

## STUDIES IN THE ISOQUINOLINE SERIES.

### PART VI. 2' AND 4',QUINOLYL-*l*-ISOQUINOLINES.

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(Read January 2, 1940.)

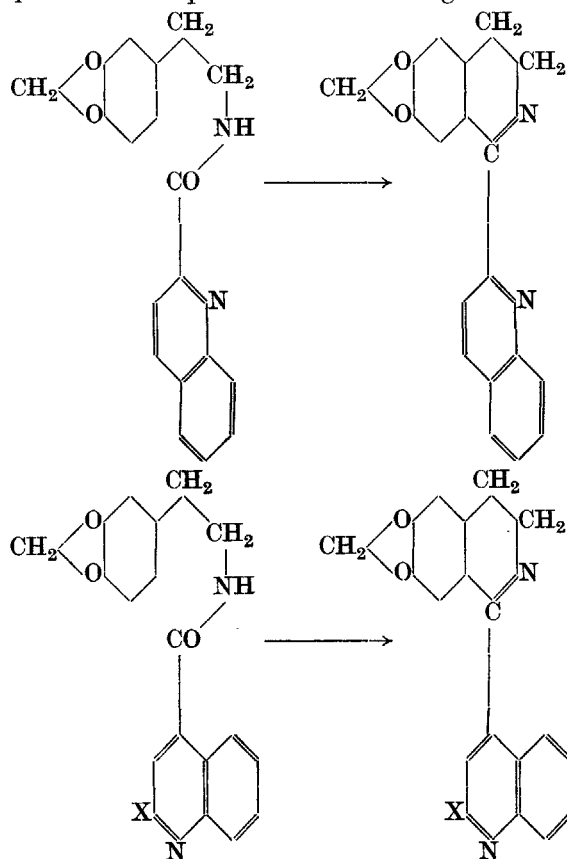
A survey of recent literature on the subject of isoquinolines brings into prominence two interesting lines of development in this field. In the first place, the syntheses of these bases have been carried out under physiological conditions, i.e. conditions approximating to those existing in nature (cf. Späth and Kréuts, *Monatsch*, 1928, 50, 341; Späth and Berger, *Ber.*, 1930, 63, 2098; Schöpf and Bayerle, *Ann.*, 1934, 513, 190; Hahn and Schales, *Ber.*, 1935, 68, 24, etc.), the results contributing to a clearer understanding of the phytochemical mechanism of the formation of alkaloids containing this ring system in plants, and secondly, new types of isoquinolines have been synthesized with a view to press them into service in the treatment of amoebic dysentery, malaria and other diseases. The realization particularly of the magnitude and complexity of the malaria problem has led in recent years to the inauguration of a series of important investigations having for their object the syntheses of chemical specifics, mostly derivatives of quinolines and acridines but a few belonging to the isoquinoline group as well, and a study of their antimalarial, amoebicidal and other possible therapeutic properties. [Barger and Robinson, *Journ. Chem. Soc. London*, 1929, 2947, 2952, 2959, 2965; Kermack and co-workers, *ibid.*, 1930, 1356; 1931, 3089, 3096; 1935, 1143, 1421; Ray and co-workers, *ibid.*, 1931, 976; *J. Indian Chem. Soc.*, 1932, 9, 215; 1933, 10, 197; *J. Amer. Chem. Soc.*, 1932, 54, 3988; *J. pr. Chem.*, 1933, ii, 136, 117; Robinson and co-workers, *Journ. Chem. Soc. London*, 1933, 1467; *ibid.*, 1934, 1264, 1267, 1322, 1520, 1524; Magidson and co-workers, *J. Gen. Chem. Russ.*, 1934, 4, 1047; *Arch. Pharm.*, 1935, 273, 320; Kritschewski and Meerson, *J. Immunität*, 1933, 79, 180, 438; Mietzsch and Mauss, *Angew. Chem.*, 1934, 47, 633; Fieldman and Kopeliovitzsch, *Arch. Pharm.*, 1935, 273, 488; Goodall and Kermack, *Journ. Chem. Soc. London*, 1936, 1546; Berkenheim, *J. Gen. Chem. Russ.*, 1936, 6, 1039, 1043; Basu and Das-Gupta, *J. Indian Chem. Soc.*, 1937, 14, 468; Child and Pyman, *Journ. Chem. Soc. London*, 1931, 36.]

