

SYNTHESIS OF 8-AMINOQUINOLINES. PART VI*

BY ACHINTYA K. SEN AND U. P. BASU

The preparation of 5-chloro- and 7-chloro-8-aminoquinolines, which are necessary intermediates in the synthesis of antimalarials in the 8-aminoquinoline series, has been described,

The chloroquinolines required for the present work were prepared by the method of Doebner and Miller (*Ber.*, 1881, 14, 2816; 1883, 16, 2404; 1884, 17, 1669) as modified by Utermohlen (*J. Org. Chem.*, 1943, 8, 544) and Bowen *et al.* (*J. Amer. Chem. Soc.*, 1953, 75, 4307). Utermohlen (*loc. cit.*) has described a valuable modification of the Skraup and Doebner-Miller synthesis using *m*-nitrobenzenesulphonic acid as water-soluble acid oxidising agent. Applying the procedure with a slight further modification Spivey and Curd (*J. Chem. Soc.*, 1949, 2656) obtained a maximum yield of 60% of the usual mixed 5- and 7- isomers in the preparation of chloroquinolines from *m*-chloroaniline. In the original procedure of Utermohlen equimolecular amounts of amine and aldehyde were employed and the yields varied between 40 and 60%. It has been recently shown by Bowen *et al.* (*loc. cit.*) that using the ratio of aldehyde to amine as 1.67:1, instead of equimolecular amounts, the yields rose as high as 80%. Following the above modifications the mixture of chloroquinolines has been isolated in the present work in 80% yield.

The mixture was directly nitrated with potassium nitrate and 100% sulphuric acid, without separating the isomeric 5- and 7-chloroquinolines. The less basic 7-chloro-8-nitroquinoline separated out on pouring the reaction mixture from nitration operation into ice-water. The mother-liquor, after removing the 7-chloro-8-nitroquinoline, was basified to yield the corresponding 5-chloro derivative. The position of the nitro group in 7-chloro-8-nitroquinoline was established by its reduction to known 8-aminoquinoline by red phosphorus and hydriodic acid. The structure of 7-chloro-8-aminoquinoline has been further confirmed by converting the aminoquinoline to 7:8-dichloroquinoline through the Gatterman reaction and comparing the product with an authentic sample of 7:8-dichloroquinoline, prepared by the modified Doebner-Miller reaction upon 2:3-dichloroaniline. The structure of 5-chloro-8-nitroquinoline was ascertained from its direct synthesis from 5-chloro-2-nitroaniline. The aminoquinolines were obtained by reduction of the nitro compounds with iron and acetic acid, "Sulfo-mix" (a solution of *m*-nitrobenzenesulphonic acid in sulphuric acid), which was required in the present work, was prepared as described by Utermohlen (*loc. cit.*).

*The present work was completed in 1953 on a project under the auspices of the Council of Scientific and Industrial Research. The publication was delayed due to one of the authors' (A. K. S.) mission to U. S. A.

E X P E R I M E N T A L

5-*δ*-7-Chloroquinaldines.—In an one-litre, 3-necked flask, equipped with a mercury-sealed stirrer, thermometer and a condenser provided with a dropping funnel at the top, were placed 100 c.c. of water and 404 g. of 'sulfo-mix'; *m*-chloroaniline (127.5 g.) was added to the mixture with stirring. The mixture was then heated in an oil-bath to 105° and crotonaldehyde (117 g.) was added with vigorous stirring over a period of 45 minutes while the mixture was held at 105-10° by intermittent heating and cooling. The temperature was then slowly raised to 125° during one hour. The foaming, when became excessive, was controlled by momentarily removing the oil-bath from time to time. The reaction mixture was then cooled, poured into about 1500 g. of ice and basified with a slight excess of caustic soda solution. The crude product was then distilled with steam and about 20 litres of distillate was collected. The oily layer was separated and the aqueous layer was once extracted with ether. The solvent was then removed from the dried (CaCl₂) extract and the residual oil was distilled at ordinary pressure to furnish a slightly yellow oily liquid in 80% yield; b.p. 275-82°.

