Hz, H-6], 3.83 (d, $J_{4,5}$ = 16 Hz, H-4), 6.47 (s, H-9), 7.37 (q, H-2), 7.97 [s (b), CH_3-7], 8.88 (t, H-1).

3,6-Dimethyl-3,5-octadien-7-yn-2-one (12). A solution of the aldehyde **6** (2.43 g, 0.026 mol) in acetic acid (8 mL) was added dropwise over 15 min to a stirred solution of 2-butanone (**10**, 8.0 g, 0.11 mol) and concentrated sulfuric acid (2 mL) in acetic acid (100 mL). The resultant dark solution was stirred for a further 18 h, and then cautiously poured into saturated aqueous potassium carbonate. The residue after solvent removal was chromatographed on a column of alumina (11 × 4 cm) with 5% ethyl acetate–petrol as eluent. Early fractions afforded the ketone **12** (2.24 g, 59%) as a yellow solid. It formed yellow prisms, mp 41–43 °C from pentane: mass spectrum *m/e* 148.089 (M^+, calcd 148.089), 133 ($M^+ - 15$), 119 ($M^+ - 29$), 105 ($M^+ - 43$), 103 ($M^+ - 45$); UV (Et_2O) λ_{max} ~277 nm sh (ϵ 17 000), 295 (26 600), ~307 sh (22 200); IR (CCl_4) 3250 m (C≡CH), 2100 w (C≡C), 1660 s (C=O), 1620 cm^{-1} m (C=C); ^1H NMR (60 MHz, $CDCl_3$) τ 2.47 [d (b), $J_{4,5}$ = 11 Hz, H-4], 3.30 [d (b), $J_{5,4}$ = 11 Hz, H-5], 6.40 (s, H-8), 7.62 (s, H-1), 7.93 [s (b), CH_3-6], 8.10 [s (b), CH_3-3].

2,5,10-Trimethyl-6,8-bisdehydro[13]annulenone[4b] (4) and 3,6,11,14-Tetramethyl-3,5,11,13-hexadecatetraene-7,9-diyne-2,15-dione (14) from 12. A solution of potassium hydroxide (0.4 g) in ethanol (5 mL) was added to a solution of the ketone **12** (2.15 g, 0.015 mol) in dry tetrahydrofuran (45 mL), and a solution of the aldehyde **6** (2.15 g, 0.023 mol) in dry tetrahydrofuran (15 mL) was then added during 30 min, with stirring. After 3 h, the reaction was quenched by the addition of acetic acid (3 mL), the resulting solution was poured into water (500 mL), and the mixture was extracted with ether. Chromatography of the residue after solvent removal on a column of alumina (10 × 4 cm), with 5% ethyl acetate–petrol as eluent, afforded a yellow gum (2.34 g). Spectroscopic examination of this material showed that it was a mixture of **12** and **13**.

A solution of the mixture of **12** and **13** (2.34 g) in dimethylformamide (40 mL) was added dropwise during 1 h to a stirred mixture of cupric acetate monohydrate (18.9 g) in dimethylformamide (100 mL) at 60 °C (bath). After a further 0.5 h at 60 °C, the mixture was cooled, diluted with water (1 L), and extracted with ether, and the extracts were washed with water. The residue after solvent removal was chromatographed on a column of alumina (6 × 4 cm), with 5–15% ethyl acetate–petrol as eluent.

