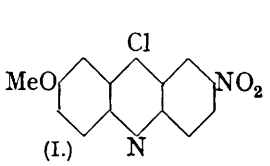
60. *Acridine Derivatives. Part I.*

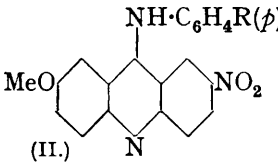
By Moti Lal Dhar, Kartar S. Narang, and Jnanendra N. Ray.

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

In view of the fact that the diaminoacridines possess bactericidal properties, it was thought interesting to synthesise acridines with an anilino- or substituted anilino-group in position 5 and an amino-group in one of the aromatic rings. For this purpose, 2-chloro-5-nitrobenzoic acid was condensed with *p*-anisidine and the 4-nitro-4'-methoxydiphenylamine-2-carboxylic acid thus formed was cyclised with phosphoryl chloride to 5-chloro-3-nitro-7-methoxyacridine (I). Magidson and Grigorowsky (*Ber.*, 1936, **69**, 404) prepared



(I.)



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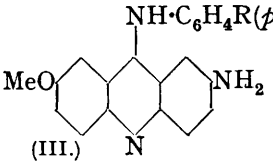

(III.)

the diphenylaminecarboxylic acid in 33% yield, but under our conditions a yield of 60% is obtainable. We have also improved the preparation of the related chloroacridine. The above authors prepared 3-nitro-5-γ-diethylamino-β-hydroxypropylamino-7-methoxyacridine *via* the phenoxy-compound, but we found no difficulty in directly condensing (I) with *p*-anisidine, *p*-aminoacetanilide, *p*-phenetidine, *n*-butylamine, and piperidine in amyl-alcoholic solution. The products, of the type (II), were smoothly reduced to the corresponding amines (III) in most cases by the stannous chloride reagent described by Albert and Linnell (J., 1936, 1617).

The bactericidal properties (against *streptococci*) of these compounds are under examination.

Experimental.

4-Nitro-4'-methoxydiphenylamine-2-carboxylic Acid.—A mixture of *p*-anisidine (6 g.) and 2-chloro-5-nitrobenzoic acid (5 g.) was stirred at 170—180° for 6—7 minutes and the dark mass thus obtained was triturated with dilute hydrochloric acid. The insoluble material crystallised from glacial acetic acid in bright yellow, parallelepiped plates (4·2 g.), m. p. 225° (Magidson and Grigorowsky give m. p. 216—220°) (Found: N, 9·7. Calc.: N, 9·5%).

5-Chloro-3-nitro-7-methoxyacridine.—The foregoing acid (1·0 g.) was heated with phosphoryl chloride (6 c.c.) at 110—115° for 45 minutes. The product, when cold, was washed with ligroin, and the residue treated with ice-cold 10% aqueous ammonia. The yellow substance was collected and stirred with cold acetone (12 c.c.); the insoluble portion crystallised from toluene in yellow plates (0·75 g.), m. p. 223° (Magidson and Grigorowsky give m. p. 220—221°) (Found: C, 58·4; H, 3·2; N, 9·9. Calc.: C, 58·2; H, 3·1; N, 9·7%).

Condensation of 5-Chloro-3-nitro-7-methoxyacridine with p-*Anisidine.*—A mixture of the acridine derivative (0·58 g.), *p*-anisidine (0·25 g.), and amyl alcohol (2·5 c.c.) was heated at 115—120° 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 *3-nitro-5-p-anisidino-7-methoxyacridine*, isolated by means of ethyl acetate, crystallised from alcohol in bright scarlet needles, m. p. 212° (Found: N, 11·0. $C_{21}H_{17}O_4N_3$ requires N, 11·2%).

Reduction. The hydrochloride of the foregoing substance (1·0 g.) was gradually stirred into

the anhydrous stannous chloride reagent (30 c.c.; Albert and Linnell, *loc. cit.*, p. 1617). The mixture was left for 12 hours at 0°, and the precipitated tin double compound then collected and washed with acetic acid. Its carmine-red aqueous solution was basified, and extracted with chloroform. The well-washed chloroform solution was extracted with 1·5% hydrochloric acid (75 c.c.); the acid extract deposited orange-red needles of the amine hydrochloride, which could be recrystallised from water. It decomposed from 205° onwards. The *3-amino-5-p-anisidino-7-methoxyacridine* liberated from the hydrochloride by aqueous ammonia crystallised from 5% aqueous alcohol in bright yellow needles, m. p. 182° (decomp.), which tenaciously retained water of crystallisation (Found for material dried at 140—150° in a high vacuum: N, 11·8. $C_{21}H_{19}O_2N_3$ requires N, 12·1%). Its *acetyl* derivative, prepared by means of warm acetic anhydride and acetic acid, crystallised from dilute alcohol in yellowish-orange needles, m. p. 258° (decomp.) (Found for material dried at 200° in a high vacuum for 2 hours: N, 10·9. $C_{23}H_{21}O_3N_3$ requires N, 10·85%).

