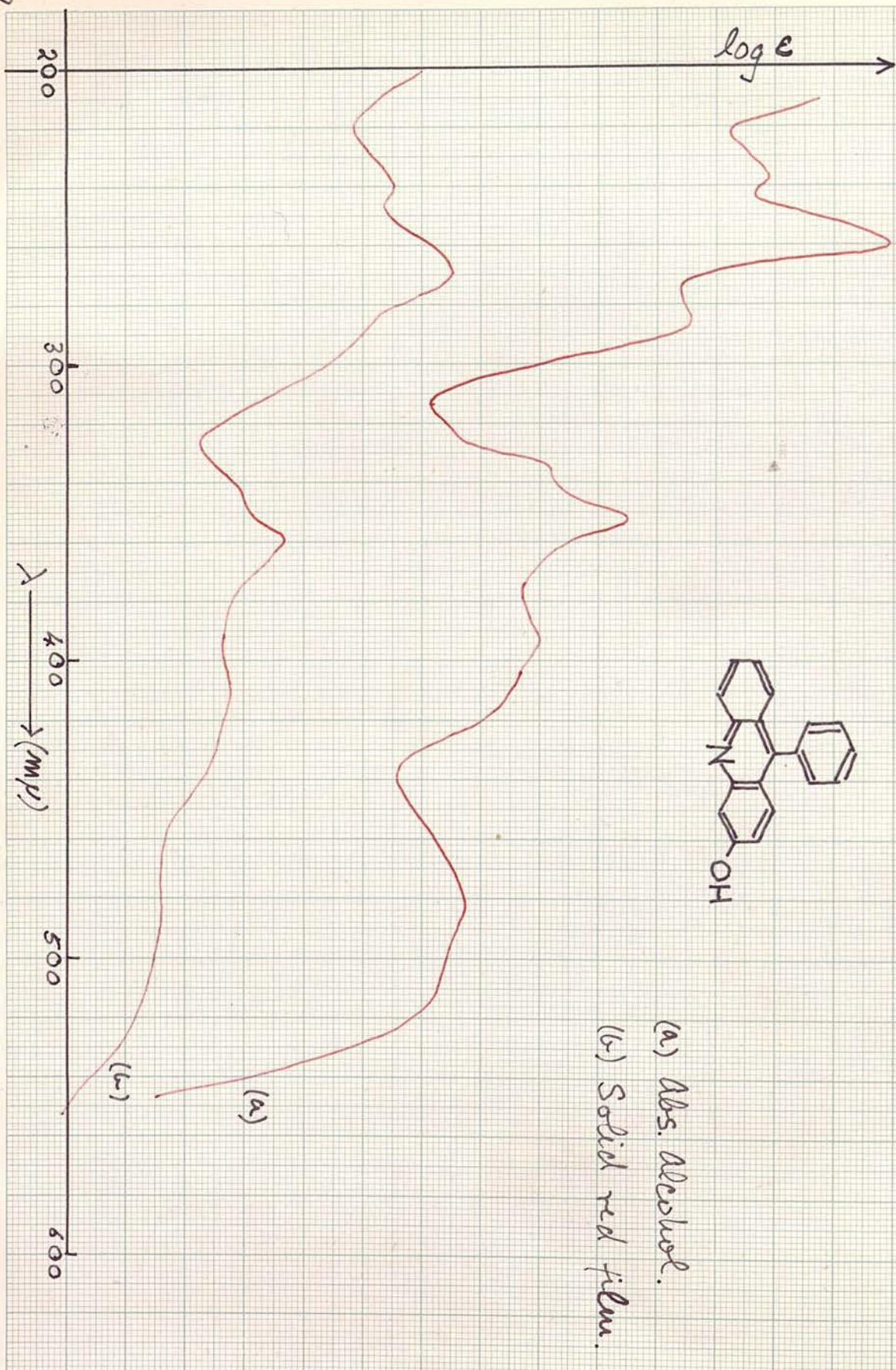
In fig. (5) (a), (b) and (c) another three curves, obtained from thinner films of the yellow form, are shown. Here, in addition to the features already discussed, maxima at about 266 $m\mu$ and shoulders at 240 $m\mu$ may be seen. The features at 240 in the spectra of the solid films are of doubtful significance, however, since although this is the position of an important lactam maximum, there are small shoulders to be seen here in the spectra of the O-methyl compound both in solution (fig.(1)) and in the solid (fig.5d)

The above points may be summarised as follows:

(1) The spectrum of the yellow form of 2-hydroxy-5-phenylacridine resembles that of its O-methyl derivative. (The difference in the region 400 - 450 will be discussed later.)

(2) The spectrum of the red form resembles the spectrum of the compound in absolute alcohol. It is "mixed". The seven principal features which can be seen in the spectrum

Fig. 6



in alcohol (at 483, 394, 352, 338, 286, 258 and 238 $m\mu$) have their counterpart in the spectrum of the red solid (at 480, 408, 358, 344, 290, 268 and 240 $m\mu$): and there are no other significant features visible. These two curves are shown together in Fig. 6.

The immediate conclusions to be drawn are:

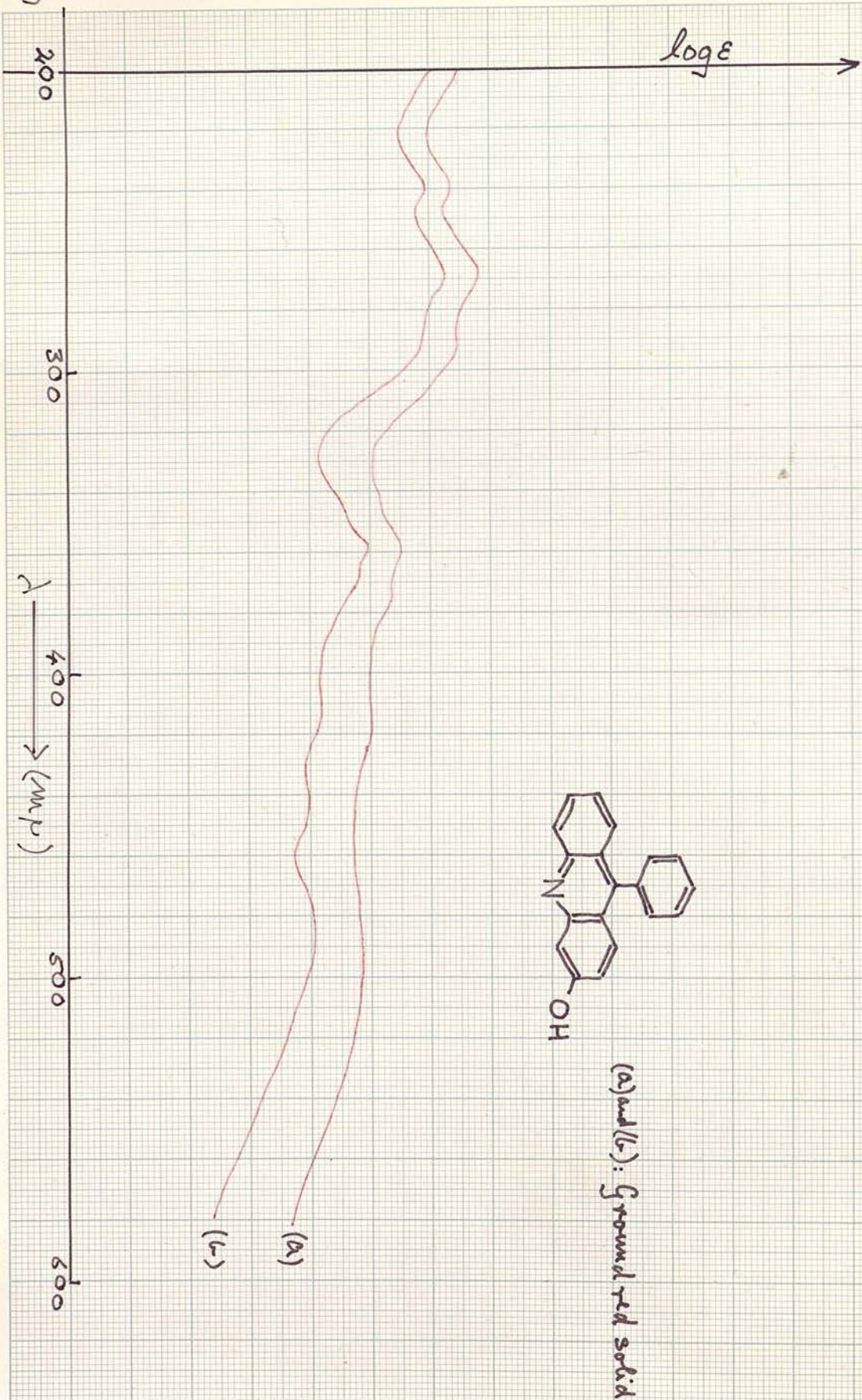
(1) In the yellow form of 2-hydroxy-5-phenylacridine the molecules are principally or entirely in the lactim form:

(2) In the red form of 2-hydroxy-5-phenylacridine both "lactam" and "lactim" molecules are present.

The second conclusion is surprising and might suggest that the sublimed films consist of a mixture of the "true" red and yellow forms. That this is not the case is shown by the two curves in fig. 7 which are the spectra of solid films obtained by grinding the "true" red form (which is obtained by grinding in any case) onto silica plates. The particle size in these films was much greater and the greater resultant scattering has produced a pronounced levelling out of the spectra; but again the "mixed" nature of the absorption is apparent.

It should be stressed that these solid film absorption spectra are essentially qualitative. No reliance can be placed upon the absolute intensities of the absorption maxima since no attempt was made to assess quantitatively the effect of scattering. As already mentioned fig. 7 illustrates the

Fig. 7



(a) and (b): Ground red solid

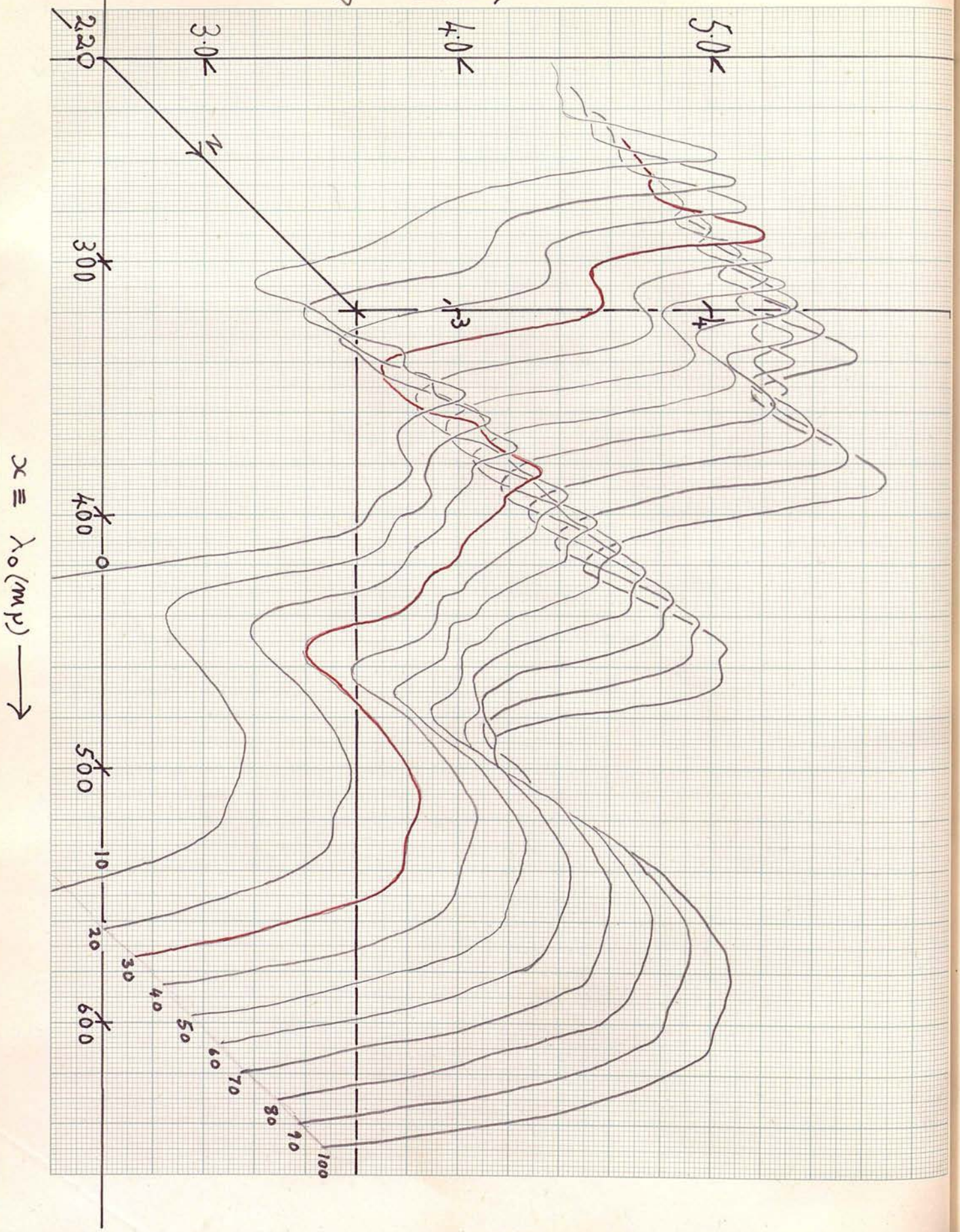
qualitative effect. Scattering may also account for one or two minor deviations in the curves, for example the maximum at 445 $m\mu$ in fig. 7b and the shoulder at 320 $m\mu$ in fig. 5b. But the features which have been discussed have been those common to all the four "yellow" absorption curves (figs. 4 and 5) on the one hand and all the four "red" curves (figs. 4 and 6) on the other. These were obtained from different films in which the particle size, and hence the effect of scattering, should have been different.

Absolute intensities are meaningless, but the relative intensities of maxima, particularly where they are close together, may be of some significance. It is probably significant, for example, that whereas the maxima at 360 $m\mu$ and 410 $m\mu$ in the yellow form (Fig. 4(a)) have approximately the same intensity, in the red form (Fig. 4(b)) the maximum at 410 $m\mu$ is considerably lower. This is consistent with the view that the red form contains a smaller proportion of molecules in the lactim state. It should be possible from the general shape of the curves to obtain some idea of the relative contribution of the lactam and lactim absorption to the spectrum of the red form.

The set of curves in fig. 8 show the purely geometrical effect of adding together the absorption curves of the O-methyl and N-methyl derivatives in different proportions. These have been drawn with their origins displaced diagonally.

Fig. 8

$$y \equiv \log \epsilon_0$$



In this way the set of curves represents a surface, points on which correspond to values of λ , $\log \epsilon$ and Z , where λ is the wavelength, ϵ the molar extinction coefficient and Z the "%age N-methyl contribution" to the composition. (The Z -axis being represented as a 45° diagonal the values on the vertical and horizontal scales allow the λ and $\log \epsilon$ to be read using the formula

$$\lambda = x - Z, \quad \log \epsilon = y - \frac{Z}{100}).$$

These curves show that the differences in the region 400 - 450 $m\mu$ between the absorption of the O-methyl compound and that of the yellow form cannot be accounted for by assuming that in this form there is a small lactam contribution. From the surface it can be seen that no such contribution would give the observed shape. The difference appears to be due to a shift of the peaks, which in the spectra of the O-methyl compound occur at 380 and 395 $m\mu$, to 410 and 440 $m\mu$ respectively. These shifts may be due to hydrogen bonding which can occur in the unmethylated compound. The spectrum in absolute alcohol suggests similar but smaller shifts to 395 and 420 $m\mu$. The cyclohexane spectrum on the other hand has maxima near their "normal" position (381 and 400 $m\mu$) together with a smaller shoulder in the "shifted" position of 430 $m\mu$. This would suggest that in cyclohexane most of the molecules are free but that some (intermolecular) hydrogen

bonding is also taking place. Similar bathochromic shifts of absorption maxima in the near ultra-violet spectrum of β -naphthol have been noted (Nagakura and Gouterman 1957) (4) on the addition, to solutions in n-heptane, of solvents capable of acting as proton acceptors in hydrogen bond formation.

A comparison between the absorption curves of the red form in fig. (4) and the set of curves in fig. 8 suggests that in the red form the lactam structure is present to an extent of between 10% and 40%, and almost certainly less than 50%. The spectrum of 2-hydroxy-5-phenylacridine in absolute alcohol, however, still gives a closer approach to that of the red solid than any of the "synthetic" curves in fig. 8. (Again the region 400 - 440 $m\mu$ cannot fit any mixture of N-methyl and O-methyl absorption curves). This spectrum in absolute alcohol shows that here the lactam structure is present to an extent of 22%. (This figure was calculated by taking the intensity of the visible absorption maximum of the N-methyl compound as the standard of "100% lactam".) Again this suggests a preponderance of lactim over lactam molecules in the red solid. The proportion of lactam molecules may be different in the films obtained by grinding the red powder on to silica plates, but it is probably still less than 50%.

Whatever may be the exact quantitative relationship between the lactam and lactim structures present in the solids, three facts seem to be established:

(1) The colour change which occurs on rubbing the yellow crystals of 2-hydroxy-5-phenylacridine is due to a tautomeric change.

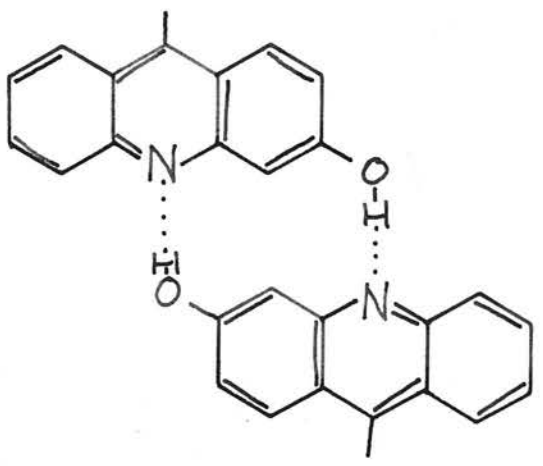
(2) The mobile hydrogen atom is attached to the oxygen in the yellow solid.

(3) In the red solid a substantial proportion of the hydrogen atoms are attached to the nitrogen.

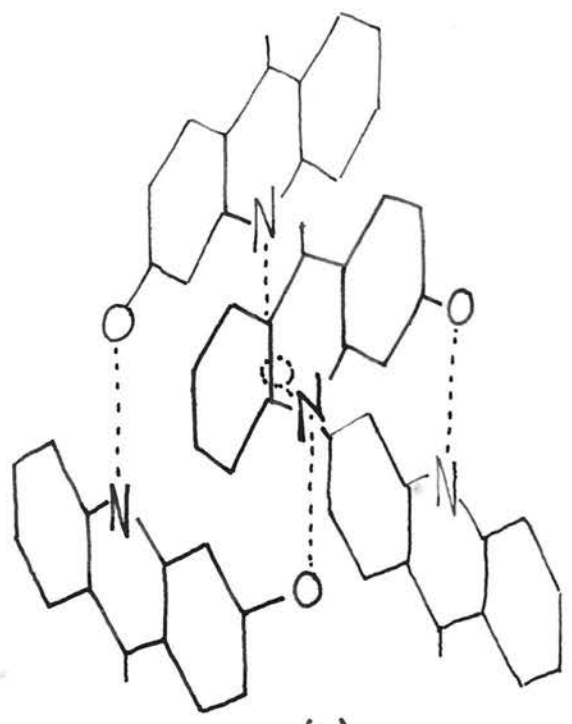
The first two of these conclusions are in accordance with Kehrman's theory: we can now consider seriously the question: "How can this tautomeric change occur so readily in the solid?" But we have found, in the third conclusion, that Kehrman oversimplified the matter by assigning the lactam structure to the red solid and that there is now another question to answer: "How is it that the change is only partial: what is the nature of the red solid that it can contain both lactam and lactim molecules together?"

At this stage a working hypothesis was proposed in an attempt to answer at least the first question. The hypothesis leads to the second subject.

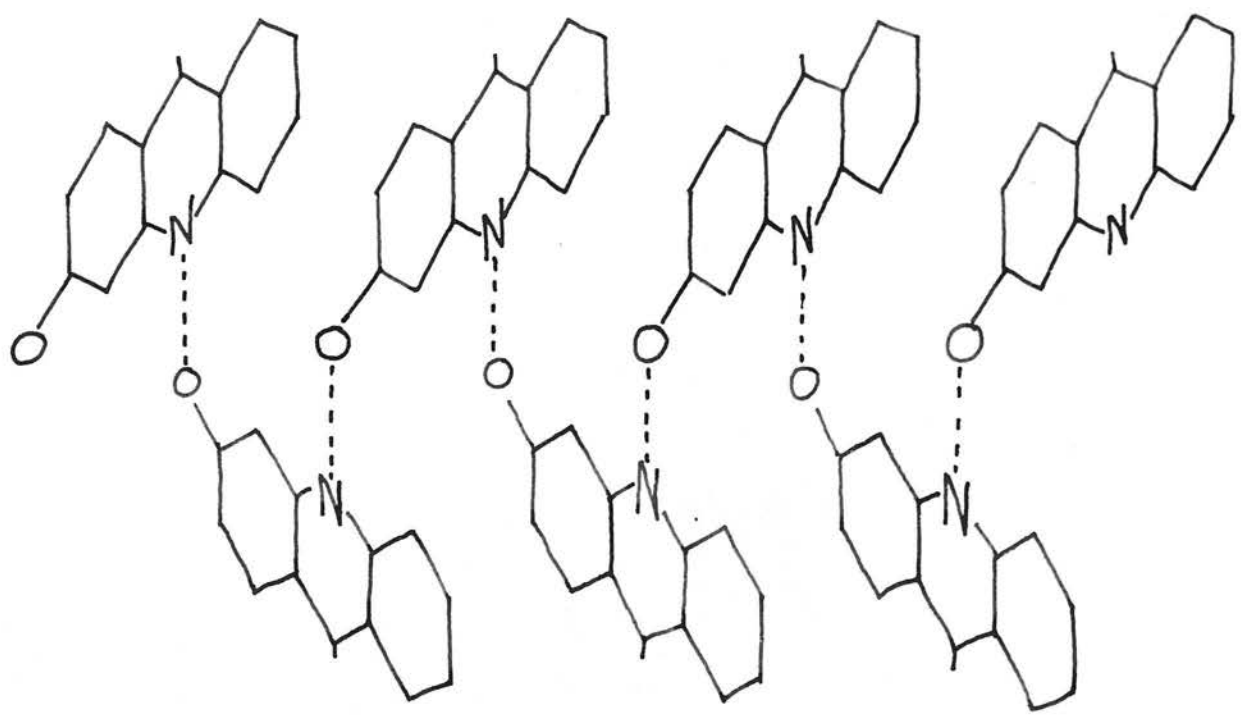
Fig. 9



(a)



(b)



(c)

TRANSITION

Hypothesis: "The yellow crystals of 2-hydroxy-5-phenyl-acridine consist of a lattice of molecules in the lactim form in which all the hydroxyl groups are engaged in short hydrogen bonds with the nitrogen atoms of adjacent molecules. Tautomeric changes can occur in the solid by the transfer of protons along these hydrogen bonds."

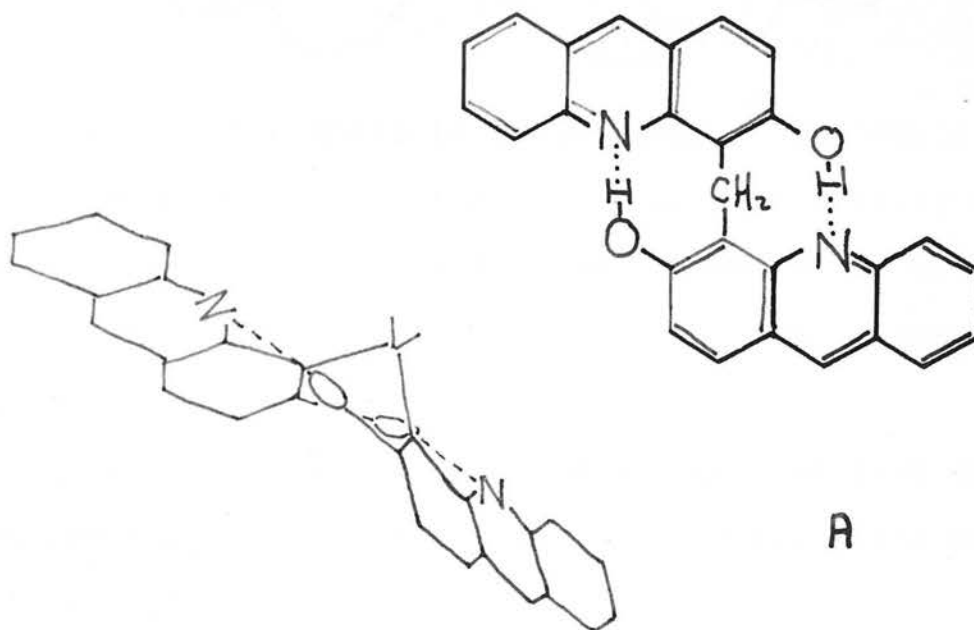
Two possible arrangements are shown in Fig. 9 (b and c). (Fig. 9a illustrates the simplest arrangement to imagine but one which is unlikely to occur in fact since the minimum possible length of the hydrogen bonds must be approximately the same as the distance between the carbon atoms in the 1-positions of the two molecules. This cannot be less than about 3.5 Å).

We have found already an indication, from the ultra-violet spectra, that the yellow solid contains hydrogen bonds which are somewhat stronger than those which occur in alcohol solution. This is not strong evidence and it does not indicate whether the hydrogen bonds are formed between oxygen and nitrogen atoms or entirely between oxygen atoms. Only X-ray analysis, or some similar technique, could decide between these alternatives; but it should be possible to prepare another 2-hydroxyacridine derivative in which the

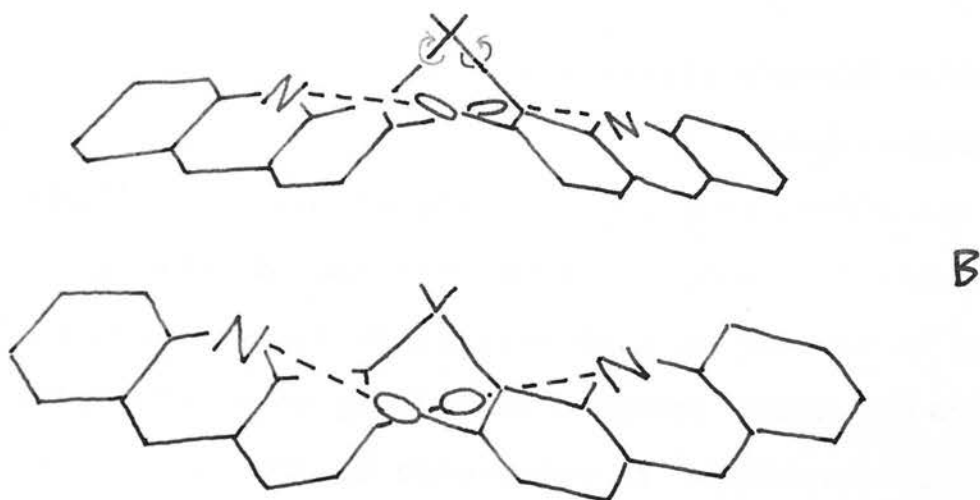
existence of oxygen to nitrogen hydrogen bonds in the crystal is highly probable and to see whether this compound behaves like 2-hydroxy-5-phenylacridine. Since crystal structure is almost impossible to predict from molecular structure, the only way in which this can be done is to arrange that hydrogen bonds of the type required will form within a single molecule. The hypothetical dimer (Fig. 9a) suggests how this can be done.

