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ABSOLUTE CONFIGURATIONS OF DIASTEREOISOMERIC METHIODIDES IN THE LYCORINE-TYPE ALKALOIDS

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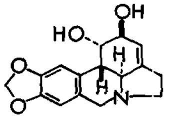
In the previous communication (1) we reported the studies on the stereochemistry of lycorine and related compounds by newer physical methods using the NMR, CD and ORD spectroscopies, and demonstrated the conclusive evidences for their stereochemistry and absolute configurations. Furthermore, Koyama et al. (2) carried out the x-ray analysis of dihydrolycorine hydrobromide, showing that the stereochemistry proposed by our group (3) was correct.

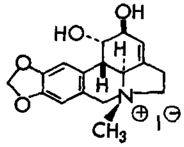
In 1938, Kondo et al. found that treatment of lycorine (I) with methyl iodide in refluxing methanol gave two diastereoisomeric methiodides, named lycorine α- and β-methiodides (4). In 1954, Uyeo et al. converted these two methiodides to the corresponding (-)- and (+)- anhydrolycorine methiodides respectively, which differ only in the configuration about the quaternary nitrogen atom (5).

We will report herein the absolute configurations of diastereoisomeric methiodides in the lycorine-type alkaloids, which have not been determined yet.

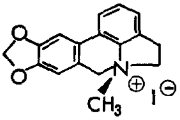
Reinvestigation of quaternarization of dihydrolycorine (II) with methyl iodide in refluxing methanol shows that dihydrolycorine methiodide, m.p. 283°, $[\alpha]_D$ -4.6°, is obtained as a sole reaction product, as reported in the literature (6). With the stereochemistry and the absolute configuration of dihydrolycorine established by the NMR α-series



(I)

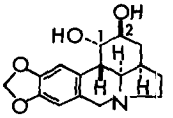


$[\alpha]_D$ -46.1°
(III)

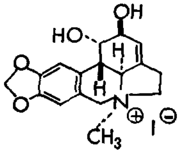


$[\alpha]_D$ -56°
(V)

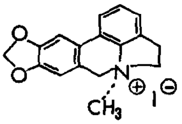
β-series



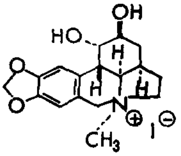
(II)



$[\alpha]_D$ +128.1°
(IV)



$[\alpha]_D$ +53°
(VI)



$[\alpha]_D$ -4.6°
(VII)

study and the x-ray analysis of dihydrolycorine hydrobromide (1,2), it is quite clear that the lone pair electrons on the nitrogen atom of dihydrolycorine should be orientated towards the rear site of the molecule.

Accordingly, the N-methyl group in dihydrolycorine methiodide has α-configuration as shown in the formula VII. Hydrogenation of lycorine β-methiodide with platinum oxide in ethanol affords dihydrolycorine methiodide (VII). This fact shows that the configurations of the N-methyl groups in both lycorine β-methiodide (IV) and dihydrolycorine methiodide should be the same. Considering the afore-mentioned chemical relation between the diastereoisomeric lycorine methiodides and anhydrolycorine methiodides, it is readily concluded that the absolute configurations of the N-methyl groups in lycorine α-methiodide, (-)- and (+)-anhydrolycorine methiodides should be depicted as the formulae III, V and VI, respectively.

The similar conclusion was recently deduced by our group from the comparison of the ORD curve of (+)-anhydrolycorine methiodide with that of nantenine which belongs to the aporphine alkaloids (7, 8). The CD curves of (+)-anhydrolycorine methiodide, nantenine*[1] and its hydrochloride (FIG. 1) show the similar high-intensity positive effect at about 240 mμ. This fact clearly indicates that the effect of the lone pair electrons on the nitrogen atom is not so large and then the positive effect near 240 mμ is dependent on only the absolute configuration of the asymmetric carbon atom, in other words, the conformation of the twisted biphenyl system. This result is in good agreement with that of ORD study.

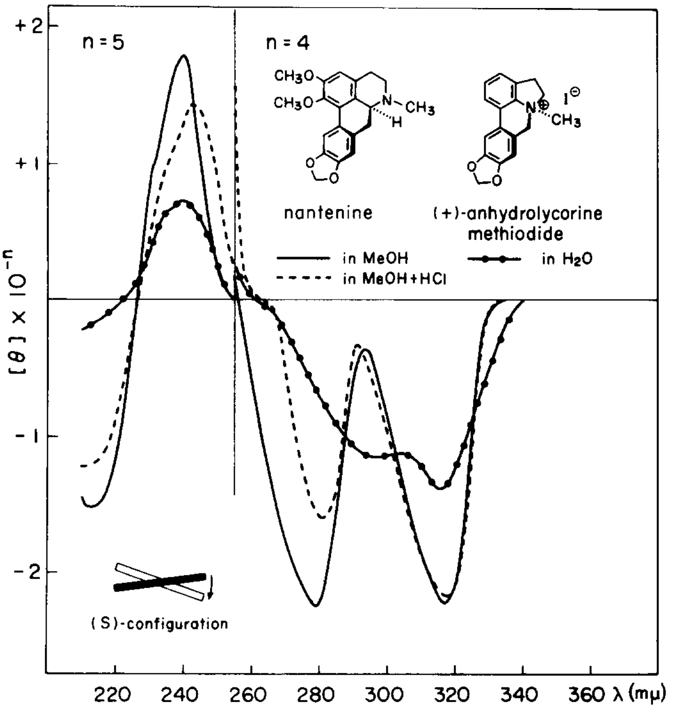


FIG. 1 CD curves of nantenine and (+)-anhydrolycorine methiodide.

