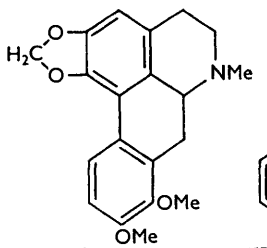
197. *Synthesis of (±)-Crebanine.*

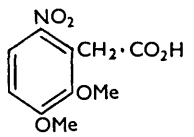
By T. R. GOVINDACHARI, K. NAGARAJAN, and C. V. RAMADAS.

The synthesis of (±)-crebanine is reported.

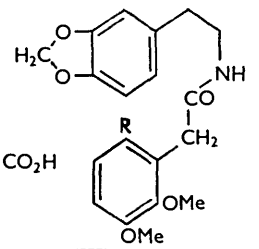
THE alkaloid, crebanine, $C_{20}H_{21}O_4N$, isolated by Japanese workers from *Stephania sasakii* and *S. capitata*, has been assigned structure (I) on the basis of degradative studies.[1] Manske,[2] considered that the methoxy-groups were in positions not accountable for by known biosynthetic routes and that the structure should be accepted with reserve. However, this structure has now been established by synthesis.



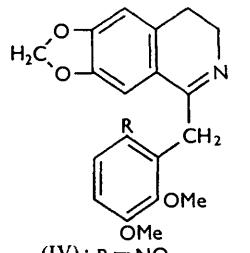
(I)



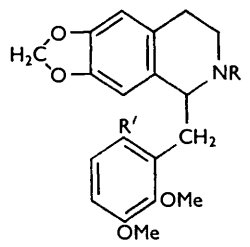
(II)



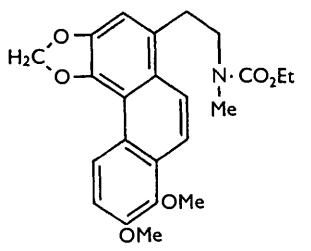
(III): R = NO_2
(IIIa): R = H



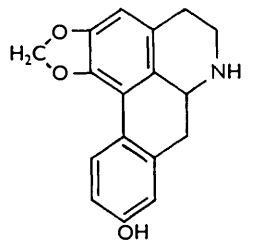
(IV): R = NO_2
(IVa): R = H



(V): R = Me, R' = NH_2
(Va): R = R' = H
(Vb): R = Me, R' = H



(VI)



(VII)

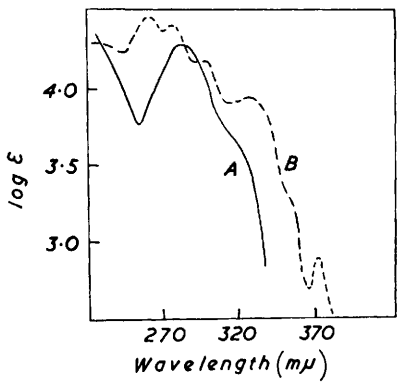
2 : 3-Dimethoxy-6-nitrophenylacetic acid (II) was obtained from 2 : 3-dimethoxy-6-nitrobenzaldehyde, through the benzyl alcohol, chloride, and nitrile, and condensed with homopiperonylamine to yield the amide (III). Cyclisation with phosphorus pentachloride in chloroform gave the dihydro*iso*quinoline (IV) which, by reduction of its methiodide, furnished 1-(6-amino-2 : 3-dimethoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinoline (V). Pschorr reaction of this base gave a product isolated as the hydriodide, m. p. 250° (decomp.), from which the free base, m. p. 123—123·5°, was obtained and identified, as indicated below, as (±)-crebanine. The ultraviolet spectra of both the hydriodide and the base (see Figure) showed only one maximum (at 280 mμ), whereas aporphines generally exhibit two maxima (near 275 and 300 mμ). The possibility of the Pschorr product's being a mere tetrahydro*iso*quinoline derivative, arising from (V) by deamination, alone or with simultaneous *N*-dealkylation,[3] was therefore considered. The tetrahydro*iso*quinoline derivatives (Va and b) were synthesised from the amide (IIIa) through the dihydro*iso*quinoline (IVa), reduction of which furnished the base (Va); the

[1] Tomita, *J. Pharm. Soc. Japan*, 1939, **59**, 207; Tomita and Shirai, *ibid.*, 1942, **62**, 27; 1943, **63**, 233; Shirai, *ibid.*, 1942, **62**, 517.

[2] Manske, " The Alkaloids, Chemistry and Physiology," Part IV, Academic Press Inc., New York, 1954, p. 129.

[3] Hey and Turpin, *Chem. and Ind.*, 1954, 216; *J.*, 1954, 2471; Govindachari and Arumugam, *J. Sci. Ind. Res., India*, 1955, **14**, *B*, 250.

methiodide of the dihydro-compound (IVa) gave the corresponding 2-methyl compound (Vb). Neither of the two was however identical with the hydriodide, m. p. 250° (decomp.), obtained in the Pschorr reaction. The ultraviolet absorption spectrum of the base, m. p. 123—123·5°, was superposable on that of natural crebanine, kindly provided by Professor Tomita. Treatment of either the synthetic or the natural base with ethyl chloroformate yielded the same compound (VI) (m. p. and mixed m. p.), with the expected spectrum



Ultraviolet absorption of (A) synthetic or natural crebanine and (B) product (VI) *from synthetic or natural crebanine, all in* EtOH.