SECOND SUBJECT.

If two 2-hydroxyacridine molecules are joined by a methylene bridge between the 1-positions the resulting molecule should contain a pair of internal hydrogen bonds. This is illustrated below. For the most symmetrical

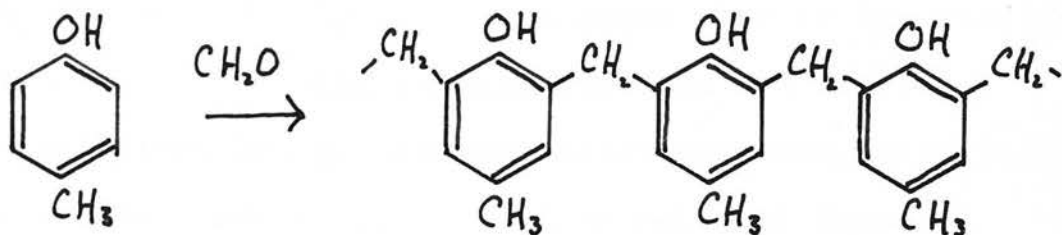


possible conformation of the molecule the distance between the nitrogen and oxygen atoms will be 2.5 Å. This is somewhat shorter than is normal for an oxygen to nitrogen hydrogen bond (5), but there should be a reasonably good approximation to ideal hydrogen bond angles (6). A pair of equal hydrogen bonds of more normal length would also be possible in which the two C-C bonds of the methylene bridge have been rotated in opposite directions, (see diagram B below) but here the hydrogen bond angles will have deviated



further from the ideal (linear) state. One would expect the true situation to be represented most closely by some compromise between these extremes in which the nitrogen and oxygen atoms in the molecule are joined by internal hydrogen bonds somewhat shorter than normal.

Phenols may react with formaldehyde to give methylene bridged compounds. For example, p-cresol gives linear polymers (7).



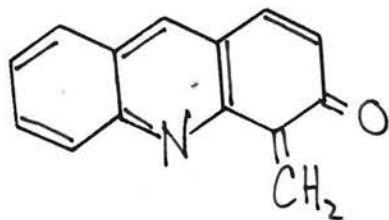
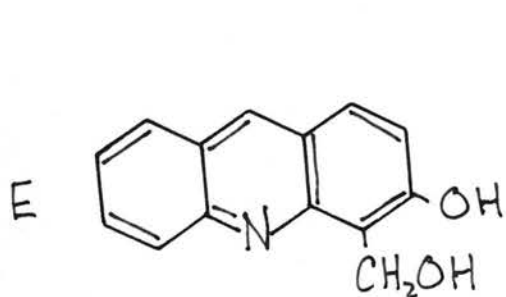
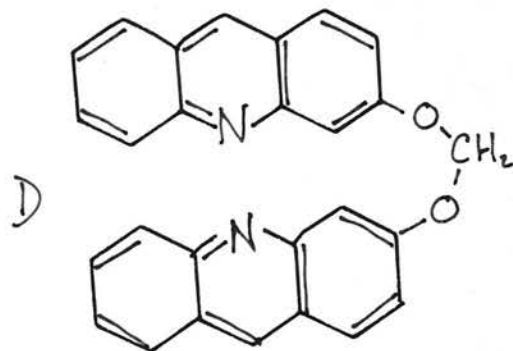
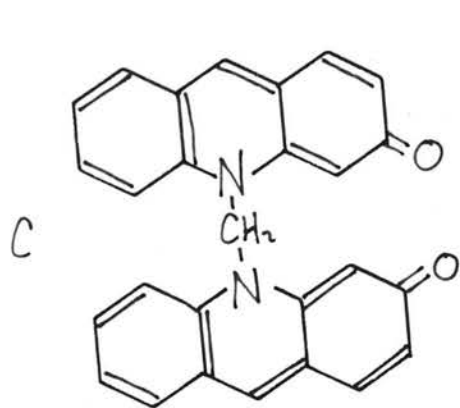
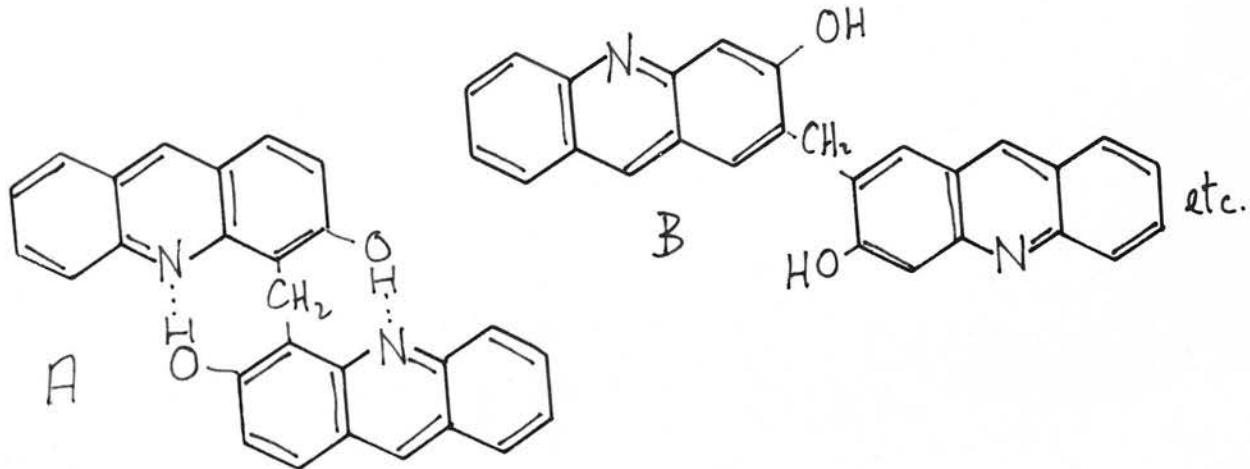
Where there is more than one reactive position in the phenol, and an excess of formaldehyde, polymerisation will occur.

But if the phenol has one position which is considerably more reactive than any other, then a simple molecule, consisting of two of the phenol molecules joined by a methylene bridge, may be produced. This is illustrated most clearly in the

case of β -naphthol which reacts quantitatively with formaldehyde (8) to give 1:1' methylene bis- β -naphthol. The analogy between the structure of β -naphthol and that of 2-hydroxyacridine suggested that the action of formaldehyde on 2-hydroxyacridine might provide a simple way of preparing the internally hydrogen bonded compound which was required.

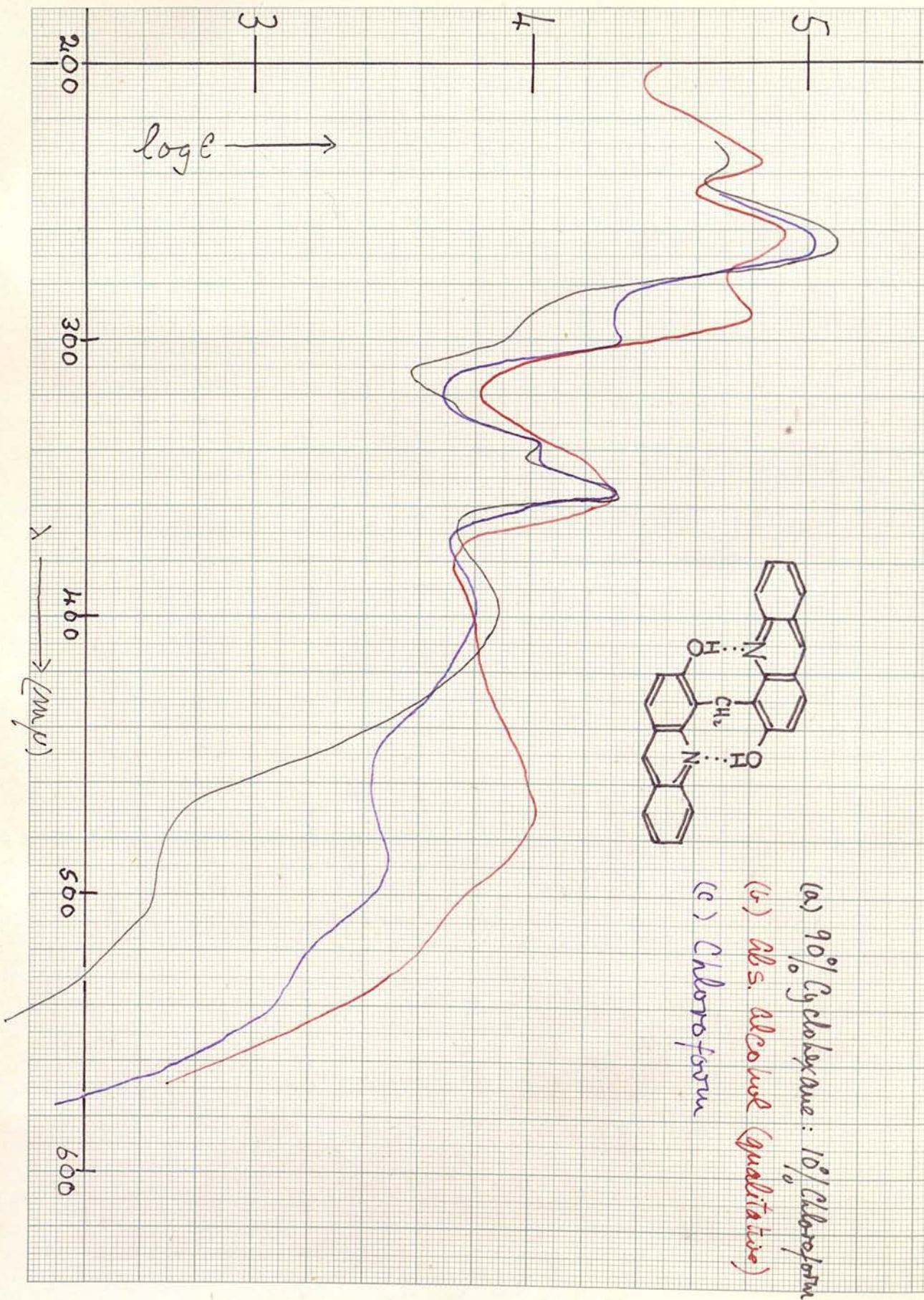
When an alcoholic suspension of 2-hydroxyacridine was warmed in the presence of sodium acetate and an excess of formaldehyde, a deep red solution was formed from which a red solid precipitated within one or two minutes. This crude product was obtained almost quantitatively and could be recrystallised without further purification, indicating that there was only one major component present. Chromatography on alumina supported this view and showed in particular that little or no polymerisation had occurred.

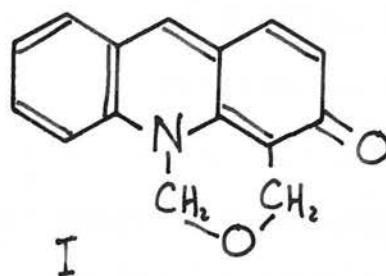
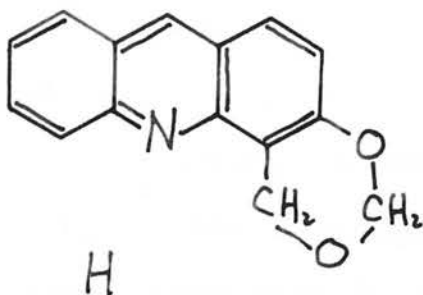
The absence of polymerisation shows that if the reaction of 2-hydroxyacridine with formaldehyde has the effect of forming methylene bridges between molecules then, with respect to such bridge formation, there can be only one reactive position in the 2-hydroxyacridine molecule. Examples of possible bridged compounds are shown below (Fig. 10, A - D). Alternatively some unbridged product might have been produced (E - I).



G

Fig. 11





The analysis of the product for carbon, hydrogen and nitrogen showed that there is only one oxygen atom present in the molecule for every nitrogen atom. This means that if formaldehyde has entered the molecule water must have been eliminated, either intermolecularly to form a methylene bridged compound (A - D) or intramolecularly to give a product like G.

Ultra-violet spectra of the product in three different solvents are shown in Fig. 11. These resemble the spectra of 2-hydroxyacridine (or 2-hydroxy-5-phenylacridine). All the typical "lactam" and "lactim" peaks can be seen and their relative intensities are changed by a change in the solvent. The only substantial difference is that in this product the lactam structure appears to be slightly more stable than in 2-hydroxyacridine (compare the spectra in alcohol for example).

The spectra show that the complete 2-hydroxyacridine nucleus is present in the formaldehyde product - that the acidic hydrogen atom has not been substituted. The reaction then, must have the effect of joining two 2-hydroxyacridine

molecules by a methylene bridge between carbon atoms (i.e. the spectra allow us to eliminate C, D and G (Fig. 10)).

We should expect the carbon atoms involved to be those in the 1-position: there is the obvious analogy between this reaction and the corresponding one which occurs under the same conditions with β -naphthol, and the analogy is not only empirical. The unique character of the 1-position in β -naphthol has been attributed to the relatively higher stability of excited states in which a negative charge is localised at the 1-position (9). Arguments of this type apply with added force in the case of 2-hydroxyacridine.

Fig. 12 illustrates various electromeric states which might be important in the formaldehyde reaction. (It has been assumed, since the reaction is base-catalysed, that the negative ion is the reacting species and also that this reaction, like phenol-formaldehyde reactions in general, involves electrophilic attack on the phenol).

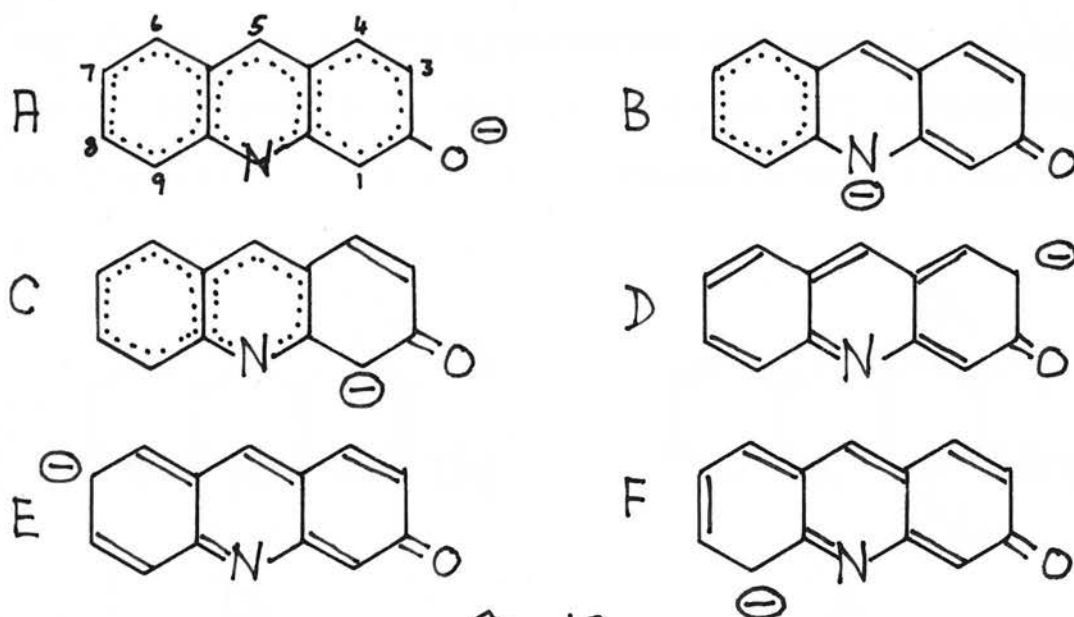
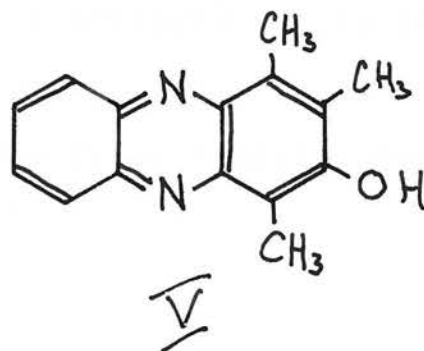
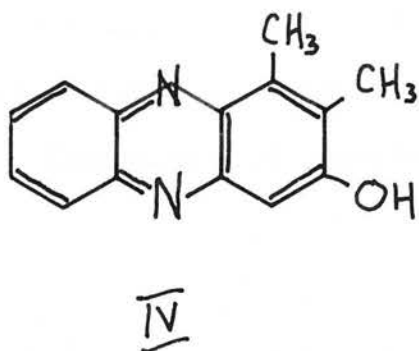


fig. 12

To localise a negative charge on C₃, C₇ or C₉ all the π -electrons in the molecule must be partially localised in seven quinonoid double bonds as shown (Fig. 12 D, E and F). On the other hand a negative charge can appear at the 1-position (Fig. 12 C) to form an excited state in which only two such bonds occur and in which a fully aromatic quinoline nucleus remains. This should require considerably less energy and we should expect electrophilic reaction to occur at C₁ much more rapidly than at any other carbon atom. Thus the absence of polymerisation and the purity of the product obtained from the reaction of 2-hydroxyacridine with formaldehyde can be explained even although, as we know from other evidence, this reaction involves the formation of methylene bridges between carbon atoms: there is effectively only one reactive position and this is at C₁; the product is 1:1' methylene-bis-2-hydroxyacridine.

In the course of work which will be discussed later it was found that 2-hydroxyphenazine undergoes a similar reaction with formaldehyde as does its 3:4-dimethyl derivative (IV). On the other hand there is no reaction with 1:3:4-trimethyl 2-hydroxyphenazine (V).

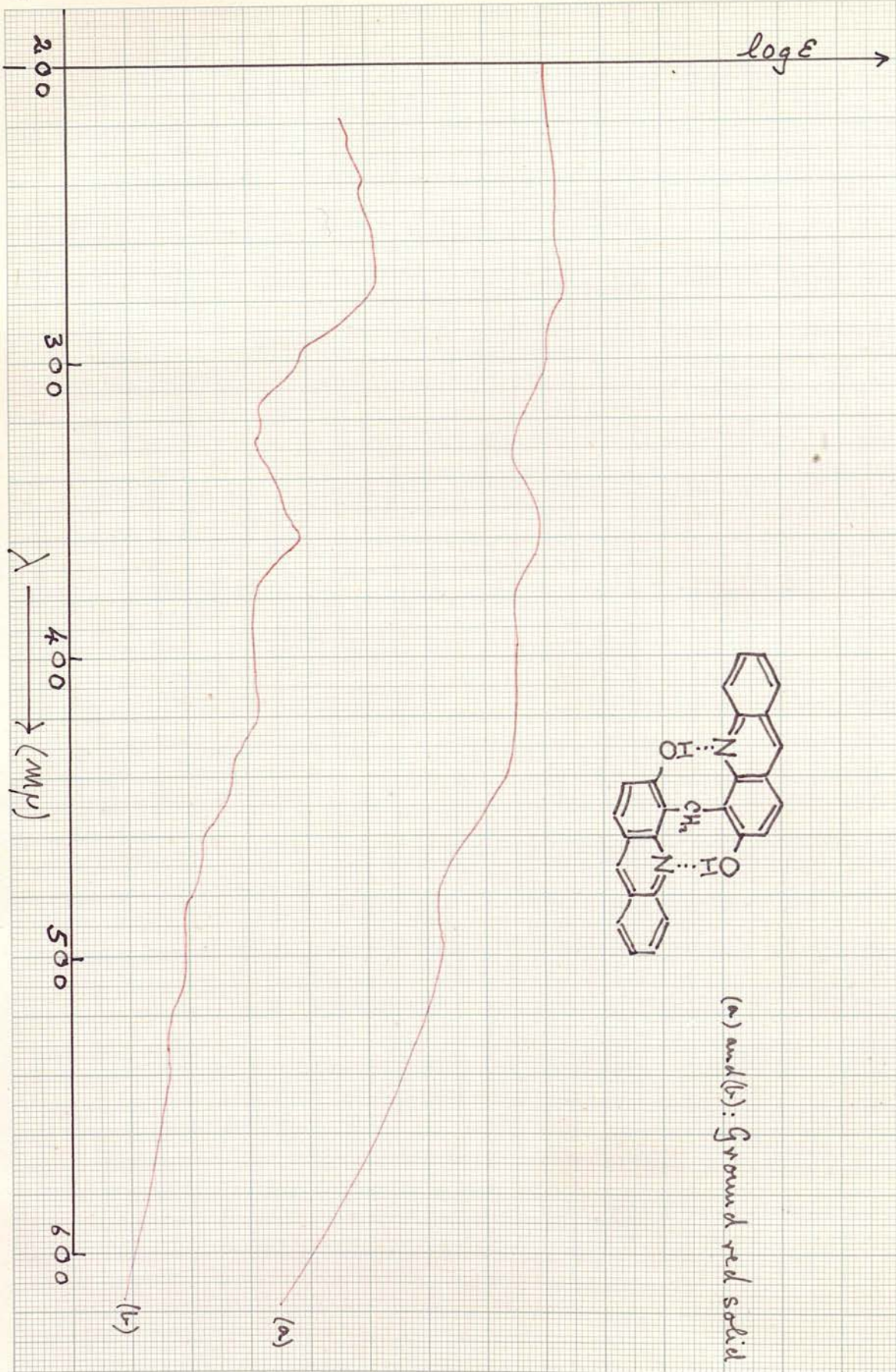


As mentioned already the stereochemistry of 1:1'-methylene bis-2-hydroxyacridine would lead us to expect the existence of fairly strong internal hydrogen bonds in the molecule. There is some experimental support for this. The bridged compound is more soluble in chloroform and runs more rapidly on alumina than 2-hydroxyacridine itself. On the other hand it is less soluble in alcohol and quite insoluble in hot caustic soda solution. This last point is in marked contrast to 2-hydroxyacridine, which is soluble even in sodium carbonate solution, and it might by itself suggest that the mobile hydrogen atom is no longer present. But the spectra show clearly that this is not the case. The apparent contradiction can be resolved by assuming the presence of strong internal hydrogen bonds which allow movement of the protons between the oxygen and nitrogen atoms while preventing their removal from the molecule as a whole.

The evidence outlined above establishes with reasonable certainty the structure of the 2-hydroxyacridine-formaldehyde product. The most interesting property of the compound is this: when formed under different conditions, crystals of different shapes and shades may be obtained ranging from red (chlorobenzene) to pale orange (chloroform). All of these give similar red powders on grinding.

Ultra-violet spectra of solid films (Fig.13) were less

Fig. 13



satisfactory in this case - they could only be obtained by grinding the material on to silica plates. But "mixed" spectra are indicated.

On heating various samples of 1:1-methylene-bis-2-hydroxyacridine no distinct colour change, comparable to the red \rightarrow yellow change, which occurs in 2-hydroxyacridine, could be observed: there was a reduction in the colour of the red powder on heating at 120°C for several hours and what appeared to be the reformation of crystals by sublimation could be seen in the region of 250°C in all samples, but the individual crystals formed were of varying shades and remained orange or red until decomposition occurred in the region of 350°C .

The important point is the qualitative one that the new compound is a second polychromic free acridine. The different colours of the various samples cannot all be due to differences in crystal habit or the state of subdivision. Grinding the orange crystals gives a red powder. This is abnormal. Generally the colours of crystalline samples become lighter when the particle size is reduced. The spectra of the solid may be insufficiently clear to draw definite conclusions from these alone, but the crystals, if we can judge from their colours, do not appear to be composed entirely of lactim or entirely of lactam molecules. The colours of all the

crystalline samples are intermediate between the yellow and red of the alternative tautomeric structures.

The colour of the orange crystals of 1:1' methylene-bis-2-hydroxyacridine is abnormal as is the effect of grinding them: in the context the simplest and most probable explanation is that, like 2-hydroxy-5-phenylacridine, this compound can undergo tautomeric changes in the solid and that it can exist as a mixture of the lactim and lactam structures in this state. There are still two problems but they are the same as those encountered before.

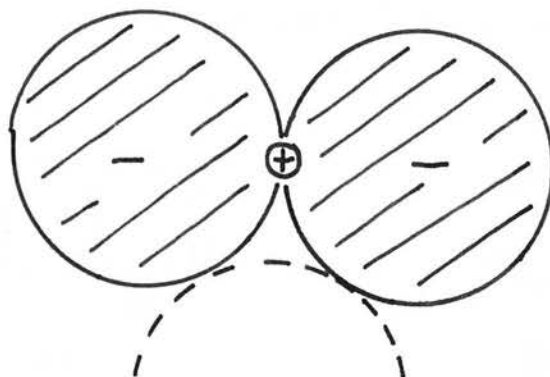
The hypothesis put forward to explain the tautomerisation in the solid of 2-hydroxy-5-phenylacridine required the (fortuitous) existence of oxygen to nitrogen hydrogen bonds in the yellow crystals. The similar behaviour of the methylene bridged compound strengthens the idea that such bonds are intimately involved. It is possible that the existence of nitrogen to oxygen hydrogen bonds in the crystal can also explain the mixed nature of the spectra. This point will be considered in the next section which starts with a short review of hydrogen bonding in general.

REFERENCES.

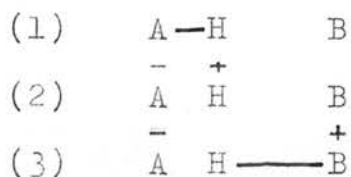
- (1). Kehrman and Matusinsky, Ber., 1912, 45, 3498.
- (2). Albert and Short, J., 1945, 760.
- (3). O'Shaughnessy and Rodebush, J.Amer.Chem.Soc., 1940, 62, 2906.
Williamson and Rodebush, ibid., 1941, 63, 3018.
Rodebush and Feldman, ibid., 1946, 68, 896.
See also Gillam and Stern "An Introduction to
Electronic Absorption Spectroscopy" (1954), P.239.
- (4). S. Nagakura and M. Gouterman, J.Chem.Phys., 1957, 26, 881.
- (5). Pauling, "The Nature of the Chemical Bond" (1940) 334.
- (6). L. Hunter, "The Stereochemistry of the Hydrogen Bond"
in "Progress in Stereochemistry" (Klyne 1954) 224.
- (7). Koebner, Angew. Chem., 1933, 46, 250.
- (8). Fries and Hubner, Ber., 1906, 39, 440.
- (9). Dewar, "Electronic Theory of Organic Chemistry" (1949) 175

SECTION 2 (DEVELOPMENT)1. THE HYDROGEN BOND.

Pauling showed in 1928 (1)(2) that a hydrogen atom can have only one stable orbital and cannot therefore form more than one pure covalent bond. He concluded that the attraction of two atoms by a hydrogen atom, as observed in hydrogen bond formation, must be due to ionic forces. The unique ability of hydrogen in this respect could be attributed to the very small size of the proton which could attract two (but not three) negatively charged groups to itself. (See diagram).

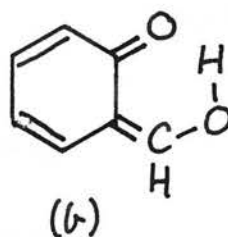
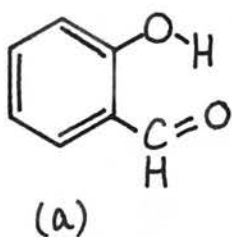


The inability of hydrogen to form two covalent bonds does not preclude the possibility of resonance forces contributing to the stability of the hydrogen bond. In a hydrogen bond between two atoms, A and B, there are at least three structures which might contribute to a resonance hybrid:

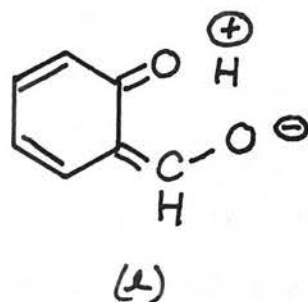
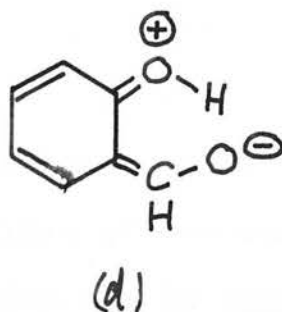
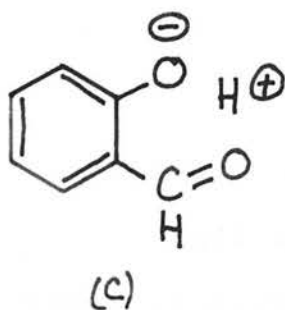


According to Pauling only (1) and (2) will make a significant contribution: the force between the hydrogen atom and the atom B will be purely electrostatic. The other extreme view is that the hydrogen bond is a resonance structure in which the attraction of the hydrogen atom for the alternative atom is due to the contribution of forms like (3).