Early fractions gave the annulenone **4** (136 mg, 4% based on **12**) as an orange solid. It formed orange rods, mp 83–84 °C, from petrol: mass spectrum *m/e* 222.105 (M^+, calcd 222.105), 207 ($M^+ - 15$), 194 ($M^+ - 28$), 179 ($M^+ - 43$); UV (Et_2O) see Table I; UV (CF_3COOH) see Table II; IR (KBr) 2165 w and 2100 w (C≡C), 1640 s, 1620 m and 1600 s (C=O, C=C), 980 cm^{-1} m (trans HC=CH); ^1H NMR (100 MHz, $CDCl_3$ 27 °C, see Figure 2 and Table III) τ 0.45 (d, $J_{3,4}$ = 11 Hz, H-3), 2.37 (m, H-12, H-13), 3.46 (d, $J_{4,3}$ = 11 Hz, H-4), 3.82 (m, H-11), 8.20 [s (b) CH_3-2, CH_3-5, CH_3-10]; ^1H NMR (100 MHz, $CDCl_3$ −60 °C, see Figure 2) τ 0.27 (d, $J_{3,4}$ = 11 Hz, H-3), 2.10 (d, $J_{13,12}$ = 16 Hz, H-13), 2.51 (dd, $J_{12,13}$ = 16, $J_{12,11}$ = 6 Hz, H-12), 3.39 [d (b), $J_{4,3}$ = 11 Hz, H-4], 3.76 [d (b), $J_{11,12}$ = 6 Hz, H-11], 8.17 [s (b), CH_3-2, CH_3-5, CH_3-10]; ^1H NMR (100 MHz, CF_3COOD, see Table III) τ −0.50 (d, $J_{3,4}$ = 11 Hz, H-3), 1.74–2.18 (m, H-12, H-13), 3.50 (d, $J_{4,3}$ = 11 Hz, H-4), 3.84 [d (b), $J_{11,12}$ = 7 Hz, H-11], 8.18 [s (b), CH_3-2], 8.28 [s (b), CH_3-5, CH_3-10]; ^{13}C NMR (20 MHz, $CDCl_3$) δ 195.5 (C-1), 139.8, 139.6, 138.6, 138.2, 137.4, 129.2, 127.2, 123.5 (C-2, C-3, C-4, C-5, C-10, C-11, C-12, C-13), 97.6, 97.1 (C-6, C-9), 88.3 (C-7, C-8), 21.2, 20.0 (CH_3-5, CH_3-10), 12.20 (CH_3-2).

Later fractions afforded the diketone **14** (442 mg, 21%) as a yellow solid. It formed yellow needles, mp 110–112 °C, from ethanol: UV (Et_2O) λ_{max} 248 nm sh (ϵ 11 800), 259 (14 000), 286 sh (31 700), 325 sh (30 000), 342 (34 600), 366 (32 100), 393 (22 400); IR (KBr) 2180 w (C≡C), 1660 s (C=O), 1610 m (C=C); ^1H NMR (100 MHz, $CDCl_3$) τ 2.53 [d (b), $J_{4,5}$ = $J_{13,12}$ = 11 Hz, H-4, H-13], 3.23 [d (b), $J_{5,4}$ = $J_{12,13}$ = 11 Hz, H-5, H-12], 7.60 (s, H-1, H-16), 7.90 [s (b), CH_3-6, CH_3-11], 8.10 [s (b), CH_3-3, CH_3-14].

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.62; H, 7.54.

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Registry No.—**3**, 55338-03-9; **4**, 61966-94-7; **6**, 52421-93-9; **7**, 6153-05-5; **8**, 58964-85-5; **9**, 61966-95-8; **10**, 78-93-3; **11**, 61966-96-9; **12**, 61966-97-0; **13**, 61966-98-1; **14**, 61966-99-2; **15**, 61967-00-8; **16**, 61967-01-9.

References and Notes

(1) Unsaturated Macrocyclic Compounds. 122. For part 121, see N. Darby, T. M. Cresp, and F. Sondheimer, *J. Org. Chem.*, **42**, 1960 (1977).
(2) P. D. Howes, E. LaGoff, and F. Sondheimer, *Tetrahedron Lett.*, 3691 (1972).
(3) R. L. Wife and F. Sondheimer, *J. Am. Chem. Soc.*, **97**, 640 (1975).
(4) IUPAC nomenclature: (a) 5,10-dimethyl-2,4,10,12-cyclotridecatetraene-6,8-diyn-1-one; (b) 2,5,10-trimethyl-2,4,10,12-cyclotridecatetraene-6,8-diyn-1-one.
(5) Inter alia, see P. J. Beeby, R. T. Weavers, and F. Sondheimer, *Angew. Chem.*, **86**, 163 (1974); R. L. Wife and F. Sondheimer, *Tetrahedron Lett.*, 195 (1974).
(6) For a preliminary report, see J. Ojima and F. Sondheimer, Abstracts, 30th Annual Meeting of the Chemical Society of Japan, Osaka, April 1974.
(7) For a review of annulenones, see T. M. Cresp and M. V. Sargent, *Top. Curr. Chem.*, **No. 57**, 111 (1975).
(8) (a) E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 937 (1946); (b) I. M. Heilbron, E. R. H. Jones, and M. Julia, *ibid.*, 1430 (1949); (c) J. Ojima, T. Katakami, G. Nakaminami, and M. Nakagawa, *Bull. Chem. Soc. Jpn.*, **49**, 292 (1976).
(9) We found substance **5** to be obtained most conveniently from methyl β-chlorovinyl ketone by reaction with ethynylmagnesium bromide in tetrahydrofuran instead of sodium acetylide in liquid ammonia.[8a,b]
(10) E. E. Boehm, V. Thaller, and M. C. Whiting, *J. Chem. Soc.*, 2535 (1963).
(11) See G. Eglinton and A. R. Galbraith, *J. Chem. Soc.*, 889 (1959); G. Eglinton and W. McCrae, *Adv. Org. Chem.*, **4**, 225 (1963).
(12) See H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 10.
(13) The values are τ 0.40 and 0.36, respectively, in CD_2Cl_2–CS_2 at −60 °C.
(14) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).
(15) E. Spath, *Sitzungsber. Akad. Wiss. Wien*, **120**, 1117 (1911).

