Tetrahedron Letters,Vol.24,No.24,pp 2441-2444,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

PHENYLCAMPHORIC ACID: STEREOCHEMISTRY AND EPIMERIZATION

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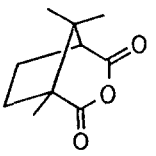
Abstract: Since it was first prepared in 1894, phenylcamphoric acid has been assigned a variety of structures and configurations. We have been led to revise the presently accepted stereochemistry on the basis of difference NOE experiments. Our new assignment is confirmed by x-ray crystallography. Base treatment of methyl phenylcamphorate results in equilibration with its previously unknown epimer, methyl epiphenylcamphorate.

When Bürcker first reported that camphoric anhydride (1) reacts with aluminum chloride and benzene to produce the monobasic phenylcamphoric acid, he assigned the entirely plausible structure **2** to this product.[1]



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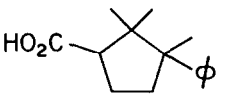

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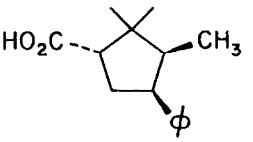
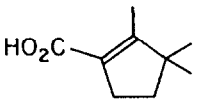


3

This assignment was revised to 3 on the basis of a variety of arguments, and an "isomeric" acid similarly derived from isolaurolonic acid (**4**) and originally considered to have structure **5**,[2] was assigned the structure and all cis configuration **6**.[3] More recently, the isolaurolonic product has been recognized to be simply the racemic form of phenylcamphoric acid.[4]



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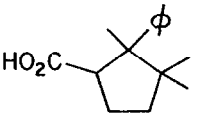

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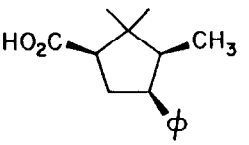
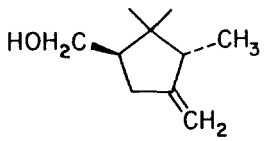


6

We became interested in phenylcamphoric acid because of the close relationship of its postulated structure and stereochemistry to that of β-necrodol (**7**), a novel terpenoid alcohol which we have recently characterized from the defensive secretion of a carrion beetle.[5] We hoped that this readily available acid might serve as a synthetic precursor of **7**.



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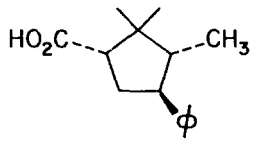

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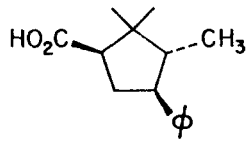

9

A sample of (+)-phenylcamphoric acid was prepared as previously described, and in order to confirm its formulation as **3**, we carried out a difference NOE experiment on the corresponding methyl ester. Surprisingly, irradiation of the methine proton α- to the methyl group resulted in a dramatic enhancement of intensity of the methine proton α- to the methoxycarbonyl substituent, indicating a cis relationship between these two groups. The stereochemistry of phenylcamphoric acid must therefore be that shown in formula **8**. (Earlier evidence required a trans relationship between the carboxyl and phenyl substituents, so that it is the relative configuration of the methyl group that requires revision.)

To confirm this assignment, we have carried out a single-crystal x-ray diffraction study on methyl phenylcamphorate. This study supports our NMR analysis, and yielded the stereochemistry shown in Fig. 1 for **8**. [6]

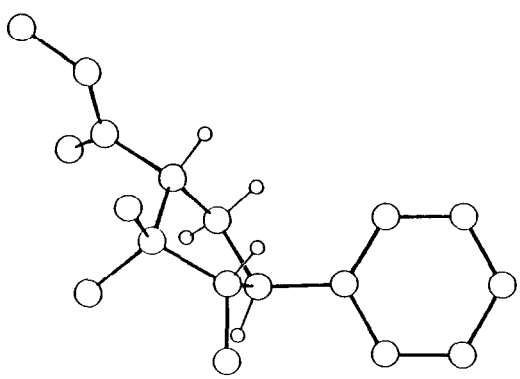

Figure 1. Structure of methyl phenylcamphorate.

Preliminary x-ray photographs displayed monoclinic symmetry and lattice constants of a=7.778 (2), b=6.277 (1), c=14.946 (3) Å and β=104.037° (2) were obtained from a least squares analysis of fifteen diffractometer measured 2θ-values. Systematic extinctions and density considerations were uniquely accommodated by space group $P2_1$ with one molecule of $C_{15}H_{22}O_2$ per asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were recorded using 1° ω-scan and graphite monochromated Cu Kα radiation (1.54178Å). After correction for Lorentz, polarization and background effects, 1115 (97%) of the 1150 reflections were considered observed ($|F_o| \geq 3\sigma|F_o|$). A phasing model was achieved by a multisolution weighted tangent formula approach and the resulting E-synthesis was interpreted without difficulty.[7] Full matrix least squares refinements with anisotropic temperature factors for carbon and oxygen and fixed isotropic temperature factors for hydrogen have converged to a final unweighted crystallographic residual of 0.048 for the observed reflections.

