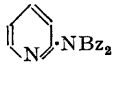
32. *The Acetylation of Some 5-Aminoacridines.*

By J. H. Wilkinson and I. L. Finar.

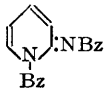
It has been shown that 5-aminoacridine forms a diacetyl derivative, as well as 5-acetamidoacridine (Albert and Goldacre, *J.*, 1943, 454). The orientation of the former has been studied, and the evidence obtained is in favour of structure (I). The acetylation of a number of substituted 5-aminoacridines has also been carried out, and a series of mono- and di-acetyl derivatives obtained.

During a study of the effect of fluorine substitution on the properties of 5-aminoacridine and similar compounds, a number of chlorine and methyl substituted 5-aminoacridines were acetylated by the method described by Albert and Goldacre (*loc. cit.*) for 5-acetamidoacridine. The 4-methyl derivative did not give the required acetyl compound, and a product was isolated which proved to be the diacetyl derivative. Later, it was found that 5-aminoacridine and a number of related compounds gave diacetyl derivatives, though somewhat more rigorous conditions than for 5-amino-4-methylacridine were found necessary.

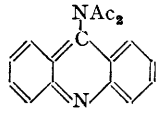
The observation of Tschitschibabin and Bylinkin (*Ber.*, 1922, **55**, 998) on the dibenzoyl derivative of 2-aminopyridine seems relevant to the study of the structure of this new derivative of 5-aminoacridine. These authors point out that their compound may have either of the structures, (*a*) or (*b*).



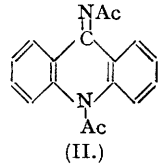
(*a*.)



(*b*.)



(I.)

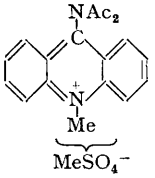


(II.)

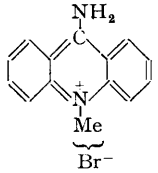
A similar reservation must be made in the case of the acridine derivative which may have either structure, (I) or (II).

It has been shown by Albert and Goldacre (*loc. cit.*) that in the case of the monoacetyl derivative of 5-aminoacridine the acetyl group is in the 5 position since, on treatment with methyl *p*-toluenesulphonate and subsequent hydrolysis, it gives 5-amino-10-methylacridinium bromide, (IV). Similarly, if the diacetyl derivative has structure (I), it should be possible to convert it to the quaternary salt (IV) by a similar series of reactions, whereas it is improbable that structure (II) would quaternise in view of the inductive effect exerted by the carbonyl groups on the " lone pair " electrons of the nitrogen atoms (Ingold, *Ann. Rep.*, 1926, **23**, 139).

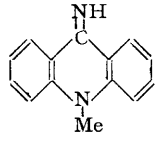
When quaternisation with methyl *p*-toluenesulphonate [Albert and Goldacre (*loc. cit.*); Albert and Ritchie (*J.*, 1943, 458)] was attempted an unworkable black tar was obtained, but it was achieved by the use of dimethyl sulphate in nitrobenzene at 130°. The product (III), on hydrolysis with hydrobromic acid, gave 5-amino-10-methylacridinium bromide (IV), which, on treatment with alkali, gave 5-amino-5-hydroxy-10-methylacridan. When this was heated at 130°, 5-imino-10-methylacridan (V) was obtained. No reaction with methyl iodide occurred either with the diacetyl compound or with 5-acetamidoacridine.



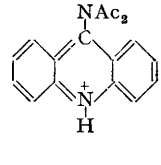
(III.)



(IV.)



(V.)



(VI.)

It is thus established that the structure of the diacetyl derivative is correctly represented by (I), but the possibility of molecular rearrangement, though remote, cannot be excluded.

All the acetyl derivatives dissolve in dilute mineral acid giving deep yellow solutions, thus indicating not only their basic nature, probably due to the ionic form (VI) (cf. Albert and Ritchie, *J.*, 1943, 458), but also the similarity in structure between the mono- and di-acetyl compounds.

Further confirmatory evidence based on a study of the ultra-violet absorption spectra of some of these compounds will be published elsewhere shortly by King, Gilchrist, and Tárnoky.

