Model Lactones Related to Eudesmanolides and Guaianolides[1]

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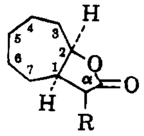
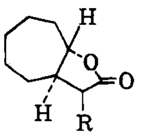
Six of the eight possible lactones of 2-hydroxy-α-methylcyclohexaneacetic and 2-hydroxy-α-methylcycloheptaneacetic acids have been synthesized. Configurations have been assigned to the products and relative stabilities are discussed.

In an earlier paper the synthesis and thermodynamic properties of the *cis*- and *trans*-cycloheptane lactones **1** and **2** were reported and contrasted with those of the cyclohexane analogs.[3] Because of the presence of α-methyl groups in guaianolides and pseudoguaianolides,[4] synthesis of the lactones **3**–**6** was also of interest. Previously reported compounds of this type[7] were of indeterminate stereochemistry and undoubtedly represented complex mixtures.

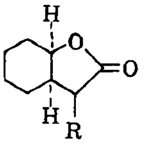
Compounds **3**–**6** were to be contrasted with the corresponding γ-lactones of the cyclohexane series **9**–**12**. In view of the controversy[8] over the configuration of the C-11 methyl group in the santonin series it was surprising that no stereospecific syntheses of **9**–**12** had been recorded.



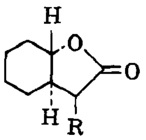
1,[9] R = H
3, R = —CH$_3$
4, R = . . . CH$_3$



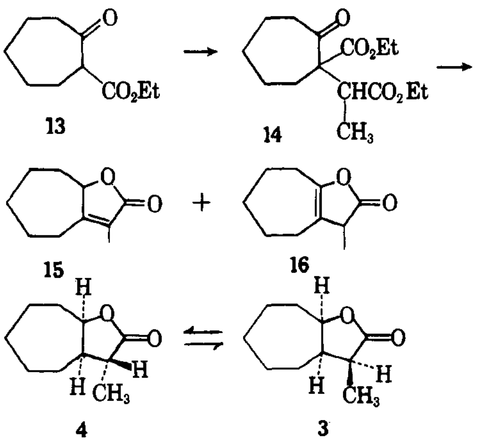
2, R = H
5, R = —CH$_3$
6, R = . . . CH$_3$



7, R = H
9, R = —CH$_3$
10, R = . . . CH$_3$



8, R = H
11, R = —CH$_3$
12, R = . . . CH$_3$



Lactone **3** was synthesized from 2-carbethoxycycloheptanone in the manner shown. In contrast to our experience with **1**,[3] hydrolysis of **14** led directly to the unsaturated lactone (**15**) contaminated by a small amount of the β,γ-unsaturated isomer (**16**). The facile cyclization exemplifies the operation of the Thorpe–Ingold effect. High-pressure hydrogenation of **15** led to a saturated lactone which was homogeneous as shown by g.l.c., infrared, and n.m.r. spectroscopy. The nonidentity of the product and of its α-C epimer (**4**) with that of the *trans* lactone (**5**) indicated that the hydrogenation was stereospecific and had led, by the usually accepted mechanism *via cis* addition, to the all-*cis* isomer (**3**).

It might be argued that in the present instance hydrogenation of **15** could proceed in a *cis*-1,4 manner and that the resulting enol could have rearranged to the presumably more stable **4**. This is contraindicated by the observation that equilibration of the hydrogenation product (**3**) with anhydrous potassium carbonate in xylene resulted in the formation of an equilibrium mixture containing 30% of starting material and 70% of a new substance (**4**) homogeneous by g.l.c., infrared, and n.m.r. spectroscopy. The two lactones were separated by chromatography over neutral alumina, the new isomer being eluted first. This is in agreement with the structure assignment since inspection of Dreiding models indicates that lactone **4** would present more hindrance to surface absorption near the carbonyl group. Further evidence for the assignments will be given subsequently.

A lactone of probable formula **5** was synthesized as shown on p. 614, col. 1).

The very sluggish condensation of **17** with diethyl sodiomethylmalonate resulted in recovery of much starting material and, surprisingly enough, directly in the isolation of a small amount of **5**. Saponification of the nonvolatile residue, presumably **18**, led to the isolation of additional **5** and the lactone acid (**19b**). The latter on heating above its melting point decarboxylated smoothly with formation of **5** which was shown to be homogeneous by g.l.c., infrared, and n.m.r. spectroscopy.

