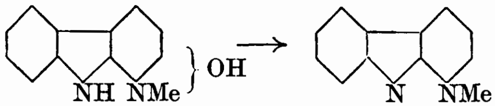
CCCI.—*Polynuclear Heterocyclic Aromatic Types. Part III. Pyrroloquinoline Derivatives.*

By Reginald Clifford Fawcett and Robert Robinson.

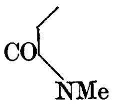
In Part II of this series (Armit and Robinson, J., 1925, **127**, 1604) several anhydronium bases of the carboline type were described, and 3-carboline methohydroxide (I), for example, was shown to be dehydrated with the formation of the anhydride (II). An attempt was made to reproduce this phenomenon in the case of a base in which the pyridine and pyrrole rings were separated by a naphthalene nucleus, but without definite result; we have now made similar trials with compounds in which the separation of the heterocyclic nuclei is by a benzene nucleus. A study of the literature showed that the particular combinations of fused

(I.)

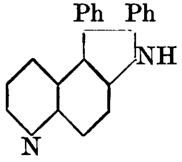


(II.)

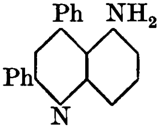
rings which we wished to examine are not contained in known substances, and some difficulty has been experienced in effecting the necessary syntheses. 6-Aminoquinoline and benzoin (compare Japp and Murray, J., 1894, **65**, 889) could be condensed with formation of a *diphenylpyrroloquinoline* (III), but the *methosulphate* of this base, on treatment with aqueous potassium hydroxide, does not appear to yield an anhydro-base. It was thought that less ambiguous results would be obtained if the quinoline ring were phenylated in positions 2 and 4 in order to stabilise the α- and γ-carbinols and thus prevent oxidation to quinolones. The condensation of dibenzoylmethane and *p*-aminoacetanilide could not, however, be effected. With *m*-phenylenediamine the isomeric *aminodiphenylquinolines* (IV, V) were obtained, although in such poor yield that further work along these lines was prohibited.



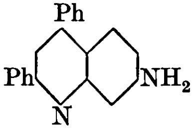
(IIIA.)



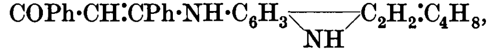
(III.)

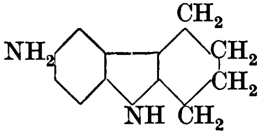


(IV.)

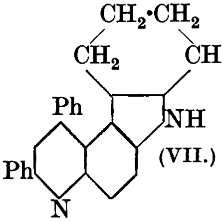


(V.)

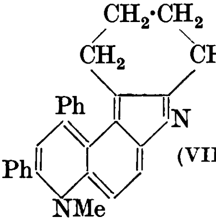
We therefore turned our attention to a scheme in which the quinoline ring is the last to be introduced. 6-Aminotetrahydrocarbazole (VI) (Plant and Edwards, J., 1923, **123**, 2393) and dibenzoylmethane give rise to the intermediate *phenyl tetrahydrocarbazylaminostyryl ketone*,  $COPh{\cdot}CH{:}CPh{\cdot}NH{\cdot}C_6H_3\underset{NH}{\diagdown\!\!-\!\!\diagup}C_2H_2{:}C_4H_8$, which may be dehydrated by means of phosphoryl chloride with formation of a *diphenyltetrahydroindoloquinoline* (VII). This



(VI.)



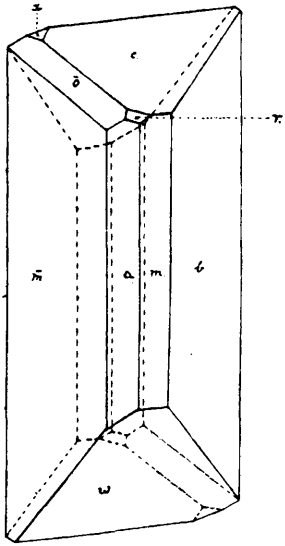
(VII.)



