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THE PREPARATION OF A KEY INTERMEDIATE IN THE SYNTHESIS OF AJACONINE AND ATIDINE[1,2]

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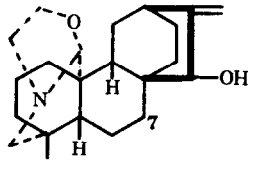
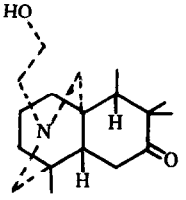
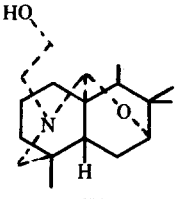
We have previously described[4] our approach to the synthesis of the diterpenoid alkaloid atisine(I) beginning with the readily available and previously synthesized diterpene, podocarpic acid. We now wish to describe a modification of this approach which can be used to



I



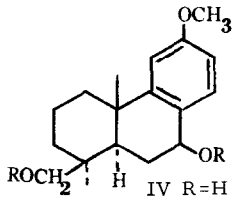
II



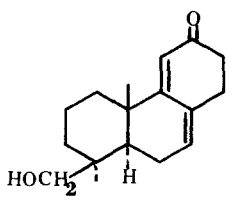
III

synthesize atidine(II) and ajaconine(III)[5].

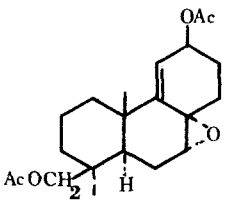
Methyl-O-methyl-7-ketopodocarpate, prepared as previously described[6], was reduced with lithium aluminum hydride to give the diol IV, which gave the expected diacetate V. Reduction of IV with sodium, absolute ethanol or tetrahydrofuran with a small amount of ethanol and liquid ammonia followed by hydrolysis in methanolic hydrochloric acid gave VI [m. p. 132-134°; λ_{max}^{KBr} 2.9, 6.05μ; λ_{max}^{EtOH} 289 mμ, ϵ 17,500; $\delta_{ppm}^{CDCl_3}$ 1.0 (3H), 1.05 (3H),



IV R=H
V R=COCH$_3$



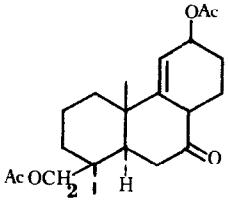
VI



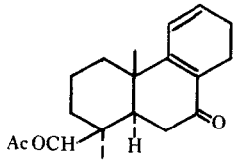
VII

3.75 (2H, doublet of doublets, J=10 cps), 5.88 (1H, 1/2 band width 3 cps), 6.10 (1H, broad signal) in 57% yield (single peak by g.l.c.) after separation with Girard's T reagent. Reduction of VI with sodium borohydride (g.l.c. indicated ~ 1:1 mixture of isomers) followed by acetylation gave the diacetate, which on treatment with m-chloroperbenzoic acid gave epoxydiacetate VII [λ_{max}^{film} 5.75μ; $\delta_{ppm}^{CCl_4}$ 1.0 (3H), 1.05 (3H), 1.75 (3), 1.78 (3), 4.74 (2H, doublet of doublets, J=10 cps), 5.70 (1H, 1/2 band width 4 cps)] as a viscous gun (quantitative yield) which was used without further purification.

Treatment of VII with BF_3·etherate gave ketone VIII (λ_{max}^{film} 5.72, 5.80, 6.0μ) which after chromatography on alumina gave dienone IX [λ_{max}^{film} 5.75, 6.02μ; $\lambda_{max}^{diox.}$ 308 mμ, ϵ 6,040; $\delta_{ppm}^{CCl_4}$ 1.0 (3), 1.15 (3), 2.01 (3), 4.16 (2H, doublet of doublets, J=10 cps), 6.30 (2H, 1/2 band width 3 cps)] as a viscous gum which could not be crystallized (yield 80% from VII).



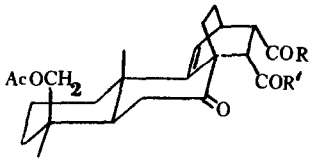
VIII

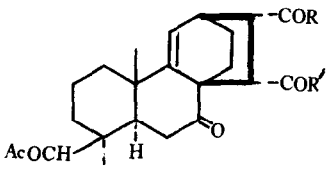


IX

On treatment with maleic anhydride in refluxing toluene IX gave two crystalline adducts X

[m.p. 200-203°; λ_{max}^{KBr} 5.45, 5.65, 5.80, 5.85μ; $\delta_{ppm}^{CDCl_3}$ 1.01 (3), 1.18 (3), 2.05 (3), 6.1 (1H, d, J=7 cps)] and XI [m.p. 270-272°; λ_{max}^{KBr} 5.40, 5.62, 5.80, 5.85; $\delta_{ppm}^{CDCl_3}$ 1.02 (6),





X R≡R'=O

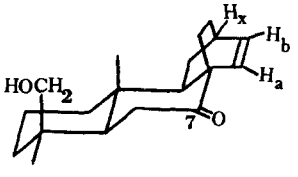
XIII R=R'=OCH_3

XI R≡ R'=O

XII R=R'=OCH_3

2.08 (3), 6.1 (1H, d, J=7 cps)] in 53% yield in a ratio of 3:2 respectively, which were separated by recrystallization from chloroform.

