Tetrahedron, 1964, Vol. 20, pp. 2895 to 2901. Pergamon Press Ltd. Printed in Northern Ireland

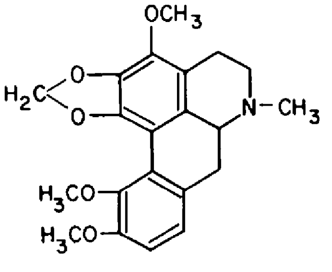
SYNTHESIS OF (±) THALICMINE (OCOTEINE)

T. R. GOVINDACHARI,* B. R. PAI and G. SHANMUGASUNDARAM
Presidency College, Madras 5

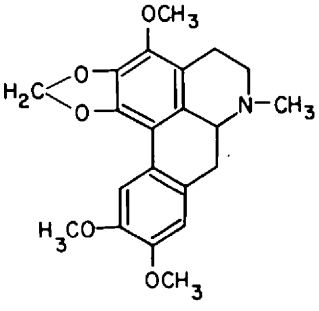
(*Received* 18 *July* 1964)

Abstract—The structure of the alkaloid thalicmine has been proved to be 1,2-methylenedioxy-3,9,10-trimethoxyaporphine by a synthesis of the racemic form of the alkaloid on classical lines.

THE alkaloid thalicmine, $C_{21}H_{23}O_5N$, was isolated by Yunusov and Progressov[1] from *Thalictrum minus*. According to these authors, Hofmann degradation of the alkaloid yielded 2,5,6-trimethyl-3,4-methylenedioxy-1-vinylphenanthrene, so that structure I was proposed for the alkaloid.[2] The alkaloid ocoteine, isolated from *Ocotea puberula* by Iacobucci[3] was originally considered to be isomeric with but different from thalicmine. Vernengo *et al.*[4] carried out extensive degradation studies on ocoteine and found a surprising agreement between the m.p. of several of the degradation products with the corresponding products obtained from thalicmine by the Russian workers. While this was so, the specific rotation of ocoteine was found to be +37·6 (EtOH) whereas the Russian workers reported for thalicmine a value of +255·3° (EtOH). However, Vernengo[5] was able to effect a direct comparison between thalicmine and ocoteine and found them to be identical.



I



II

On the basis of UV and NMR spectra and of the optical rotation Vernengo[5] considered that thalicmine cannot be substituted both at the 1- and 11-positions and that structure I is inconsistent with the data. Vernengo proposed that thalicmine is 1,2-methylenedioxy-3,9,10-trimethoxyaporphine (II). A synthesis of this structure (I) proposed by Yunusov and Progressov (*loc. cit.*) for thalicmine was reported earlier from this laboratory.[6] The synthetic compound shows a single maximum at 280 mμ

---

* CIBA Research Centre, Goregaon, Bombay 62.

[1] S. Yunusov and N. N. Progressov, *J. Gen. Chem., U.S.S.R.* **20**, 1151 (1950).

[2] S. Yunusov and N. N. Progressov, *Zh. Obshch. Khim.* **20**, 1151 (1950); *Chem. Abstr.* **45**, 1608 (1951).

[3] G. A. Iacobucci, *Ciencia Invest., Buenos Aires* **7**, 48 (1951); *Chem. Abstr.* **45**, 7129 (1951).

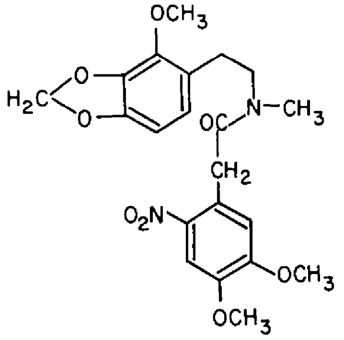
[4] M. J. Vernengo, A. S. Cerezo, G. A. Iacobucci and V. Deulofeu, *Ann. Chim.* **610**, 173 (1957).

[5] M. J. Vernengo, *Experimentia* **19**, 294 (1963).

