Synthesis of Diterpenoid Acids. V.[1] Insertion of Two Quaternary Methyl Groups

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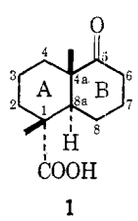
A general approach to the synthesis of diterpenoid acids is outlined. Keto lactone **5a** has been converted to thioethers **9b** and **10a**. Methyl groups have been inserted in positions 1 and 4a of thioether **10a**. Dimethyl compound **10b** has been transformed into dimethyl compound **7b**, and trimethyl compounds **7c** and **7d**. Neither of the latter two trimethyl keto lactones is identical with the trimethyl keto lactone obtained from marrubiin. The stereochemistry and conformations of the intermediates are discussed.

For some years[2-5] we have been trying to devise a general synthesis of diterpenoid acids[6] by making first the portion of the skeleton which is common to all diterpene acids. As the diterpene acids fall into two groups, epimeric at C_4, the two main objectives of the work are **1** and **2** or compounds related to them, *e.g.*, **4b** and **5b**. Ketones **1** and **4b** would be precursors for the acids related to abietic acid; ketones **2** or **5b** would be starting materials for the members of the podocarpic acid family. In addition, the approach could be used in making compounds with naphthalene skeletons, *e.g.*, marrubiin (**3**), as well as acids based on phenanthrene.[7]



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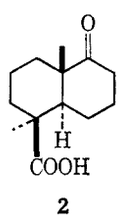

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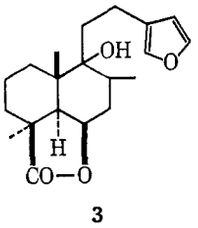

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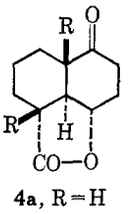

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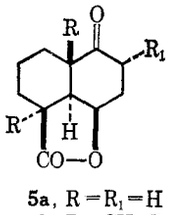
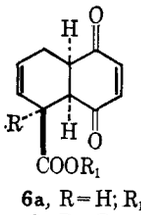
b, R = CH_3

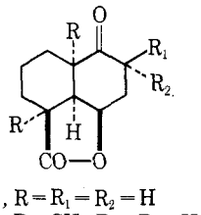


5a, R = R_1 = H
b, R = CH_3; R_1 = H
c, R = R_1 = CH_3

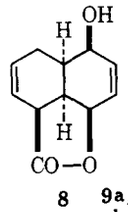


6a, R = H; R_1 = CH_3
b, R = R_1 = H
c, R = CH_3; R_1 = H

We started our synthesis with adduct **6a**[10,11] which we converted into keto lactone **5a**.[3] In making this compound, the critical point was the selective epimerization of C_{4a} (**7a** → **5a**).[12,13] In the present work, we report an alternative route to **7a**. Compound **6a** was hydrogenated to the corresponding saturated diketo ester **11**, which was then reduced under Meerwein–Ponndorf conditions and the resulting hydroxy lactone **12** was oxidized to **7a**. This new route avoids enolisation to hydroquinol **13** which we observed in attempts to improve the yield of hydroxy lactone **8** from the Meerwein–Ponndorf reduction of **6a**. Keto lactone **7a** is unstable on standing and decomposes partly to **5a**. Contrary to our earlier experiments[3] on small scale, basic conditions are better than acidic for the conversion of **7a** to **5a**. The epimerization was not complete as had been reported earlier; equilibrium mixtures were formed. We were not able to determine the relative amounts of the epimers at equilibrium since they started to interconvert on passage down a Florisil column. However, it is clear that the presence of the lactone ring changes the relative stability of the *cis* and *trans* decalones and so the energy difference between **5a** and **7a** is not large.



7a, R = R_1 = R_2 = H
b, R = CH_3; R_1 = R_2 = H
c, R = R_1 = CH_3; R_2 = H
d, R = R_2 = CH_3; R_1 = H



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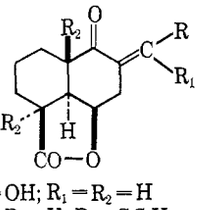
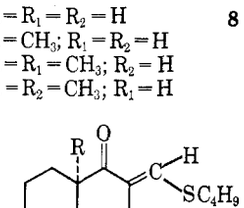
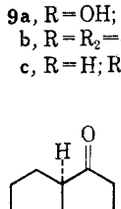


9a, R = OH; R_1 = R_2 = H
b, R = R_2 = H; R_1 = SC_4H_9
c, R = H; R_1 = SC_4H_9; R_2 = CH_3



10a, R = H
b, R = CH_3



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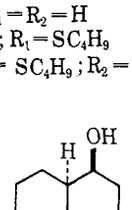

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We next wished to insert methyl groups at positions 1 and 4a in the skeleton of **5a**. To protect the 6 position,[15] keto lactone **5a** was condensed with ethyl formate

(1) (a) References 2–5 constitute parts I–IV of this series. (b) A preliminary account of part of this work has been given: S. K. Roy and D. M. S. Wheeler, Abstracts of the 146th National Meeting of the American Chemical Society, Denver, Colo., 1964, p 41C.

(2) D. M. S. Wheeler and M. M. Wheeler, *J. Org. Chem.*, **27**, 3796 (1962).

