AN INVESTIGATION OF SOME QUINOLINE AND ACRIDINE DERIVATIVES OF POSSIBLE THERAPEUTIC VALUE.

A Thesis Submitted in Fulfilment of the Requirements for the Degree of Doctor of Philosophy in the Faculty of Science of Glasgow University

By

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1937.

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The author wishes to express his gratitude to Professor F.J.Wilson, D.Sc., Ph.D., F.I.C., and to Doctor M.M.J.Sutherland, D.Sc., F.I.C., for their kindly direction throughout this research and much valuable advice.

He also wishes to thank Professor C.H. Browning, F.R.S., of the Pathological Department of Glasgow University, for his generous co-operation, and the Governors of the Royal Technical College for the Research Assistantship granted to him during the Sessions 1934-37.

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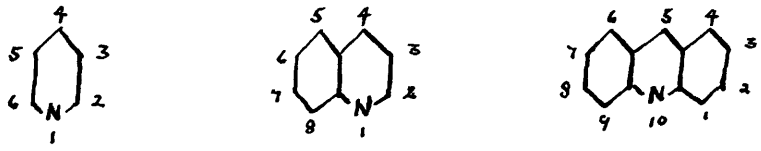
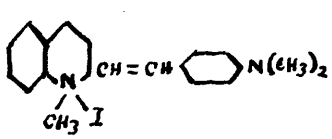
NOTES ON THE NOMENCLATURE ADOPTED.

The pyridine, quinoline, and acridine rings have been numbered as follows :-

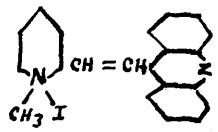


Derivatives of 2-methyl quinoline have been referred to as such, and also as "quinaldine" compounds for the sake of brevity.

Browning and his collaborators studied a series of unsaturated compounds which they regarded as derived from styrene , thus compound (1) was named "2(p-dimethylamino styryl) quinoline methiodide ".



(I)

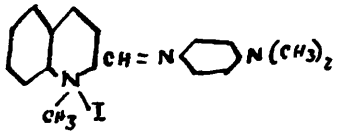


(II)

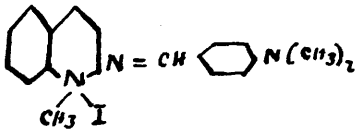
As the compounds prepared by the author posess a heterocyclic ring on either side of the unsaturated linkage, they cannot properly be regarded as derived from styrene, and have been considered as derivatives of ethene. Compound (11) is named " s-(2-pyridyl methiodide)-5-acridylethene." Since the "ethene" nomenclature is more generally applicable than adopted by Browning, the latter's compounds have been re-named on this system, so that (1) becomes :-

" s-(2-quinolyl methiodide)-(p-dimethylamino phenyl)ethene." To avoid confusion, and also for the sake of emphasising the very real connection between Browning's compounds and those prepared by the author the ethene system has been employed throughout this thesis. (In one case however, it was considered too complicated, and the styryl system was used since it happened to be applicable to the case in question, cf. Section III(c).)

Browning's "anil quinoline" nomenclature has been adopted for the naming of all compounds to which it can be applied; thus (III) is "2(p-dimethylamino anil) quinoline methiodide".



(III)



(IV)

In the case of the anils of 2:8-diamino acridine described in Section I, the "benzylidene" nomenclature has been adopted , since these compounds are different in character to those prepared by Browning. Thus, (IV) is of a type analogous to the 2:8-diaminoacridine anils and would be described as "2-p-dimethylaminobenzylideneamino quinoline methiodide" since it is different to (III).

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NOTE: The majority of these references appear again in their appropriate places throughout this thesis. The papers by Browning and his collaborators have been referred to under the first name only for the sake of brevity, although Professor Browning was not responsible for the chemical sections.

INTRODUCTION.

Chemotherapy is still a comparatively young science, but during its thirty years of existance it has achieved many remarkable successes.

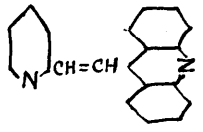
It was Paul Ehrlich who first placed chemotherapy on a scientific basis, by endeavouring to correlate the chemical and pharmacological properties of the drugs used. Unfortunately, few relationships of a general nature have been found to exist, so that it is still impossible to predict the pharmacological properties of a compound from a mere study of its molecular architecture.

Every chemotherapeutically active substance does not stand alone however, without any pharmacological relationship to its analogues. In a series of compounds it is frequently found that a certain therapeutic property is common to all members, so that it is possible to trace the influence of various substituent groups; but it is often the case that the rules which are established for one series do not hold for another.

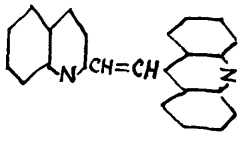
The chemotherapeutic agents of the acridine and quinoline ethene groups lend themselves to the study of the relationship between chemical and pharmacological properties, as the influence of substituent groups is often very marked.

In this thesis, some new acridine and quinoline ethene derivatives are described, and these compounds will now be considered in detail. Each series has been confined to a separate section for the sake of clarity, and each of these sections is, as far as possible, complete in itself.

In Section I a series of anil compounds of 2:8-diamino acridine is discussed, while sections II, III, and IV are concerned chiefly with a series of ethene derivatives prepared from 5-aldehyde acridine. Thus Section II contains pyridine-acridine ethenes of type (a), while Section III deals with analogous quinoline-acridine ethenes of type (b).

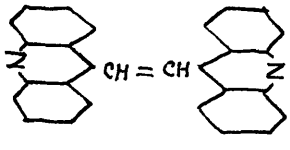


(a)



(b)

In Section IV an unsuccessful attempt was made to prepare acridine-acridine ethenes of the following type :-



The means whereby substituent groups can be introduced into the acridine ring of the ethene compounds prepared are also

briefly discussed in this section.

In addition to the compounds mentioned above, a few quinoline ethene and anil derivatives of the type studied by Browning and his collaborators have been prepared.

The theoretical portion of this thesis has been reserved largely for discussions of a general nature, results of biological tests, and consideration of negative results or cases of especial difficulty arising out of the preparation of the various compounds studied. It contains therefore, little information on the methods of preparation employed, since this is available "in extenso" in the experimental section, together with any relevant theoretical considerations.

SECTION 1. DERIVATIVES OF 2:8-DIAMINOACRIDINE.

The best known antiseptic for the treatment of bacterial infections is 2:8-diaminoacridine methochloride, or "Euflavine"; but there are many other chemically related compounds on the market , and the acridine molecule appears to be capable of great therapeutic activity if suitable substituent groups are present.

In 1921 , Browning and his collaborators tried to trace the source of the antiseptic power of "Euflavine", but were forced to the conclusion that the activity was due to the molecule as a whole , and connected with the presence of the free amino groups. (Proc. Roy. Soc. (1922) B. 93. 330.) Later, the same workers prepared and examined several anil derivatives of quinoline, and found some of them therapeutically active.

In view of Browning's work, it was thought that it would be of interest to prepare some anils of 2:8-diaminoacridine , and examine their chemical and pharmacological properties. A search through the literature was made, and it was found that no anil derivatives of 2:8-diaminoacridine were known , but a bisbenzylidene anil of 3:7-diaminoacridine was mentioned. (Coll. Czech. Chem. (1930) 2, 385.)

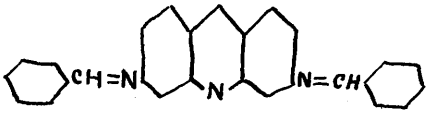
An "anil" or "Schiff's base" is formed when an aromatic aldehyde condenses with a primary amine. For example, benzaldehyde and aniline react to form benzylidene aniline :-

$$C_6H_5 \cdot CHO + C_6H_5 \cdot NH_2 \longrightarrow C_6H_5 \cdot CH{=}N \cdot C_6H_5 + H_2O$$

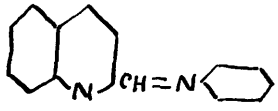
There is , however, an alternative method of preparation ; compounds containing the anil group -CH=N- can also be prepared by condensing nitroso compounds with substances posessing a reactive methyl group , as follows :-

$$R \cdot CH_3 + ON \cdot C_6H_4 \cdot N(CH_3)_2 \longrightarrow R \cdot CH{=}N\,C_6H_4 \cdot N(CH_3)_2 + H_2O$$

The author prepared the anil derivatives of 2:8-diaminoacridine by the first of these methods , whereas Browning prepared his anil-quinoline compounds by the second.



(1)



(2)

The anil (1) is derived from 2:8-diaminoacridine and is a true "Schiff's base" of the acridine compound; while (2) is not a "Schiff's base" of aminoquinoline, but of aniline, since the nitrogen atom of the anil group is not attached to the quinoline nucleus. Thus , Browning's products are anils

of relatively simple bases such as aniline, p-amino acetanilide, and p-amino dimethylaniline ; whereas the author's compounds are anils of the more complex diamino-acridine, and their complexity is reflected in their compartive instability.

Anils vary greatly in their ease of hydrolysis by acids, some are readily decomposed while others are not. It was found that the anils of 2:8-diaminoacridine were extremely easily hydrolysed , so that even exposure to the slightly acidic atmosphere of a chemical laboratory was sufficient to cause partial decomposition. The anils prepared by Browning's collaborators appear to be much more stable , and a "sulphonation product" of an anil has been described, (Proc.Roy.Soc. (1926);B.100; 312.)The author considers that this compound cannot possibly have been an anil , but if it was, it must have posessed very exceptional stability.

The available methods for the preparation of anils, and the conditions which favour condensations with aromatic aldehydes were examined , and found to be numerous and very varied. In some cases condensation takes place readily in the cold , while in others elevated temperatures and catalysts are required. Extreme examples were found in which condensations required days or even weeks for their completion, (Ber. 35. 2591.) , although anil condensations were almost invariably rapid.

Various catalysts were employed by different workers. Reddelein used small quantities of halogen hydracids or zinc chloride,(Ber. 47. 1355. & Ber. 43. 2477.) ; while Knoevenagel worked with iodine (J. Pr. Chem. (1914),2, 89, 1-50.). Various primary and secondary amines , and heterocyclic bases have also been used to make aldehydes condense, such as ethylamine, diethylamine, and piperidine, (Ber. 35, 1143.) or pyridine and alcoholic ammonia , (Ber. 31. 2604.)

The author found that zinc chloride inhibited the formation of anils of 2:8-diaminoacridine ; while iodine, pyridine, and alcoholic ammonia appeared to have no effect on the reaction. Piperidine and diethylamine on the other hand, both exerted a catalytic action , and the former was found to be a very efficient condensing agent and was used for the preparation of all the anils of diaminoacridine.

Numerous experiments were performed in order to determine the best conditions for the reaction, and it was found essential to purify the aldehydes used for the various condensations , as any traces of acid present had a very deleterious effect. The best yields were obtained by boiling the reagents in alcoholic solution on the waterbath. Higher boiling solvents and higher temperatures generally gave less pure products and lower yields.

2:8-Diaminoacridine was readily obtained from the commercial antiseptic "Proflavine" which is the sulphate of the base ; but as it was costly , experiments were performed on a comparatively small scale.

The anils of 2:8-diaminoacridine all posessed similar chemical and physical properties ; and as they were too sparingly soluble in water , and their salts too readily hydrolysed, for biological tests , only the following five examples were prepared :-

2:8-Bisbenzylideneaminoacridine.

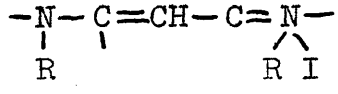
2:8-Biscinnamylideneaminoacridine.

2:8-Bisanisylideneaminoacridine.

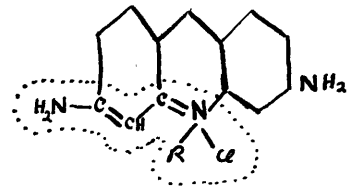
2:8-Bis-salicylideneaminoacridine.

2:8-Bis-p-dimethylaminobenzylideneaminoacridine.

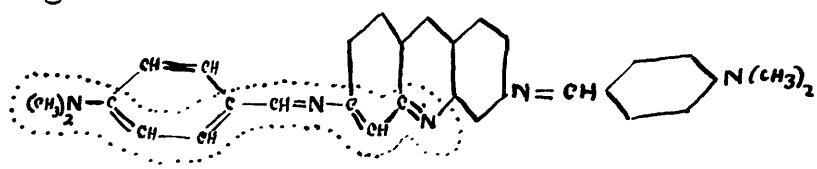
The last of these is the most interesting , as it is more likely to be therapeutically active than the others , since it contains free amino groups in addition to the anil linkages. Pope suggested that the photo-sensitising action of certain dyes may be connected with the presence of such a group as the following :-



a group which is also present in 2:8-diaminoacridine methochloride, as Browning pointed out (B. 96. 318. Proc.Roy.Soc.)



Similar arrangements are present in Browning's styryl and anil quinoline compounds , which posess long chains of alternate single and double bonds linking a "ring" nitrogen atom with an amino group , and attention has been drawn to the possible influence of these groups on the antiseptic properties of the compounds mentioned. 2:8-Bis-p-dimethyl-aminobenzylideneaminoacridine contains a considerably extended chain of alternate double linkages joining two nitrogen atoms :-



and had it posessed more suitable chemical and physical properties the corresponding p-amino and p-acetylamino derivatives would have been prepared.

It has already been stated that the anils were too readily hydrolysed to attempt the preparation of salts such as sulphates or hydrochlorides, so that the only method whereby they could be rendered more soluble in water was to convert the ring nitrogen atom of the acridine molecule to a quaternary alkyl salt , such as a methochloride or methiodide. This can be accomplished in two different ways:-

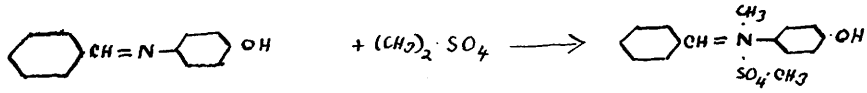
(1) Methylation of the anils already prepared.

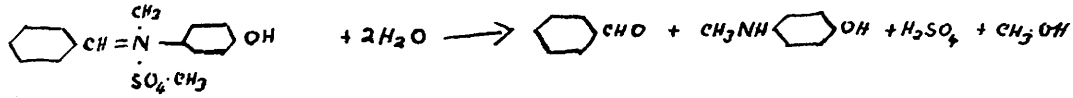
(2) Condensation of aldehydes with 2:8-diaminoacridine methochloride.

Both methods were investigated, but neither of them was found to be suitable.

The first method posses some inherent disadvantages. There is danger of the methylating agent attacking the anil linkage or the substituent groups present. Thus, 2:8-bis-p-dimethylaminobenzylideneaminoacridine could not be methylated for the latter reason , as the dimethyl-amino group would be attacked.

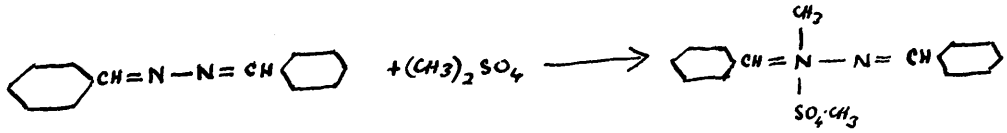
There are three well known methylating agents in general use, dimethyl sulphate, methyl p-toluene sulphon-ate, and methyl iodide. The first of these was not employed since it is known to attack the anil linkage; it has been used industrially (private communication) for the conversion p-amino phenol to p-methylamino phenol, the process being effected by forming the benzylidene derivative and methylating with dimethyl sulphate, and finally hydrolysing the addition product obtained by means of a steam distillation.

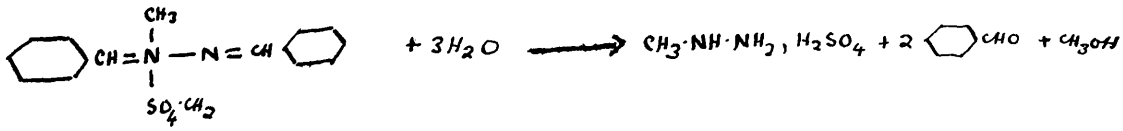




An analogous reaction is made use of in the preparation of

methylhydrazine sulphate, (Thiele. Ann. 376, 244. (1910.)). Benzalazine is treated with dimethyl sulphate, and the addition product decomposed by cold water, as follows:-





It was thought advisable to avoid methyl p-toluene sulphonate and all the more vigorous methylating agents, so that experiments were confined to the action of methyl iodide on 2:8-bisbenzylideneaminoacridine.

On examining the literature for information on the reaction of benzylidene anils with alkyl iodides, it was found that some of the earlier workers stated that no alkyl bases were formed, (Borodin. Ann.,111, 254.), while later it was claimed that extremely unstable addition products had been obtained. (Hansch & Schwab. Ber.,34, (1901), 825.) These addition products were very readily decomposed by water, and the anil group was ruptured with regeneration of the free base and benzaldehyde; thus with benzylidene-p-toluidine ethiodide the reaction took the following course :-

$$C_6H_5\cdot CH=\underset{\underset{I}{|}}{\overset{\overset{Et.}{|}}{N}}-C_7H_7 + 2H_2O \longrightarrow C_6H_5\cdot CHO + C_7H_7\cdot NH_2 + HI + Et\cdot OH.$$

The hydrolysis of the addition product was stated to occur so readily, that on exposure to the atmosphere sufficient moisture was absorbed to cause decomposition.

Thus it appeared that it would be impossible to methylate the ring nitrogen atom in 2:8-bisbenzylideneamino-acridine by means of methyl iodide, without causing rupture of the anil linkages. The method was nevertheless considered worth investigating, and several experiments were performed. It was found that even in absence of moisture the anil was very readily decomposed by the action of methyl iodide, and products were obtained which were thought to be methylated 2:8-diaminoacridine methiodides.

As the first method had proved unsuccessful attempts were next made to condense aldehydes with 2:8-diaminoacridine methochloride.

Commercial "Euflavine" has been shown to be a mixture of 2:8-diaminoacridine methochloride and 2:8-diamino-acridine hydrochloride, (Gaillot, Bull. Soc. Chim., (1934), 796.). It was therfore decided to prepare 2:8-diaminoacridine methochloride using the original method described by Benda (Ber.,45, 1787.); but when this was done it was found that an impure mixture similar to the commercial product was obtained. Thus the impurities in the commercial product are not due to the process of manufacture, but to the inherent faults in the method as originally described by Benda; and

this observation was separately confirmed by another worker. (Marshall., Quaterly Journal of Pharmacy, VII, 1934, 514.) As the preparation has been fully discussed in the experimental section, it will not receive further consideration here.

A specimen of pure 2:8-diaminoacridine methochloride was obtained from "Euflavine" using the separation described by Gaillot. (Bull. Soc. Chim., 1934, 796.) The product was analysed, and was satisfactory in every way. Here again the method has been discussed in the experimental section, so that further comment is unnecessary.

An attempt was made to condense the purified 2:8-diaminoacridine methochloride with p-dimethylamino benzaldehyde, using the fusion method which had been found more efficacious than boiling in alcohol in cases of refractory condensation. (cf. Section III(c).) No reaction took place however, and all the diaminoacridine methochloride was recovered unchanged. It has already been explained that this anil, had it been formed, would have been of especial interest, and it was for this reason that p-dimethylamino benzaldehyde was chosen for the attempted condensations in preference to other aldehydes.

Finally, a few attempts were made to condense aldehydes with unpurified commercial "Euflavine", for it was

thought that on condensation of an aldehyde with "Euflavine" a mixture of two anils would be obtained, one methylated and the other unmethylated; and since examples of the latter type had been prepared and characterised, it seemed that it might be possible to separate the products of the reaction. Negative results were obtained with benzaldehyde and cinnamaldehyde, but with salicylaldehyde the case was different.

It was found that on addition of salicylaldehyde and piperidine to an alcoholic solution of commercial "Euflavine" there was an almost immediate precipitation of 2:8-bis-salicylideneaminoacridine, and when this precipitate of the unmethylated anil was filtered off, it was possible to isolate unchanged 2:8-diaminoacridine methochloride from the filtrate. The practical details have been discussed in the experimental section, but it should be mentioned here that a comparatively large quantity of piperidine must be added, instead of a mere few drops. The function of the piperidine is twofold, it liberates the 2:8-diaminoacridine from its hydrochloride, and then catalyses the condensation of the free base with the aldehyde.

Pure 2:8-diaminoacridine methochloride gives no precipitate with salicylaldehyde under the conditions indicated above, so that the unmethylated product can be readily separated from the methylated; and the reaction may

have important qualitative and quantitative applications.

Hall and Powell, (Quarterly Journal of Pharmacy, (1934), VII, 523.) have criticised the two official tests given in the British Pharmacopoeia for 2:8-diaminoacridine compounds. These authors point out that neither of the tests is capable of detecting the presence of unmethylated 2:8-diaminoacridine hydrochloride in "Euflavine" or "Acriflavine", although "Acriflavine" can be detected in presence of 2:8-diaminoacridine dihydrochloride. ("Euflavine" is 2:8-diaminoacridine methochloride, but commercial products generally contain about 30% of 2:8-diaminoacridine hydrochloride."Acriflavine" is 2:8-diaminoacridine methochloride hydrochloride, but again commercial specimens are impure, and generally contain upwards from 30% of 2:8-diaminoacridine dihydrochloride.)

On adding salicylaldehyde to commercial specimens of "Euflavine" and "Acriflavine" in the manner indicated above, it was found that the presence of unmethylated diaminoacridine was readily detected in both, so that the "salicylaldehyde test" is applicable in just those cases where the official tests fail. The author has not attempted to put this reaction on a quantitative basis, as that was considered outside the scope of this thesis; but the reaction may have possibilities as a limiting test for the purity of commercial products.

Hall and Powell also point out that the test for unmethylated compounds of 2:8-diaminoacridine described in the British Pharmacopoeia is applicable only to "Proflavine", (diaminoacridine sulphate), and is of no value for the detection of 2:8-diaminoacridine hydrochloride. In this instance too, the salicylaldehyde test is superior to the official one, as it was found to be equally applicable to 2:8-diaminoacridine sulphate, and 2:8-diaminoacridine hydrochloride and dihydrochloride.

As has been stated already, salicylaldehyde did not react with 2:8-diaminoacridine methochloride, thus confirming the negative result obtained with p-dimethylamino benzaldehyde. The quaternary ammonium group appears to have a steric effect.

The above is not an isolated case, for there are a few examples in the literature of steric hindrance due to the presence of a quaternary ammonium group. Hamer, (J.C.S. 1930, 997.), found that the methyl group of 5-methyl acridine methiodide would not react with p-nitroso dimethylaniline although 5-methyl acridine itself condenses readily. The author had a similar experience with 5-methyl acridine methochloride,(cf. Section IV.). Again, Hamer, (J.C.S.,1921, 2 , 1432.) found that 8-acetylamino quinoline and 8-acetylamino quinaldine would not form alkyl iodides because of the steric

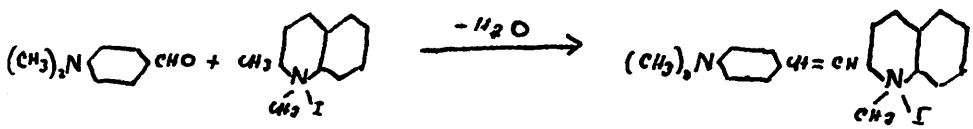
influence of the acetylamino group. The last example, although somewhat different from the case in question, serves to illustrate the intimate connection which may exist between a quaternary ammonium group and another substituent group in the same molecule. It has been shown that the presence of a quaternary ammonium group sometimes promotes condensation,(Mills and Smith, J.C.S., 1922, 121, 2724.), so that it is not unreasonable to suppose that given a different molecular arrangement and different conditions, the presence of the same group might have the reverse effect.

SECTION II. DERIVATIVES OF PYRIDINE.

In 1924 Browning and his collaborators made an extensive study of the therapeutic properties of the quinoline dyes, and in addition to the anils mentioned in Section I., a series of quinoline derivatives of ethene was prepared and examined.

It was generally found that the members of the anil series were strong antiseptics, but weak trypanocidal agents, while in the ethene series the reverse was the case and the members were strongly trypanocidal and weakly antiseptic.

On account of their very valuable trypanocidal properties, the quinoline ethenes received much attention, and many examples were synthesised by the condensation of various aldehydes with 2-methyl quinoline derivatives. For example, 2-methyl quinoline methiodide was condensed with p-dimethylaminobenzaldehyde as follows:-



The resulting condensation product contains the unsaturated -CH= CH- group characteristic of ethene compounds.

Since the quinoline ethenes had proved such active therapeutic agents, it seemed profitable to prepare and examine a series of acridine derivatives of similar type.

There are two possible methods for the preparation of acridine ethenes:-

(1) Aldehydes can be condensed with acridine compounds containing reactive methyl groups.

(2) Acridine aldehyde derivatives can be condensed with substances containing reactive methyl groups.

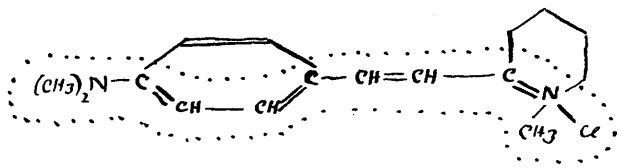
A search was made through the literature, and it was found that an acridine ethene compound had been prepared by the condensation of m-nitro benzaldehyde with 5-methyl acridine. The method did not appear to be a satisfactory one, as the 5-methyl group is comparatively unreactive, and it has been shown by Friedlander (Ber., (1905), 38, 2840.) that when aldehydes react with 5-methyl acridine addition products are formed which are not unsaturated compounds, but alcohols. (This reaction will be considered in Section IV.)

As no other acridine derivatives are known to contain reactive methyl groups, attention was focussed on the second of the two methods mentioned above. It was found that although 5-aldehyde acridine already existed, no ethene derivatives had been prepared from it, and it was therefore decided to condense this substance with heterocyclic compounds containing reactive methyl groups.

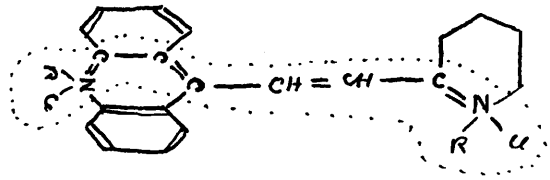
Since Browning and his collaborators had investigated the quinoline dyes so thoroughly, it was

thought that for purposes of comparison attention should be confined to compounds of similar type, and so pyridine-acridine ethene and quinoline-acridine ethene derivatives were prepared.

The possible influence of long chains of alternate single and double bonds uniting two nitrogen atoms has already been referred to in Section I. An alternate linkage system somewhat similar to that contained in Browning's quinoline ethene derivatives is common to both the pyridine-acridine and quinoline-acridine compounds prepared by the author:-



p-dimethylamino pyridine ethene compound. (Browning).



Acridine-pyridine ethene compound.

In the case of Browning's quinoline ethene (and pyridine ethene) compounds, the alternate linkages unite a basic trivalent nitrogen atom to a pentavalent nitrogen atom of a quaternary ammonium group, while in the author's compounds a slightly shorter alternate linkage system unites two quaternary ammonium pentavalent nitrogen atoms. In the pyridine-acridine series described in this section

water-soluble examples were prepared containing no quaternary ammonium group in the acridine nucleus. These compounds resemble Browning's quinoline ethene derivatives even more closely, for here too the alternate linkages unite a basic trivalent nitrogen atom and a pentavalent nitrogen of a quaternary ammonium group, and the difference between the two types is in the length of the linkage system, and the fact that the trivalent nitrogen atom is a member of a heterocyclic ring.

As the quaternary salts of a base containing a reactive methyl group are, in general, more reactive than the base itself (Mills. J.C.S. (1922). 121, 2724), the pyridine-acridine ethene compounds described in this section were all prepared by the condensation of 5-aldehyde acridine with the quaternary ammonium alkyl salts of 2-methyl pyridine. The alternative method of condensing the aldehyde with the free base in presence of zinc chloride and subsequently methylating the ethene obtained, was not employed by the author, although it has been used by other workers. (J.A.C.S. (1920). 42. 2309.) (Proc.Roy.Soc., (1931), B.109, 52.) The condensations were effected in boiling alcoholic solution, using piperidine as catalyst, in an analogous manner to that described by Browning and his collaborators for the preparation of their quinoline ethene compounds.

The following examples were prepared:-

s-(2-Pyridyl methiodide)-5- acridylethene.
s-(2-Pyridyl methiodide)-(5-acridyl hydrochloride) ethene.
s-(2-Pyridyl methiodide)-(5-acridyl methiodide) ethene.
s-(2-Pyridyl ethiodide)-5-acridylethene.
s-(2-Pyridyl ethiodide)-(5-acridyl methiodide) ethene.

The ethiodides were considerably more soluble in water than the corresponding methiodides, and this was especially marked in the case of those compounds which contained no quaternary ammonium group in the acridine nucleus. The latter class of compounds is interesting, and of a new type, since the acridine ring nitrogen remains basic in character and un-neutralised by salt formation. Acridine derivatives containing a free ring nitrogen atom are generally too insoluble for biological tests.

The methiodide group was introduced into the acridine nucleus by methylation with dimethyl sulphate and subsequent treatment of the methosulphate formed with saturated potassium iodide solution.

The unsaturated ethene linkage -CH= CH- is considerably more stable than the corresponding anil group, and is not hydrolysed by acids; it is also unaffected by methylation, so that ethene compounds can be treated with

even the most reactive methylating agents without rupture of the molecule.

The fact that a certain chemical grouping was common to some antiseptics and many photographic sensitisers led Browning and his collaborators to examine the therapeutic properties of the sensitising apocyanine, carbocyanine, and isocyanine dyes, and it was found that many of them were powerfully antiseptic. (Proc.Roy.Soc., B. 96. 317.)

As many photographic sensitisers containing quaternary ammonium ethiodide groups are more efficient than the corresponding methiodides (private communication), it was thought advisable to introduce an ethyl radicle into the quaternary ammonium group of the pyridine nucleus, and compare the antiseptic action with that of the corresponding methiodide. In the pyridine series of acridine ethene compounds the substitution of an ethyl for a methyl radicle produced no increase in antiseptic power, but in the analogous quinoline series a marked increase was recorded, (cf. Section III.)

All the pyridine-acridine ethene compounds were moderately antiseptic towards staphylococcus in dilute peptone water (inhibition of growth at a concentration of 1 : 40,000 of the substances), while in serum all suffered some diminution of action (inhibition of growth with concentration of 1 : 10,000 to 1 : 20,000). For B. coli

the antiseptic action was much weaker than for staphylococcus as was found to be the general rule with Browning's quinoline ethene compounds (Proc.Roy.Soc.,(1926), B. 100.293); but the action on B. coli was intensified in serum medium as compared with peptone water.

All the substances were only moderately toxic for mice on subcutaneous injection, but were devoid of trypanocidal action. (The tests for trypanocidal action were carried out on mice experimentally infected with T. brucei.)

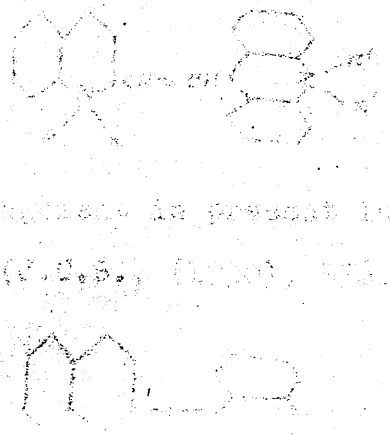
The biological tests were performed by Professor C.H. Browning and his staff, using the methods described by them, (Brit. J. Exp. Path., 1921, 2, 95; Proc. Roy. Soc., (1929), B, 105, 99.)

The presence of amino or acetylamino groups in a chemotherapeutic agent, though often beneficial, does not always appear to be essential for the development of powerful antiseptic properties, and cases have even been recorded where the introduction of amino groups into an antiseptic substance has resulted in diminished activity. (Browning, Proc. Roy. Soc., (1924), B. 96. 318). The presence of basic groups is desirable, however, for the production of trypanocidal properties, (cf. Section III b.), and the available methods for the introduction of amino groups

into the pyridine nucleus were examined.

It was found that 2-methyl-6-amino pyridine and 2-methyl-3:6-diamino pyridine were known, but a recent paper by Feist (Arch. der Pharm.(1936), 274. 418.) states that the presence of an amino group in the 6 position of the pyridine ring renders the 2-methyl group unreactive.

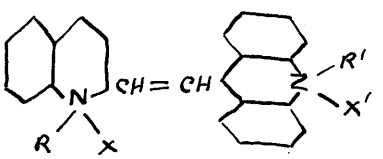
In view of this alleged inactivity of the methyl group, and also because of the fact that Browning had made no amino pyridine ethenes , it was decided that it would be more profitable to concentrate on the quinoline-acridine ethenes. Work on the pyridine series has therefore been suspended for the present.



