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A SYNTHETIC ROUTE TO ASPIDOSPERMINE AND QUEBRACHAMINE*

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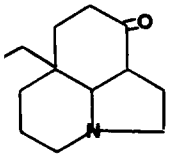
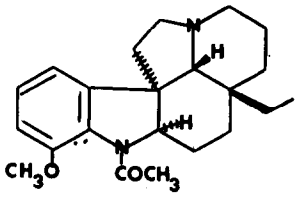
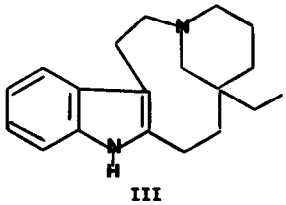
This communication describes the synthesis of the key tricyclic intermediate I with stereochemistry Ia and Ib, which can be transformed to aspidospermine II or quebrachamine III through a Fischer indole reaction and reduction sequence. Previously the tricyclic intermediate I with stereochemistry Ic (1) and Id (2) had been obtained by two variants of a completely different route and both stereoisomers had been converted to the natural products.



I



II



III

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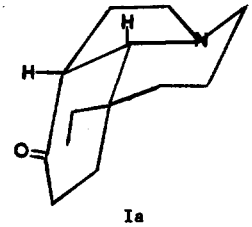
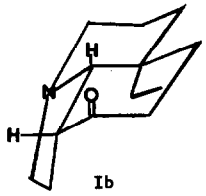
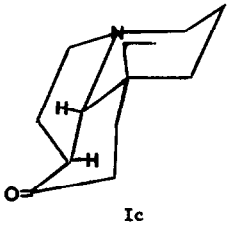


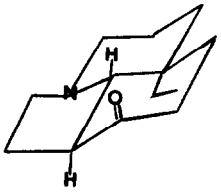
Ia



Ib



Ic



Id

The alkylation of proline ethyl ester IV with γ-bromoethylbutyrate gave the pyrrolidinodiester V (b.p. 103-105°/0.1 mm., 80% yield. Anal. calcd. for $C_{12}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.54; H, 8.95; N, 5.72). This was cyclized by treatment with sodium hydride and the crude product hydrolyzed and decarboxylated to the very unstable aminoketone VI (b.p. 64-66°/1 mm., 60% yield; picrate m.p. 157-158°. Anal. calcd. for $C_{14}H_{16}N_4O_8$: C, 45.66; H, 4.38; N, 15.21. Found: C, 45.80; H, 4.50; N, 15.25.). A Wittig reaction of the aminoketone with triphenylphosphineethylene led to the aminoolefin VII (b.p. 64-65°/3 mm.,

40% yield; λ max 1600 cm^{-1} for C = C; n.m.r. δ 5.0 p.p.m., one proton quartet for CH_3 - CH = C$\lessgtr$; picrate m.p. 146-147°. Anal. calcd. for $C_{16}H_{20}N_4O_7$: C, 50.52; H, 5.30; N, 14.73. Found: C, 50.51; H, 5.42; N, 14.69.). Conversion of the aminoolefin VII to the isomeric enamine VIII (b.p. 81-82°/7 mm. Anal. calcd. for $C_{10}H_{17}N$: C, 79.38; H, 11.33; N, 9.26. Found: C, 79.65; H, 11.59; N, 9.51. λ max 1680 cm^{-1}, 230 mμ for C = C - N, n.m.r. three proton triplet at δ 0.75 p.p.m. for CH_3CH_2-; perchlorate m.p. 182-184°. Anal. calcd. for $C_{10}H_{18}Cl\,N\,O_4$: C, 47.72; H, 7.21; N, 5.57. Found: C, 47.46; H, 7.35; N, 5.52.) was only possible through mercuric acetate oxidation (60% yield) of the product IX (b.p. 62-63°/5 mm., 69% yield; picrate m.p. 161-163°. Anal. calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.66. Found: C, 50.41; H, 5.89; N, 14.76.) obtained on catalytic reduction with a palladium catalyst.

A condensation of the enamine VIII with methylacrylate led to the vinylogous lactam X (chromatographed on silica gel with methanol and acetone, dist. bath temp. 186-190°/0.001 mm., 41% yield; λ max 1610, 1580 cm^{-1}, 325 mμ (ε 19,000) -CO-C = C-N$\lessgtr$.).

Hydrogenation of the tricyclic enone X in ethanol and acetic acid over a platinum catalyst gave an aminoalcohol which was oxidized to the tricyclic aminoketone Ib with aluminum isopropoxide and acetone. The isomeric aminoketone Ia was obtained from a lithium aluminum hydride reduction of the vinylogous amide X. The two stereoisomeric products Ia and Ib and the other two isomers* Ic and Id of known stereochemistry showed identical vapor phase chromatographic retention times on four

*Kindly provided by Profs. Y. Ban and G. Stork for this purpose.

different column packing materials. However, the mass spectra* of the four stereoisomers, while quite similar, could be divided into two groups Ia and Ic vs. Ib and Id. The two geometrically similar isomers with trans fused six membered rings Ib and Id showed almost identical fragmentation patterns throughout the spectra, the two isomers with cis fused six membered rings showed several differences below m/e 174. At those points isomer Ic resembled the isomers Ib and Id. Comparisons of the infrared spectra again allowed the same groupings of isomers and also showed a small difference in the fingerprint region between the isomers with angular cis protons Ia and Ib and those with angular trans protons Ic and Id. The complete stereochemical purity of the new products Ia and Ib could not yet be rigorously established, however, since all four stereoisomers are not crystalline and usual methods of purification such as salt formation and chromatography promote epimerization of the aminoketones.

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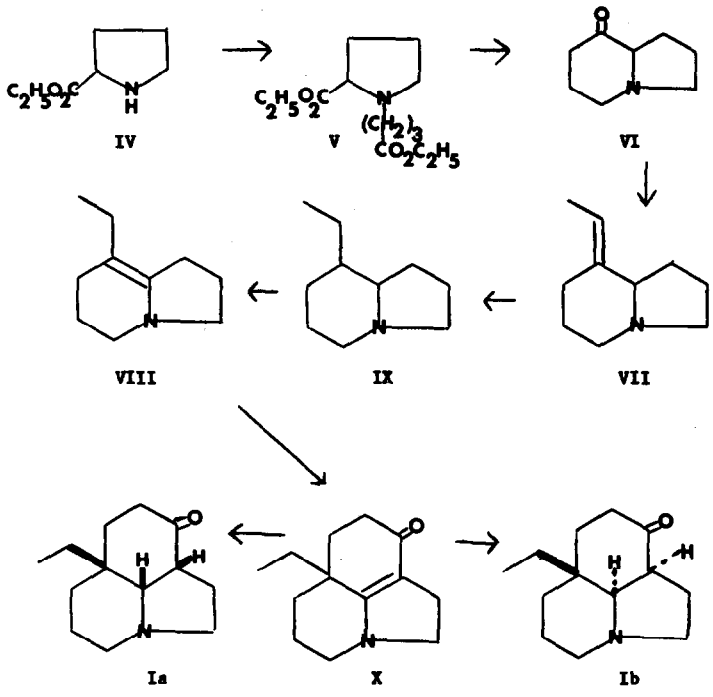
*We thank Dr. J. Dudek of Harvard Univ. for the mass spectra.



1. Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu and Y. Kanaoka, Tetrahedron letters 27 2261 (1965).

2. G. Stork and J. E. Dolfini, J. Am. Chem. Soc. 85 2872 (1963).