A MECHANISTIC STUDY OF THE NUCLEOPHILIC AROMATIC SUBSTITUTION OF SOME SUBSTITUTED 10-METHYLACRIDONES

A THESIS

PRESENTED FOR THE DEGREE OF

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UNIVERSITY OF ADELAIDE

by

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CONTENTS

STATEMENT

The work described in this thesis incorporates no material previously submitted for a degree in any University and, to the best of my knowledge and belief, contains no material previously published or written by another person except where due reference is made in the text.

(Daryl K. C. Hodgeman)

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Finally, I wish to thank the Department of Supply for granting leave during which this work was carried out.

SUMMARY

This thesis is presented in four parts.

In Part I the preparation and some of the properties of the mono-bromo-, amino-, and piperidino-10-methylacridones, most of which are new compounds, are described.

In Part II the reactions of the isomeric bromo-10-methylacridones with potassamide and with lithium piperidide are described. Reaction of 2- and 4-bromo-10-methylacridone occurs via aryne intermediates and rearranged products are observed. Reaction with 1- and 3-bromo-10-methylacridone generally occurs by the addition-elimination mechanism and no rearranged products are observed. The reaction of 1-bromo-10-methylacridone with potassamide is exceptional and the acridone nucleus is cleaved at the carbonyl group in a Haller-Bauer-type reaction. 10-Methylacridone is observed as a significant by-product in many of these reactions.

In Part III the reactions of the bromo-10-methyl-acridones with sodium methoxide are described. With sodium methoxide in methanol-free dimethyl sulphoxide 1- and 3-bromo-10-methylacridone undergo substitution by the addition-elimination mechanism and substitution occurs

faster in the 3-position than in the 1-position. With sodium methoxide in methanol the bromo-10-methylacridones are reduced to 10-methylacridone and this has been found to occur by a free radical mechanism.

In Part IV the reactions of some polyalkoxy-10-methylacridones with sodium methoxide are discussed. With sodium methoxide in methanol the dimethoxymethylenedioxy-10-methylacridones undergo nucleophilic attack at both aromatic and side chain carbon leading to a variety of products. With sodium methoxide in methanol-free dimethyl sulphoxide substitution occurs entirely by the addition-elimination mechanism on aromatic carbon and the rates of methylenedioxy ring-opening of the different dimethoxymethylenedioxy-10-methylacridones have been measured. An hypothesis is proposed to explain the observed results. With polyalkoxy-10-methylacridones nucleophilic substitution by methoxide ion is found to occur faster in the 1-position than in the 3-position.

INTRODUCTION

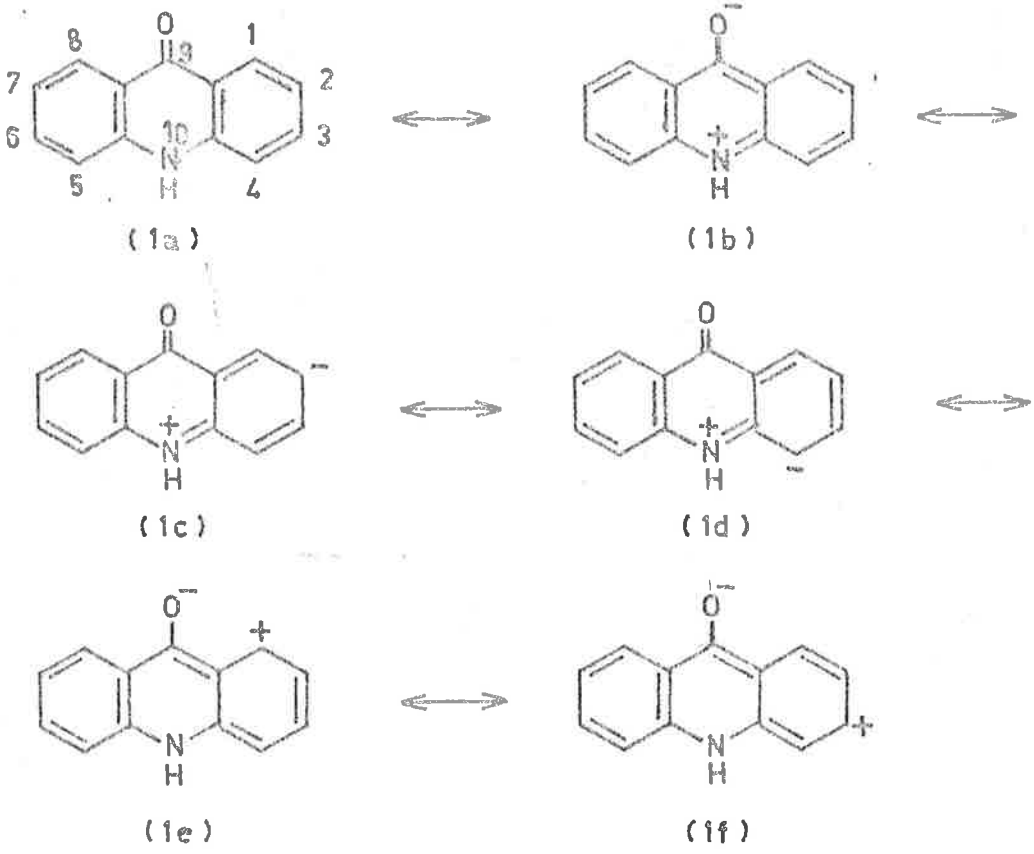
Substitution reactions in aromatic compounds have been known for a long time and the mechanisms by which these reactions occur have been the subject of extensive study. Aromatic substitution reactions fall into three principal mechanistic types - nucleophilic, electrophilic, and free radical substitution. Each of these different types of substitution is characterized by a different type of attacking species and in each case the ease of substitution depends on a number of factors governed both by the nature of the substrate and by the nature of the attacking species.

In nucleophilic substitution it is the negative pole of the attacking species, the nucleophile, which attacks the aromatic ring system. Nucleophiles are generally anions or species with a lone pair of electrons so that substitution occurs most readily at sites of low π-electron density. In electrophilic substitution it is the positive pole of the attacking species, the electrophile, which attacks the aromatic ring so that electrophilic substitution is favoured at sites of higher π-electron density. In free radical substitution the attacking species is a free radical.

The influence of substituents already present in the aromatic substrate on the direction and rate of substitution by all three mechanisms has been extensively studied over many years. Both mesomeric and inductive effects influence the direction and rate of substitution, particularly in nucleophilic and electrophilic aromatic substitution reactions. Generally mesomeric effects are considerably more important than are inductive effects. Sometimes special effects such as steric crowding and hydrogen bonding also influence the direction and rate of substitution. Nucleophilic aromatic substitution, since it involves attack by a negative species, is favoured by electron-withdrawing substituents in the aromatic ring, particularly in the positions ortho- and para- to the site of substitution, and is retarded by electron-donating substituents, again particularly when these substituents are situated ortho- or para- to the site of substitution. Conversely, electrophilic substitution, since it involves attack by a positive species, is favoured by electron-donating substituents and is retarded by electron-withdrawing substituents, again particularly when these substituents are situated ortho- or para- to the site of substitution.

An examination of the canonical forms (Scheme 1) contributing to the structure of acridone (1a) indicates

the π-electron densities on the benzenoid carbon atoms alternate from one position to the next, the 2- and the 4-positions*, and the corresponding positions in the



SCHEME 1

* The I.U.P.A.C. system of numbering the acridine (and acridone) nucleus is used throughout this thesis. This numbering system is illustrated in formula (1a) in Scheme 1. Other numbering systems which have been used in the past and now appear less frequently are discussed by Albert[1a].

other benzenoid ring, having a higher π-electron density than the 1- and the 3-positions. This alternation of π-electron density in the benzenoid rings of acridone is further substantiated by Hückel molecular orbital calculations[2] which give for acridone the π-electron densities shown in Fig. 1.

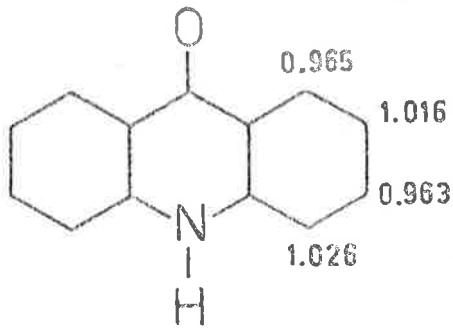
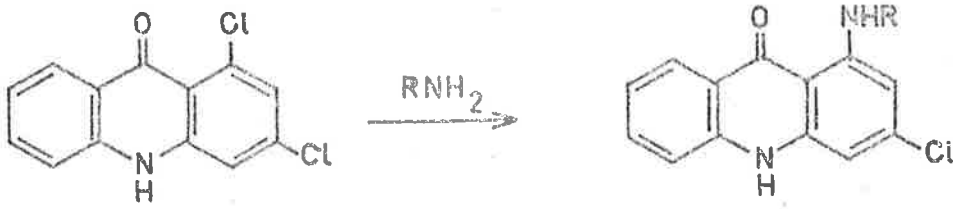


FIG. 1

The higher π-electron densities at the 2- and the 4-positions suggest that these would be the sites of electrophilic substitution and, indeed, this is borne out by experiment. Bromination[3,4,5] and nitration[6], both aromatic electrophilic substitution reactions, of acridone and 10-methylacridone have been well studied and substitution is found to occur preferrentially in the 2- and 4-positions and also in the corresponding positions in the other benzenoid ring.

The lower π-electron densities at the 1- and the 3-positions suggest that, if suitable leaving groups

are present, these will be the sites of attack by nucleophiles. Again this expectation is borne out by experiment. A number of instances of nucleophilic substitution of halogen in 1- and 3-halogenoacridones by hydroxide ion and by amines have appeared in the literature[7-11]. 1,3-Dichloroacridone (2) has been found to react[9] with the primary amine (4) by nucleophilic substitution only in the 1-position giving the disubstituted acridone (3). Thus, with primary amines,

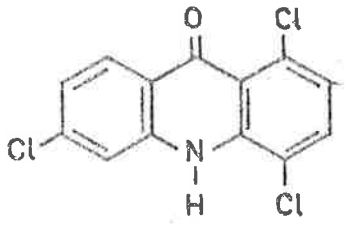


(2) (3)

(4) $RNH_2 = (C_2H_5)_2NCH_2CHOHCH_2NH_2$

substitution of chlorine appears to occur very much faster in the 1-position than in the 3-position of the acridone nucleus. 1,4,6-Trichloroacridone (5) behaves in a similar manner[9] and undergoes nucleophilic substitution only in the 1-position with the amine (4). Substitution of chlorine in the 3-position by ammonia has been achieved [11] but requires far more forcing conditions

than does substitution of chlorine in the 1-position by primary amines. In addition substitution of the 3-chlorine by ammonia required the use of copper sulphate as catalyst and it is possible that this substitution proceeds by a free radical mechanism rather than by nucleophilic substitution.



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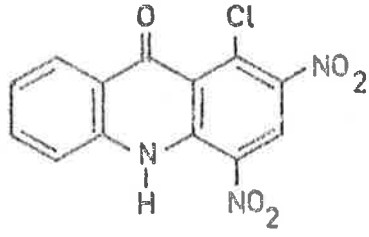


(6)

1-Chloro-2,4-dinitroacridone (6) reacts with hydroxide ion[7] giving the corresponding 1-hydroxy compound, 1-hydroxy-2,4-dinitroacridone. However, in this case the activating influence of the acridone carbonyl group would be insignificant compared to the powerful electron-withdrawing effects of the two nitro groups so that this substitution does not reflect the activating influence of the acridone carbonyl group.

Nucleophilic substitution by alkoxide ion has been observed in reactions of the acridone alkaloids with alcoholic solutions of potassium hydroxide. The two naturally occurring dimethoxymethylenedioxy-10-methyl-acridones melicopidine (7) and melicopine (9) have both

been observed to undergo nucleophilic substitution in the 3-position on reaction with alcoholic potassium hydroxide[12]. Reaction of melicopidine (7) and melicopine (9) with alcoholic potassium hydroxide results in ring-opening of the methylenedioxy ring with formation of the phenols (8) and (10) respectively.

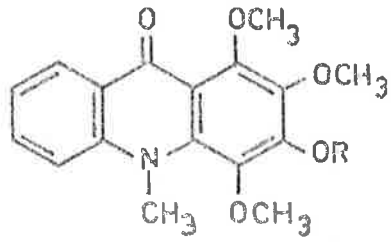
(7) (8)

(9) (10)

Melicopine (9) has also been observed to undergo nucleophilic substitution in the 1-position since on treating with sodium ethoxide in ethanol a mixture of the 3-ethoxy and 1,3-diethoxy derivatives of the phenol (10) has been obtained[13].

Similar observations have been made in the reaction of the alkaloid melicopicine (11) with ethanolic potassium

hydroxide[14] where, among other products, some of the 3-ethoxy derivative of melicopicine, 3-ethoxy-1,2,4-trimethoxy-10-methylacridone (12), was obtained. No indication is given in the literature whether or not substitution also occurs in the 1-position.



(11) R = CH_3

(12) R = CH_2CH_3

Although a number of instances of nucleophilic substitution occurring in substituted acridones have appeared in the literature, and there is ample evidence that nucleophilic substitution occurs preferrentially in the 1- and 3-positions, most of the past work has been directed towards the synthesis of substituted acridones or towards elucidation of the structure of naturally occurring substituted acridones. No detailed study of the effects of the acridone system on aromatic nucleophilic substitution have appeared in the literature. In particular, no rate data for nucleophilic substitution with various nucleophiles in the 1- and 3-positions of substituted acridones is available and no studies of the nucleophilic substitution reactions of the halogenated acridones with strong bases, where aryne intermediates are

a possible feature, have appeared. It was towards these ends that the present research was directed.

Before proceeding further it is pertinent at this stage to consider the mechanisms by which nucleophilic substitutions occur in aromatic compounds. Unlike aromatic electrophilic substitution, where hydrogen (as the proton) is the usual leaving group, hydrogen (as hydride ion) is rarely displaced in aromatic nucleophilic substitution. Hydride ion acts as a leaving group in nucleophilic substitution only in cases where considerable activation exists as in the methylation of aromatic compounds with the methylsulphinylcarbanion[15,16] and related carbanions[17] and in aminations of aromatic compounds with hydroxylamine[18]. Nucleophilic substitutions involving displacement of hydride ion are also known to occur under oxidizing conditions and these are discussed in detail by Bunnett and Zahler[19] and by Miller[20]. The first essential feature for facile aromatic nucleophilic substitution is, therefore, a suitable leaving group which can be displaced either as a neutral molecule or as a relatively stable anion. The most common leaving groups employed in aromatic nucleophilic substitution are the halide ions, although many other substituents are successful, and sometimes better, leaving groups.

There are two principal mechanisms by which nucleo-

philic substitution occurs in aromatic compounds:

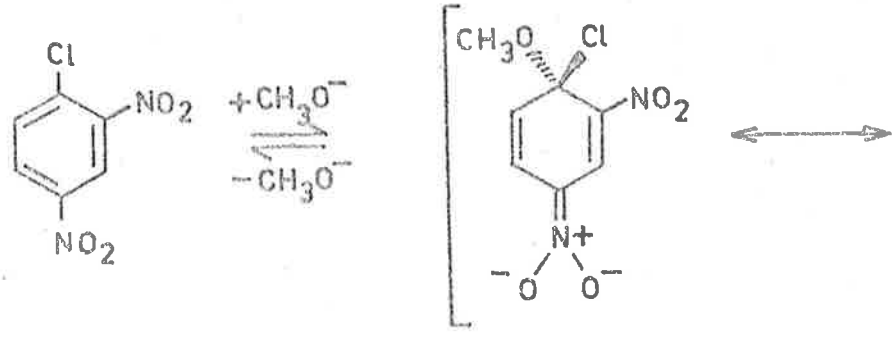
(1) the addition-elimination (AE) mechanism, (vide infra), which is favoured when suitably oriented activating groups are present, and

(2) the elimination-addition (EA) mechanism, (vide infra), which occurs in the presence of strong bases which generally also act as the nucleophile.

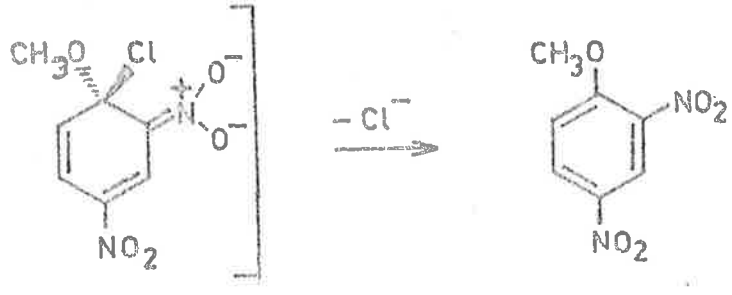
The field of aromatic nucleophilic substitution has been well reviewed for reactions occurring by both the addition-elimination mechanism[19-25] and for reactions occurring by the elimination-addition mechanism[26-30]. The most extensive reviews dealing principally with substitutions occurring by the addition-elimination mechanism are those of Bunnett and Zahler[19] and of Miller[20] and the most extensive review of substitutions occurring by the elimination-addition mechanism is that of Hoffmann[26]. A recent review dealing with nucleophilic substitution reactions occurring by both mechanisms and also photonucleophilic substitution reactions is that by Pietra[40]. Only a brief discussion of the two mechanisms and their principal features would appear pertinent in the present discussion.

Nucleophilic substitution in aromatic compounds occurs by the addition-elimination mechanism when suitable electron-withdrawing substituents are situated

ortho- or para- to the leaving group in the substrate. Perhaps the most familiar example of this type of substitution reaction is the methoxydechlorination of 1-chloro-2,4-dinitrobenzene with methoxide ion and this is a suitable reaction to illustrate the pathway of the addition-elimination substitution mechanism in general. The nucleophile, methoxide ion, attacks 1-chloro-2,4-dinitrobenzene at C-1 (Scheme 2) entering from above the plane of the aromatic ring forming the resonance stabilized intermediate (13a↔13b) in which the orbital hybridization at C-1 has changed from sp^2 to sp^3. There is ample



(13a)

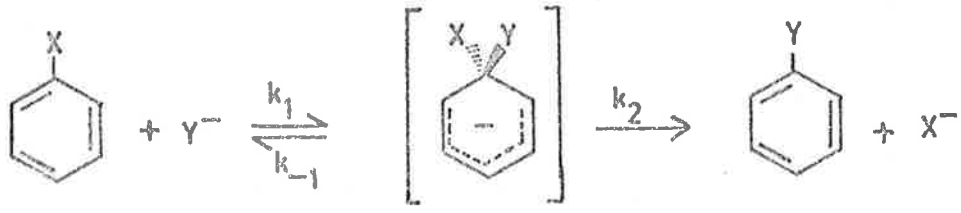


(13b)

SCHEME 2

evidence[23] that the species (13) is an intermediate in the reaction and not merely a transition state. Indeed, many compounds with structures analogous to that of the species (13), the so-called Meisenheimer complexes, have actually been isolated as crystalline salts or have been detected by spectroscopic methods[31,32]. The formation of Meisenheimer complexes under the conditions generally employed for nucleophilic aromatic substitution does not, however, prove the intermediacy of these complexes in the substitution reaction but does provide excellent evidence that they may participate as intermediates in the reaction. Elimination of chloride ion from the intermediate (13) gives 2,4-dinitroanisole.

Substitution by the addition-elimination mechanism is a two-step process involving two transition states and an intermediate of some stability. Either the first or the second step may be rate determining. However, with good leaving groups and with good nucleophiles the first step, attack by the nucleophile on the aromatic compound to give an intermediate analogous to the species (13), is generally the slow step. In cases where the first step is the rate determining step the reaction follows simple second order kinetics. The free-energy profile for such a reaction is illustrated in Fig. 2. Not all substitutions occurring by this mechanism are as straight forward as the



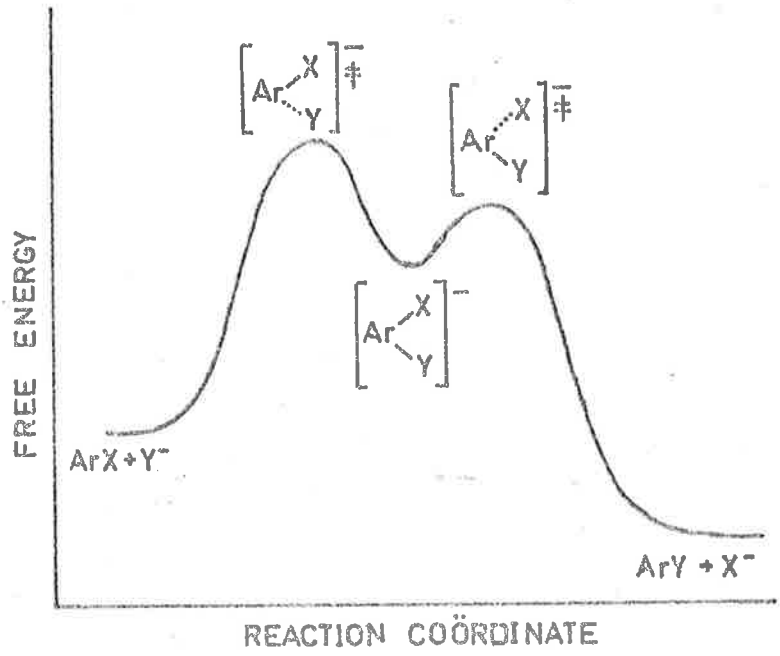
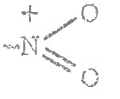


FIG. 2

simple description given above and a range of mechanisms may be possible, depending on the number and type of activating groups present, the nature of the nucleophile, and the nature of the leaving group. Nucleophilic substitution by the addition-elimination mechanism often exhibits kinetics more complex than the second order kinetics mentioned above and this is particularly the case when amines are used as the nucleophile.

The most common leaving groups in aromatic nucleophilic substitution, and those of particular importance in the present work, are the halide ions. The rate of the substitution reaction is found to depend on the nature of the halogen used as the leaving group and, with nucleophiles for which the nucleophilic atom is in the first horizontal row of the Periodic Table the rate of substitution is found to be in the order[20a] F > Cl > Br > I. Any group which is able to form a reasonably stable anion may function as a leaving group so that alkoxy groups, also of importance in the present work, may also serve this purpose. Many other substituents may also act as leaving groups and are discussed in detail by Bunnett and Zahler[19] and by Miller[20].

A large number of electron-withdrawing substituents in the positions ortho- and para- to the leaving group may act as activating groups for nucleophilic substitutions occurring by the addition-elimination mechanism and are discussed in detail by Miller[20b]. Relevant to the present work are Miller's Class 3 substituents[20c], those electron-withdrawing substituents which have multiply bonded atoms conjugated with the aromatic ring and able to withdraw electrons from the site of attack by the nucleophile. Typical examples of these groups are the nitro (), the acyl (), the cyano (-C≡N), and

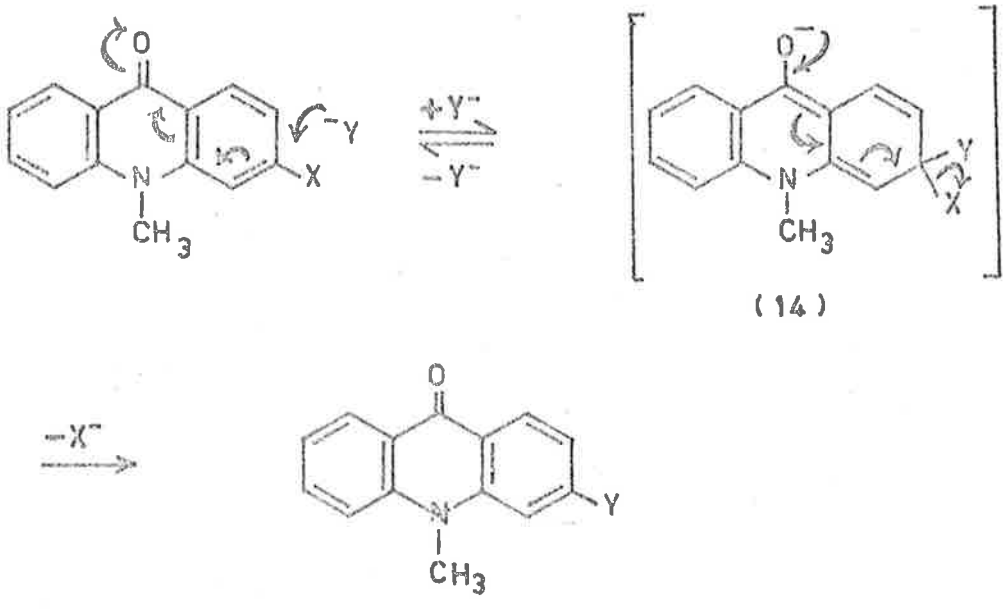
the nitroso (-N=O) groups. When these substituents are situated ortho- or para- to the leaving group they are able, by virtue of their -M effects, to withdraw electrons from the site of nucleophilic attack. The activating influence of these groups depends, of course, on the magnitude of the -M effect. It is found for the following substituents in the para- position that the activation for reaction of the aryl chloride 1-chloro-2-nitro-4-X-benzene with methoxide ion in methanol is in the relative order[20d] $NO_2 \gg COPh > CONH_2$. With activating substituents in the position ortho- to the leaving group special proximity effects often come into play and have considerable effects on the rate of reaction. These proximity effects include relief of steric strain in formation of the first transition state, which closely resembles the intermediate typified by the species (13), and stabilization of the transition state by hydrogen bonding or internal solvation[23, 33,34,35] with the ortho- activating group. This latter effect is particularly marked in the reactions of primary and secondary amines with ortho- substituted substrates. Relief of steric strain in positions remote from the site of nucleophilic attack has also been found to influence the rate of reaction[36]. In cases where no special steric or hydrogen bonding effects occur with the ortho- activating group it is generally found that the same substituent

has a greater activating influence in the para- position than in the ortho- position. This is attributed to the greater conjugative effect of the substituent in the para-position[20e]. In cases where the inductive effect is more important than the mesomeric effect a substituent in the ortho- position has the greater effect[20e].

Having discussed the principal features of aromatic nucleophilic substitution by the addition-elimination mechanism it is now pertinent to consider the influence of the acridone system as an activating group in this type of substitution reaction. As shown in the canonical forms (1e) and (1f) (Scheme 1) which contribute to the structure of acridone the mesomeric effect of the acridone carbonyl group lowers the π-electron density at the 1- and the 3-positions. As stated previously, these positions are expected to be the sites of attack by nucleophiles. The reaction pathway for nucleophilic substitution in the 3-position of a 3-substituted 10-methylacridone is illustrated in Scheme 3. The intermediate (14) is analogous to the intermediate (13) in the methoxydechlorination of 1-chloro-2,4-dinitrobenzene (Scheme 2).

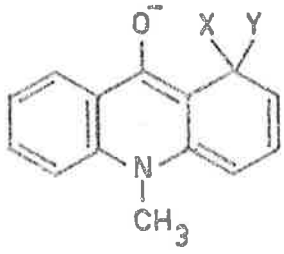
Nucleophilic substitution in the 1-position of 1-substituted acridones occurs by a pathway analogous to that shown in Scheme 3 and involves intermediates typified by the general structure (15). The acridone carbonyl

group is essentially a substituent situated ortho- to the 1-position so that the special proximity effects mentioned above may influence the rate of substitution



(14)

SCHEME 3



(15)

in this position. It is evident that this occurs from the reaction of 1,3-dichloroacridone (2) with the primary amine (4) mentioned previously where substitution occurs exclusively in the 1-position. The activating effect of

the acridone carbonyl group due to its -M effect would be expected to be of similar magnitude in both the 1- and 3-positions so that this greatly enhanced relative rate of substitution by primary amines in the 1-position must be due to one of the proximity effects mentioned above. This question of special ortho- activation in the reaction of 1-substituted acridones with amines will be discussed in more detail in Part II.

We now come to the question of the magnitude of the activating effect of the acridone system on nucleophilic substitution in the 1- and 3-positions. The acridone carbonyl group comes under Miller's Class 3 activating substituents which have been discussed above. It is therefore of interest to compare the activating effects of the acridone carbonyl group with those of other Class 3 substituents. Due to resonance of the type (1a ↔ 1b) (Scheme 1) the electron-withdrawing effect of the acridone carbonyl group is somewhat reduced compared to the electron-withdrawing effect of the carbonyl group in, say, benzophenone where this type of resonance does not occur. There is considerable evidence[1b,37] that a significant proportion of the zwitterionic canonical form (1b) contributes to the resonance hybrid of acridone. The activating effect of the acridone carbonyl group would, therefore, more closely resemble that of the amide group

($-CONH_2$) than that of the acyl group (-COR). Indeed, acridone can be regarded as a vinylogous amide[1c,38]. As has been mentioned above the amide group is a weak activating substituent for nucleophilic substitution and is weaker than the acyl group and very much weaker than the nitro group. It follows that the acridone carbonyl group would also be expected to be a weak activating group for substitutions occurring by the addition-elimination mechanism. This is borne out by the results described in this thesis where, in many cases, alternative reaction pathways compete with nucleophilic substitution in the 1- and 3-positions.

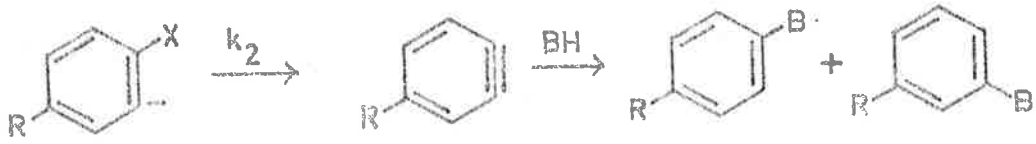
One further site for attack by nucleophiles is the acridone carbonyl group. This will form the species (16) in a reversible reaction which will generally lead to no change in the acridone molecule. This equilibrium

(16)

is not established with hydroxide ion since the carbonyl oxygen of acridone is not exchanged with O^{18}-labelled hydroxide ion[39].

The other principal mechanism by which nucleophilic substitution occurs in aromatic compounds is the elimination-addition (or aryne) mechanism. In substitutions occurring by this process the new substituent is found not only in the position originally occupied by the leaving group but also in the positions ortho- to this site. Substitutions of this type resulting in rearrangement to the ortho-position are termed 'cine-substitutions'. Nucleophilic substitutions by this mechanism require the use of a strong base and, in this instance, occur only when hydrogen is adjacent to the leaving group. This reaction proceeds for aryl halides by elimination of hydrogen halide to give an intermediate aryne (18) (Scheme 4). The nucleophile (B^-), or the conjugate acid

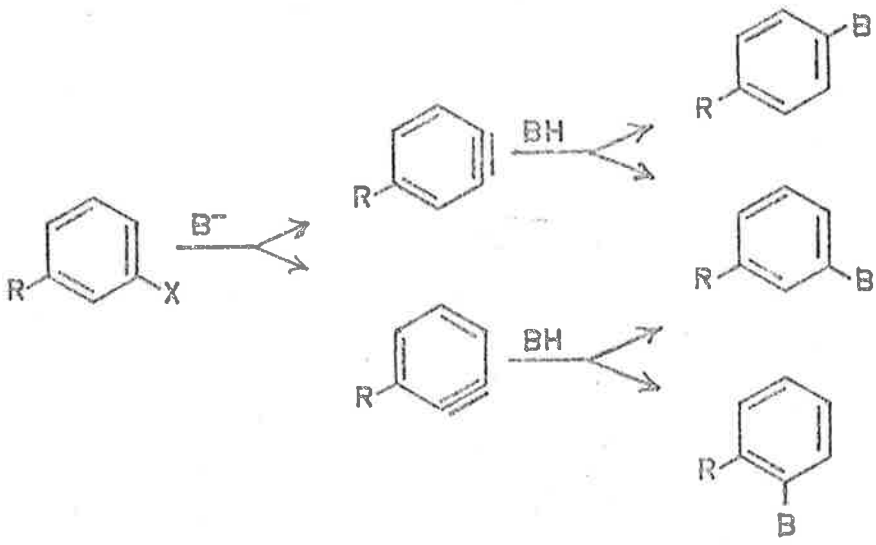
(17)



(18) (19) (20)

SCHEME 4

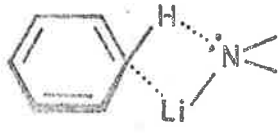
of the nucleophile (BH), then attacks at either end of the formal triple bond of the aryne giving the unrearranged product (19) and the rearranged product (20). Ortho- and para-substituted aryl halides form only one aryne and may lead to two substitution products. Meta-substituted aryl halides form two arynes (Scheme 5) which in turn lead to three possible substitution products. Substitutions of this type may be divided into two



SCHEME 5

distinct processes, first elimination of hydrogen halide via the carbanion (17) to give the aryne (18) and, second, addition of the conjugate acid of the base or, indeed, any other nucleophile present, to the aryne to give the substitution products. The factors affecting these two processes will be briefly discussed separately.

The first factor that will be considered is the nature of the base. Since aromatic hydrogen is only weakly acidic strong bases are required. These include organometallic compounds such as phenyllithium and butyllithium and the metal amides such as potassamide, lithium piperidide and lithium diethylamide. The reactions with these bases are generally carried out in ethereal solvents or, with the metal amides, in the free amine as solvent. Although phenyllithium is far more basic than the dialkylamides the latter bases are found to react considerably faster with bromobenzene than phenyllithium[41]. This is attributed to assistance by the lone pair of electrons on nitrogen in removal of the proton as shown in formula (21)[41]. Reaction of aryl bromides with dialkylamides is



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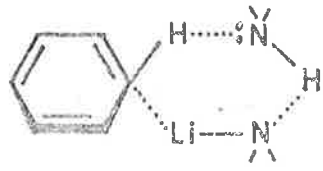


(22)

observed to be catalyzed by the free amine and the transition state for this assisted metalation is visualized in formula (22)[41]. The metalation of aryl halides is not subject to severe steric requirements neither from the standpoint of the substrate[42] nor of the metalating agent[26a].

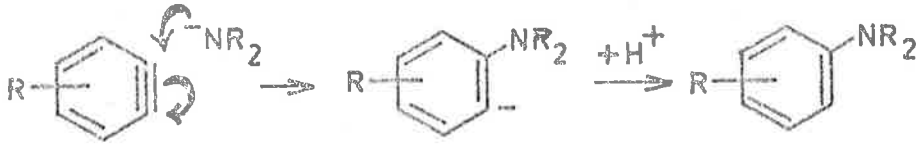
The most common leaving groups in elimination-

addition substitution reactions with strong bases are the halide ions although other leaving groups have been used and are discussed by Hoffmann[26]. The nature of the halogen will affect two steps in the reaction (Scheme 4), formation of the o-halogenoaryl anion (17) and formation of the aryne (18). The different halogens are expected to have opposing effects on each of these processes. First, formation of the carbanion (17) involves removal of a proton from the aryl halide by attack of the strong base from within the plane of the aromatic ring. The acidity of the ortho- hydrogen depends on the electronegativity of the adjacent halogen so that the rate of formation of the carbanion (17) from the aryl halide is, therefore, in the order[28] F > Cl > Br > I. The second step involves loss of halide ion and the expected sequence for this process is[28] I > Br > Cl > F. In the case of aryl fluorides k_1 (Scheme 4) is very much greater than k_2 so that these compounds very rapidly exchange ortho-hydrogen but only very slowly form the aryne. With aryl bromides k_2 is considerably greater than k_1 so that formation of the aryne from these compounds is a near synchronous process. Aryl chlorides are intermediate in reactivity and the aryne forms in a distinct two-step process.

When arynes are generated from the aryl halide

with a strong base as described above the aryne is formed in the presence of a strong nucleophile with which it rapidly reacts. This presents little opportunity for study of the reactions of arynes with other reagents. Numerous methods are available for the generation of arynes in the absence of nucleophiles[26] enabling the reactions of arynes with reagents such as dienophiles[26] to be studied. However, this topic is beyond the scope of the present discussion.

The final step in nucleophilic substitution by the elimination-addition mechanism is addition of the nucleophile to the formal triple bond of the aryne. Nucleophilic anions such as dialkylamides attack arynes to give the carbanion (23) which on subsequent protonation gives the substitution products. If the proton of the



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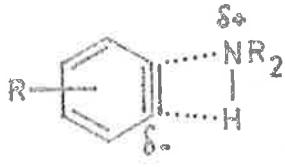
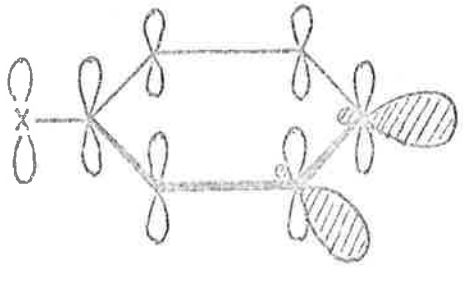


(24)

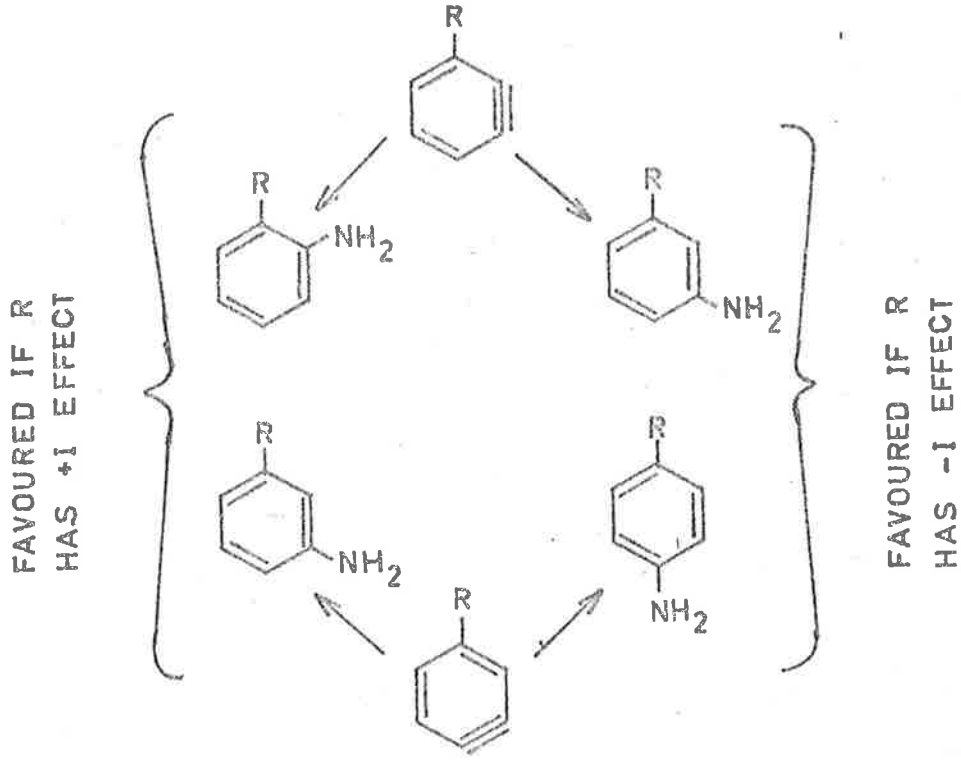
conjugate acid of the nucleophilic anion, the free amine in the present example, is sufficiently acidic the compound will add bidentally[26b] as illustrated in formula (24). It has been shown[43] that both lithium piperidide and piperidine add to 9,10-phenanthryne at similar rates. Therefore, in substitutions carried out with metal amides in the free amine as solvent it is probably mainly the free amine which adds to the aryne.

