Some Chemistry of Methyl 12,14-(2-Oxapropano)abiet-8,9-enoate[1]

D. K. BLACK[2] AND G. W. HEDRICK

Naval Stores Laboratory,[3] Olustee, Florida 32072

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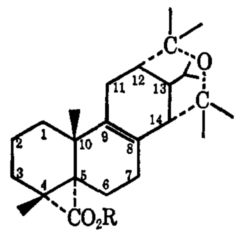
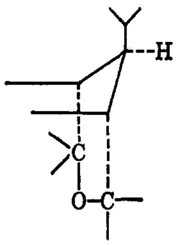
In an earlier paper, some reactions of 12α-hydroxymethylabiet-7,8-enoic acid with formaldehyde were described. The major product when the reaction was run in acetic acid with sulfuric acid present was believed to be 12,14-(2-oxapropano)abiet-8,9-enoic acid (**1a**). In the present paper, consideration is given to the stereochemistry and oxidative studies needed for chemical evidence to support the structure initially assigned. Treatment of **1b** with N-bromosuccinimide gave the transoid diene methyl 12,14-(2-oxapropano)abiet-7,9(11)-dienoate (**3a**). Reduction of the 7-keto derivative (prepared by CrO_3 oxidation and ozonolysis of **1b**) and cleavage of the 8,9 epoxide both gave diene **3a**, which by a series of degradation oxidation steps gave a tetrahydropyran substituted by isopropyl, aldehyde, and hydroxyl (hydroxymethyl) groups and is depicted as **7**.

In studies on the preparation of polyols from resin acids derivatives[4,5] 12,14-(2-oxapropano)abiet-8,9-enoic acid (**1a**) was obtained from the condensation of 12-hydroxymethylabiet-7,8-enoic acid with paraformaldehyde in acetic acid containing sulfuric acid.[4] Similar products may be formed in reactions of resin acids and rosin used commercially. At the time the results of this reaction were published, structural assignments were based on elemental analyses and spectral data. There was an increase in the neutral equivalent of **1a** and in the infrared (ir) spectrum there were no absorbance bands for hydroxyl, ketone, or acetate groups. The purpose of this report is to consider the stereochemistry of the molecule as it relates to the isopropyl-substituted pyran ring, **1a**, and describe the results of some oxidative studies made involving the 8,9 double bond to obtain chemical evidence in support of the structure initially assigned.

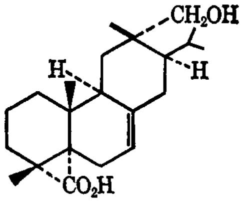
To assign a configuration to the pyran ring and isopropyl group in **1a**, consideration of the stereochemistry of the starting material **2** is necessary since it was not described clearly in the initial publication. Parkin and Hedrick[6] synthesized hydroxymethylabietic acid and from the method of synthesis and spectral data concluded the hydroxymethyl group had an α configuration. Herz and coworkers[7] demonstrated preference for α attack when 12α-hydroxyabietic acid was reduced catalytical with Adam's catalyst. The same hydrogenation of 12-hydroxymethylabietic acid would be expected to proceed in an analogous manner leading to a structure with α-hydroxymethyl- and β-isopropyl groups as in **2**. In the mechanism initially proposed by Black and Hedrick[4] the methylene carbonium ion attacked the C-14 carbon forming an α-pyran ring. This is the only possibility if **2** has the structure depicted. There is strong evidence for a β-oriented isopropyl group in the nuclear magnetic resonance (nmr) spectrum. The observed difference in chemical shift for the two methyls of the isopropyl group together with the change in shift of one methyl with alterations in ring B require this configuration. An α-isopropyl group would be in an essentially symmetrical environment well removed from the rest of the molecule.



1a, R = H
b, R = CH_3



1c



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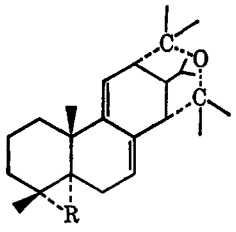

3a, R = CO_2Me
b, R = CH_2OH

Chemical evidence to support the assigned structure was obtained by degradative studies of **1b** using three different oxidation reactions which gave the transoid diene structure **3a**. The pyran **7** was obtained from cleavage of **3a** by ozonolysis and subsequent reactions of the ozonide.

Treatment of **1b** with N-bromosuccinimide resulted in allylic bromination and dehydrobromination to give the transoid diene methyl 12,14-(2-oxapropano)abiet-7,9(11)-dienoate (**3a**), the nmr spectrum of which showed a broad signal at 5.41 ppm for the H-7 and H-11 vinyl protons.

