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Preparation of Some Bicyclic Ethers

Steven Wolff, Amos B. Smith, III, and William C. Agosta*

Laboratories of The Rockefeller University, New York, New York 10021

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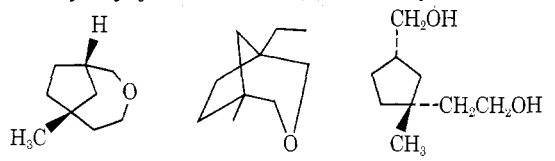
Synthetic routes to 1 and 2 are described. Noteworthy reactions are the formation of bicyclic seven-membered lactone 21 promoted by ethyl chloroformate and the cyclizations leading to ethers 17–20 *via* intramolecular Michael processes.

In the course of verifying the structures of certain photochemically derived compounds, we required authentic samples of bicyclic ethers 1 and 2. We describe here routes to these substances by way of the related glycols, along with structural information concerning other bicyclic systems encountered in this work.

The glycol 3, which is related to ether 1, was prepared by two different routes. In the first approach condensation of 4-benzoyloxycyclohexanone (4)[1] with cyanoacetic ester



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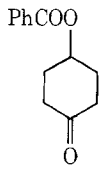

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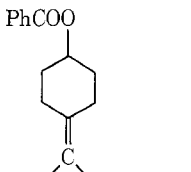

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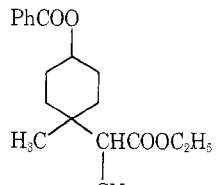

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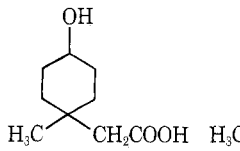

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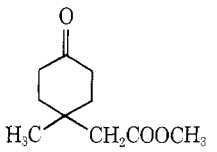

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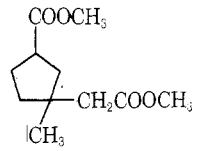

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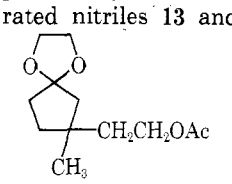
yielded 5, which reacted with methylmagnesium iodide in the presence of tetrakisiodo(tributylphosphine)copper(I)[2] to give 6.[3] Saponification and decarboxylation then furnished hydroxy acid 7, which was converted directly to 8[4] by Jones oxidation[5] and esterification with diazomethane. Keto ester 8 underwent clean ring contraction on treatment with thallium(III) nitrate in acetic acid,[6] and the product was conveniently isolated after conversion to diester 9. Reduction with lithium aluminum hydride then furnished the mixture of epimeric diols. The desired diol 3 was separated from its epimer by preparative vapor phase chromatography (vpc) of the bis(trimethylsilyl)[7] ether and characterized as the diacetate. The stereochemical assignment rests on comparison of this deacetate and the epimeric trans compound with the diacetate of 3 prepared by the second route to be described below. This latter approach yields a single isomer of clearly defined configuration.

The inconvenience of this sequence, particularly the tedious purification of 3, which we found no way to avoid,[8] led us to develop an alternative synthesis. The previously described[9] ketal acetate 10 was converted through ketone 11 to cyanohydrin 12. This was dehydrated using phosphorus oxychloride and pyridine to a mixture of unsaturated nitriles 13 and 14. Hydrogenation of this mixture



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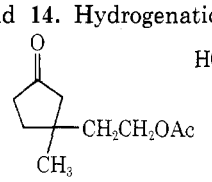

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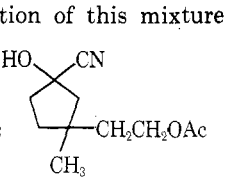

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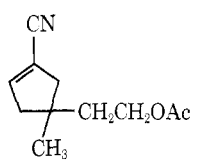

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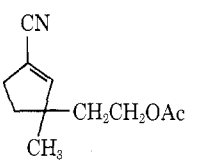

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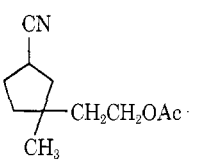

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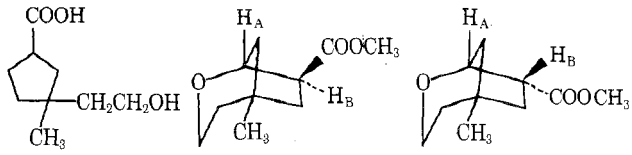
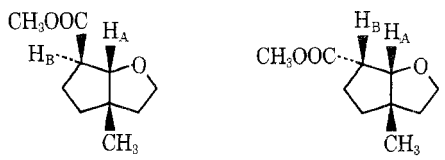
furnished the cyanoacetate 15, which could be hydrolyzed to the mixture of epimeric hydroxy acids 16.

Hydrolysis of 13 and 14 before hydrogenation of the double bond led to a mixture of bicyclic carboxylic acids which was esterified with diazomethane and then separated by vpc to furnish esters 17–20. These compounds presumably arise from initial saponification of the ester function of 13 and 14, intramolecular Michael addition of the hydroxyl group thus formed, and subsequent hydrolysis of the bicyclic nitrile.

The structures 17–20 are based on the origin of these compounds, spectroscopic evidence, and base-catalyzed interconversion of each pair of esters. For 19 and 20 the environment of the unique low field carbinyl proton H_A was substantiated by double irradiation at H_B. Under



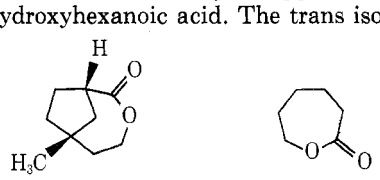
16 17 18



19 20

these conditions the signal for H_A collapses to a singlet. The results presented in Table I also lead to assignment of stereochemistry for the carbomethoxyl group through application of the Karplus equation.[10] In support of these assignments equilibration in base of the less stable endo isomers **18** and **20** led to mixtures containing predominantly exo epimers **17** and **19**, respectively. Cis ring fusion in **19** and **20** is required, since these cyclizations occur under conditions favoring formation of the stabler isomer, and the alternative trans-fused system is quite strained.[11]

Conversion of *cis*-**16** into the seven-membered lactone **21** permitted separation of isomers at this point. Although ϵ-caprolactone (**22**) can be obtained[12] by treatment of 6-hydroxyhexanoic acid with benzenesulfonic acid in a large volume of benzene using a water separator, these conditions converted **16** only to polymeric ester. We found successful conditions for preparation of **21** in the exposure of **16** first to 2 equiv of triethylamine and then 1 equiv of ethyl chloroformate at −18°, all in dichloromethane at high dilution. This procedure afforded approximately 60% of **21** based on the estimated amount (nmr) of cis isomer present in the mixture **16**. It gave approximately 50% of **22** from 6-hydroxyhexanoic acid. The trans isomer present



21 22

in **16** was converted to polymeric ester under these conditions; this material could be recovered, saponified, and then recycled in the lactonization reaction after base-catalyzed partial epimerization of the derived methyl ester. Similar use of ethyl chloroformate in forming esters from carboxylic acids and alcohols has been known for some years,[13] but we are unaware of its prior application in selective preparation of medium ring lactones.

