free as shown by the absence of infrared absorption maxima or shoulders at 1700–1720 cm^{-1}.

A solution of the acetate mixture obtained above (4.0 g) in ether (40 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.8 g) in ether (50 ml); after completion of the addition, the reaction mixture was refluxed 2 hr more. The reaction mixture was cooled and treated slowly with water (0.7 ml), 15% sodium hydroxide (1.0 ml), and water (3 ml), and stirred for 1 hr. The white salts were filtered and washed well with ether; the combined filtrates were dried and concentrated to give the mixture of ring alcohols and as a colorless, slightly cloudy oil (1.2 g); ir (film) 3450–3500 cm^{-1}.

The mixture of ring alcohols (1.2 g) in reagent grade acetone (30 ml) was treated with Jones reagent (1.3 ml, 8 *N* in oxygen at 25–30° and stirred at ambient temperature for 5 hr. Evaporation of the solvent, treatment with water, and extraction as usual gave, after evaporation of the solvent and distillation, 0.82 g (16% overall) of colorless liquid, ir (film) 1712 cm^{-1}. This mixture of ring ketones showed four peaks on column E at 170°. The retention times of these and the per cent of total peak area represented by each are (a) 5.5 (63%); (b) 6.5 (12%); (c) 7.4 (16%); and (d) 8.3 min (9%). Peaks a and b were collected from column C, on which they were partially resolved. Rechromatography on column A afforded first 4-isopropylcyclohexanone, identical (ir, gc on two columns, mixture melting point of 2,4-DNP) with material prepared from authentic 4-isopropylphenol by a hydrogenation–oxidation sequence. Peak b was identical with a sample of 4-ethylcycloheptanone prepared by ring expansion with diazomethane of authentic 4-ethylcyclohexanone. Peaks c and d both exhibited gc retention times which were significantly different from that of authentic cyclononanone and of 4-*n*-propylcyclohexanone. It seems most likely that at least one of these compounds is 4- or 5-methylcyclooctanone; however, samples of these isomers were not available for comparison.

Registry No.—**2**, 27921-40-0; 2 semicarbazone, 27921-41-1; **3**, 27921-42-2; **4**, 27921-43-3; **5**, 27921-44-4; *cis*-cyclononene, 933-21-1; acetylcyclononane, 19207-40-0; acetylcyclononane semicarbazone, 27921-46-6.

Acid-Catalyzed Cyclization of 4-(2,6,6-Trimethylcyclohexenyl)-2-methylbutanal. X-Ray Structure Analysis of the Major Product

GABRIEL SAUCY*

Chemical Research Department, Hoffmann-La Roche Incorporated, Nutley, New Jersey 07110

ROBERT E. IRELAND,[1] JON BORDNER, AND RICHARD E. DICKERSON

Contribution No. 4052 from the Norman W. Church Laboratories of Chemical Biology, California Institute of Technology, Pasadena, California 91109

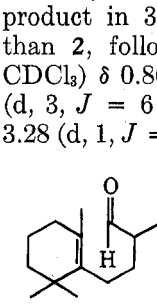
Received July 28, 1970

The cyclization of 4-(2,6,6-trimethylcyclohexenyl)-2-methylbutanal (luciferin aldehyde) with phosphoric acid has been found to give (±)-1,2,3,4,4a,7,8,8a-octahydro-2α,4aβ,5,8aβ-tetramethylnaphthalen-1β-ol as the major product. The structure and stereochemistry of this bicyclic alcohol, the formation of which involves an interesting Wagner–Meerwein rearrangement, was established by X-ray analysis of the 4-bromobenzoate derivative. The alcohol is probably identical with a product obtained (cyclization and degradation) from β-monocyclofarnesic acid by Kitahara, *et al.*

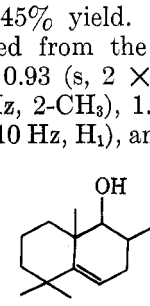
Some time ago, we became interested in the cyclization of the aldehyde **1** which is readily available from the "β-C_{14}-aldehyde"[2] by partial hydrogenation with palladium on charcoal in acetone solution. The same aldehyde (**1**, "luciferin aldehyde") has recently been obtained[3] upon hydrolysis of luciferin, which is the enol formate derived from **1**, and by subsequent synthesis[4,5] from dihydro-β-ionone. It was hoped that the aldehyde **1** might cyclize to give the bicyclic alcohol **2**, thus offering a new approach to the preparation of certain sesqui- and higher terpenoids. A precedent for this type of reaction is the well-known cyclization of citronellal, which affords isopulegol.[6]

