CCCXCV.—*Benzquinazocolines.*

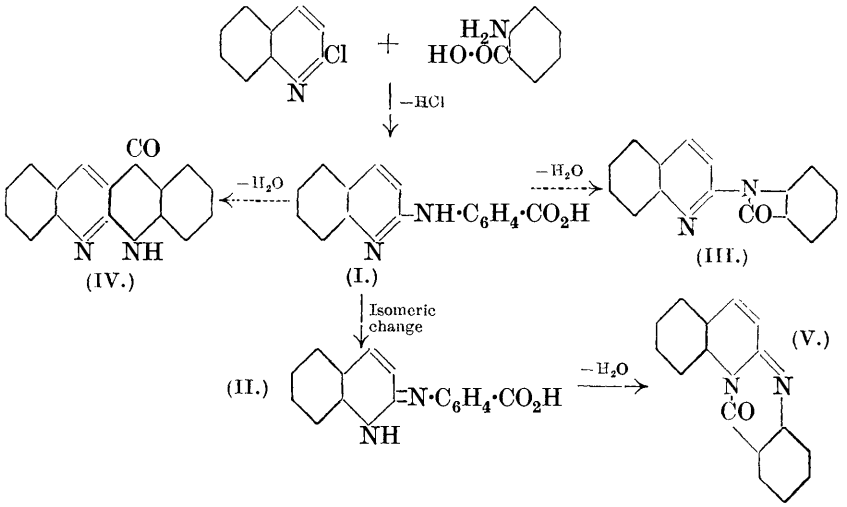
By Prafulla Kumar Bose and Dines Chandra Sen.

The object of the present investigation was to synthesise polynuclear heterocyclic compounds containing the quinazoline and quinoline rings. These substances were expected to possess appreciable therapeutic value, since compounds containing the compo-

nent rings have been known to exhibit pronounced physiological properties.

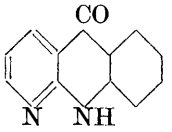
We first sought to condense 2-quinolone and anthranilic acid (or its methyl ester) after the method of Sen and Rây (J., 1926, 646), which has made it possible to fuse a quinazoline residue to a carboline (Asahina, Manske, and Robinson, J., 1927, 1708) and to a quinazoline ring (Aggarwal and Rây, *J. Indian Chem. Soc.*, 1929, **6**, 722); under the conditions described by Aggarwal and Rây, however, we failed to isolate the compound (V). 2-Pyridone and 4-methyl-2-quinolone likewise failed to react with anthranilic acid in presence of phosphorus trichloride. From methyl anthranilate and 2-quinolone, a yellow crystalline *product* (m. p. 226°), which appeared to be (I) or (II), was once isolated in extremely poor yield. The failure of 2-quinolone to condense with anthranilic acid may be due to the fact that the imino-group is directly attached to a benzene nucleus : in the substances that have been condensed by the authors mentioned above (*locc. cit.*), the imino-group is attached to a pyrrole or a benzene ring through a carbonyl group.

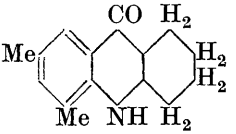
The interaction of 2-chloroquinoline and anthranilic acid, which might produce one or more of the isomerides (III), (IV), and (V), was next investigated. The condensation proceeded smoothly when



the components in equimolecular proportion were heated over a small flame, and the yield was fairly good. 2-Chloropyridine also reacted with anthranilic acid under similar conditions, yielding the quinoquinolone (VI) which Reissert had obtained by decarboxylating the product of interaction of 2-chloronicotinic acid and anthranilic

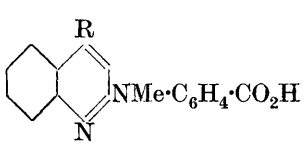
acid (*Ber.*, 1895, **28**, 119). This compound, like dimethyltetrahydroacridone (VII), exhibited a violet-blue fluorescence in very

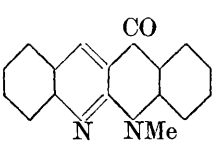
(VI.) 

