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THE STRUCTURE OF GLOBICIN

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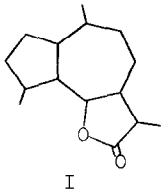
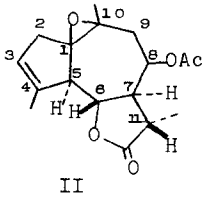
PARTIAL structure I has been forwarded[1] for globicin, a crystalline sesquiterpenoid from Matricaria globifera. We wish to present further evidence, which has led to structure II for globicin.



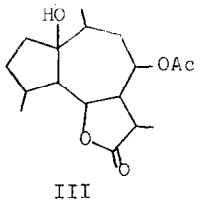
-OAc
-O-
Double bond

I

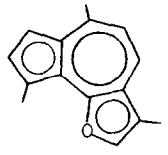


II

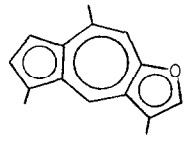
Globicin takes up two moles of hydrogen in acetic acid with Adams' catalyst, giving III[2], which is clearly a tertiary alcohol (resistance to oxidation and acetylation). III was reduced to an oxidodiol which gave a 3:1 mixture of artemazulene (IV) and linderazulene (V) on dehydrogenation, showing the presence of oxygen functions at C_6 and C_8 in globicin.



III



IV



V

[1] Z. Čekan, V. Procházka, V. Herout and F. Šorm, Coll. Czech. Chem. Comm., 25, 2553 (1960).

[2] This structure is favored over the alternative with the hydroxyl group at C_{11} for reasons which, since they are involved and irrelevant to the arguments given herein for the structure of globicin, will be deferred until the detailed report of this study.

To establish the position of the γ-lactone ring, III was selectively saponified and the resulting dihydroxylactone (which could be reconverted to III with acetic anhydride and pyridine, showing that the direction of lactonization had not changed) oxidized to a hydroxyketolactone (ketone carbonyl at 1720 cm.$^{-1}$). The ketone carbonyl was converted to a methylene group *via* the thioketal, and lithium aluminum hydride reduction of the hydroxylactone followed by selenium dehydrogenation of the triol gave only IV, showing the lactone and acetoxyl functions to be located as in II.

The NMR spectrum of globicin (Figure 1) was examined using the double resonance technique[3] to clarify coupling patterns; the positions of the double bond and oxide ring were apparent from this spectral study. A key feature was the eight-line absorption pattern for the proton at C_8, indicating strong coupling with three nearby protons, and thus the presence of two protons at C_9; the double bond, which bears one proton (4.45 τ) and one methyl group (8.07 τ), can then only be between C_3 and C_4. This is supported by the production of iodoform from globicin on successive treatment with osmium tetroxide, periodate, and hypoiodite. The oxide bridge must be between two tertiary carbons, since there is no absorption below 7 τ other than that for the protons on C_3, C_6, and C_8. Carbons 5, 6, 7, 8, and 11 each clearly bear one hydrogen, and globicin must be a 1,10-epoxide.

The relative configurations shown for globicin (II) are tentatively forwarded on the basis of the large coupling constants observed between the protons at C_5 and C_6 (10 cps), C_6 and C_7 (10 cps), and C_7 and C_{11} (11 cps). These relatively large values for vicinal protons suggest dihedral angles of close to 0° (*cis* arrangements with protons held in an

[3] F. Bloch, *Phys. Rev.*, 102, 104 (1956).

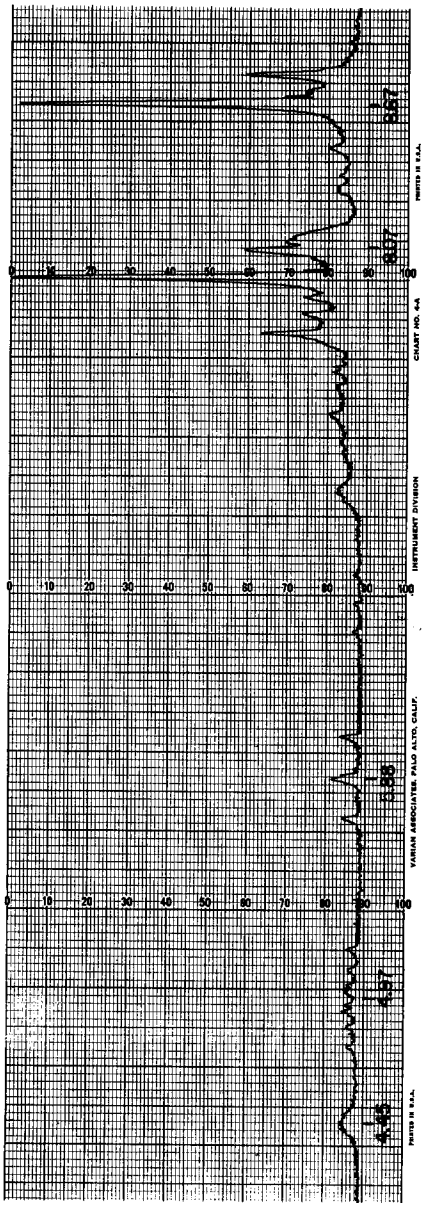


Figure 1. NMR spectrum of globicin at 60 Mc. in $DCCl_3$, with chemical shifts in τ units.

eclipsed conformation[4,5] or 150-180° (*trans* arrangements of the protons[5]). After examination of Dreiding models of the globicin stereoisomers, it is clear that C_5-C_6 *cis*, C_6-C_7 *cis* stereoisomers could not have the observed coupling constants and can definitely be excluded, and is evident that the relative configurations shown in II (in which the critical dihedral angles are 150-180°) are the most probable.

The absolute configurations shown are favored on biogenetic grounds: practically all of the sesquiterpenoids of known configuration at their carbon corresponding to C_7 in II have this configuration.[6,7]

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[4]F. A. L. Anet, *Can. J. Chem.* 39, 789 (1961); A. Hassner and M. J. Michelson, *J. Org. Chem.* 27, 3974 (1962).

[5]M. Karplus, *J. Chem. Phys.* 30, 11 (1959); H. Conroy in *Advances in Organic Chemistry* Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p. 311.

[6]M. Sumi, *J. Am. Chem. Soc.* 80, 4867 (1958); R. B. Bates, G. Büchi, T. Matsuura, and R. R. Schaffer, *ibid.* 82, 2332 (1960); V. Herout, M. Suchý, and F. Sorm, *Coll. Czech. Chem. Comm.* 26, 2615 (1961); R. B. Bates and R. C. Slagel, *Chem. and Ind.* 1715 (1962).

[7]This work was supported in part by the U. S. Public Health Service.