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(1) Supported in part by a grant from the National Science Foundation (NSF-G 14396).

(2) Abstracted from a dissertation of L. A. Glick submitted in partial fulfillment of the requirements for the degree Doctor of Philosophy, 1963.

(3) W. Herz and L. A. Glick, *J. Org. Chem.*, **28**, 2970 (1963).

(4) We are adopting this term, suggested by Dr. V. Herout, for the sesquiterpene lactones based on the "abnormal" carbon skeleton of parthenin[5] and constituents of *Helenium* species.[6]

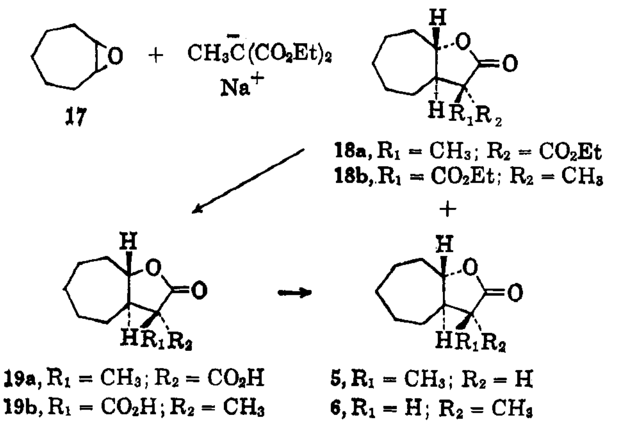
(5) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962).

(6) W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman, and N. Viswanathan, *ibid.*, **84**, 3857 (1962); W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *ibid.*, **85**, 19 (1963).

(7)(a) L. Mangoni and M. Belardini, *Ric. sci. Suppl.*, **29**, 1542 (1959); *Chem. Abstr.*, **54**, 8763 (1959); (b) L. Mangoni and M. Belardini, *Ann. chim.* (Rome), **50**, 309, 322 (1960); (c) L. Mangoni and G. Bandiera, *Gazz. chim. ital.*, **90**, 947 (1960); (d) S. Naito, *J. Pharm. Soc. Japan*, **75**, 325 (1955).

(8) W. Cocker and T. B. H. McMurry, *Tetrahedron* **8**, 181 (1960). This recently has been settled, J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.*, 111 (1962); D. H. R. Barton, T. Miki, J. T. Pinhey, and R. J. Wells, *ibid.*, 112 (1962); M. Nakazaki and H. Arakawa, *ibid.*, 151 (1962); J. D. M. Asher and G. A. Sim, *ibid.*, 335 (1962).

(9) All compounds synthesized and described in this paper are racemates, although the formulas depict only one enantiomer.



The simultaneous formation of **5** and **19b** from the mixture of lactone esters (**18**) may be explained in the following manner. Saponification of **18** followed by acidification should result in the two isomeric lactones **19a** and **19b**. The models indicate that there is more crowding between the bulky carboxyl group and the C-7 protons of **19a** than of **19b**. Hence **19a** should be of higher energy and should be decarboxylated more readily by the commonly accepted mechanism[10] to the enol which is then protonated in such a way so as to yield the more stable methyl configuration. Decarboxylation of **19b** at higher temperatures would give the same enol and hence lactone **5** also. Similar observations during the decarboxylation of two closely related isomeric α-methyllactone acids have been reported.[11]

Assignment of structure **5** to the stable lactone is based on n.m.r. spectroscopy. Efforts to correlate **5** with one of the two lactones (**3** or **4**) by chemical means in order to place this assignment on a more secure footing were not successful. Similarly, several attempts to prepare less stable isomer **6** have so far been unproductive.

The literature[12] records the isolation of **9** or **10**, but the reaction sequence used permits no decision between the two formulas and indeed suggests that the product might have been a mixture. Adaptation of the method used for the preparation of **3** led to lactone **9**, whose purity was established by g.l.c., infrared, and n.m.r. spectroscopy.