(VIII.)

yellow base gives red salts, and when dissolved in organic solvents it absorbs a molecular proportion of oxygen so as to produce a *dioxy-compound*, $C_{27}H_{22}O_2N_2$. The *substance* derived from the *methosulphate* of (VII) by the action of aqueous potassium hydroxide has, apparently, the composition $C_{28}H_{24}N_2,2H_2O$. In view of its deep green colour and the avidity which it displays for oxygen, it is better regarded as a hydrate of the anhydro-base (VIII) than of the methohydroxide of (VII) (which should be red, like the methosulphate). Probably the most satisfactory conception of the nature of these intensely-coloured, hydrated anhydro-bases, several of which have now been found to exist, is that which would class them with the pyranhydrones and flavanhydrones as quinhydrones. Thus the substance under discussion would, on this hypothesis, have the composition, $C_{28}H_{24}N_2,C_{28}H_{26}N_2O,3H_2O$. The first component would be the fractional dipolar anhydronium base (compare Part II, *loc. cit.*), whilst the second would be a partly dissociated carbinol-amine, also a fractional dipole, balancing the first and cohering to it through electrostatic attraction. Such a conception of the molecular combination seems to be generally applicable to the quinhydrones.

Fig. 1.



EXPERIMENTAL.

5 : 6 - (2′ : 3′ - *Diphenylpyrrolo*)(4′ : 5′) - *quinoline* (III).—This base may be obtained from *p*-nitroaniline in an over-all yield of 43%, the yield in the last stage described below being 95%. A mixture of 6-aminoquinoline (7 g.), its hydrochloride (3 g.), and benzoin (15·5 g.) was heated for 4 hours at 150—160°. On cooling, the mass set to a hard cake which was ground with aqueous ammonia, and the yellow powder collected, washed, dried, and crystallised from methyl alcohol and then from ethyl acetate; short, yellow prisms (19 g.), m. p. 167—168° (Found, in material dried at 100° : C, 81·4; H, 5·4; in material dried at 140° in a high vacuum : C, 86·0; H, 5·3. $C_{23}H_{16}N_2,H_2O$ requires C, 81·6; H, 5·3; $C_{23}H_{16}N_2$ requires C, 86·2; H, 5·0%). The molecule of water is tenaciously held and only removed very slowly at 110—120° in a vacuum. Solutions of the substance in most organic solvents are yellow and exhibit a green fluorescence.

A sample of this base was crystallised from ethyl acetate, and the following crystallographic description was kindly supplied by Mr. H. E. Buckley, of the Crystallography Department of this University :

Symmetry : anorthic, pinacoidal. Habit : short prisms, parallel to zone (001). Forms developed : *a*(100), *b*(010), *c*(001), *m*(110), $\overline{m}$(1$\bar{1}$0), $\bar{o}$(1$\bar{1}$1), *w*(11$\bar{1}$), *r*(101), *x*(0$\bar{1}$3).

Table of Observed Angles.

Faces.	Angle.	No. of measurements.	Limits.
(010—$\bar{1}$10)	59° 41′	11	59° 20′—59° 56′
(100—110)	47° 50′	3	47° 45′—47° 57′
(100—1$\bar{1}$0)	33° 7′	5	33° 0′ —33° 13′
(110—010)	39° 28′	2	39° 28′ (each)
(001—010)	74° 51′	8	74° 35′—75° 3′
(001—$\bar{1}$10)	95° 56′	5	95° 46′—96° 6′
(001—1$\bar{1}$1)	42° 0′	7	41° 42′—42° 11′
(1$\bar{1}$1—1$\bar{1}$0)	42° 2′	6	41° 46′—42° 8′
(010—1$\bar{1}$1)	54° 13′	6	54° 5′ —54° 23′
(110—1$\bar{1}$1)	43° 13′	3	43° 4′ —43° 18′
(00$\bar{1}$—11$\bar{1}$)	69° 1′	6	68° 51′—69° 10′
(001—0$\bar{1}$3)	17° 29′	1	17° 29′

Axial angles: $\alpha = 80° 37'$; $\beta = 70° 8'$; $\gamma = 77° 3'$.
$a : b : c = 0{\cdot}601 : 1 : 0{\cdot}530$.