While the cinchona alkaloids still retain their undoubted pre-eminence in this field, recent work has brought to light many important facts concerning their true values and also their limitations, and synthetic drugs like Plasmoguin and Atebrin appear to have proved their superiority to the natural alkaloids in the treatment of certain special types of malaria. Attention has thus been drawn to the possibilities of employing different types of *l*, substituted isoquinolines in the treatment of various kinds of malarial infections and with this end in view, heterocyclic acids like picolinic and nicotinic acids have been

condensed with  $\beta$ -phenyl ethyl amines for the synthesis of isoquinolines with a pyridine ring in 1, position. (Clemo, McIlwain and McG. Morgan, *J.C.S.*, 1936, 610; Sugawara and Kuriyagawa, *Ber.*, 1936, 69 [B], 2068.)

In pursuance of the systematic studies in the isoquinoline series which have been undertaken in this laboratory, attempts have now been made with success to link two new heterocyclic ring systems, viz.: (a) quinoline, and (b) benzo- $\alpha$ -pyrone, to carbon atom 1 in the isoquinoline ring. The quinoly-isoquinolines form the subject matter of the present investigation. The coumaryl isoquinolines have been described in Part V of this series.

The condensation of quinaldine and of 2,methyl- and 2,phenyl-cinchoninic acids with homopiperonylamine resulted in the formation in good yields of the respective amides which underwent smooth cyclization to the corresponding 3,4,dihydro-isoquinolines as explained in the following scheme:—



The quinoly-isoquinolines are well-defined bases which are colourless but which form deep yellow salts with mineral acids. While the 2,quinoly-isoquinolines function as monacid bases yielding stable monohydrochlorides, the 4,quinoly derivatives are found to be diacidic and form, in accordance

with expectation, stable dihydrochlorides. The preparation of analogous isoquinolines with other heterocyclic substituents and of their reduction products is in progress.

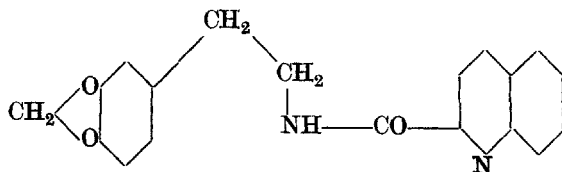
#### EXPERIMENTAL.

Quinaldinic acid was prepared both by the method of Besthorn and Ibele (*Ber.*, 1906, 39, 2329) from quinaldine and formalin and by the method of Reissert (*Ber.*, 1905, 38, 1603) from quinoline, benzoyl chloride, and potassium cyanide. The former method was preferred on account of the simplicity of the process and the better yield of the product.

The methyl ester was prepared according to the direction given by Hammick (*Journ. Chem. Soc.*, 1923, p. 2883). 5.4 g. of methyl quinaldinate crystallizing from ligroin in long needles, M.P. 86°, were obtained from 6 g. of the acid.

Homopiperonylamine was prepared in the usual way by the method of Buck and Perkin (*J. Chem. Soc.*, 1924, 125, 1693). 10 g. of the pure amine, B.P. 162°/22 mm. were obtained starting from 20 g. of piperonal. Attempts were made to prepare the amine by the electrolytic reduction process from piperonylidene nitromethane but none of them were very successful, only poor yields of the amine being obtained at the end.

#### *α,quinolinoyl-β-3,4,methylene dioxy-phenyl ethylamide.*



This was prepared by the following three methods:—

- (a) Powdered quinaldinic acid (1.73 g.) was heated with homopiperonylamine (1.65 g.) at 160°–170° on an oil-bath for five hours. The oily reaction product was triturated with alcohol when it solidified and the solid residue was finally crystallized twice from alcohol (norit-charcoal). Yield, 0.5 g. of amide. M.P. 110°.
- (b) Quinaldinic acid (1 g.) was covered with dry chloroform (50 c.c.), thionyl chloride (1 g.) added, and the mixture refluxed on the steam bath for three hours. After removing the chloroform and excess of thionyl chloride under reduced pressure, dry benzene (10 c.c.) and homopiperonylamine (0.92 g.) were successively added, the mixture heated on a steam bath for an hour and the product treated with crushed ice, basified with ammonia, extracted thrice with benzene and the benzene extract dried over potassium carbonate. On distilling off the benzene, a reddish oil was left behind which solidified on rubbing with

alcohol. Crystallization from alcohol gave thin plates. M.P. 110°. Yield, 0.7 g. The alcoholic mother liquor, on dilution with water, gave a further 0.5 g. of the slightly impure amide.

