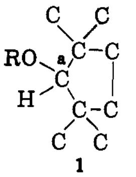
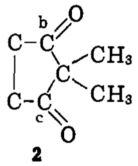


1



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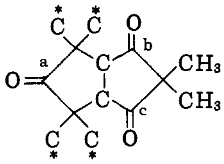

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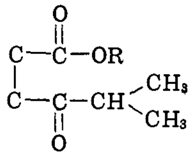
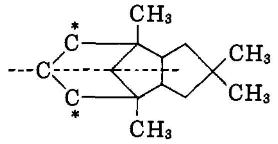


3a, R = H
b, R = CH_3



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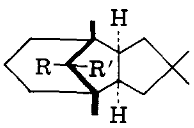

6, R = OH; R′ = H
7, R = H; R′ = OH

epi-α-alcohol (*e.g.*, benzoate, 3,5-dinitrobenzoate, nitrite) the signal for the proton attached to the oxygenated carbon (carbon a) is a singlet. The adjacent centers are therefore fully substituted (partial structure **1**, R = ester unit).

Previous work showed that α-alcohol nitrite and epi-α-alcohol nitrite are photorearranged to the same oximino alcohol, which was hydrolyzed to a keto alcohol (ν 1733 cm.$^{-1}$).[2,6] Oxidation with chromium trioxide now gave the related diketone ($C_{15}H_{22}O_2$, m.p. 98.5–99°, overlapping carbonyl bands at 1745 cm.$^{-1}$), which proved stable to hot alcoholic alkali and thereby excluded a 1,3-relationship of the two carbonyl groups. From the known structural requirements of the Barton reaction[4b] the second ketone group (carbonyl b) is in a 1,4-relationship to carbonyl a and the infrared data indicate that b is also in a 5-membered ring. To introduce a third function (carbonyl c) the keto alcohol was converted to its nitrite ($C_{15}H_{23}O_3N$, m.p. 73.5–74°), and photoisomerized in benzene. The derived keto oximino alcohol was hydrolyzed with acid to a diketo alcohol ($C_{15}H_{22}O_3$, ν 1751, 1706 cm.$^{-1}$ in CS_2, m.p. 149–149.5°) which was oxidized to the corresponding triketone ($C_{15}H_{20}O_3$, m.p. 132°, ν 1754, 1713 cm.$^{-1}$).

The following evidence establishes that carbonyls b and c are in the same ring and separated from each other by one carbon that carries two methyl groups (part structure **2**). Alkaline cleavage of the diketo alcohol gave a noncrystalline hydroxy keto acid, which was oxidized (CrO_3) to the related diketo acid ($C_{15}H_{22}O_4$, m.p. 129–130°, ν in CS_2 3400–3030, 1748, 1701 cm.$^{-1}$; methyl ester, b.p. 145–155° (0.1 mm.), ν in CS_2 1748, 1730, 1704 cm.$^{-1}$). This diketo acid (part structure **3a**) was also obtained by alkaline cleavage of the triketone. The methyl ester (**3b**) contains three enolizable hydrogens (2.49 D incorporated by treatment with sodium methoxide in methanol-*d*) and its n.m.r. spectrum indicated an isopropyl ketone unit (a six-proton doublet at δ 1.23 assigned to the *gem*-dimethyl group and a one-proton septet at δ 2.76 assigned to the adjacent methine hydrogen; $J \cong 7.5$ c.p.s.). The facts require that the fragments **1** and **2** have two atoms in common and uniquely define their mode of attachment as that illustrated for the triketone by the C_{14} fragment **4**.

The n.m.r. of all the tricyclic compounds reveal the presence of four quaternary methyl groups. In α-alcohol and epi-α-alcohol (and their esters), and in the ketone, the diketo alcohol, and the triketone two of the methyl groups are equivalent. For example, the methyl signals in α-alcohol appear as singlets at δ 0.87 (6H), 0.90 (3H), and 1.05 (3H). It follows that the 15th carbon as well as two of the starred carbons of skeleton **4** must be part of the third ring, which itself must be symmetrically disposed (as in **5**) to account for the equivalence of the bridgehead methyl groups.[7]

The two intramolecular photorearrangements that functionalize centers b and c are possible only if the five-membered rings have a *cis* fusion and have the junction hydrogens projecting away from the hydroxylated carbon bridge (**6** and **7**). The configuration of the OH group in α-alcohol (**6**) and in epi-α-alcohol (**7**) follow, from earlier findings.[2]

When commercial caryophyllene was treated in ether with D_2SO_4 the derived α-alcohol contained 2.73 D. The absorption patterns in the 1395–1360 cm.$^{-1}$ region of the infrared spectra (taken in CCl_4 or KBr) and in the δ 0.8–1.1 region of the n.m.r. spectra are identical in detail with those regions in the spectra of nondeuterated α-alcohol. These results establish the absence of the structural unit $-CH_2D$, which would have formed had α-alcohol arisen from caryophyllene. Humulene[8] is the only other constituent present in sufficient quantity to account for the α-alcohol produced.[9,10] Mechanistic studies of the cyclization and of various aspects of the nitrite photolyses are in progress.

