109. *Acridine Derivatives. Part II.*

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Further 5-substituted 3-amino-7-alkoxyacridines have been synthesised with the object of ascertaining their antiseptic activity.

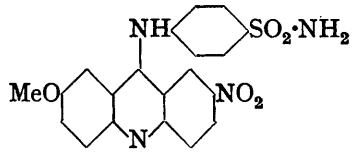
Linnell *et al.* (*Brit. J. Exp. Path.*, 1938, **19**, 41) have found the aminoacridines to be good antiseptics.

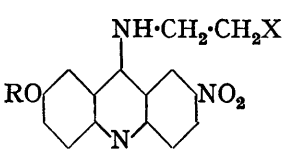
In view of the fact that the sulphonamide group in certain substances possesses excellent bacteriostatic and bactericidal properties, we have synthesised the *substance* (I) by the method described in Part I (J., 1938, 304). The related amine obtained by reduction was acetylated.

The *substance* (II; X = OH, R = Me or Et), synthesised in an analogous manner, has

been converted into the related *chloro*-compound (II, X = Cl), and this condensed with diethylamine and with piperidine. The *products* have been reduced to the corresponding *amino*-compounds and in some cases the amine was acetylated.

The bactericidal properties of these compounds are under investigation.

(I.) 

 (II.)

Experimental.

3-Nitro-5-p-amidosulphonylanilino-7-methoxyacridine (I).—A mixture of 5-chloro-3-nitro-7-methoxyacridine (3·0 g.), *p*-aminobenzenesulphonamide (1·79 g.), and amyl alcohol (20 c.c.) was heated at 110—115° for 2 hours, an orange-coloured hydrochloride separating. After cooling, the mixture was diluted with light petroleum, and the precipitate collected and decomposed with aqueous ammonia. The liberated *base* (I) crystallised from ethyl alcohol–chloroform (2 : 1) in bright scarlet plates, m. p. 298—300° (decomp.); after drying at 100—110° for 1 hour, at 150—160° for 2 hours, and at 190—200° for 2 hours, these had m. p. 304° (decomp.) (Found: N, 12·8; S, 7·2. $C_{20}H_{16}O_5N_4S$ requires N, 13·2; S, 7·5%).

Reduction. The foregoing nitro-compound (1·0 g.) in acetic acid (40 c.c.) was slowly added with stirring to the anhydrous stannous chloride reagent (30 c.c.; Albert and Linnell, J., 1936, 1617). The mixture was left for 12 hours at 0°, and the precipitated tin double compound then collected and washed with acetic acid. An aqueous solution of the double compound was basified and extracted with ethyl acetate. The base recovered from the ethyl acetate layer crystallised from dilute alcohol in yellow plates (0·3 g.), m. p. 263—265° (decomp.). A slightly better yield (0·4 g.) of the amine was obtained by reducing the nitro-compound (1·0 g.), suspended in alcohol (100 c.c.), with hydrated ferrous sulphate (7·0 g.) in water (18 c.c.) and aqueous ammonia (40 c.c.). The *hydrochloride* crystallised in dark red plates when an alcoholic solution of the base was heated with concentrated hydrochloric acid; recrystallised from water and dried for 9 hours in a high vacuum at 150—160°, it had m. p. 315° (decomp.) (Found: N, 12·3; HCl, 16·0. $C_{20}H_{18}O_3N_4S,2HCl$ requires N, 12·0; HCl, 15·6%). The *acetyl* derivative, prepared by means of warm acetic anhydride and acetic acid, crystallised from dilute alcohol in yellow rectangular prisms, m. p. 185° (Found for material dried at 150—160° in a high vacuum for 6 hours: N, 12·8. $C_{22}H_{20}O_4N_4S$ requires N, 13·05%).

3-Nitro-5-β-hydroxyethylamino-7-methoxyacridine (II; R = Me, X = OH), obtained from 5-chloro-3-nitro-7-methoxyacridine (4·7 g.) and β-hydroxyethylamine (2·0 g.) in amyl alcohol (20 c.c.) (120°, 2½ hours), crystallised from alcohol in scarlet needles, m. p. 237° (decomp.) (Found for material dried at 190° in a high vacuum for 10 hours: N, 13·0. $C_{16}H_{15}O_4N_3$ requires N, 13·4%). The corresponding *-7-ethoxyacridine* formed hair-like, curved, reddish needles, m. p. 226° (decomp.) (Found in material dried at 190° for 8 hours: N, 12·6. $C_{17}H_{17}O_4N_3$ requires N, 12·8%).

3-Nitro-5-β-chloroethylamino-7-methoxyacridine (II; R = Me, X = Cl).—The hydroxy-compound (1·0 g.) was treated with thionyl chloride (7 c.c.), and the mixture warmed on the steam-bath for 45 minutes and cooled. After filtration and evaporation, the residue was washed with dry light petroleum, left in a vacuum over sodium hydroxide for 48 hours, suspended in water, and stirred with aqueous ammonia for ½ hour. Ethyl acetate extracted the *chloro*-compound, which crystallised from benzene in stout red needles, m. p. 191° (Found in material dried at 150—155° for 6 hours: N, 12·3; Cl, 10·7. $C_{16}H_{14}O_3N_3Cl$ requires N, 12·7; Cl, 10·7%).

3-Nitro-5-β-chloroethylamino-7-ethoxyacridine crystallised from benzene in bunches of reddish needles, m. p. 176° (decomp.) (Found in material dried at 130—140° in a vacuum for 8 hours: N, 12·2. $C_{17}H_{16}O_3N_3Cl$ requires N, 12·2%).

