The Condensation of Paraformaldehyde with Abietic Acid and Some of Its Derivatives

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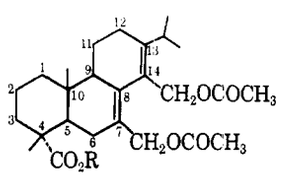
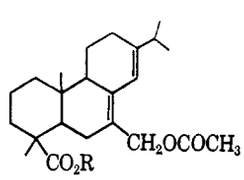
Abietic acid, 12-hydroxymethylabietic acid, and 12-hydroxymethylabiet-7,8-enoic acid react with paraformaldehyde in acetic acid to give mixtures of mono- and diacetates. The isolation and characterization of some of these products are described.

The reaction of paraformaldehyde with conjugated dienes and monoterpenes has been widely studied,[2] the predominant products (*m*-dioxanes, 1,3-diols, or unsaturated acetates) being dependent on the reaction conditions. However, the reaction with diterpenes has largely been ignored. Royals and Greene[3] recognized the heterogeneous nature of the condensation products of the abietic acid–paraformaldehyde reaction but only isolated 7,14-dihydroxymethylabietic acid. This reaction has now been studied further, together with the condensation of paraformaldehyde with 12-hydroxymethylabietic acid,[4] 12-hydroxymethylabiet-7,8-enoic acid,[5] and levopimaric acid.

Abietic acid (1 equiv) and paraformaldehyde (2 equiv) in acetic acid under reflux 24 hr gave a mixture of at least six products as shown by gas–liquid partition chromatography of the esterified product. Chromatography over neutral alumina gave a 65% yield of methyl 7,14-diacetoxymethylabietate (**1b**) having ultraviolet maxima at 245, 252 (ϵ 20,700), and 260 mμ, typical of a heteroannular diene. Earlier chromatographic fractions afforded methyl abietate (*i.e.*, unreacted material, ~5%) and a mixture of monoacetates. Rechromatography of the latter gave methyl 7-acetoxymethylabietate (**2b**) as the major monoacetate product,[6]



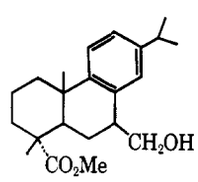
1a, R = H
b, R = Me



2a, R = H
b, R = Me

having an ultraviolet maximum at 244 mμ (ϵ 12,800) which is in approximate agreement with the value predicted by Woodward's[7] rule for a monosubstituted diene. The structure is supported by its nuclear magnetic resonance (nmr) spectrum which showed a shielded H-14 singlet at 5.45 and a two-proton singlet at 1.92 ppm assigned to the uncoupled protons of the C-7 acetate methylene group.

Saponification of the crude abietic acid–paraformaldehyde reaction mixture, esterification, extraction with *n*-hexane, and chromatography of the hexane-soluble fraction afforded (a) methyl abietate, λ_{max} 241 mμ (ϵ 22,800); (b) methyl dehydroabietate, λ_{max} 267 and 275 mμ (ϵ 770); and (c) methyl 7-hydroxymethyldehydroabietate (**3**), λ_{max} 265 and 273 mμ (ϵ 680). The