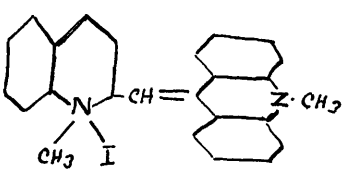
SECTION III (a). UNSUBSTITUTED DERIVATIVES OF QUINOLINE.

The theoretical and other considerations set forth in Section II are also applicable to the compounds about to be described here, for the connection between the pyridine-acridine ethenes and the quinoline-acridine ethenes is of the most intimate nature. Both series of compounds contain a common arrangement of alternate single and double linkages, as has been already pointed out, and they also possess similar chemical, physical, and pharmacological properties.

The members of the quinoline-acridine series are especially interesting because of their close relationship with Browning's quinoline ethenes, and the compounds described in this section are the parent substances of a series containing the group:-



A very similar arrangement is present in an isocyanine dye prepared by Hamer, (J.C.S., (1930), 996.) :-



and it would be of interest to compare the therapeutic

properties of this compound with those of the acridine-quinoline derivatives described in this thesis.

The author did not prepare any ethene compounds by the condensation of 5-aldehyde acridine with 4-methyl quinoline derivatives. One quinoline ethene of this type, and the corresponding anil, were prepared by Browning, (Proc.Roy. Soc., B. 100. 293, 1926.), but they were found to possess antiseptic properties which were inferior to those of the analogues prepared from 2-methyl quinoline derivatives. Browning suggested that the diminution in antiseptic power was possibly due to an alteration in the length of the system of single and double bonds. The author considers that these two negative results should not preclude further research among the ethenes and anils derived from 4-methyl quinoline compounds, especially as amino derivatives of 4-methyl quinoline are readily accessible, (Besthorn. Ber., (1898), 31. 796. and Pechmann. ibid., (1899), 32, 3686.)

The condensation of 5-aldehyde acridine and the quaternary ammonium alkyl salts of 2-methyl quinoline was effected in the usual way in boiling alcoholic solution, using piperidine as catalyst. The condensation products, unlike the corresponding pyridine derivatives, were too insoluble in water for biological tests, so that it was necessary to form the quaternary ammonium salt of the basic

nitrogen atom in the acridine ring. The following examples were prepared:-

s-(2-Quinolyl methiodide)-5-acridylethene.

s-(2-Quinolyl methiodide)-5-acridylethene hydrochloride.

s-2-Quinolyl-5-acridylethene dimethosulphate.

s-2-Quinolyl-5-acridylethene dimethochloride.

s-2-Quinolyl-5-acridylethene dimethiodide.

s-(2-Quinolyl ethiodide)-(5-acridyl methiodide) ethene.

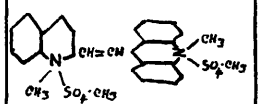
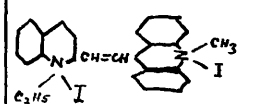
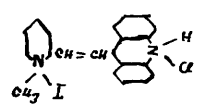
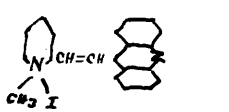
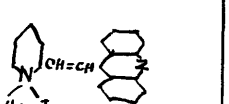
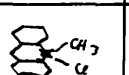
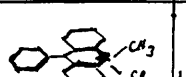
Various alterations were made in the radicles present in the quaternary ammonium groupings of both the quinoline and acridine nucleii, but the antiseptic properties were not affected one way or the other except in the case of the ethiodide compound which was distinctly more active towards staphylococcus.

Apart from the ethiodide, the quinoline-acridine ethene compounds resembled the pyridine analogues in their antiseptic properties and lack of trypanocidal action.

In Table I., the antiseptic properties of some of the compounds prepared in sections II and III(a) have been tabulated , together with those of a few related dyes for purposes of comparison.

The antiseptic results were read after contact of the substances and the organisms for 48 hours at 37°C., and the figures show the concentrations of the substances required to produce the various effects. (6 & 7 were copied from Browning, Proc. Roy. Soc., B. 93 , 329. 1922.)

TABLE I.

	SUBSTANCE.	STAPHYLOCOCCUS.						BACILLUS COLI.						APPROXIMATE MAXIMUM TOLERATED DOSE FOR 20 GRAM MOUSE (SUBCUTANEOUSLY.)
		DILUTE PEPTONE WATER.			SERUM.			DILUTE PEPTONE WATER.			SERUM.			
		FULL GROWTH.	INHIBITION.	STERILE.	FULL GROWTH.	INHIBITION.	STERILE	FULL GROWTH	INHIBITION.	STERILE	FULL GROWTH	INHIBITION.	STERILE.	
1.		1/100,000	1/40,000	1/10,000	1/20,000	1/10,000	1/4,000	1/1000	?	?	1/20,000	—	1/10,000	1/500 gms.
2.		1/1000,000	1/400,000	1/100,000	1/20,000		1/10,000	1/10,000	1/4,000	1/2,000	1/4000	1/2,000	?	1/200
3.		1/100,000	1/40,000	1/10,000	1/20,000	—	1/10,000	1/2,000	1/1000	?	1/20,000	1/10,000	1/4,000	1/600
4.		1/100,000	1/40,000	1/10,000	1/20,000	—	1/10,000	1/2,000	1/1000	?	1/20,000	1/10,000	1/4,000	1/300
5.		1/100,000	1/40,000	1/10,000	1/40,000	1/20,000	1/10,000	1/10,000	?	?	1/10,000	—	1/4,000	1/250
6.		1/10,000	—	1/1000	1/10,000	—	1/2,000	1/10,000	—	1/1,000	1/20,000	—	1/4,000	—
7.		1/1,000,000	—	1/40,000	1/200,000	—	1/20,000	1/4,000	—	1/2,000	1/20,000	—	1/10,000	—

(pg. 29.)

SECTION III. (b). 6 AMINO QUINOLINE DERIVATIVES.

As has been already stated, the quinoline-acridine ethene series of compounds was considered especially worthy of study, as it bears a close relationship to the series examined by Browning and his collaborators. Having investigated the parent substances, the question now arose as to which groups should be introduced into the molecule, and as the introduction of substituent groups into the acridine portion is too complex a problem (cf. Section IV) only the effect of substitution in the quinoline nucleus has been considered.

Browning and his co-workers introduced various groups into both the benzene and quinoline nucleii of their ethene and anil compounds, and found that in general, amino groups, or substituted amino groups, proved the most effective.

These workers also found that antiseptic action and trypanocidal action did not go hand in hand. Thus, the anil quinolines generally had little trypanocidal action, although they mostly possessed powerful antiseptic properties; and the quinoline ethenes were much more effective than the anils as trypanocidal agents, although the most powerful trypanocides were usually only weakly antiseptic against bacteria.

Since the acridine-quinoline derivatives prepared by the author contained an ethene linkage, and the latter

had been shown to favour trypanocidal rather than antiseptic action, it was decided to incorporate those groups which were most likely to enhance trypanocidal properties.

A study of the relationship between the trypanocidal action and the chemical structure of Browning's anil and ethene derivatives reveals that the orientation of the substituent groups in the quinoline nucleus is of great importance. Thus, s-(6-acetylamino-2-quinolyl methochloride)-(p-dimenthylamino phenyl) ethene is a powerful trypanocide, while the corresponding 7 isomer is much less active, and the 4 isomer has no action at all. Compare (Browning. Proc. Roy. Soc. B.105, 102. (1929).) and (Browning. Proc. Roy. Soc. B.113, 295. (1933).).

Another striking example of the way in which the orientation of the groups in the quinoline nucleus affects trypanocidal action is afforded by a series of ethene and anil quinoline compounds containing a carboxylamide group, $\cdot CO \cdot NH_2$. It was found that only those compounds substituted in the 6 position were trypanocidal, the anils being only slightly less effective than the ethene analogues. The 3, 4, 5 and 8 isomers were all inactive. (Proc. Roy. Soc. B. 110. 250. 1932.).

When the antiseptic properties of the ethene and anil quinolines are examined, it is found that the question of orientation assumes much less importance. The position

of the substituent groups in the quinoline nucleus does, however, have a certain influence, and the most effective antiseptics were generally substituted in the 6 position. There is also strong evidence that 4 amino quinoline derivatives are much less effective antiseptics than the 6 isomers (Browning. Proc. Roy. Soc. B. 113. 293. (1933).)

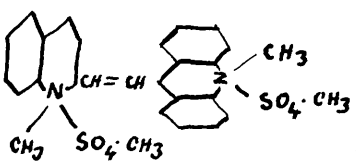
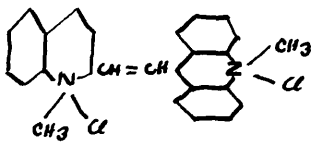
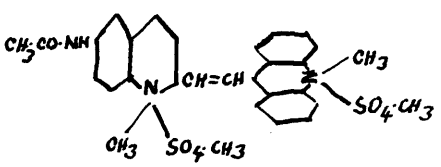
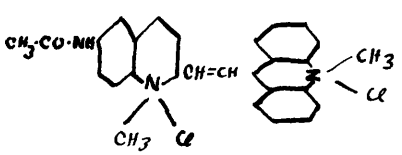
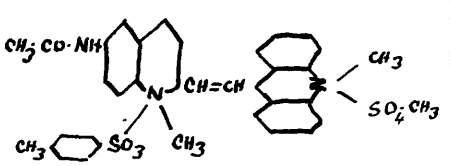
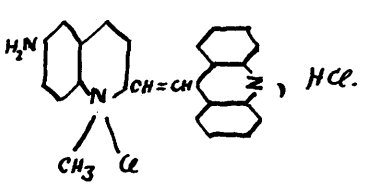
Thus it appears that the introduction of basic groups into the 6 position of the quinoline nucleus is essential for the production of marked trypanocidal properties, and accordingly a series of acridine-quinoline ethene compounds, possessing 6-amino, 6-acetyl amino, and 6-dimethyl-amino groups, was prepared.

All these compounds showed trypanocidal action (cf. Table II) and in the case of number (4) only a very late relapse was recorded.

The greatest reserve must be maintained in drawing conclusions from biological tests, as the individual mouse plays an important part in the chemotherapeutic effect, and results sometimes differ slightly from animal to animal. However, the results obtained for the quinoline-acridine ethenes prepared by the author do show that the introduction of an amino or acetylamino group into the 6 position of the quinoline nucleus produces marked trypanocidal activity (compare (4) and (6) with (2)). Further, the activity is due in part to the acridine portion of the molecule, and not merely to the presence of a 6 amino derivative of

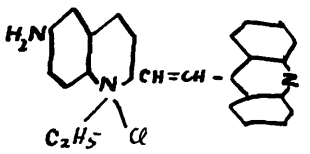
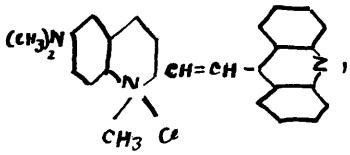
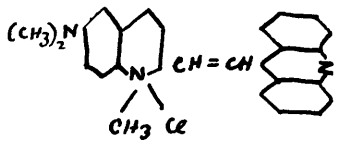
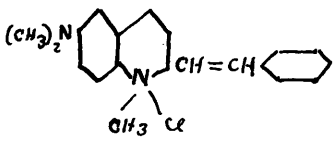
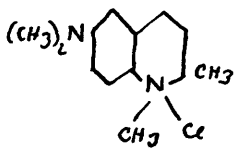
TABLE II.

TRYPANOCIDAL PROPERTIES OF 6-AMINO QUINOLINE DERIVATIVES.

No.	SUBSTANCE.	DOSE.*	RESULT.	REMARKS.
1.		$\frac{1}{300}$	0	-
2.		$\frac{1}{100}$	0	-
3.		$\frac{1}{1000}$	Distinct.	-
4.		$\frac{1}{100}$	Marked.	Blood remained free from parasites for 40 to 50 days.
5.			Slight.	-
6.		$\frac{1}{400}$	Marked.	-

* (gms. of substance per 20 gms. body weight of mouse.)

TABLE II. (contd.)

No.	SUBSTANCE.	DOSE.	RESULT.	REMARKS.
7.		$\frac{1}{600}$	Trace.	-
8.		$\frac{1}{600}$	Trace.	-
9.		$\frac{1}{400}$	Trace.	-
10.		$\frac{1}{9000}$	0	Reference:- Proc. Roy. Soc., B.105, 111,(1929.)
11.		$\frac{1}{5500}$	0	Reference:- Proc. Roy. Soc., B. 105, 111. (1929)

"Trace" prolongation of life for several days beyond that of the untreated controls.
"Slight" disappearance of parasites from the blood for several days to a week.
"Marked" absence of parasites from the blood for 10 days or longer.
The mice were experimentally infected with T. brucei, and the untreated controls usually died 3 days after innoculation.

quinoline methochloride and an ethene linkage, for (9) is active while (10) and (11) are not.

Browning frequently found marked differences between the trypanocidal actions of compounds containing 6-amino, 6-acetylamino, and 6-dimethylamino groups in the quinoline nucleus, but one of these three substituents was almost invariably present in the most effective trypanocides. As far as can be judged from the results obtained with the quinoline-acridine ethenes, a dimethyl-amino group in the 6 position is less effective than an amino or acetylamino group (compare (4) (6) and (8).).

It is interesting to note that the substitution of an ethyl for a methyl radicle in the quaternary ammonium grouping in the quinoline nucleus caused an apparent reduction in trypanocidal action, for this same change produced enhanced antiseptic properties when the parent unsubstituted substances were examined. (Section IIIa). The tests for antiseptic properties of the 6 amino series have not yet been completed, but it will be interesting to see whether the change from methochloride to ethochloride produces increased antiseptic activity.

The preparation of the compounds studied presented a few difficulties. It was found convenient to condense quinaldine methiodide compounds with 5-aldehyde acridine, as better yields and more workable products were obtained. In cases where the methochloride was desired, the methiodide

of the ethene compound was boiled with silver chloride in the usual way. The following condensation products of 5-aldehyde acridine and 6 substituted quinaldine derivatives were prepared:-

s-(6-Acetylamino-2-quinolyl methiodide)-5-acridyl ethene.

s-(6-Acetylamino-2-quinolyl ethiodide)-5-acridyl ethene.

s-(6-Acetylamino-2-quinolyl metho-p-toluene sulphonate) -5-acridylethene.

s-(6-Dimethylamino-2-quinolyl methiodide)-5-acridylethene.

The last of these compounds could not be methylated, as methylating agents would attack the 6 dimethylamino group. It was therefore converted to the methochloride which was sufficiently soluble for biological tests. A specimen of the hydrochloride was also prepared, and found to have similar trypanocidal properties.

In order to obtain a direct comparison between the trypanocidal action of the dimethylamino and amino groups, the 6 amino analogue of the preceding compound was prepared, and the following series studied:-

s-(6 Dimethylamino-2-quinolyl methochloride)-5 acridylethene, hydrochloride.

s-(6-Amino-2-quinolyl methochloride)-5 acridylethene, hydrochloride.

s-(6-Amino-2-quinolyl ethochloride)-5 acridylethene, hydrochloride.

The last compound enabled a comparison to be made between

an ethyl and a methyl radicle in the quaternary ammonium group of the quinoline nucleus. All the members of this series were monohydrochlorides, and it was not known whether the acid was attached to the acridine "ring"nitrogen atom, or to the quinoline amino group, but the question was considered unimportant.

The compounds containing free amino groups were prepared by hydrolysis of the corresponding acetylamino derivatives. In spite of Browning's observation that the 6 amino group is unreactive (Proc. Roy. Soc. B 100. 311. (1926)) it is considered unwise to attempt the condensation of quinaldine compounds containing free amino groups with aldehydes, as it is possible that a mixture of anil and ethene derivatives will be obtained.

s-(6-Acetylamino-2-quinolyl methiodide)-5-acridyl ethene was methylated with excess of methyl sulphate, in a manner entirely analogous to that described for the methylation of the corresponding unsubstituted compound, s-(2-quinolyl methiodide)-5-acridyl ethene.

It was found that in this case, the presence of the acetyl amino group caused difficulties, and the products obtained invariably gave slightly low results when their nitrogen content was estimated. Browning and his collaborators experienced considerable trouble when they methylated compounds containing free amino groups, and obtained products of somewhat indefinite constitution. (Proc. Roy. Soc. B. 109.

(1931) 51.) But these, and other workers record no trouble when methylating acetylamino compounds, and Benda, (Ber.45, 1787. and Section I of this thesis) experienced no difficulty when he methylated 2 : 8 bis-acetylamino acridine with a large excess of methyl-p-toluene sulphonate.

However, the acetylamino group is not always passive, and methyl aniline has been prepared from acetanilide by the following process:-

$$C_6H_5 \cdot NH \cdot CO \cdot CH_3 \xrightarrow{CH_3 \cdot I} C_6H_5 \cdot N(CH_3) \cdot CO \cdot CH_3$$

$$C_6H_5 \cdot N(CH_3) \cdot CO \cdot CH_3 \xrightarrow{\text{hydrolysis}} C_6H_5 \cdot NH(CH_3) + CH_3 \cdot COOH$$

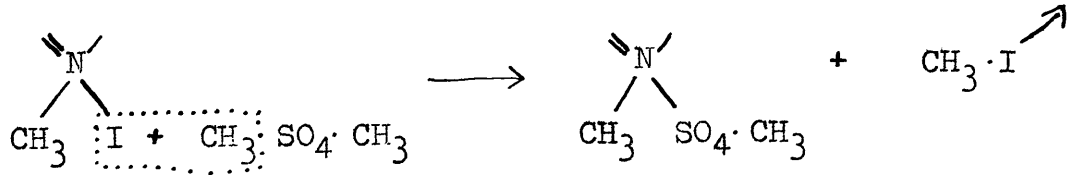
(Ber. 10. 328.)

The compound obtained from the methylation of s-(6-acetylamino-2-quinolyl methiodide)-5-acridylethene was a dimethosulphate, and was converted to the dimethochloride in the usual manner. Both products were active trypanocides.

Since the methylation was not entirely satisfactory, it was thought that perhaps the large excess of methyl sulphate used was proving harmful, and accordingly methylations were attempted using one molecular proportion of methyl sulphate and one of s-(6-acetylamino-2-quinolyl methiodide)-5-acridylethene. The resulting product should have been s-(6-acetylamino-2-quinolyl methiodide)-(5-acridyl methosulphate) ethene, but the product of the methylation could always be resolved into two portions, one containing

iodine, and the other containing no iodine.

It appeared that the methyl sulphate was attacking the methiodide group in preference to the free "ring" nitrogen atom, and this was attributed to the volatile nature of methyl iodide:-



Hence, to methylate s-(6-acetylamino-2-quinolyl methiodide) -5-acridylethene completely, two molecules of dimethyl sulphate, at least, are required, and the employment of large quantities of methyl sulphate which might harm the acetylamino group cannot be avoided.

A more satisfactory product was obtained by the following method, which avoided the employment of two molecules of dimethyl sulphate:-
s-(6-acetylamino-2-quinolyl metho-p-toluene sulphonate) -5-acridylethene was prepared, and methylated with one molecular proportion of methylsulphate + 30% excess. As methyl-p-toluene sulphonate is a solid, there was no volatile product to split off, and large quantities of the methylating agent were avoided.

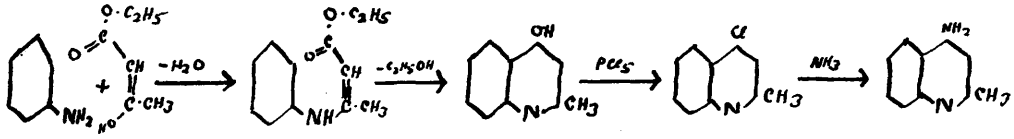
SECTION III(c). DERIVATIVES OF 4-AMINO QUINOLINE.

It has been pointed out that the anil and ethene derivatives of 4-amino quinoline were generally found to be less effective therapeutic agents than the corresponding 6 isomers, so that before proceeding to a consideration of the compounds described in this section, the reasons for undertaking their preparation will be explained.

It seemed advisable to introduce more than one amino group into the quinoline nucleus of the quinoline-acridine ethenes, and so the literature was examined and it was found that 2-methyl-3:4-diaminoquinoline had been prepared by Conrad and Limpach in 1888, (Ber., 21 , 1938.), and that a process had been patented in 1934 for the preparation of 2-methyl-4:8-diaminoquinoline and 2-methyl-4:6-diaminoquinoline, (D.R.P. 591,480. and E.P. 414,105.). Further, the last of these compounds, 2-methyl-4:6-diaminoquinoline, yields 2-methyl-3:4:6-triaminoquinoline when nitrated and subsequently reduced.

The details given in the patented process for the synthesis of the diaminoquinoline derivatives are very inadequate, but the method specified is entirely analogous to that employed for the preparation of 2-methyl-4-aminoquinoline. 2-Methyl-4-aminoquinoline is prepared as follows:-

Aniline is condensed with ethyl acetoacetate and the resulting ethyl B-phenylaminocrotonate ring closed to form 2-methyl-4-hydroxyquinoline. The phenolic group in the last compound is then replaced by chlorine by heating with phosphorus pentachloride, and the resulting chloro compound yields 2-methyl-4-aminoquinoline on treatment with ammonia.



The 4:6- and 4:8-diamino-2-methyl quinolines are prepared by identical processes starting from p-amino acetanilide and o-amino acetanilide respectively; while 2-methyl-3:4-diamino quinoline is prepared by the nitration of 2-methyl-4-hydroxy quinoline (in the 3 position) , followed by replacement of the phenolic group by an amino group in the manner indicated above , and reduction of the 3-nitro-4-amino-2-methyl quinoline to the diamino compound.

Thus, the 4-amino group is common to all the known 2-methyl diamino quinolines and to the triamino compound, and the preparation of all these derivatives involves a series of reactions closely paralleled in the synthesis of 2-methyl-4-amino quinoline.

It was proposed to prepare 4:6-diamino and 3:4:6-triamino-2-methyl-quinoline, and to condense these compounds with 5-aldehyde acridine and various other aldehydes and nitroso compounds, and also to prepare the corresponding 3-amino and 4-amino-2-methyl-quinoline derivatives for purposes of comparison.

It seemed advisable to examine the mono-amino quinoline derivatives before proceeding to the synthesis of the more complex diamino and triamino compounds , and so the preparation of 2-methyl-4-amino quinoline and its derivatives was undertaken by the author , while another worker is at present examining the 3-amino analogues. It was also thought that the experience gained in the preparation of 2-methyl-4-amino quinoline would be extremely valuable for the proposed synthesis of the 4:6-diamino analogue.

As Browning and his collaborators had investigated several anil and ethene derivatives of 4-amino, 4-acetylamino, and 4-dimethylamino quinoline and found them therapeutically inactive, (Proc. Roy. Soc., B. 113, 1933.) , the author confined his attention to the slightly different 4-phenyl amino analogues.It was proposed to condense 5-aldehyde acridine with 4-phenylamino, 4-p-acetylamino-phenylamino, and 4-dimethylamino-phenylamino-2-methyl-quinoline, and to

prepare also anil and ethene compounds of the type studied by Browning. The latter series is interesting as it is very closely related to the cancer-producing quinoline dyes discovered by Browning and his collaborators. (Proc. Roy. Soc. B. 113, 300.)

It was found impossible to condense 5-aldehyde acridine with 2-methyl-4-phenylamino-quinoline methiodide or methochloride by boiling the reagents together in alcoholic solution in the usual way. It was similarly found impossible to condense p-dimethylamino benzaldehyde with 2-methyl-4-phenylamino quinoline methiodide or 2-methyl-4-p-acetylamino-phenylamino quinoline methiodide in alcoholic solution , although these last two condensations were eventually effected by fusing the reagents together at 140° C. in presence of piperidine.

The presence of substituent groups in the 4 position of the quinoline nucleus appears, therefore, to have a depressing effect on the reactivity of the 2-methyl group. Further evidence of this was obtained when p-dimethyl-amino benzaldehyde was fused in presence of piperidine with 2-methyl-4-phenylamino quinoline methiodide and 2-methyl-4-p-acetylamino-phenylamino quinoline methiodide. In the first case condensation was complete after two hours, while in the second case there was hardly any condensation after

two hours, and the period of fusion had to be increased up to nine hours in order to complete the reaction. From this it appears that the entry of the p-acetylamino group into the 4-phenylamino radicle has had a pronounced steric effect.

It was rather surprising that the anil condensations could be effected in the usual manner in alcoholic solution; but the yields were poor, and a protracted time of heating was required. Browning and his collaborators similarly record low yields for their 4-amino quinoline anils , and point out that they found it necessary to heat the reaction mixtures for longer periods than usual. (Proc. Roy. Soc.,(1933),298,B.113) As a general rule, Browning and his co-workers found that anil condensations took place much more rapidly than the corresponding ethene condensations, (Proc. Roy. Soc., (1926), B. 100. 306.), and this fact may explain why, in the cases cited above, the author found it possible to prepare the anils in alcoholic solution, but not the corresponding ethene derivatives.

It is interesting to note that although Browning and Cohen prepared their 4-amino quinoline anils in alcoholic solution in the usual manner, the corresponding ethene derivatives were obtained by fusion of the quinaldinium salt with p-dimethylamino benzaldehyde. (Proc. Roy. Soc., (1933), B. 113, 298.). These authors do not record any attempts to prepare the ethene compounds in alcoholic solution, but in

view of the fact that the 6 isomers were all successfully prepared in this manner, it is significant that the more unorthodox fusion method was resorted to for the preparation of the 4-amino quinoline ethene derivatives.

The chlorine atom of 2-methyl-4-chloroquinaldine is very reactive, and condenses readily with amino compounds to give derivatives of 2-methyl-4-amino quinoline. This reaction appears to be a general one, and capable of very wide extension, so that it may well prove of value for the future synthesis of many chemotherapeutic agents. The author condensed 2-methyl-6aminoquinoline with 2-methyl-4-chloro quinoline in this manner, and it therefore appears that various other heterocyclic groups can be introduced into the 4 position of the quinoline molecule. It would be extremely interesting to condense quinoline with amino arsenicals in this way.

Although 2-methyl-4-hydroxyquinoline was readily prepared by ring closing ethyl B-phenylaminocrotonate, the yields were unsatisfactory and could not be improved upon. Some work was also done on the preparation of 2-methyl-4-hydroxy-6-acetylamino quinoline by the ring closure of ethyl B-p-acetylamino-phenylaminocrotonate, but here again the yields were not good; and in this case the matter is more serious since no information is available in the literature. The yield of ethyl B-p-acetylamino-phenylamino

crotonate was found to be extremely good, however, so that if the difficulties attending its ring closure can be overcome, 2-methyl-4-hydroxy-6-acetylamino quinoline may yet prove to be an accessible substance.

Several new "intermediate" compounds were prepared, and modifications made in the methods of preparation of those already known, but since all these compounds are fully discussed in the experimental section they will not be considered here.

As the 2-methyl group of 4-amino-2-methyl quinoline compounds had been found unreactive, the 4-p-dimethylamino phenylamino derivatives were not made.

The following anil and ethene compounds were prepared:-

s-(4-Phenylamino-2-quinolyl methiodide)-(p-dimethylamino-phenyl)ethene.

s-(4-Phenylamino-2-quinolyl methochloride)-(p-dimethylamino-phenyl)ethene.

s-(4-p-acetylamino phenylamino-2-quinolyl methiodide)-(p-dimethylamino phenyl)ethene.

s-(4-p-Acetylamino phenylamino-2-quinolyl methochloride)-(p-dimethylamino phenyl)ethene.

2(p-Dimethylamino anil)-4(p-acetylamino phenylamino) quinoline methiodide.

2(p-Dimethylamino anil)-4-phenylamino quinoline methiodide.

2(p-Dimethylamino styryl)-6(4-(2(p-dimethylamino styryl)) quinolyl methiodide)amino-quinoline methiodide.

The tests for the antiseptic properties of these compounds have not been completed yet, and it is still too soon to state whether any of them causes sarcoma, since the development of the latter requires many months.

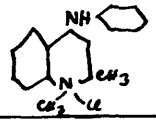
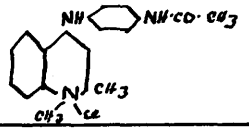
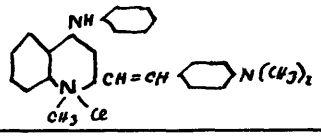
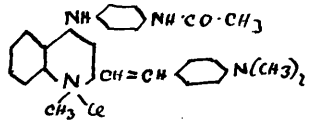
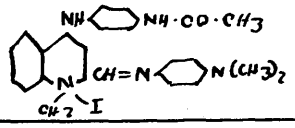
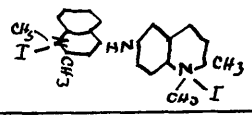
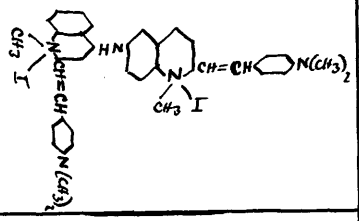
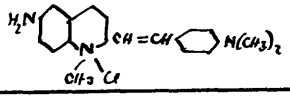
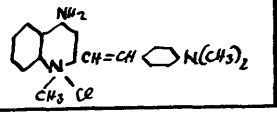
The tests for trypanocidal properties have been completed, and the results have been tabulated, (Table III.). It is interesting to note that all the derivatives of 4-amino quinoline prepared are inert except no. (7) which contains a 6-amino quinoline group.

This compound, no. (7), is at the one time a derivative of 4-amino quinoline and 6-amino quinoline. On comparing it with the related substances (8) and (9) it appears that the activity of the molecule as a whole can be attributed to the presence of the 6-amino group, although the unsaturated linkages and the p-dimethylamino groups play their part too, since (6) is inactive. It is interesting to note that (6) is comparatively toxic, whereas (7) is non toxic.

The activity of (7) furnishes further evidence that the presence of a 6-amino group is desirable in quinoline ethene derivatives, if the latter are to show marked trypanocidal action.

TABLE III.

TRYPANOCIDAL PROPERTIES OF 4-AMINO QUINOLINE DERIVATIVES.

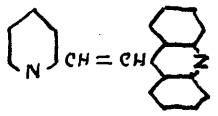
	SUBSTANCE.	DOSE.*	RESULT.	REMARKS.
1.		1/2500	O	–
2.		1/300	O	–
3.		1/1,000	O	–
4.		1/600	O	–
5.		1/500	O	–
6.		1/1,500	O	Comparatively toxic.
7.			Marked.	
8.		1/6000	Slight.	Reference :- Proc. Roy. Soc., B. 105, 100.
9.		1/2,000	O	Reference :- Proc. Roy. Soc., B. 113, 294.

* (Grammes of substance per 20 gms. body weight of mouse.)

SECTION IV. DERIVATIVES OF 5-ALDEHYDE ACRIDINE.

In sections II and III ethene compounds have been described containing an acridine nucleus united to various other groups by an unsaturated linkage. All these substances contain an acridine ring in common, so that it seems profitable to discuss the means whereby substituent groups may be introduced into this portion of the molecule.

It has been already pointed out that there are, theoretically, two methods available for the preparation of acridine ethene compounds. Thus, the substance :-



could be prepared by the condensation of 2-aldehyde pyridine with 5-methyl acridine, or by the condensation of 5-aldehyde acridine with 2-methyl pyridine.

Reactions of the first type do not appear to be general, since the methyl group of 5-methyl acridine does not condense very readily with aldehydes. Friedlander, (Ber., 1905, 38, 2840.), obtained not an ethene derivative, but an addition product when he condensed benzaldehyde with 5-methyl acridine, and the author obtained a compound of similar type on condensing 5-aldehyde acridine with 5-methyl acridine. On the other hand, Friedlander (ibid.)

found that no condensation appeared to occur between cinnamaldehyde and 5-methyl acridine, while an ethene derivative was obtained quite readily from m-nitro benzaldehyde; so that the type of product obtained appears to depend to a great extent on the aldehyde employed for the condensation.

The best method for the preparation of acridine ethene compounds is, therefore, the second of those mentioned, viz. the condensation of aldehyde acridine derivatives with substances containing reactive methyl groups; and this is the only method which will be considered here.

As has been explained, the presence of basic groups in chemotherapeutic agents is very desirable, and the only means whereby they can be introduced into the acridine nucleus of the ethene compounds under consideration appears to involve the preparation and condensation of substituted derivatives of 5-aldehyde acridine. (The direct introduction of amino or nitro groups into the acridine-ethene compounds prepared in sections II and III, by the action of sodamide, nitration, or other means, is not considered here, as the method is thought to be unsuitable.)