The formation of 5-*diacetylaminoacridine* suggests that in the un-ionised state, 5-aminoacridine does not exist to any great extent in the imino form (see Craig and Short, *J.*, 1945, 419, for evidence from absorption spectra).

The Fluorescence of the Acetyl Derivatives.—None of the acetylated aminoacridines examined exhibited fluorescence in alcoholic solution by daylight but, in ultra-violet light, all were fluorescent, the colours and intensities varying according to the reaction of the solution. Under ultra-violet light, all the acetylated compounds showed a blue fluorescence in the solid state, 1-*chloro*-5-*diacetylaminoacridine* being exceptionally vivid under these conditions.

Experimental.

(M. ps. are corrected unless over 300°.)

Preparation of Bases.—Since this work was completed, Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169) have reported the preparation of the monomethyl- and monochloro-5-aminoacridines. The m. ps. reported are somewhat lower than those recorded in this paper, possibly because the former may be uncorrected. The corresponding 5-chloroacridines were converted to the 5-aminoacridines by the standard method (Albert and Ritchie, *Org. Syn.*, 1942, **22**, 5). The bases were isolated by precipitating the hydrochlorides with acetone, dissolving the latter in hot water and precipitating with sodium hydroxide. The yields varied from 80 to 90%.

1 : 5-*Dichloroacridine* was prepared by refluxing 2′-chlorodiphenylamine-2-carboxylic acid (Ullmann, *Annalen*, 1907, **355**, 312) (16 g.) with phosphorus oxychloride (35 c.c.) for 2 hours, followed by removal of the excess of the latter by distillation under reduced pressure. The residue was dissolved in chloroform, and washed free from acid with aqueous ammonia. The solvent was removed under reduced pressure. The product (14·9 g.) crystallised from a mixture of 90 parts of alcohol and 10 parts of 2N-ammonia in white plates, m. p. 100° (Found: N, 5·6. $C_{13}H_7NCl_2$ requires N, 5·6%).

1-*Chloro*-5-*aminoacridine* crystallised from 50% alcohol in small bright yellow prisms, m. p. 235° (Found: C, 68·2; H, 4·0; N, 12·5; Cl, 15·6. $C_{13}H_9N_2Cl$ requires C, 68·3; H, 3·9; N, 12·3; Cl, 15·5%). The *hydrochloride* was obtained as small lemon-yellow prisms, soluble in about 500 parts of water, m. p. over 360°, charring *ca.* 330° (Found: N, 10·45. $C_{13}H_9N_2Cl,HCl$ requires N, 10·6%).

2-Chloro-5-aminoacridine crystallised from chlorobenzene in small bright yellow prisms, m. p. 277° (U.S.P. 2,092,131 gives m. p. 277°). The *hydrochloride* crystallised in pale yellow plates, sparingly soluble in water, m. p. *ca.* 360° (decomp.) (Found: N, 10·25; Cl, 25·9. $C_{13}H_9N_2Cl,HCl,\frac{1}{2}H_2O$ requires N, 10·2; Cl, 25·9%).

3-Chloro-5-aminoacridine crystallised from chlorobenzene in small prisms, m. p. 288—289° (G.P. 364,035 gives 273—274° and U.S.P. 2,092,131 gives 269—270°) (Found: N, 12·2%). The *hydrochloride* was obtained as yellow rectangular prisms, soluble in about 1000 parts of water. It had m. p. over 360°, charring *ca.* 300° (Found: N, 10·75%).

4-*Chloro*-5-*aminoacridine* crystallised from chlorobenzene in small bright yellow prisms, m. p. 270° (Found: C, 67·8; H, 4·2; N, 12·4; Cl, 15·7%). The *hydrochloride* crystallised in lemon-yellow plates, soluble in about 150 parts water, m. p. 303° (corr., decomp.) (Found: N, 10·5%).

5-*Amino*-3-*methylacridine* crystallised from chlorobenzene in flat rectangular prisms, m. p. 252° (Found: C, 80·6; H, 5·6; N, 13·3. $C_{14}H_{12}N_2$ requires C, 80·75; N, 5·75; N, 13·5%). The *hydrochloride* was obtained in small lemon-yellow prisms, soluble in about 1000 parts of water, m. p. 328—329° (decomp.) (Found: N, 11·45. $C_{14}H_{12}N_2,HCl$ requires N, 11·4%).