(3) S. K. Roy and D. M. S. Wheeler, *J. Chem. Soc.*, 2155 (1963).

(4) K. Mori, S. K. Roy, and D. M. S. Wheeler, *ibid.*, 5815 (1964).

(5) K. Mori, D. M. S. Wheeler, J. O. Jilek, B. Kakáč, and M. Protiva, *Collection Czech. Chem. Commun.*, **30**, 2236 (1965).

(6) For a summary of the extensive literature on other approaches to the synthesis of diterpenoid acids, see N. A. J. Rogers and J. A. Barltrop, *Quart. Rev.* (London), **16**, 117 (1962).

(7) Since we started this work other groups[8,9] have reported similar approaches.

(8) T. A. Spencer, T. D. Weaver, M. A. Schwartz, W. J. Greco, and J. L. Smith, *Chem. Ind.* (London), 577 (1964); T. A. Spencer, T. D. Weaver, and W. J. Greco, *J. Org. Chem.*, **30**, 3333 (1965).

(9) C. T. Mathew and P. C. Dutta, *Proc. Chem. Soc.*, 135 (1963); C. T. Mathew, G. C. Banerjee, and P. C. Dutta, *J. Org. Chem.*, **30**, 2754 (1965); S. L. Mukherjee and P. C. Dutta, *J. Chem. Soc.*, 3554 (1964).

(10) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(11) Attempts to make the adduct **6c** failed.[4]

(12) All compounds in our synthesis are racemates. In our diagrams we have always drawn the mirror image related to our ultimate synthetic objectives. This sometimes necessitates going from one mirror image series to the other in discussing an epimerization, *e.g.*, ref 13. In naming our compounds the 8a hydrogen is always assumed to be up.[2]

(13) By an analogous series of reactions involving epimerization at 8a (*cf.* ref. 2) we[14] converted acid **6b** into the keto lactone **4a**.[12] We hope to obtain **4b** from **4a**.

(14) A. C. Ghosh, R. C. Matejka, and D. M. S. Wheeler, unpublished work.

(15) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).

to give hydroxymethylene compound **9a**.[16] The *trans* stereochemistry of the ring junction in **9a** is assigned on the basis of the width of the nmr signal at δ = 4.8 ppm (corresponding to the hydrogen at C_8).[18] The nmr signal corresponding to the vinyl proton appears at δ = 7.26 ppm. Applying Garbisch's ideas[20,21] we conclude that the product is a mixture, with 80% in the hydroxymethylene form and 20% in the aldenol form. Garbisch[20] reported that hydroxymethylene cyclohexanone has the reverse composition. The difference between the two compounds may be due to ring B in **9a** being forced into a half-boat form by the lactone. At first we always isolated **9a** and the hydroxy acid corresponding to it. Avoiding addition of alkali in the work-up eliminated the by-product. The hydroxymethylene compound was also formed directly from the *cis*-keto lactone **7a** and this preparation was used routinely. Treatment of **9a** with a slight excess of *n*-butyl mercaptan gave a mixture of thioethers A (mp 139–139.5°) and B (mp 122–123°) which were separated by careful chromatography on Florisil. The thioethers were clearly stereoisomers either at C_{4a} or across the double bond or at both of these points. The ultraviolet spectra of both isomers (λ_{max} 310 mμ) fit well with the value calculated[22] (315 mμ) for α,β-unsaturated ketones with the substitution pattern shown in **9b**. The high intensity of the ultraviolet peak in both of the spectra (ϵ 16,900 and 17,200) and the strongly deshielded nmr signal for the vinyl protons (δ = 7.6 ppm in both spectra) suggested that in both thioethers the butylthio group is *trans* to the carbonyl. The fact that both thioethers were converted on methylation to the same dimethyl thioether (see below) confirmed that they are epimers at the 4a position and not isomers about the double bond. A *trans* addition of the butyl mercaptan followed by *trans* elimination of water explains the exclusive formation of isomers with the thioether *trans* to the ketone. To distinguish between the C_{4a} epimers we used our nmr criterion[18] to assign structure **10a** to thioether A (isolated in greater amount) and **9b** to thioether B. The formation of stereoisomers has not been noted in previous use of the thiomethylene blocking group. As indicated above, the epimeric pairs **5a** and **7a**, and **9b** and **10a** have similar stabilities, but **9a** is apparently much more stable then its corresponding *cis* isomer. This suggests that the presence of the hydroxy group *cis* to the ketone in **9a** destabilizes the *cis*-fused epimer. The reason for this is not clear from a study of models. As the thioethers were stereoisomers at 4a the methylations were routinely done on mixtures of the ethers.

After much work, successful conditions were developed for the methylation of the thioethers. The unsuccessful reactions are noted in the Experimental Section. A dimethyl compound was obtained by adding methyl iodide to the dianions formed from the thioethers by treatment with sodium hydride in dimethylformamide solution, under strictly anhydrous conditions. The dimethyl thioether was obtained by chromatography of the crude reaction product on Florisil. The same dimethyl thioether was obtained from methylation of either thioether A or B and is assigned structure **10b** (see below).