(see Figure). The structure (I) for crebanine is thus established. It is possible that nuclear oxidation of anolobine (VII) followed by *O*- and *N*-methylation gives crebanine.

Experimental

2 : 3-*Dimethoxy*-6-*nitrophenylacetic Acid.*—2 : 3-Dimethoxy-6-nitrobenzaldehyde [4] (18 g.) in dry *iso*propyl alcohol (150 ml.) was added to aluminium *iso*propoxide (4·5 g.) in the same solvent (50 ml.), and the solution distilled at the rate of 2—3 drops per min., till 90—100 ml. of distillate had been collected. More *iso*propyl alcohol (70 ml.) was then added and the distillation continued until the distillate was free from acetone (10 hr.) and then to remove the remaining solvent. The cooled residue was treated with concentrated hydrochloric acid (20 ml.) in water (150 ml.), to give 2 : 3-dimethoxy-6-nitrobenzyl alcohol (16 g.), pale yellow needles (from alcohol), m. p. 91—91·5°. The alcohol (10 g.) was added slowly to thionyl chloride (20 ml.) at 0°. When the initial vigorous reaction had ceased, the solution was boiled under reflux for ½ hr., cooled, and poured on ice (200 g.) to yield an oil which solidified to give 2 : 3-dimethoxy-6-nitrobenzyl chloride (12 g.), forming white crystals [from benzene–light petroleum (b. p. 40—60°)], m. p. 132°. The crude benzyl chloride (10 g.) was converted into the cyanide by refluxing it with potassium cyanide (18 g.) in water (18 ml.) and alcohol (160 ml.). The cyanide (5 g.) was converted [5] into the imidoate by saturating its methanol solution (6 ml.) with hydrogen chloride, and thence by hydrolysis into 2 : 3-*dimethoxy*-6-*nitrophenylacetic acid* (2 g.), needles (from benzene), m. p. 181·5° (Found: C, 50·3; H, 4·4. $C_{10}H_{11}O_6N$ requires C, 49·8; H, 4·6%).

N-(2 : 3-*Dimethoxy*-6-*nitrophenylacetyl*)-3 : 4-*methylenedioxyphenethylamine.*—The foregoing acid (0·5 g.) in chloroform (7 ml.) was warmed with thionyl chloride (2 ml.) at 40° for 2 hr. and the solvents then removed at 30° *in vacuo*. The residue was taken up in benzene (15 ml.) and added with stirring to homopiperonylamine (0·5 g.) in benzene (5 ml.), and the mixture made alkaline after some time and left at 0° overnight, to give the colourless *amide* (0·8 g.), m. p. 195° (from alcohol) (Found: C, 58·7; H, 5·2. $C_{19}H_{20}O_7N_2$ requires C, 58·8; H, 5·2%).

1-(2 : 3-*Dimethoxy*-6-*nitrobenzyl*)-3 : 4-*dihydro*-6 : 7-*methylenedioxy*isoquinoline.—The foregoing amide (0·5 g.) in chloroform (7 ml.) was left with phosphorus pentachloride (0·8 g.) for 72 hr. The chloroform was then removed *in vacuo* and the residue extracted with hot water and filtered. Addition of concentrated aqueous ammonia precipitated the iso*quinoline* (0·15 g.), m. p. 169° (from methanol) (Found: C, 61·4; H, 5·0. $C_{19}H_{18}O_6N_2$ requires C, 61·6; H, 4·9%). The yellow *methiodide*, prepared by methyl iodide in hot chloroform, separated from alcohol and had m. p. 192° (decomp.) (Found: C, 47·1; H, 4·3. $C_{20}H_{21}O_6N_2I$ requires C, 46·9; H, 4·1%).

[4] Perkin, Robinson, and Stoyle, *J.*, 1924, **125**, 2358.
[5] Kay and Pictet, *J.*, 1913, **103**, 947.

1-(6-*Amino*-2 : 3-*dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*-6 : 7-*methylenedioxy*isoquinoline.—The above methiodide (1·7 g.) in methanol (65 ml.) containing Adams catalyst (0·15 g.) was shaken with hydrogen at 56 lb./sq. in. for 2 hr. The solution was filtered from the catalyst and evaporated. The residue was triturated with dilute sodium hydroxide solution and extracted with ether. The dried (K_2CO_3) ether extract was treated with hydrogen chloride, and the gummy precipitate triturated with alcohol, to give a *dihydrochloride* (0·65 g.), which, after recrystallisation from alcohol–ether, had m. p. 224° (decomp.) (Found: C, 54·9; H, 6·6. $C_{20}H_{26}O_4N_2Cl_2,\frac{1}{2}H_2O$ requires C, 54·8; H, 6·2%).

