Experiments on the Synthesis of Tetrahydroworenine.

By JOHN A. D. JEFFREYS.

[Reprint Order No. 5676.]

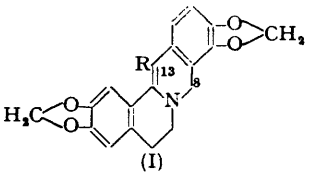
Attempts to synthesise tetrahydroworenine (I; R = Me) led as far as 5 : 6 : 13 : 13*a*-tetrahydro-2 : 3 : 10 : 11-tetrahydroxy-8*H*-dibenzo[*a*, *g*]pyridocoline hydrochloride (cf. XI; R = H), but no further.

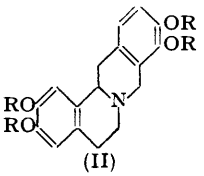
WORENINE, isolated as its tetrahydro-derivative from *Coptis japonica* by Kitasato (*J. Pharm. Soc. Japan*, 1927, No. 542, 28; *Chem. Abs.*, 1927, **21**, 2700), is a homologue of coptisine (I; R = H), whose tetrahydro-derivative has been synthesised (Späth and Posega, *Ber.*, 1929, **62**, 1029); it has been shown not to be the 8-methyl compound (Kitasato, *Acta Phytochim., Tokyo*, 1927, **3**, 175; *Chem. Abs.*, 1928, **22**, 1780), and hence was assigned structure (I; R = Me). Corydaline (II; R = Me) has been synthesised (Späth and Kruta, *Ber.*, 1929, **62**, 1024) by methylating the corresponding tetrahydric phenol, which in turn was prepared from methylenepapaverine (III). It was proposed to prepare compound (II; R = H), and thence the presumed tetrahydroworenine.

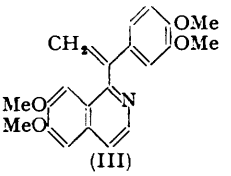
3 : 4-Dimethoxyhydratroponitrile was prepared by alkylation of homoveratronitrile, and hydrolysed to the acid, which had previously been prepared by Bougault from methyleugenol (*Ann. Chim.*, 1902, **25**, 562). The alkylation gave a quantity of oil as well as the crystalline nitrile, and hydrolysis of the oily mixture gave an oily acidic fraction, and a crystalline neutral compound. Separation of the acids by fractional liberation from their sodium salts gave, in order of increasing basicity, α-(3 : 4-dimethoxyphenyl)*iso*butyric acid (IV; R = Me), 3 : 4-dimethoxyhydratropic acid (IV; R = H), and homoveratric acid,

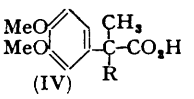
the first of these being present in relatively small amount. The neutral compound could also be prepared by treating α-(3 : 4-dimethoxyphenyl)*iso*butyric acid with thionyl chloride, then with ammonia, showing it to be the corresponding amide. The neutral compound gave analyses consistently and accurately two hydrogen atoms short for the amide, probably owing to the splitting off of methane from the *gem*-dimethyl group during combustion.

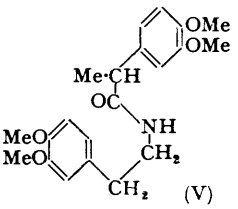
Reaction of 3 : 4-dimethoxyhydratropoyl chloride with 2-(3 : 4-dimethoxyphenyl)-ethylamine gave the amide (V), which on treatment with phosphorus oxychloride, either alone or, better, in chloroform, was converted into the hydrochloride of the dihydro*iso*-quinoline (VI). Liberation of the free base gave an oil which did not crystallise but on

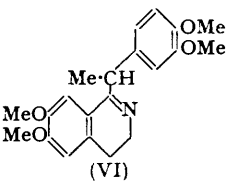

(I)

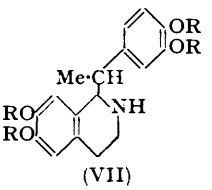

(II)


(III)


(IV)

