Tetrahedron Letters No. 40, pp 3687 - 3690, 1971. Pergamon Press. Printed in Great Britain.

SYNTHESIS AND STEREOCHEMISTRY OF 4a-METHYL-1,2,3,4,4a,9a-HEXAHYDROCARBAZOLE AND ITS RELATIVES

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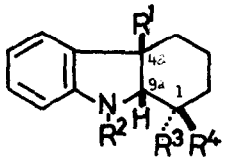
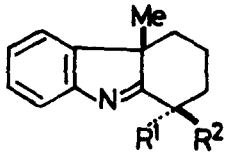
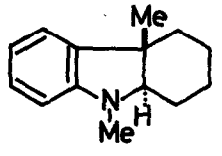
(Received in Japan 7 July 1971; received in UK for publication 15 August 1971)

The recent publication on the stereochemistry of cis-9-acetyl-4a-ethyl-1,2,3,4,4a,9a-hexahydrocarbazole(Ia) by S. McLean et al.[1] prompted us to report our results in this field.

In connection with the synthetic studies on the aspidosperma and strychnos alkaloids from a common intermediate,[2] it was necessary to establish the stereochemistry of 4a-alkyl-hexahydrocarbazoles, mainly based on the nmr spectral measurement. For this purpose, 4a-methyl-1α-hydroxymethyl-1,2,3,4,4a,9a-hexahydrocarbazole[(Ib), colorless crystals, m.p. 65-75°, M^+=217; picrate, m.p. 187.5-190.5°] and the 1β-hydroxymethyl isomer[(Ic), colorless crystals, m.p. 62-67°, M^+=217; picrate, m.p. 166-168°] were synthesized by $LiAlH_4$ reductions of the corresponding carbazolenines, (IIa) and (IIb), respectively, the latters of which had been obtained by Bernauer,[3] because the spatial situation of the vicinal protons at C_{9a} and C_1 of Ib and Ic could be expected to be simply analysable on comparison of the coupling constants between them.





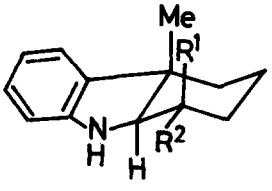


(VI)

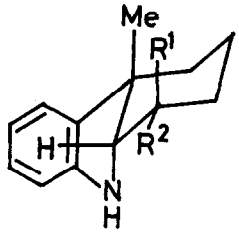
Ia R^1=Et, R^2=COMe, R^3=R^4=H
Ib R^1=Me, R^2=H, R^3=CH_2OH, R^4=H
Ic R^1=Me, R^2=R^3=H, R^4=CH_2OH
Id R^1=Me, R^2=CHO, R^3=R^4=H
Ie R^1=Me, R^2=R^3=R^4=H
If R^1=Me, R^2=COMe, R^3=R^4=H
Ig R^1=R^2=Me, R^3=R^4=H

IIa R^1=CH_2OH, R^2=H
IIb R^1=H, R^2=CH_2OH
IIc R^1=R^2=H

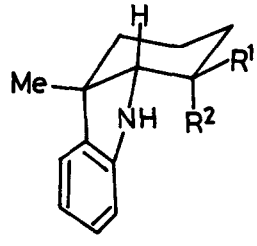
For argument of stereochemistry of these compounds, the chair and its slightly distorted forms for ring C were mainly considered by analogy with stereochemistry of cis- and trans-hydrindane ring systems,[4] since the six-membered ring of these compounds(Ib∿Ig) is fused to the nearly planar indoline ring with an angular methyl group. Furthermore, although a boat form was excluded in cis-hydrindane,[4] the possibility of taking a similar form was taken into accounts for the present case in cis-configuration. Thus, one pair of the possible trans-isomers with α- and β-hydroxymethyl groups at C_1-position are indicated as IIIa and IVa, and two pairs of the cis-isomers are delineated as IIIb, IIIc, IVb and IVc in Fig. 1. The coupling constants between vicinal protons at C_1 and C_{9a} were calculated due to the observed dihedral angles on examination of molecular models, by utilizing the modified Karplus equation,[5] which are described below the respective formulas in Fig. 1, together with the approximate values for boat forms inside parentheses.



IIIa R^1=H, R^2=CH_2OH
Calcd. J=10 Hz
IVa R^1=CH_2OH, R^2=H
Calcd. J=0 2 Hz



IIIb R^1=H, R^2=CH_2OH
Calcd. J=5.2 Hz
(J=3 Hz)
IVb R^1=CH_2OH, R^2=H
Calcd. J=0 1 Hz
(J=2 Hz)
Vb R^1=R^2=H



IIIc R^1=H, R^2=CH_2OH
Calcd. J=5.8 Hz
(J=7 Hz)
IVc R^1=CH_2OH, R^2=H
Calcd. J=8 Hz
(J=13 Hz)
Vc R^1=R^2=H

Figure 1. Possible Conformations for Ib, Ic and Ie.