To take a specific example, salicaldehyde contains an internal hydrogen bond: the stability of this has been attributed to resonance between the structures (a) and (b).(3).

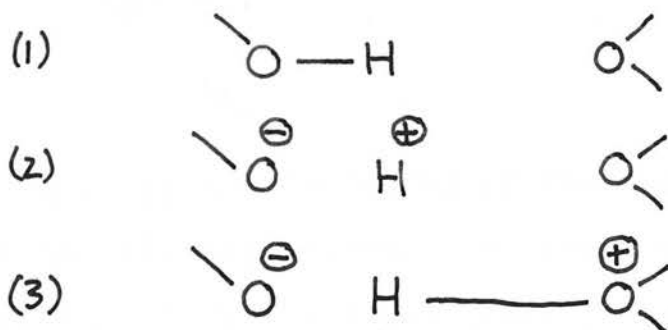


On Pauling's view the existence of this bond is regarded as being due entirely to the electrostatic attraction of the positively charged hydrogen atom for the negatively charged carbonyl oxygen: the significant structures are (c), (d), and (e). In none of these is there a covalent bond between the carbonyl oxygen and the acidic hydrogen atom.



The "electrostatic" theory is now generally regarded (4) as being the closest approximation to the truth. Many of the results which are described in this thesis can only be interpreted readily on such a basis.

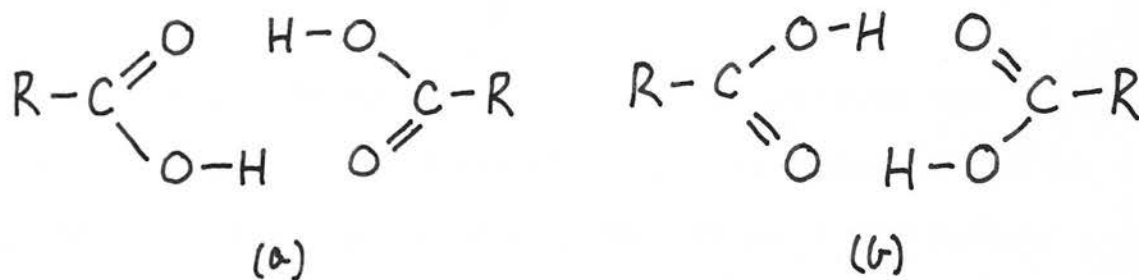
Coulson (4a) quotes the results of a calculation by Danielsson on the relative weights w_1 , w_2 and w_3 to be attributed to the structures (1), (2) and (3) in accounting for the energy of an isolated oxygen to oxygen hydrogen bond.



For the equilibrium distance between the oxygen atoms these are given as $w_1 = 65\%$, $w_2 = 31\%$, $w_3 = 4\%$. For certain short hydrogen bonds, such as occur in β -oxalic acid, w_3 was found to be 12%.

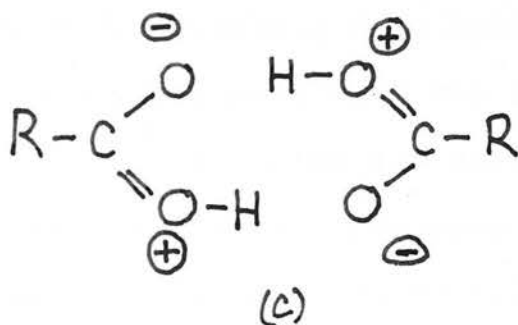
Danielsson's calculations are only approximate, but they are consistent with the general view that resonance plays a minor part in contributing to the energy of the hydrogen bond. The calculations show, however, that it is difficult to generalise about the origin of the energy of the hydrogen bond: the resonance contribution may be small, but it is there, and it appears to be very variable. It could be argued that tautomeric hydrogen bonds must be regarded as a special class.

The carboxylic acid dimers are examples of structures containing a pair of (secondary) tautomeric hydrogen bonds. Here the energy of the two structures (a) and (b) might be at

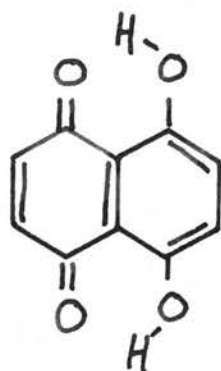


least similar, and identical if the hydrogen atoms take up positions half-way between the oxygen atoms. In fact the arrangement of the hydrogen atoms is almost certainly not symmetrical (5), but the greater strength of these over normal oxygen to oxygen hydrogen bonds (4a)(6) might suggest that here such resonance is important. Pauling (7) however gives another explanation which seems equally satisfactory. The extra strength of these bonds is due to resonance, but this is

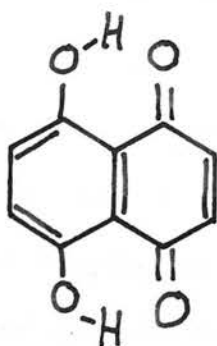
confined to each of the carboxylic acid molecules. Hydrogen bonds in general are favoured by the existence of positive charge on the atom which is covalently bonded to the hydrogen, and negative charge on the other atom with which the bond is being formed. In carboxylic acid dimers contributions such as (c) are possible. These will increase the strength of the hydrogen bond. This point is important because it is



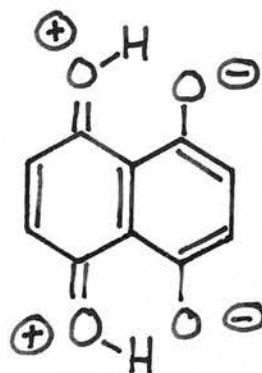
general: It is always impossible to say whether the increased strength of tautomeric hydrogen bonds is due to long bond resonance such as (b) or charge distribution resonance such as (c). That tautomeric hydrogen bonds are generally strong does not necessarily mean - as Hunter implied (8) - that these hydrogen bonds owe their stability to resonance between alternative uncharged covalent structures. The internal hydrogen bonds in naphthazarin are strong (9): this may be due to resonance between (a) and (b) (below). Equally it may be due to resonance between (b) and (c). In



(a)

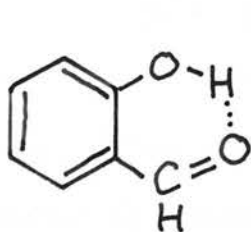


(b)

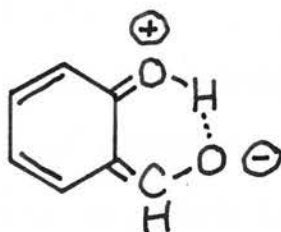


(c)

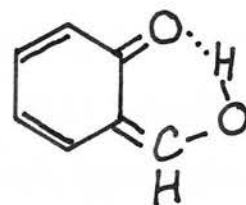
all cases where we are dealing with hydrogen bonds in which the energies to be associated with the two alternative positions for the hydrogen atom are similar - that is where we are dealing with tautomeric hydrogen bonds - this ambiguity inevitably arises. Let us consider salicaldehyde again, and a hypothetical experiment with it. Suppose that we could



(a)



(b)



(c)

start with the uncharged structure (a) and add progressively increasing contributions of (b): as we did so the strength of the hydrogen bond would increase due to the electrostatic attraction across the hydrogen bond. But another thing would happen: the alternative tautomeric structure (c) would become more stable. This must be so since the point would be

reached when the hydrogen atom, by the mutual action of the positive charge on the phenolic oxygen and the negative charge on the carbonyl oxygen, would move across to the carbonyl oxygen atom - and remain there: we would then say that the tautomeric form (c) had become more stable. Thus a strong contribution of the type (b) is inexorably linked with a high relative stability of the alternative tautomeric structure: in such a case there will be a strong hydrogen bond, but it is impossible to conclude from this alone that the hydrogen bond is a resonance hybrid of the tautomeric structures. The additional strength may equally be due to the electrostatic effect which is inevitably linked with such bonds.

Hunter's theory of mesohydric tautomerism depends on the idea that tautomeric hydrogen bonds are resonance structures. According to Hunter (J.1945, 806) (8), tautomeric compounds, in which the tautomerism is due to a mobile hydrogen atom moving between oxygen, nitrogen or sulphur atoms, will associate in solution to form complexes in which there are hydrogen bonds between the oxygen, nitrogen or sulphur atoms in question.

Hunter considered the general case of a molecule



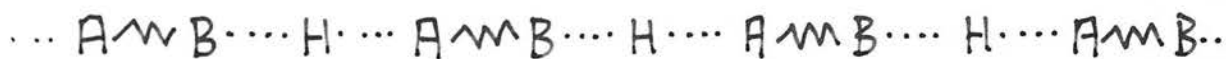
in which the tautomeric hydrogen atom could be attached

either to A or B. An isolated molecule can have two

structures: $A\text{---}H\text{---}B$ or $H\text{---}A\text{---}B$. But if in solution the

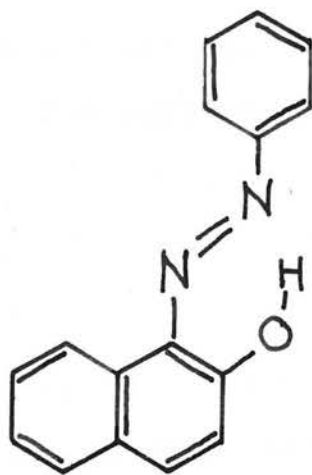
molecules are associated by hydrogen bonds between A and B

(see diagram) then the compound will be essentially

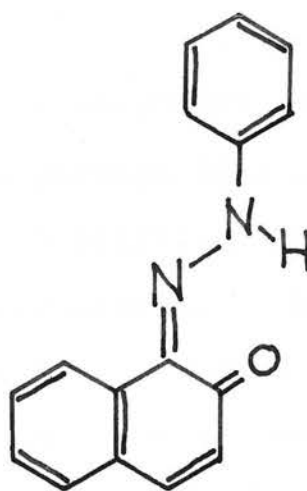


homogeneous, the hydrogen atom being uniquely associated neither with A nor B. Only a single tautomeric type will exist in solution - the mesohydric tautomer - in which a "half-hydrogen" is attached to each of A and B. The mesohydric tautomer is thus a resonance hybrid of the $A \sim B H$ and the $H A \sim B$ tautomers and the latter have no more independent existence than the different Kekulé structures of benzene.

According to Hunter, mesohydric tautomerism can occur as the result of an internal tautomeric hydrogen bond. 1-phenylazo-2-naphthol is an example of such a compound which should be regarded as a resonance hybrid rather than an equilibrium mixture of (a) and (b).



(a)



(b)

One of the difficulties with Hunter's theory is in the interpretation of ultra-violet spectra. 2-hydroxyacridine (and 2-hydroxy-5-phenylacridine) should be mesohydric compounds; yet the spectra of these can readily be interpreted as resulting from a mixture of the "classical" tautomeric types: the spectrum of the mesohydric tautomer would not be expected to be simply the sum of the "lactam" and "lactim" spectra and the variation in the relative intensities of these with change in solvent cannot be explained on the mesohydric theory.

It might be argued that the theory is fundamentally sound, but that with 2-hydroxyacridine the degree of association is not sufficiently great. But 1:1' methylene-bis-2-hydroxyacridine behaves in the same way: here again the individuality of the lactim and lactam structures is preserved in solution and here the internal hydrogen bonds should have allowed the molecule to retain a mesohydric state at any dilution - if such a state exists.

But perhaps there is still a loophole: the methylene bridged compound is not planar, perhaps this prevents a large "tautomeric resonance" from blurring the distinction between the lactim and lactam structures. From the work of Burroway and co-workers (10) it is clear that neither is this satisfactory. Burroway showed that by suitable substituting

1-phenylazo-2-naphthol, compounds could be prepared in which the stabilities of the two alternative tautomeric structures were sufficiently close for the relative amounts of these in solution to change with change in solvent. Here also there must be two distinct positions for the hydrogen atom on the hydrogen bond.

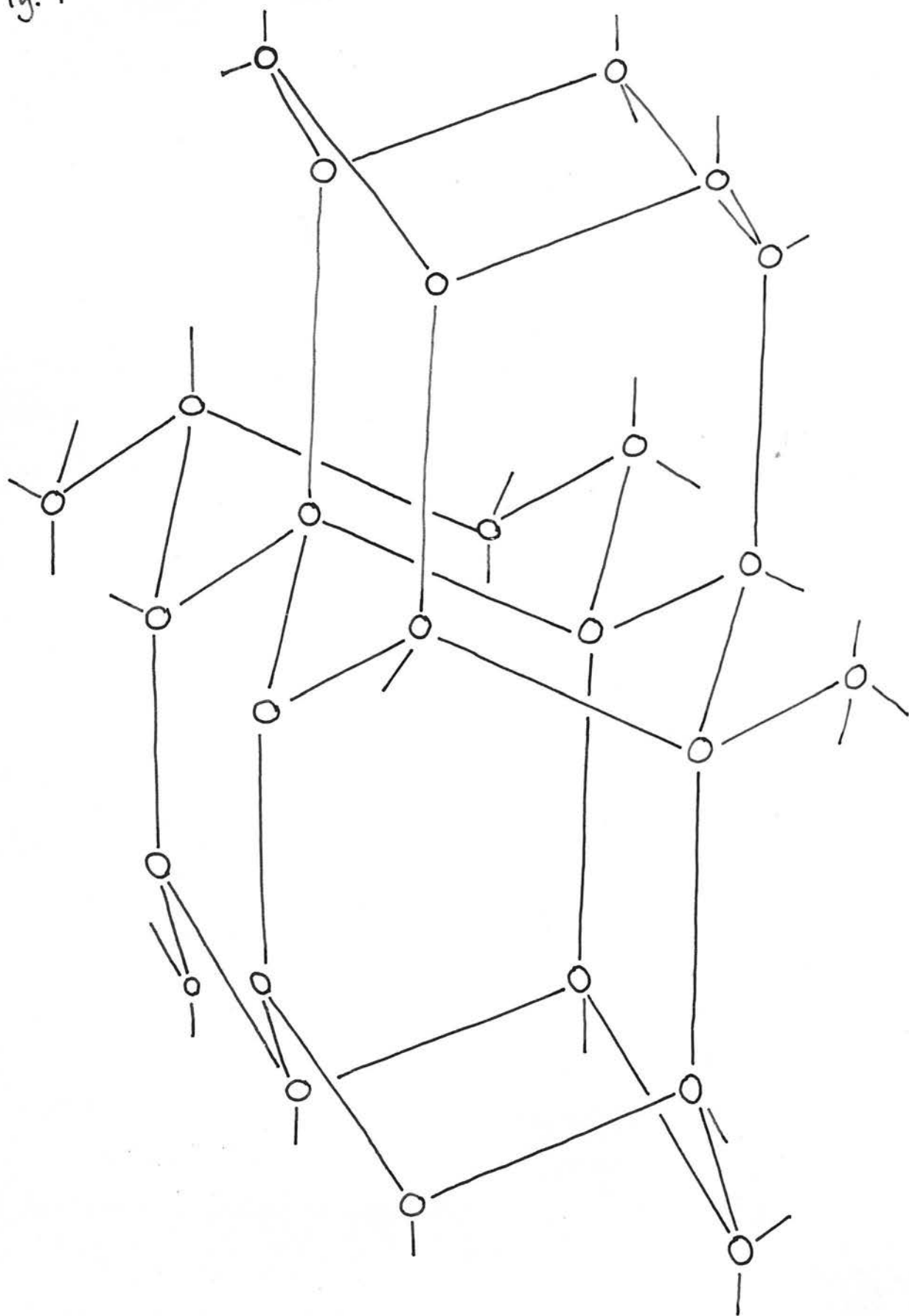
The origin of the energy of the hydrogen bond has been considered at some length because of its relevance to the main subjects of this thesis. The other important features of hydrogen bonding will be considered now by using ice as an example.

To say that ice contains a large number of hydrogen bonds is to miss the point: ice is a large number of hydrogen bonds.

In normal ice (ice I) the oxygen atoms are arranged such that the four nearest neighbours of any one atom are disposed tetrahedrally and at equal distances (2.76 Å)(11). The structure resembles that of diamond although in ice the crystal type is hexagonal rather than cubic. Fig. 1 illustrates the arrangement.

The hydrogen atoms lie on hydrogen bonds between the oxygen atoms. But their positions are not symmetrical: this is shown by the absence of any large change in the vibration frequencies of water on changing from the vapour to the solid: only a small increase in bond length is indicated (from 0.96 Å - 1.0 Å) (12). A symmetrical arrangement would require an

Fig. 1



O-H bond length of 1.38 Å.

With the hydrogen atoms arranged in this way the lattice cannot have a regular structure and lack piezo- and pyro-electric properties unless the unit cell is improbably large - containing 96 molecules (13). Bernal and Fowler (12) suggested that the arrangement is random or glass-like.

Pauling calculated (14) that the number of random arrangements for the hydrogen atoms, in which two hydrogen atoms are attracted to each oxygen atom, will be $(\frac{3}{2})^N$. By ignoring any interactions except those of the four nearest neighbours of any one oxygen atom (i.e. by ignoring all interaction except hydrogen bonding) the energy of each random arrangement should be the same. Thus even at absolute zero there will be $(\frac{3}{2})^N$ a priori equally probable arrangements for the molecules. From the fundamental relationship of statistical mechanics:

$$S = K \log \Omega$$

the entropy at absolute zero should be $K \log(\frac{3}{2})^N$ (i.e.) 0.806 cal./mole degree. The experimental value for the residual entropy of ice is 0.82 ± 0.01 cal./mole degree.

Pauling's brilliantly simple calculation confirms that the general picture for the structure of ice, obtained from X-ray and infra-red data, is correct. More recent neutron diffraction measurements (15) also favour the random hydrogen

structure: these indicate that there are two "half-hydrogens" on each of the hydrogen bonds.

Using this structure we can now summarise briefly the important features of hydrogen bonding and see how some of these may be related to macroscopic properties in ice.

(1) The length of the hydrogen bond is intermediate between that of normal covalent bonds and normal Van der Waals approach distances, (i.e.) about 2.7 Å.

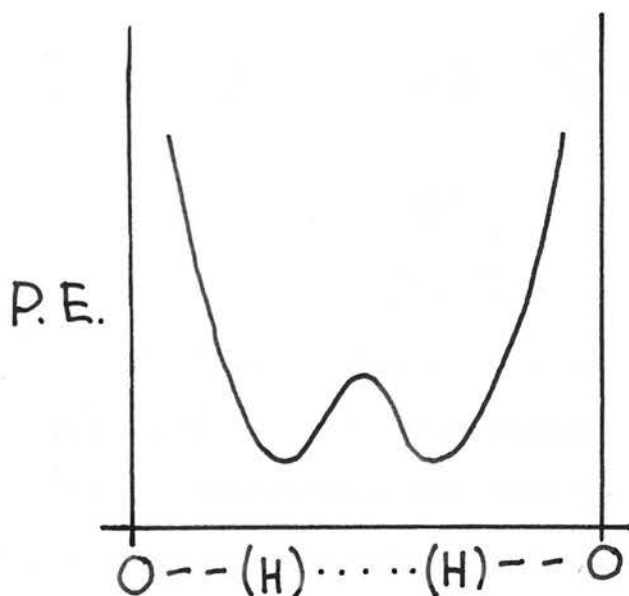
(2) The low density of ice is evidently due to the very open structure which is maintained by the molecules in spite of the close approach of the oxygen atoms which hydrogen bonding allows. This suggests that the hydrogen bond is much more strongly directional than normal crystal forces, that in this case the optimum direction is tetrahedral and that therefore the lone pairs are involved in the bond formation.

(3) The high melting point of ice indicates that hydrogen bonds are stronger than normal Van der Waals forces. From the heat of sublimation of ice the energy of each bond has been found to be about 4.5 K.cals./mole (16).

(4) By assuming that charges of $\frac{1}{2}e$. and $-e$. are located at the hydrogen and oxygen atoms respectively - and this arrangement would give rise to the observed dipole moment of water - Bernal and Fowler (12) calculated the lattice

energy for ice. That this was near the observed value supports the view that the energy of the hydrogen bond is mainly electrostatic in origin (4a).

(5) As we have seen, the residual entropy of ice may be accounted for by assuming that the hydrogen atoms do not take up a symmetrical position on the hydrogen bonds: that is that there are two minima in the potential energy diagram for the movement of the protons between the oxygens (Fig.2). (The diagram is somewhat formal since the minima will only



be equal if the charges on the oxygen atoms remain constant: this could happen by the co-operative transfer of a number of protons (at least six) as illustrated in Fig. 3. The transfer of a single proton (Fig. 3b) must lead to a separation of charges and an unsymmetrical diagram.)

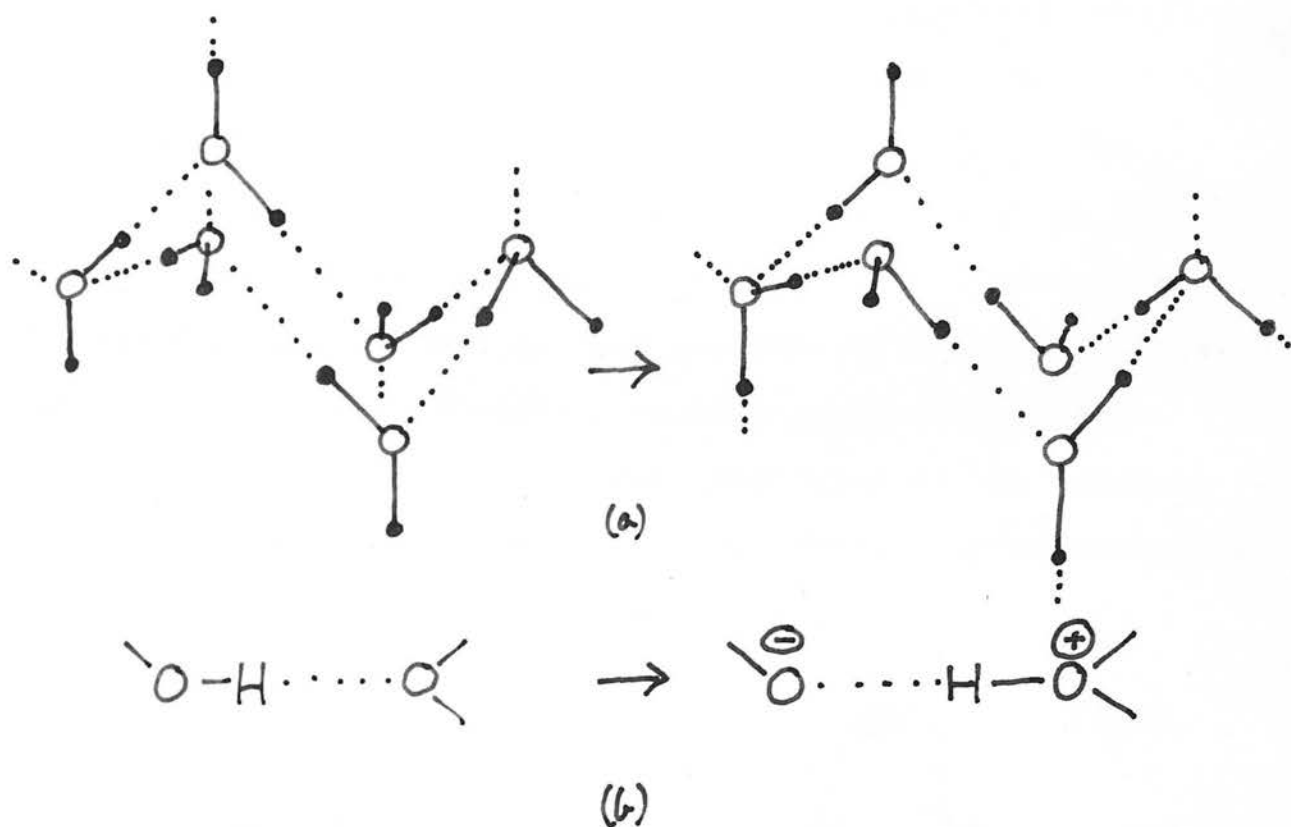


Fig. 3.

(6) The dielectric constant of ice at 0°C is about 80; this decreases with fall in temperature to a value of 4 at -60°C ; below this temperature the behaviour is that of a normal solid (17). Pauling suggested (14) that the high value for the dielectric constant near the melting point is due to the co-operative "switching" of the hydrogen atoms between the alternative positions which can occur most readily at higher temperatures. Such switching of the hydrogen atoms allows the dipoles to rotate without breaking the hydrogen bonds.

The alternative theory to explain this dielectric effect

is that the molecules as a whole rotate: this would require the breaking of hydrogen bonds and would seem to be less probable, but the point is still in dispute (18). The dielectric absorption studies of Meakin (1955)(19) on some di-ortho substituted phenols suggest that rotation can occur. It was found, for example, that di-ortho-nitrophenol (Fig.4(a)) showed appreciable absorption whereas ortho-nitrophenol (Fig. 4(b)) did not. This was attributed to the movement of the hydrogen atom between the two possible hydrogen bonded states in the di-ortho substituted compounds.

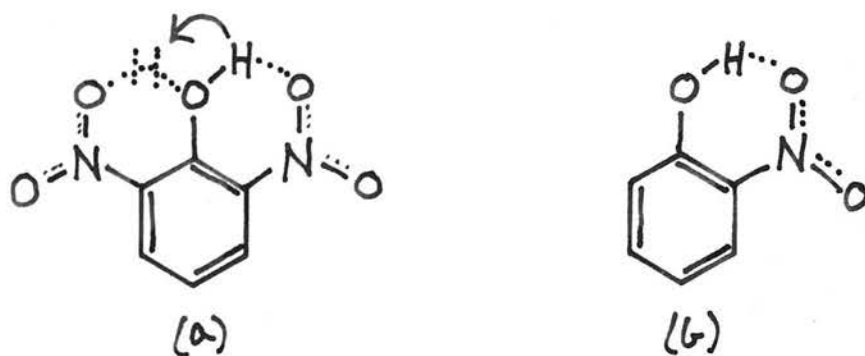


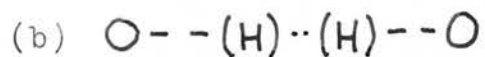
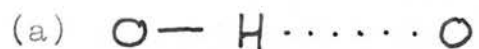
Fig. 4.

In ice it is possible that both the "switching" and the "rotation" occur (20).

Potassium dihydrogen phosphate undergoes a second order transition at 132° K - the so-called ferroelectric point - which corresponds to the disordering of the protons on short O-O hydrogen bonds which are present in these crystals (21). Below the transition temperature the protons are all associated with one of the alternative oxygen atoms. By the application



of an electrostatic field the protons can be made to move into the alternative positions. Above the transition temperature the protons are statistically distributed between the two possible positions. The hydrogen bonds in the two phases can be represented formally as (a) and (b).