The addition of nucleophiles to arynes which are not symmetrically substituted with respect to the formal triple bond leads to two substitution products (Scheme 4). The two products are generally not found in a statistical ratio and one of the two isomers predominates. The direction of addition of nucleophiles to substituted arynes is found to depend on the nature of the substituent present and the substituent effect can be explained on the basis of electronic effects. Since the orbitals of the formal triple bond at which the polar addition occurs are orthogonal to the aromatic π-system, as shown in formula (25), the major influence of the substituent is through its inductive effect. The influence of substituents with



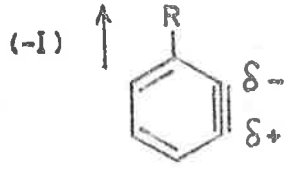
(25)

different inductive effects on the direction of addition of nucleophiles to substituted arynes is summed up by Roberts' rule[44] which is illustrated diagrammatically in Scheme 6. This substituent effect is explained in terms



SCHEME 6

of polarization of the formal triple bond of the aryne by the substituent as shown in formulas (26) and (27)[26c,45]. The nucleophile attacks the formal triple bond at the site



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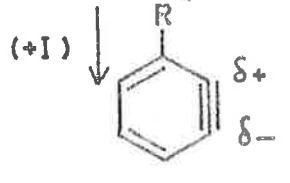


(27)

of lower electron density. An alternative hypothesis considers stabilization of the carbanion (23) by the inductive effect of the substituent. According to this explanation the more acidic of the two possible products predominates[26d,44]. However, this reaction is more likely to be kinetically than thermodynamically controlled so that the former explanation is favoured. Although both hypotheses satisfactorily explain the direction of addition in carbocyclic arynes only the former hypothesis explains the direction of addition in hetarynes[26c].

The nucleophilicity of the attacking reagent also determines to a minor degree the product ratio on addition of nucleophiles to substituted arynes[26e]. The stronger the nucleophile the more likely it is to react on the first encounter[26e] which will shift the product ratio towards the statistical value. Steric effects on the isomer ratio are of little importance and occur only in extreme cases[26e]. The direction of addition of nucleophiles depends, therefore, primarily on the inductive effect of the substituent. If the aryne contains two substituents the inductive effects are additive and the combined effect determines the direction of addition[26f].

The formation of arynes is not restricted to carbocyclic aromatic compounds but also occurs with heterocyclic compounds, where the aryne intermediates are known

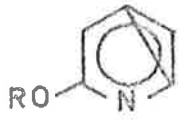
as hetarynes. The chemistry of hetarynes has been well reviewed[46,47]. Although acridone is regarded as a heterocyclic compound the acridonynes, where the formal triple bond is in the carbocyclic ring, are better considered as substituted carbocyclic arynes than as hetarynes.

When the strong base used for reactions proceeding by the aryne mechanism is also a good nucleophile, as is the case with the metal amides, then substitution by the addition-elimination mechanism may become a competing process. The unrearranged product may, therefore, be derived from both elimination-addition and addition-elimination substitution mechanisms.

The main feature of reactions occurring by the elimination-addition mechanism is the occurrence of products derived from cine-substitution. However, the occurrence of cine-substitution is not restricted to reactions occurring via arynes. Other base catalyzed reactions involving cine-substitution are the Smiles and Sommelet rearrangements and the von Richter reaction which have been reviewed by Shine[48]. These rearrangements are not related to the present work. The rearrangement of trihalogenobenzenes with sodamide and potassium anilide, which is also reviewed by Shine[48], is more closely related to the present work. Other cine-substitution reactions

are reviewed by Pietra[40] and include the reaction of 2-bromothiophene with potassamide to give 3-amino-thiophene[49]. Although this reaction occurs under conditions in which arynes are usually formed it has been shown that arynes are not intermediates in this substitution.

Rearrangements in which the incoming group has been found further removed than the position ortho- to the site of the leaving group have been observed in some instances under conditions where arynes are normally formed. Thus some 6-alkoxy-2-bromopyridines have been found to react with potassamide in ammonia giving the 6-alkoxy-2-aminopyridine and the 6-alkoxy-4-amino-pyridine[50]. The 1,3-rearrangement forming the latter compound has been termed 'tele-substitution' and a possible intermediate[50] in this rearrangement is the 1,3-dehydropyridine (28).

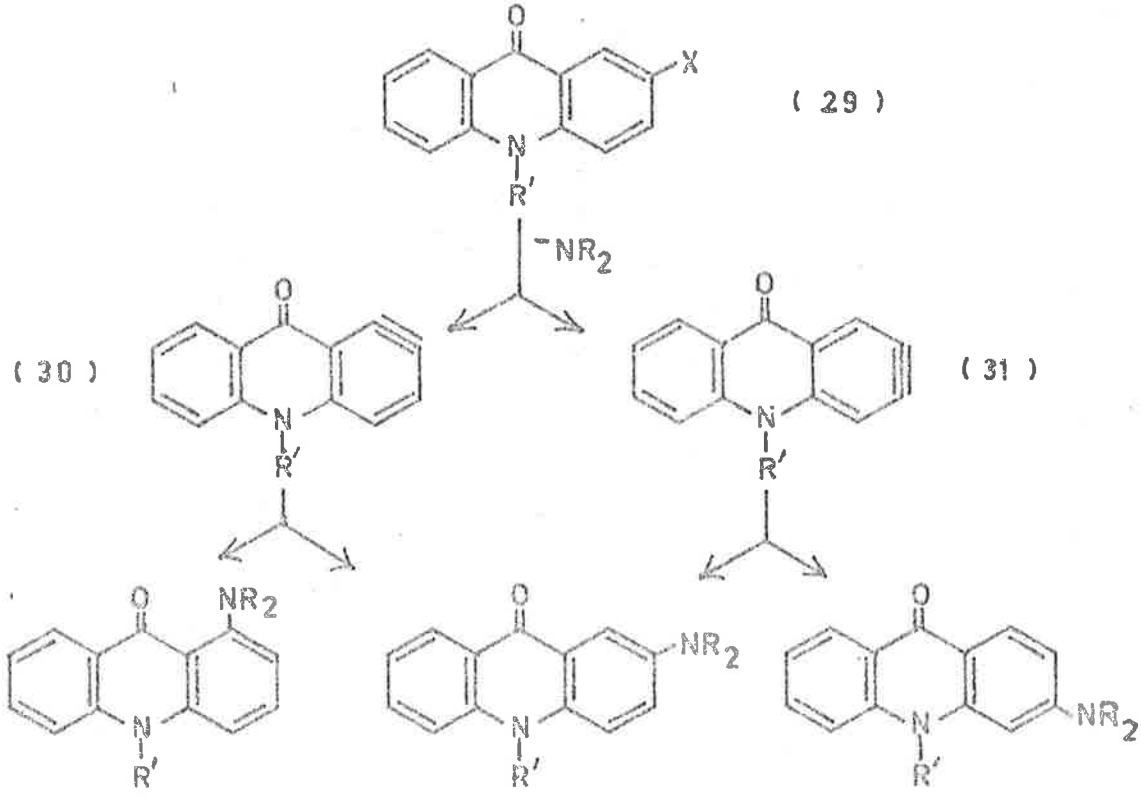


(28)

The chemistry of 1,3- and 1,4-dehydroaromatic intermediates has been reviewed by Hoffmann[26g].

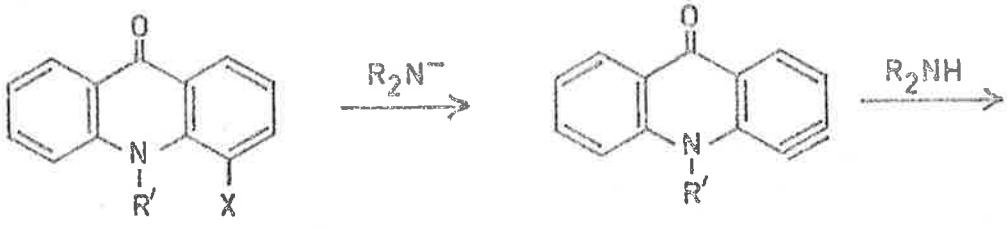
The halogeno-acridones would be expected to react

with strong bases such as the metal amides in a different manner depending on the nature and position of the halogen. Since the 1- and 3-positions are activated by the carbonyl group substitution is expected to occur in these positions entirely by the addition-elimination mechanism as this pathway would be expected to have a much lower activation energy than the elimination-addition pathway. Only the 2- and 4-halogenoacridones, excluding the fluoro compounds, would be expected to undergo substitution by the aryne mechanism. The 2-halogenoacridones



SCHEME 7

(29) are able to form two arynes, the 1,2-acridonyne (30) and the 2,3-acridonyne (31) which subsequently lead to three substitution products (Scheme 7). The 4-halogeno-acridones (32) can form only one aryne, the 3,4-acridonyne (33), which may subsequently give two substitution products (Scheme 8).



SCHEME 8

In the present work the reactions were performed with the bromo-10-methylacridone using as strong bases potassamide in liquid ammonia-dimethoxyethane and lithium piperidide in piperidine and in piperidine-dimethoxyethane. With these reagents the substitution products are the amino- and piperidino-10-methylacridones respectively. In work of this nature, where rearrangements may occur and some products may be present in very low yield, it is important to have on hand samples of the expected products as

reference materials. For this reason the amino- and piperidino-10-methylacridones were synthesized.

DISCUSSION

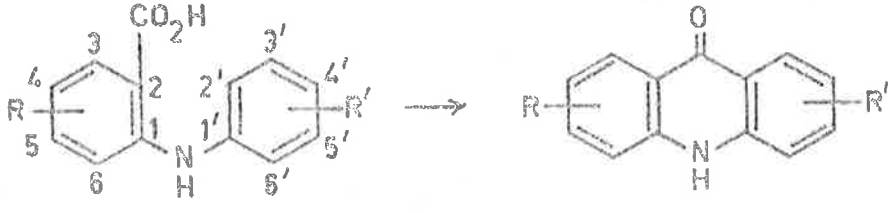
PART I

PREPARATION AND PROPERTIES OF THE MONO-BROMO-, AMINO-, AND PIPERIDINO-10-METHYLACRIDONES

General Principles of Acridone Synthesis

There are two approaches to the synthesis of substituted acridones, (1) by substitution on the acridone nucleus and (2) by synthesis from suitably substituted precursors of the acridone nucleus. The latter method has found the greater application and was used in the preparation of most of the acridones in the present work. The preparations and properties of the acridones have been well reviewed by Albert[1] and by Acheson[51].

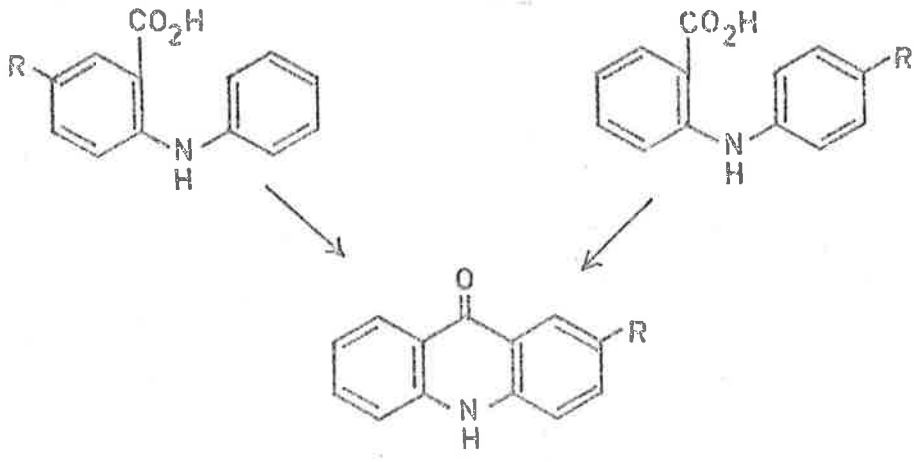
The most useful general method for the preparation of substituted acridones is by cyclization of an appropriately substituted diphenylamine-2-carboxylic acid (Scheme 9), the usual cyclizing agents being phosphoryl chloride and sulphuric acid. Both reagents generally give



SCHEME 9

very high yields of the acridone, although sulphuric acid sometimes causes sulphonation, particularly when electron releasing substituents are present, and in one instance cyclization with phosphoryl chloride has resulted in replacement of a nitro group by chlorine[52]. When phosphoryl chloride is used as the cyclizing agent the acridone or the 9-chloroacridine can be obtained by varying the work-up procedure.

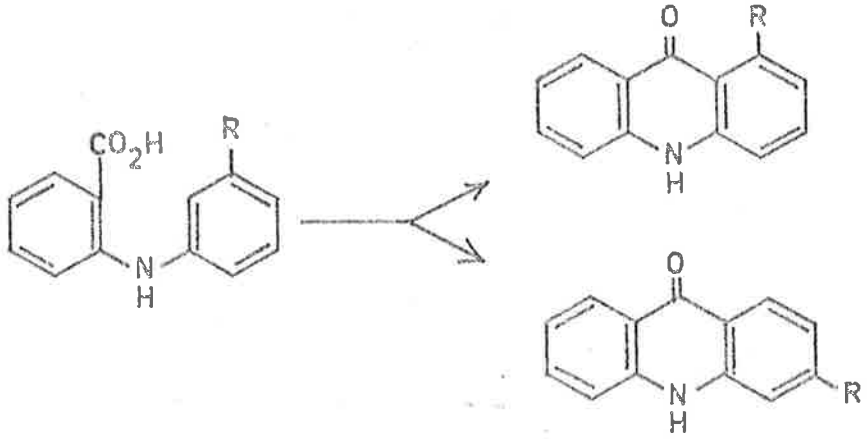
A given acridone can arise by cyclization of two different diphenylamine-2-carboxylic acids (Scheme 10) depending in which ring the substituent is situated.



SCHEME 10

Cyclization of 3'-substituted diphenylamine-2-carboxylic acids results in a mixture of the 1- and 3-substituted acridones (Scheme 11), the isomer ratio depending on the nature of the substituent. Electron releasing substituents,

such as NH_2 and OCH_3, favour ring closure at the 6'-position[1d] giving principally the 3-substituted acridone, whereas electron withdrawing substituents, such as Cl and NO_2, favour cyclization at the 2'-position[1d] giving mainly the 1-substituted acridone. Obviously 1- and 3-substi-

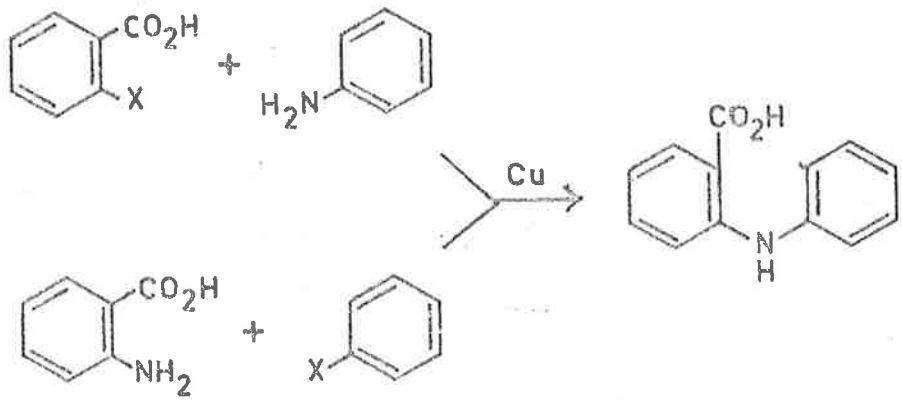


SCHEME 11

tuted acridones would be better prepared by cyclization of diphenylamine-2-carboxylic acids substituted in the same ring as the carboxyl group, but this is not always possible, particularly in the preparation of 1-substituted acridones.

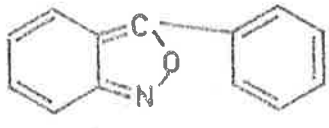
Diphenylamine-2-carboxylic acids are prepared by the Ullmann condensation of an aniline with a 2-halogeno-benzoic acid or of an anthranilic acid with a halogeno-benzene (Scheme 12). This reaction is a copper catalysed aromatic nucleophilic substitution and the effects of substituents on the rate and yield of the reaction follow the general trends for this type of substitution reaction.

The reaction is favoured by electron-withdrawing substituents in the halogenobenzene and by electron-donating substituents in the aniline. The yields are variable and depend to a considerable extent on the nature of the copper catalyst. Freshly precipitated copper has been found most satisfactory in this work.



SCHEME 12

Another reaction which has found considerable application in the preparation of substituted acridones is the reaction of 2-nitrobenzaldehydes with substituted benzenes[le] in sulphuric acid. The acridone arises by rearrangement of an intermediate phenylanthranil (34) and its N-oxide.



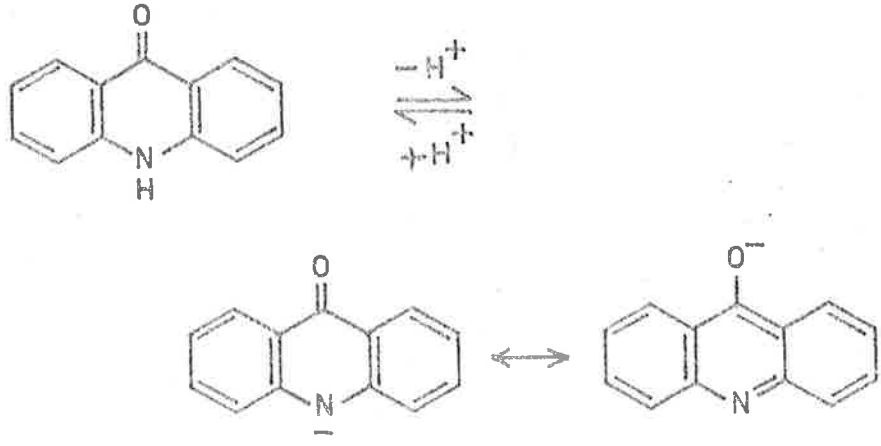
(34)

Substituted acridones can also be produced by nucleophilic and electrophilic substitution on the acridone nucleus. Nucleophilic substitution in acridones, the subject of this thesis, requires the presence of a suitable leaving group and is only of synthetic use in certain specific cases.

Electrophilic substitution is sometimes of use in the preparation of mono-substituted acridones substituted in the 2-position. As mentioned in the Introduction to this thesis the higher π-electron densities at the 2- and 4-positions, and also the corresponding positions in the other benzenoid ring, favour electrophilic substitution at these sites. Bromination of acridone with bromine in acetic acid results in mixtures of 2-bromo-, 2,7-dibromo-, and 2,4,5,7-tetrabromoacridones[4] and it is not possible to stop the reaction at the mono-bromo- stage. The reaction of 10-methylacridone with bromine in acetic acid[4] gives 2,7-dibromo-10-methylacridone and under more vigorous conditions further bromination is accompanied by demethylation[4]. 2-Bromo-10-methylacridone has been prepared in good yield by bromination of 10-methylacridone in chloroform[5] but in methanol 2,7-dibromo-10-methylacridone is obtained[3]. 2-Nitro-10-methylacridone can be obtained by nitration of 10-methylacridone with nitric acid in acetic acid[6] but is contaminated with numerous by-products.

Substituted 10-methylacridones can be prepared either by cyclization of the N-methyldiphenylamine-2-carboxylic acid or by N-methylation of the acridone. Little is known about the preparation of N-methyl-diphenylamine-2-carboxylic acids by the Ullmann condensation and, because of the availability of a number of other excellent methods, this procedure generally offers little advantage. Several N-methyldiphenylamine-2-carboxylic acids have been prepared from N-methylanthranilic acid and the halogenobenzene[53,54,55] and these include N-methyl-2'-nitrodiphenylamine-2-carboxylic acid[53]. Attempts to prepare N-methyldiphenylamine-2-carboxylic acids from N-methylanilines and 2-halogenobenzoic acids have met with little success[1f,6,55].

Acridones are weakly acidic and form the resonance stabilized anion (35a ↔ 35b) on treatment with base. This anion can be methylated on nitrogen with methyl iodide or



(35a) (35b)

dimethyl sulphate[1g,6] and this method was found to be the most useful in the present work. An alternative method via the 9-chloroacridine is less satisfactory[1h].

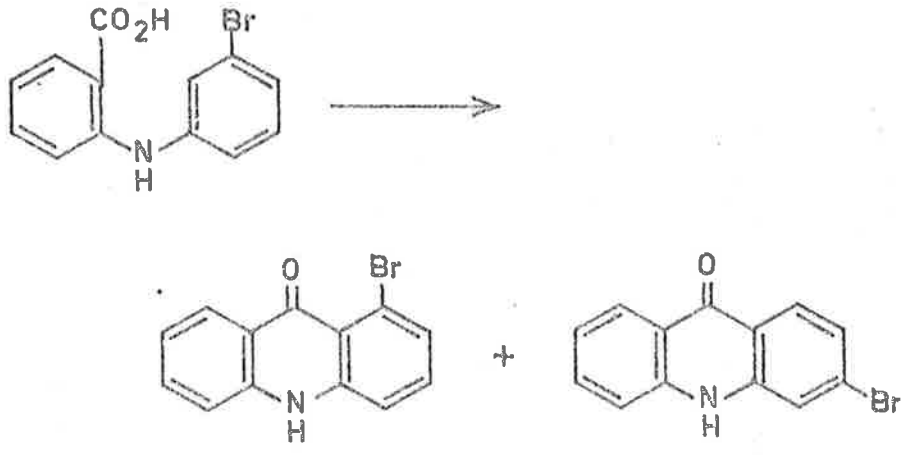
Discussion

Although the four mono-bromoacridones[1j] and the four mono-aminoacridones[1j] have been described in the literature only two of the N-methyl derivatives, 2-bromo-10-methylacridone[5] and 2-amino-10-methylacridone[6], have been prepared. The piperidino-10-methylacridones have not been described. In all but one case the substituted 10-methylacridones were obtained in the present work by N-methylation of the respective acridone. The amino-10-methylacridones were obtained by reduction of the corresponding nitro compound and the piperidino-10-methylacridones were prepared by reaction of the corresponding amino compound with 1,5-dibromopentane. In most cases the substituted acridone was obtained by cyclization of the respective diphenylamine-2-carboxylic acid with phosphoryl chloride. The diphenylamine-2-carboxylic acids were prepared by the Ullmann condensation.

N-Methylation was generally achieved by reaction of the respective acridone anion (35) with methyl iodide or dimethyl sulphate. Although the possibility of

O-methylation exists, as seen in the canonical form (35b), this has not been observed, even in the case of 4-nitro-acridone which does not readily undergo N-methylation. High yields of 10-methylacridones are generally obtained on reaction of the acridone with sodium hydride and dimethyl sulphate in dimethylformamide. The weaker base sodium methoxide is also able to remove the acridone proton but with this base there exists the possibility of nucleophilic substitution occurring, particularly in the preparation of 1- and 3-bromo-10-methylacridones. As later work has shown this would indeed have been the case in dipolar aprotic solvents, but in methanol as solvent reduction of the bromo compounds to 10-methylacridone occurs. Non-nucleophilic sodium hydride presented none of these problems.

Cyclization of 3'-bromodiphenylamine-2-carboxylic acid with phosphoryl chloride or sulphuric acid leads to a mixture of 1- and 3-bromoacridones (Scheme 13). By analogy with cyclization of 3'-chlorodiphenylamine-2-carboxylic acid, which gives a mixture of 1- and 3-chloroacridones in the ratio[56] 4 : 1, 1-bromoacridone would be expected to be the major product on cyclization of 3'-bromodiphenylamine-2-carboxylic acid. Indeed, Tanasescu and co-workers[57] have obtained 1-bromoacridone in very low yield by fractional crystallization of this mixture of 1-



SCHEME 13

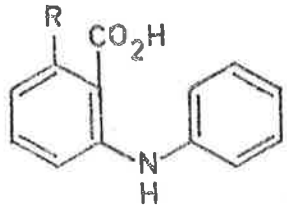
and 3-bromoacridones. Attempts to separate the 1- and 3-bromoacridones on a preparative scale by chromatography, both before and after N-methylation, were unsuccessful. 1-Bromo-10-methylacridone was finally obtained pure in reasonable yield by fractional crystallization of the mixture of isomers after N-methylation with sodium hydride and dimethyl sulphate in dimethylformamide. However, 3-bromo-10-methylacridone could not be obtained pure by this method. Since 3-bromo-10-methylacridone is readily obtained by other routes this procedure constitutes the best method of preparing 1-bromo-10-methylacridone.

Although the mixture of 1- and 3-bromo-10-methyl-acridones could not be separated on a preparative scale by chromatography it was possible to separate them on an analytical scale. Analysis of the crude mixture of

1- and 3-bromo-10-methylacridones by quantitative thin layer chromatography showed the 1- and 3-bromo compounds to be present in the ratio 61 : 39, respectively. Thin layer chromatography of the product from N-methylation of the mixture of 1- and 3-bromoacridones showed the yield of the 1- and 3-bromo-10-methyl compounds to be essentially quantitative, although only 85% yield was recovered on work-up. Therefore, it is expected that the 1- and 3-bromoacridones obtained on cyclization of 3'-bromodiphenylamine-2-carboxylic acid would be formed in the ratio 61 : 39.

An excellent separation of the 1- and 3-bromo compounds was obtained by thick layer chromatography after conversion to the bromo-9-chloroacridines. Separation of this mixture gave 1- and 3-bromo-9-chloroacridines in the approximate ratio 5 : 3 which is in agreement with the ratio obtained for the 1- and 3-bromo-10-methylacridones. The bromo-9-chloroacridines were converted to the bromo-10-methylacridones both directly and via the bromoacridones.

A possible method for avoiding the mixture of isomers and obtaining only 1-bromoacridone would be by cyclization of 3-bromodiphenylamine-2-carboxylic acid (36). However, it is of significance that 3-nitrodiphenylamine-2-carboxylic acid (37) cannot be cyclized with either

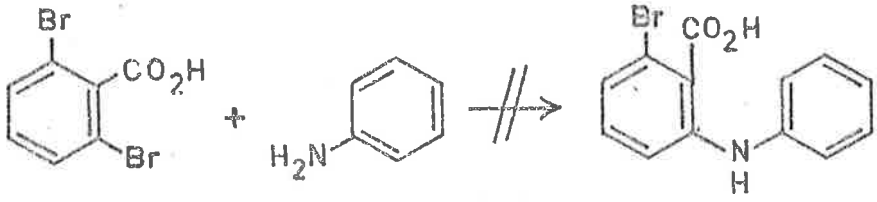


(36) R = Br

(37) R = NO_2

(38) R = CH_3

phosphoryl chloride or sulphuric acid[8] and undergoes decarboxylation under the conditions of the reaction. 3-Methyldiphenylamine-2-carboxylic acid (38) has been successfully cyclized[55] with phosphoryl chloride to 1-methylacridone. An attempt to prepare 1-bromoacridone by this route failed in the Ullmann condensation prior to cyclization. Attempts to prepare 3-bromodiphenylamine-2-carboxylic acid (36) by the Ullmann condensation of aniline with both 2,6-dibromobenzoic acid (Scheme 14) and its amide were unsuccessful. When this reaction was carried out with the acid a complex mixture of products was obtained and i.r. spectroscopy showed that none of these products contained a carbonyl group and could not be the desired 3-bromodiphenylamine-2-carboxylic acid. When this condensation was attempted with the amide only starting material was recovered. It is known that 2,6-dichlorobenzoic acid undergoes dehalogenation under the conditions of the Ullmann condensation with aniline and it is probable that this also occurs with 2,6-dibromo-



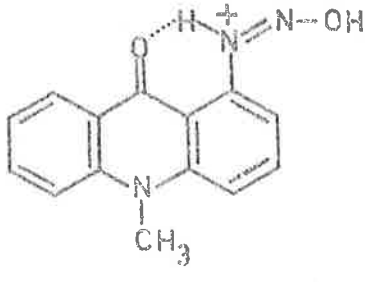
SCHEME 14

benzoic acid although it appears that decarboxylation is also occurring.

4-Bromo-10-methylacridone has been prepared both by N-methylation of 4-bromoacridone and by a Sandmeyer reaction with 4-amino-10-methylacridone. The latter is the method of choice since 4-amino-10-methylacridone is readily obtained in good yield in several steps from N-methylanthranilic acid and 2-bromonitrobenzene. The Sandmeyer reaction gives an excellent yield (82%) of 4-bromo-10-methylacridone. By contrast, this compound is obtained in very poor yield in several steps from 2-chlorobenzoic acid and 2-bromoaniline. The Ullmann reaction consistently proceeded in poor yield (17%), although other workers[58] have obtained a somewhat higher yield (33%). This low yield is probably due to the reduced nucleophilicity of the amino nitrogen due to the electron-withdrawing inductive effect of the adjacent bromine atom. N-Methylation of 4-bromoacridone with sodium hydride and dimethyl sulphate in dimethylformamide

proceeded in low yield (41%) and a considerable amount of the 4-bromoacridone was recovered unchanged. This is in marked contrast to methylation of the other bromoacridones by this procedure where a high yield of the bromo-10-methylacridone was always obtained. The low yield on N-methylation of 4-bromoacridone is best explained on steric grounds, the 4-bromine atom inhibiting approach of dimethyl sulphate to the 4-bromoacridone anion.

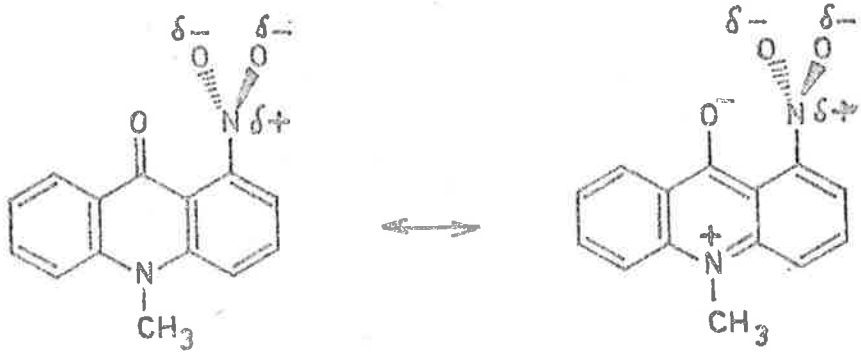
Although 4-bromo-10-methylacridone was prepared in excellent yield by the Sandmeyer reaction this was not the case in an attempt to prepare the 1-bromo compound by this method. When the Sandmeyer reaction was carried out on 1-amino-10-methylacridone a poor yield (16%) of 1-bromo-10-methylacridone was obtained. Much of the starting material was unaccounted for and appears to have been water soluble. It would seem possible that hydrogen bonding may impart special stability to the protonated diazotic acid intermediate (39) in the diazotization process and may retard formation of the diazonium salt. However, no evidence is presented in support of this hypothesis.



(39)

Cyclization of 3'-nitrodiphenylamine-2-carboxylic acid leads to a mixture of 1- and 3-nitroacridones in the ratio[56] 4 : 1. Since 3-nitrodiphenylamine-2-carboxylic acid (37) cannot be cyclized[8], the above cyclization is the only route to 1-nitroacridone. This mixture of 1- and 3-nitroacridones has been poorly resolved by fractional crystallization[1k,56]. Fortuitously, in the present work this separation was found unnecessary since the mixture of isomers was readily separated after N-methylation, pure 1-nitro-10-methylacridone crystallizing from the reaction mixture.

The properties of 1-nitro-10-methylacridone, in particular its relatively high melting point and very low solubility in organic solvents, suggest a larger than usual contribution of the acridinium form (40b) to the structure



(40a) (40b)

of this compound. Examination of appropriate molecular models shows the nitro group of 1-nitro-10-methylacridone

to be twisted out of the plane of the aromatic ring and the higher electron density on the carbonyl oxygen may be somewhat stabilized by electrostatic attraction of the peri- nitrogen atom. This is probably an example of the well known field effect[59,60]. Some evidence for this hypothesis is seen in the i.r. spectrum of this compound. The carbonyl and nitro group stretching frequencies of the nitroacridones and the nitro-10-methylacridones are collected in Table 1. The carbonyl stretching band of 1-nitro-10-methylacridone occurs at lower frequency than in the other nitro-10-methylacridones. This indicates a lower bond order for this carbonyl group and is evidence for an increased contribution of the acridinium form (40b) to the structure of 1-nitro-10-methylacridone. It is apparent that the nitro group is not coplanar with the aromatic ring from a comparison of the 1-nitro and 3-nitro stretching frequencies. If the 1-nitro group were coplanar with the aromatic ring the conjugation effects would be similar to those occurring in the 3-nitro compound so that the nitro stretching frequencies would be very nearly the same in these compounds. However, for all but the asymmetric stretching band of 1-nitro-10-methylacridone, the 1-nitro stretching frequencies of 1-nitroacridone and 1-nitro-10-methylacridone are significantly higher than the corresponding 3-nitro stretching frequencies. This is

consistent with the 1-nitro group being twisted out of the plane of the aromatic ring with consequent reduction in resonance[61].

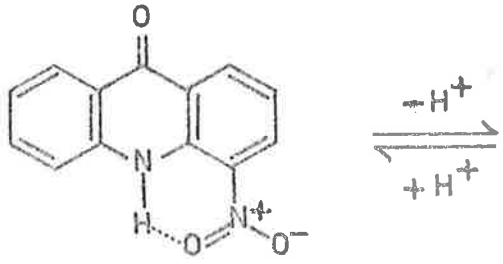
TABLE 1.

Infra-red stretching frequencies (cm^{-1}) of the nitroacridones and nitro-10-methylacridones (nujol mull).

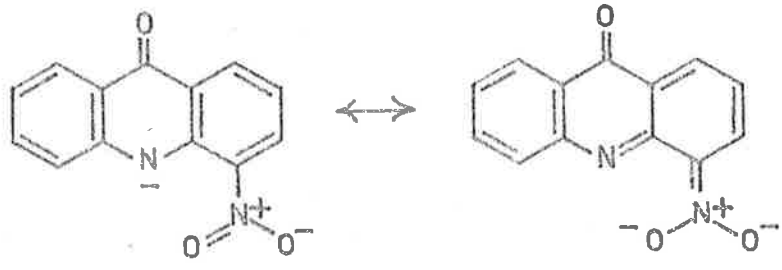
	C=Ostr	NO_2str	
		asym.	sym.
Nitroacridones			
1-nitro	1635	1545	1360
2-nitro	1635	1518	1338
3-nitro	1630	1535	1353
4-nitro	1639	1515	1303
Nitro-10-methylacridones			
1-nitro	1635	1530	1385
2-nitro	1640	1519	1337
3-nitro	1640	1535	1353
4-nitro	1643	1530	1356

Several attempts were made to prepare 4-nitro-10-methylacridone by N-methylation of 4-nitroacridone, but in each case only starting material was recovered, even with sodium hydride and dimethyl sulphate in dimethylformamide at 100°. Lehmstedt and Hundertmark[6] obtained 4-nitro-10-methylacridone in very poor yield from 4-nitroacridone with sodium methoxide and methyl iodide in refluxing ethanol, the majority of the starting material being recovered unchanged. Evidence that the anion of 4-nitroacridone (42a ↔ 42b) does form under the conditions used is indicated by the red solution produced when sodium hydride is added to a suspension of 4-nitroacridone in dimethylformamide. This observation is confirmed by the very similar changes occurring in the u.v. spectra of both acridone and 4-nitroacridone on addition of alkali (Table 7, page 143). In both cases there is a bathochromic shift of all bands in the alkaline solution. The u.v. spectra of the 2- and 3-nitroacridones change in a similar manner on addition of alkali. The inability of the anion of 4-nitroacridone to undergo N-methylation is readily explained on electronic and steric grounds. In both 4-nitroacridone (41) and its anion (42a ↔ 42b) the nitro group is coplanar with the aromatic ring and is conjugated with the heterocyclic nitrogen atom. However, examination of molecular models shows that in 4-nitro-10-methylacridone (43) steric

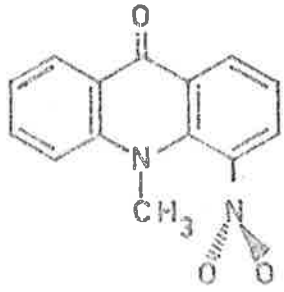
interaction of the peri situated nitro and methyl groups forces the nitro group out of the plane of the ring with consequent loss of resonance. Therefore, both steric interaction and loss of resonance stabilization, both of which raise the energy of the transition state, must be overcome on introduction of the methyl group.



