

CRYSTAL AND MOLECULAR STRUCTURE OF LYCORINE-CHLOROHYDRIN:
REVISION OF THE STEREOCHEMISTRY

Jun Toda and Takehiro Sano

Showa College of Pharmaceutical Sciences, Setagaya-ku, Tokyo 154, Japan

Yoshisuke Tsuda* and Miyuki Kaneda

Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa 920, Japan

Yoichi Iitaka

Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo 113, Japan

Action of POCl_3 and HCl on 1-O-acetyllycorine gave, quantitatively, O-acetyllycorine-chlorohydrin, which was convertible, in good yield, to lycorene- α -oxide and so-called lycorine-*cis*-chlorohydrin. The configuration of the latter compound was revised establishing as *trans* by a single crystal X-ray analysis.

So-called lycorine-*cis*-chlorohydrin was first prepared by Takeda et al¹⁾ by action of POCl_3 and HCl on lycorine (I). The proposed *cis*-configuration (IIa) of the chlorohydrin moiety was supported by Wildman²⁾ from the observation of an intramolecular hydrogen bonding between the hydroxyl group and the chlorine atom. Although its yield from lycorine was low (~10%) because of major path of dehydration to anhydrolycorinium chloride (III) (~70%), the compound is particularly important as a synthetic precursor of lycorene- α -oxide (IV)²⁾, a key intermediate in synthesizing various lycorine congeners including stereospecifically labelled compound such as [2β -³H]caranine (V)²⁻⁴⁾ (see Chart 1).

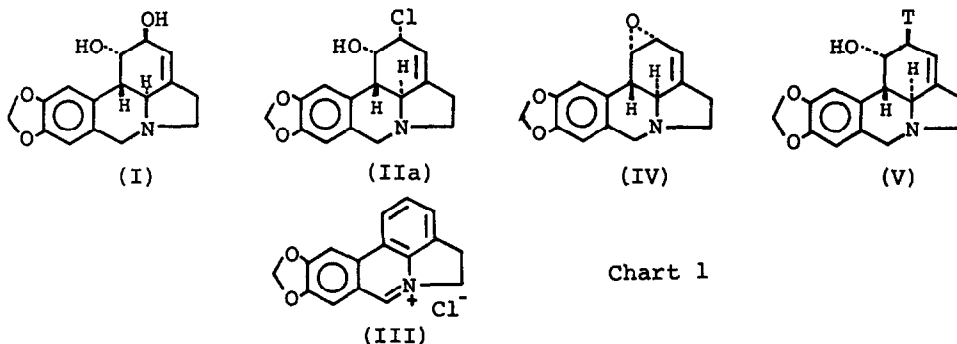
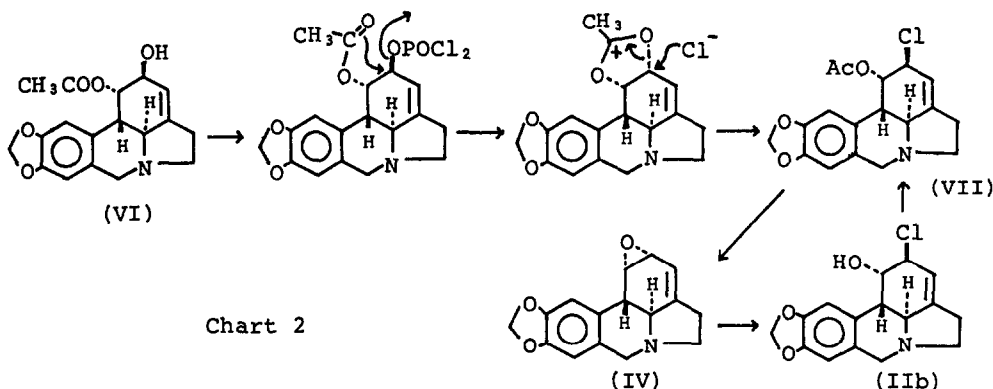


Chart 1

We found that 1-O-acetyllycorine (VI)⁵⁾, on the same treatment with POCl_3 and HCl gave, in almost quantitative yield, a chlorohydrin-acetate (VII), m.p. 185-187° (IR: 1745 cm^{-1}), which on treatment with NaOMe at 0° for short time (20 min.) furnished the α -oxide (IV), m.p. 152-154°, in 62% yield. Action of dry HCl on the α -oxide (IV) in CHCl_3 afforded a compound, m.p. 150° (decomp.) identical with the above *cis*-chlorohydrin (m.p., TLC, and IR comparisons), which

regenerated the acetate (VII) (m.p., TLC, IR, and NMR comparisons) on acetylation with pyridine and acetic anhydride. The sequence of these reactions and the mechanistic consideration that the chlorohydrin-acetate may be formed through the pathway shown in Chart 2 suggest, contrary to the previous proposal, that the chlorohydrin has *trans*-configuration (IIb).



Difinite conclusion was, however, still required since the chlorine atom is at a labile allylic position.

Conclusive evidence, confirming our revised assignment of the stereochemistry, was obtained from X-ray crystallography of the chlorohydrin.

Lycorine-chlorohydrin, when crystallized from ether, formed orthorhombic crystals of space group $P2_12_12_1$ with $a=13.867$, $b=10.822$, $c=9.339$ Å and $Z=4$. The intensity data were collected on a Philips PW-1100 diffractometer using graphite-monochromated Cu-K α radiation. The structure was solved by direct methods using the MULTAN program⁶⁾. Block-diagonal least-squares refinement of positional and

thermal parameters reduced R to 0.082 for 915 observed reflections. The resulting structure was shown in the Figure, which rigidly established *trans*-configuration of the chlorohydrin moiety in lycorine-chlorohydrin, hence supporting our mechanistic consideration of the formation of the chlorohydrin-acetate from 1-O-acetyllycorine.

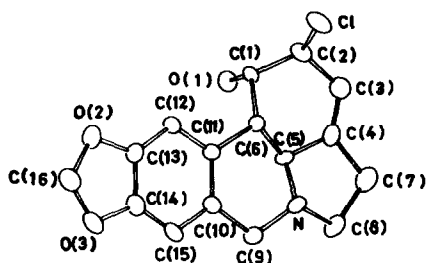


Figure. A computer-generated perspective drawing of lycorine-chlorohydrin

REFERENCES

- 1) K. Takeda, K. Kotera and S. Mizukami, *J. Am. Chem. Soc.*, **80**, 2562 (1958).
- 2) W. C. Wildman and N. E. Heimer, *J. Am. Chem. Soc.*, **89**, 5265 (1967).
- 3) C. Fuganti and M. Mazza, *J. C. S. Chem. Comm.*, **1972**, 936.
- 4) I. T. Bruce and G. W. Kirby, *J. C. S. Chem. Comm.*, **1968**, 207.
- 5) S. Uyeo, Y. Nakagawa and H. Yajima, *Chemistry and Industry*, **1956**, 1238.
- 6) G. Germain, P. Main and M. M. Woolfson, *Acta Cryst.*, **A27**, 368 (1971).

(Received in Japan 15 October 1979)