Results

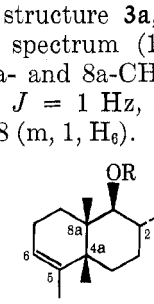
Upon mixing the aldehyde **1** with 85% phosphoric acid, a solid mass was produced in an exothermic reaction. After alkaline work-up and crystallization, the bicyclic alcohol **3a** was obtained as the major product in 35–45% yield. The structure **3a**, rather than **2**, followed from the nmr spectrum (100 mc, $CDCl_3$) δ 0.86, 0.93 (s, 2 × 3, 4a- and 8a-CH_3), 0.94 (d, 3, J = 6 Hz, 2-CH_3), 1.60 (t, J = 1 Hz, 5-CH_3), 3.28 (d, 1, J = 10 Hz, H_1), and 5.38 (m, 1, H_6).



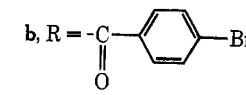
1



2



3a, R = H

b, R = 

In order to assign the stereochemistry unambiguously, the alcohol **3a** was converted into its 4-bromobenzoate **3b** and the latter subjected to single crystal X-ray structure analysis. As a result, proof for the relative stereochemistry shown in formula **3a** was obtained. A product with the same structure and "tentative" relative stereochemistry was recently described by Kitahara, Kato, and Kanno.[7] These authors obtained **3a** *via* its acetate by lead tetraacetate oxidation of the bicyclic acid **6**. The latter was formed as a

(1) The portion of this work carried out at the California Institute of Technology was made possible by a grant from the Hoffmann-La Roche Foundation, and this support is gratefully acknowledged.

(2) Intermediate of the technical synthesis of vitamin A; *cf.* O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947).

(3) O. Shimomura and F. H. Johnson, *Biochemistry*, **7**, 1734 (1968).

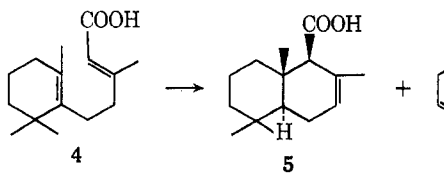
(4) M. G. Fracheboud, O. Shimomura, R. K. Hill, and F. H. Johnson, *Tetrahedron Lett.*, 3951 (1969).

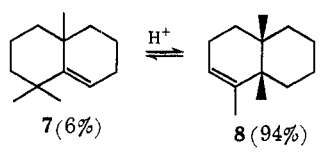
(5) F. Nakatsubo, Y. Kishi, and T. Goto, *ibid.*, 381 (1970).

(6) A. R. Pinder, "The Chemistry of the Terpenes," Wiley, New York, N. Y., 1960, p 38.

(7) Y. Kitahara, T. Kato, and S. Kanno, *J. Chem. Soc. C*, 2397 (1968).

minor product together with the unrearranged acid **5** upon cyclization of β-monocyclofarnesic acid **4** with boron trifluoride in benzene. On the basis of the published[7] nmr data, the two products (**3a**) seem to be identical, although we found a somewhat higher melting point (79–80° *vs.* 71–73°) for our sample. From a study of models, it would appear that the stereochemical result of the cyclization **1** → **3a** is consistent with a concerted mechanism. However, Marshall and Hochstettler[8] have very recently shown that the analogous octalins **7** and **8** are interconvertible *via* acid-catalyzed equilibration, **8** being the predominant isomer. Therefore, the hydroxy octalin **3a** may arise from its isomer **2**, which could be the primary cyclization product. Treatment of the hydroxy octalin **3a** and its acetate with sulfuric acid in acetic acid[8] has so far failed to produce the isomeric octalin **2**, other products forming instead.