5-*Amino*-4-*methylacridine* was prepared from 4-methylacridone (Gleu and Nitzsche, *J. pr. Chem.*, 1939, **153**, 200). It crystallised from 50% alcohol in small orange-yellow prisms, m. p. 248—249° (Found: C, 80·6; H, 6·0; N, 13·2%). The *hydrochloride* separated from acetone in small lemon-yellow prisms, soluble in about 30 parts of water, and highly soluble in alcohol. It had m. p. *ca.* 320° (decomp.) (Found: N, 11·1; Cl, 14·2. $C_{14}H_{12}N_2,HCl,\frac{1}{2}H_2O$ requires N, 11·05; Cl, 14·0%).

Preparation of 5-*Diacetylamino*-4-*methylacridine.*—5-Amino-4-methylacridine (1 g.) was heated at 105° for 30 minutes with acetic anhydride (2 c.c.) and allowed to cool. No precipitate was obtained on the addition of benzene, but in a repeat preparation, the reaction mixture was diluted with water (20 c.c.) and the resulting suspension neutralised with 2N-ammonia. The solid was separated, washed with water and dried at 90°. The *diacetyl derivative* crystallised from 50% alcohol in irregular white plates, m. p. 144° (Found: N, 9·6. $C_{18}H_{16}O_2N_2$ requires N, 9·7%).

Preparation of Monoacetyl Derivatives.—It was found that the other bases examined behaved in a similar manner to 5-aminoacridine when acetylated by the method of Albert and Goldacre (*loc. cit.*), although a larger proportion of acetic anhydride was found to facilitate the reaction. The base (4 g.) was heated at 105° in acetic anhydride (12 c.c.) for 30 minutes. After cooling, benzene (40 c.c.) was added and the solid separated, washed with alcohol and ammonia, and dried at 90°. The various 5-acetamidoacridines were crystallised from alcohol, the yields being of the order of 85 to 95%.

1-*Chloro*-5-*acetamidoacridine* crystallised from 90 volumes alcohol in long white needles, m. p. 267° (Found: N, 10·2. $C_{15}H_{11}ON_2Cl$ requires N, 10·35%). 2-*Chloro*-5-*acetamidoacridine* crystallised in cream–white, long feathery needles from 120 volumes alcohol, m p. 281° (Found: N, 10·4%). 3-*Chloro*-5-*acetamidoacridine* crystallised in pale yellow fine silky needles from 130 volumes alcohol, m. p. 297° (Found: N, 10·3%). 4-*Chloro*-5-*acetamidoacridine* crystallised in cream–white feathery needles from 45 volumes alcohol, m. p. 231° (Found: N, 10·4%). 5-*Acetamido*-3-*methylacridine* crystallised in colourless needles from 80 volumes alcohol, m. p. 268° (Found: N, 11·2. $C_{16}H_{14}ON_2$ requires N, 11·2%).

Preparation of Diacetyl Derivatives.—The base (2 g.) was refluxed with acetic anhydride (12 c.c.) for 30 minutes and, after cooling, the mixture was poured into water (30 c.c.). After neutralising with 2N-ammonia the product was separated, washed with water and dried at 90°. The crude diacetyl derivatives (yields 90—95%) were crystallised from aqueous alcohol. All were readily soluble in alcohol and benzene.

