CCLXXIII.—*The Synthesis of* iso*Indenoquinolines. Part I.*

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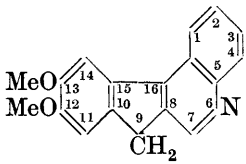
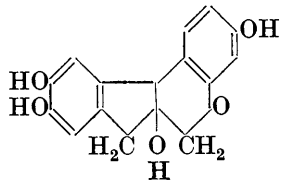
THE present interest in quinoline derivatives, particularly as antimalarials (compare Barger and Robinson, J., 1929, 2947), together with the fact that 4-keto-1 : 2 : 3 : 4-tetrahydroquinoline (J., 1924, **125**, 1608), subsequently referred to as the quinolone, has a local anæsthetic action, made it of interest to attempt to convert the latter into *iso*indenoquinolines (I) with a view to testing the physiological properties of the resulting compounds. Indenoquinoline (III) has been described by Noelting and Blum (*Ber.*, 1901, **34**, 2471) and Ruhemann and Levy (J., 1913, **103**, 563), who prepared it by condensing *o*-aminobenzaldehyde and α-ketohydrindene.

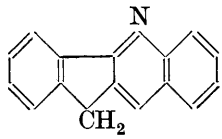
Further, the replacement of the nitrogen in 6 : 7 : 8 : 16-tetrahydro-3 : 12 : 13-trimethoxy*iso*indenoquinoline by oxygen by the method of von Braun (*Ber.*, 1905, **38**, 850) offers possibilities for the introduction of a hydroxyl group into position 8 as demanded by the brazilin formula (II). Pfeiffer and Oberlin (*Ber.*, 1927, **60**, 2142) and Perkin, Rây, and Robinson (J., 1927, 2094) have described the synthesis of trimethylanhydrobrazilin, but apparently have not yet succeeded in converting the latter into brazilin itself.

(IA.)  (IB.)

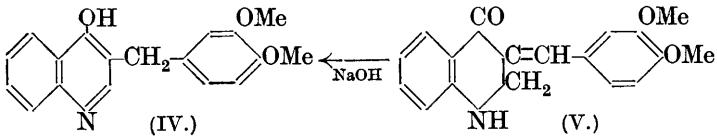
This communication describes the synthesis of both forms of 12 : 13-*dimethoxy*iso*indenoquinoline* (IA & B). In the first place the quinolone was condensed with veratraldehyde in ethyl-alcoholic solution by using sodium hydroxide as catalyst. A colourless compound resulted which could not be reduced by either sodium amalgam or palladium and hydrogen, and, as it was soluble in sodium hydroxide, and on treatment with phosphorus oxychloride gave a chloro-derivative by replacement of a hydroxyl group, it was clearly 4-*hydroxy*-3-*homoveratrylquinoline* (IV). Treatment

with cold concentrated sulphuric acid did not effect ring closure, but gave a *sulphonic acid* in which the substituent has in all probability entered in the 6′-position, *i.e.*, para to the 3′-methoxyl group in the veratryl residue. A like assumption is made below for the constitution of the monobromo-products. The sulphonic acid crystallises from water, and is then readily soluble in ethyl alcohol and acetic acid, but it immediately separates from the solutions and is then no longer soluble in these solvents, indicating intramolecular salt formation.

(II.) 

 (III.)

Bromination of (IV) in acetic acid gave 4-*hydroxy*-3-(6′-*bromo-homoveratryl*)*quinoline*, whilst the action of bromine on 4-*chloro*-3-*homoveratrylquinoline* in chloroform solution gave the 6′-*monobromo*-derivative, but in acetic acid a mixture of this mono- and a *dibromo*-compound resulted. Attempts to effect ring closure by the action of aluminium chloride on 4-chloro-3-homoveratrylquinoline, and by Ullmann copper treatment of 4-chloro-3-(6′-bromohomoveratryl)quinoline were unsuccessful, the latter compound being recovered unchanged.



When, however, the quinolone and veratraldehyde were condensed in glacial acetic acid by means of hydrogen chloride, 4-*keto*-3-*veratrylidene*-1 : 2 : 3 : 4-*tetrahydroquinoline* (V) resulted, which is readily converted into the isomeride (IV) by means of alcoholic sodium hydroxide. In order to eliminate this possibility in subsequent work, the N-*acetylquinolone* was used in the above condensation, whereby the N-*acetyl* derivative of (V) was produced. Reduction of this compound in acetic acid by means of palladised charcoal and hydrogen gave 4-*keto*-1-*acetyl*-3-*homoveratryl*-1 : 2 : 3 : 4-*tetrahydroquinoline*, although Perkin, Rây, and Robinson (J., 1926, 943) state that palladium and hydrogen convert 3-veratrylidene-7-methoxychromanone mainly into 3-homoveratryl-7-methoxychroman. Pfeiffer and Oberlin (*loc. cit.*) showed, however, that when platinum was used as catalyst the keto-group was left intact.