Optics. When the crystal is laid on face $\overline{m}(1\bar{1}0)$, which is usually the largest face, there is an extinction, in parallel polarised light, practically parallel to the edge given by the *c*(001) face and the prism. From observations in convergent polarised light, it appears that the birefringence is very strong and positive, whilst the dispersion appears to be of the type $\rho > \nu$.

The *hydrogen sulphate* and the *hydrochloride* crystallise from water and from dilute hydrochloric acid respectively in stellar clusters of pale yellow plates. The solution in concentrated sulphuric acid is both colourless and non-fluorescent. The *picrate* crystallises from alcohol in bright yellow needles, m. p. 218° (decomp.).

The Methosulphate.—Pure methyl sulphate (4 g.) in dry benzene (10 c.c.) was added to a solution of diphenylpyrroloquinoline (5 g.) in hot dry benzene (100 c.c.), and the mixture boiled. Bright yellow needles soon appeared and in 10 minutes filled the liquid. The salt was isolated and crystallised from water in yellow needles (5 g.), m. p. 218—219° (Found: S, 7·1. $C_{25}H_{22}O_4N_2S$ requires S, 7·2%). The orange-yellow, alcoholic solution exhibits a faint fluorescence, but the light yellow acetic acid solution has a vivid light green fluorescence. The colourless solution in concentrated sulphuric acid is not fluorescent, but on the addition of water the yellow colour and green fluorescence appear. The solubility in water is approximately: at 25°, 1 part in 70 parts; at 95°, 1 part in 7 parts. Decomposition of this methosulphate with 50% aqueous potash yielded an amorphous red powder.

2-*Keto*-1-*methyl*-5 : 6-(2′ : 3′-*diphenylpyrrolo*)(4′ : 5′)-1 : 2-*dihydroquinoline* (III, modified as in IIIA).—A cold concentrated aqueous solution of the above methosulphate (4 g.) was added to a 10% sodium hydroxide solution (50 c.c.) containing potassium ferricyanide (5·9 g.), and the mixture was kept for an hour and frequently shaken. The product was isolated by means of ether and then extracted with boiling light petroleum; the solutions on concentration to a small volume deposited a pale yellow powder. The *quinolone* crystallised from ether in pale yellow needles, m. p. 195·5° (Found: C, 78·8; H, 5·2. $C_{24}H_{18}ON_2,H_2O$ requires C, 78·3; H, 5·4%); it is readily soluble in most organic solvents.

5- *and* 7-*Amino*-2 : 4-*diphenylquinoline* (IV, V).—*p*-Aminoacetanilide condenses with dibenzoylmethane to an anil, but ring closure of this could not be effected under a variety of conditions. The action of sulphuric acid on the anil, followed by treatment with aqueous sodium hydroxide gave a *substance*, m. p. 237·5—238·5°, crystallising from alcohol. This appeared to be the sodium salt of a sulphonic acid of the required base. 70% Sulphuric acid and also zinc chloride gave no useful results. We therefore directed our attention to *m*-phenylenediamine derivatives, but here too the experiments met with little success, since the yields of the desired aminodiphenylquinolines were only 5%. A mixture of *m*-phenylenediamine (6 g.) and dibenzoylmethane (12 g.) was heated at 140° for 1 hour; powdered zinc chloride (10 g.) was then introduced, and the temperature maintained at 175—180° for 5 hours. The bases produced were rendered to benzene, and the dried extract on concentration and keeping deposited a mixture of short, thick, prismatic needles and fine, silky needles. These were separated, and after many crystallisations from alcohol and benzene the two forms were obtained pure, their m. p.'s not being altered by further crystallisation; the former variety had m. p. 168·5° (Found: C, 85·0; H, 5·5%), and the latter had m. p. 187° (Found: C, 84·5; H, 5·8. $C_{21}H_{16}N_2$ requires C, 85·1; H, 5·4%); by analogy with other 5- and 7-substituted quinoline derivatives, the substance, m. p. 168·5°, should be the 5-substituted isomeride. The yellow colour of the base, m. p. 187°, is the paler of the two, but in other respects the properties of these substances are closely similar; a mixture had m. p. 142°. The bases may be diazotised, and then couple with β-naphthol to give bright red azo-compounds.

