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SYNTHESIS OF LYCOPODIUM ALKALOIDS. II.
DEVELOPMENT OF STEREOSPECIFIC SYNTHETIC METHODS

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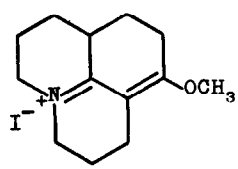
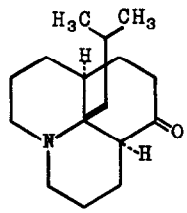
Recently, we reported the preparation of the salt I and its conversion into II by a reaction with isobutyllithium (1). The all-trans stereochemistry of ketone II followed from its physical properties and from its correlation with the alkaloid lyconnotine (1). We now wish to report the facile transformation of I into the tetracyclic amine III, which contains all but one of the asymmetric carbon atoms of the alkaloid lycopodine (IV) (2,3).



I



II

Treatment of I, m.p. 112-114°,* with an excess of allyl

* All reported compounds gave a correct elementary analysis.

magnesium bromide in boiling ether gave a mixture of products, from which the oily ketone V, $C_{15}H_{23}NO$, picrate m.p. 168–170°, I.R. max. (CCl_4) 1715 (ketone), 1640 and 920 cm^{-1} (allyl), could be isolated after a mild acid hydrolysis of the intermediate enol ether followed by a counter-current distribution (ether–buffer pH 5) and a rapid chromatography on basic alumina. The yield of pure ketone was 15%.* The stereochemistry of ketone V follows unambiguously from the presence of Bohlmann bands (4) in its infrared spectrum, from the fact that the axial alcohol formed from V by reduction with $LiAlH_4$ forms a cyclic bromoether on treatment with N-bromosuccinimide and from the following transformations.

A prolonged adsorption of V on basic alumina (grade 1) converted it into a 1:1 mixture (preparative thin-layer chromatography) of V and the isomeric ketone VI,** $C_{15}H_{23}NO_3$, m.p. 118°, I.R. max. (CCl_4) 1715 (ketone), 1643 and 926 cm^{-1} (allyl). Pure ketone VI was isolated by crystallization from petroleum ether and the oily residue was again subjected to epimerization. An almost complete conversion of V into VI could thus be achieved in a series of equilibrations. In agreement with the indicated trans–cis stereochemistry

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* Experiments now in progress show that a yield of about 50% can be achieved when the methoxyl group in I is replaced by an isopropoxyl group.

** The same equilibrium was obtained on treatment of V with KOH in methanol.

ketone VI showed no pronounced Bohlmann bands in its infrared spectrum.

The final cyclization could be achieved in a remarkably simple fashion. Treatment of VI with 70% sulfuric acid at room temperature for 70 hours gave an almost quantitative yield of alcohol VII,* $C_{15}H_{23}NO$, m.p. 140-141°, I.R. max. (CCl_4) 3690, 3340 (hydroxyl) and 1665 cm^{-1} (double-bond), N.M.R. ($CHCl_3$) 4.5 τ (multiplet; 2 olefinic H's). Alternately, treatment of VI with boiling conc. HBr for 70 hours resulted in a complete conversion to a 54:46 mixture of alcohol VII and the bromocompound VIII, $C_{15}H_{22}NBr$, m.p. 101-102°, I.R. max. (CCl_4) 1656 cm^{-1} (double-bond), N.M.R. ($CHCl_3$) 4.3 τ (multiplet; 2 olefinic H's). The two compounds were cleanly separated by chromatography on neutral (grade 1) alumina.

Finally, reduction of VIII with 6% sodium amalgam in ethanol-acetic acid at room temperature gave a high yield of the oily amine III, $C_{15}H_{23}N$, picrate m.p. 207-209°, I.R. max. (CCl_4) 1656 cm^{-1} (double-bond).** The trans-cis stereochemistry of compounds III, VII and VIII follows

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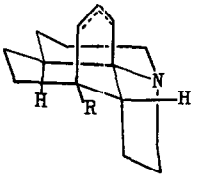
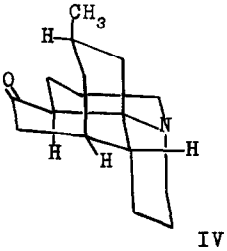
* As indicated in the formulae, the position of the double-bond in compounds III, VII and VIII is as yet not rigorously determined. We believe that the hydride transfer observed in our second synthetic series (vide infra) did not occur here, since it would most probably have resulted in the more stable trisubstituted double-bond.