Oxidation of **1b** with chromic acid in acetic acid[8] gave methyl 7-keto-12,14-(2-oxapropano)abiet-8,9-enoate (**4**) as the major product,[9] the presence of the α,β-unsaturated ketone chromophore being shown by the uv maximum at 249 mμ and ir bands at 1610 and 1660 cm^{-1}. That oxidation had occurred at the less hindered C-7 site rather than at C-11 is apparent from the nmr spectrum which showed the AB portion of an ABX pattern in the region 1.90–2.60 ppm, attributed to the coupling of the two protons adjacent to the carbonyl group with the angular C-5 proton.[10] A broad doublet centered at 2.12 ppm is assigned to the geminal coupling ($J \sim 12$ cps) of the equatorial 6α

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[2] National Research Council Posdoctoral Resident Research Associate.

[3] One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

[4] D. K. Black and G. W. Hedrick, *J. Org. Chem.*, **32**, 3763 (1967).

[5] D. K. Black and G. W. Hedrick, *ibid.*, **32**, 3758 (1967).

[6] B. A. Parkin and G. W. Hedrick, *ibid.*, **30**, 2356 (1965).

[7] W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *ibid.*, **30**, 3190 (1965).

[8] L. Ruzicka, E. Rev, and A. C. Muhr, *Helv. Chim. Acta*, **27**, 472 (1944).

[9] Intermediate chromatographic fractions showed ultraviolet (uv) maxima at approximately 260 mμ, suggesting the presence of some enedione.

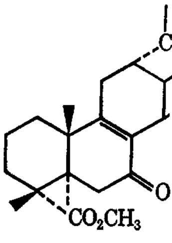
[10] R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 73.

proton, the broadening being due to axial–equatorial coupling with the 5α proton. The 6β axial proton gives rise to a pair of doublets, centered at 2.36 and 2.58 ppm, the larger coupling ($J \sim 13$ cps) again corresponding to the geminal interaction, and the smaller splitting ($J \sim 10$–11 cps) being due to the axial–axial coupling with the 5α proton. Although no deuterium incorporation experiments were carried out, these assignments are in agreement with examples found in the literature for 7-keto steroids.[11]

Lithium aluminum hydride reduction of **4** gave 12,14-(2-oxapropano)abiet-7,9(11)-dienol (**3b**), formed by 1,4-dehydration of the unstable intermediate allylic alcohol.

Ozonolysis of **1b** gave a complex mixture of products. The major component was found to be the 7-keto compound **4**, suggesting preferential allylic attack rather than oxidation of the hindered double bond. However, some epoxide formation was observed. Enzell and Thomas[12] obtained epoxides from the anomalous ozonolysis of araucarolene diacetate, containing a 7,8 double bond.

Epoxidation of methyl 12,14-(2-oxapropano)abiet-8,9-enoate with *m*-chloroperbenzoic acid gave a low yield of an epoxide which on hydrolysis, using lithium iodide in collidine,[13] was accompanied by opening of the oxirane ring and elimination[14] to give the corresponding 7,9(11)-diene (**3a**).



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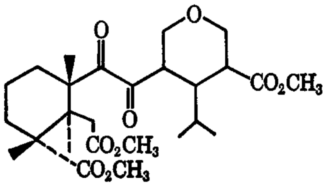

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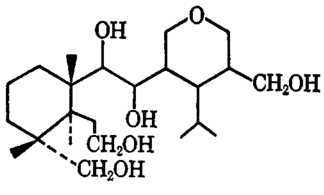

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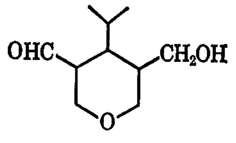

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Ozonolysis of **3a** followed by esterification gave, presumably, the diketone (**5**) which was reduced with lithium aluminum hydride to the corresponding pentaol (**6**). Lead tetraacetate cleavage indicated the presence of a 1,2-diol system and gave the pyran (**7**), isolated by preparative glpc and characterized by ir and nmr.

Experimental Section[15]

Methyl 12,14-(2-Oxapropano)abiet-7,9(11)-dienoate (3a).—Methyl ester **1b** (2.0 g) in dry carbon tetrachloride (50 cc) was refluxed 2 hr with recrystallized N-bromosuccinimide (2.0 g). The mixture was filtered cold; the filtrate was washed with 5% aqueous sodium hydroxide solution and water, dried, and concentrated *in vacuo* to give a resinous solid (1.6 g). Chromatography over alumina (50 g) and elution with *n*-hexane ether (19:1) gave ester **3a** as a colorless solid (1.5 g, 76%): mp 106–108°; λ_{max} 237, 244 mμ (ϵ 15,000), and 253; $[\alpha]^{24}_{D}$ +103° (*c* 1.33); glpc showed a single peak at *t* 4.8 min; nmr (CDCl$_3$) signals appeared at 0.86 and 0.76 and 0.99 and 0.88 (doublets for isopropyl group, J = 6.5 cps), 1.02 (C-10 Me), 1.20 (C-4), 3.63 (ester Me), and a broad signal centered at 5.41 ppm (H-7 and H-11).