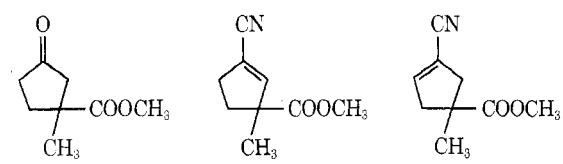
Lactone **21** was then reduced with sodium borohydride in the presence of boron trifluoride etherate. Previous experience[14] suggested that these or various other conditions favoring conversion of esters and lactones directly to ethers might well yield only diol **3** from **21**. In the event **21** was reduced largely to **3** and about 1–2% of bicyclic ether **1**.[15] Glycol **3** was characterized as its diacetate, and this material was employed in distinguishing the epimeric diacetates prepared nonstereospecifically above. This second sequence thus provided a more convenient pathway to **3**, assured its stereochemistry, and even furnished a small amount of **1** directly from lactone **21**. Treatment of **3** first with 1 equiv of tosyl chloride in pyridine and then with sodium hydride in tetrahydrofuran gave the desired ether **1**.

Preparation of bicyclic ether **2** started with the known[16] keto ester **23**, which was converted to the mixture of unsaturated nitriles **24** and **25** by way of the cyanohydrin as detailed above for **13** and **14**. Hydrogenation of this mixture then gave the saturated nitriles **26a** and **27a** which were separated by vpc for characterization. The configuration of these isomers is discussed below. For preparative purposes they were alkylated without separation using ethyl iodide and lithium dicyclohexylamide[17] in dimethoxyethane, first at −78° and then at room temperature, to give **26b** and **27b** which were also separated by vpc and characterized.

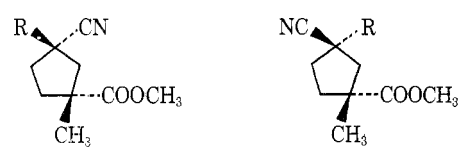
Table I
Nmr Data for H_A and H_B in 17–20

Compd	Signal, δ H_A	H_B
17	4.28 (br s, $w_{1/2}$ = 6 Hz, 1 H)	2.97 (ddd, $J_1 \sim J_2 \sim 6.5$, $J_3 \sim 1$ Hz, 1 H)
18	4.37 (br s, $w_{1/2}$ = 10 Hz, 1 H)	2.91 (m, $w_{1/2}$ = 25 Hz, 1 H)
19	4.01 (d, J = 2 Hz, 1 H)[a]	2.71 (m, 1 H)
20	3.94 (d, J = 6 Hz, 1 H)[a]	2.66 (m, 1 H)

[a] Collapses to singlet on spin decoupling from H_B.



23 24 25

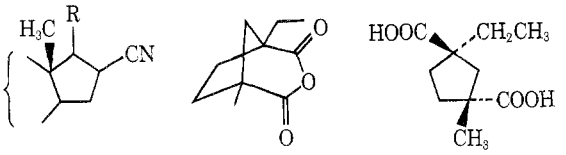


26 27

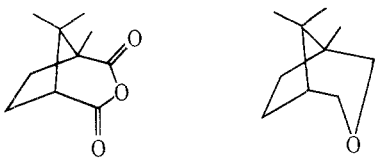
a, R = H
b, R = CH_2CH_3

A provisional stereochemical assignment for **26b** and **27b** was made from their nmr spectra. In one isomer the protons of the C(2) methylene group isolated between the two quaternary centers appear as a pair of doublets at δ 1.39 and 2.80 ppm (J = 14 Hz). In the epimeric compound the lower field doublet is at 2.27 ppm (J = 14 Hz), with the other signal lost in an upfield multiplet. We assumed that the unique signal at 2.80 ppm was due to the proton flanked by both cis-cyano and cis-carbomethoxy groups and that this isomer was then **26b**. This assignment proved to be correct, as will be clear from transformations described in the next paragraph. A tentative assignment of configuration can also be made for **26a** and **27a** on the basis of nmr spectra. One isomer (**26a**) has its methyl signal at 1.24 ppm and methoxyl signal at 3.71 ppm, while the other isomer, **27a**, shows these protons at 1.37 and 3.67 ppm, respectively. These changes in chemical shift with inversion of the nitrile are rationalized as long range deshielding by the polar nitrile function of the group (methyl or methoxyl) in a 1,3-cis relation to it. The effect is also apparent in **26b** (methyl, 1.27; methoxyl, 3.72 ppm) and **27b** (methyl, 1.42; methoxyl, 3.66 ppm), and it has been noted previously in 16α- and 16β-cyano steroids.[18] In these latter compounds (*cf.* **28**) the C(18) methyl signal is shifted downfield upon inversion of the nitrile from 16α (trans) to 16β (cis). An element of uncertainty remains in this assignment for **26a** and **27a**, however; long range nmr effects of the nitrile group are known[19] to be complex and sensitive functions of molecular geometry, and these cyclopentanes are conformationally mobile systems.

Hydrolysis of **26b** in hot aqueous ethylene glycol containing potassium hydroxide, followed by dehydration in acetic anhydride furnished cyclic anhydride **29**, thus confirming the stereochemistry assigned above to **26b**. Similar saponification of **27b** yielded the trans diacid **30**. Hydride reduction of **29** gave the corresponding diol, and this was converted to **2** on treatment with 1 equiv of tosyl chloride in pyridine, first at 4° and then at reflux.[20] The yield in this step was materially improved by isolation of the product after reaction at 4° and use of fresh, dry pyridine as solvent for the final treatment. This led to the desired cyclic ether **2** in 56% yield from **29**.[21]



28 **29** **30**



31 **32**

It was convenient to work out conditions for this last sequence using camphoric anhydride (**31**) as substrate, and this gave the corresponding bicyclic ether **32**.

Experimental Section

Materials and Equipment. All vpc was carried out using a Varian Aerograph Model A-90-P3 with one of the following columns: A, 15% QF-1, 15 ft × ⅜ in.; B, 30% DEGS, 10 ft × ⅜ in.; C, 25% PDEAS, 48 ft × 0.25 in.; D, 15% SE-30, 15 ft × ⅜ in. All columns were prepared using 45–60 Chromosorb W in aluminum tubing. Ir and nmr spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237B spectrophotometer and the latter on a Varian A-60 (60 MHz) or HR-220 (220 MHz) spectrometer. Mass spectra were obtained on a Du Pont 21-492 double-focusing mass spectrometer with a resolution of 10^4; results were processed with an AEI DS-30 data system. Boiling points are uncorrected; melting points are corrected. Solutions were dried over $MgSO_4$. All products were obtained as colorless oils unless otherwise indicated.

