144. N-*Substituted* 5-*Aminoacridines.*

By D. J. Dupré and F. A. Robinson.

Twenty derivatives of 5-aminoacridine, substituted only in the amino-group, have been prepared by reaction of the appropriate amine with 5-chloroacridine, or of the amine hydrochloride with 5-phenoxyacridine. In their bacteriostatic and toxic properties, these compounds are not superior to 5-aminoacridine.

Secondary and tertiary derivatives of 5-aminoacridine, containing aliphatic and aromatic substituents in the amino-group, have been prepared in order to determine the effect of such substituents on their bacteriostatic and toxic properties. These compounds have the general structure (I), where R_1 is methyl, ethyl, propyl, *iso*propyl, butyl, *iso*butyl, *iso*amyl, phenyl, *o*-, *m*-, or *p*-tolyl, *o*- or *p*-anisyl, *o*-phenetyl, β-hydroxyethyl, carboxymethyl, β-diethylaminoethyl or γ-diethylamino-*n*-propyl, and R_2 is hydrogen, or where both R_1 and R_2 are methyl or ethyl.

(I.)

Of these compounds, four have been described by Albert and his co-workers since the present research was undertaken, namely, 5-methyl-, 5-dimethyl-, 5-phenyl- (Albert and Ritchie, J., **1943**, 458), and 5-*n*-butylaminoacridine (Albert, Goldacre, and Heymann, *ibid.*, p. 651). Two others—5-ethyl- and 5-β-hydroxyethylaminoacridine—are described in a series of patents granted in the years 1922 and 1923 (D.R.-PP. 360,421, 364,031, 364,032, 364,034, 367,084; B.PP. 176,038, 199,870; Swiss Pat. 94,950). These patents are the first publications dealing with compounds of this type, and describe the preparation of numerous aminoacridines—usually containing other nuclear substituents—by the interaction of 5-halogeno-, 5-alkoxy-, or 5-aryloxyacridines with amines or their salts. The yields obtained are not reported, and no detailed account is given of their bacteriological properties, though they are stated to be of value as antimalarials. Eisleb (*Med. und Chem.*, 1936, **3**, 41; *Chem. Zentr.*, 1937, I, 604; *Chem. Abs.*, 1937, **31**, 5802) describes the preparation and pharmacological properties of over 200 acridines substituted in the 5-position but, since the original paper is not available and the abstracts do not contain an exhaustive list of the compounds prepared, it is uncertain whether the compounds now described are included in the earlier publication.

Several simple alkylaminoacridines not included in the present series have been described. These are 5-*cyclo*hexyl-, 5-heptyl, 5-dodecyl-, and 5-hexadecyl-aminoacridines, prepared by Albert, Goldacre, and Heymann (*loc. cit.*), 5-piperidinoacridine, described by Mietzsch and Mauss (U.S.P., 2,092,131/1937), and 5-β-diethylaminoethyl-ethylaminoacridine, described in D.R.-P. 488,890/1930 (to I.G.-Farbenind.). In addition, there is an extensive literature dealing with related compounds containing a variety of other nuclear substituents (*e.g.*, Ishihara, *J. Chem. Soc. Japan*, 1934, **55**, 458; Drozdov, *J. Gen. Chem. U.S.S.R.*, 1936, **6**, 1641; Goodall and Kermack, J., 1936, 1546; Dhar, Narang, and Ray, J., 1938, 304).

In the present work, the 5-aminoacridine derivatives were prepared by reaction of the appropriate amine or its hydrochloride, usually in phenolic solution, with 5-chloro- or 5-phenoxy-acridine (cf. Drozdov, *loc. cit.*). It was found most satisfactory to use either the free base with chloroacridine or the amine hydrochloride with phenoxyacridine; other combinations of the reactants gave poor yields. The former method was used principally with the less volatile bases, the reaction being carried out in an open vessel, but it was also found necessary to prepare 5-diethylaminoacridine by this route, using a sealed tube. In general, the monohydrochloride of the new base was obtained when the reaction product was poured into ether. In the preparation of the diethylaminoalkylaminoacridines, however, of which the monohydrochlorides do not appear to exist, this procedure led to precipitation of half the base as dihydrochloride.