(41)



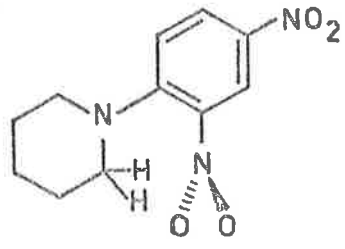
(42a) (42b)



(43)

Evidence that the nitro group of 4-nitro-10-methylacridone is not coplanar with the aromatic ring is derived from the i.r. and u.v. spectra of this compound. The nitro group absorption frequencies (Table 1) of 4-nitro-10-methylacridone occur at much higher frequency than those of 4-nitroacridone, where the nitro group is able to remain coplanar with the aromatic ring. This shift to higher frequency indicates the nitro group of 4-nitro-10-methylacridone is twisted out of the plane of the ring[61]. Evidence that this shift in the nitro bands is due to twisting of the nitro group and not some other effect of the methyl group is seen in a comparison of the i.r. spectra of 2-nitroacridone and 2-nitro-10-methylacridone where the nitro stretching frequencies are essentially the same. Further evidence for the non-coplanarity of the nitro group of 4-nitro-10-methylacridone is seen in a comparison of the u.v. spectra of 4-nitroacridone and 4-nitro-10-methylacridone (Table 7, page 143). After allowing for the small electronic effects of N-methylation it is seen that the u.v. spectra of 4-nitroacridone and 4-nitro-10-methylacridone differ considerably, particularly in the position of the long wavelength band where there is a considerable hypsochromic shift on introduction of the N-methyl group. This shift is due to decreased resonance of the 4-nitro group of 4-nitro-10-

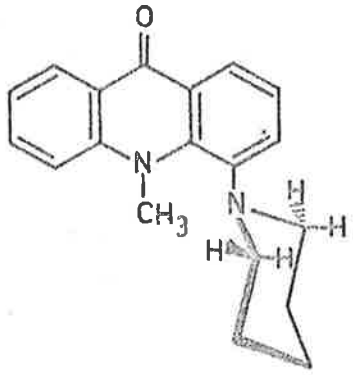
methylacridone. Spectroscopic measurements[62] have shown that the 2-nitro group of N-2,4-dinitrophenylpiperidine (44) is forced out of the plane of the benzene ring whilst the piperidino group remains coplanar and conjugated



(44)

with the 4-nitro group. This system must have very similar steric requirements to 4-nitro-10-methylacridone.

Similar effects are observed for the 1- and 4-piperidino-10-methylacridones and here examination of the stereochemistry is amenable to study by n.m.r. spectroscopy. Examination of molecular models shows that the piperidino groups of these two compounds cannot be coplanar with the aromatic ring. The n.m.r. spectrum of 4-piperidino-10-methylacridone shows two separate resonances for the α-methylene protons, both appearing as broad signals at δ 2.6 and δ 3.2. This strongly suggests that the plane of the piperidino group is perpendicular to the plane of the aromatic ring and is fixed approximately in the conformation (45), the two signals being due to the non-equivalent axial and



(45)

equatorial ∝-protons. The n.m.r. spectrum of 4-piperidinoacridone, in which the 4-piperidino group is able to rotate freely, shows only a single broad signal at δ 2.97 for the ∝-methylene protons.

The n.m.r. spectrum of 1-piperidino-10-methylacridone shows a single broad triplet at δ 3.13 for the ∝-methylene protons indicating these protons are equivalent. Free and rapid rotation of the 1-piperidino group would be expected to give a single broad signal as occurs with 4-piperidinoacridone. Therefore it appears that rotation of the 1-piperidino group is restricted by steric interaction with the peri- carbonyl oxygen.

In the preparation of 4-piperidino-10-methylacridone from 4-amino-10-methylacridone and 1,5-dibromopentane a considerable amount of demethylation occurred giving 4-piperidinoacridone. This demethylation is probably a result of the forcing conditions required to

prepare 4-piperidino-10-methylacridone and it is possible that this reaction is related to the demethylation occurring on bromination of 10-methylacridone under forcing conditions[4]. No demethylation was observed on prolonged heating of 4-amino-10-methylacridone in boiling hydrobromic acid. There seems to be no simple explanation for this interesting observation and it was not pursued further.

PART II

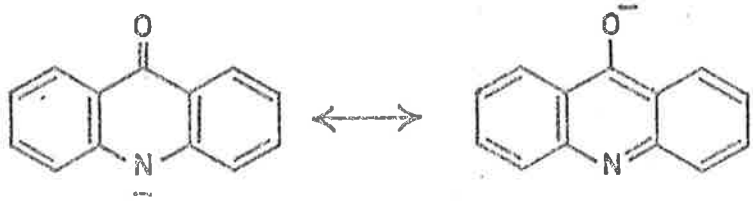
REACTION OF THE ISOMERIC BROMO-10-METHYLACRIDONES WITH POTASSAMIDE AND LITHIUM PIPERIDIDE

Aromatic halogen compounds react with strong bases producing arynes and undergo nucleophilic substitution accompanied by rearrangement of the substituent. If the strong base is also a good nucleophile competition by the addition-elimination mechanism occurs, and if suitably oriented activating groups are present, this becomes the exclusive process. Substitution by the addition-elimination process is generally not accompanied by rearrangement.

In this section the reactions of the bromo-10-methylacridones with potassamide in liquid ammonia-dimethoxyethane and with lithium piperidide in piperidine and in dimethoxyethane are discussed. The reactions of the bromo-10-methylacridones with piperidine alone are also discussed in relation to the principal topic. These reactions have been found, with one exception, to follow the general principles of aromatic nucleophilic substitution.

Acridones are weakly acidic and react with bases forming the resonance stabilized anion (46a $\longleftrightarrow$ 46b). For this reason the present study was carried out with the

10-methylacridones. A further advantage of 10-methylacridones is their greater solubility in organic solvents.



(46a) (46b)

The bromo compounds were chosen in preference to the other halogeno compounds principally for the ready lability of bromide ion in substitutions occurring by the elimination-addition mechanism. With strong bases the loss of hydrogen bromide from aryl bromides is a near synchronous process[63] whereas the loss of hydrogen chloride from aryl chlorides is a two-step process[63] and formation of the aryne is slower. Bromide ion is also a good leaving group in the addition-elimination mechanism, although not as good as chloride and fluoride[20f].

2-Bromo-10-methylacridone reacts rapidly with excess potassamide in liquid ammonia-dimethoxyethane giving a deep red solution which changes to yellow on neutralization of excess potassamide. The products found by analysis were 1-, 2- and 3-amino-10-methylacridones and 10-methylacridone (Table 2). Experiments to determine the stabilities of the amino-10-methyl-

acridones showed that 1- and 2-amino-10-methylacridone decomposed under the conditions of the reaction, the latter compound quite rapidly. The initial yields were therefore found from a series of reactions of increasing reaction time by extrapolation of a plot of the yields vs. reaction time (Fig. 3) and it is these yields which are quoted in Table 2. Several observations can be made from

TABLE 2.[a]

Yields (%) of products from the reaction of the bromo-10-methylacridones with 10 equiv. of potassamide in liquid ammonia-dimethoxyethane

	1-NH_2	2-NH_2	3-NH_2	4-NH_2	10-Me
1-Bromo-	0	0	0	0	some
2-Bromo-[b]	57	32	3.3	0	~0
3-Bromo-	0	0	93	0	0
4-Bromo-[c]	0	0	88	0	1.5

a) Results are tabulated in full in Tables 16 - 19, pages 189 - 191.
b) Yields by extrapolation.
c) Based on unrecovered starting material.

Fig. 3. (1) The high initial total yield (ca. 92%)

indicates no significant side reactions are occurring in the reaction. (2) Since no starting material was recovered, even after a reaction time of only 30 seconds, the reaction is very rapid. Indeed, the red colour, which was found to be due to 1-amino-10-methylacridone, is formed immediately the 2-bromo-10-methylacridone comes into contact with the potassamide solution. (3) The steady

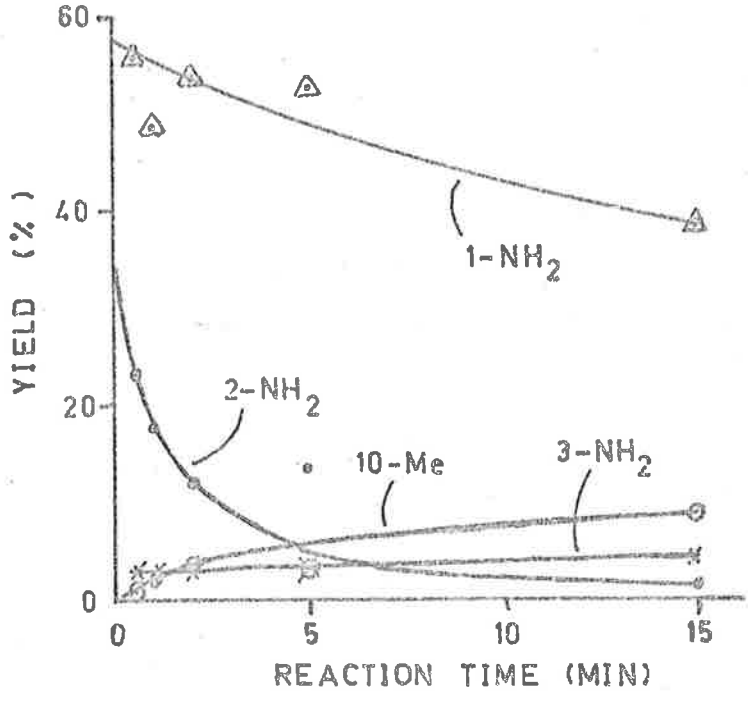
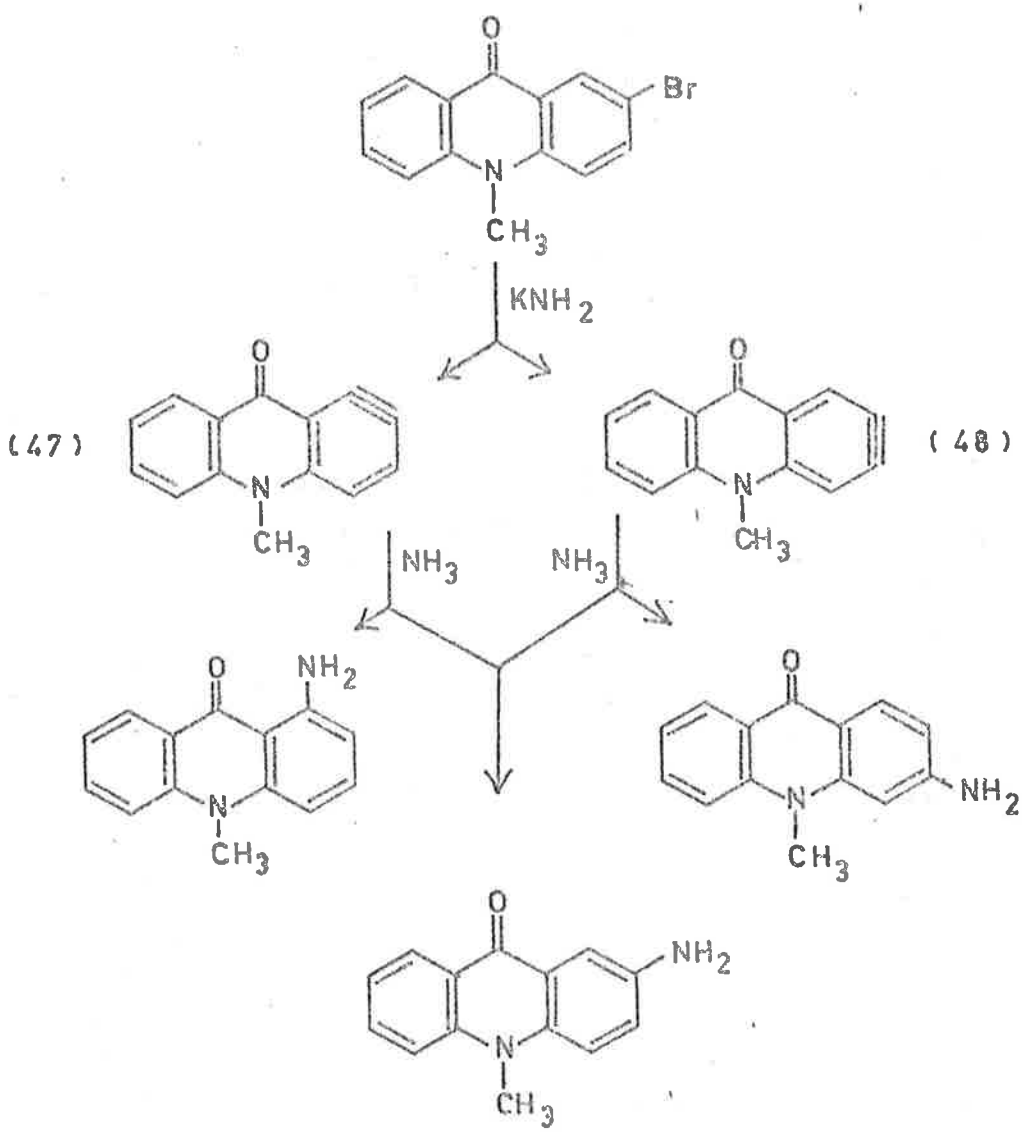


Fig. 3. Yields of products in reaction of 2-bromo-10-methylacridone with KNH_2 - NH_3 - dimethoxyethane.

increase in the yield of 10-methylacridone indicates it is formed from one of the products rather than from the starting material. Exposure of 2-amino-10-methylacridone to the reaction conditions gave a significant yield of

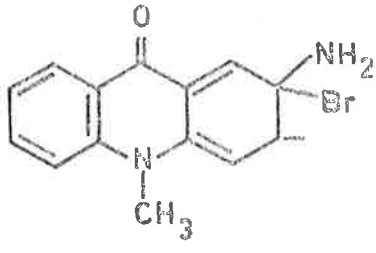
10-methylacridone, together with much intractable material, and this appears to be the source of the 10-methylacridone in the reaction. None of the other amino-10-methyl-acridones gave 10-methylacridone under these conditions.



SCHEME 15

(4) The yield of 3-amino-10-methylacridone was probably constant, the slight rise can be accommodated within the experimental error.

Formation of the rearranged products, 1- and 3-amino-10-methylacridone, clearly indicates that substitution is occurring by the elimination-addition mechanism, the products being formed by addition of ammonia to the arynes (47) and (48) (Scheme 15). 2-Amino-10-methylacridone could conceivably arise by addition of ammonia to both arynes and also by competing addition-elimination substitution by amide ion at C-2 via the intermediate (49). The high yield of rearranged products and the deactivation of the 2-position by the heterocyclic nitrogen would suggest that competing addition-elimination substitution is no more than a minor process.

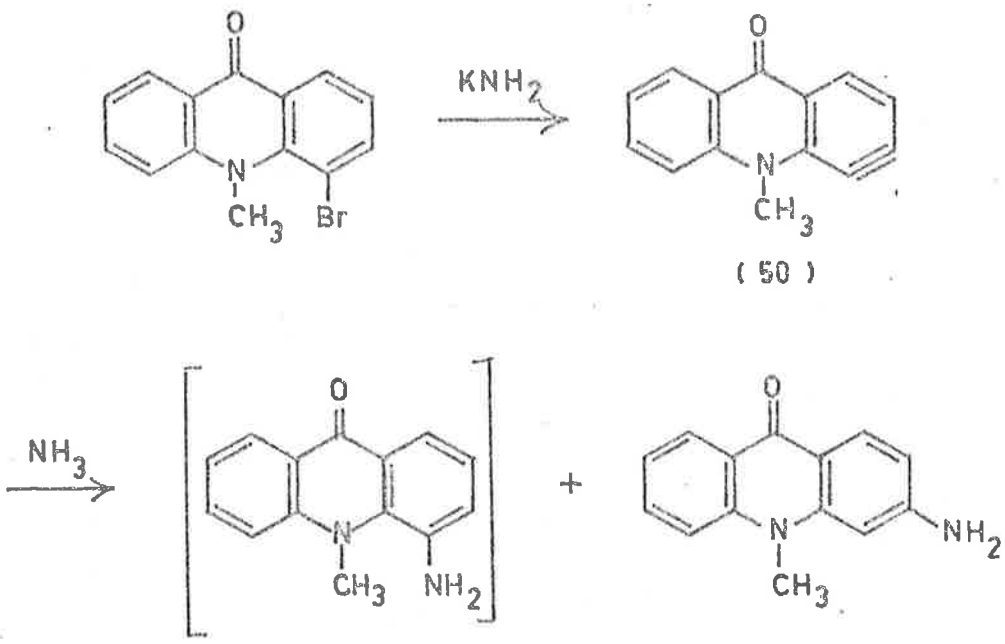


(49)

4-Bromo-10-methylacridone reacts with excess potassamide in liquid ammonia-dimethoxyethane giving a deep orange solution which changes to pale yellow on neutralization. This reaction appears to be somewhat slower than the reaction of the 1-bromo compound since 11%

of the starting material was recovered unchanged after a reaction time of 30 seconds. The products (Table 2) formed in the reaction were 3-amino-10-methylacridone, some 10-methylacridone and some intractable material which remained at the base of the chromatography plate. No 4-amino-10-methylacridone was observed, although control experiments showed this compound was very unstable under the reaction conditions and was entirely converted to intractable materials. However, on the basis of the recovered products 4-amino-10-methylacridone could have been formed in no more than 10% yield. The formation of 3-amino-10-methylacridone indicates the substitution is occurring by the elimination-addition mechanism via the aryne (50) (Scheme 16). Again, due to the large amount of rearrangement occurring, competing addition-elimination substitution could be no more than a minor process.

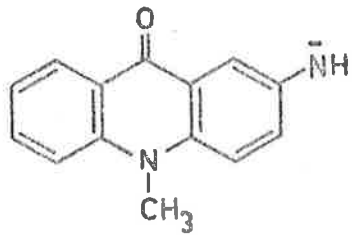
As has been mentioned in the above discussion the 2- and 4-amino-10-methylacridones are unstable under the reaction conditions and decompose with the formation of intractable materials which remained at the base of the chromatography plates. The only product identified on treatment of the amino-10-methylacridones with potassamide in liquid ammonia-dimethoxyethane was some 10-methylacridone from 2-amino-10-methylacridone although this did not account for all of the unrecovered 2-amino compound.



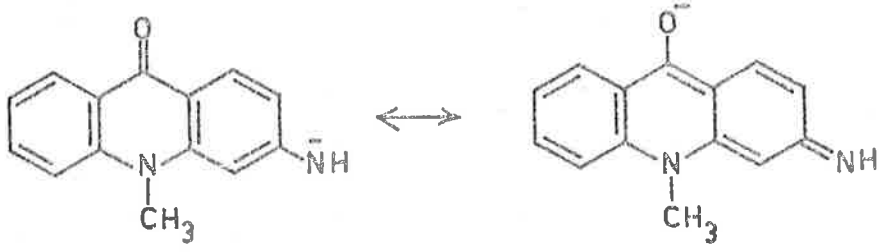
SCHEME 16

The other amino compounds and 10-methylacridone are all far more stable under these conditions, although 1-amino-10-methylacridone decomposes slowly to intractable materials. The stabilities of the amino compounds, which are present in the potassamide solution as the anion (e.g. 51, 52a↔52b), appear to be related to their resonance stabilization. However, it is only possible to speculate on the processes occurring in the decomposition of these compounds.

3-Bromo-10-methylacridone reacts with potassamide in liquid ammonia-dimethoxyethane giving a high yield of 3-amino-10-methylacridone (Table 2). No 2- or 4-amino-



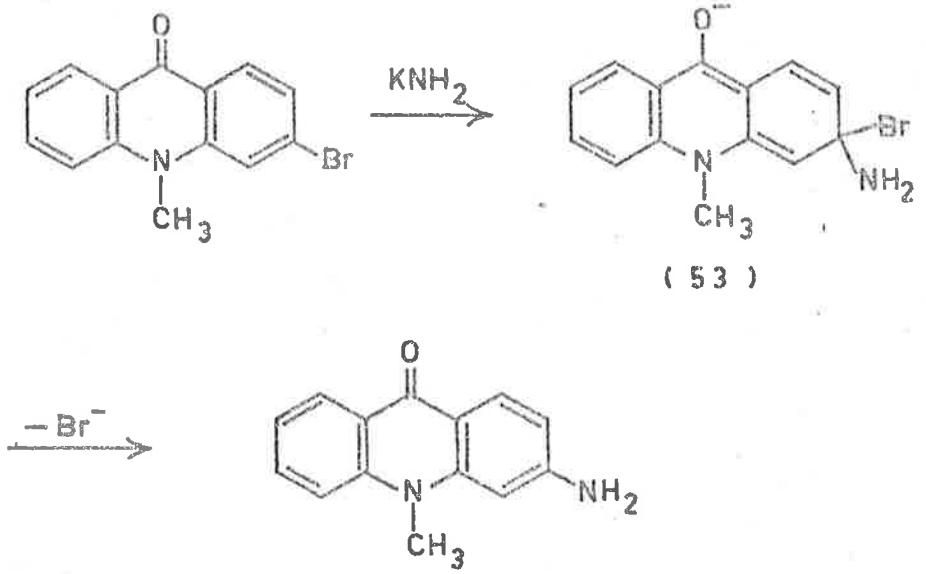
(51)



(52a) (52b)

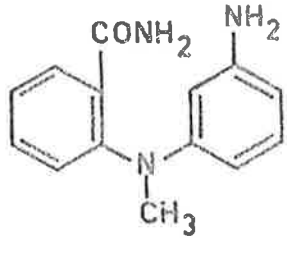
10-methylacridones or 10-methylacridone were observed. The high yield of unrearranged product indicates this substitution occurs entirely by the addition-elimination mechanism via the intermediate (53) (Scheme 17). The absence of 2-amino-10-methylacridone precludes any participation by the elimination-addition mechanism since this compound is sufficiently stable under the reaction conditions for a significant proportion to have been recovered after a reaction time of 6 minutes (c.f. Fig. 3). 4-Amino-10-methylacridone, if formed, is too unstable under the reaction conditions to have been detected.

1-Bromo-10-methylacridone reacts with potassamide in liquid ammonia-dimethoxyethane, but does not give 1-amino-10-methylacridone as would be expected from an



SCHEME 17

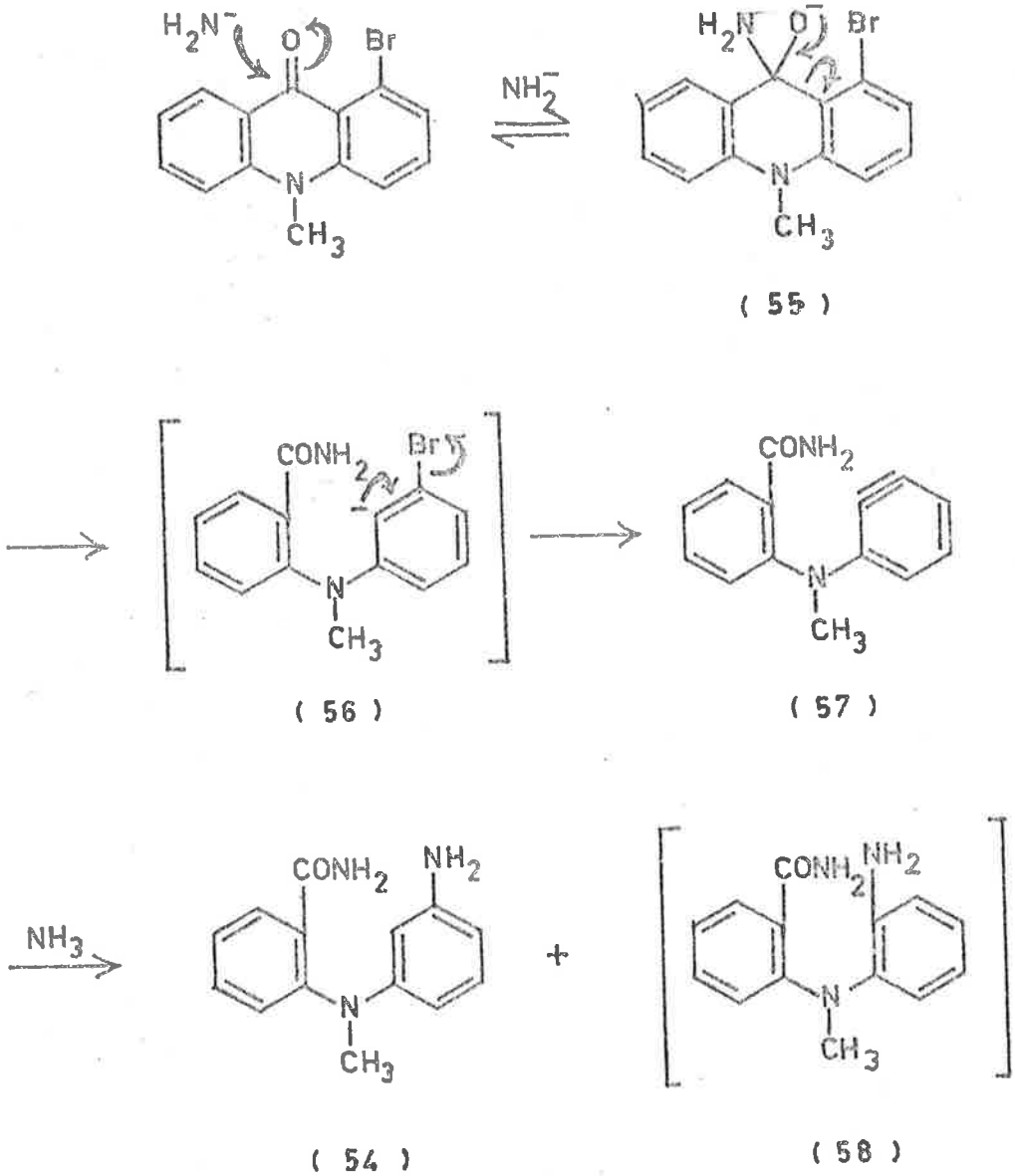
addition-elimination substitution at the activated 1-position. Instead, amide ion attacks the acridone carbonyl group giving a high yield of the amide (54). This product was identified by n.m.r., i.r. and mass spectrometry and the structure and position of the amino group comfirmed by unambiguous synthesis of the amide (54) from 3'-nitrodiphenylamine-2-carboxylic acid.



(54)

No 1- or 2-amino-10-methylacridone was detected indicating that no substitution occurs in the benzenoid ring of the acridone by either addition-elimination or elimination-addition mechanisms. In the analytical scale reaction a 22% yield of 10-methylacridone was obtained and some 10-methylacridone was also obtained in the preparative scale reaction. The reaction is best rationalized in terms of attack of amide ion at the acridone carbonyl group (Scheme 18) giving the intermediate (55) which then undergoes ring cleavage to the carbanion (56). Rapid loss of bromide ion from this carbanion gives the aryne (57). Addition of ammonia to the aryne (57) is expected to occur principally in the meta position[26d,44] giving the amide (54). Thin layer chromatography of the crude product showed a small spot with slightly higher R_f and similar appearance to the amide (54) on staining with iodine. This spot may well have been the amide (58) formed by attack of ammonia at the ortho position in the aryne (57). However, there was too little of this compound to isolate and characterize. Ring cleavage of 1-bromo-10-methylacridone with potassamide is similar to the Haller-Bauer reaction[64] and is closely related to the cleavage of o-halogenobenzophenones with potassamide in liquid ammonia[65] where aryne products have been observed. The driving force for this reaction is the electron-withdrawing

inductive effect of the 1-bromine atom, which assists formation of the carbanion (56), and the irreversible formation of the aryne (57).



SCHEME 18

The bromo-10-methylacridones react with lithium piperidide in piperidine in a similar manner to the reactions with potassamide, with the notable exception of 1-bromo-10-methylacridone. The reactions are very much slower with lithium piperidide in piperidine at 27° than with potassamide in liquid ammonia-dimethoxyethane at -33° as seen from the recovery of considerable amounts of starting material. The results of the reactions of the bromo-10-methylacridones with lithium piperidide in piperidine at 27° are collected in Table 3.

1-Bromo-10-methylacridone reacts with lithium piperidide in piperidine by substitution of the 1-bromine atom rather than by attack at the carbonyl group as occurs with potassamide. Attack by lithium piperidide at the acridone carbonyl group appears to be sterically unfavourable.

As seen from Table 3 substitution of the 1- and 3-bromo-10-methylacridones with lithium piperidide in piperidine is not accompanied by rearrangement and proceeds entirely by the addition-elimination mechanism, giving high yields of 1- and 3-piperidino-10-methylacridones, respectively. It is also seen that 1-bromo-10-methylacridone undergoes substitution somewhat faster than does the 3-bromo compound. Both 1- and 3-bromo-10-methylacridone react with boiling piperidine alone giving the

TABLE 3.[a]

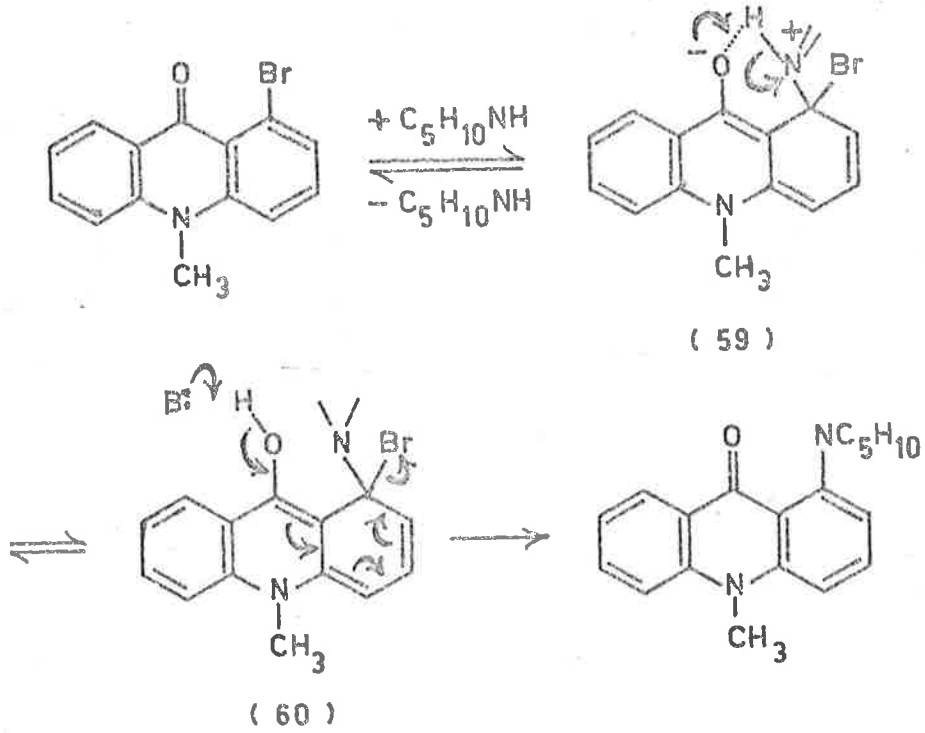
Products from reaction of the bromo-10-methylacridones with 5 equiv. of lithium piperidide in piperidine at 27°.

	% reactn. in 10 min.	Yields (%)[b]				
		1-Pip	2-Pip	3-Pip	4-Pip	10-Me
1-Bromo-	65	74	0	0	0	13
2-Bromo-	9	<1	72	10	0	18
3-Bromo-	39	0	0	73	0	12
4-Bromo-	46	0	0	31	0	25

a) Results collected in full detail in Tables 10 - 13, pages 180 - 182 .
b) Based on unrecovered starting material.

respective piperidino-10-methylacridones, but in this case the 1-bromo compound reacts a great deal faster than does the 3-bromo compound; the reaction is complete in 20 minutes with the 1-bromo compound whereas only 5.7% substitution product is obtained from the 3-bromo compound after 5.25 hours. 1-Bromo-10-methylacridone also reacts slowly with piperidine at room temperature, but the reaction is very much slower than that with lithium piperidide in piperidine at room temperature. The greatly enhanced rate

of reaction of 1-bromo-10-methylacridone with piperidine, as compared with the 3-bromo compound, can be explained in terms of hydrogen bonding. The reaction pathway for this substitution is shown in Scheme 19. Hydrogen bonding of the amino proton with the acridone carbonyl group will lower the free energy of the first transition state,

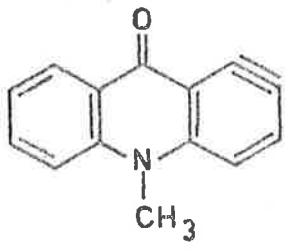


SCHEME 19

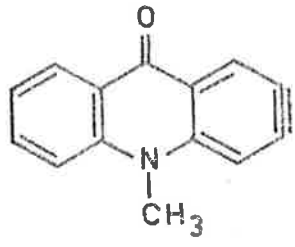
which resembles the intermediate (59), and will probably also assist in removal of the quaternary proton as shown in the equilibrium (59⇌60) making bromide the better leaving group. Hydrogen bonding of this type has been proposed[23,33,34] to explain similar ortho-para effects in the nucleophilic substitution of o- and p-nitrohalogeno

aromatic compounds with primary and secondary amines. With o-chloronitrobenzene this phenomenon has also been interpreted in terms of electrostatic interaction[35] or internal solvation. On transferring to lithium piperidide in piperidine, where the nucleophile is much stronger and hydrogen bonding of the type shown in formula (59) will not occur, the rates of substitution become more nearly the same for the 1- and 3-bromo compounds.

2-Bromo-10-methylacridone reacts with lithium piperidide in piperidine at 27° much slower than the 1- and 3-bromo compounds and gives 1-, 2- and 3-piperidino-10-methylacridone and 10-methylacridone (Table 3). Again rearrangement products, although present in low yield, indicate the intermediacy of the arynes (61) and (62).



(61)

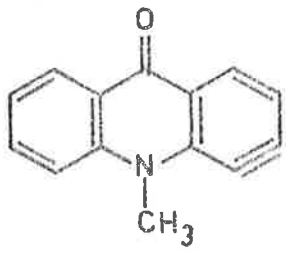


(62)

The yield of 1-piperidino-10-methylacridone is very much lower in this reaction than is the yield of 1-amino-10-methylacridone in the potassamide reaction. This

observation is discussed in detail below. The products of the reaction were found to be reasonably stable under the reaction conditions (Table 14, page 183).

4-Bromo-10-methylacridone reacts with lithium piperidide in piperidine giving 3-piperidino-10-methylacridone, 10-methylacridone and a considerable amount of intractable material which remained at the base of the chromatography plate. No 4-piperidino-10-methylacridone was detected although this compound was shown to be stable under the reaction conditions. The formation of 3-piperidino-10-methylacridone indicates the intermediacy of the aryne (63) as occurs in the reaction of 4-bromo-10-methylacridone with potassamide.



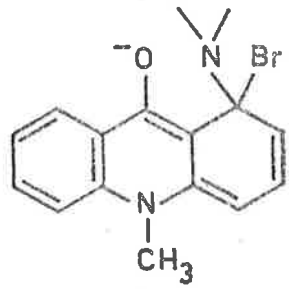
(63)

Prior to carrying out these reactions with lithium piperidide in piperidine they were performed with lithium piperidide and excess piperidine in refluxing dimethoxyethane. In these reactions the lithium piperidide was generated *in situ* by addition of phenyllithium to a solution

of the bromo-10-methylacridone and piperidine in dimethoxyethane. The products and product ratios from the reactions in dimethoxyethane were essentially the same as those obtained in piperidine as solvent. A troublesome substance with green fluorescence which streaked the length of the thin layer chromatography plates prevented quantitative analysis being carried out for the reactions with 2- and 4-bromo-10-methylacridone. In the reactions with the 2- and 4-bromo compounds the phenyllithium was added all at once to the solution of the bromo compound and piperidine in dimethoxyethane and it is possible that the phenyllithium could have been reacting directly, to some extent, with the bromo-10-methylacridone to produce the substance with green fluorescence.

Although 1-bromo-10-methylacridone reacts readily with lithium piperidide and excess piperidine in refluxing dimethoxyethane, giving 77% yield of the 1-piperidino compound in 75 minutes, this was not the case with lithium piperidide in dimethoxyethane alone. When 1-bromo-10-methylacridone was refluxed for 9 hours with excess lithium piperidide in dimethoxyethane the starting material was recovered quantitatively and the only product of the reaction was a trace of 10-methylacridone. This strongly suggests that stabilization of the transition state, which closely resembles the intermediate (64), by hydrogen bond-

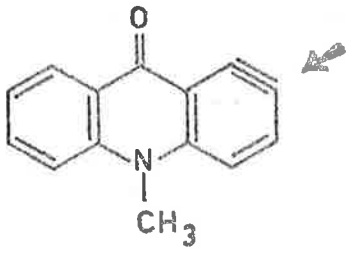
ing with piperidine is an essential feature of substitution of the 1-bromine by lithium piperidide. Without this solvation of the transition state the activation energy is too high for the substitution to occur.



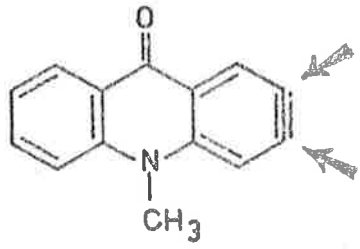
(64)

So far the reactions of the bromo-10-methylacridones with potassamide and with lithium piperidide have been discussed in terms of the products formed and the mechanism by which the substitution occurs. No attempt has been made to explain the product ratios observed in the reactions occurring by the elimination-addition mechanism. The effects of substituents on the direction of addition of nucleophiles to arynes have been well studied and are reviewed by Hoffmann[26d] and have been discussed in the Introduction of this thesis. The general principle of the directing influence of substituents is that of Roberts[44] in which the direction of addition is controlled by the inductive effect of the substituent.

The substituents in the 10-methylacridonynes which will affect the direction of addition of nucleophiles are the heterocyclic nitrogen atom and the carbonyl group, and these both have electron-withdrawing (-I) inductive effects. Therefore, employing Roberts' rule[44] (see page 27) the three 10-methylacridonynes (65), (66) and (67) are expected to add nucleophiles preferrentially in the positions indicated by the arrows, addition to the aryne (66) being expected to occur approximately equally in each position.