9 was not affected by refluxing with potassium carbonate in xylene but was successfully equilibrated at the temperature of boiling tetralin. The reason for the increased stability of **9** as compared with **3** is not immediately apparent but may entail greater steric hindrance to proton removal by base. The equilibrium mixture contained 40% of **9** and 60% of a new lactone. For chemical work the isomers were separated by column chromatography. The more rapid elution of the new isomer and the established stereochemistry of lactone **9** (mode of preparation and n.m.r. analysis) show that the new isomer is **10**.

The Canadian workers[12] also reported the preparation of a lactone (**11** or **12**) by reaction of cyclohexene oxide with diethyl methylmalonate followed by hydrolysis. Repetition of this work led to a substance which appeared to be homogeneous by g.l.c. criteria. However, while the n.m.r. spectrum (*vide infra*), established the absence of **9** or **10**, it indicated the presence of 10% of another isomer. Composition of the mixture was unchanged by chromatography or treatment with potassium carbonate. Hence the material appears to be an equilibrium mixture containing 90% of what is probably **11** and 10% of **12** which could not be removed with the means at hand.

N.m.r. peaks of lactones **3**–**5** and **9**–**11** are listed in Table I and confirm the assignments. In **3** and **9** where C-1–H, C-2–H, and α-H are on the same side of the ring system, α-H is a multiplet near 2.85 and the methyl group is found at 1.12 p.p.m. In **4** and **10**, α-H is shifted upfield to 2.3 and the methyl signal is shifted downfield to 1.23 p.p.m. This is in agreement with the assignments made earlier, the methyl group of **3** and **9** being screened more effectively by the ring bonds than the methyl group of **4** and **10**. Conversely, α-H of **4** and **10** is shielded more effectively than α-H of **3** and **9**. The multiplicity and chemical shift of C-2–H in **9** and **10** suggest it is equatorial.[13] In accord with the models, lactone **10** seems to be more flexible than lactone **9** as indicated by the envelope of the methylene region. As expected **4** is more flexible than **3** as indicated by the narrowing of the methylene envelope which is centered at 1.88 p.p.m.

TABLE I[a]

N.M.R. PEAKS OF LACTONES

Lactone	C-2-H[b]	H[c]	CH_3[d]	$-CH_2$[e]$-$
3	4.64 dt (9,5.5)[f]	2.88 m[g](7)	1.12 d (7.5)	1.4–2.0 e
4	4.58 dt (8,4)[f]	2.3[h]	1.24 d (7)	1.88 s
5	4.22 n	2.5[h]	1.22 d (6.5)	1.66 s
9	4.65 m[f]	2.85 m(7)[g]	1.12 d (7)	1.3–2.0 e
10	4.53 m[f]	2.07–2.58[h]	1.23 d (6.5)	1.4–1.8 e 1.5 s
11	3.76 n	2.4[h]	1.22 d (7)	1.4–2.4 e

[a] Spectra determined on Varian A-60 and HR-60 spectrometers in carbon tetrachloride. Values given in p.p.m. relative to tetramethylsilane as internal standard. Multiplets are described as follows: d, doublet; t, triplet; m, multiplet of uncertain multiplicity; n, unresolved multiplet; s, relatively sharp signal corresponding to several protons; usually superimposed on envelope, e. Numbers in parentheses denote coupling constants in c.p.s. [b] Intensity one proton. [c] Intensity two protons. [d] Intensity three protons. [e] Ring protons other than C-2–H. [f] X of AB_2X. [g] Five bands of multiplet visible and separated by value given. [h] Signal partially or completely superimposed on ring protons.

The chemical shifts of α-H and the methyl group of lactone **5** suggest (compare with **4**) that C-1–H and α-H bear a *trans* relationship to each other. The relatively sharp band of the ring protons, as compared with the broad envelope exhibited by **11**, again illustrates the flexibility of the *trans* fused seven-membered ring.[3] In the n.m.r. spectrum of **11**, C-2–H was shifted upfield to the position occupied by C-2–H of the *trans* lactone **8** (H axial).[3] Methyl appeared as a doublet at 1.22 p.p.m. (note similarity to **4**, **5**, and **10**), but the presence of a weak doublet at 1.15 p.p.m. suggested that **11** was an equilibrium mixture containing about 10% of

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(10) J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 304.