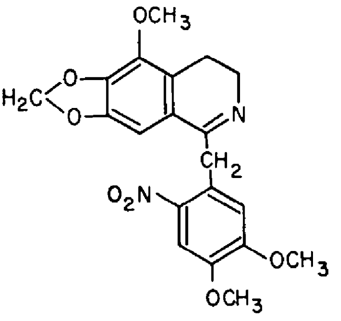
[6] T. R. Govindachari, S. Rajadurai, C. V. Ramadas and N. Viswanathan, *Chem. Ber.* **93**, 360 (1960).

and not two maxima at 283 and 300 mμ as reported for thalicmine. From this it is clear that structure I for thalicmine is untenable even though no direct comparison was made. We now report the synthesis along classical lines of (±) 1,2-methylenedioxy-3,9,10-trimethoxyaporphine (II).

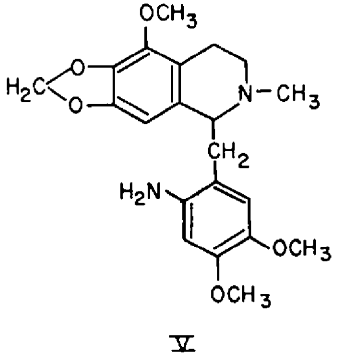
One of the starting materials for the synthesis was β-(2-methoxy-3,4-methylenedioxyphènyl) ethylamine. This was earlier obtained by conversion of croweacinaldehyde to the nitrostyrene followed by reduction with lithium aluminium hydride but the yield was extremely poor and inconsistent.[6] The amine has now been prepared in excellent over-all yield, through the alcohol, chloride, nitrile and final reduction. Condensation of the amine with 6-nitro-3,4-dimethoxyphenylacetyl chloride yielded the amide (III) which was cyclized by phosphorous oxychloride in benzene at room temperature to 1-(6-nitro-3,4-dimethoxybenzyl)-5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline (IV). The methiodide of this compound was reduced with zinc and hydrochloric acid to the amino tetrahydroisoquinoline (V), which on diazotization and Pschorr reaction yielded (±) 1,2-methylenedioxy-3, 9, 10-trimethoxyaporphine (II). The UV absorption spectrum of the synthetic sample (as the hydriodide) exhibits maxima at 283 and 300 mμ (log ε 4·25, 4·27) in excellent agreement with the values reported[4] for thalicmine (Fig. 1). The base liberated from the hydriodide was submitted to the Gadamer reaction. The neutral product obtained in this reaction exhibits the characteristic spectrum of a phenanthrene compound. A comparison



III



IV



V

of the IR (Fig. 2) NMR spectra (Fig. 3) of the synthetic base and the natural alkaloid establishes their complete identity.* Thalicmine (Ocoteine) should therefore be formulated as 1,2-methylenedioxy-3,9,10-trimethoxyaporphine.

EXPERIMENTAL

1. (a) *2-Methoxy-3,4-methylenedioxybenzyl alcohol.* Croweacin aldehyde (6 g) was suspended in methanol (60 ml) and $NaBH_4$ (2 g) was added in small portions during 2 hr. The resulting solution was refluxed on a water-bath for 1 hr and the solvent removed. Cold water was added to the residue and the solution extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and the ether distilled off to give a colourless liquid (5·8 g), b.p. 110/0·1 mm characterized as the 3,5-dinitrobenzoate (from benzene), m.p. 145–147°. (Found: C, 51·3; H, 3·2. Calc. for $C_{16}H_{12}O_9N_2$: C, 51·1; H, 3·2%).