Crystal Structure of Tetrahymanol Hemihydrate

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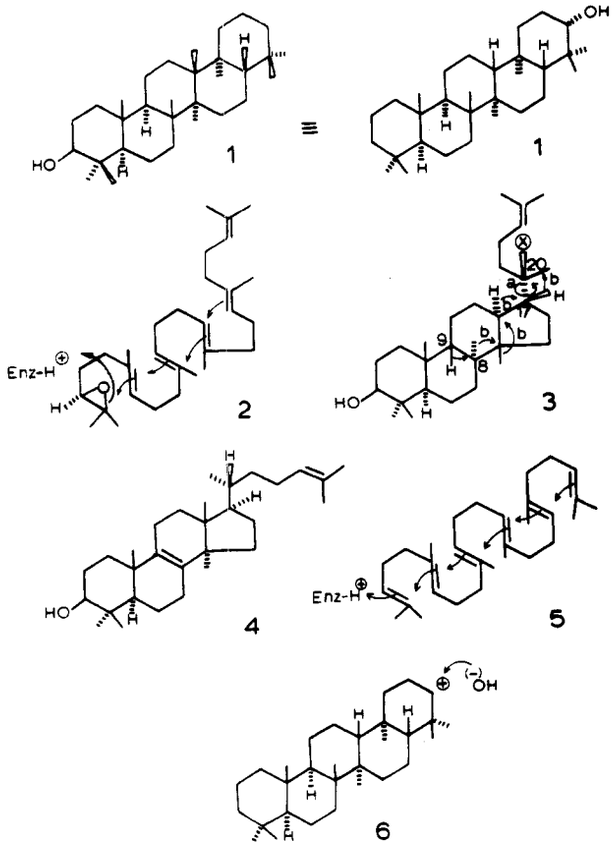
The crystal structure of a hemihydrate of the pentacyclic triterpenoid tetrahymanol, $C_{30}H_{52}O \cdot \frac{1}{2}H_2O$ [monoclinic, $P2_1$, a = 7.417 (1) Å, b = 11.438 (2), c = 30.248 (4), β = 91.95°, Z = 4, R = 0.076] has been determined. Steric overcrowding warps the gross conformation of the two molecules in the asymmetric unit and generates unusually long carbon–carbon single bonds. The observed weakening of the C8–C14 bond, whose average length is 1.61 Å, is consistent with its scission observed in mass spectral experiments. Although the molecular skeleton possesses rotational symmetry, the observed conformations are markedly asymmetric, appear to be independent of the hydroxyl moiety, and suggest the presence of conformational isomers in solution.