(11) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi, and T. Toga, *J. Am. Chem. Soc.*, **78**, 1422 (1956).

(12) E. H. Charlesworth, H. J. Campbell, and D. L. Stachiw, *Can. J. Chem.*, **37**, 877 (1959).

(13) Compare with C_2-H (eq.) of **1** at 4.60 and C_2-H (ax.) of **2** at 3.87 p.p.m.[3]

12. Transparency of the 4.5-p.p.m. region indicated the absence of lactones **9** and **10**.

In summary, among the model *cis* lactones considered in this paper, the α-methyl group is in the more stable position when *cis* to the adjacent ring hydrogen, whether the ring be six- or seven-membered. The preference is so slight, however (ΔF approximately -0.2–-0.3 kcal./mole), that other factors will undoubtedly exercise an overriding influence in more complex systems like the eudesmanolides and guaianolides.

In the *trans* lactones the overwhelming preference is for one of the two possible isomers. The n.m.r. evidence suggests that this is the isomer where the α-methyl group is *trans* to the adjacent ring hydrogen, whether the ring be six- or seven-membered. This stability relationship is not the one which prevails in the α- and β-tetrahydrosantonins[8] or some pseudoguaianolides.[14]

Experimental[15]

Ethyl 1-Carbethoxy-α-methyl-2-oxocycloheptaneacetate (14).—To an ice-cooled mixture of 40 g. of 2-carbethoxycycloheptanone, 39.3 g. of ethyl α-bromopropionate, 0.3 g. of potassium iodide, and 140 ml. of ethanol was added dropwise over 1 hr. a solution of sodium ethoxide (4.9 g. of sodium in 175 ml. of ethanol). The slurry was allowed to warm to room temperature and was refluxed for 1 hr. until the pH did not decrease further. Distillation of 300 ml. of ethanol was followed by cooling, dilution with water, and extraction with ether. The washed and dried ether extracts were concentrated and distilled. Three fractions were collected: b.p. 31–35° (3 mm.), 5 g. (2-carbethoxycycloheptanone); b.p. 88–130° (0.4 mm.), 10 g. (mainly ethyl α-bromopropionate); b.p. 136–139° (0.4 mm.), 26.6 g. (**14**, 45%). The last fraction was redistilled in a nitrogen atmosphere, b.p. 145° (0.1 mm.), n^{25}D 1.4694, n^{20}D 1.4707, infrared bands at 1750 (ester) and 1720 cm.$^{-1}$ (cycloheptanone).

Anal. Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.12; H, 8.20.

Lactones of 2-Hydroxy-α-methylcycloheptane-$\Delta^{1,2}$-acetic Acid (15) and 2-Hydroxy-α-methyl-1-cycloheptene-1-acetic Acid (16).—A mixture of 20 g. of **14** was refluxed with 80 ml. of concentrated hydrochloric acid for 12 hr., an additional 20 ml. of acid was added, and the mixture was refluxed overnight. Most of the water was removed at reduced pressure. The residue was taken up in water and ether, the ether layer was separated, and the water layer was extracted several times with ether. The combined ether layers were dried, concentrated (wt. of residue, 12.6 g.), distilled, and the fraction, b.p. 123–126° (0.8 mm.), 10.2 g., n^{26}D 1.5092, was collected; infrared bands were at 1770 and 1670 cm.$^{-1}$ (α,β-unsaturated lactone), and at 1800 and 1630 cm.$^{-1}$ (β,γ-unsaturated lactone, these bands were relatively weak). Since the presence of **16** did not interfere with the planned reaction, the mixture was used immediately for the following step.

Lactone of *cis*-2-Hydroxy-*cis*-α-methylcycloheptaneacetic Acid (3).—Hydrogenation of 7.5 g. of the above in 300 ml. of ethanol with freshly prepared Raney nickel at 100° and 1400-lb. hydrogen pressure resulted in 13 g. (74%) of **3**, b.p. 92–93° (0.3 mm.); homogeneous by g.l.c.; infrared bands at 1780, 1175, 1170, and 1020 cm.$^{-1}$ (relative intensities of the last two bands were the same).

Anal. Calcd. for $C_{10}H_{16}O_2$; C, 71.39; H, 9.59. Found: C, 71.22, 71.54; H, 9.42, 9.40.