Experimental Section[9]

(±)-4-(2,6,6-Trimethylcyclohexenyl)-2-methylbutanal (1, Luciferin Aldehyde).—The C_{14} β aldehyde[2] (200 g) was dissolved in acetone (400 ml) and hydrogenated under normal conditions using 5% palladinum/carbon catalyst (30 g). After takeup of 1 mol of hydrogen, the hydrogenation was stopped and the catalyst was removed by filtration. The crude aldehyde **1** (200.5 g) obtained upon evaporation of the filtrate was found to be sufficiently pure (95% or better by gc) for the cyclization step. A pure sample of **1** was obtained by fractional distillation on a spinning-band column, bp 93.5° (1.6 mm), $n^{21}D$ 1.4821. The ir, nmr, and mass spectra of **1** were identical with those reported[3-5] for luciferin aldehyde.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.59; H, 11.31.

(±)-1,2,3,4,4a,7,8,8a-Octahydro-2α,4aβ,5,8aβ-tetramethylnaphthalen-1β-ol (3a) from 1.—The aldehyde **1** (100 g, crude hydrogenation product) was mixed, with stirring, with 85% phosphoric acid (100 ml). A red emulsion was obtained and the temperature rose to about 50° within 15 min. After standing at room temperature for 24 hr, the reaction mixture had solidified. Water (200 ml) was added and the solid residue was broken up with a spatula. The solid material (probably a phosphoric ester) was filtered and washed with three 100-ml portions of hot water. The solid residue was placed in a flask with ice (200 g), ether (500 ml), and concentrated sodium hydroxide solution (100 ml) and stirred until all solids had dissolved. The ether phase was washed with 3 *N* sodium hydroxide (200 ml) and three 100-ml portions of water. All of the aqueous washings were back extracted in two separatory funnels with more ether (500 ml each). The combined, neutral ether extracts were dried over sodium sulfate and evaporated *in vacuo* at 60° to give 95–98 g of a yellow oil. This was crystallized from petroleum ether (200 ml, boiling range of 40–60°) at Dry Ice temperature. After filtration, washing with cold (−50°) petroleum ether (50 ml), and drying *in vacuo* at room temperature, the alcohol **3a** was obtained as a crystalline, colorless solid (35–54 g), mp 77–80°. An analytically pure sample, mp 79–81°, was made by repeated crystallization from the same solvent.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.64; H, 11.92.

(±)-1,2,3,4,4a,7,8,8a-Octahydro-2α,4aβ,5,8aβ-tetramethylnaphthalen-1β-ol 4-Bromobenzoate (3b).—To a solution of 600 mg (2.88 mmol) of the alcohol **3a** in 60 ml of dry pyridine was added 1.188 g (5.40 mmol) of 4-bromobenzoyl chloride and, after brief agitation, the homogeneous mixture was allowed to stand at 23° for 36 hr under a nitrogen atmosphere. After the mixture was treated with ice and 3 *N* hydrochloric acid, the precipitated ester was isolated by ether extraction. The ethereal extract was washed successively with water, three 100-ml portions of 2% aqueous sulfuric acid, water, and saturated salt solution and then dried (Na_2SO_4). The residue (1.185 g), obtained after evaporation of the ether, was chromatographed on 50 g of silica gel and 825 mg (76%) of the ester **3b**, mp 79–81°, was eluted with 500 ml of 1:1 ether–petroleum ether (bp 30–60°). Analytically pure material suitable for single crystal X-ray analysis was obtained after two crystallizations from hexane and melted at 80.0–81.5°: ir ($CHCl_3$) 1710 (ester C=O) and 1590 cm^{-1} (aromatic absorption); nmr ($CDCl_3$) δ 0.83 (d, 3, J = 5 Hz, C_2 CH_3), 0.99 (s, 3, C_{8a} CH_3), 1.09 (s, 3, C_{4a} CH_3), 1.13 (m, 3, C_5 CH_3), 5.15 (d, 1, J = 10 Hz, C_1 H), 5.50 (m, 1, C_6 H), and 7.50, 7.64, 7.85, 8.00 (A_2B_2q, 4, para-substituted ArH).

Anal. Calcd for $C_{21}H_{27}BrO_2$: C, 64.45; H, 6.96; Br, 20.42. Found: C, 64.51; H, 6.84; Br, 20.35.

X-Ray Analysis of 3b.—Suitable crystals of the 4-bromobenzoate derivative **3b** were grown from a mixture of methanol–ether by slow evaporation. The resulting plate-like crystals were cut to a size of 0.05 × 0.15 × 0.20 mm and surveyed on a precession camera. Both the survey and data collection were performed at ambient room temperature. The survey is summarized in Table I.

