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SYNTHESIS OF 5- AND 8-METHOXY-YOBYRINES

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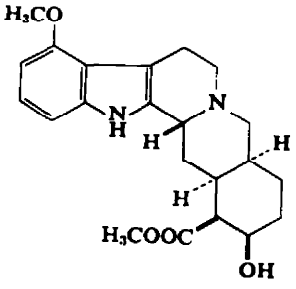
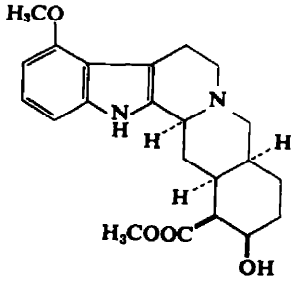
Abstract—5- and 8-Methoxy-yobyrines have been synthesized. The methoxy-yobyrine obtained by dehydrogenation of venenatic acid has been shown to be 5-methoxyyobyrine.

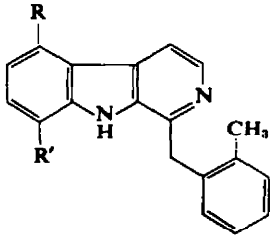
IN THE preceding paper[1] structures I and II were advanced for venenatine and isovenenatine, two indole alkaloids isolated from the bark of *Alstonia venenata* R.Br. The methoxyl group was assigned position 9 in the yohimbine skeleton mainly on the basis of physical evidence. Position 12 in the template was considered to be a less likely location for the methoxyl group:



I



II



III R = OCH_3; R′ = H

IV R = H; R′ = OCH_3

Selenium dehydrogenation of venenatic acid yields a methoxy-yobyrine, m.p. 229°. This has been identified as 5-methoxy-yobyrine by the synthesis of the two possible yobyrines (III and IV) and direct comparison of the dehydrogenation product with the synthetic samples.

[1] T. R. Govindachari, N. Viswanathan, B. R. Pai and T. S. Savitri, *Tetrahedron* **21**, 2951 (1965).

The synthesis of the methoxy-yobyrines was carried out by the method of Clemo and Swan.[2] 4-Methoxytryptamine needed for the synthesis of 5-methoxy-yobyrine was prepared from 4-methoxyindole by the standard method. 7-Methoxytryptamine was available by the method of Späth and Lederer.[3] The tryptamines were converted into the N-*o*-methylphenacetyl derivatives and cyclized to give the dihydroyobyrines. Dehydrogenation of these with Pd-black gave the methoxyyobyrines (III and IV). The selenium dehydrogenation product of venenatic acid was found to be identical in all respects (m.p., mixed m.p., UV and IR spectra) with III, thus confirming chemically the position of methoxyl group in venenatine and isovenenatine.

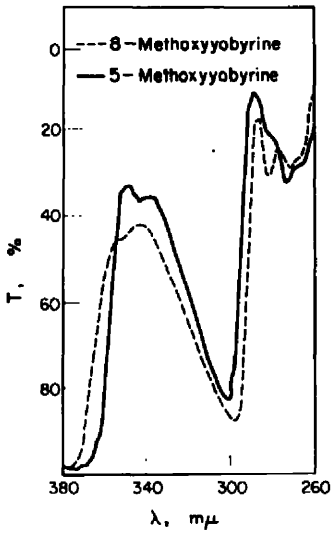


FIG. 1.

EXPERIMENTAL

All m.ps are uncorrected. IR and UV spectra were determined in CH_2Cl_2 and EtOH solutions respectively.

2-Methoxy-6-nitrotoluene. 2,6-Dinitrotoluene was reduced to 2-amino-6-nitrotoluene by H_2S in alcoholic ammonia solution. This was converted to 2-hydroxy-6-nitrotoluene by the procedure described by Noelting.[4] But the methylation of the phenol to the title compound by his method was found to be less successful than the one described below.

A solution of 2-hydroxy-6-nitrotoluene (3·06 g) in MeOH (50 ml) was mixed with a solution of $NaHCO_3$ (3·36 g) in water (50 ml), treated with MeI (8·5 g) and refluxed for 12 hr. After evaporation of the MeOH, the solution was diluted with water and extracted with ether. The ether layer was washed with dil. alkali, then with water, dried (Na_2SO_4) and the solvent evaporated. Crystallization of the residue from aqueous MeOH after treatment with animal charcoal gave 2-methoxy-6-nitrotoluene (2·1 g), m.p. 51°.

2-Methoxy-6-nitrophenylpyruvic acid. The condensation of diethyl oxalate with 2-methoxy-6-nitrotoluene was carried out according to the general method of Stoll *et al.*[5] To a solution of K (15·6 g) in abs. alcohol (70 ml) and ether (320 ml) was added a solution of 2-methoxy-6-nitrotoluene (33·4 g) and diethyl oxalate (58·4 g) in xylene (100 ml) with cooling (below 8°) and stirring. The

[2] G. R. Clemo and G. A. Swan, *J. Chem. Soc.* 617 (1946).
[3] E. Späth and E. Lederer, *Ber. Dtsch. Chem. Ges.* **63B**, 2102 (1930).
[4] E. Noelting, *Ber. Dtsch. Chem. Ges.* **37**, 1015 (1904).
[5] A. Stoll, F. Troxler, J. Peyer and A. Hofmann, *Helv. Chim. Acta* **38**, 1452 (1955).