(4-Benzoyloxycyclohexylidene)cyanoacetic Acid Ethyl Ester (5). This was prepared from **4**[1] following a procedure previously described:[3] mp 59–60.5° from ether–pentane; ir 2225 (w), 1730 (s); nmr (220 MHz) δ 7.98 (d, J = 6 Hz, 2 H), 7.55–7.27 (m, 3 H), 5.25 (m, 1 H), 4.23 (q, J = 6.5 Hz, 2 H), 3.41–2.71 (br m, 4 H), 2.21–1.88 (m, 4 H), 1.36 (t, J = 6.5 Hz, 3 H); mass spectrum m/e 313.1320 (M^+, calcd for $C_{18}H_{19}NO_4$, 313.1313).

1-Methyl-4-oxocyclohexaneacetic Acid Methyl Ester (8). Cyano ester **5** (14.835 g) was converted to **6** (15.600 g) and subsequently hydrolyzed and decarboxylated, all following a procedure previously described.[3] The crude acid obtained was esterified with CH_2N_2 and this ester (9.33 g) was taken up in acetone (225 ml), titrated with Jones reagent (~30 ml) at 15°, and worked up in the usual way to give 3.188 g of colorless oil after distillation, bp 91–95° (0.7 mm) (38% overall yield). An analytical sample of **8** was obtained on column D (165°, 120 ml/min): ir 2955 (m), 1740 (s), 1720 (s), 1428 (m), 1250 (w), 1155 (m), 1000 (m) cm^{-1}; nmr (220 MHz) δ 3.65 (s, 3 H), 2.36 (s, 2 H), 2.29 (t, J = 6.5 Hz, 4 H), 1.91–1.68 (m, 4 H), 1.19 (s, 3 H); mass spectrum m/e 184.1109 (M^+, calcd for $C_{10}H_{16}O_3$, 184.1099).

Reaction of Keto Ester 8 with Thallium(III) Nitrate. The keto ester **8** (7.080 g, 11.3 mmol) in glacial acetic acid (10.0 ml) was treated with thallium trinitrate (5.12 g, 11.5 mmol) according to the published procedure of Taylor and McKillop.[6] The crude acid ester was esterified with diazomethane and distilled bulb-to-bulb (120–130°, 0.7 mm) to yield 1.461 (61%) of diester. The cis and trans epimers (3:2 by nmr) could not be separated by vpc and the following data are reported for the mixture **9**: ir 2955 (m), 2880 (w), 1742 (s), 1430 (m), 1350 (w), 1190 (m), 1165 (m), 1005 (w) cm^{-1}; nmr (60 MHz) δ 3.59 (s, 6 H), 2.71 (br m, 1 H), 2.33, 2.25 (two s, 2 H), 2.21–1.21 (br m, 6 H), 1.13, 1.06 (two s, 3 H).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.73; H, 8.50.

Reduction of Diester 9. The epimeric mixture of diester **9** was reduced with $LiAlH_4$ (300 mg) in anhydrous ether and after standard work-up yielded a colorless residue (212.6 mg) which was treated with *N,O*-bis(trimethylsilyl)acetamide for 1 hr at room temperature. Pentane extraction after water had been added to the reaction, and then distillation of the residue (130°, 0.5 mm), yielded 370.7 mg (90%) of the bis(trimethylsilyl) derivative of the epimeric alcohols. The major, cis isomer (first eluted) could be obtained pure with great difficulty by preparative vpc on column E (120°, 90 ml/min). Acid hydrolysis of 13.2 mg followed by ether extraction from the NaCl-saturated solution gave **3**. This material was acetylated in the usual way to yield 17.8 mg of material, identical with the diacetate of **3** described below from the second route. The trans diacetate was obtained free of the cis isomer but not analytically pure. It showed the following nmr spectrum: (220 MHz) δ 4.01 (t, J = 7 Hz, 2 H), 3.89 (d, J = 7 Hz, 2 H), 2.42–2.20 (m, 2 H), 1.96 (s, 3 H), 1.94 (s, 3 H), 1.88–1.05 (br m, 7 H), 1.04 (s, 3 H).

3-(2-Acetoxyethyl)-3-methylcyclopentanone (11). A mixture of the acetoxy ketal **10** (5.71 g, 25 mmol) and 10% HCl (30 ml) was stirred rapidly for 0.75 hr. The reaction was saturated with NaCl, and the aqueous phase was extracted three times with ether. The combined ethereal phases were washed once with brine and dried. The aqueous phase and brine wash were combined and continuously extracted with ether overnight. This extract was dried and combined with the original. After filtration and removal of solvent *in vacuo*, the residue was acetylated with acetic anhydride (5 ml) in pyridine (10 ml) overnight at 4°. The mixture was worked up in the usual way; distillation afforded the product **11** (3.77 g, 82%), bp 91–94° (1.0 mm). An analytical sample was obtained by preparative vpc on column A (190°, 135 ml/min): ir 2960 (m), 1748 (s), 1405 (w), 1362 (m), 1235 (s), 1026 (m) cm^{-1}; nmr (220 MHz) δ 4.17–3.99 (symmetrical ten line m, 2 H), 2.27–1.64 (br m, 8 H), 1.96 (s, 3 H), 1.10 (s, 3 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.32; H, 8.80.

3-(2-Acetoxyethyl)-3-methyl- and 4-(2-Acetoxyethyl)-4-methyl-1-cyclopentenecarbonitrile (14 and 13). To a mixture of **11** (3.77 g, 20.3 mmol), NaCN (3.97 g, 81 mmol), and water (11.5 ml), magnetically stirred and cooled in an ice–salt bath, was added a solution of $NaHSO_3$ (4.17 g, 40 mmol, dissolved in 11.5 ml of water) over a period of 20 min. The reaction mixture was stirred for 2.5 hr at −5 to 0° and then stirred vigorously with ether (25 ml) for 5 min. The organic phase was separated and the aqueous phase was extracted three times with ether. The combined organic phases were washed twice with brine and dried. Removal of solvent *in vacuo* gave 4.30 g of cyanhydrin as a colorless oil: ir 3600 (a), 3450 (br s), 2960 (s), 2870 (m), 2230 (w), 1747 (s), 1722 (m), 1368 (m), 1230 (s), 1040 (m) cm^{-1}.

