

REACTIONS AT C-9 OF ACRIDINE DERIVATIVES. PART XXV¹.Stanisław Skonieczny

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Abstract - The kinetic data and mechanisms of the reactions occurring at the position 9 and/or 10 of the 9-substituted acridines have been reviewed. The mechanisms of hydrolysis and condensation reactions have been discussed and annelation effect considered where comparative data for the corresponding quinoline and pyridine derivatives were available. Some spectral and basicity data have been included to interpret the reaction mechanisms. Special attention has been paid to compounds of biological importance. The review falls into the following chapters according to the substituents undergoing substitution and/or types of the reactions being considered:

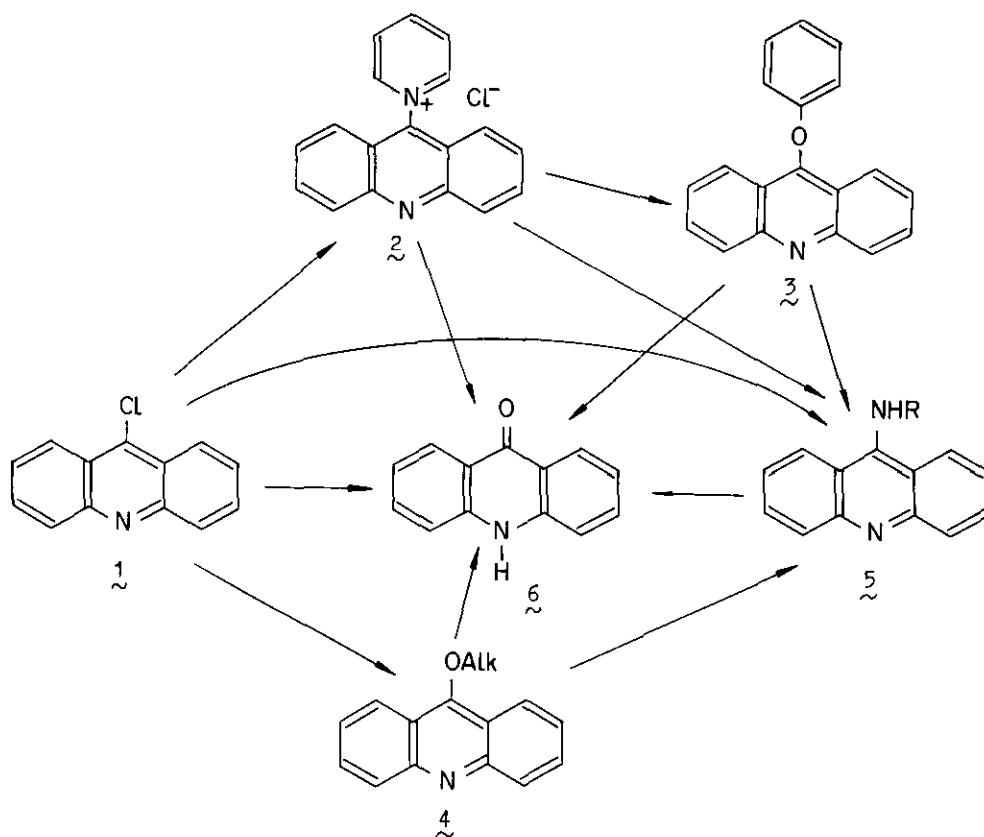
1. Introduction
2. 9-Aminoacridines
3. 9-Chloroacridines
4. 9-Phenoxyacridines
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1. INTRODUCTION

Interest in the acridine series is due to the useful chemotherapeutic properties of certain derivatives², and also to their very interesting interactions with DNA³, which have led to the understanding of the genetic code. The most widely known acridine derivatives are atabrin, proflavine, acridine orange, rivanol, and acriflavine². Most recently, however, two more derivatives have attracted most attention; ledakrin⁴ - an antitumour drug registered in Poland in 1974, and m-AMSA which also

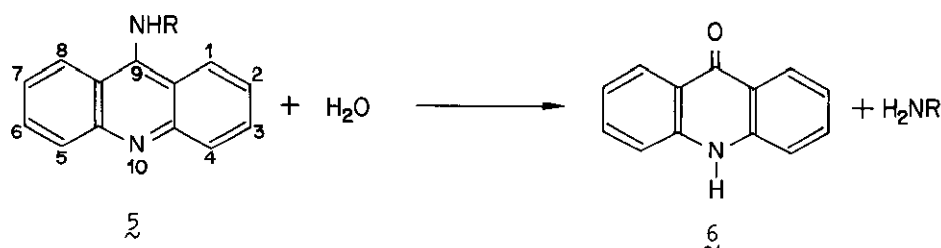
shows antitumour activity⁵ and has passed all pre-clinical evaluations with good results. Both latter compounds and the overwhelming majority of others of biological interest are 9-aminoacridine derivatives. The main pathways leading to the synthesis of 9-aminoacridines (5) are schematically shown in the scheme below. Owing to the molecular-orbital picture of the π -electron densities round the acridine molecule^{6,7} nucleophilic attack takes place at position 9 and, therefore, most reactions, in which acridine derivatives are involved, occur at this position^{8,9}

The previous review⁹ dealt with synthetic works on the 9-substituted acridines and the intent of this account is to survey recent developments that extend our understanding of the mechanism of hydrolysis and similar nucleophilic reactions in the acridine series. An attempt will also be made to provide a thorough historical review of the reactions under consideration and include some comparative data for the corresponding pyridine and quinoline derivatives.



2. 9-AMINOACRIDINES

2.1. Hydrolysis of 9-aminoacridines. The general properties of 9-aminoacridines and their chemical behaviour are very different from those of the corresponding derivatives with the amino group in other positions. The chemistry of 9-aminoacridines will be understood better if one bears in mind that they are vinylogues of amidine. First of all, they are far the most basic of the monoaminoacridines¹⁰ due to a considerable conjugation of the 9 and 10 position, and for this reason and unlike their isomers they undergo relatively rapid hydrolysis to give the corresponding 9-acridone derivatives 6:



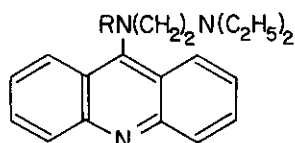
Comparison of the basicity of N-heterocyclic amines and their amino derivatives in aqueous solutions at room temperature

Acridine ¹⁰		Quinoline ¹¹		Pyridine ¹²	
Substituent	pK _a	Substituent	pK _a	Substituent	pK _a
-	5.60	-	4.94	-	5.23
1-amino	6.04	5-amino	5.51		
2-amino	5.88	6-amino	5.62		
3-amino	8.04	7-amino	6.65		
4-amino	4.40	8-amino	3.93		
9-amino	9.99	4-amino	8.46	4-amino	9.17
		2-amino	7.34	2-amino	6.86
		3-amino	4.95	3-amino	5.98

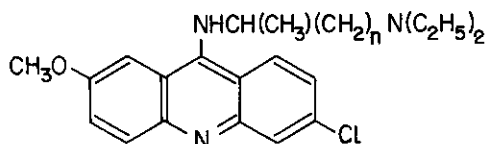
A list of works on the hydrolysis of 9-aminoacridines was opened simultaneously and independently by Mietzsch and Mauss¹³ as well as by Magidson and Grigorovski¹⁴ in 1936. Both groups and several others working shortly afterwards were particularly interested in acridine antimalarials, i.e., atabrin 8, which was commercially available from 1932, and its congeners. Mietzsch and Mauss¹³ have re-

ported that atabrin dihydrochloride is hydrolyzed in aqueous solutions to 2-methoxy-7-chloro-9-acridone, the hydrolysis being complete when a 5% solution is refluxed for 60 hr. Magidson and Grigorovski¹⁴ have described the same decomposition route involving a splitting off of the diamine chain and formation of 9-acridone and, moreover, they have found that the decomposition follows another route on heating with concentrated hydrochloric acid under pressure for several hours at 120-125°C leading to either 2-methoxy- or 2-hydroxy-7-chloro-9-aminoacridine. Furthermore, they observed that the hydrolysis occurred with special ease when the 9-substituent was a secondary amine residue.

The latter observation was confirmed by Goodall and Kermack¹⁵ shortly afterwards. They found that compounds 7 (R = Pr or Me) were much more easily hydrolyzed in neutral or slightly acid solutions than the corresponding secondary amines (7, R = H).



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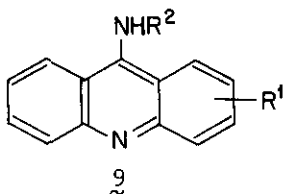
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In 1943 Albert and Ritchie¹⁶ reported qualitative studies to compare the reactivities of 1-, 2-, 3-, 4-, and 9-amino-, 9-methylamino-, and 9-dimethylamino-acridines. When they boiled the unmethylated monoaminoacridines with 5N-potassium hydroxide, 9-aminoacridine alone was hydrolyzed evolving ammonia and giving 11% of 9-acridone in 2 hr. Similarly, 9-methylamino- and 9-dimethylaminoacridines gave 24 and 68% yields, respectively. On the other hand, 2-aminoacridine could be fused with moist sodium hydroxide for 2 hr. at 200°C without decomposition.

The first kinetic investigation of the hydrolysis of 9-aminoacridines was published by Hammick, Mason, and Meacock¹⁷ in 1952. They determined the rates at which the acridine antimalarials (8, n = 1 - 4) were hydrolyzed under the temperature and pH conditions of the human blood stream (37°C and pH 7.3). The hydrolyses were of the first-order with respect to the acridine derivatives and the rate constants for the four homologues 8, (n = 1 - 4) were found to be 1.6×10^{-3} , 1.5×10^{-3} , 1.1×10^{-3} , and 0.25×10^{-3} hr⁻¹, respectively.

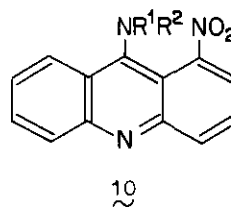
A similar influence of the side chain length on the rate of hydrolysis was described by Ledóchowski and Żytkiewicz¹⁸. They studied hydrolysis of 61 compounds of general formula 9 (substituents R¹ in positions 1, 2, 3, and 4) in 1% aqueous

solutions at 80°C for the nitro compounds and at 100°C for all others, drawing the following conclusions: (a) the shorter the side chain, the greater the rate of hydrolysis, (b) the order of ring substituent (R^1) reactivity is $\text{NO}_2 \gg \text{CH}_3 > \text{H} > \text{OCH}_3 > \text{N}(\text{CH}_3)_2$ in all positions, (c) the mesomeric effect of the ring substituents is of greater consequence on the reaction rate than the inductive effect, (d) the influence of ring substituents is identical for the 9-chloro- and 9-amino-acridines.



R^1 : H, OCH_3 , CH_3 , NO_2 , $\text{N}(\text{CH}_3)_2$

R^2 : $(\text{CH}_2)_{2-4}\text{N}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)(\text{CH}_2)_3\text{N}(\text{C}_2\text{H}_5)_2$



The kinetics of the hydrolytic deamination of aminoacridines with alkali have been studied by Kalatzis¹⁹. The deamination of 9-amino-, 9-methylamino-, and 9-dimethylaminoacridine was of first-order with respect to the amine, but of zeroth-order with respect to the hydroxide concentration. The addition of a methyl group near the reaction centre seemed to have little, if any, effect on the spatial requirements of the transition state, whilst the addition of a second methyl group seemed to increase the freedom associated with it, since the entropy of activation had a somewhat larger positive value. The increase in the value of $\Delta S^\ddagger$ together with the decrease in the value of E_a account for the greater rate of hydrolysis of 9-dimethylaminoacridine over that of the other amines, but the decrease in the value of E_a only accounts for the higher rate of deamination of 9-methylaminoacridine over that of 9-aminoacridine.

U.v. spectral data and ionization constants confirm the steric inhibition of conjugation in 9-dimethylaminoacridine but not in 9-methylaminoacridine²⁰.

Ledóchowski et al.²¹ have extended the work of the previous authors^{14-16,19} studying the reaction over a wider pH range (1 - 13) and including 9-dimethylaminopropylaminoacridine. The pH-hydrolysis rate profile for the latter compound (Fig. 1) seems to be a typical one for most 9-aminoacridines excluding 1-nitro derivatives. The hydrolysis is more facile in the presence of alkali than in acidic media where the reaction is very slow or unnoticeable.

When the bulky 1-nitro group was introduced near the reaction centre²², the addition of a methyl or butyl group or even two methyl groups to the amino group

of 9-aminoacridine (10) did not cause great differences in either reaction parameters or in the rate constants. It is likely that even in 1-nitro-9-aminoacridine the amino nitrogen atom is sufficiently out off the acridine plane to prevent appreciable conjugation of the nitrogen electron pair with aromatic ring. Moreover, it was suggested that the bulk steric effects of the 1-nitro group undoubtedly accounted for both widening of the pH range, in which hydrolysis can be carried out, and the diminution of the influence of the 9-amino substituent on the reaction rate. The former effect, however, can also be explained, at least partly, in terms of the electron-withdrawing power of the 1-nitroacridine nucleus.

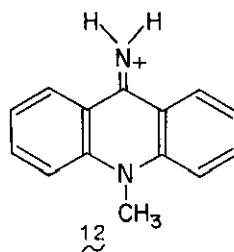
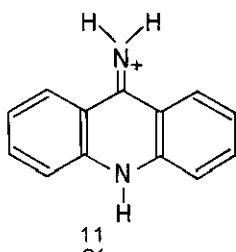
Skonieczny and Ledóchowski²³⁻²⁷ have extensively studied the hydrolysis of 1-nitro-9-aminoacridines which exhibit a high antitumour activity in a wide variety of tests and one of them, viz. 1-nitro-9-(3-dimethylaminopropylamino)-acridine dihydrochloride⁴, was registered as an effective antitumour drug and named ledakrin.