** It is also found that the conversion of alcohol VII to the corresponding chlorocompound with thionyl chloride and the subsequent chemical reduction of the chlorine atom present no difficulties.

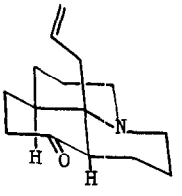
from the finding that ketones V and VI do not epimerize under strongly acidic non-cyclizing conditions;* cyclization of VI would thus not be expected to involve isomerization, especially since the stereochemically pure products VII and VIII are formed in a high yield and their infrared spectra show no Bohlmann bands.



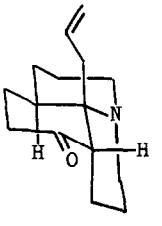
III: R = H
VII: R = OH
VIII: R = Br



IV



V



VI

A second approach to similar systems was carried out as follows: Dihydroorcinol IX (5) was converted into compound X, $C_{10}H_{17}O_2N$, m.p. 89°, picrate m.p. 129°, by refluxing in benzene with 3-aminopropanol for 20 hours. Compound X was cyclized by heating with an equal amount of pyridine

* The interconversion of V and VI involves an inversion at a carbon atom α to the carbonyl group and at the nitrogen atom; the inhibition of this inversion in a medium in which virtually all nitrogen atoms are protonated is thus readily explicable.

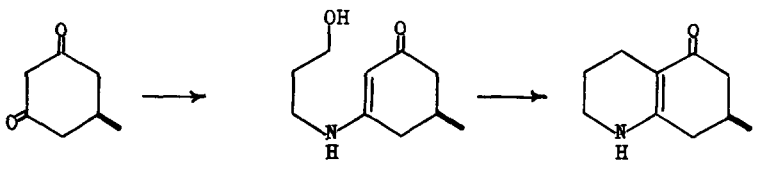
hydroiodide for 2 hours at 140°C. without solvent to the secondary vinylogous amide XI, $C_{10}H_{15}ON$, m.p. 176°, I.R. max. ($CHCl_3$) 3450, 1580, 1520 cm^{-1}, U.V. (neutral) $\lambda^{EtOH}_{max.}$ 306 mμ (ε 14,200), (acidic) $\lambda^{EtOH}_{max.}$ 292 mμ (ε 13,300). Methylation of XI in tetrahydrofuran with 2.5 mols of sodium hydride and 2.5 mols of methyl iodide yielded the oily compound XII, $C_{11}H_{17}ON$, I.R. max. ($CHCl_3$) 1605, 1550 cm^{-1}, U.V. (neutral) $\lambda^{EtOH}_{max.}$ 311 mμ (ε 17,000), (acidic) $\lambda^{EtOH}_{max.}$ 298 mμ (ε 14,000).

Compound XII was converted by the procedure of Alt and Speciale (6) into the perchlorate of XIIIa, m.p. 167°, I.R. max. ($CHCl_3$) 1625, 1605, 1090 cm^{-1}, U.V. $\lambda^{EtOH}_{max.}$ 276 mμ (ε 9,600). The perchlorate of XIIIb was prepared in an analogous manner using phosphorus tribromide instead of phosphorus pentachloride. It was a crystalline compound which could not be recrystallized; I.R. max. ($CHCl_3$) 1625, 1600, 1090 cm^{-1}, U.V. $\lambda^{EtOH}_{max.}$ 282 mμ (ε 11,000). The isopropyl ether XIIIc was prepared by refluxing XII for 48 hours with isopropyl iodide in benzene. It was not characterized but its I.R. spectrum (1580, 1100, 975, 960 cm^{-1}) was comparable to the spectra of analogous ethers described previously (1). The reaction of XIIIa and XIIIb with an excess of allyl magnesium bromide gave a good yield of XIVa, $C_{14}H_{22}NCl$ (80%) and XIVb, $C_{14}H_{22}NBr$ (65%), respectively. These compounds gave crystalline picrates (XIVa, m.p. 146°; XIVb, m.p. 164°) and their N.M.R. spectra were in full agreement with the structures assigned.