(65)



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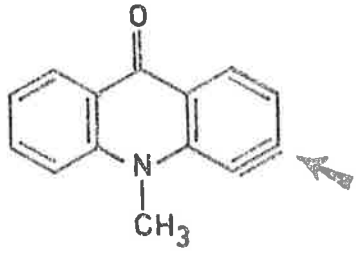


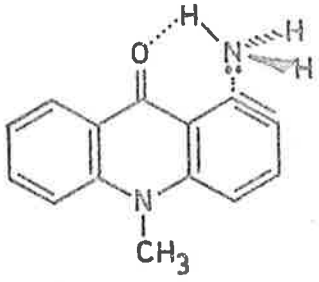
(67)

The reactions with lithium piperidide in piperidine follow this principle well if it is assumed that 2-bromo-10-methylacridone forms preferrentially the aryne (65).

This is a reasonable assumption since with the combined inductive effects of the carbonyl group and the bromine atom the 1-hydrogen of 2-bromo-10-methylacridone would be expected to be more acidic than the 3-hydrogen[26h] and there would be little, if any, steric hindrance by the carbonyl group preventing removal of the 1-hydrogen atom to form the carbanion prior to aryne formation. Therefore, with a greater proportion of the 1,2-aryne (65) than of the 2,3-aryne (66) the principal product from the reaction of 2-bromo-10-methylacridone with lithium piperidide in piperidine is expected, and observed, to be 2-piperidino-10-methylacridone (Table 3).

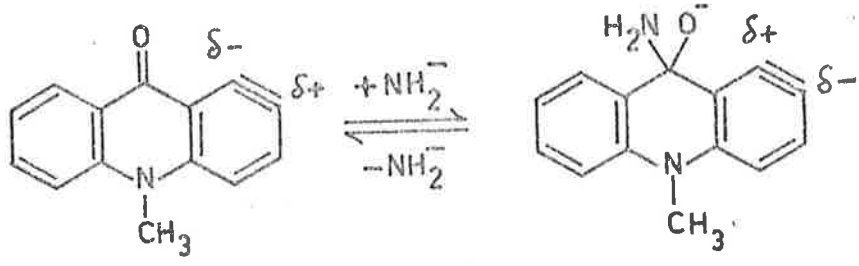
The principal product from the reaction of potassamide in liquid ammonia with 2-bromo-10-methylacridone is the 1-amino compound (Table 2) rather than the 2-substituted product as was obtained with lithium piperidide in piperidine. 2-Bromo-10-methylacridone would be expected to give approximately the same ratio of arynes (65) and (66) with potassamide as with lithium piperidide. Therefore, it is evident from the results (Table 2) that the aryne (65) reacts with ammonia preferrentially in the 1-position whereas with piperidine it reacts preferrentially in the 2-position. This 'abnormal' addition of ammonia to the aryne (65) can be explained in two ways. Hydrogen bonding of ammonia to the carbonyl group of the aryne (65),

giving the species (68), favourably situates the ammonia for addition at the 1-position. The increased steric



(68)

requirements of piperidine would prevent this occurring in the addition of piperidine to the aryne (65). An alternative hypothesis requires the conversion of the aryne (65) to the species (69) by attack of amide ion at the acridone carbonyl group. The substituent in the aryne (69) now has a strong electron-donating (+I) inductive effect and directs addition of ammonia to the 1-position giving preferrentially 1-amino-10-methylacridone. Evidence that the equilibrium



(65) (69)

(65 ⇌ 69) may occur in potassamide solution can be seen from the reaction of 1-bromo-10-methylacridone with potassamide where attack of amide ion at the acridone carbonyl group results in cleavage of the acridone nucleus (Scheme 18). Formation of an adduct analogous to the species (69) has been proposed[65] to explain the abnormal directing effects of the carbonyl group in addition of ammonia to 2,3-dehydrobenzophenone with sodamide and liquid ammonia. As evident from the reaction of 1-bromo-10-methylacridone with lithium piperidide in piperidine this equilibrium is not established with piperidide ion.

The results of the reaction of 2-bromo-10-methylacridone with potassamide in liquid ammonia-dimethoxyethane do not distinguish between the two hypotheses which explain the abnormal addition of ammonia to the aryne (65). Intuitively, it might be thought that the equilibrium concentration of the species (69) might be very low. Indeed, 10-methylacridones do not exchange the carbonyl oxygen with labelled hydroxide ion[39], but amide ion is a stronger nucleophile than hydroxide ion[20g].

Addition of both ammonia and piperidine to the 3,4-aryne (67) occurs in the predicted manner giving the 3-substituted product.

The only identifiable by-product observed in the

reactions of the bromo-10-methylacridones with potassamide and with lithium piperidide was 10-methylacridone. Most of the reactions also gave varying amounts of intractable polymeric materials, an observation that is quite common in reactions of aryl halides with strong bases.

When the reaction of 2-bromo-10-methylacridone with five equivalents of 0.1M lithium piperidide in piperidine (Table 11, page 181) was carried out at 75° there was found to be no significant change in the relative yields of the products compared with those obtained at 27°; the only change was an increase in the rate of reaction. At temperatures of 75° and below 10-methylacridone was obtained in yields of 7-18% but, on performing the reactions in refluxing piperidine with five equivalents of 0.25M lithium piperidide, or with a more dilute solution of lithium piperidide, the yield of 10-methylacridone rose to ca. 70%, and the yields of the substitution products decreased but remained in approximately the same relative ratios. However, with ten equivalents of a 1M solution of lithium piperidide in refluxing piperidine the yield (5.2%) of 10-methylacridone was again quite low. These observations indicate that the formation of 10-methylacridone from 2-bromo-10-methylacridone is favoured by high temperatures and low concentrations of lithium piperidide.

With 4-bromo-10-methylacridone there was no significant difference in the relative yields of the products on performing the reaction with lithium piperidide in piperidine at 27° and at reflux temperature, other conditions being the same (Table 13, page 182). There was not the large increase in yield of 10-methylacridone at reflux temperature as might have been inferred from the observations with 2-bromo-10-methylacridone.

In the early reactions of the bromo-10-methylacridones with lithium piperidide in piperidine the reactions of the 2- and 4-bromo compounds at reflux temperature were very slow and gave high yields of 10-methylacridone (Table 8, page 175), 2-bromo- and 4-bromo-10-methylacridone giving respectively 61 and 89% yield of 10-methylacridone under the same conditions. 1-Bromo- and 3-bromo-10-methylacridone also gave some 10-methylacridone but the yields (Table 8, page 175) were very much lower since these compounds readily undergo substitution by the addition-elimination mechanism and prolonged heating was not necessary. Indeed the products from the reaction of 1-bromo-10-methylacridone were essentially the same as those obtained on reaction with refluxing piperidine alone (Table 15, page 184).

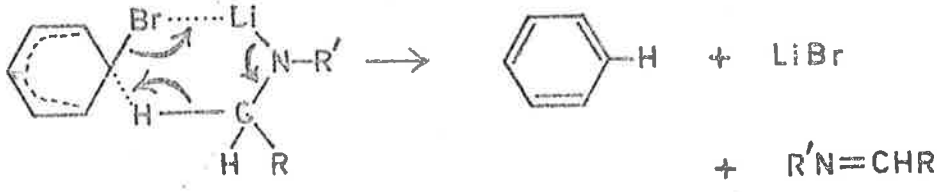
In these early reactions with lithium piperidide in piperidine there was some doubt that the piperidine was

completely dry, although the solvent had been purified by methods adapted from the literature[69]. To test the possibility that the large yield of 10-methylacridone in these reactions of the 2- and 4-bromo-10-methylacridones was due to reaction of lithium hydroxide with the bromo compound the 2- and 4-bromo compounds were heated under reflux with lithium hydroxide in piperidine. On refluxing 2-bromo-10-methylacridone with lithium hydroxide in piperidine no trace of 10-methylacridone was observed after six hours and the starting material was, within experimental error, recovered quantitatively. No trace of any piperidino-10-methylacridone was observed indicating that lithium hydroxide is not a strong enough base to form the arynes. However, 4-bromo-10-methylacridone slowly reacted with lithium hydroxide in refluxing piperidine giving 10-methylacridone, but qualitative experiments showed the reaction to be very much slower than that with lithium piperidide in 'wet' piperidine. Again, no piperidino-10-methylacridones were observed.

The results of the early reactions of 2-bromo-10-methylacridone with lithium piperidide in 'wet' piperidine are consistent with the results discussed above in 'dry' piperidine where the 2-bromo compound is reacting, at reflux temperature, with low concentrations of lithium piperidide. Indeed, the formation of substitution products,

although in low yield, indicates that significant amounts of lithium piperidide were present. Possibly traces of lithium hydroxide co-ordinate with lithium piperidide to give a less basic reagent, thereby reducing the amount of aryne formation.

The reduction of aryl halides by lithium dialkylamides is well known[26j] and two mechanisms have been proposed[66,67], one of which is applicable to the reduction of the bromo-10-methylacridones with lithium piperidide. In this mechanism[66] the lithium dialkylamide reacts with the aryl bromide via the six-membered transition state (70) which, in the case of lithium piperidide, leads to the imine (71). However, in the present work no attempt was made to detect the presence of this imine.



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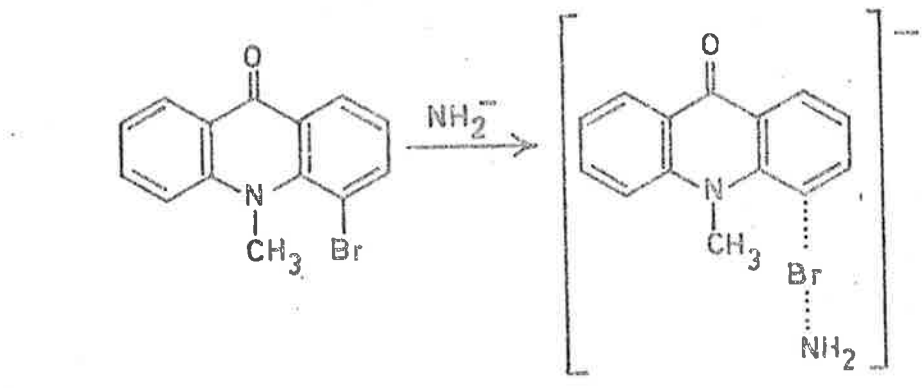
(71)

10-Methylacridone was also obtained on reaction of potassamide in liquid ammonia-dimethoxyethane with 1-, 2- and 4-bromo-10-methylacridones but not with the 3-bromo compound (Table 16-19, pages 189 - 191). As has been mentioned above the 10-methylacridone formed in the reaction of 2-bromo-10-methylacridone comes not from the starting material but from decomposition of the product 2-amino-10-methylacridone. Reduction of 1- and 4-bromo-10-methylacridones to 10-methylacridone probably occurs by nucleophilic attack of amide ion on the bromine atom as has been proposed for the reduction of aryl halides with alkyllithiums[68]. This reaction would be facilitated for the 1- and 4-bromo compounds by relief of steric strain on lengthening of the carbon-bromine bond in the transition state (72) (Scheme 20).

10-Methylacridone was also observed in low yield among the products from the reaction of 1- and 4-bromo-10-methylacridones with refluxing piperidine (Table 15, page 184).



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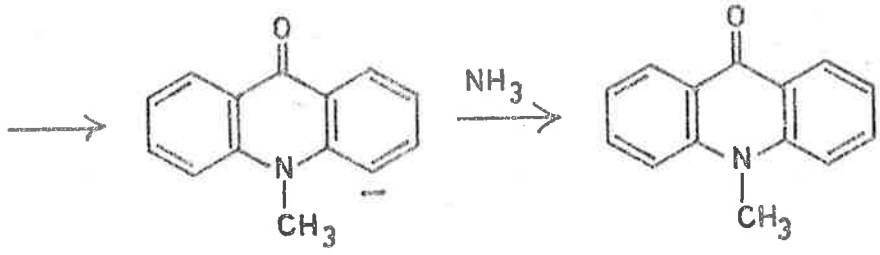


SCHEME 20

PART III

REACTION OF THE ISOMERIC BROMO-10-METHYLACRIDONES WITH SODIUM METHOXIDE IN METHANOL AND IN DIMETHYL SULPHOXIDE

In the previous section the reactions of the bromo-10-methylacridones with strong bases were discussed where nucleophilic substitution was found to occur by both addition-elimination and elimination-addition mechanisms. In continuing the study of nucleophilic substitution in substituted acridones the reactions of the bromo-10-methylacridones with methoxide ion were investigated. This work was directed towards determination of the relative rates of addition-elimination substitution in the 1- and 3-positions.

The reactions of 1- and 3-bromo-10-methylacridone with piperidine have been discussed in Part II and it was found that substitution occurred by the addition-elimination mechanism and was very much faster in the 1-position than in the 3-position. The enhanced rate of substitution by piperidine in the 1-position was explained in terms of hydrogen bonding with the acridone carbonyl group in the transition state. It was therefore pertinent to determine the relative rates of nucleophilic substitution in the 1- and 3-positions with a nucleophile which could

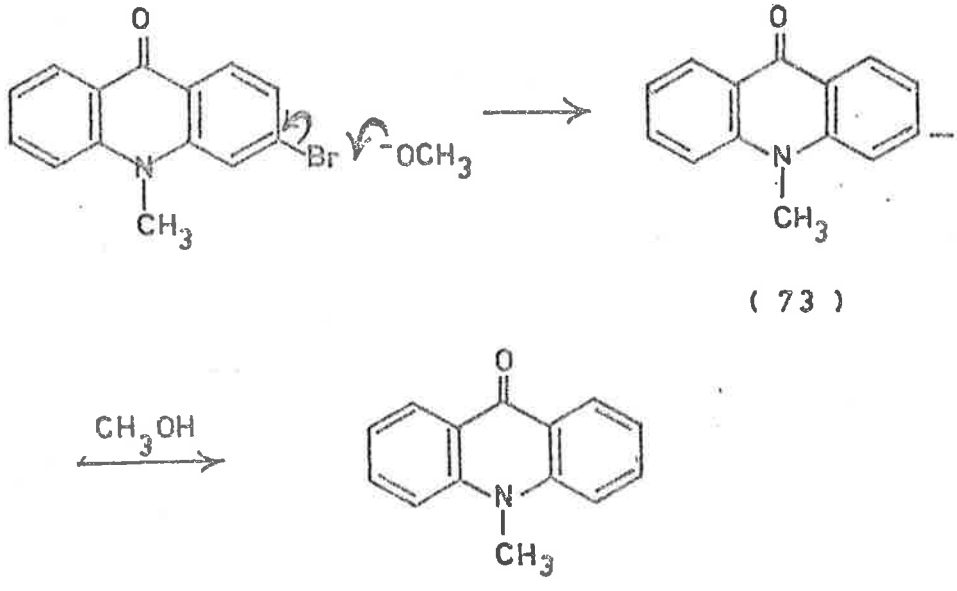
not undergo hydrogen bonding with the carbonyl group in substitutions occurring in the 1-position. It was for this reason that the reactions of 1- and 3-bromo-10-methylacridone with sodium methoxide in methanol were investigated.

1-Bromo- and 3-bromo-10-methylacridone were treated with sodium methoxide in refluxing methanol fully expecting the products to be the 1- and 3-methoxy-10-methylacridones respectively. However, this was not the case. In both reactions the product was found to be 10-methylacridone and no more than trace amounts of the expected substitution products were observed. These reactions were slow, 1-bromo-10-methylacridone giving a 96% yield of 10-methylacridone after refluxing for 18 hours in 0.5M sodium methoxide in methanol and 3-bromo-10-methylacridone giving an 85% yield of 10-methylacridone after 20 hours.

Since this reaction was obviously not a simple nucleophilic substitution of bromine by methoxide ion the reactions of the 2- and 4-bromo compounds were also investigated under the same conditions. Reduction of the bromo compound to 10-methylacridone was again found to occur but there was a vast difference in the relative rates of reduction of the 2- and 4-bromo isomers. 2-Bromo-10-methylacridone reacted extremely slowly with sodium methoxide

in refluxing methanol giving only trace amounts of 10-methylacridone after 48 hours whereas 4-bromo-10-methylacridone reacted quite rapidly, and faster than the 1- and 3-bromo compounds, giving a quantitative yield of 10-methylacridone after only 3.5 hours. Any mechanism proposed to explain these reductions must be consistent with the observations on the relative rates of reaction of the different bromo-10-methylacridones.

One possible mechanism for the reduction of the bromo-10-methylacridones with sodium methoxide in methanol is nucleophilic attack of methoxide ion on the bromine atom (Scheme 21) to give the acridone carbanion (73). Protonation of the carbanion will give 10-methylacridone. This mechanism is similar to that proposed for the reaction



(73)

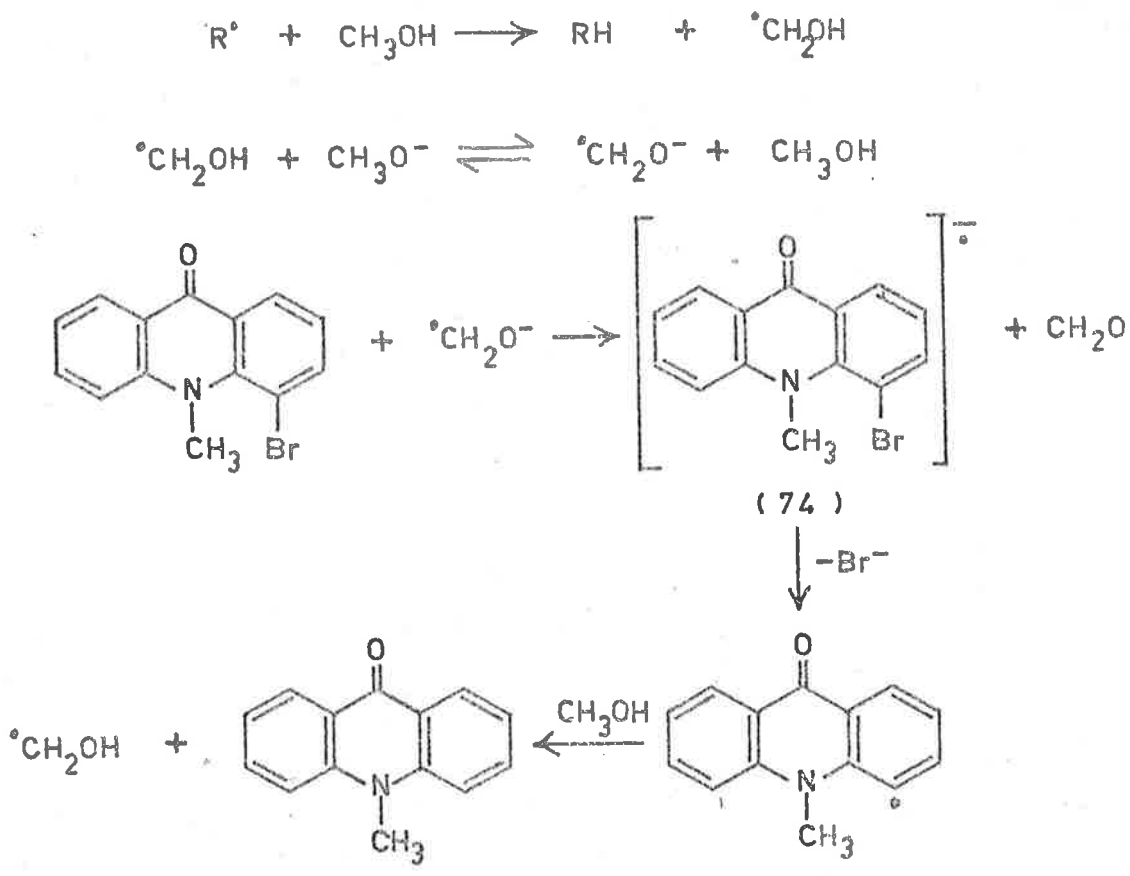
SCHEME 21

of halogenoacetylenes with bases[70]. Reduction by this mechanism would be favoured by any factors inductively effecting polarization of the carbon-bromine bond or inductively stabilizing the carbanion intermediate (73). On both counts the lower electron densities at C-1 and C-3 of the acridone nucleus would favour reduction at the 1- and 3-positions by the mechanism shown in Scheme 21. The unexpectedly rapid reduction of 4-bromo-10-methylacridone could be explained in terms of relief of steric strain in the transition state due to lengthening of the carbon-bromine bond as was proposed in Part II for the formation of 10-methylacridone from potassamide and 4-bromo-10-methylacridone.

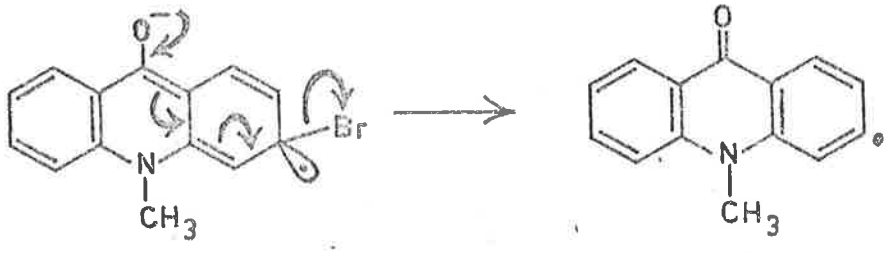
It is also possible to envisage the reduction occurring by a free radical mechanism. Although the reactions were carried out under an atmosphere of nitrogen, the solvent was not degassed and air was not rigorously excluded and may well have entered on removing samples for chromatographic analysis. Therefore, the reduction may be occurring by a free radical mechanism initiated by traces of atmospheric oxygen. Radical chain reactions in the absence of oxygen or other initiators are known[71]. Aryl iodides have been found to undergo deiodination with sodium methoxide in methanol in the presence of radical initiators[72] and it has been proposed that this is a

radical chain reaction occurring via the formaldehyde radical anion, $^{\bullet}CH_2O^{-}$. It has been suggested[72] that the reduction of some aryl halides occurring on prolonged heating with alcoholic alkoxides occurs by the same mechanism in which the radical reaction is initiated by atmospheric oxygen. It seems likely that the present reductions of the bromo-10-methylacridones with sodium methoxide in methanol are a further example of this type of reaction. The mechanism of the reduction, adopted from that of Bunnett and Wamser[72], is shown in Scheme 22. The different rates of reduction of the bromo-10-methylacridones must reflect the differing stabilities of the bromo-10-methylacridone radical anions (e.g. (74)). Addition of one electron to 3-bromo-10-methylacridone will give the stabilized radical anion (75) which will readily lose bromide ion giving the 10-methylacridone radical (76). A similar process will apply in the reduction of the 1-bromo compound and accounts for the faster reactions of the 1- and 3-bromo compounds compared with the 2-bromo compound. Again, removal of bromide ion from the 4-position is probably assisted by relief of steric strain in the transition state.

One further possibility for the mechanism of reduction of the bromo-10-methylacridones with methoxide ion in methanol is hydride transfer from methoxide ion to



SCHEME 22



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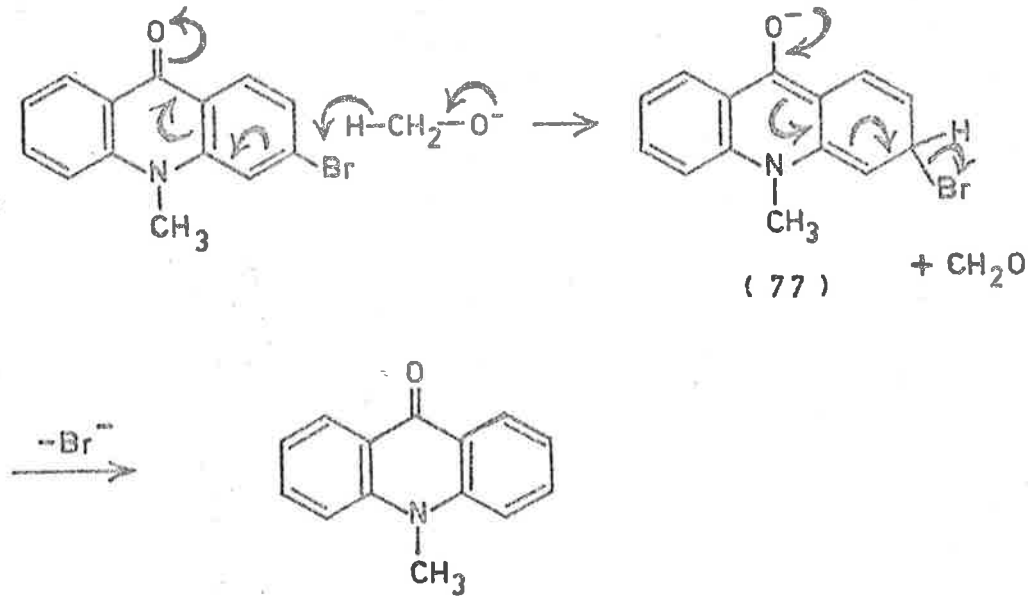


SCHEME 23

the bromo-10-methylacridone forming an intermediate such as (77) and formaldehyde (Scheme 23). This mechanism is essentially an addition-elimination substitution, and, although it could account for the reduction of 1- and 3-bromo-10-methylacridone to 10-methylacridone, it would not satisfactorily account for the relatively rapid reduction of the 4-bromo compound which has not been observed to undergo nucleophilic substitution by the addition-elimination mechanism in other reactions.

In order to distinguish between the ionic and free radical mechanisms the reaction was carried out with 4-bromo-10-methylacridone and sodium methoxide in methanol-d_1 (CH_3OD) where, if the reduction is occurring by the ionic

mechanism (Scheme 21) the 10-methylacridone would contain deuterium but by the free radical mechanism (Scheme 22) no deuterium would be introduced. The 10-methylacridone obtained in this reaction was found by mass spectrometry to contain no deuterium and it can be inferred that for 4-bromo-10-methylacridone the reduction is occurring by the free radical mechanism. The reduction almost certainly occurs by the same mechanism with the other bromo-10-methylacridones. The occurrence of the free radical mechanism has been confirmed[73] by carrying out the reduction of 4-bromo-10-methylacridone with sodium methoxide in methanol in the presence of azobisisobutyronitrile and in the presence of hydroquinone. The rate of formation of 10-methylacridone was found to be enhanced in the presence of azobisisobutyronitrile and diminished in the presence of hydroquinone. This distinguishes the free radical mechanism from the less likely hydride transfer mechanism.

Since 1- and 3-bromo-10-methylacridone underwent very little nucleophilic substitution with sodium methoxide in methanol the reaction was carried out with sodium methoxide in methanol-free dimethyl sulphoxide. In the latter solvent the products were found to be exclusively the 1- and 3-methoxy-10-methylacridones respectively. Since methoxide ion is not solvated in dimethyl sulphoxide[74] the activation energy for nucleophilic substitution is much

lower in dimethyl sulphoxide than in methanol, where methoxide ion is strongly solvated. Nucleophilic substitution, therefore, occurs very much faster in dimethyl sulphoxide than in methanol. The second order rate constants at 40° determined for the nucleophilic substitution of 1- and 3-bromo-10-methylacridone with sodium methoxide in methanol-free dimethyl sulphoxide are recorded in Table 4. It is seen that 3-bromo-10-methylacridone undergoes nucleophilic substitution faster than

TABLE 4.

Second order rate constants for reaction with sodium methoxide in methanol-free dimethyl sulphoxide at 40°.

	k ($l.mole^{-1}.sec^{-1}$)
1-Bromo-10-methylacridone	0.046
3-Bromo-10-methylacridone	0.15

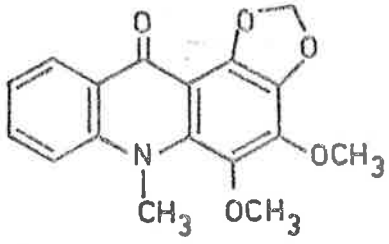
1-bromo-10-methylacridone. This appears to be the normal pattern of ortho and para activating effects[20e,20h] for addition-elimination substitutions in which activation is due to the electron-withdrawing (-M) mesomeric effect of the substituent and in which no special hydrogen bonding

or steric effects influence the rate of substitution in the position ortho to the activating group. The greater rate of substitution with the para-isomer is generally ascribed to the somewhat greater conjugative effect at the para-position than at the ortho-position[20e].

PART IV

REACTION OF SOME POLYALKOXY-10-METHYLACRIDONES WITH SODIUM METHOXIDE IN METHANOL AND IN DIMETHYL SULPHOXIDE

In this section the mechanisms of the reactions of some polyalkoxy-10-methylacridones with sodium methoxide are discussed and, in particular, the reactions of the methylenedioxyacridones, 3,4-dimethoxy-1,2-methylenedioxy-10-methylacridone (78), melicopidine (79), and melicopine



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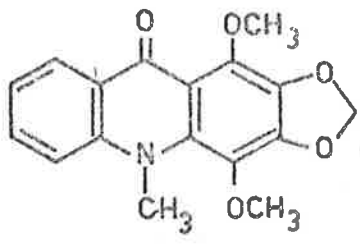

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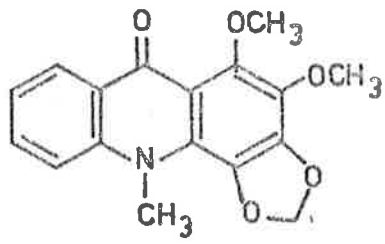
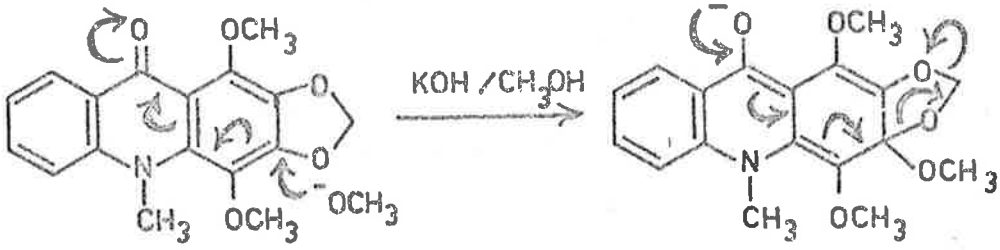


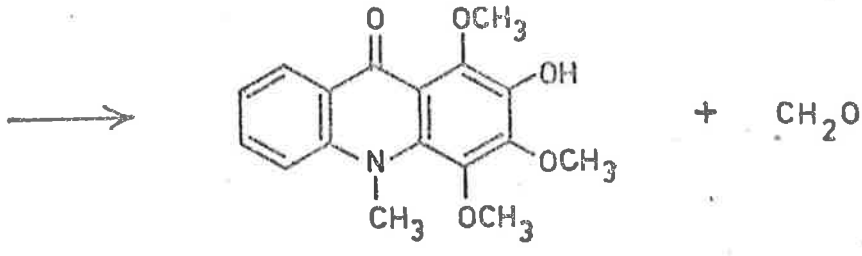
(80)

(80) with sodium methoxide are considered. This work was again directed towards an examination of nucleophilic substitution by the addition-elimination mechanism in the 1- and 3-positions of the acridone nucleus.

In their elucidation of the structures of the acridone alkaloids Crow and Price found that melicopidine (79) and melicopine (80) reacted with methanolic potassium hydroxide[12] to open the methylenedioxy ring giving the phenols (82) and (83) respectively. It is well known that



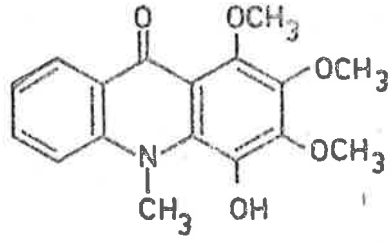
(81)



(82)

SCHEME 24

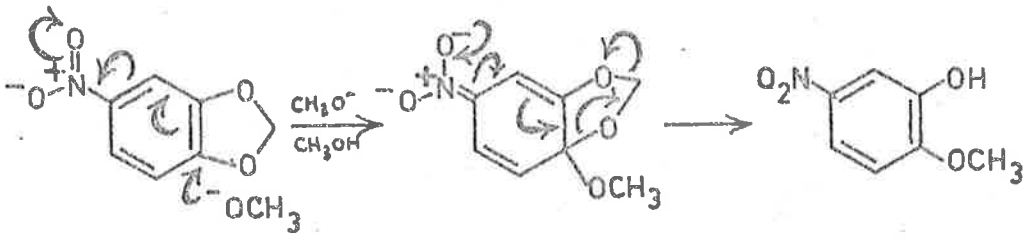
the nucleophilic species in alcoholic alkali is the alkoxide ion and this reaction obviously occurs for melicopidine by nucleophilic substitution at the 3-position by the addition-elimination mechanism via the intermediate (81) (Scheme 24). Ring opening of the methylenedioxy ring of melicopine (80) occurs by the same type of mechanism again involving nucleophilic attack by methoxide ion at the 3-position.



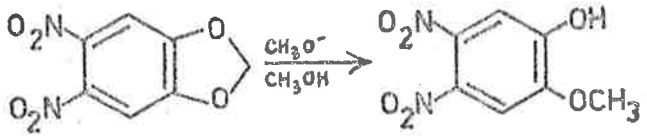
(83)

Nucleophilic substitution of this type at methylenedioxy substituents is also known to occur in the reactions of the methylenedioxynitrobenzenes (84) and (87) which, on treatment with sodium methoxide in methanol, undergo opening of the methylenedioxy ring giving the phenols (86) and (88) respectively[75,76]. Again this is interpreted in terms of an addition-elimination substitution via intermediates such as the species (85) where methoxide ion has attacked the aromatic ring at the position activated

by the nitro group.



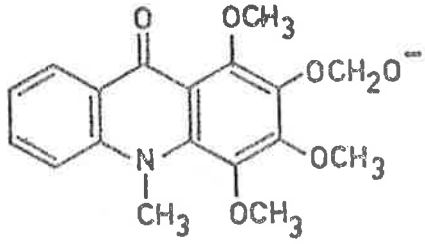
(84) (85) (86)



(87) (88)

It is difficult to decide whether or not the formaldehyde is lost from intermediates such as (81) and (85) in a synchronous process or if it occurs by a two-step process via a second intermediate such as the species (89) in the case of melicopidine. Since the species (89) would be expected to lose formaldehyde very rapidly the corresponding alcohol would not be expected to be observed among the products of the reaction. The results do not distinguish between the two modes for loss of formaldehyde from the first formed intermediate, but, in view of the stability of formaldehyde, the synchronous process would be favoured. Since the elimination of formaldehyde occurs after the rate determining step, it is unimportant in the present

work by which process this elimination occurs.

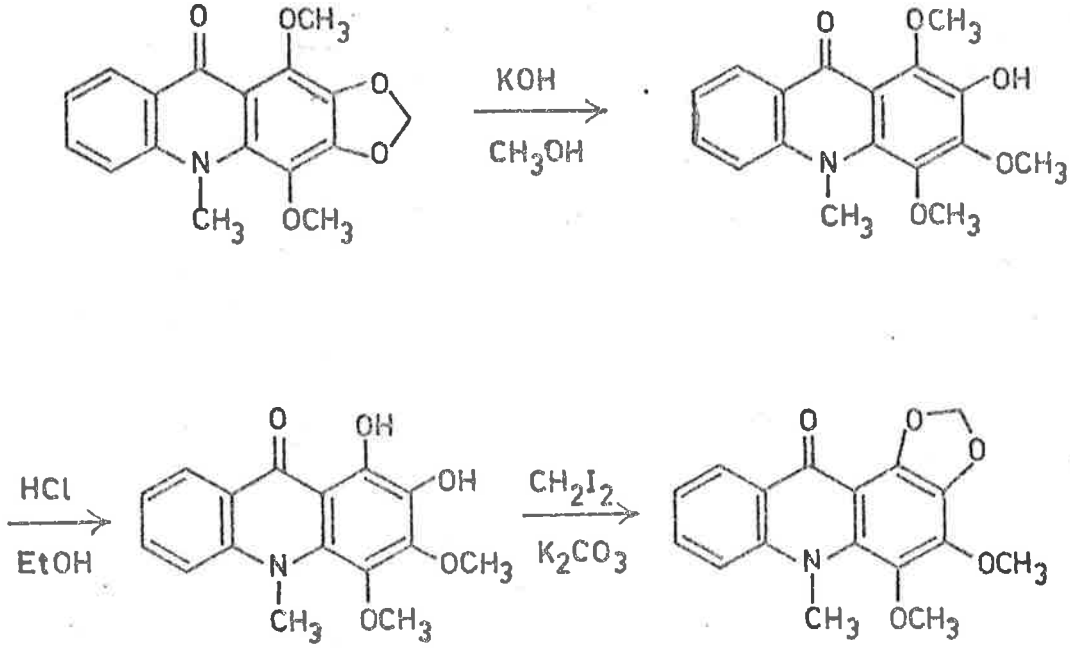


(89)

The present work was directed towards determining the rates at which the three isomeric dimethoxymethylenedioxy-10-methylacridones (78), (79) and (80) undergo nucleophilic substitution with methoxide ion with opening of the methylenedioxy ring. Loss of formaldehyde from intermediates such as the species (81) by either the synchronous or two-step process would be expected to have a lower activation energy than the reverse process, loss of methoxide ion. Therefore, the first step in these reactions, nucleophilic attack by methoxide ion on aromatic carbon, would be expected to be the rate determining step and the reaction would be expected to follow second order kinetics.