The hydrolysis of 1-nitro-9-(3-dimethylaminopropylamino)-acridine in buffered solutions within a pH range of 0 to 8.5 was studied²³. At a pH above 9 some side-reactions, most likely involving the 1-nitro group, were observed. The hydrolysis followed simple first-order kinetics below 4 and above 8 pH. Within the pH range from 4 to 7 the pseudo-first-order consecutive reaction seemed to describe the process better than simple first-order kinetics. Most recently, however, a reinvestigation²⁷ has pointed out that the latter conclusion was wrong due to the fact that the compounds studied within the pH range of 4 to 7 existed as a mixture of mono- and di-cations and their u.v. spectra were very sensitive to the temperature. An improved method of concentration measurements excluded the possibility of any true intermediate existing in this reaction because first-order plots were satisfactory and well-formed isosbestic points were observed in the whole ranges of both pH and wave lengths (cf. Fig. 2).

The most striking observation in these last studies was that that the pH-rate profiles for the antitumour active 1-nitro-9-aminoacridines (Fig. 1) were dissimilar to those for the nitro-free analogues and even different from those of their 2-, 3-, or 4-nitro isomers²⁵. Particularly interesting conclusion can be drawn from a comparison of the hydrolysis rate constants of the two isomers with the nitro group in position 1 or 3. The observed trend of dependence of rate constants upon the pH is opposite (Fig. 1), though the direction of both inductive and mesomeric effects is still the same in these compounds.

The observed phenomenon may be explained in terms of tautomerism. The question of whether 9-aminoacridines exist as the amino or imino form was controversial for a long time. Attempts to decide it from chemical reactions have not been successful and could at best provide only negative evidence in favour of one formulation²⁸. Although physical methods are usually a better approach to questions of imine-amine tautomerism²⁸, dipole-moment determinations were inconclusive in this case^{29,30}. The similarity of the ultra-violet absorption spectra of 9-aminoacridine and 9-aminoanthracene led Craig and Short³¹ to conclude that the imine form of the acridine played an insignificant part under the conditions of the examination. Moreover, the infra-red spectra²⁹ of 9-aminoanthracene, 9-aminoacridine, and various other amino-heterocycles confirmed the earlier view that the 9-aminoacridine did not contain appreciable quantities of the imino form. More recently, the i.r. spectra of 9-amino- and 9-dideuteroamino-acridine have provided further support for the amino form³².

Contrary to the conclusions reached by other workers using the above methods, ultra-violet absorption measurements on solutions of 9-dimethylamino-, 9-imino-10-methyl-9,10-dihydro-, and 9-amino-acridine indicate that the last compound is largely present in the tautomeric form of 9-iminoacridan under the experimental conditions³³. Nevertheless and in spite of other spectral data available³⁴ it is now accepted that 9-aminoacridines are amino compounds³⁵. But, when a strongly electron-withdrawing group is attached to the amino-nitrogen, as in 9-trichloroacetamidoacridine or 9-benzenesulfonylamidoacridine, the compounds adopt the imino form³⁶.



Recently, singly protonated 9-aminoacridine has also been shown to exist in aqueous solution as the protonated iminoacridan 11^{37,38}. Comparison of electronic spectral shifts induced through changes in the state of protonation or solvent environment as well as dissociation constants of 9-aminoacridine and 2-aminoacridine (the latter being assumed to be a quite purely aromatic) were used to show that 9-aminoacridine behaves differently from arylamines and heterocyclic arylamines in particular³⁷. The occurrence of the second absorption band in the long-wavelength

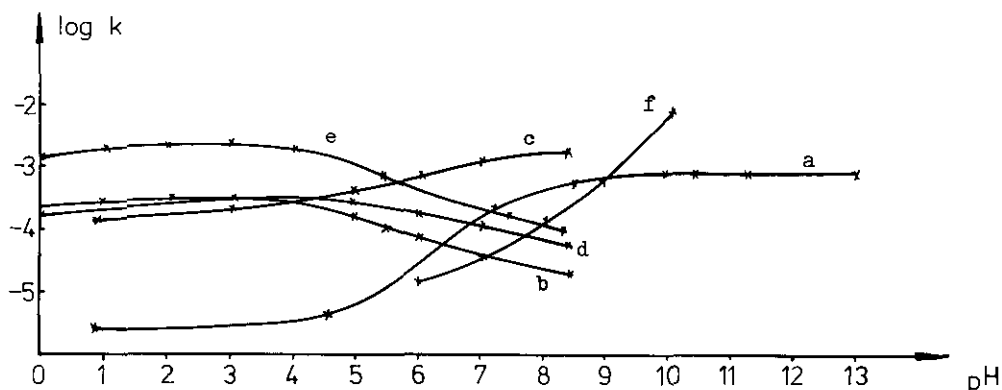


Fig. 1. The pH-rate profiles for the hydrolysis at 80°C; (a) 9-(3-dimethylaminopropylamino)-acridine, (b) 1-nitro-9-(3-dimethylaminopropylamino)-acridine, (c) 3-nitro-9-(3-dimethylaminopropylamino)-acridine, (d) 1-nitro-9-(5-dimethylaminopentylamino)-acridine, (e) 1-nitro-9-(2-dimethylaminoethylamino)-acridine, and (f) 3'-(9-acridinylamino)-methanesulfonanilide.

spectrum of 11 indicated a disruption of the aromaticity of the central ring of the singly charged cation and the imine-like dissociation. The spectral behaviour of the N-methylated monocation 12 supported the assignment of structure 11 as that of singly protonated 9-aminoacridine and thus confirmed the previous report by Acheson et al.³³ This conclusion was also supported by an X-ray diffraction study of 9-aminoacridine hydrochloride monohydrate³⁹, in which it was shown that the length of the bond joining the amino group to the aromatic ring is indicative of a double bond as represented in structure 11.

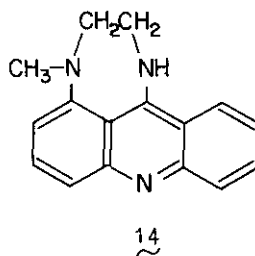
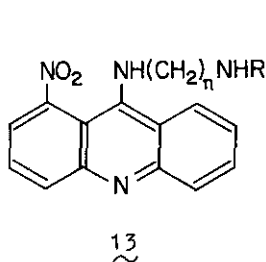
Hydrolysis of all antitumour active 1-nitro-9-alkylaminoalkylaminoacridines²⁷ follows pseudo-first-order kinetics over the whole pH range studied. The rates of reaction vary with changes in pH but the function is not linear (Fig. 1). The hydrolysis proceeds somewhat more easily in an acidic medium. It indicates that nucleophilic attack at position 9 is more favourable in the case of doubly protonated molecules, i.e., when the pH is below 4. In strongly acidic media, however, a slight drop in rate constants is observed because of a decrease in concentration of unprotonated water which seems to be a nucleophile in the hydrolysis process.

Fig. 1 shows that the side chain length affects the reaction rate. The pH-rate profile for compound (e) possessing a 1,2-diaminoethyl side chain is identical with that of compound (b) with a 1,3-diaminopropyl side chain with the only

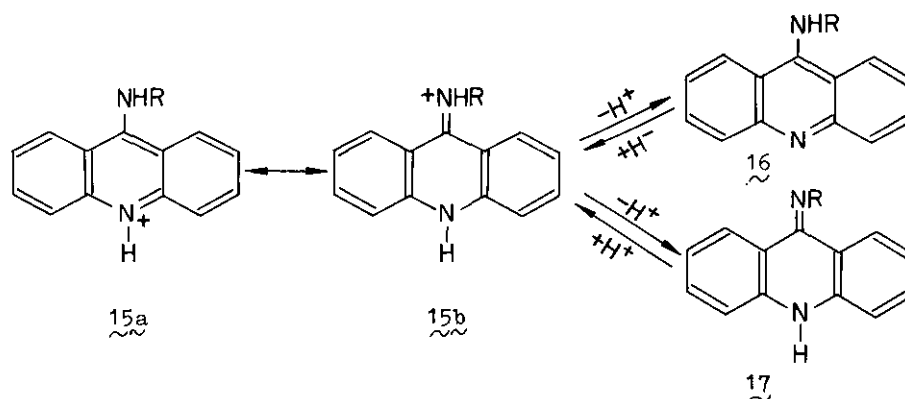
exception that the former is shifted upward. The observed phenomenon is explicable on the ground that an inductive effect of the protonophilic amino group is being transmitted through three bonds in 1,2-diaminoethyl compounds and therefore is much more effective than that in 1,3-diaminopropyl derivatives where it is transmitted through four bonds. Support for this conclusion comes from the u.v. spectra of these compounds where the influence of side chain length on the absorption bands is manifest and unmistakable⁴⁰. For instance, the dication of 1-nitro-9-(3-dimethylaminopropylamino)-acridine shows an absorption band at 437 nm while that of 1-nitro-9-(5-dimethylaminopentylamino)-acridine at 406 nm²⁷. This inductive effect is also well reflected by the differences in pK_a values of the compounds under consideration⁴. The same effect is observed when the terminal dialkylamino group is replaced by a hydroxyl group, i.e. in the 1-nitro-9-(hydroxyalkylamino)-acridines.

Similar influence of the side chain on the reaction rate was reported by Hammick et al.¹⁷ for the atabrin-like derivatives. A tendency observed by them was analogous to that described above, but in case of the 1-nitro-9-alkylamino-alkylaminoacridines this influence is more pronounced.

Alkyl substituents on the terminal amino nitrogen atom (R in 13) have a minor influence on both u.v. spectra of the compounds and their hydrolysis rates over a wide range of substituents from cyclohexyl and isopentyl to methyl. In one case, however, viz. when 1-nitro-9-(2-methylaminoethylamino)-acridine (13: R=CH₃, n=2) was hydrolyzed in neutral aqueous solution, the reaction did not result in the formation of 1-nitro-9-acridone but afforded compound 14, which was isolated and its structure confirmed by its elemental analysis, i.r. and high resolution mass spectra⁴¹.



The above dependence of rate constants of 9-aminoacridines upon the pH may be interpreted by assuming the existence of the following species in equilibria^{25,26}:



The 1-nitro-9-aminoacridinium cation can be written as for 9-aminoacridine³⁵ in the resonance forms 15a and 15b (the latter being predominant)³⁸. In weakly basic solutions, however, 1-nitro-9-aminoacridines may exist either as the amino form 16 or as the imino tautomer 17. The crystal structures of 1-nitro-9-(3-dimethylaminopropylamino)-acridine as a hydrogen iodide salt⁴² and dihydrochloride⁴³ showed that this compound existed as the iminoacridan in the crystal. The iminoacridan structure also appears to exist in chloroform solution in the presence of europium(III), for the n.m.r. spectrum of their complex shows shifts of signals corresponding to a hydrogen atom attached to the heterocyclic nitrogen⁴⁴.

The present kinetic data suggest that some 1-nitro-9-alkylaminoacridines also exist in the imino form 17 in water solutions. This would explain while they are so stable in neutral and weakly basic solutions, because the C(9)-N bond which is to be broken is of double bond character. On the other hand, 9-aminoacridines which exist in the amino form 16 under these conditions exhibit the opposite dependence of $\log k$ against pH (cf. compound (a) in Fig. 1).

The question is why we observe a different dependence of rate constants upon the pH for 1-nitro-9-(3-dimethylaminopropylamino)-acridine and its nitro-free congeners. First explanations²⁵ of this phenomenon were based on steric reasons. The usually unfavourable imino-acridan form 17 has less steric hindrance from the nitro group than the amino structure 16 would have in the case of 1-nitro compounds. Alternatively, in the case of the 3-nitro isomer, in the absence of obvious steric interference, the compound was assumed to be of aminoacridine type and to have a very strong tendency to remain that way. Two reasons for this were advanced:

(a) The shape of a plot of $\log k$ versus pH for the 3-nitro compound (Fig. 1) rather resembles those of nitro-free analogues though this one is shifted considerably to the left; the 3-nitro group decreases the electron density at the reaction site and makes nucleophilic substitution much easier over the whole pH range. (b) The hydrolysis rate constants are similar under strongly acidic conditions indicating that the acridinium cations are of identical character or nearly so.

Thus it was suggested that steric demands of the substituents in 1-nitro-9-aminoacridine competed with the electronic requirements of aromaticity preventing the full adoption of one or another of the alternative (16 or 17) structures.

Most recently²⁷, however, it has been pointed out that not all the observed pH-rate profiles for 1-nitro-9-aminoacridines can be explained in terms of steric repulsion. If so, we would have observed the same profiles for 1-nitro-9-butylaminoacridine²⁴, 1-nitro-9-(4-hydroxybutylamino)-acridine⁴⁵, 1-nitro-9-(5-dimethylaminopentylamino)-acridine²⁷, 1-nitro-9-(3-dimethylaminopropylamino)-acridine²⁷, and 1-nitro-9-(2-diethylaminoethylamino)-acridine²⁴. But it is not the case. Moreover, some support for a considerable electronic influence of the terminal amine group comes from X-ray data for 1-nitro-9-(3-dimethylaminopropylamino)-acridine in the form of dication⁴³, monocation⁴² (in both cases the terminal amine group is protonated) and free base⁴³. In the first two cases the compound adopts a typical iminoacridan structure whereas in the form of the free base two kinds of structures are observed: one similar to those in dication and monocation, i.e., iminoacridan, and another typical for planar 9-aminoacridines, e.g., 2-nitro-9-(3-dimethylaminopropylamino)-acridine⁴⁶. These data indicate that there are two structures almost energetically equal from the point of view of steric requirements and that the electronic effects must also be taken into account to explain all the kinetic results²⁷. So, the existence of the antitumour active 1-nitro-9-aminoacridines in the form of structure 17 is not solely due to the steric demands.

2.2. Other reactions of 9-aminoacridines. There are few reports in the literature dealing with the reactions of 9-aminoacridines occurring at the position 9 and not involving hydrolysis. The possible explanation is that 9-aminoacridines are of most important biological interest and, therefore, are final compounds of most syntheses and multistage reactions⁹.