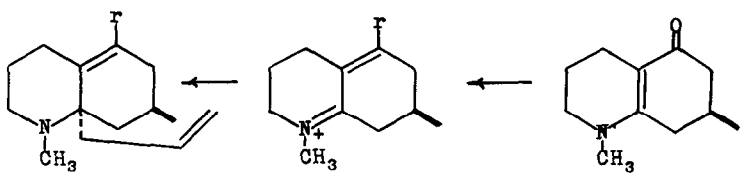
In the case of the Grignard reaction of XIIIa, a second isomeric product was obtained (picrate m.p. 160°) in which the allyl and the methyl group were assigned the cis configuration. The yield of this product was very small (3-5%) and the configurational assignment was made on the ground that if stereospecificity is observed in the Grignard reaction, there is no reason why the cis rather than the trans isomer should be favoured. By analogy, it was also assumed that XIVb and XIVc are the trans compounds. In these cases, the second isomer could not be isolated.

The reaction of the iodide of XIIIc with an excess of allyl magnesium bromide gave the product XIVc in a yield of 50%. This compound remained oily, but it was homogeneous in thin-layer chromatography. The N.M.R. spectrum of XIVc was in complete agreement with the structure assigned to it and its hydrolysis with dilute hydrochloric acid furnished an oily ketone, I.R. max. ($CHCl_3$) 1705, 1645, 918 cm^{-1}.

Treatment of XIVc with 75% sulfuric acid for 12 hours resulted in the cyclization (70% yield) to a crystalline compound, $C_{14}H_{23}ON$, m.p. 122-132°, I.R. max. ($CHCl_3$) 3600 and 1670 cm^{-1}, homogeneous in thin-layer chromatography. This compound, evidently a mixture of double-bond isomers, did however not have the expected structure XV but rather structure XVI which resulted from a hydride transfer in the course of the cyclization. The correctness of formula XVI for the product followed from the N.M.R. spectrum which showed a methyl singlet at 8.2 τ and only one vinylic hydrogen at



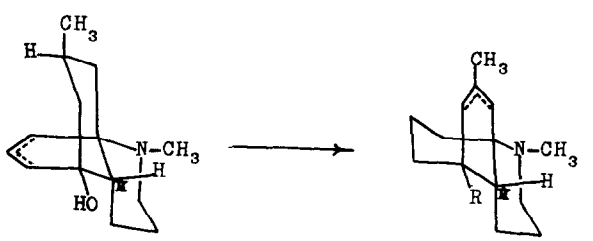
IX X XI



XIVa: r = Cl
XIVb: r = Br
XIVc: r = -O-CH(CH3)2

XIIIa: r = Cl
XIIIb: r = Br
XIIIc: r = -O-CH(CH3)2

XII



XV

XVI: R = OH
XVII: R = H

4.6 τ. Hydrogenation of XVI with PtO_2 in acetic acid yielded a dihydro derivative, $C_{14}H_{25}ON$, which melted sharply at 159°. The reduction of the bridge-head hydroxyl was accomplished by treatment of XVI with thionyl chloride followed by reduction with sodium in liquid ammonia. The resulting product XVII, $C_{14}H_{23}N$, was characterized as the crystalline picrate, m.p. 196°. The stereochemistry of C* in formula XVI is not proved but is favoured as written by both kinetic and thermodynamic conformational arguments.

The occurrence of the hydride transfer in the cyclization reaction proves conclusively the assumed stereochemistry of our initial Grignard products XIVa, b, c. While the transfer admittedly frustrated our plans to synthesize the Lycopodium alkaloids via the intermediate XV, it is now possible to utilize this reaction deliberately in a very simple modification of our synthetic methods. Experiments in this direction are in progress.

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