Melicopidine (79) and melicopine (80) both occur naturally as alkaloids of several species of the family Rutaceae[14]. However, the 1,2-methylenedioxy isomer, 3,4-dimethoxy-1,2-methylenedioxy-10-methylacridone (78),

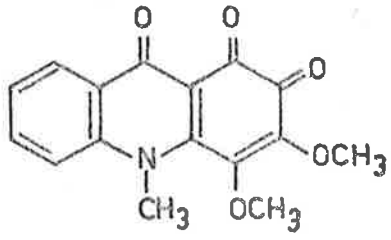
has not been observed to occur naturally and has not been described in the literature. In order to carry out a complete study of the relative rates of ring opening of the methylenedioxy rings of the methylenedioxyacridones this compound was required and was synthesized from melicopidine by the route shown in Scheme 25. The first two steps were carried out by procedures described by Crow and Price[12]. The 1,2-dihydroxy-3,4-dimethoxy-10-methyl-acridone (90) obtained in the present work was found to have a sharp melting point some 42 degrees higher than that



(90) (91)

SCHEME 25

recorded in the literature. The mass spectrum of this compound showed only a very small molecular ion at m/e 301, that expected for the dihydroxy compound (90) and a large peak at m/e 299. It appears that the molecular ion of the dihydroxy compound (90) readily loses hydrogen giving the molecular ion of the o-quinone (92). Evidence that the compound prepared was not the quinone (92) was



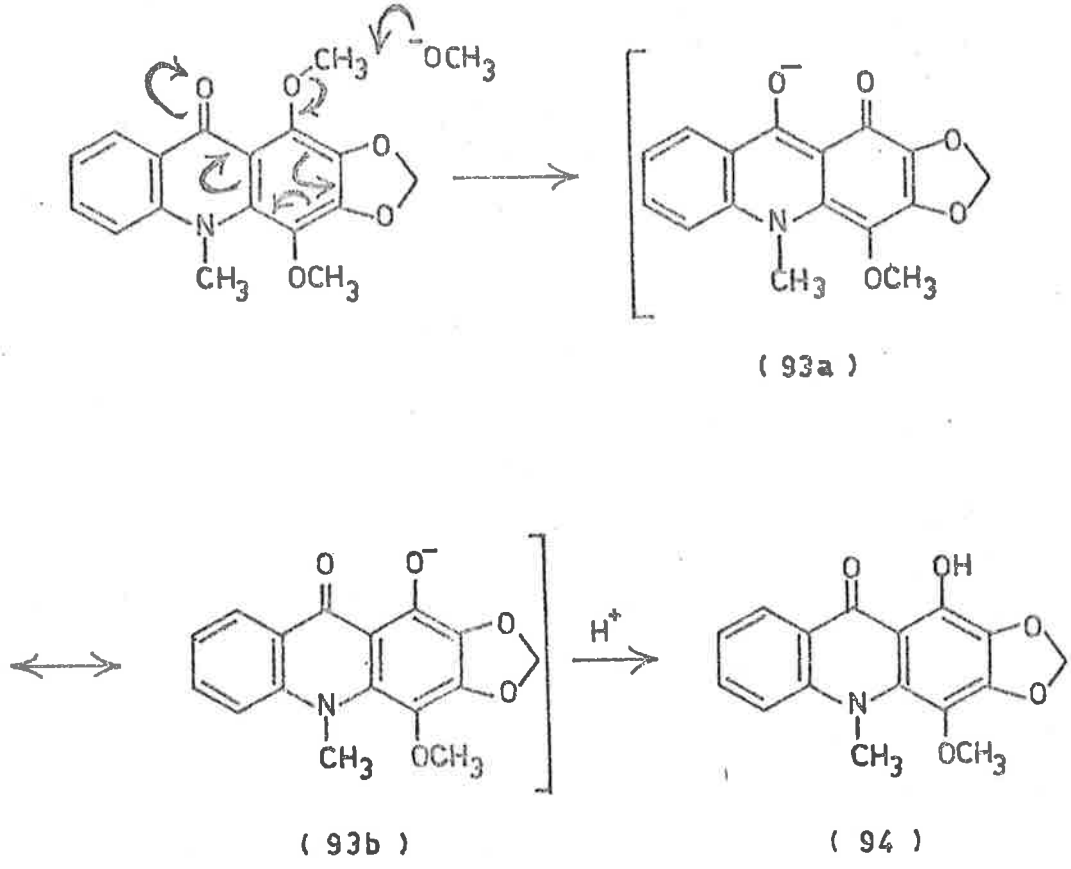
(92)

obtained from the broad O-Hstr band in the i.r. spectrum and from the positive phenol test with ferric chloride. Furthermore, the melting point recorded in the literature[77] for the quinone (92) is 30 degrees higher than that obtained in this work for the melting point of the dihydroxy compound (90). Reaction of the dihydroxy compound (90) with di-iodomethane and potassium carbonate in refluxing acetone gave a good yield of the 1,2-methylenedioxy compound (91).

The reactions of the methylenedioxyacridones (78), (79) and (80) with sodium methoxide in refluxing methanol were examined in order to determine whether this was a

suitable system for measuring the rates of methylenedioxy ring-opening with methoxide ion. These reactions were very slow and it was only in the case of melicopidine (79) that ring-opening of the methylenedioxy ring by the expected process was the principal reaction. With melicopine (80) and the 1,2-methylenedioxy compound (78) a complex mixture of products was obtained and the nature of these products warranted further investigation. It was qualitatively observed that reaction with methoxide ion occurs somewhat faster with melicopidine (79) than with the other two methylenedioxyacridones (78) and (80), an observation also made by Crow and Price for the reactions of melicopidine and melicopine with methanolic potassium hydroxide[12].

Melicopidine reacted with 1M-sodium methoxide in refluxing methanol giving, after 6 days, a 97% yield of the phenol (82) together with a 3% yield of normelicopidine (94). The phenol (82) arises by nucleophilic substitution by methoxide ion in the 3-position as shown in Scheme 24. Normelicopidine must arise from attack of methoxide ion on the methoxyl carbon in the 1-position (Scheme 26). Since the product of this reaction is present in the alkaline solution as the resonance stabilized anion (93a$\leftrightarrow$93b) further attack by methoxide ion, which would result in opening of the methylenedioxy ring, would



(93a)

(93b)

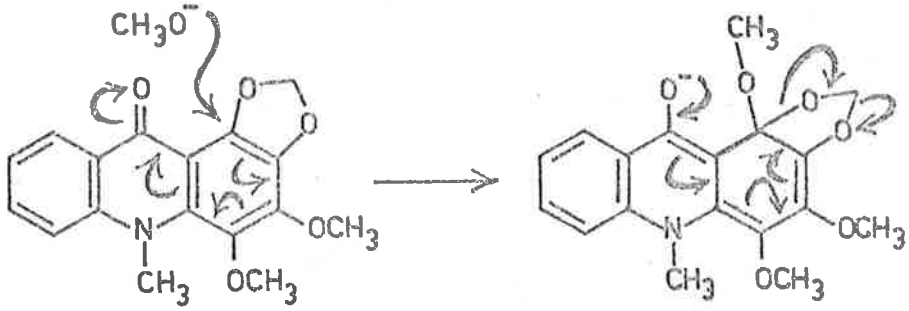
(94)

SCHEME 26

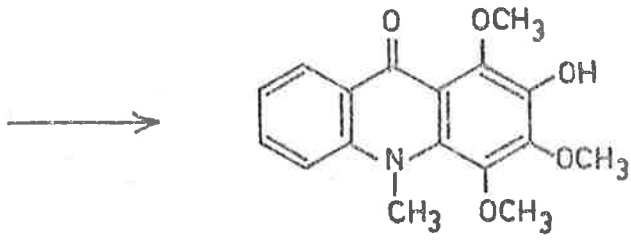
be unlikely to occur. Crow and Price obtained the phenol (82) in 82% yield on reaction of melicopidine with methanolic potassium hydroxide[12] but did not observe normelicopidine (94) as a product. However, normelicopidine was observed as a minor product on reaction of melicopidine with ethanolic potassium hydroxide[12].

3,4-Dimethoxy-1,2-methylenedioxy-10-methyl-

acridone (78) reacted with 1M-sodium methoxide in refluxing methanol more slowly than did melicopidine and after 14 days 3% of the starting material remained. Only 39% yield of the normal product, the phenol (96), was obtained. This product is formed by nucleophilic attack of methoxide ion at the 1-position (Scheme 27) giving the intermediate (95) which, on loss of formaldehyde, gives the phenol (96). The other products obtained in this reaction were



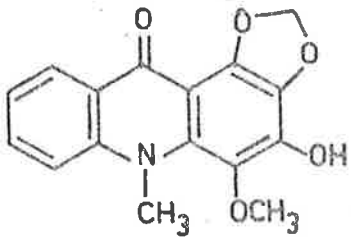
(95)



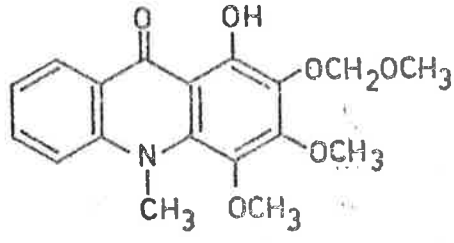
(96)

SCHEME 27

3-hydroxy-4-methoxy-1,2-methylenedioxy-10-methylacridone (97), which was obtained in 25% yield, and 3,4-dimethoxy-1-hydroxy-2-(∝-methoxy)methoxy-10-methylacridone (98), which was obtained in 13% yield.



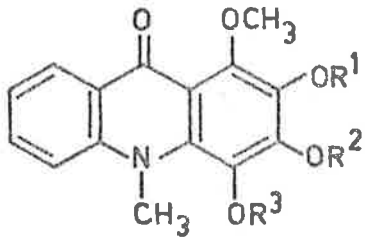
(97)



(98)

The phenol (97), in which the methylenedioxy ring remained intact, was identified from its mass spectrum, which showed that demethylation had occurred, and by re-formation of 3,4-dimethoxy-1,2-methylenedioxy-10-methylacridone (78) on methylation with diazomethane. This evidence does not distinguish between the 3-hydroxy compound (97) and its isomer in which the hydroxyl group is in the 4-position. Since compound (97) could be formed from the 1,2-methylenedioxy compound (78) by a process analogous to the formation of normelicopidine from melicopidine (Scheme 26) this demethylation would be expected to occur preferrentially in the activated 3-position. The position of the hydroxyl group in compound (97) was confirmed by u.v. and mass spectrometry. The

u.v. spectrum of compound (97) showed very similar changes to the u.v. spectrum of the 3-hydroxy-acridone (100) in



(99) $R^1 = H$, $R^2 = R^3 = CH_3$

(100) $R^2 = H$, $R^1 = R^3 = CH_3$

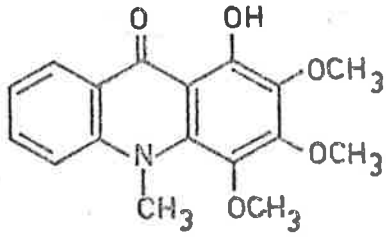
(101) $R^3 = H$, $R^1 = R^2 = CH_3$

neutral and alkaline solution and, in particular, a hypsochromic shift and increase in intensity of the long wavelength band was observed for both of these compounds on transferring from neutral to alkaline solution. The u.v. spectra of the 2-hydroxy-acridone (99) and the 4-hydroxy-acridone (101) showed totally different changes in neutral and alkaline solution where, for the long wavelength band, there was a bathochromic shift and decrease in intensity in alkaline solution.

Further evidence for the position of the hydroxyl group in compound (97) was obtained from the mass spectrum of the 3,4-dimethoxy-1,2-methylenedioxy-10-methylacridone obtained on methylation with dideuterodiazomethane. The mass spectrum of this methylation product showed specific loss of CH_3 rather than CD_3. Since the molecular ions of methoxy-10-methylacridones preferrentially lose methyl

radical from the 2- or 4-positions[39] methylation with dideuterodiazomethane must have occurred in the 3-position. This evidence added to that of the u.v. spectra unequivocally places the hydroxyl group of compound (97) in the 3-position.

The structure of compound (98) was determined from its u.v., n.m.r. and mass spectra. Compound (98) had the same R_f and appearance as normelicopicine (102) on thin layer chromatography and, in particular, did not fluoresce under u.v. light, an observation characteristic of acridones with a 1-hydroxyl substituent. In addition



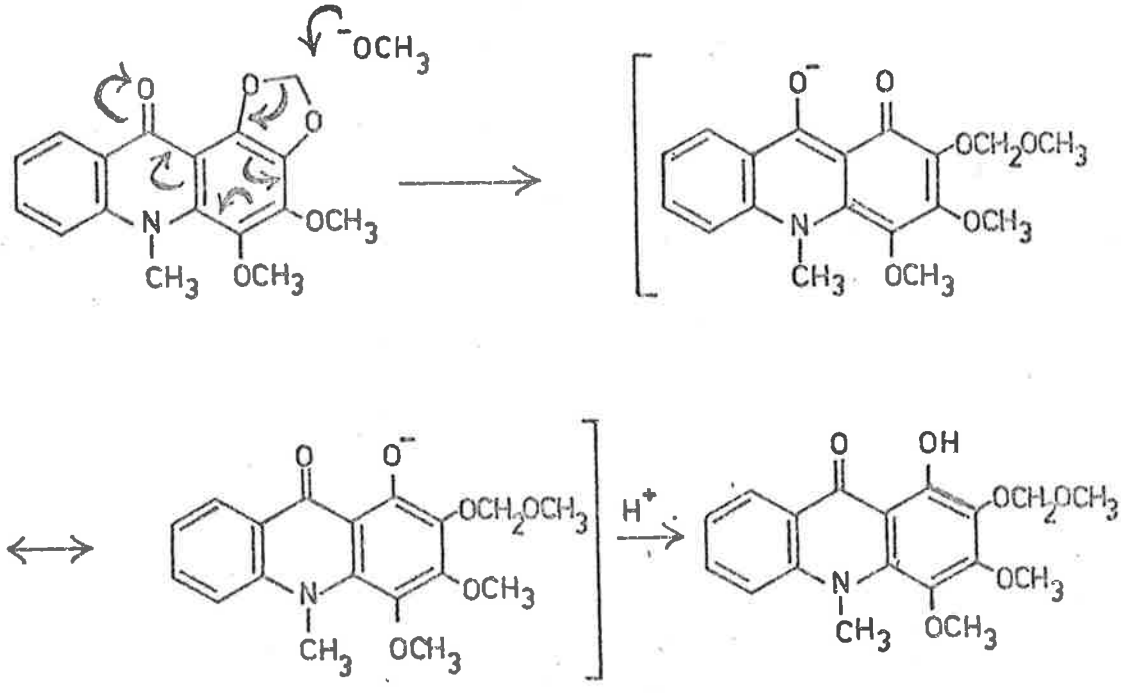
(102)

the u.v. spectra of compound (98) in neutral and alkaline solution were identical with those of normelicopicine (102) under the same conditions. Clearly compound (98) is very closely related to normelicopicine (102) and, in particular, appears to contain a 1-hydroxyl group. These two compounds could differ only in the nature of the substituent in the 2-position. The n.m.r. spectrum of compound (98) clearly showed the four methyl groups on oxygen or nitrogen and

the methylenedioxy group. The hydroxyl group was at very low field (δ 14.5) which again is characteristic of 1-hydroxy-acridones. The mass spectrum showed the molecular ion at m/e 345 and the base peak at m/e 300 which is consistent with the loss of the CH_2OCH_3 radical from the 2-position of the acridone nucleus.

Compound (97) clearly must form by attack of methoxide ion on the methyl carbon of the 3-methoxyl group in a process analogous to that shown in Scheme 26 for the formation of normelicopidine from melicopidine.

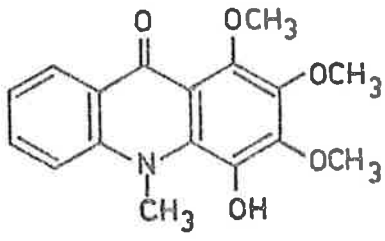
Compound (98) forms in a similar manner to compound (97) but, in this case, the attack by methoxide ion occurs at the methylenedioxy carbon (Scheme 28). Ring-opening of



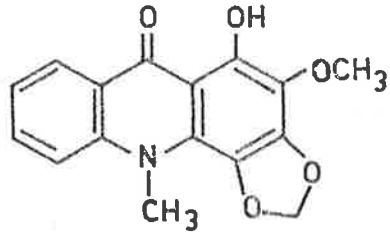
SCHEME 28

the methylenedioxy ring occurs only in the direction assisted by the carbonyl group. This type of ring-opening with alkoxides, resulting in the formation of alkoxymethyl ethers, has been observed in the reactions of aromatic methylenedioxy compounds which are not activated towards nucleophilic attack on aromatic carbon[78,79].

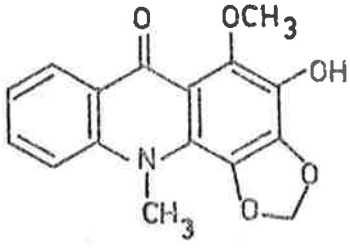
Melicopine (80) reacts with sodium methoxide in methanol much more slowly than does melicopidine and results in a mixture of products even more complex than that obtained from the 1,2-methylenedioxy compound (78). The principal product of the reaction is the phenol (103)



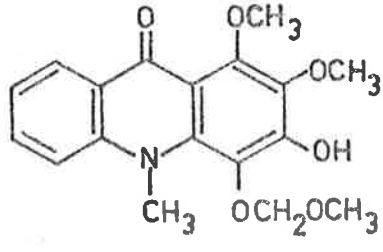
(103)



(104)

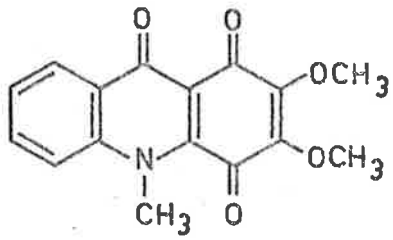


(105)



(106)

which is the normal product of ring opening and is formed in a process analogous to that shown in Scheme 24. A large fraction of the product, which appeared to be a mixture of several compounds, remained unidentified. Among the minor products of the reaction were normelicopine (104), 2-hydroxy-1-methoxy-3,4-methylenedioxy-10-methylacridone (105), 1,2-dimethoxy-3-hydroxy-4-(α-methoxy)-methoxy-10-methylacridone (106) and the dimethoxyquinone (107). The last compound appears to come from the phenol (103) during separation by demethylation and oxidation on the silica gel plates. Normelicopine (104) must be formed by attack of methoxide ion on the 1-methoxyl group in a process analogous to that shown in Scheme 26 for the formation of normelicopidine.



(107)

The 2-hydroxy compound (105), which was identified from its mass spectrum, gave melicopine on methylation with diazomethane. Since the compound (105) differed from normelicopine (104) the hydroxyl group could only be in the 2-position. This was confirmed by methylation with

dideuterodiazomethane. The mass spectrum of the melicopine from this methylation showed specific loss of the CD_3 radical indicating methylation had occurred in the 2-position[39]. The 2-hydroxy compound (105) must result from attack of methoxide ion on the 2-methoxyl carbon although this demethylation is not activated by the carbonyl group as are similar demethylations occurring in the 1- and 3-positions.

The compound (106) was identified from its mass spectrum which showed the molecular ion at m/e 345 and a large fragment ion at m/e 300 corresponding to loss of the fragment CH_2OCH_3 from the 4-position[39]. This compound must be formed by attack of methoxide ion on the methylenedioxy carbon in a process analogous to that shown in Scheme 28 and, again, methylenedioxy ring-opening occurs in the direction assisted by the carbonyl group.

Crow and Price[12] found melicopine reacted very slowly with methanolic potassium hydroxide giving variable yields of the phenol (103) and some normelicopine[14] (104). A large proportion of the starting material was recovered unchanged.

The slower reactions of melicopine (80) and the 1,2-methylenedioxy compound (78) with sodium methoxide in methanol and the large number of by-products formed com-

pared with the reaction of melicopidine (79) indicate that the activation energy for nucleophilic substitution by the addition-elimination mechanism at the methylenedioxy ring is higher for melicopine and the 1,2-methylenedioxy compound (78) than for melicopidine. Since nucleophilic attack by methoxide ion occurs at C-3 in both melicopidine and melicopine there must be some factor other than electronic activation by the carbonyl group influencing the rate of this reaction.

The large number of products formed in the reactions of the 1,2-methylenedioxy compound (78) and melicopine with sodium methoxide in methanol prevented determination of the rates of methylenedioxy ring-opening for these compounds in methanol as solvent. However, the reaction of melicopidine was sufficiently specific that the rate of methylenedioxy ring-opening could be satisfactorily determined. In refluxing methanol (65^{o}) the second order rate constant for ring-opening of the methylenedioxy ring of melicopidine was found to be 4.0×10^{-6} l. $mole^{-1}.sec^{-1}$.

When these reactions were carried out in methanol-free dimethyl sulphoxide as solvent the reactions of the 1,2-methylenedioxy compound (78) and melicopine were now found to be far more specific and the products were almost entirely the phenols (96) and (103) respectively. It was therefore possible, in this system, to determine the rates

of ring-opening of all three dimethoxymethylenedioxy-10-methylacridones. The second order rate constants for these reactions at 40^{o} are recorded in Table 5 where it can be seen that the relative rates of ring-opening of the

TABLE 5.

Second order rate constants for reaction of the dimethoxymethylenedioxy-10-methylacridones with sodium methoxide in methanol-free dimethyl sulphoxide at 40^{o}.

	k $l.mole^{-1}.sec^{-1}$.
3,4-dimethoxy-1,2-methylenedioxy-10-methylacridone	0.090
melicopidine	0.180
melicopine	0.040

methylenedioxy rings are in the order

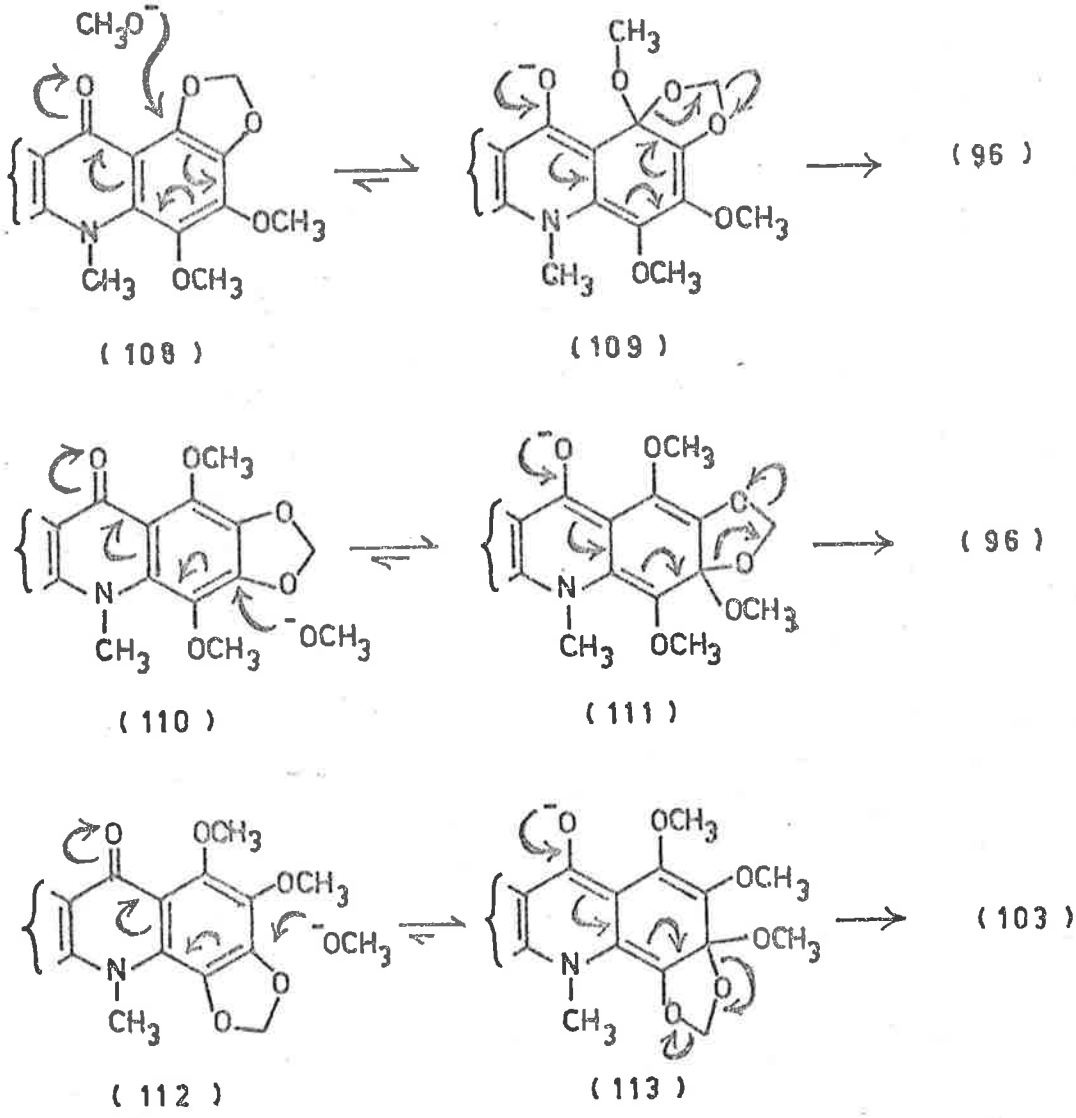
2,3-methylenedioxy > 1,2-methylenedioxy > 3,4-methylenedioxy.

There is also seen to be an approximately 4×10^{4} -fold rate enhancement on transferring the reaction with meli-

copidine from methanol to methanol-free dimethyl sulphoxide as solvent. The rate enhancement in dimethyl sulphoxide would actually be somewhat higher than the above figure as the reaction in methanol was carried out at 65° whereas that in dimethyl sulphoxide was carried out at 40°. For reactions between anions and neutral molecules the reaction is normally very much faster in dipolar aprotic than in protic solvents[74].

Reaction of the methylenedioxyacridones with methoxide ion is a two-step process for which the pathways for the different methylenedioxy isomers are shown in Scheme 29. As has been mentioned previously the second step in this reaction, loss of formaldehyde from the intermediate, is expected to be a very rapid process and to occur to the virtual exclusion of the reverse process, loss of methoxide ion. The first step is, therefore, expected to be the rate determining step and since formation of the intermediates (109), (111) and (113) is an endothermic process the transition states for these reactions will closely resemble the respective intermediates[80]. It is possible to rationalize the observed differences in rate of methylenedioxy ring-opening for the different isomers in terms of electronic activation effects and in terms of the geometry of the transition states.

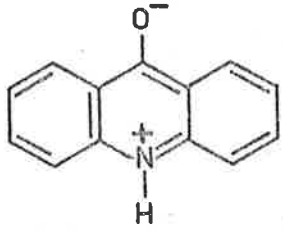
Since reaction of methoxide ion with melicopidine



SCHEME 29

and melicopine both involve nucleophilic attack of methoxide ion at C-3, where it is expected that the electronic activating effects of the carbonyl group are the same in each compound, it is necessary to look for other factors which may affect the rate of formation of the intermediate. It

is possible to rationalize the slower rate of reaction with melicopine, compared with that of melicopidine, in terms of the carbon-carbon bond lengths in the benzenoid ring of the acridone nucleus. There is considerable evidence that a significant proportion of the acridinium canonical form (114) contributes to the structure of acridone[1b] so that acridone would be expected to exhibit similar bond fixation to that occurring in acridine. The bond lengths



(114)

of acridine have been measured[81] and it has been found that the $C_1 - C_2$ and $C_3 - C_4$ bonds are somewhat shorter than the $C_2 - C_3$ bond. This same alternation in carbon-carbon bond lengths would be expected to occur in acridone. In addition, Hückel molecular orbital calculations[2] have shown the $C_1 - C_2$ and $C_3 - C_4$ bonds of acridone to have a higher bond order than the $C_2 - C_3$ bond, again indicative that the $C_1 - C_2$ and $C_3 - C_4$ bonds of acridone are shorter than the $C_2 - C_3$ bond.

Examination of appropriate molecular models shows the five-membered methylenedioxy ring of the methylene-dioxyacridones to be considerably strained and, furthermore,

shows that this strain should decrease as the carbon-carbon bond of the five-membered ring is shortened. Since the $C_3 - C_4$ bond of acridones is expected to be shorter than the $C_2 - C_3$ bond the methylenedioxy ring of melicopine will be less strained than that of melicopidine. Melicopine will therefore have a lower ground state energy than melicopidine. However, on forming the intermediates (111) and (113), which closely resemble the respective transition states, the 3-carbon becomes sp^3 hybridized and the carbon-carbon bonds of the five-membered methylenedioxy rings are now single bonds in both (111) and (113) and are of the same length. The strain energy of the methylenedioxy rings will, therefore, be the same in both intermediates and nearly the same in both transition states. This will result in a higher activation energy (Fig. 4) and a slower rate of reaction for melicopine than for melicopidine.

Since the $C_1 - C_2$ and $C_3 - C_4$ bonds of acridone are expected to be of very nearly the same length the ground state energies of the 1,2-methylenedioxy compound (108) and melicopine (112) are expected to be very nearly the same and the changes in ring strain of the methylenedioxy ring in formation of the intermediate will be essentially the same for both compounds. The observed difference in reaction rate of these two compounds must, therefore, reflect the electronic activation effects of the carbonyl group on

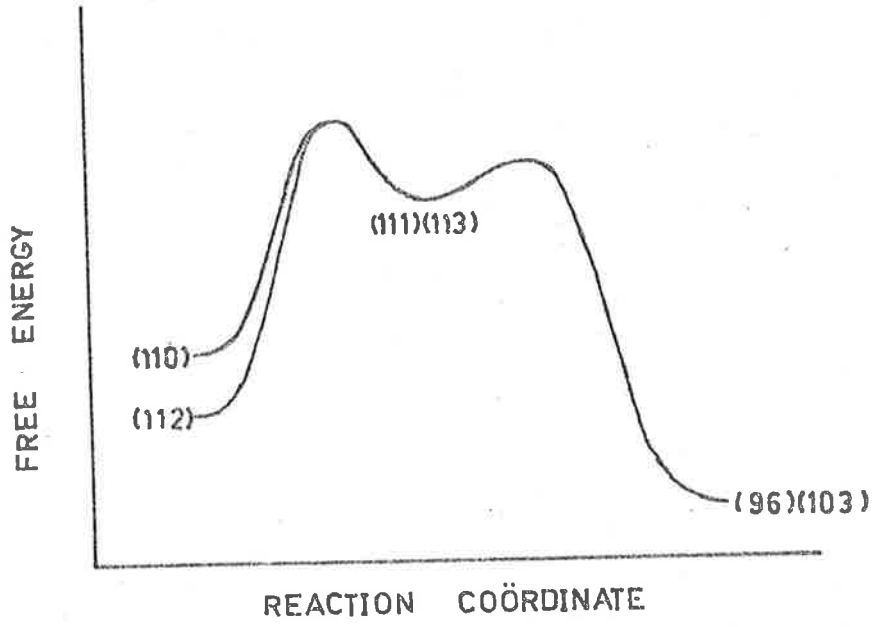
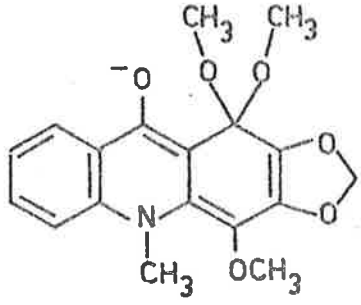


FIG. 4

addition-elimination substitution by methoxide ion in the 1- and 3-positions of the dimethoxymethylenedioxy-10-methylacridones. The results indicate that, with alkoxy leaving groups, substitution occurs faster in the 1-position than in the 3-position, the reverse of that obtained with the bromo-10-methylacridones.

In the reactions of the dimethoxymethylenedioxy-10-methylacridones with methoxide ion a reaction which may compete with ring-opening of the methylenedioxy ring is methoxide exchange at the other position activated towards nucleophilic substitution. Methoxide exchange at the 1-

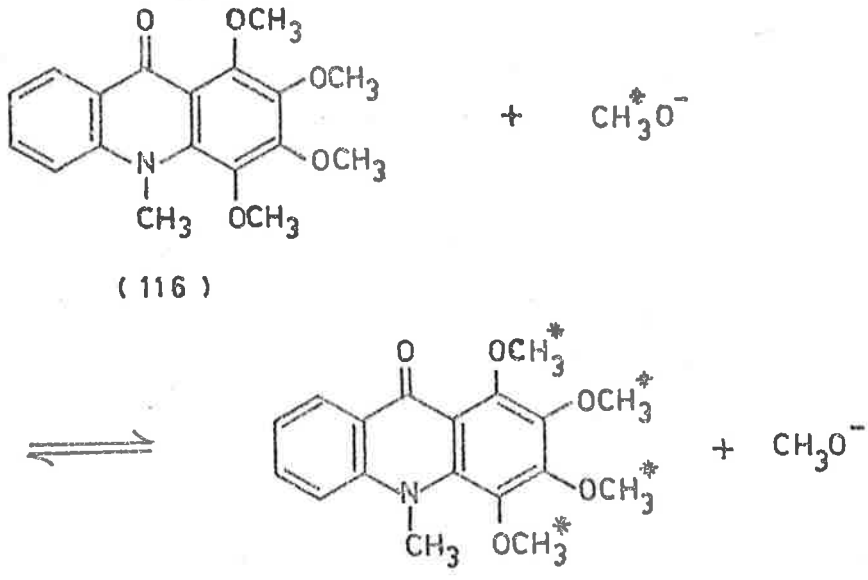
position of melicopidine will occur via the intermediate (115) and will occur via similar intermediates for the other dimethoxymethylenedioxy-10-methylacridones. However, methoxide exchange results in no chemical change in the molecule and could only be observed with the use of isotopically labelled methoxide ion. Since the dimethoxymethylenedioxy-10-methylacridones undergo chemical change



(115)

with methoxide ion the exchange process was examined for the tetra-methoxy acridone, melicopicine (116). This work was carried out with the view to determining the rates of exchange of the methoxyl groups in each of the four positions and, in particular, the rates of exchange in the 1- and 3-positions. So that the results obtained in the exchange reactions might be directly compared with those obtained for the rates of ring-opening of the different dimethoxymethylenedioxy-10-methylacridones the exchange reaction with melicopicine was carried out under the same

conditions employed to determine rates of ring-opening of the different methylenedioxy rings. Melicopicine was treated with tritium-labelled sodium methoxide (CH_3^*ONa) in methanol-free dimethyl sulphoxide at 40°. However, under these conditions, the exchange reaction was found to be too fast to follow by standard sampling techniques and equilibrium (Scheme 30) was established before the first sample had been removed. Samples removed after 4, 6 and 8 minutes all had, within experimental error, the same activity. Obviously methoxide exchange in melicopicine occurs very much faster with sodium methoxide in methanol-



(116)

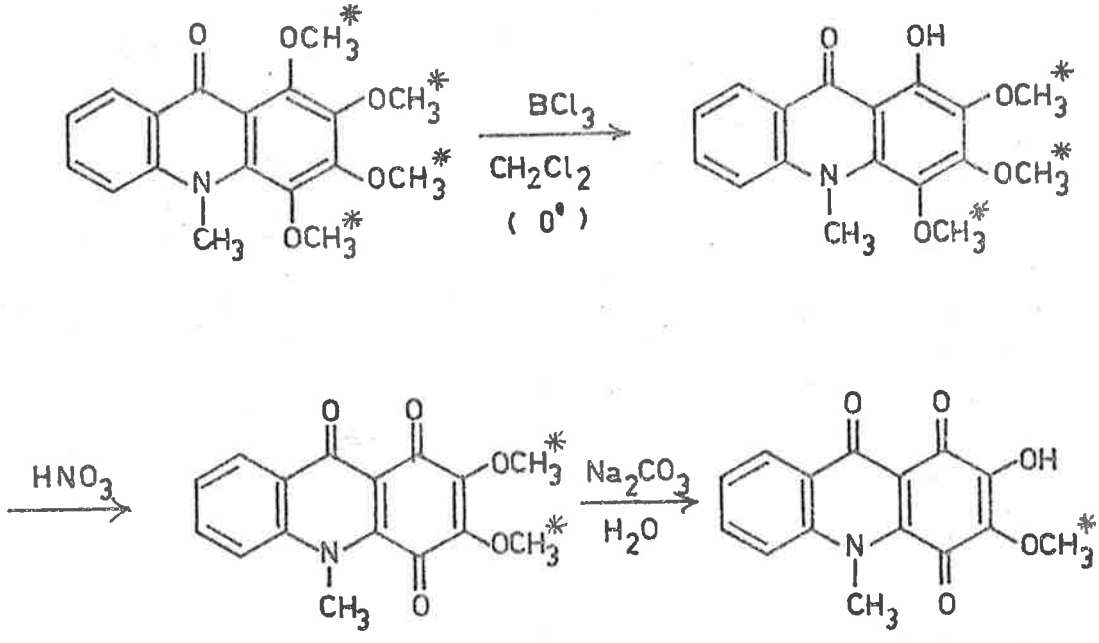
SCHEME 30

free dimethyl sulphoxide than methylenedioxy ring-opening occurs in the dimethoxymethylenedioxy-10-methylacridones.

The rate of methoxide exchange in melicopicine could be slowed to a measurable rate by performing the reaction with sodium methoxide in a mixture of dimethyl sulphoxide and methanol. Reactions which proceed at a greatly enhanced rate in dipolar aprotic solvents are also found to proceed at an enhanced rate in mixtures of protic and dipolar aprotic solvents but in a somewhat dampened form[74]. The rate of exchange of methoxide in melicopicine has been determined[73] with tritium-labelled sodium methoxide in dimethyl sulphoxide - methanol (5 : 1, V/V) and the second order rate constant for the overall exchange process at 50° found to be 6.0×10^{-3} l. $mole^{-1}$. sec^{-1}. This overall rate constant represents the sum of the four rate constants for exchange of each of the methoxyl groups in melicopicine.