The pentacyclic triterpene tetrahymanol (**1**) was first isolated from the protozoan *Tetrahymena pyriformis*.[2] Later, it was also obtained from the fern *Oleandra walichii*.[3] Initially, tetrahymanol (**1**) was thought to be an "isomer of cho-

lesterol",[2] but, subsequently, it was recognized that the product is a triterpene.[4] Its structure was finally determined by interrelating tetrahymanol with known triterpenes of the gammacerane type.[5]

The available evidence indicates that the biosynthesis of C-3 oxygenated triterpenes and sterols requires molecular oxygen[6] and proceeds via 2,3(*S*)-oxidosqualene[7-9] (**2**). It is assumed that an enzymatic "cationic" cleavage of the epoxide (**2**) will generate an electron deficiency at C-3 and initiate the cyclization process. In many species (rat, yeast, *F. coccineum*, *D. lanata*, etc.) a free[10] or transiently stabilized[11] C-20 cation[12] (**3**) is thought to be formed. In rat livers (and in yeasts), following the rotation of the side chain around the C17–C20 bond (**3a**), the indicated backbone rearrangement (**3b**) takes place to yield a C8 cation.[13] Finally, elimination of the 9β hydrogen from the C8 cation results in lanosterol (**4**).[14] Accordingly, it was found that the oxygen atom of the hydroxyl of lanosterol (**4**) originates from *molecular oxygen* and not from the *water of the medium*.[15]



In contrast, we have proven that the biosynthesis of tetrahymanol (**1**) is *not oxygen dependent* and proceeds under *anaerobic conditions*.[16,17] Most likely, the biosynthesis involves a proton attack on a terminal double bond of squalene (**5**) which initiates the cyclization and results in the formation of the cation (**6**). Acquisition by the cation (**6**) of a hydroxyl moiety from the medium will yield tetrahymanol[17] (**1**). In fact, when a mixture of [^{3}H][2,3]oxidosqualene and [$^{14}C_6$]squalene was incubated with *T. pyriformis*[18] or an enzyme preparation of *T. pyriformis*,[16,17] the obtained tetrahymanol (**1**) contained only ^{14}C. However, when [$^{14}C_6$]squalene was incubated with an enzyme preparation suspended in deuterium oxide or $^{18}OH_2$, the biosynthesized tetrahymanol (**1**) contained one atom of deuterium[17,19] or one atom of oxygen-18,[17,20] respectively.

It is apparent that the biosynthesis of tetrahymanol (**1**) involves a nonoxidative cyclization of squalene. The overall process is equivalent to the acquisition of a molecule of water by squalene.[17]

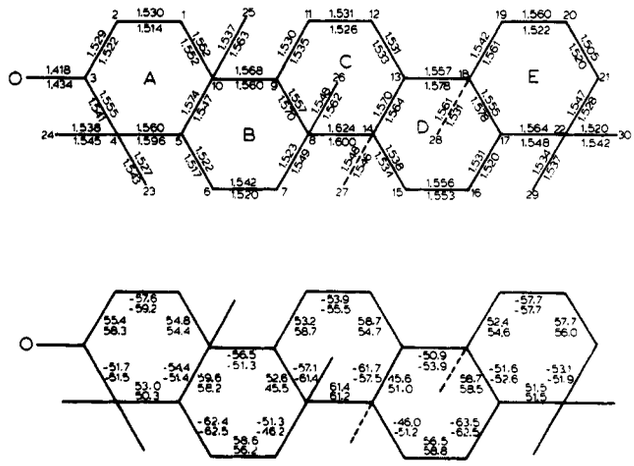


Figure 1. Observed bond lengths and endocyclic torsion angles in molecules I (above) and II of tetrahymanol. The average estimated standard deviation in the bond lengths and angles are 0.008 Å and 0.4°, respectively.

At present, it is considered likely that the biosynthesis of all 3-deoxytriterpenes proceeds via the nonoxidative mechanism of squalene cyclization.[3,21]

For the extension of studies on the mechanism of nonoxidative squalene cyclization, we required an x-ray crystal structure of tetrahymanol. The results of the crystallographic studies are reported in this paper.

Experimental Section

Tetrahymena pyriformis was grown in 15-L batches for 48–60 h and the organisms were harvested at 4 °C by continuous flow centrifugation.[16] The packed cells (ca. 20–30 g per 15-L batch) were freeze dried and extracted and the recovered lipids saponified under nitrogen.[18] The isolated tetrahymanol was extensively purified by thin layer chromatography,[17] sublimed, and crystallized.[18]

Cell dimensions of a crystal were determined by a least-squares procedure of 15 well-centered reflections. Cell data: a = 7.417 (1) Å, b = 11.438 (2) Å, c = 30.248 (4) Å, β = 91.95°, V = 2564.6 Å^3, monoclinic, $P2_1$, Z = 4. Three-dimensional data were collected on a Syntex P$\bar{1}$ automated diffractometer in a θ–2θ scan mode with Cu Kα radiation to a 2θ value of 137°. Of the 5020 data collected, 3134 were classified as observed ($>1.5\sigma$).