To the crude cyanhydrin (**12**) (4.53 g) in 15 ml each of pyridine and benzene, cooled in an ice bath and stirred, was added dropwise a solution of $POCl_3$ (15 ml) in pyridine (15 ml). The reaction mixture was stirred at room temperature overnight, then heated on a steam bath for 0.5 hr, cooled, and poured onto ice. The mixture was extracted three times with ether. The combined extracts were washed successively with saturated aqueous $NaHCO_3$, brine, water, $NaHCO_3$, and brine and dried. After removal of ether, the residue was distilled to give 3.48 g (83%) of colorless oil: bp 117–121° (1.7 mm); ir 2965 (m), 2220 (m), 1748 (s), 1620 (w), 1362 (m), 1228 (s), 1048 (m), 1020 (m) cm^{-1}.

Hydrolysis of the Unsaturated Nitriles 13 and 14 to Form Ethers 17–20. A mixture of the mixed unsaturated nitriles (4.19 g), KOH (6 g), ethylene glycol (25 ml), and water (10 ml) was purged of oxygen with nitrogen and heated to reflux for 3 days under a nitrogen atmosphere. After cooling and diluting with water, the reaction mixture was extracted twice with ether, cooled in an ice bath, acidified with concentrated HCl, saturated with NaCl, and extracted three times with ether. The combined extracts were washed with brine and dried. After removal of solvent *in vacuo*, 3.07 g of a slightly yellow oil was obtained (88% from **11**), an nmr of which indicated virtually no olefinic protons. A portion was esterified with diazomethane; four compounds were obtained upon preparative vpc on column B (162°, 135 ml/min) and were identified as the following (in order of elution).

cis-5-Methyl-2-oxabicyclo[3.3.0]octane-*exo*-8-carboxylic acid methyl ester (**19**, 35%): ir 2950 (s), 2860 (m), 1738 (s), 1450 (m), 1428 (m), 1190 (m), 1168 (m), 1055 (s), 1020 (w), 985 (w), 960 (w),

cm^{-1}; nmr (220 MHz) δ 4.01 (d, J = 2 Hz, 1 H), 3.80 (ddd, J_1 = 16, $J_2 = J_3$ = 6 Hz, 1 H), 3.71–3.60 (m, 1 H), 3.65 (s, 3 H), 2.71 (m, 1 H), 2.05–1.55 (m, 6 H), 1.22 (s, 3 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.27; H, 8.79.

exo-5-Methyl-2-oxabicyclo[3.2.1]octane-7-carboxylic acid methyl ester (**17**, 47%): ir 2955 (s), 2925 (m), 2860 (m), 1738 (s), 1450 (m), 1428 (m), 1375 (w), 1355 (m), 1330 (m), 1187 (s), 1168 (s), 1112 (s), 1072 (m), 1030 (m), 910 (w) cm^{-1}; nmr (220 MHz) δ 4.28 (br s, $w_{1/2}$ = 6 Hz, 1 H), 3.81–3.50 (m, 2 H), 3.65 (s, 3 H), 2.97 (ddd, $J_1 = J_2$ = 6.5, $J_3 \sim$ 1 Hz, $w_{1/2}$ = 18 Hz, 1 H), 1.86–1.15 (br m, 6 H), 1.13 (s, 3 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.30; H, 8.82.

endo-5-Methyl-2-oxabicyclo[3.2.1]octane-7-carboxylic acid methyl ester (**18**, 6%): mp 54.5–55.5°; ir 2952 (s), 2925 (m), 1745 (s), 1430 (m), 1345 (m), 1300 (w), 1198 (s), 1160 (s), 1127 (m), 1075 (m), 1050 (s) cm^{-1}; nmr (220 MHz) δ 4.37 (br s, $w_{1/2}$ = 10 Hz, 1 H), 3.83–3.53 (m, 2 H), 3.70 (s, 3 H), 2.91 (m, $w_{1/2}$ = 25 Hz, 1 H), 2.19 (ddd, J_1 = 13, J_2 = 6, J_3 = 2 Hz, 1 H), 1.69–1.19 (m, 5 H), 1.11 (s, 3 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.12; H, 8.78.

cis-5-Methyl-2-oxabicyclo[3.3.0]octane-*endo*-8-carboxylic acid methyl ester (**20**, 12%): ir 2952 (s), 2860 (m), 1740 (s), 1450 (w), 1432 (m), 1235 (m), 1195 (m), 1075 (m) cm^{-1}; nmr (220 MHz) δ 3.94 (d, J = 6 Hz, 1 H), 3.83 (ddd, J_1 = 16, $J_2 = J_3$ = 6 Hz, 1 H), 3.63 (s, 3 H), 3.62 (m, 1 H), 2.66 (m, 1 H), 2.14–1.93 (m, 1 H), 1.82–1.65 (m, 4 H), 1.49–1.29 (m, 1 H), 1.19 (s, 3 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.27; H, 8.82.

Treatment of **18** in refluxing anhydrous methanol containing a small amount of $NaOCH_3$ for 4.5 hr gave, after work-up with pentane and water, an 85:15 mixture of **17** and **18**. Similar treatment of **20** for 3.33 hr gave a 59:41 mixture of **19** and **20**.

Hydrogenation of Unsaturated Nitriles 13 and 14. A solution of distilled unsaturated nitriles (3.386 g, 17.55 mmol) in absolute MeOH was hydrogenated at atmospheric pressure in the presence of 5% Pd/C (205 mg) for ~2 hr. The catalyst was removed by filtration and the solvent removed *in vacuo* to give 3.456 g of a colorless oil (**15**) which was used without further purification: ir 2960 (s), 2872 (m), 2242 (m), 1747 (s), 1452 (w), 1362 (m), 1230 (s), 1025 (m) cm^{-1}; nmr (60 MHz) δ 4.10, 4.07 (two sets of t, J = 7 Hz, 2 H), 2.88 (m, 1 H), 2.44–1.30 (br m, 8 H), 1.98 (s, 3 H), 1.17, 1.00 (2 s, 3 H).