TABLE I

DETAILS OF CRYSTAL SURVEYS

Solvent system	Methanol–ether
a(Å) = 6.67 ± 0.01	
b(Å) = 13.60 ± 0.01	
c(Å) = 21.05 ± 0.01	
β (degrees) = 95.84 ± 0.08	
Systematic extinctions	$h0l$, l odd $0k0$, k odd
Space group	$P2_1/c$
Molecules/unit cell	4
Density calculation	1.368 g/cm³
Density observed	1.38 g/cm³
Number of reflections	1986
Nonzero reflections	1837

One-angstrom intensity data were collected on a General Electric Datex diffractometer using nickel-filtered copper radiation and a scintillation counter. A θ–2θ scan technique was employed, the background was counted for 30 sec at each end of the scan, and the scan rate was 2° per minute in 2θ. A single check reflection (023) was monitored every 30 reflections; this reflection indicated no crystal damage and was reproducible well within counting statistics.

The diffractometer output was processed using subprograms of the CRYRM crystallographic computer system.[10] The processing included corrections for background and for Lorentz and polarization effects. Absorption effects on the relative intensities would be less than 2% and, therefore, no corrections for this effect were made. The data processing also included calculation of the F^2 value and its standard deviation for each of the 1986 reflections (149 reflections having observed intensities less than or equal to zero were assigned a value of zero intensity). The standard deviations were assigned on the basis of the following equation

$$\sigma^2(I) = S + (B_1 - B_2)\alpha^2 + (dS)^2$$

(8) J. A. Marshall and A. R. Hochstettler, *J. Amer. Chem. Soc.*, **91**, 648 (1969).

(9) Boiling and melting points are uncorrected. Nmr spectra were determined with Varian Model A-60 and HA-100A spectrometers at 60 MHz and 100 MHz, respectively. The mass spectra were determined on a Consolidated Electrodynamics Corp. mass spectrometer, Model 21-110.

(10) D. J. Duchamp, Annual Meeting of the American Association of Crystallographers, Abstracts, Paper B-14, Bozeman, Mont., 1964, p 29.

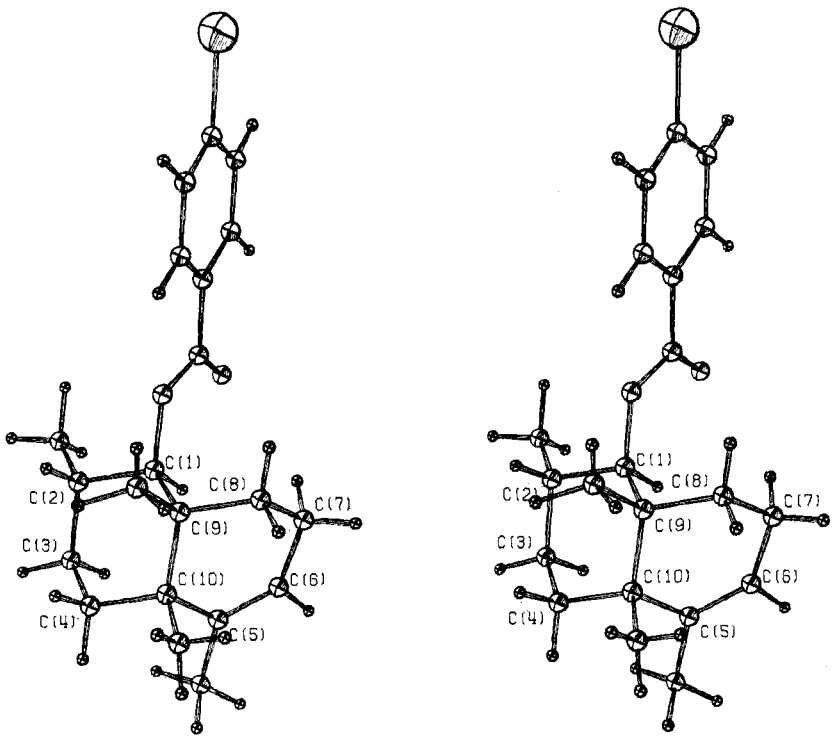


Figure 1.—Stereoplot of the *p*-bromobenzoate **3b**.

where S is the scan count, B_1 and B_2 are the background counts, d is an empirical constant equal to 0.02, and $\alpha = n/2mt$ where n = scan range, m = scanning speed, and t = time for background count in seconds. Finally, the data were placed on an absolute scale by means of Wilson statistics.[11] The atomic scattering factor for bromine includes the real part of the anomalous dispersion correction.