7-Chloro-8-nitro and 5-Chloro-8-nitroquinaldines.—The above mixture of chloroquinaldines (35.7 g.) was dissolved in a mixture of 15 c.c. of fuming sulphuric acid (60% SO₃) and 100 c.c. of concentrated sulphuric acid. To the stirred and well-cooled mixture potassium nitrate (27 g.) was added during one hour while the temperature was maintained at 0° to -5°. After stirring at that temperature for 3 hours, the mixture was kept overnight at room temperature and poured into 500 g. of crushed ice, stirred well, filtered and the solid was washed thoroughly till free of acid. The crystalline product obtained was recrystallised from rectified spirit to afford 18 g. of pure 7-chloro-8-nitroquinaldine melting at 145-46°. (Found: N, 12.34. C₁₀H₇O₂N₂Cl requires N, 12.58%).

The acid solution after removal of 7-chloro isomer was basified with a slight excess of caustic soda when a solid separated. This was collected, washed and crystallised from rectified spirit to yield 8 g. of 5-chloro-8-nitroquinaldine, m.p. 131-32°. (Found: N, 12.81. C₁₀H₇O₂N₂Cl requires N, 12.58%).

Reduction of 7-Chloro-8-nitroquinaldine with Red Phosphorus and Hydriodic Acid to 8-Aminoquinaldine.—A mixture of 7-chloro-8-nitroquinaldine (5 g.), potassium iodide (6 g.), red phosphorus (4 g.) and constant boiling hydriodic acid (40 c.c.) was heated under reflux. After the initial vigorous reaction had subsided, a further quantity of hydriodic acid was added and the heating under reflux was continued for 5 hours. After the period was over, 10 c.c. of water was added to the mixture, heated to boiling and filtered hot. The cooled solution was then basified with a slight excess of caustic soda, filtered and the solid was washed thoroughly with water and crystallised from ligroin, m.p. 55-56°. The mixed m.p. with an authentic sample was 56°, prepared according to Doebner and Miller (*Ber.*, 1884, 17, 1701), recorded no depression.

5-Chloro-8-nitroquinaldine from 5-Chloro-2-nitroaniline.—In a 100 c.c. bolt headed flask fitted with a short air-condenser, dropping funnel and a thermometer dipping below

the surface of the liquid were placed water (5 c.c.) 'sulfo mix' (20 g.) and 2-nitro-5-chloroacetanilide (7.2 g.). The solution was heated in an oil-bath at 130° for 30 minutes and the mixture was then cooled to 105° and crotonaldehyde (4 g.) was added with vigorous shaking (temperature was maintained at 105-110°) during 20 minutes. When the addition was over, the temperature was gradually raised to 125° and then to 130° and kept at that temperature for half an hour. The mixture was then poured into iced caustic soda solution, filtered, washed thoroughly with water, dried and extracted with ether. Ether was evaporated off and the residue was crystallised from rectified spirit, m.p. 128-30°. The mixed m. p. with a sample, prepared by the nitration procedure described earlier, recorded no depression.

7-Chloro-8-aminoquinaldine.—A mixture of 7-chloro-8-nitroquinaldine (13.3 g.) and 50% acetic acid (120 c.c.) was heated on a steam-bath. Powdered iron (80 mesh, 10 g.) was added in small portions over a period of 1½ hours to the vigorously stirred mixture. The heating was continued for one hour more after the last portion of iron added. The mixture was cooled, made alkaline with aqueous NaOH and the 7-chloro-8-aminoquinaldine was distilled with steam. The oily layer was separated from about 4 litres of the distillate which was collected, and the aqueous portion was extracted once with ether. After distilling off the ether from the dried extract, the residual oil was distilled under reduced pressure, yield 9.5 g., b.p. 170°/5 mm. (Found: N, 14.00. $C_{12}H_9N_2Cl$ requires N, 14.54%).

The *picrate* was prepared by adding an alcoholic solution of picric acid to a solution of 7-chloro-8-aminoquinaldine; the picrate which separated out immediately was collected and recrystallised from rectified spirit in shining yellow crystalline solid, m.p. 197-99°.