Since no substituted 5-aldehyde acridine derivatives are known, and it seems unlikely that basic or other groups could be introduced into the acridine ring with the aldehyde group "in situ", the problem resolves itself into

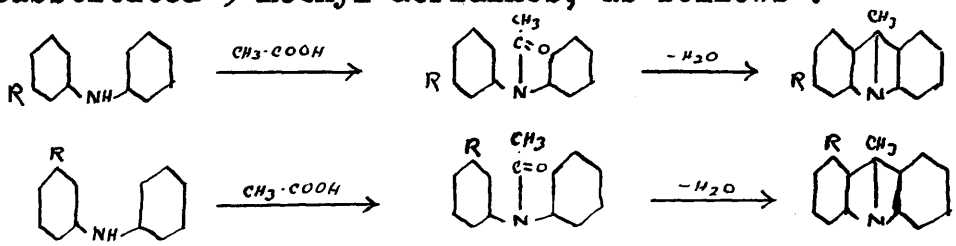
the preparation of amino or nitro derivatives of 5-methyl acridine, followed by replacement of the methyl group by an aldehyde group.

No amino 5-methyl acridines are known, but 2-phenylamino-5-methyl acridine, (Besthorn, Ber.,24, 2039.), and 3-nitro-5-methyl acridine, (Jensen & Rethwisch, J.Am.C.S., (1928), 114.), have both been prepared. Neither of these compounds is accessible however, although this is a difficulty which could be perhaps overcome.

When 5-methyl acridine is nitrated, the methyl group is oxidised to a carboxyl group,(Bernsthen, Ann., B 224, 40.), but it is possible that by further experiment, conditions could be found under which the methyl acridine could be nitrated without oxidation of the methyl group. Alternatively the carboxyl group could perhaps be reduced to the desired aldehyde group.

Hess and Bernsthen,(Ber., 18 , 689.), attempted to prepare 3-amino-5-methyl acridine from p-amino diphenylamine and acetic acid, by a method that was analogous to that employed for the preparation of 5-methyl acridine, but the experiment was not successful. The method is theoretically a good one for the preparation of acridine compounds from ortho and para substituted diphenylamine derivatives, but is less useful when meta diphenylamine derivatives are considered,

for the latter are liable to give a mixture of 2 and 4 substituted 5-methyl acridines, as follows :-



There is still another possible method for the preparation of 5-methyl acridine derivatives, and as it appears to be a promising one, the author intends to investigate it at a future date. Many nitro and amino compounds of 5-chloro acridine are known, and as the 5 chlorine atom is very reactive, it seems reasonable to suppose that it could be replaced by a methyl group.

The introduction of amino groups into the acridine nucleus of the acridine-ethene derivatives described in this thesis is, therefore, a big problem in itself, and it was considered best to postpone this for the present since two other workers are at present investigating the seventeen unknown diamino acridines, (Albert & Linnell, J.C.S., (1936), 88.). When their work is completed, it will be possible to say with a greater degree of certainty into which positions the substituent amino groups should be introduced in order to produce the maximum therapeutic activity in the acridine molecule.

Since p-amino acetanilide dissolves in water, it was hoped that the anil formed by condensing it with 5-aldehyde acridine, viz. 5(p-acetylamino anil)-acridine, would be sufficiently soluble for therapeutic tests, but when it was prepared it was found to be unsuitable. A few more somewhat similar anils have been made by various workers, but they are all too sparingly soluble in water to be of any value as therapeutic agents.

It was pointed out in Section I that anils are not generally stable towards methylating agents, so that there are two methods available for the preparation of water-soluble anils derived from 5-aldehyde acridine and containing quaternary ammonium groups :-

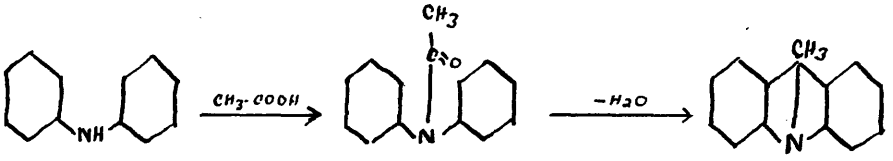
(1) Nitroso compounds can be condensed with 5-methyl acridine methochloride, methiodide, etc.

(2) 5-Aldehyde acridine methochloride can be condensed with primary amines.

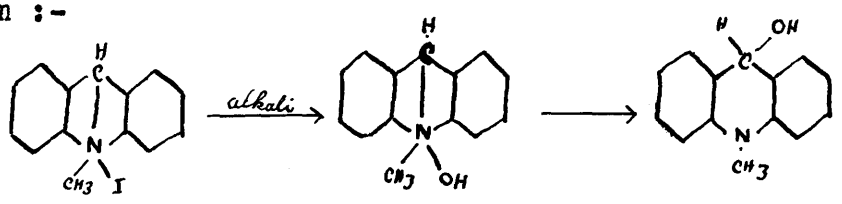
The first of these methods does not appear to be applicable. Hamer, (J.C.S., 1930, 995.), found that although 5-methyl acridine condenses readily with p-nitroso dimethylaniline, 5-methyl acridine methiodide would not condense; and the author had a similar experience when an attempt was made to condense 5-methyl acridine methochloride with p-nitroso dimethyl aniline.

The steric effect of the quaternary ammonium group is interesting. There appears to be an intimate connection between the ring nitrogen atom and the 5 carbon atom of acridine compounds, indeed the formula of acridine is often written to show this :-

and the connection is again apparent in the synthesis of methyl acridine described in the practical section :-



When quaternary ammonium salts of acridine compounds are treated with alkali, the acid radicle is replaced by a hydroxyl group, and the latter migrates to the 5 carbon atom :-



There are many other examples of this connection in the literature, so that it appears that a change in the state of the ring nitrogen atom could be expected to produce a change

in the reactivity of the methyl group attached to the 5 carbon atom.

There remains therefore, only the second method for the preparation of the quaternary ammonium salts of anils derived from 5-aldehyde acridine, and this has not been investigated. The hitherto unknown 5-aldehyde acridine methochloride has been prepared however, and is described in the experimental section. As this aldehyde could not be synthesised from p-nitroso dimethyl aniline and 5-methyl acridine methochloride for the reasons stated above, it was prepared by direct methylation of 5-aldehyde acridine.

The compounds prepared in this section are in the nature of "intermediates", and only 5-aldehyde acridine methochloride and its phenylhydrazone were subjected to biological tests. Both these compounds were found to be non trypanocidal.

EXPERIMENTAL SECTION.

SECTION I. DERIVATIVES OF 2:8-DIAMINO ACRIDINE.

GENERAL.

Before proceeding to a detailed discussion of the compounds described in this section, some general remarks on the work can be made.

Very few of the compounds prepared have definite melting points since most of them contain quaternary ammonium groups. It is characteristic of quaternary ammonium salts to have high melting points, and much often depends on the rate of heating. Most of the compounds prepared by the author decompose at their melting points, and as the latter are so indefinite they have usually been quoted over comparatively wide ranges.

It was found that the quantities of solvents used had to be carefully noted in order to obtain consistent results.

The compounds prepared have been confined to sections which are numbered to correspond with the theoretical portion of this thesis.

PREPARATION OF 2:8-DIAMINOACRIDINE FROM "PROFLAVINE".

2:8-Diaminoacridine was prepared from commercial "Proflavine", or 2:8-diaminoacridine sulphate, by treatment with dilute ammonia.

$$C_{13}H_{11}N_3 , H_2SO_4 + 2\,NH_4OH \longrightarrow C_{13}H_{11}N_3 + (NH_4)_2SO_4 \quad (+2H_2O)$$

5 Grammes of "Proflavine" were dissolved in 200 c.c. of hot water, and the free base precipitated by addition of excess 5N ammonia solution. The precipitate was left in contact with the ammoniacal liquid until it was quite cool, and was then filtered off , washed with water , and well drained at the pump. It was finally washed with a little alcohol to remove water , and then with ether, and dried in a vacuum desiccator over sulphuric acid. The base was kept out of contact with the air as much as possible while wet , so that there was no oxidation.

Golden yellow needles ; m.p. 283°C. (not sharp.)

Yield 3.3 gms. (97 %.)

It was found that water was not a satisfactory solvent for the recrystallisation of diamino acridine , as unwieldy volumes of boiling water were required , and there was evidence of decomposition. (Benda advocates a recrystallisation from "much boiling water" , (Ber. 45 . 1787.), which gives brown needles.)

In cases where recrystallisation was considered necessary alcohol was employed as solvent, but it was found that the product obtained as above was pure enough for all practical purposes when well washed with water, so that recrystallisation was seldom required.

2:8-Diaminoacridine is not "readily soluble" in alcohol as stated by Benda , it is only moderately soluble. It is very sparingly soluble in water , ether , isopropyl ether, dioxan , benzene , and toluene. It dissolves readily in nitrobenzene , pyridine , and ethylene glycol monoethyl ether.

There were noticable variations in the purity of the different batches of "Proflavine" obtained from the manufacturers. Some specimens were much darker in colour than others, and the free base liberated from these darker specimens was also dark in colour. This dark colour is probably due to the presence of nitrogenous decomposition products , as these are stated to be present in some commercial products, (Quarterly Journal of Pharmacy , 7 , 523.) Whenever possible , these impure specimens were rejected.

Pure 2:8-diamino-acridine is golden-yellow , and not "brownish-yellow" as stated by Benda , but on exposure to the atmosphere it oxidises and turns brown.

Reference.

Benda. Ber. 45. 1787.

INVESTIGATION OF THE EFFECTS OF VARIOUS CATALYSTS AND CONDITIONS ON THE CONDENSATION OF AROMATIC ALDEHYDES WITH 2:8-DIAMINOACRIDINE.

In addition to the work done with the object of finding the most efficient catalysts for the condensation of aromatic aldehydes with 2:8-diaminoacridine , a number of preliminary experiments were performed with benzaldehyde and cinnamaldehyde, in order to establish the best conditions for the reaction.

It was found that the most satisfactory results were obtained when the reagents were condensed in absolute alcoholic solution on the waterbath. Various higher-boiling solvents were tried , but in all cases the yields were inferior to those obtained in alcohol. When the alcoholic solution of the reagents was refluxed over a small flame , instead of on the waterbath , there was a reduction in the yield , due possibly to local over-heating.

Considerable difficulty was at first experienced on account of the impurities present in the aldehydes. Both benzaldehyde and cinnamaldehyde oxidise readily forming benzoic and cinnamic acids , and these acids were found to inhibit condensation with 2:8-diaminoacridine. The following experiment illustrates this :-

Pure cinnamaldehyde, diaminoacridine, and a little cinnamic acid were boiled under reflux in alcoholic solution, and a few drops of piperidine added as catalyst. A red

solution was obtained which deposited a red tarry substance from which biscinnamylideneaminoacridine could not be isolated. A control experiment performed in a similar manner, but omitting to add cinnamic acid , yielded the anil readily.

The aldehydes employed for the various condensations described in this thesis were carefully purified before use, and in view of the ease with which they undergo oxidation it seemed advisable to effect the condensations rapidly and to exclude air. The method adopted for the preparation of the anils of 2:8-diaminoacridine prevented air from entering the reaction vessel to any extent, as the latter was always filled with alcohol vapour. It was found unnecessary to carry out the condensation in an atmosphere of carbon dioxide , as advocated by Reddelein. (Ber. 46. 2718.)

Various catalysts were now tried , and their effects on the yields of the benzylidene and cinnamylidene anils noted. It was found that both these anils could be obtained in about 40 % yield without the addition of a catalyst, if care was taken to have the reagents pure and the other conditions properly adjusted. Of the catalysts tried, only piperidine was found to increase the yield , and its influence was very marked. Zinc chloride on the other hand was found to have an adverse effect, and the benzylidene anil could not be obtained in its presence.

EXPERIMENTAL.

The experiments to determine the effect of the various catalysts were carried out on a small scale. In the case of the benzylidene anil , the general method was as follows:-

1 gm. of 2:8-diaminoacridine was suspended in 20 c.c. of absolute alcohol and 1.3 c.c. of benzaldehyde. The catalyst was then added , and the mixture boiled under reflux on the waterbath for one hour, and then set aside to crystallise. The anil which separated was filtered off, dried , and weighed. The following results were obtained:-

Preparation of 2:8-Bisbenzylideneaminoacridine.

Time: 1 hour. Solvent: 20 c.c. alcohol.

Experiment No.	Catalyst.	Yield.
(1)	None.	45 %.
(2)	Iodine.	40 %.
(3)	Piperidine.	80 %.
(4)	Zinc Chloride.	Nil.

The cinnamylidene anil was prepared in a similar way:-

1 gm. of 2:8-diaminoacridine was suspended in 6 c.c. of ethylene glycol monoethyl ether and 1.3 c.c. of cinnamaldehyde added. The mixture was then heated on the waterbath, and the catalyst added. After half an hour the reaction mixture was cooled, and the anil which separated filtered off, dried, and weighed. (Ethylene glycol monoethyl ether was substituted for alcohol as 2:8-diaminoacridine is more soluble in it; the yields, however, are slightly less than those obtainable from alcohol.)

Preparation of 2:8-Biscinnamylideneaminoacridine.

Time: 1 hour. Solvent: 6 c.c. ethylene glycol monoethyl ether.

Experiment No.	Catalyst.	Yield.
(1)	None.	40%
(2)	Alcoholic Ammonia.	40%
(3)	Diethylamine.	40%
(4)	Pyridine.	40%
(5)	Piperidine.	70%

2:8-Bis-salicylideneaminoacridine is a very insoluble anil , and is precipitated from alcoholic solutions whenever it is formed in appreciable quantity. The following qualitative tests show that piperidine is a more efficient catalyst than the others tried.

2:8-diaminoacridine was dissolved in alcohol and salicylaldehyde added , the solution was mixed and divided into six portions:-

(1) Warmed gently , there was no precipitate of anil. This showed that condensation did not take place readily without addition of a catalyst.

(2) Added a few drops of piperidine , there was an immediate precipitation of the anil. This showed that condensation took place whenever the catalyst was added.

(3) Added a few drops of diethylamine , the solution turned red , and after a few seconds a precipitate of the anil was formed showing that diethylamine was also an efficient catalyst.

(4) Added a few drops of pyridine, there was no precipitate. This showed that pyridine was not a condensing agent.

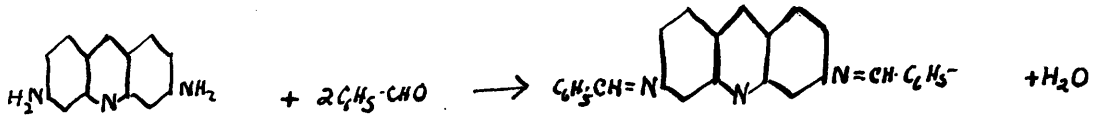
(5) Added a crystal of iodine. There was no precipitate.

(6) Added a little solid zinc chloride. The solution became red in colour, but there was no precipitate.

(7) Added a few drops of saturated alcoholic ammonia solution to (1) , but no precipitate was formed.

The above experiments show that piperidine and diethylamine are both efficient condensing agents. Piperidine appears to be the best catalyst , as it gave the best yields in the case of the benzylidene and cinnamylidene anils , and seems to act a little more rapidly than diethylamine.

PREPARATION OF 2:8-BISBENZYLIDENEAMINOACRIDINE.



209 212 385

3.0 gms. of 2:8-diamino-acridine.
4.0 c.c. of benzaldehyde, (excess.)
60 c.c. of absolute alcohol.

The diamino-acridine was suspended in the alcohol, and the benzaldehyde added together with 6 drops of piperidine. The mixture was now boiled under reflux for one hour , on the waterbath, and the solid gradually dissolved, giving a reddish-brown solution. About 35 c.c. of alcohol was then distilled off, and the reaction mixture allowed to cool. The anil crystallised, and was filtered off and washed with absolute alcohol followed by ether. The mother liquor was concentrated, and a second crop obtained.

Yield , about 80 % (5 gms.)

The product was recrystallised repeatedly from alcohol, and was obtained in lemon-yellow needle shaped prisms which melted sharply at 220°. The crystals formed felted layers on the filter.

The product was insoluble in ether and in water , sparingly soluble in alcohol , and readily soluble in pyridine and ethylene glycol monoethyl ether. The alcoholic

solution of the anil was not fluorescent , while the alcoholic solution of 2:8-diamino-acridine was found to be strongly fluorescent.

The anil is extremely readily hydrolysed by acids, and even appeared to hydrolyse to a slight extent when boiled with water. It was much more stable towards caustic soda than towards acids, the former reagent did not appear to cause marked hydrolysis in the cold , but on boiling decomposition took place, and benzaldehyde was liberated.

A specimen was treated with sulphuric acid , it began to turn red immediately , and liberated benzaldehyde which was identified by preparing the 2:4-dinitrophenyl-hydrazone .

Analyses.

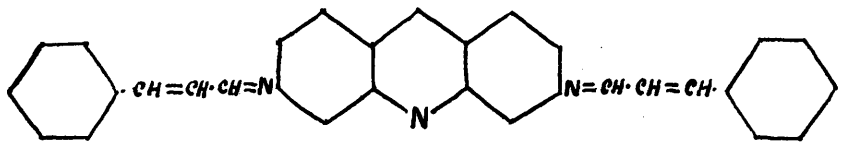
$C_{27} H_{19} N_3$ requires N , 10.9 %.

Found :- N , 10.9 , 11.1 %.

Purification of Benzaldehyde.

The benzaldehyde used for the preparation was carefully purified; it was shaken with sodium carbonate to remove benzoic acid, washed with water, and redistilled in a current of carbon dioxide to prevent oxidation.

PREPARATION OF 2:8-BISCINNAMYLIDENEAMINOACRIDINE.



437

2.0 gms. of 2:8-diamino-acridine.
3.5 c.c. of cinnamaldehyde,(excess.)
60 c.c. of absolute alcohol.

The reagents were added to the alcohol, with 5 drops of piperidine, and the mixture boiled under reflux on the waterbath. After about five minutes the solid dissolved, and a clear solution was obtained. The solution was boiled for half an hour, at the end of which the anil began to separate out from the hot reaction mixture. Heating was discontinued, and the product was filtered off when quite cold, and washed with alcohol. The mother liquor was concentrated , and a second crop obtained.

Yield 3 gms. (75% of theoretical.)

The product was insoluble in water and in ether, and very sparingly soluble in alcohol. It dissolved readily in hot pyridine or ethylene glycol monoethyl ether, and crystallised well from both of these solvents.

Microscopic golden-yellow needles were obtained from ethylene glycol monoethyl ether , melting at 252°C.

The anil was readily hydrolysed by mineral acids, which liberated free cinnamaldehyde. The aldehyde was identified by preparing the phenylhydrazone which melted at 168°C.

Analyses.

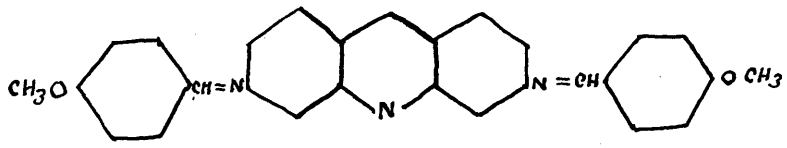
$C_{31} H_{23} N_3$ requires N, 9.6 %.

Found :- N, 9.7 %, 9.7 %.

Purification of Cinnamaldehyde.

The cinnamaldehyde used for the above preparation was purified as follows:- First the aldehyde was shaken with sodium carbonate to extract cinnamic acid; it was then washed with water and dried over sodium sulphate in a sealed flask from which the air had been displaced by carbon dioxide. After standing over sodium sulphate for two days, the aldehyde was filtered , and redistilled under reduced pressure in an atmosphere of carbon dioxide.

PREPARATION OF 2:8-BISANISYLIDENEAMINOACRIDINE.



445

1.0 gm. of diamino-acridine.
2.0 c.c. of anisaldehyde, (excess.)
15 c.c. of absolute alcohol.

The reagents were dissolved in the alcohol, and 3 drops of piperidine added. The mixture was boiled for half an hour under reflux on the waterbath , and a brownish-red solution was obtained. About 9 c.c. of alcohol were now distilled off, and the mixture cooled and allowed to stand for 48 hours. The anil which separated was filtered off, and washed with alcohol and ether. Yield , almost theoretical , 2.1 gms.

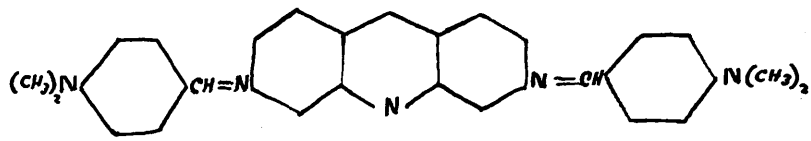
The product was recrystallised twice from ethylene glycol monoethyl ether , washed with ether , and finally dried in a vacuum desiccator over sulphuric acid.

Microscopic , lemon-yellow , needle-shaped prisms were obtained , m.p. 241° - 242°C.

The product was insoluble in water and in ether , but readily soluble in alcohol , pyridine , and ethylene glycol monoethyl ether. It was hydrolysed by acids.

$C_{29}H_{23}O_2N_3$ requires N, 9.4 % Found N , 9.6, 9.7 %.

PREPARATION OF 2:8-BIS-p-DIMETHYLAMINOBENZYLIDENEAMINO-ACRIDINE.



471

3.0 gms. of 2:8-diamino-acridine.
7.0 gms. of p-dimethylamino benzaldehyde. (60 % excess.)
40 c.c. of absolute alcohol.

The reagents were dissolved in the alcohol , and 6 drops of piperidine added. The mixture was boiled under reflux on the waterbath for an hour, and then cooled and set aside for 24 hours. The product which separated was filtered off , and washed with alcohol.

Yield (crude) , about 5 gms. (60 % of theoretical.)

The product was purified by extracting the impurities with absolute alcohol. This was done by boiling under reflux, filtering hot , and washing with hot alcohol. The anil was finally dried in a vacuum desiccator over sulphuric acid.

Microscopic orange-yellow, needle-shaped prisms , m.p. 230°C., were obtained.

The product was insoluble in water and in ether, sparingly soluble in alcohol , and soluble in hot pyridine or ethylene glycol monoethyl ether. It oxidised readily, becoming brown , and was readily hydrolysed by acids.

Analyses.

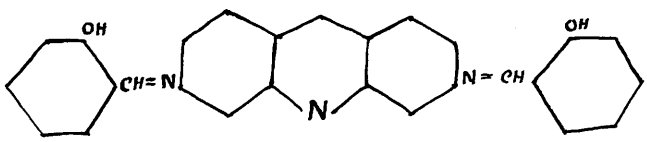
$C_{31} H_{29} N_5$ requires N 14.9 %.

Found :- N 14.9 %, 15.0 %.

The p-dimethylamino benzaldehyde used was a specially pure commercial product. It was employed in the above preparation without further purification.

PREPARATION OF 2:8-BIS-SALICYLIDENEAMINOACRIDINE.

As this anil is formed almost instantaneously , it was necessary to modify the method of preparation slightly.



417

3.0 gms. of diamino-acridine.
5.0 c.c. of salicylaldehyde , (40 % excess.)
20 c.c. of ethylene glycol monoethyl ether.

The diamino acridine was dissolved in the ethylene glycol monoethyl ether , and the hot solution filtered to remove any grit etc. present. The aldehyde was now added , and the mixture stirred so that it was thoroughly mixed. Five drops of piperidine were next added, and there was an almost immediate precipitation of the yellow anil. The product was allowed to stand for several hours , and was then filtered off , and washed with hot alcohol.

Yield , 4.3 gms. (68 % of theoretical.)

The anil was purified by refluxing with a little ethylene glycol(to remove any unchanged starting materials), and washing with hot alcohol. It was finally dried in a vacuum desiccator over sulphuric acid.

The product was a straw-coloured , microcrystalline powder which melted at 282° C.

The anil was sparingly soluble in hot alcohol , and soluble in hot pyridine , nitrobenzene , benzyl alcohol, and ethylene glycol monoethyl ether on prolonged boiling. It was insoluble in ether and in water.

On boiling with acids , the anil was readily hydrolysed liberating salicylaldehyde . The aldehyde was identified by its smell , and by the preparation of the 2:4-dinitro phenylhydrazone.

Analysis.

$C_{27} H_{19} O_2 N_3$ requires N 10.1 %.

Found :- N 10.3 % ; 10.3 %.

The anil can also be prepared in alcoholic solution , but as 2:8-diamino-acridine is not readily soluble in alcohol the preparation necessitates a large volume of solvent. The yield is better than that obtained in ethylene glycol monoethyl ether.

As this anil is so quickly and readily formed , the author suggests that its formation might be used as a test for diamino acridine. The reaction may even have quantitative applications , and is certainly capable of detecting very small quantities of 2:8-diamino.acridine in alcoholic solution.

The salicylaldehyde used was purified through the bisulphite compound.

ATTEMPTS TO METHYLATE 2:8-BISBENZYLIDENEAMINOACRIDINE.

When 2:8-bisbenzylideneaminoacridine was methylated with methyl iodide , it was found that the anil hydrolysed, and products which appeared to be methyl-amino derivatives of diaminoacridine methiodide were obtained.

Nitrobenzene and ethylene glycol monoethyl ether were both tried as solvents , and the proportion of methyl iodide and duration of methylation varied. Sometimes slight decomposition occurred , and the reaction mixture deposited carbonaceous matter.

The reaction invariably took the following course:- The anil was suspended in the solvent, methyl iodide added , and the mixture boiled under reflux. The insoluble anil gradually dissolved and a red solution was obtained ; heating was continued , and soon an insoluble red product separated out from the reaction mixture. After heating for a little time longer , the reaction was stopped , and the red product filtered off and examined.

The following is typical of the experiments tried :-

3.9 gms. of 2:8-bisbenzylideneaminoacridine.
2.0 gms. of methyl iodide , (50 % excess.)
25 c.c. of ethylene glycol monoethyl ether.

The reagents were gently boiled together under reflux , and a red solution was obtained after about

quarter of an hour. Heating was continued for a further forty-five minutes , during which a red insoluble substance separated from the hot reaction mixture. The product was cooled and filtered off, washed with alcohol and ether, and recrystallised from alcohol containing 30 % of water by volume.

On analysis it was found that the red product was not 2:8-bisbenzylideneaminoacridine methiodide , and it appeared that the anil had hydrolysed yielding a methylated derivative of 2:8-diaminoacridine.

It was thought that if the methylation were stopped before the insoluble red product separated from the reaction mixture , it might be possible to isolate 2:8-bis-benzylideneaminoacridine from the red solution. When this was tried , unmethylated bisbenzylideneaminoacridine was obtained , as is shown by the following experiment :-

3.9 gms. of 2:8-bisbenzylideneaminoacridine.
2.0 gms. of methyl iodide.
25 c.c. of ethylene glycol monoethyl ether.

The reagents were boiled together under reflux , and the anil gradually dissolved forming a red solution which was boiled for quarter of an hour , and then divided into two portions:-

Portion (1). Boiled gently for a further 45 minutes , and obtained the usual red insoluble product.

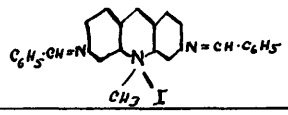
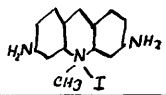
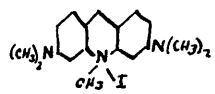
Portion (2). This was allowed to stand for some time , and

solid separated which was purified and identified as unchanged 2:8-bisbenzylideneaminoacridine.

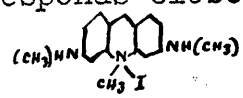
It was thought that perhaps the water added to the alcohol employed for the recrystallisation of the products had caused hydrolysis. Another sample of the red substance was therefore prepared, and purified from absolute alcohol. An orange-red powder was obtained which on analysis proved to be of a composition which approximated to those of the samples recrystallised from aqueous alcohol.

The products from the various preparations were not of uniform appearance, and ranged from orange to orange-red in colour. Some specimens crystallised readily from alcohol in needle-shaped prisms , while others could only be obtained as amorphous powders. The melting points were indefinite , and very high , (ca. 300° - 320° C. with decomposition.)

Analyses showed that the various products obtained were all of approximately the same composition , and it appears that they are mixtures of compounds posessing formulae intermediate between 2:8-diaminoacridine methiodide and 2:8-tetramethyl diaminoacridine methiodide. The analyses show that the products are not anil compounds , and this was confirmed by boiling the various specimens with hydrochloric acid, and passing the vapours into a solution of 2:4-dinitrophenylhydrazine in hydrochloric acid; in no case was there a precipitate of hydrazone.

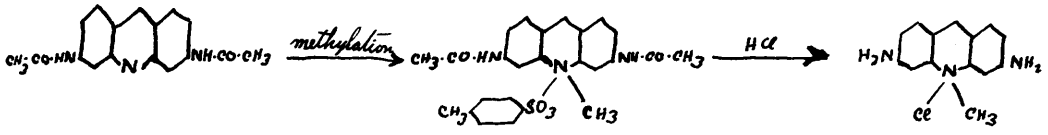
		C%	H%	N%	I%	Total.
	requires	63.8	4.2	8.0	24.1	100.1
	requires	47.8	4.0	12.2	36.2	100.2
	requires	53.0	5.4	10.5	31.1	100.0
(1)	Crystalline product. (From aqueous alcohol) found	49.2	4.0	10.5	35.2	98.9
(2)	Amorphous product. (From aqueous alcohol) found	49.7	4.5	11.2	33.5	98.9
(3)	Amorphous product. (From absolute alcohol) found	49.5	4.3	10.1	33.8	97.7
(4)	Amorphous product. (From aqueous alcohol) found			11.8 11.9		
(5)	Crystalline product. (From aqueous alcohol) found			10.8 10.7		

The samples analysed were all obtained from different preparations. Analyses (1),(2),and(3) were done by "micro" methods, while (4) and (5) were analysed by the ordinary Dumas method.

Product no.(2) corresponds closely to 2:8-dimethyl diaminoacridine methiodide,  , which requires C, 50.6 %; H, 4.8 %; N, 11.1 %; I, 33.6 %.

PREPARATION OF 2:8-DIAMINOACRIDINE METHOCHLORIDE.

The method used was that originally described by Benda, (Ber. 45, 1787.). Diaminoacridine is acetylated, to prevent methylation of the amino groups, and the di-acetyl compound is then methylated with excess of methyl p-toluene sulphonate. The product obtained is boiled with hydrochloric acid which converts the metho p-toluene sulphonate to the methochloride, and at the same time de-acetylates the amino groups.



Acetylation of 2:8-diaminoacridine.

1.25 Grammes of fused sodium acetate, 5 gms. of 2:8-diamino acridine, and 12.5 c.c. (excess) of acetic anhydride were made into a paste and heated to 80°C. A reaction commenced, and heating was discontinued, the temperature rose spontaneously to 125°C., and a dark brown solution was obtained. The temperature was maintained at 130° for 25 minutes, and then allowed to fall. The reaction mixture was diluted with 35 c.c. of water, then boiled, filtered, and left to crystallise for 24 hours.

According to Benda, greenish-yellow scales of the acetate of the acetyl compound should now have separated. The author performed several experiments, but in each of them the same difficulty occured, and the acetyl compound

remained in solution. A very small quantity of another product invariably separated out here, however, and this was filtered off from the reaction mixture. (This will be dealt with later.)

The acetyl compound was isolated from solution by adding solid sodium carbonate until an alkaline reaction was obtained. This precipitated the free di-acetyl compound as a yellow precipitate which was filtered off, and washed with water.(This method is a little shorter than Benda's , as in the latter the acetate of the acetyl compound is redissolved in water, and the free base precipitated by ammonia.)

Yield, almost theoretical, (7 gms.)

The product was recrystallised from alcohol , as this solvent was found to be the most suitable. It formed yellow prisms of indefinite melting point , (200°- 300° C.)

The product was found to crystallise from alcohol with one molecule of alcohol of crystallisation.

$C_{17} H_{15} O_2 N_3 . C_2 H_5 OH$ requires N, 12.4 %.
Found :- N, 12.5 %.

This alcohol of crystallisation was removed by heating the product for three hours in a vacuum oven at 98° C , and under a vacuum of 30" of mercury.

$C_{17} H_{15} O_2 N_3$ requires N, 14.3 %.
Found :- N, 14.4 %, 14.6 %.

The presence of this molecule of alcohol of crystallisation was also shown by the loss in weight of a sample heated in the vacuum oven:-

2.151 gms. of $C_{17} H_{15} O_2 N_3 . C_2 H_5 OH$ lost 0.295 gms.

For conversion to $C_{17} H_{15} O_2 N_3$ the calculated loss is 0.292 gms.

Very little information on the properties of 2:8-bisacetylamino acridine is available in the literature, and so the author has given the following list of solubilities:-

The product was found to insoluble in ether, and sparingly soluble in butyl acetate.It dissolved in hot methyl or ethyl alcohol, and crystallised out on cooling from both these solvents. It was very readily soluble in pyridine, ethylene glycol monoethyl ether, and propyl alcohol, and separated from all three in well defined crystals on long standing.