2-Oxo-6-methyl-3-oxabicyclo[4.2.1]nonane (21). The crude saturated acetoxynitriles, **15** (3.456 g), were hydrolyzed in the same fashion as above. Work-up gave 2.660 g (87% from unsaturated nitriles) of colorless oil whose ir and nmr spectra were consistent with a mixture of hydroxy acids **16**: ir 3615 (w), 3575–2350 (br), 2960 (m), 1700 (s), 1215 (br m) cm^{-1}. To a mixture of the crude hydroxy acids (1.388 g, 8.05 mmol, ~55% cis isomer) and triethylamine (1.63 g, 16.1 mmol) in anhydrous CH_2Cl_2 (2 l.), cooled to −10° in an ice–acetone bath, was added *via* a syringe through a rubber serum stopper ethyl chloroformate (873 mg, 8.05 mmol). The reaction mixture was immediately placed in a freezer (−18°) for 17 hr. The cold solution was washed with dilute HCl, water, saturated $NaHCO_3$, and water and dried. After removal of solvent (Vigreux column), the colorless residue was distilled bulb-to-bulb (170°, 0.5 mm) to yield 376.6 mg of viscous oil. This was analyzed by vpc on column C (175°, 120 ml/min) and found to be a 1:9 mixture; the major component was collected and identified as the ϵ-lactone, **21**, a waxy solid: mp 63–68° (hot stage); ir 2955 (m), 2870 (w), 1735 (s), 1460 (m), 1448 (m), 1383 (w), 1325 (m), 1290 (m), 1275 (m), 1242 (m), 1133 (m), 1113 (s), 1075 (s), 1025 (s), 997 (m), 962 (m), 942 (w) cm^{-1}; nmr (220 MHz) δ 4.22 (ddd, J_1 = 1.5, $J_2 = J_3$ = 13 Hz, 1 H), 4.06 (ddd, J_1 = 13, $J_2 = J_3$ = 3.5 Hz, 1 H), 3.12 (m, 1 H), 2.27–1.39 (br m, 8 H), 1.15 (s, 3 H); mass spectrum m/e 154.1005 (M^+, calcd for $C_9H_{14}O_2$: 154.0993).

The polyester residue after distillation was hydrolyzed with 10% aqueous KOH to give predominantly the trans hydroxy acid. Epimerization to a 1:1 mixture of hydroxy acids suitable for lactonization was effected by esterification with diazomethane, treatment with sodium methoxide in hot methanol overnight, and addition of water. After 1 hr of continued heating, the reaction was worked up as before to give the mixture of hydroxy acids. Epimerization could not be accomplished by treating the polyester directly with methoxide.

Lactonization of 6-Hydroxyhexanoic Acid. To a suspension of 6-hydroxyhexanoic acid (126.5 mg) in CH_2Cl_2 (200 ml) was added triethylamine (202.4 mg, 2 mmol). Ethyl chloroformate (108 mg, 1 mmol) was added after the mixture had been cooled to −5°, and this temperature was maintained for 8 hr. The cold mixture was poured into saturated $NaHCO_3$, washed with water, and dried. After removal of solvent, the residue was analyzed by calibrated vpc on column B (182°, 135 ml/min); this indicated that a 50% yield of ϵ-caprolactone (**22**) had been formed; **22** was identified by comparison with an authentic sample.

Reduction of ϵ-Caprolactone (22). To a suspension of $NaBH_4$ (750 mg, 20 mmol) in anhydrous dimethoxyethane (20 ml), magnetically stirred under a nitrogen atmosphere and cooled in an ice bath, was added ϵ-caprolactone (1.14 g, 10 mmol) dissolved in freshly distilled $BF_3 \cdot Et_2O$ (37 ml, 42.5 g, 300 mmol). After the addition had been completed, the reaction mixture was stirred at 0° for 0.75 hr, then heated to reflux (bath temperature ~75°) for 1 hr. The reaction was cooled, 5% HCl was added cautiously, and the mixture was extracted three times with pentane; the combined pentane extracts were washed three times with water and once with brine and were dried. Most of the pentane was removed (Vigreux column), and residue was analyzed by vpc on column C (115°, 86 ml/min). In addition to solvents, two new components were observed; the second (retention time = 27.5 min) major one was collected and identified as oxepane (~5% yield) by comparison of its ir spectrum with that of authentic material.

Reduction of 2-Oxo-6-methyl-3-oxabicyclo[4.2.1]nonane (21). Reduction of distilled **21** (854 mg, 5.55 mmol) by the method described for **22** above gave, after vpc analysis on column C (158°, 80 ml/min), ~1% of **1**. This material was collected by passing the vpc effluent through CCl_4 in an nmr sample tube. A 220-MHz Fourier transform nmr spectrum (512 scans) was identical with the spectrum of **1** prepared below.

The aqueous phase and washings obtained in the work-up above were combined, neutralized with $NaHCO_3$, and saturated with NaCl. Continuous extraction with ether for 20 hr gave a residue which was treated with pyridine (5 ml) and acetic anhydride (2 ml) overnight at room temperature. After the standard work-up, bulb-to-bulb distillation (145°, 0.5 mm) afforded 1.156 g (87%) of the diacetate of **3**. An analytical sample was obtained on column B (190°, 150 ml/min): ir 2960 (m), 1745 (s), 1358 (m), 1225 (s), 1025 (m) cm^{-1}; nmr (220 MHz) δ 4.03 (t, J = 7 Hz, 2 H), 3.87 (d, J = 7 Hz, 2 H), 2.42–2.20 (m, 2 H), 1.96 (s, 3 H), 1.94 (s, 3 H), 1.92–1.05 (br m, 7 H), 0.99 (s, 3 H).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.59; H, 9.28.

6-Methyl-3-oxabicyclo[4.2.1]nonane (1). To a suspension of $LiAlH_4$ (490 mg) in anhydrous ether, magnetically stirred under a nitrogen atmosphere and cooled by an ice bath, was added a solution of the *cis*-diacetate (1.100 g, 4.54 mmol) in ether (10 ml). After 0.25 hr, excess hydride was destroyed with saturated Na_2SO_4 solution, the salts were removed by filtration, and the ether layer was dried. Removal of ether *in vacuo* gave 671 mg (93%); an ir spectrum exhibited the expected hydroxyl absorption and was transparent in the carbonyl region.

Purified *p*-toluenesulfonyl chloride (404 mg, 2.12 mmol) was added to a pyridine (5 ml) solution of the diol (335 mg, 2.12/mmol) and was allowed to stand at 5° overnight. Standard work-up yielded 580 mg (87.5%) of an oil which was taken up in anhydrous tetrahydrofuran (600 ml) with protection from atmospheric moisture and treated with powdered sodium hydride (65 mg). The mixture was stirred at room temperature for 1.5 hr, then heated at reflux overnight. Nearly all of the tetrahydrofuran was removed by distillation through a Vigreux column; the residue was added to water and extracted three times with pentane. The combined extracts were washed with several portions of water and brine and dried. After filtration, the pentane solution was passed through a column containing 5 g of activity I neutral alumina. Vpc analysis of the eluted material indicated one major component which was collected and identified as ether 1 on the basis of the following data: ir 2950 (s), 2870 (m), 1460 (m), 1138 (w), 1122 (m), 1095 (s), 1025 (m), 970 (w), 918 (w) cm^{-1}; nmr (220 MHz) δ 3.62–3.36 (m, 4 H), 2.22 (m, 1 H), 2.14–1.24 (br m, 8 H), 1.10 (s, 3 H); mass spectrum m/e 140.1197 (M^+, calcd for $C_9H_{16}O$, 140.1200).