3-Nitro-5-p-phenetidino-7-methoxyacridine.—The condensation of (I) (1·0 g.) and *p*-phenetidine (0·47 g.) in amyl alcohol (10 c.c.) at 120° for 3 hours furnished the *hydrochloride* of the above substance (1·3 g.), m. p. 281° (decomp.) (Found: N, 9·5. $C_{22}H_{19}O_4N_3$,HCl requires N, 9·9%). The *base*, liberated with alcoholic ammonia, crystallised from dilute alcohol in thick plates, m. p. 181°, containing solvent of crystallisation (Found for material dried at 140—150° in a high vacuum for 6 hours: N, 10·8. $C_{22}H_{19}O_4N_3$ requires N, 10·7%).

3-Amino-5-p-phenetidino-7-methoxyacridine.—The foregoing substance was reduced with the stannous chloride reagent. The *hydrochloride* of the base crystallised from 5% alcohol in sheaves of slender orange needles, m. p. (after drying in a high vacuum at 140°) 280° (decomp.) (Found: N, 9·5; HCl, 16·8. $C_{22}H_{21}O_2N_3$,2HCl requires N, 9·7; HCl, 16·9%). The *acetyl* derivative of the base crystallised from 50% alcohol in light orange needles, m. p. 235—237° (Found for material dried in a vacuum at 200° for 2 hours: N, 10·7. $C_{24}H_{23}O_3N_3$ requires N, 10·5%).

3-Nitro-5-piperidino-7-methoxyacridine was prepared in the manner already described. The scarlet-red solid formed was boiled with toluene (5 c.c.), and the residue crystallised from hot benzene; m. p. 220° (decomp.) (Found: N, 12·2. $C_{19}H_{19}O_3N_3$ requires N, 12·5%). The substance could not be reduced without decomposition.

3-Nitro-5-p-acetamidoanilino-7-methoxyacridine (II, R = NH·CO·CH_3).—*p*-Aminoacetanilide (0·26 g.) and (I) (0·5 g.) in amyl alcohol (10 c.c.) furnished the hydrochloride (0·6 g.), m. p. 287° (decomp.), after 4 hours' heating at 120°. The *base* crystallised from alcohol in dark red, rectangular plates, m. p. 270° (decomp.) (Found for material dried at 150° in a vacuum for 3 hours: N, 13·7. $C_{22}H_{18}O_4N_4$ requires N, 13·9%).

Reduction. A solution of the foregoing nitro-compound (1·0 g.) in alcohol (100 c.c.) and aqueous ammonia (*d* 0·88, 30 c.c.) was added to a boiling solution of ferrous sulphate (11·0 g.) in water (30 c.c.). After 1½ hours' heating, the solution was filtered, diluted with water (300 c.c.), and acidified with hydrochloric acid; the hydrochloride of *3-amino-5-p-acetamidoanilino-7-methoxyacridine* slowly crystallised in long scarlet-red needles. The base crystallised from 30% alcohol in fine yellow needles, m. p. 279—280° (decomp.) (Found for material dried in a vacuum at 180° for 2 hours: N, 15·1. $C_{22}H_{20}O_2N_4$ requires N, 15·05%).

3-Nitro-5-butylamino-7-methoxyacridine.—A mixture of (I) (2·0 g.), *n*-butylamine (1·2 g.), and amyl alcohol (3 c.c.) was heated at 100° for 3 hours in a sealed tube. The product was diluted with light petroleum and the precipitate (2·1 g.) was collected and heated with alcoholic ammonia. The alcoholic solution, filtered hot, furnished on dilution an orange-red precipitate, which crystallised from 80% alcohol in long plates, m. p. 105°. The substance could not be satisfactorily dried without decomposition. The *hydrochloride* was prepared in alcoholic solution with concentrated hydrochloric acid and separated on standing; m. p. 242° (Found for material dried at 160—170° for 3 hours: N, 11·4; HCl, 9·75. $C_{18}H_{19}O_3N_3$,HCl requires N, 11·6; HCl, 10·1%).

The above compound was smoothly reduced by the "stannous chloride" reagent, but difficulty was experienced in crystallising the free base. It was purified *via* its hydrochloride, which crystallised readily in stout yellowish-orange prisms, m. p. 282°. The base was acetylated with acetic anhydride and acetic acid; *3-acetamido-5-butylamino-7-methoxyacridine* crystallised from alcohol in yellow plates, m. p. 230° (Found for material dried at 170° for 2 hours: N, 12·6. $C_{20}H_{23}O_2N_3$ requires N, 12·5%).

The analyses recorded were all done by the micro-method.

THE UNIVERSITY, LAHORE. [*Received, December 13th*, 1937.]