Acid-Catalyzed Rearrangement of 2-*endo*-Phenyl-2-*exo*-hydroxyepicamphor[1]

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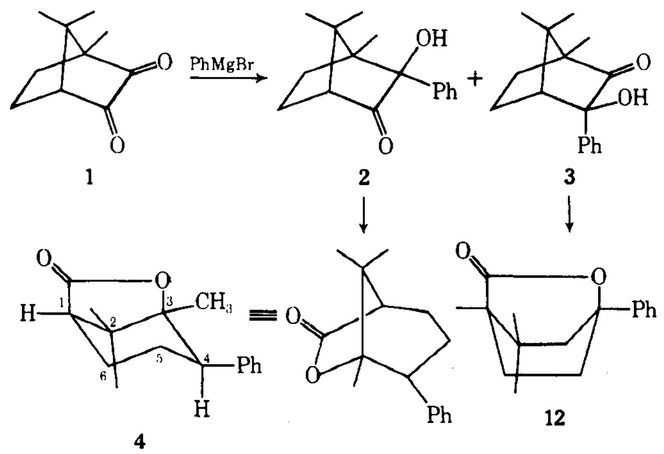
The molecular rearrangement of 2-*endo*-phenyl-2-*exo*-hydroxyepicamphor (**2**) with concentrated sulfuric acid at 0° is described. The product, isolated in yields of up to 90%, is the lactone of 3-hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylic acid (**4**). A possible intermediate in the rearrangement, 4-phenyl-2,2,3-trimethyl-3-cyclohexenecarboxylic acid (**11**), is readily converted into lactone **4** under the conditions of the rearrangement. The rearrangement of the isomeric ketol, 3-*endo*-phenyl-3-*exo*-hydroxycamphor (**3**), yields the lactone of 4-hydroxy-4-phenyl-1,2,2-trimethylcyclohexanecarboxylic acid (**12**) in low (~6%) yield.

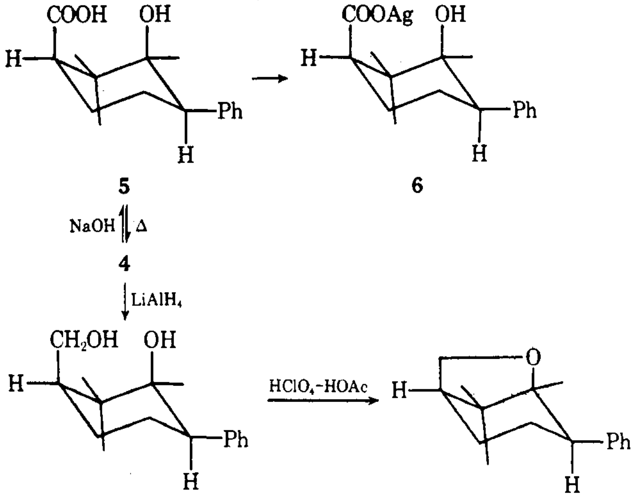
It has been known for many years that camphorquinone (**1**) in cold, concentrated sulfuric acid is converted into 4-keto-2,2,3-trimethylcyclohexanecarboxylic acid.[2] Recently an extensive study of the acid-catalyzed conversion of camphor into 3,4-dimethylacetophenone has been reported by Rodig and Sysko.[3] We wish now to report that a derivative of camphor, 2-*endo*-phenyl-2-*exo*-hydroxyepicamphor (**2**), rearranges in concentrated sulfuric acid at 0° to the lactone of 3-hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylic acid (**4**).

