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SYNTHESIS OF dl-MESEMBRINE AND ITS TRANS ISOMER

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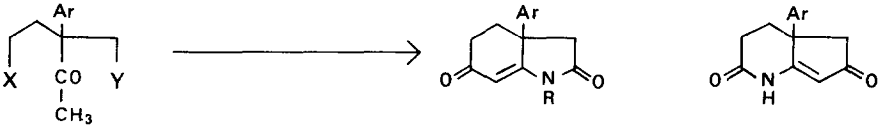
In the course of studying the hydrolytic cyclization of β-acetyladiponitriles and related compounds1), we have found that Ia(mp.117.5°), Ib(103°) and Ic(mp.111°) gave the hexahydroindole derivatives(IIa) in 60%, 72.9% and 73% yields respectively.2)



I II III

a; X = CN, Y = CN

b; X = CN, Y = COOMe

c; X = COOMe, Y = CN

a; R = H

b; R = Me

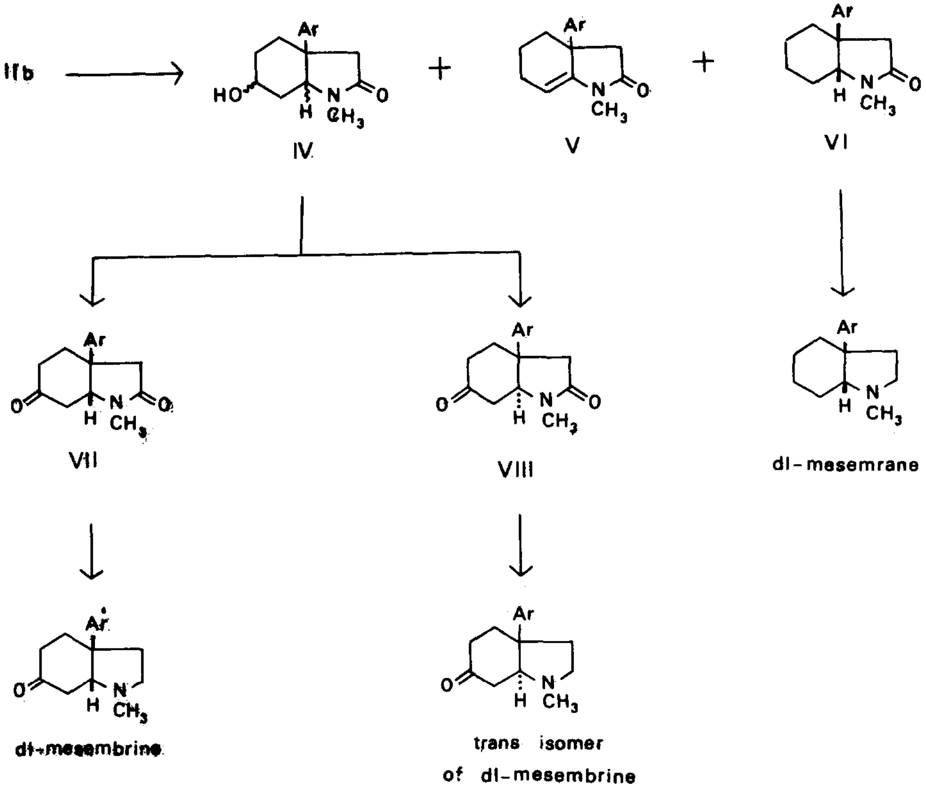
Ar = 3,4-dimethoxyphenyl

A suspension of 1g. of I in 5ml. of 65% sulfuric acid3) was heated at 140° for 5 min. and poured into ice-water. Recrystallization of the crude product from ethanol gave 3a-(3,4-dimethoxyphenyl)-2,6-dioxo-Δ^7-hexahydroindole(IIa) as a single product, mp.212°;IR(Nujol)1740, 1710cm^{-1}(five membered lactam)4), 1640cm^{-1}(enone).

N-methylation of IIa with dimethyl sulfate and KOH in ethanol gave IIb, mp.179-180°;IR(CHCl$_3$) 1745cm^{-1}(five membered lactam)4), 1625cm^{-1}(enone); NMR(CDCl$_3$) 2.86ppm. 2H, s,(3-C methylene), 5.72ppm. 1H, s,(vinyl proton).