On treatment with diazomethane in methanol-ether, XI was found to evolve nitrogen much more slowly than X, but eventually gave diester XII [m.p. 178-180°; λ_{max}^{KBr} 5.76, 5.90, 6.17 (w)μ; $\delta_{ppm}^{CDCl_3}$ 1.0 (3H), 1.31 (3H), 2.0 (3H), 3.47 (3H), 3.53 (3H), 4.16 (2H, doublet of doublets, J=10 cps), 5.78 (1H, d, J=7 cps)]. Similarly, X was converted into diester XIII [m.p. 161-163°; λ_{max}^{KBr} 5.71, 5.79, 5.88, 6.15 (w)μ; $\delta_{ppm}^{CDCl_3}$ 1.02 (3H, 1.12 (3H), 2.06 (3H), 3.51 (3H), 3.58 (3H), 4.10 (2H, doublet of doublets, J=10 cps), 5.93 (1H, d, J=7 cps)]. Diester XIII resisted hydrogenation but after hydrolysis, the resulting diacid-alcohol (m.p. 245-247°) was hydrogenated to give the dihydro derivative (m.p. 248-250°) which was acetylated and oxidatively bisdecarboxylated with lead tetraacetate in pyridine to yield XIV [m.p. 149-150°; λ_{max}^{KBr} 2.93, 5.92μ; $\delta_{ppm}^{CDCl_3}$ 0.97 (3H), 1.15 (3H), 3.65 (2H, doublet of doublets,

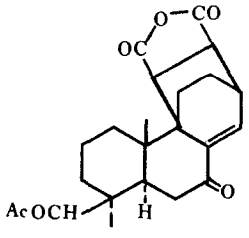


XIV

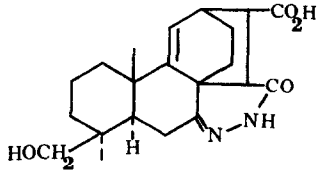
XV 7-Desoxo

J=11 cps), 6.25 (H_b, q, $J_{a,b}$ = 8 cps, J_{bx} = 6 cps), 6.74 (H_a, J_{ab} = 8 cps), mol. wt. 288 (mass spectrometry), base peak m/e 257 (M^+-31)] after saponification of the crude product. That structure XIV, and therefore structures X and XII, are correct was shown by Wolff-Kishner reduction of XIV to give the previously described[4] unsaturated alkene XV. Compound XIV is a key intermediate for the synthesis of atidine and ajaconine and should be convertible into these alkaloids by previously described procedures[4,7,8,9]. These transformations will be undertaken after sufficient supplies of XIV become available.

Adduct XI behaved in an unexpected manner. For example, the derived diester XII could not be epimerized with sodium methoxide, under conditions where XIII gave two isomeric substances (neither identical with XII or XIII). Likewise, XI, XII and the corresponding diacid-alcohol could not be hydrogenated catalytically. Diester XII showed no ultraviolet absorption characteristic of an α,β-unsaturated ketone, thus eliminating structure XVI for the anhydride adduct of m.p. 270-272°. A structure such as XVI was obtained in the sequence of reactions beginning with 7-desoxy IV.[4] In an attempt to convert XI into the corresponding 7 desoxo-XI previously reported[4], under Wolf-Kishner conditions, a product (m.p. 260-261°) was obtained to which structure XVII has been assigned on the basis of spectral information. However, Wolf-Kishner reduction of XII did lead to the previously reported[4] 7-desoxo-XII thus establishing the structure of XI and XII.



XVI



XVII

We suggest that the observed resistance of XI, XII and the derived diacid-alcohol to hydrogenation results from the fact that in these substances all of the polar groups reside on the

same face (β) of the molecule and this leads to absorption on the catalyst surface of the β side, the side remote from the double bond. A similar explanation has been suggested by Pelletier[10] for the difference in absorption on alumina of epimeric atisine derivatives. The large downfield shift observed for one of the methyl groups (C-10) in the conversion of XI to XII may arise from a change in conformation in the B ring. An examination of Dreiding models indicates that dipole-dipole repulsion between the C-7 carbonyl and the nearest anhydride carbonyl would lead to ring B assuming a boat conformation in the anhydride. In the case of diester XII, the dipole-dipole repulsion would result in ring B assuming a chair conformation. The effect of the C-7 carbonyl group on the C-10 methyl group would be shielding in the former case and deshielding in the latter case, as observed in the n.m.r. spectra of XI and XII.

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(2) Presented at the 19th Southeastern Regional Meeting of the American Chemical Society, November 1-3, 1967, Atlanta, Georgia.

(3) Taken in part from the Ph. D. Dissertation of B. Kumar, submitted to Oklahoma State University, August, 1966. This work was performed at the Georgia Institute of Technology.

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(10) Reference 9, p. 90.