Tetrahedron Letters No.20, pp. 1509-1512, 1965. Pergamon Press Ltd.
Printed in Great Britain.

THE PROBLEM OF THE 1,2,9,10-TETRAOXYGENATED APORPHINES AND THE SYNTHESIS OF (±)-1-HYDROXY-2,9,10-TRIMETHOXYAPORPHINE

Maurice Shamma and William A. Slusarchyk[1]

Department of Chemistry, The Pennsylvania State University,
University Park, Pennsylvania

(Received 12 March 1965)

In a very recent communication to this journal[2], some drastic revisions in the structural assignments for a number of 1,2,9,10-tetraoxygenated aporphine alkaloids were proposed, including those for glaucentrine, laurelliptine, rogersine, and the quaternary base from Fagara tinguassoiba.[3]

It would be otiose at this point to go through the detailed reasoning[2] for suggesting such changes, but we wish to indicate that:

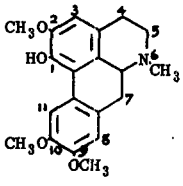
(a) The newly proposed[2] structure I (in the N-methyl quaternary form) for the base from F. tinguassoiba is indeed correct, and that

(b) Glaucentrine[4] is not a 1,2,9,10-tetrasubstituted aporphine as was believed so far. This fact is one of the causes of the confusion that has arisen regarding the structures of the 1,2,9,10-tetrasubstituted aporphines, since glaucentrine has been used in a process of elimination to prove the structures of several 1,2,9,10-tetrasubstituted aporphines, including that from F. tinguassoiba.[5]

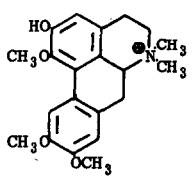
We have synthesized authentic (±)-1-hydroxy-2,9,10-trimethoxyaporphine (I) by the classical route outlined below. When this base was quaternized with methyl iodide, and the iodide ion then exchanged

for picrate, the resulting quaternary salt was identical in its uv spectrum in ethanol, its ir spectrum in acetonitrile solution, and its silica gel thin-layer R_f values in ten different solvent systems, with the quaternary alkaloid of F. tinguassoiba also in the picrate form. It follows that the old structure II for the F. tinguassoiba alkaloid[5] should be replaced by expression I (in the N-methyl quaternary form).

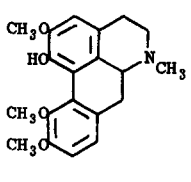
Natural glaucentrine has also been assigned structure I.[4] Comparison of our synthetic sample with natural glaucentrine showed the two compounds were not identical. We were subsequently able to prove that the natural glaucentrine we had received corresponds to corydine (III), via nmr, ir, uv, and R_f comparisons with an authentic sample of corydine. A sample of natural glaucentrine HCl, turning brown at 234° and blackening between 237-238°, as reported in the literature for this salt,[4] was also shown by us to be identical with corydine HCl.



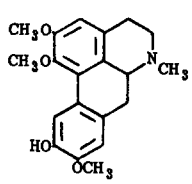
I



II



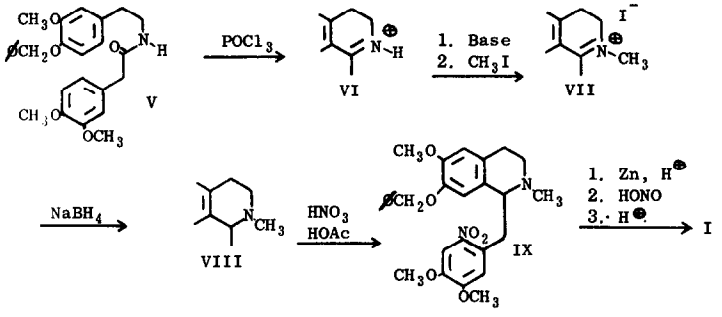
III



IV

The revised structure IV recently suggested for glaucentrine cannot therefore be correct.[2] Additionally, all 1,2,9,10-tetraoxygenated aporphines whose structures were elucidated by comparison with samples of natural glaucentrine should now have their structures reconsidered.

Synthesis of Compound I



The amide V, m.p. 124°, prepared in 65% yield by condensing 2-(4-benzyloxy-3-methoxyphenyl)ethyl amine with homoveratric acid in the presence of N,N'-dicyclohexyl carbodiimide in tetrahydrofuran, was cyclized to the salt VI in 87% yield. Both V and VI gave melting points comparable with those reported by Billek who earlier had used different procedures to prepare these two compounds.[6] Treatment of the salt VI with base and then with methyl iodide gave the immonium salt VII, m.p. 191-192°, which was reduced with sodium borohydride to oily, racemic O-benzylcodamine (VIII).

Subsequent nitration of the base VIII with nitric acid in acetic acid gave 6'-nitro-O-benzylcodamine IX, m.p. 114-116°, in 54% yield. Zinc and sulfuric acid reduction of IX afforded 6'-amino-O-benzylcodamine which when diazotized with sodium nitrite in sulfuric acid, and then treated with boiling 25% H_2SO_4 gave racemic aporphine I in 22% yield, free base m.p. 190-192°. The uv spectrum of I exhibited λ_{max}^{EtOH} 305, 280, and 220 mμ (log e 4.12, 4.12, and 4.52) characteristic of a 1,2,9,10-tetrasubstituted aporphine.[3,7]

Acknowledgements.- The authors wish to thank Drs. R.H.F. Manske and Leo Marion for the alkaloidal samples, and the National Science Foundation for Grant GF-1941.

References

1. Recipient of N.I.H. predoctoral fellowship 5-F1-GM-20, 691-02.

2. R. Tschesche, P. Welzel and G. Legler, Tetrahedron Letters, No.8, 445 (1965).

3. For a recent review on the aporphine alkaloids see M. Shamma and W.A. Slusarchyk, Chem. Reviews, 64, 59 (1964).

4. For a discussion of the chemistry of glaucentrine see R.H.F. Manske "The Alkaloids", Vol. IV, Academic Press, New York, 1954, p. 119.

5. N.V. Riggs, L. Antonaccio, and L. Marion, Can. J. Chem., 39, 1330 (1961).

6. G. Billek, Monat., 87, 106 (1956).

7. Satisfactory elemental analyses were obtained for all the synthetic compounds prepared. Melting points are uncorrected.