

SYNTHESIS IN THE SERIES OF DITERPENE ALKALOIDS VII.

A SYNTHESIS OF COMPOUNDS CLOSELY RELATED TO THE
AROMATIZATION PRODUCTS OF ACONITINE AND DELPHININE

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Some time ago we have described the degradation (1) of aconitine to compound II. Since a correlation of II with a totally synthetic product would constitute a rigorous chemical structure proof of aconitine (2) and delphinine (3) we have been engaged for some time in the development of synthetic methods (4) for compounds of this type. We wish to describe now a simple synthesis of I which places a synthetic structure proof of II by a facile modification of the functionality of both products within reach.

The starting materials for our synthesis were the methoxytetralone IV (5) and the iodo compound III (6). The tetralone IV was alkylated in methanolic solution with one mole of sodium methoxide and 1.3 moles of III at reflux for 48 hours. The product V was purified by chromatography on silica gel and was obtained in a yield of 50%. It was

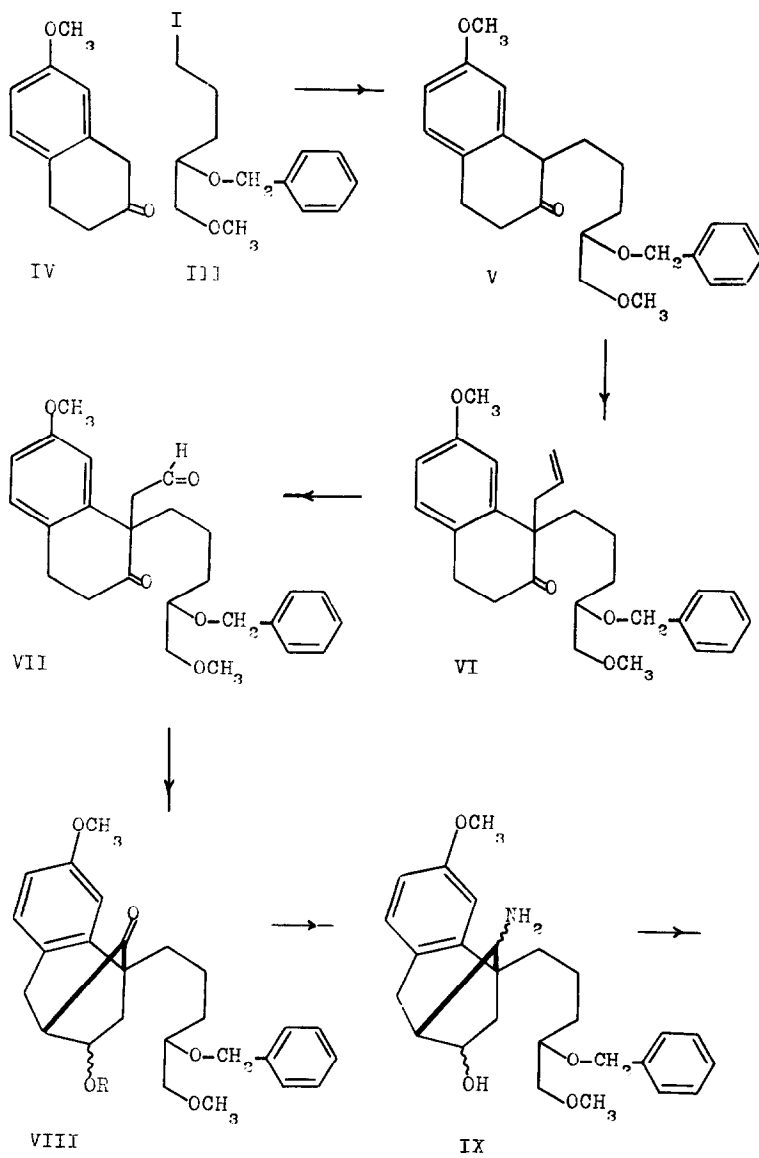
a mixture of diastereoisomers apparently homogeneous by thin layer chromatography. I.R.: ketone (1700 cm^{-1}); N.M.R.: 2 $-\text{OCH}_3$ singlets (3H) $\tau = 6.66, 6.25$ p.p.m., benzylic CH_2 singlet (2H) $\tau = 5.48$ p.p.m.