Ireland removed the thioether group by hydrolysis under alkaline conditions. Hydrolysis of the thioether mixture (**9b** and **10a**) took place under milder conditions than Ireland had used on his compounds. When these milder conditions were tried on thioether **10b** the protecting group was removed and, as expected, the lactone ring was opened. We had to use dicyclohexylcarbodiimide to reclose the lactone, but were then unable to separate the lactone from the urea formed from the diimide. However, hydrolysis of **10b** under acid conditions removed the protecting group and gave dimethyl keto lactone **7b**. Alternatively dimethyl thioether **10b** was refluxed with Raney nickel[15] to yield a trimethyl keto lactone (**7c** or **7d**). This compound on treatment with acid or with base (followed by recyclization of the lactone) gave a second trimethyl keto lactone, clearly the C_6 epimer of the first. Although the infrared spectrum of the first synthetic trimethyl compound closely resembles that of the trimethyl keto lactone **5c** obtained by degradation of marrubiin,[23] comparison of the nmr spectra showed clearly that the two lactones are different. It has been our experience that the infrared spectra of *cis* and *trans* isomers of lactones of hydrogenated 8-hydroxy naphthoic acids are frequently almost identical. The C_6 epimer of the synthetic trimethyl keto lactone is also not the same as **5c**. The stereochemistry of **5c** is secure on the basis of recent work on the stereochemistry of marrubiin.[24,25]

The assignment of stereochemistry to our methylation products is based on the following arguments. The stereochemistry of the centers at 8 and 8a should not have been affected during the alkylation. The lactone ring should have preserved the stereochemistry at 1. This leaves only 4a to be decided. If the methylation had given a *trans* ring junction, one of the trimethyl keto lactones we obtained would have been **5c**. The fact that neither was **5c** leads us to the structures **10b**, **7b**, **7c**, and **7d** for the dimethyl thioether, the dimethyl keto lactone, and the trimethyl keto lactones. We think that in the Raney nickel reduction, the hydrogen was delivered from the convex side of the *cis* decalin[10] and so the first trimethyl keto lactone is assigned structure **7c** and the epimer is assigned structure **7d**. Studies with models suggest that **7d** should be more stable. Application of our nmr criterion[18] also leads us to conclude that synthetic dimethyl and trimethyl compounds are *cis*.

Johnson and his co-workers[26] found that in the methylation at 8a of saturated 1-decalones the *cis*-fused products predominated. However, the presence of the lactone ring in thioethers **9b** and **10a** changes the

(16) Attempts to alkylate **9a** using Hauser's dianion method[17] failed.

(17) S. Boatman, T. M. Harris, and C. R. Hauser, *J. Am. Chem. Soc.*, **87**, 82 (1965).

(18) Examination[19] of the nmr spectra of the lactones reported in ref 2 and 3 shows that the nmr peak corresponding to the proton at C_8 (which usually appears at about δ = 4.8 ppm) is wider for lactones of type **5a** than **7a**. We are also able to conclude that the ring B in **5a** has a twist conformation and that the oxygen at C_8 in **7a** is axial to ring B.

(19) G. A. Gallup, S. K. Roy, and D. M. S. Wheeler, unpublished work.

(20) E. W. Garbisch, *J. Am. Chem. Soc.*, **85**, 1696 (1963).

(21) Some parts of Garbisch's treatment may require further discussion.

(22) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 58.

(23) W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward, and T. F. Holley, *J. Chem. Soc.*, 2540 (1953).

(24) J. W. B. Fulke and R. McCrindle, *Chem. Ind.* (London), 647 (1965).

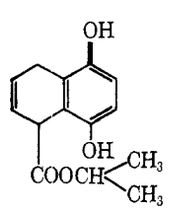
(25) W. H. Castine, M. Fetizon, M. M. Wheeler, and D. M. S. Wheeler, unpublished work.

(26) W. S. Johnson, D. S. Allen, R. R. Hindersinn, G. N. Sausen, and R. Pappo, *J. Am. Chem. Soc.*, **84**, 2181 (1962).

conformations as compared with simple 1-decalones and so it was not clear *a priori* how keto lactones would methylate. Presumably, alkylation occurs first at C_1 which we expect to be a less stable anion than that at C_{4a}. On the basis of Johnson's results we also assume that the transition state for the second alkylation closely resembles the monoanion. Examination of a model of the intermediate anion shows that there are two possible conformations. Atoms C_{4a}, C_5, and C_6, are sp^2 and are assumed coplanar: thus ring B has a flattened conformation. Ring A, however, can exist either in the chair or twist conformations. With the latter possibility, methylation to give **10b** is hindered by hydrogens at C_{8a}, C_3, and C_4; approach to give *trans* product **9c** is hindered by hydrogens at C_2 and C_4 and by the lactone. With this conformation there seems little difference in the relative ease of *cis* or *trans* attack. If ring A is a chair, attack to give the *trans* product will be hindered by the lactone ring and a hydrogen at C_3; methylation to give the *cis* product will be hindered by hydrogens at C_2, C_4, C_7, and C_{8a}. With this conformation, attack to give the *cis* product appears more likely. The fact that we isolated only *cis* product from our methylation suggests that the predominant conformation of the anion is ring A chair, ring B flattened, and that hindrance by the lactone ring played a decisive part in favoring *cis* attack.

