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SYNTHESIS OF LYCOPODIUM ALKALOIDS. PART 2.*

A METHOD FOR THE CONSTRUCTION OF SUBSTITUTED CIS-TRANS-HEXAHYDROJULOLIDINES.

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The Lycopodium alkaloids have not yet yielded to total synthesis, although advances in that direction have recently been reported (1,2). We have now developed a method for the construction of functionalized cis-trans-hexahydrojulolidines of type I which should be useful in the synthesis of tetracyclic Lycopodium alkaloids such as lycopodine (II).

The starting point for the synthesis of I (X=H or OH) was 9-methoxyjulolidine (III), b.p. 125-127°/0.2 mm (3,4), prepared by known methods (5) from thalline and 1-bromo-3-chloropropane. Reduction of III with lithium-ammonia-tert. butyl alcohol yielded the unstable dihydro derivative which was transformed immediately to the ketal immonium perchlorate (IV),

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* Part I. W. A. Ayer and K. Piers. Chem. Comm. No. 21, 541 (1965).

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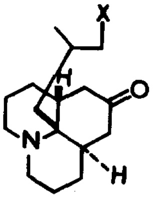
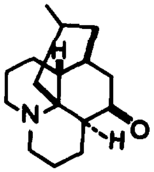
m.p. 258-259° (dec.) (4), by dissolution in ethylene glycol containing perchloric acid.

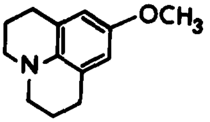
When the immonium salt IV was reacted with an excess of methallylmagnesium chloride in tetrahydrofuran the unsaturated ketal V was obtained, after chromatography of the crude product, in 50% yield. Compound V was a low melting (54-56°) solid which afforded a nicely crystalline hydroperchlorate, m.p. 247-249° (4).



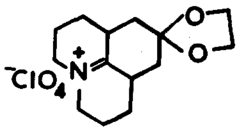
I



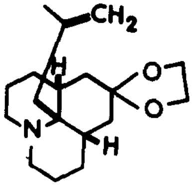
II



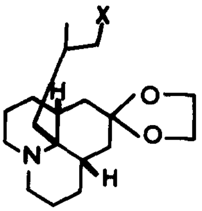
III



IV



V

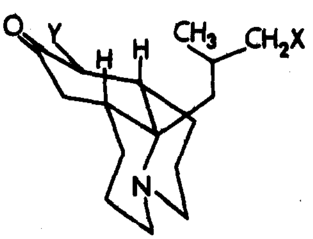


VI, X = H
VII, X = OH

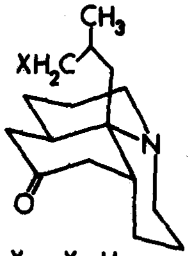
The presence of strong absorption (Bohlmann bands) in the 2700-2800 cm^{-1} region of the infrared spectrum of V showed that it possessed either the *cis-cis* or the *trans-trans* stereochemistry at the ring junctions (6). The fact that it reacted very sluggishly with methyl iodide indicated that it was the cis-cis system (7), which was expected on theoretical grounds since it results from addition of the Grignard reagent to the less hindered side of the salt IV.

Catalytic hydrogenation of V provided the saturated compound VI and hydroboration yielded the alcohol VII (dl-form, compounds V and VI are meso forms)(4). Hydrolysis of the ethylene ketal group in VI provided the ketone VIII, m.p. of hydrobromide 220° (dec.) and hydrolysis of VII yielded dl-IX, m.p. of hydroperchlorate 245-247°. It can be seen from the conformational drawing IX (the possibility that VIII and IX exist in the highly-strained conformationally inverted form is rendered unlikely by the presence of "Bohlmann bands" in the infrared spectra of these substances) that ring closure to the bicyclo[3.3.1]nonane system of lycopodine (II) is impossible from this conformation. In order to make this synthetic route a feasible path to the Lycopodium alkaloids it was necessary to develop a method for transforming cis-cis-hexahydrojulolidines of type VIII and IX into cis-trans compounds such as X and XI. The more readily prepared ketone VIII was selected as the substrate on which to study this isomerization.

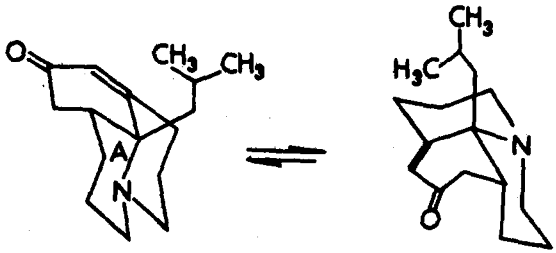
It was felt that the isomerization might be accomplished via the α,β-unsaturated ketone (XII) derived from VIII. Because of the conformational mobility at the nitrogen it should be possible for the ketone XIIa to assume the other conformation XIIb. This change involves an inversion (of ring A) at the nitrogen and a transformation of the resultant boat into a new chair form with similtaneous transformation of the unsaturated ring from one half-chair form to the other half-chair. An examination of models indicated that XIIb might in fact be the favored conformation for the unsaturated ketone.



VIII X = H, Y = H
IX X = OH, Y = H
XIII X = H, Y = Br



X X = H
XI X = OH



XIIa XIIb

Bromination of the hydrobromide of ketone VIII with one equivalent of bromine gave the hydrobromide of the equatorial bromoketone XIII. The equatorial nature of the bromine was shown by the carbonyl absorption in the infrared spectrum ($\nu^{CCl_4}_{max.}$ 1735 cm^{-1}, ketone VIII shows $\nu^{CCl_4}_{max.}$ 1710 cm^{-1}) and by the n.m.r. spectrum (doublet at τ 4.68, J = 12 cps) of the free base. Dehydrobromination of XIII proved difficult but was finally accomplished by use of semicarbazine in acetic acid (8) followed by exchange of the resulting semicarbazone with pyruvic acid in aqueous acetic acid. The unsaturated ketone XII was obtained as a low melting solid (4), $\gamma_{max.}^{CCl_4}$ 1675, 1615 cm^{-1}, $\lambda_{max.}^{EtOH}$ 242 mμ (ε 9,000), τ 4.15 (doublet, J∿1.5 cps, allylic coupling) *which did not display Bohlmann bands (6)* in its infrared spectrum, indicating that it existed predominantly in conformation XIIb.

Reduction of the unsaturated ketone XIII with lithium-ammonia provided a ketone *isomeric with ketone VIII*. The ketone obtained from the reduction (4) had a mass spectrum almost identical with that of ketone VIII (parent peak m/e 249, base peak m/e 192) but showed different chromatographic properties and a different infrared spectrum. Unlike ketone VIII the new ketone did not show Bohlmann bands and hence must be the desired *cis-trans* ketone X (*dl*-form).

With the successful completion of this phase of the work we have now turned our attention to the preparation of functionalized derivatives of X (e.g. XI) which we hope to transform into the tetracyclic ring system of lycopodine.

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