(c) Methyl quinaldinate (1.85 g.) and homopiperonylamine (1.65 g.) were heated on the steam-bath for three hours. Crystallization of the reaction product from alcohol (norit) gave colourless glistening plates. M.P. 110°. Yield, 2.6–2.7 gms.

The third method proved to be the most satisfactory and was employed for preparing larger quantities of the amide.

23.04 mg. of the substance gave 60.75 mg. of CO<sub>2</sub> and 10.86 mg. of H<sub>2</sub>O; 26.08 mg. gave 2.055 c.c. of nitrogen at 33° and 763 mm.

Found: C, 71.91; H, 5.24; N, 8.83 per cent.

C<sub>19</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub> requires C, 71.22; H, 5.037; N, 8.75 per cent.

The *hydrochloride* of the  $\alpha$ ,quinolinoyl,  $\beta$ -phenyl ethylamide was prepared by passing dry HCl gas into a suspension of the amide (0.5 g.) in dry benzene (20 c.c.). It crystallized from absolute alcohol in dark yellow prisms. M.P. 167°.

60.19 mg. required 8.2 c.c. of 1.043 N/50 NaOH.

Found: Cl, 10.08 per cent.

C<sub>19</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub> · HCl requires Cl, 9.94 per cent.

The hydrochloride is very easily hydrolyzed even in the presence of moisture.

The *picrate*, obtained by mixing alcoholic solutions of the amide and picric acid, crystallized in fibrous needles. M.P. 115°.

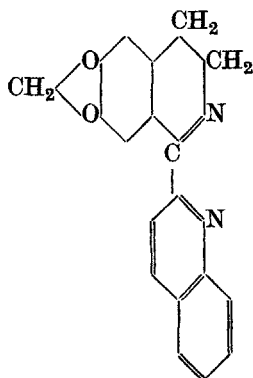
The picrate was dried in vacuum at room temperature. 42.44 mg. gave 4.752 c.c. of nitrogen at 33° and 765 mm.

Found: N, 12.58 per cent.

C<sub>19</sub>H<sub>16</sub>O<sub>3</sub>N<sub>2</sub> · C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub> requires N, 12.72 per cent.

Attempts to prepare the *methiodide* by the usual method were not successful, the unchanged amide being recovered at the end.

*1-2'- $\alpha$ ,quinolyl-6,7,methylene dioxy-3,4,dihydro-isoquinoline.*



The above amide (2 g.), phosphorus oxychloride (6 c.c.) and dry toluene (12 c.c.) were heated on an oil-bath at 120°–130° for three hours. A thick oil separated out which solidified to a hard gummy mass on cooling. Petroleum ether was added to the mixture until there was no further turbidity, the clear liquid poured off and the residue washed with petroleum ether and finally treated with water (150 c.c.) containing 1 c.c. strong HCl. The acid aqueous extract was shaken once with ether to remove any toluene, strongly cooled and basified with strong ammonia. After standing for three hours, the dirty white solid was collected and crystallized from alcohol (norit). The isoquinoline separated in bundles of colourless rectangular plates. M.P. 118°. Yield, 1.4 g.

It dissolves in cold dilute acids with a deep yellow colour which changes to deep red on addition of more acid. The acid solution, on dilution, showed a pale blue fluorescence.

18.01 mg. gave 49.46 mg. CO<sub>2</sub> and 7.97 mg. H<sub>2</sub>O, and 18.22 mg. of the base gave 1.472 c.c. of nitrogen at 33° and 760 mm.

Found: C, 74.89; H, 4.92; N, 9.02 per cent.

C<sub>19</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub> requires C, 75.44; H, 4.67; N, 9.27 per cent.

29.9 mg. of the base (dried in vacuum), dissolved in 405 mg. of camphor, depressed the melting point by 10°.

Found: M.W., 295.3.

C<sub>19</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub> requires M.W., 302.

The *platinichloride* was prepared in the usual way. Orange yellow crystals. M.P. 210°.

0.10415 mg. (dried at 110°/5 mm.) gave 0.01999 g. Pt.