In the aliphatic series, the hydrochlorides are readily soluble in water (0·5 to >20%), though the *hydrochloride* of 5-carboxymethylaminoacridine is hydrolysed to the free base too rapidly for the solubility to be estimated. The aromatic compounds are less soluble in water (*ca.* 0·1%), but dissolve more readily in alcohol. With the exception of 5-*carboxymethylaminoacridine*, for which no significant determination could be made, all the hydrochlorides gave pH values in 0·1% aqueous solution within the range 5·5—6·5. The dialkylamino-compounds undergo considerable hydrolysis at room temperature to acridone, and all are hydrolysed with more or less rapidity on heating.

The bacteriostatic properties of aqueous solutions of the hydrochlorides of 18 of these compounds have been investigated by Dr. J. Ungar, and their toxicities to mice by Mr. M. R. A. Chance, both of these laboratories. In no instance were the new compounds superior to 5-aminoacridine. 5-β-Hydroxyethylaminoacridine was not investigated, since it was prepared at a late stage in the investigation, in the hope that the free base might be appreciably water-soluble; this expectation was not realised. 5-Carboxymethylaminoacridine could not be investigated, since the free base is insoluble in water, and its hydrochloride and *sodium* salt, both of which were prepared in anhydrous conditions, are unstable in the presence of water.

Experimental.

(All m. p.'s are uncorrected.)

Method I. Interaction of 5-*Phenoxyacridine and Amine Hydrochloride.*—5-Phenoxyacridine was prepared by a modification of the method of Goodall and Kermack (*loc. cit.*). Sodium hydroxide (7·2 g.) was dissolved in phenol (120 g.) at 100°, and 5-chloroacridine (28 g.) added with stirring. The solution was kept at 100° for 1½ hours, then poured into 2N-sodium hydroxide solution (1 l.), stirred, and set aside overnight. The precipitated material was filtered off, washed with water, powdered, and dried. The resultant 5-phenoxyacridine (35 g.) had m. p. 127—128°, unchanged by crystallisation from benzene. Drozdov and Cherntzov (*J. Gen. Chem. U.S.S.R.*, 1935, **5**, 1576) record m. p. 125—126°.

(a) 5-*Monoalkylaminoacridines.* 5-Phenoxyacridine (6·3 g.) was dissolved in phenol (20 g.) at 80° in an open vessel, and an equimolecular quantity of the appropriate amine hydrochloride added. The temperature was raised to 120°, and heating continued for one hour. On cooling, the mixture was poured into ether, giving a crude hydrochloride slightly contaminated with phenol. This was filtered off, dissolved in hot methyl alcohol, and precipitated with ether. Fairly pure hydrochloride was then obtained in good yield. (The recorded yields of individual hydrochlorides refer to material obtained at this stage.) Further purification, when necessary, was effected by recrystallisation from methyl alcohol or methyl alcohol–ether. The base was liberated by treatment of an aqueous solution of the hydrochloride with dilute ammonia, followed by crystallisation from benzene, light petroleum, or a mixture of the two.

5-*Methylaminoacridine hydrochloride* was obtained in 87% yield, m. p. *ca.* 300°; crystallisation from methyl alcohol gave yellow needles, m. p. 302—303° (decomp.) (Found: Cl, 14·8. $C_{14}H_{13}N_2Cl$ requires Cl, 14·5%). The base, crystallised from benzene, had m. p. 170—171° (Found: C, 80·7; H, 5·8; N, 13·7. Calc. for $C_{14}H_{12}N_2$: C, 80·7; H, 5·8; N, 13·5%). Albert and Ritchie (*loc. cit.*) record 173—174° (sealed tube).