As the methylation failed to give the desired *trans* compound, the synthesis could not proceed according to the original plan. We now intend to convert **7b** into dehydrodeisopropylabietic acid (**14**) according to the general route used by Dutta;[9] this involves epimerizing position 8a under dehydrogenation conditions.[12] In preliminary studies we have already obtained a tricyclic compound.

In abortive work directed toward epimerizing C_8 in **7b** we reduced **7b** to the corresponding alcohol **15** and a triol **16**. Alcohol **15** was then reduced to **16**. Stereochemistries at C_5 are based on approach of hydride from the convex face.[2] Finally hydroxy lactone **17**[3] was reduced to the corresponding triol.



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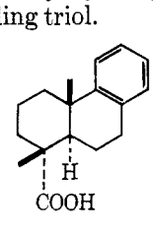

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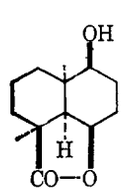

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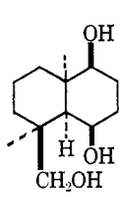

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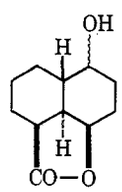

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Experimental Section[12,27]

1,4-Dihydro-5,8-dihydroxynaphthalene-1-carboxylic Acid Isopropyl Ester (13).—In an attempt to improve the yield of hydroxy lactone **8** from the Meerwein–Ponndorf reduction of **6a**,[28] a mixture of **6a** (55 g), aluminum isopropoxide (170 g), and isopropyl alcohol (1250 ml) was distilled with concurrent addition of isopropyl alcohol until no acetone could be detected in the distillate (DNP test). The mixture was worked up in the usual way[28] and 1,4-dihydro-5,8-dihydroxynaphthalene-1-carboxylic acid isopropyl ester (**13**), mp 166–168° (9.84 g), was isolated. After crystallization from ether, the analytical sample had mp 168.5–169.5°; ν_{max}^{KBr} 3380, 3065, 3010, 2960, 2900, 1715, 1670 (sh), 1627, 1610, 1495, 1470, 1430, 1390, 1377, 1338, 1312, 1276, 1205, 1149, 1100, 1060, 1018, 1007, 953, 930, 906, 825, 806, 777, 743, and 699 cm^{-1}; λ_{max} 295 mμ (ϵ 3200) and 225 mμ (ϵ 5700); nmr peaks (CD_3CN) at 61 to 67 (6 H, two doublets), 192 (2 H, multiplet), 261 (1 H, multiplet), 293 (1 H, septet?), 359 (3 H, multiplet), and 394 (3 H, singlet) cps.

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50; O, 25.78. Found: C, 67.79; H, 6.46; O, 26.01.

***cis*-Decahydro-5,8-dioxonaphthalene-1α-carboxylic Acid Methyl Ester (11).** A.—A solution of adduct **6a** (10 g) in *t*-butyl alcohol (80 ml with a few drops of methyl alcohol) was shaken under pressure (30 psi initial, 22 psi final) in an atmosphere of hydrogen in the presence of 5% rhodium on charcoal (1.5 g). Hydrogenation appeared complete after a 0.5 hr. After 1 hr, the solution was filtered and the solvent was removed under reduced pressure on a steam bath. The residual oil (9.5 g) after two crystallizations from ether and one from ether–petroleum ether (bp 60–69°) gave **11** in stout needles: mp 134–135° (4.3 g); ν_{max} 3012, 2940, 2848, 1716, 1442, 1430, 1350, 1302, 1277, 1162, 1127, 1090, 1018, 969, 938, 905, and 840 cm^{-1}; nmr peaks at 50–180 (13 H, complex), and 221 (3 H, singlet) cps.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.40; H, 7.07; O, 28.82.

Further crystallization of the mother liquors gave another 2.7 g of diketo ester **11**, mp 134–135°.

In several experiments, it was difficult to purify the saturated diketo ester. Thin layer chromatography indicated the presence of three compounds. Presumably these impurities were the result of over hydrogenation. A more reliable but slower method is given in B.

B.—A solution of **6a** (2 g) in *t*-butyl alcohol (50 ml) with 1 drop of methyl alcohol was hydrogenated in the presence of 5% rhodium on charcoal (0.8 g, 2-mole uptake over 14 hr). The reaction was worked up as above, and the crude product (1.92 g) on crystallization gave diketo ester **11**, mp 134–135° (1.28 g), identical by mixture melting point and infrared spectra with the material obtained in A.