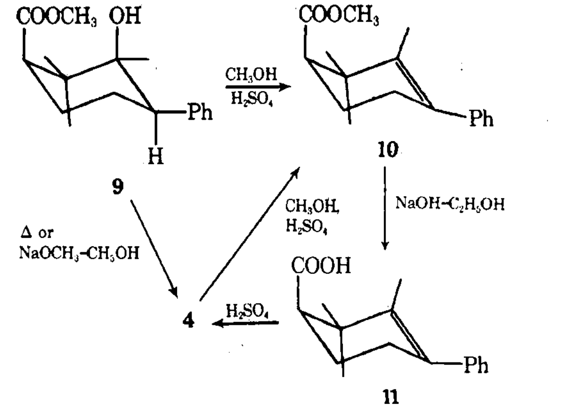
The reaction of camphorquinone with phenylmagnesium bromide afforded in good (~70%) yield and in almost equal proportions the isomeric ketols **2** and **3**, which were readily separated by fractional crystallization from methanol. To the less soluble isomer Gripenberg[4] assigned structure **2**. When ketol **2** was treated with H_2SO_4 at 0° for 30 min, lactone **4** was isolated in yields of up to 90%. The lactone exhibited carbonyl absorption in the infrared at 1763 cm^{-1}, characteristic of a five-membered ring.[5]



When the lactone **4** was hydrolyzed by alcoholic NaOH, the corresponding γ-hydroxy acid **5** was obtained following cautious neutralization. To provide the silver salt of acid **5** for an X-ray analysis, the method of Youngblood[6] was employed. The infrared spectrum of this salt exhibited an OH frequency at 3209 cm^{-1} and two typical, asymmetric and symmetric, stretching vibrations at 1530 and 1389 cm^{-1}.[7] X-Ray analysis[8] of the silver salt confirmed the structure shown in **6**. On pyrolysis of acid **5**, lactone **4** was regenerated. Reduction of either lactone **4** or acid **5** with $LiAlH_4$ gave 3-hydroxymethyl-6-phenyl-1,2,2-trimethylcyclohexanol (**7**) and reaction of diol **7** with perchloric in acetic acid (1:100) or with *p*-toluenesulfonyl chloride in pyridine afforded ether **8**, confirming the 1,3-cis-diaxial conformation of the hydroxymethyl and hydroxy groups.

On reaction with diazomethane, acid **5** gave ester **9**, methyl 3-hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylate, in good yield. The ester **9** afforded lactone **4** as the sole product when heated with sodium methoxide in methanol under reflux for 2 hr or under vacuum at 80° for 5 hr. When ester **9** was heated under reflux in methanol for 9 hr with a trace of H_2SO_4, the products were lactone **4** and the unsaturated ester **10** in a ratio of 2.7 to 1. When lactone **4** was treated under similar conditions, but for a period of 7 days, the reaction mixture contained starting material (6%), ester **10** (90%), and an unidentified compound. Ester **10** was then converted with alcoholic alkali into the corresponding acid **11** which yielded the lactone **4** under the conditions employed for rearrangement of ketol **2**. It is interesting that under none of the alkaline conditions employed was there evidence of epimerization of the carbomethoxyl group from axial to the more stable equatorial geometry. In the case of the hydroxy ester **9** it must be concluded that a competitive reaction, the formation of the tertiary alkoxide which is followed by concommitant cycli-

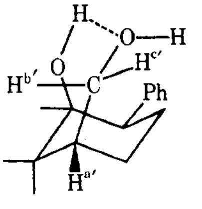




zation and expulsion of methoxide ion to regenerate lactone **4**, is fast relative to the ionization of the α-methinyl hydrogen.

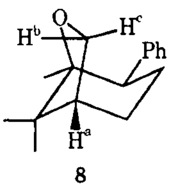
The proton nmr spectra were consistent with the structures postulated. For lactone **4**, there were three methyl singlets at δ 0.92, 1.09, and 1.19; a multiplet (4 H) centered at approximately δ 1.86; an ill-defined doubled (1 H) at δ 2.22 (J = 2.7 Hz); a doublet of doublets (1 H) at δ 2.95; and the aromatic protons at δ 7.2. The signal at δ 2.95 has been assigned to the benzyl (C_4) proton. The doublet of doublets with coupling constants J = 11.0 Hz between the C_4-benzyl proton and the C_5-axial proton, as well as the value J = 5.0 Hz between the C_4 proton and the C_5-equatorial proton, confirms the geometry of the benzyl proton as axial[9] and the aromatic ring as equatorial. The singlet at δ 2.22 has been assigned to the C_1 proton which is adjacent (α) to the carbonyl function. This signal is sharper than that of the benzyl proton, an observation which suggests that the C_1 proton occupies the equatorial position.