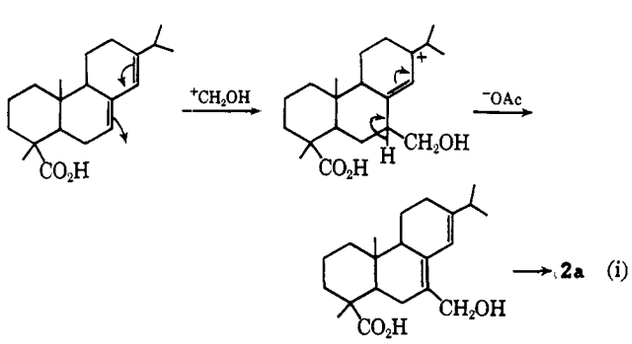


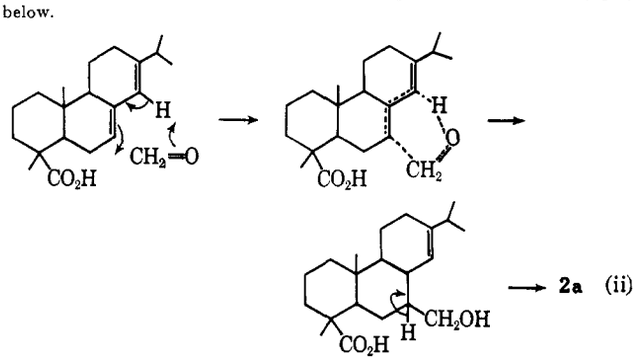
3

nmr spectrum of **3** showed a deshielded three-proton singlet at 1.10 (C-10 Me), a one-proton singlet at 6.85 (H-14), and two diffuse singlets at 6.95 and 7.10 ppm (J_{AB} = 11 cps, H-11 and H-12). Chromatography of the hexane-insoluble fraction gave methyl 7,14-dihydroxymethylabietate (**4**) as a viscous liquid, λ_{max} 245, 252 (ϵ 21,000), and 260 mμ.

Alkali hydrolysis of **1** and **4** gave 7,14-dihydroxymethylabietic acid with physical properties similar to those for the Royals and Greene product. Hydrolysis of **2b** afforded 7-hydroxymethylabietic acid. The ready hydrolysis of the carbomethoxy group is consistent with the equatorial orientation of that group.[8]

No evidence was obtained as to the presence of cyclic ethers in the reaction mixture as postulated by Royals formation of an intermediate six-membered cyclic transition state (eq ii) below.





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(2) E. Arundale and L. A. Mikeska, *Chem. Rev.*, **51**, 505 (1952).

(3) E. E. Royals and J. L. Greene, *J. Org. Chem.*, **23**, 1437 (1958).

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

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

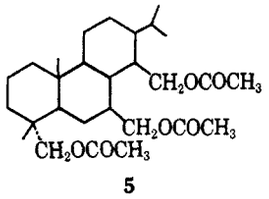
(6) This is to be expected on mechanistic grounds. Two mechanisms may be considered: attack by the resonance-stabilized carbonium ion $^{+}CH_2OH$ at C-7 followed by stabilization of the resulting cation (eq i following) and

(7) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 72 (1942).

(8) U. R. Ghatak and J. Chakravarty, *Tetrahedron Letters*, No. 22, 2449 (1966).

and Greene.[5] Under the experimental conditions used, it is possible that such products, if formed, were hydrolyzed. An attempted cyclization of methyl 7,14-dihydroxymethylabietate by dehydration with dimethyl sulfoxide[9] under reflux was unsuccessful.[10]

Low pressure hydrogenation of **1a** gave a 2:3 mixture of di- and tetrahydro derivatives. Following lithium aluminum hydride reduction and acetylation of the resulting triol mixture, preparative gas–liquid partition chromatography afforded 7,14-dihydroxymethyltetrahydroabietol triacetate (**5**) and the corresponding dihydro compound (**6**).[11] The nmr spectrum of **6** showed a singlet at 1.98 ppm for the uncoupled $-CH_2-$ of the vinyl-substituted acetoxy group and two signals at 3.80 and 3.97 ppm (J_{AB} = 11 cps) of a two-proton quartet for the equatorially oriented C-4 acetate group.[12] The tetrahydro compound **5** showed only the two-proton quartet and the common acetate Me singlet at 1.95 ppm. A low resolution mass spectrum of **6** showed a parent molecular ion at 476 and a breakdown pattern consistent with that structure.