The bisacetylamino compound gave no precipitate with salicylaldehyde and piperidine in alcoholic solution, and it is suggested by the author that this might be used as a test for the completion of acetylation. (Benda tests by diazotisation.) For the "Salicylaldehyde Test" cf. pg. 72.

The bye-product obtained from the acetylation was not exhaustively examined. It was a white substance

which melted fairly sharply at 219°C. On ignition in a platinum crucible, it burned with a smoky flame, and left no metallic residue. It contained nitrogen, but was not an acetyl compound since no acetic acid was evolved on boiling with sulphuric acid. It was insoluble in water and in ether, but very readily soluble in alcohol, pyridine, and ethylene glycol monoethyl ether. It can be recrystallised from alcohol.

The substance may be a product of the reaction, or a hitherto unknown impurity present in commercial "Proflavine". It was obtained only in small quantities, and was not examined further as it was considered outside the scope of this research.

Methylation of 2:8-Bisacetylamino-acridine.

2.9 Grammes of the acetyl compound were suspended in 25 c.c. of nitrobenzene, and the temperature raised to 175°. 2.5 Grammes of methyl p-toluene sulphonate were now added, and the solid rapidly dissolved forming a red solution. Benda does not state how long he methylated the acetyl compound, but says that on addition of the methyl p-toluene sulphonate "alkylation follows at once". Similarly Browning's collaborators omit to indicate the time required for several analogous methylations, (Proc. Roy. Soc., B. 93. 329.) It was assumed therefore that methylation was rapid, and the acetyl compound was methylated for half an hour.

The reaction mixture was allowed to stand for 24 hours, and the metho - p-toluenesulphonate filtered off, and washed with ether till free from nitrobenzene.

Yield 5 gms. Yellowish-orange crystals.

It was found that the methylation could be effected in ethylene glycol monoethyl ether solution ; and this solvent is preferable to nitrobenzene , for it is more readily got rid of, and is miscible with water in all proportions.

Hydrolysis of 2:8-Bisacetylaminoacridine Metho p-Toluene Sulphonate.

5 Grammes of the above product were dissolved in a mixture of 17 c.c. of concentrated hydrochloric acid and 17 c.c. of water, and the solution gently boiled under reflux for four hours. A deep red solution was obtained which deposited red prisms on cooling. The product was filtered off, washed with a little water, and dried in an oven at 90°C. Drying at elevated temperatures drives off hydrogen chloride and converts the hydrochloride of 2:8-diaminoacridine methochloride to 2:8-diaminoacridine methochloride.

It was found that the product gave a precipitate in alcoholic solution when piperidine and salicylaldehyde were added, thus showing that Benda's method gave an impure mixture. The proportion of unmethylated product was ca. 30 %.

(The "Salicylaldehyde Test" for unmethylated 2:8-diamino compounds is discussed in full on pg. 89).

As pure 2:8-diamino acridine methochloride can be obtained from "Euflavine" by Gaillot's method, attempts were not made to rectify Benda's preparation.

It is possible that bis-acetylaminoacridine could be methylated if other methylating agents were used and the duration of the reaction prolonged, but two criticisms of the method as it now stands can be made. Firstly, since bis-acetylaminoacridine is only moderately soluble in nitrobenzene any of it which escapes methylation will tend to be thrown out of solution if this solvent be employed. Secondly, when concentrated hydrochloric acid is added to a solution of diamino acridine hydrochloride and acriflavine , there is a preferential precipitation of the former compound , and this has even been suggested as a possible means of separation for commercial mixtures, (Marshall, Quarterly Journal of Pharmacy, 1934, 7, 514.)

Thus, the nitrobenzene used as solvent for the methylation and the hydrochloric acid employed for the subsequent hydrolysis both tend to enrich the final product in unmethylated 2:8-diamino-acridine.

PREPARATION OF PURE 2:8-DIAMINOACRIDINE METHOCHLORIDE.

Commercial preparations of 2:8-diaminoacridine methochloride are contaminated with about 30 % of 2:8-diaminoacridine hydrochloride. It was found also , that the original method described by Benda for the preparation of 2:8-diaminoacridine methochloride gave a product which was contaminated with about 30 % of unmethylated starting material.

Gaillot's method for the separation of mixtures of 2:8-diaminoacridine methochloride and hydrochloride was employed. This method depends upon the fact that when the impure mixture is treated with silver oxide , the methylated diaminoacridine remains in solution, while the unmethylated compound is precipitated as free 2:8-diaminoacridine.

A sample of commercial "Euflavine" was used , which contained about 70 to 80 % of 2:8-diaminoacridine methochloride , and about 20 to 30 % of 2:8-diaminoacridine hydrochloride. Gaillot's instructions were followed fairly closely, but it was found unnecessary to concentrate the solution of pure methochloride in order to get it to crystallise , so that prolonged boiling which tends to cause decomposition can be avoided.

Moist silver oxide was prepared by treating 10 gms. of silver nitrate with 10 c.c. of 30% sodium hydroxide solution; and the product obtained washed by

decantation , using five litres of water.

10 grammes of "Euflavine" were dissolved in 600 c.c. of warm water, and the clear solution poured upon the silver oxide and vigorously stirred for ten minutes. A yellow precipitate of free diaminoacridine was obtained, and was filtered off with the other insoluble material. The orange-red filtrate containing the methylated compound was now neutralised with dilute hydrochloric acid, thus re-converting the metho-hydroxide to the methochloride. (Note:- It was hard to judge when neutrality had been reached, as the solution was so highly coloured."Spot" tests were done with blue litmus solution ; when the solution was alkaline a green colour was obtained from the orange solution and blue litmus, and when the solution was acid an orange colour was got.) Acid was added until the solution showed a definitely acid reaction.

The solution was now concentrated on the waterbath under reduced pressure (6-7 mm.), and 100 cc. of water distilled off which deminished the volume to 500 c.c. On standing overnight , the methochloride crystallised.

The product was filtered off, and washed with a little alcohol, followed by much ether, and finally dried in a vacuum desiccator over sulphuric acid.

The yield was 5.5 gms. (55 % of the weight of "Euflavine" taken initially.) A second crop of .5 gms. was obtained on concentrating the mother liquor.

It is impossible to draw comparisons between the yield obtained by Gaillot, and that obtained by the author, since different specimens of "Euflavine" were used ; but the figures are interesting in view of the fact that Gaillot obtained his first crop of crystals from a solution which contained about 130 gms. of diaminoacridine methochloride per litre, whereas the author obtained his first crop from a solution containing only 12 gms. of diamino acridine methochloride per litre. Gaillot obtained a yield of 57.5 % for his first crop of crystals , and the author obtained a yield of 55.0 %.

From these figures it is readily seen that it is not necessary to evaporate the solution down in order to obtain the first crop of crystals; and it is probable that the product obtained by the author's method will be purer, since it crystallises from a larger volume of mother-liquor, and is not subjected to prolonged boiling which causes decomposition.

The total yield obtained by the author was 60 % , whereas Gaillot obtained 65 %.

3 Grammes of the product were recrystallised from 75 c.c. of methyl alcohol. Beautiful glistening, orange-red prisms were obtained,which were dried in a vacuum desiccator over sulphuric acid. Yield 2.5 gms.

Analysis.

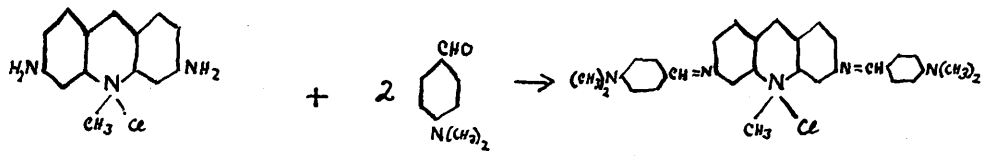
$C_{14} H_{14} N_3 Cl$	requires	Cl	13.7 %.
	Found :-		13.6 %.

Reference.

Gaillot, Bull. Soc. Chim., (1934) , 796.

ATTEMPTED CONDENSATION OF 2:8-DIAMINO ACRIDINE METHOCHLORIDE AND p-DIMETHYLAMINO BENZALDEHYDE.

The reagents were fused together instead of being boiled in alcoholic solution , as the former method is generally the more effective in cases where condensation is difficult. (cf. the 4-phenylamino-quinoline ethene compounds in this thesis.) Condensation did not take place.



260.5 298 522.5

2.6 gms. of 2:8-diamino acridine methochloride.
3.8 gms. of p- dimethylamino benzaldehyde , (25 % excess.)

The reagents were melted together on an oil bath, and the temperature raised to 130°C. Five drops of piperidine were added now , and the mixture heated for 7 hours at 130° - 145°C. The melt was then allowed to cool and solidify, and the product pulverised and extracted with ether till free from unchanged aldehyde. Yield 2.7 gms. (The slight increase in weight of the ether-insoluble matter was due to a little aldehyde which escaped extraction, and not to condensation having taken place.)

The product was recrystallised once from methyl alcohol , and then from water, and finally from

methyl alcohol again. It was finally dried in a vacuum desiccator over sulphuric acid.

The product thus obtained was an orange-red crystalline substance, which looked like unchanged 2:8-diamino acridine methochloride.

To determine the constitution of the substance , the chlorine was estimated.

2:8-Bis-p-dimethylaminobenzylideneamino acridine methochloride requires :-	Cl, 6.8 %.
2:8-Diamino acridine methochloride :-	Cl,13.7 %.
Found (micro):-	Cl,13.5 %.

Hence the substance was unchanged 2:8-diamino acridine methochloride.

THE ACTION OF SALICYLALDEHYDE ON COMMERCIAL SPECIMENS OF "EUFLAVINE", "ACRIFLAVINE", AND "PROFLAVINE".

The significance of the reaction between salicylaldehyde and unmethylated salts of 2:8-diaminoacridine has been fully discussed in the theoretical section of this thesis, and will not be considered here.

Experimental. The Action of Salicylaldehyde on "Euflavine".

1 Gramme of commercial "Euflavine" was dissolved by boiling under reflux, in 80 c.c. of alcohol and a few drops of water. One c.c. of salicylaldehyde and 0.5 c.c. of piperidine were now added to the alcoholic solution, and there was an almost immediate precipitation of yellow 2:8-bis-salicylideneaminoacridine. The anil was filtered off, and the mother liquor was treated with a further quantity of salicylaldehyde and a few more drops of piperidine, and boiled for two hours on the waterbath. Nothing separated from the reaction mixture on cooling , so that it was diluted with ether and allowed to stand overnight when red crystals of 2:8-diaminoacridine methochloride were obtained.

The 2:8-bis-salicylideneaminoacridine was recrystallised from ethylene glycol monoethyl ether, and melted at 280°C. It was further identified by boiling with sulphuric acid, when free salicylaldehyde was evolved.

The anil was tested and found to be free from chlorine.

The unchanged 2:8-diaminoacridine methochloride was recrystallised twice from methyl alcohol, filtered off, and washed with ether. It contained chlorine, and yielded no salicylaldehyde on boiling with sulphuric acid. On dissolving the product in alcohol and treating it with salicylaldehyde and piperidine as before, no precipitate was obtained.

A pure specimen of 2:8-diaminoacridine methochloride prepared by Gaillots method gave no precipitate in alcoholic solution on tratment with salicylaldehyde and piperidine.

As explained in the theoretical section, a large excess of piperidine must be added, and its function appears to be twofold. It liberates free diaminoacridine from its hydrochloride, and then catalyses the condensation with the aldehyde.

Action of Salicylaldehyde on "Acriflavine".

"Acriflavine" was found to give a precipitate in an exactly similar manner to "Euflavine" , but the quantity of piperidine taken was doubled, since in this case the free base must be liberated from the dihydrochloride

while the unmethylated compound in "Euflavine" is present as the monohydrochloride.

1 Gramme of "Acriflavine" was dissolved in alcohol, and 1 c.c. of salicylaldehyde and 1 c.c. of piperidine added. The unmethylated anil precipitated as before.

Action of Salicylaldehyde on "Proflavine".

"Proflavine" was dissolved in alcohol and treated with salicylaldehyde and piperidine in the usual manner, and there was an immediate precipitation of the anil.

A specimen of 2:8-diamino acridine dihydrochloride behaved in the same way as "Proflavine".

This test for the presence of unmethylated 2:8-diaminoacridine has been referred to as "The Salicylaldehyde Test" for the sake of brevity. It was used in order to detect the presence of unmethylated 2:8-diaminoacridine in specimens of 2:8-diaminoacridine methochloride prepared by Benda's method, and appears to be generally applicable.

As explained in the theoretical section, this reaction has not been placed on a quantitative basis, but the samples of "Euflavine" tested generally gave a precipitate of anil which corresponded to about 35% of 2:8-diaminoacridine hydrochloride.

SECTION II. DERIVATIVES OF PYRIDINE.

PREPARATION OF 2-METHYL PYRIDINE METHIODIDE.

100 c.c. of 2-methyl pyridine were placed in a large flask fitted with an efficient reflux condenser , and 70 c.c. of methyl iodide (excess) added. The reaction took place in the cold , and became almost violent. Much heat was evolved , and the flask had to be cooled. After the initial violent reaction had subsided, the reaction mixture was allowed to stand for some hours. The product was filtered off, and washed with ether till free from 2-methyl pyridine. It recrystallised from alcohol in white needles.

Yield (recrystallised) 60 - 70 %.

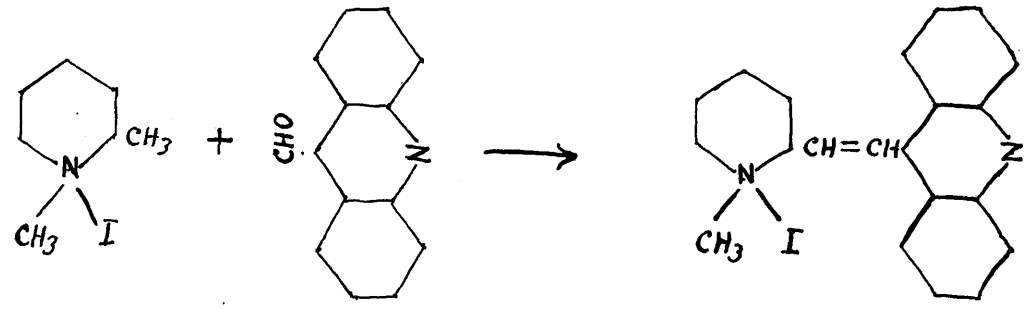
PREPARATION OF 2-METHYL PYRIDINE ETHIODIDE.

40 c.c. of 2-methyl pyridine were placed in a flask fitted with an efficient reflux condenser, and 35 c.c. of ethyl iodide added. The mixture was gently warmed to start the reaction, and finally refluxed on the waterbath for two hours. After standing overnight , the product was filtered off, washed with ether, and recrystallised from alcohol. Colourless prisms were obtained , much more readily soluble in water , and in alcohol , than the methiodide.

Yield 70 - 80 %, (recrystallised.)

PREPARATION OF S-(2-PYRIDYL METHIODIDE)-5-ACRIDYLETHENE.

This compound is new.



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35.3 gms. of 2-methyl-pyridine methiodide.
31.0 gms. (1 mol.) of 5 aldehyde acridine,
70 ccs. of absolute alcohol.

The reagents were dissolved in the alcohol , and a deep brown solution was obtained. Ten drops of piperidine were now added , and the solution boiled on the waterbath under reflux. Condensation was very rapid, and solid soon began to separate , so that after about quarter of an hour the whole mass had become practically solid. Heating was continued for 1½ hours , at the end of which the precipitate was filtered off from the hot solution , and washed with a little alcohol followed by much ether. The product was finally dried in a vacuum desiccator.

Yield 32 gms.,(50% of the theoretical.)

The product obtained was nearly pure , but contained a little unchanged methyl-pyridine methiodide. It was recrystallised from aqueous alcohol , in which it was readily soluble.

The substance was dimorphous, occurring in yellow leaflets or orange needles which were interconvertible by seeding a solution with the appropriate crystal. The melting point was rather indefinite , the substance became orange-red above 120°C. , darkened at about 215°to 220°C., and charred at 220°to 225°C. with escape of gas.

Analysis. $C_{21} H_{17} N_2 I$ requires 6.6% N.
found :- 6.6% N, 6.9% N.

Solubilities. The compound was soluble in water and in alcohol , and very soluble in aqueous alcohol or water containing a few drops of alcohol. Insoluble in ether.

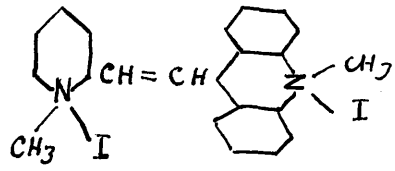
PREPARATION OF S-(2-PYRIDYL METHIODIDE)-5-ACRIDYLETHENE HYDROCHLORIDE.

The product obtained from the preceeding preparation was dissolved in hydrochloric acid , and the hot solution filtered. Red, needle-shaped prisms separated on cooling, and were filtered off , drained well, and washed with ether. The hydrochloride was recrystallised from alcohol , washed with ether , and dried in a vacuum desiccator. Orange-red prisms were obtained , readily soluble in water with an acid reaction.

$C_{21} H_{18} N_2 I Cl$ requires N 6.1 %.
found :- N 6.1 %.

PREPARATION OF S-2-PYRIDYL-5-ACRIDYLETHENE DIMETHIODIDE.

This compound is new.



8.5 gms. of s-(2-pyridyl methiodide)-5-acridylethene.
3.5 ccs. of methyl sulphate, (excess.)
10 ccs. of ethylene glycol monoethyl ether.

The ethene compound was suspended in the ethylene glycol monoethyl ether , and the dimethyl sulphate added. The mixture was agitated and the temperature slowly raised to 30° to 35°C ; the reaction then commenced , and heating was discontinued . The solid gradually dissolved , and the temperature rose spontaneously to about 70° C. The mixture was again gently heated , and the temperature at 100°C. for 10 - 15 minutes. The dark red solution was allowed to cool and stand for 24 hours , and the orange-red methosulphate which separated filtered off , and washed with a little absolute alcohol followed by much ether. A second crop was obtained from the mother liquor by precipit--ation with ether. The product was dried in a vacuum desiccator over sulphuric acid.

About 7 gms. of the orange-red methosulphate were obtained. The melting point was indefinite, (175°- 185°C)

The methosulphate was dissolved in a little hot water, in which it was very soluble , and a saturated solution of potassium iodide added . The dimethiodide precipitated at once, and was recrystallised from water. Hydrated , bright red , needle-shaped prisms were obtained, which lost water on drying in a vacuum desiccator over sulphuric acid , and became much darker; addition of water restored the bright red colour.

Analyses.

$C_{22}H_{20}N_2I_2$ requires N 5.0 %.

found :- N 5.0 %, 5.2 %.

The dimethiodide was soluble in water , giving a dark red solution.

PREPARATION OF S-(2-PYRIDYL ETHIODIDE)-5-ACRIDYLETHENE.

This compound is new ; it was prepared in a similar way to the corresponding methiodide.

10.3 gms. of 5 aldehyde acridine.
15.0 gms of 2-methyl-pyridine ethiodide, (15% excess.)
20 ccs. of absolute alcohol.

The reagents were dissolved in the alcohol , and 10 drops of piperidine added. The solution was boiled for 1¼ hours on the waterbath, and the precipitate which separated filtered off from the hot solution , and washed with alcohol followed by much ether. The product was then spread on a porous plate , and dried first in the air , and finally in a vacuum desiccator over concentrated sulphuric acid. A yellow , beautifully crystalline product was obtained.

Yield 14.5 gms. , (66% of the theoretical.)

Recrystallisation.

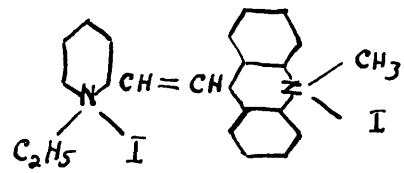
The compound showed a very marked increase in solubility when compared with the corresponding methiodide; it was very readily soluble in boiling water , from which it separated in lemon-yellow leaflets on cooling.

For analysis , a sample was recrystallised first from water , and then from alcohol. It was washed with a little alcohol , and dried in a vacuum oven at 100°C.

Analysis. $C_{22} H_{19} N_2 I$ requires N 6.4 %.
found :- N 6.5 %, 6.5 %.

PREPARATION OF S-(2-PYRIDYL ETHIODIDE)-(5-ACRIDYL METHIODIDE)ETHENE.

This compound is new.



580

6.6 gms. of s-(2-pyridyl ethiodide)-5-acridylethene.
13 ccs. of methyl sulphate , (excess.)

The ethene compound was added gradually to the methyl sulphate , and the temperature slowly raised. There was a vigorous reaction , and the temperature was allowed to rise to 100°C., and maintained at that for 5 - 10 minutes. The orange-red methosulphate which separated on cooling was filtered off, and washed with a little alcohol , followed by much ether. About 6 gms. of product were obtained.

The methosulphate was dissolved in a little hot water, in which it was very soluble , and a saturated solution of potassium iodide added. The methiodide was precipitated immediately, and was then filtered off , and washed with a little water.

For analysis, the product was recrystallised once from water, and then from alcohol. Dark red, needle-shaped prisms were obtained , which were dried in a vacuum oven at 100°C.

$C_{23}H_{22}N_2I_2$ requires N 4.8 %.
found :- N 4.8 %, and 4.9 %.

SECTION III(a). UNSUBSTITUTED DERIVATIVES OF QUINOLINE.

PREPARATION OF 2-METHYL QUINOLINE METHIODIDE.

50 c.c. of 2-methyl quinoline and 30 c.c. of methyl iodide (excess) were mixed, and heated on the waterbath for an hour in a flask fitted with an efficient reflux condenser. After standing overnight , the product was filtered off, washed with ether , and recrystallised from alcohol. Lemon-yellow needles were obtained.

Yield , (recrystallised) ,70 %.

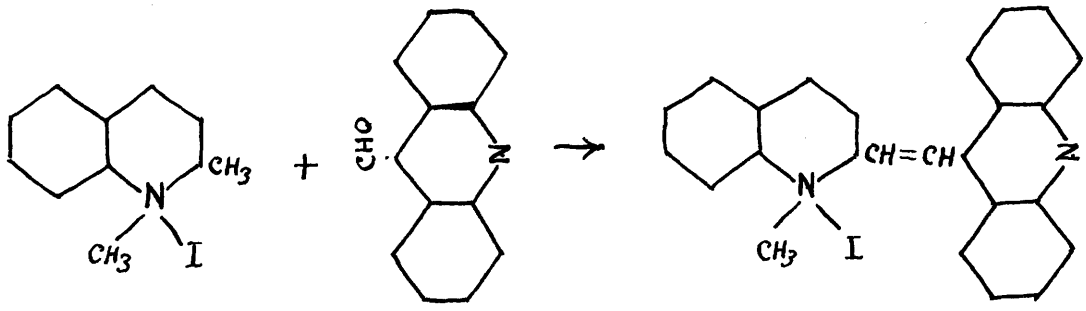
PREPARATION OF 2-METHYL QUINOLINE ETHIODIDE.

70 c.c. of 2-methyl quinoline and 40 c.c. of ethyl iodide were mixed, and heated under reflux on the waterbath for two hours. The reaction took place much less rapidly than it did in the case of the corresponding methiodide. The reaction mixture was cooled , and the flask stoppered , and allowed to stand for several days. The product was finally filtered off, washed with ether , and recrystallised from alcohol. Lemon-yellow prisms were obtained.

Yield , (recrystallised) 50 %.

PREPARATION OF 5-(2-QUINOLYL METHIODIDE)-5-ACRIDYLETHENE.

This compound is new.



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10.0 gms. of 5-aldehyde acridine.
16.5 gms. of quinaldine methiodide, (excess.)
75 ccs. of absolute alcohol.

The reagents were dissolved in the alcohol , and the dark brown solution filtered. Eight drops of piperidine were now added , and the solution boiled on the waterbath , in a flask fitted with a ground-glass joint and water condenser. Condensation was rapid, and solid soon began to separate , while the solution gradually became greenish-blue in colour. Heating was continued for five hours , at the end of which the precipitate was filtered off from the hot solution, and washed with alcohol. The product was next refluxed with 70 ccs. of absolute alcohol for 1 hour , to remove a green impurity , filtered off from the hot solution , and repeatedly washed on the filter with hot alcohol .

Yield 19 gms. , (85% of the theoretical.)

A dark brown , crystalline product was thus

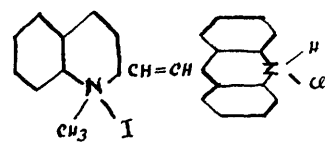
obtained, which was insoluble, or sparingly soluble in all the usual solvents. It was, however, moderately soluble in nitrobenzene, and in 50% aqueous ethylene glycol monoethyl ether, and crystallised from the latter as a dark brown, crystalline powder. The melting point was indefinite, but was about 220° - 225° C. (with decomposition).

$C_{25}\ H_{19}\ N\ I$ requires N 5.9%

found:- N 6.1%, 6.2%.

The product was readily soluble in dilute mineral acids, giving red solutions which generally deposited crystalline salts on cooling, e.g:- the nitrate, (orange-yellow needles); and the sulphate, (orange-red prisms). On boiling with concentrated nitric acid, fumes of iodine escaped.

PREPARATION OF S-(2-QUINOLYL METHIODIDE)- 5-ACRIDYLETHENE HYDROCHLORIDE.

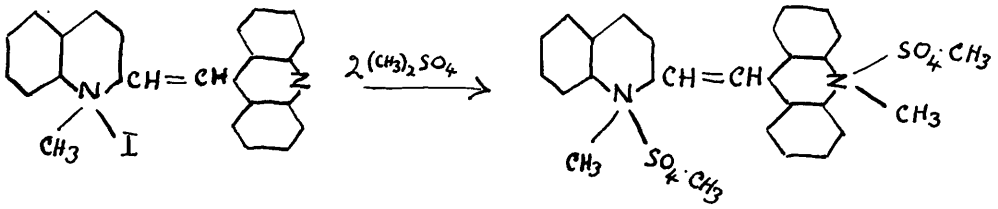


s-(2-Quinolyl methiodide)5- acridylethene was dissolved in hot, dilute, hydrochloric acid, and the red solution filtered. The hydrochloride crystallised, and was filtered off, and washed first with water, and then with alcohol, and dried in a vacuum desiccator. On drying the crystals became darker in colour, and became anhydrous.

$C_{25}\ H_{20}\ N_2\ I\ Cl$ requires N, 5.5%. Found N 5.5%

PREPARATION OF S-2-QUINOLYL-5-ACRIDYLETHENE DIMETHOSULPHATE.

This compound is new.



474 584

Twenty grammes of s-(2-quinolyl methiodide)-5-acridylethene were dissolved in 20 to 30 ccs. of methyl sulphate with gentle heating. At about 140° C., a vigorous reaction took place , and after 10 - 15 minutes at this temperature the mixture was set aside , and allowed to stand overnight. An almost solid mass was obtained , which was filtered off, and thoroughly washed with ether to remove methyl sulphate. The product was dissolved in a little hot water , in which it was extremely soluble , and the solution filtered and allowed to cool. The dimethosulphate crystallised in orange-red , needle-shaped prisms , which were filtered off , washed with water followed by ether , and dried in a vacuum desiccator.

Yield 65-70% of theoretical.

After drying in a vacuum desiccator the product became more orange in colour , and resembled potassium dichromate. This was probably due to loss of water of crystallisation.

The dimethosulphate was readily soluble in water or in alcohol , giving deep red solutions; it was insoluble in ether.

The melting point was indefinite ; darkening began at about 230° C.

The product contained no halogen , and as shown by analysis , the iodine was replaced , and a dimethosulphate obtained.

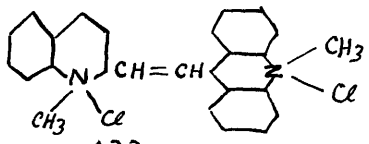
$C_{28}\ H_{28}\ O_8\ N_2\ S_2$ requires N, 4.8%; SO_4 , 32.9%.

Found :- N , 4.9% , 5.0%.

SO_4 , 33.0%, 32.4%.

(pptn. as $BaSO_4$)

PREPARATION OF S-2-QUINOLYL-5-ACRIDYLETHENE DIMETHOCHLORIDE.



433

The methosulphate was dissolved in a little hot water, and a saturated sodium chloride solution added. There was an immediate precipitation of the orange methochloride , which was filtered off after allowing the solution to cool , and washed on the filter with a little water.

The product was recrystallised from water , and filtered off , washed with water, and finally dried in a vacuum desiccator.

Orange prisms were obtained , very readily soluble in water and aqueous alcohol, less soluble in dry alcohol , and insoluble in ether.

Addition of silver nitrate to a solution of the methochloride in dilute nitric acid gave an immediate precipitation of silver chloride.

$C_{26}H_{22}N_2Cl_2$ requires N 6.5 %, and Cl 16.4 %.
Found :- N 6.7 %, 6.8 %.

The chlorine was estimated by dissolving the salt in water and precipitating the chlorine as silver chloride. .Found :- 15.9 % and 15.9 % Cl.

Preparation of s-2-quinolyl-5-acridylethene dimethiodide.

This compound was prepared in an analogous manner to the dimethochloride , using potassium iodide to precipitate the salt , instead of sodium chloride.

The product recrystallised from water in dark red , needle-shaped prisms, and was sparingly soluble in aqueous alcohol , and insoluble in ether.

$C_{26}H_{22}N_2I_2$ requires N 4.5 %.
Found :- N 4.6 %.

PREPARATION OF S-(2-QUINOLYL ETHIODIDE)-(5-ACRIDYL METHIODIDE)ETHENE.

Stage (1). Condensation of 5-Aldehyde Acridine and Quinaldine Ethiodide.

This condensation was effected using a method entirely analogous to that employed for the preparation of s-(2-quinolyl methiodide)-5-acridylethene.

17 gms. of quinaldine ethiodide were dissolved in 60 ccs. of alcohol and 10 ccs. of water, and 10 gms. (excess) of aldehyde acridine added. A brown solution was obtained, which was filtered. Ten drops of piperidine were now added, and the solution boiled for three hours under reflux , on the waterbath. The reddish-brown condensation product which separated was filtered off from the hot solution , and washed with hot alcohol to remove a green impurity. The product was next extracted twice with boiling absolute alcohol, using 50 ccs. for each extraction , filtered off from the hot solution , and finally washed with alcohol. The yield was 50 % of theoretical.

The product closely resembled the corresponding methiodide in its general properties , and was insoluble in the usual solvents.

Stage (2). Methylation of the Condensation Product.

11.5 gms. of the compound obtained above were

suspended in 20 ccs. of methyl sulphate (large excess) , and the temperature gradually raised to 70° C., there was a vigorous reaction , and the solid gradually dissolved giving a red solution. The temperature was kept at 100° - 110° for 10 to 15 minutes, and the mixture then set aside , and allowed to stand overnight. The orange-red methosulphate which separated was filtered off , and thoroughly washed with ether till quite free from methyl sulphate, and dried.

The product obtained was dissolved in a little hot water , in which it was very soluble giving a red solution , and a saturated solution of potassium iodide added. The methiodide precipitated immediately, and was filtered off, and washed with a little water, and then recrystallised from aqueous alcohol , (30 % of water.) The compound crystallised in bright red , hydrated , needle-shaped prisms which lost solvent in the air , and became darker ; it was dried first in a vacuum oven at 100° C., and then in a vacuum desiccator over sulphuric acid.

The s-(2-quinolyl ethiodide)-(5-acridyl methiodide)ethene obtained was readily soluble in water and aqueous ethylene glycol monoethyl ether , giving red solutions which deposited crystals on cooling. It was insoluble in ether.

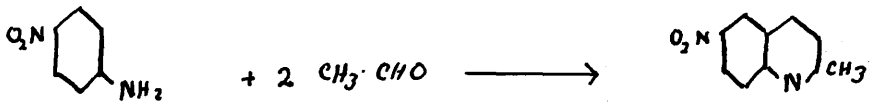
$C_{27}H_{24}N_2I_2$ requires N 4.4 %.

Found :- N 4.5 %, 4.7 %.

SECTION III(b). DERIVATIVES OF 6-AMINO QUINOLINE.

PREPARATION OF 6-NITRO-2-METHYL-QUINOLINE.

The method used was that outlined by Hamer (J.C.S. (1921) 1432.) employing the Dobner-Miller reaction. Various slight modifications were made, but large quantities of tar were obtained, and the yields were poor as is generally the case with the Dobner-Miller reaction.



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The best yield was obtained as follows:-

100 g. p-nitraniline.
80 g. paraldehyde.
100 g. concentrated hydrochloric acid.

