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SYNTHESIS OF ATHEROSPERMIDINE

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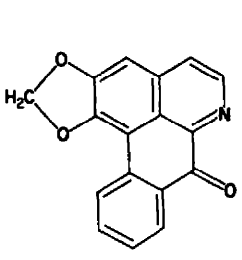
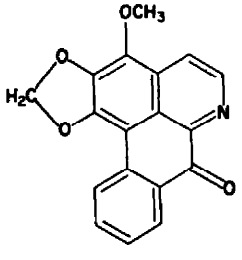
Abstract—The structure of the alkaloid atherospermidine has been proved to be 1,2-methylenedioxy-3-methoxy-7-oxo-dibenzo (de, g) quinoline. The synthesis of racemic 1,2-methylenedioxy-3-methoxy-aporphine and its oxidation to atherospermidine is also reported.

THE alkaloids spermatheridine, $C_{17}H_9O_3N$, and atherospermidine, $C_{18}H_{11}O_4N$, together with other alkaloids, were isolated by Bick *et al.*[1] from *Atherosperma moschatum* Labill. Spermatheridine was shown to be identical with liriodenine[2] (I) of known structure,[3] by a comparison of IR and UV spectra and mixed m.p. determination of the two compounds.

Atherospermidine was shown to be 3-methoxyliriodenine (II) by a comparison of its physical data with those of liriodenine.[2] Atherospermidine is the third example of a naturally occurring 7-keto aporphine, the other two being liriodenine and 1,2,9,10-tetramethoxydibenzo (de, g) quinoline-7-one (III) co-occurring with liriodenine in *Liriodendron tulipifera*.[3a,4]



I



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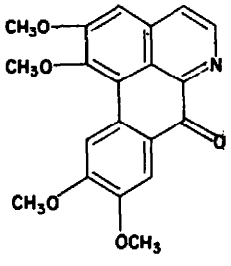
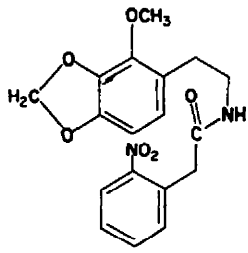


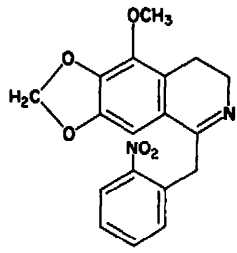
III

Since the structure assigned to atherospermidine was based entirely on spectral data, it was of interest to confirm it by a synthesis based on the principles used by Taylor[3] for liriodenine. Condensation of β-(2-methoxy-3,4-methylenedioxyphenyl) ethylamine with *o*-nitrophenylacetyl chloride yielded the amide (IV) which was cyclized by phosphorous oxychloride to 1-(2-nitrobenzyl)-5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline (V). Oxidation of V to the benzoylisoquinoline (VI) was effected in a single step using potassium dichromate and 70% acetic acid. Reduction of the nitro group with hydrogen in presence of Raney nickel gave the amine

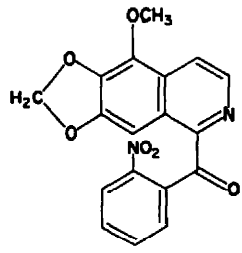
[1] I. R. C. Bick, P. S. Clezy and W. D. Crow, *Austral. J. Chem.* **9**, 111 (1956).
[2] I. R. C. Bick and G. K. Douglas, *Tetrahedron Letters* No. 25, 1629 (1964).
[3] W. I. Taylor, *Tetrahedron* **14**, 42 (1961).
[3a] M. A. Buchanan and E. E. Dickey, *J. Org. Chem.* **25**, 1389 (1960).
[4] J. Cohen, N. Von Langenthal and W. I. Taylor, *J. Org. Chem.* **26**, 4143 (1961).



IV



V



VI

which, without further characterization, was diazotized and subjected to Pschorr ring closure to yield 1,2-methylenedioxy-3-methoxy-7-oxo-dibenzo (de, g) quinoline (II). The UV absorption maxima of the synthetic sample both in alcohol and 0·1 N HCl are in excellent agreement with those reported for atherospermidine (Fig. 1). Mixed m.p. and comparison of the IR spectra of the synthetic base and the natural alkaloid (Fig. 2) established their complete identity. Thus the structure assigned to atherospermidine has been confirmed by synthesis.