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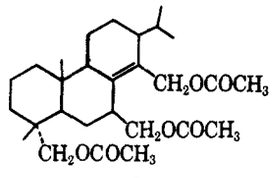

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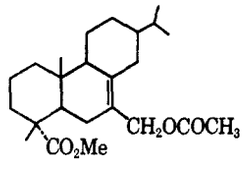

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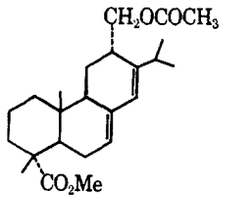
Hydrogenation of **2b** followed by preparative gas–liquid partition chromatography gave methyl 7-acetoxymethylabiet-7,8-enoate (**7**) as the major product. The nmr spectrum showed Me singlets at 0.80 (C-10), 1.17 (C-4), 1.96 (acetate Me), and 3.57 (ester Me) and a two-proton singlet at 1.91 ppm for the acetoxy $-CH_2-$ group.

The thermal condensation of 12-hydroxymethylabietic acid with paraformaldehyde in acetic acid gave a mixture of products which on alkali hydrolysis, lithium aluminum hydride reduction, acetylation, and chromatography gave dehydroabietol acetate,[13] 12-hydroxymethylabietol diacetate, a mixture of triacetates, and a very low yield of 7,12,14-trihydroxymethylabietol tetraacetate, λ_{max} 252 mμ (ε 10,700).

In order that the reaction could be studied more directly by glpc, it was thought more desirous to use methyl 12-acetoxymethylabietate (**8**) as starting material. The reaction product was found to be a mixture of four major components with retention times t = 4.5 (~15%), t = 6.2 (~20%), t = 8.5 (~40%), and t = 8.7 min (~25%).



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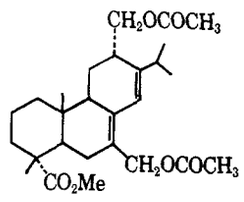

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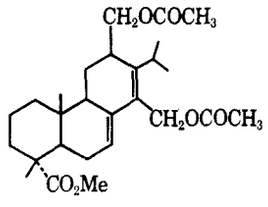

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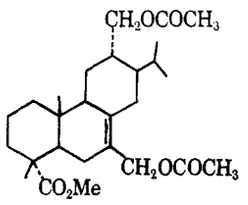
Preparative glpc afforded (a) a component with t = 4.5 min identified as methyl dehydroabietate (infrared and ultraviolet spectra); (b) a component with t = 6.2 min (unreacted **8**); (c) a component with t = 8.5 min which showed ultraviolet maxima at 244 mμ (ε 14,900) and 250 mμ, infrared bands at 1730 (ester C=O), 1725 (acetate C=O), and 828 cm^{-1} (C=CH, out-of-plane deformation), and a singlet at 6.07 ppm (H-14) in the nmr spectrum. This data suggests that the major diacetate product is methyl 7,12-diacetoxymethylabietate (**9**), formed by the Prins reaction on the less hindered and electronically more favorable C-7 site. The minor diacetate product (**10**) was isolated in an impure state only, the nmr spectrum showing a broadened doublet at 5.33 (H-7) and a singlet at 6.07 ppm (H-14) together with the expected acetate Me signals.

Hydrogenation of **9** resulted in the uptake of one molecule of hydrogen with the formation of methyl 7,12-diacetoxymethylabiet-7,8-enoate (**11**), the nmr spectrum of which showed no signals for vinyl protons.

12-Hydroxymethylabiet-7,8-enoic acid (**12a**) was comparatively much less reactive toward paraformaldehyde in acetic acid solution. After refluxing 36 hr, 50% of **12a** was recovered as the 12-acetoxymethyl



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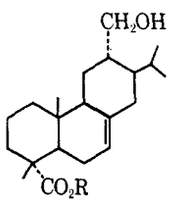
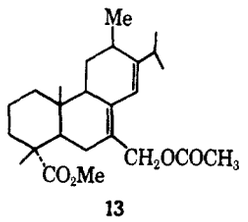


12a, R = H
b, R = Me



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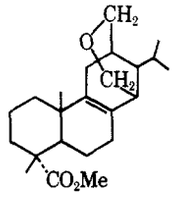


14

compound. The major product of reaction (isolated as the Me ester) was a crystalline solid which analyzed for $C_{23}H_{36}O_3$. The infrared spectrum showed no OH, ace-

(9) V. J. Traynelis, W. L. Hergenrother, J. L. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962).

