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SYNTHESIS IN THE DITERPENE ALKALOID SERIES III.

A NOVEL SYNTHESIS OF A KETO LACTAM.

A PHOTOCHEMICAL APPROACH TO THE C,D-RING SYSTEM OF ATISINE

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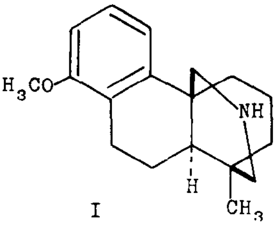
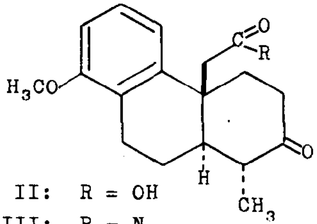
In previous communications of this series, we announced the total synthesis of the *d*,*l*-amine I (1) and its conversion to the Garrya alkaloids (2). We now report two synthetic sequences which can be anticipated to lead to a short and efficient total synthesis of the alkaloid atisine (XVIII). The first of these also constitutes a shortening of our Garrya alkaloid synthesis by five steps.

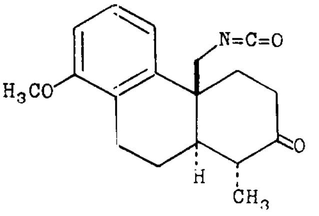


I

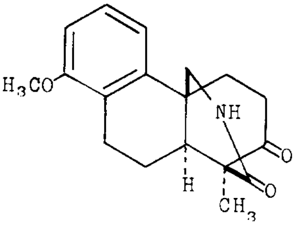


II: R = OH
III: R = N_3

The previously reported *d*,*l*-acid II, m.p. 205-210°, was converted in a good yield to the acyl azide III, infrared max. (CHCl$_3$) 2130 and 1720 cm^{-1}, on treatment with N,N'-dicyclohexylcarbodiimide and sodium azide in aqueous tetrahydrofuran. Reflux of III in anhydrous benzene for 30 minutes resulted in a complete conversion to the isocyanate IV, infrared max. (CHCl$_3$) 2270 and 1720 cm^{-1}, which without isolation was treated with anhydrous *p*-toluenesulfonic acid in refluxing dry benzene for 32 hours. Chromatography of the crude reaction mixture gave a 26% yield of the crystalline keto lactam V, m.p. 246-248°, infrared max. (CHCl$_3$) 3400, 1725 and 1670 cm^{-1}; the attachment of the new ring in V follows from the presence, in its N.M.R. spectrum, of a methyl singlet at 8.65 τ. A second keto lactam with comparable infrared absorption, isolated in about 8% yield and showing a methyl doublet at 8.90 τ in its N.M.R. spectrum, is assigned structure VI.[*]



IV



V

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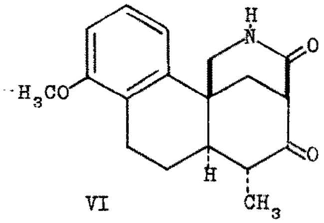
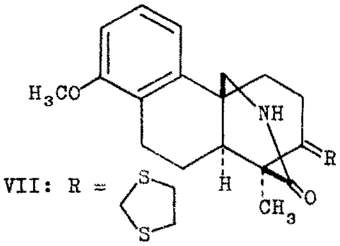
[*] The nature of further components of the reaction mixture and the dependence of yield of compound V on reaction conditions are under investigation.



VI



VII: R =

VIII: R = H_2

Treatment of the keto lactam V with ethane dithiol and boron trifluoride etherate at room temperature led to the corresponding dithioketal VII, m.p. 274-279°, which on reduction with Ra-nickel in ethanol gave the lactam VIII, m.p. 308-309°, in 84% yield based on V. Lithium aluminum hydride reduction of VIII in dioxane then gave amine I, m.p. 109-111°, picrate m.p. 273-275° in 94% yield. This compound was found to be identical in all respects with the previously reported base (1,2).

The above method can clearly be used also for the total synthesis of atisine (XVIII) and other alkaloids of this class. We now wish to report a model series which indicates a simple route for the elaboration of the C,D-ring system of atisine.

The tetracyclic d,l-olefin IX, m.p. 40-44°, N.M.R. quadruplet for 2 H's centred at 4.66 τ, was prepared by the previously reported method (1) using 2,6-dimethoxynaphthalene as starting material.[*] The isolated double-bond in IX was saturated by

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[*] The preparative details of the synthesis of IX will be reported in a full publication.

hydrogenation with Pt in ethyl acetate and the resulting oily anisol X, obtained in a quantitative yield, was subjected to a reduction with lithium in a mixture of ammonia, t-butanol and tetrahydrofuran. Acid hydrolysis of the resulting enol ether gave a 70% yield of the oily ketone XI, infrared max. (CCl_4) 1680, 1625 cm^{-1}, N.M.R. singlet (1 H) at 4.24 τ, characterized in the form of its crystalline 2,4-dinitrophenyl hydrazone, m.p. 169-180°.

