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SYNTHESIS AND STEREOCHEMISTRY OF OCTAHYDRO-4H-PYRROLO [3,2,1-i,j] QUINOLIN-9(2H)-ONE

Yoshio Ban, Masao Akagi and Takeshi Oishi

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

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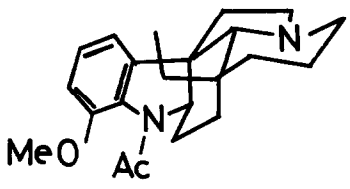
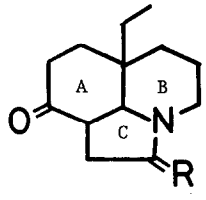
The total syntheses of dl-aspidospermine(I) were reported by G. Stork et al. in 1963 (1), and by Y. Ban et al. in 1964 (2,3). The key intermediates of the same plane formulas (II and III) in both syntheses were prepared in the independent ways, whose physico-chemical properties are quite different and proved to be the stereoisomers. Thus, IIa and IIIa were given by Stork to their compounds (1), and IIb and IIIb were preferred by us for our intermediates on taking Stork's assignment into consideration, although the possibility of IIa to our compound was alternatively considered based on n.m.r. spectral data (2). For confirmation of this point, trans-7-keto-decahydroquinoline(IV), m.p. 90-92°, was prepared by the method of Grob (4) and was converted to the lactam-ketone(VI), m.p. 98-99°, colorless needles, through V (semicarbazone, m.p. 214-215°) in the same way as our synthesis of dl-aspidospermine (2).

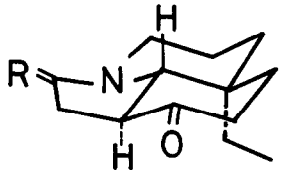


(I)



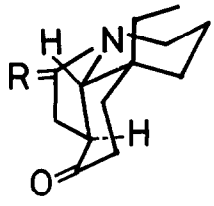
(II) R=O

(III) $R=H_2$



(IIa) R=O

(IIIa) $R=H_2$



(IIb) R=O

(IIIb) $R=H_2$

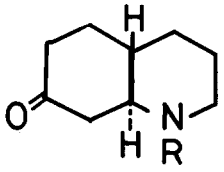
Contrary to our expectation, the n.m.r. spectrum of VI was well similar to that of our compound(II), but not to Stork's one(5). Therefore, we could not help suspecting the previous assignments to the conformations of these compounds. Accordingly, the conformational analyses of the present compounds(VI and others) have been conducted in reference to determination of stereochemistry of the above intermediates(II and III).

Based upon Grob's evidences for the trans configuration of IV (4), two isomeric structures for VI have deserved serious consideration; these are VIa and VIb, in which the lactam nitrogen forms the flat structure (6) and ring A of VIa may constitute a twist boat form, as it is supposed to be preferable to a classical chair form (7).

The tricyclic keto-lactam(VI) was converted to the ketal(VII), colorless prisms, m.p. 92-94°, IR ν_{max}^{Nujol} 1678 cm^{-1}(the absorption at 1710 cm^{-1} disappeared), which was reduced with lithium aluminum hydride to afford the ketal-amine(VIII) as a pale yellow oil, not indicating the Bohlmann's absorption (8) in its IR spectrum. This compound may be delineated as VIII involving the tetrahedral nitrogen and ring B of a chair form. The ketal(VIII) was readily hydrolyzed to the corresponding ketone(IX), colorless pillars, m.p. 53-56°, which demonstrated the Bohlmann's absorptions and indicated two close spots on TLC, but could not be isolated by column chromatography. These results suggest that the initial compound should have the conformation of VIa, but not VIb, and at the final step, epimerization must have occurred at C-9a coupled with the facile inversion of the electron pair of nitrogen at N-3. Thus, the tricyclic ketoamine(IX) could be assumed to be an equilibrium mixture of two stereoisomers, IXa and IXb.

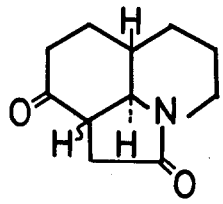
Furthermore, the keto-lactam(VI) was reduced with sodium borohydride to the alcohol(X), m.p. 128-130°, (tosylate, m.p. 116-117°, TsO-C<u>H</u> δ 4.85, W/2 = 20 cps). It could be expected that the axial hydroxyl group at C-9 (in the twist boat form) initially produced under the kinetic control of this reduction should be readily converted to the equatorial on inversion of that ring to a flattened chair form, in which the axial hydrogen at the same carbon should indicate ca. 20 cps at the half-width of that proton signal (4,9). The experimental result well agreed with this anticipation. The lactam-alcohol(X) was reduced with lithium aluminum hydride to yield the amine(XI-D)*1, involving no Bohlmann's bands in the IR spectrum, which

*1 The compound(XI-D) was identified with one of the products obtained by reduction of IX.