[6] In the photorearrangement it is the α-epimer that undergoes configurational change so that the keto alcohol has its OH in the epi configuration (ref. 2).

[7] The equivalence of the two ring-junction hydrogens (singlet at δ 3.06) is also evident in the n.m.r. of the diketo alcohol.

[8] S. Dev, *Tetrahedron*, **9**, 1 (1960); V. Benesova, V. Herout, and F. Sorm, *Collection Czech. Chem. Commun.*, **26**, 1832 (1961); M. D. Sutherland and O. J. Waters, *Australian J. Chem.*, **14**, 596 (1961), and references cited there.

[9] The commercial caryophyllene ordinarily contained *ca.* 10–15% humulene and traces of several unknown components (total <5%). Typical yields of α-alcohol were 3–5%.

[10] On acid hydration of humulene S. Dev [*Current Sci.* (India), **20**, 296 (1951)] obtained an alcohol (m.p. 116°) which he suggested might be α-caryophyllene alcohol. Dr. Dev kindly sent us his compound and we confirmed its identity with α-alcohol by melting point, mixture melting point, and infrared spectral comparisons.

[11] This work was supported by The National Institutes of Health (Grant GM06304) and by the Alfred P. Sloan Foundation.

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RECEIVED FEBRUARY 1, 1964

The Structure of α-Caryophyllene Alcohol

Sir:

Discordant reports concerning α-caryophyllene alcohol[1] prompted us to reinvestigate the source and struc-

[1] Y. Asahina and T. Tsukamoto, *J. Pharm. Soc. Japan*, **484**, 463 (1922); E. Deussen, *J. prakt. Chem.*, **114**, 121 (1926); J. Bell and G. G. Henderson, *J. Chem. Soc.*, 1971 (1930); L. Ruzicka and D. T. Gibson, *Helv. Chim. Acta*, **14**, 573 (1931); D. H. R. Barton, T. Bruun, and A. S. Lindsey, *J. Chem. Soc.*, 2210 (1952); D. H. R. Barton and A. Nickon, *ibid.*, 4665 (1954).

ture of this compound. Treatment of commercial caryophyllene with sulfuric acid in ether produced variable, but always small, amounts of the crystalline alcohol together with clovene and β-caryophyllene alcohol. Since commercial caryophyllene contains up to 10% of humulene, the reported acid-catalyzed conversion[2] of humulene to a crystalline alcohol seemed to us significant.

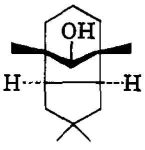
G.l.c. pure caryophyllene on treatment with concentrated sulfuric acid in ether produced no detectable amount of the α-alcohol, whereas both α- and β-humulene[3] were converted to the required alcohol in approximately 40% yield. The physical constants of this compound and its derivatives were in agreement with those reported by Nickon.[4]

The α-alcohol readily formed a *p*-bromobenzenesulfonate which was obtained from ether solution as monoclinic crystals, m.p. 147.5–148°, with cell dimensions $a = 12.65$, $b = 10.82$, $c = 16.43$ Å., $\beta = 109°13'$. There are four molecules of $C_{21}H_{29}O_3BrS$ in the unit cell and the space group is $P2_1/c$. Three-dimensional X-ray intensity data were recorded on equi-inclination Weissenberg photographs and estimated visually; in all 2100 F_o values were derived.

The coordinates of the bromine and sulfur atoms were obtained from Patterson syntheses and the remaining atoms, apart from hydrogen, were then located by evaluating successive three-dimensional electron-density distributions. Further refinement of the atomic coordinates is being continued by the method of least squares; the value of R is now 16%.

The results of the crystallographic analysis unambiguously define the constitution and stereochemistry of the alcohol to be as in I. The cyclohexane ring has the usual chair conformation with the hydroxyl group axial.

The average valency angle in the six-membered ring is 109°. In the five-membered rings, however, the average valency angle is 104°, distinctly smaller than tetrahedral and in good agreement with values reported for five-membered rings in other molecules.[5]



I

Acknowledgment.—The calculations were performed on the Glasgow University Deuce computer with programs[6] devised by Dr. J. S. Rollett and Dr. J. G. Sime. We are grateful to Prof. J. Monteath Robertson, F.R.S., and Prof. R. A. Raphael, F.R.S., for their constant interest and encouragement. We thank D.S.I.R. for a studentship (J. S. R.) and the Carnegie Trust for a scholarship (K. W. G.).