This substance was first prepared by reduction of 0.25 g. of the lactone mixture with platinum oxide in acetic acid at room temperature and standard pressure (ethanol was not satisfactory). Attempts to repeat the preparation subsequently in this way or in a Parr hydrogenator were not successful.

Lactone of *cis*-2-Hydroxy-*trans*-α-methylcycloheptaneacetic Acid (4).—A solution of 4.39 g. of **3** in 50 ml. of xylene was refluxed with 0.44 g. of potassium carbonate for 4 hr., the solvent was distilled, the residue was taken up in ether and water, and the ether layer was dried and fractionally distilled to yield 3.1 g. (71%) of product, b.p. 77–84° (0.3 mm.). G.l.c. on a 2-ft. Degs column indicated the presence of 30% of starting material and 70% of the epimer (**4**); more prolonged heating had no effect on the composition.

Preparative scale g.l.c. on a 4 × 0.5 in. Degs or silicone SF-96 column gave incomplete separation, but column chromatography on neutral alumina (40 g. of absorbent /1 g. of sample) was successful. **4** was eluted with benzene–pentane (2:3); **3** was eluted with benzene–pentane (4:1). Redistillation of **4** furnished material, b.p. 82° (0.3 mm.); infrared bands at 1780, 1148, 1020, and 1008 cm.$^{-1}$ (intensity of last two bands greater than band at 1148 cm.$^{-1}$); homogeneous on g.l.c. and easily distinguishable from **3** by n.m.r. spectroscopy.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39: H, 9.59. Found: C, 71.54; H, 9.40.

Lactone of *trans*-2-Hydroxy-α-methylcycloheptaneacetic Acid. (5).—The condensation of 14.36 g. of cycloheptene oxide with 23.4 g. of diethyl methylmalonate using sodium ethoxide (from 3.06 g. of sodium) in 100 ml. of ethanol was carried out as described previously[3] for diethyl malonate. After 48 hr. of reflux the solution was poured on ice, the neutral portion was extracted with ether, and the ether was dried and concentrated; the residue weighed 18.5 g. The base-soluble material was acidified, and the oil was extracted with ether, dried and concentrated; the residue weighed 8.7 g.

Distillation of the neutral fraction furnished 3.05 g. of cycloheptene oxide, 10.3 g. of diethyl methylmalonate, and 1.6 g. of lactone **5**, b.p. 80° (0.07 mm.), n^{24}D 1.4767. Redistillation of the lactone furnished material, b.p. 74° (0.14 mm.), n^{25}D 1.4757, which was chromatographed over neutral alumina. Elution with benzene–pentane (4:1) furnished pure **5**, b.p. 97–98° (0.8 mm.); infrared bands at 1780, 1180, and 1010 cm.$^{-1}$ (last two bands of equal intensity); the substance was homogeneous on g.l.c.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.65.

The residue from the distillation of the neutral fraction was hydrolyzed with 40 ml. of 5% sodium hydroxide solution for 3 hr., cooled, and acidified. A solid precipitated and was recrystallized several times from hot water to yield 0.38 g. of **19b**, m.p. 151–152.5° dec., infrared bands at 1770 (γ-lactone) and 1730 cm.$^{-1}$ (acid). The lactone acid decarboxylated slowly on standing at room temperature and gave poor analytical results.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.26; H, 7.60. Found C, 63.23; H, 7.51.

When **19b** was heated in an oil bath at 180°, **5** was formed. Distillation of the acid fraction gave 2.15 g. of material, b.p. 81–92° (0.2 mm.), n^{25}D 1.4410; infrared bands at 1795, 1750, 1720 cm.$^{-1}$ (acid –OH); neut. equiv. 217, which was not further investigated, but may have been the isomeric lactone acid. The residue was heated overnight at 135–140° with 15 ml. of concentrated hydrochloric acid; the solvents were removed at reduced pressure; the residue was heated at 180° for 3 hr. until carbon dioxide evolution had ceased and was distilled. An additional 1.5 g. of **5** was obtained in this way, identical in all respects with the material previously isolated.