3-Carbomethoxy-3-methyl- and 4-Carbomethoxy-4-methyl-1-cyclopentene-1-carbonitrile (24 and 25). These nitriles were prepared from 3-carbomethoxy-3-methylcyclopentanone (**23**)[16] following the procedure given above for **13** and **14** and purified on column A. The first nitrile eluted was **24**: ir 3025 (w), 2970 (m), 2950 (m), 2220 (m), 1735 (vs), 1618 (w), 1455 (m), 1430 (m), 1240 (m), 1185 (m), 1165 (m), 1140 (m), 1090 (m) cm^{-1}; nmr (220 MHz) δ 1.36 (s, 3 H), 1.77–1.96 (m, 1 H), 2.46–2.77 (m, 3 H), 3.69

(s, 3 H), 6.55 (m, 1 H); mass spectrum m/e 165.0792 (M^+, calcd for $C_9H_{11}NO_2$, 165.0789). The second was **25:** ir 3025 (w), 2950 (m), 2220 (m), 1735 (vs), 1430 (m), 1270 (m), 1210 (m), 1115 (m) cm^{-1}; nmr (220 MHz) δ 1.35 (s, 3 H), 2.32–2.50 (m, 2 H), 3.03–3.23 (m, 2 H), 3.70 (s, 3 H), 6.56 (m, 1 H); mass spectrum m/e 165.0792 (M^+, calcd for $C_9H_{11}NO_2$, 165.0789).

cis- **and** *trans*-**3-Cyano-1-methylcyclopentanecarboxylic Acid Methyl Ester (26a and 27a).** A solution of 8.21 g of **24** and **25** in 50 ml of methanol was hydrogenated over 250 mg of palladium on carbon. Work-up and preparative vpc on column C gave two products in the ratio ~1:2. The first eluted minor product was assigned trans structure **27a:** ir 3110 (w), 2960 (s), 2948 (s), 2870 (m), 2240 (m), 1735 (vs), 1465 (m), 1445 (m), 1430 (m), 1265 (m), 1185 (m), 1155 (s) cm^{-1}; nmr (220 MHz) δ 1.37 (s, 3 H), 1.64–1.82 (m, 2 H), 1.91–2.27 (m, 3 H), 2.60 (dd, J_1 = 13, J_2 = 8 Hz, 1 H), 2.82–3.00 (m, 1 H), 3.67 (s, 3 H); mass spectrum m/e 167.0950 (M^+, calcd for $C_9H_{13}NO_2$, 167.0946). For the major isomer (**26a**) the following were obtained: ir 3110 (w), 2960 (s), 2950 (s), 2875 (m), 2240 (m), 1735 (vs), 1460 (m), 1445 (m), 1430 (m), 1185 (s), 1120 (s) cm^{-1}; nmr (220 MHz) δ 1.24 (s, 3 H), 1.41–1.59 (m, 1 H), 1.82–2.55 (m, 5 H), 2.75–2.95 (m, 1 H), 3.71 (s, 3 H); mass spectrum m/e 167.0943 (M^+, calcd for $C_9H_{13}NO_2$, 167.0946).

cis-**3-Cyano-***trans*-**3-ethyl- and** *trans*-**3-Cyano-***cis*-**3-ethyl-1-methylcyclopentanecarboxylic Acid Methyl Ester (26b and 27b).** To a stirred solution containing 19.75 ml of methyllithium (1.6 *M*) dissolved in 32 ml of dimethoxyethane (freshly distilled from $LiAlH_4$) and cooled in an ice bath was added dropwise under nitrogen 5.73 g (0.0316 mol) of dicyclohexylamine. After the addition was complete and the evolution of methane stopped, the mixture was cooled in a Dry Ice–acetone bath, and a solution containing 4.8181 g (0.0288 mol) of **26a** and **27a** and 2.56 ml (0.0316 mol) of ethyl iodide dissolved in 32 ml of dimethoxyethane was added dropwise. After the addition was complete, the mixture was allowed to warm to room temperature over a period of 0.5 hr. The resultant mixture was then poured onto a mixture of ice and 10% (v/v) aqueous HCl. After extraction with ether and drying, 4.37 (78%) of an oil was isolated. Vpc on column C indicated the formation of two products in the ratio of ~2.5:1, in addition to unalkylated material. Preparative vpc gave a sample of each. The first was **27b:** ir 3025 (w), 2970 (s), 2950 (m, sh), 2875 (m), 2230 (w), 1735 (vs), 1462 (m), 1195 (s), 1120 (s) cm^{-1}; nmr (220 MHz) δ 1.10 (t, J = 7 Hz, 3 H), 1.42 (s, 3 H), 1.55–2.36 with d (J = 14 Hz) at 2.27 (m, 8 H), 3.66 (s, 3 H); mass spectrum m/e 195.1259 (M^+, calcd for $C_{11}H_{17}NO_2$, 195.1258). The second was **26b:** ir 3025 (w), 2970 (s), 2950 (m), 2875 (m), 2230 (w), 1735 (vs), 1460 (m), 1195 (s), 1163 (m) cm^{-1}; nmr (220 MHz) δ 1.10 (t, J = 7 Hz, 3 H), 1.27 (s, 3 H), 1.39 (d, J_{AB} = 14 Hz, 1 H, H_A), 1.50–1.77 (m, 4 H), 2.09–2.30 (m, 1 H), 2.36–2.51 (m, 1 H), 2.80 (d, J_{AB} = 14 Hz, 1 H, H_B), 3.72 (s, 3 H).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.48; H, 8.80; N, 6.98.

1-Ethyl-3-methylcyclopentane-1,3-dicarboxylic Acid Anhydride (29). A solution containing 468 mg of **26b**, 2 ml of H_2O, 10 ml of ethylene glycol, and 3.0 g of KOH was heated at reflux for 95 hr under nitrogen. After acidification, work-up with ether and isolation gave the dicarboxylic acid as a semisolid. A solution of 18.7 mg of this acid in 1 ml of acetic anhydride was heated at reflux for 12 hr. After this period the acetic anhydride was removed by distillation. The residue yielded upon short path distillation (~150° at 1.0 Torr) a white solid, which after two recrystallizations from cyclohexane was pure **29:** mp 69–71°; ir 2980 (m), 2940 (w), 2980 (w), 1810 (m), 1770 (vs), 1135 (m), 1025 (m), 1010 (m), 990 (s), 970 (m), 955 (m) cm^{-1}; nmr (220 MHz) δ 0.99 (t, J = 7 Hz, 3 H), 1.36–1.68 with s at 1.39 (m, 5 H), 1.73–2.18 (m, 6 H).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.88; H, 7.67.