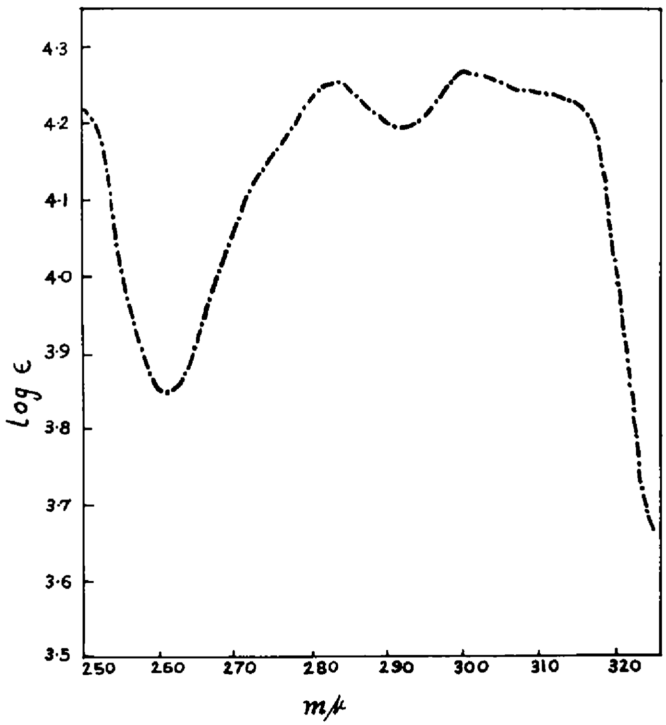


Fig. 1

(b) *2-Methoxy-3,4-methylenedioxybenzyl chloride.* Thionyl chloride (3·1 g; 0·075 mole) in dry benzene (5 ml) was added with stirring to a solution of 2-methoxy-3,4-methylenedioxybenzyl alcohol (3·2 g; 0·05 mole) in dry benzene (20 ml) during 0·5 hr. The mixture was kept at room temp for 1·5 hr, then heated on a boiling water bath for 10 min, two-thirds of benzene was removed under red. press. and the resulting solution was washed with water, dil. Na_2CO_3 aq and water, dried (Na_2SO_4) and the solvent removed. Distillation of the residue gave the chloro compound as a colourless liquid (2·9 g; 90%) b.p. 108°/0·1 mm undergoing decomposition very quickly.

(c) *2-Methoxy-3,4-methylenedioxybenzyl cyanide.* A solution of the foregoing chloride (2·4 g) in dry benzene (10 ml) was added dropwise to a solution of NaCN (2·7 g) and $Hg(CN)_2$ (0·1 g) in water (4 ml), heated and stirred on a steam-bath. The mixture was refluxed with stirring for 6 hr and the

---

* The comparisons were carried out by Professor M. Shamma with a sample of the alkaloid obtained from Dr. Vernengo. We express our grateful appreciation for this help.