Found: Pt, 19.20 per cent.

[C<sub>19</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub>]<sub>2</sub> · H<sub>2</sub>PtCl<sub>6</sub> requires Pt, 19.23 per cent.

The *hydrochloride* was prepared by passing dry HCl gas into a solution of the base (0.5 g.) in benzene (8 c.c.), rubbing the deep red sticky solid with a little absolute alcohol and then crystallizing from the same solvent. Clusters of yellow needles. M.P. 241°.

0.17007 g. requires 18.1 c.c. of 0.555 N/20 caustic soda.

Found: Cl, 10.47 per cent.

C<sub>19</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub> · HCl requires Cl, 10.49 per cent.

The base appears therefore to be mono-acidic.

The *picrate* was prepared by mixing alcoholic solutions, crystallized in prisms. M.P. 210°.

7.65 mg. of the picrate gave 0.84 c.c. of N<sub>2</sub> at 764.75 mm. and 27°C.

Found: N, 12.63 per cent.

C<sub>19</sub>H<sub>14</sub>O<sub>2</sub>N<sub>2</sub> · C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub> requires N, 13.18 per cent.

The *methiodide* was prepared by heating the components in a closed bottle at 100° for four hours, washing the sticky product with alcohol and finally crystallizing it from alcohol or water. Long rectangular plates. M.P. 245°.

0.09225 g. gave 0.04441 g. AgI.

Found: I, 26.0 per cent.

$C_{19}H_{14}O_2N_2 \cdot CH_3I$  requires I, 28.6 per cent.

The reduction of the dihydro base with zinc and sulphuric acid or with tin and hydrochloric acid could not be effected satisfactorily. Catalytic reduction with palladized—norit was ultimately found to be the most successful method.

A solution of 0.5 g. of the base in 10 c.c. of glacial acetic acid containing 0.2 g. of the catalyst in suspension was shaken in an atmosphere of hydrogen until there was no more absorption of gas. The catalyst was filtered and the colourless solution diluted and basified with ammonia. The white precipitate was filtered and crystallized from alcohol. It melted at 160°. Yield, 0.4 g.

The tetrahydro base was dried in vacuum at 30°. 18.12 mg. gave 49.66 mg. of  $CO_2$  and 8.98 mg. of water.

Found: C, 74.73; H, 5.51 per cent.

$C_{19}H_{16}O_2N_2$  requires C, 74.98; H, 5.30 per cent.

The *platinichloride*, prepared in the usual way, melted to a clear red liquid at 204°.

0.1167 g. of the double salt gave 0.0221 g. of Pt.

Found: Pt, 18.93 per cent.

$[C_{19}H_{16}O_2N_2]_2 \cdot H_2PtCl_6$  requires Pt, 19.16 per cent.

The *hydrochloride*, which was hygroscopic, melted at 142°.

0.1231 g. of the hydrochloride dried in vacuum required 13.55 c.c. of 1.292 N/50 sodium hydroxide solution.

Found: Cl, 10.08 per cent.

$C_{19}H_{16}O_2N_2 \cdot HCl$  requires Cl, 10.41 per cent.

The *picrate*, crystallized from dilute alcohol, melted to a thick liquid at 96°–98°.

22.64 mg. gave 2.618 c.c. of nitrogen at 33° and 758 mm.

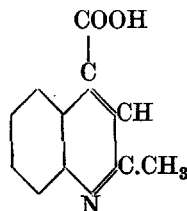
Found: N, 12.87 per cent.

$C_{19}H_{16}O_2N_2 \cdot C_6H_3O_7N_3$  requires N, 13.13 per cent.

The reduced base is therefore mono-acidic.

#### *Syntheses of 4',quinolyl-L-isoquinolines.*

$\alpha$ , *Methyl-cinchoninic acid*,

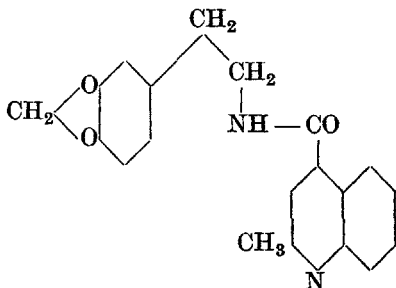


This was prepared by the method of Pfitzinger (*J. Prakt. Chem.*, 1897, 56, 284) by refluxing isatin with acetone and alkali for several hours. Nearly

16 g. of the cinchoninic acid crystallizing from boiling water in needles, M.P. 241°, were obtained from 15 g. of isatin.

