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THE TOTAL SYNTHESIS OF dl-N(a)-ACETYL-7β-ETHYL-5-DESETHYL-ASPIDOSPERMIDINE

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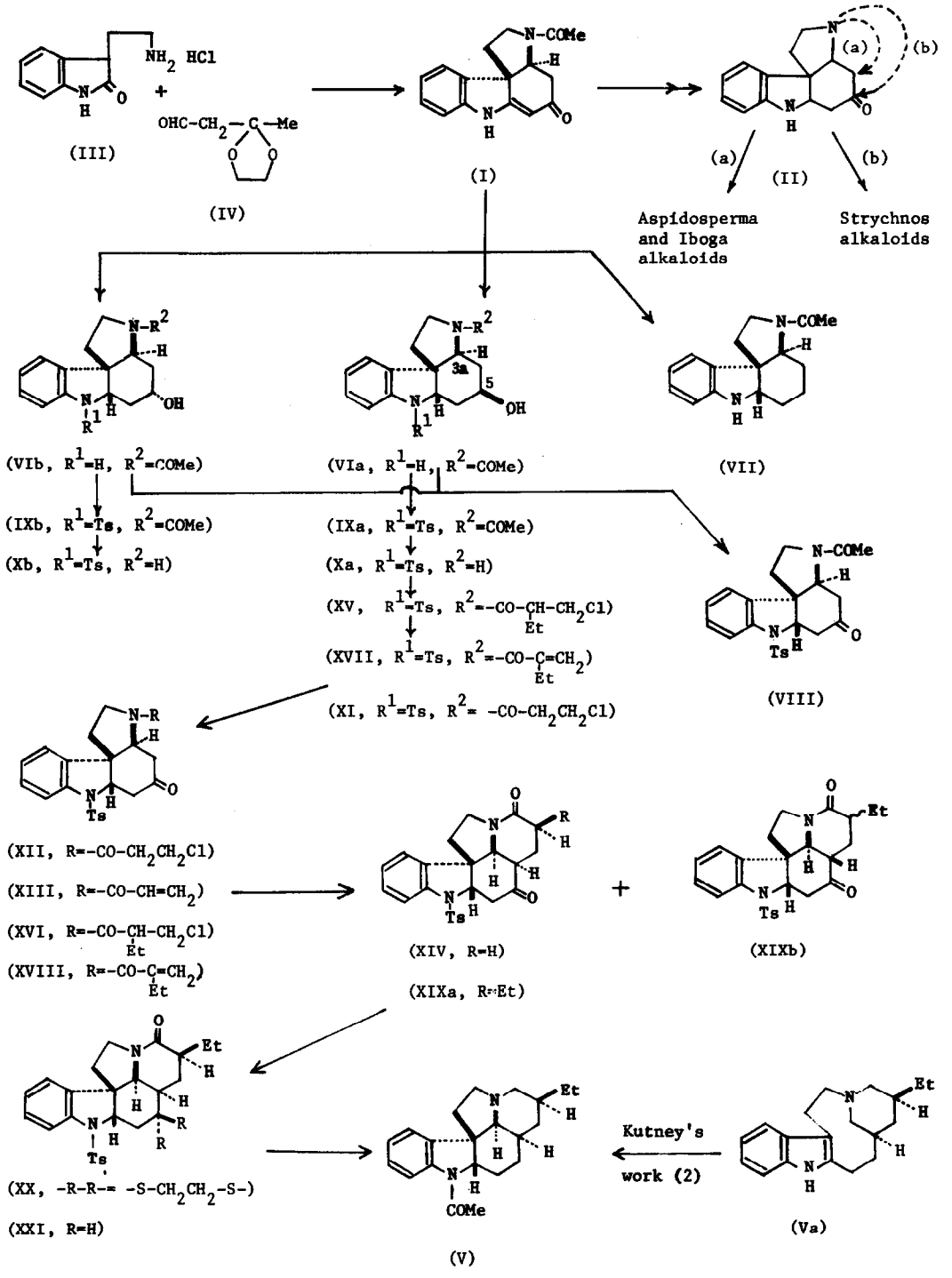
The synthesis of the vinylogous amide(I) which might be available as a common intermediate to synthesize the Aspidosperma and Iboga alkaloids by formation of the (a)-chain and the Strychnos family by construction of the (b)-bridge as are shown in Formula(II), was reported by us, starting from condensation of 2-hydroxytryptamine hydrochloride(III) with 3-oxobutanal ethylene ketal(IV), followed by cyclization at C-2 position by activation of the oxindole lactam with the Meerwein reagent (1). We now describe the stereoselective total synthesis of the entitled compound(V) of the established stereochemistry (2a) from the above intermediate(I), which not only constitutes the first significant conversion of oxindole derivatives to the Aspidosperma skeleton, coupled with the preceding paper (1c) and with the recent interests in biosynthetic reactions (3), but also establishes the validity of the present approach to the above purpose.*