5-*Ethylaminoacridine hydrochloride* (crude yield 89%) was obtained as a yellow, microcrystalline powder, m. p. 283—284° (decomp.) in 76% yield on crystallisation from methyl alcohol–ether (Found: Cl, 13·2. $C_{15}H_{15}N_2Cl$ requires Cl, 13·7%). The free base crystallised from benzene as yellow needles, m. p. 126° (Found: C, 81·0; H, 6·3; N, 12·9. Calc. for $C_{15}H_{14}N_2$: C, 81·1; H, 6·35; N, 12·6%). D.R.-P. 364,032 gives m. p. 129°.

5-iso*Propylaminoacridine hydrochloride,* crude m. p. 295° (82% yield), gave the pure compound as yellow prisms, m. p. 306° (decomp.), on crystallisation from methyl alcohol–ether (Found: Cl, 13·0. $C_{16}H_{17}N_2Cl$ requires Cl, 13·0%). The free *base* crystallised from benzene–light petroleum as large yellow prisms or flat plates, m. p. 119° (Found: C, 81·3; H, 6·8; N, 12·0. $C_{16}H_{16}N_2$ requires C, 81·3; H, 6·8; N, 11·9%).

5-n-*Propylaminoacridine hydrochloride,* crude m. p. 247—248° (78% yield), gave the pure compound, m. p. 249° (decomp.), on crystallisation from methyl alcohol (Found: Cl, 13·7). The free *base* did not solidify spontaneously, but was obtained as a yellow solid, m. p. 98—99°, by extraction of the oil with ether, evaporation of the dried extract, and refrigeration of the residue; large yellow prisms, m. p. 99°, were obtained from benzene–light petroleum (Found: C, 81·1; H, 7·1; N, 11·6%).

5-iso*Butylaminoacridine hydrochloride,* crude m. p. 266—268° (80% yield), on crystallisation from methyl alcohol gave the pure compound, m. p. 269—271°, in 71% yield (Found: Cl, 12·3. $C_{17}H_{19}N_2Cl$ requires Cl, 12·4%). The *base* crystallised from benzene–light petroleum as small, yellow prisms, m. p. 144—145° (Found: C, 81·1; H, 7·2; N, 11·6. $C_{17}H_{18}N_2$ requires C, 81·6; H, 7·25; N, 11·2%). 5-*n*-Butylaminoacridine hydrochloride, crude m. p. 189° (79% yield), raised to 190° by recrystallisation from methyl alcohol–ether (Found: Cl 12·4%). Albert, Goldacre, and Heymann (*loc. cit.*) record a lower yield of this compound, m. p. 189—190°, by reaction of 5-chloroacridine with *n*-butylamine. The free base crystallised from benzene as yellow cubes, m. p. 104—104·5° (Found: C, 81·8; H, 7·25; N, 10·9%). Albert, Goldacre, and Heymann record m. p. 100—102°.

(b) 5-*Dimethylaminoacridine.* The reaction conditions were modified in that special precautions were taken to dry the reactants, and the reaction time was increased to 9 hours. Direct purification of the hydrochloride obtained on pouring the reaction mixture into ether was not attempted owing to its ready hydrolysis; instead, it was dissolved in water, filtered from insoluble material, and treated with dilute ammonia. The liberated base was extracted with light petroleum (b. p. 40—60°), the extract yielding a syrup from which 5-*dimethylaminoacridine* was obtained as orange crystals, m. p. 59—61° (46% yield). Crystallisation from light petroleum gave very large, orange-yellow prisms, m. p. 61—61·5° (Found: C, 80·4; H, 6·4; N, 12·6. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·35; N, 12·6%). Albert and Ritchie (*loc. cit.*) do not record the properties of the base, which they did not obtain crystalline. The hydrochloride, obtained by treatment of an ethereal solution of the base with an equivalent of alcoholic hydrogen chloride, crystallised from absolute alcohol as fibrous needles, m. p. 267—268° (decomp.) (Found: Cl, 14·2. Calc. for $C_{15}H_{15}N_2Cl$: Cl, 13·7%). Albert and Ritchie record m. p. *ca.* 275° (decomp.).