The actual signal of C_{9a}-H of the 1α-hydroxymethyl isomer(Ib) appeared at 6.39τ as a doublet with J=3.4 Hz (in $CDCl_3$), which is apparently different from the corresponding proton signal due to C_{9a}-H at 6.92τ (d., J=8.7 Hz) of the 1β-hydroxymethyl isomer(Ic). The fact that the splitting of C_{9a}-H of the latter compound(Ic) is almost 9 Hz indicates that this compound takes a non-steroidal conformation(B/C:cis) represented by formula(IVc), since the calculated value of the coupling constant for IVc is 8 Hz (13 Hz with a boat form), and the values for

the other forms(IVa and IVb) are about 0~2 Hz. On the other hand, if the 1α-isomer(Ib) were trans, the splitting of C_{9a}-H should be expected to be 8~9 Hz, for the dihedral angle between C_1-H and C_{9a}-H in the trans-form(IIIa) is almost same as that in the cis-form(IVc) of the 1β-isomer(Ic). Nevertheless, the fact that the observed value is 3.4 Hz, distinctly suggests that the 1α-isomer(Ib) should be IIIb or IIIc, either of which is cis. This conclusion was further supported by the subsequent studies on stereochemistry of 4a-methyl-1,2,3,4,4a,9a-hexahydrocarbazole(Ie), the formyl derivative(Id) of which was generated as one of the products on the Fischer indolization of 2-methylcyclohexanone phenylhydrazone with formic acid, followed by a concurrent reduction according to the standard procedure.[6)]

The formyl derivative(Id) was hydrolyzed to Ie as a brownish oil, which was identified with the product obtained by $LiAlH_4$ reduction of the carbazolenine(IIc) by direct comparison of the spectral data. The identity was further confirmed by conversion of Ie to the acetyl derivative(If), m.p. 85-87°. The fact that the identical product(Ie) was obtained by either (a) hydrolysis of Id or (b) $LiAlH_4$ reduction of IIc, strongly suggests that the hexahydrocarbazoles (Id, Ie and If) should be in the cis-configuration at B/C ring juncture, because the cis-isomers(Ib and Ic), the configuration of which was established by the present work, were exclusively obtained by the same reductions of IIa and IIb, respectively. This assumption was supported by measurement of nmr spectra, in which the signal due to C_{9a}-H of Ie appeared at 6.72τ as a triplet(J=3.4 Hz), and the corresponding proton of the N-acetyl derivative(If) gave rise to a broad signal with a half-band width of 18 Hz centered at 6.16τ. This observation could be attributed to a facile ring inversion or its equilibrium with If, that is compatible only with the cis-configuration at C_{4a} and C_{9a}.

Furthermore, as for the conformation of Ie, the C_{9a}-proton signal appearing as a triplet clearly suggests that it approximately bisects the angle between C_1-methylene protons, as in a perfect chair form, which is indicative of a "steroidal form(Vb)" for Ie. In relation to this result, the 1α-hydroxymethyl isomer(Ib) whose C_{9a}-H appears at 6.39τ as a doublet with the vicinal coupling constant(J=3.4 Hz), equal to the corresponding value with Ie(C_{9a}-H, t., J=3.4 Hz), might be assumed to prefer a "steroidal form(IIIb)" in a solution. It is interesting to note that the 1β-hydroxymethyl isomer(Ic) seems to prefer a "non-steroidal form(IVc)" to a "steroidal form(IVb)", in which there should exist the acute 1,3-diaxial interaction between C_{4a}-methyl and C_1-hydroxymethyl substituents. The cis-configuration for these compounds was further confirmed by direct comparison of Ig(oil; picrate, m.p. 126-129°) which was obtained by $LiAlH_4$ reduction

of Id, with trans-1,2,3,4,4a,9a-hexahydro-4a,9-dimethylcarbazole(VI)[7] (oil; picrate, m.p. 181-183°), prepared by following Chapman's photoisomerization of the N-aryl enamine.[8] In the trans-isomer(VI), the C_{9a}-proton resonates at a relatively high field position in the methylene envelope(9.0~7.37τ), while with the former(Ig), the corresponding signal appearing at a downfield of 7.2τ is apart from the methylene proton signals which are appreciably sharpened like a singlet centered at 8.55τ, which is reasonably explained by a ring inversion in the cis-configuration.

Thus, the present results on stereochemistry of Ib, Ic and Ie in solutions could be compatible with the result from the X-ray analysis of 9-acetyl-4a-ethyl derivative(Ia) in a solid state, although it is a "non-steroidal form" involving an ethyl group at C_{4a}, a bulkier substituent equatorial to ring C.

Satisfactory elemental analyses have been obtained on all characterized compounds.

Acknowledgements This work was financially supported by the Toyo Rayon Science Foundation, which is gratefully acknowledged.

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