X-Ray Crystal Structure and Configuration of Enhydrin Bromohydrin

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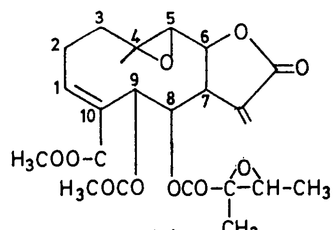
Summary An X-ray study has shown that $C_{23}H_{29}O_{10}Br$ is a germacronolide sesquiterpene lactone having a *cis* stereochemistry at the double bond C-1–C-10, and an epoxide ring at positions C-4,C-5 which has a *trans* configuration; enhydrin thus falls into group 2 of the classification recently proposed by Neidle and Rogers.[1]

The sesquiterpene lactone named enhydrin was first isolated from *Enhydra fluctuans*[2] a herb which has been used for the treatment of skin diseases and nervous ailments, and also as a laxative.[3] The gross structure (I)† of enhydrin was reported[4] on the basis of degradative and spectroscopic evidence.†

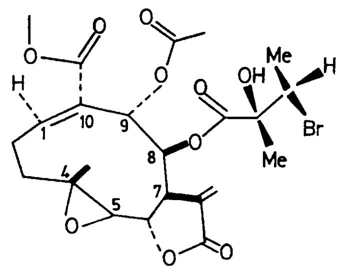


(I)

An X-ray study was undertaken to determine the detailed configuration of the enhydrin molecule and to make use of the assignment of groups at C-8 and C-9. X-ray crystallographic studies were made on the bromohydrin obtained by reaction of enhydrin with 40% HBr in methanol, which reaction opened the epoxide ring of the side chain.

Crystals of enhydrin bromohydrin $C_{23}H_{29}O_{10}Br$ are orthorhombic and have a space group $P2_12_12_1$, $a = 10{\cdot}08$, $b = 26{\cdot}97$, $c = 8{\cdot}94$ Å and $Z = 4$. Intensity data were collected manually on a diffractometer with Cu-K_α radiation to a Bragg angle of 75°, using the stationary-crystal stationary-counter method and balanced Ni and Co filter pairs. Of the 2957 reflections measured, 2474 were considered observed. The structure was solved by direct methods[6,7] and refined by block-diagonal least-squares to an R value of 0·148, the bromine atom alone being ascribed anisotropic thermal parameters.

A view of the molecule and the stereochemistry of bromo-



(II)

Table. *Torsional angles about the bonds in the ten-membered ring*

C-1–C-2–C-3–C-4	+75°	C-6–C-7–C-8–C-9	−63°
C-2–C-3–C-4–C-5	−92°	C-7–C-8–C-9–C-10	−56°
C-3–C-4–C-5–C-6	+147°	C-8–C-9–C-10–C-1	+132°
C-4–C-5–C-6–C-7	−119°	C-9–C-10–C-1–C-2	+13°
C-5–C-6–C-7–C-8	+95°	C-10–C-1–C-2–C-3	−97°

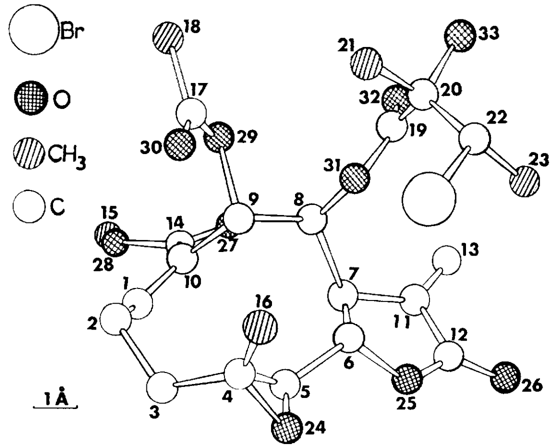


Figure. *The bromohydrin enhydrin molecule viewed approximately normal to the macrocycle.*

† Drawn according to the convention of Rogers *et al.*[5]

enhydrin (II)† is shown in the Figure. The general features agree with those suggested by Joshi *et al.*[4] and confirm the assignment of the acetyl and α-methyl-α,β-epoxy-butyl group group at positions C-8 and C-9 of the ring respectively. The occupancy of *cis* and *trans* configurations within the ring make the ten-membered macrocycle very distorted. The torsion angles[8] about the bonds in this ring (Table) show that the epoxide ring at position C-4,C-5 is *trans* fused whereas the double bond C-1–C-10 has a *cis* stereochemistry. Thus enhydrin falls in the group 2 classification of Neidle[1] *et al.*, and in this respect resembles melampodin, the only germacronolide with this pattern of endocyclic double bond previously studied by *X*-ray diffraction. As in melampodin whose stereochemistry it resembles closely, it is seen that C-14 and C-16 are *anti* with respect to the plane of macrocycle. The relative configurations about the asymmetric atoms are 4*R*, 5*R*, 6*S*, 7*S*, 8*S*, 9*S*, 20*S*, and 22*S*. We plan to determine the absolute configuration using anomalous scattering from the bromine atom.

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