The individual rate constants for exchange of each of the methoxyl groups have been obtained[73] by determination of the fraction of the tritium label in each methoxyl group. Melicopicine was treated with tritium-labelled sodium methoxide in dimethyl sulphoxide - methanol under the above conditions and the reaction quenched well before equilibrium was established. The fraction of the label in each

methoxyl group was then determined by selectively removing each methoxyl group of melicopicine by the procedure shown in Scheme 31. The individual rate constants for exchange of the methoxyl groups of melicopicine are recorded in Table 6. The rate of exchange of the methoxyl groups



SCHEME 31

of melicopicine is seen to be in the relative order

$$1\text{-}OCH_3 \gg 3\text{-}OCH_3 > 4\text{-}OCH_3 > 2\text{-}OCH_3.$$

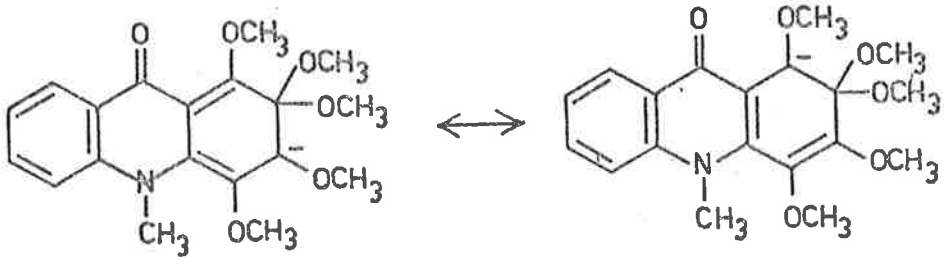
Again, with alkoxy substituents, substitution is found to occur faster in the 1-position than in the 3-position. Furthermore, the difference in the rates of substitution in the 1- and 3-positions is found to be very much greater

TABLE 6.

Second order rate constants for methoxide exchange in melicopicine with sodium methoxide in dimethyl sulphoxide - methanol (5 : 1, V/V) at 50°.

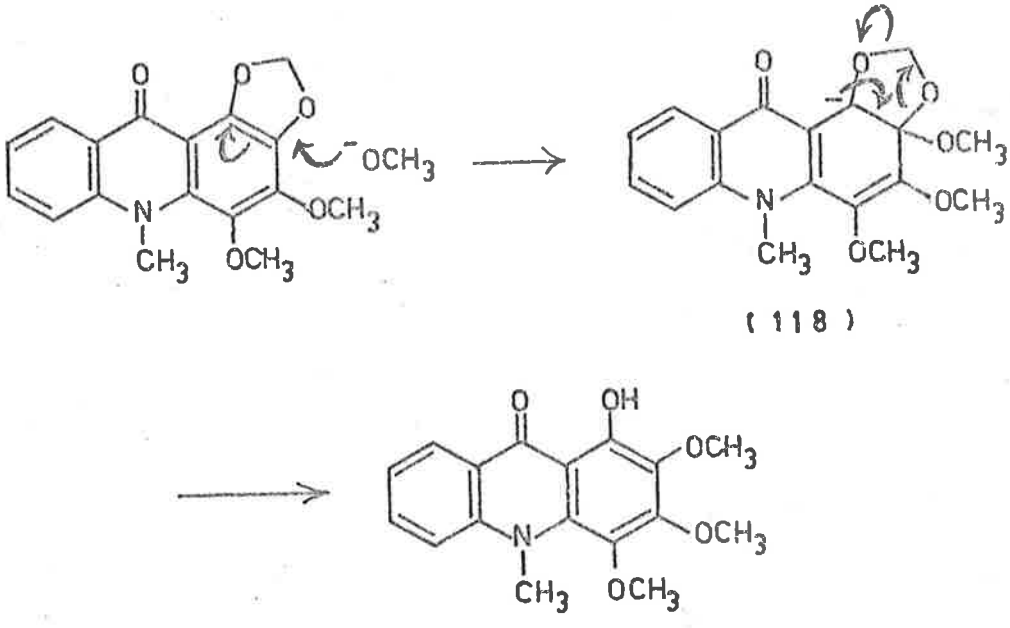
Methoxyl group	k x 10^4 (l. $mole^{-1}$. sec^{-1}.)
1-OCH_3	55
2-OCH_3	0.67
3-OCH_3	3.6
4-OCH_3	0.94

in the exchange of methoxyl groups than in the ring-opening of methylenedioxy rings. Methoxide exchange in melicopicine is also observed to occur in the 2- and 4-positions. Methoxide exchange in the 2-position will occur via the intermediate (117a ⇔ 117b) and via a similar intermediate



(117a) (117b)

in the 4-position. Although melicopicine has been observed to exchange methoxide in the 2- and 4-positions no evidence has been obtained for attack of methoxide ion at the unactivated position of the methylenedioxy ring of the methylenedioxyacridones in dimethyl sulphoxide or methanol as solvent. This would proceed, for the 1,2-methylenedioxy compound (78), by attack of methoxide ion at C-2 and would lead to normelicopicine via the intermediate (118) (Scheme 32).

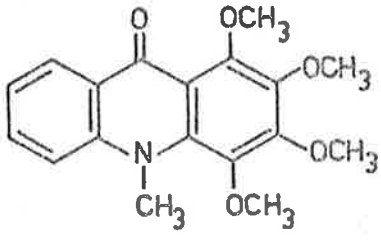


(118)

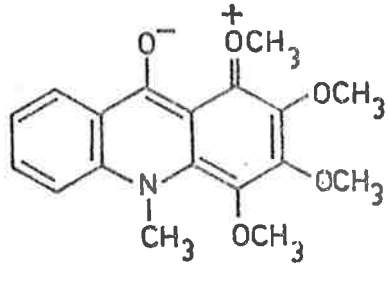
SCHEME 32

In the reactions of the bromo-10-methylacridones with sodium methoxide in dimethyl sulphoxide it was found that substitution occurred faster in the 3-position than in the 1-position. This was considered to be the normal order of relative rates of substitution as the conjugative

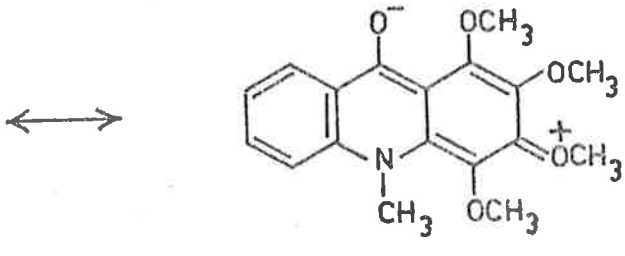
activation by the carbonyl group is expected to be greater at C-3 than at C-1. However, with the alkoxy-10-methyl-acridones the reverse order was observed and substitution was found to occur faster in the 1-position than in the 3-position. It is possible to rationalize this reversal in substitution rates for the alkoxy compounds in terms of resonance involving the canonical forms (119b) and (119c). The non-bonding electrons of the small oxygen atom are situated in orbitals which may overlap with the aromatic π-orbitals giving rise to resonance of the type (119a ↔ 119b ↔ 119c) in which the positive charge is partly distributed in the 1- and 3-methoxyl groups. With the larger bromine atom this overlap occurs to a very much smaller extent. Since the canonical form (119b) involves a much



(119a)



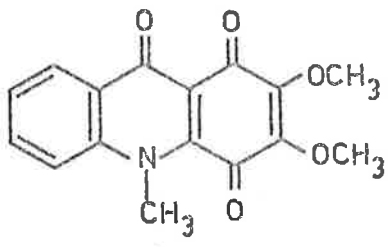
(119b)



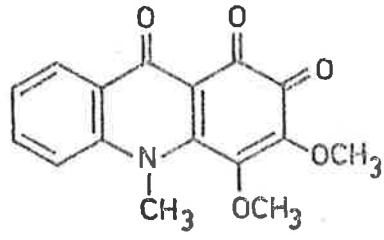
(119c)

smaller physical separation of charges than does (119c) it might be argued that the former canonical form would contribute to a greater degree to the overall structure than would the latter canonical form. This would favour nucleophilic substitution in the 1-position in the alkoxy-10-methylacridones.

In the elucidation of the structures of the acridone alkaloids Crow and Price[14] observed that the dimethoxyquinone (120) gave different products on treatment with cold 5% sodium hydroxide and with hot sodium carbonate solution. They made similar observations with the o-quinone (121). With both o- and p-quinones cold 5% sodium hydroxide result-

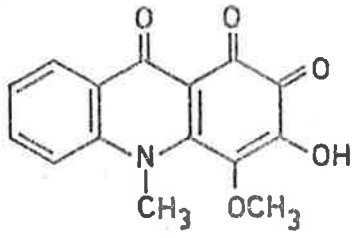


(120)

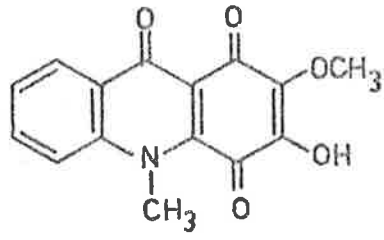


(121)

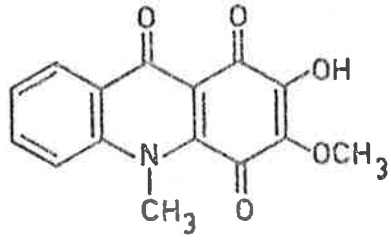
ed in demethylation at the 3-position giving the 3-hydroxy-4-methoxy-o-quinone (122) and the 3-hydroxy-2-methoxy-p-quinone (123), respectively. In the case of both dimethoxyquinones reaction with hot aqueous sodium carbonate gave the 2-hydroxy-3-methoxy-p-quinone (124). Since these reactions appeared to offer a method for ascertaining the



(122)



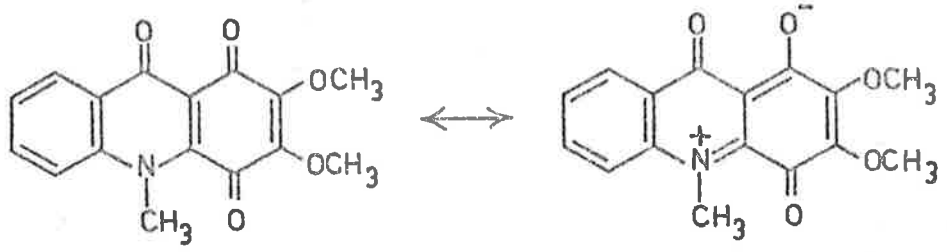
(123)



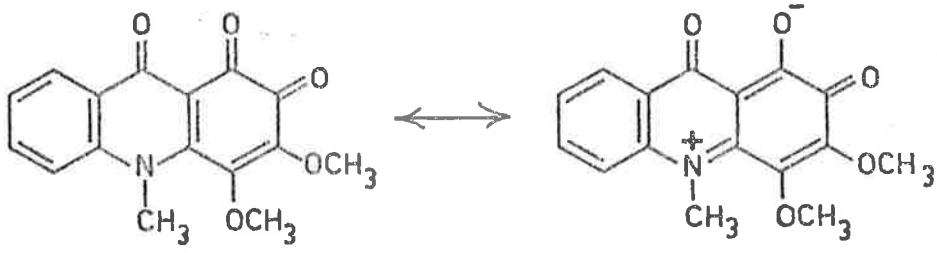
(124)

relative ratio of methoxide exchange using tritium-labelled methoxide ion at the 1- and 3-positions of melicopicine (Scheme 31), for comparison with the rates obtained with the methylenedioxy compounds, some further investigation of these observations seemed merited. In particular, since the hydroxyquinones (123) and (124) appear to complex with silica gel and alumina and could not be purified by chromatography and also could not be satisfactorily purified by crystallization, it was necessary to determine the specificity of these reactions. In addition, an attempt to determine the reason for demethylation at different positions under the different conditions appeared to be a challenging problem.

Crow and Price pointed out that in both quinones the influence of the carbonyl group in the 1-position is diminished by resonance, the structures (125a ⟷ 125b) and (126a ⟷ 126b) contributing towards the structures of the dimethoxyquinones.

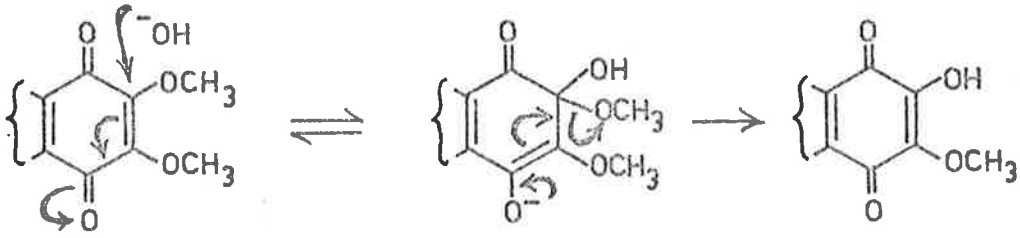


(125a) (125b)

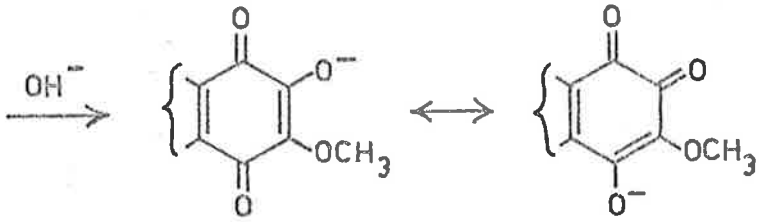


(126a) (126b)

Two mechanisms can be envisaged for demethylation of these quinones with alkali: (a) attack of hydroxide ion at the ring carbon with loss of methanol by an addition-elimination mechanism (Scheme 33), and (b) attack by hydroxide ion on the methoxyl carbon (Scheme 34). · Since the hydroxymethoxyquinone is present in the alkaline solution as the resonance stabilized anion (128a ⟷ 128b)

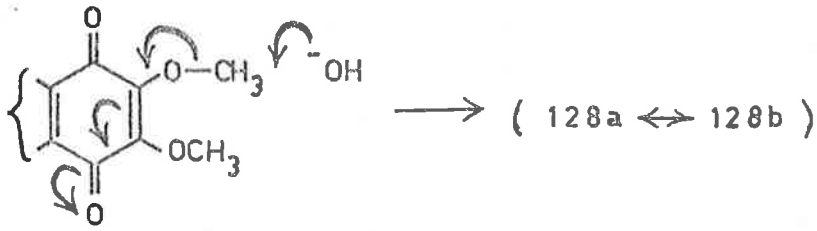


(127)



(128a) (128b)

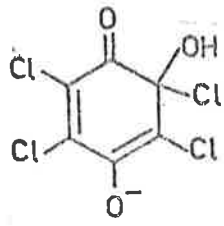
SCHEME 33



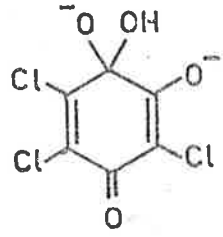
SCHEME 34

further attack by hydroxide ion is not likely to occur. The more unlikely mechanism of Scheme 34 can be immediately ruled out from the observation that the 2,3-dimethoxy-p-quinone (120) rapidly gave a quantitative yield of the 2,3-diethoxy-p-quinone with sodium ethoxide in ethanol. It is

well known that anion forming substituents in quinones can be readily displaced by nucleophiles[82-85] and that these substitutions most likely occur by an addition-elimination mechanism analogous to the activated addition-elimination substitutions in aromatic compounds[20j] involving intermediates like the species (127). Indeed, Hancock and co-workers[86] claim to have spectroscopic evidence for the formation of the species (129) from chloranil on treatment with cold alkali. However, this is discounted by Bishop and Tong[87] who suggest that what Hancock and co-workers actually observed was the species (130).



(129)



(130)

In the present work the specificity of the reaction of the 2,3-dimethoxy-p-quinone (120) with hot sodium carbonate solution to give the 2-hydroxy-3-methoxy-p-quinone (124) has been examined and the factors determining the position of demethylation investigated.

Since the hydroxymethoxyquinones could not be chromatographed the nature of the product was determined from the i.r. spectrum. The i.r. spectra of the 2,3-

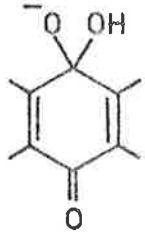
dimethoxy-p-quinone (120) and the two hydroxymethoxy-p-quinones (123) and (124) differed considerably, particularly in the region 1500 - 1700 cm^{-1}. It was therefore possible to determine which hydroxymethoxy-p-quinone was formed and whether or not it was contaminated with the other isomer. The i.r. spectrum of the 2,3-dimethoxy-p-quinone (120) included bands at 1663(s), 1625(s), 1600(s), 1585(s)(sh), and 1525 cm^{-1}(s); that of the 2-hydroxy-3-methoxy-p-quinone (124) included bands at 1670(s), 1598(s) and 1527 cm^{-1}(w); and that of the 3-hydroxy-2-methoxy-p-quinone (123) included bands at 1660(w)(sh), 1630(s), 1580 (m) and 1540 cm^{-1}(m). The spectra also showed characteristic bands below 1500 cm^{-1}. In addition, the three compounds have totally different appearance, the 2,3-dimethoxy-p-quinone (120) is red, the 2-hydroxy-3-methoxy-p-quinone (124) is pale brown, and the 3-hydroxy-2-methoxy-p-quinone (123) is greenish-brown.

The reactions of the 2,3-dimethoxy-p-quinone (120) with cold 5% sodium hydroxide and hot sodium carbonate solution were re-examined and the yields of the hydroxymethoxyquinones determined. Reaction of the 2,3-dimethoxy-p-quinone (120) with hot aqueous sodium carbonate solution was found to give a quantitative yield of the 2-hydroxy-3-methoxy-p-quinone (124) which was not contaminated with the 3-hydroxy isomer. This reaction was, therefore,

suitable for the selective demethylation of melicopicine shown in Scheme 31. Reaction with cold 5% sodium hydroxide was found to give a 69% yield of the 3-hydroxy-2-methoxy-p-quinone (123), but the nature of the remainder of the product could not be determined from the i.r. spectrum.

In continuing this investigation of the factors influencing the position of demethylation, the 2,3-dimethoxy-p-quinone (120) was treated with hot 0.1M sodium hydroxide and gave a 79% yield of the 2-hydroxy-3-methoxy-p-quinone (124) and with hot 1M sodium hydroxide a 78% yield of the 2-hydroxy-3-methoxyquinone was obtained. With cold 0.05M sodium hydroxide a 81% yield of the 2-hydroxy-3-methoxy-p-quinone was recovered. Thus, the 3-hydroxy-2-methoxy-p-quinone (123) is formed under the conditions used only with cold 1M sodium hydroxide. With hot 1M sodium hydroxide and with hot or cold less concentrated sodium hydroxide, or sodium carbonate solution the 2-hydroxy-3-methoxy-p-quinone (124) was formed. Thus, both heat and low hydroxide ion concentration appear to favour demethylation at the 2-position. This indicates that the position of substitution by hydroxide ion is controlled by some equilibrium occurring prior to substitution.

Bishop and Tong[87] have shown that quinones react rapidly with hydroxide ion to form the adduct (131) and



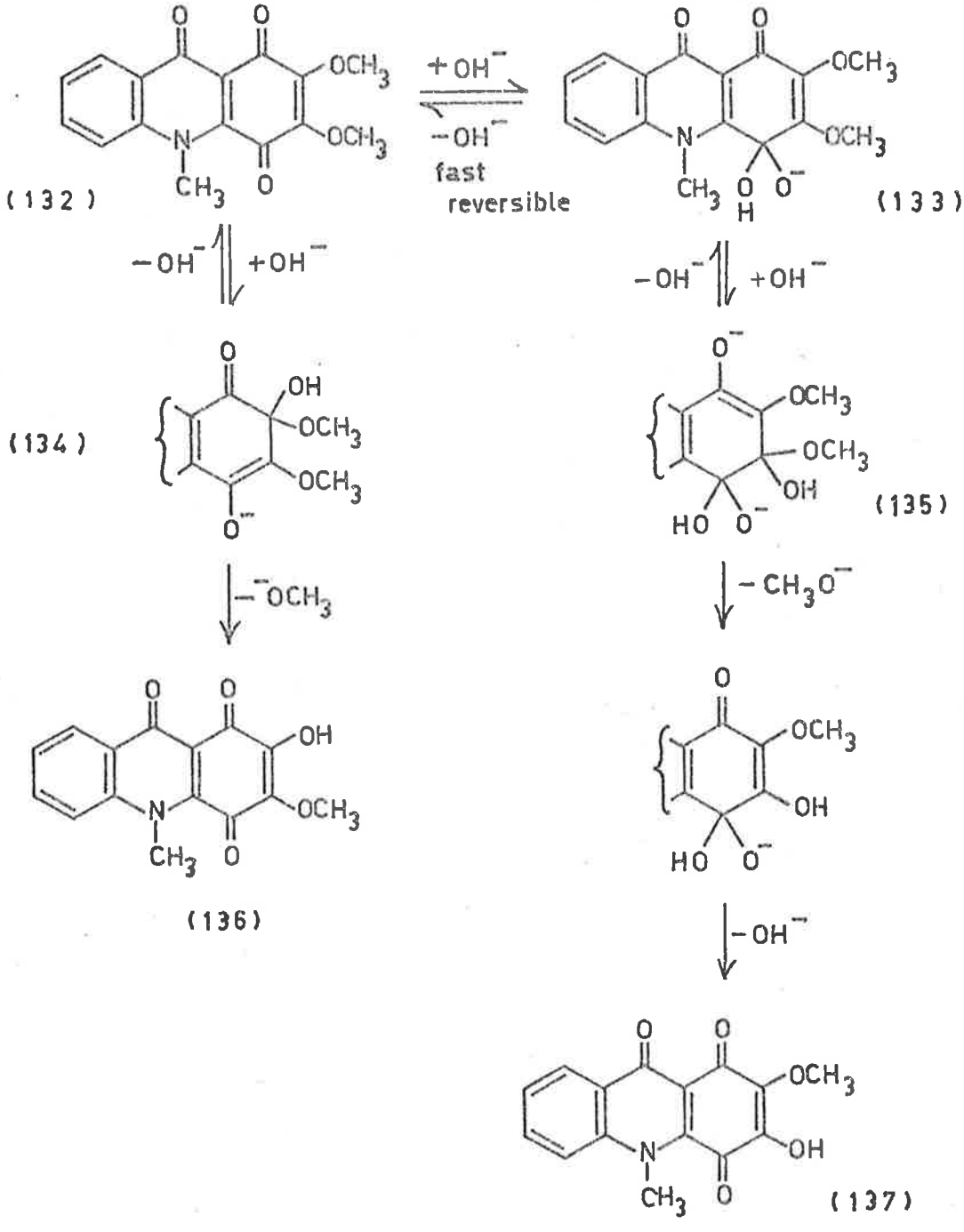
(131)

that formation of this adduct is promoted by strong electronegative groups attached to the ring. Indeed, with chloro-p-benzoquinone formation of the adduct is complete at pH 12.2. They also found that equilibrium was established in less than twelve milliseconds. It is possible to rationalize the position of demethylation of the 2,3-dimethoxy-p-quinone (120) in terms of formation of a similar adduct. Since the influence of the carbonyl group in the 1-position of the 2,3-dimethoxy-p-quinone (132) is reduced by resonance (125a ↔ 125b), hydroxide ion will react preferrentially with the 4-carbonyl group giving the adduct (133) (Scheme 35). The free quinone (132) and the adduct (133) would then undergo demethylation in different positions. Due to the reduced carbonyl character of the 1-carbonyl group of the 2,3-dimethoxy-p-quinone (132) hydroxide ion would attack preferrentially at C-2 giving the intermediate (134) which, in turn, gives the 2-hydroxy-3-methoxy-p-quinone (136). However, with the adduct (133) hydroxide ion can attack only at C-3 giving the intermediate (135) which leads to

the 3-hydroxy-2-methoxy-p-quinone (137). At the relatively low pH of 0.05M sodium hydroxide and sodium carbonate solution the 2,3-dimethoxyquinone is expected to be present mainly as the free quinone (132) so that demethylation is expected to occur at C-2. At the high pH of 1M sodium hydroxide the quinone must be present mainly as the adduct (133) so that demethylation occurs at C-3. It is expected that the essential equilibrium step (132 $\rightleftharpoons$ 133) will be driven to the left with an increase in temperature thus explaining the above observations.

An attempt was made to observe the adduct (133) by scanning the u.v. spectrum immediately after adding concentrated sodium hydroxide to a solution of the 2,3-dimethoxy-p-quinone (132) in water. However, the u.v. spectrum observed was identical with that of the 3-hydroxy-2-methoxy-p-quinone (137) in alkali. The reaction is too fast to observe the u.v. spectrum of the adduct by this technique.

Attempts have been made[73] to confirm the above postulate that the difference in product composition is a result of the first order dependence in $[OH^-]$ for the formation of the 2-hydroxy isomer, and a second order dependence in $[OH^-]$ for the formation of the 3-hydroxy isomer by kinetic measurements, but the second reaction is too rapid even at 30^o for rate measurements to be made by


(132)
+OH⁻
−OH⁻
fast
reversible
(133)
−OH⁻
+OH⁻
(134)
(135)
−⁻OCH₃
−CH₃O⁻
(136)
−OH⁻
(137)

SCHEME 35

non-flow methods. The first reaction has indeed been shown to be first order in both [quinone] and [OH^-] and independent of salt effects and general base catalysis.

EXPERIMENTAL

Melting points were determined on a Leitz hot-stage microscope and are uncorrected. Ultra-violet spectra were measured on a Perkin-Elmer Uvispek 137 or Unicam SP. 800 recording spectrophotometer and absorbance measurements at fixed wavelength for quantitative analysis measured with a Hilger manual spectrophotometer. Infrared spectra were recorded in nujol mulls on a Perkin-Elmer Infracord 237 or Unicam SP.200 infrared spectrophotometer.

Nuclear magnetic resonance spectra were measured with a Varian T-60 N.M.R. spectrometer in solution in deuterochloroform unless stated otherwise; each signal is described in terms of multiplicity, intensity, chemical shift in ppm from tetramethylsilane, assignment, and coupling constant in that order with the use of the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; (b), broad.

Mass spectra were determined with a Hitachi Perkin-Elmer RMU 6D mass spectrometer at 70eV. Analyses were carried out by the Australian Microanalytical Service, Melbourne. Radioactive samples were counted on an Ekco N664A liquid scintillation counter in toluene using POP and POPOP[88] as solutes.

Whatman SG31 silica gel and Spence alumina were used for column chromatography. Thin layer chromatography was carried out on 0.25mm layers of Merk silica gel G or

Merk aluminium oxide G. Thick layer chromatography was carried out on 2mm layers of an equal mixture of Merk silica gel G and HF_{254}.

Yields reported in the analytical scale reactions are based on unrecovered starting material.

Light petroleum refers to the fraction of b.p. 55-65°.

The products of the reactions were determined by quantitative thin layer chromatography on 0.25mm layers of Merk silica gel G or Merk aluminium oxide G. The plates were dried at 110° for ca. 30 min after preparation but were generally not reactivated before use.

The reaction mixture was worked up and prepared for analysis in the following manner. On completion of the reaction volatile solvents, such as dimethoxyethane and ammonia, were removed and water added to the residue. The organic material was extracted into chloroform and the extract filtered and evaporated. High boiling solvents such as piperidine and dimethyl sulphoxide, which would interfere with the chromatographic separation, were removed at 0.01mmHg. The residue was dissolved in chloroform or chloroform-ethanol and made up to a suitable volume in a volumetric flask.

The products were characterized by qualitative thin layer chromatography by comparison with standards and examination of fluorescence. Iodoplatinate spray[89] was often found useful in assisting identification as many of the substituted acridones gave characteristic colours with this reagent. In cases of doubt of identity of a product the full u.v.-visible spectrum of the eluted material was determined and in some cases the identity was confirmed by isolation and characterization by mixed m.p.

The adsorbent layer and solvent system used for analysis is described in each experiment. Solvent systems based on benzene with various amounts of ethyl acetate to increase the polarity had the best resolving properties with acridones.

To determine the yield of each product an aliquot of the product solution (10 - 100μl), measured with Drummond 'microcap' micropipettes, was applied as a strip to the base of the thin layer plate and the plate developed. The products were located and, after drying, were removed with a small glass 'vacuum cleaner' with water-pump suction, the adsorbent being collected on a sintered glass disc. The compound was eluted with 95% ethanol directly into a 5ml volumetric flask. A blank plate was treated in the same manner and the eluent from the same area of adsorbent used as the spectroscopic reference. The yield was determined from the absorbance at λ_{max} (table 7) of the eluted compound. Each analysis was carried out in duplicate. The accuracy of this technique is generally quoted as $\pm$ 10%.

ULTRA-VIOLET SPECTRA OF SOME SUBSTITUTED ACRIDONES

The u.v. spectra were determined in 95% ethanol. Those absorbance maxima marked with an asterisk (*) were used in the quantitative analysis and for these absorbances log ε was determined from a Beer's law plot which was found to give straight lines for all compounds in the absorbance range ca. 0.05 - ca. 1.2.

TABLE 7.

Acridone	Conditions	Absorbance maxima (nm)(log ε)
Unsubstituted	neutral	250(4.76[a]), 254(4.78[a]), 294(3.33[a]), 306(3.05[a]), 378(3.93[a]), 397(3.95[a])
	alkaline	262(sh)(4.73), 267(4.76), 326(3.51), 341(3.60), 390(3.92), 409(4.00), 434(3.86)
10-Methyl-	neutral	255(4.740)*, 293(3.43[a]), 304(3.09[a]), 384(3.92[a]), 402(3.98[a])

TABLE 7 (CONT.)

Acridone	Conditions	Absorbance maxima (nm)(log ε)
1-Bromo-10-methyl-	neutral	259(4.638)*, 389(3.77), 406(3.86)
2-Bromo-10-methyl-	neutral	253.5(4.632)*, 261(4.63), 268(sh)(4.53), 276(4.47), 388(3.80), 407(3.85)
3-Bromo-10-methyl-	neutral	263(4.714)*, 268(4.69), 382(3.77), 398(3.88)
4-Bromo-10-methyl-	neutral	258.5(4.623)*, 402(3.75)
1-Nitro-	neutral	255(4.59), 382(3.79), 400(3.81)
2-Nitro-	neutral	237(4.55), 294(4.17), 352(4.14), 394(3.97),
	alkaline	246(4.50), 318(4.24), 376(sh)(4.06), 390(4.09), 481(3.94)
3-Nitro-	neutral	263(4.54), 420(3.67)
	alkaline	287(4.51), 318(4.09), 382(3.72), 474(3.52)
4-Nitro-	neutral	244(4.61), 263(4.30), 336(3.67), 428(4.00)

TABLE 7 (CONT.)

Acridone	Conditions	Absorbance maxima (nm)(log ε)
4-Nitro-	alkaline	252(4.57), 273(4.50), 450(3.80)
1-Nitro-10-methyl-	neutral	259(4.59), 395(3.77), 409(3.82)
2-Nitro-10-methyl-	neutral	241(4.54), 257(sh)(4.35), 297(4.13), 358(4.16), 395(3.94)
3-Nitro-10-methyl-	neutral	268(4.53), 275(sh)(4.49), 434(3.69)
4-Nitro-10-methyl-	neutral	249(4.55), 337(3.57), 412(3.91)
1-Amino-10-methyl-	neutral	250.5(4.661)*, 270(4.49), 323(4.05), 430(3.91)
	acidic	255(4.69), 259(4.69), 412(3.84)
2-Amino-10-methyl-	neutral	258(4.644)*, 285(4.47), 438(3.88)
3-Amino-10-methyl-	neutral	255(4.648)*, 275(4.44), 285(4.49), 358(4.18)
4-Amino-10-methyl-	neutral	268(4.631)*, 319(3.77), 423(3.59)

TABLE 7 (CONT.)

Acridone	Conditions	Absorbance maxima (nm)(log ε)
1-Piperidino-10-methyl-	neutral	250(4.54), 261(4.611)*, 320(3.44), 422(3.74)
2-Piperidino-10-methyl-	neutral	262(4.609)*, 294(4.46), 430(3.64)
3-Piperidino-10-methyl-	neutral	260(4.634)*, 280(sh)(4.36), 289(4.51), 370(4.29)
4-Piperidino-10-methyl-	neutral	267.5(4.625)*, 414(3.67)
1,2-Methylenedioxy-3,4-dimethoxy-10-methyl-	neutral	277(4.644)*, 305(sh)(3.89), 424(3.84)
Melicopidine	neutral	277(4.668)*
Melicopine	neutral	270.5(4.668)*
Normelicopicine	neutral	249(4.36[a]), 273(4.63[a]), 309(4.02[a]), 421(3.76[a])
	alkaline	250(4.43), 276(4.45), 323(4.02), 434(3.79)
2-Hydroxy-1,3,4-trimethoxy-10-methyl-	neutral	274(4.60), 414(3.83)
	alkaline	297(4.50), 460(3.67)
3-Hydroxy-1,2,4-trimethoxy-10-methyl-	neutral	272(4.54), 392(3.70)
	alkaline	253(4.41), 275(4.38), 291(4.20), 368(4.12)

TABLE 7 (CONT.)

Acridone	Conditions	Absorbance maxima (nm)(log ε)
4-Hydroxy-1,2,3-trimethoxy-10-methyl-	neutral	270(4.93), 305(4.23), 410(4.13)
	alkaline	253(4.65), 283(4.76), 330(4.36), 456(3.94)

a) These values of log ε were taken from reference 105.

PREPARATION OF THE MONO-BROMO-, AMINO-, AND PIPERIDINO-10-METHYLACRIDONES

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1. Preparation of 1-Bromo-10-methylacridone

1.1 3'-Bromodiphenylamine-2-carboxylic acid

Anhydrous potassium carbonate (52.5g) was added to a hot mechanically stirred solution of 2-chlorobenzoic acid (39.3g) in isoamyl alcohol (75ml). Solvent was then distilled over until the temperature of the vapours reached 126°. 3-Bromoaniline (65.4g), precipitated copper[90] (1.0g), and cupric oxide (0.5g) were introduced and the mixture heated under reflux with stirring for 5 hr. Solvent and excess 3-bromoaniline were removed by steam distillation and the hot residue filtered and acidified. The precipitate was extracted with boiling water leaving insoluble 3'-bromodiphenylamine-2-carboxylic acid (43.5g, 60%), m.p. 170-172° (ex aqueous ethanol)(lit.[57] m.p. 172°).

1.2 Preparation of a mixture of 1- and 3-bromoacridones

A mixture of 3'-bromodiphenylamine-2-carboxylic acid (43.5g) and phosphoryl chloride (150ml) was heated under reflux for 1.5 hr in an oil-bath at 120°. Most of the excess phosphoryl chloride was removed under reduced pressure

and 1N-hydrochloric acid cautiously added. The suspension was vigorously stirred for 1.5 hr on a boiling water-bath and filtered giving a mixture of 1- and 3-bromoacridones (41.5g, 100%).

1.3 Preparation of a mixture of 1- and 3-bromo-10-methyl-acridones

The mixture of 1- and 3-bromoacridones (3.8g) was slowly added to a suspension of sodium hydride (1.9g of 1 : 1 dispersion with oil) in dimethylformamide (40ml). When evolution of hydrogen ceased dimethyl sulphate (5.0ml) was introduced dropwise so that the temperature of the mixture did not rise above about 50°. When the reaction was complete excess sodium hydride was destroyed with acetic acid and the solution concentrated under reduced pressure. Water was added and the precipitate filtered, dried and washed with light petroleum (to remove oil from the sodium hydride dispersion) giving a mixture of 1- and 3-bromo-10-methylacridones (3.4g, 85%) in the ratio 61 : 39 (by quantitative thin layer chromatography on silica gel developed with benzene - ethyl acetate, 4 : 1).

1.4 1-Bromo-10-methylacridone from the mixture of 1- and 3-bromo-10-methylacridones

1-Bromo-10-methylacridone was obtained pure from the

mixture of 1- and 3-bromo-10-methylacridones by fractional crystallization. The mixture of 1- and 3-bromo-10-methylacridones (47g) was crystallized three times from benzene giving pure (one spot by thin layer chromatography) 1-bromo-10-methylacridone (11.9g), m.p. 221-221.5° (Found: C, 58.8; H, 3.6; N, 4.7. $C_{14}H_{10}BrNO$ requires: C, 58.4; H, 3.5; N, 4.9%). The mass spectrum showed the molecular ion at m/e 287/289. N.m.r. spectrum: s,3,3.66, ($N-CH_3$); m, 6, 6.9-7.7, (aromatic H); d of d, 1, 8.30, (H-8), 7Hz, 1.5Hz.

1.5 Preparation and separation of a mixture of 1- and 3-bromo-9-chloroacridines

3'-Bromodiphenylamine-2-carboxylic acid was cyclized with phosphoryl chloride as described in section 1.2 above. After removing excess phosphoryl chloride the residue was dissolved in chloroform. The chloroform solution was slowly poured into a vigorously stirred mixture of dilute ammonia and crushed ice kept basic to phenolphthalein by addition of concentrated ammonia. Stirring was continued for 45 min. The crude product was recovered from the chloroform and partially purified by extraction with light petroleum in a Soxhlet apparatus giving 93% yield of a mixture of 1- and 3-bromo-9-chloroacridines. The mixture (200mg) was separated by thick layer chromatography on silica gel (20 x 20 x 0.2cm) developing with benzene - ether

(9 : 1). Two principal fractions were obtained. The upper band with grey fluorescence was 3-bromo-9-chloroacridine (65mg), m.p. 175-176° (ex light petroleum)(lit.[91] m.p. 170-170.5°). The lower band with yellow fluorescence was 1-bromo-9-chloroacridine (100mg), m.p. 138.5-140° (ex ethanol). The remainder of the mixture of 1- and 3-bromo-9-chloro-acridines had undergone hydrolysis to the acridones.

1.6 Preparation of 2,6-dibromobenzoic acid

1.6(a) 4-Amino-3,5-dibromobenzenesulphonic acid (barium salt)

This compound was prepared from sulphanilic acid by the method of Heinichen[92] using the modification of Orton and Pearson[93].

1.6(b) 2,6-Dibromoaniline

This was prepared in 76% yield by desulphonation of the barium salt of 4-amino-3,5-dibromobenzenesulphonic acid according to the method of Orton and Pearson[93].

1.6(c) 2,6-Dibromobenzonitrile

This was prepared in 72% yield from 2,6-dibromo-aniline by the method of Olivier[94].

1.6(d) Hydrolysis of 2,6-dibromobenzonitrile

This hydrolysis was carried out by the method of Sudborough[95] using sulphuric acid and sodium nitrite. Hydrolysis of the amide formed was incomplete and both 2,6-dibromobenzamide and 2,6-dibromobenzoic acid were obtained

in an overall yield of 80%.