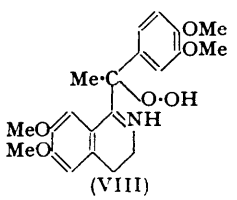

(V)

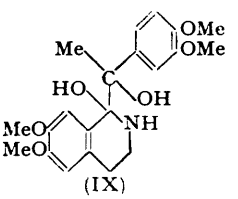

(VI)

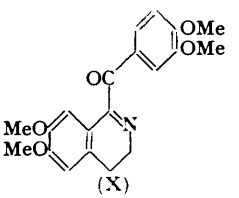

(VII)

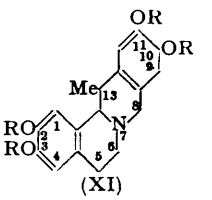
exposure in ethereal solution to air gave an unstable crystalline material; this may be (VIII) or less probably (IX); its colour reaction with acetic anhydride is similar to that of the ketone (X) prepared by aerial oxidation of the corresponding 1-(3 : 4-dimethoxybenzyl) derivative (Buck, Perkin, and Stevens, *J.*, 1925, 1470). Reduction of the dihydro*iso*-quinoline hydrochloride with Adams catalyst in dilute hydrochloric acid gave the hydrochloride of the tetrahydro*iso*quinoline (VII; R = Me).

For comparison, the hydrochloride of the tetrahydric phenol (XI; R = H) was prepared by condensing the tetrahydro*iso*quinoline (VII; R = Me) with formaldehyde, and demethylating the product with hydriodic acid and red phosphorus, and replacing the iodide ion by chloride ion. Similar demethylation of the *iso*quinoline (VII; R = Me) gave the hydrochloride of the phenol (VII; R = H), previously prepared by Späth and Kruta (*loc. cit.*), but not well characterised: it was unusually sensitive to oxidation. Condensation of the phenol (VII; R = H) with a slight excess of formaldehyde was accompanied by a marked colour change, and under the conditions used by Späth and Kruta (*loc. cit.*), a good yield of a highly crystalline product was generally obtained. Attempts to carry out the reaction under physiological conditions gave only amorphous material, as did one of a series of identical runs under Späth and Kruta's conditions. The reason for this is not known.


(VIII)


(IX)


(X)


(XI)

Though the only crystalline material Späth and Kruta obtained by methylation of this product was corydaline (II; R = Me), it is likely that the condensation with formaldehyde yielded a mixture of the hydrochlorides of (XI and II; R = H). The evidence from the very indefinite melting points is of no help in this matter; the compounds became

increasingly gummy with rising temperature, and the melting points recorded may, in fact, be the temperatures at which the compounds dissolved in their water of crystallisation.

Attempts to introduce the methylenedioxy-group into the free base by means of methylene halides or methylene sulphate were unsuccessful, and attempts to brominate the compound (XI; R = H) to the tetrabromo-derivative, with a view to oxidising the product to the bis-*o*-quinone which could be treated with diazomethane (cf. Horner and Lingnau, *Annalen*, 1951, **573**, 30), resulted in the destruction of the compound before the theoretical amount of bromine had been taken up.

Experimental

Alkylation of Homoveratronitrile.—To a solution of sodamide, prepared from sodium (4·3 g.), in liquid ammonia (500 c.c.) homoveratronitrile (30 g.) was added. After 10 minutes' swirling, methyl iodide (14 c.c.) was added dropwise, with swirling. The ammonia was evaporated, water added to the residue, and the insoluble material collected and pressed between filter papers to remove oil. Recrystallisation of the solid from light petroleum (b. p. 40—60°) gave rhombic tablets of 3 : 4-*dimethoxyhydratroponitrile* (16·7 g., 52%), m. p. 71° (Found : C, 68·9; H, 6·9; N, 7·6. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%). The yield in this alkylation was unchanged when potassium was substituted for sodium. The treatment of the oily material is described later.

