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A TOTAL SYNTHESIS OF CORUNNINE

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Recently we have reported the isolation from Glaucium flavum Cr. var. vestitum of a new oxoaporphine alkaloid with an unusual dipolar structure (I), named corunnine (1). The study of the aporphine and oxoaporphine alkaloids are of current interest mainly because of their pharmacological properties as tumor inhibitors (2,3).

Although we could establish from chemical and spectral studies that corunnine is derived from a 1,2,9,10 tetraoxygenated 7-oxoaporphine, however, the placement of these three methoxy groups in the 2,9 and 10 positions of the aporphine skeleton needed further support since this assignment was based uniquely on the fact that only the aporphine alkaloids which carry a phenolic group in C-1 or C-11, or two phenolic proups in C-10 and C-11 give unusual green dipolar compounds on oxidation (4).

In this communication we wish to report a synthesis of corunnine as shown in the scheme of Fig. 1. It involves the preparation of the intermediate (VI) having a distinct substituent in C-1 in comparison to the 2,9 and 10 positions, and its subsequent deethylation to give (I). Thus establishing that the three methoxy groups in corunnine alkaloid must be in the 2,9 and 10 positions of the oxoaporphine skeleton and that the reported novel demethylation of this type of methiodides (1), occurs in the C-1 position.

N-β-(4-ethoxy-3-methoxy-phenetyl)-3,4-dimethoxy-6-nitro-phenylacetamide (6) was cyclised by the Bischler-Napieralski reaction using P.P.E.(7) to give the corresponding 3,4-dihydroisoquinoline (II) (6) (70% yield), which on oxidation by slowly adding CrO_3 in acetic acid to the compound (II), afforded the desired benzoyl derivative (III) (8) in 53 % yield.According to the procedure described (5) by adding (II) to the chromic anhydride in acetic acid on oxidation a mixture containing a substantial quantity of (IV; R=NO_2, X=2H), m.p. 192-94ºC, in addition to the desired compound (III) was produced, which was readily resolved by column chromatography. Dehydrogenation of (III) by treatment with hot alcoholic alkali afforded (IV; R=NO_2, X=0) (5) (60% yield), which was hydrogenated with Raney nickel to the Ketoamine (IV; R=NH_2, X=0)(90%) and this without further purification cyclised by the Pschorr reaction to the oxoaporphine (V)(5)(58 % yield) . Quaternisation of (V) with methyl Iodide in boiling acetone for two hours afforded

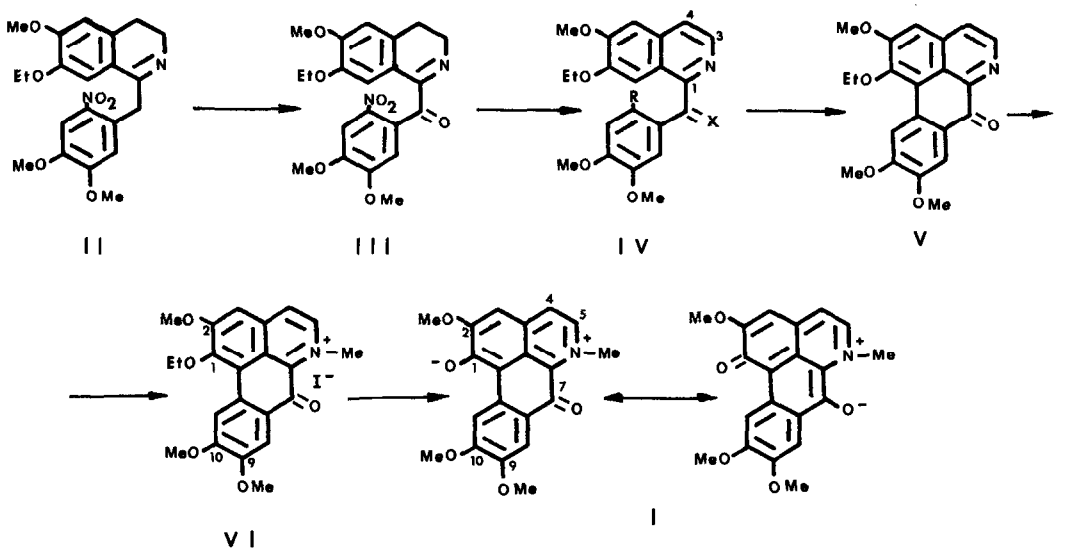

Fig. 1

a quantitative yield of the desired methiodide (VI) as reddish-brown colored needles, m.p. 186-88 °C.

As we have recently shown that the methiodide of 1,2,9,10 tetramethoxy 7-oxoaporphine is readily demethylated (1), we decided to heat (VI) under different conditions. In this way we found that by heating the quaternary salt (VI) in boiling benzene or N,N-dimethylformamide for several hours,or briefly heating the compound to nearly melting point, a highly colored compound of high yield lacking the ethoxy group as shown by its NMR resulted.Its identity with corunnine was proved by direct comparison with a sample of authentic material.

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REFERENCES

1. I.Ribas, J. Sueiras, and L.Castedo, Tetrahedron Letters, 3093 (1971).
2. D.Warthen, E.L.Gooden, and M.Jacobson, J. Pharm.Sci.,58, 637 (1969).
3. P.E.Sonnet, and M. Jacobson, J.Pharm. Sci,, 60, 1254 (1971).
4. V.Preininger,J.Hrbek jun., Z.Samek, and F.Santavý, Arch.Pharmaz.,302,808 (1969).
5. I.R.C.Bick,J.H.Bowie,and G.K.Douglas, Aust. J. Chem. , 20, 1403 (1967).
6. R.H.F.Manske, E.H.Charlesworth, and W.R.Ashford, J.Amer.Chem.Soc.,73,3751 (1951).
7. M.P.Cava, M.V.Lakshmikanthan, and M.J.Mitchell,J.Org.Chem., 34, 2665 (1969).
8. The structures of all new compounds were fully compatible with spectral and analytical data.