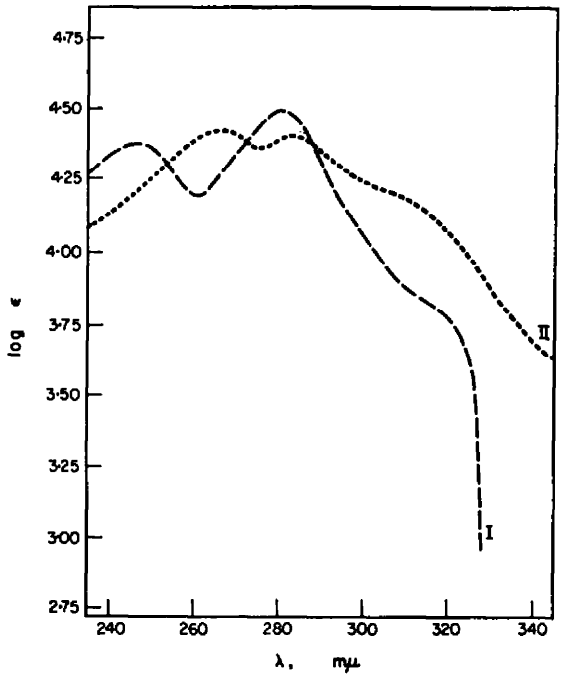
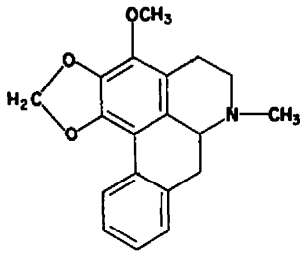


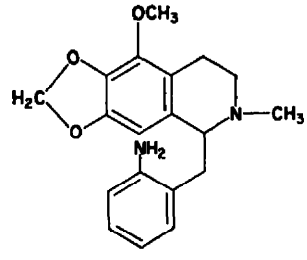
FIG. 1. I—In ethanol. II—In 0.1 N ethanolic hydrochloric acid.

Cohen *et al.*[4] have suggested that liriodenine (I) and its co-occurring 1,2,9,10-tetramethoxydibenzo (dc, g) quinoline-7-one (III) could be derived in the plant oxidatively from roemerine or glaucine or their nor compounds. This hypothesis was further supported by their isolation of glaucine from *Liriodendron tulipifera* L. Oxidation of aporphine by chromium trioxide–pyridine complex to 7H-dibenzo (de, g)

quinoline-7-one skeleton is well known[5,6] and having successfully synthesized atherospermidine, it was of interest to synthesize 1,2-methylenedioxy-3-methoxyaporphine (VII) which on oxidation should give atherospermidine. The aporphine (VII) was



VII



VIII

synthesized along the classical lines. The methiodide of the readily available 1-(2-nitrobenzyl)-3,4-dihydro-5-methoxy-6,7-methylene-dioxyisoquinoline (V) was reduced with Adams catalyst to the amino tetrahydroisoquinoline (VIII) which on diazotization and Pschorr reaction yielded (±)-1,2-methylenedioxy-3-methoxyaporphine (VII). The UV absorption spectrum of the aporphine (as the hydriodide) exhibits maxima at 240, 279 and 312 (sh) mμ (log ε 4·46, 4·41, 3·59) (Fig. 3). The base liberated from the hydriodide was submitted to the Gadamer reaction. The neutral product thus obtained

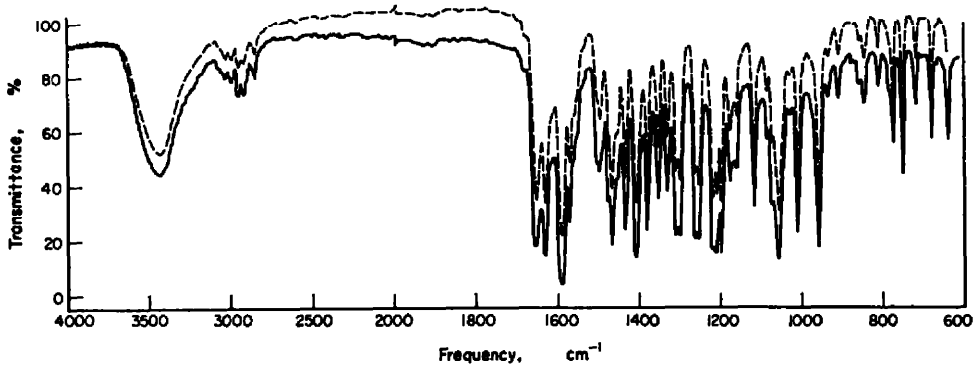


FIG. 2

exhibits the characteristic spectrum of a phenanthrene compound. The base liberated from the aporphine hydriodide was oxidized with chromium trioxide–pyridine complex. The product obtained was identical with atherospermidine, thus supporting Taylor's suggestion that the keto bases are oxidatively formed in the plants from the normal aporphines.