1-Ethyl-3-methyl-*trans*-**1,3-cyclopentanedicarboxylic Acid (30).** Saponification of **27b** following the above procedure gave **30**, mp 169–171° from ethyl acetate.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.09; H, 7.95.

1-Ethyl-5-methyl-3-oxabicyclo[3.2.1]octane (2). To a suspension of 600 mg of $LiAlH_4$ in 40 ml of ether was added 1.0684 g of **29** in 15 ml of ether. After heating the mixture at reflux for 22 hr, work-up gave 849 mg of an oil. This was dissolved in 25 ml of pyridine and 940 mg (4.94 mol) of *p*-toluenesulfonyl chloride was added. The resultant mixture stood at 4° for 8 hr and then warmed to 25° overnight. It was poured onto a mixture of ice and 10% (v/v) aqueous HCl and extracted with ether. After washing and drying, removal of the solvent gave 511 mg of oil (56% from **29**). Vpc on column C indicate the formation of one major product. Preparative vpc on columns C and F gave a pure sample of **2:** ir 2950 (s), 2850 (s), 2835 (m), 1455 (m), 1320 (m), 1115 (m), 1100 (m), 1082 (m), 1068 (m), 920 (m) cm^{-1}; nmr (220 MHz) δ 0.827 (t, J = 7 Hz, 3 H), 0.886 (s, 3 H), 1.09–1.50 (m, 6 H), 1.59–1.76 (m, 2 H), 3.12 (d, J = 10 Hz, 1 H), 3.14 (d, J = 10 Hz, 1 H), 3.31 (dd, J_1 = 10, J_2 = 2 Hz, 1 H), 3.39 (dd, J_1 = 10, J_2 = 2 Hz, 1 H); mass spectrum m/e 154.1367 (M^+, calcd for $C_{10}H_{18}O$, 154.1357).

1,8,8-Trimethyl-3-oxabicyclo[3.2.1]octane (32). This ether was prepared from 500 mg of camphoric anhydride following the above procedure and purified on column C: mp 174–176°; ir 2960 (s), 2870 (s), 1465 (m), 1385 (m), 1368 (m), 1170 (m), 1125 (m), 1080 (m), 1012 (m), 920 (m), 915 (m) cm^{-1}; nmr (220 MHz) δ 0.719 (s, 3 H), 0.860 (s, 3 H), 1.06 (s, 3 H), 1.43–1.89 (m, 5 H), 2.96 (d, J = 11 Hz, 1 H), 3.30 (dd, J_1 = 11, J_2 = 3 Hz, 1 H), 3.56 (br d, J = 10 Hz, 1 H), 3.89 (br d, J = 10 Hz, 1 H); mass spectrum m/e 154.1336 (M^+, calcd for $C_{10}H_{18}O$, 154.1357).

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Registry No.—**1**, 51096-78-7; **2**, 51096-79-8; **3** diacetate, 51096-80-1; *cis*-**3** diacetate, 51096-81-2; **5**, 51096-82-3; **8**, 51096-83-4; *cis*-**9**, 51096-84-5; *trans*-**9**, 51096-85-6; **10**, 49664-69-9; **11**, 51096-86-7; **12**, 51096-87-8; **13**, 51157-39-2; **14**, 51157-40-5; *cis*-**15**, 51096-88-9; *trans*-**15**, 51096-89-0; *cis*-**16**, 51096-90-3; *trans*-**16**, 51096-91-4; **17**, 51096-92-5; **18**, 51096-93-6; **19**, 51096-94-7; **20**, 51154-46-2; **21**, 51096-95-8; **22**, 502-44-3; **23**, 32436-10-5; **24**, 51096-96-9; **25**, 51096-97-0; **26a**, 51096-98-1; **26b**, 51096-99-2; **27a**, 51097-00-8; **27b**, 51097-01-9; **29**, 51097-02-0; **30**, 51097-03-1; **32**, 51097-04-2; 6-hydroxyhexanoic acid, 1191-25-9.

References and Notes

(1) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).
(2) J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626 (1970).
(3) For references to previous use of this sequence on other cyclohexanones, see S. Wolff, W. L. Schreiber, A. B. Smith, III, and W. C. Agosta, *J. Amer. Chem. Soc.*, **94**, 7797 (1972).
(4) A different synthesis of the related butyl ester is described by C. Chuit, *Tetrahedron*, **28**, 4797 (1972), concerning which we thank Dr. Hugh Felkin, Gif-sur-Yvette, for helpful correspondence.
(5) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).
(6) A. McKillop, J. D. Hunt, and E. C. Taylor, *J. Org. Chem.*, **37**, 3381 (1972), and references cited therein.
(7) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).
(8) Efforts to effect separation of esters **9** or the diacetates of **3** and its epimer were unsuccessful, as were attempts to prepare the monomeric anhydride from **9**.
(9) R. L. Cargill, D. F. Bushey, P. D. Ellis, S. Wolff, and W. C. Agosta, *J. Org. Chem.*, **39**, 573 (1974).
(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, pp 281–301, and references cited therein.
(11) From heats of combustion *trans*-2-oxabicyclo[3.3.0]octane is destabilized by 4.5 kcal/mol relative to the cis isomer; for discussion and references see M. Procházka, J. V. Černý, and M. Smíšek, *Collect. Czech. Chem. Commun.*, **31**, 1315 (1966). For references concerning Michael addition of alcohols, see H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 596.
(12) M. Stoll and A. Rouvé, *Helv. Chim. Acta*, **18**, 1087 (1935). We confirmed this preparation of ϵ-caprolactone.
(13) D. A. Johnson, *J. Amer. Chem. Soc.*, **75**, 3636 (1953).
(14) G. R. Pettit, B. Green, T. R. Kasturi, and U. R. Ghatak, *Tetrahedron*, **18**, 953 (1962); G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **27**, 2127 (1962); G. R. Pettit and J. R. Dias, *Chem. Commun.*, 901 (1970).
(15) Reduction of ϵ-caprolactone (**22**) under these same conditions gave approximately 5% of oxepane.
(16) J. D. Roberts, A. K. Jeydel, and R. Armstrong, *J. Amer. Chem. Soc.*, **71**, 3248 (1949); P. T. Lansbury, N. Y. Wang, and J. E. Rhodes, *Tetrahedron Lett.*, 1829 (1971).
(17) Use of lithium diethylamide led to complete conversion of the ester to the diethylamide, while lithium dicyclohexylamide is totally unreactive toward the carbomethoxy group under the conditions employed. The advantages and utility of this base were first noted by R. A. Olofson and C. M. Daugherty, *J. Amer. Chem. Soc.*, **95**, 582 (1973).