The *methyl ester* of 2-methyl-cinchoninic acid crystallized from ligroin in colourless needles. M.P. 60°-61°.

*α, methyl-γ, quinolinoyl-β-3 : 4-methylene dioxy-phenyl ethylamide.*



A mixture of the methyl ester of cinchoninic acid (2 g.) and homopiperonylamine (1.6 g.) was heated at 100° for five hours. The reaction product was a gum which solidified on rubbing with alcohol. Crystallization from 50 per cent alcohol gave the amide as colourless thin plates. M.P. 153° (after drying). Yield, 1.8-1.9 g. The amide is a strong base dissolving readily in cold dilute acids. (The *hydrochloride* was prepared by saturating a benzene solution of the amide with HCl gas. It crystallized from absolute alcohol as pale yellow scales. M.P. 194°.)

22.30 mg. of the amide gave 58.69 mg. of CO<sub>2</sub> and 11.30 mg. of H<sub>2</sub>O. 16.61 mg. gave 1.148 c.c. of nitrogen at 33° and 762 mm.

Found: C, 71.78; H, 5.63; N, 8.10 per cent.

C<sub>20</sub>H<sub>18</sub>O<sub>3</sub>N<sub>2</sub> requires C, 71.83; H, 5.43; N, 8.38 per cent.

0.20497 g. of the hydrochloride required 22.55 c.c. of 1.291 N/50 caustic soda.

Found: Cl, 10.07 per cent.

C<sub>20</sub>H<sub>18</sub>O<sub>3</sub>N<sub>2</sub> · HCl requires Cl, 9.57 per cent.

The *picrate* crystallized from dilute alcohol as small plates. M.P. 190°.

16.69 mg. gave 1.84 c.c. of nitrogen at 31° and 761 mm.

Found: N, 12.28 per cent.

C<sub>20</sub>H<sub>18</sub>O<sub>3</sub>N<sub>2</sub> · C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub> requires N, 12.43 per cent.

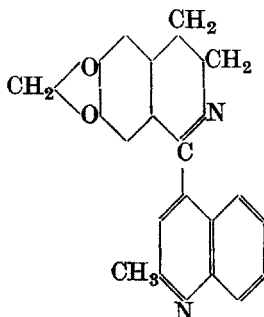
The *methiodide* was prepared by heating the components in a closed bottle for five hours on a steam bath. It crystallized from alcohol in clusters of yellow plates. M.P. 197°.

0.18216 g. gave 0.08433 g. AgI.

Found: I, 25.02 per cent.

C<sub>21</sub>H<sub>21</sub>O<sub>3</sub>N<sub>2</sub>I requires I, 26.65 per cent.

*α*,methyl-quinolyl- $\gamma$ ,6 : 7,methylenedioxy-3,4,dihydro-isoquinoline.



The  $\gamma$ -quinolinoyl-phenyl ethylamide (1 g.), phosphorus oxychloride (3.5 c.c.) and dry toluene (10 c.c.) were refluxed for three hours on an oil-bath at 120°–130°. On cooling, 20 c.c. petroleum ether was added and after standing for an hour the clear supernatant liquid was decanted off and the gummy residue ground with 50 c.c. water containing 1 c.c. HCl. After shaking the deep red aqueous acid extract with ether to remove any non-basic impurities and traces of toluene the solution was cooled in ice and basified with ammonia. The granular solid was collected and crystallized from 50 per cent alcohol (norit). The base separated in glistening, colourless, rectangular plates. M.P. 114°. Yield, 0.8 gm.

The isoquinoline is a strong base dissolving instantly in cold dilute acids and giving crystalline precipitates with Meyer's reagent and with potassium dichromate solution.

17.38 mg. gave 48.10 mg. of CO<sub>2</sub> and 8.29 mg. of H<sub>2</sub>O. 22.32 mg. gave 1.758 c.c. of N<sub>2</sub> at 34° and 761 mm.

Found: C, 75.48; H, 5.30; N, 8.73 per cent.

C<sub>20</sub>H<sub>16</sub>O<sub>2</sub>N<sub>2</sub> requires C, 75.91; H, 5.10; N, 8.86 per cent.