Anal. Calcd for C$_{23}$H$_{34}$O$_3$: C, 79.49; H, 9.86. Found: C, 79.41; H, 9.81.

Methyl 7-Keto-12,14-(2-oxapropano)abiet-8,9-enoate (4).—Ester **1b** (2.3 g) in glacial acetic acid (120 cc) was heated to 40°, chromium trioxide (1.5 g) in 90% aqueous acetic acid (15 cc) was added, and the mixture was heated at 45° for 4 hr. Methanol (10 cc) was added; the mixture was poured into water and ether extracted. The extracts were washed with aqueous NaHCO$_3$ solution and water then dried. Removal of solvent gave a low melting solid (2.0 g, 83%). Chromatography over neutral alumina and elution with ether gave the **enone** (**4**) as colorless needles: mp 115°; λ_{max} 249 mμ (ϵ 12,900); ν_{max} (CHCl$_3$) 1730 (ester C=O), 1660 and 1610 cm^{-1} ($\alpha\beta$-unsaturated C=O); glpc showed a major peak at *t* 5.5 min (*ca.* 95%) together with unreacted material at *t* 4.0 min; nmr signals appeared at 0.87 and 0.76 and 0.97 and 0.85 (doublets for isopropyl group, J = 6.5 cps), 1.13 (C-10 Me), 1.25 (C-4 Me), 3.65 (ester Me), and doublets centered at 2.12 (J = 12 cps) and 2.37 ppm (H-5 and H-6); mass spectrum *m/e* (rel intensity) 374 (100), 329 (26), 314 (20), 298 (28), 223 (28), 158 (37), 145 (40), 119 (31), 107 (22), 105 (38), 91 (54), 77 (22), 55 (35), 43 (44), and 41 (46).

Anal. Calcd for C$_{23}$H$_{34}$O$_4$: C, 73.73; H, 9.15. Found: C, 73.64; H, 9.07.

The **enone** gave a 2,4-dinitrophenylhydrazone derivative as an orange-red solid: mp 212–214°; λ_{max} 384 mμ (ϵ 22,000).

Anal. Calcd for C$_{29}$H$_{38}$N$_4$O$_7$: C, 62.80; H, 6.91; N, 10.10. Found: C, 62.37; H, 6.78; N, 9.97.

Lithium Aluminum Hydride Reduction of 4.—Ketone **4** (0.60 g) in ether (50 cc) was refluxed for 2 hr with lithium aluminum hydride (0.5 g). Addition of water followed by dilute HCl (1:1) to pH 2.0, ether extraction, washing with aqueous NaHCO$_3$ and water, concentration, and filtration gave 12,14-(2-oxapropano)-abiet-7,9(11)-dienol (**3b**, 0.4 g, 73%): mp 204–205°; λ_{max} 238, 244.5 mμ (ϵ 13,600), and 255; ν_{max} 3300 cm^{-1} (OH).

Anal. Calcd for C$_{22}$H$_{34}$O$_2$: C, 79.93; H, 10.37. Found: C, 79.95; H, 10.37.

Epoxidation of Methyl 12,14-(2-Oxapropano)abiet-8,9-enoate.—Ester **1b** (0.4 g) in dry chloroform (50 cc) was refluxed for 48 hr with *m*-chloroperbenzoic acid. The resulting solution was washed with aqueous potassium iodide solution, aqueous sodium thiosulphate solution, and water and then dried. Removal of solvent gave a semisolid mass. Addition of ether precipitated a colorless solid (*m*-chlorobenzoic acid). Concentration of the filtrate gave a viscous liquid (0.3 g) which on glpc showed two major components at *t* 4.0 (starting material) and 7.0 min, with minor components having longer retention times. Chromatography of the mixture (0.3 g) over alumina (20 g) and elution with hexane–ether (9:1) gave unreacted ester followed by the epoxidized product as a viscous liquid (60 mg, 20%): nmr signals appeared at 0.87 and 0.77 and 0.92 and 0.82 (doublets for isopropyl group, J = 6.5 cps), 1.15 (C-10 Me), 1.26 (C-4 Me), and 3.65 ppm (ester Me).