Structure Solution and Refinement. Although Patterson interpretation readily yielded the correct orientations of the two independent molecules in the asymmetric unit, attempts to achieve a solution by use of translation functions were not successful. Initial direct methods results obtained through the program MULTAN[22] were also discouraging and the structure was finally solved by a global fixed point phase refinement procedure, QTAN.[23] A structure factor calculation based on the 60-atom model located in the E map having the best figures of merit[24,25] produced a residual of 0.30.

After isotropic full-matrix least-squares refinement to a residual of 0.17, a single water of hydration was detected in a difference electron density synthesis. Hydrogen atoms, excluding methyl protons, were introduced in fixed theoretical positions with isothermal temperature factors of 5.0 Å^2. The positions of methyl protons were determined by difference electron density syntheses. The maximum coordinate shift in the last least-squares cycle (R = 0.076, wR = 0.087) corresponded to less than three-quarters of its estimated standard deviation. The estimated standard deviation in an observation of unit weight was 0.97.

The final atomic corrdinates and anisotropic thermal parameters for the nonhydrogen atoms and the positional coordinates of the hydrogen atoms appear in the microfilm edition.

Discussion

Intramolecular bond distances and torsion angles derived from the refined atomic coordinates of the crystal structure are presented in Figure 1 for the two crystallographically in-

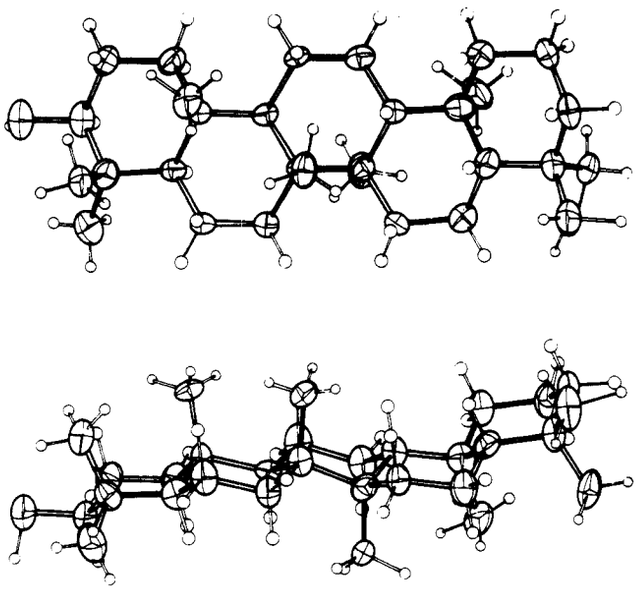


Figure 2. Observed conformation of molecule I of tetrahymanol with 50% probability thermal vibrational ellipsoids.

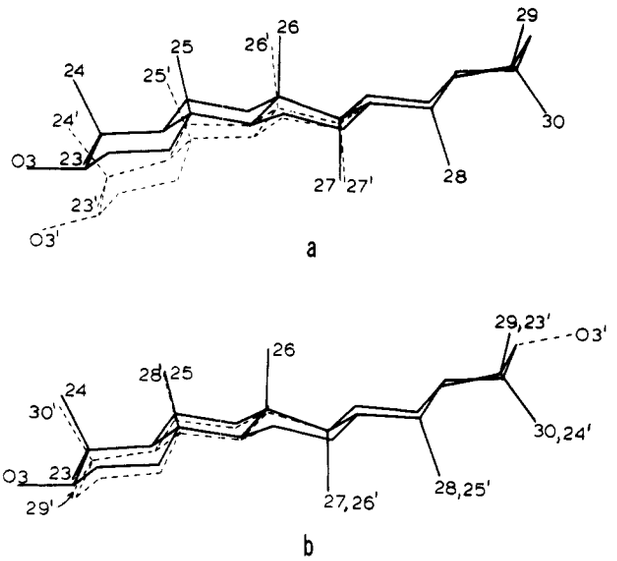


Figure 3. (a) Relative conformations of molecules I and II contrasted by superimposing the D and E rings of each as a reference element. (b) Similarity of conformations of molecule I and II illustrated by superimposing rings D and E of molecule I on rings B and A of molecule II.

dependent tetrahymanol molecules. The average carbon–carbon bond length is 1.546 (16) Å.