The *platinichloride*, prepared in the usual way, decomposes gradually without melting, above 250°.

0.06959 g. dried at 110°, gave 0.01836 g. platinum.

Found: Pt, 26.37 per cent.

C<sub>20</sub>H<sub>16</sub>O<sub>2</sub>N<sub>2</sub> · H<sub>2</sub>PtCl<sub>6</sub> requires Pt, 26.8 per cent.

It behaves therefore as a diacidic base.

The *hydrochloride*, prepared from a benzene solution of the base and dry HCl gas, separated from alcohol as orange yellow crystals. M.P. 234° (decomp.).

0.10140 g. required 21 c.c. of 1.291 N/50 caustic soda.

Found: Cl, 18.95 per cent.

C<sub>20</sub>H<sub>18</sub>O<sub>2</sub>N<sub>2</sub>Cl<sub>2</sub> requires Cl, 18.23 per cent.

The *methiodide*, prepared in the usual way, crystallized from absolute alcohol as rectangular prisms. M.P. 254° (decomp.).



15.83 mg. gave 31.85 mg. of  $\text{CO}_2$  and 5.98 mg. of water.  
 11307 g. of substance dried at  $100^\circ$ , gave 0.5248 g. AgI.

Found: C, 54.87; H, 4.20; I, 25.08 per cent.

$\text{C}_{20}\text{H}_{16}\text{O}_2\text{N}_2 \cdot \text{CH}_3\text{I}$  requires C, 55.01; H, 4.18; I, 27.7 per cent.

The base therefore forms a mono-methiodide.

The *picrate* crystallized from a small quantity of alcohol melting at  $221^\circ$  (decomp.).

24.26 mg. gave 3.083 c.c. of  $\text{N}_2$  at  $33.5^\circ$  and 762 mm.

Found: N, 14.20 per cent.

$\text{C}_{20}\text{H}_{16}\text{O}_2\text{N}_2 \cdot 2\text{C}_6\text{H}_3\text{O}_7\text{N}_6$  requires N, 14.46 per cent.

#### *Reduction with zinc and sulphuric acid.*

The dihydro base (1 g.) and zinc spangles (3 g.) in water (30 c.c.) containing copper sulphate (0.05 g.) was warmed on the water-bath ( $50^\circ$ - $60^\circ$ ) with the gradual addition of concentrated sulphuric acid in the course of two hours. The orange yellow solution became colourless in about 20 minutes. The excess of zinc was filtered off and the filtrate with the washings was cooled and basified with ammonia. The white precipitate was filtered, dried and extracted with hot benzene. The pale yellow oil (0.8 g.), after removing the solvent, solidified on rubbing with a few drops of alcohol. Crystallized from dilute alcohol, the tetrahydro base separated in colourless rhombic plates melting at  $81^\circ$ .

17.40 mg. gave 48.06 mg. of  $\text{CO}_2$  and 9.02 mg. of water.

Found: C, 75.32; H, 5.76 per cent.

$\text{C}_{20}\text{H}_{18}\text{O}_2\text{N}_2$  requires C, 75.56; H, 5.70 per cent.

The *hydrochloride*, crystallized from absolute alcohol, melted at  $275^\circ$ .

0.1054 g. required 23.8 c.c. of 1.108 N/50 sodium hydroxide solution.

Found: Cl, 17.72 per cent.

$\text{C}_{20}\text{H}_{18}\text{O}_2\text{N}_2 \cdot 2\text{HCl}$  required Cl, 18.18 per cent.

The *picrate* separated from alcohol, melting at  $202^\circ$ . 12.71 mg. gave 1.62 c.c. of  $\text{N}_2$  measured at  $33^\circ$  and 759 mm.

Found: N, 14.21 per cent.

$\text{C}_{20}\text{H}_{18}\text{O}_2\text{N}_2 \cdot 2\text{C}_6\text{H}_3\text{O}_7\text{N}_3$  requires N, 14.42 per cent.

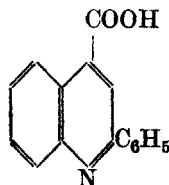
The *benzoyl derivative* crystallized from acetone-alcohol mixture and melted at  $226^\circ$ .

20.27 mg. gave 1.146 c.c. of  $\text{N}_2$  at  $33^\circ$  and 764 mm.

Found: N, 6.38 per cent.