The p-nitraniline and the paraldehyde were mixed in a large flask fitted with a reflux condenser, and the acid added gradually. Heat was evolved, and the flask was cooled. When all the acid had been added, the mixture was heated for 30 to 40 minutes on the waterbath, and then poured into 300 ccs. of water and allowed to cool. When cool, the yellow liquid was filtered free from tar, and solid crystalline sodium acetate added which precipitated the 6-nitro-quinaldine as a thick, yellow mass. The product was filtered off, drained well, and washed with water. It was found that when the nitroquinaldine was not washed free of sodium acetate,

a/

a green oxidation product was gradually obtained on standing.

Purification.

The product obtained was made into a thick cream with water, and heated on the waterbath. Dilute nitric acid was then carefully added with stirring, until the solid was just dissolved, and care was taken to avoid excess of acid as recommended by Browning, (Proc. Roy. Soc. B. 96 (1924) pg 325.) the solution not being acid to Congo Red paper at the end of the operation, Browning's observation that excess acid converted the product to tar was confirmed, but it was found a distinct advantage to heat on the waterbath and agitate efficiently. The solution was filtered free from any tar which separated, boiled with animal charcoal, filtered again, and finally concentrated in a large evaporating basin on the waterbath till a crystalline crust of the nitrate of 6 nitro quinaldine began to form. The deep orange-red liquid was set aside to cool, when the nitrate crystallised. The nitrate was filtered off, drained, and washed with a little cold water.

The nitrate was dissolved in hot water, boiled with a little animal charcoal, and filtered, and ammonia added to precipitate the free base. It was found that the base precipitated as a yellow solid, but on addition of excess ammonia, a second, red product was obtained. It was found that this red substance could be entirely eliminated if the ammonia/

ammonia was added till the solution was alkaline to Congo Red paper, but acid to litmus.

The product thus obtained was pale yellow, and generally melted at 163° to 165°C., so that it was seldom necessary to recrystallise it. When recrystallisation was necessary, alcohol was used as solvent. Sometimes the nitro quinaldine was contaminated with traces of a greenish substance, it was found that the latter could be removed by boiling the alcoholic solution with animal charcoal prior to crystallisation.

The yields were poor, and were usually between 30% and 35% of the theoretical. (About 45 grammes of product were generally obtained from 100 grammes of p-nitraniline.)

There seems to be some doubt as to the colour of 6-nitro-2-methyl quinoline. Cohn & Springer describe it as "pale yellow", and Browning and his collaborators describe it as "grey". The purified product was found to be very pale yellow in colour, but liable to contamination with a little green matter.

REFERENCES.

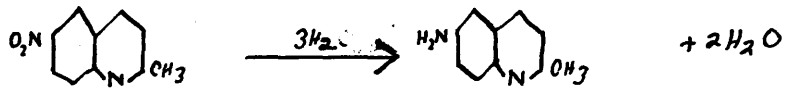
Hamer. J.C.S. (1921), 2. 1432.

Browning. Proc. Roy. Soc. B. 96, 325, (1924).

Cohn & Springer. Monatsheft, 24, 87, (1903).

PREPARATION OF 6-AMINO-2-METHYL QUINOLINE.

The method outlined by Hamer was used, but the details available in the literature are very scanty.



188 158

40 g. 6-nitro quinaldine.
190 g. Stannous chloride.(excess.)

The nitro compound was dissolved in 100 ccs. of concentrated hydrochloric acid and 100 ccs. of water, by warming gently on the waterbath. The stannous chloride ($SnCl_2 \cdot 2H_2O$) was dissolved in 300 ccs. of concentrated hydrochloric acid, and a little tin added to clear the solution if turbid. The solution of Stannous chloride was now added gradually, with stirring, to the solution of the nitro quinaldine which had been previously cooled. Heat was developed, and the tin double salt of the amine tended to separate. The reaction mixture was poured while hot into excess of 40% sodium hydroxide, and allowed to cool. When cool, the precipitated base and tin hydroxide were filtered off, and drained well on a Buchner funnel, and finally washed with cold water. The precipitate was now spread on porous plates, and dried. (If the precipitate is not dried well, any sodium chloride present is extracted along with the base, when/

when the precipitate is treated with alcohol, and separates out again when the alcoholic extracts are finally concentrated thus contaminating the amino quinaldine.)

The extractions with alcohol were carried out as follows:-

The precipitate was extracted with alcohol by boiling in a large flask fitted with a reflux condenser, on the waterbath, the base being readily soluble. The solution was filtered through a Buchner funnel, and the precipitate extracted again with a fresh portion of alcohol. The first extract was transferred to a large distilling flask, and the alcohol distilled off on the waterbath, and the recovered alcohol used to extract the precipitate a third time. Meanwhile the second alcoholic extract was transferred to the distilling flask, and the recovered alcohol used to extract the precipitate the fourth time. The process was continued until the alcoholic extracts were almost colourless. By employing this method, large quantities of alcohol need not be used, and the extracts are continuously concentrated in a closed vessel. It was found that on concentration of the extracts in an open basin, the product was less pure, and liable to be contaminated with a little tarry water. The concentrated liquor was finally filtered, and on cooling the base crystallised.

The 6-amino quinaldine was filtered off, washed with

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a little alcohol followed by ether, and finally dried on a porous plate. An almost colourless, crystalline, product was obtained, melting at 185° to 186° C., quite pure.

On further concentration of the mother liquor, a second crop was obtained, melting around 170°C. This is sufficiently pure for most purposes, but further purification can be effected by boiling with alcohol and a little charcoal, filtering, and recrystallising.

Yield

Crop (1)	about	15 gms.
Crop (2)	"	11 gms.
Total	"	26 gms. (77% of theoretical)

A third crop can be obtained by precipitating the tartrate of the base from the mother liquor.

6-AMINO QUINALDINE TARTRATE.

It was found that on addition of an alcoholic solution of tartaric acid to an alcoholic solution of 6-amino quinaldine, a yellow precipitate of the tartrate, sparingly soluble in alcohol, was obtained. The precipitate was filtered off, drained well, and finally washed with a little alcohol.

The tartrate is sparingly soluble in alcohol, but very readily soluble in water. It crystallises from the latter solvent in yellow, needle-shaped prisms, which darken about 200°/

200°C., but are still unmelted at 300°C.

By dissolving the tartrate in a little hot water, and adding excess of ammonia, the free base is precipitated almost completely in colourless small needles.

By precipitating the tartrate from alcoholic solutions of impure or tarry 6-amino quinaldine, it was found that it was possible to purify the base, as the tartrate can be readily recrystallised from water, after boiling with animal charcoal, if necessary.

Alcoholic solutions of 6-nitro quinaldine gave no precipitates of tartrate under similar conditions.

REFERENCES.

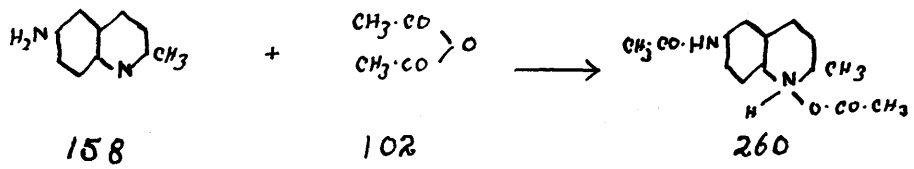
Hamer. J.C.S. (1921),1432.

Browning. (1924), Proc. Roy. Soc. B.96, 325.

Browning. (1926), " " " B.100,304.

PREPARATION OF 6-ACETYLAMINO-2-METHYL QUINOLINE.

The acetylation of 6-amino quinaldine was carried out as indicated by Hamer, using twice the theoretical quantity of acetic anhydride. As the acetate of the acetyl compound is the first product obtained, the quantities taken were based on the following reactions:-



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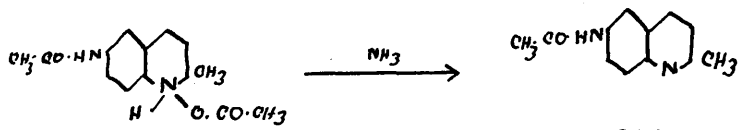


260 200

15.8 g. of 6-amino quinaldine
20.4 g. of acetic anhydride.

The acetic anhydride was added to the base which dissolved rapidly with evolution of heat. The mixture was heated on the waterbath for 20 minutes, cooled, and diluted with much cold water. (If the amino quinaldine used is quite pure, the acetate of the acetyl compound tends to separate out at the end of the 20 minutes heating on the waterbath.) Excess of ammonia was now added to precipitate the free acetyl-amino quinaldine, which was filtered off when quite

cold/

cold, and washed with cold water. The product was recrystallised from much boiling water, using charcoal to decolourise when necessary.

The purified product was obtained in colourless needles which were filtered off, washed with water, and spread on a porous plate and dried in an oven at 70°C.

Yield, about 18 gms. (90% of theoretical.)

The product obtained before drying is a hydrate which melted generally between 90° and 100°C., then solidified and melted finally about 164°C. quite sharply. If, however, the product is dried in the oven, it melts at 168° to 169°C., a few degrees higher, and does not melt around 100°C.
Browning gives the melting point at first 100° to 110°C., melting finally at 163° to 164°C.
Hamer gives the melting point as 168.5°C.
Care must be taken to dry the hydrate at a temperature below its melting point.

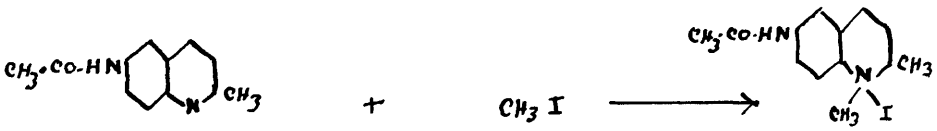
REFERENCES.

Hamer. J.C.S. (1921),1432.

Browning. Proc. Roy. Soc. B, 96, 325, (1924)

PREPARATION OF 6-ACETYLAMINO-2-METHYL QUINOLINE METHIODIDE.

This compound has been prepared by Hamer by heating the acetylamino quinaldine with methyl iodide in a sealed tube, and also by Browning and his collaborators who heated the reagents together in nitrobenzene solution, dispensing with the sealed tube. Browning's method was used, and the yield was improved from 70% up to 80% by altering the conditions slightly.



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20 g. of 6-acetylamino quinaldine.
8 ccs. of methyl iodide (28% excess.)
100 cc. of nitrobenzene.

The acetylamino quinaldine was dissolved with gentle warming, in the nitrobenzene, and the solution cooled. The methyl iodide was now added, and the mixture heated on the waterbath under efficient reflux for two hours. (Browning gives ½ to 1 hr. with 10% excess of methyl iodide). The yellow methiodide soon began to separate, and the whole mass was practically solid after about 1 hour's heating. The reaction mixture was now allowed to cool, and the flask stoppered, and allowed to stand overnight. The product was then filtered off on a Buchner funnel, drained well, and washed with ether till free of nitrobenzene. Finally, it was pressed on a porous plate.

The yield was 27.5 gms. (80% of the theoretical) and the product obtained was light yellow in colour, crystalline, and sufficiently pure for most purposes. It can be further purified, if desired as follows:-

Recrystallisation.

The 27.5 gms. of product obtained above were dissolved in a mixture of 100 ccs. of alcohol and 40 ccs. of water, by heating gently in a flask fitted with a reflux condenser, on the waterbath. The solid dissolved gradually, and the amber coloured solution was filtered and allowed to cool. The methiodide separated in well-defined crystals, which were filtered off, drained well, and washed first with a little absolute alcohol, followed by ether.

24 gms. of pale yellow crystals were obtained. A second crop is obtainable by concentrating the mother liquor.

The melting point was indefinite, the substance appeared to start to change about 255° C., and melted finally with decomposition around 270° C. (Hamer gives "about 254° C.")

SOLUBILITIES:- The 6-acetylamino quinaldine methiodide was insoluble in ether, very sparingly soluble in dry alcohol, and soluble in water. The solubility in alcohol is much increased by the addition of a little water.

REFERENCES.

Browning. Proc. Roy. Soc. B., Vol. 96, 325 (1924)

Hamer. J.C.S. (1921) 1432.

PREPARATION OF 6-ACETYLAMINO-2-METHYL QUINOLINE ETHIODIDE.

This compound is new. The method employed for the preparation is similar to that used for the corresponding methiodide.

200 156 356

10 gms. of 6-acetylamino quinaldine.
5 c.c. of ethyl iodide, (25% excess.)
50 c.c. of nitrobenzene.

The acetylamino quinaldine was dissolved in the nitrobenzene in a flask fitted with an efficient reflux condenser. The ethyl iodide was added, and the mixture heated on the waterbath for two hours, cooled, and allowed to stand overnight. The yellow, crystalline solid which separated was filtered off, drained well, and washed with ether till free from nitrobenzene.

Yield (crude) 12.8 gms. (72% of the theoretical).

Recrystallisation.

Aqueous alcohol was found to be the most suitable solvent for the recrystallisation of 6-acetylamino-2-methyl quinoline ethiodide. Five gms. of the crude product were dissolved in 55 c.c. of aqueous alcohol by boiling under reflux on the waterbath. (The alcohol contained 10% of water

by volume.) The amber coloured solution was filtered and allowed to cool, and the crystalline product which separated was filtered off and washed on the filter with a little alcohol.

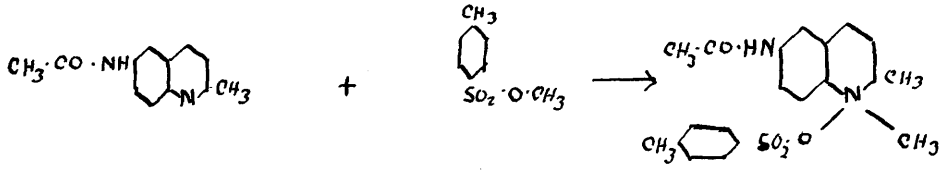
The yellow prisms obtained were finally dried in a vacuum desiccator over sulphuric acid. The melting point was indefinite, the substance darkened at ca. 250 °, and melted finally with decomposition at about 265 ° - 270 °.

Analysis.

$C_{14} H_{17} O N_2 I$	requires	N, 7.9 %.
	Found :-	N, 8.1 %.

PREPARATION OF 6-ACETYLAMINO-2-METHYL QUINOLINE METHO p-TOLUENE SULPHONATE.

This compound was prepared by Browning by heating 6-amino quinaldine with the theoretical quantity of methyl p-toluene sulphonate in nitrobenzene solution at 130° - 140°C for 1½ hrs. As the analysis given for the nitrogen in the product was high, it was feared that methylation might have been incomplete, and so the time of methylation was increased to two hours.



200 186 386

10 gms. of 6-acetylamino quinaldine.
9.3 gms. of methyl p-toluene sulphonate.
40 ccs. of nitrobenzene.

The reagents were dissolved in the nitrobenzene, and heated on an oil bath for two hours at 130° to 140° C., noting the temperature every ten minutes. The flask was removed from the oil bath, cooled, stoppered, and allowed to stand overnight. A yellow product separated which was filtered off on a Buchner funnel, drained well, and washed with ether till free of nitrobenzene.

Yield (crude) 13 gms. (67% of theoretical). (Browning does not state the yield.)

Recrystallisation.

The 13 gms. of product obtained above were dissolved in 25 ccs. of alcohol and a few drops of water, by heating under reflux on the waterbath. The orange-red solution obtained was filtered, and left to stand for a few days. Yellow, glistening prisms separated, which were filtered off, and washed with ether. (9.3 gms. were obtained.)

The melting point of the product obtained as above was 209° to 211° C., with decomposition. No melting point is given in the literature.

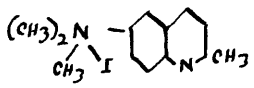
REFERENCE.

Browning. Proc. Roy. Soc. B, Vol. 100, pg. 305.

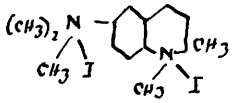
PREPARATION OF 6-DIMETHYLAMINO-2-METHYL QUINOLINE METHIODIDE .

This compound was first prepared by Barbier in 1920; later Browning and his co-workers prepared it by a different method, and it appears that they were not aware that the compound was already known.

Barbier first prepared 6-dimethylamino quinaldine by the Dobner-Miller method, and then boiled it with methyl iodide. He isolated two isomeric products, the first of which he identified as 6-dimethylamino quinaldine methiodide, which formed orange-red crystals melting at 230° C. The second compound melted at 190° C., and had no methyl iodide attached to the ring nitrogen atom, but had an extra molecule of methyl iodide attached to the 6-amino group, (compound I.). He also found that by using excess of methylating agent, compounds of type II were obtainable.



(I)



(II)

Browning methylated 6-amino quinaldine in presence of sodium carbonate, with the theoretical quantity of methyl iodide to give 6-dimethylamino quinaldine methiodide, and also mentions that the methylation can be similarly effected by methyl p-toluene sulphonate.

Browning's method of preparation was tried, following the instructions given very closely. It was assumed

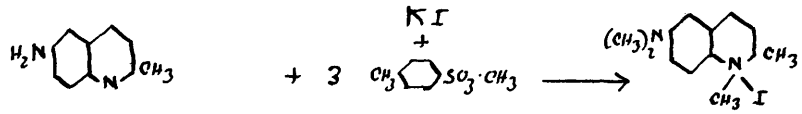
the directions to "boil for 5 hours under reflux" did not mean that the water present had to be at boiling point, but that the mixture had to be heated to a temperature at which the methyl iodide would reflux gently without escaping from the system. The mixture was accordingly refluxed on the waterbath. After refluxing for five hours, a clear deep orange solution was not obtained, but a deep red oil which on refluxing for a further three hours did not go into solution. It was assumed that some methyl iodide had escaped, and some more was therefore added, and the oil went into solution giving a deep-orange liquid which deposited orange crystals on cooling.

A second experiment gave a similar result, in spite of all precautions to prevent the escape of methyl iodide. The method was considered quite unsatisfactory, because if the volatile methyl iodide escapes, then the methylation will be incomplete; and if excess methyl iodide be added, the methylation may go a stage further, as shown by Barbier.

Non-volatile methyl p-toluene sulphonate was used as methylating agent. Methylation was rapid, and a satisfactory product was obtained. The melting point was slightly higher than that given by Barbier, but the melting points of these compounds are all rather indefinite, and there was no indication of the presence of the low-melting isomer. The following was the method used:-

PREPARATION OF 6-DIMETHYLAMINO QUINALDINE METHIODIDE

(USING METHYL p-TOLUENE SULPHONATE.)



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5.25 g. of 6-amino quinaldine.
15.27 g. of methyl p-toluene sulphonate (theoretical).
3.5 g. of sodium carbonate.
50 ccs. of water.

The reagents were mixed together in an open flask, and gently heated. The solution darkened rapidly, becoming deep red, while the amino quinaldine went into solution. A vigorous reaction took place, which seemed to be complete after about ten minutes. Gentle heating was continued for a further twenty minutes, and then the solution was cooled, and potassium iodide added to precipitate the methiodide. There was an immediate precipitation of the desired compound, and the precipitate was allowed to stand for several hours before being filtered off. It was washed on the filter with a little water, and then recrystallised from 25 ccs. of water.

Yield about 3 gms. (30% of theoretical).

Yellow powder, melting indefinitely at 235° to 240° C. with decomposition.

The product obtained by the method indicated above was entirely satisfactory, and condensed with 5-aldehyde acridine to yield s-(6-dimethylamino-2-quinolyl methiodide)-5-acridylethene, cf. page

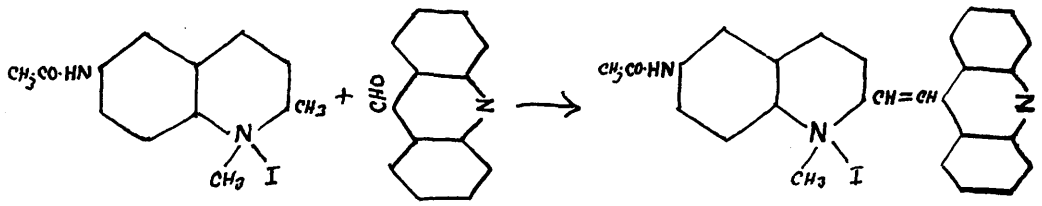
REFERENCES.

Browning, Proc. Roy. Soc., B. 100, 304, (1926).

Barbier, Bull. Soc. Chim., (1920), (4), 427. & Brit. Chem. Abstracts, (1920), 1 , 568.

PREPARATION OF 5-(6-ACETYLAMINO-2-QUINOLYL METHIODIDE)-5-ACRIDYLETHENE.

This ethene compound is new, and as it was insoluble in the usual solvents it was purified by extracting the impurities with alcohol, instead of by recrystallisation. Precautions had to be taken therefore to exclude all dust, grit &c. from the reaction mixture.



342 207 531

10.7 gms. of 6-acetylamino-2-methyl quinoline methiodide.
8.0 gms. of 5-aldehyde acridine. (25% excess.)
80 c.c. of alcohol.
30 c.c. of water.

The reagents were dissolved in the alcohol and water and the resulting dark brown solution filtered. The mixture was refluxed on the waterbath in a flask fitted with a ground-glass joint and water condenser, and a porcelain chip was added to prevent "bumping". Five drops of piperidine were now added to the reaction mixture, and the whole boiled for two hours. The solution soon began to turn red in colour, and after about quarter of an hour solid separated. (If adequate precautions were not taken, the mixture "bumped" violently.)

After the two hours boiling, the acridine ethene

derivative was filtered off from the hot solution , drained, and washed on the filter with hot , filtered , alcohol. The product thus obtained was brick-red , and crystalline, while the mother liquor was green in colour.

The compound was now boiled on the waterbath with alcohol , in a flask fitted with a ground-glass joint and water condenser. (The alcohol was previously filtered to remove any dust or solid impurities present.) The etheme was filtered off from the hot solution , washed with alcohol, and extracted once again with alcohol, before being finally filtered off and dried. The last traces of alcohol were removed in a vacuum desiccator.

Yield , 12.5 to 14.5 gms. (75 to 85 %.)

Red , crystalline , powder, of indefinite melting point. It started to darken about 140°C. , and was quite black by 230°C., and melted finally , with decomposition between 233°and 240°C.

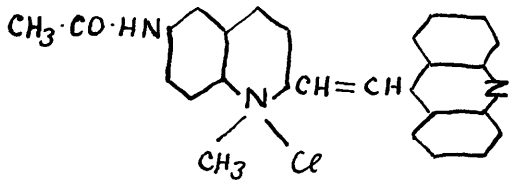
Analyses.	$C_{27} H_{22} O N_3 I$	requires	N	7.91 %.
		found (1)	N	8.1 %.
		(2)	N	8.1 %.

Solubilities. Insoluble in ether and in butyl acetate. Moderately soluble in nitrobenzene , from which it separated crystalline on cooling. Almost insoluble in water , alcohol, and ethylene glycol monoethyl ether. Moderately soluble in a hot 50% aqueous-alcoholic mixture , separating as a jelly on cooling.

The ethene dissolved readily in warm dilute sulphuric or hydrochloric acid , giving an orange-red solution which deposited an orange-red jelly on cooling. On prolonged boiling , however, the solution became darker in colour , and nothing separated on cooling, presumably this was due to the fact that the acetyl group had been hydrolysed off. On boiling with moderately concentrated sulphuric acid, there is a smell of acetic acid.

On boiling with nitric acid , fumes of iodine were observed, while on addition of silver nitrate to a solution of the ethene in dilute nitric acid, there was an immediate precipitate of silver iodide.

PREPARATION OF S-(6-ACETYLAMINO-2-QUINOLYL METHOCHLORIDE) -5-ACRIDYLETHENE.



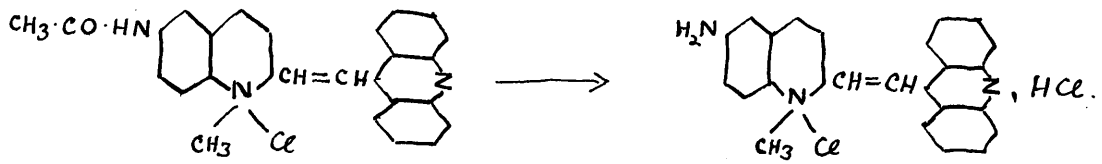
Four grammes of s-(6-acetylamino-2-quinolyl methiodide) -5-acridylethene were suspended in 100 ccs. of aqueous methyl alcohol, and excess of freshly precipitated , washed , silver chloride added. The mixture was then boiled under reflux for 6 hours,on the waterbath. The methiodide gradually went into solution , and the orange-red colour disappeared and was replaced by the yellower colour of the methochloride. The solution was filtered hot, and the residue of silver salts extracted several times with methyl alcohol; the filtrate and extracts were then combined , and refluxed again with a fresh portion of silver chloride for a few hours. The solution was finally filtered , and concentrated on the waterbath , then cooled and left to stand overnight. The methochloride separated as an orange powder, which was recrystallised from aqueous methyl alcohol , and dried in an oven at 90°C.

The melting point was indefinite, the compound darkened from 190°to 210°C., and melted finally at 220°to 228°, with decomposition and escape of gas.

$C_{27}H_{22}ON_3Cl$ requires N 9.6 %.
Found :- N 9.5 %.

$C_{27}H_{22}ON_3Cl$ requires N 9.6 %.
Found :- N 9.5 %.

PREPARATION OF S-(6-AMINO-2-QUINOLYL METHOCHLORIDE)-5-ACRIDYLETHENE HYDROCHLORIDE.



The s-(6-acetylamino-2-quinolyl methochloride)-5-acridylethene , obtained from the preceeding preparation , was gently boiled under reflux for 3 to 4 hours with concentrated hydrochloric acid and a little water. The dark red solution obtained was cooled , and allowed to stand overnight , but nothing separated from it . Most of the acid was now neutralised with dilute sodium carbonate , and a dark red powder precipitated. The solution was still strongly acidic after the addition of the sodium carbonate. The product was filtered off , drained well , and washed first with a little water , and then with ether, till free from acid. Addition of more sodium carbonate to the mother liquor did not give a second precipitate of red powder.

The product was recrystallised from methyl alcohol containing a little water , and washed with a small quantity of methyl alcohol , followed by much ether.

Dark red prisms were obtained , of indefinite melting point. (The compound started to darken about 280°C., and melted finally at 205°- 210°, with decomposition.)

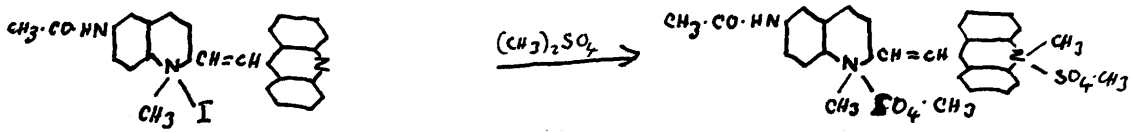
$C_{25}H_{20}N_3Cl$, HCl requires N, 9.7 %.
Found :- N, 9.6 %, and 9.8 %.

The product was insoluble in ether, but dissolved readily in water or ethyl alcohol yielding red solutions.

On boiling with sulphuric acid no acetic acid was evolved, indicating that the de-acetylation of the amino group had been complete.

The presence of a free amino group was also demonstrated by diazotising the product, and coupling it with B-naphthol.

PREPARATION OF S-(6-ACETYLAMINO-2-QUINOLYL METHOSULPHATE)-(5-ACRIDYL METHOSULPHATE)ETHENE.



s-(6-Acetylamino-2-quinolyl methiodide)-5-acridylethene was methylated with excess of dimethyl sulphate in nitrobenzene solution. As was the case with the analogous s-(2-quinolyl methiodide)-5-acridylethene compound, the iodine was replaced, and the dimethosulphate obtained. It was found that nitrobenzene had to be employed as solvent , as dimethyl sulphate alone gave a supersaturated solution from which the product could not be induced to separate; but otherwise the preparation was entirely analogous to that described for the corresponding s-(2-quinolyl methosulphate)-(5-acridyl methosulphate)ethene.

Several preparations were made, and it was found that the nitrogen estimations were all consistent, but slightly low when compared with the percentage of nitrogen required by theory. It was thought that the methyl sulphate was attacking some other portion of the molecule, and that the large excess of this reagent used was proving harmful. Methylations were therefore tried using the theoretical quantity of methyl sulphate (one mole.) required for the preparation of the compound:- s-(6-acetylamino-2-quinolyl

methiodide)-(5-acridyl methosulphate)ethene. These preparations gave a mixture of products which was resolved into two portions. One portion contained iodine, while the other contained no iodine, and the method was therefore considered unsatisfactory.

The methylation was carried out using a large excess of methyl sulphate as follows :-

9.0 gms. of s-(6-acetylamino-2-quinolyl methiodide)-5-acridylethene.
7.0 c.c. of dimethyl sulphate, (excess.)
30 c.c. of nitrobenzene.

The ethene compound was suspended in the nitrobenzene, the methyl sulphate added , and the temperature raised to 120° C. The solid began to turn red , and gradually dissolved forming a red solution. After about 15 minutes solid began to separate out from the reaction mixture , and the temperature was raised to 130°, and maintained at 130° to 140° for a further 25 minutes. The mixture was allowed to stand overnight , and the solid that separated was filtered off, and washed with ether till free from nitrobenzene.

The orange-red powder obtained was dissolved in 25 c.c. of alcohol and 5 c.c. of water , and the solution filtered and allowed to crystallise. The powder which separated was filtered off, and washed with a little cold alcohol followed by much ether, and recrystallised again

from 12.5 c.c. of alcohol and 2.5 c.c. of water. The product was finally filtered off, washed with alcohol and ether , and dried in a vacuum desiccator over sulphuric acid.

An orange-red powder was obtained. The melting point was indefinite ; the product started to darken at 200°, was quite black at 220°, and melted finally with decomposition at 225°- 235° C.

For analysis, the compound was recrystallised once again from alcohol.

Analyses.

$C_{30} H_{31} O_9 N_3 S_2$	requires :-	N 6.5 %.	
	Found:- (1)	6.4 %.	6.3 %.
	(2)	6.2 %.	
	(3)	6.3 %.	6.3 %.

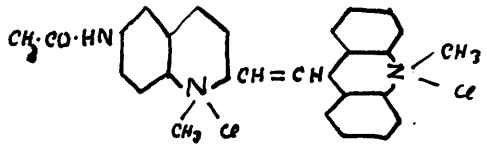
The specimens (1), (2), and (3) were all obtained from different preparations. The analyses were all done by the usual Dumas method except the second one done on (3) which was a "micro" estimation.

Properties.

The product was insoluble in ether, but readily soluble in water or alcohol giving red solutions.

The substance contained no halogen. On boiling with sulphuric acid , the acetyl group was hydrolysed , and acetic acid was evolved.

PREPARATION OF S-(6-ACETYLAMINO-2-QUINOLYL METHOCHLORIDE)-(5-ACRIDYL METHOCHLORIDE)ETHENE.



s-(6-Acetylamino-2-quinolyl methosulphate)-(5-acridyl methosulphate)ethene was dissolved in hot water, and treated with saturated sodium chloride solution in the usual manner. An orange precipitate was obtained which was filtered off when cold , and washed with a little water, followed by alcohol. The product was crystallised once from water to remove any sodium chloride present , and then from aqueous alcohol. The orange-red powder obtained was filtered off , drained well, and washed with a little alcohol followed by much ether, and finally dried in a vacuum desiccator over sulphuric acid.

$C_{28}H_{25}ON_3Cl_2$ requires N 8.6 %.
Found :- N 8.5 %.

The nitrogen is again slightly low , but has risen from 6.5 % required by the dimethosulphate to 8.5 % required by the dimethochloride.

The Cl can be precipitated from nitric acid

solutions of the product on addition of silver nitrate.

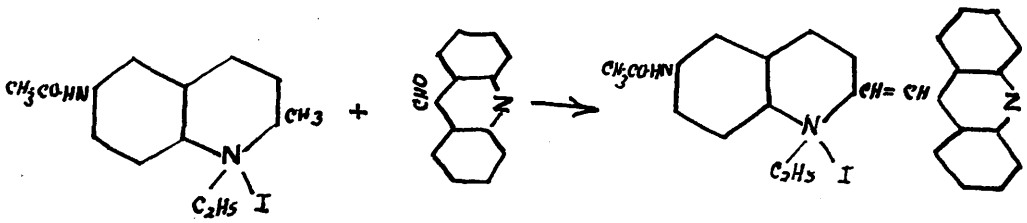
The dimethochloride was readily soluble in water and in alcohol , yielding red solutions.

The dimethonitrate (orange precipitate) and the dimethiodide (dark red precipitate) were similarly prepared by salting out with potassium nitrate and potassium iodide.

S-(6-Acetylamino-2-quinolyl ethochloride) (5-acridyl methochloride)ethene was prepared in an analogous manner by methylating s-(6-acetylamino-2-quinolyl ethiodide) -5-acridylethene with dimethyl sulphate , and salting out with sodium chloride. It possesed physical properties similar to those of the dimethochloride.

PREPARATION OF S-(6-ACETYLAMINO-2-QUINOLYL ETHIODIDE) -5-ACRIDYLETHENE.

This compound is new.