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RECEIVED FEBRUARY 1, 1964

(2) S. Dev, *Current Sci.* (India), **20**, 296 (1951).

(3) V. Benešová, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.*, **26**, 1832 (1961). We are indebted to Dr. V. Herout for a sample of humulene.

(4) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, **26**, 3617 (1961). Workers at Johns Hopkins University have independently arrived at the same structure by an elegant degradation sequence, and simultaneous publication was arranged [A. Nickon, F. J. McGuire, J. R. Mahajan, B. Umezawa, and S. A. Narang, *J. Am. Chem. Soc.*, **86**, 1437 (1964)].

(5) See, *inter alia*, I. C. Paul, G. A. Sim, T. A. Hamor, and J. M. Robertson, *J. Chem. Soc.*, 4133 (1962); J. A. Hamilton, T. A. Hamor, J. M. Robertson, and G. A. Sim, *ibid.*, 5061 (1962); J. Donohue and K. Trueblood, *Acta Cryst.*, **5**, 419 (1952).

(6) "Computing Methods and the Phase Problem in X-ray Crystal Analysis," R. Pepinsky, J. M. Robertson, and J. C. Speakman, Ed., Pergamon Press, Oxford, 1961; J. S. Rollett, p. 87; J. G. Sime, p. 301.

High Resolution Mass Spectra of Natural Products.[1,2] Vinblastine[3] and Derivatives

Sir:

We wish to present an example illustrating the usefulness of high resolution mass spectrometry[4] for the determination of the structure of a molecule as complex as the "dimeric" indole alkaloid vinblastine (VLB)[5] where this technique was used to establish the correct elemental composition,[6] to provide completely independent additional information regarding the point of attachment of the two parts, and to corroborate other features of the molecule.

Conventional mass spectra of VLB indicated a molecular weight 838 which was incompatible with the earlier structure.[7] However, high resolution mass spectrometry, employed in a fashion[8] that permits detecting any thermal changes taking place in the sample,[10] showed that vinblastine is, in fact, thermally labile. When it begins to vaporize, mass 810 predominates, but peaks at $m/e = 824$ and even $m/e = 838$ appear immediately and increase with time. The determined mass of these species (Table I) differ, in fact, by CH_2, ruling out any nonhomologous contaminants. Fractionation of contaminants is eliminated by the fact that under conditions favoring thermal reactions (slow

(1) Application of Mass Spectrometry to Structure Problems. Part XIX[2]; this investigation was supported by grants from the National Science Foundation (G-21037) and the National Institutes of Health, Public Health Service (GM-09352).

(2) Part XVIII: W. Benz and K. Biemann, *J. Am. Chem. Soc.*, in press.

(3) This A.M.A. approved generic name refers to the alkaloid vincaleukoblastine.

(4) For reviews of previous work in this field using a different technique (see ref. 8 below), see J. H. Beynon, "Advances in Mass Spectrometry," Vol. II, R. M. Elliot, Ed., Pergamon Press, Oxford, 1963, pp. 216–229; and R. A. Saunders and A. E. Williams, "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press, New York, N. Y., 1963, pp. 343–396, and references therein.

(5) N. Neuss, *et al.*, *J. Am. Chem. Soc.*, **86**, 1440 (1964).

(6) Neither the usual analytical data (see footnote 9 in ref. 5) nor conventional mass spectrometric data (discussed below) gave unambiguous results.

(7) N. Neuss, M. Gorman, H. E. Boaz, and N. J. Cone, *J. Am. Chem. Soc.*, **84**, 1509 (1962).

(8) The sample (0.1–0.2 mg.), as a thin layer on glass wool, was introduced through a vacuum lock and vaporized directly into the ion source of a CEC 21-110 mass spectrometer. With this instrument, and in contrast to the earlier work,[4] all ions are focused simultaneously and recorded immediately on a photographic plate optimizing the chance of obtaining, in the first exposure, the complete spectrum (from mass 35 to 850) of the unaltered sample.

Exposure times varied from 3 to 18 min., Perfluorokerosene, admitted coincidently with the sample, provided the calibration lines required for the mass determination which is performed after taking the spectrum and not while the substance resides in the instrument,[4] a procedure much too slow to permit the measurement of the mass of many ions of a thermally decomposing substance. The accuracy of the mass measurement was within a few p.p.m. (see Table I) with the resolution set for 1:15,000. The principle of the measuring technique has been discussed previously.[9]

(9) K. Biemann, Conference on Mass Spectrometry, San Francisco, Calif., May, 1963, pp. 235–240.

(10) Such pyrolytic reactions had previously led to complications with another dimeric indole alkaloid voacamine: G. Büchi, R. E. Manning, and S. A. Monti, *J. Am. Chem. Soc.*, **85**, 1893 (1963).