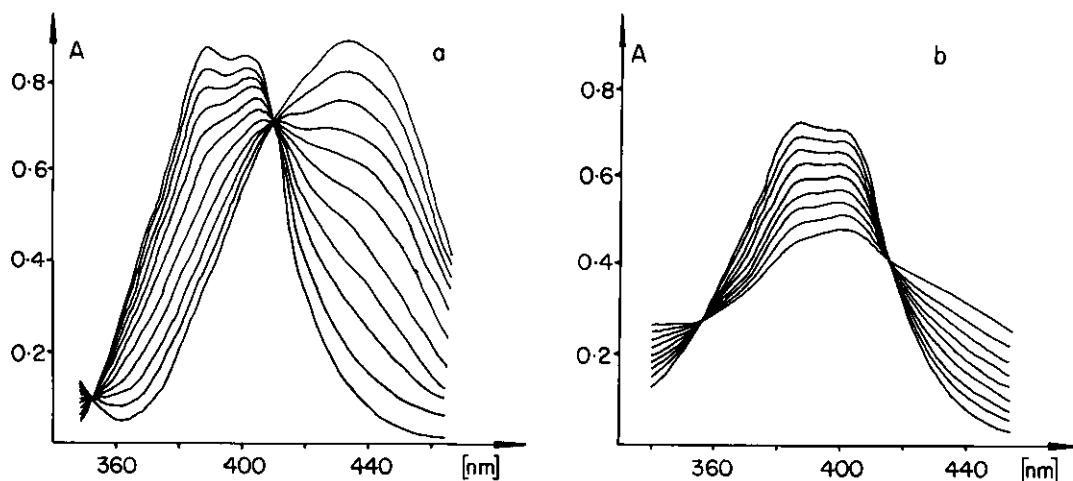
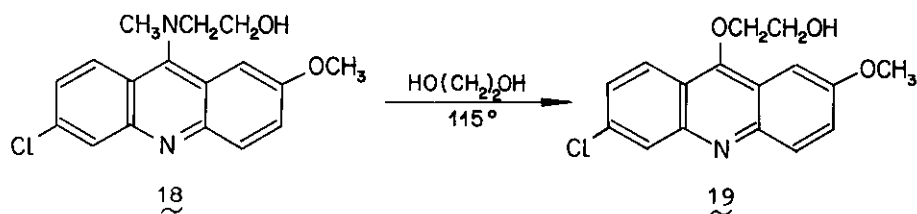


Fig. 2. U.v. spectra of the reaction mixture during hydrolysis of 1-nitro-9-(3-dimethylaminopropylamino)-acridine at 90°C at pH 1 (a) and pH 7 (b).

Of these several papers, the following should be mentioned. The loss of stability of 9-aminoacridines associated with increased steric hindrance was reflected in the results of Peck⁴⁷, who found that 6-chloro-9-(2-hydroxyethyl)-methylamino-2-methoxyacridine reacted with a series of simple glycols to yield 9-acridinyl ethers, e.g. 19. All the reactions occurred rapidly at 115°C and apparently were uncomplicated by side reactions, except in the case of ethylene chlorohydrin, where too long a reaction time led to alkylation of the nucleus. However, less bulky substituent at position 9 (e.g., morpholine) reacted with ethylene glycol in a similar way but at higher temperatures. So, N,N-disubstitution was found again to labilize the aromatic amino bond of 9-aminoacridine to permit substitution by alcohols. An analogous reaction in similarly N,N-disubstituted 4-aminoquinolines was not observed, though a pronounced effect on base strength and u.v. spectra upon increasing the bulk of the substituents in the latter case was noted.



9-Methylaminoacridine with nitrous acid forms 9-nitrosomethylaminoacridine, which, unlike secondary aromatic nitrosoamines, is completely hydrolyzed in very

dilute acidic solutions to the original acridine⁴⁸. Hydrogen sulfide in alcoholic ammonia attacks 9-methylaminoacridine, but not 9-aminoacridine, to give 9-acridanthione in good yield⁴⁹. 1-Nitro-9-(3-dimethylaminopropylamino)-acridine readily reacts with hydrogen sulfide in pyridine at -10°C affording various derivatives of 9-acridanthione⁵⁰, while with piperidine 1-nitro-9-piperidinoacridine and its derivatives are formed⁵¹. The reactions with hydrogen sulfide and sulphydryl compounds are supposed to be of biological importance⁵¹⁻⁵³.

2.3. Hydrolysis and stability of 2- and 4-aminoquinolines. The aminoquinolines yield the corresponding quinolinones when heated at 200°C with concentrated hydrochloric acid⁵⁴. On the other hand, 2- and 4-aminoquinolines afford the corresponding quinolinones merely by boiling with dilute acid or alkali or with concentrated alkali in the cold⁵⁵.

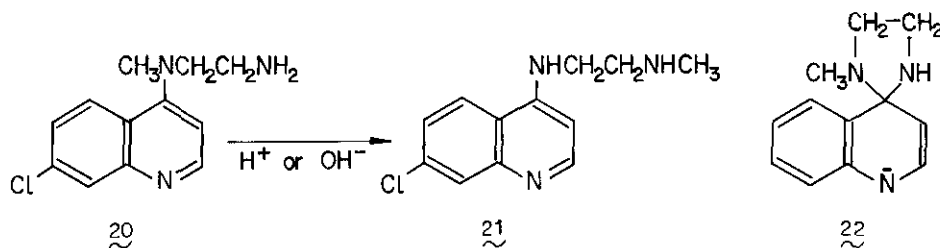
From analogy with the similar findings for 9-aminoacridines one could expect 4-aminoquinoline to exist in the amino form under basic conditions, i.e., when we consider the free base of 4-aminoquinoline, and this is the case. The ultra-violet spectra of the 2- and 4-aminoquinolines in solution closely resemble those of the corresponding N,N-dimethylaminoquinolines⁵⁶. This is strong evidence that the amines exist in the amino- and not the imino-form. This has been confirmed by infra-red spectra of aminoquinolines⁵⁷. Finally convincing evidence has been provided by the p.m.r. examination of methylated 4-aminoquinoline derivatives⁵⁸.

The spectroscopic evidence thus supplies abundant evidence that the 4-aminoquinoline exists in the amino form and this conclusion applies also to 2-aminoquinoline and its derivatives. However, this is not true when 2- and/or 4-aminoquinolines are protonated. The basic strengths have been carefully measured by Albert et al.¹¹, who found that all aminoquinolines fall into three classes. One class contains the 2- and 4-isomers, which are much stronger bases than is quinoline (cf. the Table). The second class is made up of the 3-, 5-, and 6-isomers, the basicities of which are only slightly greater than that of quinoline. The third class consists only of the 8-isomer which is considerably less basic than quinoline, and approximately equal in this respect to α -naphthylamine, pK_a 4.00. The authors show that such an increase of basic properties in the 2- and 4-isomers is readily explicable in terms of mesomerism of the cations⁵⁹ in which the positive charge is distributed over the two nitrogen atoms without disruption of the benzene ring.

Steck and Eving⁵⁶ have reported u.v. spectra of aminoquinolines in ethanol, 0.01 N hydrochloric acid, and 0.01 N sodium hydroxide. The spectra of 2- and 4-aminoquinolines show little resemblance to those of the other isomers. The authors have also found that the close resemblance between the spectra of the free amine and its dimethyl derivative is particularly significant in assigning the structures. However, spectrophotometric evidence is in essential agreement with other physical and chemical data⁵⁶ in the assignment of an imino structure to the 2- and 4-aminoquinolines. So, in dilute acid solution only one proton is taken up and that by the ring nitrogen rather than by the substituent group⁵⁹. The other isomers exhibit the characteristics of the naphthylamines, the amino group being aromatic in character.

Not infrequently, however, the results for 2- and 4-aminoquinolines studied in the form of the free bases⁵⁶⁻⁵⁸ are set against those for protonated forms^{56,59,60} in order to find one 'universal' structure responsible for all the reactions and properties. Such attempts lead nowhere and the criticism⁵⁵ of the imino forms of 2- and 4-aminoquinolines seems to be overhasty. Even the key spectral evidence is doubtful. A close examination of the spectra of 4-aminoquinoline and its N,N-dimethylamino derivative⁵⁶ shows that the spectrum of the former compound in ethanol and 0.01 N NaOH is really almost identical with that of the latter. Under acidic conditions, however, the absorption is somewhat greater and the long-wave absorption band is complex. One maximum does correspond to that of 4-dimethylaminoquinoline but there is still another one shifted toward longer wave lengths and its substantial contribution is clearly seen. Instead of this second maximum we can see only an inflexion point in the spectrum of 4-dimethylamino compound.

Of other curious reactions of 4-aminoquinolines, it is worth to note a 'surprising rearrangement'⁶⁰ of 7-chloro-4-[N-methyl-N(2-aminoethyl)]-aminoquinoline (20) to 7-chloro-4-(2-methylaminoethylamino)-quinoline (21) occurring in the presence of either acid or alkali. I would suggest an intermediate 22 for this reaction since a number of similar Meisenheimer complexes are known as intermediates in nucleophilic aromatic substitution⁶¹ and the whole process is known as Smiles⁶² rearrangement. Similar reactions were also reported for the quinoline series, e.g., replacement of alkylated amino groups in the 2- and 4-positions by the amino group can be effected by the action of potassium amide and liquid ammonia⁶³, 2-dimethylaminoquinoline thus yielding 2-aminoquinoline.



2.4. Stability and structures of 2- and 4-aminopyridines. The aminopyridines occupy an important position in the field of pyridine chemistry. They serve as useful intermediates for medicinals and dyes, and as starting materials for further synthesis. 2-Amino- and 4-aminopyridines are very stable to both base and acid even under severe conditions. The 2- and 4-amino groups can be replaced by diazotization⁶⁴, in the presence of a strong acid the 2- and 4-amino groups can be converted to the various halogeno⁶⁵, cyano or thiocyno derivatives⁶⁶. In weak acid, however, the diazotization apparently leads to the corresponding pyridone derivatives. Direct hydrolysis takes place only in the case of 2,6-diaminopyridines where a second amine group, being protonated in concentrated acid, acts as a powerful activating substituents; one amine group is hydrolyzed after several hours of refluxing⁶⁷ in 50-70% H₂SO₄ and two groups are hydrolyzed⁶⁸ after a prolonged heating in 75% H₂SO₄ at 150-175°C.

Quaternisation of the ring nitrogen enhances still further its electron-attracting capability; pyridinium salts and N-oxides are thus more susceptible than the parent pyridines to nucleophilic attack at the 2- and 4-positions. The N-oxide group increases rate constants at the 2-position by four orders of magnitude and at the 4-position by three orders of magnitude, while N-methyl group increases them by thirteen and ten orders of magnitude, respectively⁶⁹. Quantitative measurements of the reactivities of pyridine derivatives towards various nucleophiles, and comparison of pyridines with other heterocyclic systems, are summarized by Miller^{70,71}.

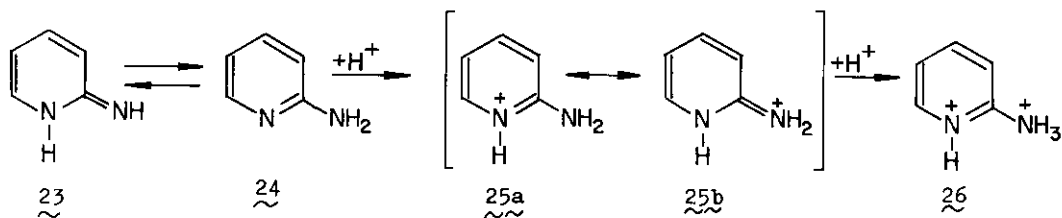
The kinetics of the reactions of 2- and 4-amino-, methylamino-, and dimethylamino-pyridine methiodides with hydroxide ions in water have been studied⁷². At room temperature, 2-dimethylaminopyridine methiodide was ca. 10^4 times more reactive than the 4-isomer, owing to a lower energy of activation (by $26 \text{ kJ} \times \text{mol}^{-1}$).

Barlin and Young⁷³ have also prepared trimethylammonio-derivatives of pyridine, purine⁷⁴, and quinoline⁷⁵ and reported kinetic studies of their reactivity towards

hydroxide ions. Examination of the effect of annelation in quinolin-2-yltrimethylammonium iodide relative to 2-pyridyltrimethylammonium iodide reveals that at 20°C the quinoline is 1100 times more reactive; this is due mainly to its lower energy of activation (84.5 compared with 114 kJ mole⁻¹). This higher reactivity of the annelated compounds was attributed to the larger area available for delocalisation of the charge in the transition state⁷⁶.

The pK_a value of quinolin-2-yltrimethylammonium iodide is 2.94 units higher than that relating to dication formation in 2-dimethylamino-1-methylquinolinium iodide⁷⁵. As in the pyridine series⁷³, this difference, which is of the same order, is taken as a measure of the loss in mesomeric stabilization of the monocation and any differences associated with protonation at a dimethylamino-group or ring nitrogen atom.

The loss of the aromatic resonance energy in going from the amino to the imino form is the most important feature of the tautomerization. As a consequence, the amino form 23 would be expected to be more stable. From the dissociation constants of the cationic forms of 2-aminopyridine and 1,2-dihydro-2-imino-1-methylpyridine, Angyal and Angyal²⁸ have calculated that the ratio of amino form to imino form in 2-aminopyridine exceeds 1000:1. Similarly, 2- and 4-aminopyridine-1-oxides exist mainly as such and not as the 1-hydroxypyridine-imine tautomers⁷⁷.



On the other hand, the mono-cations of 2- and 4-aminopyridines exist largely in the amidinium forms⁷⁸. Monoprotonation of aminopyridines occurs on the ring nitrogen rather than on the amino group^{11,28}. Furthermore, while the monoprotonated species of 25 is only weakly acidic, pK_a 6.86, the diprotonated species 26 for which the reported pK_a value is -7.6 is formed with considerable difficulty and can only be obtained in strongly acidic solutions⁷⁹. All these observations indicate that the monoprotonated species is usually stable⁸⁰⁻⁸² and that this stability is destroyed by diprotonation. A substantial resonance contribution by structures 25a and 25b increases the barrier to free rotation around the carbon-nitrogen bond of the amino group⁸³.