3-Nitro-5-β-piperidinoethylamino-7-methoxyacridine (II; R = Me, X = NC_5H_{10}), prepared from the hydrochloride of 3-nitro-5-β-chloroethylamino-7-methoxyacridine (2·7 g.), piperidine (2·1 g.), and amyl alcohol (4 c.c.) by the general method (100°, 4 hours), crystallised from acetone in ruby-red hexagonal prisms, m. p. 171° (decomp.) (Found in material dried at 130—150° in a high vacuum for 8 hours: C, 66·3; H, 6·3; N, 14·7. $C_{21}H_{24}O_3N_4$ requires C, 66·4; H, 6·6; N, 15·0%).

3-*Nitro*-5-β-*piperidinoethylamino*-7-*ethoxyacridine* crystallised from alcohol in hair-like needles, m. p. 221° (decomp.) (Found in material dried at 180—190° in a vacuum for 6 hours: N, 14·1. $C_{22}H_{26}O_3N_4$ requires N, 14·2%).

3-*Amino*-5-β-*piperidinoethylamino*-7-*methoxyacridine*, prepared by reduction of the foregoing nitro-compound (1·0 g.) in acetic acid (40 c.c.) by the stannous chloride reagent (30 c.c.) at 0°, crystallised from ethyl acetate and recrystallised from 50% alcohol, formed bright yellow, rectangular plates, m. p. 170° (decomp.) (Found in material dried at 130—140° in a high vacuum for 9 hours: N, 16·0. $C_{21}H_{26}ON_4$ requires N, 16·0%). The *acetyl* derivative crystallised from 50% alcohol in golden-yellow plates, m. p. 206° (Found in material dried at 130—160° for 11 hours: N, 14·6. $C_{23}H_{28}O_2N_4$ requires N, 14·3%).

3-*Amino*-5-β-*piperidinoethylamino*-7-*ethoxyacridine* crystallised from 40% alcohol in light brown prisms, m. p. 180° (Found in material dried in a vacuum at 60—70° for 1 hour, at 110° for 2 hours, and at 130—140° for 4 hours: N, 15·6. $C_{22}H_{28}ON_4$ requires N, 15·4%).

3-*Nitro*-5-β-*diethylaminoethylamino*-7-*methoxyacridine* (II; R = Me, X = NEt_2), prepared in a similar manner to the piperidino-compound, crystallised from 90% alcohol in rectangular plates, m. p. 155° (decomp.) (Found in material dried in a high vacuum at 110—140° for 8 hours: N, 15·1. $C_{20}H_{24}O_3N_4$ requires N, 15·2%).

3-*Amino*-5-β-*diethylaminoethylamino*-7-*methoxyacridine*, crystallised five times from 50% alcohol and dried at 100° for 6 hours, had m. p. 128—134° (decomp.) (Found: N, 15·8. $C_{20}H_{26}ON_4$ requires N, 16·5%).

3-*Nitro*-5-p-*anisidino*-7-*ethoxyacridine*.—The condensation of 5-chloro-3-nitro-7-ethoxyacridine (3·03 g.) (Magidson and Grigorowsky, *Ber.*, 1933, **66**, 870) and *p*-anisidine (1·23 g.) in amyl alcohol (20 c.c.) at 110—115° for 3 hours furnished the *hydrochloride*, m. p. 315° (decomp.) (Found in material dried in a vacuum at 150—160° for 5 hours: N, 9·6; HCl, 8·7. $C_{22}H_{19}O_4N_3$,HCl requires N, 9·9; HCl, 8·6%), of the above substance. The base, liberated by alcoholic ammonia, crystallised from ethyl alcohol in ruby-red needles, m. p. 185° (decomp.).

3-*Amino*-5-p-*anisidino*-7-*ethoxyacridine* crystallised from 50% alcohol in bright yellow, stout needles, m. p. 168° (after drying) (Found in material dried in a vacuum at 60° for 2 hours, then at 105° for 8 hours: N, 12·0. $C_{22}H_{21}O_2N_3$ requires N, 11·7%). The *acetyl* derivative crystallised from 80% alcohol in light brown, thick rods, m. p. 257° (Found in material dried in a vacuum at 100° for 1 hour, at 150° for 6 hours, and at 200° for 2 hours: N, 10·3. $C_{24}H_{23}O_3N_3$ requires N, 10·5%).

3-*Nitro*-5-n-*butylamino*-7-*ethoxyacridine*.—A mixture of 5-chloro-3-nitro-7-ethoxyacridine (1·01 g.), *n*-butylamine (0·65 g.), and amyl alcohol (1·5 c.c.) was heated at 100° for 5 hours in a sealed tube. The product was diluted with light petroleum, and the precipitate (0·9 g.) collected and heated with alcoholic ammonia. The alcoholic solution was filtered hot; on dilution it furnished an orange-red precipitate, which crystallised from 80% alcohol in red stout needles. The *hydrochloride* was prepared in alcoholic solution with concentrated hydrochloric acid; it separated on standing and crystallised from 50% alcohol in yellow needles, m. p. 265° (decomp.) (Found in material dried in a vacuum at 100° for 2 hours and at 150—160° for 7 hours: N, 10·7; HCl, 9·5. $C_{19}H_{21}O_3N_3$,HCl requires N, 11·2; HCl, 9·7%).

3-Amino-5-*n*-butylamino-7-ethoxyacridine was prepared from the foregoing nitro-compound by reduction with the stannous chloride reagent; difficulty was experienced in crystallising it. The *acetyl* derivative crystallised from dilute alcohol in hexagonal yellowish prisms, m. p. 193° (decomp.) (Found in material dried in a vacuum at 100° for 2 hours and at 150° for 12 hours: N, 12·0. $C_{21}H_{25}O_2N_3$ requires N, 12·0%).

The analyses recorded were done by the micro-method.

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