Lactones of 2-Hydroxy-α-methyl-1-cyclohexene-1-acetic Acid and 2-Hydroxy-α-methyl-Δ^1-cyclohexaneacetic Acid.—Condensation of 2-carbethoxycyclohexanone with ethyl α-bromopropionate proceeded far more slowly than the condensation of 2-carbethoxycycloheptanone to give a 31% yield after 96 hr., b.p. 96–121° (0.2 mm.). This material was hydrolyzed with acid in the usual manner to give a 27% yield of product, b.p. 74–86° (0.2 mm.), infrared bands at 1770 and 1620 cm.$^{-1}$ (α,β-unsaturated lactone) and 1805 and 1700 cm.$^{-1}$ (β,γ-unsaturated lactone, ratio approx. 4:1), λ_{max} 217 mμ (ϵ 9300).

Lactone of *cis*-2-Hydroxy-*cis*-α-methylcyclohexaneacetic Acid (9).—The hydrogenation of the above mixture required more vigorous conditions than hydrogenation of the cycloheptane analogs. A solution of 3.6 g. of the lactone mixture in ethanol was hydrogenated with W-2 Raney nickel at 1800 lb. and 135° for 24 hr. The usual work-up gave 2.5 g. of material, b.p. 77–79° (0.5 mm.), which was taken up in ether, extracted with 5%

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(14) W. Herz, A. R. de Vivar, J. Romo, and N. Viswanathan, *Tetrahedron*, **19**, 1359 (1963); E. Dominguez and J. Romo, *ibid.*, **19**, 1415 (1963).

(15) Melting points and boiling points are uncorrected. Analyses are by Dr. F. Pascher, Bonn, Germany. Gas-liquid chromatograms were run on an F & M Model 500 instrument using 0.25 × 2 in. copper tubing programmed from 85–220° at 11°/min. and held at the higher temperature; carrier gas was helium at 60 ml./min.

sodium bicarbonate solution, washed, dried, and distilled to yield 2.07 g. of product, b.p. 79–80.5° (0.6 mm.); infrared bands at 1780, 1175, and 970 (last two bands of equal intensity); homogeneous on g.l.c.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.61; H, 9.18.

Lactone of *cis*-2-Hydroxy-*trans*-α-methylcyclohexaneacetic Acid. (10).—Attempted epimerization of 9 with potassium carbonate in refluxing xylene was unsuccessful. However, it was found that equilibration was complete when 1.0 g. of 9 was refluxed with 10 ml. of tetralin and 0.1 g. of potassium carbonate for 12 hr. Further heating caused no change in the infrared spectrum or gas–liquid chromatogram of the product except for an increase in the proportion of α-tetralone (*vide infra*). The solvent was removed by distillation; the residue was taken up in ether, washed, dried, and distilled to give 0.5 g. of product, b.p. 75–76° (0.6 mm.); g.l.c. analysis of the distillate indicated the presence of α-tetralone and 9 and 10 in a ratio of 2:3.

The distillate was chromatographed over 20 g. of alumina. Benzene–pentane (2:3) eluted 0.04 g. of α-tetralone, identified by comparison with an authentic sample (g.l.c. and infrared spectrum). This was followed, with some overlap, by 10, 0.094 g., eluted with benzene–pentane (1–1), and then by 9, 0.092 g., eluted with benzene–pentane (4:1). The remainder of the product could not be removed from the column, possibly because of cleavage to the hydroxy acids. Distillation of 10 furnished material, b.p. 78° (0.6 mm.); infrared bands at 1780, 1185, and 1025 cm.$^{-1}$ (last band weaker than band at 1185 cm.$^{-1}$); this was homogeneous on g.l.c. analysis.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; Found: C, 70.18; H, 9.15.

Lactone of *trans*-2-Hydroxy-α-methylcyclohexaneacetic Acid (11).—This lactone was prepared by refluxing 28.8 g. of cyclohexene oxide and 54 g. of diethyl methylmalonate in 250 ml. of sodium ethoxide solution (from 7.25 g. of sodium) for 6 hr. The usual work-up and hydrolysis by the literature method[6] gave 16.2 g. of a lactone, b.p. 80–83° (0.4 mm.), lit.[6] 125–128° (10 mm.); infrared bands at 1790, 1180, and 1020 cm.$^{-1}$ (last band more intense than band at 1180 cm.$^{-1}$). This material appeared to be homogeneous when subjected to g.l.c. analysis using a number of different columns, but the n.m.r. spectrum indicated the presence of about 10% of 12.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.00; H, 9.28.

