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THE CONVERSION OF OXINDOLES TO THE ASPIDOSPERMA SKELETON
THE SYNTHESIS OF dl-N(a)-ACETYL-DESETHYLASPIDOSPERMIDINE

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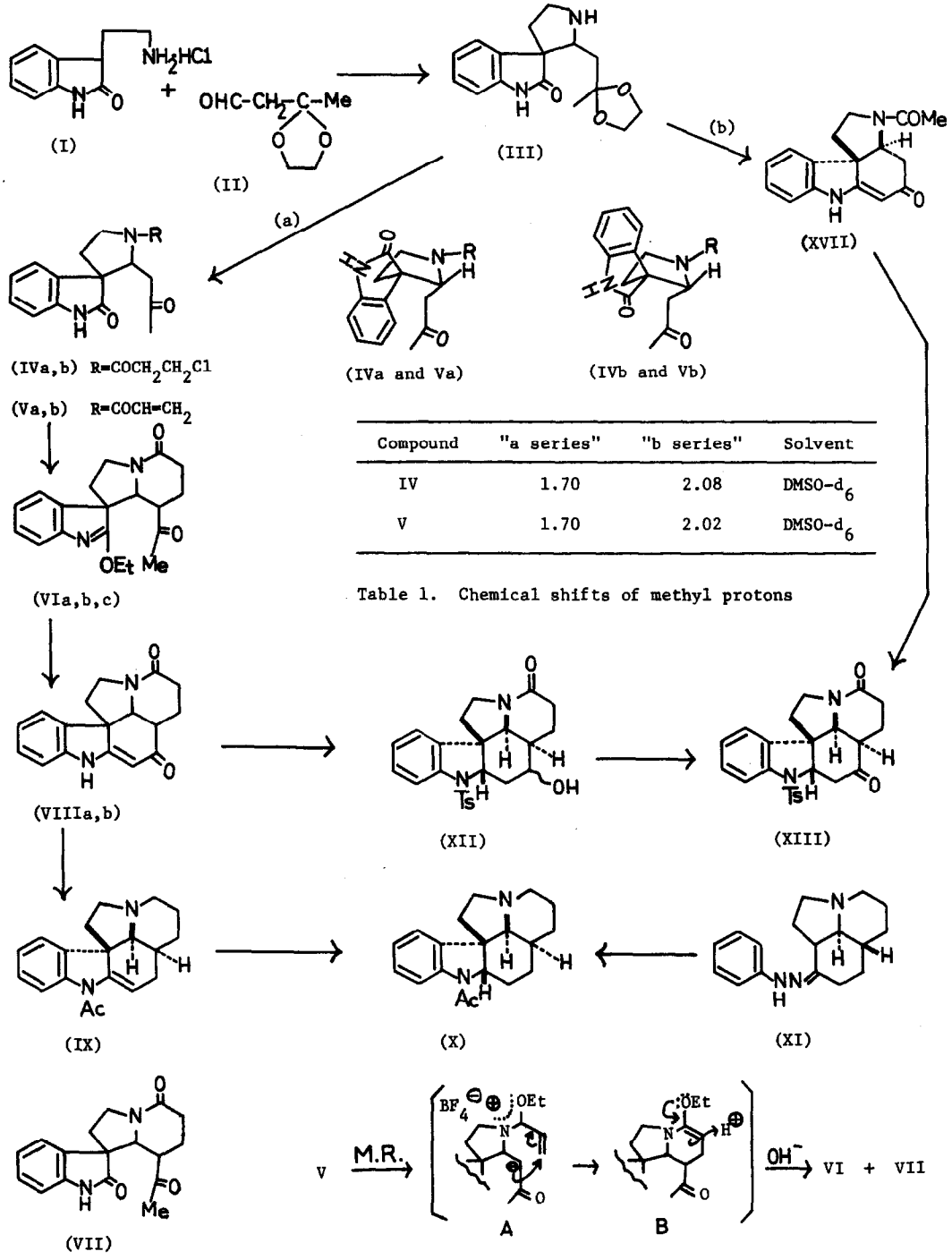
Although many alkaloids of complex structures belonging to the Aspidosperma family have been described increasingly (1), the synthetic works are limited to several kinds of alkaloids and the related compounds constituting the fundamental skeleton (2). In an attempt to create the general method for syntheses of the complex alkaloids in this family, the oxindole(III) which was prepared by us according to condensation of 2-hydroxytryptamine hydrochloride(I) with 3-oxobutanal ethylene ketal(II) (3), has been converted to the entitled compound(X) possessing the stereochemistry of the natural product (4). The present work coupled with the subsequent communication (5), establishes the validity of the proposed method for syntheses of the various Aspidosperma alkaloids, through (a) or (b) routes from III.

An isomeric mixture of III was acylated with β-chloropropionyl chloride and deketalized with acid to afford an oil which was separated by chromatography on alumina into two diastereoisomers(IVa, m.p. 198°, M^+336, 334 and IVb, m.p. 88-89°, M^+336, 334). A solution of IVa in EtOH-CH_2Cl_2 was stirred with solid NaOH (1 mol. eq.) at a room temperature overnight to give the acryloyl derivative(Va, m.p. 204°, 89%). Similarly, IVb gave Vb(m.p. 159°, 70%) on treatment with K_2CO_3(0.5 mol. eq.). The chemical shifts of methyl protons of these compounds are shown in Table 1, in which the proton signals of "a series" appeared in the higher magnetic field due to anisotropy of the phenyl ring than "b series", suggesting that the methyl groups in the formers should exist over the phenyl ring as are illustrated. The compound(Va) was treated with $Et_3O^+BF_4^-$(6 mol. eq.) in 1,2-dichloroethane at 65-70° for 20 hr to give the cyclized iminoether as two isomers(VIa, pale yellow powder, m.p. 97-100°, and VIb, colorless prisms, m.p. 121°) in 51% yield after chromatography on silica-gel eluted with the mixed solvents of ethyl acetate:methylene chloride:ethanol=10:2.5:1. The isomeric acryloyl compound(Vb) gave the other isomeric product(VIc, colorless needles, m.p. 112-113°, 21%) with a mixture of VIa and VIb(4%) under a similar condition. The stereochemistry of these three isomers is still not clear, but