Observations of note include the relative lengthening of the endocyclic carbon–carbon single bonds which directly link the 1,3-diaxial methyl groups [average 1.565 (12) Å], and the abnormal lengthening of the C8–C14 bond to the average value of 1.612 Å.[27] Apparently bond angle and torsion angle deformations are insufficient to relieve steric overcrowding of the methyl groups and consequently bond lengths are also distorted from commonly observed values. In the structure of zeorin[26] the 1,3-diaxial methyl groups cause a similar lengthening of the C8–C14 bond to 1.63 Å. This bond lengthening is consistent with mass spectal data on tetrahymanol suggesting a scission of the C8–C14 bond.[17]

The tetrahymanol molecule possesses an approximate twofold axis which passes through the midpoints of the C8–C14 and C11–C12 bonds. This intramolecular symmetry extends to include the observed conformations of the methyl groups (Figure 2) and is broken only by the hydroxyl substituent. The axial methyl groups on carbons 4, 8, 14, and 22 are rotated by as much as 30° counterclockwise with respect to a staggered conformation with the molecular skeleton, and the axial groups on 10 and 18 are rotated clockwise so that all adjacent methyl groups have two symmetrical hydrogen contacts between them. Although the tetrahymanol backbone possesses compositional symmetry, the observed conformation is not symmetric as indicated in the torsion angles (Figure 1). An overlap of the chemically equivalent portions of molecule I with molecule II illustrates the conformational differences between the two molecules in the asymmetric unit (Figure 3a). However, if molecule II is rotated 180° about the axis through the midpoints of the C8–C14 and the C11–C12 bonds, the overlap of the polycyclic portions is almost exact (Figure 3b).

These observations are consistent with the hypotheses that (a) the most stable conformation of the symmetric portion of the molecule is in fact the asymmetric form observed, (b) the hydroxyl substituent does not alter this conformational asymmetry but permits the detection of two conformational isomers, and (c) in solution, tetrahymanol molecules oscillate between the two conformers that have been cocrystallized.

The polar ends of the molecules and the water of hydration form a left-handed helical hydrogen-bonding arrangement about one of the screw axes. Although the gross packing of the molecules in the unit cell is such that molecule I is approximately related to molecule II by pseudoorthorhombic symmetry operators, strict orthorhombic symmetry would require that either molecule I or II be rotated to exchange the polar and nonpolar ends, and as such the hydrogen bonding structure observed in the hemihydrate would be destroyed.

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Registry No.—Tetrahymanol hemihydrate, 61899-97-6.

Supplementary Material Available. The final atomic coordinates and anisotropic thermal parameters for the nonhydrogen atoms and the positional coordinates of the hydrogen atoms (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Medical Foundation of Buffalo; (b) Institute for Cancer Research; (c) Worcester Foundation for Experimental Biology.
(2) C. M. McKee, J. D. Dutcher, V. Groupe, and M. Moore, *Proc. Soc. Exp. Biol. Med.*, **65**, 326 (1947).
(3) J. M. Zander, E. Caspi, G. N. Pandey, and C. R. Mitra, *Phytochemistry*, **8**, 2265 (1969).
(4) F. B. Mallory, J. T. Gordon, and R. L. Conner, *J. Am. Chem. Soc.*, **85**, 1362 (1963).
(5) Y. Tsuda, A. Morimoto, T. Sano, Y. Innubushi, F. B. Mallory, and J. T. Gordon, *Tetrahedron Lett.*, 1427 (1965).
(6) T. T. Tchen and K. Bloch, *J. Biol. Chem.*, **226**, 921 (1957).
(7) E. E. van Tamelen, J. D. Willett, R. B. Clayton, and K. E. Lord, *J. Am. Chem. Soc.*, **88**, 4752 (1966); E. J. Corey, W. E. Russey, and P. R. Ortiz de Montellano, *ibid.*, **88**, 4750 (1966).
(8) R. B. Boar and K. Damps, *Tetrahedron Lett.*, 3731 (1974).
(9) D. H. R. Barton, T. R. Jarman, K. G. Watson, D. A. Widdowson, R. B. Boar, and K. Damps, *J. Chem. Soc., Chem. Commun.*, 861 (1974).
(10) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).
(11) J. W. Cornforth, *Angew. Chem.*, **7**, 903 (1968).
(12) E. Caspi and L. J. Mulheirn, *J. Am. Chem. Soc.*, **92**, 404 (1970); L. J. Mulheirn and E. Caspi, *J. Biol. Chem.*, **246**, 2494 (1971).
(13) L. J. Mulheirn and E. Caspi, *J. Biol. Chem.*, **246**, 3948 (1971).
(14) J. W. Cornforth, R. H. Cornforth, C. Donninger, G. Popjak, Y. Shimizu, S. Ichii, E. Forchielli, and E. Caspi, *J. Am. Chem. Soc.*, **87**, 3224 (1965).