EXPERIMENTAL

1. N-(*2-Nitrophenylacetyl*)-*2-methoxy*-3,4-*methylenedioxy-phenethylamine*. A mixture of *o*-nitrophenylacetic acid (0·75 g), $SOCl_2$ (1·5 ml) and dry benzene (3 ml) was refluxed gently for 2 hr on a steam-bath. The benzene and excess $SOCl_2$ were removed at 10° *in vacuo*. Dry benzene (10 ml) was added and distilled off under the same conditions to remove traces of $SOCl_2$. The acid chloride

[5] T. H. Yang, *J. Pharm. Soc. Japan* **82**, 794 (1962).
[6] M. Tomita, T. H. Yang, H. Furukawa and H. M. Yang, *J. Pharm. Soc. Japan* **82**, 1574 (1962).

dissolved in abs. $CHCl_3$ (15 ml) was added gradually to a vigorously stirred mixture of β-(2-methoxy-3,4-methylenedioxyphenyl) ethylamine (0·5 g) in $CHCl_3$ (5 ml) and 1 N NaOH (50 ml) which was cooled in ice. After stirring for 1 hr, the $CHCl_3$-layer was separated. The aqueous layer was extracted with $CHCl_3$ and the combined $CHCl_3$-extracts were washed with dil. HCl aq and water, dried (Na_2SO_4) and the solvent removed. The residue was triturated with MeOH, heated with more MeOH, cooled and filtered to give a colourless amide (0·5 g), m.p. 157° from benzene. (Found: C, 60·6; H, 4·7. $C_{18}H_{18}N_2O_6$ requires: C, 60·3; H, 5·0%.)

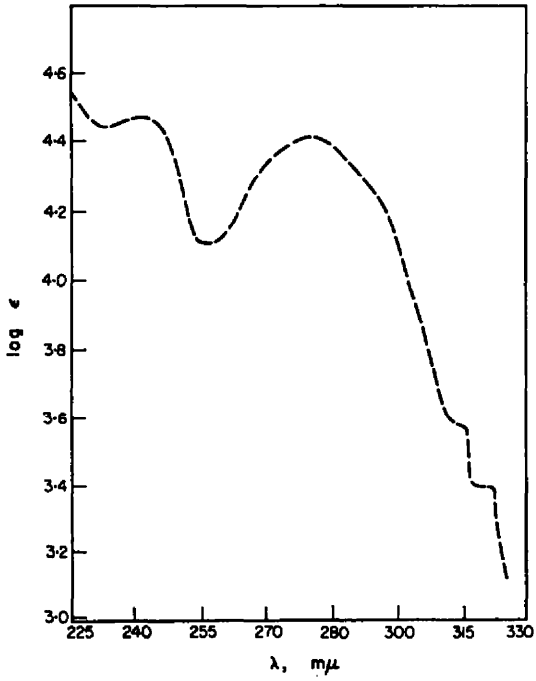


FIG. 3

2. 1-(2-*Nitrobenzyl*)-3,4-*dihydro*-5-*methoxy*-6,7-*methylenedioxyisoquinoline*. The above amide (400 mg) suspended in dry benzene (3 ml) was treated with $POCl_3$ (1 ml) and allowed to stand at room temp (30°) for 60 hr. The resulting brown solution was poured onto crushed ice and left for 2 hr. The benzene was removed *in vacuo* and the residue extracted repeatedly with hot water. The yellow aqueous extract was filtered, cooled, washed with ether and basified with conc. NH_4OH. The liberated base was extracted with ether and the ether extract washed with water and dried (K_2CO_3). The solvent was removed, the residue adsorbed on a small column of alumina (1 cm) and eluted with benzene. Removal of benzene yielded a pale yellow solid which crystallized from benzene–petrol to give brownish-yellow granules (160 mg), m.p. 137°; λ_{max}^{EtOH} 273 mμ (log ε 4·04). (Found: C, 63·5; H, 4·7. $C_{18}H_{16}N_2O_5$ requires: C, 63·5; H, 4·7%.)

