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The Synthesis of erythro- and threo-N-methyl 7-Hydroxy-1,2,9,10-tetramethoxyaporphine

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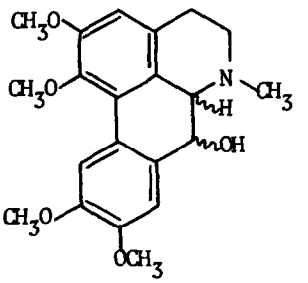
Abstract: The total synthesis of the title compounds is described.

A few naturally occurring 7-hydroxyaporphine alkaloids possessing antiparkinsonian activity have recently been isolated.[1,2] The parent ring system, shorn of oxygenation except for the 7-position, has been synthesized,[3] but the generality of that synthetic route as applied to its more highly functionalized analogues is not certain.[4] We report here, in preliminary fashion, a general route for the synthesis of 7-hydroxyaporphine alkaloids and apply that route to the synthesis of erythro- (R,S and S,R)- and threo- (R,R and S,S)-N-methyl-7-hydroxy-1,2,9,10-tetramethoxyaporphine (1a,b).



(1a,b)

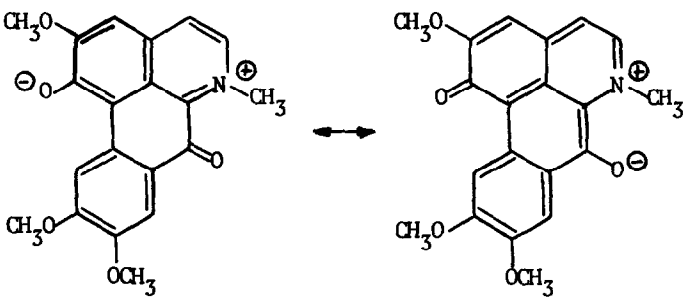
As shown in the Scheme, nitration of (3,4-dimethoxyphenyl)acetic acid (2, R = H) in concentrated nitric acid at 0 - 5°C proceeded smoothly (92%) to the corresponding nitro-derivative (2, R = NO_2, mp 207-208°C).[5] Condensation of 2 (R = NO_2) with (3,4-dimethoxyphenyl)ethylamine in dichloromethane at 0 - 5°C using N,N'-carbonyldiimidazole, produced the amide 3 (80%, mp 174-175°C).[6] In this connection, it is interesting to note that the usual Schotten-Baumann techniques[7] or application of other condensing reagents[8] met with notable lack of success.

Bischler-Napieralski cyclization of the amide 3 to 1-(2'-nitro-4',5'-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (4) (80%, mp 124-125°C) was accomplished using the Langheld ester (PPE)[9]

in refluxing chloroform (48 hrs). Rose Bengal catalyzed photooxidation of 4 in oxygen saturated absolute methanol[10] provided (82%) the ketone 5. Unreacted starting material (18%) could be recovered. The corresponding, bright orange, N-methyl derivative, 6, obtained in quantitative yield (iodomethane, acetone, reflux 24 hrs) was catalytically reduced (Pd/C, 5%, methanol, 50 psi) to the diamine 7 in 80% yield.