These spectral data of IIa and IIb excluded the other possible structure III for the cyclization product. The ultraviolet spectrum of IIa was likewise in accordance with the vinylogous imide structure1), showing an absorption maximum at 273mμ (ε 26,200) in ethanol, which shifted to 325mμ (ε 39,020) in alkaline ethanol.

We now wish to report a successful transformation of the above cyclization product to dl-mesembrine5) and its trans isomer by the following sequence of reactions ;

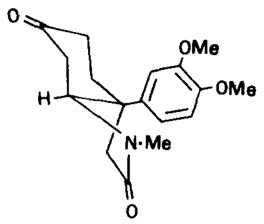


Hydrogenation of IIb with Raney Ni at 110-120° under initial 105atm. pressure of hydrogen gave a mixture of at least three compounds as revealed by TLC. This mixture was chromatographed on alumina, and elution with benzene gave V as an oil, bp$_{0.1}$183° ;IR(CHCl$_3$) 1710,1665cm^{-1}; UV(ethanol)λ_{max}231mμ (ε 16,030)6); NMR(CDCl$_3$) 1H centered at 5.13ppm. t, J=3.0cps.(vinyl proton) 2H centered at 2.68ppm. d, J=2.0cps.(3-C methylene). Further elution with benzene:ether(10:1) gave VI, mp.87°; IR(Nujol) 1690cm^{-1}, which was converted to dl-mesembrane5) by reduction with LAH in refluxing tetrahydrofuran in 72.3% yield, bp $_{0.1}$140°; hydrochloride, mp.194° ;picrate, mp.173°, identical in all respects with an authentic sample provided by Dr. A. Popelak7). Further elution with ether:ethanol(20:1) gave in 30-46% yield the hydroxy derivative(IV) as amorphous powder, which was a mixture of two or more stereoisomers ; IR(CHCl$_3$) 3600-3200cm^{-1},1690cm^{-1}.

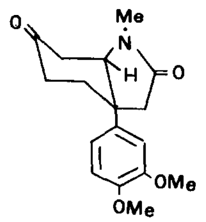
IV, without being resolved, was subjected to Jones oxidation at -5° to give a nearly 1:1 mixture of the ketolactam(VII)and (VIII) as crystals in a combined yield of 54.4%. The mixture was chromatographed on alumina. Early part of the eluate with acetone contained the trans isomer (VIII), mp.205-208°; IR($CHCl_3$) 1705(shoulder), 1690cm^{-1}. Subsequent elution with the same solvent gave the cis isomer (VII), mp.129-131°; IR($CHCl_3$) 1720, 1685cm^{-1}.

Structural assignment to the isomers was made on the basis of NMR spectra. C-7a methine proton of VIII appeared as a multiplet at 4.11-3.62ppm. Although the methoxy group(3.87ppm.) obscured this signal partly, it revealed a large coupling constant with one of the C-6 protons (10cps.). With this only, however, the trans structure is not sufficiently discernible because this pattern of signal might also be ascribable to the C-7a methine proton of the cis form in conformation (B). Distinction became obvious when the other isomer (VII) showed a signal of the proton at 4.30ppm., triplet, J=4.5cps, almost inconceivable for the axial-oriented C-7a proton of the trans structure. The signal of the C-7a proton seen with VII seems to provide some information concerning the favored conformation of the cis structure. Dreiding models show that (A) is more favored than (B) for the spectral evidence.

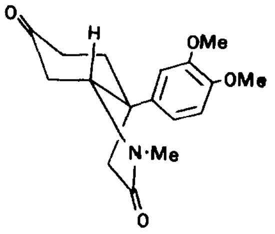
VIII (trans)



VII (cis)



(A)



(B)

The cis isomer (VII) was ketalized with 2-methyl-2-ethyl-dioxolane-1,3 and p-toluene sulfonic acid. Reduction of the crude oily ketal with LAH in tetrahydrofuran followed by treatment with 10% HCl gave dl-mesembrine as a colorless oil in 72.5% overall yield from VII, bp $_{0.07}$178°; IR(CCl_4) 1725cm^{-1} ; hydrochloride, mp.179-181°, which was identical in melting point, IR and NMR spectra with authentic dl-mesembrine furnished by Dr. A. Popelak[7)].