Method II. Interaction of 5-*Chloroacridine and Amine.*—(a) 5-*Arylaminoacridines.* 5-Chloroacridine (5 g.) in phenol (20 g.) was heated with an equimolecular quantity of the appropriate free base for one hour at 120°. The crude material obtained by pouring the mixture into ether gave the required hydrochloride in 80—90% yield on crystallisation from ethyl or methyl alcohol–ether. A small rise in m. p. was generally produced by further crystallisation from alcohol alone or, with better recovery, alcohol–acetone. The recorded m. p.'s were obtained after preheating to *ca.* 200°.

The free bases were best obtained by treatment of a hot alcoholic solution of the hydrochloride with concentrated aqueous ammonia. The base was dissolved by heating the solution to boiling, and sufficient water was then added to cause crystallisation of the base on cooling. Purification was effected by crystallisation from aqueous alcohol.

5-*Phenylaminoacridine hydrochloride* was obtained as yellow prisms, m. p. 305—307° (decomp.) (Found: Cl, 11·9. $C_{19}H_{15}N_2Cl$ requires Cl, 11·6%). The free base had m. p. 224°, in agreement with Albert and Ritchie's m. p. (*loc. cit.*) (Found: C, 83·9; H, 5·4; N, 11·0. Calc. for $C_{19}H_{14}N_2$: C, 84·3; H, 5·2; N, 10·4%).

5-o-*Tolylaminoacridine hydrochloride* was obtained as a yellow microcrystalline powder, m. p. 292—293° (Found: Cl, 11·2. $C_{20}H_{17}N_2Cl$ requires Cl, 11·1%). The free *base,* m. p. 170°, formed small, orange needles (Found: C, 84·6; H, 5·7; N, 9·9. $C_{20}H_{16}N_2$ requires C, 84·5; H, 5·7; N, 9·9%). 5-m-*Tolylaminoacridine hydrochloride,* m. p. 287°, crystallised as orange prisms (Found: Cl, 10·9. $C_{20}H_{17}N_2Cl$ requires Cl, 11·1%). The free *base* crystallised from aqueous alcohol as orange-yellow platelets containing solvent of crystallisation and melting, when heated slowly, at 157°. When the solvent was removed by gentle heating in a vacuum, the colour changed to orange-red, the m. p. remaining at 157°. An orange-red form of slightly lower m. p. was obtained on crystallisation from benzene–light petroleum (Found: C, 83·8; H, 5·9; N, 9·9%). 5-p-*Tolylaminoacridine hydrochloride,* m. p. 285—287°, formed yellow fibrous needles (Found: Cl, 11·2%). The free *base* crystallised as orange-yellow, monoclinic prisms, m. p. 174° (Found: C, 84·5; H, 5·65; N, 9·6%).

5-o-*Anisylaminoacridine hydrochloride,* m. p. 272—274°, formed orange-yellow, fibrous needles (Found: Cl, 11·2. $C_{20}H_{17}ON_2Cl$ requires Cl, 10·5%). The *base,* m. p. 169—170°, crystallised as orange-yellow platelets (Found: C, 80·1; H, 5·4; N, 9·3. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·4; N, 9·3%). 5-p-*Anisylaminoacridine hydrochloride,* m. p. 274°, was obtained as orange-red prisms (Found: Cl, 10·1%), and the *base,* m. p. 151°, as a voluminous mass of small orange crystals (Found: C, 80·2; H, 5·5; N, 9·4%).