6-*Amino*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (VI).—*p*-Nitrophenylhydrazine (the method of Hodgson and Beard, *J. Soc. Chem. Ind.*, 1926, **45**, 56T, gives almost theoretical yields) was converted into 6-nitrotetrahydrocarbazole, as described by Borsche, Witte, and Bothe (*Annalen*, 1908, **359**, 53) (yield, 80%), but the recorded processes for the reduction of this substance (compare Perkin and Plant, J., 1921, **119**, 1833; Plant and Edwards, *loc. cit.*) gave only 20—40% yields. The use of sodium sulphide as the reducing agent led to still lower results, but a 73% yield was obtained by means of iron powder and hydrochloric acid in alcoholic solution (compare West, J., 1925, **127**, 494). 6-Nitrotetrahydrocarbazole (20 g.), dissolved in boiling 90% alcohol (70 c.c.) (reflux condenser, mechanical stirrer, and wide, stoppered side-tube) and concentrated hydrochloric acid (1 c.c.), was reduced by the gradual addition of iron powder (24 g.) during 45 minutes and subsequent boiling for 3—4 hours. The mixture was filtered hot and the residue washed with boiling alcohol; the amine (12·5 g.) was isolated from the filtrate by precipitating neutral impurities with concentrated hydrochloric acid (50 c.c.) and separating the hydrochloride by the further addition of hydrochloric acid (100 c.c.). Extraction of the neutral substances by water yielded some more amine hydrochloride, and the final acid mother-liquor was concentrated, basified with ammonia and the crude base crystallised from water.

Phenyl α-Tetrahydrocarbazylamino(6)*-styryl Ketone.*—A mixture of dibenzoylmethane (9·5 g.), 6-aminotetrahydrocarbazole (7·6 g.), and acetic acid (35 c.c.) was refluxed for 1 hour, and the solvent then removed by distillation under diminished pressure. The residue crystallised from alcohol in yellow prisms (8 g.), m. p. 229·5—230° (Found: C, 82·1; H, 6·2. $C_{27}H_{24}ON_2$ requires C, 82·6; H, 6·1%). This substance has very feebly basic properties, and when boiled with hydrochloric acid it first gives a red substance and is then slowly hydrolysed. Its solution in concentrated sulphuric acid is yellow and non-fluorescent, but on keeping the colour fades and a bright violet fluorescence develops; on the addition of water a red salt is precipitated.

2 : 4-*Diphenyl*-5 : 6-(4′ : 5′ : 6′ : 7′*-tetrahydroindolo*)(2′ : 3′)*-quinoline* (VII).—This substance may be obtained from the foregoing ketone in several ways, *e.g.*, (1) by keeping a cold sulphuric acid solution for 24 hours, (2) by heating a sulphuric acid solution to 60—65° for 5 minutes, (3) by passing hydrogen chloride into a solution in acetic acid, and (4) by heating it with half its weight of zinc chloride or phosphoric anhydride. The best procedure is the following: A mixture of the ketone (12·5 g.) and phosphoryl chloride (80 c.c.) was boiled for 1 hour, and the red liquid then gradually added to ice and water with stirring. The dull red solid was collected, washed with water, and triturated with ammonia; the resulting light yellow powder was collected, washed, dried at 105°, and extracted with ether in a Soxhlet apparatus from which air was excluded by means of carbon dioxide; the ethereal solution, on keeping, deposited yellow crystals which were collected and washed in an atmosphere of carbon dioxide, and finally dried in a vacuum desiccator (total yield, 9·5 g., 76%) (Found: C, 86·4; H, 6·1. $C_{27}H_{22}N_2$ requires C, 86·6; H, 5·9%). 2 : 4-*Diphenyl*-