3. 1-(2-*Nitrobenzoyl*)-5-*methoxy*-6,7-*methylenedioxyisoquinoline*. A mixture of the above dihydro isoquinoline (100 mg), acetic acid (70%; 0·8 ml) and very finely powdered pure $K_2Cr_2O_7$ (200 mg) was refluxed gently for 4 hr. The resulting solution was cooled and diluted with water. The precipitated solid was collected, washed thoroughly with dil. acetic acid followed by water and dried. It was adsorbed on a small column of alumina (2 cm) and eluted with benzene–$CHCl_3$ (1:1). The solvent was removed and the bright yellow residue crystallized from EtOH–benzene as pale yellow needles (40 mg), m.p. 197°; λ_{max}^{EtOH} 235, 270 and 353 mμ (log ε 4·68, 4·80 and 3·98).

The green solution left after removal of the benzoylisoquinoline was diluted with water and extracted with $CHCl_3$. The $CHCl_3$-extract was washed with water, dried (Na_2SO_4) and the solvent removed. The residue on chromatography followed by crystallization from EtOH gave a further

crop (5 mg) of the above benzoylisoquinoline. (Found: C, 61·2; H, 3·6. $C_{18}H_{12}N_2O_6$ requires: C, 61·4; H, 3·45%.)

4. 1,2-*Methylenedioxy*-3-*methoxy*-7-*oxo*-*dibenzo* (*de*, *g*) *quinoline*. The above nitrobenzoylisoquinoline (100 mg) was suspended in EtOH (25 ml) and shaken in an atm. of H_2 at 15 lb in the presence of Raney Ni in a Parr reaction vessel for 18 hr. The catalyst was filtered off and the solvent removed *in vacuo*. To the resulting solid (40 mg) as a fine suspension in abs. MeOH (3 ml), 2 N H_2SO_4 (2 ml) was added. The mixture became warm and the resulting solution was cooled in a freezing mixture with stirring for 10 min. It was treated with $NaNO_2$ aq (0·15 ml containing 18 mg $NaNO_2$), the addition being done rapidly dropwise. The pale brown solution was stirred at −5° for 15 min and then at 0° for 15 min. As the temp of the solution was raised to 30°, the brownish-yellow solution turned red with the evolution of N_2. It was kept at room temp (30°) for the next 15 min then heated on a water-bath for a further period of 15 min. The bright red solution was cooled, basified with conc. NH_4OH and extracted with CH_2Cl_2. The CH_2Cl_2-layer was washed with water, dried (K_2CO_3) and the solvent removed. The reddish-yellow residue was adsorbed on a small column of alumina (1 cm) and eluted with CH_2Cl_2. Removal of CH_2Cl_2 followed by crystallization of the residue from $CHCl_3$ gave slender orange–yellow needles (3 mg), m.p. 274–276° (dec); λ_{max}^{EtOH} 247, 281 and 312 (sh) mμ (log ε 4·37, 4·49 and 3·89). (Found: C, 70·5; H, 3·7. $C_{18}H_{11}O_4N$ requires: C, 70·8; H, 3·6%.)

5. 1-(2-*Nitrobenzyl*)-3,4-*dihydro*-5-*methoxy*-2-*methyl*-6,7-*methylenedioxyisoquinolinium iodide*. Methyl iodide (2 ml) was added to a solution of 1-(2-nitrobenzyl)-3,4-dihydro-5-methoxy-6,7-methylenedioxyisoquinoline (0·5 g) in dry $CHCl_3$ (6 ml). The mixture was gently refluxed for 3 hr with separation of the *methiodide* of isoquinoline as a yellow spongy solid. This was filtered off, washed with ether, dried and crystallized from MeOH to yield the methiodide as pale yellowish-brown fluffy needles (0·5 g), m.p. 205° (dec). (Found: C, 47·7; H, 4·3. $C_{19}H_{19}O_6N_2I$ requires: C, 47·3; H, 4·0%.)