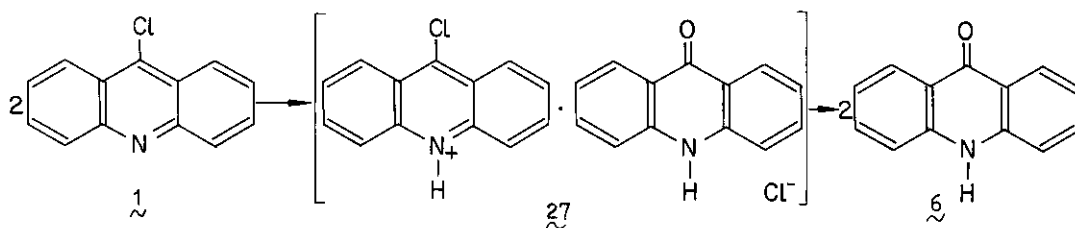
Summing up the main features of the amines in the acridine, quinoline, and pyridine series, it is possible to say that all these compounds exist in the amino forms as free bases while the imino forms predominate over the amino forms in protonated species⁸⁴. This conclusion was well illustrated by INDO theoretical studies of 4-aminopyridine and protonated 4-aminopyridine^{85,86} as well as by the u.v. spectra of these compounds^{56,87}.

The stability of these compounds decreases on annelation: aminopyridines are very stable⁶⁷, aminoquinolines are much more reactive⁷⁵, and 9-aminoacridines are still more reactive^{27,48}.

3. 9-CHLOROACRIDINES

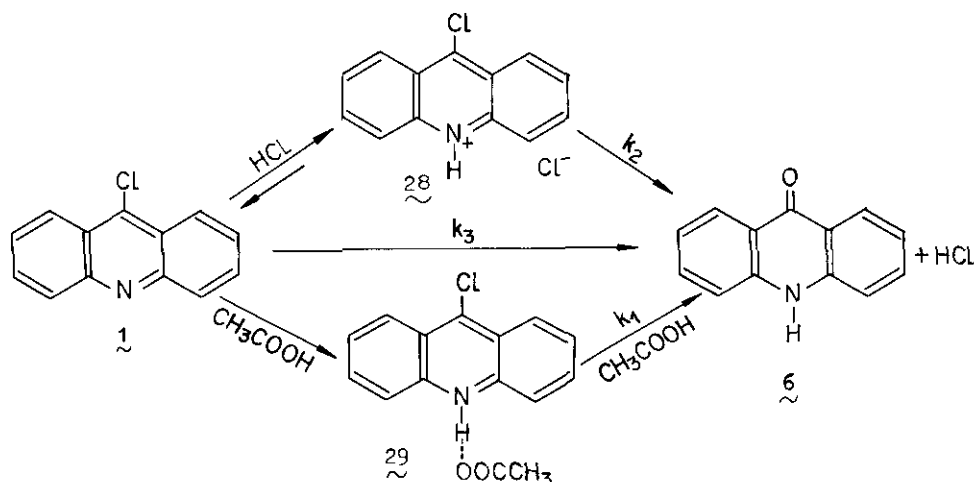
3.1. Hydrolysis of 9-chloroacridines. 9-Chloroacridine (1) and its derivatives are still the most widely used starting materials in the syntheses of many biologically active acridine derivatives⁹ due to the facile replacement of the chlorine atom⁸⁸. 9-Chloroacridines are often extremely sensitive to acid hydrolysis and even a pure sample suffers autocatalyzed decomposition to the corresponding 9-acridone derivatives.

The first kinetic studies of hydrolysis of 9-chloroacridine were reported by Magidson and Grigorovski⁸⁹. The reaction was performed in 50% aqueous acetic acid employing titration of chloride anions liberated in the process and the reaction was found to be pseudo-first-order with respect to the substrate up to 50 or 60% conversion. Ledóchowski^{90,91} has extensively extended the investigations varying concentration of both acetic acid and 9-chloroacridine and following the reaction up to over 80% conversion. He has pointed out⁹¹ that the hydrolysis occurs in a pseudo-first-order two-step consecutive reaction according to the following scheme:



The intermediate addition compound, a hydrate of 27, was isolated⁹¹. Moreover, such compounds, which precipitated from concentrated solutions of 9-chloroacridine, had earlier been described by Drozdov and Leznova⁹² when 10% aqueous hydrochloric acid was used as a hydrolysis medium⁹³. However, the hydrolysis of compound 27 did not confirm it to be an intermediate existing in the solvolysis process in aqueous acetic acid⁹⁴.

Aqueous acetic acid was chosen as a reaction medium⁸⁹⁻⁹¹ owing to its unique feature of dissolving 9-acridone (6). More recently, however, Inoue et al.⁹⁵ have described the reaction of carboxylic acids with 9-chloroacridine. The comparative investigations⁹⁶ of 9-chloroacridine hydrolysis in aqueous hydrochloric acid permitted me to suggest 9-chloroacridinium chloride (28) to be, contrary to the previous suggestion⁹¹, the true intermediate and the hydrolysis to proceed according to the following scheme:



9-Chloroacridine dissolved in acetic acid forms hydrogen bonded 'acridinium acetate' 29 which reacts with another molecule of acetic acid, k_1 , affording 6 and, according to findings of Inoue et al.⁹⁵, acetyl chloride which hydrolyzes to give acetic acid and HCl. The hydrochloride 28 is then formed and undergoes hydrolysis yielding 6, k_2 . Thus we observe a two-step consecutive kinetics in this reaction. This explanation is supported by other experiments of Ledóchowski⁹¹ who found that an addition of HCl to the reaction mixture retarded the total hydrolysis rate. Moreover, u.v. spectra of the reaction mixtures excluded the possible existence of any traces of the suggested π -complex 27 (well-formed isosbestic points)⁹⁶. In view of the above, it seems reasonable to consider the reaction in acetic acid as solvolysis and not hydrolysis with 9-chloroacridine hydrochloride being an intermediate.

The above reaction sequence also explains the influence of sodium acetate on the 9-chloroacridine solvolysis rate in aqueous acetic acid described by Ledóchowski⁹¹. According to recent results⁹⁶, the hydrolysis of 28 is a much slower process than the reaction of 9-chloroacridinium acetate with acetic acid ($k_1 > k_2$). An addition of sodium acetate to the reaction mixture decreases the concentration of 9-chloroacridine hydrochloride (28) and thus increases the solvolysis rate. After reaching a certain excess of CH_3COONa , a further addition of this reagent produces no effect. The ionic character of the intermediate 28 may also be responsible for salt effects reported for this reaction⁹¹.

The influence of 9-chloroacridine and acetic acid concentration on both k_1 and k_2 can also be explained. The higher the concentration of 1 or acetic acid,

the higher the rate constants for the reaction of acetic acid with 9-chloroacridine, k_1 . The more HCl is formed and the higher the concentration of 1, the more the equilibrium $\text{1} + \text{HCl} \rightleftharpoons \text{28}$ is shifted to the right and the smaller the mole fraction of 1 reacting via the pathway described by k_1 .

On the other hand, in the presence of hydrochloric acid 9-chloroacridine is almost completely converted into its hydrochloride 28 which hydrolyzes according to simple first-order kinetics⁹⁶. The hydrolysis rate constants in aqueous hydrochloric acid at pH 1 surprisingly turned out to be almost identical with those for the second-step reaction found for the solvolysis of 1 at the same concentration in 80% aqueous acetic acid. As the pH value of 80% acetic acid is just equal to 1, the conclusion is that 9-chloroacridinium chloride 28 is the intermediate in both processes.

When the solvolysis of 9-chloroacridine was performed in a 1:4 v/v solution of DMF-H₂O (the DMF component had to be introduced because 9-chloroacridine was completely insoluble in water), the reaction followed a typical three-step mechanism characteristic of catalysis by the reaction product ($k_3 > k_2$)⁹⁷. The uncatalyzed step was very slow, 1% of conversion at 90°C was observed after 40 min. A similar catalysis by acids was described for halogenopyridines by Reinheimer et al.⁹⁸ who had demonstrated that, in a typical case, the rate of reaction was proportional to the fraction of the halogenopyridine which was protonated. Analogous results have been observed for 4-chloroquinoline and its derivatives^{99,100}.

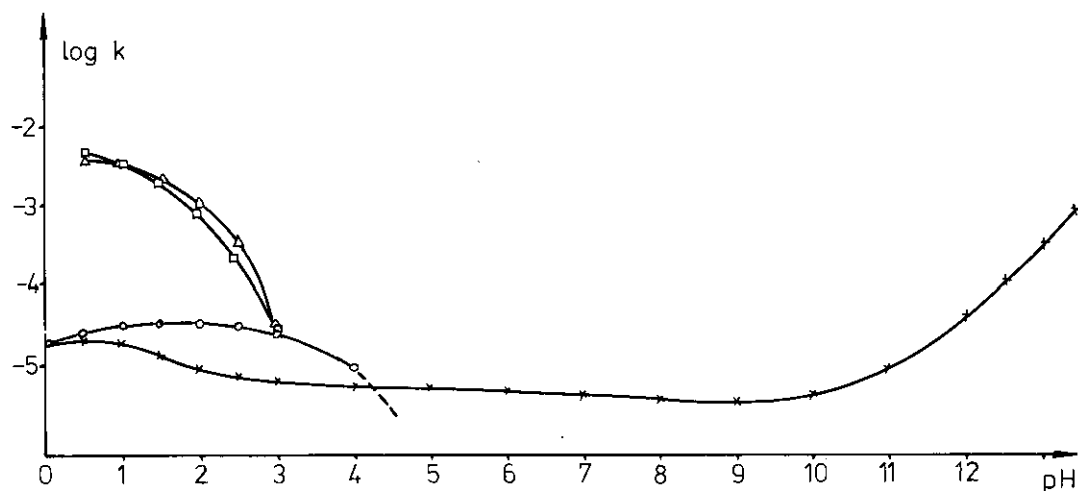


Fig. 3. The pH profiles of the logarithm of pseudo-first-order rate constants for hydrolysis of 9-chloroacridine (○—○—○), 9-chloroacridine-10-oxide (×—×—×), 1-nitro-9-chloroacridine (△—△—△), and 3-nitro-9-chloroacridine (□—□—□)¹⁰¹.

3.2. Hydrolysis of 1-nitro- and 3-nitro-9-chloroacridines. The pH-rate profiles for 1-nitro- and 3-nitro-9-chloroacridines (Fig. 3) are of the same shape as that of 9-chloroacridine with displacement upwards characteristic of the influence of nitro groups. Such an influence of the nitro group is not unexpected for this reaction. Electron-accepting substituents are known to facilitate the substitution of halogens in halogenopyridines, e.g., 4-chloro-3-nitropyridine liberates chloride ions simply by reaction with ethanol at 30°C whereas the corresponding substitution in 4-chloropyridine itself requires the use of the alkoxide¹⁰⁰. Similarly, the 8-nitro group in 4-chloro-8-nitroquinoline has a pronounced activating influence and the halogen is much more easily replaced by the amino group than that in 4-chloroquinoline¹⁰².

A comparison of the reactivity of 9-chloroacridine and its 1-nitro and 3-nitro derivatives at 40°C and pH 1 revealed that the 1-nitro compound was 150 times more reactive and the 3-nitro isomer ca. 200 times more reactive than 9-chloroacridine itself. This higher reactivity of nitro compounds is associated with lower energies of activation: 62 kJ × mole⁻¹ for 1-nitro-9-chloroacridine, 55 kJ × mole⁻¹ for 3-nitro-9-chloroacridine and 83 kJ × mole⁻¹ for 9-chloroacridine¹⁰¹. By chance, however, all these compounds have similar reactivities at pH 3 (cf. Fig. 3). This is due to much lower pK_a's of nitro compounds as compared with that of 9-chloroacridine. The latter compound is still partly protonated at pH 3 and, therefore, its hydrolysis rate constants are greater than those of nitro derivatives at a pH > 3. The reaction mechanism for nitro-9-chloroacridines seems to be identical with that proposed for 9-chloroacridine¹⁰¹.

The plot of log k against pH (Fig. 3) indicates that the hydrolysis is appreciably catalyzed by hydrogen ions. The curve for 1-nitro-9-chloroacridine is almost identical with that of the 3-nitro isomer. This was unexpected as 1-isomers were reported to react with pyridine much more readily than 3-isomers and, moreover, the reaction with pyridine was proposed as a preparative method for separation of 1-nitro-9-chloroacridine from 3-nitro-9-chloroacridine¹⁰³, and the method has successfully been used for ten years in both laboratories and industry¹⁰⁴. However, the kinetic data do not reveal any differences in rate constants or reaction parameters. A possible explanation is that the marked differences in solubility between 1- and 3-nitro isomers and not mobility of the chlorine atom might be responsible for the phenomenon observed.

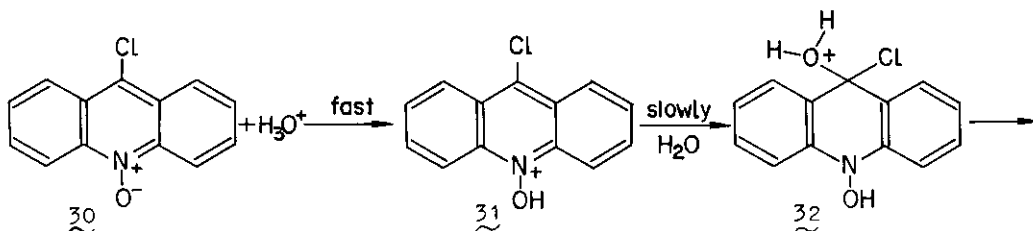
3.3. Hydrolysis of 9-chloroacridine-10-oxide. The hydrolysis of this compound was undertaken to elucidate the disagreement in the literature. The first report¹⁰⁵ on 9-chloroacridine-10-oxide solvolysis in aqueous acetic acid showed considerably lower rate constants for this reaction as compared with those for 9-chloroacridine solvolysis under the same conditions⁹⁰. It was very surprising since N-oxides of the pyridine series show a high susceptibility towards nucleophilic substitution in the 'gamma' position¹⁰⁶. Many reports have been made on the reaction of halogen atoms at the 2- and 4-positions of amine oxides of the pyridine series with various nucleophiles, and the 4-halogen of amine oxide was found to be more reactive, in general, than that of the corresponding amine¹⁰⁷.