The nmr data for the δ 3.5–4.5 region of compounds **7** and **8** are summarized below. The protons H^b, $H^{b'}$, and $H^{c'}$ appear to be doublets of doublets, while H^c has only doublet character since the dihedral angle between it and H^a is approximately 90°.[10] The presence of different chemical shifts for protons $H^{b'}$ and $H^{c'}$ is evidence for a strong hydrogen bond between the two hydroxyl groups of **7** which prevents freedom of rotation of the hydroxymethyl group. The structure of **11** has been established by the proton nmr trace of the corresponding methyl ester **10**. A significant feature of the spectrum is the three-proton absorption at δ 1.50 which has been assigned to the C_3-olefinic methyl group. This methyl group is coupled with the two C_5 protons (the homoallylic position) with small coupling constants.



7

$H^{b'}$, δ 4.42; $H^{c'}$, δ 4.00
$J_{b',c'} = 11$ Hz
$J_{a'b'(c')} = 5.2$ Hz
$J_{a'c'(b')} = 3.3$ Hz

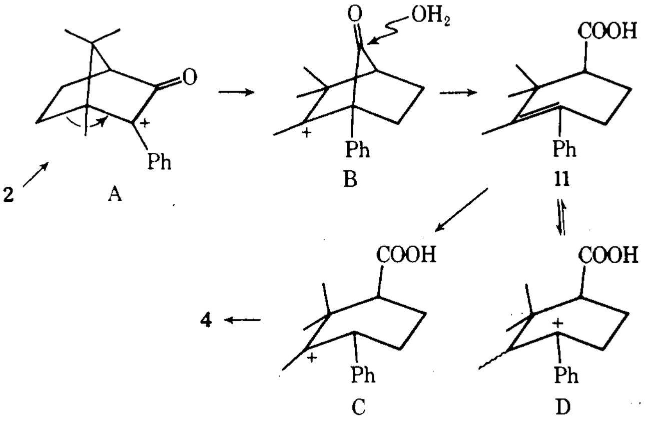


8

$\theta_{ab} = 18°$; $\theta_{ac} \approx 90°$
H^b, δ 4.02; H^c, δ 3.77
$J_{b,c} = 7.5$ Hz
$J_{a,b} = 4.5$ Hz
$J_{ac} \simeq 0$ Hz

A route for the molecular rearrangement of 2-*endo*-phenyl-2-*exo*-hydroxyepicamphor (**2**) is suggested in Scheme I.

Scheme I



Protonation of the carbinol provides the carbonium ion A which undergoes a Wagner–Meerwein rearrangement to give B. Attack of water at the carbonyl carbon of B accompanied by a concerted collapse of the C_1–C_7 σ bond yields the unsaturated acid **11**. Reprotonation of **11** provides the ions C and D and product **4** is obtained from what would appear to be the less stable carbonium ion C since high strain inherent in the boat conformation from D militates against lactonization. Formation of lactone **4** from the unsaturated acid **11** is consistent with the mechanism suggested above.