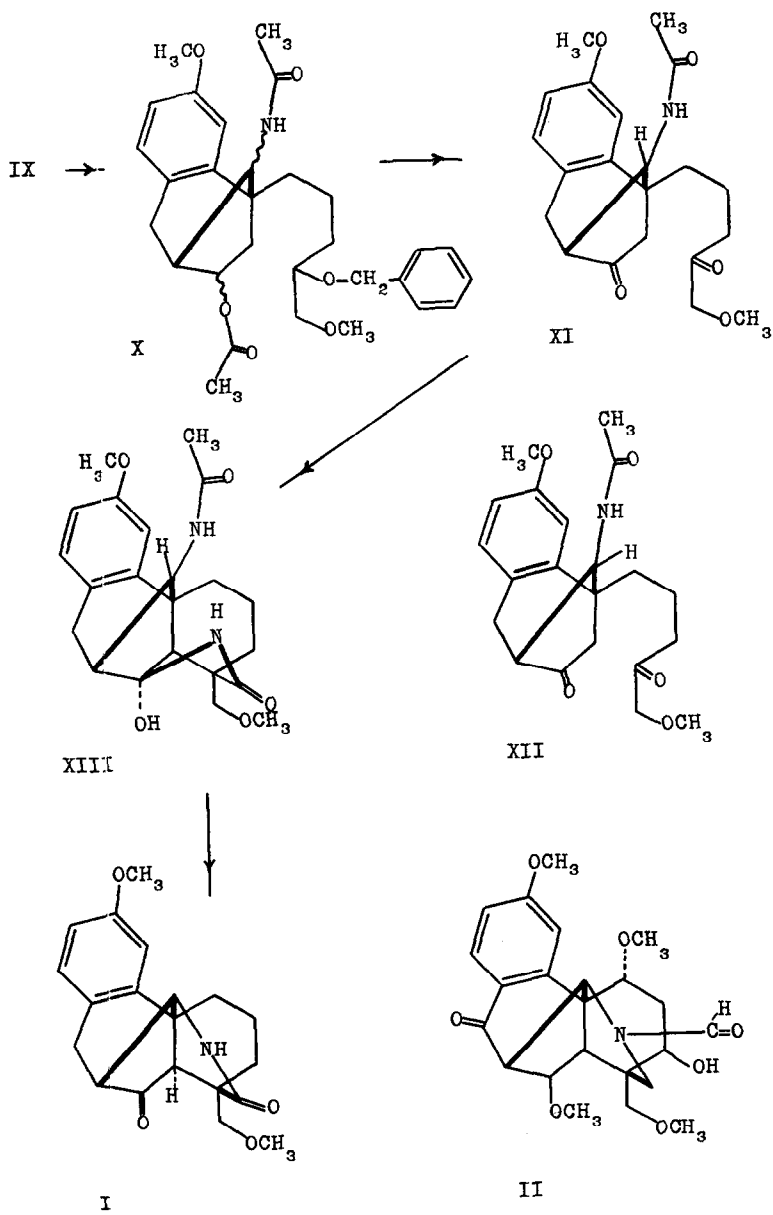
Compound V was treated with one mole of sodium hydride and two moles of allyl bromide in benzene at 50°C . for 24 hours.

The product VI was purified by chromatography on silica gel. It was obtained in a yield of 90% and was apparently homogeneous by T.L.C. I.R.: ketone (1720 cm^{-1}), allyl (928 cm^{-1}); N.M.R.: 2 $-\text{OCH}_3$ singlets (3H) $\tau = 6.68, 6.23$ p.p.m., benzyl CH_2 singlet (2H) $\tau = 5.53$ p.p.m., allyl typical multiplet (3H) around $\tau = 5.06, 5.31$ p.p.m.

Compound VI was catalytically osmlyated in T.H.F. with 5×10^{-3} moles of osmium tetroxide and 1.2 moles of sodium chlorate (4) and the crude product was cleaved by an excess of sodium periodate in a T.H.F. water mixture. The oily aldehyde VII was isolated in a yield of 97% and was apparently homogeneous in T.L.C. without chromatography. I.R.: ketone (1725 cm^{-1}), aldehyde ($1730, 2710\text{ cm}^{-1}$); N.M.R.: 2 $-\text{OCH}_3$ singlets (3H) $\tau = 6.70, 6.24$ p.p.m., aldehyde (1H) $\tau = 0.61$ p.p.m., benzyl CH_2 singlet (2H) $\tau = 5.50$ p.p.m.

