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THE STEREOCHEMISTRY OF INTERMEDIATES IN THE TOTAL SYNTHESIS OF dl-ASPIDOSPERMINE

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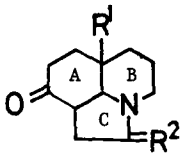
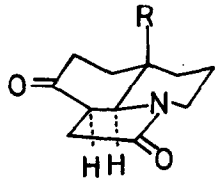
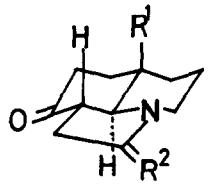
In the preceding papers (1), we reported that trans-7-keto-decahydroquinoline was synthesized by the method of Grob (2) and derived to I in a similar way for synthesis of dl-aspidospermine(V) (3,4). The structure of the compound(I) was proved to be Ia, whose n.m.r. spectrum was well similar to that of our compound(III) (3), but not to Stork's one (4). We therefore suspected the previous stereochemical assignments for the intermediates in the syntheses of dl-aspidospermine (3,4,5), in which III-A and IV-A were given by Stork to their compounds(A/B: trans), while IIIc and IVc were preferred by us for our intermediates(A/B: cis), and Kuehne adopted IVd and IVf for their isomeric ketones(IV) on direct comparison with Stork's and our substances (5). Based upon the following experiments, we propose the new assignment that A/B ring juncture in our compounds(III and IV) should be trans as they are demonstrated by the formulas, IIIa(A/C: cis) and IV-A(A/C: trans).



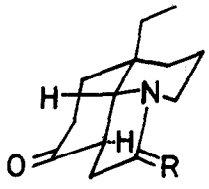
(I) R^1=H, R^2=O
(II) R^1=H, R^2=H_2
(III) R^1=Et, R^2=O
(IV) R^1=Et, R^2=H_2



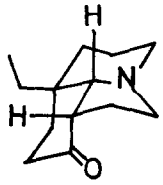
(Ia) R=H
(IIIa) R=Et



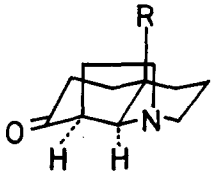
(III-A) R^1=Et, R^2=O
(IV-A) R^1=Et, R^2=H_2
(II-A) R^1=H, R^2=H_2



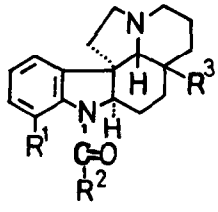
(IIIc) R=O
(IVc) R=H_2



(IVd)