(15) T. T. Tchen and K. Bloch, *J. Biol. Chem.*, **226**, 931 (1957).
(16) E. Caspi, J. J. Greig, and J. M. Zander, *Biochem. J.*, **109**, 931 (1968).
(17) J. M. Zander, J. B. Greig, and E. Caspi, *J. Biol. Chem.*, **245**, 1247 (1970).
(18) E. Caspi, J. M. Zander, J. B. Greig, F. B. Mallory, R. L. Conner, and J. R. Landrey, *J. Am. Chem. Soc.*, **90**, 3563 (1968).
(19) E. Caspi, J. B. Greig, J. M. Zander, and A. Mandelbaum, *Chem. Commun.*, 28 (1969).
(20) J. M. Zander and E. Caspi, *Chem. Commun.*, 210 (1969).
(21) D. H. R. Barton, A. F. Gosden, G. Mellows, and D. A. Widdowson, *Chem. Commun.*, 184 (1969).
(22) G. Germain, M. M. Woolfson, and P. Main, *Acta Crystallogr., Sect. A.*, **27**, 368 (1971).
(23) D. A. Langs and G. T. DeTitta, *Acta Crystallogr., Sect. A*, submitted.
(24) G. T. DeTitta, J. W. Edmonds, D. A. Langs, and H. Hauptman, *Acta Crystallogr., Sect. A*, **31**, 472 (1975).
(25) J. Karle and I. L. Karle, *Acta Crystallogr., Sect. B*, **21**, 849 (1966).
(26) T. Nakanishi, H. Yamauchi, T. Fujimara, and K. Tomita, *Tetrahedron Lett.*, 1157 (1971).
(27) The standard deviation of this average calculates as ±0.017 Å when based upon the deviation of the individual observations from the average or ±0.005 Å when based on the standard deviations of the individual observations. Since the two observations differ by greater than twice the lower of these values (0.005 Å), the standard deviations of the individual observations must be slightly underestimated and the standard deviation of the average value probably lies somewhere between 0.006 and 0.017 Å.

γ-Alkylation of α,β-Unsaturated Carbonyl Compounds

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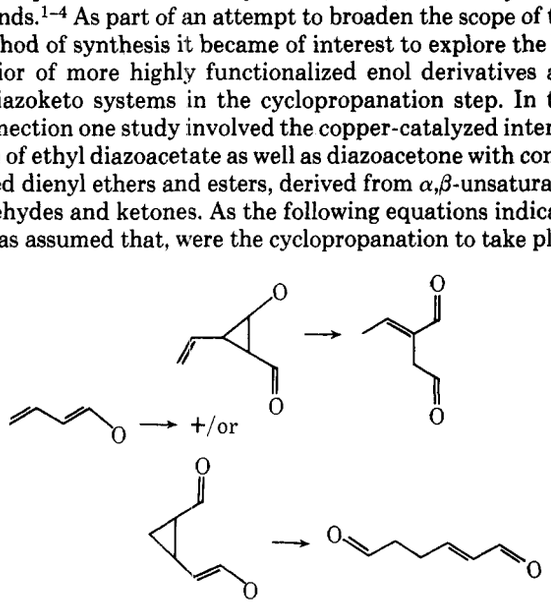
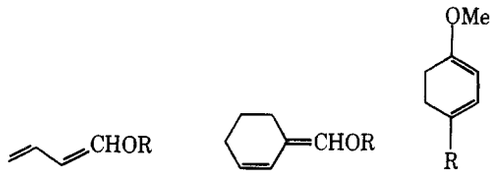
The copper-catalyzed reactions of ethyl diazoacetate and diazoacetone with the dienol derivatives 1-methoxy- and 1-trimethylsilyloxy-1,3-butadiene, 3-acetoxymethylene- and 3-trimethylsilyloxymethylenecyclohexene, and 1-methoxy-1,3-cyclohexadiene and its 4-methyl analogue are described. Hydrolysis of the olefinic cyclopropane adducts is shown to lead to α- and γ-alkylated α,β-unsaturated aldehydes and ketones.