(10) This was somewhat unexpected in view of the close proximity of the two OH groups and of the strain-free nature of the would-be product.

(11) It was assumed that 1,4 addition of hydrogen to the diene system had occurred. However, the position of the double bond is only tentative, it being difficult to assign a definite position on physical data alone.

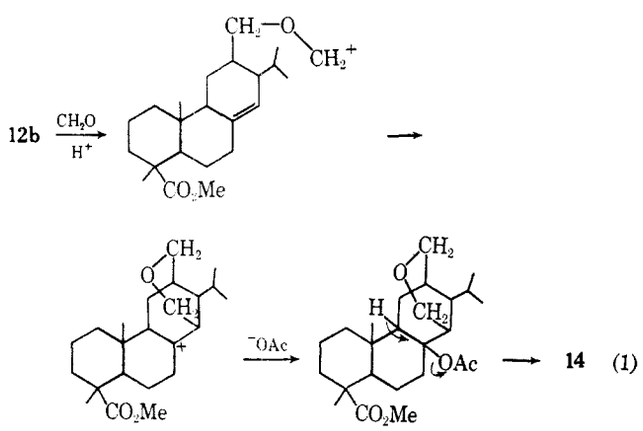
(12) A. Gaudemer, J. Polonsky, and E. Wenkert, *Bull. Soc. Chim. France*, **5**, 28 (1964).

(13) Formed by the α elimination of the 12-acetoxymethyl group on prolonged heating in acetic acid.

tate C=O, or C=CH bands; the ultraviolet region showed no absorption. The nmr spectrum showed doublets at 0.75, 0.86 and 0.81, 0.92 (isopropyl group), a singlet at 1.21 (C-4 Me), a deshielded singlet at 1.02 (C-10 Me), a three-proton singlet at 3.66 ppm (ester Me), broadened signals (2 cps) of an AB pattern at 3.23 and 3.41 ppm (J = 10.5 cps, O–CH_2–CH–), but no protons in the 4.0–10.0-ppm region (*i.e.* absence of vinyl or aromatic protons, 1,3-dioxanes, etc.). These data are consistent with structure **14**, methyl 12,14-methyleneoxyabiet-8,9-enoate. Column chromatography and preparative glpc afforded two additional products. One was identified as the diacetate (**11**) having identical infrared and nmr spectra and glpc retention time with those of the product of the hydrogenation of **9**.

The second product showed an ultraviolet maximum at 245 mμ ($E^{1\%}_{1\,cm}$ 350), infrared bands at 1730 (ester C=O), 1725 (acetate C=O), and 826 cm^{-1} (C=CH, out of plane deformation) and analyzed for $C_{25}H_{38}O_4$. The nmr spectrum showed a singlet at 5.93 (H-14) and a two-proton singlet at 1.92 ppm (uncoupled acetate –CH_2–) consistent with the structure **13**. This may be considered as being formed from **11** by elimination of a molecule of acetic acid followed by proton rearrangement.

Reaction of **12b** with paraformaldehyde in acetic acid at 90° for 4 hr in the presence of concentrated sulfuric acid gave a 74% yield of **14**. A three-step mechanism for its formation is postulated (eq 1): (a) initial rearrangement of the double bond to the 8,14 position under acid conditions and formation of an intermediate oxymethylene carbonium ion, (b) cyclization at the C-14 site with the formation of a second carbonium ion, and (c) attack by $^-$OAc and elimination of a molecule of acetic acid.