 (VII.)

dilute acid solution and was not hydrolysed by alcoholic potassium hydroxide. The product obtained from 2-chloroquinoline, on the other hand, did not show any fluorescence in acid solution and was easily hydrolysed by dilute alkali (not by acid) to a *carboxylic acid.* This reaction is difficult to explain by formula (IV), which is analogous to (VI) and (VII). An attempt to synthesise the compound (IV) from 2-chloroquinoline-3-carboxylic acid and aniline was unsuccessful.

An indication that in the condensation of 2-chloroquinoline and anthranilic acid the β-hydrogen atom of the former is not involved under the experimental conditions has been furnished by the action of *N*-methylanthranilic acid upon 2-chloroquinoline and 2-chloro-4-methylquinoline; N-*methyl*-N-*quinolylanthranilic acid* (VIII; R = H) and its *methyl* derivative (VIII; R = Me) respectively were obtained but not a substance of type (IX).

(VIII.) 

 (IX.)

One of the *N*-hydrogen atoms in anthranilic acid therefore appears to be directly or indirectly responsible for ring closure with the carboxyl group. If the hydrogen atom reacts directly with the carboxyl group, the product from 2-chloroquinoline and anthranilic acid would be *N*-2-quinolylanthranil (III). The product could not be compared with an *N*-alkyl- or *N*-aryl-anthranil, since these are unknown, the so-called *N*-methylanthranil of Heller (*Ber.*, 1903, **36**, 4178) being really a mixture (Bamberger, *Ber.*, 1904, **37**, 966): it resembled anthranil in being easily hydrolysable by alkali to a monobasic acid, but differed from it in being unaffected by treatment with ferrous sulphate and ammonia. The acid when heated lost water and reverted to the original compound, the yield being not less than 90%. Hot acetic anhydride produced the same change. Anthranilic acid cannot be converted into anthranil by heat.

Further evidence has been brought forward against the anthranil

structure (III). Since a substituent in quinoline possesses almost identical chemical properties, whether it is in position 2 or 4, it was expected that the condensation product of 4-chloro-2-methylquinoline and anthranilic acid would have the same empirical formula and properties as the compound derived from 2-chloro-4-methylquinoline. As a matter of fact the former reaction gave *N-2'-methyl-4'-quinolylanthranilic acid*, $C_9NH_5Me{\cdot}NH{\cdot}C_6H_4{\cdot}CO_2H$, which partly decomposed when heated, yielding a tarry product. This fact indirectly supports the constitution (V) for the compound obtained from 2-chloroquinoline, which explains the most conspicuous property of the compound and also strengthens the view that under the experimental conditions the β-hydrogen atom does not take part in ring closure.

The condensation product of 2-chloro-4-methylquinoline and anthranilic acid obtained by Ephraim (*Ber.*, 1892, **25**, 2710), to which he gave an anthranil structure, has properties similar to those of the compound derived from 2-chloroquinoline. Hence it should be assigned a similar structure.

Attempts were made to synthesise the acid (I) from 2-chloroquinoline and methyl anthranilate : the product was, however, (V).

The constitution of the acid derived from the compound (V) by hydrolysis remains undecided : it must be either (I) or (II).

Experimental.

2-Chloropyridine was prepared in 62·5% yield by heating *N*-methylpyridone with phosphorus pentachloride (compare Fargher and Furness, J., 1915, **107**, 690). As we were unable to get the reported yield of *N*-methylpyridone by the method of Fargher and Furness, we adopted the following method.

Into a mechanically stirred solution of potassium ferricyanide (200 g.) in 600 c.c. of water, cooled in ice, were dropped solutions of potassium hydroxide (50 g.) in water (50 c.c.) and of pyridine methosulphate prepared by treating 20 g. of pyridine with 32 g. of methyl sulphate in the cold. The mixture was stirred for ½ hour, the potassium ferrocyanide removed, and the filtrate saturated with about 450 g. of potassium hydroxide. The mixture was then cooled, and shaken for ½ hour with 700—800 c.c. of ether. From the ethereal extract, dried over potassium carbonate, *N*-methylpyridone was obtained as a bright yellow oil, b. p. 259° (yield, 44%).