7-Chloro-8-acetamidoquinaldine.—7-Chloro-8-aminoquinaldine (0.5 g.) was acetylated by boiling in 5 c.c. of acetic anhydride for about 15 minutes and then poured in ice-water. The supernatant aqueous portion was decanted off and the semi-solid mass was treated with fresh water. The crystalline solid was collected, washed with water and recrystallised from aqueous alcohol, m.p. 142-44°. (Found: N, 11.45. $C_{12}H_{11}ON_2Cl$ requires N, 11.92%).

7:8-Dichloroquinaldine.—(a). A solution of sodium nitrite (3.2 g.) in water (10 c.c.) was added to a solution of 7-chloro-8-aminoquinaldine (8.5 g.) in aqueous HCl (80 c.c. in 60 c.c. water) at 0° to -5°. A suspension of copper-bronze (10 g.) in aqueous HCl (1 c.c. in 10 c.c. water) was added slowly to the solution of the diazotised amine. When no more gas evolved, the mixture was heated on a water-bath for half-an-hour, made strongly alkaline with ammonium hydroxide and was distilled with steam. The solid collected from the distillate was recrystallised from aqueous alcohol, m.p. 70-71°. (Found: N, 6.45. $C_{12}H_7NCl_2$ requires N, 6.60%). The m.p. remained undepressed on admixture with an authentic 7:8-dichloroquinaldine, prepared from 2:3-dichloroaniline as described in (b).

(b). In a wide pyrex test tube, fitted with a condenser and a thermometer dipping below the surface of the mixture, were placed 'sulfo mix' (22.5 g.) and water (5.5 c.c.). 2:3-Dichloroaniline (8.9 g.) was slowly added to the mixture with cooling. The tube

was then gradually heated to 105°, and 6.5 g. of crotonaldehyde was slowly added during 20 minutes with shaking, while the temperature was maintained at 105-10°. After the addition was over the temperature was slowly raised to 130°, kept at that temperature for 10 minutes, poured into ice-water, basified as above and steam-distilled. The solid was collected from the distillate and recrystallised from aqueous alcohol, m.p. 70-71°.

5-Chloro-8-aminoquinaldine.—5-Chloro-8-nitroquinaldine was similarly reduced as its 7-chloro isomer. When the reduction was completed, the mixture was cooled, made alkaline with sodium hydroxide and the aminoquinaldine was distilled with steam. The solid was collected and crystallised from aqueous alcohol, m.p. 92-93°. (Found: N, 14.12. $C_{10}H_8N_2Cl$ requires N, 14.54%).

BENGAL IMMUNITY RESEARCH INSTITUTE,
CALCUTTA.

Received June 15, 1957.

SYNTHESIS OF 8-AMINOQUINOLINES. PART VII

BY ACHINTYA K. SEN AND U. P. BASU

Synthesis of 7-chloro-2-methyl-8-amino-4-(4'-hydroxy-3'-diethylaminomethyl)-anilinoquinaldine has been described.

During the course of a previous investigation on the synthesis of 8-aminoquinoline derivatives, simultaneously substituted at the 4-position by an aminocresol side chain, 7-chloro-8-amino-4-(4'-hydroxy-3'-diethylaminomethyl)-anilinoquinoline was synthesised (Chandran *et al.*, *J. Sci. Ind. Res.*, 1951, 10B, 290). The compound showed signs of promise in the preliminary screening. From the metabolic study of quinine it is known that the drug undergoes oxidation in the system and forms a 2-hydroxy derivative (Mead and Koepfli, *J. Biol. Chem.*, 1944, 154, 104). It was then considered to be of interest to substitute at the 2-position of the quinoline nucleus by a suitable grouping, and to see how the resulting quinoline would behave. Accordingly, a compound, analogous to the above compound but substituted at its 2-position by a methyl group, *i.e.* 7-chloro-2-methyl-8-amino-4-(4'-hydroxy-3'-diethylaminomethyl)-anilinoquinoline, has now been synthesised. The results of its preliminary screening tend to indicate high efficacy.

7-Chloro-4-hydroxyquinaldine required in the present work was first prepared by Price *et al.* (*J. Amer. Chem. Soc.*, 1946, 68, 1256) by the usual Conard-Limpach

* The present work was completed in 1953 on a project under the auspices of the Council of Scientific and Industrial Research. The publication was delayed due to one of the authors' (A. K. S.) mission to U.S.A.