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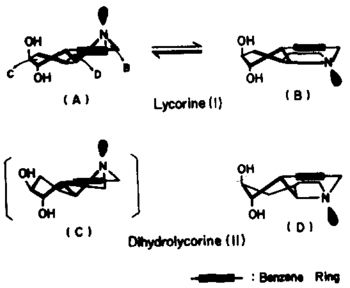
*[1] We are indebted to Prof. M. Tomita for providing the sample of nantenine.

The reason why quaternarization of lycorine affords two diastereoisomeric methiodides, whereas in dihydrolycorine there is obtained the only one methiodide, would be readily explanable by considering the difference of the conformations in both lycorine and dihydrolycorine.

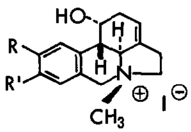


In the case of lycorine, it is possible by the model inspections to alternate easily the conformation of the B ring between half-chair (A) and half-boat (B) without the remarkable conformational changes in any other rings. Therefore, it will be expected that in solution there is an equilibrium between the two forms, which may result in the formation of two diastereoisomeric methiodides.[*2]

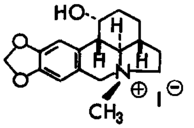
On the contrary, the conformation of dihydrolycorine should be fixed only in the D-type form as indicated by the results of the NMR study (1) and the x-ray analysis (2) of dihydrolycorine hydrobromide. Alternative conformation, the C form, would be out of consideration, since the conformational change of the D form into the C form must accompany the considerable changes in both the C- and D-rings together with in the B-ring. Actually the only one dihydrolycorine methiodide resulting from the conformation of the D-type form is obtained.

[*2] It will be considered that the conformation of the A form will be more thermodynamically favourable than that of the B form. Really it has been proved that the yield of α-methiodide (from the A form) increased with decrease of the reaction temperature.

α-series

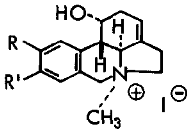


(VIII) a R:R' = $-OCH_2O-$, $[\alpha]_D$ -116.3°
b R=R' = CH_3O- $[\alpha]_D$ -129°

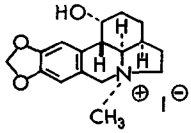


(XI) $[\alpha]_D$ -119.7°

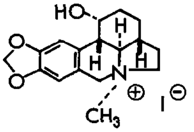
β-series



(IX) a R:R' = $-OCH_2O-$
$[\alpha]_D$ +52.2°
b R=R' = CH_3O-
$[\alpha]_D$ +38.2°



(X) $[\alpha]_D$ -14.6°



(XII) $[\alpha]_D$ +28.4°

We can readily deduce the absolute configurations of caranine and pluviine methiodides (9,10) from the comparison of their rotation values with those of lycorine and anhydrolycorine methiodides.

The more laevo-rotatory α-methiodides of caranine and pluviine are shown in the formulae VIIIa and VIIIb, respectively, similar to the cases of lycorine and anhydrolycorine methiodides (III and V), and the corresponding more dextro-rotatory β-methiodides in the formulae IXa and IXb. Quaternarization of α-dihydrocaranine (9), one of the hydrogenation products of caranine, gives the only one methiodide (X), because the conformation of α-dihydrocaranine is the same as that of dihydrolycorine. In contrast to this, treatment of β-dihydrocaranine (9), which is another reduction product of caranine, with methyl iodide gives expectedly two diastereoisomeric methiodides, named α- (XI) and β- (XII) methiodides according to their rotatory values, since, from the model inspections, the conformational change of this compound is easy just as lycorine, caranine and pluviine do.

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REFERENCES

1. K. Kotera, Y. Hamada, K. Tori, K. Aono and K. Kuriyama, Tetrahedron Letters 2009 (1966).
2. M. Shiro, T. Sato and H. Koyama, Chem. & Ind. (London) 1229 (1966).
3. K. Takeda and K. Kotera, Chem. Pharm. Bull. 5, 234 (1957).
4. H. Kondo, H. Katsura and S. Uyeo, Ber. 71, 1529 (1938).
5. L. G. Humber, H. Kondo, K. Kotera, S. Takagi, K. Takeda, W. I. Taylor, B. R. Thomas, Y. Tsuda, K. Tsukamoto, S. Uyeo, H. Yajima and N. Yanaihara, J. Chem. Soc. 4622 (1954).
6. H. Kondo and K. Tomimura, Yakugaku Zasshi 48, 223 (1928).
7. J. C. Craig and S. K. Roy, Tetrahedron 21, 395 (1965).
8. K. Kuriyama, T. Iwata, M. Moriyama, K. Kotera, Y. Hamada, R. Mitsui and K. Takeda, J. Chem. Soc., in press.
9. E. W. Wahnhoff and W. C. Wildman, J. Am. Chem. Soc. 89, 2192 (1956).
10. H-G. Boit and H. Ehmke, Chem. Ber. 89, 163 (1965); H-G. Boit, H. Ehmke, S. Uyeo and H. Yajima, Ibid. 90, 363 (1957); T. Kitagawa, S. Uyeo and N. Yokoyama, J. Chem. Soc. 3471 (1959).