The trans isomer (VIII) gave the crystalline ketal in 77.5% yield, mp.173°; IR($CHCl_3$) 1685cm^{-1}(lactam). Reduction of the ketal with LAH in tetrahydrofuran and subsequent treatment with 10% HCl likewise gave the trans isomer of dl-mesembrine in 71% yield, mp.97-99°; IR(CCl_4) 1715cm^{-1}; hydrochloride, mp.223-225°(decomposed).

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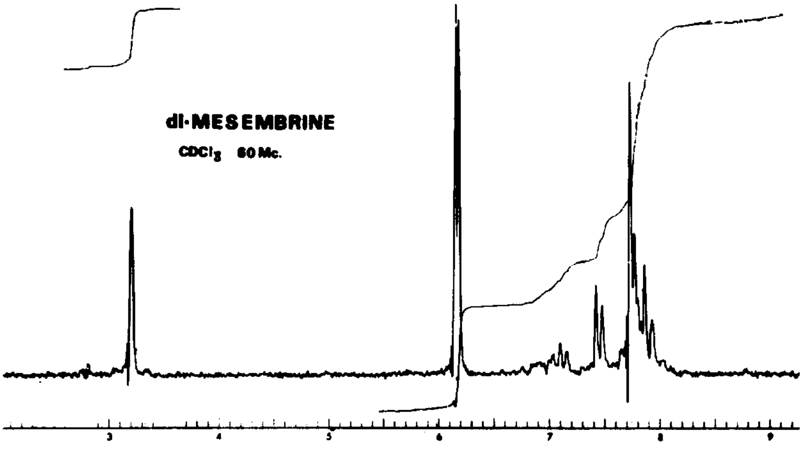

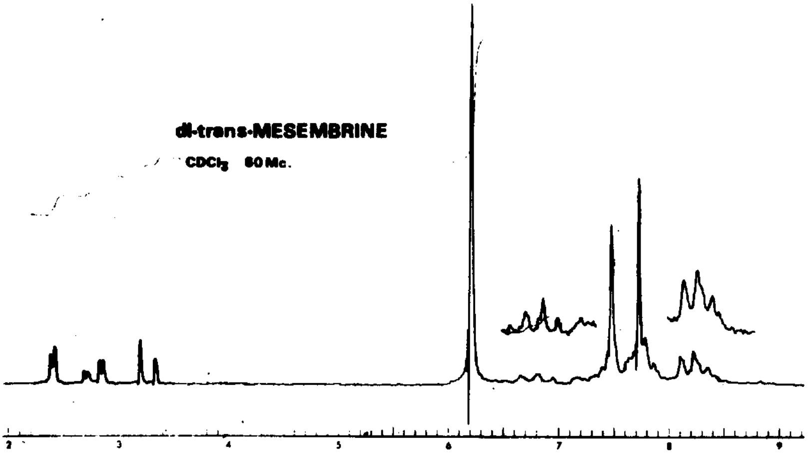

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1) For a similar acid cyclization of γ-acetylpimelonitrile, see C.F.Koelsch and H.Walker, J.Am. Chem.Soc.72,346(1950) and Y.Ban, Y.Sato, I.Inoue, M.Nagai, T.Oishi, M.Terashima, O.Yonemitsu and Y.Kanaoka, Tetrahedron Letters,2261(1965)

2) Preparations of these starting materials and a detailed account for the mechanism of this reaction will be reported in a full paper.

3) Higher concentration of sulfuric acid decreased the yield, probably because of sulfonation of the aromatic ring. Hydrochloric acid in dioxane gave IIa in a lower yield.

4) See e.g. K.Nakanishi, Infrared Absorption Spectroscopy, p.46,Holden-Day,Inc. San Francisco (1962)

5) (a) A.Popelak, E.Haack, G.Lettenbauer and H.Spingler, Naturwissenshaften,47,156,231(1960)
(b) E.Smith, N.Hosansky, M.Shamma and J.B.Boss, Chemistry and Industry,402(1961)

6) M.Uskovic and M.Gut, Helv. Chim. Acta,42,2258(1959)

7) We are indebted to Dr.A.Popelak for providing us with these samples.