Levopimaric acid with paraformaldehyde in refluxing acetic acid gave a similar mixture of products as obtained from abietic acid. 12-Hydroxyabietic acid[14] failed to react, dehydration and rearrangement readily taking place with the formation of dehydroabietic acid.

Experimental Section[15]

Reaction of Abietic Acid with Paraformaldehyde.—Abietic acid (33.3 g, 0.11 mole), paraformaldehyde (7.3 g, 0.24 mole), glacial acetic acid (160 cc), and acetic anhydride (10 cc) were refluxed 24 hr; the mixture was concentrated *in vacuo* and water (100 cc) added. After ether extraction and washing the extracts with aqueous $NaHCO_3$ solution and then water, drying ($MgSO_4$), and removal of solvent a viscous material (50 g) was obtained, λ_{max} 252 mμ, neut equiv 451 (calcd for diacetate: 450).

Esterification with ethereal diazomethane afforded a yellow viscous liquid: ν_{max} 1740, 1720, 1250 cm^{-1}; λ_{max} 252 mμ; glpc showed the presence of a major component (~65%) with retention time t = 11.0, with minor components, t = 8.6, 6.6, 5.6, and 3.4 min.

Chromatography of the mixture (10 g) on Fisher neutral alumina (150 g) and elution with *n*-hexane gave methyl abietate (component with t = 3.4 min). Elution with hexane–ether (9:1) afforded a mixture of components with t = 5.6, 6.6, and 8.6 min (4.0 g, see later) whereas elution with hexane–ether (4:1) gave 5.0 g (65%) of **methyl 7,14-diacetoxymethylabietate (1b)**: ν_{max} 1730 (ester C=O), 1716 and 1250 cm^{-1} (acetate C=O); λ_{max} 252 mμ (ε 20,700); $[\alpha]^{24}D$ +91.1° (*c* 1.08); glpc showed a major components (~99%), t = 11.0, with an impurity at t = 8.6 min; nmr signals at 1.14 and 1.25 (superimposed doublets for isopropyl group, J = 6.5 cps), 0.80 (C-10 Me), 1.17 (C-4 Me), 1.97 (acetate Me), 1.91 (four-proton singlet, acetate –CH_2–), and 3.58 ppm (ester Me).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.39; H, 8.75. Found: C, 70.43; H, 8.79.

Methyl 7-Acetoxymethylabietate (2b).—The above intermediate fractions were combined and concentrated. Chromatography of the mixture (2.0 g) over Alcoa neutral alumina (50 g) and elution with hexane–ether (19:1) gave 0.6 g of the **monoacetate 2b**: ν_{max} 1735 (ester C=O), 1720, 1240 (acetate C=O), 1650 and 822 cm^{-1} (C=CH); λ_{max} 244 (ε 12,800) and 250 mμ; glpc showed a major component (~95%), t = 5.6 min; nmr signals at 0.96 and 1.06 (isopropyl group, J = 6.5 cps), 0.86 (C-10 Me), 1.18 (C-4 Me), 1.96 (acetate Me), 1.92 (C-7 acetate –CH_2–), 3.56 (ester Me), and 5.45 ppm (H-14 singlet).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34; sapon equiv, 194. Found: C, 74.22; H, 9.29; sapon equiv, 196.

Methyl 7-Hydroxymethyldehydroabietate (3) and Methyl 7,14-Dihydroxymethylabietate (4).—The crude product (50 g) from the abietic acid—paraformaldehyde reaction was hydrolyzed by refluxing 3 hr with KOH (30 g) in ethanol (150 cc) and water (150 cc). The resulting product was treated with aqueous sodium dihydrogen phosphate solution and ether extracted. The extracts were concentrated *in vacuo*, esterified with excess ethereal diazomethane, and dried ($MgSO_4$) to give a mixture of methyl ester (55 g) which was divided into a hexane-soluble fraction (12 g) and a hexane-insoluble fraction (43 g).