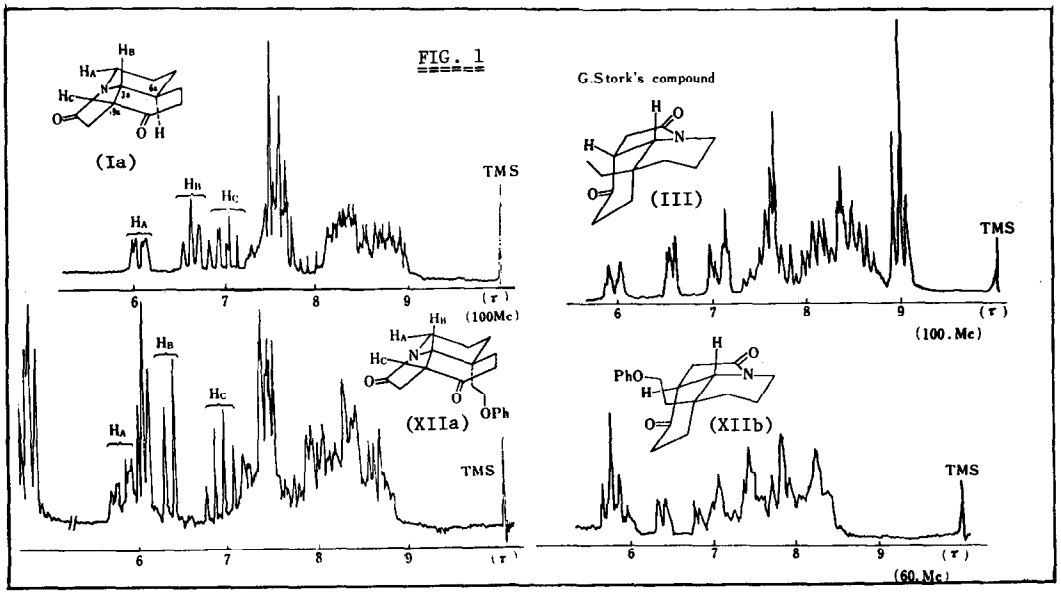
(IVf) R=Et
(IIf) R=H

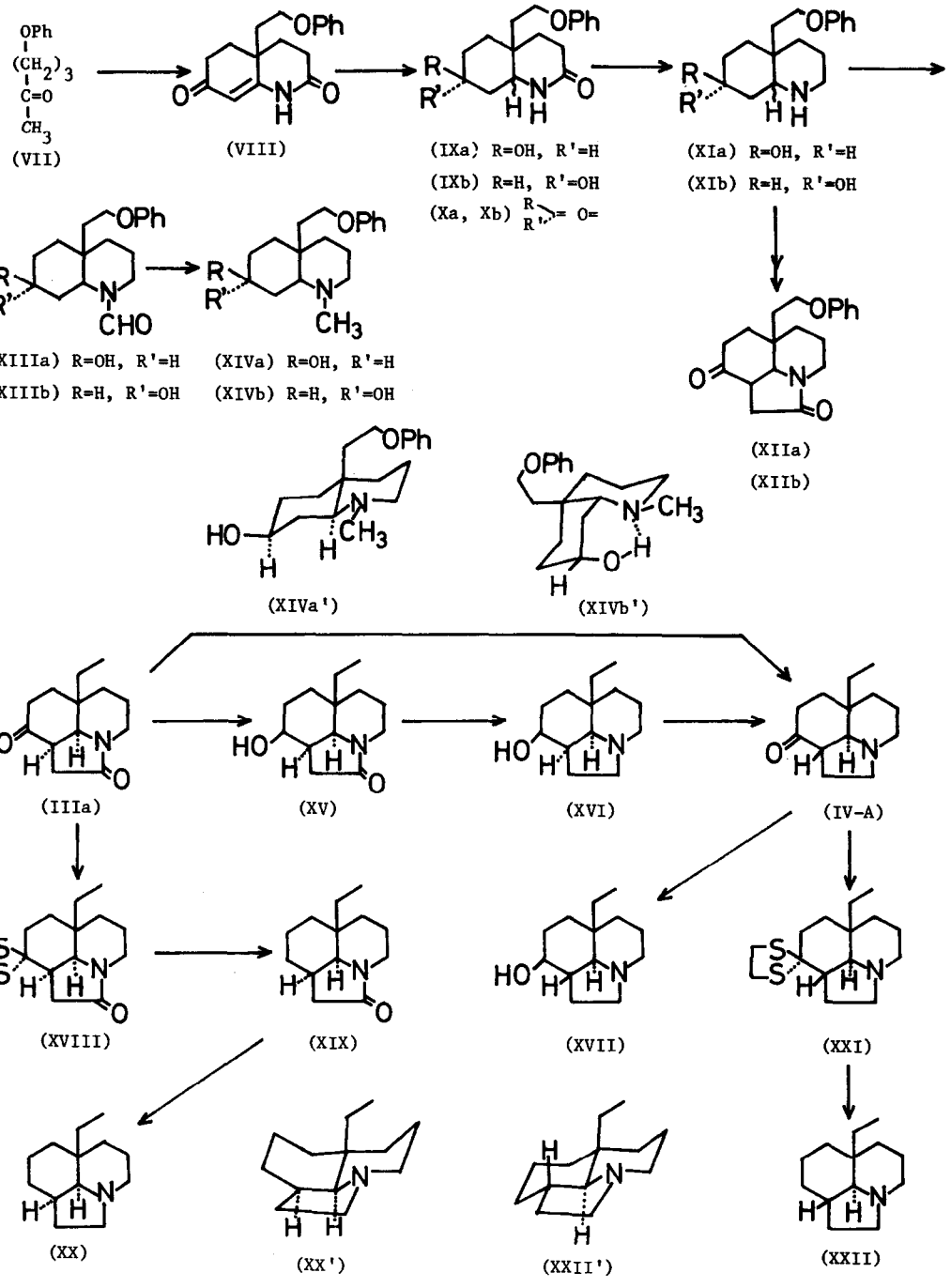


Aspidospermine(V) R^1=OMe, R^2=Me, R^3=Et
Limaspermine(VI) R^1=OH, R^2=Et, R^3=CH_2CH_2OH

Meanwhile, we(Ban and Inoue) had attempted to extend our method (3) to the syntheses of other members of aspidosperma alkaloids, for example, limaspermine(VI) (6), starting from condensation of 5-phenoxy-2-pentanone(VII) with acrylonitrile to afford the lactam-ketone(VIII), which gave two isomeric alcohols, IXa[m.p. 220-222°, (70.5% yield)] and IXb[m.p. 163-165°, (2.8% yield)] on hydrogenation. It became obvious that these alcohols are different at the configuration of ring juncture, because they furnished the different ketones, Xa(m.p. 187-189°) and Xb(m.p. 97-99°), respectively, by chromic acid oxidations. The lactam-alcohol(IXa) was reduced with $LiAlH_2(OCH_3)_2$ (7) to afford the amino-alcohol(XIa), m.p. 150-151.5°, in 76% yield. The tricyclic lactam-ketone(XIIa), m.p. 145-149°, was prepared from XIa, and the other product (XIIb), m.p. 117-118°, was obtained from IXb through XIb(oil; picrate, m.p. 164-165°). The n.m.r. spectrum of the former(XIIa) was well corresponding to that of our ethyl-lactam-ketone (IIIa), while the latter's one(XIIb) was well similar to that of Stork's intermediate(III), suggesting that stereochemistry in each pair should be the same, respectively. (See FIG. 1).

