Tetrahedron Letters No. 48, pp 4609 - 4612. 0040-4039/79/1122-4609$02.00/0

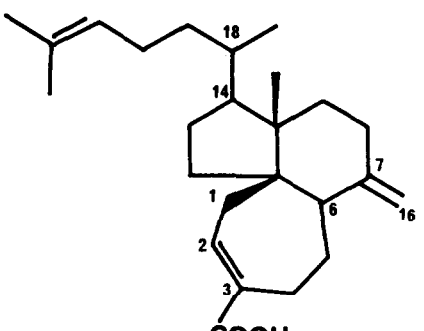
THE STRUCTURE OF GASCARDIC ACID FROM AN X-RAY DIFFRACTION STUDY

Robert K. Boeckman Jr.*,[1] and David M. Blum
Department of Chemistry, Wayne State University
Detroit, MI 48202

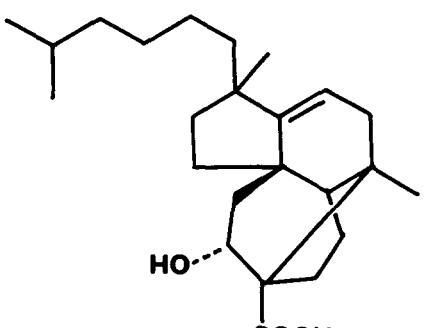
Edward V. Arnold and Jon Clardy*
Department of Chemistry, Cornell University
Ithaca, NY 14853

Summary: The complete structure of the unique tricyclic sesterterpene gascardic acid is proposed based on a single crystal x-ray diffraction analysis of the dicyclohexylammonium salt.

While the number of known sesterterpenes (C_{25} terpenes) is slowly increasing, they remain the rarest and least well understood class of terpenoid natural products. The sesterterpenes encompass a number of unique carbon skeletons, ring sizes and stereochemical relationships which have provided considerable challenges in structure elucidation and biosynthetic interpretation.[2] Gascardic acid, a lac acid isolated in the late 1950's,[3] was the subject of intensive scrutiny by Polonsky, Arigoni and their collaborators and these efforts resulted in expression 1.[3,4]



1



2

These studies clearly elucidated the gross structure of gascardic acid and the cis relationship of the central hydrindane ring fusion. The stereochemistry at C-6, the remaining ring junction center, could not be established. There was an acid catalyzed cyclization of 1 to 2 and the structure of 2 was established by spectroscopic means.[4] However, as pointed out by these authors, the mechanism of interconversion was such that a firm structural relationship could not be established. The remaining two centers, C-14 and C-18, were not assigned stereochemistries.

In view of the unique polycyclic system which is present in gascardic acid we undertook structural and synthetic studies aimed at establishing the complete stereostructure of this substance.[5] Gascardic acid itself did not crystallize in a form suitable for x-ray analysis and we wished to minimize chemical interconversions in our search for a useful derivative. After some experimentation it was found that the dicyclohexylammonium salt could be utilized. A suitable crystal of this derivative was grown from CH_2Cl_2-heptane solution. Preliminary x-ray photographs indicated the monoclinic crystal system and accurate lattice parameters of $a = 12.051(2)$, $b = 9.383(1)$, $c = 15.333(3)$ Å and $\beta = 97.48(1)°$ were obtained. Systematic extinctions were consistent with space group $P2_1$ and density considerations suggested one unit of composition $C_{25}H_{37}O_2 \cdot C_{12}H_{24}N$ per asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were measured on a four-circle diffractometer using graphite monochromated CuKα radiation (1.54178 Å) and a variable speed, 1° ω-scan technique. Of the 2631 reflections surveyed in this manner, 2479 (94%) were judged observed after correction for Lorentz, polarization and background effects. The structure was solved using a multisolution weighted tangent formula approach with five reflections from the centrosymmetric hOl zone and two general reflections as variable starting phases.[6] The most consistent set from this treatment gave an E-synthesis which revealed two plausible fragments with 30 of the 40 nonhydrogen atoms in the asymmetric unit. The structure was completed by electron density syntheses and full-matrix least-squares refinements with anisotropic nonhydrogen atoms and isotropic hydrogens. The standard crystallographic residual is 0.064 for the observed data.[7] This x-ray analysis defines only the relative stereostructure of gascardic acid.

Fig 1 is a computer generated perspective drawing of the final x-ray model. As can be seen the gross structure postulated by the original workers is fully verified and the complete stereochemistry is now that shown in 3. The hydrindane fusion is indeed cis as was expected from the degradative studies. The centers at C-14, C-6 and C-18 have the configurations shown.