Hexane-Soluble Fraction.—Chromatography of this fraction (10 g) over Fisher alumina (100 g) and elution with *n*-hexane gave a mixture (2.0 g) of methyl abietate, λ_{max} 241 mμ (ε 22,800), and methyl dehydroabietate, λ_{max} 267 and 275 mμ (ε 770). Initial elution with hexane–ether (19:1) gave a semisolid mass which on washing with cold ether left colorless needles (0.4 g), mp 187–188°, identified as **methyl 7-hydroxymethyldehydroabietate (3)**: λ_{max} 265 and 273 mμ (ε 680); nmr signals ($CDCl_3$) at 1.03 and 1.15 (isopropyl group, J = 7.0 cps), 1.22 (C-4 Me), 1.19 (C-10 Me), 3.60 (ester Me), 6.85 (H-14), and diffuse singlets at 6.95 and 7.10 ppm (H-11 and H-12; J_{AB} = 11.0 cps).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.68; H, 9.37. Found: C, 76.69; H, 9.42.

Further elution with hexane–ether (19:1) gave an unresolved mixture of monoacetates (3.5 g). Elution with hexane–ether (2:1) gave **methyl 7,14-dihydroxymethylabietate (4)** (2.2 g) as a viscous liquid: λ_{max} 245, 252 (ε 21,000), and 260 mμ; ν_{max} 3350 (OH), 1730 (ester C=O), 1060 and 1235 cm^{-1} (C—O, stretch).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.35; H, 9.64. Found: C, 73.66; H, 9.77.

Hexane-Insoluble Fraction.—Chromatography of this fraction (3 g) over Fisher alumina (50 g) and elution with hexane–ether (10:1) gave **methyl 7,14-dihydroxymethylabietate** (2.0 g).

(14) W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *J. Org. Chem.*, **30**, 3190 (1965).

(15) Melting points are uncorrected. Analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra (Nujol mulls or neat) were determined on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra and rotations were determined in 95% ethanol. Nmr spectra were run on a Varian A-60 spectrometer using CCl_4 as solvent. Frequencies are given in parts per million (ppm) measured downfield from tetramethylsilane as internal standard. J values are in cycles per second (cps). Gas–liquid partition chromatography (glpc) was carried out on a 5 ft × 3/8 in. column 20% SE-52 on Gas-Chrom Z (Applied Science Laboratories Inc., State College, Pa.) at 320° using an Aerograph Autoprep A-700 instrument and a helium flow of 120 cc/min for preparative work. A 10 ft × 3/16 in. column 10% OV-1 on 100–200 mesh Chromosorb W (Applied Science Laboratories, Inc.) at 300° using a Loenco Model 15B instrument and a helium flow of 150 cc/min was used for analytical work. Alumina for chromatography was Alcoa F-20, unless otherwise stated.

7,14-Dihydroxymethylabietic Acid. A. From 1b.—Methyl 7,14-diacetoxymethylabietate (1.5 g) was refluxed with KOH (2.0 g) in ethanol (5 cc) and water (5 cc) for 3 hr and the mixture shaken with sodium dihydrogen phosphate (4 g) in water (20 cc) and ether (30 cc). The ethereal layer was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a pale yellow solid (0.8 g). Decolorization and recrystallization twice from ethanol gave the **acid** (0.6 g) as a colorless solid: mp 190–191° (lit.[3] mp 192–193°); ν_{max} 3400 (OH), 3250–2950 (H-bonded OH), 1695 (acid C=O); λ_{max} 251.5 mμ (ε 23,800); $[\alpha]^{24}D$ +123.7° (*c* 1.20); neut equiv, 364 (calcd: 362.5).

B. From 4.—Methyl 7,14-dihydroxymethylabietate (1.0 g), KOH (1.0 g) in water (5 cc), and ethanol (5 cc) were refluxed 2 hr. Work-up as above gave **7,14-dihydroxymethylabietic acid** (0.74 g, 77%).

