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SYNTHESIS IN THE SERIES OF DITERPENE ALKALOIDS IV. DEVELOPMENT OF SYNTHETIC METHODS IN THE SERIES OF HEXACYCLIC ALKALOIDS

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In our studies on the structure of aconitine and delphinine (1) we have described a simple high yield degradation of these alkaloids to the compound I and other similar derivatives. It appears highly desirable to develop synthetic methods for this type of compound.

A synthesis of I would provide a rigorous chemical structure proof for aconitine and delphinine since the degradation of these alkaloids to I is clearly understood. Furthermore, compounds of this type are readily available from natural sources and they could conceivably serve as a relais in the synthesis of the alkaloids themselves.

We now wish to describe a facile synthesis of compounds of the type II. Such compounds with a suitable choice of the groups R should be convertible to I or its derivatives. We have chosen for this first synthesis $R_1 = CH_3$ since the precise requirements which this group has to satisfy in the eventual conversion of II to I were not clear at outset of our work. The starting material for the synthesis was the methoxytetralone III (2). The pyrrolidine enamine of III gave with ethyl iodide compound IV by the procedure of Stork (3) in a yield of 80%. IV, $C_{13}H_{16}O_2$; b.p. 112-117° (0.13 mm.); I.R. (CCl_4) 1720, 1610 cm^{-1}; N.M.R. singlet (3 H) 6.10 τ (methoxyl), triplet (3 H) 9.1 τ (C-methyl).

Compound IV was dissolved in T.H.F. and treated under nitrogen with 1.2 mols of sodium hydride and 1.7 mols of allyl bromide. A quantitative yield of V was obtained in this reaction. V, $C_{16}H_{20}O_2$; I.R. (CCl_4) 1715, 1610, 924 cm^{-1}; N.M.R. multiplet (3 H) 2.89 - 3.4 τ, multiplet (3 H) 4.79 τ, singlet (3 H) 6.2 τ, triplet (3 H) 9.4 τ. Compound V was suspended in a mixture of equal volumes of water and T.H.F. and stirred with 5 x 10^{-3} mols of osmium tetroxide and 1.2 mols of sodium perchlorate for 22 hours. The product VI was obtained in a yield of 87.5%. VI, $C_{16}H_{22}O_4$; I.R. (CCl_4) 3670 - 3500, 1720 (weak), 1610 cm^{-1}. The weakness of the carbonyl band in VI is undoubtedly due to hemiketal formation with one of the hydroxyls. Compound VI was now dissolved in a mixture of water and T.H.F. and cleaved with 8 mols of sodium periodate under nitrogen to give the aldehyde VII in a 94% yield. VII, $C_{15}H_{18}O_3$; I.R. (CCl_4) 2730, 1735, 1720, 1610 cm^{-1}; N.M.R. unresolved signal (1 H) 0.61 τ.

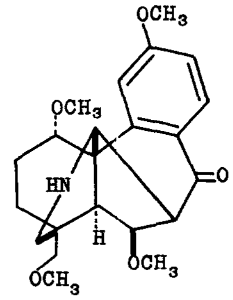
Compound VII (100 g.) was dissolved in 1.8 l. of a T.H.F.-water mixture (4:1) and heated to 55° under nitrogen for 2 hours with 200 ml. of 10% aqueous sodium hydroxide.

A 90% yield of the bicyclic ketone VIII resulted. VIII, $C_{15}H_{18}O_3$; I.R. (CCl_4) 3620 - 3500, 1755, 1610 cm^{-1}. Compound VIII was converted into the tetrahydropyranyl derivative IX which crystallized and was recrystallized to a m.p. 80 - 87°. The overall yield of this material from compound V was 52%. IX, $C_{20}H_{26}O_4$; I.R. (CCl_4) 1755, 1610, 1030 cm^{-1}.

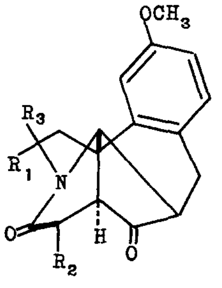
Compound IX was hydrogenated in methanol saturated with ammonia at 2,100 lbs./in.^{2}, 175°, in the presence of Ra-Ni for 6 hours. An 84% yield of a mixture of the aminoalcohols X and XI resulted.

This mixture was converted into a mixture of the epimers XII and XIII by 1) acetylation 2) $LiAlH_4$ reduction 3) treatment with dichloroacetyl chloride and aqueous alkali and 4) Jones oxidation, in an overall yield of 50%. The compounds XII and XIII were separated by chromatography on neutral alumina using 20% chloroform in benzene as eluant. They were obtained in approximately equal amounts. XII, $C_{19}H_{23}NO_3Cl_2$; m.p. 132-134°; I.R. (CCl_4) 1755, 1680, 1610 cm^{-1}. XIII, $C_{19}H_{23}NO_3Cl_2$; m.p. 142.5-144.5°; I.R. (CCl_4) 1755, 1670, 1610 cm^{-1}. Compound XII was dissolved in dry T.H.F. and stirred with 1.2 mols of sodium hydride at 65° for 3 days. The cyclization product was purified by chromatography on neutral alumina and it was obtained in a yield of 34% after recrystallization. II ($R_1 = CH_3$, $R_2 = Cl$, $R_3 = CH_2-CH_3$), $C_{19}H_{22}NO_3Cl$; m.p. 135-137.5°; I.R. ($CHCl_3$) 1750, 1690, 1610 cm^{-1}.

The molecular weights of all products were determined by mass spectroscopy and the crystalline compounds gave correct elemental analyses.



I



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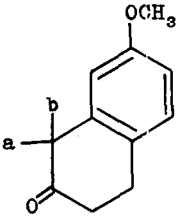


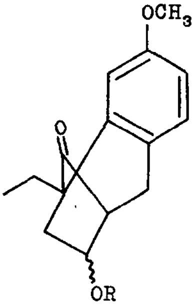
III (a, b = H)

IV (a = CH_2-CH_3; b = H)

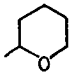
V (a = CH_2-CH_3; b = CH_2-CH=CH_2)

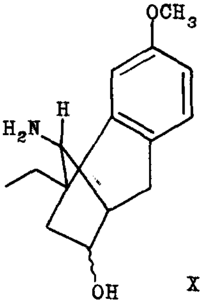
VI (a = CH_2-CH_3; b = $CH_2-\underset{OH}{CH}-\underset{OH}{CH_2}$)

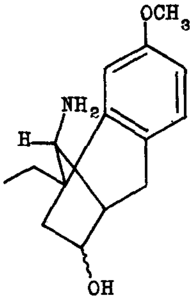
VII (a = CH_2-CH_3; b = $CH_2-\underset{H}{C}=O$)

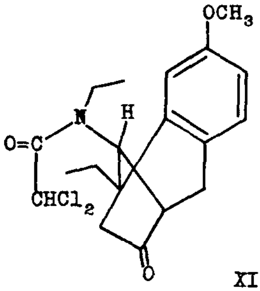


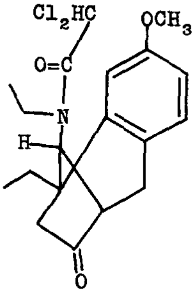
VIII (R = H)

IX (R = )


X

XI



XII

XIII


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