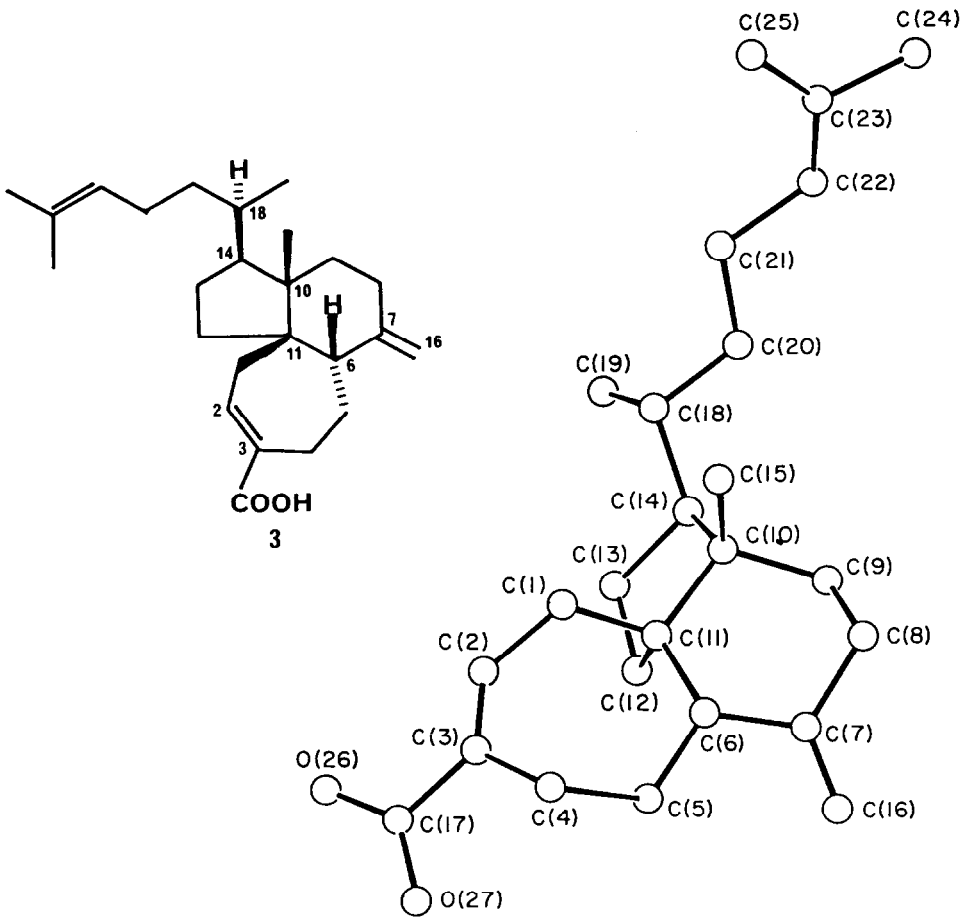


Figure 1. A computer generated perspective drawing of the final x-ray model of gascardic acid. Hydrogen atoms are omitted and the enantiomer choice is arbitrary. A conventional representation is shown in the upper left hand corner.

The six membered ring exists in a chair conformation with the seven membered ring fused in a trans fashion. The five membered ring is fused in a cis axial-equatorial manner to the cyclohexane ring with the axial branch emanating from the carbon common to all three rings (C-11). The seven membered ring is in a chair conformation with the unsaturation forming the 0° dihedral bond. The five membered ring is an envelope with C-12 serving as the flap. This conformation results in the relief of a severe nonbonded interaction between C-1 and C-18 present in alternative envelope forms. Surprisingly, the molecule adopts the apparently more encumbered hydrindane conformation in which the majority of the ring branches are equatorial about the cyclohexane ring.

The result of the x-ray analysis allows the mechanism of formation of cyclization product 2 to be specified. The epimerization at C-6 required to permit formation of 2 most plausibly arises by acid catalyzed migration of the C7-C16 double bond to C6-C7, followed by reprotonation from the β face regenerating the C-7 carbonium ion which is subsequently trapped by the unsaturation at C2-C3. This possibility was explicitly recognized by the original workers.[4]

A biogenetic model can now be suggested to accommodate the C-6, C-14 and C-18 stereochemistries. This involves cyclization of the geranyl-farnesyl pyrophosphate from a compact polyene conformation during formation of the C10-C14 and C6-C11 bonds rather than more extended conformations which can be formulated.

Acknowledgement. We wish to thank Professor D. Arigoni for encouraging us in this study, for a sample of gascardic acid and for reference 4. We also benefited from discussions with Professor A. Kende. This work was supported by NIH grants GM-25982 (RKB) and CA-24487 (JC).

NOTES AND REFERENCES

1. Fellow of the Alfred P. Sloan Foundation (1976-1980) and NIH Career Development Awardee (1976-1981) (CA 00273).

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5. R.K. Boeckman, Jr., D.M. Blum and S.D. Arthur, J. Am. Chem. Soc., 101, 5060 (1979).

6. All crystallographic calculations were done on a Prime 400 computer, operated by the Materials Science Center, Cornell University. The principal programs used were: REDUCE and UNIQUE, data reduction programs, M.E. Leonowicz, Cornell University, 1978; BLS, block diagonal least squares refinement, K. Hirotsu, Cornell University, 1978; ORFLS (modified), full matrix least squares, W.R. Busing, K.O. Martin and H.S. Levy, Oak Ridge, ORNL-TM305; ORTEP, crystallographic illustration program, C. Johnson, Oak Ridge, ORNL 3795; BOND, structural parameters and errors, K. Hirotsu, Cornell University, 1978; MULTAN-76, direct methods and fast fourier transform, G. Germain, P. Main and M. Woolfson, University of York.

7. A table of fractional coordinates and temperature factors for gascardic acid is available from the director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, and from Prof. Clardy.

(Received in USA 15 August 1979)