Condensation of 2-Chloropyridine and Anthranilic Acid : Formation of (VI).—Equimolecular quantities of the components were heated together over a small flame till a vigorous reaction set in and the mass swelled up. The horny product was heated on a water-bath with water and treated with ammonia. From the

crystalline solid obtained, 2-anilinopyridine (m. p. 108°) was removed by distillation in steam; the residue crystallised from alcohol in yellow prisms, m. p. 210°, soluble in acetone and mineral acids (violet-blue fluorescence) but insoluble in alkali. The substance (Found : N, 14·3. Calc. for $C_{12}H_8ON_2$: N, 14·3%) remained unaltered when boiled with potassium hydroxide (2—10%) for 2 hours, could not be methylated with methyl iodide and alkali in methyl-alcoholic solution, and appeared to be identical with Reissert's compound (*loc. cit.*).

Methyl anthranilate failed to react with 2-chloropyridine under the above conditions.

N-*Methylquinolone and* 2-*Chloroquinoline.*—The former was prepared by a slight modification of the method of Perkin and Robinson (J., 1913, **103**, 1977). Quinoline methosulphate solution and 10% aqueous potassium hydroxide were separately dropped into a saturated solution of potassium ferricyanide, vigorously stirred at 0°. When the mixture became turbid it was shaken for 10 minutes with 600 c.c. of ether. The ethereal solution was worked up as described by Perkin and Robinson, the yield of methylquinolone being 23·5 g. from 25 g. of quinoline.

A yield of 90—95% of 2-chloroquinoline was obtained by Perkin and Robinson's method (*loc. cit.*).

Condensation of 2-*Chloroquinoline with Anthranilic Acid : Formation of Ketobenzquinazocoline* (V).—The reactants (5 g. of each) were heated till a vigorous reaction set in and the mass swelled up. The viscous product was heated with a few c.c. of water on the water-bath for 5—10 minutes. The solution after decantation deposited crystals of 2-quinolone (mixed m. p. and analysis). The tarry residue, which solidified when treated with moderately concentrated aqueous ammonia, was extracted with a small quantity of dilute hydrochloric acid; the extract on neutralisation deposited 2-anilinoquinoline, m. p. 98°. The residue was digested with acetone (charcoal), and the filtered solution diluted with water; prismatic crystals (1·5 g.), m. p. 170°, gradually separated. These were sparingly soluble in benzene and chloroform but easily in alcohol. They were also soluble in mineral acids but not in aqueous ammonia or alkalis in the cold (Found : C, 78·5; H, 4·1; N, 11·2. $C_{16}H_{10}ON_2$ requires C, 78·05; H, 4·1; N, 11·4%).

Condensation of 2-*Chloroquinoline with Methyl Anthranilate : Formation of* (V).—The reaction (1 g. of each substance) was not so vigorous as in the previous case and required 15 minutes for completion. The dark viscous product was extracted with ether, and the residue crystallised from acetone (charcoal), light yellow, prismatic needles (0·5 g.), m. p. 170°, being obtained. The substance

resembled the previous compound (V) in properties and did not depress its m. p.

Hydrolysis of (V).—0·5 G. of the substance was refluxed with 25 c.c. of 1·6% alcoholic potassium hydroxide for 3 hours. The solution was filtered, the filtrate diluted with water and acidified with acetic acid, and the precipitate collected, dissolved in aqueous ammonia, and reprecipitated by means of acetic acid (yield, almost quantitative). The product formed colourless prisms, m. p. 198°, and dissolved in alkali in the cold, the solution showing a faint unstable bluish-violet fluorescence. The *acid* is soluble in alcohol, acetone or pyridine but not in cold dilute mineral acids. It is fairly readily soluble in hot strong mineral acids (Found : N, 10·5. $C_{16}H_{12}O_2N_2$ requires N, 10·6%).

Condensation of 2-*Chloroquinoline and* N-*Methylanthranilic Acid : Formation of* N-*Methyl*-N-*quinolylanthranilic Acid* (VIII; R = H). —The condensation was effected in the usual manner. The *product* separated from water in prisms, m. p. 190°. In aqueous solution it was acid to litmus and effervesced with potassium carbonate. It dissolved in alkali or mineral acids in the cold. When heated with concentrated sulphuric acid for 15 minutes on a water-bath, it did not suffer any appreciable change, and hot acetic anhydride had no effect on it. The substance partly sublimed but did not undergo any chemical change when heated (Found : C, 73·1; H, 5·1; N, 10·2. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·0; N, 10·1%).