5-o-*Phenetylaminoacridine hydrochloride,* m. p. 255—256°, crystallised as very large, red prisms (Found: Cl, 10·2. $C_{21}H_{19}ON_2Cl$ requires Cl, 10·1%), and the *base,* m. p. 143°, as yellow needles (Found: C, 80·3; H, 6·3; N, 8·8. $C_{21}H_{18}ON_2$ requires C, 80·2; H, 5·8; N, 8·9%).

5-*Diethylaminoalkylaminoacridines.* (*i*) β-Diethylaminoethylamine, prepared by the method of Magidson and Grigorowsky (*Ber.,* 1936, **69**, 396), and 5-chloroacridine were treated as described for the aromatic series, except that a reflux condenser was provided. When the product was poured into ether, the dihydrochloride separated. This was filtered off, dissolved in absolute alcohol, and precipitated with absolute ether, giving the crude dihydrochloride, m. p. 244° (49% yield). Doubtless, treatment of the ethereal filtrate with hydrogen chloride would have yielded additional material, as occurred with γ-diethylaminopropylaminoacridine (see below). The pure 5-(*β-diethylaminoethylamino*)-*acridine dihydrochloride* crystallised from alcohol as yellow prisms, m. p. 249° (Found: Cl, 19·8. $C_{19}H_{25}N_3Cl_2$ requires

Cl, 19·9%). The *base* separated as an oil, which was extracted with light petroleum. The residue left on evaporation of the solvent solidified on prolonged refrigeration, yielding, on crystallisation from light petroleum, the pure base, m. p. 76—76·5°, as yellow prisms (Found : C, 77·9; H, 8·0; N, 13·7. $C_{19}H_{23}N_3$ requires C, 77·8; H, 7·9; N, 14·3%).

(ii) γ-Diethylamino-*n*-propylamine was prepared as above, trimethylene bromide being used in place of ethylene dibromide, and the reaction with chloro-acridine was carried out as before. The product obtained on pouring into ether was contaminated with diethylaminopropylamine hydrochloride, and was purified by conversion into base, evaporation in a vacuum, and reconversion into hydrochloride. Fairly pure salt, m. p. 226—228°, was obtained in 30% yield by crystallisation of the product from alcohol–acetone. A further quantity (18% yield) of similar purity was obtained by addition of alcoholic hydrogen chloride to the ethereal filtrate, and similar crystallisation of the precipitate. Further recrystallisation from alcohol–acetone gave pure 5-(*γ-diethylamino*-n-*propylamino*)*acridine dihydrochloride* as fine yellow needles, m. p. 232° (decomp.) after preheating to 210°; this was apparently a *monohydrate*, though no water was lost on heating at 180° in a vacuum (Found : C, 60·6; H, 7·3; N, 10·8; Cl, 17·9. $C_{20}H_{27}N_3Cl_2,H_2O$ requires C, 60·3; H, 7·3; N, 10·5; Cl, 17·8%). The base could not be obtained crystalline, but a *dipicrate*, prepared in hot alcoholic solution, crystallised from acetone as orange-yellow platelets, m. p. 198—199° (Found : C, 50·0; H, 4·0; N, 16·7. $C_{32}H_{31}O_{14}N_9$ requires C, 50·2; H, 4·1; N, 16·5%).

(c) *Miscellaneous 5-Aminoacridines.*—*5-β-Hydroxyethylaminoacridine.* The preparation was carried out as described for the aromatic series, except that the base was prepared from a hot aqueous solution of the hydrochloride. The hydrochloride was obtained in 80% yield, m. p. 245° (decomp.), giving voluminous yellow crystals of the same m. p. on recrystallisation from methyl alcohol. The base crystallised from ethyl alcohol as yellow needles, m. p. 205—206°. D.R.-P. 360,421 gives m. p. 206°.