5-*Diacetylaminoacridine*. Large glistening white needles, m. p. 164°. These appear to be hydrated since, when heated at 130°/14 mm. for 2 hours, a loss in weight of 3·75% occurred. (*Hemihydrate* requires 3·15%). The *anhydrous* form crystallised from benzene in colourless hexagonal prisms, m. p. 164° (Found: C, 73·0; H, 5·1; N, 10·0. $C_{17}H_{14}O_2N_2$ requires C, 73·3; H, 5·05; N, 10·1%). Its orientation was verified by treatment of 1 g. with dimethyl sulphate (1 c.c.) in nitrobenzene (10 c.c.) at 130° for 30 minutes. After cooling, the mixture was treated with benzene (30 c.c.) and set aside. The precipitate was washed with benzene and dried. The crude methosulphate (1·25 g.) was dissolved in water (5 c.c.) and hydrolysed by heating at 90° with 48% hydrobromic acid (5 c.c.) for one hour. The solution was filtered (charcoal) and allowed to cool. The solid which separated was collected and crystallised from water, and proved to be 5-amino-10-methylacridinium bromide, m. p. 306—307° (decomp.) [Albert and Ritchie, *J.*, 1943, 458, give m. p. *ca.* 305° (decomp.)] (Found: N, 9·7. Calc. for $C_{14}H_{13}N_2Br$: N, 9·7%). The identity of this compound was confirmed by treatment with alkali to give the *pseudo*-base, which on drying at 130° gave the anhydro-base, 5-imino-10-methylacridan, m. p. 134—136° (Albert and Ritchie give m. p. 134—136°). A mixed m. p. with an authentic specimen showed no depression.

1-*Chloro*-5-*diacetylaminoacridine* was obtained in pale greenish–yellow square prisms, strongly fluorescent under ultra-violet light, m. p. 179·5° (Found: N, 9·1. $C_{17}H_{13}O_2N_2Cl$ requires N, 8·95%). 2-*Chloro*-5-*diacetylaminoacridine* was obtained in pale yellow regular parallelepipeds, m. p. 185° (Found: N, 8·8%). 3-*Chloro*-5-*diacetylaminoacridine* was obtained in colourless square prisms, m. p. 172° (Found: N, 9·0%). 4-*Chloro*-5-*diacetylaminoacridine* was obtained in

pale yellow plates, m. p. 155° (Found: N, 8·9%), and 5-*diacetylamino*-3-*methylacridine* in pale yellow elongated rhombs m. p. 205° (Found: N, 9·8%).

Fluorescence of Acetyl Derivatives under Ultra-violet Light.

	Base.	Monoacetyl derivative.	Diacetyl derivative.
(a) *In the solid state.*			
5-Aminoacridine	Very faint green.	Blue.	Vivid blue.
1-Cl-5-NH_2-acridine	Green	Blue	Vivid blue.
2-Cl- ,, ,,	Absent.	Blue.	Blue.
3-Cl- ,, ,,	Very faint green.	Blue.	Blue.
4-Cl- ,, ,,	Green.	Blue.	Faint blue.
5-NH_2-3-Me- ,,	Absent	Blue.	Blue.
5-NH_2-4-Me- ,,	Absent.	—	Blue.
(b) *In alcoholic solution.*			
5-Aminoacridine (acid)	Vivid blue.	Faint green.	Faint green.
,, (neutral)	Vivid blue.	Blue.	Faint violet.
,, (alkaline)	Green.	Faint green.	Faint green.
1-Cl-5-NH_2-acridine (acid)	Blue.	Bluish green.	Faint blue.
,, ,, (neutral)	Blue.	Blue.	Violet.
,, ,, (alkaline)	Green.	Vivid green.	Vivid green.
2-Cl-5-NH_2 ,, (acid)	Blue.	Green.	Very faint green.
,, ,, (neutral)	Green.	Blue.	Violet.
,, ,, (alkaline)	Green.	Vivid green.	Vivid green.
3-Cl-5-NH_2 ,, (acid)	Blue.	Discharged.	Discharged.
,, ,, (neutral)	Green.	Blue.	Violet.
,, ,, (alkaline)	Green	Vivid green.	Vivid green.
4-Cl-5-NH_2 ,, (acid)	Blue.	Faint green.	Very faint green.
,, ,, (neutral)	Green.	Blue.	Violet.
,, ,, (alkaline)	Green	Vivid green.	Green.
5-NH_2-3-Me ,, (acid)	Vivid blue.	Faint green.	Green.
,, ,, (neutral)	Bluish-green.	Blue.	Violet.
,, ,, (alkaline)	Bluish-green.	Vivid green.	Vivid green.
5-NH_2-4-Me ,, (acid)	Vivid blue.	—	Green.
,, ,, (neutral)	Blue.	—	Violet.
,, ,, (alkaline)	Blue.	—	Vivid green.

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