Condensation of 2-*Chloro*-4-*methylquinoline and Anthranilic Acid.* —The condensation was brought about after the method of Ephraim (*loc. cit.*). The product, m. p. 213°, had all the properties ascribed to it by that author.

Action of methyl iodide. The substance (0·5 g.) was heated under reflux with methyl iodide (1 g.), methyl alcohol, and potassium hydroxide (6 c.c. of 4% solution) for 3 hours. The large yellow prismatic crystals that separated were collected and boiled with a little alcohol to remove unaltered material. The *substance*, m. p. 140°, dissolved only sparingly in alcohol but easily in pyridine. It was probably the methyl ester of the following acid (Found : N, 9·5. $C_{18}H_{16}O_2N_2$ requires N, 9·6%).

Hydrolysis. The condensation product (1 g.) was refluxed with alcoholic potash (20 c.c. of 10% solution) for 2 hours. The *acid*, isolated and purified as in the previous hydrolysis, formed yellow prismatic crystals, m. p. 210° (yield, about 93%). It was faintly acid to litmus, soluble in cold alkali but not in dilute acids, and dissolved sparingly in acetone or alcohol (Found : N, 10·1. $C_{17}H_{14}O_2N_2$ requires N, 10·1%).

Condensation of 4-*Chloro*-2-*methylquinoline and Anthranilic Acid :*

Formation of N-2'-*Methyl*-4'-*quinolylanthranilic Acid.*—4-Chloro-2-methylquinoline (1·8 g.) and anthranilic acid (1·5 g.) were heated together as usual, the product was treated with methyl alcohol, and the insoluble residue dissolved in hot potassium carbonate solution, filtered, and reprecipitated with acetic acid (yield, 0·9 g.). Purified by reprecipitation of the ammoniacal solution, it formed golden-yellow prisms, m. p. 307°, soluble in acids as well as alkalis (Found: N, 10·05. $C_{17}H_{14}O_2N_2$ requires N, 10·1%).

Condensation of 2-*Quinolone with Methyl Anthranilate.*—The components (7 g. of each) were refluxed with 70 c.c. of phosphorus trichloride for 12—15 hours. The pasty residue, after the removal of phosphorus trichloride and oxychloride under reduced pressure, was decomposed with ice. The solution was filtered; it then deposited crystals of carbostyril, which were filtered off and the filtrate made slightly acid with hydrochloric acid. A granular precipitate which slowly separated was collected, washed with water, and twice crystallised from dilute acetone, giving yellow cubes, m. p. 226—227°, soluble in acids and alkalis. The *substance* was acid to litmus and gave a slow effervescence with sodium bicarbonate in aqueous-alcoholic solution (Found: N, 10·8. $C_{16}H_{12}O_2N_2$ requires N, 10·6%). The yield was too small for further investigations.

Condensation of 2-*Chloro*-4-*methylquinoline and* N-*Methylanthranilic Acid: Formation of* N : 4'-*Dimethyl*-N-2'-*quinolylanthranilic Acid* (VIII; R = Me).—The tarry mass obtained by heating equal parts of the reactants was treated with alcohol, and the yellow residue dissolved in aqueous ammonia and precipitated by means of acetic acid (yield, 30%). The white prismatic crystals, m. p. 220°, showed a slight bluish-violet fluorescence in moderately dilute ammoniacal solution (Found: N, 9·5. $C_{18}H_{16}O_2N_2$ requires N, 9·6%).

Condensation of 2-*Chloro*-4 : 7-*dimethylquinoline and Anthranilic Acid.*—The condensation product crystallised from acetone in colourless needles, m. p. 150° (yield, 0·9 g. from 2 g. of the quinoline). The *compound* was sparingly soluble in most organic solvents but easily in mineral acids (Found: N, 10·3. $C_{18}H_{14}ON_2$ requires N, 10·2%).

Hydrolysis. 10% Alcoholic potassium hydroxide brought about a smooth hydrolysis of the above substance, the yield being almost theoretical. The *acid* melted at 226° and showed the properties of other compounds of the series described above (Found: N, 9·6. $C_{18}H_{16}O_2N_2$ requires N, 9·6%).

UNIVERSITY COLLEGE OF SCIENCE AND TECHNOLOGY,
CALCUTTA.
[*Received, August 10th,* 1931.]