For determination of configuration at the ring-fusion of the above decahydroquinolines, the foregoing amino-alcohol(XIa) was formylated (8) to yield XIIIa, m.p. 150-151°, which was reduced with $LiAlH_4$ to the N-methyl alcohol(XIVa) as colorless needles[m.p. 98-99°, IR.ν ($CHCl_3$) 3580, 3400(10%); 3580 cm^{-1}(1%); picrate, m.p. 146-147°(decomp.)]. Quite similarly, the other N-methyl alcohol(XIVb) as a pale yellow oil [IR.ν($CHCl_3$) 3290 (OH, independent from the concentrations(10%, 1%, 0.5%)); picrate, m.p. 172-173°(decomp.)] was obtained from XIb




(VII)
(VIII)
(IXa) R=OH, R'=H
(IXb) R=H, R'=OH
(Xa, Xb) R, R' = O
(XIa) R=OH, R'=H
(XIb) R=H, R'=OH
(XIIIa) R=OH, R'=H
(XIIIb) R=H, R'=OH
(XIVa) R=OH, R'=H
(XIVb) R=H, R'=OH
(XIIa)
(XIIb)
(XIVa')
(XIVb')
(IIIa)
(XV)
(XVI)
(IV-A)
(XVIII)
(XIX)
(XVII)
(XXI)
(XX)
(XX')
(XXII')
(XXII)

through XIIIb. Thus, the intramolecular hydrogen bonding was observed only with the latter, proving that they could be represented by the formulas, XIVa'(trans form) and XIVb'(cis form), respectively. These assignments are compatible with the result of the studies on trans-7-keto-decahydroquinoline discussed in the preceding papers (1).

To clarify the subsequent problem about stereochemistry at A/C ring juncture of the tricyclic ketones, we returned to our ethyl derivatives.

Our lactam-ketone(IIIa) prepared by the method of Ban (1) was transformed by $NaBH_4$ in MeOH into XV, m.p. 124-125°, and thence, by reduction with $LiAlH_4$ into XVI as an oil [NMR.($CDCl_3$), δ 4.18 (HO-C-H, W/2=16 cps; picrate, m.p. 219-221°(decomp.)], indicating the Bohlmann's absorptions in its IR spectrum. This alcohol(XVI) was oxidized with chromic acid to give the ketone(IV-A) identical with the one previously obtained by us (3). Reduction of the ketone (IV-A) with $LiAlH_4$, however, gave the different alcohol(XVII) as an oil, indicating the Bohlmann's absorptions, which formed the picrate, m.p. 182-184°, and afforded the corresponding acetate, pale yellow oil [NMR.($CDCl_3$), δ4.64(HO-C-H, W/2=18 cps; picrate, m.p. 229-231°]. Although the hydroxyl substituents of XVI and XVII could be assumed to exist as the equatorial by half-widths of the proton signals at the same carbon in their n.m.r. spectra (9), they were not identical, suggesting that the configuration at A/C ring-fusion in both compounds should be different.

For further confirmation, IIIa was converted to the lactam-thioketal(XVIII) by treatment with 1,2-ethanedithiol and BF_3-etherate, and the product(XVIII) underwent desulfurization with Raney Ni to give the lactam(XIX), m.p. 49-50°, which was reduced with $LiAlH_4$ to afford the amine(XX) as an oil, IR. ν 2780, 2720 cm^{-1}, forming the picrate, m.p. 219-220°.

In a similar way, the amino-ketone(IV-A) was converted to the thioketal(XXI) [picrate, m.p. 199-200°(decomp.)], which was submitted to hydrogenolysis with Raney Ni to the other amine (XXII) [IR. ν(film) 2800, 2720 cm^{-1}], giving the picrate, m.p. 195-197°.

Thus, the isomeric amines(XX and XXII) prepared through the above respective routes, are apparently different in the fundamental ring configurations. None the less, both of them exhibit the distinct absorptions in the Bohlmann's region (10), which suggests that the above amines should be represented by the stereoformulas[XX'(A/C:cis) and XXII'(A/C:trans)].

In view of the preceding assignment that the lactam-ketone(I) is Ia and the amino-ketone(II) is a configurational equilibrium mixture of II-A and IIf (1), the formulas(IIIa and IV-A) should be given to our compounds(III and IV), respectively. The n.m.r. spectrum of IIIa accompanied

with the decoupling data published in our previous communication (3), is compatible with the present assignment. These facts let us conclude that the amino-ketone[IV-A (A/C:trans)] must have been formed on hydrolytic regeneration of the carbonyl function at C(9) from the corresponding ketal(A/C:cis) of IV with the concurrent epimerization at C(9a)-H without yielding IVf, because the acute 1,3-diaxial interaction between the ethyl group at C(6a) and the five-membered ring pictured in IVf should not permit to exist in this conformation. The similar interaction in IIIa could be relieved by taking the flat structure for the lactam part (11) and the twist boat form for the A-ring.

Satisfactory elemental analyses have been obtained on all crystalline compounds.

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