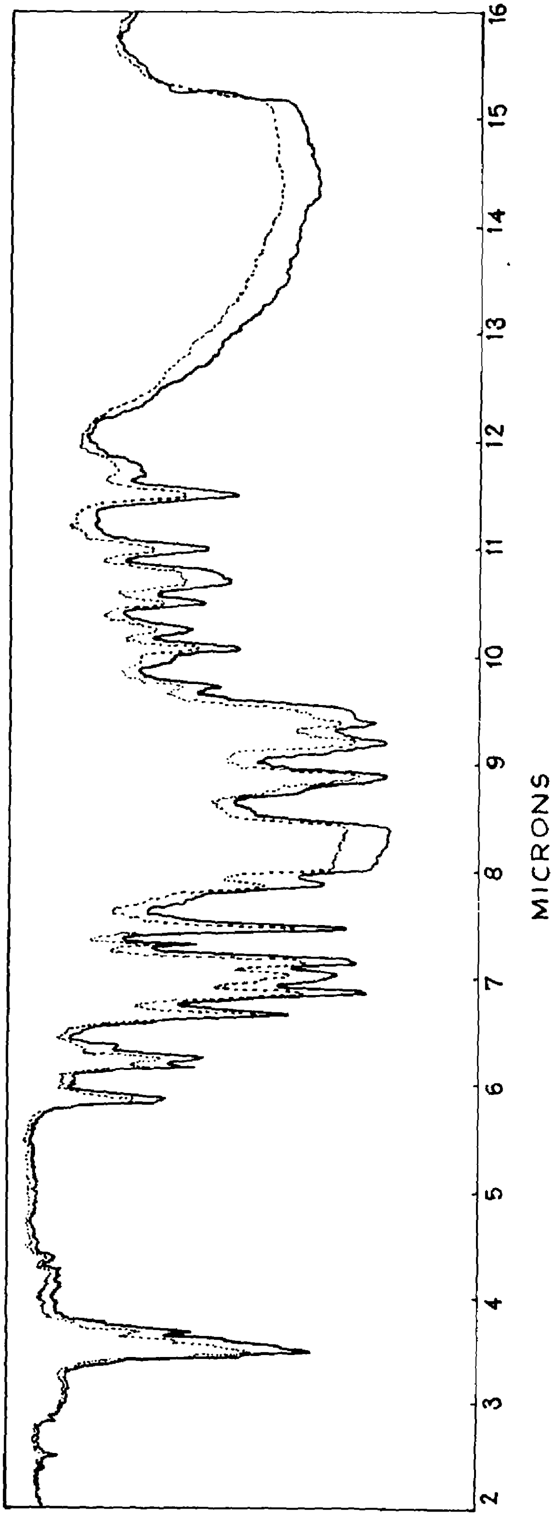


Fig. 2

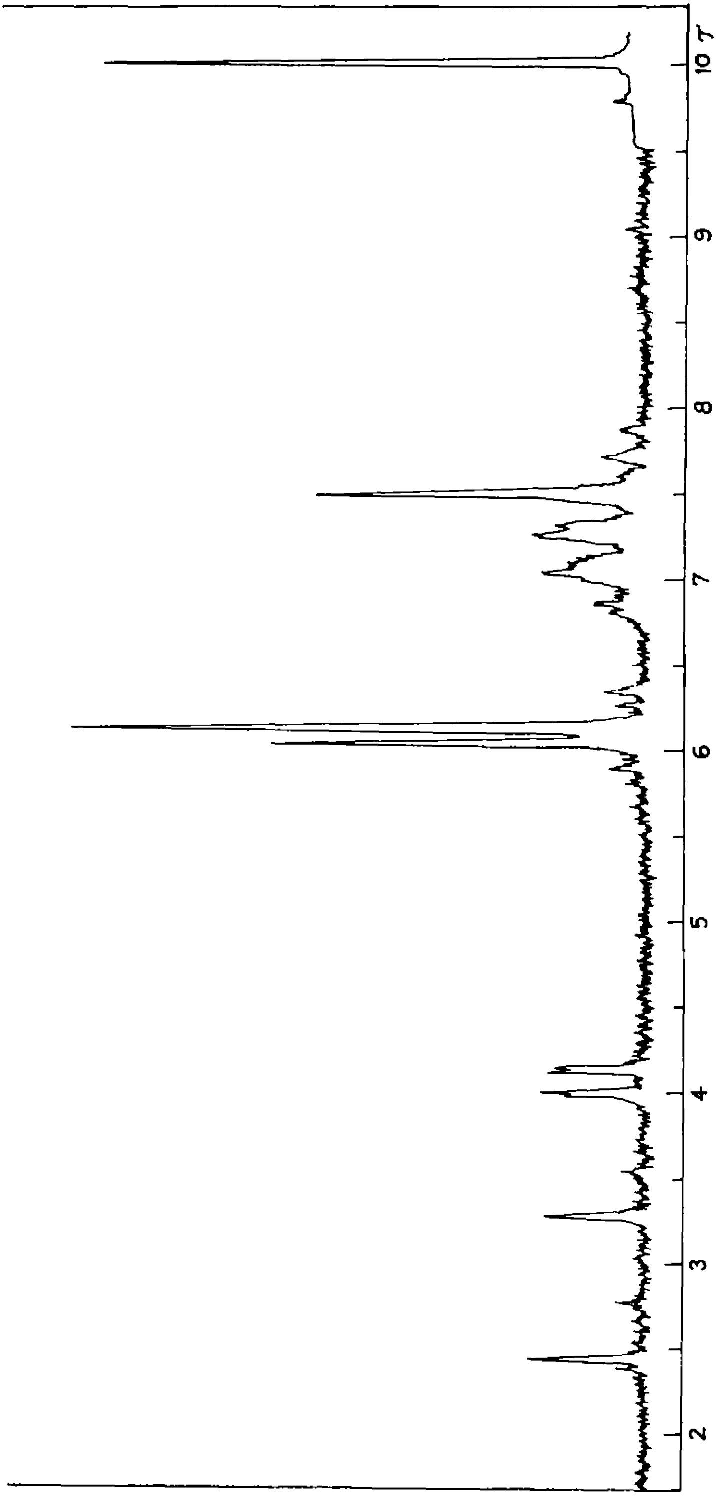


Fig. 3

benzene layer separated. It was washed thoroughly with water, dried (Na_2SO_4) and the solvent removed to give a pale yellow solid (2·2 g), m.p. 98° from ethanol. (Found: C, 63·4; H, 4·9. Calc. for $C_{10}H_9O_3N$: C, 62·8; H, 4·7%).

2. *β-(2-Methoxy-3,4-methylenedioxyphenyl) ethylamine.* A solution of the above cyanide (2 g) in methanolic potash (5%; 60 ml) was shaken in a Parr reaction vessel at 50 lbs. press. for 12 hr in presence of Raney Nickel catalyst. The solution was filtered and the solvent distilled off. Benzene was added to the residue and the benzene solution extracted with dil. HCl aq. The aqueous layer was washed once with benzene and then basified with conc. NH_4OH. The amine was extracted with chloroform and the organic layer washed with water and dried (K_2CO_3). The solvent was removed and the residue distilled to give a colourless oil (1·8 g) b.p. 114°/0·1 mm, characterized as the picrate from ethanol, m.p. 218°. Govindachari *et al.*[6] reported b.p. 180°/0·5 mm for the amine. (Found: C, 45·4; H, 4·1. Calc. for $C_{16}H_{16}O_{10}N_4$: C, 45·4; H, 3·8%).

3. N-*(3,4-Dimethoxy-6-nitrophenylacetyl)-2-methoxy-3,4-methylenedioxyphenethylamine.