5-iso*Amylaminoacridine.* 5-Chloroacridine (6 g.) and *iso*amylamine (2·5 g.) were heated under reflux (external temp. 125°) for 2 hours in amyl alcohol (35 c.c.). The product was cooled, poured into ether, and worked up in the usual way. The *hydrochloride*, obtained in 79% yield, m. p. 185—186°, crystallised from alcohol as a yellow, microcrystalline powder, m. p. 188—189° (Found : Cl, 12·4. $C_{18}H_{21}N_2Cl$ requires Cl, 12·1%). The *base* crystallised from benzene–light petroleum as yellow prisms, m. p. 118—118·5° (Found : C, 81·7; H, 7·5; N, 11·0. $C_{18}H_{20}N_2$ requires C, 81·8; H, 7·6; N, 10·6%).

5-*Diethylaminoacridine.* 5-Chloroacridine (5 g.) and dry diethylamine (8 c.c.) were dissolved in dry phenol (20 g.) and heated for 15 hours at 120° in a sealed tube. A mixture of diethylaminoacridine and diethylamine hydrochlorides was obtained by pouring the homogeneous liquid product into ether and precipitation with gaseous hydrogen chloride. The product was converted into the base and extracted with light petroleum, the dried extract yielding on evaporation a viscous oil, from which the remaining diethylamine was removed in a vacuum. The residue was treated in ethereal solution with hydrogen chloride, giving crude diethylaminoacridine hydrochloride, m. p. 176—178° (3·5 g.; 52% yield). Further purification, best effected through the base, yielded the *hydrochloride* as orange needles, m. p. 185—186° (Found : Cl, 12·6. $C_{17}H_{19}N_2Cl$ requires Cl, 12·4%). The free *base*, prepared from the pure hydrochloride, crystallised from light petroleum (b. p. 40—60°) as very large, orange-yellow prisms, m. p. 62—62·5° (Found : C, 81·8; H, 7·3; N, 11·2. $C_{17}H_{18}N_2$ requires C, 81·6; H, 7·3; N, 11·2%).

5-*Carboxymethylaminoacridine.* Glycine (2 g.) was added to a solution of 5-chloroacridine (5 g.) in phenol (20 g.), and the suspension stirred at 120—125° (bath temp.) for 2 hours. The product obtained by pouring into ether was not soluble in water. It was triturated with dilute ammonia until free from chloride, then washed with alcohol, giving fairly pure carboxymethylaminoacridine as a yellow solid, m. p. 236—238° (decomp.; efferv.), in 65% yield. It is insoluble in water and in the ordinary organic solvents, including pyridine. It dissolves in 400 parts of hot glacial acetic acid, but the substance separating in almost quantitative yield on cooling is the *acetate* (Found : C, 65·3; H, 5·2; N, 9·2. $C_{15}H_{12}O_2N_2,C_2H_4O_2$ requires C, 65·4; H, 5·2; N, 9·0%); this melts at 240° (efferv.), presumably after loss of acetic acid.

The *sodium* salt was prepared by trituration of carboxymethylaminoacridine with an equivalent of sodium hydroxide in absolute alcohol. Addition of ether led to slow crystallisation of the salt, which had no definite m. p. (Found : N, 9·8; Na, 8·0. $C_{15}H_{11}O_2N_2Na$ requires N, 10·2; Na, 8·4%). It is readily soluble in water, but rapid hydrolysis occurs, leading to almost immediate quantitative deposition of the free base. This fact was utilised to prepare a specimen of the *base* (Found : C, 70·7; H, 4·9; N, 11·4. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8; N, 11·1%). Pure *hydrochloride* was obtained by dissolving the pure base or its acetate in alcoholic hydrogen chloride, followed by precipitation with ether (Found : N, 9·2; Cl, 11·6. $C_{15}H_{13}O_2N_2Cl$ requires N, 9·7; Cl, 12·3%). Heated rapidly, this compound melted with effervescence at 196° after some sintering at 190°. Slow heating raised the m. p. to 220°, presumably owing to loss of hydrogen chloride. The hydrochloride is readily soluble in water, but the solution is unstable, separation of the base being perceptible in 2 hours and almost complete in 15 hours.

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