2. PROTON TRANSFER THERMOCHROMISM.

The study of 2-hydroxy-5-phenylacridine showed that the polychromism of this compound was due to tautomerism and it led to the suggestion that O - N hydrogen bonds might play an important part in allowing tautomerisation to occur in the solid: the discovery of a second compound with similar properties and which might be expected to have internal O - N hydrogen bonds strengthened this view: a consideration of the general properties of hydrogen bonds supports the assumption of internal hydrogen bonds in the second compound. It also suggests an explanation for the mixed nature of the solid absorption spectra. We have seen that disordered hydrogen bonds have been shown to occur in ice and in potassium dihydrogen phosphate. In these cases no visible effect is produced. The tautomerism is between identical end-atoms. But if tautomeric hydrogen bonds were to be disordered in the solid where the end atoms were not identical and where the colours to be associated with the alternative structures were different then a visible effect would be produced. The absorption spectrum of the crystals would be "mixed". The degree of disorder would depend on the crystal structure: the compound if polymorphic would be polychromic.

This then is an extension to the hypothesis put forward on page 24: "the red form of 2-hydroxy-5-phenylacridine, and all the forms of 1:1'methylene-bis-2-hydroxyacridine, contain

disordered O-N hydrogen bonds." It can be tested.

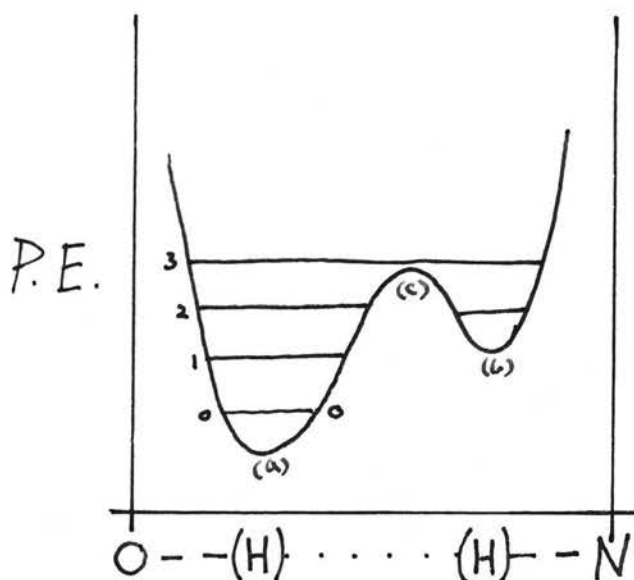
Disordered crystal structures in general become ordered at low temperatures: this may be gradual and partial, as in ice, or sudden and complete as in potassium dihydrogen phosphate. In any case it should occur without a major change in crystal structure and in our case it should be accompanied by a colour change. Since the lactim form appears to be dominant at room temperature this should be the structure that exists exclusively at absolute zero. The red form of 2-hydroxy-5-phenylacridine and all samples of 1:1' methylene-bis-2-hydroxyacridine should turn yellow when cooled to a sufficiently low temperature.

At the temperature of liquid nitrogen the "red" crystals of 1:1' methylene-bis-2-hydroxyacridine are pale orange: the "orange" crystals are yellow. These changes occur rapidly and they are immediately reversible. There is no sharp transition temperature. Examination under the microscope showed that no major change in crystal structure is involved. The effect does not occur in solution. Even in the crystal the effect depends to some extent on the sample. The state of perfection of the lattice appears to be important: samples crystallised slowly are more strongly thermochromic. Grinding the crystals reduces the effect whereas heating a poor sample

at 100°C for a few hours will improve it.

No thermochromic sample of 2-hydroxy-5-phenylacridine could be prepared.

The potential energy diagram in fig. 5 may be used to discuss the behaviour of 1:1'-methylene-bis-2-hydroxyacridine. It describes the movement of the protons between the oxygen and nitrogen atoms within the molecule. The lactim and lactam structures are represented by the minima (a) and (b) in the diagram. These are separated by a barrier (c). The



minimum near the oxygen atom is taken as being lower since the lactim is evidently the dominant structure.

The diagram may be used to describe the thermochromism of the compound. At absolute zero the protons will occupy the lowest energy sites near the oxygen atom: this corresponds to the (yellow) lactim structure. As the

temperature increases transitions to higher energy states will occur and some of these (for example (3)) will allow the protons to move into the site near the nitrogen atom, producing a change towards orange or red in the colour of the crystals. The number of molecules in the higher energy (lactam) state will increase with increasing temperature.

3. RE-EXAMINATION OF 2-HYDROXY-5-PHENYLACRIDINE.

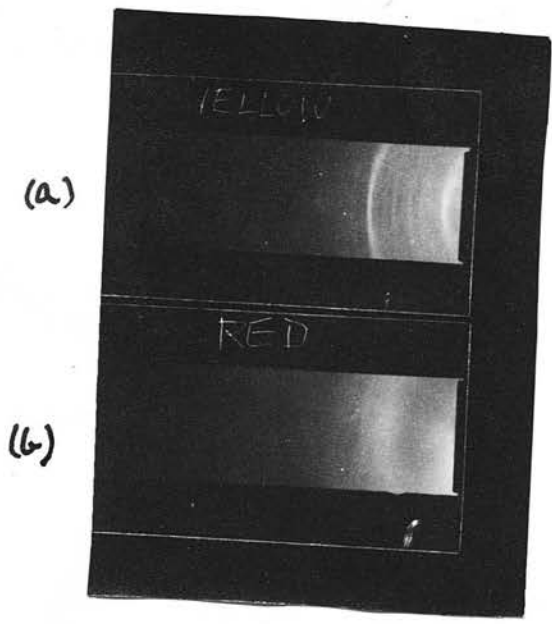
The absence of thermochromism in the red form of 2-hydroxy-5-phenylacridine suggests that here the simple disordered hydrogen bond idea is inadequate. The red form cannot be the disordered structure corresponding to the yellow form if it is the lower energy modification. There must be some major difference in the crystal structure of the red and yellow forms. Powder photographs of the two forms showed that there is indeed a difference between them, but one which was not expected: the yellow form has a crystal structure, the red form is almost amorphous. These photographs are shown in fig. 6. Fig. 6(a) is of the yellow form and 6 (b) is of the same sample after being ground for half an hour. Only one faint line, corresponding in position to the principal line of the yellow form, can be seen in the photograph of the red powder. Crystallographically the only difference between the two forms appears to be in the degree of crystallinity.

The problem of the mixed nature of the red form of 2-hydroxy-5-phenylacridine is solved - there is no reason to expect a largely amorphous state to favour exclusively one of the tautomeric forms. But this problem has been replaced by another.

There can be little doubt that the two principal effects of grinding the yellow crystals of 2-hydroxy-5-phenyl-

Faint, illegible text at the top of the page, possibly bleed-through from the reverse side.

Fig. 6



3. RE-EXAMINATION OF 2-HYDROXY-5-PHENYLACRIDINE.

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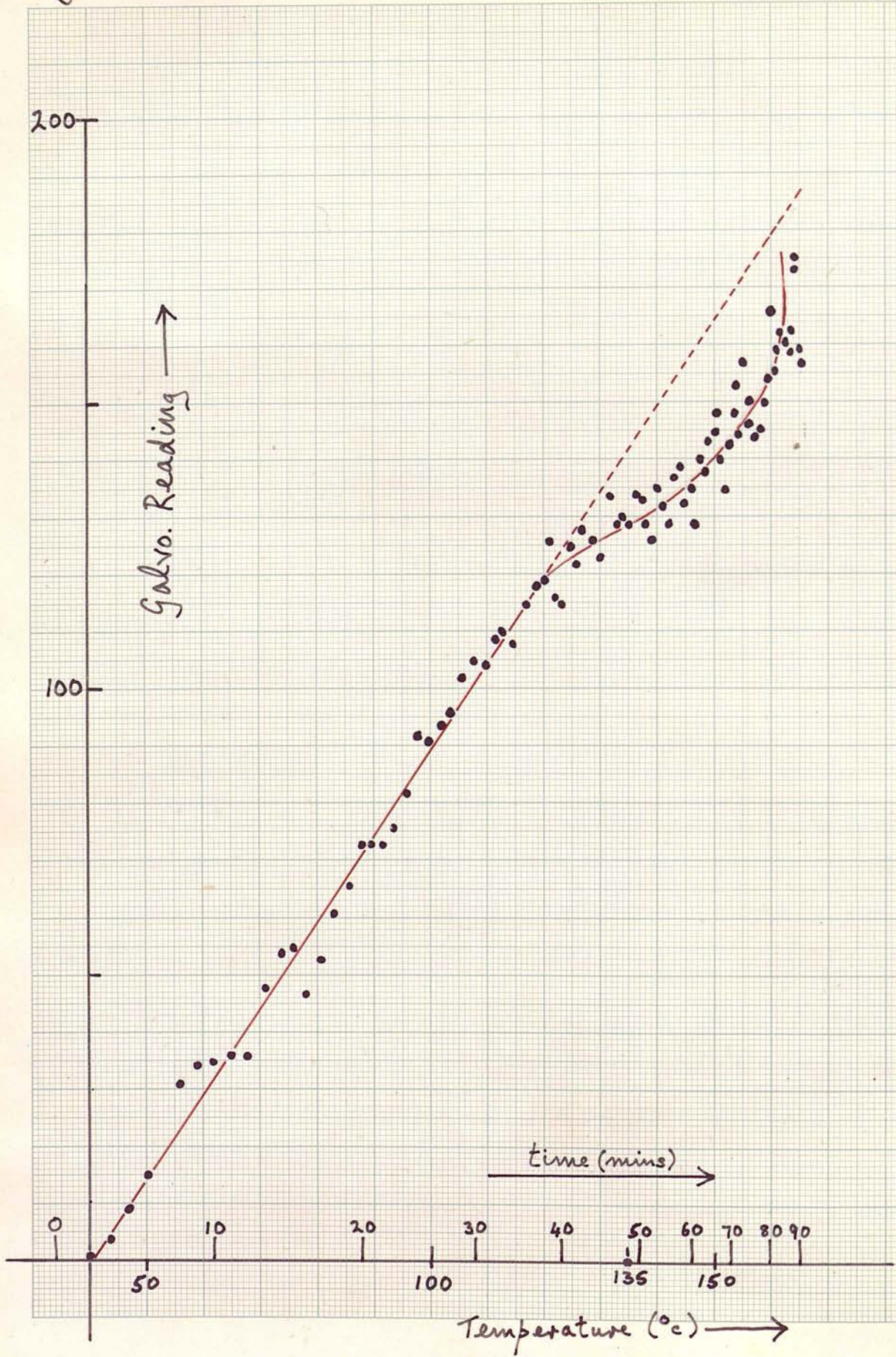
The problem of the mixed nature of the red form of 2-hydroxy-5-phenylacridine is solved - there is no reason to expect a largely amorphous state to favour exclusively one of the tautomeric forms. But this problem has been replaced by another.

There can be little doubt that the two principal effects of grinding the yellow crystals of 2-hydroxy-5-phenyl-

acridine - tautomerisation and lattice disintegration - are connected. A more detailed discussion of this will be given later. In the meantime it is important to establish the fact of disintegration further. It does not fit with Kehrman's conclusion that the red form is a lower energy structure than the yellow. If the red form is amorphous it should certainly be the higher energy form.

Preliminary studies had thrown some doubt on Kehrman's observations: a transition temperature could not be found. The reason for this failure now seems to be that there is no such temperature - that the red form is always metastable. There are other points which support this. The red form turns yellow in the presence of solvents in which it is sparingly soluble: it is in general more soluble than the yellow form: it will dissolve in cold cyclohexane and precipitate as the yellow form on heating. A similar effect occurs with benzene, the yellow form crystallising out of a cold solution of the red. This shows that the brick-red prisms reported by Kehrman to crystallise from cold benzene, if they are genuine, are not the same as the red form obtained by grinding the yellow crystals. But Kehrman's red crystals were probably an artefact. 2-hydroxy-5-phenylacridine, like acridines in general and hydroxyacridines in particular, can readily form supercooled liquids. If evaporated even quite

Fig. 7

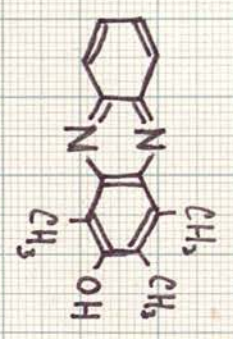
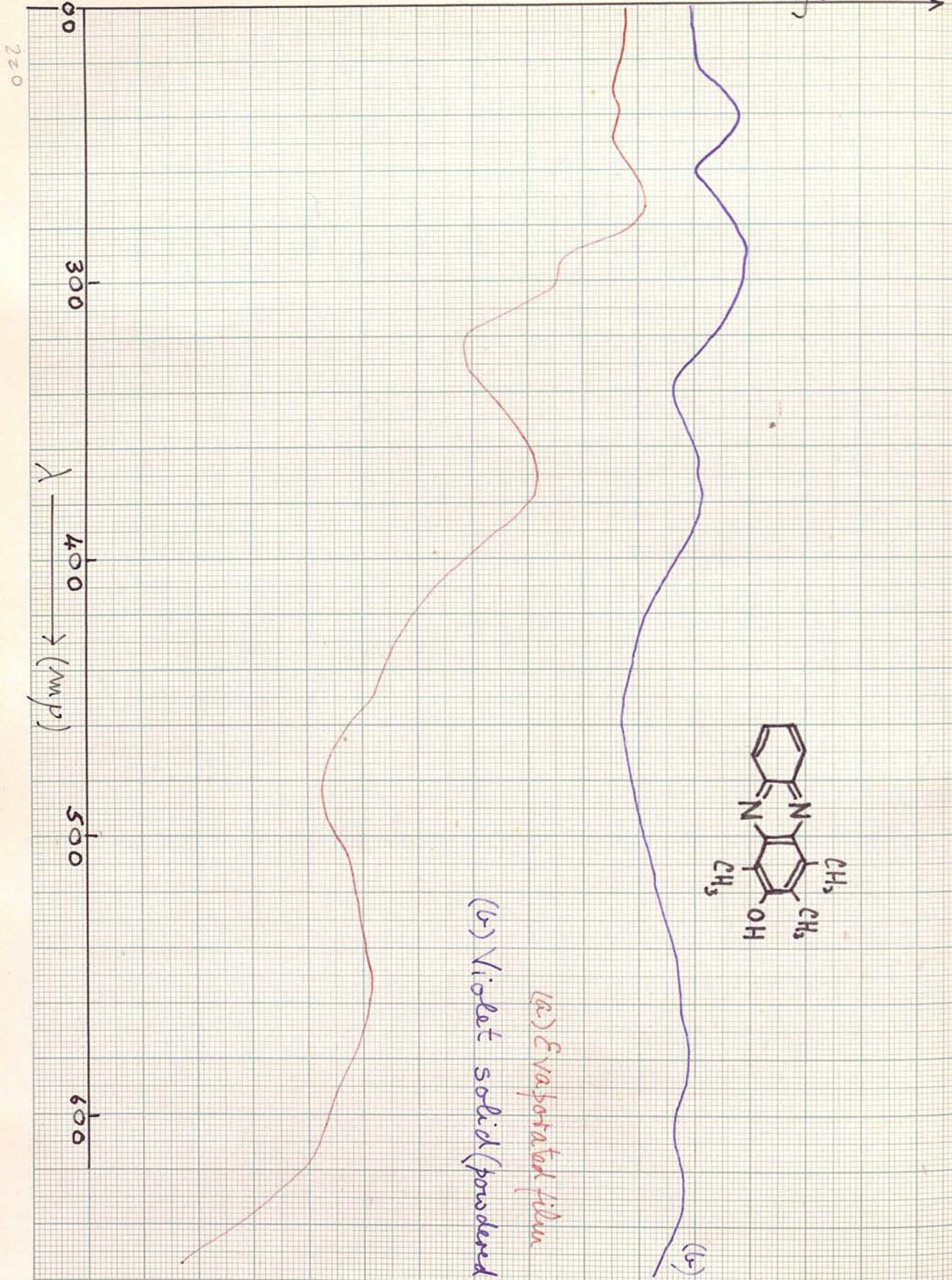


slowly, a solution in benzene will deposit some yellow crystals together with a large amount of red supercooled glass. This glass crystallises only very slowly but the effect may be accelerated by heating and it proceeds fairly rapidly at about 130°C - 140°C. In addition to the yellow crystals and the red glass slow evaporation may indeed produce "brick red crystals with a yellow glance"; but one end of an individual crystal may conform to this description while the other is pure yellow. There can be little doubt that Kehrman's red crystals are the yellow ones with a layer of supercooled liquid covering them. Probably, 2-hydroxy-5-phenylacridine has no crystalline red modification.

A differential heating curve of 2-hydroxy-5-phenylacridine against sodium chloride is shown in Fig. 7. Sodium chloride is evidently not an ideal standard in this case as the base line is far from horizontal, but the curve does show a deviation in the exothermic direction in the region of the transition which indicates that the red is the higher energy form. There is however another observation which is simple and conclusive. On Kehrman's theory the grinding would be regarded as accelerating the transition to the stable state. Below the transition temperature this produces the red form. Above the transition temperature it should give the yellow. This is not so. Even at 150°C, which is certainly above any

Fig. 8

$\log \epsilon$ →



(a) Evaporated film

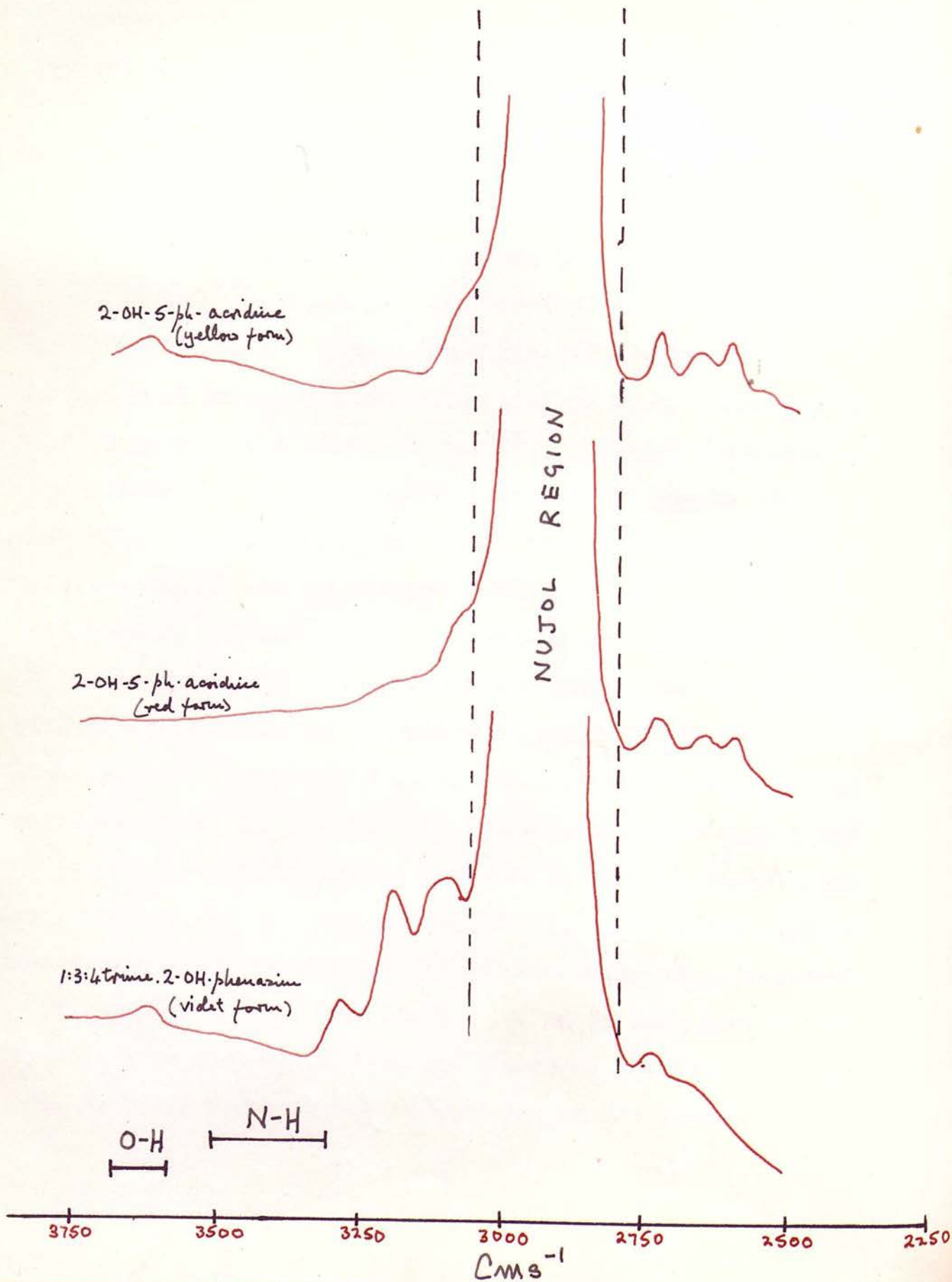
(b) Violet solid (powdered)

possible transition temperature, the yellow form becomes red on grinding or compression. It reverts to the yellow again on removing the stress. Clearly, grinding and compression have the effect of producing a metastable state. By itself this would be surprising, but it is consistent with the powder photographs and it is consistent with the mixed spectra: grinding destroys the lattice.

1:3:4 trimethyl-2-hydroxyphenazine was mentioned in the introduction (page 8) as a polychromic compound in which the polychromism appears to be due to proton tautomerism (22). A sample of the compound was prepared and it was confirmed that it exists in a pale yellow and deep violet modification. Both of these were certainly crystalline and grinding did not affect the colour of either. Neither form was thermochromic. An ultra-violet absorption spectrum was taken from an evaporated film and from a sample of the purple form lightly ground on to a silica plate (fig. 8). The spectrum (a) of the evaporated film is mixed but that (b) of the crystalline form resembles that of the pure lactam structure (compare Badger, 1951, (23)). The yellow form was not examined, but from its light colour any contribution from the highly coloured lactam form must be small. Here, then, the polychromism appears to be due to simple tautomerism as John suggested (22), but, as already stated, tautomerisation does not occur in the

Fig. 9

I.R. Spectra (Nujol smears)



solid state. The methyl groups adjacent to the oxygen atom may prevent the formation of sufficiently short hydrogen bonds.

Infra-red spectra of both forms of 2-hydroxy-5-phenyl-acridine (Fig. 9) show no absorption in the O-H and N-H region indicating that these groups are involved in very strong hydrogen bonds.* 1:3:4 trimethyl-2-hydroxyphenazine, on the other hand, does show absorption here the position of the maxima suggesting that the groups are involved in moderately strong hydrogen bonds.

John (22) prepared a large number of 2-hydroxyphenazine derivatives and it may be significant that only those with a group in the 1-position were polychromic. The polychromism in all cases was between yellow and deep violet forms.

* Infra-red spectra were also taken of 1:1' methylene-bis-2-hydroxyacridine; again negative results indicated strong hydrogen bonding. Unfortunately, the spectra were very complex and it was not found possible to use them to assess the relative amounts of the tautomeric forms present.

4. THE PREPARATION OF FURTHER THERMOCHROMIC COMPOUNDS.

1:1' Methylene-bis-2-hydroxyacridine appears to be an example of a new type of thermochromic compound; one in which thermochromism can occur in the solid as a result of proton transfer along hydrogen bonds. To prepare further compounds of this type it would seem that the following minimum conditions should be satisfied.

(1) The molecule must contain short, approximately linear, internal, tautomeric hydrogen bonds (or a single such bond).

(2) The stabilities of the structures with the protons in the alternative positions must be similar.

(3) The colours of the alternative tautomeric structures must be different.

These conditions are sufficiently restrictive to account for the rarity of the phenomenon, and even when they would appear to hold for an isolated molecule there is no guarantee that they will hold in the solid.*

We shall now consider attempts which were made to prepare further compounds satisfying the above conditions as far as possible.

* Hadzi (24) has reported recently that 2-phenylazo-1-naphthol, from its ultra-violet spectrum in the solid, appears to exist in that state as a mixture of the azo- and hydrazo-tautomers. The possible thermochromism of this compound has not been investigated.

1:1' Methylene-bis-2-hydroxy-5-phenylacridine I was prepared by the reaction of 2-hydroxy-5-phenylacridine with formaldehyde. It was found to be polychromic, crystallising from benzene as pale orange needles and from dioxan as compact red crystals. Both forms were thermochromic. The orange needles became yellow and the red blocks orange on cooling to the temperature of liquid nitrogen.

8:8' Methylene-bis-7-hydroxyquinoline II was prepared similarly. It was not thermochromic. In 7-hydroxyquinoline the (colourless) lactim structure appears to be much more stable than the lactam (25). 7-hydroxyquinoline is colourless in most solvents. In aq. alcohol or water it has a greenish colour. The N-methyl ether of 7-hydroxyquinoline was prepared and found to be bright yellow with a very intense green fluorescence. It was highly deliquescent and difficult to purify. The green colour observed in the parent compound may well be due to the existence of lactam molecules in aqueous solvents, but probably at a low concentration.

A similar situation appears to exist in 1:1' Methylene-bis-2-hydroxyphenazine III which was also prepared for study. 2-hydroxyphenazine, like 2-hydroxyacridine, exists in solution as an equilibrium mixture of lactim and lactam tautomers (Badger 1951 (23)), but the lactam structure is less stable

here than in the acridine: there is still a considerable lactim absorption visible even in aqueous solution. The methylene bridged compound is yellow and is not thermochromic below room temperature. It becomes gradually and reversibly dull orange, however, between 200°C and 300°C. This shift in the temperature range over which thermochromism occurs is consistent with the greater stability of the lactim structure of 2-hydroxyphenazine compared to that of 2-hydroxyacridine.

The substitution of methyl groups in the 2-hydroxyphenazine molecule appears to increase the stability of the lactam structure. 1:3:4 trimethyl-2-hydroxyphenazine, for example, gives a purple solution in water whereas 2-hydroxyphenazine is dull orange in this solvent. In alcohol the colours are dull orange and yellow respectively.

1:1' Methylene-bis-3:4 dimethyl-2-hydroxyphenazine IV was prepared and found to be polychromic and thermochromic. Rapid crystallisation from toluene solution gave yellow needles which showed no thermochromism. On crystallising slowly, however, compact "brick orange" crystals were obtained which were thermochromic both in the higher temperature and in the lower temperature regions. At the temperature of liquid nitrogen these crystals are yellow. Heating causes the colour of the crystals to change through

dull orange and brick red to chocolate brown (at about 280°C). These effects are immediately reversible.

That the colour of the crystals should change to brown rather than to red is consistent with the tautomeric theory of the thermochromism of these compounds in view of the known deep violet colour of the lactam form of 2-hydroxyphenazine derivatives.