***cis*-Decahydro-5α,8α-dihydroxynaphthalene-1α-carboxylic Acid γ-Lactone (12).**—A solution of freshly distilled aluminum isopropoxide (*ca.* 60 g) in isopropyl alcohol (200 ml) at 50° was added to a stirred solution of saturated diketo ester **11** (8 g) in isopropyl alcohol (150 ml) at 50–55°. After the solution had been stirred at 50–55° for 1 hr, isopropyl alcohol (about 200 ml) was removed by distillation under reduced pressure during 1.5 hr. The cooled solution was treated with cooled sulfuric acid (100 ml, 10%), which was added slowly while the temperature was kept at 5–10°. A precipitate, which separated at first, dissolved on further addition of aqueous acid. The mixture was kept for 1 hr and was then extracted with chloroform (six 150-ml portions). The chloroform solution was washed with saturated aqueous sodium chloride and with water and was dried (Na_2SO_4), and the solvent was removed. The oily residue (5.2 g) crystallized from ether–petroleum ether in stout needles to give **12**: mp 146–147° (3.6 g) raised to 150–151° on further crystallization; ν_{max} 3660, 3530, 3042, 2967, 2918, 2895, 1770, 1454, 1429, 1368, 1358, 1316, 1139, 1064, 1018, 976, 965, 892, and 829 cm^{-1}. The nmr and infrared spectra are almost identical with those of hydroxy lactone **12**, mp 143–144° previously reported.[3]

***cis*-Decahydro-8α-hydroxy-5-oxonaphthalene-1α-carboxylic Acid Lactone (7a).**—Hydroxy lactone **12** was oxidized[3] to *cis*-keto lactone **7a**, mp 108–109°.

***trans*-Decahydro-8α-hydroxy-5-oxonaphthalene-1α-carboxylic Acid Lactone (5a).**—The *trans* compound (**5a**) had mp 118–120°. On a large scale, the epimerization of **7a** to **5a** under acid condi-

(27) General experimental details as in ref 3. Nmr spectra were taken on a Varian A-60 spectrometer using deuteriochloroform as solvent (unless otherwise specified). Shifts are in cycles per second relative to tetramethylsilane. Melting points are uncorrected. Nomenclature is as in ref 2 and 3.

(28) The most satisfactory procedure for this reaction was that described by Protiva and his co-workers[29] except that isopropyl alcohol should not be removed by distillation after acidification of the reaction mixture.

(29) E. Alderová, L. Bláha, M. Borovička, I. Ernest, J. O. Jílek, B. Kakáč, L. Novak, M. Rajsner, and M. Protiva, *Collection Czech. Chem. Commun.*, **25**, 221 (1960).

tions was complicated by a side reaction which involved cleavage of the lactone to an unsaturated acid. For this reason, alkaline conditions were normally used for the epimerization. Contrary to our previous work,[3] both epimers (approximately 30% of pure **5a**) were obtained in the work-up under both sets of conditions. The separation was complicated because the epimers interconvert on Florisil.[30]

trans-**Decahydro-8α-hydroxy-6-hydroxymethylene-5-oxonaphthalene-1α-carboxylic Acid Lactone (9a). A. From *trans*-Keto Lactone 5a.**—A solution of **5a** (1.0 g) and ethyl formate (3.60 ml) in dry benzene (60 ml) was added, rapidly, to a cold (5°) stirred suspension of sodium methoxide (1.60 g) in dry benzene (60 ml). The reaction mixture was kept under nitrogen at room temperature with occasional mixing for 19 hr. After the reaction mixture had been thoroughly mixed with ice (200 g), the organic and aqueous layers were separated. The organic layer was washed with water and the aqueous layer was washed with ether. The aqueous portions were combined, chilled in an ice bath, acidified to pH 1 (Hydrion paper) with 10% aqueous hydrochloric acid, saturated with sodium chloride, and extracted with ethyl acetate. The ethyl acetate solution was dried (Na_2SO_4). Removal of the solvent gave hydroxymethylene compound **9a**, which on crystallization from ether had mp 160–162° (0.412 g); ν_{max} 2930, 2850, 1775, 1660, 1590, 1440, 1415, 1325, 1275, 1210, 1140, 1070, 1055, 1020, 980, 970, 890, and 860 cm^{-1}; λ_{max} 267 mμ (ε 8400); nmr peaks at 50–200 (11 or 12 H, complex multiplets), 287 (1 H, broad multiplet; width at base 23, $W_{1/2}$ = 21 cps), and 436 (1 H, singlet) cps.

The analytical sample was obtained after several crystallizations from acetone as needles, mp 161–162°.

Additional material (0.379 g, mp 148–160°, a mixture of **9a** and the corresponding hydroxy acid, mp 135–136°) was isolated as a second crop. The acid was recyclized to **9a** by treatment with *p*-toluenesulfonic acid in benzene (refluxed with water removal), giving additional **9a**, mp 155.5–158° (0.148 g).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; O, 28.80. Found: C, 64.71; H, 6.46; O, 28.74.

If the benzene solution from the reaction was washed with aqueous sodium hydroxide which was then added to the other aqueous material, the crude material on crystallization from acetone–ether gave the hydroxy acid corresponding to **9a** in fine needles: mp 135–136°; ν_{max} 3500–2500, 1710, 1640, 1592, 1453, 1350, 1250, 1155, 1100, 1056, 1025, 900, and 815 cm^{-1}. In preparative runs, the crude reaction mixture from the hydroxy methylation was refluxed in benzene with *p*-toluenesulfonic acid to reform the lactone from the hydroxy acid.

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71; O, 33.30. Found: C, 59.88; H, 6.49; O, 33.47.

B. From *cis*-Keto Lactone 11a.—A solution of unrecrystallized *cis*-keto lactone **11a** (3 g) in benzene (150 ml) was refluxed with water removal until no more water separated. Ethyl formate (11 ml) and then sodium methoxide (5 g) were added to the cold, stirred solution, and the resulting mixture was stirred at room temperature under nitrogen for 12 hr. A work-up similar to A gave the hydroxymethylene compound, mp 160–162° (1.71 g), which was shown to be **9a** by mixture melting point and comparison of infrared spectra.