356 207 545

7.1 gms. of 6-acetylamino-2-methyl quinoline ethiodide.
5.2 gms. of 5-aldehyde acridine. (25% excess.)
90 c.c. of alcohol.
7.5 c.c. of water.

The reagents were dissolved in the mixture of water and alcohol, and the solution filtered. Five to ten drops of piperidine were now added, and the mixture boiled under reflux on the waterbath for three to three and a half hours. (On addition of the piperidine the dark brownish-green solution became redder in colour, and after five or six minutes , solid began to separate, and precautions had to be taken to prevent the reaction mixture from bumping.)

The precipitate which separated was filtered off from the hot alcoholic solution, drained well, and washed with successive quantities of hot, filtered, alcohol. The precipitate was next washed with a little hot, filtered,

water to remove any unchanged acetylamino quinaldine ethiodide present, and finally washed again with alcohol, drained , and dried in a vacuum desiccator over sulphuric acid.

The product was of a yellowish-brown colour , but on drying in a vacuum desiccator, the colour changed to reddish-orange. The yellow colour could be restored by leaving the product in the air for some time , or by adding alcohol - presumably the colour change was due to solvent of crystallisation.

Yield about 8 gms. (70 % of theoretical.)

The melting point was rather indefinite, the material started to darken about 235°C. , and melted finally with decomposition , about 238°C.

Analyses.

$C_{28} H_{24} N_3 I O$ requires N 7.7 %.

Two different samples were analysed , the first gave :- N 7.8 % , and N 7.9 %.

The second sample gave :- N 7.9 % , and 7.9 %.

Solubilities.

The compound was insoluble or sparingly soluble in the usual solvents. It dissolved to a certain extent in aqueous alcohol, separating again as a jelly on cooling.

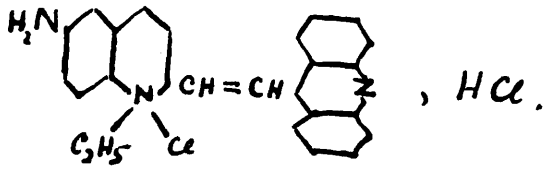
CONVERSION OF THE PRECEEDING COMPOUND TO THE ETHOCHLORIDE.

Six grammes of s-(6-acetylamino -2-quinolyl ethiodide)-5-acridylethene were suspended in 80 ccs. of methyl alcohol and 40 ccs. of water , and excess of freshly precipitated , washed , silver chloride added , and the mixture boiled under reflux for 6 hours on the waterbath. The solution became yellower in colour. The precipitate of silver iodide and chloride was filtered off, and extracted with more methyl alcohol , and the extract added to the filtrate. The orange solution of the ethochloride was boiled with a little fresh silver chloride , to make sure that no ethiodide remained , and after about an hours boiling , filtered and cooled.

On cooling a brown jelly-like mass was obtained , which could not be induced to crystallise. The solution was therefore evaporated to dryness on the waterbath , and an orange mass was obtained , with a distinctly metallic sheen.

When quite dry , the product was pulverised , and used for the preparation of s-(6-amino -2-quinolyl ethochloride)-5-acridylethene hydrochloride.

PREPARATION OF S-(6-AMINO-2-QUINOLYL ETHOCHLORIDE)-5-ACRIDYLETHENE HYDROCHLORIDE.



The s-(6-acetylamino-2-quinolyl ethochloride)-5-acridylethene, obtained from the preceeding preparation , was gently boiled with concentrated hydrochloric acid for three hours, in a flask fitted with a reflux condenser. The deep red solution was cooled , but nothing separated, and most of the acid was neutralised with sodium carbonate. (The solution was strongly acid after addition of the sodium carbonate , but if made alkaline , a flocculent orange-red base precipitates.) A dark red powder was obtained which was filtered off, drained well , and washed with a little alcohol.

The product was recrystallised from 50% aqueous-alcohol , filtered off , and washed with a little alcohol , followed by much ether , and finally dried over sulphuric acid in a vacuum desiccator.

Dark red , glistening , needle-shaped prisms were obtained, readily soluble in ethyl or methyl alcohol and in water , giving a dark red solution neutral to Congo red.

The melting-point was indefinite , and depended on the rate of heating , but was between 280°and 300°C. , the

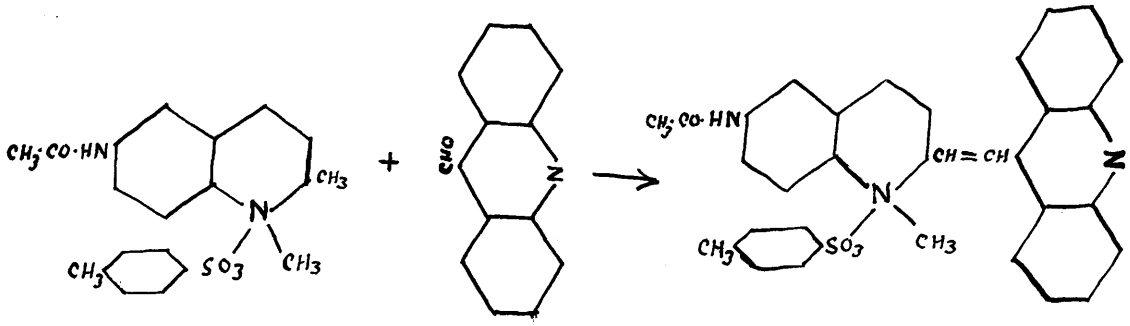
compound swelling up and decomposing , with escape of gas.

Analyses.

$C_{26} H_{22} N_3 Cl$, HCl	requires	N	9.4 %.
	found :- (1)	N	9.5 %.
	(2)	N	9.5 %.

PREPARATION OF S-(6-ACETYLAMINO-2-QUINOLYL METHO p-TOLUENE SULPHONATE)-5-ACRIDYLETHENE.

This compound is new.



386 207 575

9.3 gms. of 6-acetylamino-2-methyl quinoline metho p-toluene sulphonate.
6.1 gms. of 5-aldehyde acridine. (20% excess.)
75 c.c. of alcohol.

The reagents were dissolved in the alcohol and the solution filtered. Eight drops of piperidine were now added, and the mixture boiled under reflux on the waterbath for three hours. Considerable quantities of solid separated, and the alcoholic solution became green in colour.

The precipitate was filtered off hot, and then washed on the filter with hot alcohol. A yellow, crystalline solid was obtained. Yield 6.5 gms.

Purification

The product was extracted with 25 c.c. of alcohol by boiling for half an hour under reflux, then filtered off hot, and washed with hot alcohol. 5.6 Grammes of product were

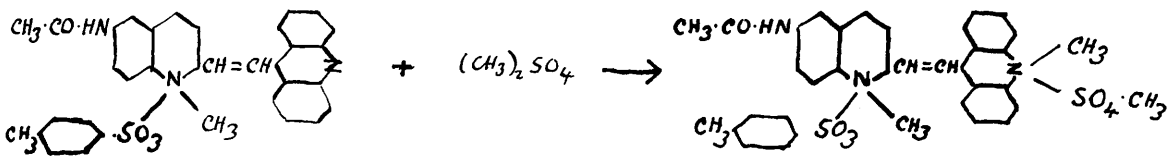
thus obtained , quite free from the green impurity. The 5.6 gms. obtained were recrystallised in three batches from a mixture of 60 ccs. of water and 30 ccs. of alcohol, washed with alcohol, and dried first in an air oven at about 100°C., and then in a vacuum desiccator.

A yellow , crystalline , powder was obtained, of indefinite melting point. It began to darken about 240°C., shrank, and melted finally with decomposition around 250°C.

Analysis. $C_{34} H_{29} O_4 N_3 S$ requires N 7.3 %.
found N 7.4 %.

Properties. The compound was insoluble in ether, sparingly soluble in alcohol, and moderately soluble in aqueous alcohol or hot water. Addition of sodium chloride to an aqueous solution of the ethene gives a flocculent orange-yellow precipitate of the corresponding methochloride. Potassium iodide similarly precipitates a dark red methiodide. Moderately soluble in hot nitrobenzene.

PREPARATION OF S-(6-ACETYLAMINO-2-QUINOLYL METHO P-TOLUENE SULPHONATE)-(5-ACRIDYL METHOSULPHATE)ETHENE.



575 126 701

3.7 gms. of s-(6-acetylamino-2-quinolyl metho p-toluene sulphonate)-5-acridylethene.

0.8 ccs. of methyl sulphate, (approximately 30% excess.)

23 ccs. of nitrobenzene.

The ethene compound was suspended in 20 c.c. of nitrobenzene, and the methyl sulphate added and washed in with 3 c.c. of nitrobenzene. The mixture was heated at 100°C. for ¼ hour , and the temperature then raised to 120° to 130° for a further ¼ hour. The reaction mixture was allowed to stand overnight , and the product which separated filtered off, drained , and washed with a little alcohol followed by much ether till free from nitrobenzene.

Yield (crude) 2.2 gms.

Recrystallisation.

The 2.2 gms. of product dissolved in a mixture of 30 ccs. of alcohol and 30 ccs. of water , and gave a dark red solution which was filtered and allowed to stand overnight. Orange-yellow , small needles separated, which were filtered off, and washed with alcohol and then with ether.

Melting Point.

The product darkened about 240° C., and melted finally at 245-248° , with decomposition.

Solubilities.

The compound was moderately soluble in alcohol, and the solubility was much increased by addition of water. It dissolved in water giving an orange solution , which gave an orange precipitate on addition of sodium chloride , and an orange-red precipitate on addition of potassium iodide. These two precipitates were,presumably, the dimethochloride, and the dimethiodide.

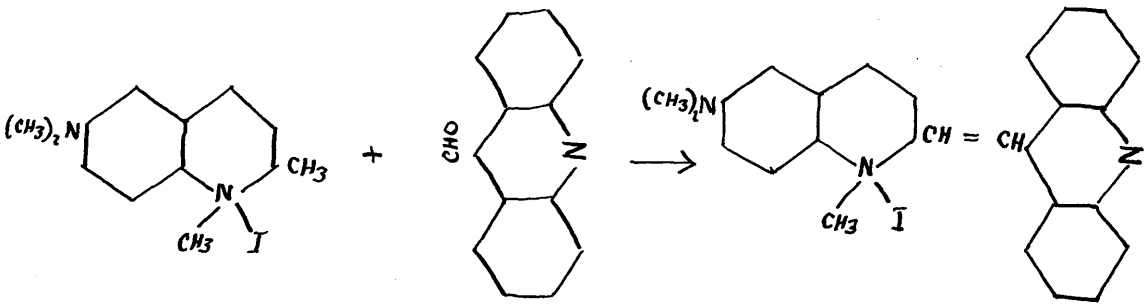
Analyses.

$C_{36}H_{35}O_8N_3S_2$ requires C, 61.6 %; H, 5.0 %; S, 9.1 %.

Found :- C, 62.0 %; H, 5.3 %; S, 8.8 %.

PREPARATION OF S-(6-DIMETHYLAMINO-2-QUINOLYL METHIODIDE) -5-ACRIDYLETHENE.

This compound is new.



328 207 517

2.0 gms. of 6-dimethylamino-2-methyl quinoline methiodide.
1.5 gms. of 5-aldehyde acridine. (25% excess.)
30 c.c. of alcohol.

The reagents were dissolved in the alcohol, and the solution filtered. Four drops of piperidine were now added, and the mixture boiled under reflux in a flask fitted with a ground-glass joint and water condenser, for four hours on a waterbath. The solution became red in colour, and solid separated.

The product was filtered off hot, and washed with hot, filtered alcohol. It was now extracted with filtered alcohol by boiling under reflux on the waterbath, filtered off hot, and again washed with hot alcohol, and finally dried in a vacuum desiccator.

Yield, 60 % of theoretical.

Dark red crystalline powder, moderately soluble in methyl and in ethyl alcohol, sparingly soluble

in hot water, and insoluble in ether. Very soluble in hot nitrobenzene, but does not separate again on cooling.

Analysis. $C_{27} H_{24} N_3 I$ requires I 24.5 %.
found I 25.0 %.

CONVERSION OF THE PRECEEDING COMPOUND TO THE METHOCHLORIDE.

Two grammes of the methiodide were suspended in 40 ccs. of aqueous methyl alcohol, and excess of freshly precipitated , washed , silver chloride added, and the whole boiled for five hours on the water bath under reflux. The solution was then filtered hot , and the precipitate of silver chloride and iodide extracted with boiling methyl alcohol , and the extract added to the filtrate. The deep red solution of the methochloride was concentrated on the water bath , filtered , and allowed to crystallise.

A red crystalline solid was obtained. The melting point was indefinite , the substance started to darken about 150° C. or so , and was quite black at 200° C., melting finally between 200°C and 210°C. , swelling up and decomposing.

Analysis. $C_{27} H_{24} N_3 Cl$ requires N 9.9 %.
found :- N 10.0 % , and 10.0%

Moderately soluble in hot water giving a red solution which deposits crystals on cooling.

The hydrochloride was prepared as follows:- s-(6-Dimethylamino-2-methyl quinoline methochloride)-5-acridylethene was dissolved in hot dilute hydrochloric acid and the solution left to crystallise. The solid which separated was recrystallised from methyl alcohol.

A purple powder, melting above 300°C. was obtained. It was readily soluble in water , and in alcohol, yielding dark red solutions.

SECTION III(c). DERIVATIVES OF 4-AMINO QUINOLINE.

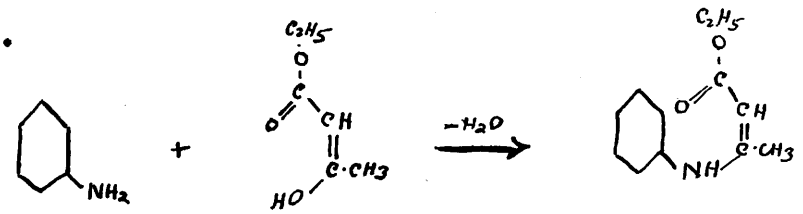
PREPARATION OF 4-HYDROXY QUINALDINE.

The preparation of 4-hydroxy quinaldine involves two separate stages. The first of these is the preparation of ethyl B-phenylamino crotonate; and the second the ring-closure of this crotonate under conditions which favour the formation of hydroxy quinaldine.

Ethyl B-Phenylaminocrotonate.

This compound has been prepared from aniline and ethyl acetoacetate by a number of different methods. These methods have been summarised in a recent paper by Coffey , Thomson , and Wilson, (J.C.S.(1936) 856.) , and it was pointed out that the reaction was best carried out at ordinary temperature in presence of acid catalysts .

The method of Coffey and his collaborators was employed , and it was confirmed that small traces of hydrochloric acid greatly accelerated the reaction. It was found unnecessary, however , to centrifuge the reaction mixture in order to separate the water, as this separation can be effected more expeditiously in an ordinary separating funnel.



93 130 205

186 Grammes of aniline were mixed with 260 grammes of ethyl acetoacetate , and 4 drops of concentrated hydrochloric acid added. Water soon began to separate. The mixture was transferred to a large separating funnel , and allowed to stand overnight. Next morning, the aqueous layer was separated from the crotonate, and the latter dried over sodium sulphate . The ethyl B-phenylaminocrotonate thus obtained was finally filtered free from sodium sulphate , and used without further purification for the preparation of hydroxy quinaldine.

It was found that when no acid catalyst was added , the reaction was much slower, so that the mixture had to be left for 10 days before separating off the water. Otherwise, the preparation was identical to the one described above.

The product obtained was a pale yellow oil.

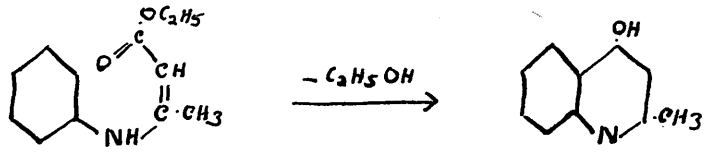
Commercial ethyl acetoacetate of good quality was used without further purification. The aniline was dried over caustic soda and redistilled.

Principal References for Ethyl B-Phenylaminocrotonate.

Coffey. (J.C.S. (1936) 856.)

Limpach. Ber. 64. 969. (1931.)

4-Hydroxy Quinaldine.



205 159

Limpach first prepared 4-hydroxy quinaldine in 1887, but as he himself points out , the yields were poor and seldom more than 30 %. The method was to heat ethyl B-phenylaminocrotonate rapidly to a high temperature so that alcohol was split off, and the ring closed. There were, however, numerous side-reactions , and much tar was obtained. In 1931 , the same worker described another method whereby the ring-closure of the crotonate was effected by heating in liquid paraffin, and almost theoretical yields obtained. (Ber. 64. 969.)

The author has not been able to confirm the high yields recorded by Limpach, and so the latter's method is quoted in full:-

Limpach: " 93 Parts of aniline and 130 parts of acetoacetic ester were mixed at room temperature and left for several days. After elimination of the water which separated, the crotonic ester was introduced into about four times its volume of paraffin oil heated to 260° to 280°, and the whole then heated further for 15 to 20 minutes at 240° to 250°. When alcohol

ceased to separate , the mass was allowed to cool, and the crystalline hydroxy quinaldine separated from the liquid paraffin by centrifuging or suction filtration. Recrystallised from boiling water. Yield 90 to 95 %."

The author understands from the above that the yield of recrystallised product was 90 % for the two processes, viz. the preparation of the crotonate and its ring-closure. This is extremely good, as if the yield of crotonate was say 90% , and the yield for the ring-closure 90 %, the yield for the two processes combined would only be about 80 %. It is assumed that Limpach did not overlook the fact that 4-hydroxy quinaldine crystallises with two molecules of water.

The author's yields of pure , anhydrous , 4-hydroxy quinaldine were consistently about 30 % for the two processes, that is , 30 % calculated on the quantity of aniline taken initially.

It was thought that perhaps the small trace of acid added in the preparation of the crotonate was interfering with the ring-closure, but specimens of crotonate prepared without the addition of a catalyst did not give better yields of hydroxy quinaldine , and so the cause of the trouble must be looked for elsewhere.

Various slight modifications in the experimental method were tried. The duration of heating was varied, and also the temperature. The crotonate was gently warmed before introducing it into the paraffin , so that there would be no great fall in temperature. The hot paraffin was decanted off from the product at the end of the reaction so that the hydroxy quinaldine was subjected to a high temperature for as short a time as possible. Finally , experiments were performed with , and without , mechanical agitation. These variations had no apparent effect on the yield, which remained low.

The reaction was carried out in an open vessel to facilitate the escape of the alcohol. The following is typical of the many experiments performed:-

A litre of liquid paraffin was heated to 280°, and efficiently agitated with a glass stirrer and electric motor. 250 c.c. of ethyl B-phenylaminocrotonate warmed to 70° , were now introduced into the hot paraffin in one addition, and the temperature maintained at 240°-245° for 20 minutes. Agitation was discontinued, and the product allowed to settle as a dark oil at the bottom of the reaction vessel. The hot paraffin was now decanted off, and the product extracted several times with benzene to remove paraffin. A little benzene was allowed to remain in contact with the

hot, molten , hydroxy quinaldine , so, that it boiled and aerated the mass ; in this manner , the product was obtained in a granular state , and not in a solid block , when it solidified. The product was finally washed with benzene and drained well.

The hydroxy quinaldine thus obtained was dark brown in colour , and impure. It was extracted with boiling water, and the solution filtered from the insoluble tarry residue, boiled with charcoal, and cooled. A supersaturated solution was obtained which deposited glistening prisms of hydroxy quinaldine on scratching or seeding. The crystals were filtered off, washed with water , and dried in an oven at 120°C. , to remove water of crystallisation. The mother liquor was used to extract the tarry residue again.

The product was colourless, and quite pure , melting at 230°- 231°.

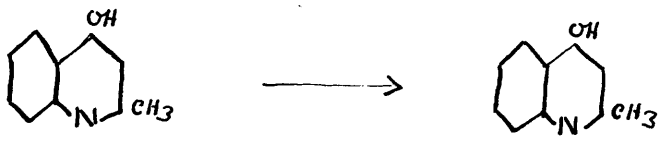
Limpach stated that the 4-hydroxy quinaldine separated in a crystalline form from the reaction mixture. It can be obtained crystalline if the liquid paraffin is not decanted off from the hydroxy quinaldine at the end of the reaction, and the whole mass is efficiently agitated . The 4 - hydroxy quinaldine solidifies gradually, and is got in a distinctly crystalline form.

<u>Principal References</u>.

Limpach. Ber. <u>20</u>. 944, (1887.)

" Ber. <u>64</u>. 969, (1931.)

PREPARATION OF 4-CHLOROQUINALDINE.



159 177.5

This compound was first prepared by Conrad and Limpach in 1887. "Hydroxy quinaldine was mixed with the theoretical quantity of phosphorus pentachloride , and heated on an oil bath at 130°to 140° , with addition of phosphorus oxychloride, as long as hydrogen chloride was evolved. A brown, semi-solid mass was obtained."

Later Fischer prepared it by a slightly modified method. "Equivalent quantities of phosphorus pentachloride and hydroxy quinaldine together with some phosphorus oxychloride, were heated in an open flask for half an hour at 110°to 115°, and a light brown crystalline mass was obtained." Fischer notes that "it is not advisable to heat for a longer time than half an hour , or at the higher temperatures advocated by Conrad and Limpach, otherwise a violet dye is obtained in considerable quantities."

Finally , Ashley prepared it by heating hydroxy quinaldine with four times its weight of phosphorus oxychloride at 140°to 150°.

The author tried all three methods , and in every case , the product was contaminated with the violet

dye. The method of Ashley gave the best results , but it was soon realised that the other two methods were incapable of yielding the brown products claimed by the authors. Various modifications of Limpach's method were made , and eventually it was possible to obtain the chloroquinaldine pure , and free from the violet dye.

Phosphorus pentachloride reacts with hydroxy quinaldine as follows :-

$$\underset{159}{C_{10}H_8N\cdot OH} + \underset{208}{PCl_5} \longrightarrow C_{10}H_8N\cdot Cl + POCl_3 + HCl$$

$$2\ C_{10}H_8N\cdot OH + POCl_3 \longrightarrow 2\ C_{10}H_8N\cdot Cl + H_3PO_4 + HCl$$

The quantities taken were based on the first reaction, so that the phosphorus oxychloride generated acted merely as a solvent.

32 gms. of 4-hydroxy quinaldine.
42 gms. of phosphorus pentachloride.
10 c.c. of phosphorus oxychloride.

The hydroxy quinaldine and the phosphorus pentachloride were intimately mixed in an open flask.(It is essential that this mixing is thorough, and that no lumps of phosphorus pentachloride remain.)The reaction mixture was not heated , as advocated in the methods mentioned above. The phosphorus oxychloride was now added very gradually ,

drop by drop, and the mixture was vigorously stirred after each drop had been added. The temperature was kept as low as possible, and this slow addition of the phosphorus oxychloride and vigorous stirring prevented any local overheating. After about quarter of an hour , all the phosphorus oxychloride had been added , and the temperature of the reaction mixture had risen spontaneously to about 90°C., while hydrogen chloride was evolved. After all the phosphorus oxychloride had been added , the reaction mixture was allowed to stand for quarter of an hour , and was then transferred to an oil bath , and heated to 100° C. The temperature was finally raised gradually from 100°up to a maximum of 115°, over a period of half an hour. A brown semi-solid melt was thus obtained , without a trace of the violet impurity.

The reaction mixture was allowed to cool , and then treated gradually with cold water, keeping the temperature low. A solution was obtained which was filtered, and made alkaline with sodium carbonate. The chloroquinaldine precipitated as an oil which soon solidified , and the aqueous liquor was decanted off. The product was washed several times as follows:- Hot water was added to the chloroquinaldine which melted, the mixture was shaken , and then allowed to cool so that the product re-solidified , and the aqueous liquor was readily decanted off. The chloroquinaldine was finally melted , and vigorously shaken with cold water , so that it was obtained in a granular form when it solidified.

The product was filtered off, washed with water , and dried on a porous plate at room temperature.

A 90 % yield of 4-chloroquinaldine hydrate , $C_{10} H_8 N \cdot Cl$, $H_2 O$, was obtained. (35 gms.)

The product was putty-coloured, and dissolved in dilute hydrochloric acid without any violet colouration. It was pure enough for all ordinary purposes, so that further purification was unnecessary. It melted at 41° - 42°.

When work was first started on the preparation of 4-chloroquinaldine , the author thought that perhaps the violet colouration obtained was due to impurities in the hydroxyquinaldine employed. It was found, however , that carefully purified specimens of hydroxyquinaldine still gave this colouration, and so this theory was abandoned.

The violet dye appears to be a condensation product which is formed at high temperatures , and so local overheating must be avoided in the preparation of chloroquinaldine. For this reason , it was found inadvisable to perform the preparation on a larger scale which renders temperature control difficult.

Purification of 4-Chloroquinaldine.

Steam distillation was employed by Conrad and Limpach, and also by Fischer, for the purification of chloroquinaldine which distills over as a colourless oil which solidifies to a white solid. The author tried this method, but found that the chloroquinaldine distilled over

very slowly indeed. As chloroquinaldine is completely decomposed when boiled with water for two hours, (Ber. 20 , 952.), it would appear that the method is not entirely satisfactory. In carrying out a steam distillation , it seems advisable to add the chloroquinaldine gradually to the distillation flask, so that it is left in contact with the boiling water for as short a time as possible.

The following alternative method of purification was devised by the author:-

4-Chloroquinaldine Tartrate.

14 Grammes of 4-chloroquinaldine hydrate were dissolved in 30 c.c. of hot alcohol, and a hot solution of 14 gms. (excess) of tartaric acid in 50 c.c. of alcohol added. There was an almost immediate precipitation of 4-chloroquinaldine tartrate. The mixture was allowed to cool a little , and the tartrate filtered off from the lukewarm solution , and washed with alcohol , followed by ether; 20 to 23 gms. of tartrate were obtained.

(If the tartrate is impure , it can be recrystallised from alcohol at this stage , but this is generally unnecessary unless the original sample of chloroquinaldine was very impure.)

The tartrate was dissolved in boiling water, and the solution filtered and afterwards made alkaline with sodium carbonate. The chloroquinaldine precipitated as a

colourless oil which soon solidified to a white solid.

The yield depends on the initial purity of the 4-chloroquinaldine hydrate, but was generally about 70 %. It was the author's experience that the tartrate method of purification compared favourably with the steam distillation method, both for yield and general convenience.

Notes on the Purification of 4-Chloroquinaldine by the Tartrate Method.

The two impurities liable to be present in crude chloroquinaldine are the violet dye , and unchanged hydroxy quinaldine. It was found that the tartrate method could eliminate considerable quantities of the violet dye, as the dye remained in the alcoholic solution, while the tartrate precipitated colourless, or almost colourless. It was found also , that 4-hydroxyquinaldine did not give a precipitate with tartaric acid under the conditions specified for the purification , so that it is readily eliminated.

Impure chloroquinaldine tartrate can be purified by recrystallisation from alcohol or water, after boiling the alcoholic or aqueous solution with animal charcoal. Ten grammes dissolve in 100 c.c. of boiling alcohol, or 350 c.c. of boiling water. It is insoluble in ether.

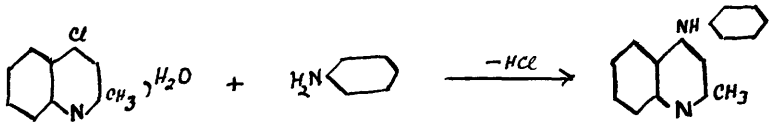
A sample of 4-chloroquinaldine tartrate recrystallised from water in silky , colourless needles , which melted at 138° to 142°.

Principal References for 4-Chloroquinaldine.

Conrad & Limpach. Ber. 20, 952.	(Preparation.)
Fischer. J. Pr. Chem. 109, 59.	(" ")
Ashley. Proc. Roy. Soc. B. 113, 293.	(" ")
Conrad & Limpach. Ber. 22, 77.	(Methiodide.)
(Ber. 41 , 2699.) & (Ber. 53, 1025.)	(Properties.)

PREPARATION OF 4-PHENYLAMINO QUINALDINE.

This compound was first prepared by Conrad & Limpach by heating aniline and chloro-quinaldine together under pressure. Later Fischer and others prepared it by heating the reagents together in an open flask, and this was the method employed for the preparation.



195.5 93 234

20.0 gms. of 4-chloroquinaldine hydrate.
9.3 gms. of aniline.

The reagents were gently heated together in an open flask on an oil-bath, until a solution was obtained. The temperature was then gradually raised to about 110° C., when a vigorous reaction commenced. Heating was stopped, and the temperature rose spontaneously to about 170° C., and the whole mass finally solidified. The solid was allowed to cool, and was then pulverised, and extracted with boiling water till only a very little residue remained undissolved. The aqueous solution of the hydrochloride of the phenyl amino quinaldine was allowed to cool slightly, and then treated with excess of dilute caustic soda to precipitate the free base. The phenyl amino quinaldine precipitated as a colourless, flocculent mass which was allowed to consolidate before filtering off and washing with water. The product was spread on a porous plate, and allowed to dry.

Recrystallisation.

The mixture of ether and benzene recommended in the literature was found unsuitable for the recrystallisation of the product, but very satisfactory results were obtained with methyl alcohol, while ethyl alcohol was found to be much less suitable.

The phenylamino quinaldine crystallised well from methyl alcohol, in colourless prisms, melting between 153° and 155°C. (This agrees with the melting point given by Fischer.)

Yield, (recrystallised), 18 gms. (77% of theoretical).

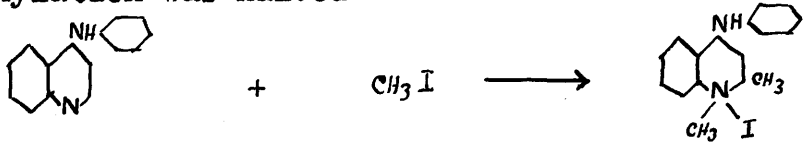
References :-

Fischer, J. Pr. Chem., 109 , 59.

Ephriam, Ber., 26 , 2228.

PREPARATION OF 4-PHENYLAMINO QUINALDINE METHIODIDE.

This compound was prepared by Fischer by heating phenylamino quinaldine with excess methyl iodide in a sealed tube for two hours. It was found by the author, that a much purer product could be obtained by using nitrobenzene as solvent and dispensing with the sealed tube. The yield was very satisfactory, and the time required for the methylation was halved.



234 142 376

10 gms. of 4-phenylamino quinaldine.
6 ccs. of methyl iodide (large excess).
20 ccs. of nitrobenzene.

The phenylamino quinaldine was dissolved in the nitrobenzene, in a flask fitted with an efficient reflux condenser, and the methyl iodide added. The mixture was then gently heated on the waterbath. Methylation was very rapid, and solid methiodide soon began to separate. Heating was continued for an hour, after which the mixture was allowed to cool, and set aside to crystallise. The methiodide was finally filtered off on a Buchner funnel, drained well, and washed with ether till free of nitrobenzene.

Yield (crude), 12.5 gms. (78% of theoretical). Golden yellow prisms, melting indefinitely between 254° and 260° C. (Fischer gives the melting point as 254° C.)

Recrystallisation.

Water, aqueous methyl alcohol, or aqueous ethyl alcohol are all suitable for the crystallisation of phenylamino quinaldine methiodide; the second of these was used as it dissolved the product most readily. The crystals obtained were filtered off, drained well, and washed with ether.

It was found that the addition of a little water to an alcoholic solution of the product greatly increased the solubility.

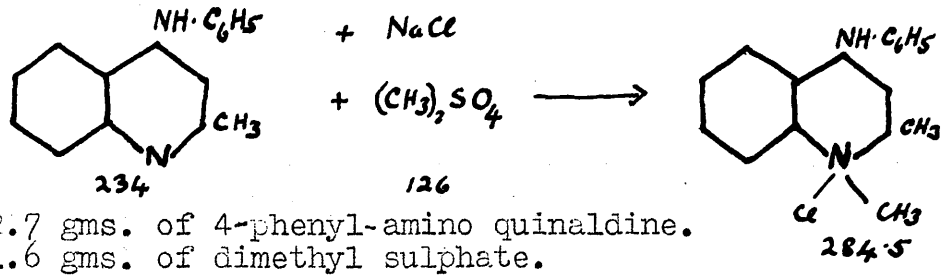
The crude product obtained from the nitrobenzene solution is pure enough, without further recrystallisation, for most purposes.

Reference.

Fischer, J. Pr. Chem., 109, 59.

PREPARATION OF 4-PHENYL-AMINO-QUINALDINE METHOCHLORIDE.

This compound is new.



2.7 gms. of 4-phenyl-amino quinaldine.
1.6 gms. of dimethyl sulphate.
2 ccs. of nitrobenzene.