3 : 4-*Dimethoxyhydratropic Acid.*—This acid was produced by refluxing the nitrile with aqueous-ethanolic sodium hydroxide till ammonia ceased to be evolved (about 20 hr.). The ethanol was evaporated, an excess of hydrochloric acid added, and the acid extracted with ether. Evaporation of the dried extract left the acid as an oil which was recrystallised from light petroleum (b. p. 40—60°), giving ill-defined plates, m. p. 50°, of the anhydrous acid (Found : C, 63·0; H, 6·8. Calc. for $C_{11}H_{14}O_4$: C, 62·9; H, 6·7%); Bougault (*loc. cit.*) gives m. p. 50°, but says that it can be obtained crystalline only by dehydrating a crystalline sample of the monohydrate.

N-1-(3 : 4-*Dimethoxyphenylethyl*)-3 : 4-*dimethoxyhydratropamide* (V).—The crude acid from 13·4 g. of nitrile was refluxed with thionyl chloride (20 c.c.) in chloroform (25 c.c.) for 1 hr., the chloroform evaporated, and the residual thionyl chloride removed by evaporation with toluene. The acid chloride was taken up in dry ether and added to 2-(3 : 4-dimethoxyphenyl)-ethylamine (12 g.) in dry pyridine–ether (30 + 200 c.c.). Next day sufficient chloroform and water were added to dissolve all precipitated material, and the non-aqueous phase was washed with dilute hydrochloric acid, sodium carbonate solution, and water. Evaporation of the dried solvents left crude N-1-(3 : 4-*dimethoxyphenylethyl*)-3 : 4-*dimethoxyhydratropamide* (17·6 g., 70% based on the nitrile). Recrystallisation from toluene gave needles, m. p. 117° (Found : C, 67·7; H, 7·2; N, 3·9. $C_{21}H_{27}O_5N$ requires C, 67·6; H, 7·2; N, 3·8%).

1-[1-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-3 : 4-*dihydro*-6 : 7-*dimethoxy*isoquinoline *Hydrochloride* (VI).—A mixture of the foregoing amide (3·6 g.) and phosphorus oxychloride (30 c.c.) was refluxed for 45 min., then evaporated under reduced pressure on the water-bath. To the residue ice and dilute hydrochloric acid were added, the mixture was filtered, and the filtrate was extracted with ether. The acid liquor was made alkaline with aqueous sodium hydroxide, the base extracted with ether, then re-extracted with dilute hydrochloric acid, and this procedure repeated. The acid liquid gradually deposited the required *hydrochloride* (2·9 g.) as yellow crusts. Repeated recrystallisation from dilute hydrochloric acid gave hygroscopic yellow needles, m. p. 91—93° (Found : C, 63·9; H, 7·0; N, 3·7; Cl, 8·9. $C_{21}H_{26}O_4NCl$ requires C, 64·4; H, 6·6; N, 3·6; Cl, 9·1%). In later runs a mixture of phosphorus oxychloride (1 part) and chloroform (3 parts) was used, refluxing continued for 2 hr., and during subsequent working up, the temperature kept below 70°; a cleaner product was so obtained. The *methiodide*, which was very soluble in methanol or acetone, crystallised from acetone–ether in yellow nodules, m. p. 173° (slight decomp.) (Found : I, 25·7. $C_{22}H_{28}O_4NI$ requires I, 25·5%).

Attempts to isolate the free base gave an oil, which did not crystallise even when its solution in ether was stored at 0° for several weeks. Exposure of its solutions in moist ether to the air caused the separation of colourless needles. This material was unstable, decomposing on storage or on being heated in solution, and had m. p. 90—110° (decomp.), depending on rate of heating {Found, on two samples : (i) (crystallised from ether), C, 64·9; H, 7·1; (ii) [crystallised from benzene–light petroleum (b. p. 60—80°)], C, 65·5; H, 7·0. $C_{21}H_{25}O_6N$ requires C, 65·1; H, 6·5. $C_{21}H_{27}O_6N$ requires C, 64·8; H, 6·9%}. The substance gave a yellow solution in dilute

hydrochloric acid; its solution in acetic anhydride was deep yellow at first, but faded on boiling, then became intense green.