The Rearrangement of Limonene and Carvomenthene Epoxides

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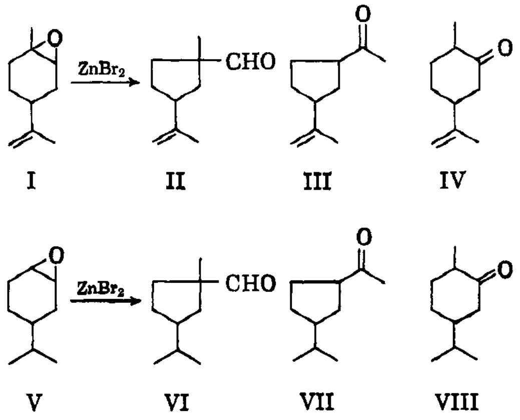
The monocyclic terpene oxides, limonene oxide, and carvomenthene oxide have been reported previously to yield a variety of six-membered ring products by reaction with alumina or Lewis acid catalysts. It has been found that limonene oxide in the presence of zinc bromide rearranges with ring contraction to 1-methyl-3-isopropenylcyclopentyl-1-carboxaldehyde and methyl (3-isopropenylcyclopentyl) ketone and isomerizes to dihydrocarvone. Similarly, carvomenthene oxide rearranges to 1-methyl-3-isopropylcyclopentyl-1-carboxaldehyde and methyl (3-isopropylcyclopentyl) ketone and isomerizes to carvomenthone. Structural elucidation of the rearranged products was achieved by chemical synthesis and supported by nuclear magnetic resonance. Several alcohol and acetate derivatives of rearranged products were prepared.

During our investigation of the chemical composition of Florida orange oil (Valencia), limonene oxide (I), a constituent of this oil, was found to undergo acid-catalyzed rearrangement. This reaction of I was observed to occur during both its gas chromatographic analysis on acid-washed support and in the presence of Lewis acid catalysts. Thus, reaction of limonene oxide (I) with zinc bromide in refluxing benzene yielded three products, an aldehyde (II, 30%), a ketone (III, 10%), and dihydrocarvone (IV, 59%). An analogous reaction with carvomenthene oxide (V) yielded an aldehyde (VI), a ketone (VII), and carvomenthone (VIII) in similar proportions (Chart I). That the reaction does proceed in a similar manner is shown by the catalytic hydrogenation of II, III, and IV to VI, VII, and VIII, respectively.

The formation of dihydrocarvone and carvomethone from limonene oxide and carvomenthene oxide, respectively, has been the subject of previous investigations[3,4]; however, there has been no report of materials having a cyclopentane structure, although in this case, they constitute 40% of the reaction mixture.

The isomerization or rearrangement of epoxides to carbonyl compounds is a general reaction.[5–9] The structures of the rearranged products depend on a variety of factors, *i.e.*, the direction of oxide ring opening, the relative migratory aptitudes of the different substituent groups,[10] and the steric requirements

CHART I



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[1] Naval Stores Laboratory, Olustee, Fla.

[2] One of the laboratories of the Southern Utilization Research and Development Division, Agriculture Research Service, U. S. Department of Agriculture. References to specific products of commercial manufacture are for illustration only and do not constitute endorsement by the U. S. Department of Agriculture.

[3] E. E. Royals and L. L. Harrell, Jr., *J. Am. Chem. Soc.*, **77**, 3405 (1955).

[4] A. Kergomard and M. Th. Geneix, *Bull. soc. chim. France*, 390 (1958).

[5] S. M. Naqvi, J. P. Horwitz, and R. Filler, *J. Am. Chem. Soc.*, **79**, 6283 (1957).

[6] E. A. Braude, A. A. Webb, and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3328 (1958).

[7] B. A. Arbuzov, *Ber.*, **68**, 1430 (1935).

[8] L. C. King and H. Farber, *J. Org. Chem.*, **26**, 326 (1961).

[9] R. Dulou, Y. Chretien-Bessiere, and J. P. Montheard, *Compt. rend.*, **254**, 3374 (1962).

[10] S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, R. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 1.