5 : 6-(4′ : 5′ : 6′ : 7′-*tetrahydroindolo*)(2′ : 3′)-*quinoline* crystallises from ether in yellow prisms, m. p. 235°, and dissolves in most organic solvents to yellow solutions exhibiting a greenish-blue fluorescence. Its salts are red and sparingly soluble in water. The red solution in acetic acid gives a pink precipitate on addition of water, whilst the colourless solution in sulphuric acid exhibits a brilliant violet fluorescence. The *picrate*, prepared in alcoholic solution in an atmosphere of carbon dioxide, crystallised in orange-red needles, m. p. 241° (decomp. 243°). The most characteristic property of the base is the ease with which it absorbs oxygen from the air when in solution in organic solvents, especially ether or chloroform; it appears to be relatively stable in the solid state. The product, *dioxydiphenyltetrahydroindoloquinoline*, is readily isolated and crystallises from ether in long, colourless needles which decompose suddenly with bright incandescence at 168°, but without melting (Found: C, 79·4; H, 5·6; N, 6·7. $C_{27}H_{22}O_2N_2$ requires C, 79·8; H, 5·4; N, 6·9%). The dirty green solution in concentrated sulphuric acid slowly develops a most intense green fluorescence, giving the effect of opacity. The incandescence observed on heating suggests that this curious substance is a peroxide.

Metho-derivatives.—A mixture of the base (5 g.), pure methyl sulphate (3·6 g.), and benzene (140 c.c.) was boiled for 2·5 hours, air being displaced from the apparatus by nitrogen. The solvent was removed by distillation, the residual red oil dissolved in dry acetone (about 20 c.c.), and on keeping, red needles separated. These were collected (3·5 g.), and a further quantity (0·6 g.) could be obtained from the mother-liquor by concentration to two-thirds of its volume (further concentration gave uncrystallisable material). The separated *methosulphate* is sparingly soluble in acetone and moderately readily soluble in water. On heating, it decomposes at a high temperature without melting. The colourless solution in concentrated sulphuric acid exhibits a brilliant violet fluorescence. The related *methopicrate* crystallised from acetone in long, slender, meshed, orange-red needles, m. p. 252—254° (decomp.).

The methosulphate (4 g.) was added to benzene (100 c.c.) and 50% aqueous potassium hydroxide (50 c.c.), and the mixture heated for 1½ hours with occasional shaking; air in the apparatus was displaced by nitrogen. The bright red colour in both layers disappeared, the aqueous solution becoming colourless and the benzene layer intense brilliant green. In all the subsequent operations access of air was prevented by nitrogen. The aqueous layer was siphoned off and potassium hydroxide (35 g.) added to the benzene layer, which was then boiled for 1 hour, filtered, and dried for 12 hours over potassium hydroxide. The solution was filtered, heated, and the base precipitated by the addition of boiling light petroleum (b. p. 60—80°) as a bright green solid, which was collected and dried in a vacuum. At this stage there was for the first time a momentary contact with air, but the desiccator had been previously filled with nitrogen and was quickly evacuated. Weighing was carried out with the utmost dispatch, since absorption of oxygen was obviously indicated during the operation (Found: C, 79·3, 78·8; H, 6·4, 6·3. $C_{28}H_{28}O_2N_2$ requires C, 79·2; H, 6·6%). The dark green powder becomes brown and then black when exposed to air. Treatment with acids gives red salts resembling the metho-salts mentioned above, and the solution in sulphuric acid exhibits violet fluorescence.

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