(18) J. Romo, L. Rodriguez-Hahn, P. Joseph-Nathan, M. Martinez, and P. Crabbé, *Bull. Soc. Chim. Fr.*, 1276 (1964); A. D. Cross and P. Crabbé, *J. Amer. Chem. Soc.*, **86**, 1221 (1964).
(19) A. D. Cross and I. T. Harrison, *J. Amer. Chem. Soc.*, **85**, 3223 (1963).
(20) References to related reactions are given by J. Jacobus, *J. Org. Chem.*, **38**, 402 (1973).
(21) The photochemical work for which **2** was required has recently appeared: A. B. Smith, III, and W. C. Agosta, *J. Amer. Chem. Soc.*, **96**, 3289 (1974).

Synthesis and Conversion of 2-Methyl-2-(3-oxobutyl)-1,3-cyclopentanedione to the Isomeric Racemic Ketols of the [3.2.1]Bicyclooctane and of the Perhydroindan Series

Zoltan G. Hajos*[1] and David R. Parrish

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

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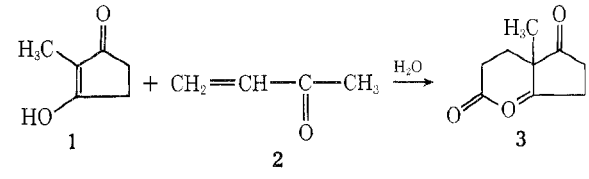
Michael addition of 2-methylcyclopentane-1,3-dione to methyl vinyl ketone in water gives 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (**3**), an important intermediate of natural product chemistry. Neutral piperidinium acetate in water cyclizes **3** to the bridged ketol **4** of the [3.2.1]bicyclooctane series. Additional piperidine epimerizes the C-4 center of **4** to give the more stable bridged ketol **5**. The C-8 keto group of **5** can be reduced to give the dihydroxy ketone **6**. The structure and the stereochemistry of **4**, **5**, and **6** have been proven by ir and nmr spectroscopy and by chemical correlation. A skeletal isomer, the bicyclic ketol **7** of the perhydroindan series, could be obtained by cyclizing **3** with pyrrolidinium acetate in anhydrous ether. A discussion of the reaction mechanism for each of the three selective cyclization reactions is presented.

In connection with the stereocontrolled total synthesis of 19-norsteroids[2] it became necessary to prepare certain CD-bicyclic steroidal intermediates. The triketone **3** [2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione] was considered the key intermediate of the synthesis provided that it could be prepared in reasonably good yield and be selectively cyclized to the desired CD-bicyclic ketol (**7**) of the perhydroindan series. The possibility of an asymmetric conversion of the triketone **3** had also been considered at the outset of our studies; this problem, however, shall be discussed in the accompanying publication.[3] This communication deals with the problem of an improved synthesis of the triketone **3**, and with its selective conversions to the isomeric racemic ketols **4**, **5**, and **7** *via* directed aldol cyclization reactions.

The preparation of the triketone **3** from 2-methylcyclopentane-1,3-dione (**1**) and methyl vinyl ketone (**2**) in refluxing methanol and a catalytic amount of potassium hydroxide had been reported in the literature.[4] The compound **3** had been described as a crystalline solid, mp 117–118°. Upon repeating the literature procedure we found the triketone **3** to be an oil, and confirmed its structure by ir and nmr spectroscopy.[5] We could also isolate a very small amount of a crystalline by-product from the reaction mixture, mp 121–122°. It was different from the triketone **3** by thin layer chromatography, and corresponded to the bridged ketol **4**, whose synthesis shall be described below. We have also found that the best way to prepare the triketone **3** is to allow the dione **1** and methyl vinyl ketone (**2**) to react in water.[6] The previously reported[5] yield of 54% was thus increased to 87.6% of pure triketone **3**. The reaction may be considered a Michael addition under slightly acidic reaction conditions due to the enolic nature of the dione **1** (Scheme I).

Next we investigated the chemical properties of the triketone **3** under a variety of reaction conditions. We, therefore, dissolved the compound **3** in water, added a neutral solution of piperidinium acetate in water, and stirred the solution at 20° for 3 days. The reaction mixture was then worked up to give a crystalline product **4**, mp 114–116.5°, in 51% yield. Microanalysis indicated an empirical formula of $C_{10}H_{14}O_3$. Infrared spectroscopy in chloroform showed a hydroxyl band at 3600 cm^{-1}, a five-membered ring ketone at 1762 cm^{-1} and a six-membered ring ketone at 1720 cm^{-1}. Its nmr spectrum in $CDCl_3$ indicated the bridged ketol structure **4**: δ 1.07 (s, 3, 1-CH_3), 1.45 (s, 3, 4-CH_3), 1.78 (m, 4, -CH_2CH_2-), 2.18 (s, 1, -OH), 3.10, 2.55, 2.85 (AMX, 3, J_{AM} = 18, J_{AX} = 0, J_{MX} = 7 Hz, -$CHCH_2CO$-). The stereochemical assignment at C-4 is the result of a comparison of the nmr spectra of **4** with that of the isomeric bridged ketol **5**, as will be discussed below. The infrared spectrum of **4** in Nujol was identical with the spectrum published for the compound of mp 118.5–120.5°, to which the triketone structure **3** had been erroneously assigned, despite a strong band at 3.1 μ in the infrared.[7]

Scheme I



The bridged ketol structure **4** was thus proven to be the correct formula for the previously reported mp 118.5–120.5° "triketone" of the literature. It remained to be seen, however, if our bridged ketol **4** could be converted to the higher melting substance (mp 157–159°) under the reaction conditions described by the same group of investigators.[7] Therefore, we dissolved the compound **4** in water, added 1 molar equiv of piperidine, and then added enough glacial acetic acid to neutralize the system. The solution was then allowed to stand for 3.5 days at 20°. It should be noted that in the course of the preparation of the bridged ketol **4** we added neutral piperidinium acetate to the triketone **3**, whereas here we first added basic piperidine to the aqueous solution of the compound **4** to be isomerized. Work-up of the reaction mixture gave a product **5**, mp 154–158°, in 57% yield. Microanalysis agreed with an empirical formula of $C_{10}H_{14}O_3$, and indicated that compound **5** was an isomer of the bridged ketol **4**. The nmr spectrum of **5** in $CDCl_3$ showed the following peaks: δ 1.07 (s, 3, 1-CH_3), 1.43 (s, 3, 4-CH_3), 1.60–2.30 (m, 4, -CH_2CH_2-), 2.63, 2.85 (A′M′X′ = A_2X, 3, J_{AX} = 4.5 Hz, -$CHCH_2CO$-). This spectrum clearly indicated