Although methyl phenylcamphorate does not have the desired stereochemistry for a β-necrodol synthesis, there was still the chance that the carboxyl substituent could be inverted to give the methyl ester of the previously unknown epiphenylcamphoric acid (**9**). The epimerization, reported earlier to be unsuccessful,[3b] actually occurs smoothly on refluxing a sample of the methyl ester of **8** with methanolic sodium methoxide for several days, giving a 1:1 mixture of the methyl esters of **8** and **9**. The desired methyl ester of **9** can then be isolated by preparative HPLC.[8,9] The synthesis of β-necrodol and its cis epimer from these precursors, as well as from 5-ketobornyl acetate, will be described elsewhere.

Acknowledgments: We are indebted to Dr. Braden Roach for carrying out the initial difference NOE measurements. We thank Gayle Matsumoto for invaluable help with the x-ray structure determination. Acknowledgment is given to the National Science Foundation Instrumentation Program (CHE7904825 and PCM8018643) for support of the Cornell Nuclear Magnetic Resonance Facility. Support from the NIH (grant no. AI-12020) and the Schering-Plough Corporation are acknowledged with pleasure.

References and Notes

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3. (a) J.R. Bantick and E. Rothstein, J. Chem. Soc.(C), 2512 (1971); (b) R.B. Mane and G.S. Krishna Rao, Ind. J. Chem., **12**, 932 (1974).

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5. Braden Roach, unpublished results; T. Eisner and J. Meinwald, Psyche, in press.

6. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (d, 3H), 0.76 (s, 3H), 1.16 (s, 3H), 1.66 (dq, 1H), 1.87 (ddd, 1H), 2.61 (ddd, 1H), 2.74 (ddd, 1H), 2.79 (dd, 1H), 3.68 (s, 3H), 7.21 (m, 5H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 11.69, 16.93, 27.00, 34.21, 45.30, 49.83, 51.26, 54.53, 54.89, 125.98, 127.41, 128.38, 145.77, 174.38.

7. All crystallographic calculations were performed on a PRIME 400 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were REDUCE and UNIQUE, data reduction programs, Leonowicz, M.E., Cornell University, 1978; BLS78A, anisotropic block diagonal least squares refinement, Hirotsu, K. and Arnold E., Cornell University, 1980; XRAY76, the X-ray System of Crystallographic Programs, edited by Stewart, J.M., University of Maryland, Technical Report, TR-445, March 1976; ORTEP, crystallographic illustration program, Johnson, C.K. Oak Ridge, ORNL-3794; BOND, molecular metrics program, Hirotsu, K., Cornell University, 1978; MULTAN-68, "A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data," University of York, England. Principal author P. Main. For literature description of MULTAN, see: Germain, G.; Main, P.; Woolfson, M.M.; Acta Crystallogr. Sect. B, **1970**, 26, 274-85 and Woolfson, M.M., Acta Crystallogr. Sect. A, **1977**, 33, 219-225.

8. High performance liquid chromatography was performed utilizing a Waters M6000A solvent delivery system, Rheodyne Model 7120 injection valve fitted with a 20 μL (analytical) or 100μL (semi-preparative) sample loop, Perkin Elmer Model LC-65T variable wavelength ultraviolet detector and Waters Model R401 Refractive Index detector. Analytical separation was achieved on a Supelco LC_{18} octadecyldimethylsilyl reverse phase column (5μm, 4.6mm X 25 cm) at a flow rate of 1.5 mL/min, and semi-preparative separations were achieved on a Supelco LC_{18} octadecyldimethylsilyl reverse phase column (5μm, 10mm X 25 cm) at a flow rate of 6.0 mL/min. The solvent system used was 1:1:2 water/methanol/acetonitrile, and ultraviolet detection at 254 nm was employed.

9. ^{1}H NMR of 9 (300 MHz, $CDCl_3$): δ 0.65 (d, J=6.8Hz, 3H), 0.92 (s, 3H); 0.95 (s, 3H), 1.80 (dq, J=6.8, 11.5Hz), 7.12 (m, 2H), 2.56 (m, 2H), 3.65 (s, 3H), 7.22 (m, 5H).

(Received in USA 21 March 1983)