

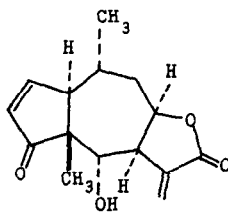
TRANSFORMATIONS OF HELENALIN : CRYSTAL STRUCTURE ANALYSIS OF THE OXIDE FROM THE
REACTION WITH HYDROGEN CHLORIDE

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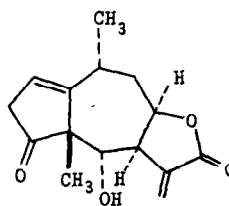
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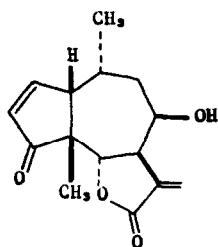
During the course of the recent re-investigations¹ on the reactions of helenalin(I) with hydrogen chloride-chloroform and deactivated neutral alumina a new crystalline oxide having composition $C_{15}H_{18}O_4$ was obtained in addition to the known mexicanin A(II) and 1-epiallohelenalin(III). In contrast to earlier reports²⁻⁴, no neohelenalin(IV) was found to be produced under these conditions. Structures (V) and (VI) were postulated for this new compound with the former being favored on the basis of reactions and spectra but definite structure proof was not obtained. Since the structure and stereochemistry of the oxide bear on the mechanism of transformations between the above compounds, we have subjected it to single crystal X-ray analysis in order to define its constitution unambiguously.



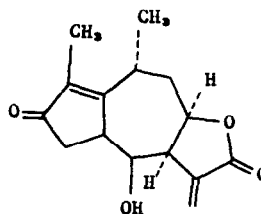
(I)



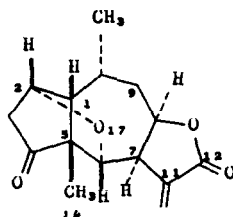
(II)



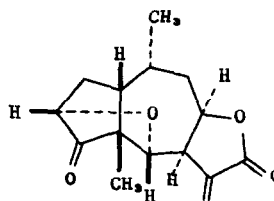
(III)



(IV)



(V)

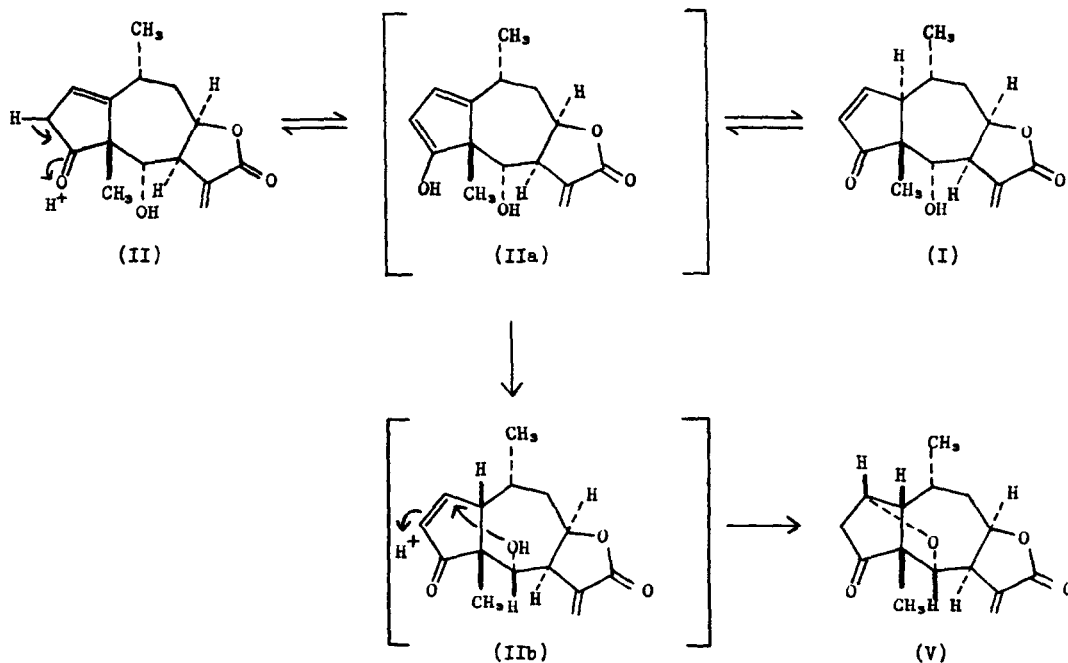


(VI)

The oxide crystallizes in the orthorhombic system, space group $P2_12_12_1$, $a = 8.57(1)$, $b = 15.79(2)$, $c = 9.95(1)$ Å, $Z = 4$. The structure was solved by direct phase-determining methods using MULTAN⁵ and 29⁴ $|E|$ values ≥ 1.2 . Full-matrix least-squares refinement of the molecular parameters (hydrogen atoms not included) has produced a current R of 0.13 over 1303 independent observed reflexions from photographic data.

The X-ray analysis proves that (V) correctly represents the structure and stereochemistry for the oxide. In addition, since helenalin(I) was also obtained from the reaction of (II) with $HCl-CHCl_3-Al_2O_3$, the result of this study provides some insight into the probable mechanism of formation of (I) and (V) from the common precursor (II) through the postulated intermediate (IIa) as shown in the scheme below.

In (V) the cycloheptane ring adopts a conformation which is intermediate between a twist-chair(C_2) and chair(C_s) forms^{6,7} and characterized by torsion angles $\theta_{1,5} = -78^\circ$, $\theta_{5,6} = 89^\circ$, $\theta_{6,7} = -52^\circ$, $\theta_{7,8} = -23^\circ$, $\theta_{8,9} = 65^\circ$, $\theta_{9,10} = -66^\circ$, $\theta_{1,10} = 68^\circ$, and with intramolecular non-bonded separations $C_{11} \dots C_{14} = 3.25$ and $C_9 \dots O_{17} = 2.96$ Å. Formation of (V) from (II) via (IIa)



and (IIb) may be rationalized nicely if (IIb) and (V) are assumed to adopt similar conformations i.e. a distorted C_7 twist-chair⁸ which has C_2 and the OH group 1,3-diaxially oriented. Indeed, non-bonded repulsive interactions between the C_{14} methyl and C_{11}, C_{12} of the γ -lactone ring, and between the C_9 -aH and the OH group will serve to decrease the $C_2 \dots OH$ distance in (IIb) and thus facilitate ring closure to give product (V).

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References and Footnotes

1. K. H. Lee, H. Furukawa, S. H. Kim, and C. Piantadosi, J. Pharm. Sci., 62, 987 (1973).
2. W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, J. Amer. Chem. Soc., 85, 19 (1963).
3. W. Herz, M. V. Lakshmikantham, and R. N. Mirrington, Tetrahedron, 22, 1709 (1966).
4. A. Romo de Vivar, L. Rodriguez-Hahn, J. Romo, M. V. Lakshmikantham, R. N. Mirrington, J. Kagan, and W. Herz, Tetrahedron, 22, 3279 (1966).
5. G. Germain, P. Main, and M. M. Woolfson, Acta Cryst., A27, 368 (1971).
6. J. B. Hendrickson, Tetrahedron, 19, 1387 (1963).
7. A. T. McPhail and G. A. Sim, Tetrahedron, 29, 1751 (1973).
8. C_7 is the unique axis carbon atom which lies on the approximate C_2 axis of the distorted twist-chair cycloheptane conformer.