Finally, under conditions identical with those employed for the rearrangement of ketol **2**, 3-*endo*-phenyl-3-*exo*-hydroxycamphor (**3**) gave lactone **12**, but in only a 6% yield because of the strain inherent in the boat form of **12**. The major product was polymeric ester from intermolecular esterification. The infrared spectrum of **12** exhibited C–O–C stretching at 1176 and 1121 cm^{-1} and a carbonyl absorption at 1741 cm^{-1}, characteristic of six-membered lactones.[5] In the nmr trace, there were three methyl singlets at δ 0.84, 1.05, and 1.16; a multiplet (5 H) centered at δ 7.25; and no absorption between δ 2.2 and 7.0.

Experimental Section

Melting points and boiling points are uncorrected. Analyses are by Galbraith Laboratories, Knoxville, Tenn., or M-H-W Laboratories, Garden City, Mich. Analytical glpc analyses were performed on a Varian aerograph Series 1200 instrument; preparative glpc analyses were performed on an Aerograph Model A-700 autoprep. Nmr spectra were recorded on a Varian T-60 spectrometer and infrared spectra were obtained with Perkin-Elmer Models 137 and 237 spectrometers.

2-*endo*-Phenyl-2-*exo*-hydroxyepicamphor (2) and 3-*endo*-Phenyl-3-*exo*-hydroxycamphor (3). The method of Gripenberg[4] with the following modifications was employed. A solution of 50 g (0.30 mol) of camphorquinone (1) in 250 ml of dry ether was added to phenylmagnesium bromide (70.6 g, 0.45 mol, of bromobenzene and 10.2 g, 0.45 mol, of magnesium turnings) in 200 ml of ether at such a rate that slow reflux was maintained. The mixture was heated overnight under reflux; it was cooled in an ice bath and cold 10% HCl solution was added. Sufficient benzene in several portions was added to dissolve all solid material. The combined organic solutions were washed with 10% $NaHCO_3$ solution and with water and were then dried over $MgSO_4$. Benzene was removed under vacuum and the residue was dissolved in methanol (~600 ml). On cooling, a crop of 32.3 g of the crude isomer **2**, mp 184–190°, was obtained. On recrystallization from 400 ml of methanol, the yield was 28.0 g (38.2%) of ketol **2**, mp 193–194° (reported 193°). The volume of the filtrate was reduced and the residue was dissolved in hot hexane. On cooling, the yield of crude ketol **3** was 29.7 g, mp 109–113°. Recrystallization from 5:1 hexane–methanol yielded 25.5 g (34.8%) of **3**, mp 111–113° (reported 114–115°).

Lactone 4 of 3-Hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylic Acid. To 100 ml of concentrated H_2SO_4 at 0° was added in one portion 13 g (0.053 mol) of the ketol **2**. The mixture was stirred vigorously for 30 min at 0° and was poured into 1500 ml of an ice–H_2O mixture. The mixture was saturated with NaCl and extracted several times with ether. The combined ether layers were washed with saturated $NaHCO_3$ and H_2O and were then dried over magnesium sulfate. Removal of solvent afforded 10.85 g of crude product. Recrystallization from methanol–water afforded 10.7 g (92.5%) of the lactone **4**, mp 110.5–111°.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.61; H, 8.24.

Reaction of the Lactone 4 with NaOH. 3-Hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylic Acid (5) and Its Silver Salt 6. A mixture of 5.0 g (0.020 mol) of the lactone and 4 g of NaOH in 70 ml of 50% ethanol was heated under reflux for 4 hr, was cooled, and then was acidified with concentrated HCl. The aqueous mixture was saturated with NaCl and extracted with ether. The combined ether solutions were washed with H_2O and dried over magnesium sulfate. Removal of solvent afforded 5.1 g (94%) of hydroxy acid **5**, mp 89–92°. Two recrystallizations from acetone–water gave a sample, mp 93–94°. The acid was characterized as its silver salt **6**, which was prepared by the method of Youngblood.[6] To a suspension of acid **5** in water was added enough aqueous NH_3 to dissolve the acid and to make the solution just slightly basic to litmus. An equivalent amount of $AgNO_3$ in water was added slowly with stirring. The white solid which resulted was separated by filtration and was washed with water, ethanol, and then ether. Recrystallization from 95% ethanol afforded crystals for X-ray analysis.[8]

When heated at 100–110° for 30 min under house vacuum, the acid **5** (0.50 g) gave a residue which on recrystallization from methanol–water yielded lactone **4** (0.40 g, 87%), mp 110.8–112°. A mixture melting point with an authentic sample of **4** was not depressed.

