

THE STRUCTURE OF HETEROPHYLLOIDINE AND PANICUTINE

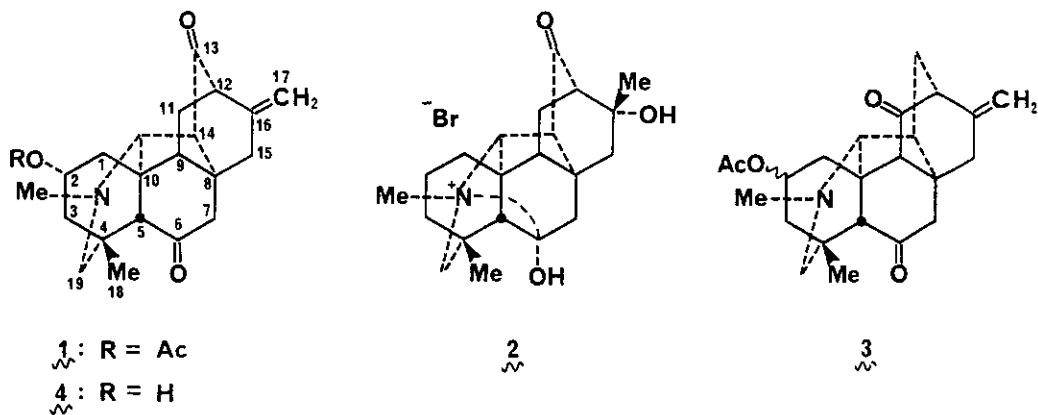
S. William Pelletier*, Balawant S. Joshi, Haridutt K. Desai, and Al Panu
 Institute for Natural Products Research and the Chemistry Department
 University of Georgia, Athens, Georgia 30602, U.S.A.

Alfred Katz*

Laboratorium der Holbein-Apotheke, Oberwilerstrasse 7
 CH-4054 Basel, Switzerland

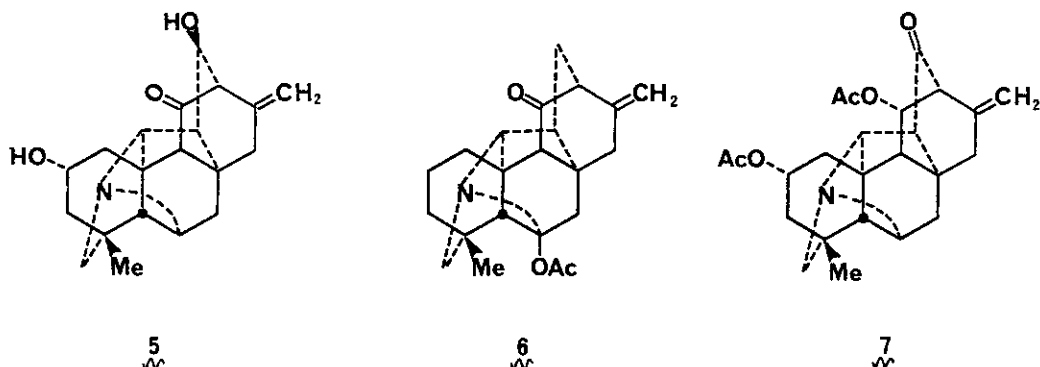
Abstract - Heterophylloidine (*Aconitum heterophylloides* Stapf) and panicutine (*A. paniculatum* Lam.) have been shown to be identical. CD measurements on derivatives of heterophylloidine and hetisine indicate that the keto groups in panicutine must be located at C(6), C(13) and not at C(6), C(11) as previously reported. The structure of panicutine is therefore **1**, as proposed earlier for heterophylloidine.

An amorphous diterpenoid alkaloid, heterophylloidine (**1**, $[\alpha]_D^{24} -82.0^\circ$ in CHCl_3), was reported in 1981 from the Indian plant *Aconitum heterophylloides* Stapf.¹ The ^1H and ^{13}C nmr spectra exhibited features characteristic of atisine-type alkaloids. On the basis of nmr data and an X-ray analysis of a bromine derivative (**2**), the structure and absolute configuration was assigned to heterophylloidine (**1**). Later Katz and Staehelin², unaware of the publication on heterophylloidine, described the isolation of an alkaloid panicutine from the European species *Aconitum paniculatum* Lam. (mp 160-165°C; $[\alpha]_D^{26} -141.1^\circ$ in CHCl_3). They assigned structure **3** from the uv, mass, ^1H and ^{13}C nmr spectra. This structure differs from that of heterophylloidine (**1**) in locating one of the keto groups at C(11) rather than C(13) and leaves the stereochemistry at C(2) undecided. At this point alkaloids heterophylloidine (**1**) and panicutine (**3**) appeared to be different. However, the ^{13}C nmr spectra reported for the two compounds are practically identical.