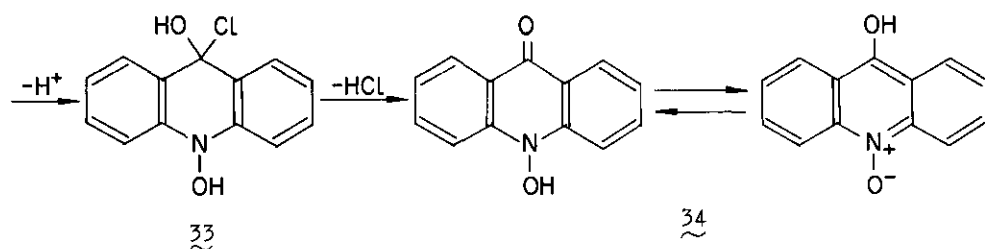
The most recent data^{101,108} seem to support both previous reports, which were contradictory to each other. Thus, 9-chloroacridine does hydrolyze more readily than its N-oxide but only in acid solutions (pH 0-4). Under alkaline conditions, however, 9-chloroacridine-10-oxide still undergoes hydrolysis and, moreover, shows a specific base catalysis (by OH^-) at a pH above 12 while the 9-chloroacridine hydrolysis is not observed at a pH above 6.

The general view on the reactivity of N-oxides of the pyridine series generally involves such reactions as aminolysis, alcoholysis, alkaline hydrolysis, alkylation, etc.¹⁰⁹, i.e. all the reactions occur under alkaline conditions. Thus, this general rule that N-oxides are more reactive than the corresponding amines also applies for the acridine series as far as the basic medium is concerned. However, in acid solutions, at a pH below 4, the opposite reactivity is observed and conclusions of both previous reports were correct.

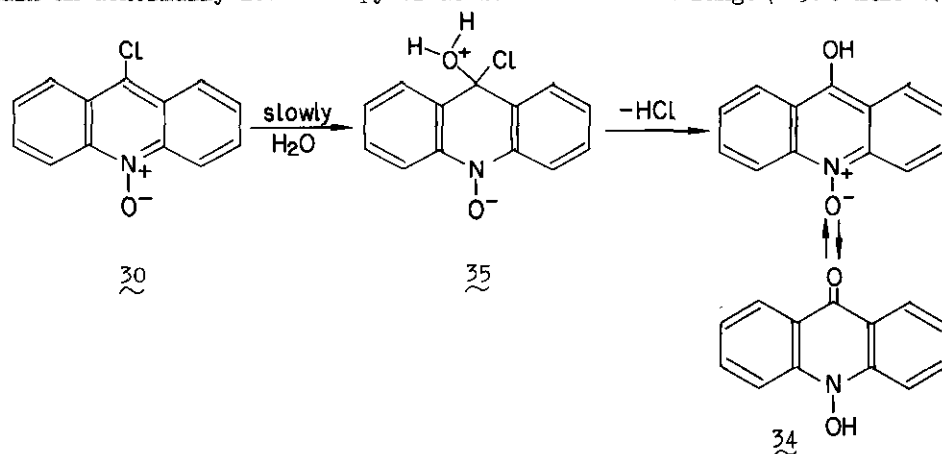
The pH-rate profile for 9-chloroacridine-10-oxide (cf. Fig. 3) differs significantly from those of both 9-chloroacridine itself and its nitro derivatives. The relationship between the rate constants and pH can be explained on the assumption that the hydrolysis may take place via the three following reactions¹⁰¹:

In the pH range 0-1.5 there is a slight maximum rate and the proposed reaction mechanism is shown below:

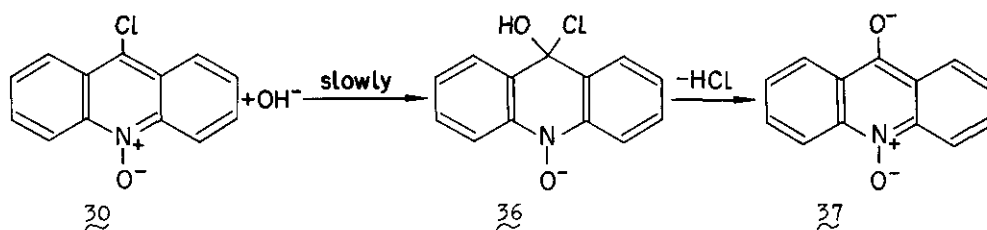




Over the pH range 2-11 the reaction rate changes insignificantly and the proposed reaction sequence is shown below. The charges are well separated in the transition state 35 permitting substantial solvation of each centre. This can explain an abnormally low entropy of activation in this range ($-190 \text{ J} \times \text{mole}^{-1} \times \text{deg}^{-1}$).



In the pH range 12-14 the hydrolysis is catalyzed appreciably by hydroxyl ions according to the scheme below:



3.4. General remarks. Annulation normally increases the reactivity of 2- and 4-substituted 1-azaheterocycles¹¹⁰ and this effect also operates in the following series: (a) 4-chloropyridine¹¹¹, 4-chloroquinoline^{102,112,113} and 9-chloroacridine; (b) 4-chloropyridine-1-oxide¹¹⁴ and 9-chloroacridine-10-oxide¹⁰¹; and (c) 4-chloro-3-nitropyridine¹⁰⁰, 4-chloro-5-nitroquinoline¹⁰², and 1-nitro-9-chloroacridine¹⁰¹.

The increased ease of hydrolysis, or other nucleophilic attacks^{76,115}, at the 9-position of 9-chloroacridine in comparison with the 4-position of 4-chloropyridine and quinoline has been ascribed to annelation, which leads to a decrease in the charge density at the site of attack¹¹⁶ and an increased possibility of delocalization of charge in the transition state. The delocalization approach was used to interpret the above kinetic behaviour of N-heterocyclic halogeno derivatives in nucleophilic aromatic substitution¹¹⁷. On the other hand, the much faster rate of hydrolysis of 9-chloroacridine when compared with 9-chloro-10-nitroanthracene has been attributed to steric inhibition of resonance by the peri hydrogens in the latter compound¹¹⁸.

The ring substituent order of reactivity observed in the acridine series over the pH range 0-3 was found to be nitroacridine > acridine > acridine N-oxide. There is a straightforward explanation of this order. As expected, electron-withdrawing nitro substituents promote nucleophilic attack, while electron-donating groups have a reverse effect. The influence of the nitro group is well known in both the pyridine series (4-chloro-3-nitropyridine liberates chloride ion by reaction with ethanol at 30°C while the corresponding substitution in 4-chloropyridine requires the use of the alkoxide)¹⁰⁰ and the quinoline series (the halogen in 4-chloro-8-nitroquinoline is much more readily replaced than that in 4-chloroquinoline)¹⁰². Surprisingly, N-oxide formation appears to reduce the reactivity of the chlorine atom at C-9¹¹⁹. The electron-withdrawal by a protonated N-oxide group includes a large electromeric component, but there must still be a residual electron-release by oxygen which reduces the reactivity of the gamma position with the result observed. In neutral and basic solutions, however, only 9-chloroacridine-10-oxide undergoes hydrolysis owing to a powerful conjugative effect of the N-oxide group.

In the case of solvolysis of 9-chloroacridine^{90,91}, methyl- and methoxy-9-chloroacridines^{120,121} as well as nitro-9-chloroacridines¹²² in 80% aqueous acetic acid, the ring substituent order of reactivity is $\text{OCH}_3 < \text{CH}_3 < \text{H} < \text{NO}_2$ for the 2- and 3-derivatives. The same reactivity order was observed in the pyridine series¹²³ where electron-donating substituents facilitated the substitution.

The positional order of reactivity was $1 > 4 > 3 \approx 2$ in the series of methyl- and methoxy-9-chloroacridines and $4 > 2 > 3 \approx 1$ for nitro derivatives. The following explanation may be proposed: 9-Chloroacridine and its methyl and methoxy derivatives react according to a different mechanism than that for nitro compounds. The former acridines react with acetic acid in the first stage of a two-step reaction, k_1 , and their hydrochlorides undergo hydrolysis in the second step, k_2 . The k_2/k_1 ratio

remains unchanged on going from methoxy-9-chloroacridines to 9-chloroacridine itself. Thus, protonation and substituents increasing basicity of the compounds retard the reaction rate and one can observe the following order of reactivity: $\text{OCH}_3 < \text{CH}_3 < \text{H}$.

On the other hand, nitro-9-chloroacridines seem to hydrolyze under these conditions and not to react with acetic acid. The authors¹²² reported some difficulty in the determination of the reaction component concentrations due to deep colours of titrated solutions and slight solubility of both nitro-9-chloroacridines and nitro-9-acridones in the reaction medium. Moreover, the k_2/k_1 ratio ranges from 0.3 to 0.5 and such values are within the error of calculation according to simple first-order reaction equations. A support of this suggestion comes from the comparison of rate constants for 1-nitro- and 3-nitro-9-chloroacridines hydrolysis in acetic acid¹²² and hydrochloric acid¹⁰¹, e.g., $k_{40^\circ\text{C}}$ for 3-nitro-9-chloroacridine in acetic acid is $2.1 \times 10^{-3} \text{ s}^{-1}$ and $k_{40^\circ\text{C}}$ in hydrochloric acid at pH 1.5 is $1.8 \times 10^{-3} \text{ s}^{-1}$.

The comparative solvolysis of 9-chloro-, 9-bromo-, and 9-iodo-acridines¹²⁴ in 80% aqueous acetic acid showed the highest reactivity for 9-chloro and the lowest for 9-iodo derivatives; the following rate constants at 52.5°C were reported: 2.44, 1.82, and $0.77 \times 10^{-4} \text{ s}^{-1}$, respectively. The above reaction order is reflected in the increasing energy of activation: 84, 89, and $93 \text{ kJ} \times \text{mole}^{-1}$, respectively. Ethanolic solution of 9-chloro-, 9-bromo-, and 9-iodo-acridines have been irradiated with 365-nm light¹²⁵. The hydrolysis rate of these acridinium ions in the dark was 100 times that of the acridines themselves¹²⁶. Hydrolysis in light in the presence of oxygen was also 100 times as fast as that in the dark.

3.5. Condensation reactions of 9-chloroacridines. The facile replacement of a 9-halogen from a protonated acridine is widely exploited in syntheses. 9-Chloroacridine can react with a wide variety of compounds to give 9-substituted acridines. The many reactions of 9-chloroacridines are dealt with in connection with the corresponding 9-acridyl derivatives in several review articles^{2,9,127-132}. The objective of this account is not to provide a comprehensive list of possible products, but to throw some light onto the mechanism of the reactions. The most studied reaction is with amines. The first preparations of 9-aminoacridines from 9-chloroacridines were achieved by heating with amines, or suitable derivatives, at about 140°C in the presence of copper salts⁸⁸. Although phenol had been used as a solvent for the

reaction of 9-chloroacridine with a number of amines, its importance in facilitating the reaction was not generally recognized until the work of Magidson and Grigorovski⁸⁹. Best results are usually obtained when 9-chloroacridine is condensed with a free amine⁸⁸ in phenol at 100-120°C. A very large number of substituted 9-aminoacridines were prepared in this way for testing as antimalarials², potential carcinostatic drugs^{2,4,5} and other useful biological agents⁸⁸ by the same route.

Following the recognition of acid catalysis in the above condensations, it was found that 6,9-dichloro-2-methoxyacridine reacted with aromatic amines or morpholine¹³³, but not with ethylamine, in aqueous acid to yield the 9-aminoacridines. The rate of formation of the aminoacridine was increased by increasing the acid concentration, but so also was the rate of hydrolysis of the 9-aminoacridine to 9-acridone. The reaction was thought to proceed by initial protonation of the ring nitrogen, facilitating nucleophilic attack¹³³, this giving a useful method when it is necessary to avoid the use of phenol¹³⁴. It has also been used successfully in the preparation of 9-phenoxyaminoacridines from aminophenols¹³⁵.

Other solvents have also been used for the reaction of 9-chloroacridines with amines. 6,9-Dichloro-2-methoxyacridine does not appear to react with 2-aminobenzyl-diethylamine in phenol, but does so in boiling toluene¹³⁶. The reverse is usually found to be true for primary amines¹³⁷. Atabrin, for example, is formed from this chloroacridine and the appropriate diamine in 92% yield in phenol, but in less than 25% yield in toluene¹³⁶. Methylcellosolve at reflux temperature has also been used as a solvent with some success¹³⁸. An interesting case of a change of solvent bringing about the formation of a different product occurs in the reaction of 9-chloroacridine with aminophenols. In aqueous acids¹³⁵ or in phenol¹³⁹, the products are phenoxyaminoacridines, whereas in refluxing methanol the aminophenoxyacridine is formed¹⁴⁰.

A kinetic study has been made of the reaction between 9-chloroacridine and piperidine in toluene¹⁴¹. The reactions were carried out under second-order and pseudo-first-order conditions and the results were compared with those of other N-heterocycles, viz. chloropyridines¹⁴², chloroquinolines^{143,144}, and many others^{141,145}. Again, an annelation effect is observed on going from 2-chloropyridine to 4-chloroquinoline and 9-chloroacridine, reflected in lowering the activation energy: 72, 68, and 61 kJ×mole⁻¹, respectively. The behaviour of 4-chloropyridine in its pseudo-first-order reaction with piperidine is worthy of special mention. In typical runs with this pair of reactants it was found that the reaction 'rate constant'

was continually increasing with time. However, the reaction does not appear to be purely autocatalytic. The authors¹⁴¹ ascribed this to unique properties of 4-chloropyridine among the compounds examined, e.g., it readily dimerizes to form 4-chloro-1-(4-pyridyl)-pyridinium chloride and this reaction also appears to be somewhat autocatalytic.