The inclusion of the partial double bond, between C_2 and C_3 in the lactam form of 7-hydroxyquinoline, in an aromatic ring, may account for the increased stability of the lactam form in 2-hydroxyacridine (Fig.10). An attempt was made to prepare the unknown 5:6-benz-7-hydroxyquinoline (V) as

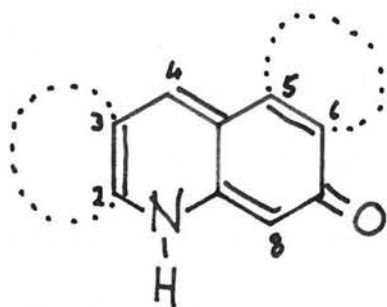
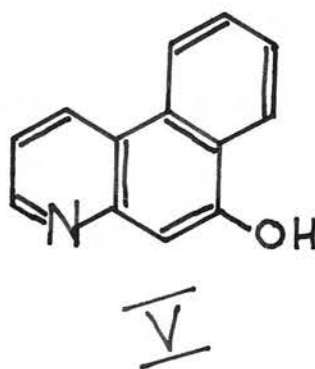
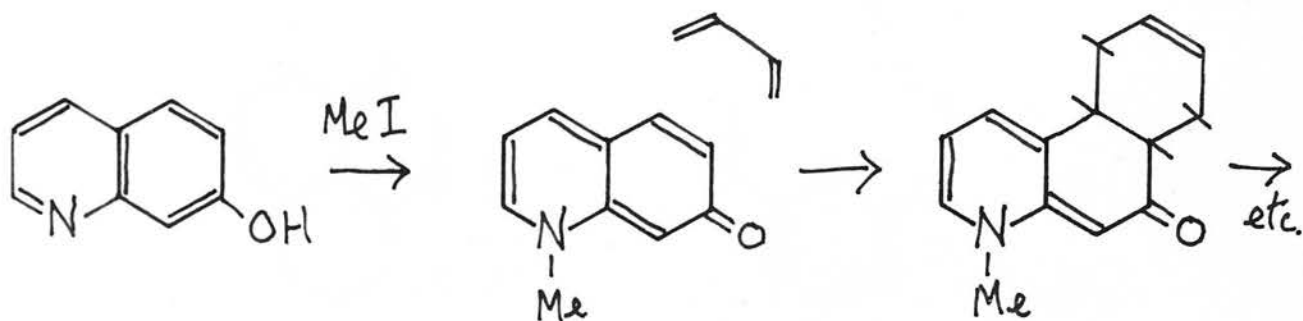


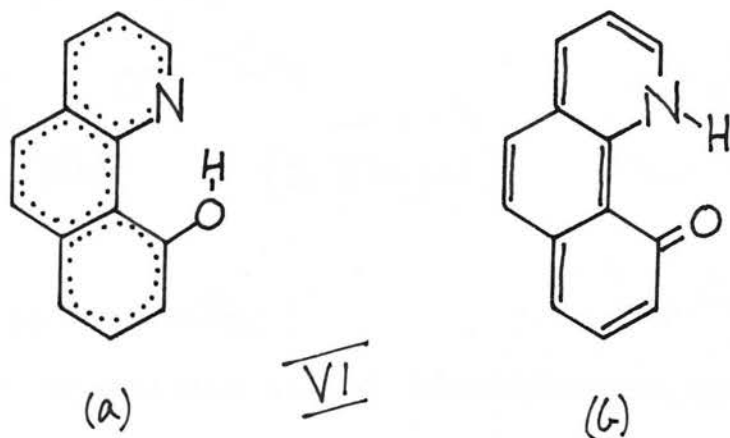
Fig. 10



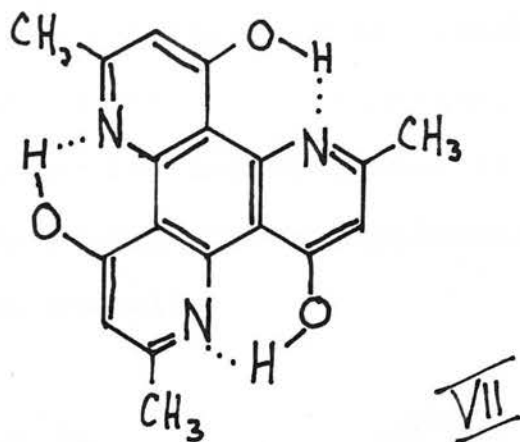
an alternative "parent" compound for the preparation of a potential proton transfer thermochrome. The method which was tried is indicated below. The butadiene reaction was unsuccessful.



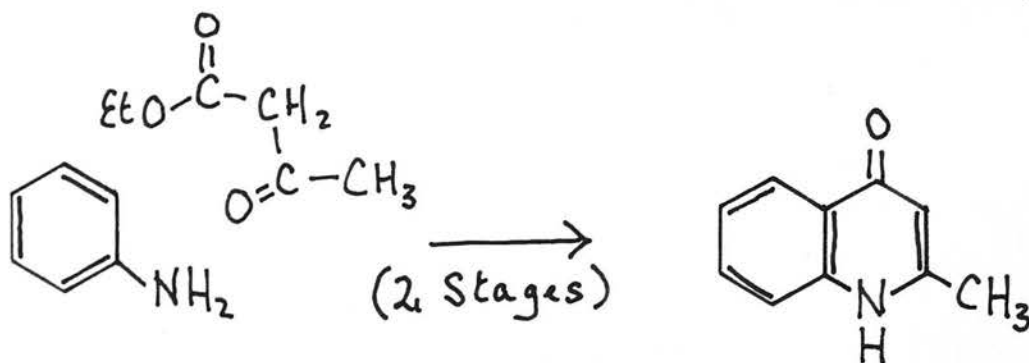
5-hydroxy-4-azaphenanthrene (VI) was prepared since this compound would be expected to have an internal hydrogen bond, but it was not thermochromic. Schenkel-Rudin (1944)(26) has discussed the structure of this compound and he concluded that the hydrogen atom is attached to the nitrogen (VI b). His arguments - among which are that the compound is a very weak acid, is difficult to methylate and does not form complexes with metals, as does 8-hydroxyquinoline - are not very convincing. No mention is made of the possibility that an internal hydrogen bond may account for these effects. The colour of 5-hydroxy-4-azaphenanthrene is very pale yellow which would suggest the phenolic structure (VI a). The compound does not show any differences of colour in different solvents so the absence of thermochromism is not surprising.



An attempt was made to prepare VII in which the lactam structure, being analogous to γ -pyridone, might be expected to be more stable.



Sym-triaminobenzene was substituted for aniline in the reaction (27):



- but without success.

2-hydroxyacridine is not thermochromic, but its tautomeric nature makes it an ideal "parent" for such compounds. To derive a "solid state proton transfer thermochrome" a mechanism must be provided whereby a proton may move (effectively) between the oxygen and nitrogen atoms without requiring the movement of the molecule as a whole. 1:1' methylene-bis-2-hydroxyacridine is the simplest such derivative; but it is not the most general type. A range of unsymmetrical potential thermochromes is possible. 2-hydroxy-1-(2-methylene-5:5-dimethylcyclohexane-1:3-dione)-acridine VIII is an example.

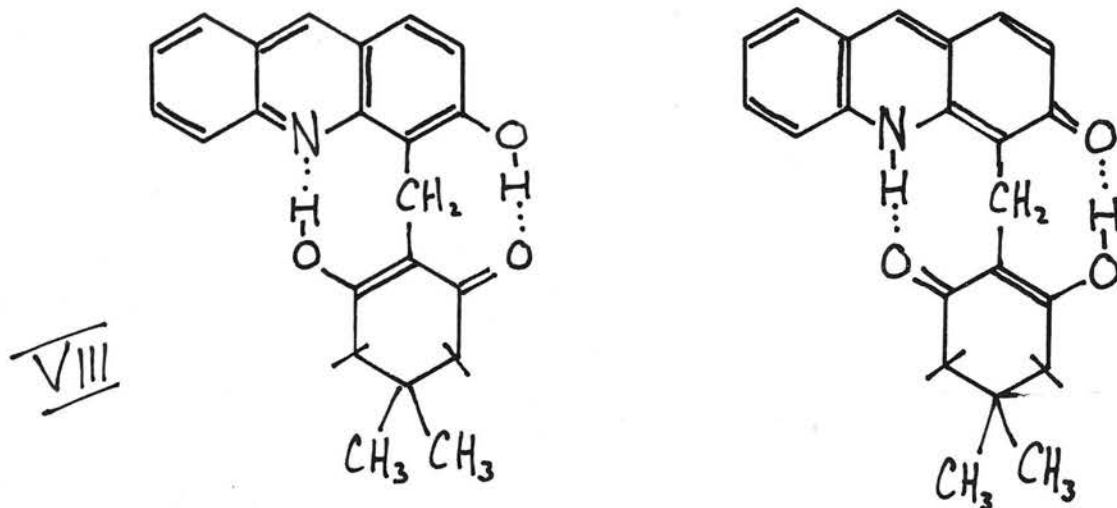
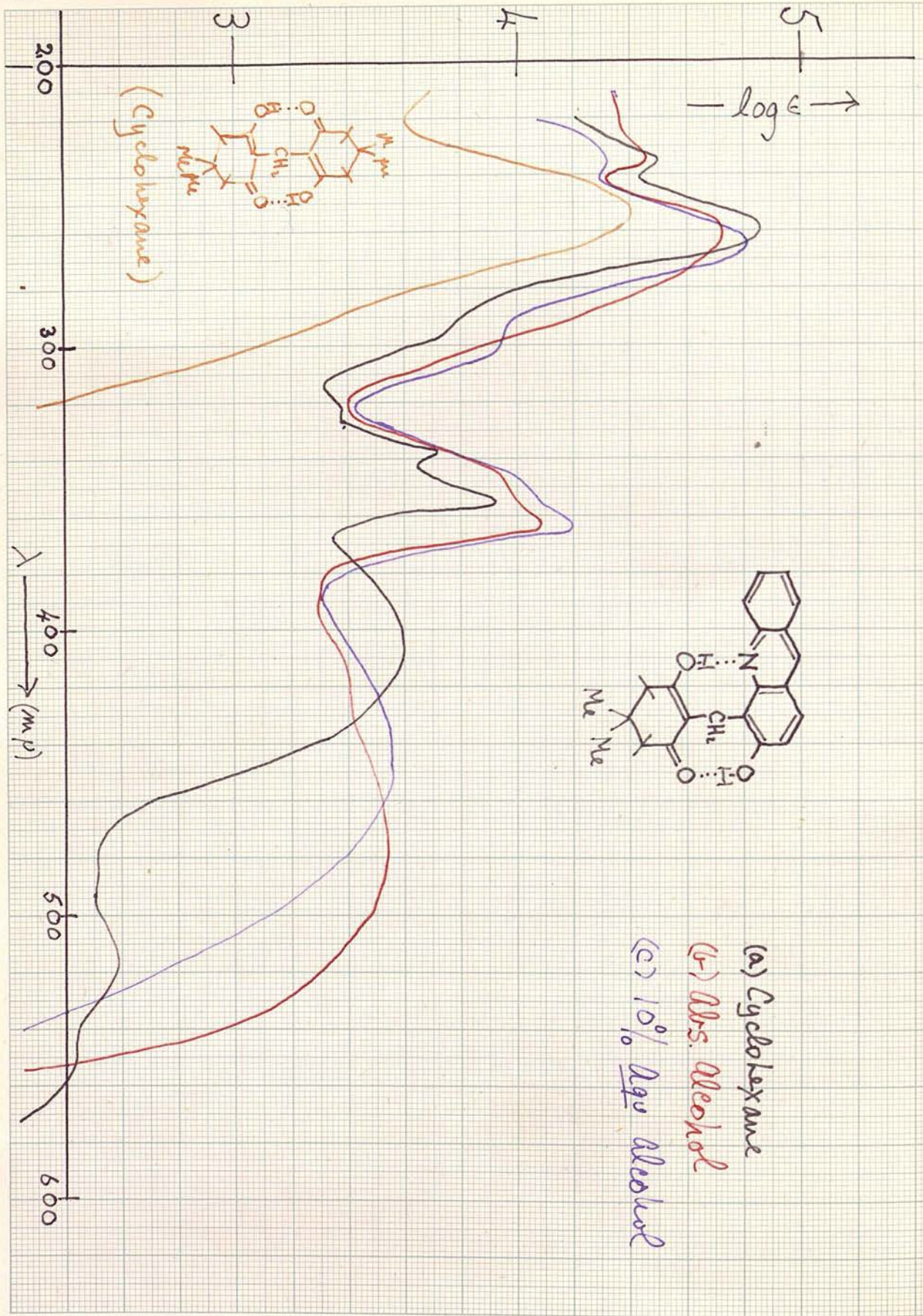


Fig. 11

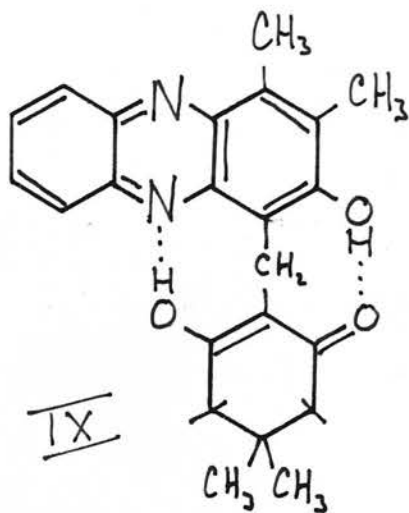
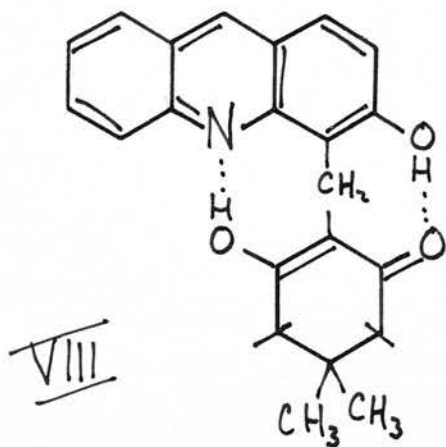
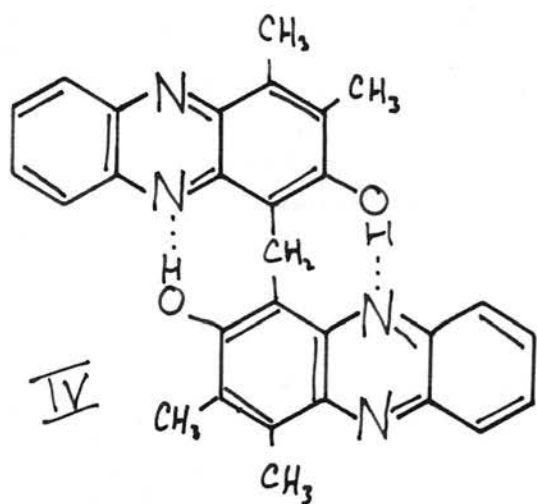
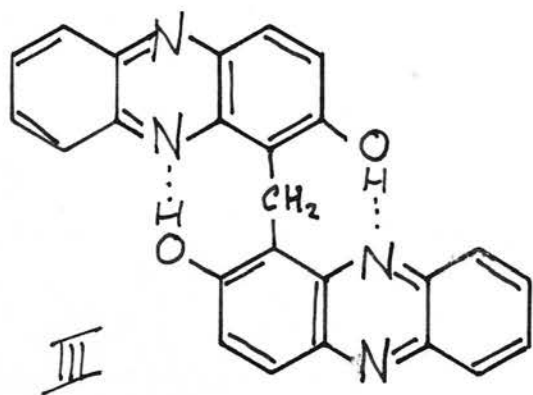
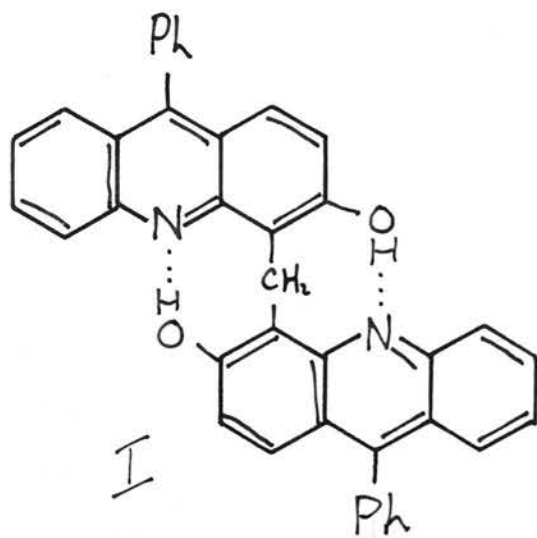
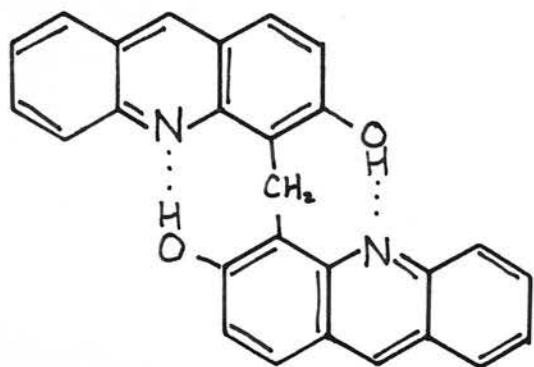


The analogy between the reaction of 2-hydroxyacridine with formaldehyde and the well known reaction of dimedone suggested that a mixture of 2-hydroxyacridine and dimedone might yield, in addition to symmetrical products, the unsymmetrical compound required. By using a large excess of dimedone it was found that a highly crystalline red compound was produced in 50% yield. This compound was found to be generally more soluble in organic solvents than either 2-hydroxyacridine or 1:1'-methylene-bis-2-hydroxyacridine. Its analysis was consistent with the structure VIII. Ultra-violet spectra in three different solvents are shown in Fig. 11, together with that of dimedone-formaldehyde. Here again the tautomerism of the 2-hydroxyacridine nucleus is evident. (The position of the visible lactam absorption peak depends more strongly on the solvent here than in 2-hydroxyacridine, otherwise the spectra are similar.)

But the most important point is that the compound is thermochromic, the bright red crystals becoming reversibly pale orange on cooling to the temperature of liquid nitrogen.

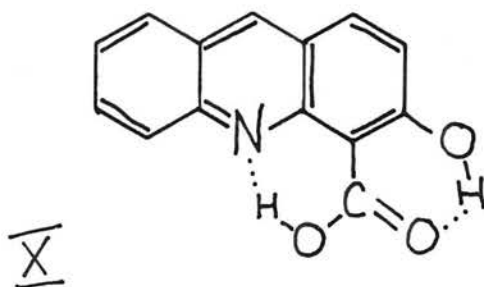
Under similar conditions, but substituting 3:4 dimethyl-2-hydroxyphenazine for 2-hydroxyacridine, 2-hydroxy-3:4-dimethyl-1-(2-methylene-5:5-dimethylcyclohexane-1:3-dione)-phenazine IX was prepared. The crude product was slightly thermochromic in the low temperature region. Recrystallisation

Fig. 12



from toluene gave dull yellow crystals which were still only slightly thermochromic, but a very pure sample of these changed, over a period of a few weeks, into dark reddish brown crystals which were strongly thermochromic, becoming bright yellow on cooling to the temperature of liquid nitrogen.

Unsuccessful attempts were made to prepare the simplest possible derivative of 2-hydroxyacridine incorporating a proton carrier mechanism, namely 2-hydroxyacridine-1-carboxylic acid (X).

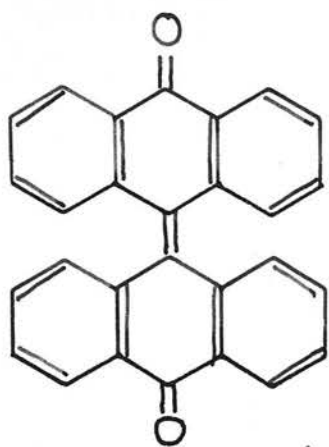


The six compounds which were prepared and found to be thermochromic are shown in fig. 12. They are all tautomeric compounds in which the transfer of protons between the oxygen and nitrogen atom should require neither solvent nor catalyst. None of the "parent" compounds - 2-hydroxyacridine, 2-hydroxy-5-phenylacridine, 2-hydroxyphenazine nor 3:4-dimethyl-2-hydroxyphenazine - is thermochromic. The colours of many of

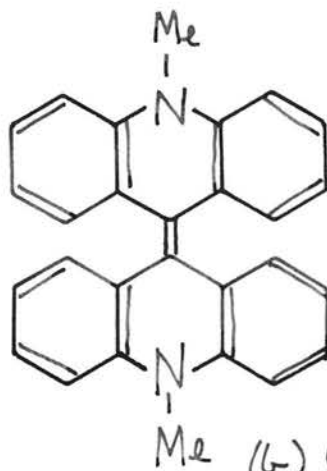
the solid samples of these methylene bridged compounds are intermediate between those of the alternative tautomeric structures, and the nature and direction of the colour changes are consistent with the known colours and relative stabilities of these structures. All this is evidence, independent of any analogy with the behaviour of 2-hydroxy-5-phenylacridine, that the thermochromism of these methylene bridged compounds is due to proton transfer in the solid.

In the last part of this section we shall consider briefly the subject of thermochromism in general to assess the possibility that in our cases it may yet have some other origin.

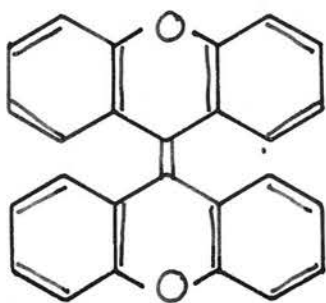
Fig. 13



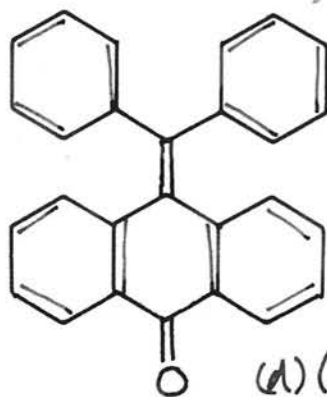
(a) (30)



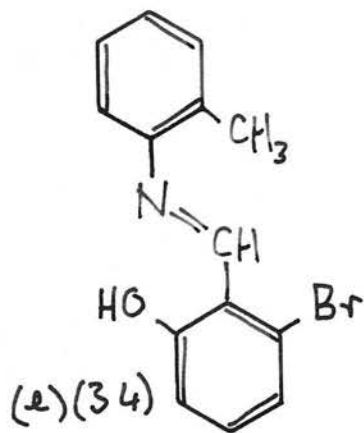
(b) (37)



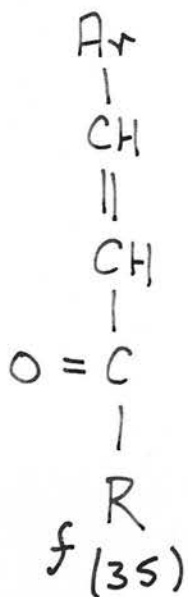
(c) (37)



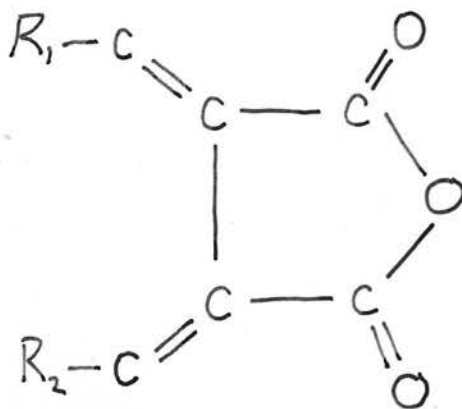
(d) (30)



(e) (34)



f (35)



g (36)

5. THERMOCHROMISM

The first point to notice is that the electronic absorption of a molecule usually depends, to some extent, on temperature (28). This does not mean that most organic compounds are thermochromic, since the effect is usually small and the term is reserved for those cases in which a marked colour change is involved. But there is still a large number of compounds which show thermochromism. The effect occurs most frequently in solution and it is here that it has been most effectively studied. The origin of thermochromism is not understood in all cases but it has been found possible, from more or less empirical classification to predict many new thermochromic compounds.

Fig. 13 shows some cases of compounds which have been found to be thermochromic in the solid.

Schonberg (28) proposed as a working hypothesis that "in overcrowded molecules in which planarity is hindered the degree of non-planarity changes with temperature. This is associated with change of colour, one reason being that resonance is related to planarity. If the molecules absorb in the visible region, thermochromism may be observed with the naked eye." That there is some connection between "hindered planarity" and thermochromism is a reasonable

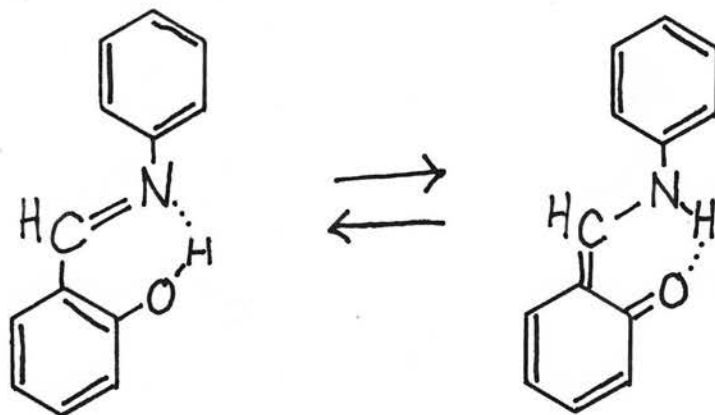
hypothesis in view of the structure of many thermochromic compounds, but the exact nature of this connection is not perfectly clear. The simplest idea is that molecules like bianthrone Fig. 13(a) can exist in thermally excited states which are planar (28)(29) and in which conjugation between the two halves of the molecule is possible. Grubb and Kistiakowsky (30), however, consider that the energy of such a state would be too great and prefer the view that a diradical excited state is involved. According to these authors thermochromism occurs here because the difference between the energy of the ground state and the triplet state has been reduced by torsion in the double bond (31).

Grubb and Kistiakowsky also studied the thermochromism in solution of diphenyl-methyleneanthrone (Fig. 13 d). They found that the only effect on the spectra with rise in temperature was the "trivial" one of a broadening of the visible absorption band, there being no change in the area under the curve. They concluded that here thermochromism was due to a change in the distribution of the molecules between different vibrational states. At higher temperatures there will be a larger number of possible ground states for any given electronic transition and hence a broadening of the corresponding absorption band. (As Schonberg points

out however (28) these authors have not ruled out a possible connection with steric hindrance: they do not explain why "thermal broadening" should be particularly pronounced in this case).

Brand and Davidson (32) have partly attributed the thermochromism of some thiocarbonyl compounds and disulphides, which they studied in solution, to a similar thermal broadening. As these authors say such an effect should be a property of the isolated molecule. It is unlikely therefore to be of importance where thermochromism occurs only in the solid. (In 1:1' methylene-bis-2-hydroxyacridine there is in fact a small thermochromic effect in solution, as there is with 2-hydroxy-5-phenylacridine, but this is in the opposite direction from that shown in the solid: it is not uncommon for an equilibrium between tautomers in solution to be influenced by temperature).

A large number of anils of aromatic aldehydes are thermochromic (33)(34). Of these the anils of O-hydroxy-benzaldehydes appear to be the most common. This might suggest a proton transfer mechanism:

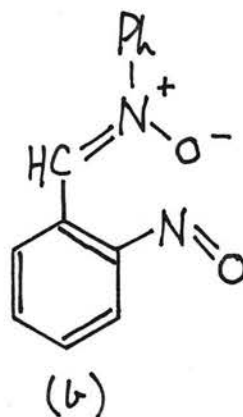
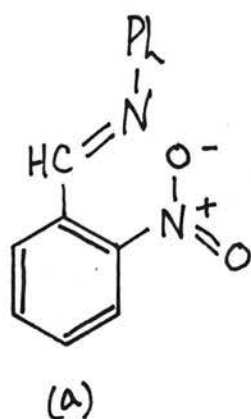


But there are also some p-hydroxy compounds which are thermochromic (which weakens the theory) and three anils of O-nitrobenzaldehyde (which kills it^{*}). (See 34). It is probable that the double bond rather than the hydrogen bond is responsible for the effect.

Thermochromism in the solid has also been reported in semicarbazones and thiosemicarbazones (fig. 13 f) (35), and in the fulgide series (fig. 13 g)(36). In these cases also the origin of the thermochromism is obscure, but it would seem that here again it is conjugated double bonds which provide the necessary link between thermal excitation and electronic absorption.