(±)-*Crebanine*.—The above dihydrochloride (0·6 g.) in 2N-sulphuric acid (10 ml.) and methanol (10 ml.) was treated at 0°, with stirring, with sodium nitrite (0·15 g.) in water (2 ml.). After 1 hr. the solution was allowed to rise to room temperature. Freshly precipitated copper powder (0·2 g.) was added and stirring continued for ½ hr. at that temperature and for another ½ hr. at 100°. Zinc dust (1 g.) and concentrated hydrochloric acid (2 ml.) were then added and after being heated and stirred for 20 min. the mixture was filtered. The filtrate was basified with aqueous sodium hydroxide and extracted with ether. The ether extract was shaken with N-hydrochloric acid (3 × 20 ml.). The acid extracts were neutralised by solid sodium hydrogen carbonate, made just acidic with acetic acid, and treated with excess of potassium iodide. The gummy precipitate, on two recrystallisations from methanol, gave (±)-*crebanine hydriodide* (0·1 g.), as colourless needles becoming pink on storage, m. p. 250° (decomp.) with preliminary blackening, $\lambda_{max.}$ 280 mμ (log ε 4·38) (Found: C, 51·2; H, 4·8. $C_{20}H_{22}O_4NI$ requires C, 51·4; H, 4·7%), yielding, by basification and ether-extraction, (±)-*crebanine*, stout needles [from light petroleum (b. p. 40—60°)], m. p. 123—123·5°, $\lambda_{max.}$ 280 mμ (log ε 4·29) (Found: C, 70·8; H, 6·3. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·2%).

8-(2-N-*Ethoxycarbonyl*-N-*methylaminoethyl*)-1 : 2-*dimethoxy*-5 : 6-*methylenedioxyphenanthrene*.—(±)-Crebanine (80 mg.) in chloroform (10 ml.) containing potassium hydroxide (60 mg.) and ice was shaken with ethyl chloroformate (0·07 ml.) in chloroform (3 ml.). After 1 hr., more potassium hydroxide and ethyl chloroformate were added. Next day the chloroform solution was separated, washed with water, dilute acid, and water, dried (Na_2SO_4), and evaporated, to yield the *phenanthrene* (70 mg.), slender needles with a violet tint [from ether–light petroleum (b. p. 40—60°)], m. p. 125°, undepressed by a specimen (7 mg.), m. p. 125°, obtained by the same procedure from natural crebanine (10 mg.); this had $\lambda_{max.}$ 260, 275, 295, 325, 370 mμ (log ε 4·46, 4·40, 4·17, 3·93, 2·87) (Found: C, 67·5; H, 6·5. $C_{23}H_{25}O_6N$ requires C, 67·2; H, 6·1%).

N-(2 : 3-*Dimethoxyphenylacetyl*)-3 : 4-*methylenedioxyphenethylamine*.—*o*-Homoveratric acid (2 g.) was converted into the chloride and treated with homopiperonylamine, yielding the *amide* (2·5 g.), colourless needles (from methanol), m. p. 100—101° (Found: C, 66·1; H, 6·3. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·1%).

1-(2 : 3-*Dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*methylenedioxy*isoquinoline.—The above amide (1 g.) in toluene (15 ml.) was refluxed with phosphoryl chloride (4 ml.) for 2 hr. and the whole poured on ice. The yellow solution was shaken with ether to remove toluene and non-basic material, then cooled and basified with aqueous sodium hydroxide. The liberated dihydro*iso*quinoline was taken up in ether, and the dried (K_2CO_3) ether extract saturated with hydrogen chloride, to give the hygroscopic hydrochloride (0·5 g.). This was reduced in alcohol (20 ml.) by Adams catalyst (0·15 g.). The solution was filtered and evaporated. An aqueous solution of the residue was treated with excess of potassium iodide, and the precipitate recrystallised from alcohol–ether, to give the *tetrahydro*isoquinoline *hydriodide* as needles, m. p. 196—197° (Found: C, 50·4; H, 5·0. $C_{19}H_{22}O_4NI$ requires C, 50·1; H, 4·8%).

1-(2 : 3-*Dimethoxybenzyl*)-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*-6 : 7-*methylenedioxy*isoquinoline.—The crude dihydro*iso*quinoline base from cyclisation of the amide (2 g.) was converted into the gummy methiodide by methyl iodide in chloroform. Reduction of the methiodide (0·35 g.) in methanol (20 ml.) with Adams catalyst (0·15 g.) during 2 hr. gave, after filtration, evaporation, and crystallisation of the residue from alcohol–ether, the *tetrahydro*-2-*methyl*isoquinoline *hydriodide* (0·2 g.), m. p. 175—176° (Found: C, 51·2; H, 5·4. $C_{20}H_{24}O_4NI$ requires C, 51·2; H, 5·1%).

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PRESIDENCY COLLEGE, MADRAS. [*Received, August 26th,* 1957.]