The compound(I) was reduced with $NaBH_4$ in isopropanol by refluxing for 25 hr (4) to afford the three reduced products(VIa, m.p. 215-217°, M^+272, 60%), (VIb, m.p. 199-201°, M^+272, 9%) and (VII, m.p. 173-175°, M^+256, 9%). Both of the alcohols(VIa and VIb) gave the same ketone(VIII, pale yellow oil, M^+270) by mild oxidation with DCC-DMSO (5), indicating that they are the stereoisomers on the hydroxyl substituent. The compound(VIa) was selectively tosylated at N(a) with TsCl in CH_2Cl_2 and 10% aq. NaOH to give IXa, m.p. 228-229°, M^+426, usually 20-40% yields,** which was heated at reflux in a mixture of 5% aq. KOH and ethanol(7:2 by volume) for 20 hr to afford the amine(Xa, m.p. 242-244°, M^+384, 82%). Similarly, VIb gave IXb(m.p. 222-224°, M^+426, 70%), which was hydrolyzed under a similar condition, but after a longer heating over a period of 3 days, furnishing Xb(m.p. 184-186°, M^+384, 83%). As for the stereochemistry of B/C ring juncture of these compounds, the cis-configuration was assigned to all substances excluding the

* Kutney reported the total synthesis of dl-4β-dihydrocleavamine[(±)-Va] (2b), and the optically active compound(Va) derived from the natural source had been led to V by himself (2a). These works constitute the first total synthesis of the entitled compound.

** The yield was later improved to 75% by the new general method. [T. Oishi, K. Kamata, S. Kosuda and Y. Ban, Chem. Comm., in press.]


(III)
(IV)
(I)
(II)
(a)
(b)
Aspidosperma and Iboga alkaloids
Strychnos alkaloids
(VIb, R1=H, R2=COMe)
(VIa, R1=H, R2=COMe)
(VII)
(IXb, R1=Ts, R2=COMe)
(Xb, R1=Ts, R2=H)
(IXa, R1=Ts, R2=COMe)
(Xa, R1=Ts, R2=H)
(XV, R1=Ts, R2=-CO-CH(Et)-CH2Cl)
(XVII, R1=Ts, R2=-CO-C(Et)=CH2)
(XI, R1=Ts, R2= -CO-CH2CH2Cl)
(VIII)
(XII, R=-CO-CH2CH2Cl)
(XIII, R=-CO-CH=CH2)
(XVI, R=-CO-CH(Et)-CH2Cl)
(XVIII, R=-CO-C(Et)=CH2)
(XIV, R=H)
(XIXa, R=Et)
(XIXb)
(XX, -R-R-= -S-CH2CH2-S-)
(XXI, R=H)
(V)
Kutney's work (2)
(Va)

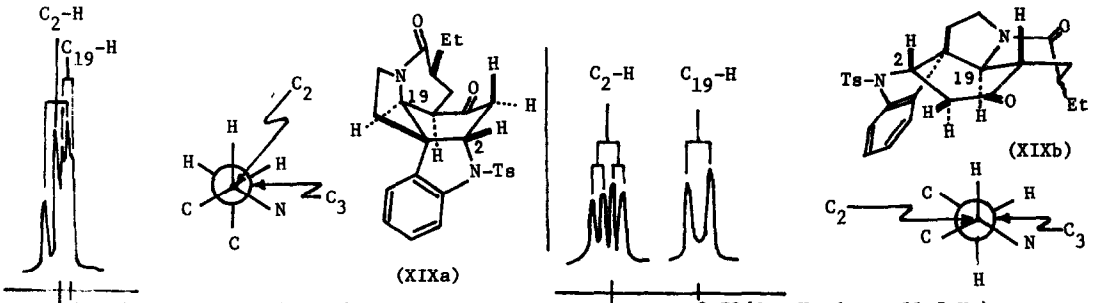


FIGURE 1

trans-orientation, based upon the related studies on hexahydrocarbazoles carried out by us for the present work (6). The configurations of the hydroxyl substituents of VIa and VIb were determined to be in the β[cis to the C_{3a}-N(b) bond] and α[trans to the same bond], respectively, by observation of the absorptions in their infrared spectra due to the intramolecular hydrogen bonding with VIb[C_5-O-H····N(a)] and Xa[C_5-O-H····N(b)]. Thus, the stereochemistry of these compounds could be fully delineated.