Determination and Refinement of Structure.—The trial structure was derived by the usual Patterson and Fourier techniques in three dimensions. Full-matrix least-squares refinement of coordinates, isotropic temperature factors (bromine anisotropic), and scale factor reduced the R index to 14.4%. The quantity minimized by the least-squares procedure is $\Sigma w(F_o^2 - F_c^2)^2$, where $w = \sigma^2(F_o^2)$. The difference Fourier indicated no misplaced or missing Br, C, or O atoms. The difference Fourier was also utilized to locate the hydrogen atoms. The addition of the hydrogen atoms, without refinement, to the structure factor calculation and the application of anisotropic temperature factors and secondary extinction factor[12] to the refinement reduced the R index to its final value of 8.7%.

Results of X-Ray Analysis.—The structure obtained in the analysis was stereographically plotted (Figure 1) using the ORTEP computer program of C. K. Johnson.[13] An estimate of errors in positional parameters, bond lengths, and bond angles is summarized in Table II. Bond distances and bond angles found together with the crystallographic numbering are given in Figure 2. Other pertinent crystallographic data and parameters may be found in the microfilm addition.[14]

TABLE II
DATA FIT AND DEVIATIONS

Final R index ($\Sigma(\|\|F_o - F_c\|\|)/\Sigma\|F_o\|$)	0.087
Standard deviations[a] of coordinates	
Br	0.001 Å
C, O	0.008 Å
Uncertainties in C, O, Br bond lengths	0.01 Å
Uncertainties in C, O, Br bond angles	0.5°

[a] Standard deviations in the coordinates were derived from the residuals and the diagonal elements of the inverse matrix of the final least-squares cycle.

(11) A. J. C. Wilson, *Nature*, **150**, 152 (1942).
(12) A. C. Larson, *Acta Crystallogr.*, **23**, 664 (1967).
(13) C. K. Johnson, ORTEP, ORNL-3794, Oak Ridge National Laboratories, Oak Ridge, Tenn.

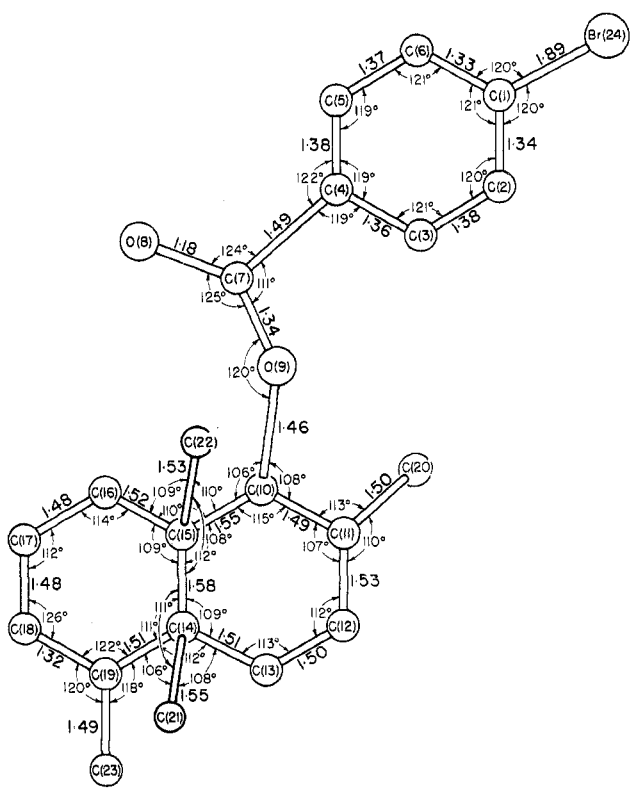


Figure 2.—Plot of bond distances and angles for the *p*-bromobenzoate **3b**.

Registry No.—**1**, 28058-97-1; **3a**, 28058-98-2; **3b**, 28058-99-3.

(14) F tables, atomic coordinates, anisotropic temperature factors, bond angles, and distances appear immediately following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.