Treatment of 4-keto-1-acetyl-3-homoveratryl-1 : 2 : 3 : 4-tetrahydroquinoline (which gives an *oxime*) with warm sulphuric acid (80%) effected ring closure with simultaneous deacetylation and oxidation, giving 12 : 13-dimethoxy*iso*indenoquinoline (I). When this compound is rapidly crystallised from benzene and then methyl alcohol, long, thin, faintly yellow prisms are obtained, but slow crystallisation from benzene leads to a mixture of this form with stout reddish-brown prisms, both melting, alone or mixed, at 193—194°. The fact that the mixed crystalline deposit in benzene is not transformed completely into one form, taken in conjunction with the fluorescence data given in the experimental section, appears to rule out the possibility that the two forms are polymorphic. As the ring structure (I) appears to be a stable one, and a model indicates that it is uniplanar, thus ruling out stereoisomeric possibilities, it seems that the occurrence of the two forms is due to tautomerism in the 7 : 8 : 9 three-carbon system. The form (IB), having an *o*-quinonoid structure, would be expected to be coloured.

EXPERIMENTAL.

4-Keto-1-acetyl-1 : 2 : 3 : 4-tetrahydroquinoline.—4-Keto-1 : 2 : 3 : 4-tetrahydroquinoline (5 g.) was refluxed with ether (75 c.c.) and acetic anhydride (7·5 c.c.) for 18 hours. The bulk of the ether was removed, and solid potassium carbonate and then water were added, followed by the removal of the residual ether. The pale yellow solid was collected, washed with water, then with ether, and dried (5·6 g.). The *compound*, which crystallised from a small volume of methyl alcohol in stout colourless prisms, m. p. 94°, was pure enough for subsequent operations (Found : C, 69·9; H, 6·1. $C_{11}H_{11}O_2N$ requires C, 69·8; H, 5·8%).

4-Hydroxy-3-homoveratrylquinoline (IV).—A solution of the quinolone (5·8 g.) and veratraldehyde (6·8 g.) in ethyl alcohol (60 c.c.) containing sodium hydroxide (1·2 g.) was refluxed for 18 hours on the water-bath, the bulk of the alcohol removed under reduced pressure, and water and a slight excess of acetic acid were added. The pale yellow solid was collected, dried (10 g.), and crystallised from ethyl alcohol, giving slender colourless prisms, m. p. 225° (Found : C, 73·1; H, 6·0. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8%).

4-Hydroxy-3-homoveratrylquinoline is sparingly soluble in most organic solvents, soluble in warm dilute sodium hydroxide, and gives a faint purple solution in sulphuric acid. Bromination in acetic acid gave *4-hydroxy-3-(6′-bromohomoveratryl)quinoline*, colourless irregular prisms, m. p. 233°, from alcohol (Found : Br, 21·3. $C_{18}H_{16}O_3NBr$ requires Br, 21·4%).

4-Hydroxy-3-homoveratrylquinoline-6'-sulphonic Acid.—4-Hydroxy-3-homoveratrylquinoline (0·5 g.) was stirred into solution in cold concentrated sulphuric acid (2 c.c.), left over-night, ice added, the precipitate dissolved in sodium hydroxide, again precipitated by hydrochloric acid, collected, and dried (0·7 g.). The *compound* was crystallised from boiling water (200 c.c.) and then from acetic acid; colourless rhombic prisms, m. p. 308° (decomp.) (Found: C, 57·85; H, 4·7. $C_{18}H_{17}O_6NS$ requires C, 57·6; H, 4·6%). It dissolves easily in cold sodium bicarbonate solution.

4-Chloro-3-homoveratrylquinoline.—The above hydroxy-compound (8 g.) was dissolved in phosphoryl chloride (24 c.c.), heated on the water-bath over-night, part of the excess solvent removed under reduced pressure, and ice and then an excess of sodium hydroxide were added. The resulting colourless gum which soon solidified was collected and dried (8 g.); it crystallised from light petroleum (b. p. 80—100°) as colourless well-formed prisms (7·3 g.), m. p. 96° (Found: C, 69·1; H, 5·2; N, 4·4; Cl, 11·3. $C_{18}H_{16}O_2NCl$ requires C, 69·0; H, 5·1; N, 4·5; Cl, 11·2%). The *chloro*-compound is easily soluble in most organic solvents, and in dilute hydrochloric acid, giving a light green fluorescent solution. *4-Chloro-3-homoveratrylquinoline methiodide*, formed with methyl iodide in acetone, crystallises from ethyl alcohol in orange prisms, m. p. 208° (decomp.) (Found: C, 49·9; H, 4·4. $C_{18}H_{16}O_2NCl,MeI$ requires C, 50·0; H, 4·2%).

