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THE TOTAL SYNTHESIS OF (±)-MESEMBRINE

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The alkaloid (-)-mesembrine (I) was originally isolated from *Mesembryanthemum tortuosum* in 1957,[1] and its structure was derived from degradative processes and the synthesis of the deoxy compound mesembrane (II).[2] We would now like to report on the total synthesis of (±)-mesembrine (I).

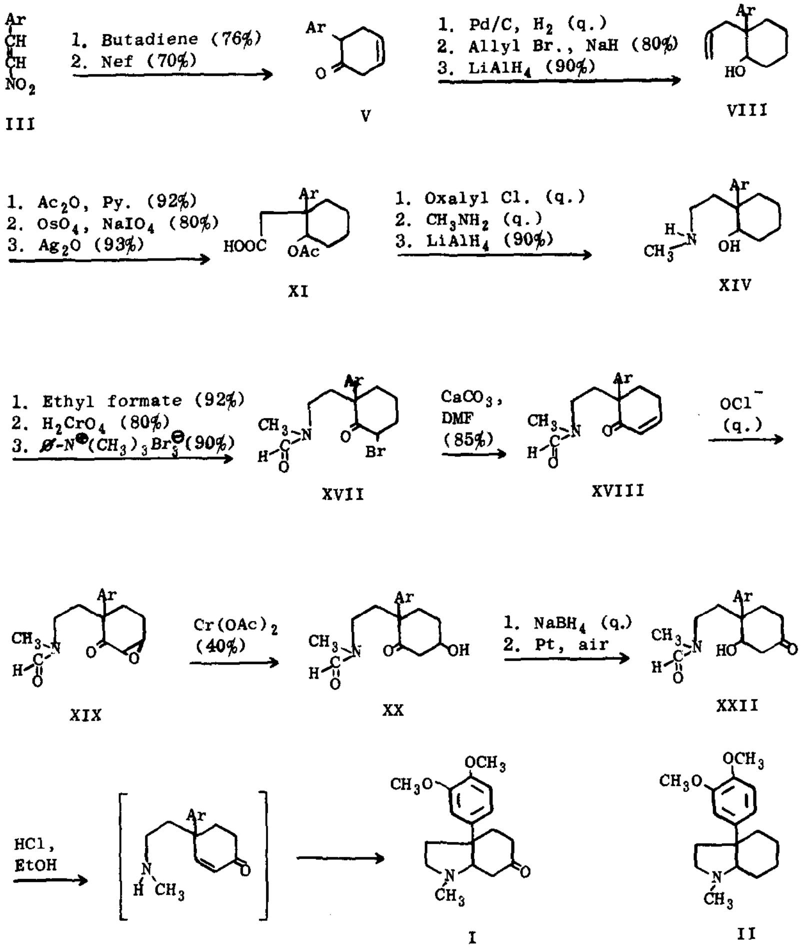
The starting material for the synthesis was the nitrostyrene III.[3] Diels-Alder condensation with butadiene resulted in the adduct IV, m.p. 113-114.5°.[4] Treatment of the sodium salt of IV with ethanolic hydrochloric acid yielded the ketone V, $C_{14}H_{16}O_3$, m.p. 73.5-75°.[4] Hydrogenation over 5% Pd/C then selectively reduced the double bond and resulted in formation of the saturated ketone VI, $C_{14}H_{18}O_3$, m.p. 65°, i.r. 5.90 μ.

Monoalkylation of VI with NaH and allyl bromide gave the oily ketone VII, $C_{17}H_{22}O_3$, i.r. 5.88 and 6.10 μ. Reduction of the oil with $LiAlH_4$ in ether yielded the alcohol VIII, $C_{17}H_{24}O_3$, m.p. 115-116.6°, i.r. 2.88 and 6.11 μ. Oxidative cleavage of the acetate IX, $C_{19}H_{26}O_4$, with OsO_4 and $NaIO_4$ in dioxane/water[5] produced the aldehyde acetate X, m.p. 94-95°, $C_{18}H_{24}O_5$, i.r. 3.72 and 5.85 μ.

The acid acetate XI, $C_{18}H_{24}O_6$, m.p. 137-140°, obtained from oxidation of X with alkaline silver oxide, was treated with excess oxalyl chloride in benzene. The acid chloride XII so obtained was not purified or analyzed, but was immediately treated with CH_3NH_2 to give the amide acetate XIII, $C_{19}H_{27}NO_5$, m.p. 142-143°, i.r. 2.99, 5.82 and 6.03 μ. Complete reduction with excess $LiAlH_4$ gave XIV, $C_{17}H_{27}NO_3$, which exhibited extensive hydrogen bonding in the i.r. from 3.0 to 4.2 μ. From this point onward all of the intermediates we had to deal with were oils.

The amide alcohol XV, $C_{18}H_{27}NO_4$, i.r. 2.90 and 6.05 μ, formed by treatment of XIV with ethyl formate, was oxidized with Jones reagent[6] to the ketoamide XVI, $C_{18}H_{25}NO_4$, i.r. 5.92 and 6.07μ, which was brominated with phenyltrimethylammonium tribromide[7] to give XVII. Dehydrohalogenation then produced the eneone XVIII, $C_{18}H_{23}NO_4$, i.r. 6.05μ.

Epoxidation of XVIII in the cold with 1:1 pyridine/chlorox[8] was followed by reduction with $Cr(OAc)_2$.[9] The product was a mixture of starting compound XVIII and the β-hydroxyketone XX. Oily XX was separated from the mixture by preparative TLC, and exhibited i.r. peaks at 2.88, 5.90 and 6.06 μ. Reduction with $NaBH_4$



Ar = 3,4-Dimethoxyphenyl

(q.) = Essentially quantitative yield

in ethanol gave quantitatively the diol XXI, $C_{18}H_{27}NO_5$, i.r. 2.89, and 2.90-3.40 μ.

Oxidation of XXI over Pt/air preferentially oxidized the less hindered alcohol to give the N-formyl ketoalcohol XXII which was both dehydrated and hydrolyzed with ethanolic hydrochloric acid to give an overall 50% yield (from XXI) of (±)-mesembrine. Both natural and synthetic mesembrine are oils, but the two materials were found to be identical in terms of their i.r. spectra in $CHCl_3$ and in CS_2 solution, and also on the basis of their R_f TLC (Adsorbosil-1) values in twelve different solvent systems.

The synthesis of mesembrine by the above route points to the accessibility of similarly substituted octahydroindoles. Accordingly, work is presently in progress on the synthesis of some of the Amaryllidaceae type alkaloids which are structurally related to mesembrine. All i.r. spectra were run in $CHCl_3$ solution, except where specified otherwise. Satisfactory analyses were obtained for all key intermediates.

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