

THE ABSOLUTE CONFIGURATION OF (-)-CREBANINE

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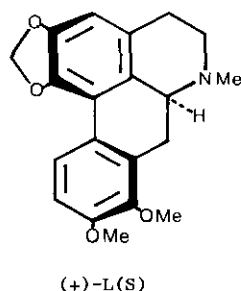
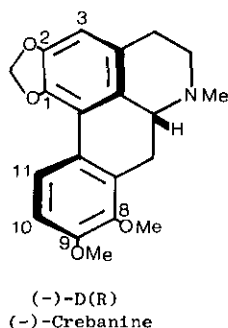
The aporphine (-)-crebanine, found in Stephania spp. (Menispermaceae), possesses the D(R) absolute configuration.

The absolute configuration of aporphine alkaloids can be correlated along broad general lines with the substitution pattern in ring D. One rule states that "aporphines substituted at both C-10 and C-11, or at both C-9 and C-10, are usually dextrorotatory and belong to the L(S) series. Aporphines unsubstituted or monosubstituted in ring D can belong to either the L(S) or the D(R) series."¹ No mention has been made, however, about substitution at both C-8 and C-9. There is presently only one naturally occurring aporphine incorporating this pattern, which is crebanine (1,2-methylenedioxy-8,9-dimethoxyaporphine). The isolation of crebanine from Stephania capitata and S. sasakii (Menispermaceae) had been originally reported some forty years ago, at which time the specific rotation in chloroform had been recorded as -56° or -57.5° .² In 1969, the reisolation of crebanine from S. sasakii was reported, and the specific rotation was determined to be -61° ($c = 0.44$, CHCl_3).³ In view of the fact that the sign of the specific rotation in the aporphine series is diagnostic of the chirality,⁴ the negative value for crebanine pointed to the D(R) absolute configuration.

Very recently, as part of a general screening of the flora of Thailand for alkaloids, we have been able to reisolate this relatively rare aporphine base from Stephania venosa Spreng. The CDCl_3 nmr spectrum at 60 MHz, which had never been recorded previously, shows an N-methyl singlet at $\delta 2.55$, two O-methyl singlets at 3.75 and 3.82, and a methylenedioxy doublet of doublets at 5.82 and 5.98 ($J = 2$ Hz). A singlet at 6.45 represents H-3, while a doublet of doublets at 6.80 and 7.75 ($J = 8$ Hz) is due to H-10 and 11, respectively.

To settle conclusively the absolute configuration of crebanine, its specific rotation was measured in three different solvents, and in each case the value was found to be definitely negative. The values recorded were $[\alpha]_D^{25} -64.2^\circ$ ($c = 0.45$, MeOH), $[\alpha]_D^{25} -67.5^\circ$ ($c = 1.05$, CHCl_3), and $[\alpha]_D^{25} -64.8^\circ$ ($c = 1.36$, CH_3CN); pointing again to the D(R) rather than the L(S) configuration.

For further confirmation of these results, the circular dichroism spectrum of crebanine in methanol was recorded, and the following $\Delta\epsilon_{\text{nm}}$ values were determined: $+14.47_{275}$, -56.28_{237} , and $+28.94_{216}$. The strong negative Cotton effect in the short wave length region which shows a trough at 237 nm is another strong proof for the D(R) absolute configuration.⁵



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References and Footnotes

1. M. Shamma and J.L. Moniot, Isoquinoline Alkaloids Research 1972-1977, Plenum Press, New York (1978), p. 146. Since several biogenetic rules have their exceptions, it is a substantiated fact that dicentrine, which is a 1,2,9,10-tetrasubstituted aporphine occurs in both the dextro and the levo forms.
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3. J. Kunitomo, Y. Okamoto, E. Yuge and Y. Nagai, J. Pharm. Soc. Japan, **89**, 1691 (1969).
4. K.W. Bentley and H.M.E. Caldwell, J. Chem. Soc., 3252 (1955).
5. J.C. Craig and S.K. Roy, Tetrahedron, **21**, 395 (1965).

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