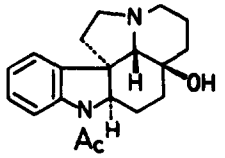


Compound	"a series"	"b series"	Solvent
IV	1.70	2.08	DMSO-d_6
V	1.70	2.02	DMSO-d_6

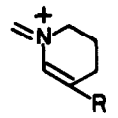
Table 1. Chemical shifts of methyl protons

the observation which VIa and VIb indicates the very close spots on tlc and VIb is readily converted to VIa, suggests that they are isomeric on the orientation of the acetyl substituent, and VIc must be a spiro-isomer at C-3(1') position. This novel Michael type of cyclization could be assumed to proceed via (A) and (B), inducing the nucleophilic attack to the β-position of acryl amide, and further examples are described in the following paper (5). This reaction was superior in the yield to cyclization of IVa or IVb with potassium tert. butoxide affording VII as three isomers(VIIa, colorless cubes, m.p. 228-229°; VIIb, colorless prisms, m.p. 212-216° and VIIc, colorless prisms, m.p. 165-168°), a mixture of which in turn, was converted to the iminoether(VI) in at best 56% yield.

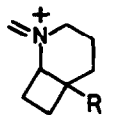
At the subsequent step, a mixture of VIa and VIb was heated with NaH in DMSO for 60 hr to give the pentacyclic products, [VIIIa, m.p. 247-249°; u.v. λ_{max}^{EtOH} 298.5, 342.5 mμ; n.m.r.(DMSO-d_6) δ4.32(C_{19}-H, d, J=8.2 Hz; 31-50%] and [VIIIb, m.p. 230-232°; u.v.λ_{max}^{EtOH} 295, 338 mμ; n.m.r. (DMSO-d_6) δ4.02(C_{19}-H, d, J=11 Hz; 3%]. On a similar treatment, VIc gave a trace of VIIIa as a sole identifiable product. Thus, the main product(VIIIa) was reduced with $LiAlH_4$ in THF on heating at reflux and acetylated to give the colorless caramel[IX, picrate, m.p. 212°(decomp.)], which was hydrogenated with Adams catalyst to provide N(a)-acetyl-desethylaspidospermidine[X, colorless amorphous powder; M^+296; Bohlmann's absorptions were observed in the range of 2700-2780 cm^{-1} of the infrared spectrum; u.v. λ_{max}^{EtOH} 254, 282 and 290 mμ; picrate, m.p. 148-151°], suggesting that the synthetic compound(X) constitutes the stereochemistry of the natural product (4). Furthermore, the compound(X) was identified with the product [picrate, m.p. 147-150°(decomp.)] which was obtained as a minor product on the Fischer indolization of the phenylhydrazone(XI, A/B ring juncture: trans) with acetic acid, followed by $LiAlH_4$ reduction and acetylation(6).



(XIV)



(XV)



(XVI)

It is interesting to note that Ikeda and Djerassi isolated deoxyaspidodispermine from Aspidosperma dispermum, whose complete structure was established by X-ray crystallography (4c, 4d) to be 5-desethyl-5-hydroxyaspidospermidine(XIV) lacking the angular ethyl group of aspidospermine skeleton. The spectral data[mass: m/e 96(base peak; XV, R=H), 124(XVI, R=H);

n.m.r.($CDCl_3$) δ 2.24($NCOCH_3$, s), 4.04(C_2-H, q, J=5 and 10 Hz) of the present synthetic sample (X) well correspond with those [mass: m/e 112(base peak; XV, R=OH), 140(XVI, R=OH); n.m.r. δ 2.26($NCOCH_3$, s), 4.04(C_2-H q)] of 5-desethyl-5-hydroxyaspidospermidine(XIV)(4d).

Finally, VIIIa was reduced with $NaBH_4$ in isopropanol on heating at reflux for 2 hr to give the alcohol(XII) as an isomeric mixture, which without isolation, was tosylated in CH_2Cl_2 at N(a) and oxidized with the Jones reagent to yield the keto-lactam(XIII, colorless needles, m.p. 203~204°), which was identified with the product synthesized via (b) route through XVII, which is published in the following communication (5). In line with the initial project, the method is being extended to syntheses of the polycyclic indole alkaloids.

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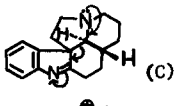
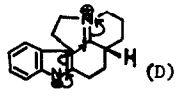
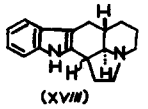
6) Y. Ban and M. Akagi, Unpublished work. The phenylhydrazone(XI) was heated with acetic acid under a stream of nitrogen for 8 hr, and the product was treated with $LiAlH_4$ to afford X in 6.1% yield and the indole(XVIII) of two different conformations in 51.2% yield, during which reaction through the fission and recombination processes, the A/B ring juncture became cis from trans like in (C) and (D). [cf. M. Akagi, T. Oishi and Y. Ban, Tetrahedron Letters, 2063 (1969)].


(C)


(D)


(XVIII)