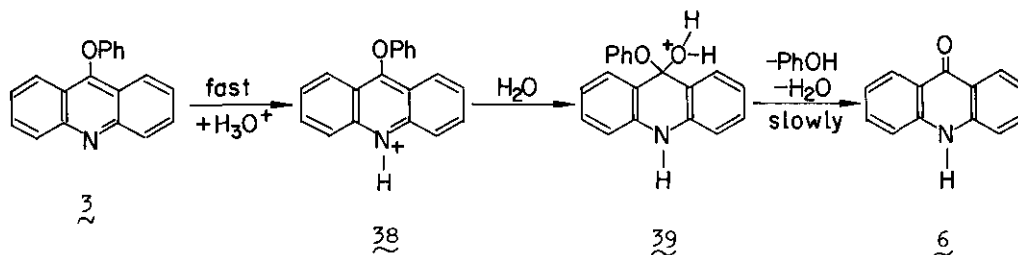
Most recently, the kinetics of condensation of 9-chloroacridine with pyrrolidine in p-xylene and DMSO have been reported¹⁴⁶. The condensation was found to proceed according to a second-order equation in DMSO while third-order kinetics were observed in p-xylene. A three-molecule mechanism is suggested in the latter case with a cyclic transition state similar to that described by Illuminati and LaTorre¹⁴⁷. In the former case, however, the DMSO molecules facilitate the reaction playing the same part as a second amine molecule in p-xylene¹⁴⁸. Thus we observe higher rate constants when a polar solvent is used.

Of other solvents used in the condensation reactions of 9-chloroacridine with amines, the following were successfully used: an excess of the reacting amine¹⁴⁹, methanol¹⁵⁰, ethanol¹⁴¹ or ethanol with a few drops of concentrated HCl^{151,152}, absolute methanol¹⁵³ or 2-ethoxyethanol¹⁵² or N-methylpyrrolidine¹⁵⁴ with a few drops of methanesulphonic acid, butanol¹⁵⁵, cresol¹⁵⁶, and ethylene glycol¹⁵⁷. Recently, n-pentanol, chlorobenzene, xylene, pyridine, N,N-dimethylaniline, and DMF have also been used and two last solvents gave the highest yields of 9-aminoacridines¹⁵⁸.

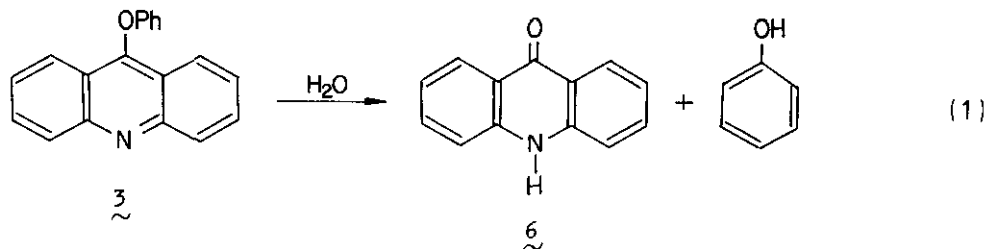
9-Chloroacridine also reacts with other nucleophiles yielding dozens of different products^{2,9}, but there are no kinetic or comparative studies of these reactions.

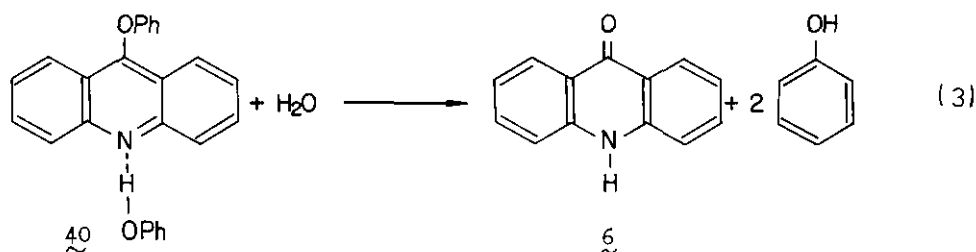
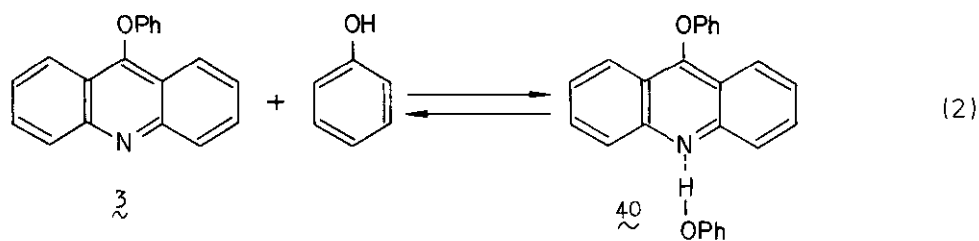
4. 9-PHENOXYACRIDINES

4.1. Hydrolysis of 9-phenoxyacridines. 9-Phenoxyacridines are the second most widely used intermediates in syntheses of all 9-acridine derivatives⁹ and, in particular, in syntheses of biologically active 9-aminoacridines⁸⁸. Nevertheless, there has been no report in the literature of stability of 9-phenoxyacridine and/or its derivatives until the preceding paper in this series¹. Fig. 4 depicts the pH-rate profiles for 9-phenoxyacridine, 1-nitro-9-phenoxyacridine, and 1-nitro-9-phenoxyacridine-10-oxide. The hydrolysis of 9-phenoxyacridine follows pseudo-first-order kinetics over a pH range 0 to 2, i.e., when the compound undergoing hydrolysis is 9-phenoxyacridinium chloride. The following mechanism was suggested for this reaction¹:



On the other hand, the hydrolysis is susceptible to autocatalysis under less acidic conditions, viz. at a pH above 2.5. The kinetic data for 1-nitro-9-phenoxyacridine indicate that the nitro derivative is subject to a stronger autocatalysis than that observed for 9-phenoxyacridine at the same pH value¹. This is most likely due to the fact that the 1-nitro compound, having much smaller pK_a value, is even less protonated under the same conditions. The autocatalysis followed a typical three-step mechanism⁹⁷ characteristic of catalysis by a reaction product:





Reaction (1) in the above scheme represents an uncatalytic step of the process. This reaction step is very slow due to very weak interactions of 9-phenoxyacridine with water (compound $\sim$ is insoluble in aqueous solutions at pH above 3). Therefore, the reaction was carried out in water-methanol (1:1, v/v) solution and surprisingly the reaction rate constants were slightly higher than those found for an aqueous buffer though the concentration of water was twice as high in the latter case. The rate-enhancing effect of methanol in the N-heterocyclic substrates is well-established¹⁵⁹ and H-bonding interaction is responsible for this phenomenon. The same effect is observed in the case of phenol-acridine interactions and, therefore, the H-bonded compound 40 was suggested to be the intermediate.

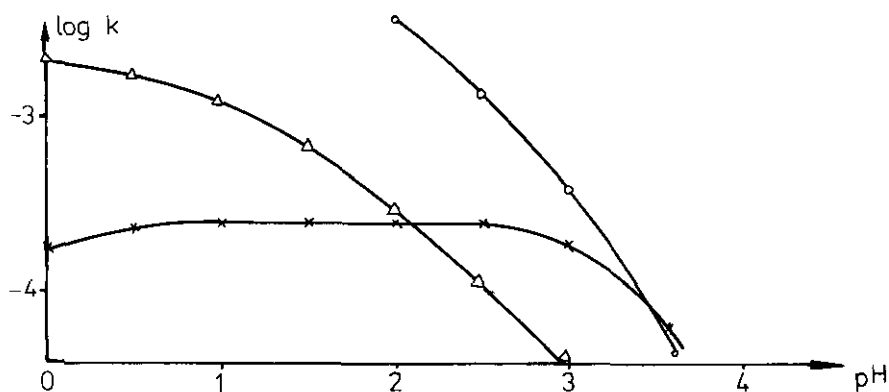
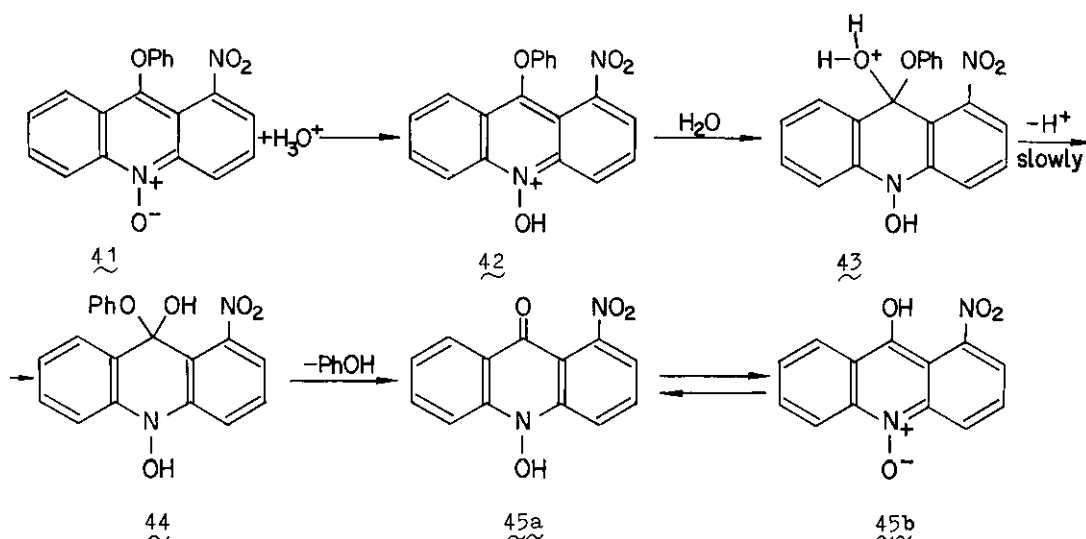


Fig. 4. The pH profile of the logarithm of pseudo-first-order rate constants for hydrolysis of 9-phenoxyacridine (—x—x—x—), 1-nitro-9-phenoxyacridine (—○—○—○—), and 1-nitro-9-phenoxyacridine-10-oxide (—△—△—△—)¹.

The pH-rate profile for the hydrolysis of 1-nitro-9-phenoxyacridine-10-oxide is shown above. In this case no autocatalytic effect was observed over the whole pH range studied. The plot shows, however, that the hydrolysis is catalyzed appreciably by hydrogen ions. The proposed reaction mechanism is shown in the scheme below. The abnormally low entropy of activation for this reaction ($-120 \text{ J} \times \text{mole}^{-1} \times \text{deg}^{-1}$) may be due to substantial solvation of the transition state ⁴³ and considerable molecular overcrowding in the vicinity of the reaction centre¹.

In aqueous solution, the tautomeric composition of 9-hydroxyacridine-10-oxide (⁴⁵) resembles that of 4-hydroxypyridine-1-oxide¹⁶⁰ in that each co-exists with a comparable amount of the N-hydroxy form. This pattern differs from that found in the corresponding non-N-oxides¹⁶¹ where annelation of one or two benzene rings considerably increases the relative stability of the oxo form. There is, however, a considerable contribution from the charge-separated form which is also stabilized by annelation of the benzene rings¹⁶². Spectra and basicity measurements indicate that in aqueous solution of 9-hydroxyacridine-10-oxide exists in equilibrium with an approximately equal amount of 10-hydroxyacridone¹⁶³.



The above findings explain why we observe a considerable decrease of reactivity on going from 1-nitro-9-phenoxyacridine to its N-oxide (Fig. 4). The N-oxide group has a large electromeric effect, but there must be an even greater electron release by oxygen which reduces the reactivity of the 'gamma' position with the result observed. The strong electron-withdrawing effect of the 1-nitro group is well known in the acridine series (cf. Chapter 3.2). We therefore observe the fol-

lowing ring substituent order of reactivity: 1-nitro-9-phenoxyacridine > 1-nitro-9-phenoxyacridine-10-oxide > 9-phenoxyacridine.

The solvolysis of 9-phenoxyacridine in 80% aqueous acetic acid was also found to follow pseudo-first-order kinetics¹⁰⁴. The rate constants reported for the solvolysis were about five times lower than those for hydrolysis in hydrochloric acid at pH 1 (pH of 80% acetic acid is about 1) and this ratio corresponds to a five times lower concentration of water in the former case¹. Energies of activations were very close in both cases.

It is worth noting that hydrolysis rate constants for 9-phenoxyacridine are almost exactly ten times as higher as those for 9-chloroacridine under the same conditions over the whole pH range examined. The higher reactivity of the 9-phenoxy derivatives is also reflected in, in general, lower values of energy of activation, e.g., E_a for 9-phenoxyacridine¹ is $77 \text{ kJ} \times \text{mole}^{-1}$ while for 9-chloroacridine¹⁰¹ it is $85 \text{ kJ} \times \text{mole}^{-1}$; for the 1-nitro derivatives they are 53 and 64 $\text{kJ} \times \text{mole}^{-1}$, respectively. The phenoxy group is thus a better leaving group than Cl^- . This higher reactivity of 9-phenoxyacridine and the catalytic nature of phenol might explain the common use of phenol as a solvent or at least as a facilitating agent for most of the syntheses to which reference is made below.

4.2. Condensations of 9-phenoxyacridines. Most syntheses, involving 9-chloro- or 9-phenoxy-acridines and leading to 9-aminoacridines⁸⁸ and other 9-substituted acridines, have hitherto been carried out in phenol. Best results are usually obtained when the 9-phenoxyacridine is condensed with an amine hydrochloride¹⁵⁵ in phenol whereas in the case of 9-chloroacridine, an acridine derivative is condensed with the free amine⁸⁸. In 1935, Drozdov and Chernzov¹⁶⁵ concluded that heating of 9-chloroacridine with an excess of phenol resulted in the formation of HCl salts of 9,9-diphenoxy-9,10-dihydroacridine as the first reaction product. Since then 9,9-diphenoxyacridan has been considered as being formed in most similar reactions^{88,127-132}. Recently, however, it was pointed out^{166,167} that not 9,9-diphenoxyacridan but 9-phenoxyacridine hydrochloride is an intermediate existing in the course of nucleophilic substitution in 9-phenoxyacridine. This conclusion was drawn on the basis of a crossover experiment involving 9-phenoxy- and 9-p-cresoxy-acridines and was supported by n.m.r. and u.v. spectra¹⁶⁷.

