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THE CONSTRUCTION OF THE SUBSTITUTED C/D RING SYSTEM OF DELPHININE-TYPE ALKALOIDS

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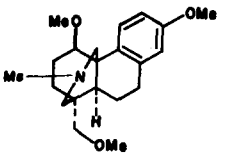
We have recently perfected simple and stereospecific methods for the preparation of the intermediates i[1] and ii[2]. While these compounds are being accumulated on a large scale, it became imperative to explore various possible routes for their conversion into alkaloids of the delphinine type - talatisamine and chasmanine.

In the present communication we wish to disclose a process of unexpected simplicity and general utility which is based on our photochemical synthesis of the atisine skeleton[3].

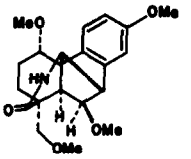
Methoxy tetraline iii was converted into the known[4] compound iv. This material gave the oily homogeneous allene adduct (1) in a yield of 95%[3].* Proceeding exactly as described in our atisine synthesis the intermediate (3) was obtained and converted stereospecifically (thermodynamic control) into the hydroxy ketone (4) (m.p. 128.5-130°) in a high yield. Compound (4) was methylated in refluxing dioxane with sodium hydride and methyliodide to yield the homogeneous oily methoxy ketone (5a) in quantitative yield. A solution of compound (5a) (10.5 g), t-butyl perbenzoate (9.72 g) and cuprous bromide (10 mg) in absolute benzene (100 ml) was refluxed for 24 h.

Chromatography on silica gel yielded 6.5 g of the starting material (5a) and 2.25 g (60% on the basis of starting material consumed) of the oily homogeneous product (6).

* All compounds gave molecular ions in mass spectroscopy, I.R. and N.M.R. spectra compatible with the structures assigned to them. All crystalline compounds gave correct elemental analyses.



i



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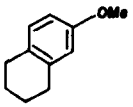

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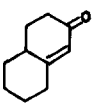

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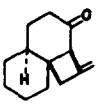

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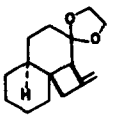

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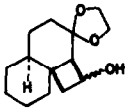

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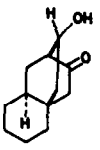

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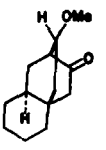
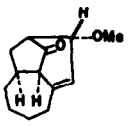


5a



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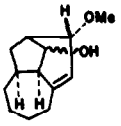

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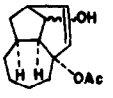

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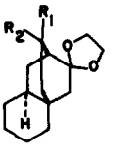
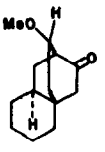


9 R_1=OH, R_2=H

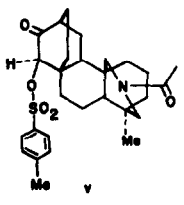
10 R_1=H, R_2=OH

11 R_1=OMe, R_2=H

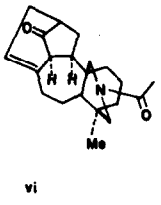
12 R_1=H, R_2=OMe



5b



v



vi

[I.R. (CCl_4) 1738 cm^{-1} (ketone), 1640 cm^{-1} (strong) (double bond); N.M.R. ($CDCl_3$) singlet (3H) τ = 6.4 p.p.m. (methoxyl), doublet (1H) τ = 5.18, 5.22 p.p.m. (vinylic hydrogen)].

Reduction of (6) with lithium aluminum hydride gave one epimer of the oily alcohol (7) and this compound on heating with glacial acetic acid and p-toluene sulphonic acid underwent the typical pyro-isopyro rearrangement of the delphinine alkaloids[5] to yield the product (8) (m.p. 115°-116°, 78%). [I.R. (CCl_4) 3470 cm^{-1} (hydroxyl), 1735 cm^{-1} (acetate); N.M.R. ($CDCl_3$) singlet (3H) τ = 8.00 p.p.m. (acetyl methyl), multiplet (2H) τ = 4.85 p.p.m. (vinylic protons), no methoxyl].

The configuration of the methoxyl in (5a) was deduced as follows. Ketalization of (4) with ethylene glycol and p-toluene sulphonic acid in benzene yielded an equilibrium mixture of the oily hydroxyketals (9) and (10) readily separable by chromatography on silica gel.

Compound (9) had a larger R_f, a hydroxyl band at 3550 cm^{-1} in the I.R. and a multiplet (1H) at τ = 6.33 p.p.m. for the proton R_2 in the N.M.R. spectrum. Compound (10) had a smaller R_f, a hydroxyl band at 3620 and 3450 cm^{-1} in the I.R. and a multiplet (1H) at τ = 5.77 p.p.m. for the proton R_1 [unshielded by the dioxolane and by the hydroxyl] in the N.M.R. spectrum.

Methylation followed by acidic hydrolysis converted the ketal (9) into the previously described compound (5a) and the ketal (10) into its epimer (5b).

The epimers (5a) and (5b) differ very strongly in T.L.C. and thus their stereochemical purity is assured. A rearrangement of the type (5a) → (6) has been postulated many years ago as a step in the biogenesis of delphinine alkaloids[6]. More recently a rearrangement of the epimer v derived from atisine to the product vi on pyrolysis has been observed by Johnston and Overton[7].

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REFERENCES

1. Unpublished results by the present authors.
2. K. Wiesner, Pak-tsun Ho, D. Chang and J. F. Blount, Experientia 28, 766 (1972); Pak-tsun Ho, S. Oida and K. Wiesner, Chem. Comm. p. 883 (1972); K. Wiesner, Pak-tsun Ho, R. C. Jain, S. F. Lee, S. Oida and A. Philipp, Can. J. Chem. (in the press).
3. R. W. Guthrie, Z. Valenta and K. Wiesner, Tetrahedron Letters No. 38, 4645 (1966).

4. C. Mannich, W. Koch and F. Borkowsky, Ber., 70, 355 (1937).

5. K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Gotz, Tetrahedron 9, 254 (1960).

6. c.f. K. Wiesner and Z. Valenta in L. Zechmeister, Progress in the Chemistry of Organic Natural Products Vol. XVI p. 26 Springer-Verlag Wien (1958).

7. J. P. Johnston and K. H. Overton, J. Chem. Soc. p. 1490 (1972).