* 6-Nitrohomoveratic acid (0·6 g) was suspended in freshly distilled absolute chloroform (6 ml) kept in a two-necked flask fitted with a Hg-seal and $CaCl_2$ guard-tube and cooled in ice. Phosphorus pentachloride (1·2 g) was gradually added with stirring until all the PCl_5 and the acid passed into solution (½ hr). The solution was slowly added to a vigorously stirred mixture of the amine (0·5 g) in chloroform (5 ml) and NaOH aq (1N; 50 ml) which was cooled in ice. After about ½ hr, the chloroform layer was separated, the aqueous layer extracted with chloroform and the combined chloroform solutions washed with dil. HCl aq, dried (Na_2SO_4) and the solution removed. The residue was triturated with methyl alcohol, boiled for 1 min, cooled and filtered to give a colourless powder (0·4 g) m.p. 175° from methanol. (Found: C, 57·2; H, 5·3. Calc. for $C_{20}H_{22}N_2O_8$: C, 57·4; H, 5·3%).

4. *1-(4,5-Dimethoxy-2-nitrobenzyl)-3,4-dihydro-5-methoxy-6,7-methylenedioxyisoquinoline.* A mixture of the amide (2 g) and a solution of $POCl_3$ (1·5 ml) in dry benzene (20 ml) was kept in a closed vessel at room temp (30°) for 120 hr. The solvent was next removed *in vacuo* and the contents decomposed by adding crushed ice and leaving for 1 hr. The hydrochloride that formed was repeatedly extracted with hot water. The combined yellow aqueous extract was filtered, cooled and basified with NH_4OH aq. It was extracted with benzene and on removal of the solvent, the base was obtained as a pale yellow powder. It crystallized from benzene–petrol as pale brown needles (0·8 g) m.p. 193–6°. (Found: C, 59·7; H, 5·1. Calc. for $C_{20}H_{30}N_2O_7$: C, 60·0; H, 5·0%).