Reduction of the Lactone 4 with $LiAlH_4$. 3-Hydroxymethyl-6-phenyl-1,2,2-trimethylcyclohexanol (7). A mixture of 7.0 g (0.028 mol) of lactone **4** and 0.4 g (0.011 mol) of $LiAlH_4$ in 140 ml of dry ether afforded 4.0 g (56%) of the diol **7**. Recrystallization from methanol gave the pure diol, mp 168.5–169.8°.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.13; H, 9.76.

Reduction of Hydroxy Acid 5 with $LiAlH_4$. Crude diol **7** (1 g) was obtained from 1 g of the hydroxy acid and $LiAlH_4$ in dry ether. Recrystallization from methanol–water afforded 0.7 g (74%) of the diol **7**, mp 168.5–169.8°. A mixture melting point with the diol prepared in the reduction above was not depressed.

Reaction of 3-Hydroxymethyl-6-phenyl-1,2,2-trimethylcyclohexanol (7) with $HClO_4$–HOAc. Preparation of the Ether 8. A mixture of 0.4 g of the diol **7** and 20 ml of a solution of $HClO_4$ in HOAc (1:100) was stored with occasional stirring at ambient temperature for 19 hr. A standard work-up afforded 0.29 g (78%) of the ether **8**, bp 95–100° (0.3 mm).

Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.25; H, 9.77.

Reaction of 3-Hydroxymethyl-6-phenyl-1,2,2-trimethylcyclohexanol (7) with *p*-Toluenesulfonyl Chloride in Pyridine. The diol (1.2 g, 0.005 mol) dissolved in 10 ml of pyridine was cooled in an ice–salt bath and a solution of 1.20 g (0.0063 mol) of *p*-toluenesulfonyl chloride in 7 ml of pyridine was added slowly. The reaction mixture was stirred at 0° for 4 hr and was then stored in a refrigerator for 2 days. The mixture was poured into ice-cooled 10% HCl solution and was extracted several times with ether. Removal of solvent afforded 0.7 g (70%) of ether **8**, bp 95–100° (0.3 mm).

Methyl 4-Phenyl-2,2,3-trimethyl-3-cyclohexenecarboxylate (10). A mixture of 1.95 g of lactone **4**, 75 ml of dry methanol, and 7.5 ml of concentrated H_2SO_4 was refluxed for 5 days. The reaction mixture was cooled to room temperature and was then poured into 300 ml of an ice–H_2O mixture. The aqueous mixture was extracted several times with ether and the combined ether layers were washed with 10% $NaHCO_3$ and H_2O and dried over magnesium sulfate. Removal of the solvent afforded 1.7 g of the crude oil which consisted of 90.5% of the ester **10**, 5.6% of the lactone **4**, and 3.9% of an unknown substance, determined by glpc on a SE-30 column at 180°. The ester **10** was purified through preparative glpc.

Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.63. Found: C, 79.22; H, 8.68.

4-Phenyl-2,2,3-trimethyl-3-cyclohexenecarboxylic Acid (11). (A) Saponification of Methyl 4-Phenyl-2,2,3-trimethyl-3-cyclohexenecarboxylate (10). The mixture of 0.8 g (0.003 mol) of the ester **10** and 0.8 g of NaOH in 10 ml of 50% ethanol was refluxed for 5 hr and then cooled. A standard work-up gave 0.6 g (79%) of the unsaturated acid which on recrystallization from ethanol–water exhibited mp 163.5–165.5°.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 79.05; H, 8.25.