1:1' methylene-bis-2-hydroxyacridine contains no "sensitive double bond": the only structural features which it has, and which are not shared by 2-hydroxyacridine, are a methylene bridge and a pair of hydrogen bonds. The proton

* But perhaps not stone dead. In theory at least ^{anils of} O-nitro benzaldehyde should be capable of nitro-nitroso tautomerism. (Resonance between (a) and (b) might stabilise an "oxygen bridge" arrangement.)



transfer theory is still the best one.

It might be argued that an objection to the "chemical" proton transfer theory (and which does not apply to "physical" theories) is that it requires that two different molecules should be able to exist in the same lattice: the overall shapes of the lactim and lactam molecules may be very similar, but the electronic structures - the dipoles and polarisabilities - of the two will be quite different and hence also the Van der Waal's forces which play so important a part in determining crystal structure. The "structure of intermolecular interactions" must change when lactam molecules appear in an otherwise "lactim" lattice. How then does the original crystal survive ?

To this we may ask: "How do you know that the electronic structures of the tautomers are different ?" We should expect a reply such as "Their difference in colour is visible evidence of it." This reveals the fallacy in the argument. That thermochromism can occur at all in the solid shows that a crystal lattice can sometimes tolerate changes in the electronic structure of its component molecules. The "objection" holds equally against any possible theory.

REFERENCES.

- (1) Pauling, Proc. Nat. Acad. Sci., 14, 359 (1928);
J. Amer. Chem. Soc., 1931, 53, 1367.
- (2) Pauling, "The Nature of the Chemical Bond" (1940) 286.
- (3) Watson, "Modern Theories of Organic Chemistry" (1941), 242.
- (4) For example:
(a) Coulson, "Valence" (1952), 302-5.
(b) Robertson, "Organic Crystals and Molecules" (1953),
230.
- (5) M. M. Davies and G. B. B. M. Sutherland, J. Chem. Phys.
1938, 6, 755.
J. D. Morrison and J. M. Robertson, J., 1949, 980.
- (6) (a) A. S. Coolidge, J. Amer. Chem. Soc., 1928, 50, 2166.
(b) F. H. MacDougall, ibid., 1936, 58, 2585.
- (7) Pauling, "The Nature of the Chemical Bond" (1940), p.307.
- (8) L. Hunter, J., 1945, 807.
- (9) Hadzi and Shepherd, Trans. Faraday Soc., 1954, 50, 916.
- (10) Burroway, Salem, Thompson, J., 1952, 4793.
See also J., 1955, 3727.
- (11) Dennison, Phys. Rev., 1921, 17, 20.
W. H. Bragg, Proc. Phys. Soc., 1921, 34, 98.
Barnes, Proc. Roy. Soc., 1929, A 125, 670.
- (12) Bernal and Fowler, J. Chem. Physics, 1933, 1, 515.
- (13) Owston, Quart. Rev., 1951, 5, 348.
- (14) Pauling, J. Amer. Chem. Soc., 1935, 57, 2680.
- (15) Wollan, Davidson and Schull, Phys. Rev., 1949, 75, 1348.
- (16) Pauling, "The Nature of the Chemical Bond" (1940), p.304.
- (17) Smyth and Hitchcock, J. Amer. Chem. Soc., 1932, 54, 4642.
- (18) Zaromb, J. Chem. Phys., 1956, 25, 350.
- (19) Trans. Faraday Soc., 1955, 51, 371.
- (20) Owston, Quart. Rev., 1951, 5, 350-353.
- (21) Bacon and Pease, Proc. Roy. Soc., 1955, 230, 359.
- (22) John, Angew. Chem., 1947, 59, 188.
- (23) Badger, J., 1951, 3199.

- (24) Hadzi, J., 1956, 2143.
- (25) Ewing and Steck, J.Amer.Chem.Soc., 1946, 68, 2181.
- (26) Schenkel-Rudin, H.C.A., 1944, 1459.
- (27) Limpach, Ber., 1931, 64, 969.
- (28) Schonberg, Mustafa and Asker, J.Amer.Chem.Soc., 1954, 76, 4134.
- (29) Hirschberg, et al., Bull.Soc.chim.France, 1951, 88-90.
- (30) Grubb and Kistiakowsky, J.Amer.Chem.Soc., 1950, 72, 419-24.
- (31) Mullikan and Roothan, Chem.Rev., 1947, 41, 219.
- (32) Brand and Davidson, J., 1956, 15.
- (33) Brewster and Millam, J.Amer.Chem.Soc., 1933, 55, 763.
- (34) Chalkley, Chem.Rev., 1929, 6, 230.
- (35) Gheorghin, Bull.Soc.chim.France, 1934 (5) 1, 97-105.
- (36) H. Stobbe, Ann., 380, 1-129.
ibid. Ber., 1904, 37, 2239.
- (37) Schonberg, Ismail and Asker, J., 1946, 442.

SECTION 3 (RECAPITULATION)

The first and second subjects of the thesis diverged during the development section: we are now concerned with two rather different problems. The first subject has become, "the tautomerisation and lattice disintegration of the crystalline 2-hydroxy-5-phenylacridine on grinding", and the most significant part of the second subject is now "the thermochromism of 1:1'-methylene-bis-2-hydroxyacridine and related compounds". In the exposition the first subject led to the second: now, in this section, we shall consider in greater detail the simpler question of the thermochromism before finally returning to the original problem.

SECOND SUBJECT

In the last section we considered briefly an "isolated molecule" theory for the thermochromism of 1:1'-methylene-bis-2-hydroxyacridine according to which this molecule is regarded as existing in different energy states corresponding to the lactim and lactam positions for the protons. At high temperatures the higher energy (lactam) state is more fully occupied.

For any lattice to be stable above 0°K . the molecules of which it is composed must be capable of absorbing energy.

This is usually in the form of vibrational energy. In some cases, particularly where the molecules are highly symmetrical, rotation may be possible within the lattice. It seems that the tautomeric nature of our methylene bridged compounds, and the ease with which the tautomers can interchange without any appreciable alteration in the overall conformation of the molecules, is the origin of the thermochromism: these molecules have an additional degree of freedom which is effective in the lattice.

We have already considered the objection that a lattice which was "designed" for lactim molecules is not likely to tolerate many lactam types in its midst: we have seen that this, as an objection to the proton transfer theory in particular, is disingenuous: the phenomenon ^{of} λ thermochromism in the solid may seem unlikely - but it nevertheless exists. Indeed this "objection", far from destroying the proton transfer theory, touches on an essential part of it. An "isolated molecule" theory cannot explain why the thermochromism observed in the solid should not also occur in solution (even less does it explain why it should occur in reverse!). In a "lactim crystal" one would expect a resistance to the appearance of lactam molecules: if all the molecules have identical environments (or if there are a small number of sets of molecules with identical environments) then one would expect

RED GROUND
FORM

RED

ORANGE

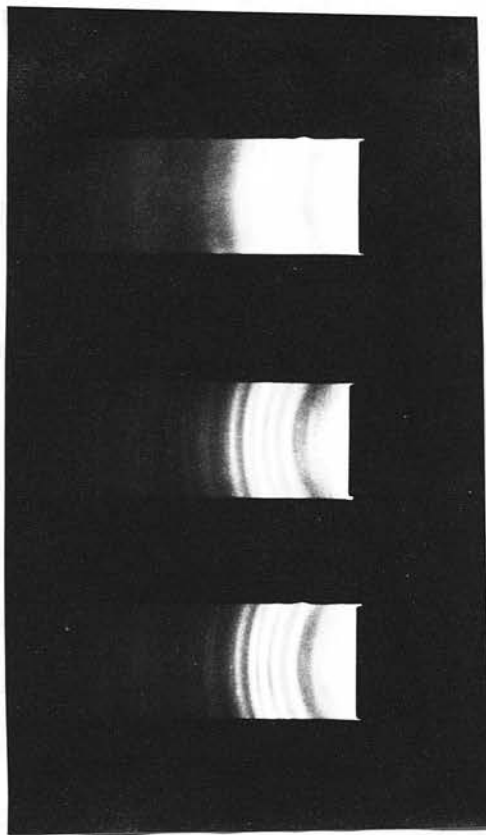


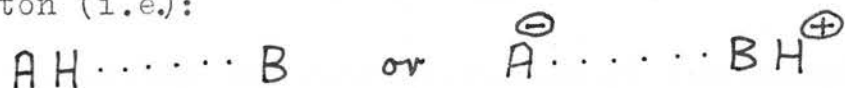
Fig. 1

that the molecules (or members of one set of molecules) would either all prefer a lactim or all prefer a lactam structure. We may say that a lattice will exert an organising effect on the tautomeric states of the molecules. Against this there is the disorganising effect of temperature. The thermochromism in the crystal results from the conflict between these two effects. Except in the crystal the first is absent: in a solution or glass each molecule has a different environment and there is no reason to suppose that either tautomer will be preferred exclusively.

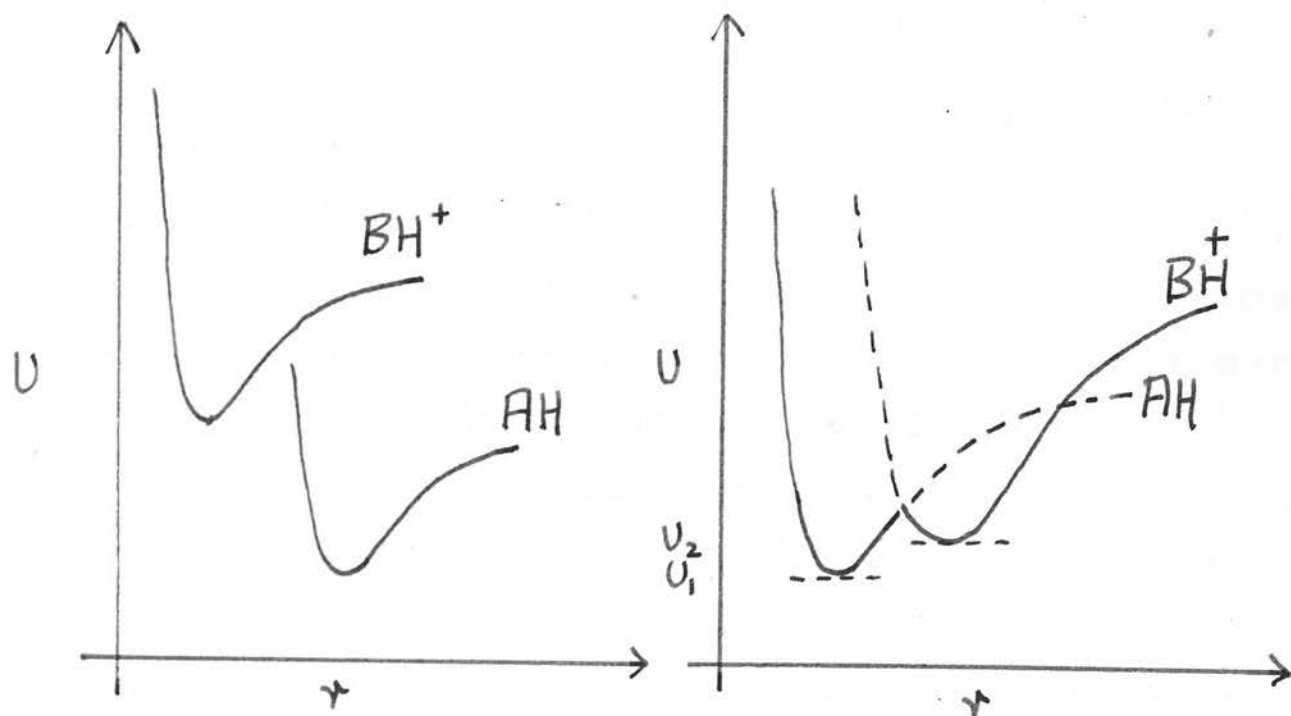
Powder photographs of 1:1'-methylene-bis-2-hydroxyacridine showed that the orange and red crystals and the red powdered form had the same crystal structure (Fig. 1). This suggests that the difference in colour between these samples is due to a difference in the degree of perfection of the crystals (the photograph of the ground form is somewhat more hazy than the others, but this may not be significant). We have mentioned already a possible connection between lattice perfection and the strength of the thermochromism. In a perfect crystal the organising effect referred to will be a maximum: the crystal will be yellow at absolute zero and paler than any other sample at any other temperature. In a glass, to take the other extreme, the organising effect will

be absent; the sample will be red at absolute zero, show no thermochromism and always be deeper in colour than any other sample. Any real crystalline sample will be in a state intermediate between that of the perfect crystal and that of the glass: hence also will its colour and the extent of its thermochromism. The ground red form appears to be a particularly imperfect sample: heating this for a period of hours should have the effect of improving the crystallinity and hence improving the thermochromism and lightening the colour of the sample. This is what is observed. Such behaviour can also be seen in apparently well crystallised samples: annealing always improves the thermochromism and lightens the colour of the sample.

Ubbelohde and Gallagher (1955)(1) have discussed hydrogen bonds in crystals from the point of view of the modern theory of acids and bases. For a hydrogen bond between an acid A-H and a base B there will normally be two positions for the proton (i.e.):



Hydrogen bonding will be strong where there is a considerable overlap between the dissociation curves for the acids AH and BH⁺, (see fig. 2); under these conditions the energy difference between the two basic sites will be comparatively small and above 0°K. some of the protons will be found in the



(a) Negligible hydrogen bonding. (b) Strong hydrogen bonding.

Fig. 2.

higher energy sites. The fraction of "isolated proton transfer defect sites" will be given by:

$$\frac{n}{N - n} = e^{\frac{-(U_2 - U_1)}{KT}}$$

If in considering the thermochromism of 1:1'methylene-bis-2-hydroxyacridine we can substitute the term "lactam defect site" (i.e. pair of proton transfer defect sites) for Ubbelohde and Gallagher's "isolated proton transfer defect site", then it would follow from the above equation that the colour of the crystals will depend on temperature and on the relative

stabilities of the tautomers in the solid. Ubbelohde and Gallagher have taken the crystal as their unit and have described proton transfer as producing defects in the crystal. We have rather concentrated attention on the molecules (which is possible where the hydrogen bonds are internal) and have regarded proton transfer as raising the molecules to higher energy states. But in modifying the original "isolated molecule" theory and taking into account the "organising effect" of the lattice we reached a description very close to the "lactam defect" picture. That the thermochromism can be predicted to some extent (one can predict "potential" proton transfer thermochromes) shows that the structure of the molecule is important in quite a detailed way; but the absence of thermochromism in one of the polymorphic forms of 1:1'-methylene-bis-3:4 dimethyl-2-hydroxyphenazine and the anomalous behaviour in solution shows that the lattice too is important. Neither the molecule nor the lattice is alone responsible for the thermochromism.

TRANSITION

For a very short hydrogen bond (about 2.3 Å) the proton will be symmetrically placed between the end atoms. As the bond becomes longer the proton will move closer to one of the end atoms until finally it is at a normal covalent distance

Fig. 3

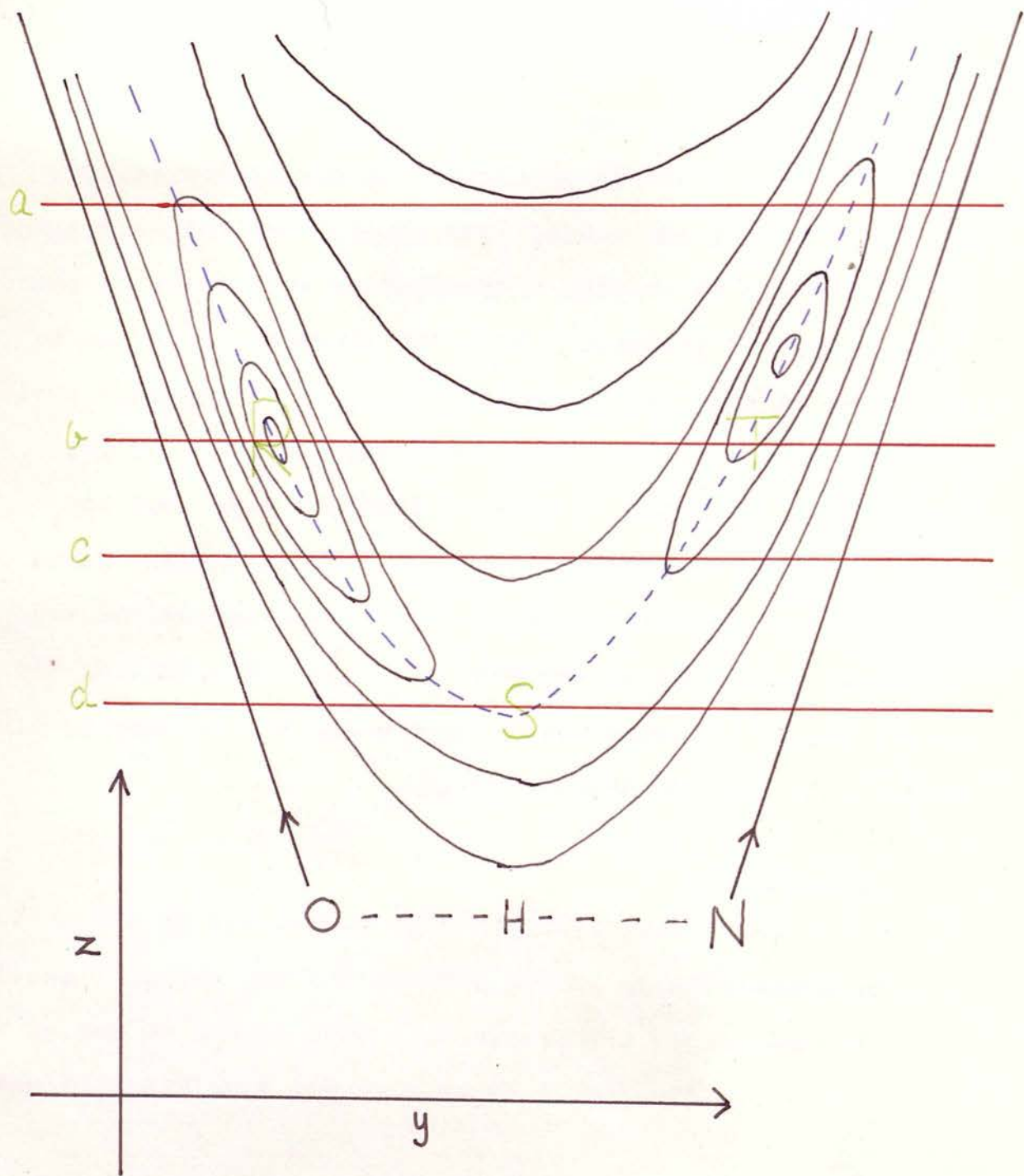
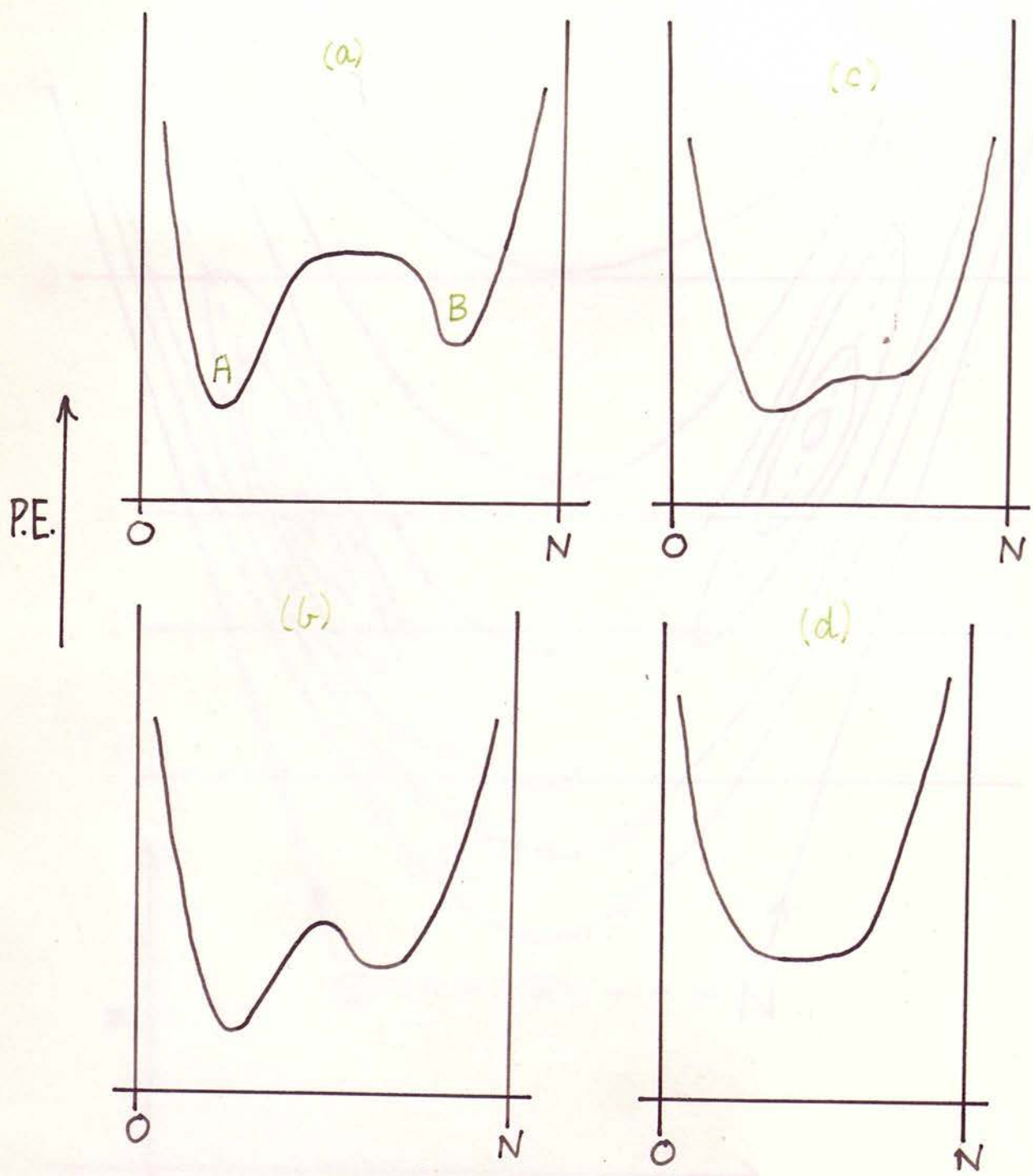


Fig 4



from it (2). When there are two possible positions for the proton, transfer between them may occur; but the potential energy barrier to be overcome will increase with increase in the length of the hydrogen bond. This situation may be summarised by means of a potential energy surface such as that shown in Fig. 3. The movement of the proton between fixed end atoms is represented by the y-axis and sections such as (a) - (d) correspond to potential energy diagrams like (a) - (d) (Fig. 4). Variation in the overall length of the bond is represented by the z-axis.

The surface may be used to illustrate the two extreme ways in which a proton may be transferred across a hydrogen bond. The bond length may remain constant and the system move horizontally, say along the line RT. Alternatively if the two end atoms are free to approach each other then the proton may be transferred by the system moving along the line RST. (If you start with the proton in minimum A (Fig. 4(a)), and then move through (b) and (c) to (d) and back again, you may find that the proton is now in the other minimum (B) - the compression of the bond allows the proton to "get round" the potential energy barrier.) In the first case transfer results from thermal excitation of the proton; in the second, transfer may occur as a result of compression of the hydrogen bond. Ubbelohde and Gallagher (1) suggested that the

piezoelectric properties of Rochelle salt might be attributed to an effect of compression on short hydrogen bonds since in the compressed state the protons will move more readily between their alternative positions.

FIRST SUBJECT.

Grinding will have two important effects on a crystalline material: it will give rise to various mechanical stresses and it will produce local regions of high temperature. Either or both of these may be responsible for the yellow to red change in 2-hydroxy-5-phenylacridine.

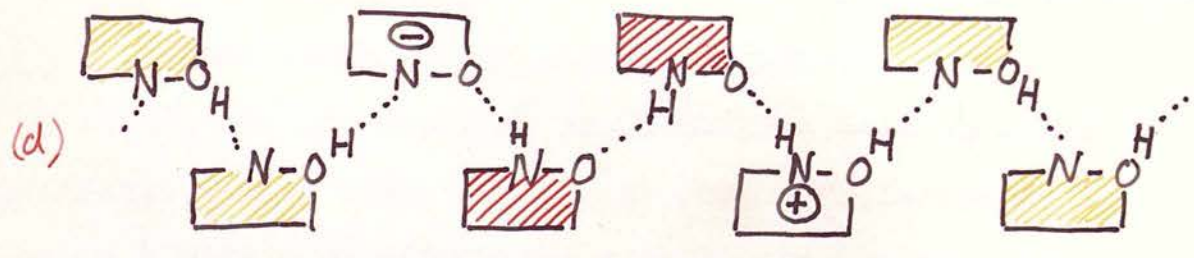
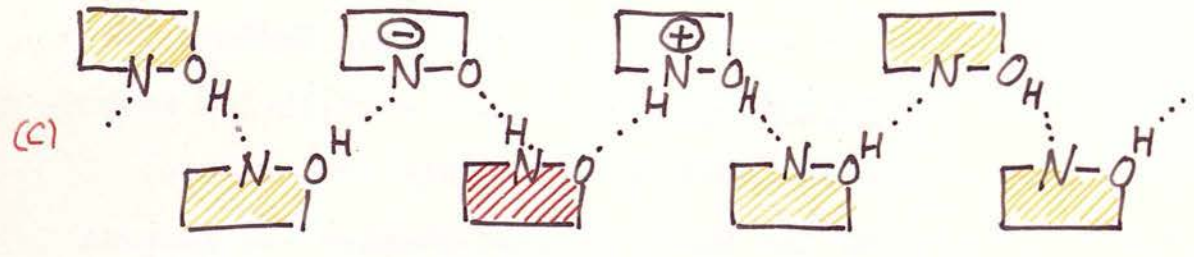
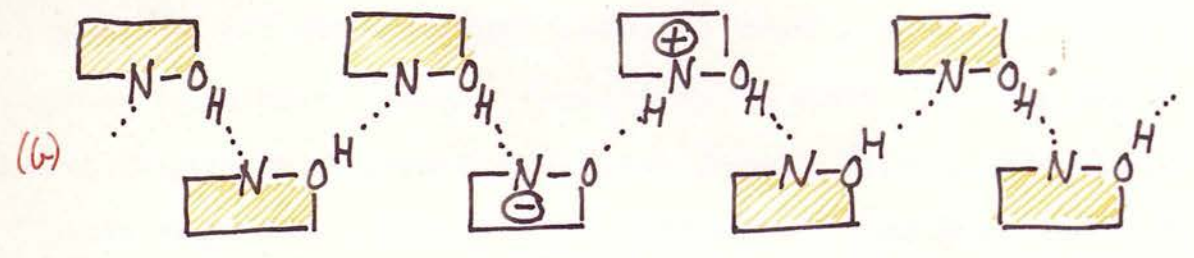
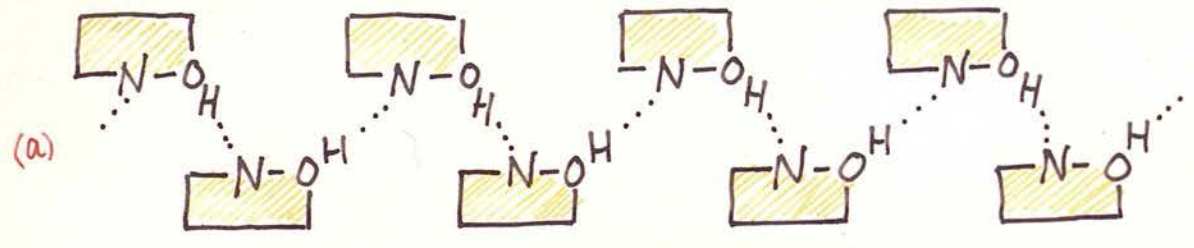
Generally, apart from the minor effect of subdivision, grinding does not raise a solid sample to a higher energy state; with 2-hydroxy-5-phenylacridine it does, and a detailed description of the behaviour of this compound must show exactly how some of the mechanical energy of grinding becomes "caught" as potential energy in the sample instead of being converted into heat. We know already the state of the ground material; we know that it is in a higher energy state because it is largely amorphous and because it contains both lactim and lactam tautomers: we have seen from the thermochromic compounds that tautomerisation in the solid is possible by thermal excitation, and, from the potential energy surface, how it could also occur as a result of the compression of hydrogen bonds. Now we can try to be more precise about

the mechanism of the yellow to red change in 2-hydroxy-5-phenylacridine.