1-[1-(3 : 4-*Dimethoxyphenyl*)*ethyl*]-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*isoquinoline *Hydrochloride* (VII; R = H).—A solution of the corresponding dihydro*iso*quinoline in dilute hydrochloride acid was shaken with hydrogen in presence of Adams platinum oxide till uptake of hydrogen ceased. After filtration from the catalyst, evaporation of the solution gave the *hydrochloride* of the tetrahydro-base as needles, m. p. *ca.* 108° (Found : C, 63·6; H, 7·6; N, 3·6; Cl, 8·9. $C_{21}H_{28}O_4NCl$ requires C, 64·0; H, 7·1; N, 3·6; Cl, 9·0%). Acetylation with acetic anhydride and pyridine in the cold gave an *acetyl derivative*, as felted needles (from methanol), m. p. 151° (Found : C, 69·0; H, 7·2; N, 3·8. $C_{23}H_{29}O_5N$ requires C, 69·2; H, 7·2; N, 3·5%).

5 : 6 : 13 : 13a-*Tetrahydro*-2 : 3 : 10 : 11-*tetramethoxy*-13-*methyl*-8H-*dibenzo*[a, g]*pyridocoline* (XI; R = Me) (Ring Index no. 2703).—The preceding hydrochloride (0·8 g.), concentrated hydrochloric acid (1 c.c.), water (5 c.c.), and 40% aqueous formaldehyde (2·4 c.c.) were heated on the water-bath for 45 min., the solution was evaporated, and the residue taken up in water. Addition of aqueous sodium hydroxide in excess, followed by extraction with chloroform and evaporation of the solvent, left a crystalline residue. Recrystallisation from methanol gave the *dibenzopyridocoline* as tablets (0·65 g.), m. p. 150° (decomp.) (Found : C, 71·5; H, 7·2; N, 4·0. $C_{22}H_{27}O_4N$ requires C, 71·6; H, 7·3; N, 3·8%). The *hydrochloride* was very soluble in water, and was obtained by treatment of a solution of the free base in dry ether with dry hydrogen chloride as a somewhat hygroscopic white powder, m. p. 150—165° (Found : C, 64·9; H, 7·1; N, 3·5; Cl, 8·5. $C_{22}H_{28}O_4NCl$ requires C, 65·0; H, 6·9; N, 3·5; Cl, 8·8%).

5 : 6 : 13 : 13a-*Tetrahydro*-2 : 3 : 10 : 11-*tetrahydroxy*-13-*methyl*-8H-*dibenzo*[a,g]*pyridocoline Hydrochloride* (XI; R = H).—The above base (0·5 g.) was boiled under reflux with concentrated hydriodic acid (7 c.c.) and red phosphorus for 6 hr., the solution evaporated *in vacuo* on a water-bath, and the residue taken up in water and treated with excess of silver chloride. After filtration from the silver salts, the solution was concentrated, and the phenol *hydrochloride* (0·32 g., 68%) was deposited as prisms which on being dried *in vacuo* collapsed to a white powder, m. p. *ca.* 213° (shrinking from 200°), which tenaciously retained one molecule of water of crystallisation (Found, in a sample dried for 6 hr. at 100° *in vacuo* : C, 59·5; H, 6·1; N, 3·9; Cl, 9·7. $C_{22}H_{20}O_4NCl,H_2O$ requires C, 58·8; H, 6·0; N, 3·8; Cl, 9·7%). In attempts to brominate this compound in dilute aqueous or acetic acid solution containing free hydrobromic acid, less than 2 mols. of bromine were taken up. Evaporation of the solutions left brown materials from which small amounts of crystalline products could be isolated.

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dihydroxy*-1-[1-(3 : 4-*dihydroxyphenyl*)*ethyl*]iso*quinoline* (cf. Späth and Kruta, *loc. cit.*).—The compound was prepared by demethylation of the tetramethoxy*iso*quinoline with hydriodic acid and red phosphorus, followed by conversion into the hydrochloride. This salt, crystallised from dilute hydrochloric acid, had m. p. 241° (decomp.) (lit., 241°); it was very sensitive to oxidation, and with ferric chloride gave a green colour, which rapidly changed through red to purple, the colours becoming more intense (Found : C, 60·4; H, 6·1; N, 4·0; Cl, 10·5. Calc. for $C_{17}H_{20}O_4NCl$: C, 60·5; H, 5·9; N, 4·1; Cl, 10·5%). With cold acetic anhydride and pyridine it gave a *penta-acetyl derivative*, as prisms (from methanol–ether), m. p. 137° (Found : C, 63·5; H, 6·0; N, 2·7. $C_{27}H_{29}O_9N$ requires C, 63·4; H, 5·7; N, 2·9%).