The above conclusion was confirmed by recent studies of the kinetics of formation of 9-phenoxyacridines from 9-chloroacridines and various phenols¹⁶⁸. The reactions were carried out under second-order conditions in CCl_4 as a solvent. Under these conditions a hydrogen bonded complex, 9-phenoxyacridine-phenol, was suggested as being formed in the first reaction step. The different reactivities observed for variously substituted phenols were explained on the ground of various strengths of hydrogen bonds formed by these phenols with 9-chloroacridine. However, such a complex is unlikely to be stable under preparative conditions where 9-chloroacridine disappears immediately after dissolution in liquid phenol.

The kinetics of condensation of 9-phenoxyacridine with pyrrolidine in DMSO and p-xylene have also been reported¹⁴⁶. The reaction has been carried out under second-order conditions and second-order kinetics were observed in DMSO. In p-xylene, however, autocatalysis similar to that described earlier¹ for the hydrolysis of 9-phenoxyacridine was observed and addition of phenol did increase the reaction rates. A deuterium isotope effect was also reported for this reaction and $k_{\text{H}}/k_{\text{D}}$ appeared to be 0.84 and 0.81 in p-xylene and DMSO, respectively.

5. 9-ALKOXYACRIDINES

9-Methoxyacridine and its derivatives were reported to react with amine salts to give approximately theoretical yields of 9-aminoacridines¹⁵⁰. Kitani¹⁶⁹ has also reported that 9-alkoxyacridines react readily with amines in presence of acids affording 9-aminoacridines in excellent yields and suggested that nucleophilic attack at the 9-position was facilitated by the formation of the acridinium ion. 9-Alkoxyacridines very readily undergo acid-catalyzed substitutions but these reactions have little preparative value¹⁷⁰, as substitution of the more readily available 9-chloroacridines is usually preferred.

A few papers deal with the hydrolysis of 9-alkoxyacridines. The base hydrolysis of 9-methoxyacridine-10-oxide has been described^{171,172}. More recently, the kinetics of hydrolysis of 9-methoxyacridine and its 1-nitro and 1-nitro-10-oxide derivatives have been studied¹⁷³.

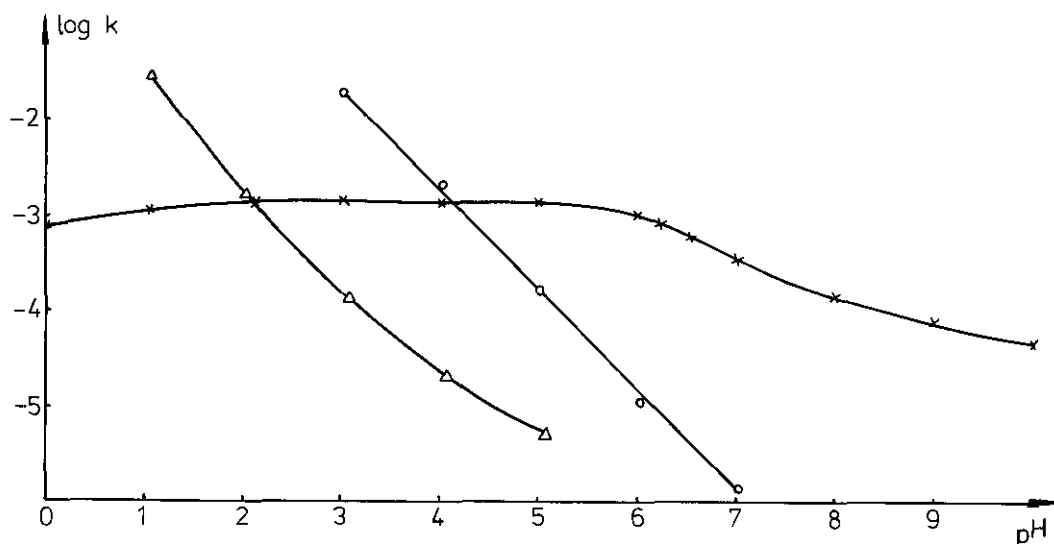
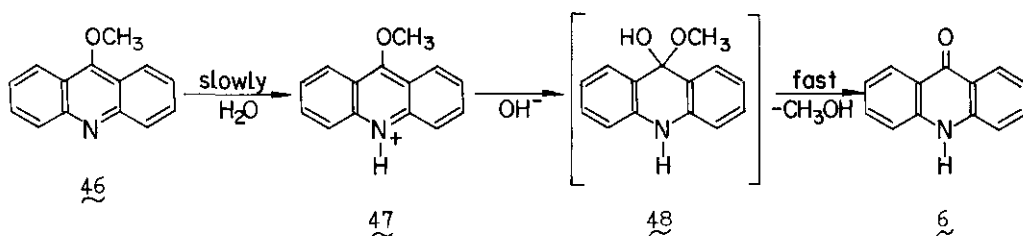


Fig. 5. The pH profile of the logarithm of pseudo-first-order rate constants for hydrolysis of 9-methoxyacridine (x), 1-nitro-9-methoxyacridine (o), and 1-nitro-9-methoxyacridine-10-oxide (Δ)¹⁷³.

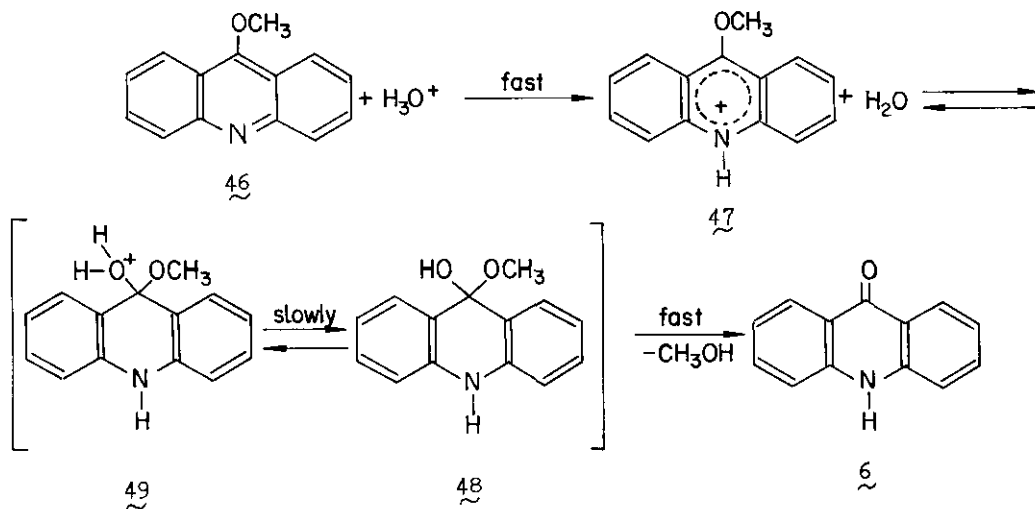
Fig. 5 shows acid-catalysis of the hydrolysis of 1-nitro-9-methoxyacridine and 1-nitro-9-methoxyacridine-10-oxide. 9-Methoxyacridine also shows a decrease of rate constants at a pH between 6 and 10 but the dependence is not proportional. The inflexion point of the $\log k = f(\text{pH})$ plot for this compound corresponds quite well to its pK_a value determined spectrophotometrically, 6.2. This suggests the mechanism by which acids catalyze the hydrolysis. The simplest view is that of

Kitani¹⁶⁹ who suggested that nucleophilic attack at position 9 was facilitated by the formation of the acridinium ion due to the decrease of the electron density at the C-9 at which the reaction occurs. The following mechanism for the acid-catalyzed hydrolysis was suggested¹⁷³:



The initial and rate-determining step is proton transfer from the reaction medium to the substrate. A substantial negative entropy of activation is quite reasonable for the above mechanism and many similar rate-determining proton transfers in aqueous solutions giving rise to negative values of $\Delta S^\ddagger$ are described in the literature^{174,175}.

In the pH range 1 to 6 rate constants for 9-methoxyacridine do not depend upon pH. This implies that a water molecule and not OH^- ion is the nucleophile reacting with the acridinium moiety. Therefore, the following reaction sequence was suggested¹⁷³:



Under acidic conditions 9-methoxyacridine exists in the form of acridinium ions 47 and/or 49 as can be seen in Fig. 6 [absorption bands at 370-400 nm indicate a considerable contribution of a structure similar to that of 9-acridone 6]. Deprotonation of 49 seems to be a rate-determining step because at a pH below 2 we observe a decrease of reaction rate with an increase of H^+ concentration (Fig. 5). Moreover, positive values of entropy of activation at a pH below 6 suggest a transition state somewhat less highly solvated than the starting state. The kinetic runs carried out at various buffer concentrations indicate that specific acid catalysis by H_3O^+ takes place.

In neutral and base solutions the u.v. spectrum shows that compound 46 represents the structure existing in a solution. The free base of 1-nitro-9-methoxyacridine-10-oxide hydrolyzes more slowly than its N-oxide-free analogue, which is in agreement with previous reports for other 9-acridine series (cf. Chapter 4.1). The significant increase in rate constants observed for 1-nitro-9-methoxyacridine in comparison to 9-methoxyacridine itself is due to the electron-attracting effect of the nitro group decreasing the electron density at the C-9 atom. However, the electron-donating N-oxide group suppresses the hydrolysis, so that the ring substituent order of reactivity in 9-methoxyacridines is exactly the same as that observed in 9-phenoxyacridines.

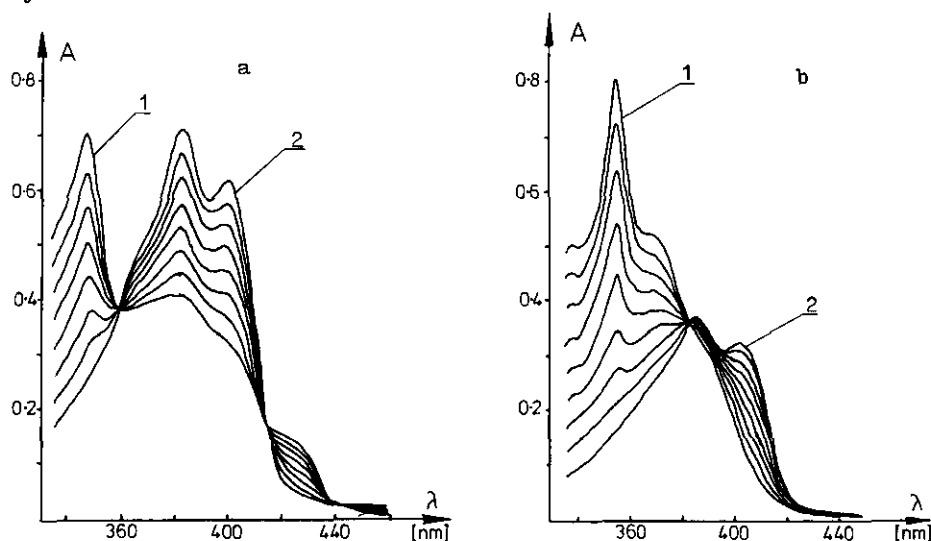
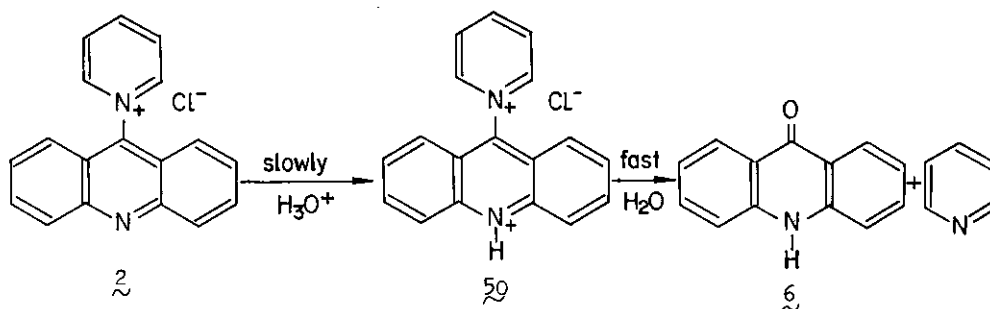


Fig. 6. Absorption spectra of the mixtures of 9-methoxyacridine (1) and 9-acridone (2) during hydrolysis at pH 3 (a) and pH 7 (b) at 40°C.

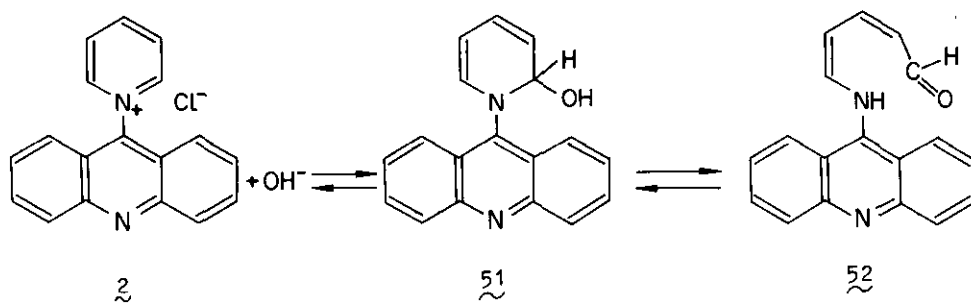
6. OTHER 9-SUBSTITUTED ACRIDINES

6.1. Hydrolysis of 1-(9-acridyl)-pyridinium chlorides. Before the potentialities of pyridine-1-oxide were realized 1-(4-pyridyl)-pyridinium chloride was the main route to certain 4-substituted pyridines¹⁷⁶. The importance of 1-(9-acridyl)-pyridinium chloride was not generally recognized until the work of Gruszecki and Borowski¹⁰³ even though pyridinium salts, being more reactive to nucleophilic attack than unquaternised pyridines, react with weaker nucleophiles than do the pyridines themselves¹⁷⁷. Gruszecki and Borowski¹⁰³ found that 1-isomers reacted much more readily with pyridine than did 3-isomers of 9-chloroacridines and this reaction was suggested as a synthetic method¹⁰⁴ for separating the mixtures of isomers which are formed in the course of cyclization of diphenylamine-2-carboxylic acids¹⁷⁸. Since then, hundreds of antitumour active 9-aminoacridines have been synthesized following this route⁴.