The conversion of mechanical energy into heat, when two surfaces are rubbed together, occurs in the first place at the comparatively small number of points of contact between the surfaces. This may produce local temperatures of a very high order. There is, for example, a relationship between the rate of frictional wear of metal surfaces and the melting point of the metal. When a crystalline organic sample is ground, local melting will almost certainly occur. Prolonged grinding would convert any such sample into an amorphous mass were it not for a simultaneous recrystallisation process. This suggests an explanation for the behaviour of 2-hydroxy-5-phenylacridine: grinding produces local melting, tautomerisation then occurs in the hot melt to give an equilibrium mixture of the tautomers and the melt cools to room temperature. Crystallisation of the glass is slow because the general temperature is low and because the melt contains two different types of molecule.

There are several objections to the above theory. Grinding will also produce local "melting" in the glass: annealing too will be accelerated and since during crystallisation the system moves from a metastable to a stable state

Fig 5



it is this process that would be expected to be the more rapid. There is nothing in the theory to show why grinding should be more effective in converting the crystals into the glass than in the reverse process. Also there are many crystalline compounds - such as sugars - which form comparatively stable supercooled liquids and yet which do not become amorphous on grinding.

The alternative theory is that tautomerisation occurs before the disintegration of the lattice. Let us return to the hypothesis put forward on page 24 and consider a general polymeric arrangement for the molecules, represented diagrammatically in fig. 5(a). The transfer of a single proton would produce a pair of ions in the crystal Fig. 5(b). If further protons were transferred on adjacent bonds lactam molecules would appear between the separating charges. (Fig. 5(c) and (d).) The production of lactam molecules here would cause more disturbance in the lattice than with 1:1'-methylene-bis-2-hydroxyacridine and it is perhaps not surprising that the compound is not thermochromic. If proton transfer were to occur on a large scale the lattice would probably disintegrate. This may indeed be the first stage in the normal melting process: disordering the hydrogen bonds would provide a means of absorbing energy similar to the rotation of molecules which sometimes occurs before melting (3). We

could then understand the behaviour of 2-hydroxy-5-phenyl-acridine. Grinding momentarily raises small parts of the crystals to high temperatures. This has the effect, in the first place, of disordering the hydrogen bonds. The crystal then melts and the hydrogen bonds which provided the mechanism for the transfer of the protons become broken or disorganised. The resulting melt contains both the lactam and the lactim structures. The arrangement forms a kind of "energy trap": the system is raised to a higher energy state by the disordering of the protons and then the mechanism by which the system might have returned to the original state is destroyed.

Of the two methods described by Kehrmann - pressing and rubbing - pressing is the more efficient in causing the yellow to red change, but rubbing also will produce local pressures in the crystals. It is possible then that pressure is the principal agency in disordering the hydrogen bonds - that the protons move along the line.RST rather than RT in Fig. 3.

Suppose a chain of molecules such as is shown in fig. 5(a) were to be compressed in the line of the hydrogen bonds: the stage would be reached (comparable to position S in fig. 3) when the protons would take up a symmetrical position between the nitrogen and oxygen atoms. The molecules would be neither "lactim" nor "lactam": their electronic structures

would have changed (probably towards the state of the negative ion). If this were to occur in the crystals of 2-hydroxy-5-phenylacridine on grinding, the effect might well be what is observed - disintegration of the lattice with a mixture of tautomers in the resulting amorphous state. The possibility of reversible "proton transfer piezochromism" in a suitable (and so far unknown) case is inherent in fig. 3 as is the (realised) possibility of thermochromism: the piezochromism may fail to be reversible in 2-hydroxy-5-phenylacridine because of an unfortunate side effect: the compressed lattice is unstable as a result of the change in the electronic structure of its component molecules - and hence in the Van der Waal's forces between the molecules - and it disintegrates, destroying the mechanism whereby the original state might have been regained.

Possibly both the "thermal" and the "compression" mechanisms operate, either independently or in conjunction. Both explain why the rate of disintegration of the lattice is greater than the rate of recrystallisation. Both require that tautomerisation occurs (or at least starts) before the crystal breaks down. It is in the system of tautomeric hydrogen bonds, which exist extensively only in the crystal that the mechanical energy of grinding, which leads eventually to the destruction of the lattice, is absorbed.

REFERENCES.

1. Ubbelohde and Gallagher, Acta. Cryst., 1955, 8, 71.
2. See for example Lippincott and Schroeder, J.Chem.Phys.,
1955, 23, 1099.
3. See for example Staveley, Quart. Rev., 1949, 6, 65.

SECTION 4 (CODA)

The transfer of a proton across a hydrogen bond is one of the simplest possible chemical reactions. It is also one of the most important. Acids and bases function by the transfer of protons: where, as is usual, the transfer is between atoms capable of forming hydrogen bonds then, at least in solution, it is very rapid (1). In biological systems the co-operative transfer of more than one proton may prove to be of fundamental importance.

In 2-hydroxy-1-(2-methylene-5:5-dimethylcyclohexane-1:3-dione)-acridine the dimedone unit acts as a catalyst for the tautomerisation of the 2-hydroxyacridine unit. It is possible

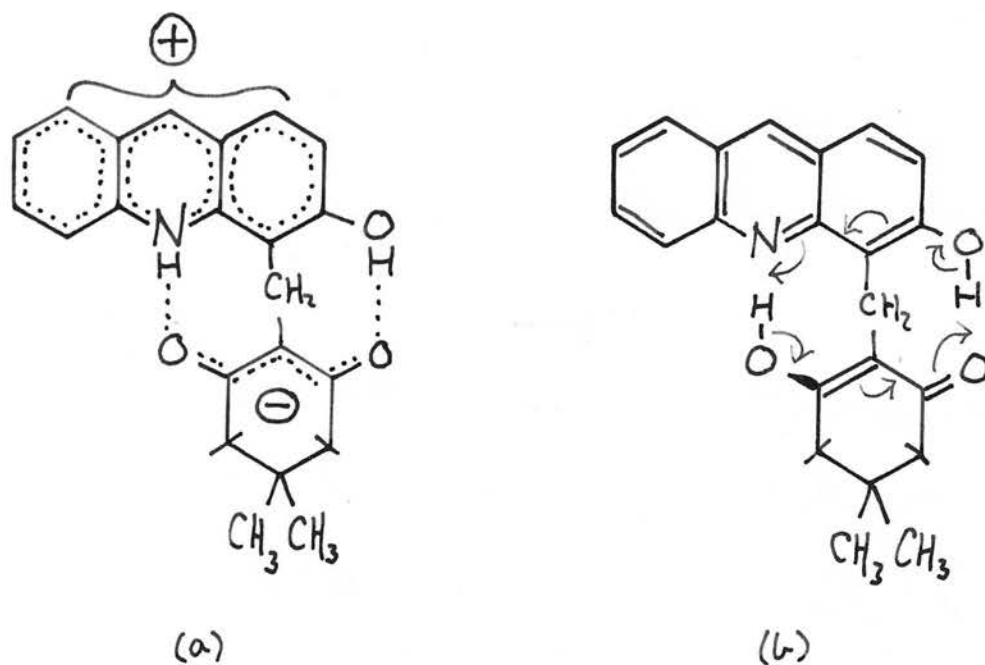


Fig. 1

that the reaction is acid catalysed, the ionic structure fig. 1(a) being formed as an intermediate; but the fact that the thermochromism is restricted to compounds containing a pair of hydrogen bonds suggests that the protons move co-operatively. In this way no ions need be formed during the reaction (see fig. 1(b)) and the dimedone unit will be neither an acidic nor a basic catalyst; neither one in which a proton is donated nor one in which it is abstracted first, but a catalyst in which donation and abstraction occur simultaneously. In principal it is not necessary that the dimedone unit should be attached to the 2-hydroxyacridine molecule, and one could imagine an independent dimedone molecule catalysing the tautomerisation reaction. (Fig. 2).

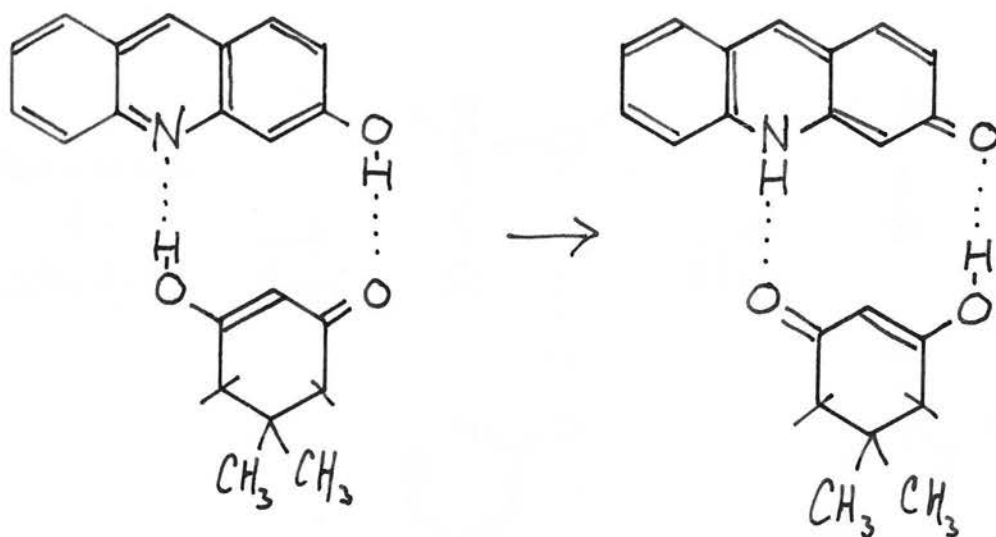
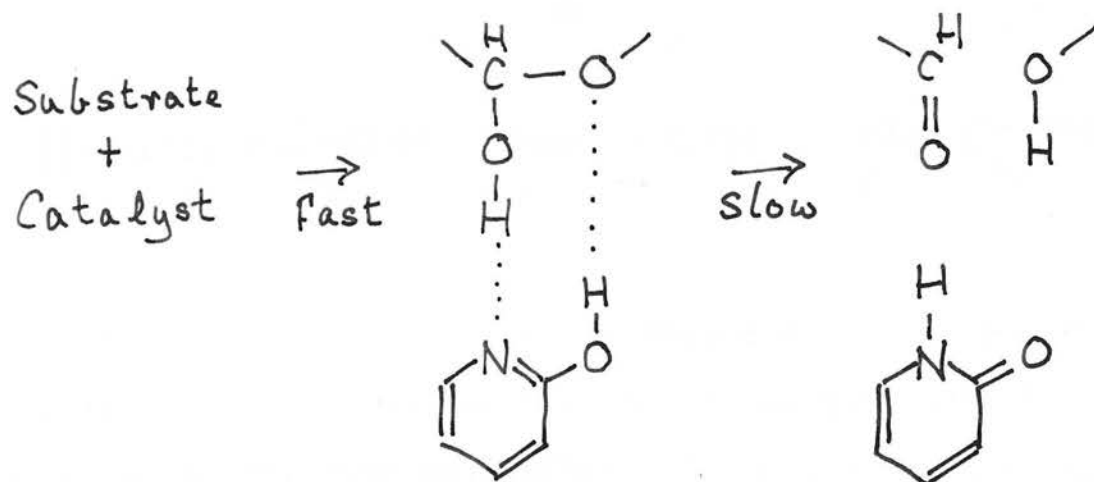


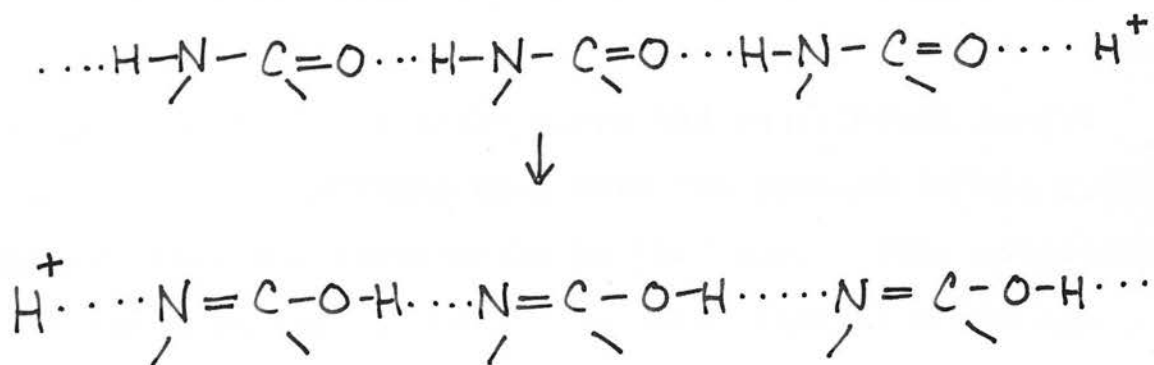
Fig. 2.

(For the sake of argument we are ignoring the impossibility of forming sufficiently short hydrogen bonds in this case.) Catalysts of this type could be highly specific and, to judge from the rate at which the thermochromic changes occur even at very low temperatures, the activation energy required may be very small. Brown and Swain (2) discovered such a catalyst. They found that the mutarotation of tetramethylglucose in benzene was catalysed by α -pyridone to an extent far greater than would have been expected from the acidic or basic strength of the catalyst. γ -pyridone was much less active. From this and other evidence they concluded that they were dealing with a catalyst whose action depended on the concerted attack of its acidic and basic groups on the substrate: this they described as a polyfunctional catalyst.



Brown and Swain suggested that there were important resemblances between enzymes and polyfunctional catalysts: "(1) they have both nucleophilic and electrophilic groups but none of high general reactivity; (2) they excel especially in near neutral solution at low temperatures and in high dilution; (3) they show high catalyst-substrate specificity; (4) they have polar rather than free radical-like reactivity; and (5) they form catalyst-substrate complexes prior to reaction."

It has been suggested (3) that proteins may be capable of transferring protons over a considerable distance by co-operative tautomeric changes in the molecule. In enzymic reactions this would allow a proton to be transferred from one



part of a substrate to another within a comparatively rigid complex. Internal proton transfer in co-operative hydrogen bonds has indeed been put forward (3) as a general energy

transfer mechanism (analogous to electron transfer in the π -electron systems of aromatic compounds) whereby distant groups within the same molecule may affect each other. We might well look for some sort of nervous system in the enormous and yet significantly complex molecules of biological systems.

The energy storage capacity of tautomeric hydrogen bonds may be significant in the functioning of biologically important molecules. A protein, for example, should be capable of existing in a very large number of different high energy states of comparatively long life corresponding to "defect positions" for the protons. The energies and accessibilities of such states will depend on the structure and conformation of the molecule since these will affect the length, angles and electrostatic environment of the hydrogen bonds. Conversely the position of the proton on a hydrogen bond may affect the conformation of the molecule since the equilibrium length and angles for a hydrogen bond with the protons in the different positions will not necessarily be the same. (The potential energy wells in fig. 3(Section 3) were drawn at different levels to illustrate this point - the O-H \cdots N bond is generally stronger and shorter than the O \cdots H-N bond.)

The two chains of the D.N.A. molecule are held together by pairs of tautomeric hydrogen bonds (4) which are similar to those which occur in 1:1'methylene-bis-2-hydroxyacridine.

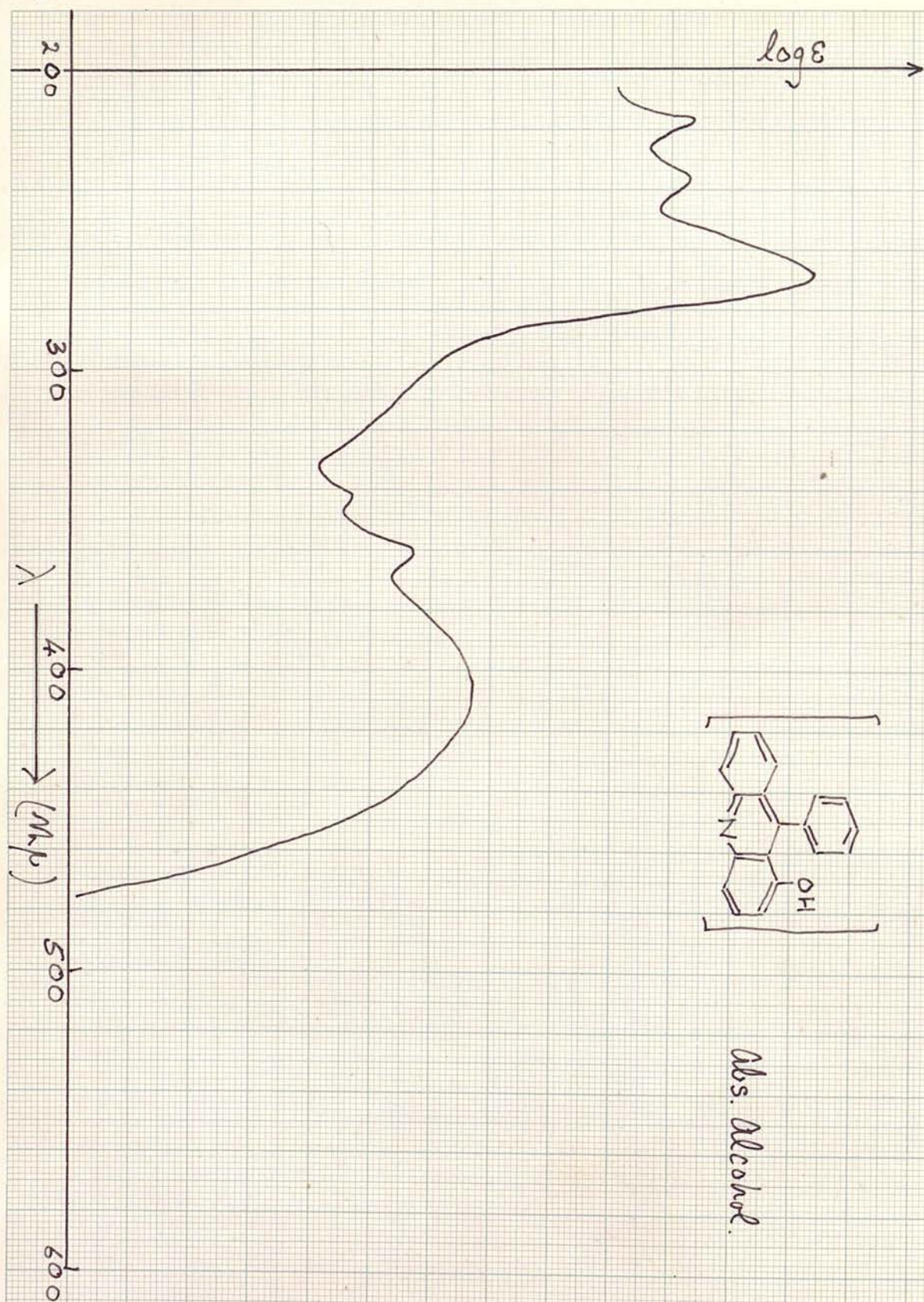
These may provide the molecule with an energy storage mechanism.

In this thesis we have been concerned with model systems for the transfer of protons across hydrogen bonds: as such we cannot say dogmatically that internal proton transfer is important in proteins etc. But our work helps to provide a foundation for theories which require this effect.

REFERENCES

- (1) Ingold, "Structure and Mechanism in Organic Chemistry" (1953), p.723.
- (2) Brown and Swain, J.Amer.Chem. Soc., 1952, 74, 2538-43.
- (3) See Bucher, "Energietransport Innerhalb Lebenden zellen" in Advances in Enzymology, 1953, 14, 22.
- (4) Watson and Crick, Proc.Roy.Soc., 1954, 223, 80.

Fig 1.



EXPERIMENTAL DETAILS.1. ORGANIC PREPARATIONS.PREPARATION OF 2-HYDROXY-5-PHENYL ACRIDINE.

This was carried out using the reaction conditions described by Kehrmann and Matusinsky (Ber., 1912, 45, 3498) but with a modification of their procedure for isolating the product. The crude brick red powder was purified further by chromatography on alumina, with chloroform and alcohol as solvents. With chloroform a very slow moving red band and a fast moving dark yellow band were visible. The yellow band was eluted with the chloroform and the larger red band then removed with alcohol. (The yellow band was probably the unidentified by-product reported by Kehrmann and Matusinsky: a qualitative spectrum of its solution in chloroform is shown in Fig. 1 and the close resemblance of this to the spectrum of 4-hydroxyacridine (Albert and Short, J., 1945, 760) suggests that the by-product is 4-hydroxy-5-phenyl-acridine. Also the colours of the cation and anion of the by-product - orange and red - are those of 4-hydroxy-acridine. The amount of this by-product, however, was comparatively small and the subject was not pursued further.)

The red band yielded 5 g. of material which after recrystallisation from benzene gave 3 g. (10%) of fine yellow needles, m.p. 264°C (with decomposition) which became red on powdering.

2-METHOXY-5-PHENYL-ACRIDINE.

2-Hydroxy-5-phenylacridine (0.1 g.), dissolved in 3 mls. of chloroform, was added in six portions to a solution of diazomethane in ether (prepared from 1 g. of N-nitroso dimethyl urea as described in Vogel. "Practical Organic Chemistry" (1956) p.971). The resulting solution was left in the refrigerator overnight, allowed to warm to room temperature and then the solvent was removed. The residue was dissolved in a minimum volume of chloroform and chromatographed on alumina with chloroform as solvent. There were two principal bands. The first moved rapidly and was pale yellow with a blue fluorescence; it yielded 0.4 g.(40%) of a yellow-green oil. The other band was the red slow moving one of the starting material.

The yellow-green oil could be obtained as crystals, m.p. 137 - 8°C., from absolute alcohol or petrol ether.

THE N-METHYL ETHER OF 2-HYDROXY-5-PHENYLACRIDINE.

2-Hydroxy-5-phenylacridine (0.2 g.) was added to 10 mls. of methyl alcohol and 10 mls. of methyl iodide and the resulting mixture heated under reflux for 20 hours, after which it was evaporated to dryness. The residue was shaken with a solution of caustic soda and then extracted into chloroform. The chloroform solution was reduced in volume and then chromatographed on alumina, eluting with chloroform.

The first band was yellow and probably consisted of a small amount of the O-methyl ether: it was followed by a large deep red band of the N-methyl ether. In addition there was a considerable amount of unchanged starting material forming a dark red band which remained at the top of the column. The product was recrystallised from benzene. Yield 0.1 g. (50%) m.p. 230°C (literature: 231°C : Kehrman and Matusinsky, Ber., 1912, 45, 3498).

3-HYDROXY-5-PHENYLACRIDINE.

(Reference: Hess and Bernthsen, Ber., 1885, 18, 693).

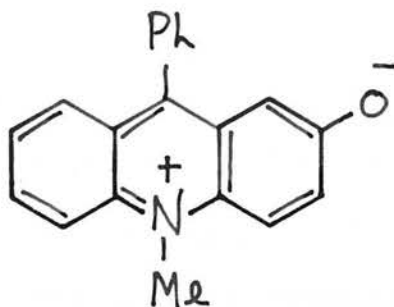
40 g. of p-hydroxydiphenylamine and 80 g. of benzoic acid were mixed intimately with 120 g. of powdered zinc chloride. The mixture was heated at $220 - 240^{\circ}\text{C}$ for half an hour, then at $200 - 220^{\circ}\text{C}$ for four hours and finally at 260°C for half an hour. The residue was dissolved in a minimum volume of alcohol and $1\frac{1}{2}$ litres of a solution of ammonia and ammonium chloride in water added. The residue was extracted with boiling N/5 hydrochloric acid, reprecipitated at 90°C with ammonia, digested at this temperature for 5 mins., cooled, filtered and dried. Crude yield 32 g. The crude product was recrystallised from 300 ml. of absolute alcohol: Yield 20 g. (35%): decomposes at about 270°C .

This procedure is preferable to that of Hess and Bernthsen (24 hours at $220 - 240^{\circ}\text{C}$) who reported their yield as being "slight".

N-METHYL ETHER OF 3-HYDROXY-5-PHENYLACRIDINE.

A sample of this compound was prepared for examination in solution using the same conditions as for the preparation of the N-methyl ether of 2-hydroxy-5-phenylacridine. The chloroform extract was turquoise blue: in water the product was pink, in alcohol purple and in benzene deep green.

The great differences in the absorption of this compound in different solvents is in contrast to the behaviour of the corresponding 2-hydroxy-compound; they are doubtless due to the betaine character of the N-methyl derivative of 3-hydroxy-5-phenylacridine.



(See Nitzsche (Ber., 1943, 76, 1187; ibid. 1944, 77, 377) for discussion of N-methyl ethers of hydroxy-acridines.)

PREPARATION OF 1;1'-METHYLENE-BIS-2-HYDROXYACRIDINE.

2-Hydroxyacridine was prepared according to the method of Albert (J., 1948, 1227) by the reaction of formic acid on

m-hydroxydiphenylamine in the presence of hydrochloric acid.

3 g. of 2-hydroxyacridine and 2 g. of anhydrous sodium acetate were added to 50 mls. of alcohol and the mixture warmed to boiling point. 25 mls. of 40% aq. formaldehyde were then added and the mixture refluxed for 10 mins. The resulting red precipitate was separated by filtration, washed with water and dried. Crude yield 2.8 g. The product could be recrystallised from chloroform or dioxan (although not very efficiently) to give orange needles or red prisms respectively. Yield 2.3 g. m.p. 350°C (with decomposition).

Analysis: Found : C - 80.8% : H - 4.7% : N - 6.3%.

Required: C - 80.6% : H - 4.5% : N - 7.0%.

1:1'METHYLENE-BIS-2-HYDROXY-5-PHENYLACRIDINE.

The same conditions as above were used here, 2-hydroxy-5-phenylacridine being substituted for 2-hydroxyacridine. Crude yield 90%. The product crystallised from benzene as light orange needles and from dioxan as red prisms, m.p. 333 - 5°C (with decomposition).

Analysis: Found : C - 84.8% : H - 4.8% : N - 4.6%.

Required: C - 84.5% : H - 4.7% : N - 5.1%.

1:1'METHYLENE-BIS-2-ACETOXYACRIDINE.

1 g. of 1:1'methylene-bis-2-hydroxyacridine was heated under reflux for 15 minutes with 1 g. of anhydrous sodium

acetate and 20 mls. of acetic anhydride. The reaction mixture was cooled, poured into water, neutralised with bicarbonate and the resulting mixture extracted with chloroform. The product, obtained from the chloroform extracts, was recrystallised from dioxan, m.p. $263 - 5^{\circ}\text{C}$.

Analysis: Found : C - 75.7%: H - 4.5%: N - 4.8%.

Required: C - 76.5%: H - 4.6%: N - 5.8%.

PREPARATION OF 1:3:4 TRIMETHYL-2-HYDROXYPHENAZINE.

Pseudocumoquinone (2:3:5-trimethylbenzoquinone.)

Pseudocumoquinone was prepared using the method of Karrer and Hoffmann (Helv., 1939, 22, 654).