Condensation of the Phenol with Formaldehyde (cf. Späth and Kruta, *loc. cit.*).—The foregoing phenol hydrochloride (1·46 g.) in water (40 c.c.) was heated with 5% aqueous formaldehyde (2·20 c.c.) in a sealed tube at 100° for 5 hr. Immediately on addition of the formaldehyde, the solution became orange, but soon changed to purple, then intense yellow. At room temperature the purple lasted several hours, but at 100° the change was complete in less than 15 min. The liquid was filtered hot from traces of dark amorphous material, and acidified with hydrochloric acid. Grey prisms (1·34 g.) were deposited, which after two recrystallisations from very dilute hydrochloric acid formed white prisms, m. p. 194—196° (shrinking from 180°); mixed with the hydrochloride of (XI; R = H), it melted at *ca.* 205°. The crystals, which tenaciously retained water, did not collapse on being dried, as did those of the hydrochloride of (XI; R = H) (Found : in a sample dried for 12 hr. at 100° *in vacuo* : C, 58·8; H, 5·6; N, 4·2; Cl, 10·7. Calc. for $C_{18}H_{20}O_4NCl,H_2O$: C, 58·8; H, 6·0; N, 3·8; Cl, 9·7%).

(ii) A solution of the hydrochloride (0·33 g.) and 5·85% aqueous formaldehyde (0·55 c.c.) in air-free water (100 c.c.) was kept at room temperature for 2 days under carbon dioxide. This solution, which remained at pH 5·5, showed the colour changes described above, but yielded only amorphous material on concentration. Longer duration of the experiment gave an identical result.

Isolation of α-(3 : 4-*Dimethoxyphenyl*)iso*butyric Acid and its Amide.*—The oily material collected from a number of alkylations (p. 81) was boiled with sodium hydroxide solution till ammonia evolution ceased. An oil remained undissolved, which crystallised under ether. Recrystallisation from ether (first analysis), in which it was very sparingly soluble, or from benzene (second analysis), gave the amide as needles, m. p. 137° (Found : C, 65·1, 65·0; H, 6·9, 6·9; N, 6·1, 6·4. $C_{12}H_{17}O_3N$ requires C, 64·6; H, 7·6; N, 6·3%).

The acids were liberated and partly crystallised during several weeks at −20°. They neutralised 37·7 c.c. of N-sodium hydroxide, and from this solution they were fractionally liberated into chloroform by addition of 11 portions of acid, the last portion being an excess. Each chloroform extract was evaporated, and the residue taken up in light petroleum (b. p. 40—60°), and set aside to crystallise. Fractions 6—11 showed increasing insolubility, and crystallised fairly readily; the others tended to deposit an oil with the crystals. Fractions 8—11 gave homoveratric acid, fractions 1—6 gave 3 : 4-dimethoxyhydratropic acid. In fractions 1—4 there appeared prisms, which were hand-picked and recrystallised from carbon tetrachloride–light petroleum (b. p. 40—60°), to give α-(3 : 4-*dimethoxyphenyl*)iso*butyric acid* as prisms, m. p. 80—81° (Found : C, 64·3; H, 7·1. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·1%). Treatment of this acid with thionyl chloride in light petroleum (b. p. 80—100°), followed by concentrated aqueous ammonia, gave the amide, as needles (from benzene), m. p. 136°, undepressed on admixture with a sample isolated as described above.

The author is grateful to Mr. J. M. L. Cameron and Miss M. W. Cristie for the microanalyses.

GLASGOW UNIVERSITY. [*Received, August 23rd,* 1954.]