Reaction of 4-Phenyl-2,2,3-trimethyl-3-cyclohexenecarboxylic Acid (11) with Concentrated H_2SO_4. To 2.5 ml of concentrated H_2SO_4 at 0° was added in one portion 0.2 g of the unsaturated acid and the solution was stirred at 0° for 30 min. Work-up afforded 0.16 g (80%) of the crude lactone **4** which was contaminated with less than 2% impurity, according to a glpc analysis. Two recrystallizations from methanol–water afforded pure lactone **4**, mp 110–111°. A mixture melting point with the sample obtained from the rearrangement of 2-*exo*-hydroxy-2-*endo*-phenylepicamphor was not depressed.

Methyl 3-Hydroxy-4-phenyl-2,2,3-trimethylcyclohexanecarboxylate (9). Diazomethane was prepared by the action of NaOH on bis(*N*-methyl-*N*-nitroso)terephthalamide. To the freshly prepared diazomethane in ether was added 1.50 g (0.0057 mol) of the hydroxy acid **5** in dry ether at room temperature. The mixture was stirred for 20 min and excess diazomethane was destroyed by addition of formic acid. The ether solution was filtered, washed with 3% $NaHCO_3$ and H_2O, and was then dried. Removal of solvent afforded 1.4 g (95%) of the crude ester **9**. Three recrystallizations from cold ligroine gave an analytical sample, mp 58.0–59.5°.

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.04; H, 8.89.

Attempted Epimerization of Methyl Ester 9. A mixture of the hydroxy ester **9** and $NaOCH_3$ in MeOH was heated under reflux for 2 hr. Work-up gave the lactone **4**.

Pyrolysis of Methyl Ester 9. The ester was heated at 80° under house vacuum for 5 hr. The product was identified as the lactone **4** by comparison of its nmr, ir, and melting point with an authentic sample.

Reaction of Methyl Ester 9 with MeOH and H_2SO_4. A mixture of 0.5 g of the ester **9**, 4 ml of CH_3OH, and 10 drops of concentrated H_2SO_4 was heated under reflux for 9 hr. Work-up gave a 1:2.7 ratio of **10** to **4** according to a glpc analysis.

Lactone 12 of 4-Hydroxy-4-phenyl-1,2,2-trimethylcyclohexanecarboxylic Acid. To 80 ml of concentrated H_2SO_4 at 0° was added in one portion 7.8 g (0.040 mol) of the ketol **3**. The mixture was stirred vigorously for 30 min at 0° and poured into 1300 ml of an ice–H_2O mixture. The mixture was saturated with NaCl and extracted several times with ether. The combined ether solution was washed with saturated $NaHCO_3$ and H_2O and then was dried over magnesium sulfate. Removal of solvent afforded 6.6 g (85%) of the crude residue which was distilled under reduced pressure. The fraction, bp 143–145° (0.4 mm), was collected and crystallized from hexane. The yield was 0.50 g (6.4%) of lactone **12**, mp 87.9–89°.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.67; H, 8.25.

The residue, a polymeric material, was recrystallized from acetone–water, mp >190°. An ir trace exhibited typical ester bands at 1111, 1171, and 1729 cm^{-1} and hydrolysis gave a nonuniform product.

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Registry No.—**1**, 465-29-2; **2**, 35202-03-0; **3**, 53684-40-5; **4**, 53684-41-6; **5**, 53684-42-7; **7**, 53684-43-8; **8**, 53684-44-9; **9**, 53684-45-0; **10**, 53684-46-1; **11**, 32623-12-4; **12**, 53684-47-2; bromobenzene, 108-86-1.

References and Notes

(1) Taken from a dissertation submitted by W.-C. Hsieh to the Graduate School of Duke University in partial fulfillment of the requirement for the Ph.D. degree, 1970. The partial support of this research by a grant (CA-4298) from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service, is acknowledged with gratitude.

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