4-Chloro-3-(6'-bromohomoveratryl)quinoline.—Bromine (0·15 c.c.) in chloroform (1 c.c.) was added to 4-chloro-3-homoveratrylquinoline (0·8 g.) in cold chloroform (5 c.c.). The solution was kept for some hours, the solvent removed, dilute sodium hydroxide added, and the colourless solid collected and dried; it crystallised from light petroleum (b. p. 80—100°) as thin, colourless, glistening prisms, m. p. 112° (Found: N, 3·8; Cl, 9·0; Br, 20·3. $C_{18}H_{15}O_2NClBr$ requires N, 3·6; Cl, 9·1; Br, 20·4%). When acetic acid was substituted for chloroform in the above bromination, and the monobromo-compound was extracted with light petroleum from the reaction mixture, a *dibromo*-compound was left, giving well-formed light yellow prisms from ethyl alcohol, m. p. 220° (decomp.) (Found: Cl, 7·3; Br, 33·6. $C_{18}H_{14}O_2NClBr_2$ requires Cl, 7·5; Br, 33·9%).

4-Keto-3-veratrylidene-1 : 2 : 3 : 4-tetrahydroquinoline (V).—4-Keto-tetrahydroquinoline (0·45 g.) and veratraldehyde (0·45 g.) were dissolved in glacial acetic acid (3 c.c.), saturated with dry hydrogen chloride with ice cooling, and left over-night. The resulting red solution was poured on ice, and the solid collected (0·6 g.); it crystallised from ethyl alcohol as light red plates, m. p. 177—178°

(Found : C, 73·2; H, 5·95. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8%). The *compound* (V) gives a persistent, intensely magenta solution in sulphuric acid, in marked contrast to the faint coloration given by the isomeride (IV). It is sparingly soluble in most organic solvents, and when its suspension in alcohol is boiled with a little sodium hydroxide it is quickly converted into (IV).

4-*Keto*-1-*acetyl*-3-*veratrylidene*-1 : 2 : 3 : 4-*tetrahydroquinoline*.—The acetylquinolone (2 g.) and veratraldehyde (1·9 g.) were condensed in acetic acid (15 c.c.) as above, giving 3·5 g. of a solid, which crystallised from ethyl alcohol in bright yellow plates, m. p. 164° (Found : C, 71·1; H, 5·7; N, 4·0. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·6; N, 4·2%). This *compound* gives a sulphuric acid solution exactly like that given by the preceding compound.

4-*Keto*-1-*acetyl*-3-*homoveratryl*-1 : 2 : 3 : 4-*tetrahydroquinoline*.—The previous acetyl compound (1 g.) was dissolved in glacial acetic acid (30 c.c.), palladised charcoal (0·5 g.; Houben–Weyl, **2**, 324, 3rd edn.) added, and the mixture well stirred in an atmosphere of hydrogen for 6 hours. The acetic acid was then removed under reduced pressure from the colourless filtrate, ice added, and the colourless precipitated gum left over-night. The resinous mass was then collected and crystallised from methyl alcohol (1 c.c.) by partial evaporation, giving stout colourless rhombs (0·5 g.), m. p. 89° (Found : C, 70·8; H, 6·4. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·2%). The *compound* is sparingly soluble in ether but readily so in most organic solvents, and gives an intense reddish-brown sulphuric acid solution. The *oxime* crystallised from alcohol in colourless irregular prisms, m. p. 208° (Found : C, 67·4; H, 6·3. $C_{20}H_{22}O_4N_2$ requires C, 67·8; H, 6·2%).

12 : 13-*Dimethoxy*iso*indenoquinoline* (IA and IB).—The above reduced compound (0·4 g.) was dissolved in sulphuric acid (4 c.c.; 80%) and heated for 30 minutes in the water-bath, the initial brownish-red solution becoming deep brownish-yellow. Ice and an excess of ammonia were added, the light grey precipitate was collected, washed with water, and dried on a porous plate (0·3 g.). The solid was extracted first with ether, then with boiling benzene (5 c.c.), and the extract filtered from a trace of brown insoluble matter. The benzene solution was evaporated to 1 c.c., whereupon light yellow prisms, m. p. 188—190° (0·15 g.), quickly separated. Rapid recrystallisation from a small volume of methyl alcohol gave long, very faintly yellow prisms, m. p. 193—194°. On standing, a benzene solution of this compound deposited compact brownish-red prisms in addition to the light yellow form. These were separated by hand picking, and melted at 193—194°, alone or when mixed with the yellow form (Found : for yellow form, C, 77·9; H, 5·6;

for brown form, C, 78·1; H, 5·4; N, 5·0. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4; N, 5·1%).

Both forms of 12 : 13-*dimethoxy*iso*indenoquinoline* give a violet fluorescence in benzene or ethereal solution, whilst in commercial absolute alcohol the fluorescence is intense green, changed to violet on the addition of a fragment of anhydrous potassium carbonate. If the green-fluorescing alcoholic solution is heated for 30 minutes on the water-bath, a reddish-brown solution results, which, on cooling, deposits the compound in reddish-brown prisms; no such change takes place if a piece of potassium carbonate is present. Concentrated nitric acid gives a non-fluorescent deep yellow solution, in contrast to the eosin colour given by trimethylanhydrobrazilin (Perkin, Rây, and Robinson, *loc. cit.*), and in sulphuric and hydrochloric acids yellow solutions with intense green fluorescences result.

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