Irradiation* of a 1% solution of ketone XI in dry tetrahydrofuran in the presence of a large excess of allene (3) at -80° for 13 hours resulted in a complete conversion to compound XII, infrared max. ($CHCl_3$) 1695 (ketone), 895 cm^{-1} (double-bond), N.M.R. signal (2 H) at 5.10 τ. Contrary to expectations (3), the four-membered ring of XII could not be opened by base or acid in a reasonable yield. The system was therefore elaborated in the following way.

The carbonyl function in XII was protected by a treatment with ethylene glycol and p-toluenesulfonic acid in boiling benzene and the resulting ketal XIII, m.p. 130-132°, infrared max. (KBr) 1675 and 890 (double-bond), 1105 cm^{-1} (ketal), was oxidized with 1 mol of OsO_4 and a large excess of $NaIO_4$ in aqueous tetrahydrofuran at room-temperature for 18 hours to give ketone XIV, infrared max. ($CHCl_3$) 1780 cm^{-1}. The indicated stereochemistry of the four-membered ring in compounds XII - XIV follows from the fact that the compounds appear

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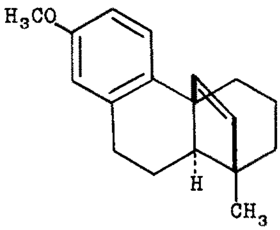
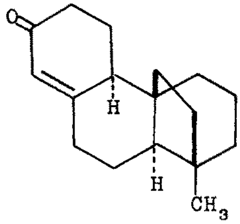
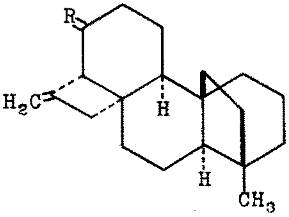
* A quartz mercury arc immersion lamp (Hanovia, 100 watts) in a Pyrex well cooled with circulating cyclohexane was used as a light source.



IX

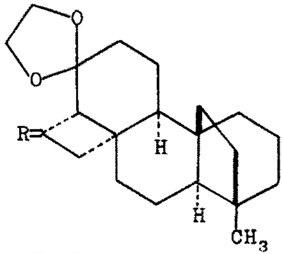


XI



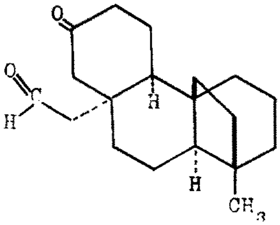
XII: R = O

XIII: R = 

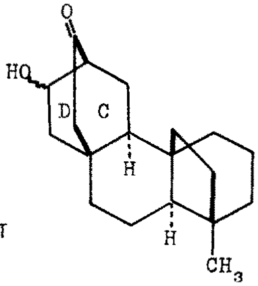


XIV: R = O

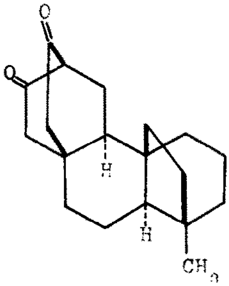
XV: R = $<^{H}_{OH}$



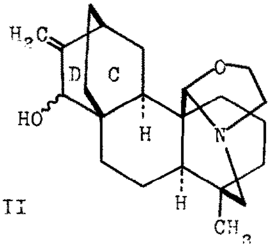
XVa



XVI



XVII



XVIII

homogeneous (T.L.C., m.p. of XIII) and the photoaddition is therefore stereospecific. A _cis_ addition to the less hindered side of ketone XI is therefore clearly indicated.

Reduction of ketone XIV with $NaBH_4$ in refluxing methanol for 1 hour yielded the hydroxyketal XV, which without purification was subjected to hydrolysis with dilute sulfuric acid in tetrahydrofuran at room-temperature. Chromatography of the product on silica gel gave the mixture of epimeric alcohols XVI, m.p. 210-215°, infrared max. (KBr) 3400, 1710 cm^{-1}, clearly formed by the hydrolysis of the ketal followed by a reverse aldol reaction to the keto aldehyde XVa and a subsequent aldol condensation. The composite yield of the last three steps (XIII → XVI) was approximately 45%. Finally, oxidation of XVI with CrO_3 in H_2SO_4-acetone gave a good yield of the crystalline diketone XVII, m.p. 130-132°, M.W. (mass-spec.) 286, infrared max. (KBr) 1750 and 1710 cm^{-1}.

Since the conversion of a ketol comparable to XVI to a compound containing the C/D ring-system of atisine has already been accomplished by Bell and Ireland (4), the photoaddition described above provides a useful synthetic approach to this alkaloid. The use of other olefins in the photoaddition is under active study.

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(4) R. A. Bell and R. E. Ireland, _Tetrahedron Letters_, 269 (1963).