6-*n*-Butylthiomethylenedecahydro-8α-hydroxy-5-oxonaphthalene-1α-carboxylic Acid Lactones.—After a solution of crude hydroxymethylene compound from **5a** (1.7 g) in dry benzene (50 ml) had been refluxed with some crystals of *p*-toluenesulfonic acid for seveal hours, *n*-butyl mercaptan (0.7 ml) was added and the mixture was refluxed overnight. The solvent was removed under reduced pressure. The residue was taken up in ethyl acetate which was washed with 1% aqueous sodium hydroxide and saturated aqueous sodium chloride, dried (Na_2SO_4), and removed to leave a yellowish white solid (2.0 g).

The crude material was chromatographed on Florisil (100 g) and the column was eluted with benzene–ether (9:1). The early fractions contained thioether A (415 mg) which crystallized from ether–petroleum ether in needles: mp 122–123° (250 mg); λ_{max} 310 mμ (ε 16,900); ν_{max} 2850, 1778, 1685, 1565, 1453, 1365, 1320, 1300, 1150, 1085, 1017, 979, 900 and 865 cm^{-1}; ν_{max}^{KBr} 3020–2860, 1774, 1676, 1569, 1439, 1381, 1295, 1231, 1188, 1155, 1088, 1069, 1016, 976, 891, 874, 866, 830, 805, and 729 cm^{-1}; nmr peaks at 45–200 (20 H, complex), 288 (1 H, multiplet; width at base 25, $W_{1/2}$ = 19 cps), and 458 (1 H, doublet, J = 2.5 cps) cps.

(30) A. E. Lickei, unpublished work.

Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.29; H, 7.53; O, 16.31; S, 10.87. Found: C, 65.51; H, 7.29; O, 16.24; S, 10.85.

Later fractions from the column contained thioether B (559 mg) which crystallized from acetone–ether in needles: mp 139–139.5° (320 mg); λ_{max} 310 mμ (ε 17,200); ν_{max} 1776, 1677, 1573, 1460, 1365, 1350, 1295, 1160, 1019, 985, 951 and 895 cm^{-1}; ν_{max}^{KBr} 3010–2860, 1762, 1663, 1570, 1446, 1362, 1278, 1164, 1023, 980, 951, 891, and 802 cm^{-1}; nmr peaks at 40–210 (20 H, complex), 293 (1 H, complex triplet, width at base 18, $W_{1/2}$ = 12 cps), and 458.5 (1 H, doublet, J = 2.5 cps) cps.

Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.29; H, 7.53; O, 16.31; S, 10.87. Found: C, 65.49; H, 7.44; O, 16.21; S, 10.91.

In addition to the fractions discussed above, the remaining fractions were thioether A mixed with a little B (367 mg), and thioether B mixed with a little A and a saturated ketone (558 mg). The identification of the thioethers was based on infrared bands at 976 (A) and at 951 cm^{-1} (B).

In another experiment starting with pure **9a** (1.85 g), the crude product (2.59 g) was chromatographed twice on Florisil and the yields of the ethers were estimated by quantitative infrared spectroscopy as thioether A (455 mg), B (1.229 g), and by-products (462 mg). On the basis of nmr evidence,[18] thioether A is assigned structure **9b** and thioether B is given structure **10a**.

cis-*n*-**Butylthiomethylenedecahydro-8α-hydroxy-1,4a-dimethyl-5-oxonaphthalene-1α-carboxylic Acid Lactone (10b).**—In a nitrogen atmosphere, a solution of the thioethers A and B (500 mg) in dimethylformamide (30 ml) was added over 45 min to an ice-cold, stirred suspension of sodium hydride (0.4 g dispersed in mineral oil) in dimethylformamide (20 ml). After the addition was complete and the mixture was greenish brown in color, methyl iodide (4 ml) was added over a period of 8 min. The mixture was stirred at room temperature (2 hr) and 70° (1 hr), and then poured onto ice. The aqueous mixture was saturated with sodium chloride and the product was isolated through extraction with ethyl acetate. The crude material in benzene was refluxed with *p*-toluenesulfonic acid for 8.5 hr and the product was isolated from the benzene. Chromatography on Florisil gave the dimethyl thioether (290 mg) which on crystallization from ether gave **10b**, mp 120–121° (51 mg). For analysis the material had mp 120–121°; λ_{max} 309 mμ (ε 17,100); ν_{max}^{KBr} 3010–2870, 1773, 1665, 1559, 1408, 1385, 1345, 1294, 1273, 1233, 1212, 1191, 1136, 1103, 1071, 1044, 1012, 998, 983, 934, 895, 800, and 734 cm^{-1}; nmr peaks at 40–200 (24 H, complex; strong singlets at 70 and 78; doublet at 141, J = 6 cps), 297 (1 H, multiplet, width at base 17.5, $W_{1/2}$ = 14 cps), and 458 (1 H, broad singlet) cps.