The aldehyde VII was treated in aqueous methanol with one mole of sodium hydroxide at 55°C . for 22 hours under nitrogen. It was converted into the aldol VIII ($R = H$) in a yield of 86%. This compound was immediately transformed





into the tetrahydropyranyl derivative VIII (R = tetrahydropyranyl) by treatment with dihydropyran and a trace of hydrochloric acid in chloroform for three days. Compound VIII (R = tetrahydropyranyl) was extensively chromatographed on a column of alumina from which it was eluted by 50% petroleum ether-chloroform. It was an oil apparently homogeneous in T.L.C. and was obtained in a yield of 72%. I.R.: ketone (1760 cm^{-1}), no hydroxyl band; N.M.R.: 2 $-\text{OCH}_2$ singlets (3H) $\tau = 6.57, 6.24$ p.p.m., benzyl CH_2 singlet (2H) $\tau = 5.34$ p.p.m.

Compound VIII (R = tetrahydropyranyl) was dissolved in absolute methanol and the solution saturated with ammonia at -20°C . The solution was then hydrogenated with Raney nickel at 2,500 p.s.i. and 165°C . for 8 hours. The basic material was separated in the usual manner and the crude compound IX thus obtained was immediately acetylated at room temperature in ethylene dichloride with acetyl chloride and triethylamine. The diacetate X obtained in this manner was chromatographed on silica gel. Compound X was thus obtained as an oil apparently homogeneous in T.L.C. in a yield of 76% from VIII. I.R.: amide (1670 cm^{-1}), ester (1730 cm^{-1}). Compound X was then hydrolysed with methanolic KOH (2.5 moles) at reflux for one hour, the benzyl group removed by hydrogenolysis with Pd-charcoal in ethanol acidified with glacial acetic acid and finally the product oxidized with the Jones reagent. The material so obtained in a yield of 33% showed two clear spots on T.L.C. and it was

separated by careful repeated chromatography on a column of silica gel (adsorbent 100 x the weight of substance) into the homogeneous epimeric products XI and XII. The ratio of XI to XII was 4:1 and the synthesis thus was almost stereospecific. Compound XI was a low-melting crystalline solid which could not be recrystallized from solvents. I.R.: ketones (1750, 1725 cm^{-1}), amide (1675 cm^{-1}); N.M.R.: 2 $-\text{OCH}_3$ singlets (3H) $\tau = 6.54, 6.12$ p.p.m., CH_2 unshielded by primary methoxyl singlet (2H) $\tau = 5.93$ p.p.m., acetyl methyl singlet (3H) $\tau = 7.93$ p.p.m., NH doublet (1H) $\tau = 5.28, 5.43$ p.p.m. The comparison of this last doublet with the model compounds prepared earlier (4) gave the first indication that the nitrogen of XI has the desired configuration anti to the anisole ring. Compound XI was now converted in one step and a yield of 50% into the highly crystalline diamide XIII. This conversion was accomplished by refluxing XI in ethanol-water (9:1) for 40 hours with five moles of potassium cyanide. It clearly involved an aldol condensation, β addition of a cyanide ion to the α, β -unsaturated ketone thus formed, hydrolysis of the resulting nitrile to a primary amide and the formation of the hemiketal-like compound XIII. This material was purified by recrystallization from benzene to a m.p. of 236-238°C. ($\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_5$) I.R. (KBr pellet): amides (1670, 1715 cm^{-1}); N.M.R.: 2 $-\text{OCH}_3$ singlets (3H) $\tau = 6.7, 6.2$ p.p.m., CH_2 unshielded by primary methoxyl singlet (2H) $\tau = 6.54$ p.p.m., acetyl methyl singlet (3H) $\tau = 8.1$ p.p.m. The mass-spectrum of XIII gave a strong peak

at 382 ($m-H_2O$). Finally compound XIII was converted to I by reflux in a solution of 30% methanol and 70% concentrated hydrochloric acid for 24 hours. Compound I was purified by chromatography on alumina and recrystallization to a m.p. of 185-186°C. from methanol. It was obtained in a yield of 50%. ($C_{20}H_{23}NO_4$) I.R.: ketone (1750 cm^{-1}), lactam (1665 cm^{-1}), lactam NH (3400 cm^{-1}); N.M.R.: 2 $-OCH_3$ singlets (3H) $\tau = 6.67, 6.22$ p.p.m., CH_2 unshielded by primary methoxyl singlet (2H) $\tau = 6.55$ p.p.m., aromatic hydrogens (3H) $\tau = 3.08, 3.21$ p.p.m. Mass-spectrum: strong molecular ion peak at 341. Both crystalline compounds I and XIII gave correct elemental analyses.

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