The amine(Xa) was reacted with β-chloropropionyl chloride in CH_2Cl_2 and 5% aq. NaOH to give the N(b)-acyl derivative (XI, m.p. 180-181°, M^+476, 474; 72%), which was oxidized with the Jones reagent in acetone to yield the ketone(XII, m.p. 153-154°, M^+474, 472; 81%). The acryloyl derivative (XIII, m.p. 147-149°, M^+436, 84%) which was readily obtained by treating XII with K_2CO_3 in CH_2Cl_2-ethanol, was submitted to cyclization with $Et_3O^+BF_4^-$ (4.5 mol. eq.) at reflux in 1,2-dichloroethane for 18 hr to afford XIV, colorless needles, m.p. 203-204°, as a sole isolated product in 52.5% yield. The stereochemistry of this compound was indicated as XIV, since it was identified with the sample derived from III via the other route, which furnished desethylaspidospermidine constituting the stereochemistry of the natural product (7).

Based upon these results, the amine(Xa) was condensed with α-chloromethyl-butyryl chloride (b.p.$_{30}$72-74°) which had been prepared from ethyl α-bromobutyrate via four steps, to give the amide (XV, m.p. 188-189°, M^+504, 502, 80%). As the dehydrohalogenation of the ketone(XVI, m.p. 204-205°, M^+500, 77%) derived from XV, did not proceed, the amide(XV) was treated with a mixture of ethanol and 5% ethanolic KOH(180:6.6 by volume) at 70° for 5 hr to yield the acryl amide(XVII, m.p. 184-185°, M^+466, 96%), which was carefully oxidized with the Jones reagent in acetone at -2° for 2.5 hr and at a room temperature for 3 hr to yield the corresponding ketone(XVIII, m.p. 188-189°, M^+464, 81%). The ketone(XVIII) in 1,2-dichloroethane was refluxed with $Et_3O^+BF_4^-$

(4.5 mol.eq.) for 24 hr, and the crude product was purified by chromatogaphy on alumina. Elution with the mixed solvents of ethyl acetate-ether-ethanol(1:4:0.1) afforded a pale yellow oil, which solidified on standing in benzene-ether to give XIXb(m.p. 228-229°, M^+464, 4%), and the later fraction gave XIXa(m.p. 191-193°, M^+464, 20%). The n.m.r. spectrum of XIXa was similar to that of XIV, and the proton signals due to C_{19}-H and C_2-H are shown in FIGURE 1, demonstrating that the stereochemistry of XIXa should be same as that(C/D ring juncture:cis) of the natural aspidospermine (8) and XIXb should have a similar stereochemistry to that(C/D:trans) of the diastereoisomer of aspidospermine whose structure was established (9). The assignment was proved to be correct particularly with XIXa by the further reaction sequence.

The keto-lactam(XIXa) was stirred with 1,2-ethanedithiol in the presence of boron trifluoride etherate at a room temperature for 14 hr to yield XX(m.p. 225-227°, M^+540, 64%), which was subjected to the hydrogenolysis with Raney Ni in ethanol at reflux for 1.5 hr to provide XXI(m.p. 216-218°, M^+450, 41%). The lactam(XXI) was reduced with $LiAlH_4$ in refluxing tetrahydrofuran for 2 hr and then acetylated with acetyl chloride in pyridine to yield the entitled compound(V), m.p. 109-111°, M^+324.2191 (error -0.8 mu), whose n.m.r. and i.r.($CHCl_3$) spectra were identical with those of N(a)-acetyl-7β-ethyl-5-desethyl-aspidospermidine, but different from those of the 7α-ethyl-isomer on direct comparison with the authentic samples (2).

Other spectral data supported the assignments of the intermediates newly described with satisfactory elemental analyses.

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