Anal. Calcd for $C_{18}H_{26}O_3S$: C, 67.06; H, 8.13; O, 14.89; S, 9.92. Found: C, 66.97; H, 8.19; O, 15.00; S, 9.84.

Methylation of thioether A (1.67 g) gave after chromatography (several times) on Florisil and crystallization, the same dimethyl thioether as above, mp 118–119° (80 mg) and 113–115° (50 mg). There was evidence that a second dimethyl thioether was present in the products but this was not isolated.

Methylation of thioether B (1.07 g) gave, after chromatography on Florisil (twice) and crystallization of the fractions (302 mg) eluted in benzene–ether (9:1), the same dimethyl thioether, mp 118–119° (145 mg) (melting point, mixture melting point, and infrared spectra).

The refluxing of the crude product with *p*-toluenesulfonic acid may be omitted.

The methylation was tried without success by the following methods: treating the thioethers with potassium amide in liquid ammonia followed by removal of the ammonia and methylation in ether or dimethylformamide solutions; by carrying out the reaction in dimethyl sulfoxide in the presence of sodium hydride; and by carrying out the reaction with potassium amide in ether. The latter conditions led to a monomethyl compound.

cis-**Decahydro-8α-hydroxy-1β,4a-dimethyl-5-oxonaphthalene-1α-carboxylic Acid Lactone (7b).**—A mixture of compound **10b**, ethanol (15 ml), and concentrated hydrochloric acid (70 ml) was refluxed for 2.5 hr and then kept at room temperature for 18 hr. The mixture was concentrated to half-volume, diluted with 50 ml of water, saturated with sodium chloride, and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated under reduced pressure. Crystallization of the residue from ether–petroleum ether gave dimethyl keto lactone **7b**, mp 106–110° (270 mg). Further crystallization from ether–petroleum ether and sublimation under vacuum gave the analytical sample: mp 110–11°; ν_{max} 2900, 1780, 1710, 1460, 1420, 1385, 1345,

1180, 1140, 1095, 1045, 1030, 1015, 1000, 995, 985, 970, 948, 900, 870, and 825 cm^{-1}; [nmr peaks at 50–100 (10 H, complex; strong singlets at 75 and 79), 112–140 (3–4 H, multiplet), 148 (3–4 H, singlet), and 296 (1 H, multiplet, width at base 16, $W_{1/2}$ = 12 cps) cps, and in benzene the methyl singlets were at 48 and 57, the C_8 proton at 254 (width at base 19, $W_{1/2}$ = 12 cps), and the peak at 148 cps had broken into multiplets.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; O, 21.59. Found: C, 70.37; H, 8.30; O, 21.35.

***cis*-Decahydro-8α-hydroxy-1β,4a,6α-trimethyl-5-oxonaphthalene-1α-carboxylic Acid Lactone (7c).**—Thioethers **9b** and **10a** (0.5 g) were methylated in presence of sodium hydride in dimethylformamide as described above. A solution of the crude reaction product (0.4 g after chromatography on Florisil), in alcohol (40 ml) was refluxed with Raney Nickel (W-2, 3 g) for 4.5 hr. The solution was filtered and the residue was washed with methanol. The combined alcoholic solutions upon concentration left a colorless oily prduct (0.33 g). This product after repeated chromatography on Florisil afforded an oily solid (120 mg), which crystallized from petroleum ether in needles, giving **7c**: mp 117–119° (40 mg), raised on further crystallization to 120–121°; ν_{max} 2930, 1765, 1708, 1460, 1385, 1350, 1128, 1100, and 995 cm^{-1}; nmr peaks at 50–175 (19 H, multiplets, methyl singlets at 78 and doublet at 75, J = 6 cps), and 294 (1 H multiplet, width at base 20, $W_{1/2}$ = 14 cps) cps. The infrared spectrum was similar to the spectrum of keto lactone **5c** obtained by ozonolysis of anhydrotetrahydromarrubiin.[33] The nmr spectra were different.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; O, 20.31. Found: C, 71.21; H, 8.64; O, 19.91.

***cis*-Decahydro-8α-hydroxy-1β,4a,6β-trimethyl-5-oxonaphthalene-1α-carboxylic Acid Lactone (7d).** A.—Trimethyl compound **7c** (70 mg) was refluxed with methanolic potassium hydroxide (20 ml 5%) for 3 hr. The solvent was removed and the residue was acidified with hydrochloric acid (6 *N*); the solution was saturated with sodium chloride and extracted with ethyl acetate (40 ml). Evaporation of the ethyl acetate gave an oil (63 mg), which was refluxed with *p*-toluenesulfonic acid in benzene for 8 hr. The benzene solution was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and concentrated to leave an oily residue (40 mg), which distilled at 130–135° (0.08 mm) and was then chromatographed on Florisil (5 g). Elution with benzene gave a solid (32 mg) which on sublimation under reduced pressure had mp 71–74° (27 mg). Repeated crystallization from petroleum ether gave **7d** as colorless needles: mp 76.5–77.5°; ν_{max} 2940, 1765, 1705, 1468, 1386, 1347, 1127, 1100, and 982 cm^{-1}; nmr peaks at 50–170 (19 H, complex with methyl singlets at 73 and 81, doublet at 72, J = 6 cps), and 298 (1 H, multiplet, width at base 17, $W_{1/2}$ = 14 cps) cps.