The phenyl amino quinaldine was dissolved in the nitrobenzene, and the dimethyl sulphate added to the yellow solution. The temperature was now gradually raised, and at about 50° C., a reaction commenced. Heating was discontinued, and the temperature rose spontaneously , while the liquid first became red in colour , and then paler. When the reaction seemed to be complete, the mixture was heated for one hour more on the waterbath , then allowed to cool and stand overnight. The methosulphate separated as an almost colourless, crystalline, precipitate which was filtered off, and washed free of nitrobenzene with ether.

The methosulphate was dissolved in a little warm water, in which it was very soluble, and a saturated sodium chloride solution added. The methochloride precipitated , and was filtered off , drained well , and washed with ether.

The methochloride was recrystallised from a very little moist alcohol , to remove organic impurities , and then from water to remove traces of sodium chloride, and

finally from alcohol again. The methochloride was washed with ether , and dried in a vacuum desiccator over sulphuric acid.

The 4-phenyl-amino quinaldine methochloride obtained was a colourless , distinctly crystalline , compound, very readily soluble in water , soluble in alcohol, and insoluble in ether. The aqueous solution of the compound on acidification with nitric acid and addition of silver nitrate, gives a precipitate of silver chloride.

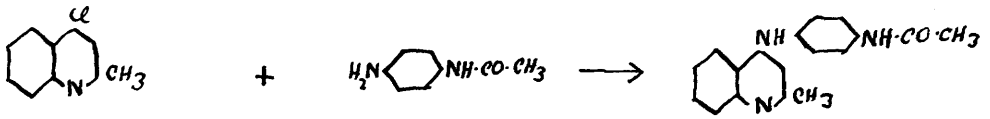
The methochloride melted fairly sharply between 259°and 261°C , to a dark red liquid , although it started to go at a much lower temperature, viz. 175°C.

Analysis.

$C_{17} H_{17} N_2 Cl$	requires	N 9.8 %.
	found	N 10.0 %.

PREPARATION OF 4-(p-ACETYLAMINO PHENYLAMINO) - QUINALDINE.

This compound is new.



195.5 + 150 → 291

20 gms. of 4-chloroquinaldine hydrate.
15 gms. of p-amino acetanilide.

The reagents were intimately mixed and heated to about 100° C. on an oil bath, when a vigorous reaction commenced. Heating was discontinued, and the temperature rose spontaneously to about 165° C., and a hard, yellow mass was obtained. After cooling, the product was pulverised, and extracted with hot water. An orange red solution was obtained which deposited yellow crystals of the hydrochloride of 4-(p-acetylamino phenylamino)-quinaldine if allowed to cool. The hot solution was diluted with cold water, and the free base precipitated by addition of excess dilute caustic soda. A bulky yellowish-white precipitate was obtained which was filtered off, and washed free of alkali with hot water.

As p-amino acetanilide is readily soluble in hot water, it was thought that the product might be contaminated with any unchanged amino acetanilide which had not reacted with the chloroquinaldine. The product was therefore extracted twice with about 200 ccs. of hot water, by agitating on the waterbath at 90° C. (5 gms. of p-amino

acetanilide were found to dissolve readily in 35 ccs. of water at 90° C.) The product was finally filtered off, drained well, and dried on a porous plate.

Yield, 28 gms. (96% of the theoretical).

Pale yellow (almost colourless) powder, which darkened at 260° C., and melted finally at 280° to 285° C. (uncorr.)

Solubilities:-

Readily soluble in pyridine, nitrobenzene and ethylene glycol mono ethyl ether. Moderately soluble in ethyl or methyl alcohol, amyl alcohol, or diacetone alcohol. Very slightly soluble in benzene, ether, and butyl acetate. Almost insoluble in water.

Recrystallisation.

Alcohol was found to be the most suitable solvent, although the product was not very soluble. Small, buff-coloured, glistening crystals were obtained.

Analyses:-

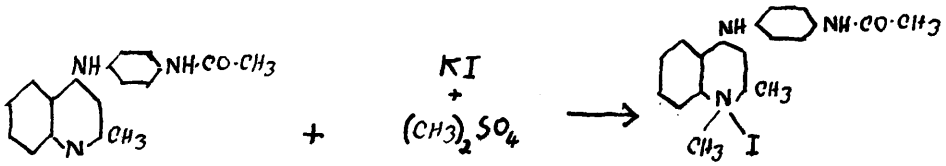
$C_{18}H_{17}ON_3$ requires N 14.4%

found:- (1) ..... N 14.3%

(2) ..... N 14.3%

PREPARATION OF 4-(p-ACETYLAMINO PHENYLAMINO)-QUINALDINE METHIODIDE.

This compound is new. A small test experiment indicated that the desired compound was obtainable on refluxing 4-(p-acetylamino phenylamino)-quinaldine with excess of methyl iodide in nitrobenzene solution, but this method was not employed owing to the insoluble nature of the starting material. The methiodide of 4 (p-acetylamino phenylamino) quinaldine was prepared via the methosulphate as follows:-



291 126 433

14.6 gms. of 4-(p-acetylamino phenylamino) quinaldine.
7.0 gms. of dimethyl sulphate (10% excess).
100 ccs. of nitrobenzene.

The quinaldine compound was suspended in the nitrobenzene, and the dimethyl sulphate added. The temperature was now gradually raised to 120° to 130° C., and the solid slowly dissolved. When all the solid had dissolved, the mixture was heated for a further half hour on the water bath at 90° C., and was then allowed to cool. The methosulphate did not crystallise, so that ether was added to precipitate it. The methosulphate precipitated in a somewhat tarry form, but was eventually obtained solid

by scratching and agitating. The mother liquor was decanted off, and the precipitate extracted once or twice with fresh portions of ether before it was finally filtered off. The precipitate was well drained on the filter, and washed with ether.

The methosulphate was dissolved in hot water, and the solution filtered. A saturated solution of potassium iodide was now added, and the methiodide precipitated immediately. The methiodide was filtered off, and washed on the filter with a little water, followed by a little alcohol, and much ether to remove traces of nitrobenzene.

The yield was almost theoretical, but the crude product thus obtained is liable to contain impurities.

Recrystallisation.

The 21 gms. of crude product obtained above were recrystallised in two batches from a mixture of 100 ccs. of alcohol and 25 ccs. of water. A third crop was obtained by evaporating down the mother liquor. The methiodide was thus obtained in lemon-yellow crystals.

The melting point was indefinite, the product started to darken at about 260° C., and melted finally with decomposition between 270° and 284° C.

Solubility.

4-(p-acetylamino phenylamino)-quinaldine methiodide is insoluble in ether, and soluble in water, ethyl alcohol, and methyl alcohol. It is only sparingly soluble in ethyl

or methyl alcohol alone, but on addition of a little water, the solubility was very much increased. The product is more readily soluble in aqueous methyl alcohol than in aqueous ethyl alcohol.

The methiodide gives a precipitate of silver iodide in dilute nitric acid solution, when silver nitrate is added.

Analysis.

$C_{19} H_{20} O N_3 I$	requires	N	9.7%
	found	N	9.9%

PREPARATION OF 4-(p-ACETYLAMINO PHENYLAMINO)-QUINALDINE METHOCHLORIDE.

This compound is new; and it was prepared via the methosulphate by a method entirely analogous to that used for the preparation of the corresponding methiodide.

A filtered solution of 4-(p-acetylamino phenyl amino) quinaldine methosulphate was prepared, and a little saturated sodium chloride solution added to it. The methochloride precipitated at once, and was filtered off, and washed well with ether. It was then recrystallised from water to remove traces of sodium chloride, and finally recrystallised from methyl alcohol.

Lemon yellow powder, very soluble in water, and in alcohol. Insoluble in ether.

Analysis.

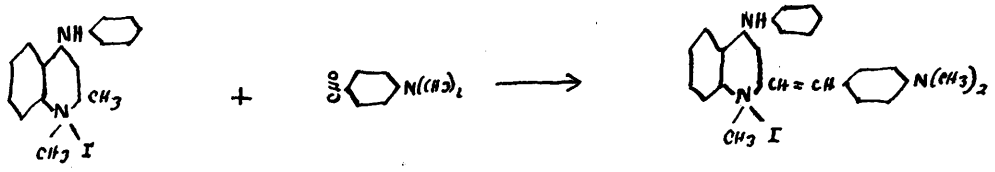
$C_{19}H_{20}ON_3Cl$	requires	N,	12.3 %.
	Found :-	N,	12.2 %.

Melting Point.

The melting point was indefinite, and appeared to depend on the rate of heating. The substance started to change about 270 ° C., and melted finally with decomposition between 278° and 285° C.

PREPARATION OF S-(4-PHENYLAMINO-2-QUINOLYL METHIODIDE)-(p-DIMETHYLAMINO PHENYL)ETHENE.

This compound is new.



376 149 507

5.0 gms. of 4-phenylamino quinaldine methiodide.
2.5 gms. of p-dimethylamino benzaldehyde. (25% excess.)

The reagents were melted together, and a deep-red, semi-solid melt was obtained. Five drops of piperidine were now added, and the mixture heated to 140°C. for two hours on an oil bath. Towards the end of the two hours, the melt became almost solid. The mixture was allowed to cool, then pulverised, and extracted with ether by boiling on the waterbath under reflux. The ether removed the unchanged aldehyde, and the residue was filtered off, and washed with ether.

A brick-red, crystalline solid was thus obtained, which was probably contaminated with unchanged quinaldine compound.

Yield (crude) 6 gms., 89 % of theoretical.

Purification.

The 6 gms of product were extracted with 30 ccs of alcohol , by boiling under reflux , filtered hot , and washed with a little alcohol. The product was thus free from the last traces of aldehyde, but was still liable to contain unchanged quinaldine compound and was purified further by boiling for an hour under reflux , with a mixture of 10 ccs. of water and 25 ccs of alcohol. The solid which remained undissolved was filtered off from the hot solution , and washed with a little alcohol. The product was now free from unchanged 4-phenylamino quinaldine methiodide , since 3 gms. of the latter dissolve completely in a mixture of 25 ccs. of alcohol and 4 ccs. of water.

For analysis , some of the product obtained above was extracted with 200 ccs. of 50% aqueous alcohol , and the extract filtered hot , and allowed to crystallise. The solid which separated was filtered off , washed with a little alcohol , followed by ether , and finally dried in a vacuum desiccator over sulphuric acid.

Red , felted , needle shaped prisms were obtained. The melting point was indefinite , the substance started to darken about 200° C. and melted finally with decomposition around 250° to 260° C.

(Better crystals are obtainable from nitrobenzene , but for analysis , the aqueous alcoholic mixture was considered preferable.)

Analysis.

$C_{26} H_{26} N_3 I$ requires N 8.3 % , and I 25.1 %.

found :- N 8.6 % , and I 25.4 %.

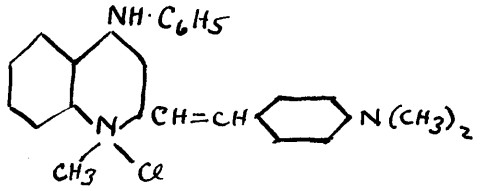
Solubilities.

Insoluble in ether. Moderately soluble in water , giving a red solution which deposited a red powder on standing. Moderately soluble in ethyl and methyl alcohol ; the solubility is increased by addition of water , and better crystals are obtained on cooling.

Readily soluble in nitrobenzene , from which it crystallised well.

Readily soluble in aqueous ethylene glycol monoethyl ether , which deposited a crystalline solid on cooling.

PREPARATION OF S-(4-PHENYLAMINO-2-QUINOLYL METHOCHLORIDE) -(P-DIMETHYLAMINO PHENYL)ETHENE.



415.5

The s-(4-phenylamino-2-quinolyl methiodide)-(p-dimethylamino phenyl)ethene obtained from the preceeding preparation was suspended in aqueous methyl alcohol , and excess of freshly precipitated , washed , silver chloride added. The mixture was now boiled under reflux on the water bath for six hours , and the precipitate of silver iodide and chloride filtered off from the hot solution and extracted with methyl alcohol. The extracts were added to the filtrate, and the solution concentrated on the waterbath , filtered , and left to crystallise. An orange-red solid was obtained , much lighter in colour than the corresponding methiodide , and much more readily soluble in water.

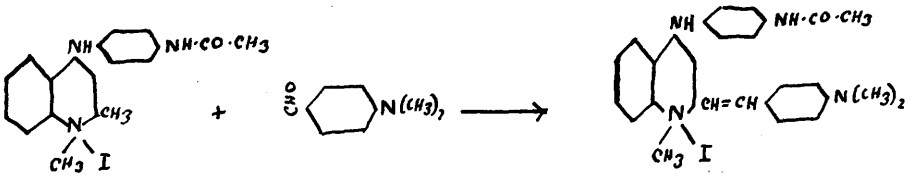
The product was recrystallised from nitrobenzene , and thoroughly washed with ether.

Red prisms were obtained , which darkened about 260°C., and melted at 280° to 285°, decomposing and turning black.

$C_{26}H_{26}N_3Cl$ requires N 10.1 %., found N 10.2 %.

PREPARATION OF S-(4-p-ACETYLAMINO PHENYLAMINO-2-QUINOLYL METHIODIDE)-(p-DIMETHYLAMINO PHENYL)ETHENE.

This compound is new.



433 149 564

4.3 gms of 4-(p-acetylamino phenylamino)-quinaldine methiodide.
5.0 gms. of p-dimethylamino benzaldehyde, (large excess.)

The reagents were intimately mixed, and gently heated to melt the aldehyde which was present in large excess, so that it acted as solvent. Five drops of piperidine were added, and the melt rapidly became red in colour, and less viscous. The mixture was now heated for nine hours on an oil bath at 130° to 140° C., then cooled, and the dark red crystalline mass obtained was pulverised, and boiled with ether under reflux. The ether extracted the unchanged aldehyde, and the solid residue was filtered off and washed with ether. Several extractions were made, and finally the product was obtained free from aldehyde.

Yield 4.7 gms. (84 % of theoretical).

The crude product thus obtained was liable to contain unchanged quinaldine compound, and was further purified as follows :-

The 4.7 gms of crude product were boiled for an hour with 20 ccs. of alcohol , and the residue which did not dissolve filtered off from the hot solution , and washed with a little alcohol. This treatment removed the last traces of aldehyde present. The product was now boiled for half an hour with a mixture of 50 ccs. of methyl alcohol and 25 ccs. of water, and the undissolved ethene compound filtered off from the hot solution , and washed with a little alcohol followed by much ether. (The quantity of aqueous alcohol used for the last extraction is sufficient to dissolve 5 gms. of 4-(p-acetylamino phenylamino) - quinaldine methiodide.)

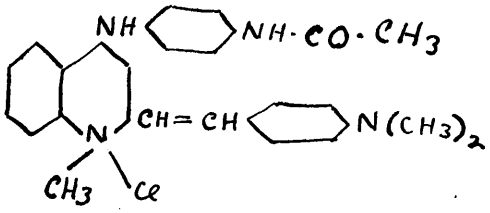
The product thus obtained was free from unchanged starting materials. A portion was recrystallised from 50 % aqueous ethyl alcohol , but it was found that much better crystals were obtained by recrystallising from nitrobenzene and then washing first with alcohol,and next with ether till quite free from nitrobenzene.

Dark red prisms were obtained. The melting point was indefinite , and depended on the rate of heating. The compound darkened slowly , and about 260°C . shrank , and became quite black , and melted finally about 270°to 275°C., with decomposition.

$C_{28} H_{29} O N_4 I$ requires N 9.9 %.

found :- N 10.0 %. and N 10.0 %.

PREPARATION OF S-(4-P-ACETYLAMINO PHENYLAMINO-2-QUINOLYL METHOCHLORIDE)-(P-DIMETHYLAMINO PHENYL)ETHENE.



472.5

1.5 gms of s-(4-p-acetylamino phenylamino-2-quinolyl methiodide)-(p-dimethylamino phenyl)ethene were suspended in a mixture of 30 ccs. of methyl alcohol and 20 ccs. of water. Excess of freshly-precipitated , washed , silver chloride was then added , and the mixture boiled under reflux on the waterbath for six hours. The precipitate of silver salts was filtered off from the hot solution , and extracted several times with boiling methyl alcohol , and the extracts added to the filtrate. The combined filtrate and extracts were refluxed with a fresh portion of silver chloride for a further two hours , to make sure that no methiodide had remained unconverted to methochloride , and the solution finally concentrated , filtered , and left to crystallise.

An orange-red product was obtained , which was recrystallised from nitrobenzene , washed with alcohol , and finally washed with ether till free of nitrobenzene , and dried in a vacuum desiccator.

The compound was also recrystallised from aqueous alcohol , but the crystalline form was not so pronounced as it was in the product obtained from nitrobenzene.

Orange-red prisms were obtained from nitrobenzene, which started to darken about 280°C. , and became quite black at 300°C. , but remained unmelted at 310°C.

Insoluble in ether. Moderately soluble in water , alcohol , and nitrobenzene , giving red solutions.

$C_{28} H_{29} O N_4 Cl$	requires	N	11.9 %.
	found	N	11.7 %.

ATTEMPTED CONDENSATION OF 4-PHENYLAMINO QUINALDINE METHIODIDE AND p-DIMETHYLAMINO BENZALDEHYDE IN ALCOHOLIC SOLUTION.

It was found impossible to prepare s-(4-phenylamino-2-quinolyl methiodide)-(p-dimethylamino phenyl)ethene by this method.*

2.6 gms. of 4-phenylamino quinaldine methiodide.
1.6 gms. of p-dimethylamino benzaldehyde. (60 % excess.)

The reagents were dissolved in 20 c.c. of alcohol and 3 c.c. of water, five drops of piperidine were added , and the mixture boiled under reflux on the waterbath for nine hours. A red solution was obtained which deposited clusters of red crystals on standing overnight. The crystals were filtered off, and washed with alcohol followed by ether, and were finally boiled under reflux with ether , in order to remove traces of unchanged aldehyde. Yield , 1.5 gms.

The crystals obtained were recrystallised from alcohol containing a little water, and formed red needle-shaped prisms. These red crystals were dissolved in alcohol, and the solution boiled under reflux with animal charcoal and filtered. A lemon-yellow solution was obtained which deposited yellow needle-shaped prisms which proved to be unchanged phenylamino quinaldine methiodide.Melting point about 260°.

Another condensation was attempted, using the

* (The preparation of this compound is described on pg. 174)

minimum quantity of water necessary to effect complete solution of the quinaldine compound, since it was feared that the presence of water might interfere with the reaction. This experiment also gave a negative result.

5.0 gms. of 4-phenylamino quinaldine methiodide.
2.5 gms. of p-dimethylamino benzaldehyde. (25 % excess.)
30 c.c. of alcohol.
1 c.c. of water.
6 drops of piperidine.

The mixture was boiled for nine hours, and a red solution obtained as before. On cooling red crystals were deposited which on purification gave lemon-yellow needle shaped prisms of unchanged 4-phenylamino quinaldine methiodide , melting about 260°.

It is interesting that this condensation could be effected by the fusion method , but not by the more usual method of boiling the reagents in alcoholic solution.

It is possible that s-(4-phenylamino-2-quinolyl methiodide)-(p-dimethylamino phenyl)ethene was formed in small quantities in the above experiments, as a red colour was developed , and this compound was subsequently found to be red. It could only be present in extremely small amounts, however, as its solubility in alcohol is only slight and nothing separated out from the hot reaction mixtures.

ATTEMPTED CONDENSATION OF 4-(p-ACETYLAMINO PHENYLAMINO) QUINALDINE METHIODIDE AND p-DIMETHYLAMINO BENZALDEHYDE IN ALCOHOLIC SOLUTION.

This condensation was only attempted on the small scale. It was found impossible to prepare s-(4-p-acetyl amino phenylamino-2-quinolyl methiodide)-(p-dimethylamino phenyl)ethene by the following method:-*

0.9 gms. of 4-(p-acetylamino phenylamino)quinaldine methiodide.
0.4 gms. of p-dimethylamino benzaldehyde,(30 % excess.)
15 cc. of alcohol.
2 c.c. of water.
2 drops of piperidine.

The reagents were suspended in the aqueous alcohol, the piperidine added , and the mixture boiled under reflux on the waterbath. A deep red solution was soon obtained which was boiled for six hours, and then allowed to stand overnight. Orange crystals separated which were filtered off and washed with ether. Yield 0.7 gms.

The product was dissolved in methyl alcohol and a little water, and boiled under reflux with animal charcoal. After filtration , a yellow solution was obtained which deposited yellow prisms. The crystals were filtered off and washed with alcohol.

The product was unchanged 4-(p-acetylamino phenylamino)quinaldine methiodide , melting at 270°- 284° with decomposition. This was confirmed by a mixed melting point.

* (For the preparation of this compound cf. pg. 178.)

ATTEMPTED CONDENSATION OF 4-(p-ACETYLAMINO PHENYLAMINO) QUINALDINE METHIODIDE AND p-DIMETHYLAMINO BENZALDEHYDE BY FUSING TOGETHER FOR TWO HOURS.

When 4-phenylamino quinaldine methiodide and p-dimethylamino benzaldehyde are fused together for a period of two hours , they condense readily , and a 90 % yield of the condensation product is obtainable. The following experiment shows that when 4-(p-acetylamino phenylamino) quinaldine methiodide and p-dimethylamino benzaldehyde are fused together under similar conditions, there is scarcely any condensation. It was found that to effect this latter condensation, the period of fusion had to be increased from 2 hours up to 9 hours. The p-acetylamino group appears, therefore, to have a steric effect.

8.7 gms. of 4-(p-acetylamino phenylamino)quinaldine methiodide.
7.0 gms. of p-dimethylamino benzaldehyde, (large excess.)

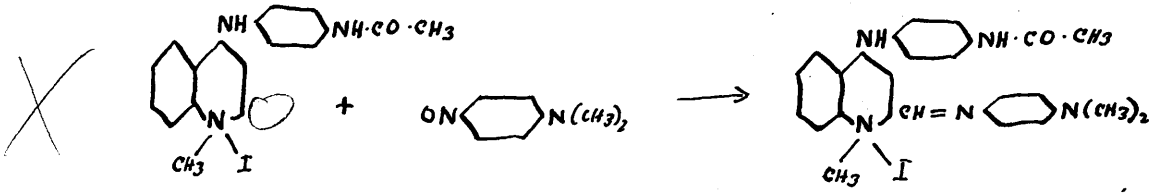
The reagents were fused together, and 6 drops of piperidine added. The melt became red in colour, and was heated for 2 hours on an oil bath at 140°. The melt was then allowed to cool , and solidify, after which it was pulverised and repeatedly extracted with ether to remove unchanged aldehyde. The red product was repeatedly boiled out with water, and a very small residue of the condensation product was obtained. Most of the quinaldine compound was recovered unchanged from the aqueous extracts, and when purified melted at 270°- 284°.

Another experiment using 4-phenylamino quinaldine methochloride in place of the methiodide gave a similar result :- After 10 hours boiling nothing separated from the reaction mixture on long standing. Most of the alcohol was evaporated off, and the solid which separated filtered off, and washed with alcohol and ether. The product was now extracted with ether, and from the etherial extract 5-aldehyde acridine was recovered. The residue which did not dissolve in ether was dissolved in water, boiled with animal charcoal, and "salted out" with a little saturated sodium chloride solution, and a white precipitate of unchanged 4-phenylamino quinaldine methochloride obtained.

Two higher boiling solvents, viz. ethylene glycol monoethyl ether and nitrobenzene, were tried, but again, negative results were obtained.

PREPARATION OF 2(p-DIMETHYLAMINO ANIL)-4(p-ACETYLAMINO PHENYLAMINO) QUINOLINE METHIODIDE.

This compound is new.



433 150 565

4.3 gms. of 4-(p-acetylamino phenylamino) quinaldine methiodide.
1.9 gms. of p-nitroso dimethylaniline, (25% excess.)
40 c.c. of alcohol.
2.5 c.c. of water.

The reagents were suspended in the alcohol and water, five drops of piperidine added, and the mixture boiled under reflux for ten hours on the waterbath. A deep red solution was obtained which deposited dark red crystals on standing overnight. The product was filtered off, drained well, and washed with a little alcohol; it was then boiled under reflux with ether to remove unchanged p-nitroso dimethyl aniline, and finally filtered off and washed with ether.

Yield 2.3 gms. (ca. 40 % of theoretical.)

The crude product was insoluble in ether, moderately soluble in water giving a red solution, and readily soluble in alcohol or nitrobenzene. It separated crystalline from the last two solvents, but the crystalline

form of the specimens obtained from nitrobenzene was more pronounced than that of the specimens recrystallised from alcohol.

Dark red prisms of indefinite melting point were obtained from both solvents.

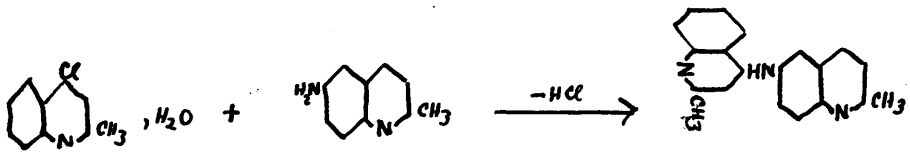
Analysis.

$C_{27}H_{28}ON_5I$	requires	N,	12.4 %.
	Found :-	N,	12.6 %. (micro.)

2(p-Dimethylamino anil)-4-phenylamino quinoline methiodide was prepared in an analogous manner to the above compound which it resembled in physical and chemical properties. It was not examined therapeutically since 2(p-dimethylamino anil) -4(p-acetylamino phenylamino) quinoline had proved inactive.

PREPARATION OF 2-METHYL-6(4-2-METHYL-QUINOLYL)AMINO-QUINOLINE.

This compound is new.



195.5 158 299

7.9 gms. of 6-amino quinaldine.

9.8 gms. of 4-chloroquinaldine hydrate.

The reagents were intimately mixed, and heated in an open flask until a brown melt was obtained. The mass was stirred and the temperature gradually raised to 170°- 180° when a reaction took place and heating was discontinued. The temperature rose spontaneously to about 270°. The reaction mixture was allowed to cool , and the hard mass obtained pulverised and extracted with boiling water. The aqueous extract was filtered and boiled with animal charcoal, filtered again, and made alkaline with sodium carbonate in order to liberate the free base from the hydrochloride. A flocculent buff-coloured precipitate was obtained, contaminated with a pink impurity. The precipitate was filtered off, and washed well with water, then spread on porous plates and dried.

Yield (crude) 9 gms. (60 % of theoretical.)

The product was dissolved in 25 c.c. of boiling alcohol, and after refluxing with animal charcoal, the solution was filtered and allowed to stand overnight. A putty-coloured product separated, and was filtered off, washed with a little alcohol followed by much ether, and finally dried.

For analysis the product was recrystallised twice more from alcohol, and dried in a vacuum desiccator over sulphuric acid.

A colourless powder melting between 100° and 110° was obtained. (The melting point was not sharp.)

Analyses.

$C_{20} H_{17} N_3$	requires	N,	14.1 %.
	Found :-	N,	14.1 %.
		N,	14.1 %.

Solubilities.

The product was very readily soluble in absolute alcohol, but the solubility was much decreased by the presence of a little water.(Unlike both of the starting materials, it gave no precipitate with tartaric acid in alcoholic solution.) It was readily soluble in ethylene glycol monoethyl ether and in nitrobenzene, almost insoluble in ether, and insoluble in water.

Notes on the reaction.

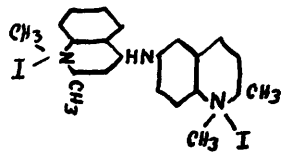
4-Chloroquinaldine decomposes at high temperatures

forming a blue dye, and as the reaction is carried out at a comparatively high temperature, it is inevitable that some of this dye is obtained. The reaction mixture at the end of the condensation was always blue in colour, and the pink impurity which appears along with the product on neutralising with sodium carbonate is the free base of the violet dye; this pink compound was eliminated afterwards by the treatment with alcohol and animal charcoal.

It was found that the condensation of 6-amino quinaldine and 4-chloroquinaldine could be effected in glacial acetic acid solution , by heating for five hours on the water bath. The reaction mixture was diluted with water, and neutralised with ammonia. The product which separated was filtered off and washed with hot water, and finally recrystallised from alcohol as before. By this method the pink impurity was entirely eliminated.

PREPARATION OF 2-METHYL-6(4-2-METHYL-QUINOLYL METHIODIDE) AMINO-QUINOLINE METHIODIDE.

This compound is new. It can be prepared by the action of methyl iodide or methyl sulphate on the base in nitrobenzene solution.



Methylation by Methyl Iodide.

3.0 gms. of 2-methyl-6(4-2-methyl-quinolyl)amino-quinoline.
5.0 c.c. of methyl iodide, (large excess.)
10 c.c. of nitrobenzene.

The base was dissolved in the nitrobenzene and the methyl iodide added. The mixture was boiled for two hours on the waterbath in a flask fitted with an efficient reflux condenser. Solid soon separated from the hot reaction mixture. When cold, the product was filtered off, and washed with ether till free from nitrobenzene.

Yield, (crude), 4.9 gms. (84 % theoretical.)

Methylation by Methyl Sulphate.

3.0 gms. of 2-methyl-6(4-2-methyl-quinolyl)amino-quinoline.
2.0 c.c. of methyl sulphate, (theoretical quantity.)
20 c.c. of nitrobenzene.

The base was dissolved in the nitrobenzene, and added to the methyl sulphate. The temperature was gradually raised, and at about 110° a reaction commenced, and heating was discontinued. The temperature rose spontaneously to 130°,

the liquid became redder in colour, and solid separated. When the temperature fell to 100°, the reaction mixture was transferred to a waterbath, and heated for a further 45 minutes. The product was filtered off when cold, and washed on the filter with ether till free from nitrobenzene.

Yield of crude methosulphate 5.6 gms. (almost theoretical.)

The methosulphate was dissolved in a little hot water, and the methiodide precipitated by addition of saturated potassium iodide in the usual manner. The precipitate was filtered off when cold, and washed first with water, then with alcohol, and finally with ether. It was then dried on a porous plate.

Purification of 2-methyl-6(4-2-methyl-quinolyl methiodide) amino-quinoline methiodide.

The products obtained from both the above preparations were reddish in colour, and somewhat tarry, they were purified as follows:- The methiodide was dissolved in hot water and boiled with animal charcoal; the aqueous solution lost its red colour, and became yellow, it was filtered and cooled. The methiodide separated from the aqueous solution as an amorphous yellow powder, and this was recrystallised from alcohol containing a little water.

Beautiful yellow prisms were obtained, which were filtered off, washed with a little alcohol and much ether,

and dried in a vacuum desiccator over sulphuric acid. (On drying in the desiccator, the crystals became darker in colour, due to loss of solvent of crystallisation. The lighter colour could be restored by addition of water, or by letting the product stand in the air.

The melting point was indefinite. The substance started to darken ca. 220°, and melted finally with charring and decomposition at 230° to 275°.

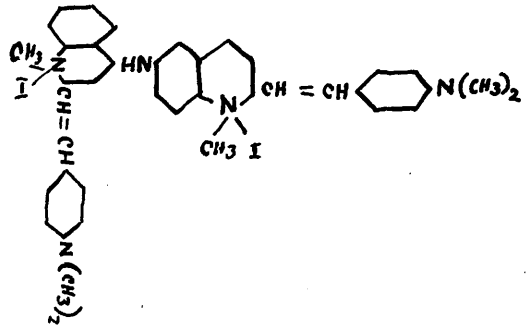
The product was insoluble in ether, soluble in water, and very sparingly soluble in absolute alcohol. The solubility in alcohol was greatly increased on addition of a little water.

Analyses.

$C_{22} H_{23} N_3 I$	requires	N, 7.2 %.
	Found :-	N, 7.3 %.
		N, 7.4 %.

PREPARATION OF 2(p-DIMETHYLAMINO STYRYL)-6(4-(2(p-DIMETHYLAMINO STYRYL))QUINOLYL)AMINO QUINOLINE METHIODIDE.

This compound is new.



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4.1 gms. of 2-methyl-6(4-2-methyl-quinolyl methiodide)amino quinoline methiodide.
8.5 gms. of p-dimethylamino benzaldehyde, (large excess.)

The reagents were melted together in a flask, and five drops of piperidine added. The melt was heated for 9 hours at 130° to 140° on an oil bath, and rapidly became purple in colour. The product was pulverised, and repeatedly extracted with ether to remove unchanged p-dimethylamino benzaldehyde; (the extractions were effected by boiling under reflux).

Yield, (crude) 4.8 gms. (80 % theoretical.)

The product thus obtained is liable to contain unchanged 2-methyl-6(4-2-methyl-quinolyl methiodide)amino quinoline methiodide, as well as a little aldehyde. It was freed from the former compound by extracting twice with hot water, using 50 c.c. each time. These extractions were performed as follows :-

The product was thoroughly pulverised, and then agitated with hot water at 90° C., by heating for quarter of an hour on the waterbath. The process was repeated, and the residue was considered free from starting materials. It was further purified by extraction with a little hot alcohol, and the residue recrystallised from much methyl alcohol and a little water.