Anal. Calcd for C$_{23}$H$_{36}$O$_4$: C, 73.35; H, 9.64. Found: C, 72.98; H, 9.54.

Hydrolysis of the Above Epoxide.—The epoxidized material (0.2 g) and anhydrous lithium iodide (1.5 g) in collidine (15 cc) was refluxed for 18 hr in a nitrogen atmosphere, cooled, acidified, and ether extracted. The extracts were washed, decolorized, dried, concentrated, and reesterified with excess ethereal diazo-

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[11] N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1966, p 63.

[12] C. R. Enzell and B. R. Thomas, *Tetrahedron Lett.*, No. **4**, 225 (1965).

[13] F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960); E. Wendert, P. Peak, R. W. J. Carney, J. W. Chamberlin, D. R. B. Johnston, C. D. Roth, and A. Tahara, *Can. J. Chem.*, **41**, 1924 (1965).

[14] W. Herz and H. J. Wahlborg, *J. Org. Chem.*, **30**, 1881 (1965).

(15) Melting points are uncorrected. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Ir spectra were determined as neat liquids or in solution; uv spectra and rotations were determined in 95% ethanol. Nmr spectra were run in CCl$_4$, unless otherwise stated, using a Varian A-60 spectrometer. Frequencies are given in parts per million (ppm) measured downfield from tetramethylsilane as internal standard. J values are in cycles per second. Mass spectra were obtained with A CEC 21-104 spectrometer using a direct insertion probe. Gas–liquid partition chromatography (glpc) was carried out on a 10 ft. $\times \frac{3}{16}$ in. column 10% Dow Corning silicone grease on 60–80 mesh Diatoport S (F & M Scientific Division of Hewlett-Packard, Avondale, Pa.) at 280° using a Loenco, Inc., Model 15B instrument and a helium flow of 110 cc min. Alumina for chromatography was Alcoa F-20.

methane. Removal of solvent and chromatography over alumina, eluting with hexane-ether (19:1), gave **7,9(11)-diene 3a** (0.15 g): mp 106–108°; λ_{max} 237, 244 mμ (ϵ 12,000), and 253; glpc showed a major component (~90%), *t* 4.8 min.

Ozonolysis of Diene 3a.—Ozonized oxygen (from a Welsbach ozonizer) was passed into a solution of **3a** (0.8 g) in chloroform (50 cc) at 0° until no further ozone was absorbed. Hydrogen peroxide 20% (20 cc) was added to the concentrated solution (residue taken up in methanol) and left at 20° for 24 hr. Water (50 cc) was added, the mixture was concentrated to remove methanol, and the mixture was ether extracted. The extracts were washed with aqueous ferrous sulfate solution and water and then dried. Removal of solvent gave a colorless resinous solid (0.9 g), neut equiv 231 (theory for diacid 227).

The above diacid was esterified with excess ethereal diazomethane to give the triester **5** as a viscous liquid: ν_{max} 1735 (ester C=O), 1715 (1,2 diketone), 1710–1715 (CH_2CO), and 1430 cm^{-1} (CH_2 deformation); glpc showed a major peak, *t* 8.5 min, with two impurities having shorter retention times.

Anal. Calcd for $C_{25}H_{38}O_9$: C, 62.10; H, 7.92. Found: C, 61.80; H, 7.65.

Lithium Aluminum Hydride Reduction of Triester 5.—Triester (0.3 g) was refluxed 2 hr with lithium aluminum hydride (0.5 g) in dry ether (50 cc). Addition of water and dilute hydrochloric acid (1:1) to pH 2.0, ether extraction, and concentration *in vacuo* gave the crude pentaol **6** as a resinous solid (0.21 g), which was not purified.

Lead Tetraacetate Oxidation of 6.—The crude pentaol (0.20 g) was left at room temperature with lead tetraacetate (0.2 g) in acetic acid (10 cc) for 3 hr. Addition of a few drops of ethylene glycol, standing 10 min, dilution with water, ether extraction, and washing gave a viscous liquid (0.2 g). Glpc showed the presence of three major components, *t* 4.5, 7.5, and 12.5 min. Preparative glpc (similar conditions) gave the component having *t* 7.5 min as a viscous liquid (65 mg) identified as the pyran (**7**): ν_{max} (CCl_4) 3400 (OH), 2800 (CHO), 1720 (aldehyde C=O), 1360 and 1380 (Me_2CH), and 1090 cm^{-1} (COC); nmr signals appeared at 0.98 and 0.85 (broad, isopropyl group, J = 7.0 cps), 2.95 (OH), and a doublet centered at 9.56 ppm (J = 2 cps, CHO).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.12; H, 9.64.