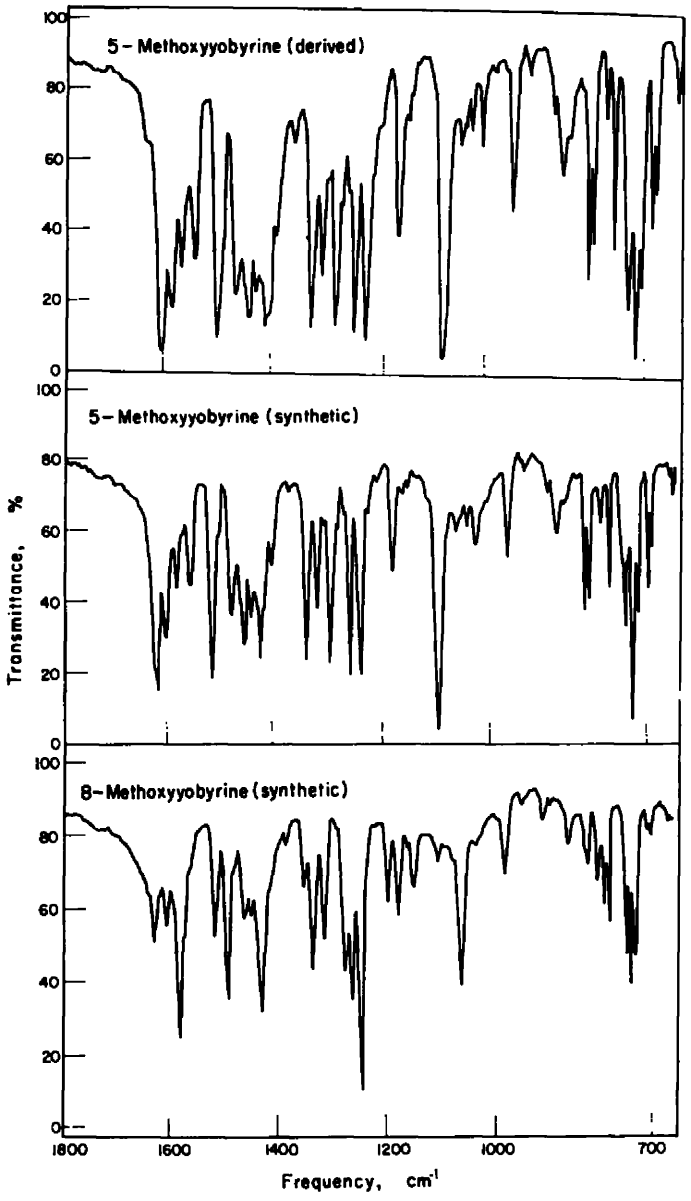


FIG. 2

solution was left overnight at 0° and then for 3 days at room temp. The potassium salt which had crystallized out was extracted with water (700 ml), 2 N NaOH (120 ml) and ether (400 ml) were added and the whole stirred vigorously for 2 hr. The aqueous solution was separated, extracted again with ether (400 ml) and acidified with conc. HCl. The acid which separated was extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and evaporated to yield the acid (41·5 g) m.p. 40–50°.

4-Methoxyindole. 2-Methoxy-6-nitrophenylpyruvic acid was converted to 4-methoxyindole-2-carboxylic acid in 73% yield as described by Blaikie and Perkin.[6] The decarboxylation of the acid to

[6] K. G. Blaikie and W. H. Perkin, *J. Chem. Soc.*, **125**, 328 (1924).

the indole by pyrolysis[8] could be achieved only in 35–40% yield. Results of refluxing the acid in quinoline in presence of $CuSO_4$ for decarboxylation were no better.

3-(N,N-*Diethylaminomethyl*)-4-*methoxyindole*. A solution of diethylamine (2·2 g) in acetic acid (4 ml) and water (1 ml) was added in one lot with formalin (38%, 3 ml) to 4-methoxyindole (4·4 g) and the mixture stirred at room temp for 3 hr. It was filtered, the filtrate basified with dil. NaOH aq and the liberated base extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and evaporated. The residue was crystallized from ether–hexane mixture to yield 3-(N,N-*diethylaminomethyl*)-4-*methoxyindole* (5·5 g), m.p. 132–134°. (Found: C, 72·56; H, 9·02; N, 12·25. $C_{14}H_{20}N_2O$ requires: C, 72·38; H, 8·68; N, 12·06%.)