The product from the steam distillation (7 g.) from 20 g. of 2:3:5-trimethylphenol in 2 stages) was used for the next stage in the synthesis, without further purification.

1:3:4-trimethyl-2-hydroxyphenazine was obtained from pseudocumoquinone according to the method of John (Angew. Chem. 1947, 59, 193): it crystallised from ethyl acetate as yellow needles. These were converted to deep violet needles by heating at 135°C : m.p. 213°C .

PREPARATION OF 1:1'-METHYLENE-BIS-2-HYDROXYPHENAZINE.

(1) PREPARATION OF 2-HYDROXYPHENAZINE FROM p-CHLORONITROBENZENE.

p-nitroanisole was prepared according to the method of Blom (Helv. 1921, 4, 1029).

2-methoxyphenazine was prepared by the reaction of p-nitroanisole with aniline in the presence of potassium hydroxide

according to the method of Yoshioka (Chem. Abst., 1953, 6427(b)). Yield 20%. m.p. 123 - 4°C. (recrystallised from 60 - 80° petrol ether). Yoshioka's procedure for demethylation with hydrogen bromide was followed also. Yield of 2-hydroxyphenazine 60%, m.p. 248 - 50°C.

The above method of preparing 2-hydroxyphenazine was found to be both time consuming and - with an overall yield of 12% from p-nitroanisole - inefficient.

(2) PREPARATION OF 2-HYDROXYPHENAZINE FROM BENZOQUINONE.

1:2:4-Triacetoxybenzene.

This compound was prepared by Thiele's reaction on benzoquinone (Thiele, Ber., 1898, 31, 1247). Yield: 80 g. (from 50 g. of benzoquinone) i.e. 60%.

1:2:4-Trihydroxybenzene.

The hydrolysis of 1:2:4-triacetoxybenzene was effected by hydrochloric acid in methyl alcohol according to the method of Robinson and Healy (J., 1934, 1626). Yield 16 g. (from 50 g.) i.e. 70%.

Hydroxybenzoquinone.

The oxidation 1:2:4-trihydroxybenzene was carried out according to the method of Willstatter and Muller (Ber., 1911, 44 2180) by means of silver oxide. Yield 2.5 g. (from 3 g.) i.e. 85%.

2-Hydroxyphenazine.

This compound was prepared according to the method of

Kehrmann and Cherpillod (Helv. 1924, 7, 973) by the condensation of hydroxybenzoquinone with o-phenylenediamine.

(3) ATTEMPTED PREPARATION OF 2-HYDROXYPHENAZINE FROM RESORCINOL.

2-NITROSORESORCINOL.

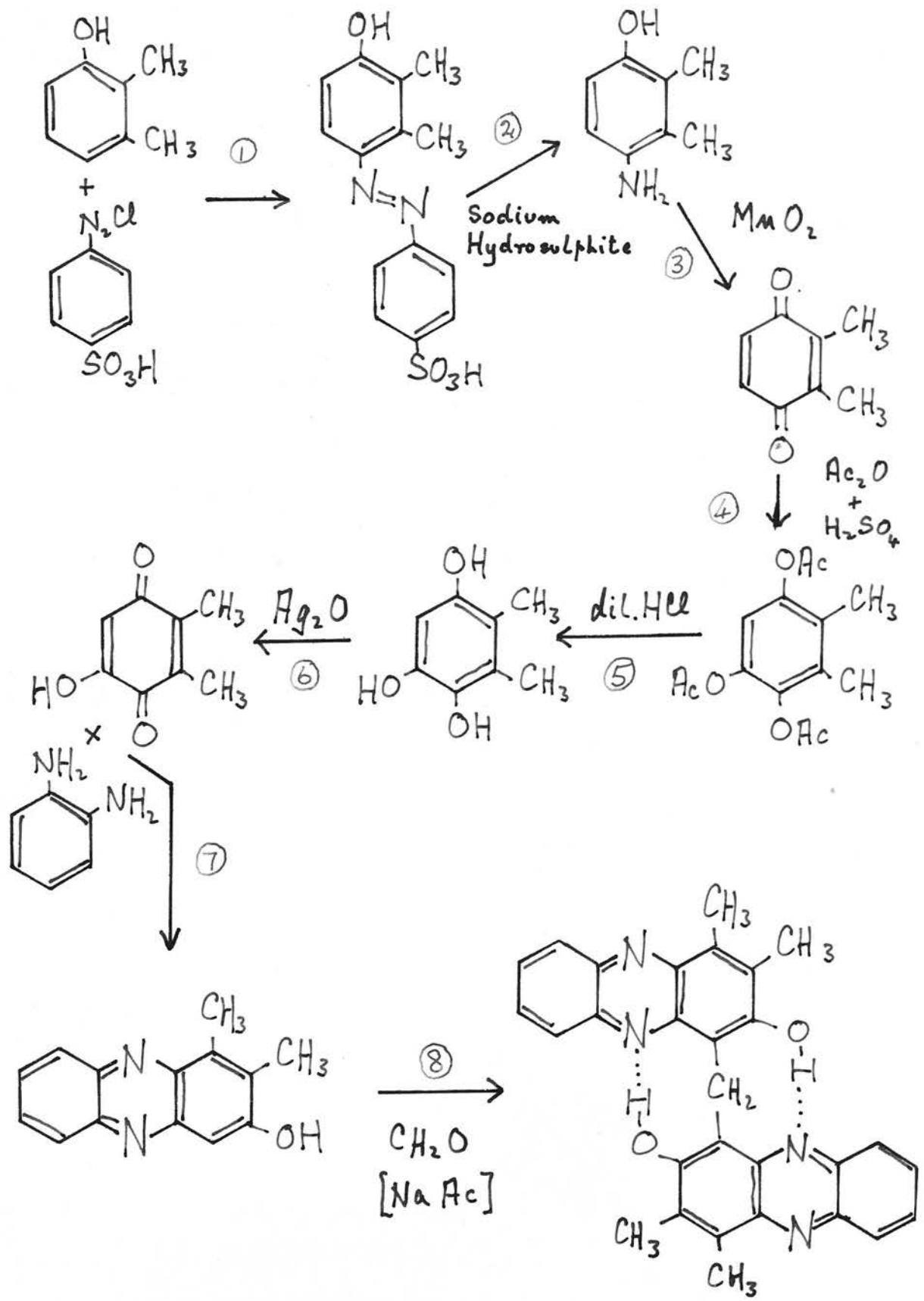
A sample of 2-nitrosoresorcinol was prepared by the action of amyl nitrite on resorcinol according to the method of Ferd (Ber., 1902, 35, 4192). The yield was only 30% instead of quantitative as reported in the literature.

HYDROXYBENZOQUINONE (attempted).

It had been hoped that 2-nitrosoresorcinol would undergo hydrolysis (reacting as a mono-oxime of hydroxybenzoquinone) to give hydroxybenzoquinone in a manner analogous to that whereby 2:3:5-trimethylbenzoquinone was obtained from 2:3:5-trimethyl-4-nitrosophenol. (cf. Karrer and Hoffmann, Helv., 1939, 22, 654).

Mononitrosoresorcinol (0.8 g.) was added to 25 mls. of 1:5 dilute hydrochloric acid together with 3 mls. of hydrogen peroxide, and the mixture refluxed gently over a small flame. Initially the reaction mixture was dark red: after two minutes this colour had disappeared and after ten minutes the solution was red again. The experiment was stopped after 25 minutes. At each of the above stages samples of the reaction mixture were removed, neutralised with bicarbonate, and the solutions extracted with ether. The absence of a bright yellow colour

Fig. 2



in the ether layers showed that the amount of hydroxyquinone formed was negligible. The subject was not pursued further.

PREPARATION OF 1:1'-METHYLENE-BIS-2-HYDROXYPHENAZINE.

The same reaction conditions were used as for the corresponding acridine. The product appeared as a yellow precipitate which was separated, dried and recrystallised from chlorobenzene as yellow needles which darkened reversibly to dull orange above about 200°C and decomposed at 331 - 334°C.

Analysis: Found: C - 74.6%: H - 4.1%: N - 13.3%.

Required: C - 74.2%: H - 4.0%: N - 13.9%.

PREPARATION OF 1:1'-METHYLENE-BIS-3:4-DIMETHYL-2-HYDROXYPHENAZINE FROM 2;3-DIMETHYL PHENOL.

The eight stages of this synthesis are outlined in fig. 2.

O-Xyloquinone (Stages (1) (2) and (3)).

(See Arnold and Zang, J.Amer.Chem.Soc., 1941, 63, 1318.)

Yield 7 g. from 12 g. of phenol (i.e.) 50% : m.p. 55°C.

3:4-dimethyl-2-hydroxyphenazine (stages (4) - (7)).

The general procedure of John (Angew. Chem., 1947, 59, 193) for the preparation of the 1:3:4-trimethyl compound was used again here with modifications in stages (4) and (7).

For the Thiele reaction (stage (4)) the conditions used by Thiele for the preparation of 1:2:4-triacetoxybenzene (Ber., 1898, 31, 1247) were used rather than those of John.

Yield 18 g. (from 9 g. of o-xyloquinone) i.e. 88%: colourless prisms m.p. 88°C.

Hydroxyxyloquinone (stages (5) and (6)).

3.2 g. of this were obtained from 8 g. of 1:2:4-triacetoxy-5:6-dimethylbenzene: (i.e.) 80% yield. Yellow needles, m.p. 114°C.

3:4-dimethyl-2-hydroxyphenazine (stage (7)).

The condensation of o-phenylenediamine with hydroxyxyloquinone was carried out under conditions similar to those described by Kehrmann and Cherpillod (Helv., 1924, 7, 973) for the preparation of 2-hydroxyphenazine. Using molecular proportions the yield was poor but was improved when an excess of o-phenylenediamine was employed.

1.52 g. of hydroxy-o-xyloquinone were dissolved in 15 mls. of warm glacial acetic acid and 2.1 g. of o-phenylene diamine added to the solution over a period of 15 mins. while the solution was being heated on a water bath. The mixture was left on the water bath for another 15 minutes and then allowed to cool to room temperature and left for an hour. The product was then separated and washed with ether. Yield 0.8 g. (i.e.) 30%: recrystallises from toluene as yellow needles; decomposes at about 250°C.

1:1'METHYLENE-BIS-3:4-DIMETHYL-2-HYDROXYPHENAZINE.

350 mgs. of 3:4-dimethyl-2-hydroxyphenazine and

500 mgs. of anhydrous sodium acetate were added to 25 mls. of alcohol. The suspension was warmed to the boiling point and then 5 mls. of 40% aq. formaldehyde added. A yellow precipitate formed almost immediately. The mixture was heated under reflux for a further 20 mins. The precipitate was separated, washed with water, dried (crude yield 85%) and recrystallised from toluene. The first crystals to appear from the rapidly cooled solution were fine yellow needles: on being left to stand overnight without filtering these converted into compact brick-orange crystals. The orange crystals could also be obtained directly by cooling the original toluene solution slowly. Both forms melt with decomposition in the region of 350°C. The orange form darkens reversibly on heating; the yellow form does not.

Analysis: Found : C - 75.1%: H - 5.1%: N - 11.2%.
 Required : C - 76.0%: H - 4.8%: N - 12.2%.

PREPARATION OF 2-HYDROXY-1-(METHYLENE-5:5-DIMETHYL-
 CYCLOHEXANE-1:3-DIONE)-ACRIDINE.

5 g. of 2-hydroxyacridine, 5 g. of anhydrous sodium acetate and 10 g. of dimedone were added to 250 mls. of alcohol and the suspension warmed on a water bath. 50 mls. of 40% aq. formaldehyde were then added. After a minute the 2-hydroxyacridine had dissolved and a deep red colour appeared. The solution was then heated under reflux for 10 mins. It

was then poured into 2 litres of cold water, with stirring, and left to stand for 15 minutes. The red solid was separated, washed with water, dried and dissolved in 200 mls. of benzene. The solution was placed on a short column of alumina and a solution of 1% of alcohol in benzene used for elution. The first deep red band was taken. (The principal coloured by-product, 1:1'-methylene-bis-2-hydroxyacridine moves more slowly on alumina under the above condition: it is also very much less soluble in benzene.) The volume of the fraction from the alumina column was reduced to 30 mls. and the solution left to crystallise. Yield 4.5 g. (i.e. 50%): m.p. 200 - 202°C. Recrystallisation from benzene gave 3.4 g. of large red prisms (m.p. 202 - 203°C) whose colour changed reversibly to pale orange on cooling in liquid nitrogen.

Analysis: Found : C - 76.0%: H - 5.8%: N - 3.2%.

Required: C - 76.1%: H - 6.1%: N - 4.0%.

PREPARATION OF 2-HYDROXY-3:4-DIMETHYL-1-(²METHYLENE-5:5-DIMETHYLCYCLOHEXANE-1:3-DIONE)-PHENAZINE.

1 g. of 2-hydroxy-3:4-dimethylphenazine, 2.g. of dimedone and 1 g. of anhydrous sodium acetate were mixed with 50 mls. of alcohol and heated almost to boiling. 10 mls. of 40% aq. formaldehyde were then added: the suspension dissolved to some extent and the colour of the solution deepened. The mixture was heated under reflux for 20 mins. after which 500 mls. of

water was added to precipitate the products which were separated by filtration washed with water, dried and passed through a short alumina column in benzene. The product obtained by evaporating the resulting benzene solution was recrystallised several times from toluene to give small dull yellow needles, m.p. 219°C. Yield 0.2 g. (i.e.) 20%. Further recrystallisation gave larger yellow needles which slowly turned brown on standing. The brown crystals changed reversibly to yellow on cooling in liquid nitrogen.

Analysis: Found : C - %: H - %: N - %.
 Required: C - %: H - %: N - %.

PREPARATION OF 8:8'-METHYLENE-BIS-7-HYDROXYQUINOLINE.

A sample of 7-hydroxyquinoline was prepared according to the method of Bradford, Elliot and Rowe (J., 1947, 44).

0.85 g. of 7-hydroxyquinoline and 0.85 g. of anhydrous sodium acetate were dissolved in 25 mls. of alcohol and 10 mls. of 40% aq. formaldehyde added. The mixture was heated under reflux for two hours after which 100 mls. of water were added. The crude product was separated, washed with water and dried. Yield 0.5 g. (crude): recrystallised from chlorobenzene 0.3 g. i.e. 35%. Very pale greenish-yellow prisms: m.p. 244 - 5°C.

ATTEMPTED PREPARATION OF 2-HYDROXYACRIDINE-1-CARBOXYLIC ACID.

Attempts to introduce a substituent into the 1-position of 2-hydroxyacridine by the following methods were unsuccessful:

- (1) A Fries rearrangement using 2-acetoxyacridine and aluminium chloride.
- (2) A Friedel-Crafts reaction with acetylchloride and aluminium chloride.
- (3) Bromination.
- (4) Hydroxymethylation (with formaldehyde under various conditions.).
- (5) Chloromethylation (with aq. formaldehyde and conc. hydrochloric acid; also with paraformaldehyde and gaseous hydrogen chloride in benzene.).
- (6) Aminomethylation.

Paper chromatography, using methylethyl-ketone saturated with water as solvent, was used to investigate the reaction mixtures in (4) (5) and (6).

PREPARATION OF 2-HYDROXYACRIDINE-1-ALDEHYDE

(Reimer-Tiemann Reaction).

A solution of 4 g. of sodium hydroxide in 10 mls. of water was added to a suspension of 2 g. of 2-hydroxyacridine in 20 mls. of alcohol. 2 mls. of chloroform were added over a period of 10 minutes. The temperature of the mixture was kept just below the boiling point during the addition and for a further hour. The mixture was then heated under reflux for $1\frac{1}{2}$ hours and the excess chloroform and most of the alcohol removed under reduced pressure. The solid material was separated by filtration, suspended in water and the suspension

acidified with hydrochloric acid. The mixture was warmed slightly and filtered to remove tarry material. The filtrate was then neutralised with bicarbonate and the resulting yellow precipitate separated and recrystallised twice from water. Yield of yellow needles: 0.4 g. (i.e. 20%): m.p. 232 - 3°C.

Analysis: Found : C - 75.1%: H - 4.0%: N - 6.1%.

Required: C - 75.3%: H - 4.1%: N - 6.3%.

This product gave a dark red precipitate with 2:4-dinitrophenylhydrazine, but this was very insoluble and difficult to purify.

ATTEMPTED OXIDATION OF 2-HYDROXYACRIDINE-1-ALDEHYDE.

Paper chromatography with methylethylketone saturated with water as solvent was used here to detect the presence of oxidation products. The following methods were tried:

(1) Treatment with boiling nitric acid at concentrations of up to 80% for periods of 1 - 3 hours. This had little or no effect on the aldehyde.

(2) Treatment with manganese dioxide (compare J., 1956, 4686). Again no new compound was produced.

(3) Treatment with boiling very dilute hydrogen peroxide solution. This produced a complex mixture of products. When a trace of ferrous sulphate was added the solution very soon became colourless.

(4) Aerial oxidation of a hot alkaline solution. This gave a complex mixture of products.

An attempt to prepare the carboxylic acid directly by substituting carbon tetrachloride for chloroform in the Reimer-Tiemann reaction was also unsuccessful.

Fig. 3

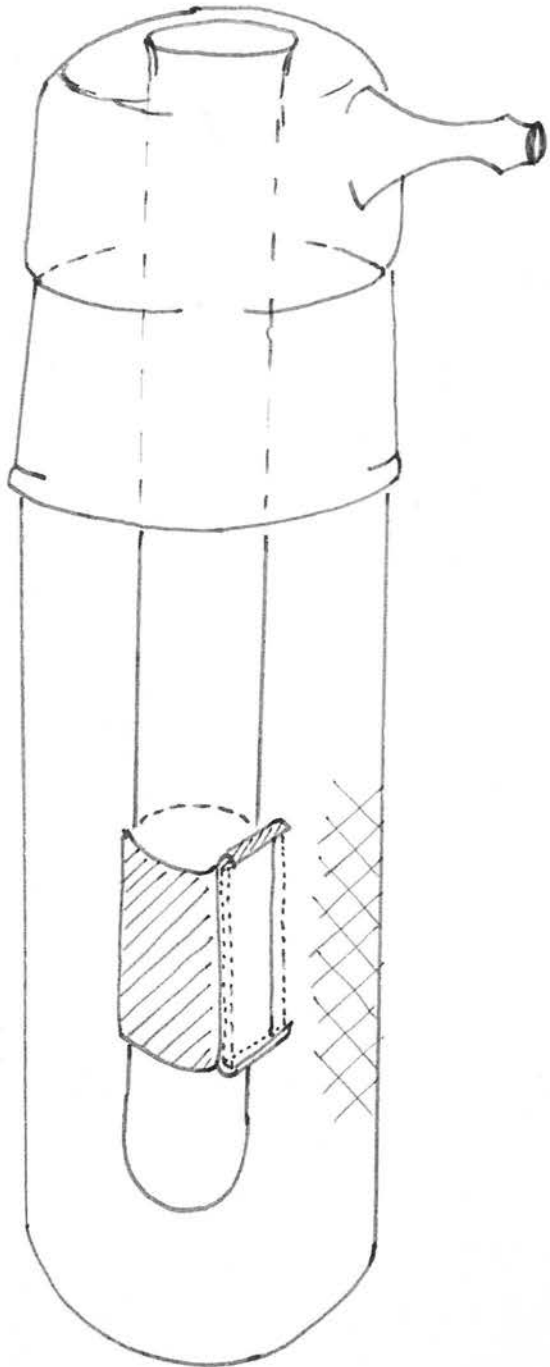
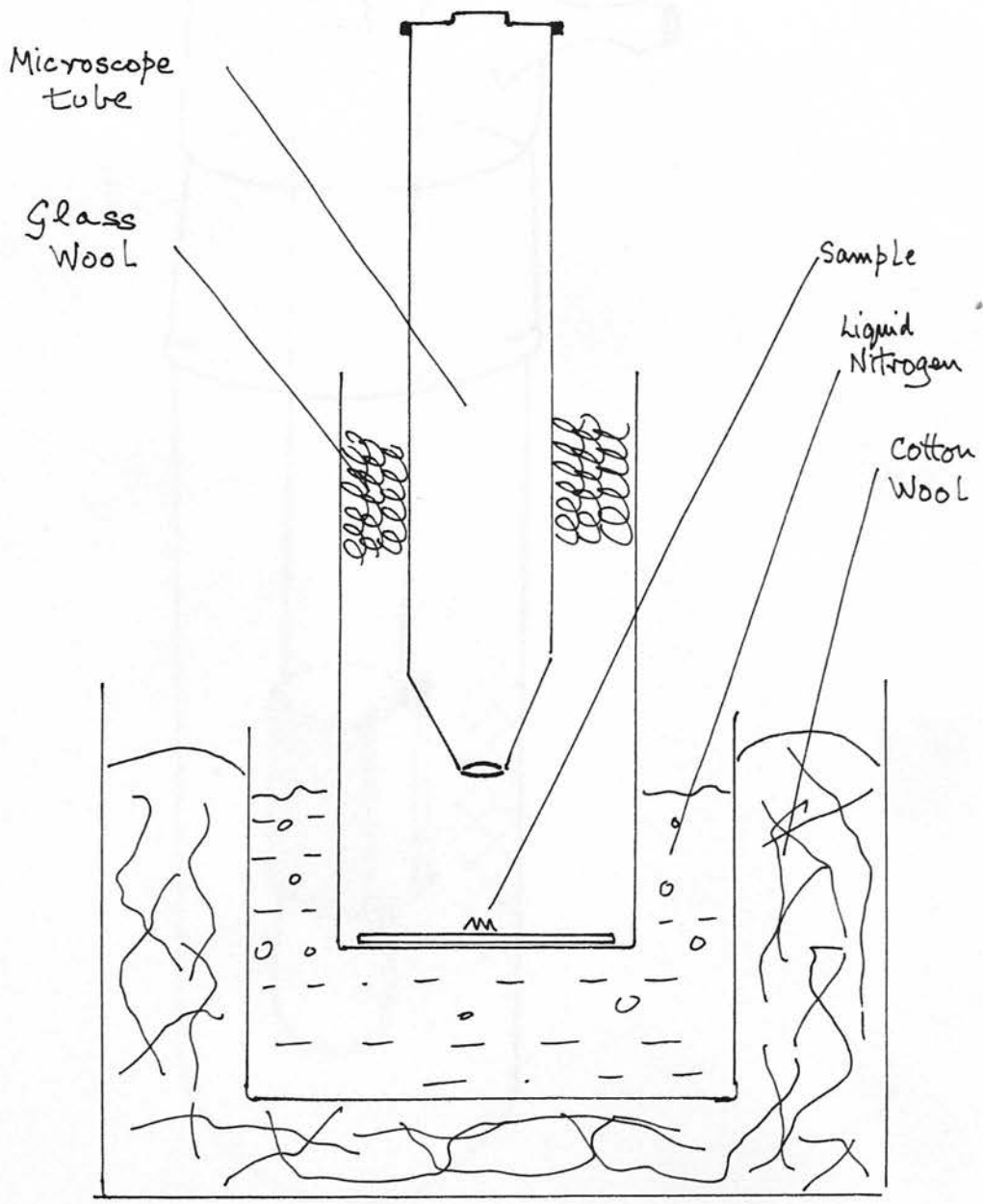


Fig 4



2. PHYSICAL MEASUREMENTS AND OBSERVATIONS.

Ultra-violet spectra were determined using a Unicam S.P. 500 spectrophotometer.

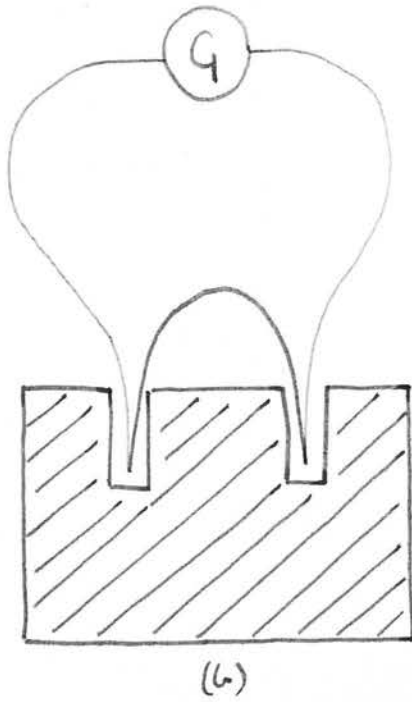
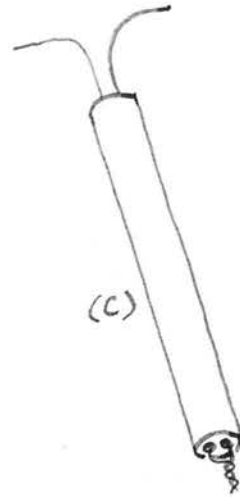
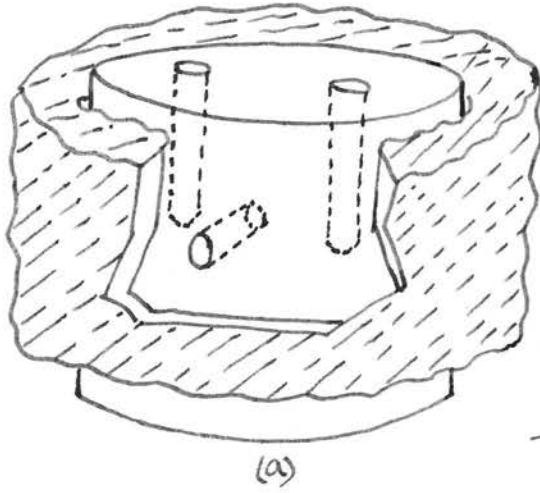
PREPARATION OF SOLID FILMS OF 2-HYDROXY-5-PHENYLACRIDINE.

For the preparation of sublimed films an ordinary "cold finger" apparatus for sublimation under reduced pressure was used (see fig. 3). Some 2-hydroxy-5-phenyl-acridine was dissolved in a little chloroform and the solution evaporated on the vertical inside wall of the outer tube. A silica plate (1 cm. x 3 cms.) was attached to the inner tube by means of a copper carrier to ensure even cooling of the plate. A mixture of solid carbon dioxide and acetone was placed in the inner tube and the outer tube heated in an oil bath at 180 - 200°C while the space between the inner and outer tubes was evacuated to 0.4 mms. Under these conditions a film of the required thickness was formed in 1 - 2 minutes.

A Kofler hot stage microscope was used to determine melting points and to examine the behaviour of solid samples in the temperature range from room temperature to 350°C. In the range below room temperature an ordinary microscope tube was used and set up as shown in fig. 4. The glass wool is necessary to prevent excessive condensation of ice on the sample.

The heating curve of 2-hydroxy-5-phenyl-acridine against sodium chloride was obtained using an apparatus lent by Dr. Taylor and consisting of a large, wadded metal block with three

Fig. 5



holes bored in it (fig. 5a). A sample of the yellow form of 2-hydroxy-5-phenylacridine was placed in one of the vertical holes together with one junction of a copper-eureka-copper thermocouple. The other junction of the thermocouple was embedded in some dry sodium chloride placed in the other vertical hole. The thermocouple wires were prevented from touching the walls of the block by means of alumina tubes (fig. 5c). The horizontal hole was used for an ordinary thermometer.

When the apparatus was set up, the block was slowly heated from room temperature up to 165°C by means of a bunsen burner, the flame of which was carefully shielded from draughts. Readings of the galvanometer were taken every minute.

By heating the thermocouple junction which had been placed in the 2-hydroxy-5-phenylacridine the galvanometer was deflected to the left. In the heating curve, in which deflection to the right was plotted against time, there is a downward trend in the region of 135°C showing that here an exothermic change was taking place.

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