Ozonolysis of Methyl 12,14-(2-Oxapropano)abiet-8,9-enoate (1b).—Ester **1b** (2.0 g) in dry chloroform (100 cc) was cooled in ice and ozonized oxygen was passed through for 30 min (progress of the reaction was followed directly by glpc). Concentration *in vacuo* gave a viscous liquid (2.6 g) which on glpc showed a major peak, *t* 6.5 (~60%), and another peak at *t* 4.0 min (ester **1b**) with minor components having longer retention times.

Chromatography over alumina (50 g) and elution with hexane-ether (4:1) gave a forerun of starting material (0.3 g) followed by a mixture (0.7 g) of two components, *t* 7.0 and 7.2 min. Preparative glpc gave the component with *t* 7.0 min as a viscous liquid (0.3 g): ν_{max} ($CHCl_3$) 1725 (ester C=O) and 875 cm^{-1} (epoxide); end absorption only in the uv region; nmr spectrum very similar to that of the epoxide of **1b**.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.35; H, 9.64. Found: C, 73.21; H, 9.59.

Elution with ether gave a colorless crystalline solid (1.0 g): mp 115°; λ_{max} 249 mμ (ϵ 12,750); ν_{max} 1730 (ester C=O), 1660, and 1610 cm^{-1} (α,β-unsaturated C=O); glpc gave a major peak, *t* 5.5 min, identical with that of the product **4** from CrO_3 oxidation of **1b**.

Registry No.—**1b**, 19206-15-6; **1b** (8,9-epoxy), 19206-20-3; **3a**, 19206-16-7; **3b**, 19206-17-8; **4**, 19206-18-9; **4** (2,4-dinitrophenylhydrozone), 19237-74-2; **5**, 19206-19-0; **7**, 19203-28-2.

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Conformational Studies. II. Consequences of the Conjugate Addition of Cyanide Ion to Rigid Bicyclic Systems. A. Hexahydro-1,4a-dimethyl-2-naphthalenone[1]

Oscar R. Rodig and Norman J. Johnston

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22903

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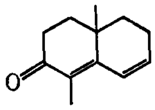
The unsaturated ketone named in the title underwent conjugate addition when treated with potassium cyanide in ethanol. In the absence of ammonium chloride, the main products were two isomeric lactamols, while in the presence of this salt the reaction yielded two epimeric ketonitriles. The structure proofs of the products entailed the use of dipole moment measurements, infrared intensity studies, and nuclear magnetic resonance spectroscopy, as well as classical chemical correlations.

Several years ago a series of publications appeared describing the introduction of a nitrile group at an angular position by the conjugate addition of potassium cyanide to an α,β-unsaturated ketone system.[2,3] In studies originally directed toward the total synthesis of certain sesquiterpenes, this reaction was likewise encountered in our laboratory at that time. The potential synthetic applications of such a cyanation procedure encouraged us to examine it in some detail as to yield, stereoselectivity, and reversibility. Our initial studies were concerned with the addition of potassium cyanide to dienone **1** for the purpose of effecting a 1,6 addition, yielding adduct **2**. The products obtained from this reaction were sufficiently complex, however,[4] that the elucidation of their struc-



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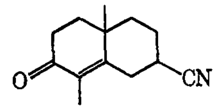

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[1] (a) Taken in part from the dissertation of Norman J. Johnston submitted for the Doctor of Philosophy Degree, University of Virginia, 1963. (b) This is part of a series of conformational studies; for earlier work, see O. R. Rodig and L. C. Ellis, *J. Org. Chem.*, **26**, 2197 (1961).

[2] Some of the more influential contributions in this field have been made by Nagata and coworkers. For a lead reference to their work, see W. Nagata, M. Narisada, and T. Sugasawa, *J. Chem. Soc., C*, 648 (1967). We wish to thank W. Nagata for sending us prior to their publication copies of some of the papers describing the work of the Shionogi group.

[3] Some other significant references are (a) A. Bowers, *J. Org. Chem.*, **26**, 2043 (1961); (b) J. A. Marshall and W. S. Johnson, *J. Amer. Chem. Soc.*, **84**, 1485 (1962); (c) W. L. Meyer and G. R. Schnautz, *J. Org. Chem.*, **27**, 2011 (1962); (d) W. L. Meyer and J. F. Wolfe, *ibid.*, **29**, 170 (1964).

[4] This reaction is described in detail in the following paper: O. R. Rodig and N. J. Johnston, *J. Org. Chem.*, **34**, 1949 (1969).