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. $C_{10}H_9N_2Cl$ requires N, 14.54%).

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Received June 15, 1957.

SYNTHESIS OF 8-AMINOQUINOLINES. PART VII

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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.

method. The only isomer obtained in 72% yield was assigned the 7-chloro structure without establishing its constitution. Later work by Spivey and Curd (*J. Chem. Soc.*, 1949, 2656) records the yield of only 35-40% of the mixed 5- and 7-chloro isomeric compounds and they have separated the isomers through their corresponding picrates. It has now been found that the procedure followed by Price *et al.* furnishes a better yield, and contrary to their observation, it has been found that the 5-chloro isomer, which is invariably formed, remains in solution in the crystallisation liquor aqueous alcohol) because of its relatively high solubility. The method described in the experimental part is found to be advantageous in our hands and it affords the desired 7-chloro isomer in a pure form in single crystallisation. A slight modification of the method of conversion of the hydroxy compound to the corresponding chloro compound has also been made in order to eliminate a violet-coloured dye which is also formed. 4:7-Dichloroquinaldine was nitrated in good yield to the corresponding 8-nitro derivative by potassium nitrate and 100% sulphuric acid. The nitro compound was reduced by stannous chloride in concentrated hydrochloric acid to the corresponding 8-amino derivative. In order to prove the position of the amino group, the amino compound was converted into 7-chloro-8-aminoquinaldine by catalytic hydrogenolysis. This was compared as picrate and as acetyl derivative with authentic samples of those derivatives from 7-chloro-8-aminoquinaldine (cf. this *issue*, p. 833). The melting points are identical and the mixed melting point determination of the sample shows no depression. The aminocresol side-chain was attached to the 4-position of the quinoline nucleus according to the method described by Burckhalter *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 1363).

Experimental

7-Chloro-4-hydroxyquinaldine.—A mixture of *m*-chloroaniline (15 g.) and ethyl acetoacetate was mixed and kept under vacuum in a desiccator over calcium chloride until the theoretical amount of water was removed. The oily crotonate was added to boiling diphenyl oxide (260 c.c.). Heating was continued for 40 minutes more after the addition was over. The product separating from cooled diphenyl oxide was collected, washed thoroughly with acetone and dried; yield 13 g. The dried product was dissolved in rectified spirit (290 c.c.); after cooling 300 c.c. of water was added, heated to boiling and filtered hot. After keeping overnight the separated crystals were collected and dried, yield 8 g., m.p. 312-14° (Price *et al.* report m.p. 313-15°).

4:7-Dichloroquinaldine.—A mixture of 7-chloro-4-hydroxyquinaldine (20 g.) and $POCl_3$ (60 c.c.) was heated in an oil-bath under reflux for one hour. About half the quantity of excess of $POCl_3$ was distilled off under reduced pressure and the residual liquid was then poured into aqueous 50% NaOH solution (100 c.c.) to which enough ice was added to prevent the rise of temperature. The dichloro compound was collected, washed thoroughly with water and dried. After recrystallisation from aqueous alcohol, the compound melted at 103-104°; lit. m.p. 103°.

4:7-Dichloro-8-nitroquinaldine.—4:7-Dichloroquinaldine (10 g.) was dissolved in ice-cooled 100% H_2SO_4 (32 c.c.). Dried and powdered potassium nitrate (7.5 g.) was then added to the well-stirred acid mixture during one hour; the temperature was

not allowed to rise above 5° throughout the experiment. After the addition was over, the mixture was stirred at that temperature for 3 hours more and then kept in the refrigerator overnight. The mixture was then poured into ice-water (500 g.). The nitro compound separating was collected, washed thoroughly with water and twice crystallised from rectified spirit, yield 3.5 g., m. p. 120-21°. (Found: N, 10.54. $C_{10}H_6O_2N_2Cl_2$ requires N, 10.90%).

4 : 7-*Dichloro*-8-*aminoquinaldine*.—The preceding compound (5.28 g.) was slowly added to a stirred solution of stannous chloride dihydrate (19 g.), dissolved in HCl (75 c.c., conc.) during an hour, care being taken to keep the temperature below 30°. The mixture was stirred for 2 hours more and then poured into aqueous 50% NaOH (125 c.c.) to which enough ice was added to keep the temperature below 20°. The solid was collected, washed thoroughly with water and recrystallised from rectified spirit in a very light yellow crystalline solid, yield 3.5 g., m.p. 115°. (Found: N, 12.07. $C_{10}H_8N_2Cl_2$ requires N, 12.33%).

7-*Chloro*-8-*aminoquinaldine*.—To a solution of the above 8-aminoquinaldine (7.3 g.) n absolute alcohol (100 c.c.) fused sodium acetate (2.7 g.) and 5% palladium (0.5 g.) on carbon were added. The mixture was hydrogenated at normal pressure; the theoretical amount of hydrogen was taken up in 3 hours. The catalyst was filtered off and washed with two 25 c.c. portions of alcohol. After removal of the solvent the residue was treated with water, basified with a slight excess of aqueous caustic soda solution and extracted with ether. Ether solution was dried with KOH, ether removed and the residue was distilled under reduced preesure; b.p. 200-205°/10 mm. The melting point and mixed melting point determination of the acetyl derivative and of the picrate, prepared according to the method described in the preceding paper (this *issue*, p. 833), recorded no depression.

* 7-*Chloro*-2-*methyl*-8 *amino*-4-(4′-*hydroxy*-3′-*diethylaminomethyl*)-*anilinoquinoline Dihydrochloride*.—A mixture of α-diethylamino-4-acetamido-*o*-cresol (5.5 g.) and HCl conc., 11 c.c.) was heated under reflux for 1 hour. After cooling and adjusting to p_H 4 with 50% caustic soda (aq.), 4 : 7-dichloro-8-aminoquinaldine (5 g.) was added and the mixture was heated under reflux for 5 hours on a water-bath. After keeping overnight, the mixture was triturated with a slight excess of ammonia (conc). The solid product was collected and washed thoroughly with water. The air-dried product was dissolved in 100 c.c. of rectified spirit and HCl (conc., 8 c.c.) was added to the solution; on stirring yellow crystalline hydrochloride of the base crystallised out. This was collected, washed with rectified spirit and finally crystallised from 70% ethyl alcohol, m.p. 258-60°. (Found: N, 11.68. $C_{21}H_{26}ON_4Cl_2HCl$ requires N, 12.21%).

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Received June 15, 1957.

* This compound was investigated by the authors and the results communicated to the Council of Scientific and Industrial Research (India) on 28 Feb., 1953. The compound has also been independently investigated by Coatney and his co-workers (Surevey of Antimalarial Agents: U.S. Public Helth Service Monograph No. 9, Jan. 1953, p. 67).