The simple, three-step scheme of conversion of aldehydes or ketones into enol ethers or esters, cyclopropanation of these olefinic intermediates with α-diazocarbonyl reagents over copper, and aqueous acid cleavage of the resultant β-oxycyclopropylketo compounds has been shown to be the equivalent of α-alkylation of aldehydo and keto substances as well as a useful procedure for the synthesis of 1,4-dicarbonyl compounds.[1-4] As part of an attempt to broaden the scope of this method of synthesis it became of interest to explore the behavior of more highly functionalized enol derivatives and α-diazoketo systems in the cyclopropanation step. In this connection one study involved the copper-catalyzed interaction of ethyl diazoacetate as well as diazoacetone with conjugated dienyl ethers and esters, derived from α,β-unsaturated aldehydes and ketones. As the following equations indicate, it was assumed that, were the cyclopropanation to take place



on the unoxygenated double bond, the new three-step scheme would be the equivalent of a γ-alkylation of α,β-unsaturated keto systems,[5] leading to 1,6-dicarbonyl compounds.[6]

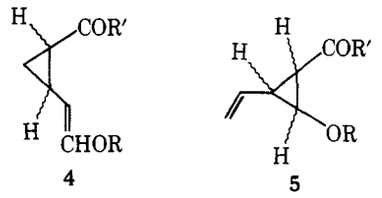
The crotonaldehyde-based dienyl ethers 1-methoxy-1,3-butadiene (**1a**) and 1-trimethylsilyloxy-1,3-butadiene (**1b**),[7,8] the enol acetate and trimethylsilyl ether from 1-cyclohexenecarboxaldehyde[9] (**2a** and **2b**, respectively), and the 1-methoxy-1,3-cyclohexadienes[10] **3a** and **3b** served as starting materials for this investigation. Diene **2a** was prepared by the acid-induced acetylation of 1-cyclohexenecarboxaldehyde with isopropenyl acetate, while diene **2b** was the result of the



1a, R = Me; **b**, R = $SiMe_3$ **2a**, R = Ac; **b**, R = $SiMe_3$ **3a**, R = H; **b**, R = Me

O-alkylation of the aldehyde with trimethylsilyl chloride in the presence of triethylamine.[7,11]

The decomposition of ethyl diazoacetate in cyclohexane or neat solutions of each of the six dienes over copper bronze at 65–85 °C led to 55–80% yields of stereo- and regioisomer mixtures of olefinic cyclopropanecarboxylates, i.e., **1a → 4a + 5a, 1b → 4b + 5b, 2a → 6a + 7a, 2b → 6b + 7b, 3a → 8a + 9a,** and **3b → 8b + 9b.** With the exception of the silyl ethers



4 **5**

a, R = Me; R′ = OEt
b, R = $SiMe_3$; R′ = OEt
c, R = R′ = Me
d, R = $SiMe_3$; R′ = Me

the regioisomers were separated into stereoisomer mixtures, no attempt having been made to fractionate the latter. Interaction of diazoacetone with each of the starting dienes under conditions similar to those of the diazoacetic ester reactions produced difficultly separable isomer mixtures of the ketone pairs **4c–5c, 4d–5d, 6c–7c, 6d–7d, 8c–9c,** and **8d–9d,** respectively.

Mild treatment of cyclopropane **4a** with aqueous acid caused the hydrolysis of its enol ether moiety leading to the aldehydo ester **10,** whereas oxycyclopropane **5a** remains un-