6. 1-(2-*Aminobenzyl*)-1,2,3,4-*tetrahydro*-5-*methoxy*-2-*methyl*-6,7-*Methylenedioxyisoquinoline*. The above methiodide (0·5 g) dissolved in MeOH (25 ml) was hydrogenated at a press. of 60 lb/in^2 in the presence of Adams catalyst (75 mg). The methanolic solution was filtered free from the catalyst, the solvent removed *in vacuo*, and the residue dissolved in water and made alkaline by adding NaOH aq. The liberated base was extracted with ether and the ether extract washed with water and dried (K_2CO_3). Dry HCl gas was passed into the ether solution and the precipitated hydrochloride crystallized from EtOH–MeOH to yield the *dihydrochloride* of the aminotetrahydroisoquinoline as a white powder (0·3 g), m.p. 243°; λ_{max}^{EtOH} 235 (sh), 286 mμ (log ε 4·33, 3·74). (Found: C, 57·0; H, 5·8. $C_{19}H_{24}O_3N_2Cl_2$ requires: C, 57·1; H, 6·0%.)

7. (±)-1,2-*Methylenedioxy*-3-*methoxyaporphine*. A solution of the foregoing dihydrochloride (240 mg) in 2 N H_2SO_4 (10 ml) and MeOH (5 ml) was cooled to 0° and treated dropwise with a solution of $NaNO_2$ (40 mg in 1 ml water). After stirring for 1 hr at 0°, the solution was allowed to come to room temp and stirred for 15 min. It was then heated at 60–80° for 30 min. The completion of the reaction was inferred when a test portion no longer gave a colour with alkaline β-naphthol Conc. HCl aq (0·4 ml) was then added followed by Zn dust (200 mg) till a colourless solution was obtained. The mixture was filtered, the filtrate cooled and rendered alkaline by the addition of conc. NH_4OH. The liberated base was extracted with ether, the ether layer washed with dil. NaOH aq to remove any phenolic material and then with water. The ethereal solution was next extracted with 1 N HCl (3 × 5 ml); the acid extract neutralized with $NaHCO_3$, rendered just acidic by the addition of acetic acid and treated with excess of KI. The precipitated *hydriodide* was washed well with water, dried and crystallized from EtOH–MeOH to give colourless clusters of needles (100 mg), m.p. 235°; λ_{max}^{EtOH} 240, 279, 312 (sh) mμ (log ε 4·46, 4·41, 3·59). (Found: C, 52·9; H, 4·8. $C_{19}H_{20}O_3NI$ requires: C, 52·2; H, 4·6%.) Better analytical values could not be obtained in spite of repeated analyses.

8. 8-(2-N-*Ethoxycarbonyl*-N-*methylaminoethyl*)-7-*methoxy*-5,6-*methylenedioxyphenanthrene*. The aporphine liberated from its hydriodide (10 mg) in $CHCl_3$ (4 ml) containing KOH (10 mg) and ice was shaken with ethyl chloroformate (0·02 ml) in $CHCl_3$ (4 ml). After 1 hr more KOH and ethyl chloroformate was added. After 24 hr, the $CHCl_3$-solution was separated, washed with water, dil. HCl aq and then again with water, dried (Na_2SO_4) and evaporated to yield the phenanthrene (3 mg) purified by chromatography; λ_{max}^{EtOH} 265, 317 and 365 mμ.

9. 1,2-*Methylenedioxy*-3-*methoxydibenzo* (de, g) *quinoline*-7-*one*. Chromium trioxide (200 mg) was added to ice-cold pyridine (2 ml) and the complex added gradually with stirring to an ice-cold solution

of the aporphine base (21 mg; liberated from the foregoing hydriodide) in pyridine (1 ml). The resulting mixture was shaken in a micro-flask shaker for 3 hr and allowed to stand at room temp (30°) for 42 hr. EtOH (0·5 ml) followed by water (5 ml) was then added with stirring and the resulting homogeneous solution allowed to stand for 30 min. It was thoroughly extracted with $CHCl_3$. The $CHCl_3$-extract was repeatedly extracted with 5% HCl aq and the acid extract saturated with conc. NH_4OH. The liberated base was extracted thoroughly with CH_2Cl_2, dried (K_2CO_3) and the solvent removed. The reddish-yellow residue was adsorbed on a small column of alumina and eluted with CH_2Cl_2. The solvent was removed and the yellow residue was crystallized from EtOH–$CHCl_3$ to give slender brownish-yellow micro-crystals (3 mg), m.p. 275–276° (dec). The m.p. was not depressed on admixture with a specimen of 1,2-*methylenedioxy*-3-*methoxydibenzo* (de, g) *quinoline*-7-*one* (atherospermidine).

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