3-*Cyanomethyl*-4-*methoxyindole*. A solution of the above Mannich base (6·9 g) in abs. tetrahydrofuran (30 ml) and glacial acetic acid (0·5 ml) was added dropwise to a mixture of dimethyl sulphate (15 ml), tetrahydrofuran (12 ml) and acetic acid (0·5 ml) with vigorous stirring and cooling below 15° in about ½ hr. The mixture was stirred for 2 hr more and left overnight. More ether was added to complete the precipitation, the supernatant liquid was decanted and the residue washed with more ether. The gummy residue was dissolved in a mixture of dioxan and water, heated with NaCN (4·5 g) and the solution stirred at 65–70° for 1 hr. It was cooled, diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried (Na_2SO_4), evaporated and the residue filtered through a column of silica gel using $CHCl_3$ as solvent. The product was crystallized from aqueous MeOH to yield the *nitrile* (3·8 g), m.p. 141–142°. (Found: C, 71·20; H, 5·63; N, 15·40. $C_{11}H_{10}N_2O$ requires: C, 70·95; H, 5·41; N, 15·05%.)

4-*Methoxytryptamine*. A solution of the above nitrile (0·5 g) in dry ether (50 ml) was added to a suspension of LAH (0·5 g) in ether (25 ml) under N_2 atm. More LAH (0·5 g) was added and the mixture refluxed for 1 hr. The complex was decomposed with water, the ether solution dried (Na_2SO_4) and evaporated to yield the tryptamine (0·5 g), m.p. 135–137°. Its IR spectrum was superimposable with that of an authentic sample of 4-methoxytryptamine.

N-(o-*Methylphenacetyl*)-4-*methoxytryptamine*. *o*-Tolyacetic acid (0·4 g) was converted to the acid chloride by treatment with $SOCl_2$. The acid chloride was dissolved in dry ether and added dropwise to a stirred solution of 4-methoxytryptamine (0·43 g) in the minimum amount of CH_2Cl_2 and diluted with excess ether. 1 N NaOH (28 ml) was added and the mixture stirred at room temp for 1 hr. The organic layer was separated, washed with alkali, water, then with acid, finally with water, dried (Na_2SO_4) and evaporated. The residue was crystallized from MeOH–ether to yield the *amide* (0·51 g), m.p. 107–109°. (Found: C, 74·25; H, 6·94. $C_{20}H_{22}N_2O_2$ requires: C, 74·51; H, 6·88%.)

5-*Methoxyyobyrine*. A solution of the above amide (0·25 g) in benzene (12 ml) was refluxed with freshly distilled $POCl_3$ (0·6 ml) under N_2 for 1 hr. The solvent was removed *in vacuo* and the residue boiled in dil. acetic acid and filtered. The filtrate was cooled and basified with ammonia. The precipitate was filtered rapidly, washed with water and dried *in vacuo* to yield the 5-methoxy-3,4-dihydroyobyrine (0·2 g) as a pale yellow solid. It was too unstable to be characterized and was used without purification, for the dehydrogenation. The dihydroyobyrine (0·2 g) was mixed with Pd black (0·2 g), heated for 30 min at 180–190° at 10 mm press. and then sublimed at 0·001 mm. The sublimate was crystallized from MeOH to yield 5-methoxyyobyrine (30 mg) as needles, m.p. 229°, λ_{max} 219, 247, 289, 335, 349 mμ (log ε, 4·58, 4·74, 4·17, 3·84, 3·89). (Found: C, 74·80; H, 5·90. $C_{20}H_{18}N_2O.H_2O$ requires: C, 74·97; H, 6·29%.) Its m.p. was undepressed by admixture with the methoxyyobyrine obtained from venenatic acid. The IR and UV spectra of the two samples were also identical.

N-(o-*Methylphenacetyl*)-7-*methoxytryptamine*. *o*-Tolyacetic acid (0·4 g) was converted to the acid chloride and treated with 7-methoxytryptamine (0·4 g) to yield the *amide* (0·55 g), needles (from MeOH–ether), m.p. 136°. (Found: C, 74·48; H, 6·95. $C_{20}H_{22}N_2O_2$ requires: C, 74·51; H, 6·88%.)

8-*Methoxy-yobyrine*. The above amide (0·3 g) was cyclized with $POCl_3$ (0·7 ml) to yield as in the previous case, the dihydroyobyrine (0·25 g) as a pale yellow solid. This was dehydrogenated with Pd black (0·2 g), the product was sublimed *in vacuo* (0·001 mm) and the sublimate crystallized from MeOH to yield 8-*methoxy-yobyrine* 90 mg) as needles, m.p. 207°, λ_{max} 213, 243, 277, 287, 342 mμ (log ε 4·56, 4·69, 3·94, 4·04, 3·74), λ_{sh} 352 mμ (log ε 3·69). (Found: C, 79·07; H, 5·92. $C_{20}H_{18}N_2O$ requires: C, 79·44; H, 6·00%.) Its m.p. was depressed to 180–185° on admixture with the methoxyyobyrine obtained from venenatic acid. Their IR spectra also showed significant differences.

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