$\text{C}_{27}\text{H}_{22}\text{O}_3\text{N}_2$  requires N, 6.63 per cent.

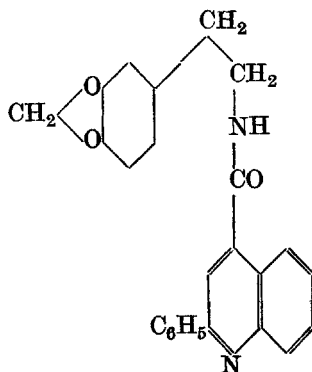
$\alpha$ ,phenyl-cinchoninic acid,



This was prepared by the method of Pfitzinger (*loc. cit.*, p. 292). 5.2 g. of pale brown needles, M.P. 208°-209°, were obtained from 5 g. of isatin.

The *methyl ester* was prepared by refluxing with methyl alcohol and sulphuric acid for three hours, basifying the diluted product with sodium carbonate and extracting with ether. It crystallized from ligroin in colourless needles. M.P. 61°. Yield, 4.7 g. from 5 g. of the acid. Claus and Brandt (*A.*, 1894, 252, 106) previously obtained this ester by the process of heating the silver salt with methyl iodide in a sealed tube at 100°.

*α,phenyl-γ,quinolinoyl-β-3 : 4,methylene dioxy-phenyl ethylamide.*



The methyl ester (4.8 g.) and homopiperonyl amine (3.0 g.) were heated for ten hours on the steam-bath. The amide began to separate out after five hours. On cooling, the hard brown mass was powdered and washed with small amounts of ether. The white residue was dried and crystallized from excess of boiling alcohol in which it was sparingly soluble. Colourless rectangular plates. M.P. 185°.

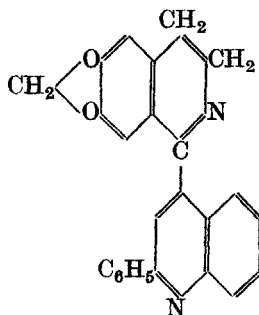
17.76 mg. gave 49.13 mg. CO<sub>2</sub> and 8.51 mg. H<sub>2</sub>O. 18.56 mg. gave 1.167 c.c. of nitrogen measured at 763.9 mm. and 33°.

Found: C, 75.44; H, 5.32; N, 7.05 per cent.

C<sub>25</sub>H<sub>20</sub>O<sub>3</sub>N<sub>2</sub> requires C, 75.71; H, 5.09; N, 7.07 per cent.

The amide behaved as a very feeble base and was quite insoluble in acids. Attempts to prepare the hydrochloride, picrate and methiodide were unsuccessful, only unchanged materials being recovered. This is obviously to be explained by the acidic influence of the phenyl group in 2, position in the quinoline ring.

*α,phenyl-quinolyl-γ,1-6 : 7-methylene dioxy-3,4,dihydro-isoquinoline.*



The amide (1.85 g.) was refluxed with phosphorus oxychloride (10 c.c.) in boiling toluene (15 c.c.) for three hours at 130°–140°. The reaction mixture was cooled, diluted with petroleum ether and allowed to stand for one hour and the clear supernatant liquid decanted off. The red gummy residue was taken up in water (40–50 c.c.) containing a few drops of hydrochloric acid and the deep red aqueous solution extracted with ether to remove traces of toluene and any non-basic matter. The ether-free solution was cooled strongly and basified with liquor ammonia. The dihydro-isoquinoline which separated as a white powder was collected and crystallized from dilute alcohol. It separated slowly in short rectangular plates, melting at 167°. Yield, 1.5 g.

It dissolves like the other two bases of this group readily in cold dilute acids with a characteristic yellow colour which changes to deep red with excess of acid. The base exhibits a feeble greenish fluorescence in dilute acid solutions.

23.53 mg. of the base gave 68.36 mg. of CO<sub>2</sub> and 10.48 mg. of H<sub>2</sub>O. 21.74 mg. gave 1.472 c.c. of N<sub>2</sub> at 34° and 761 mm.

Found: C, 79.21; H, 4.95; N, 7.53 per cent.

C<sub>25</sub>H<sub>18</sub>O<sub>2</sub>N<sub>2</sub> requires C, 79.34; H, 4.80; N, 7.41 per cent.

The *platinichloride* was obtained as a canary yellow precipitate which did not melt but decomposed above 290°.