Compound **2** was known to undergo hydrolysis in some unsuccessful condensations with amines but the kinetics of this reaction have not been studied until recently¹⁷⁹. 1-(9-Acridyl)-pyridinium chloride contains several reaction centers in both the acridine and pyridine rings. Accordingly, its reactions can be arranged into the following three main groups: (1) The attack by nucleophiles at position C-9 of the acridine ring. The result is the elimination of the pyridine ring and transfer of the acridine moiety to one of the components of the environment, followed by formation of the 9-substituted acridines, i.e., syntheses of 9-aminoacridines, 9-phenoxyacridines, etc., to which the reference was made above⁴. The hydrolysis reaction shown in the scheme below also belongs here:



(2) The attack by nucleophiles (OH^- , arylamines) at the ring α -carbon atom of pyridine resulting in so-called 'pseudobases' **51** or, more frequently, in ring opening reactions¹⁸⁰ shown in the scheme below:



(3) Reactions of other types known for various aromatic and heteroaromatic cations such as addition of nucleophiles to the pyridine ring, single electron transfer to 2 followed by radical dimerization, electrophilic substitution, and many others¹⁸¹.

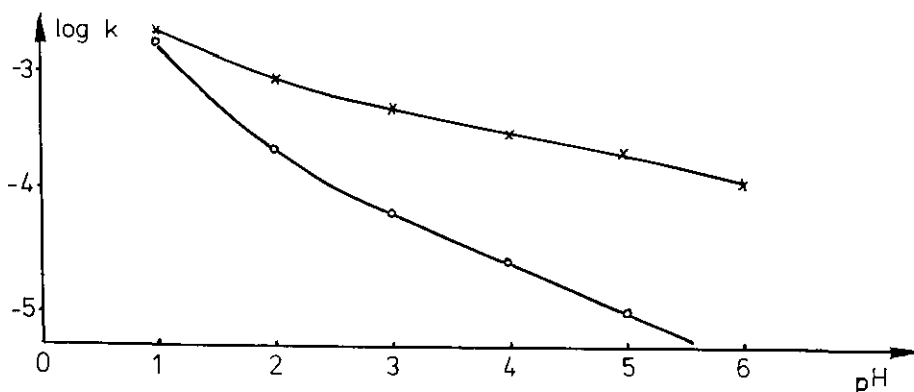


Fig. 7. The pH-rate profile for hydrolysis of 1-(1-nitro-9-acridyl)-pyridinium chloride (o-o-o) and 1-(9-acridyl)-pyridinium chloride (x-x-x-x)¹⁷⁹.

The above figure shows that compound 2 undergoes a rapid hydrolysis at a pH between 0 and 3, slowly hydrolyzes at a pH of 4 to 6, and is quite stable in neutral or weakly basic solutions. The kinetic data for reactions carried out in hydrochloric, sulphuric, and nitric acid indicate a specific acid catalysis (by H_3O^+)¹⁷⁹. In alkali, however, a deeply reddish-violet solution is formed by rupture of the pyridine ring. Reactions involving cleavage of the pyridine ring (the Zincke-Koenig reactions)¹⁸⁰⁻¹⁸² yielding glutaconic dialdehyde, its anils, and/or enamines are characteristic of quaternary pyridinium salts containing electron-withdrawing substituents at the nitrogen atom that cannot undergo transfer to the nucleophiles present in the reaction mixture. Johnson et al.^{183,184} have carried out a detailed kinetic study of ring-opening reaction of pyridinium cations in basic solutions under widely varying pH conditions. They have shown that the equilibrium formation

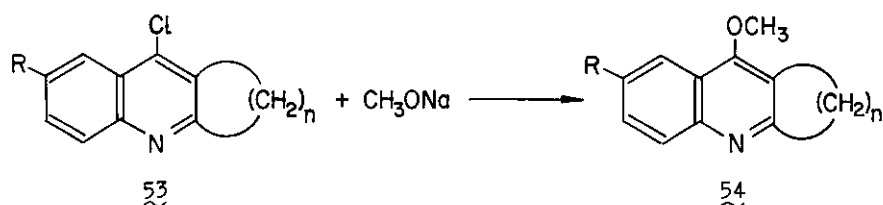
of pseudobases 51 by OH^- attack at the carbon C-2 is a faster process than ring opening.

The influence of the 1-nitro group in the acridine moiety on the relative ease of the ring-opening reaction is rather unexpected. The literature data suggest that electron-withdrawing substituents in the pyridine ring strongly influence the formation of the pseudobases, e.g., the 3-carbamido group increases rate constants by five orders of magnitude¹⁸³. Here, a transient reddish colour of 1-(1-nitro-9-acridyl)-pyridinium chloride is observed at pH 10 at elevated temperatures while the 1-nitro-free compound shows the same effect at a pH as low as 9 and at room temperature. Johnson et al.¹⁸⁴ have shown that substituents in the pyridine ring have a dramatic consequence on relative ease of reaction. There is no report in the literature, however, of such a pronounced influence of the nitro group in decreasing the reaction rate, and rather the opposite effect would be expected. The only plausible explanation seems to be that steric requirements of the 1-nitro group shield the vicinity of the reaction center and electron-rich oxygen atoms in this group make nucleophile approach to the pyridine ring difficult. Some support for this speculation may come from the crystallographic data for the two compounds.

Annulation in the acridine series was discussed in the above chapters and a similar effect is observed when comparing reactivities of 1-(4-pyridyl)-pyridinium chloride and 1-(9-acridyl)-pyridinium chloride. Although the former compound, introduced by Koenigs and Greiner¹⁸⁵, was the main route to certain 4-substituted pyridines for many years¹⁸⁶, its reactivity is much lower than that of the latter. The hydrolysis of 1-(4-pyridyl)-pyridinium chloride can be achieved either by heating with water in an autoclave¹⁸⁵ at 150°C or by working with concentrated aqueous solutions and thereby raising the boiling point to 130°C and refluxing¹⁸⁷ for 24 hr. The same reaction with compound 2 at pH 0 is completed after 30 min. at 50°C .

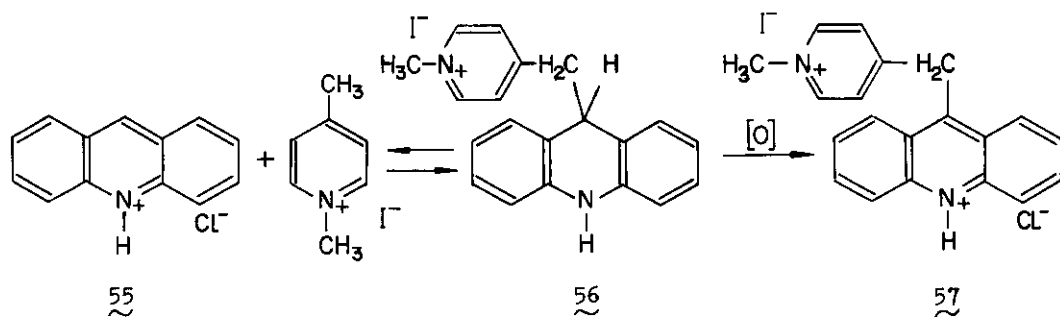
6.2. Other reactions. The kinetics of the reaction of 1,2,3,4-tetrahydro-9-chloroacridine and its 7-methyl, 7-methoxy and 7-halogeno derivatives with sodium methoxide have been studied and the results compared with those for their homologues (53, $n=3$ and 5)¹⁸⁸. The authors have found the following reactivity order of the homologues at 76.2°C : $n=3 > n=4 > n=5$ and discussed the observed results in terms of the influence of the methylene groups on electron density at

the reaction centre and the steric requirements of the methylene chain. However, the energies of activation decrease in the following order: $n = 3 > n = 5 > n = 4$ (105, 97, and 76 kJ $\times$ mole $^{-1}$, respectively) and a quite different order of rate constants could be observed at other temperatures. The substituent order of reactivity, $\text{OCH}_3 < \text{CH}_3 < \text{H} < \text{Cl} < \text{Br}$, suggests a typical mechanism of nucleophilic aromatic substitution.



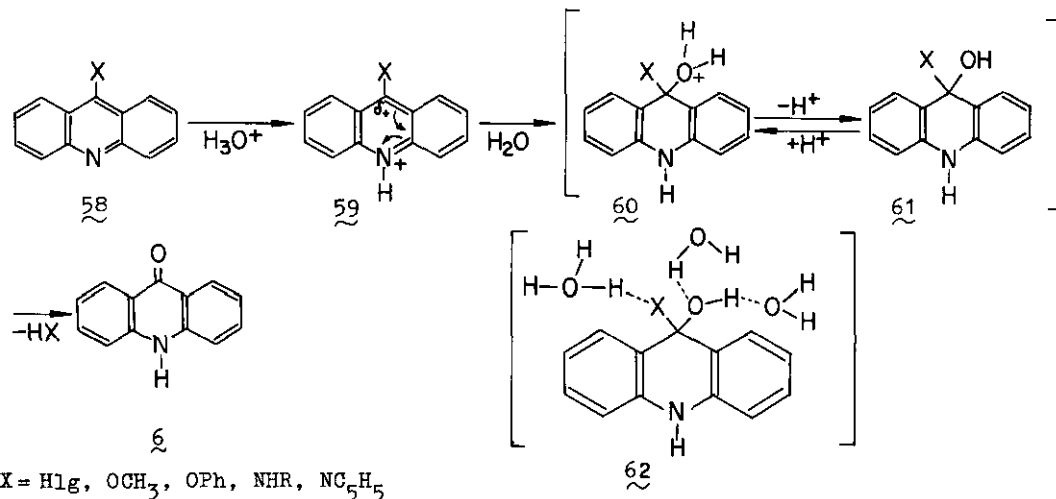
Kirichenko and Chupakhin¹⁸⁹ have reported kinetic studies of nucleophilic hydrogen atom substitution at the 9-position of acridine. The reaction of acridine and acridine hydrochloride with heterocyclic alkylidides (e.g., 1-ethyl-4-picolinium, 1,2-dimethylbenzothiazolium, 1,2,3-trimethylbenzimidazolium, picolinium iodides) was first order with respect to each reagent. The rate constants for the reaction of acridine hydrochloride were 8-fold as high as those for that of acridine itself and the lower the pK_a value for the methyl protons, the higher the rate constants. These data provide evidence for the typical addition-elimination mechanism which involves intermediate 56.

Compounds such as 56 were also found to be formed in many other similar reactions involving acridinium ions¹⁹⁰. In one case, when phenolates were used to react with acridinium chloride, the reaction resulted in the formation of 9,9-bi-acridines¹⁹¹.



CONCLUSIONS

In view of the above kinetic data and detailed discussion it is possible to suggest a general mechanism of nucleophilic aromatic substitution at the position 9 of acridine derivatives. It is suggested that specific acid-catalyzed reaction occurs in the following way:



Most acridines undergoing hydrolysis over the pH range of 0 to 10 are suggested to exist in the acridinium form 59. The suggestion is supported by the observation that a maximum hydrolysis rate is observed at pH values corresponding to pK_a 's of compounds 58, e.g., 9-methoxyacridine¹⁷³, 9-phenoxyacridine¹, 9-chloroacridine¹⁰¹, 1-nitro-9-(alkylaminoalkylamino)-acridines²⁶. Over the pH range from ca. 1 to the pK_a value, rate constants remain independent of the pH. This suggests that water molecules are nucleophiles taking part in the process. A decrease in rate constants observed under strongly acidic conditions, at a pH below 1, might be due to the fact that a good deal of the water molecules exist in the protonated form $\text{H}^+(\text{H}_2\text{O})_n$, mostly H_9O_4^+ . A decrease of rate constants is also observed at a pH above pK_a . The less soluble the free bases of 58, the steeper the slope of the plot $\log k = f(\text{pH})$.

Compounds 60 and 61 are suggested as being activated complexes rather than intermediates. Although some acridans are known to be stable, such compounds have too high internal energy to have a measurable half-life time. We usually write formulae like 60 and 61 but in fact there is not any distinguishable stage between proton splitting off and leaving group abstraction. Most unit processes are almost simultaneous and probably formula 62 describes the reality much better though not exactly since more water molecules are involved in the solvation process.

The following reactivity order is observed in the acidic media pH 0 - 6 : $C_5H_5N > C_6H_5O > Cl > OCH_3 > NHR >> H$. There is a straightforward explanation of this order. The highest reactivity of 1-9-acridyl -pyridinium chloride is not unexpected because it is diprotonated in the 9/10 conjugated system (see compound 50) and therefore interacts easily with water. Moreover, pyridine is incomparable the most stable of all these leaving groups. The phenoxy group is able to delocalize the charge by resonance, thereby decreasing the electrostatic repulsion between entering and leaving groups, and therefore it is a better leaving group than the halides. On the other hand, when the alkoxy derivatives are used, the leaving group has a substantial negative charge on it in the transition state. The 9-aminoacridines are compounds of a different class because they do not exist in form 59 in water solutions. On protonation they are transformed into protonated 9-iminoacridanes 15b and therefore are very stable. In fact this is one of their advantages as compounds used in chemotherapy because they do not decompose easily. Under neutral and basic conditions, however, 9-aminoacridines existing as such hydrolyze quite readily while the other derivatives do not interact with water at all. These features of 9-aminoacridines distinguish them from all other 9-substituted acridines described here.

It is worth emphasizing once more the significant effect of annelation in the series of pyridine, quinoline, and acridine. The addition of an extra benzene ring lowers the activation energy thereby facilitating nucleophilic substitution. The 1-nitro group in 9-acridines has a similar though much smaller effect as is evident from the preceding chapters. The N-oxide group increases the hydrolysis rate when it is protonated but decreases the rate while it exists in the unprotonated form.

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