1.7 Attempts to prepare 3-bromodiphenylamine-2-carboxylic acid

A number of attempts were made to prepare 3-bromodiphenylamine-2-carboxylic acid by the Ullmann condensation by the general method described in section 1.1 above using 2,6-dibromobenzoic acid and aniline. The solvents used were n-butanol, water and dimethylformamide (the last with N-ethylpiperidine as base). Each of these reactions gave a large number of compounds on chromatographic separation and examination of the i.r. spectra (in chloroform) of these products showed none to be the required 3-bromo-diphenylamine-2-carboxylic acid, as none of the products showed a carbonyl stretching band. Only starting material was recovered in an attempt to carry out the reaction with 2,6-dibromobenzamide and aniline in isoamyl alcohol.

2. Preparation of 2-Bromo-10-methylacridone

2.1 4'-Bromodiphenylamine-2-carboxylic acid

This was prepared from 2-chlorobenzoic acid and 4-bromoaniline by the procedure described in section 1.1 above, the stirred mixture being heated under reflux for 3 hr. The crude product was chromatographed on silica gel

eluting with chloroform giving 4'-bromodiphenylamine-2-carboxylic acid (51%), m.p. 184-186° (ex aqueous ethanol) (lit.[96] m.p. 186°).

2.2 2-Bromoacridone

This was prepared in 91% yield, m.p. >360°, by cyclization of 4'-bromodiphenylamine-2-carboxylic acid with phosphoryl chloride by the procedure described in section 1.2 above.

2.3 2-Bromo-10-methylacridone

This was prepared in 98% yield from 2-bromoacridone by the method described in section 1.3 above giving 2-bromo-10-methylacridone, m.p. 199-199.5° (ex benzene) (Found: C, 58.2; H, 3.1; N, 4.8. $C_{14}H_{10}BrNO$ requires: C, 58.4; H, 3.5; N, 4.9%). The mass spectrum included peaks at m/e 287/289 (100%)(M^+) and 272/274 (17)($M-CH_3$). N.m.r. spectrum: s, 3, 3.75, ($N-CH_3$); m, 5, 7.0-7.8, (aromatic H); d of d, 1, 8.40 (H-8), 8Hz, 2Hz; d, 1, 8.50, (H-1), 2Hz.

3. Preparation of 3-Bromo-10-methylacridone

3.1 3-Bromoacridone

This was prepared in 37% yield from 1-nitro-

benzaldehyde and bromobenzene by the method of Lehmstedt[97]. Recrystallization from nitrobenzene was omitted and purification was carried out after N-methylation.

3.2 3-Bromo-10-methylacridone

This methylation was carried out as described in section 1,3 above, the temperature of the mixture being maintained at 10°. The crude product was purified by column chromatography on alumina eluting with chloroform giving 3-bromo-10-methylacridone (95%), m.p. 157-158° (ex ethanol) which was raised to 177-178° after heating for several days at 110° (Found: C, 58.3; H, 3.7; N, 4.7. $C_{14}H_{10}BrNO$ requires: C, 58.4; H, 3.5; N, 4.9%). The mass spectrum included peaks at m/e 287/289 (100%)(M^+) and 272/274 (6)($M-CH_3$). N.m.r. spectrum: s, 1, 3.67, ($N-CH_3$); m, 5, 7.0-7.8, (aromatic H); m, 2, 8.1-8.5, (H-1 and H-8).

3.3 3-Bromo-10-methylacridone from 3-bromo-9-chloroacridine

3-Bromo-9-chloroacridine (0.87g) and dimethyl sulphate (10ml) were heated for 45 min in an oil-bath at 140°. After cooling the mixture was poured into dilute sodium hydroxide solution. Extraction with chloroform and purification by chromatography as above gave 3-bromo-10-methylacridone (0.34g, 40%), m.p. 156-158°.

4. Preparation of 4-Bromo-10-methylacridone

4.1 2'-Bromodiphenylamine-2-carboxylic acid

This was prepared from 2-bromoaniline and 2-chlorobenzoic acid using the procedure described in section 1.1 above. n-Butanol was used as solvent and the mixture heated under reflux for 4 hr. The tarry crude product was purified by column chromatography on silica gel eluting with chloroform, chloroform - ether (4 : 1) giving 2'-bromodiphenylamine-2-carboxylic acid (17%), m.p. 191-193° (ex aqueous ethanol)(lit.[58] m.p. 192-193°). The use of isoamyl alcohol as solvent gave only 15% yield.

4.2 4-Bromoacridone

This was prepared in 86% yield by cyclization of 2'-bromodiphenylamine-2-carboxylic acid with phosphoryl chloride as described in section 1.2 above.

4.3 4-Bromo-10-methylacridone from 4-bromoacridone

4-Bromoacridone was N-methylated as described in section 1.3 above. The dimethyl sulphate was introduced dropwise over 1.5 hr and stirring continued for a further 2 hr. Extraction of the crude product with chloroform left insoluble 4-bromoacridone (20%). The chloroform-soluble material was chromatographed on alumina eluting with

light petroleum - chloroform (4 :1) giving 4-bromo-10-methylacridone (41%), m.p. 91.5-93° (ex benzene - light petroleum) (Found: C, 58.0; H, 3.8; N, 4.7. $C_{14}H_{10}BrNO$ requires: C, 58.4; H, 3.5; N, 4.9%). The mass spectrum included peaks at m/e 287/289 (100%)(M^+), 272/274 (25)($M-CH_3$) and 208 (13)(M-Br). N.m.r. spectrum: s, 3, 3.14, ($N-CH_3$); m, 5, 6.1-7.2, (aromatic H); d of d, 1, 7.52 (H-8), 8Hz, 2Hz; d of d, 1, 7.58, (H-1), 8Hz, 2Hz.

4.4 4-Bromo-10-methylacridone from 4-amino-10-methylacridone

4-Amino-10-methylacridone (2.0g) was dissolved in a solution of 46% hydrobromic acid (3.3ml) in water (40ml). After cooling to 2° sodium nitrite (0.66g) in water was slowly introduced with stirring, the temperature being maintained at 2°. A bright red solution of the diazonium salt was produced. This solution was slowly added with stirring to a solution of cuprous bromide (1.3g) in 46% hydrobromic acid (12ml) yielding a brown precipitate. When the addition was complete the mixture was heated on the steam-bath until evolution of nitrogen ceased. Extraction with chloroform and purification by chromatography as described above gave 4-bromo-10-methylacridone (2.1g, 82%), m.p. and mixed m.p. 90-92°.

5. Preparation of 1-Amino-10-methylacridone

5.1 3'-Nitrodiphenylamine-2-carboxylic acid

This was prepared in 36% yield from the sodium salt of 2-chlorobenzoic acid and 3-nitroaniline by the method of Albert and Ritchie[98].

5.2 Preparation of a mixture of 1- and 3-nitroacridones

3'-Nitrodiphenylamine-2-carboxylic acid was cyclized with phosphoryl chloride as described by Lehmstedt and Schrader[56]. After removal of the phosphoryl chloride the mixture was hydrolyzed with hydrochloric acid as described in section 1.2 above to a mixture of the 1- and 3-nitroacridones.

5.3 1-Nitro-10-methylacridone

A mixture of 1- and 3-nitroacridones (4.4g) was added to a stirred suspension of sodium hydride (0.81g) in dimethylformamide (100ml) giving a deep red solution. Dimethyl sulphate (3.4ml) was introduced in portions over 15 min. The deep red solution slowly faded to deep yellow with formation of a yellow precipitate. After a further 15 min the precipitate was removed and washed with chloroform giving 1-nitro-10-methylacridone (3.2g, 70%), yellow needles m.p. 308.5-309^{o} (ex dimethyl sulphoxide). Sublim-

ation at 270°/0.01mmHg raised the m.p. to 310-311° (Found: C, 66.0; H, 4.2; N, 10.7. $C_{14}H_{10}N_2O_3$ requires: C, 66.1; H, 4.0; N, 11.0%). The mass spectrum included peaks at m/e 254 (100%)(M^+), 224 (7), 208 (60), 196 (11), 180 (18) and 152 (37). This compound was too insoluble for its n.m.r. spectrum to be determined.

Addition of water to the dimethylformamide filtrate gave a precipitate (1.5g) which on extraction with chloroform gave chloroform-soluble 3-nitro-10-methylacridone (0.7g, 15%), m.p. and mixed m.p. 215-216° and a chloroform-insoluble fraction (0.8g) which appeared to be impure 1-nitro-10-methylacridone.

5.4 1-Amino-10-methylacridone

1-Nitro-10-methylacridone (0.50g) was added to a hot solution of stannous chloride (1.8g) in concentrated hydrochloric acid (2.0ml) and the mixture heated on a steam-bath for 1 hr. Water was added and the slurry poured into dilute sodium hydroxide solution. Extraction with chloroform gave 1-amino-10-methylacridone (0.29g, 66%), m.p. 191.5-193° (ex benzene) (Found: C, 74.9; H, 5.4; N, 12.5. $C_{14}H_{12}N_2O$ requires: C, 75.0; H, 5.4; N, 12.5%). The mass spectrum included peaks at m/e 224 (100%)(M^+), 209 (13) ($M-CH_3$) and 182 (13)($M-CH_3-HCN$). N.m.r. spectrum: s, 3, 3.70, ($N-CH_3$); d, 1, 6.33, (H-2), 8Hz; d, 1, 6.53, (H-4),

9Hz; m, 6, 6.9-7.8, (H-3, H-5, H-6, H-7, NH_2); d of d, 1, 8.42, (H-8), 7Hz, 2Hz. The NH_2 signal, partly under the aromatic multiplet, disappeared on exchange with D_2O.

6. Preparation of 2-Amino-10-methylacridone

6.1 4'-Nitrodiphenylamine-2-carboxylic acid

This was prepared in 85% yield from 4-bromonitrobenzene and anthranilic acid by the method of Goldberg[99].

6.2 2-Nitroacridone

4'-Nitrodiphenylamine-2-carboxylic acid was cyclized to 2-nitroacridone in 95% yield by the method of Albert and Ritchie[98].

6.3 2-Nitro-10-methylacridone

This was prepared from 2-nitroacridone by the method described in section 1.3 above. The dimethyl sulphate was introduced over 40 min, the temperature being kept below 40°, and stirring continued for a further 1.5 hr. The crude product was purified by extraction with benzene in a Soxhlet apparatus leaving benzene-insoluble 2-nitro-10-methylacridone (81%), m.p. 282.5-284° (lit.[6] m.p. 276°).

6.4 2-Amino-10-methylacridone

This was prepared in 91% yield, m.p. 213-214° (lit.[6] m.p. 205°), from 2-nitro-10-methylacridone by the procedure described in section 5.4 above.

7. Preparation of 3-Amino-10-methylacridone

7.1 5-Nitrodiphenylamine-2-carboxylic acid

This was prepared in 71% yield from 2-Chloro-4-nitrobenzoic acid and aniline by the method of Albert and Gledhill[100].

7.2 3-Nitroacridone

5-Nitrodiphenylamine-2-carboxylic acid was cyclized with phosphoryl chloride as described in section 1.2 above. The mixture was heated under reflux for 30 min. Hydrolysis gave 3-nitroacridone (100%), m.p. >360°.

7.3 N-Methylation of 3-nitroacridone with sodium hydride and dimethyl sulphate in dimethylformamide

This methylation was carried out as described in section 1.3 above and proceeded well on a one-gramme scale giving 3-nitro-10-methylacridone (97%), orange needles, m.p. 216-217.5° (ex benzene).

However, on a fifty-gramme scale in two separate

experiments the temperature rose uncontrollably and could not be lowered by cooling in ice. A violent reaction ensued.

7.4 N-Methylation of 3-nitroacridone with sodium methoxide and methyl iodide in ethanol

3-Nitroacridone (30g) and sodium methoxide (70ml of 2.1M NaOMe in MeOH) were heated under reflux in ethanol (800 ml) giving a deep red solution. Methyl iodide (32ml) was introduced dropwise. After 1 hr a further portion of sodium methoxide solution (20ml) and methyl iodide (10ml) was introduced and heating continued for 2 hr. After concentration water was added giving a precipitate (31g). Extraction with chloroform in a Soxhlet apparatus gave chloroform-soluble 3-nitro-10-methylacridone (14.0g, 40%), m.p. 215-216° (ex chloroform) (Found: C, 66.3; H, 3.7; N, 10.9. $C_{14}H_{10}N_2O_3$ requires: C, 66.1; H, 4.0; N, 11.0%). N.m.r. spectrum (on a saturated solution in $CDCl_3$): s, 3, 4.0, ($N-CH_3$); m, 7, 7.2-8.8, (aromatic H). The mass spectrum included peaks at m/e 254 (100%)(M^+), 224 (5)(M-NO), 208 (47)($M-NO_2$) and 180 (15). The chloroform-insoluble fraction appeared to be unchanged 3-nitroacridone.

7.5 3-Amino-10-methylacridone

This was prepared in 88% yield from 3-nitro-10-methylacridone by the procedure described in section 5.4

above. 3-Amino-10-methylacridone was obtained as orange prisms, m.p. 288-293° (ex ethanol)(Found: C, 75.1; H, 5.3; N, 12.3. $C_{14}H_{12}N_2O$ requires: C, 75.0; H, 5.4; N, 12.5%). The mass spectrum included peaks at m/e 224 (100%)(M^+) and 209(9)($M-CH_3$).

8. Preparation of 4-Amino-10-methylacridone

8.1 2'-Nitro-N-methyldiphenylamine-2-carboxylic acid

This was prepared in 93% yield from N-methyl-anthranilic acid and 2-bromonitrobenzene by the method of Burton and Gibson[53].

8.2 4-Nitro-10-methylacridone

This was prepared by cyclization of 2'-nitro-diphenylamine-2-carboxylic acid with phosphoryl chloride using the procedure described in section 1.2 above. After removal of excess phosphoryl chloride the residue was poured into water and neutralized giving 4-nitro-10-methylacridone (90%), m.p. 174-177° (lit.[6] m.p. 168°).

8.3 4-Amino-10-methylacridone

This was prepared in 84% yield from 4-nitro-10-methylacridone by the procedure described in section 5.4 above. The product was extracted with chloroform in a

continuous extraction apparatus. 4-Amino-10-methylacridone was obtained as yellow needles (ex benzene), m.p. 166.5-168.5° (Found: C, 75.1; H, 5.3; N, 12.7. $C_{14}H_{12}N_2O$ requires: C, 75.0; H, 5.4; N, 12.5%). The mass spectrum included peaks at m/e 224 (80%)(M^+) and 209 (100)($M-CH_3$).

8.4 2'-Nitrodiphenylamine-2-carboxylic acid

This was prepared in 96% yield from anthranilic acid and 2-bromonitrobenzene by the method of Albert[1n].

8.5 4-Nitroacridone

This was obtained in 97% yield from 2'-nitrodiphenylamine-2-carboxylic acid by the method of Albert and Gledhill[101].

8.6 Unsuccessful attempts to N-methylate 4-nitroacridone with sodium hydride and dimethyl sulphate in dimethylformamide

These experiments were performed as described in section 1.3 above both at lower temperatures (below ca. 40°) and also by heating at 100°. In each case a red solution of the anion was formed and the red colour very slowly faded on addition of dimethyl sulphate. However, examination of the product by thin layer chromatography on silica gel (benzene - ether, 1 : 1) showed only 4-nitroacridone to be

present.

8.7 Unsuccessful attempt to N-methylate 4-nitroacridone with sodium methoxide and methyl iodide in ethanol

This was carried out as described in section 7.4 above. A red solution was obtained on adding sodium methoxide solution to 4-nitroacridone in ethanol. However, thin layer chromatography showed the product to be entirely 4-nitroacridone.

9. Preparation of the Piperidino-10-methylacridones

These were prepared by heating the respective amino-10-methylacridone (50mg), anhydrous sodium carbonate (50mg) and 1,5-dibromopentane (1.0ml) in a metal-bath at 170-180^{o} for the time specified in each preparation. After cooling, light petroleum was added and the product purified by column chromatography, eluting first with light petroleum to remove excess 1,5-dibromopentane.

9.1 1-Piperidino-10-methylacridone

Heated for 10 min. Purified by column chromatography on alumina eluting first with light petroleum and then with light petroleum - benzene and benzene - ethyl acetate (49 : 1) giving first 1-piperidino-10-methylacridone

(28%) and then 1-amino-10-methylacridone (62%), m.p. and mixed m.p. 191-193°. 1-Piperidino-10-methylacridone crystallized from aqueous ethanol as yellow prisms, m.p. 159.5-161.5° (Found: C, 77.9; H, 6.8; N, 9.8. $C_{19}H_{20}N_2O$ requires: C, 78.0; H, 6.9; N, 9.6%). N.m.r. spectrum: (b), 6, 1.5-2.1, (aliphatic CH_2); t (b), 4, 2.9-3.2, (aliphatic N-CH_2), 5Hz; s, 3, 3.66, (N-CH_3); m, 6, 6.6-7.7, (aromatic H); d of d, 1, 8.45, (H-8), 8Hz, 2Hz. The mass spectrum included peaks at m/e 292 (100%)(M^+), 277 (17) (M-CH_3), 275 (40), 273 (12), 263 (64), 249 (25), 255 (33), 223 (44), 210 (67), 209 (80) and 208 (24).

9.2 2-Piperidino-10-methylacridone

Heated for 10 min. Chromatographed on silica gel eluting with light petroleum, chloroform and chloroform-ethanol (10 : 1). The crude product eluted with chloroform-ethanol was further purified by thick layer chromatography on silica gel (benzene - ether, 1 : 1) giving 2-piperidino-10-methylacridone (100%), orange prisms m.p. 138-143° (ex benzene - light petroleum)(Found: C, 77.7; H, 7.1; N, 9.4. $C_{19}H_{20}N_2O$ requires: C, 78.0; H, 6.9; N, 9.6%). The mass spectrum showed the molecular ion at m/e 292 (100%) and very little fragmentation.

9.3 3-Piperidino-10-methylacridone

Heated for 30 min. Purified by thick layer chromatography on silica gel (benzene - ether, 1 : 1) giving 3-piperidino-10-methylacridone (54%), pale yellow plates, m.p. 198-202° (ex ether)(Found: C, 78.1; H, 6.9; N, 9.7. $C_{19}H_{20}N_2O$ requires: C, 78.0; H, 6.9; N, 9.6%). The mass spectrum included peaks at m/e 292 (100%)(M^+) and 291 (63).

9.4 4-Piperidino-10-methylacridone

Heated for 4 hr. Partially purified by chromatography on silica gel eluting with light petroleum then chloroform - ether (3 : 1). The yellow fraction eluted with chloroform - ether was purified by thick layer chromatography on silica gel (benzene - ether, 9 : 1) giving two fractions. The upper band was 4-piperidino-10-methylacridone (44%), yellow prisms m.p. 94-97° (ex light petroleum)(Found: C, 78.3; H, 6.8; N, 9.4. $C_{19}H_{20}N_2O$ requires: C, 78.0; H, 6.9; N, 9.6%). N.m.r. spectrum: s (b), 6, 1.6-2.1, (aliphatic CH_2); two s (b), each 2, 2.3-2.9 and 3.0-3.5, (aliphatic N-CH_2); s, 3, 4.1, (N-CH_3); m, 5, 7.1-7.9, (aromatic H); d of d, 1, 8.50, (H-1), 8Hz, 1Hz; d of d, 1, 8.55, (H-8), 7Hz, 2Hz. The mass spectrum showed the molecular ion at m/e 292 (100%). The lower band was 4-piperidinoacridone (28%), m.p. and mixed m.p.

181-182°.

9.5 4-Piperidinoacridone

This was prepared from 4-aminoacridone as described above, heating for 2.5 hr. The product was purified as in section 9.4 above giving 4-piperidinoacridone (43%), yellow cubes m.p. 181-182° (ex benzene - light petroleum)(Found: C, 77.6; H, 6.5; N, 9.8. $C_{18}H_{18}N_2O$ requires: C, 77.7; H, 6.5; N, 10.1%). N.m.r. spectrum: s (b), 6, 1.5-2.2, (aliphatic CH_2); s (b), 4, 2.7-3.2, (aliphatic N-CH_2); m, 5, 7.0-7.9, (aromatic H); d of d, 1, 8.30, (H-1), 6Hz, 2Hz; d of d, 1, 8.55, (H-8), 7Hz, 1Hz; s (b), 1, 9.15, (N-H). The mass spectrum included peaks at m/e 278 (100%) and 221 (65).

PART II

REACTION OF THE ISOMERIC BROMO-10-METHYLACRIDONES WITH POTASSAMIDE AND WITH LITHIUM PIPERIDIDE

SECTION A : REACTIONS WITH LITHIUM PIPERIDIDE AND PIPERIDINE

1. General

Dimethoxyethane was purified by heating with calcium hydride under reflux and was then distilled from calcium hydride.

Initially the piperidine was dried over potassium hydroxide, distilled and further dried over activated alumina. However, it appears that this method does not remove last traces of water. Solutions of lithium piperidide in this piperidine were found to be somewhat opaque at concentrations of 0.5M, due possibly to separation of lithium hydroxide. Using this lithium piperidide the reactions with the bromo-10-methylacridones were slow and the results inconsistent indicating that a proportion of the phenyllithium was converted to lithium hydroxide instead of lithium piperidide.

The piperidine was finally obtained completely dry by standing over BDH molecular sieve type 4A. Using this piperidine 1.0M solutions of lithium piperidide were quite

clear and the reactions with the bromo-10-methylacridones very much faster and reproducible.

The slightly wet piperidine was used in early trial experiments using lithium piperidide and piperidine in dimethoxyethane. In the reactions in dimethoxyethane, where only small amounts of piperidine were used, the trace of water was of little consequence. However, in piperidine as solvent this trace of water was somewhat more significant.

Phenyllithium in ether was prepared by the usual method from bromobenzene and lithium in ether[102] in an apparatus in which the solution could be filtered without exposing to the atmosphere.

Lithium piperidide in piperidine was prepared by adding a calculated amount of standardized phenyllithium in ether to piperidine and removing the ether through a short fractionating column under an atmosphere of dry nitrogen.

The yields of the products were determined by quantitative thin layer chromatography.

2. Reaction of 1-Bromo-10-methylacridone with Lithium Piperidide in Dimethoxyethane (without excess Piperidine)

Lithium piperidide (91mg, 1.0mmole) was prepared by adding 2.03M butyllithium in hexane (0.50ml, 1.0mmole) to a solution of piperidine (85mg, 1.0mmole) in dimethoxyethane. Solvent was removed in a stream of dry nitrogen leaving solid

lithium piperidide. 1-Bromo-10-methylacridone (45mg, 0.16 mmole) in dimethoxyethane (30ml) was introduced and the mixture heated under reflux for 9 hr under an atmosphere of nitrogen. Solvent was removed and water added to the residue giving a precipitate of 1-bromo-10-methylacridone (45mg, 100%), m.p. and mixed m.p. 222-223°. Extraction of the filtrate with chloroform gave a trace of 10-methylacridone (identified by thin layer chromatography and mass spectroscopy).

3. Reactions with Lithium Piperidide and Piperidine in Dimethoxyethane

The reactions with 1- and 3-bromo-10-methylacridone were performed before the piperidino-10-methylacridones were available as references and were carried out on a preparative scale. The reactions with the 2- and 4-bromo compounds were performed after the piperidino compounds were available as references and were carried out on an analytical scale. The reactions with the 2- and 4-bromo compounds were merely exploratory and quantitative results were not obtained when piperidine was found to be a superior solvent.

In these experiments the lithium piperidide was prepared *in situ* by addition of phenyllithium in ether to a solution of the bromo compound and piperidine in dimethoxyethane. In the reactions of the 2- and 4-bromo compounds,

where the phenyllithium was added rapidly, a troublesome product with green fluorescence which streaked the length of the thin layer plates was also formed. This by-product was not formed when (a) the phenyllithium was added slowly and (b) the lithium piperidide was prepared externally and would suggest that it was due to reaction of the bromo compound with phenyllithium. This substance prevented quantitative analysis being carried out, but the amount of product could be estimated qualitatively from spot size.

3.1 1-Bromo-10-methylacridone

Phenyllithium in ether (40ml of 0.38M solution, 15mmole) was added dropwise over 40 min to a refluxing solution of 1-bromo-10-methylacridone (238mg, 0.83mmole) and piperidine (2.0ml, 20mmole) in dimethoxyethane (50ml) under an atmosphere of nitrogen. A transient red colour was produced on adding the phenyllithium and this colour became permanent after about one-third of the phenyllithium had been introduced. The mixture slowly darkened to brown and after 75 min no starting material remained (by thin layer chromatography). Excess reagent was destroyed with water and the yellow solution evaporated. The products were separated by thick layer chromatography on silica gel developing with chloroform - ether (3 : 1) giving 1-piperidino-10-methylacridone (187mg, 77%), m.p. and mixed m.p.

159-161°, and 10-methylacridone (26mg, 15%), m.p. and mixed m.p. 198-200°.

3.2 3-Bromo-10-methylacridone

This was carried out as described in section 3.1 above. On adding phenyllithium the solution became orange and darkened to deep purple. After refluxing for 3 hr water was added giving an orange solution. The solvent was removed and the mixture extracted with chloroform. The products were separated by thick layer chromatography on silica gel developing with chloroform - ether (3 : 1) giving two main fractions. The upper yellow band with blue fluorescence was 10-methylacridone (58mg, 28%), m.p. and mixed m.p. 202-203°. The lower yellow band with orange fluorescence was 3-piperidino-10-methylacridone (190mg, 65%), m.p. 197-200° and identical n.m.r. and mass spectra to a later synthetic sample.

3.3 2-Bromo-10-methylacridone

Phenyllithium in ether (2.6ml of 0.8M solution, 2.0mmole) was rapidly added to a refluxing solution of 2-bromo-10-methylacridone (29mg, 0.1mmole) and piperidine (1.0ml) in dimethoxyethane (5.0ml). The solution rapidly turned brown. After 30 min water was added and the yellow solution extracted with chloroform. The products were

identified by thin layer chromatography using reference compounds. Thin layer chromatography on alumina (benzene - ethyl acetate, 49 : 1) showed the presence of 2-bromo-10-methylacridone (minor component), 10-methylacridone (minor compomemt), 2-piperidino-10-methylacridone (major component), 3-piperidino-10-methylacridone (minor component) and possibly a small amount of 1-piperidino-10-methylacridone. Thin layer chromatography on silica gel developing with ethyl acetate confirmed the presence of the 1-piperidino compound. The substance with green fluorescence mentioned above was also observed. This material streaked the length of the plate and so quantitative analysis was not carried out.

3.4 4-Bromo-10-methylacridone

This reaction was carried out as described in section 3.3 above. The mixture was heated under reflux for 13 hr and worked up in the same manner. The products were characterized by thin layer chromatography on alumina (benzene - ethyl acetate, 49 : 1) and silica gel (benzene - ethyl acetate, 4 : 1) by comparison with reference compounds. The compounds detected were 10-methylacridone (major component) and 3-piperidino-10-methylacridone (major component) together with the substance with green fluorescence mentioned above. No starting material remained and no 4-piperidino-10-methylacridone was observed. Quantitative analysis was

not carried out.

4. Reactions with Lithium Piperidide in Piperidine

4.1 Reactions in which the piperidine may have contained traces of water

These reactions were typified by the necessity for long reaction times at reflux temperature and the formation of large amounts of 10-methylacridone. The method is described for the reaction of 2-bromo-10-methylacridone and the results of all reactions are recorded in Table 8. The stabilities of the products were determined under median conditions and are recorded in Table 9. The quantitative analyses were carried out using the chromatographic systems described in section 4.2(d) below.

2-Bromo-10-methylacridone (120mg, 0.417mmole) in piperidine (4.2ml) was added to 1.0M lithium piperidide in piperidine (4.2ml, 10 equiv) and heated under reflux for 12.8 hr. Water was added and the mixture extracted with chloroform and prepared for quantitative analysis as previously described. Analysis was carried out as described in section 4.2(d) below.

TABLE 8.

Compound and conditions	% reactn	Yields (%)[a] 10-Me	1-Pip	2-Pip	3-Pip	4-Pip
1-Bromo-10-methylacridone						
10 equiv LiPip(0.25M) 20 min reflux	100	8.1	87	0	0	0
2-Bromo-10-methylacridone						
(i) 10 equiv LiPip(0.5M) 5 hr reflux	60	64	trace	7.3	1.1	0
(ii) 10 equiv LiPip(0.5M) 12.8 hr reflux	53	61	trace	17	1.2	0
(iii) as in (ii)	46	71	trace	5.4	2	0
3-Bromo-10-methylacridone						
10 equiv LiPip(0.25M) 5.75 hr reflux	45	1.5	0	0	83	0
4-Bromo-10-methylacridone						
(i) 10 equiv LiPip(0.5M) 12.8 hr reflux	77	89	0	0	1.7	0
(ii) 10 equiv LiPip(0.25M) 15 hr reflux	100	94	0	0	trace	0

a) Yields based on unrecovered starting material.

Abbreviations: LiPip - lithium piperidide

10-Me - 10-methylacridone

1-Pip - 1-piperidino-10-methylacridone

etc.

The stabilities of the products under the reaction conditions were examined by heating the compound under reflux in 0.25M lithium piperidide in piperidine for the specified time. The recovery was determined by quantitative thin layer chromatography and the results are collected in Table 9.

TABLE 9.

Compound	Reflux time (hr)	Recovery (%)
10-methylacridone	6.25	90
1-piperidino-10-methylacridone	0.33	70
2-piperidino-10-methylacridone	6.25	87
3-piperidino-10-methylacridone	5.25	99
4-piperidino-10-methylacridone	7.5	93

4.2 Reactions in which the piperidine was completely dry

In these reactions the piperidine was dried with BDH molecular sieve type 4A. The procedure used is described for three examples. The results of all reactions are collected in Tables 10 - 13.

4.2(a) 1-Bromo-10-methylacridone (at 27°)

Lithium piperidide in piperidine (0.86ml of 0.25M solution, 5 equiv) was added at room temperature (27°) to 1-bromo-10-methylacridone (12.2mg, 0.0425mmole) giving a transient deep red solution which faded after a few seconds to an orange solution. After 10 min water was added and the mixture prepared for quantitative analysis in the usual way.

4.2(b) 2-Bromo-10-methylacridone (at 75°)

Lithium piperidide in piperidine (10.5ml of 0.25M solution, 5 equiv) was added slowly over 10 min to a stirred solution of 2-bromo-10-methylacridone (150mg, 0.520mmole) in piperidine (15.0ml) maintained at 75° in an oil-bath. A transient red colour was produced during addition of the first two-thirds of the lithium piperidide but no red colour was produced during addition of the remaining one-third. After 30 min water was added to the deep orange solution and the mixture prepared for quantitative analysis.

4.2(c) 4-Bromo-10-methylacridone (at 106°)

Lithium piperidide in piperidine (0.52ml of 0.5M solution, 5 equiv) was added all at once to a refluxing solution of 4-bromo-10-methylacridone (15.1mg, 0.0523mmole) in piperidine (0.5ml) producing a transient red colour.

The mixture was heated under reflux for 5 min under an atmosphere of nitrogen during which it became deep green. Addition of water gave a yellow solution which was prepared for analysis in the usual way.

4.2(d) Chromatographic systems for quantitative analysis

(i) Reactions with 1-bromo-10-methylacridone : The compounds to be separated and determined were 1-bromo-10-methylacridone, 1-piperidino-10-methylacridone and 10-methylacridone. The separation was carried out on silica gel first developing twice with benzene - ethyl acetate (4 : 1) and then once, to just below the 10-methylacridone band, with benzene - ethyl acetate - diethylamine (4 : 2 : 1) to move the 1-piperidino-10-methylacridone from the base line.

(ii) Reactions with 2-bromo-10-methylacridone : The compounds to be separated and determined in these reactions were 2-bromo-, 1-, 2- and 3-piperidino-10-methylacridones and 10-methylacridone. The 2-bromo-, 2- and 3-piperidino-10-methylacridones and 10-methylacridone were determined on alumina (benzene - ethyl acetate, 99 : 1). 1-Piperidino-10-methylacridone was more difficult to determine. This product was formed only in very low yield and, since it does not fluoresce, was difficult to observe on thin layer

plates. On alumina it runs between the 2- and 3-piperidino compounds but could not be observed. On silica gel it required very polar solvent mixtures to make it move. In order to obtain accurate analyses of 1-piperidino-10-methylacridone it was first necessary to remove all other products which would contaminate the 1-piperidino compound by streaking. The major products were first removed by thick layer chromatography on silica gel. An aliquot (as large as possible) of the reaction product was applied to the thick layer plate and the plate developed twice with benzene - ethyl acetate (4 : 1) and then once with benzene - ethyl acetate - diethylamine (40 : 10 : 1). The yellow band moving adjacent a reference spot of the 1-piperidino compound was removed, eluted with chloroform - ethanol (3 : 1)(100ml), evaporated and made up to one ml with chloroform. The 1-piperidino compound in this solution was then determined on alumina (benzene - ethyl acetate, 49 : 1).

(iii) Reactions with 3-bromo-10-methylacridone : The compounds to be separated in these reactions were 3-bromo-10-methylacridone, 3-piperidino-10-methylacridone and 10-methylacridone. These were all determined on silica gel developed with benzene - ethyl acetate (4 : 1).

(iv) Reactions with 4-bromo-10-methylacridone : The compounds to be separated and determined in these reactions were 4-bromo-10-methylacridone, 3-piperidino-10-methylacridone and 10-methylacridone. These were all determined on silica gel developed with benzene - ethyl acetate (4 : 1).

TABLE 10.

Reaction of 1-bromo-10-methylacridone with lithium piperidide in piperidine

Conditions	Temp °C	% Reactn	Relative yields (%) 10-Me	1-Pip	2-Pip	3-Pip	4-Pip
5 equiv LiPip (0.1M), 10 min reactn time	27	65	13	74	0	0	0

TABLE 11.

Reactions of 2-bromo-10-methylacridone with lithium piperidide in piperidine.

Conditions	Temp °C	% Reactn	Relative yields (%) 10-Me	1-Pip	2-Pip	3-Pip	4-Pip
10 equiv LiPip (1.0M), 1 hr reflux	106	100	5.2	(0.7)	25	0.9	0
2 equiv LiPip (0.1M), 2 hr reflux	106	52	71	-[a]	3.6	1	0
5 equiv LiPip (0.25M), 15 min reflux	106	100	73	(0.8)	6.8	1.1	0
5 equiv LiPip (0.25M), 1 hr reflux	106	100	69	0.6	9.6	0.8	0
5 equiv LiPip (0.1M), 30 min	75	60	7.1	0.4	74	3.5	0
5 equiv LiPip (0.1M), 10 min	27	9	18	-[a]	72	10	0
5 equiv LiPip (0.1M), 30 min	27	16	11	<1	67	6.6	0

a) Not determined.

TABLE 12.

Reaction of 3-bromo-10-methylacridone with lithium piperidide in piperidine

Conditions	Temp °C	% Reactn	Relative yields (%) 10-Me	1-Pip	2-Pip	3-Pip	4-Pip
5 equiv LiPip (0.1M), 10 min	27	39	12	0	0	73	0

TABLE 13.

Reactions of 4-bromo-10-methylacridone with lithium piperidide in piperidine.

Conditions	Temp °C	% Reactn	Relative yields (%) 10-Me	1-Pip	2-Pip	3-Pip	4-Pip
10 equiv LiPip (1.0M), 1 hr reflux	106	100	19	0	0	34	0
5 equiv LiPip (0.25M), 5 min reflux	106	100	21	0	0	58	0
5 equiv LiPip (0.1M), 10 min	27	46	25	0	0	31	0

4.2(e) Stabilities of the products in lithium piperidide in piperidine

The products from the previous reactions were treated with 0.18M lithium piperidide in piperidine, those at 27° for 10 min and those at reflux temperature for 5 min. The compounds were analyzed as above and the recoveries recorded in Table 14.

TABLE 14.

Compound	Recovery (%) 27°	106°
10-Methylacridone	93	77
1-Piperidino-10-methylacridone	83	-[a]
2-Piperidino-10-methylacridone	57	-[a]
3-Piperidino-10-methylacridone	-[a]	68
4-Piperidino-10-methylacridone	85	76

a) Not determined, c.f. Table 9.

5. Reactions with Piperidine

The bromo-10-methylacridones were heated under reflux with piperidine. The product was prepared for quantitative analysis in the usual way and analyzed using the chromato-

graphic systems described above. The results are collected in Table 15.

TABLE 15.

Reaction of the bromo-10-methylacridones with refluxing piperidine

Compound	Reactn time (hr)	Analysis of product	Yield (%)
1-Bromo-10-methylacridone	0.33	1-bromo-10-methylacridone	0
		1-piperidino-10 methylacridone	81
		10-methylacridone	6.2
2-Bromo-10-methylacridone	6	2-bromo-10-methylacridone	100
3-Bromo-10-methylacridone	5.3	3-bromo-10-methylacridone	94
		3-piperidino-10-methylacridone	5.7
		10-methylacridone	trace
4-Bromo-10-methylacridone	6	4-bromo-10-methylacridone	86
		4-piperidino-10-methylacridone	0
		10-methylacridone	2.8

6. Reactions with Lithium Hydroxide in Piperidine

6.1 2-Bromo-10-methylacridone

2-Bromo-10-methylacridone (5.02mg) in piperidine (1.0ml) was heated under reflux for 6 hr with lithium hydroxide (20mg). Quantitative analysis of the product gave 2-bromo-10-methylacridone (98%). No 10-methylacridone was observed.

6.2 4-Bromo-10-methylacridone

This was carried out as above and qualitative thin layer chromatography showed that 10-methylacridone was formed slowly.

SECTION B : REACTIONS WITH POTASSAMIDE IN LIQUID AMMONIA - DIMETHOXYETHANE

1. General

Dimethoxyethane was purified by distillation and dried and stored over BDH molecular sieve type 4A.

2. Apparatus for analytical scale reactions

Analytical scale reactions were carried out in the apparatus illustrated in Fig. 5 .