5. *1-(4,5-Dimethoxy-2-nitrobenzyl)-3,4-dihydro-5-methoxy-2-methyl-6,7-methylenedioxyisoquinolinium iodide.* To a solution of the above isoquinoline (1 g) in dry benzene (50 ml) was added methyl iodide (3 ml). The mixture was gently refluxed for 6 hr and left overnight. The methiodide settled as a pale yellow powder. The solvent was decanted off and the methiodide recrystallized from ethyl acetate to give pale yellow needles (0·9 g), m.p. 204–206° with dec. (Found: C, 46·4; H, 4·3. Calc. for $C_{21}H_{23}N_2O_7I$: C, 46·5; H, 4·3%).

6. *1-(2-Amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-5-methoxy-2-methyl-6,7-methylenedioxyisoquinoline.* The foregoing methiodide (1 g) was suspended in a mixture of conc. HCl (10 ml) and water (10 ml) and heated on a water bath with gradual addition of Zn dust (15 min; 3 g) with vigorous shaking. The clear colourless solution was filtered hot from undissolved Zn, cooled, basified with NH_4OH and extracted with ether. The base was extracted from the ether solution with dil. HCl aq, the acid extract basified again with cooling and the base reextracted with ether. The ether extract was dried (K_2CO_3) and the solvent removed to give the tetrahydro base as a pale yellow liquid. It was absorbed on a small column of alumina (1 cm) and eluted with chloroform. The solvent was removed to give the base as a colourless liquid which was dissolved in dry benzene and saturated with dry HCl. The precipitated hydrochloride was washed with dry ether and recrystallized from ethanol to give a white powder (0·5 g) m.p. 234°. (Found: C, 54·8; H, 6·0. Calc. for $C_{21}H_{28}N_2O_5Cl_2$: C, 54·9; H, 6·1%).

7. *1,2-Methylenedioxy-3,9,10-trimethoxyaporphine.* The above dihydrochloride (0.4 g) in H_2SO_4 (2N, 9 ml) and methanol (6 ml) was treated at 0° with stirring with a freshly prepared solution of $NaNO_2$ (0·137 g) in water (1·1 ml). The mixture was stirred for ½ hr and kept at 0° for another ½ hr. It was allowed to come to room temp and heated on the water bath till the evolution of N_2 ceased. Conc. HCl aq (0·7 ml) was added to the solution followed by the gradual addition of Zn dust (0·3 g) during heating on the water bath. The solution was filtered hot, cooled, basified (NH_4OH) and extracted with ether. The ether solution was extracted with dil. HCl aq, the acid extract basified again with cooling, and the base re-extracted with ether. The ether extract was dried (Na_2SO_4) and the

solvent removed to give a colourless residue. It was treated with few drops HCl and a large excess of sat. KI aq. The precipitate formed was freed from mother liquor and rubbed with absolute ethanol to give the hydriodide as a colourless solid. The solid, after two crystallizations from methanol, gave (±) 1,2-methylenedioxy-3,9,10-trimethoxyaporphine hydriodide (80 mg) as white fluffy crystals, m.p. 225° (dec.), λ_{max} 283 and 300 mμ (log ε 4·25, 4·27). (Found: C, 50·8; H, 4·8. Calc. for $C_{21}H_{24}O_5NI$: C, 50·7; H, 4·8%).

8. 8-(2-N-*Ethoxycarbonyl*-N-*methylaminoethyl*)-2,3,7-*trimethoxy*-5,6-*methylenedioxyphenanthrene*. The aporphine liberated from its hydriodide (5 mg) in chloroform (2 ml) containing KOH (5 mg) and ice was shaken with ethyl chloroformate (0·01 ml) in chloroform (2 ml). After 1 hr, more KOH and ethyl chloroformate were added. Next day the chloroform solution was separated, washed with water, dil. acid and water, dried (Na_2SO_4) and evaporated to yield the phenanthrene (2 mg) purified by chromatography. The UV spectrum exhibited maxima at 265, 314, 325, 348 and 365 mμ.