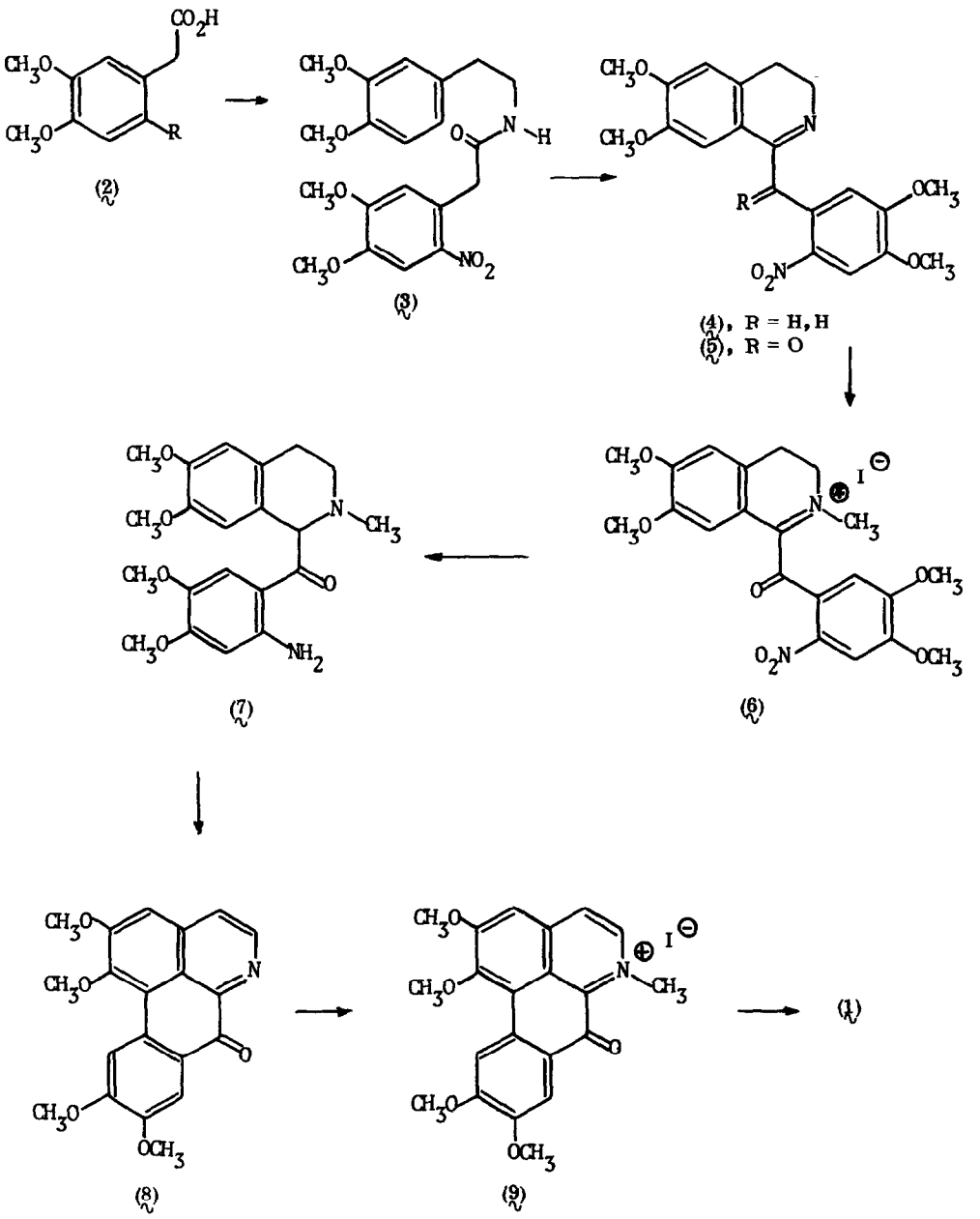
Pschorr cyclization of 7 in a mixture of glacial acetic and concentrated sulfuric acids (6:1, v/v) using sodium nitrite, followed by dilution with acetone and addition of EDTA-activated, freshly prepared, Gatterman copper provided the bright yellow oxoaporphine 8 in 20-25% yield along with numerous other products.[11,12]

Treatment of the oxoaporphine 8 with iodomethane in acetone at reflux produced exclusively[11] the known, bright green, zwitterionic alkaloid corunnine (10). However, in neat iodomethane, in the absense of moisture, at 40 - 45°C for 12 hrs, the unstable oxoaporphine methiodide 9 was, quantitatively, the sole product.



(10)

Reduction of the methiodide 9, in methanol, using a large (ca. 20 fold) excess of potassium borohydride, yielded (60%) <u>one</u> isomer of the desired N-methyl 7-hydroxy-1,2,9,10-tetramethoxyaporphine (1) along with dehydration product and corunnine (10). On the basis of the ^{1}H nmr spectrum (J_{6aH-7H} = 3 Hz) and in comparison to the known naturally occurring bases,[1,2] we assign this isomer the <u>erythro-</u> (R,S and S,R) configuration.[13] Catalytic reduction of the heterocyclic ring of the oxoaporphine methiodide 9, using platinum oxide in methanol, followed by immediate borohydride reduction in the same solvent, has yielded small quantities of the <u>threo-</u> (R,R and S,S) isomer of 1 along with major quantities of <u>erythro-</u>(1).


CO2H
CH3O
CH3O
R
(2)
N
H
O
NO2
(3)
OCH3
O2N
(4), R = H, H
(5), R = O
I⊖
CH3
NH2
(6)
(7)
(8)
(9)
(1)

Notes and References

(1) T. H. Yang, J. Pharm. Soc. (Japan), 82, 798, 804 (1962).

(2) A. Quevauviller and M. Hamonniere, C. R. Acad. Sci., Ser. D, 284 (1977).

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(4) Efforts to model the synthesis outlined here after that reported in Reference 3 were unsuccessful. We thank Professor Neumeyer for his helpful comments.

(5) G. Hahn and H. J. Schulz, Ber., 72, 1312 (1939).

(6) R. Paul and G. W. Anderson, J. Amer. Chem. Soc., 82, 4596 (1960); op cit., J. Org. Chem., 27, 2094 (1962). Satisfactory spectra (ir, uv, ms, and ^{1}H and ^{13}C nmr) and elemental analysis have been obtained for all new compounds reported here.

(7) M. P. Cava and D. R. Dalton, J. Org. Chem., 31, 1281 (1966).

(8) J. C. Sheehan and G. P. Hess, J. Amer. Chem. Soc., 77, 1067 (1966).

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(10) K. L. Wert, Master Thesis, Temple University, Philadelphia, Pa (1977).

(11) I. Ribas, J. Sueiras and L. Castedo, Tetrahedron Lett., 3093 (1971).

(12) The details, which include complete identification of all of the products, will be included in the full report of this work.

(13) The major isomer has been converted to its corresponding methiodide (mp 190°C, dec) and we are currently attempting to obtain crystals suitable for x-ray analysis.

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