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.12; H, 8.48.

B.—Trimethyl compound **7c** (30 mg) was refluxed with methanolic hydrochloric acid (10%, 11 ml) for 4 hr. The solvent was removed under reduced pressure and the residue sublimed at 130–135° (0.07 mm) as a solid, mp 72–75° (20 mg). It was identical with the alkali epimerization product by mixture melting point and infrared spectra.

***cis*-Decahydro-5α,8α-dihydroxy-1β,4a-dimethylnaphthalene-1α-carboxylic Acid γ-Lactone (15).**—Dimethyl compound **7b** (165 mg) was stirred in methanol (15 ml) with sodium borohydride (0.4 g) for 5 hr at room temperature. The mixture was cooled to 0° and treated with 10% hydrochloric acid (pH 3), and the solvent was removed under reduced pressue. Water was added to the residue, and the aqueous mixture was saturated with sodium chloride, and extracted with ethyl acetate. The ethyl acetate solution was washed with saturated aqueous sodium chloride, saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride, and was dried (Na_2SO_4) and concentrated. The partially solid residue (170 mg) was chromatographed on Florisil twice. Elution with benzene–ether (5 and 10% ether) afforded decahydro-5α,8α-dihydroxy-1β,4a-dimethylnaphthalene-1-carboxylic acid γ-lactone (**15**) as a solid (110 mg) which after crystallization from ether–petroleum ether had mp 119–120° (65 mg). Further crystallization from ether gave the analytical sample: mp 120–121°; ν_{max}^{KBr} 3498, 2970, 2880, 1744, 1463, 1387, 1358, 1322, 1295, 1252, 1215, 1172, 1155, 1087, 1056, 1005, 987, 964, 950, 921, 721, and 644 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99; O, 21.40. Found: C, 69.74; H, 9.13; O, 21.41.

***cis*-Decahydro-5α,8α-dihydroxy-1α-hydroxymethyl-1β,4a-dimethylnaphthalene (16).** A.—A solution of dimethyl keto lactone **7b** (192 mg) in dry ether (40 ml) was added to lithium aluminum hydride (300 mg) in dry ether (10 ml). The ethereal solution was refluxed for 5 hr. The excess of hydride was decomposed with ethyl acetate and water, and 10% sulfuric acid was added. Crude triol **16** (192 mg), which was isolated through extraction with ether, crystallized from ethyl acetate–ether in prisms: mp 122–123° (74 mg); ν_{max}^{KBr} 3360, 3020–2860, 1475, 1433, 1400, 1379, 1347, 1314, 1248, 1207, 1175, 1149, 1114, 1072, 1035, 1004, 986, 972, 943, 905, 886, 853, 814, and 740 cm^{-1}. The material from the mother liquors was combined with crude product (44 mg) from another reaction and crystallization from ether–petroleum ether gave additional triol **16**, mp 121–123° (85 mg).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59; O, 21.02. Found: C, 68.49; H, 10.65; O, 21.04.

B.—A solution of dimethyl hydroxy lactone **15**, (37 mg) in dry ether (15 ml) was added to lithium aluminum hydride (100 mg) in dry ether (10 ml). The mixture was refluxed for 5 hr and worked up as in A. The residue (38 mg) was crystallized from ether–petroleum ether to give triol **16**, mp 117–119° (15 mg), undepressed by addition of dimethyltriol **16** from A.

***trans*-Decahydro-5,8α-dihydroxy-1α-hydroxymethylnaphthalene.**—A solution of *trans*-decahydro-5,8α-dihydroxynaphthalene-1α-carboxylic acid γ-lactone (**17**, 210 mg)[3] in dry ether (30 ml) was added to lithium aluminum hydride (300 mg) in dry ether (10 ml). The solution was refluxed for 6 hr, and worked up as in A in the preparation above. Removal of ether yielded a partially solid residue (146 mg), which crystallized from ethyl acetate–petroleum ether in small needles, mp 158–159° (64 mg). The aqueous washings from the original ethereal extract were extracted with ethyl acetate. The product (106 mg) obtained from the ethyl acetate extract crystallized from ethyl acetate–ether–petroleum ether, mp 158–159° (70 mg). For analysis the triol crystallized from ethyl acetate–ether in prisms: mp 159–160°; ν_{max}^{KBr} 3300, 2940–2850, 1436, 1353, 1261, 1197, 1159, 1113, 1066, 1037, 1015, 955, 932, 917, 866, 816, and 717 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}O_3$. C, 65.97; H, 10.07; O, 23.97. Found: C, 66.11; H, 10.20; O, 23.44.

Registry No.—**13**, 10074-45-0; **11**, 10127-38-5; **12**, 10074-46-1; **7a**, 10074-47-2; *trans*-decahydro-5,8α-dihydroxy-1α-hydroxymethylnaphthalene, 10074-48-3; **5a**, 10074-49-4; **9a**, 10127-39-6; **9b**, 10127-40-9; **10a**, 10074-50-7; **10b**, 10074-51-8; **7b**, 10074-52-9; **7c**, 10074-53-0; **7d**, 10074-54-1; **15**, 10074-55-2; **16**, 10074-56-3.

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