A purple amorphous product of indefinite melting point was obtained. The melting point appeared to lie between 230° and 255°, the substance charring and decomposing.

Analyses.

$C_{40} H_{41} N_5 I$	requires	N,	8.3 %.
	Found :-	N,	8.4 %.
		N,	8.5 %.

Properties.

The product was moderately soluble in water and in alcohol, giving violet solutions.

It dissolved in mineral acids giving yellowish solutions which became violet on dilution with water.

On boiling with nitric acid fumes of iodine were liberated.

PREPARATION OF 2-METHYL-4-HYDROXY-6-ACETYLAMINO QUINOLINE.

As explained in the theoretical section, there are no details available in the literature for the preparation of this compound. It is merely stated that it is "obtained in the usual way from p-amino acetanilide and ethyl acetoacetate." (D.R.P., 591,480. E.P., 414,105.)

It was assumed that this "usual way" referred to was analogous to the method employed for the preparation of 2-methyl-4-hydroxy quinoline. There are , therefore , two distinct stages in the production of 2-methyl-4-hydroxy-6-acetylamino quinoline :-

(1) The preparation of ethyl B-p-acetylamino phenylamino crotonate.

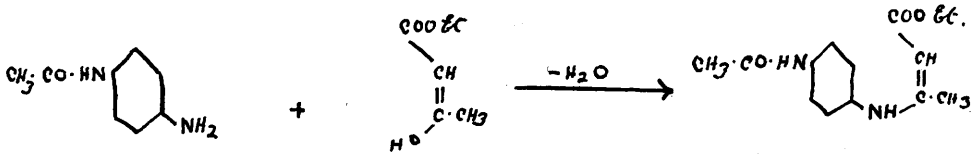
(2) The ring closure of this crotonate by some suitable means, such as heating in hot liquid paraffin.

The first of these stages was readily achieved, but the yields of 2-methyl-4-hydroxy-6acetylamino quinoline obtained from the ring closure of the crotonate were poor.

(1) Preparation of Ethyl B-p-Acetylamino Phenylamino Crotonate.

Ethyl B-p-acetylamino phenylamino crotonate was readily obtained in 90 % yield, but as p-amino acetanilide is not sufficiently soluble in ethyl acetoacetate the usual method for the preparation of ethyl esters of B-arylamino-crotonic acids was found to be inapplicable, and a solvent had to be employed. In order to keep the reagents in solution,

it was necessary to warm the reaction mixture slightly, and no deleterious effects resulted from this treatment. (Coffey, Thomson, and Wilson recommend that the reaction should be carried out in the cold, J.C.S., 1936, 856.)



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150 gms. of p-amino acetanilide.
130 gms. of ethyl acetoacetate.
500 c.c. of ethyl alcohol.

The p-amino acetanilide was dissolved in the alcohol by boiling under reflux on the waterbath, the ethyl acetoacetate and 4 drops of concentrated hydrochloric acid were now added, and the mixture removed from the waterbath and allowed to stand overnight.

The crotonate which separated was filtered off, well drained, and washed with a little alcohol. The product was then pressed on porous plates, and dried in a vacuum desiccator over sulphuric acid. (The crotonate was found to turn brown when exposed to the atmosphere in a moist condition.)

Yield 242 gms. (ca. 92% of the theoretical.)

A second crop was obtained on concentration of the mother liquor.

For analysis, the crotonate was repeatedly recrystallised from alcohol, in which it was considerably less soluble than p-amino acetanilide. The product was finally filtered off, washed with alcohol, and dried in a vacuum desiccator over concentrated sulphuric acid.

A colourless, crystalline compound was obtained, which melted at 179° - 180° C. (uncorrected.).

Analysis.

$C_{14} H_{18} O_3 N_2$ requires N, 10.7 %.

Found :- N, 10.9 %.

N, 11.0 %.

The crotonate was insoluble in water, but dissolved in acids and was readily hydrolysed by them.

As the preparation and properties of the above compound have not been published in the literature, they have been given here in full.

(2) Ring Closure of Ethyl B-p-Acetylamino Phenylamino Crotonate.

The only information available in the literature on 2-methyl-4-hydroxy-6-acetylamino quinoline is that it is "a colourless powder, soluble in dilute sodium hydroxide".

Efforts were made to prepare this compound by ring closing the crotonate in liquid paraffin, but the

product was always obtained in a tarry state, as was the case with the analogous 2-methyl-4-hydroxy quinoline. The product could not be purified by recrystallising from water, or by treatment with dilute sodium hydroxide. (Dilute mineral acids were avoided, as they would hydrolyse the acetylamino group.) The best method that was found, was to extract the impurities with alcohol, when the 2-methyl-4-hydroxy-6-acetylamino quinoline was obtained as a colourless residue. The method was wasteful, and the yield poor.

The product was unmelted at 300°C. It was insoluble in water, and sparingly soluble in alcohol, pyridine, and nitrobenzene. It dissolved in dilute mineral acids, or caustic soda. When boiled with sulphuric acid, acetic acid was evolved. It could be chlorinated in the manner indicated in the literature.

As the preparation of this product has not been satisfactory, it will not be considered further.

The ring closing of the crotonate was attempted in a manner similar to that described for ethyl B-phenylamino crotonate:-

17 gms. of Ethyl B-p-acetylamino phenylamino crotonate were heated for 20 minutes in 200 c.c. of liquid paraffin at 240° to 250°C. Alcohol was evolved, and the mixture was agitated. A brown tarry product was obtained.

ATTEMPTED CONDENSATION OF 4-PHENYLAMINO QUINALDINE METHIODIDE AND 5-ALDEHYDE ACRIDINE.

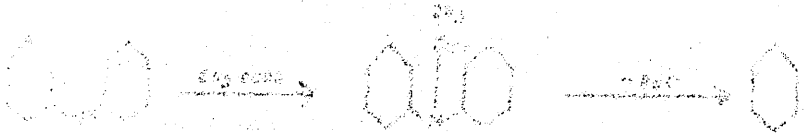
As it had been already found that 4(p-acetyl-amino phenylamino) quinaldine methiodide condensed less readily than 4-phenylamino quinaldine methiodide, experiments with 5-aldehyde acridine were confined to condensations with the latter substance and its methochloride.

In view of the fact that 4-phenylamino quinaldine methiodide did not condense with p-dimethylamino benzaldehyde in alcoholic solution, it was not surprising to obtain another negative result when attempts were made to condense it with 5-aldehyde acridine under similar conditions. As 5-aldehyde acridine does not lend itself to the fusion method of condensation, a solvent must be employed.

5 gms. of 4-phenylamino quinaldine methiodide.
5 gms. of 5-aldehyde acridine,(excess.)

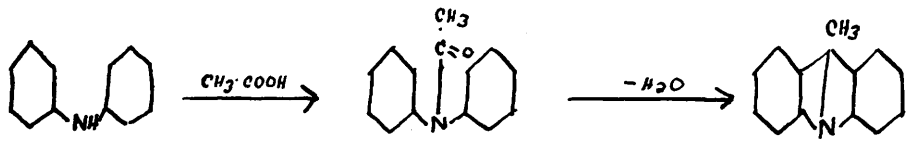
The reagents were dissolved in 40 c.c. of alcohol and 5 c.c. of water and six drops of piperidine added. The mixture was boiled for 10 hours on the waterbath in the usual manner. Nothing separated from the red solution on long standing, and most of the alcohol was distilled off. The residue was extracted with water, and lemon yellow needle-shaped prisms of the unchanged 4-phenylamino quinaldine methiodide were obtained, M.P. ca. 260°C.

SECTION IV. DERIVATIVES OF 5-ALDEHYDE ACRIDINE.



PREPARATION OF 5-METHYL ACRIDINE.

This compound was prepared by the method outlined by Bernsthen. Various modifications were made, and the yield improved from 56% up to 75% of the theoretical. There are many references available for the preparation of 5-methyl acridine, but few practical details. The following method is suitable for the preparation of large quantities of methyl acridine:-



169 193

700 gms. of diphenylamine.
1190 gms. of zinc chloride, (anhydrous.)
420 ccs. of glacial acetic acid.

The reagents were mixed in a large flask fitted with a ground-glass joint, and air-condenser having a water condenser fitted at its extreme end. A suitable thermometer was placed in the flask, the stem reaching up into the condenser. The sticks of zinc chloride were broken into small pieces, but not ground up. Gentle heating soon caused the reagents to go into solution, and the temperature was raised gradually to about 180° to 200°C., for the first hour. There was vigorous ebullition, and a slow stream of water was passed through the water condenser, so that the vapours were condensed without fear

of fracturing the glass. During the first five hours, the temperature does not generally rise much above 200° C., while the melt is greenish in colour. The temperature slowly rises to about 220° C. during the next five hours, and the reaction mixture loses its green tinge, and becomes brown in colour. Finally the temperature is allowed to rise to 220° to 240° C. for a further four hours, i.e. the melt is heated for 10 hours at 200° to 220°, and finally for four hours at 220° to 240° C.

The following modified procedure was adopted for isolating the product:-

After the 14 hours heating, the reaction mixture was allowed to cool a little, and then poured in a thin stream into 3 to 4 litres of cold water. The product was thus obtained in a comparatively finely divided state, but was broken up further, and left in contact with the water for a few days. This treatment removes large quantities of zinc chloride, while the methyl acridine remains undissolved. The water was decanted off, and the product ground up in a mortar, and extracted once again with tepid water to remove further quantities of zinc chloride. The product was then filtered off, and drained, and then extracted 5 to 8 times with warm 15% sulphuric acid. The red acid solution was made alkaline with ammonia, and the precipitated base allowed to consolidate. The base was finally filtered off, washed with water, and dried on porous plates in the air at room temperature and then over

sulphuric acid in a vacuum. It was found that drying the product at elevated temperatures in the air, caused slight darkening due to oxidation.

Yield, (crude), ca. 600 gms. (75% of theoretical)

The crude product thus obtained is liable to contain zinc oxide and diphenylamine, but further purification is not necessary if it has to be converted to 5-aldehyde acridine, as it condenses quite readily with p-nitroso dimethyl aniline, and the impurities are eliminated in the purification of the final product. The "tartrate method" devised by Koenig was found very satisfactory for the preparation of pure methyl acridine.

Purification of 5-Methyl Acridine.

100 Grammes of crude methyl acridine were dissolved in 400 c.c. of alcohol under reflux, and the solution filtered. Any Zinc oxide present remains undissolved, and is washed on the filter with a further 100 c.c. of hot alcohol, and the filtrates combined.) A solution of 100 gms. of tartaric acid in 1000 c.c. of alcohol was now added, and there was an immediate precipitation of the tartrate of 5-methyl acridine. The solution was allowed to cool, and the solid filtered off, drained, and washed with alcohol. It was found an advantage to boil the tartrate with water and animal charcoal, and recrystallise it from water at this stage. After this treatment, the

tartrate was obtained in sulphur-yellow crystals, which were filtered off, drained, and washed with a little alcohol. The melting point (153° to 154° C.) agrees with that quoted in the literature.

The base can be liberated by dissolving the tartrate in hot water and adding excess of dilute sodium hydroxide, or by making the tartrate into a cream with sodium hydroxide. Addition of sulphuric acid greatly assists the solution of the tartrate in water, and the base can be precipitated as before with solium hydroxide.

The yield depends on the initial purity of the base, but was usually about 90% of theoretical. The product obtained thus melted generally about 114° to 115° C.

The base can be further purified by crystallisation from alcohol.

Notes on the reaction:-

Acetic anhydride was tried instead of glacial acetic acid, but appeared to offer no advantage.

It was found impossible to precipitate the tartrate of 5-methyl acridine from an alcoholic extract of the crude melt.

PRINCIPAL REFERENCES.

Annalen, B. 224, 35 (1884) (Bernsthen).

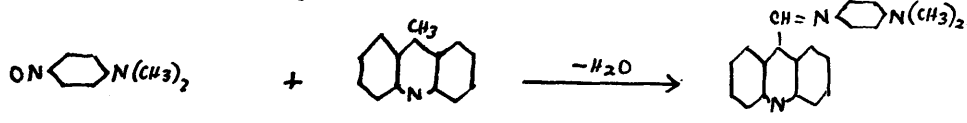
Ber. 32, 3607 (for tartrate method of purification).

Ber. 44, 2052 (Kaufmann).

PREPARATION OF 5 ALDEHYDE ACRIDINE.

This compound was first prepared by Bernsthen. A few years later, Kaufmann & Vallette prepared it by a different method, condensing methyl acridine and p-nitroso dimethyl aniline and hydrolysing the resulting anil. The method of Kaufmann was employed, and as few details are available in the literature, a full account of the preparation is given here, together with the modifications made and the yields obtained.

STAGE (1). Condensation of Methyl Acridine and p-Nitroso Dimethyl Aniline.



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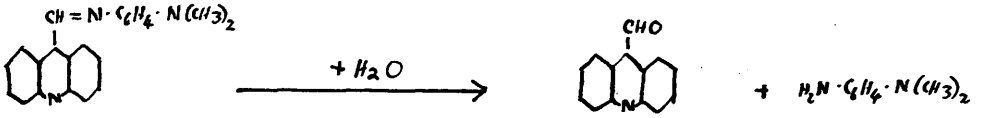
96.5 gms. of 5-methyl acridine and 75 gms. of p-nitroso dimethyl aniline were intimately mixed in a large evaporating basin, and gently heated, stirring vigorously. A dark green melt was obtained, and when the temperature reached 100° to 120° C., a reaction commenced, and heating was discontinued. The temperature rose of its own accord, and there was a brisk evolution of steam. Stirring was continued, and the melt soon began to solidify. (N.B. if the reagents are pure, the reaction can be quite violent, and care must be taken not to let the temperature rise too

much, or the product will be spoiled). A brownish-red cake was obtained, which was cooled, pulverised, and boiled under reflux with 200 ccs. of alcohol to extract impurities. The mixture was filtered hot, and drained well, and the insoluble anil washed on the filter with hot alcohol. The anil was thus obtained as a brick-red powder, melting between 235° and 237° C. (uncorrected). The melting point given in the literature is 234° C.

The yields were consistently about 60% of the theoretical (93 to 94 gms.).

STAGE (2). Hydrolysis of the Anil to 5-Aldehyde Acridine.



325 207

The anil was made into a paste with water, and dilute (5 N) hydrochloric acid added. The mixture first became black in colour, and on gentle warming and addition of a little concentrated hydrochloric acid a bulky, greenish-yellow, precipitate was obtained, which gradually became yellower in colour. The mixture was rapidly cooled, and the yellow precipitate of 5-aldehyde acridine hydrochloride filtered off, and washed with a little water. (The mother-liquor was deep red in colour.)

The hydrochloride was dissolved in hot water, and the solution filtered and made alkaline with dilute sodium hydroxide. A bulky, yellow, precipitate of the aldehyde was obtained, which was filtered off, washed with water, and spread on porous plates to dry. The product was rapidly dried by heating in a steam-oven for a short time, and the last traces of moisture removed in a vacuum desiccator, over concentrated sulphuric acid.

(Note. If the hydrochloride is greenish in colour instead of yellow, an impure brownish base is obtained on treatment with sodium hydroxide. It was found that if this precipitate was washed, and then stirred with dilute hydrochloric acid and the resulting precipitate of hydrochloride filtered off, washed, and treated with sodium hydroxide as before, the aldehyde precipitated in the pure yellow form, free from brown impurities.)

The yields for the hydrolysis were generally from 80 to 90% of the theoretical. Assuming a 60% yield of anil, and an 85% yield of aldehyde on hydrolysis, the yield for the two operations should be about 50%. That is, the yield of aldehyde calculated on the weight of methyl acridine taken initially should be about 50% of theoretical.

The yields obtained varied from 49 to 53% of theoretical (51 to 55 gms.)

Notes on the Reaction.

The product obtained by the method outlined above generally melted above 145° C., so that recrystallisation was not necessary. (Kaufmann & Vallette give the melting point as 148° C.) It is essential to wash the aldehyde well with hot water, till quite free of alkali.

As has been stated elsewhere, it was found that crude methyl acridine could be used for the preparation, so that the laborious purification by tartaric acid can be dispensed with.

Properties of 5-Aldehyde Acridine.

The aldehyde is readily soluble in alcohol, ether, nitrobenzene, and ethylene glycol monoethyl ether. Alcohol and ethylene glycol monoethyl ether are both suitable for recrystallisation of the aldehyde, and it separates also from nitrobenzene in long, yellow needles.

The sulphate of the aldehyde crystallises in yellow glistening needles, and is considerably less soluble in water than the hydrochloride.

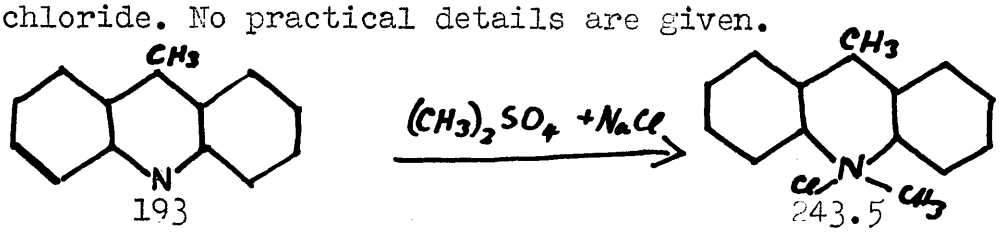
References.

Bernsthen & Muhlert, Ber. 20, 1541.

Kaufmann & Vallette, Ber. 45, 1737.

PREPARATION OF 5 METHYL ACRIDINE METHOCHLORIDE.

This compound was first prepared by Kaufmann & Albertini, by methylating methyl acridine with dimethyl sulphate , and precipitating the methochloride with sodium chloride. No practical details are given.



91 gms of methyl acridine , purified by the tartrate method , were warmed with excess of dimethyl sulphate. Between 60° and 70°C. a vigorous reaction took place and when this was over , the reaction mixture was left to cool. A solid mass was obtained, which was filtered off, and washed well with ether.

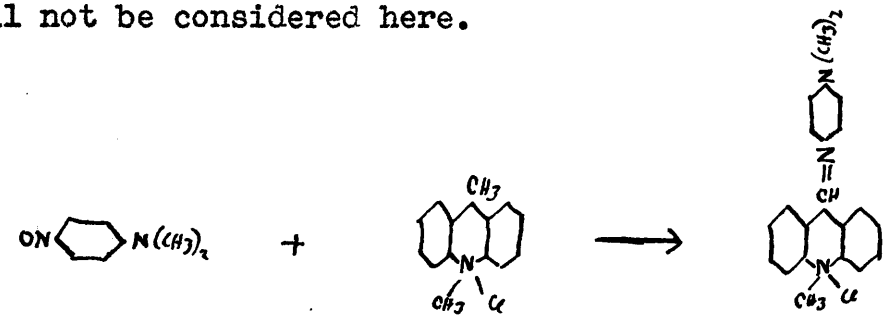
The yellow methosulphate was now dissolved in a little hot water , and the solution filtered , and a saturated sodium chloride solution added to precipitate the methochloride. The methochloride was filtered off, drained well, and washed with ether. It was then pressed on to a porous plate , and dried first in a steam oven , and then in a vacuum over concentrated sulphuric acid. When the product was thoroughly dry, it was extracted with alcohol, and the extracts boiled with charcoal, concentrated, and allowed to crystallise.

Yield, 85 gms. (75 % of theoretical.)

REFERENCE:- Kaufmann & Albertini, Ber. 44 , 2052.

ATTEMPTED CONDENSATION OF p-NITROSO DIMETHYLANILINE AND 5-METHYL ACRIDINE METHOCHLORIDE.

The reasons for undertaking this condensation have been fully discussed in the theoretical section, and will not be considered here.



150 243.5 375.5

37.5 gms. of p-nitroso dimethyl aniline, (theoretical quantity).
60.9 gms. of 5-methyl acridine methochloride.
200 c.c. of alcohol.

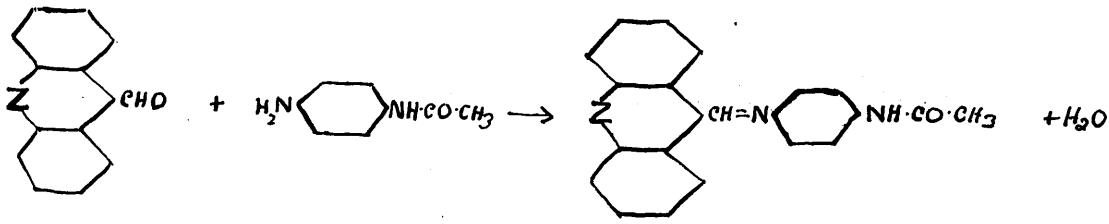
The reagents were dissolved in the alcohol, 7 drops of piperidine added, and the mixture boiled under reflux for five hours, on the waterbath. The flask and contents were then cooled, and allowed to stand overnight. A dark product separated, and was filtered off, drained well, and washed with alcohol.

Yield, 20 gms. of a blackish-brown product which contained no chlorine.

Since the compound obtained was not the desired anil, it was not examined further.

PREPARATION OF 5 (p-ACETYLAMINO ANIL)ACRIDINE.

This compound is new.



207 150 339

2.0 gms. of 5-aldehyde acridine.
1.9 gms. of p-amino acetanilide.
60 c.c. of alcohol.

The reagents were dissolved in the alcohol , a few drops of piperidine added , and the mixture boiled under reflux on the waterbath for an hour. Solid began to separate even while the mixture was hot. The product was allowed to stand overnight , and was then filtered off, and washed with alcohol.

Lemon-yellow needles were obtained, melting at 252° to 258°. The yield was 88 % , (3 gms.)

The anil was readily soluble in ethylene glycol mono ethyl ether , pyridine , and nitrobenzene, but did not separate in a well defined crystalline form from any of them. It was only moderately soluble in ethyl alcohol, amyl alcohol, and diacetone alcohol, but separated crystalline from all three.

It was insoluble in water, ether, and ethyl acetate.

A mixture of alcohol and pyridine was found to be suitable for the recrystallisation of the product. The anil was dissolved in the minimum quantity of pyridine , and the solution diluted about three times with boiling alcohol and filtered. The amber coloured solution was allowed to stand overnight, and the 5(p-acetylamino anil)acridine crystallised in lemon-yellow, well defined needles, which were filtered off, and washed with alcohol till quite free from pyridine. The product was finally dried in a vacuum desiccator over concentrated sulphuric acid.

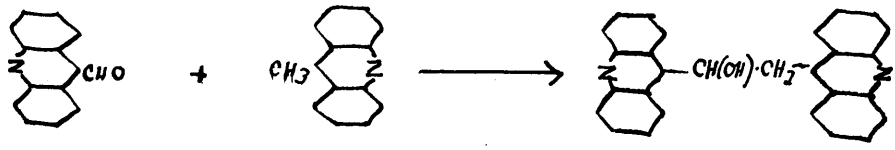
A specimine which had been twice recrystallised melted at 258°- 262°, (uncorrected.)

Analysis. $C_{22} H_{17} O N_3$ requires N 12.4 % .

Found :- N 12.5 % , 12.6 %.

CONDENSATION OF 5-ALDEHYDE ACRIDINE AND 5-METHYL-ACRIDINE.

When these reagents condense , it appears that an addition product is formed, and not an unsaturated ethene derivative.



207 193 400

10 gms. of 5-aldehyde acridine.
10 gms. of 5-methyl acridine, (excess.)

The reagents were dissolved in 60 c.c. of alcohol, and a few drops of piperidine were added to the brown solution obtained. The mixture was boiled under reflux on the waterbath for 6 hours, and then half of the alcohol was distilled off, and the reaction mixture allowed to stand overnight. A buff-coloured product separated, and this was filtered off, drained, and washed with alcohol.

Yield, (crude), 16 gms.

The product was recrystallised from pyridine containing a little water, and thoroughly washed with alcohol. Yellow, small needles were obtained, which were dried in a vacuum desiccator over concentrated sulphuric acid.

The crude product generally melted about 160°, but on recrystallisation the melting point was much higher,

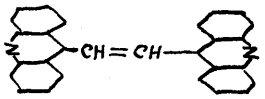
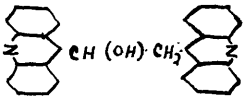
and specimens from different preparations had melting points which ranged from 160° to 184°. After drying in a vacuum desiccator, the melting point of all the products fell to 140° - 145°. This behaviour was attributed to solvent of crystallisation.

For analysis, the product was recrystallised from alcohol, and dried in a vacuum desiccator over sulphuric acid.

Analyses.

Two nitrogen estimations were performed , and the results were low when compared with the percentage of nitrogen required by the ethene compound. It was thought that perhaps the low results were due to solvent of crystallisation which had been retained in the desiccator, and the product was therefore heated at 100°C. in a vacuum oven, for 24 hours. After this treatment the nitrogen was estimated again, but the value found was similar to that obtained before heating. The compound was finally subjected to two complete micro analyses, and from the results obtained, it appears that the product contains a molecule of water of constitution.

The analyses have been tabulated, together with the percentage composition of the ethene compound and the addition product.

		C%.	H%.	N%.	O%.	Total.
1.	 requires	87.9	4.7	7.3	-	99.9
2.	 requires	84.0	5.0	7.0	4.0	100.0
3.	Nitrogen estimation, (a) (b)	-	-	7.1 7.1	-	-
4.	Nitrogen estimation, after heating sample at 100° for 24 hours in a vacuum.	-	-	7.0	-	-
5.	"Micro" analysis.	84.1	4.9	7.2	3.8*	100.0
6.	"Micro" analysis.	84.0	5.1	7.3	3.6*	100.0

* (Percentage of oxygen by difference.)

From the analyses 3,4,5, and 6, it appears that the compound has a formula corresponding to 1. The molecule of water does not appear to be present as solvent of crystallisation, since it could not be removed by prolonged heating in a vacuum at 100°C.

No evidence of unsaturation could be obtained on bromination of the product.

The physical properties of the compound, and of its salts and quaternary ammonium derivatives, were unsuitable for therapeutic tests; so that the compound will only receive brief consideration here.

The product was soluble in alcohol, but dissolved very gradually. It was soluble in ethylene glycol monoethyl ether, and very readily soluble in pyridine. It crystallised best from the last of these solvents.

The alcoholic solution of the product did not give a precipitate with tartaric acid, and the salts formed with mineral acids were all very sparingly soluble.

The compound could be methylated with dimethyl sulphate, but as the product obtained was not readily soluble it was not investigated further.

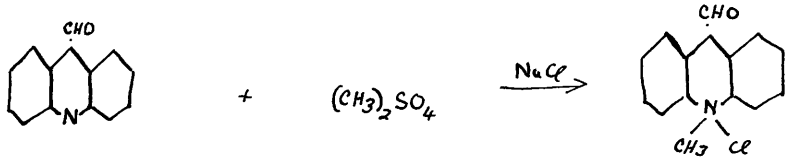
PREPARATION OF 5-ALDEHYDE ACRIDINE METHOCHLORIDE.

This compound is new , and was prepared by methylating 5-aldehyde acridine with methyl sulphate, and treating the methosulphate obtained with sodium chloride. Considerable difficulty was experienced in methylating the aldehyde acridine, and several experiments were performed to determine the best methods and conditions.

It was found that it was better to dispense with a solvent, such as nitrobenzene or ethylene glycol monoethyl ether, when methylating with dimethyl sulphate, as these solvents gave supersaturated solutions from which the methylated aldehyde did not separate.

It was found also , that it was essential to have the aldehyde quite pure and dry before attempting to methylate it , as even the smallest trace of impurity upset the reaction. The aldehyde used was always recrystallised from alcohol.

Methylation of the aldehyde by means of methyl iodide in nitrobenzene solution was found to be useless.



207 126 257.5

10 Grammes of pure 5-aldehyde acridine were made into a paste with 20 c.c. of methyl sulphate, (large

excess), and the temperature gradually raised to 70°, when a reaction commenced and the aldehyde started to dissolve. Heating was discontinued, and the temperature rose spontaneously to about 130°, and a brown solution was obtained. The temperature was maintained at 100°for quarter of an hour, and towards the end of this time , solid began to separate from the hot reaction mixture. The product was cooled , and allowed to stand overnight; it was then filtered off, drained well, and washed with ether till free from methyl sulphate. The crude 5-aldehyde acridine methosulphate thus obtained was boiled under reflux with purified absolute ether, to remove traces of dimethyl sulphate, and any unchanged aldehyde acridine, and after a few extractions was filtered off, and dried in a vacuum desiccator.

The 5-aldehyde acridine methosulphate formed golden yellow crystals. The yield was about 80 %.

The methosulphate was dissolved in a little hot water, in which it was readily soluble, and a saturated sodium chloride added . The methochloride precipitated immediately, and after standing for some time was filtered off, and washed with a little cold water. The crude methochloride thus obtained contained sodium chloride ; it was recrystallised from water and dried in a vacuum desiccator, and by this treatment was obtained nearly pure.

The 5-aldehyde acridine methochloride was further purified for analysis by recrystallising once more from water, then from alcohol, and finally from water again.

Golden yellow needle shaped prisms were obtained , which started to darken at 165°, and melted indefinitely at 173° - 176°, with decomposition and escape of gas.

The aldehyde crystallised with two molecules of water.

$C_{15} H_{12} O N Cl \cdot 2 H_2 O$ requires N 4.8 %.

Found :- N 4.8 % , 4.9 % .

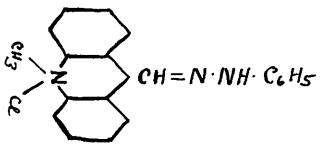
On recrystallising the product once again, found N 4.9 %

The product did not lose its water of crystallisation in a vacuum desiccator over concentrated sulphuric acid, and when an attempt was made to drive it off in a steam oven , it was found that the aldehyde decomposed.

5-Aldehyde acridine methochloride is insoluble in ether , and sparingly soluble in ethyl acetate. It dissolves readily in water and in ethyl alcohol, giving yellow solutions , which both deposit crystals on cooling.

The aldehyde forms a violet precipitate with phenylhydrazine, and a red precipitate with 2-4 dinitro phenylhydrazine. It forms a bisulphite compound , giving a precipitate with saturated sodium bisulphite solution, and reduces ammoniacal silver nitrate and Fehling's solution.

PREPARATION OF THE PHENYLHYDRAZONE OF 5-ALDEHYDE ACRIDINE METHOCHLORIDE.



347.5

5.0 gms. of 5-aldehyde acridine methochloride.
3.5 gms. of phenylhydrazine hydrochloride,(excess).

The aldehyde was dissolved in 30 c.c. of hot water, and added to a solution of the phenylhydrazine in 30 c.c. of hot water. There was an immediate precipitation of violet-blue crystals , and these were filtered off and washed with cold water. The product was recrystallised from alcohol, and the crystals filtered off , drained , and washed with cold alcohol. The yield was 70 % of the theoretical.

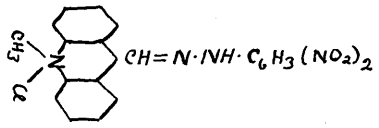
For analysis, 4.0 gms. of the purified product were recrystallised from 20 c.c. of alcohol , and dried in a vacuum desiccator over sulphuric acid.

Violet-blue crystals were obtained, with a reddish , metallic lustre. They started to darken about 140° , and melted indefinitely about 190°.

The product was insoluble in ether , but readily soluble in alcohol or water forming violet solutions.

$C_{21}H_{18}N_3Cl$ requires N,12.1 %. Found N, 12.1 ; 12.1 %.

PREPARATION OF THE 2.4-DINITRO-PHENYLHYDRAZONE OF 5-ALDEHYDE ACRIDINE METHOCHLORIDE.



437.5

2.5 gms. of 5-aldehyde acridine methochloride.
2.5 gms. of 2.4 dinitrophenylhydrazine,(25 % excess.)

The dinitrophenylhydrazine was dissolved in hot water and a little dilute hydrochloric acid, and the solution filtered and added to an aqueous solution of the aldehyde. A red precipitate was obtained immediately , and was filtered off from the hot solution and washed with hot water. The product was now extracted twice with hot alcohol, by boiling under reflux, and thus freed from unchanged starting materials. As no more suitable solvent could be found , the phenylhydrazone was recrystallised from boiling alcohol in which it was only moderately soluble. The product was finally filtered off, washed with alcohol , and dried in a vacuum desiccator over sulphuric acid.

A dull red powder was obtained , which appeared to absorb moisture from the air and became lighter in colour. The melting point was indefinite, but was about 180°.

The product was insoluble in ether, and almost insoluble in alcohol and ethyl acetate.

C_{21} H_{16} O_4 N_5 Cl requires N, 16.0 %. Found N,16.1;16.1 %.