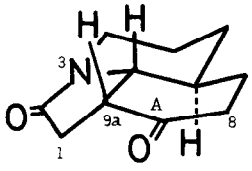


(IV) R=H

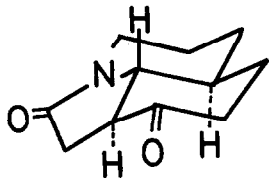
(V) R= $-COCH_2Cl$



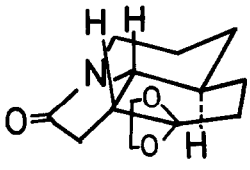
(VI)



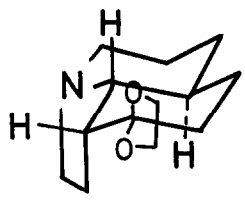
(VIa)



(VIb)

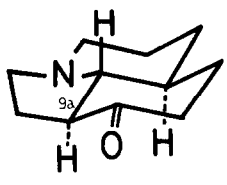


(VII)



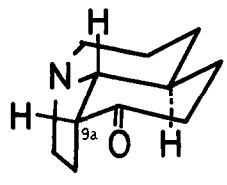
(VIII)

VI

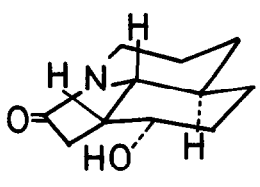


(IXa)

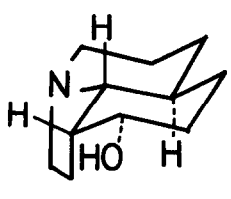
IX



(IXb)



(X)

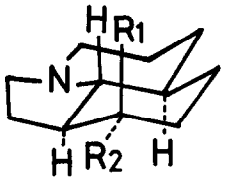


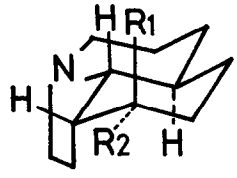
(XI-D)

TABLE I

Compound	M.p.	M.p.(Picrate of Acetate)	OH or OAc
XI-A	Oil	158-159°(decomp.)	axial
XI-B	107-108°	227-228°(decomp.)	equatorial
XI-C	119-121°	158-159.5°(decomp.)	axial
XI-D	108-110°	202-204°(decomp.)	equatorial

TABLE II





Compound	R_1	δ (W/2) (ppm,cps)	R_2	δ (W/2) (ppm,cps)	Compound	R_1	δ (W/2) (ppm,cps)	R_2	δ (W/2) (ppm,cps)
XI-A	OH	4.90	H	3.70(10)	XI-C	OH	2.46	H	4.18(5)
XI-B	H	3.45(22)	OH	3.47	XI-D	H	3.95(24)	OH	4.10
XI-A Acetate	$OCOCH_3$	2.10	H	5.05(10)	XI-C Acetate	$OCOCH_3$	2.13	H	5.24(5)
XI-B Acetate	H	4.70(20)	$OCOCH_3$	2.08	XI-D Acetate	H	5.13(21)	$OCOCH_3$	2.10

was oxidized with the Jones' reagent to give the product(IX) identical with the one obtained through the previous route.

For restraint of the easy epimerization at C-9a of IX, the compound(IX) was reduced with lithium aluminum hydride in ether or with sodium borohydride in methanol to give four isomeric alcohols (XI), which were separated by chromatography on alumina.*2 (TABLE I and II).

One pair of XI-A and XI-B revealed the Bohlmann's absorptions and the other of XI-C and XI-D involved no those bands, so that they could be classified into two groups as are shown in

*2 The production ratio of the isomeric alcohols(XI) was XI-B:XI-C:XI-D=5:1:5.8 when IX was reduced with lithium aluminum hydride, and was XI-A:XI-B:XI-D=1:3.4:2.8 when reduced with sodium borohydride.

TABLE II. Furthermore, it may be understood that the compounds(XI-A and XI-C) possess the axial hydroxyls at C-9 and the others(XI-B and XI-D) have the equatorial hydroxyl groups, being indicated by the half-widths of n.m.r. signals of the protons attached to the same carbons. (TABLE II).

These assignments were confirmed by converting these alcohols to the corresponding acetates, whose proton signals at C-9 also provide the identical results in terms of the half-widths. (TABLE II).

Thus, the present paper accounts for the whole processes of the above reaction sequences and the easy isomerization between IXa and IXb of the ketone(IX), which plays an important role in elucidation of the stereochemistry of our intermediates(II and III) in the synthesis of dl-aspidospermine(I), being discussed in the following papers.

Satisfactory elemental analyses have been obtained on all crystalline compounds.

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