Before use the apparatus was flame-dried whilst flushing with dry nitrogen. Ammonia was distilled from a cylinder into flask A, where it was dried with potassium metal and then distilled into flask B. The required amount of ammonia was forced under nitrogen pressure into the graduated funnel E. (For the reactions in which potassamide was added to a solution of the bromo-10-methylacridone in

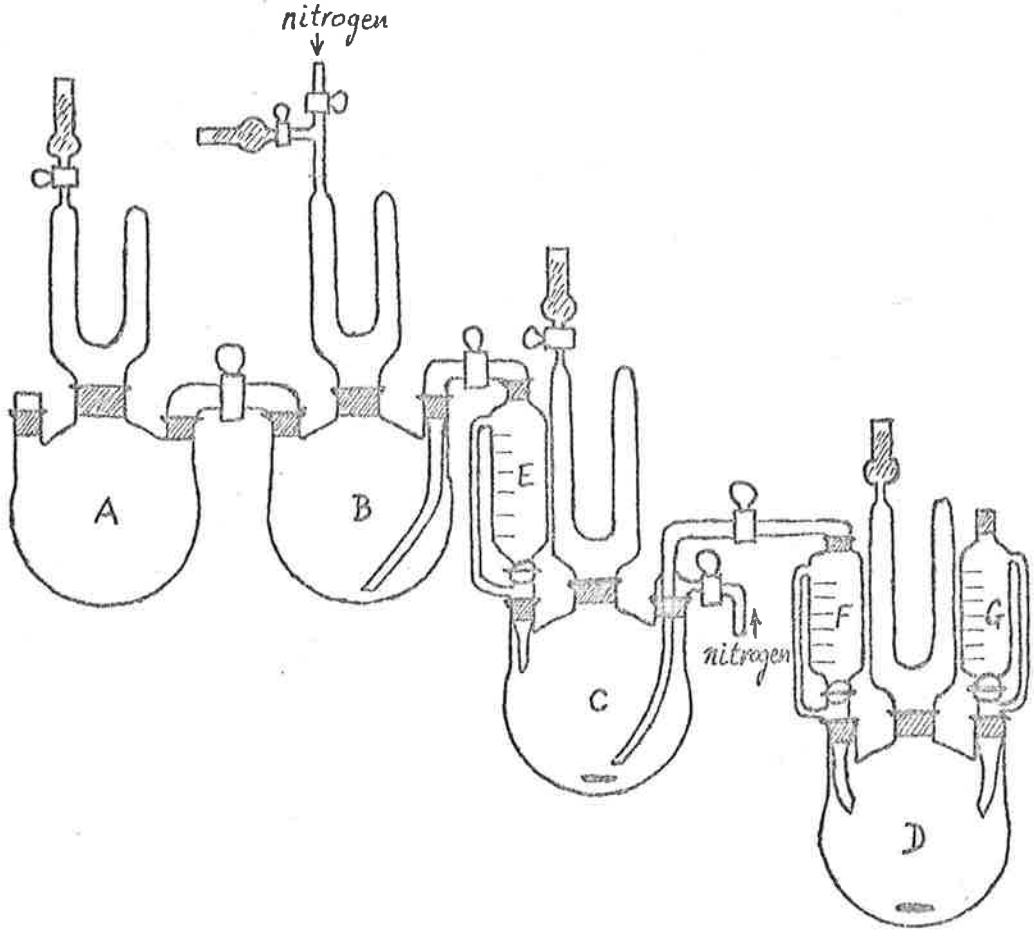

FIG. 5

ammonia - dimethoxyethane, ammonia could be forced into funnel G by means of an additional tube). The potassamide solution was formed in flask C by adding a measured amount of liquid ammonia to a weighed amount of potassium metal and dimethoxyethane with ferric nitrate as catalyst in the flask. The required amount of potassamide solution was forced into the graduated funnel F and run into the reaction vessel.

3. Chromatographic Systems for Quantitative Analysis

3.1 Reactions with 1-bromo-10-methylacridone

The compounds present in these reactions were 1-bromo-10-methylacridone, 10-methylacridone and 3'-amino-N-methyldiphenylamine-2-carbonamide. The last compound was not recognized as a product at the time the analytical reactions were performed and was not determined. Analysis was carried out on silica gel developing with benzene - ethyl acetate (9 : 1). In each case the last compound was present as a colourless spot at the base line and stained yellow with iodine.

3.2 Reactions with 2-bromo-10-methylacridone

10-Methylacridone and 1-amino-10-methylacridone were determined on silica gel developed with benzene - ethyl acetate (9 : 1). 2-Amino and 3-amino-10-methylacridone

were determined on silica gel developed with benzene - ethyl acetate - diethylamine (7 : 2 : 1).

3.3 Reactions with 3-bromo-10-methylacridone

The product, 3-amino-10-methylacridone, was not very soluble in chloroform so that the product mixture was dissolved in 2 : 1 chloroform - ethanol (25ml). Analysis was performed on silica gel developed with benzene - ethyl acetate - diethylamine (7 : 2 : 1).

3.4 Reactions with 4-bromo-10-methylacridone

Since the major product was 3-amino-10-methylacridone it was necessary to prepare the reaction mixture for analysis as described in section 3.3 above. 3-Amino-10-methylacridone was determined on the same system. 10-Methylacridone and unchanged 4-bromo-10-methylacridone were determined on silica gel developed with benzene - ethyl acetate (4 : 1).

4. Reactions of the Bromo-10-methylacridones with Potassamide in Liquid Ammonia - Dimethoxyethane

The procedure is illustrated for a typical reaction with 2-bromo-10-methylacridone. The reactions were all carried out at the temperature of refluxing ammonia.

The potassamide solution was prepared in flask C (Fig. 5) by adding liquid ammonia (50ml) to potassium metal (0.980g) suspended in dimethoxyethane (30ml) with ferric nitrate as catalyst. An aliquot (13ml, 4.0mmole of KNH_2) of this solution was transferred to the reaction vessel. 2-Bromo-10-methylacridone (56.0mg, 0.195mmole) in dimethoxyethane (20ml) was added dropwise over 10 min to the stirred potassamide solution giving a deep red solution. After 15 min excess potassamide was destroyed with ammonium nitrate and the product prepared for analysis in the usual way.

The results of the reactions are collected in Tables 16, 17, 18 and 19.

TABLE 16.

Reaction of 1-bromo-10-methylacridone with potassamide in ammonia - dimethoxyethane.

Conditions	Reactn time (min)	% Reactn	Relative yields (%) 10-Me	1-NH_2	2-NH_2	3-NH_2	4-NH_2
5 equiv KNH_2. KNH_2 added to Br-acr. soln.	60	63	22	0	0	0	0

TABLE 17.

Reaction of 2-bromo-10-methylacridone with potassamide in ammonia - dimethoxyethane.

Conditions	Reactn time (min)	% Reactn	Relative yields (%) 10-Me	1-NH_2	2-NH_2	3-NH_2	4-NH_2
10 equiv KNH_2. KNH_2 added to Br-acr. soln.	30	100	12	33	3.4	7.1	0
10 equiv KNH_2. KNH_2 added all at once to Br-acr. soln.	0.5	100	1.1	56	23	3.3	0
	1	100	2.5	49	18	3.3	0
	2	100	4.0	54	12	3.3	0
	5	100	3.6	53	14	3.7	0
	15	100	9.5	39	1.8	4.3	0
	15	100	9.5	42	1.9	5.0	0

TABLE 18.

Reaction of 3-bromo-10-methylacridone with potassamide in ammonia - dimethoxyethane.

Conditions	Reactn time (min)	% Reactn	Relative yields (%) 10-Me	1-NH_2	2-NH_2	3-NH_2	4-NH_2
10 equiv KNH_2.							
Br-acr. added to	6	100	0	0	0	93	0
KNH_2 soln.	6	100	0	0	0	92	0

TABLE 19.

Reaction of 4-bromo-10-methylacridone with potassamide in ammonia - dimethoxyethane.

Conditions	Reactn time (min)	% Reactn	Relative yields (%) 10-Me	1-NH_2	2-NH_2	3-NH_2	4-NH_2
5 equiv KNH_2.							
KNH_2 added to	35	100	9	0	0	63	0
Br-acr. soln.							
10 equiv KNH_2.	15	100	12	0	0	66	0
Br-acr. added to							
KNH_2	15	100	10	0	0	66	0
10 equiv KNH_2.							
Br-acr. added to	0.5	89	1.5	0	0	88	0
KNH_2							

5. Stabilities of the Products

The stabilities of the products were determined under median conditions by stirring the compound (20-30mg) in dimethoxyethane (10ml) with 0.14M potassamide in ammonia - dimethoxyethane (3 : 2)(15ml) for 15 min. The mixture was worked-up and analyzed as described above. The results are recorded in Table 20.

TABLE 20.

Compound	Analysis of product	Yield (%)
10-Methylacridone	10-methylacridone	92
1-Amino-10-methylacridone	1-amino-10-methylacridone	68
2-Amino-10-methylacridone	2-amino-10-methylacridone	6
	10-methylacridone	22
3-Amino-10-methylacridone	3-amino-10-methylacridone	82
4-Amino-10-methylacridone	4-amino-10-methylacridone	0[a]

a) No other products were identified. Thin layer chromatography showed a large number of fluorescent spots. About half of the starting material was recovered as a dark green unidentified solid which was insoluble in chloroform.

6. Preparative Scale Reaction of 1-Bromo-10-methyl-acridone with Potassamide in Ammonia - Dimethoxyethane

Liquid ammonia (150ml) was introduced into a 500ml 2-neck flask fitted with ammonia condenser, soda lime guard tube and magnetic stirrer. The ammonia was dried with a small amount of potassium metal. Ferric nitrate (a few crystals) and potassium metal (3.12g, 80mmole) were introduced and when formation of potassamide was complete dry dimethoxyethane (90ml) was added. Finely powdered 1-bromo-10-methylacridone (1.15g, 4.0mmole) was added in portions over 10 min to the stirred potassamide solution. Stirring was continued for a total of 20 min during which no intense colours were observed. Excess potassamide was decomposed with ammonium nitrate and the ammonia and dimethoxyethane removed. Water was added and the mixture extracted with chloroform. Evaporation yielded a pale brown solid (0.925g), m.p. 170-175°. Examination of the product by thin layer chromatography on silica gel developing with benzene - ethyl acetate (4 : 1) and ethyl acetate alone showed only trace amounts of 1-bromo-10-methylacridone and 10-methylacridone and no 1- or 2-amino-10-methylacridone to be present. A very large non-fluorescent spot of R_f 0.6 and a very small spot with slightly higher R_f in ethyl acetate were observed on treating the plate with iodine vapour. The product was purified by thick layer chromatography on silica gel

developing with ethyl acetate. The band corresponding to the spot staining with iodine was removed giving 3'-amino-N-methyldiphenylamine-2-carbonamide (67% recovery) which, after sublimation at 0.05mmHg, gave pale yellow crystals, m.p. and mixed m.p. 185-186°. The i.r. spectrum of the crude product was identical with that of the purified product so that the crude yield was 96%. The loss on purification was due to streaking and the difficulty in locating the product on the thick layer plate.

7. Preparation of 3'-Amino-N-methyldiphenylamine-2-carbonamide

7.1 3'-Nitrodiphenylamine-2-carboxylic acid

This was prepared by the method of Albert and Ritchie[98].

7.2 2-Methoxycarbonyl-N-methyl-3'-nitrodiphenylamine

3'-Nitrodiphenylamine-2-carboxylic acid (2.6g) was dissolved in dimethylformamide (20ml) and sodium hydride (1.0g of 1 : 1 dispersion in oil) added giving a deep green solution. When evolution of hydrogen ceased dimethyl sulphate (5.0ml) was added with stirring over 10 min. After a further 5 min water was added, the solution acidified and extracted with ether. The ethereal extract was washed

several times with water and chromatographed on alumina eluting with light petroleum and light petroleum - ether (4 : 1) giving 2-methoxycarbonyl-N-methyl-3'-nitrodiphenylamine (2.4g, 87%), orange cubes, m.p. 91-92° (ex petroleum b.p. 60-80°)(Found: C, 62.7; H, 5.0; N, 9.6. $C_{15}H_{14}N_2O_4$ requires: C, 62.9; H, 4.9; N, 9.8%). The mass spectrum showed the molecular ion at m/e 286 (100%). N.m.r. spectrum: two s, each 3, 3.35 and 3.65, (O-CH_3 and N-CH_3); d of d of d, 1, 6.8, (H-6), 7Hz, 2Hz, 1Hz; m, 6, 7.0-7.8, (aromatic H); d of d, 1, 8.95, (H-3), 7Hz, 2Hz.

7.3 3'-Amino-2-methoxycarbonyl-N-methyldiphenylamine

A mixture of 2-methoxycarbonyl-N-methyl-3'-nitrodiphenylamine (2.3g), stannous chloride (5.0g) and concentrated hydrochloric acid (5.0ml) was heated on a steam-bath for 15 min. Water was added, the solution neutralized with ammonia and extracted with ether. Evaporation of the ethereal extract gave an orange oil (1.8g) which was purified by thick layer chromatography on silica gel developing with benzene - ethyl acetate (4 : 1). Two pale yellow bands separated. The upper band was 3'-amino-N-methyldiphenylamine-2-carboxylic acid (0.4g, 21%), a yellow oil. The i.r. spectrum (liquid film) included absorptions at 3420 (m), 3320 (s)(N-Hstr) and 1682cm^{-1} (s)(C=Ostr). The mass spectrum included peaks at m/e 242 (82%)(M^+) and

210 (100)(M-CH_3OH). N.m.r. spectrum (in CCl_4) : s (b), 2, 3.45, (NH_2); s, 3, 3.85, (N-CH_3); m, 7, 6.1-7.4, (aromatic H); d, 1, 7.85, (H-3), 8Hz; s (b), 1, 9.3, (CO_2H). The lower band was 3'-amino-2-methoxycarbonyl-N-methyldiphenylamine (1.4g, 68%), a yellow viscous oil which was further purified by distillation at 160°/0.02mmHg (Found: C, 70.4; H, 6.4; N, 10.7. $C_{15}H_{16}N_2O_2$ requires: C, 70.3; H, 6.3; N, 10.9%). The i.r. spectrum (liquid film) included absorptions at 3420 (m), 3350 (m)(N-Hstr) and 1720cm^{-1}(C=Ostr). The mass spectrum included peaks at m/e 256 (75%)(M^+), 197 (100)(M-CO_2CH_3) and 182 (24)(M-CO_2CH_3-CH_3). N.m.r. spectrum (in CCl_4) : s (broad at base), 5, 3.20, (CH_3 and NH_2); s, 3, 3.55, (CH_3); m, 3, 5.6-6.1, (H-2', H-4', H-6'); m, 5, 6.6-7.8, (other aromatic H).

7.4 3'-Amino-N-methyldiphenylamine-2-carbonamide

Liquid ammonia (30ml) was distilled into a 250ml 2-neck flask fitted with ammonia condenser, pressure equalizing dropping funnel and magnetic stirrer. The ammonia was dried with potassium metal and, when the blue colour persisted, ferric nitrate (a few crystals) and potassium metal (1.0g) were introduced. When formation of potassamide was complete 3'-amino-2-methoxycarbonyl-N-methyldiphenylamine (0.50g) in dimethoxyethane (10ml) was introduced over 3 min and the mixture stirred for 30 min. Excess potassamide was

destroyed with ammonium nitrate and the ammonia and dimethoxyethane evaporated. Water was added to the residue and the mixture extracted with chloroform giving 3'-amino-N-methyldiphenylamine-2-carbonamide (0.37g, 79%) as a brown oil which slowly crystallized. The product was purified by thick layer chromatography on silica gel developing with ethyl acetate (recovery, 74%). Sublimation at 160°/0.01mmHg gave yellow crystals, m.p. 184.5-186.5° (Found: C, 69.8; H, 6.2; N, 16.9. $C_{14}H_{15}N_3O$ requires: C, 69.7; H, 6.3; N, 17.4%). The mass spectrum included peaks at m/e 241 (89%)(M^+), 197 (100)($M-NH_2CO$) and 182 (27)($M-NH_2CO-CH_3$) with metastable ions at m/e 161 and 169. N.m.r. spectrum: s, 3, 3.25, ($N-CH_3$); s (b), 2, 3.5, (NH_2, exchanged with D_2O); three m, 3, 5 and 2 protons respectively, 5.9-6.4, 6.9-7.6 and 8.2-8.4, (aromatic H and $CONH_2$).

PART III

REACTION OF THE ISOMERIC BROMO-10-METHYLACRIDONES WITH SODIUM METHOXIDE IN METHANOL AND IN DIMETHYL SULPHOXIDE

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1. Preparation of 1- and 3-Methoxy-10-methylacridone

1.1 3'-Methoxydiphenylamine-2-carboxylic acid

This was prepared in 19% yield by the method of Lehmstedt and Schrader[56], m.p. 143-144° (lit. m.p. 132°).

1.2 Preparation and separation of 1- and 3-methoxyacridone

3'-Methoxydiphenylamine-2-carboxylic acid was cyclized with phosphoryl chloride as described in Part I section 1.2 above and worked up to give a mixture of 1- and 3-methoxy-9-chloroacridine as described in Part I section 1.5 above. The 1- and 3-methoxy-9-chloroacridines were separated in poor yield according to Albert[1p] and hydrolyzed to the methoxyacridones with dilute acid.

1.3 1-Methoxy-10-methylacridone

This was prepared by N-methylation of 1-methoxyacridone with sodium hydride and dimethyl sulphate in dimethylformamide as described in Part I section 1.3 above and was obtained as yellow needles, m.p. 166-168° (lit.[55] m.p. 164°).

1.4 3-Methoxy-10-methylacridone

This was prepared from 3-methoxyacridone in the same way as 1-methoxy-10-methylacridone and was obtained as yellow needles, m.p. 186-187° (lit. m.p.[55] 185°).

2. Reactions of the Bromo-10-methylacridones with Sodium Methoxide in Methanol

2.1 1-Bromo-10-methylacridone

1-Bromo-10-methylacridone (11.5mg) was refluxed under nitrogen for 18 hr in 0.5M sodium methoxide in methanol. The solvent was removed, water added and the mixture extracted with chloroform. Purification of the product by thick layer chromatography on silica gel (benzene - ethyl acetate, 4 : 1) gave 10-methylacridone (8.0mg, 96%), m.p. and mixed m.p. 202-204°. Qualitative thin layer chromatography of the product showed only trace amounts of 1-bromo-10-methylacridone and 1-methoxy-10-methylacridone (by comparison with standards). Samples removed during the reaction showed no more than trace amounts of 1-methoxy-10-methylacridone at any stage.

2.2 2-Bromo-10-methylacridone

This was carried out as in section 2.1 above and, after 48 hr, qualitative thin layer chromatography showed

mainly starting material together with trace amounts of 10-methylacridone.

2.3 3-Bromo-10-methylacridone

This was carried out as in section 2.1 above, the mixture being heated under reflux for 20 hr. Analysis of the product by quantitative thin layer chromatography gave 10-methylacridone (85%) together with a small amount of 3-bromo-10-methylacridone and trace amounts of 3-methoxy-10-methylacridone.

2.4 4-Bromo-10-methylacridone

This was carried out as in section 2.1 above. The reaction was complete in 3.5 hr giving 10-methylacridone (100%), m.p. and mixed m.p. 202-204°.

2.5 Reaction of 4-bromo-10-methylacridone with sodium methoxide in methanol-d_1 (CH_3OD)

4-Bromo-10-methylacridone (15mg) was heated under reflux with 1.0M sodium methoxide in methanol-d_1 (CH_3OD) for 5 hr. Water was added giving 10-methylacridone (10mg, 92%), m.p. and mixed m.p. 202-203°. The mass spectrum included peaks at m/e 211 (2%), 210 (16), and 209 (100).

3. Kinetics of Reactions of 1- and 3-Bromo-10-methyl-acridone with Sodium Methoxide in Dimethyl Sulphoxide

3.1 Sodium methoxide in methanol-free dimethyl sulphoxide

Since sodium methoxide is very insoluble in dimethyl sulphoxide only very dilute solutions could be prepared.

Analytical grade methanol was dried with BDH molecular sieve type 3A. Sodium methoxide was prepared from sodium and dry methanol and excess methanol removed under reduced pressure. Last traces of methanol were removed by prolonged pumping at 0.01mmHg.

Redistilled dimethyl sulphoxide was dried with BDH molecular sieve type 4A.

Solutions of sodium methoxide in dimethyl sulphoxide were prepared by heating excess sodium methoxide in dimethyl sulphoxide at 100-120^{o} for several hours in a flask closed with a rubber serum cap. The mixture was equilibrated at 40^{o} and the solution separated from the excess solid and standardized with standard hydrochloric acid. It was found necessary to use this solution as soon as possible after preparation since, if left too long, sodium methoxide appeared to separate. Solutions varying in concentration from 0.002 to 0.04M were obtained.

3.2 Procedure for kinetic measurements

Kinetic runs were carried out in a constant temperature water-bath maintained at $40^{\circ} \pm 0.1^{\circ}$. The reagents were equilibrated in flasks sealed with rubber serum caps and solutions transferred and samples removed with graduated syringes.

The procedure is illustrated for the reaction with 1-bromo-10-methylacridone. Sodium methoxide in dimethyl sulphoxide (10.0ml of 0.0070M solution) was added to a solution of 1-bromo-10-methylacridone (9.91mg) in dimethyl sulphoxide (5.0ml) and samples removed after 5, 10, 15, 20, 30, 40 and 50 min. The reaction was quenched with dilute acid and the organic material extracted into chloroform. Each sample was prepared for analysis by quantitative thin layer chromatography as described previously and the concentration of 1-bromo-10-methylacridone determined on silica gel (benzene - ethyl acetate, 4 : 1).

The second order rate constants were determined from the integrated rate equation for a second order reaction which is first order with respect to each reactant[103a], and are recorded in Table 4 (page 94).

For both 1- and 3-bromo-10-methylacridone the reaction was very clean, the products being entirely the respective methoxy-10-methylacridone.

PART IV

REACTION OF SOME POLYALKOXY-10-METHYLACRIDONES WITH SODIUM METHOXIDE IN METHANOL AND IN DIMETHYL SULPHOXIDE

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1. Preparation of 3,4-Dimethoxy-1,2-methylenedioxy-10-methylacridone

1.1 2-Hydroxy-1,3,4-trimethoxy-10-methylacridone

This was prepared in 87% yield by the method of Crow and Price[12] and obtained as yellow needles, m.p. 170-171° (ex ether)(lit. m.p. 165-166°).

1.2 1,2-Dihydroxy-3,4-dimethoxy-10-methylacridone

This was prepared in 80% yield from 2-hydroxy-1,3,4-trimethoxy-10-methylacridone by the method of Crow and Price[12], m.p. 203-205° (ex ethanol)(lit. m.p. 162-163°). The product gave a dark green-brown colour with ferric chloride. The mass spectrum included peaks at m/e 301 (6%), 300 (9), 299 (64)($M-H_2$), 284 (100), 279(19), 254 (26) and 149 (69).

1.3 3,4-Dimethoxy-1,2-methylenedioxy-10-methylacridone

A mixture of 1,2-dihydroxy-3,4-dimethoxy-10-methylacridone (1.5g), di-iodomethane (10ml) and anhydrous

potassium carbonate (2.0g) was heated under reflux in acetone (50ml) for 24 hr. The solution was concentrated, water added and the mixture extracted with chloroform. Column chromatography on silica gel, eluting with chloroform, gave 3,4-dimethoxy-1,2-methylenedioxy-10-methylacridone (0.80g, 51%), m.p. 217.5-223.5° (ex acetone). Sublimation at 210°/0.01mmHg gave yellow crystals, m.p. 219-221° (Found: C, 65.4; H, 4.8; N, 4.4. $C_{17}H_{15}NO_5$ requires: C, 65.2; H, 4.8; N, 4.5%). The mass spectrum included peaks at m/e 313 (76%)(M^+), 298 (100)($M-CH_3$) and 178 (28). N.m.r. spectrum : three s, each 3, 3.75, 3.92 and 4.20, ($N-CH_3$ and two $O-CH_3$); s, 2, 6.18, ($O-CH_2-O$); m, 3, 7.0-7.8, (H-5, H-6, H-7); d of d, 1, 8.38, (H-8), 7Hz, 2Hz.

2. Reactions of the Dimethoxymethylenedioxy-10-methylacridones with sodium methoxide in methanol

2.1 3,4-Dimethoxy-1,2-methylenedioxy-10-methylacridone

3,4-Dimethoxy-1,2-methylenedioxy-10-methylacridone (246mg) in 1.0M sodium methoxide in methanol (20ml) was gently refluxed under an atmosphere of nitrogen on a water-bath for 14 days, when thin layer chromatography showed only trace amounts of starting material remained. Solvent was removed, the residue acidified and extracted with chloroform. The products were separated by thick layer

chromatography on silica gel developing with benzene - ethyl acetate (2 : 1). Four orange or yellow bands separated and are described in order of decreasing R_f.

(a) 3,4-Dimethoxy-1-hydroxy-2-(α-methoxy)methoxy-10-methylacridone (36mg, 13%), m.p. 100-102° (ex chloroform - light petroleum)(Found: C, 62.8; H, 5.5; N, 3.9. $C_{18}H_{19}NO_6$ requires: C, 62.6; H, 5.6; N, 4.0%). U.v. spectrum (in 95% ethanol): λ_{max} (neutral solution) 249, 273, 309, 419; (alkaline solution) 252, 275, 322, 433nm. The mass spectrum included peaks at m/e 345 (25%)(M^+) and 300 (100) with a meta-stable ion at m/e 261. N.m.r. spectrum : four s, each 3, 3.67, 3.75, 4.05 and 4.15 (N-CH_3 and three O-CH_3); s, 2, 5.24, (O-CH_2-O); m, 3, 7.0-7.9, (H-5, H-6, H-7); d of d, 1, 8.40, (H-8), 7Hz, 2Hz; s, 1, 14.5, (O-H, exchanged with D_2O). Methylation of this compound with diazomethane gave a non-crystalline oil identical (by thin layer chromatography) with a sample of 2-(α-methoxy)methoxy-1,3,4-trimethoxy-10-methylacridone prepared from 2-hydroxy-1,3,4-trimethoxy-10-methylacridone and chlorodimethyl ether; n.m.r. spectrum : five s, each 3; 3.56, 3.73, 3.85, 3.90 and 4.00, (N-CH_3 and four O-CH_3); s, 2, 5.05, (O-CH_2-O); m, 3, 6.9-7.7, (H-5, H-6, H-7); d of d, 1, 8.17, (H-8), 8Hz, 2Hz.

(b) 3,4-Dimethoxy-1,2-methylenedioxy-10-methylacridone (7mg, 3%), m.p. and mixed m.p. 220-221°.

(c) 2-Hydroxy-1,3,4-trimethoxy-10-methylacridone (95mg, 39%), m.p. and mixed m.p. 170-171°.

(d) 3-Hydroxy-4-methoxy-1,2-methylenedioxy-10-methylacridone (59mg, 25%), m.p. 244-246° (ex aqueous ethanol). The mass spectrum included peaks at m/e 299 (63%)(M^+), 284 (100)($M-CH_3$) and 254 (24) with meta-stable ions at m/e 270 and 230. U.v. spectrum (in 95% ethanol): λ_{max} (log ε)(neutral solution) 280 (4.52), 418nm (3.65); (alkaline solution) 252 (4.40), 289 (4.37), 370nm (4.04). Methylation with dideuterodiazomethane gave deuterated 3,4-dimethoxy-1,2-methylenedioxy-10-methylacridone, m.p. and mixed m.p. 217-218°; the mass spectrum included peaks at m/e 316 (58%), 315 (73), 314 (69), 301 (74), 300 (100) and 299 (100).

2.2 Melicopidine

Melicopidine (986mg) was heated under reflux in 1.0M sodium methoxide in methanol (50ml) for 6 days and worked up as described in section 2.1 above. Separation by thick layer chromatography on silica gel (benzene - ethyl acetate, 2 : 1) gave normelicopidine (28mg, 3%), m.p. and mixed m.p. 211-212°, and 2-hydroxy-1,3,4-trimethoxy-10-methylacridone (960mg, 97%), m.p. and mixed m.p. 170-171°.

2.3 Melicopine

Melicopine (1.05g) was refluxed under nitrogen in 1.0M sodium methoxide in methanol for 14 days and was worked up as described in section 2.1 above. The crude product (1.16g) was separated into its constituents by repeated thick layer chromatography on silica gel developing with benzene - ethyl acetate (2 : 1). All products present were isolated and are described in order of decreasing R_f.

(a) Normelicopine (65mg, 6%), m.p. and mixed m.p. 234-235°.

(b) Melicopine (45mg, 4%), m.p. and mixed m.p. 176-178°.

(c) 4-Hydroxy-1,2,3-trimethoxy-10-methylacridone (410mg, 39%), identical with a sample prepared by the method of Crow and Price[12].

(d) An unidentified fraction (380mg) which appeared to be a mixture of several compounds.

(e) A further unidentified product (15mg). The mass spectrum of this compound included peaks at m/e 322 (21%), 321 (88), 307 (30), 306 (100), 292 (37) and 262 (31).

(f) 1,2-Dimethoxy-3-hydroxy-4-(α-methoxy)methoxy-10-methylacridone (15mg, 1.3%). The mass spectrum of this compound included peaks at m/e 345 (33%) and 300 (100) with a metastable ion at m/e 261.

(g) 2-Hydroxy-1-methoxy-3,4-methylenedioxy-10-methylacridone (25mg, 2.4%). The mass spectrum of this compound included peaks at m/e 299 (100%), 284 (55), 281 (90), 280 (47), 270

(17), 256 (15), 254 (31) and 252 (22). Methylation of this compound with dideuterodiazomethane gave melicopine (identical by thin layer chromatography) of which the mass spectrum included peaks at m/e 316 (20%), 315 (30), 314 (41), 313 (32) and 298 (100).

(h) 3,4-Dimethoxy-10-methylacridone-1,4-quinone (55mg, 5.5%), m.p. and mixed m.p. 225°.

3. Kinetics of Reaction of Melicopidine with Sodium Methoxide in Methanol

Melicopidine (250mg, 0.800mmole) was refluxed under nitrogen with 1.00M sodium methoxide in methanol (25ml). Samples (5ml) were removed after 2.5, 6.75, 13.8, 23.2 and 30.6 hr and the reaction quenched with dilute hydrochloric acid. The product was extracted with chloroform, the extract evaporated and the residue dissolved in deutero-chloroform (0.7ml). The reaction was followed by n.m.r. spectroscopy by comparison of the integrated intensities of the methylenedioxy resonance (a singlet at δ6.1) and the H-8 resonance (a doublet at δ8.4) which is present in both melicopidine and in the product, 2-hydroxy-1,3,4-tri-methoxy-10-methylacridone. From this ratio the concentration of melicopidine in the reaction mixture was determined and the pseudo-first order rate constant[103b] obtained. From this the second order rate constant was found to be 4.0 x

10^{-6} l. $mole^{-1}$. sec^{-1} at 65°.

4. Kinetics of the Reactions of the Dimethoxy-methylenedioxy-10-methylacridones with Sodium Methoxide in Dimethyl Sulphoxide

The technique used for determination of the rates of opening of the methylenedioxy rings of the dimethoxy-methylenedioxy-10-methylacridones with methoxide ion in dimethyl sulphoxide was essentially the same as that used for determination of the rates of substitution of 1- and 3-bromo-10-methylacridones with methoxide ion in dimethyl sulphoxide described in Part III above. The method is briefly described for the reaction with melicopidine. The reactions were performed at 40°.

Sodium methoxide in dimethyl sulphoxide (0.042M, 10.0ml) was added to melicopidine (10.0mg, 0.064mmole) in dimethyl sulphoxide (3.0ml). Samples were removed after 0.5, 1, 1.5,2, 3 and 4 min and the reaction quenched with dilute acid. The organic material was extracted with chloroform and the extract prepared for analysis by quantitative thin layer chromatography. The reactions were followed by the decrease in concentration of the methylenedioxy compound which was determined by quantitative thin layer chromatography on silica gel (benzene - ethyl acetate, 2 : 1).

The second order rate constants are recorded in Table

5 (page 114).

5. Attempts to Measure the Rate of Methoxide Exchange of Melicopicine with Sodium Methoxide in Dimethyl Sulphoxide

Tritium labelled sodium methoxide was prepared from sodium and tritium labelled methanol, CH_2TOH^{104} (approx. 1.3 mC/mmole). A solution of labelled sodium methoxide in methanol-free dimethyl sulphoxide was prepared as described in Part III section 3.1 above. The reaction was carried out at 40° as described in Part III section 3.2 above.

Tritiated sodium methoxide in dimethyl sulphoxide (50ml of 0.0021M solution, 0.11mmole) was added to melicopicine (21.8mg, 0.066mmole) in dimethyl sulphoxide (3.0ml). Samples (5.0ml) were removed at intervals and the reaction quenched with dilute acid. Melicopicine was extracted into chloroform and the extract evaporated under reduced pressure, dimethyl sulphoxide being removed at 0.01mmHg. The residue was made up to 5.0ml in toluene and 2.0ml of this solution added to 15.0ml of scintillator solution and the radioactivity determined. The results are recorded in Table 21. Thin layer chromatography of each fraction showed no chemical change in the melicopicine.

TABLE 21.

Time (min)	Counts/1000 sec[a]
4	184001
6	168286
8	179524

a) Corrected for background count.

6. Preparation of 2,3-Dimethoxy-10-methylacridone-1,4-quinone

6.1 4-Hydroxy-1,2,3-trimethoxy-10-methylacridone

Sodium (0.7g) was dissolved in methanol (10ml) and dimethyl sulphoxide (30ml) and melicopine (2.0g) added. The mixture was heated on a steam-bath for 30 min and then poured into water and neutralized. The precipitate was removed giving 4-hydroxy-1,2,3-trimethoxy-10-methylacridone (1.6g, 80%), m.p. 193-194° (ex benzene - light petroleum) (lit.[12] m.p. 190.5-191.5°).

6.2 2,3-Dimethoxy-10-methylacridone-1,4-quinone

This was prepared by the action of nitric acid on

4-hydroxy-1,2,3-trimethoxy-10-methylacridone according to Crow and Price[14].

7. Action of Sodium Ethoxide in Ethanol on 2,3-Dimethoxy-10-methylacridone-1,4-quinone

The dimethoxyquinone (40mg) was dissolved in 1M sodium ethoxide in ethanol (2.0ml) at room temperature giving a red solution which turned reddish-brown. After 2 min the solution was acidified and extracted with chloroform giving 2,3-diethoxy-10-methylacridone-1,4-quinone (44mg, 100%), red needles m.p. 155.5-156.5° (ex benzene) (Found: C, 65.9; H, 5.2; N, 4.3. $C_{18}H_{17}NO_5$ requires: C, 66.1; H, 5.2; N, 4.3%). N.m.r. spectrum : t, 6, 1.42, (CH_2-$\underline{C}H_3$), 7Hz; s, 3, 4.00, (N-CH_3); two quartets, 4, 4.25 and 4.45, ($\underline{C}H_2$-CH_3), 7Hz; m, 3, 7.2-7.8, (H-5, H-6, H-7); d, 1, 8.36, (H-8), 8Hz.

8. Reactions of 2,3-Dimethoxy-10-methylacridone-1,4-quinone with alkali

8.1 Hot aqueous sodium carbonate

The dimethoxyquinone (46mg) was dissolved in hot 5% aqueous sodium carbonate (3ml) and heated on the water-bath giving a deep red solution. Acidification gave a reddish-brown precipitate of 2-hydroxy-3-methoxy-10-methyl-

acridone-1,4-quinone (36mg), m.p. 230-232° (lit.[104] m.p. 231-233°). The i.r. spectrum showed the O-Hstr band at 3210cm^{-1}, the C=Ostr band at 1668cm^{-1} and a strong band at 1598cm^{-1}, which is consistent with that of Crow and Price[14]. Extraction of the filtrate with chloroform gave a further 8mg of 2-hydroxy-3-methoxy-10-methylacridone-1,4-quinone (identical i.r. spectrum to the precipitate). The yield was quantitative.

8.2 Cold aqueous 1M sodium hydroxide

The dimethoxyquinone (52mg) was dissolved in 1M aqueous sodium hydroxide (3ml) at room temperature giving a deep red solution. After 30 min the solution was acidified giving an orange solution which slowly deposited a yellow-green precipitate of 3-hydroxy-2-methoxy-10-methylacridone-1,4-quinone (34mg, 69%). The i.r. spectrum showed the C=O str band at 1630cm^{-1} and the O-Hstr band at 3250cm^{-1} which is consistent with that of Crow and Price[14]. Extraction of the filtrate with chloroform yielded a brown oil (13mg) which could not be positively identified from the i.r. spectrum.

8.3 Hot aqueous 1M sodium hydroxide

1M Sodium hydroxide (3ml) was heated in a boiling water-bath and the dimethoxyquinone (74mg) added giving a

deep red solution. Acidification gave a precipitate of 2-hydroxy-3-methoxy-10-methylacridone-1,4-quinone (26mg) (identical i.r. spectrum). Extraction of the filtrate with chloroform gave a further 29mg of the 2-hydroxy-3-methoxy-quinone (identical i.r. spectrum). Total yield 78%.

8.4 Cold 0.05M aqueous sodium hydroxide

The dimethoxyquinone (65mg) was shaken with 0.05M sodium hydroxide (5ml) at room temperature for 1.5 hr giving a deep red solution. Acidification gave 2-hydroxy-3-methoxy-10-methylacridone-1,4-quinone (50mg, 81%)(identical i.r. spectrum).

8.5 Hot aqueous 0.1M sodium hydroxide

The dimethoxyquinone (53mg) was added to hot 0.1M aqueous sodium hydroxide (5ml) and heated on a boiling water-bath for 5 min giving a deep red solution. Acidification gave a precipitate of 2-hydroxy-3-methoxy-10-methylacridone-1,4-quinone (40mg, 79%)(identical i.r. spectrum). A further 7mg of brown solid was obtained on extraction of the filtrate with chloroform but the i.r. spectrum was inconclusive.

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