0.24933 g. gave, on ignition, 0.06057 g. of Pt.

Found: Pt, 24.30 per cent.

C<sub>25</sub>H<sub>18</sub>O<sub>2</sub>N<sub>2</sub> · H<sub>2</sub>PtCl<sub>6</sub> requires Pt, 24.77 per cent.

The *hydrochloride* separated from absolute alcohol in golden yellow flakes, M.P. 205°. It is extremely hygroscopic.

0.3307 g. of the salt required 64.10 c.c. of 1.108 N/50 sodium hydroxide solution.

Found: Cl, 15.23 per cent.

C<sub>25</sub>H<sub>18</sub>O<sub>2</sub>N<sub>2</sub> · 2HCl requires Cl, 15.71 per cent.

The base is diacidic in its platinum salt and its hydrochloride.

The *picrate* crystallized from acetone-alcohol mixture in hard prisms, melting at 211° (decomp.).

23.73 mg. gave 2.332 c.c. of  $N_2$  at  $32^\circ$  and 759 mm.

Found: N, 10.99 per cent.

$C_{25}H_{18}O_2N_2 \cdot C_6H_3O_7N_3$  requires N, 11.53 per cent.

The *methiodide* separated from absolute alcohol in yellow needles. M.P.  $286^\circ$  (decomp.).

16.17 mg. of the methiodide gave 35.32 mg. of  $CO_2$  and 6.14 mg. of  $H_2O$ .

0.0923 g. gave .04066 g. of AgI.

Found: C, 59.58; H, 4.22; I, 23.8 per cent.

$C_{25}H_{18}O_2N_2 \cdot CH_3I$  requires C, 59.99; H, 4.07; I, 24.4 per cent.

The base is monoacidic in its picrate and methiodide.

#### *Reduction with zinc and sulphuric acid.*

The dihydro base (1 g.) and zinc spangles (3 g.) were suspended in water (30 c.c.) containing copper sulphate (0.05 g.). The mixture was kept warm at  $50^\circ$ - $60^\circ$  and concentrated sulphuric acid (2.5 c.c.) gradually added in the course of two hours. The deep orange yellow solution became almost colourless in 20 minutes. It was allowed to remain at  $60^\circ$  for a further half hour and filtered hot from the excess of zinc. The filtrate together with the washings was cooled, basified with liquor ammonia and the precipitate collected and dried in vacuum. The dry residue containing inorganic material was extracted with ether or hot benzene. A pale yellow oil which solidified to a crisp solid was obtained. Crystallized from ether, the tetrahydro base separated in brittle flakes melting at  $92^\circ$ - $94^\circ$ , with softening at  $82^\circ$ .

16.05 mg. gave 46.25 mg. of  $CO_2$  and 7.81 mg. of water.

Found: C, 78.59; H, 5.41 per cent.

$C_{25}H_{20}O_2N_2$  requires C, 78.93; H, 5.30 per cent.

The *hydrochloride*, which is hygroscopic, sintered at  $200^\circ$  and melted completely to a clear liquid at  $225^\circ$ .

0.1033 g. requires 17.6 c.c. of 0.6348 N/25 sodium hydroxide solution.

Found: Cl, 15.34 per cent.

$C_{25}H_{20}O_2N_2 \cdot 2HCl$  requires Cl, 15.64 per cent.

The *picrate*, prepared in the usual way, crystallized from dilute acetone in irregular plates, melting at  $200^\circ$ .

21.79 mg. of the picrate gave 2.193 c.c. of  $N_2$  at  $34^\circ$  and 759 mm.

Found: N, 11.19 per cent.

$C_{25}H_{20}O_2N_2 \cdot C_6H_3O_7N_3$  requires N, 11.49 per cent.

#### SUMMARY.

A new series of isoquinolines with a quinoline ring attached to C-atom 1 in the isoquinoline ring have been synthesized. They are colourless, crystalline bases which form deep yellow salts with mineral acids, picric acid, and methyl iodide. The  $\alpha$ ,quinolyl-isoquinoline is exclusively monoacidic, whereas the

$\gamma$ -quinolyl-isoquinolines are diacidic in their salts with mineral acids. A study of the therapeutic properties of these and other similar compounds under investigation is in progress.

PRESIDENCY COLLEGE,  
MADRAS,  
*27th November, 1939.*