Although the X-ray analysis of heterophylloidine (1) may be considered unambiguous proof of structure, the possibility of a deep-seated rearrangement occurring during formation of the bromine derivative (2) could not be excluded. On the other hand, the arguments for assigning structure 3 to panicutine appeared sound. Considering the small quantity of each alkaloid available, the authors decided in this contradictory situation to cooperate in gathering additional experimental evidence about the two samples.

The alkaline hydrolysis product (4) of heterophylloidine and of panicutine have been found to be identical (tlc, mp, mmp, ir). Although heterophylloidine was originally reported to be amorphous, we have now obtained it crystalline, mp 159-161°C, cor., by purification on an alumina rotor of a "Chromatotron".³ The two alkaloids were also shown to be identical by tlc behavior and ir spectra. Since panicutine and heterophylloidine are identical, the earlier name heterophylloidine, should now be used. Aside from the unassigned stereochemistry of the C(2) acetoxy group in panicutine, the assigned structures differ in locating a keto group at C(11) in panicutine and at C(13) in heterophylloidine. The choice between these two structures was settled by application of CD measurements.⁴



CD measurements in methanol (Fig. 1) of 11-ketohetisine (5) and spiradine A acetate (6)⁵, as anticipated, show a positive Cotton effect for each compound. The 11-keto group contributes strongly to the positive Cotton effect. In contrast to the behavior of compounds 5 and 6, deacetylheterophylloidine (4) exhibits a strong negative Cotton effect (Fig. 1).⁶ On addition of HCl, the CD curve showed a negative Cotton effect with slightly lower amplitude, owing to loss of the contribution by the 6-keto group. Model compound 2,11-diacetyl-13-ketohetisine (7) also shows a strong negative Cotton effect. Clearly, the keto group in question in heterophylloidine (panicutine) is at C(13) (structure 1), rather than at C(11) (structure 3) as previously reported.¹

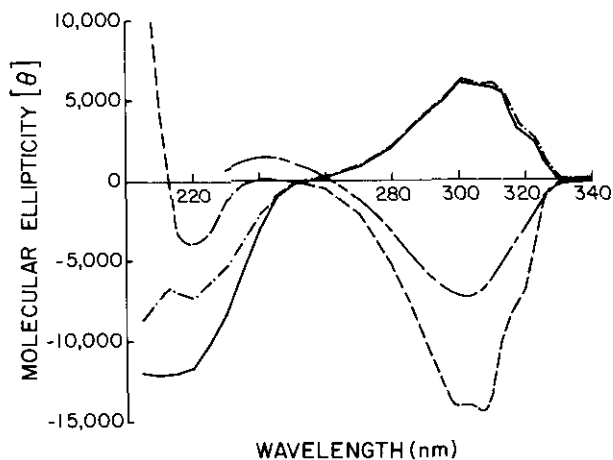


Figure 1. CD Curves: — Deacetylhetrophyllidine (4);
 - - - 2,11-Diacetyl-13-ketohetisine (7); — Spiradine
 A acetate (6); - · - · 11-Ketohetisine (5).

ACKNOWLEDGEMENT

We are grateful to Dr. P. Moser, CIBA-GEIGY Ltd, Basle for the ORD-CD measurements on compounds 5, 6 and 7.

REFERENCES

1. S. W. Pelletier, N. V. Mody, J. Finer-Moore, H. K. Desai and H. S. Puri, *Tetrahedron Lett.*, 1981, 22, 313.
2. A. Katz and E. Staehelin, *Helv. Chim. Acta*, 1982, 65, 286.
3. H. K. Desai, B. S. Joshi, A. M. Panu and S. W. Pelletier, *J. Chromatography*, 1985, 322, 223.
4. P. Crabbe, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden Day, San Francisco, 1965.
5. G. Goto, K. Sasaki, N. Sakabe and Y. Hirata, *Tetrahedron Lett.*, 1968, 1369; K. Sasaki, N. Sakabe and Y. Hirata, *J. Chem. Soc., Perkin I*, 1971, 324.
6. In a letter to A. Katz of March 25, 1985, Dr. X. T. Liang reports the CD curve for panicutine as negative ($\Delta\epsilon$ ca. -2.9 at 301 nm) and concludes that the keto group is located at C(13).
7. CD measurements were also obtained for 2,11-diketohetisine ($[\theta]_{330} +97.5$, $[\theta]_{310} +6955$, $[\theta]_{300} +6955$, $[\theta]_{260} +130$, $[\theta]_{213} -11472.5$) and 2-ketohetisine ($[\theta]_{320} -32.7$, $[\theta]_{287.5} -294.3$, $[\theta]_{255} -65.4$, $[\theta]_{225} -1798.5$, $[\theta]_{220} -1700.4$, $[\theta]_{210} +1863.9$). The 2-keto group in 2-ketohetisine exhibits only a small negative Cotton effect.

Received, 27th December, 1985