7-Hydroxymethylabietic Acid.—Monoacetate **2b** (0.2 g) was refluxed 2 hr with KOH (0.2 g) in ethanol (1 cc) and water (1 cc). Addition of sodium dihydrogen phosphate (0.5 g) in water (5 cc), ether extraction, decoloration and removal of solvent gave the *acid* as a resinous solid (0.11 g), λ_{max} 244 mμ (ε 13,700) and 250 mμ.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.81; H, 9.70. Found: C, 75.69; H, 9.68.

Methyl 7-Acetoxymethylabiet-7,8-enoate (7).—**2b** (0.1 g) in ethanol (20 cc) was hydrogenated at room temperature under pressure (20 psi) using Adams platinum oxide catalyst (0.05 g). After 1 hr, filtration and concentration *in vacuo* gave a colorless viscous liquid (0.1 g). Preparative glpc at 300° gave **7**: ν_{max} 1730 (ester C=O), 1725 and 1235 cm^{-1} (acetate (C=O); no absorption in the ultraviolet region; nmr signals at 0.89 and 1.00 (isopropyl group, J = 7.0 cps), 0.80 (C-10 Me), 1.17 (C-4 Me), 1.96 (acetate Me), 1.91 (acetate $-CH_2-$) and 3.57 (ester Me).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 12.35. Found: C, 73.72; H, 12.30.

7,14-Dihydroxymethyltetrahydroabietol Triacetate (5) and Dihydro Compound (6).—The crude abietic acid–paraformaldehyde product (25 g) was hydrogenated in glacial acetic acid (100 cc) at room temperature under pressure (30 psi) using Adams platinum oxide catalyst (1.6 g). After 12 hr, filtration and concentration *in vacuo* gave a viscous liquid (26 g) with neut equiv 443 (calcd for diacetate: 448).

Hydrolysis of the above with KOH (15 g) in ethanol (70 cc) and water (70 cc) for 2.5 hr under reflux, addition of sodium dihydrogen phosphate (60 g) in water (300 cc) and ether (300 cc), followed by ether extraction gave a semisolid mass (17 g): ν_{max} 3360 (OH), 3200–2950 (H-bonded OH), 1710 (acid C=O); neut equiv 356 (calcd: 364).

The above acid mixture (10 g) in ether (300 cc) was reduced with lithium aluminum hydride (4 g) under reflux 2 hr, excess hydride decomposed by addition of water, the pH adjusted to 2.0 with aqueous HCl (1:1), and the mixture ether extracted. The extracts were washed with cold 5% aqueous NaOH solution and water and dried. Removal of solvent gave an amorphous solid (12.8 g).

The crude triol (12 g) was refluxed 2 hr with acetic anhydride (10 cc), concentrated *in vacuo*, and poured into water. After stirring 10 min, the pH was adjusted to 8.0 with 5% aqueous NaOH solution, the mixture was ether extracted, and the extracts were washed with water. After drying, removal of solvent gave a viscous liquid (12.9 g), bp 250–260° (1.0 mm), which on glpc at 320° showed four major components, t = 4.4 (tetrahydroabietol acetate), t = 8.0 (mixture of acetates), t = 12.8 (dihydro compound **6**), and t = 14.8 min (tetrahydro compound **5**).

Preparative glpc afforded the **dihydro compound 6** as a colorless viscous liquid; nmr signals appeared at 0.89 and 1.00 (isopropyl group, J = 7.0 cps), 0.82 (C-10 Me), 1.13 (C-4 Me), 1.97 (acetate Me), 1.92 (C-14 acetate $-CH_2-$), and a 1:3:3:1 quartet centered at 3.88 ppm (C-4 acetate $-CH_2-$, J_{AB} = 10.5 cps).

Anal. Calcd for $C_{28}H_{44}O_6$: C, 70.56; H, 9.31; mol wt, 476.6. Found: C, 70.51; H, 9.27; mol wt (mass spectroscopy), 476.

7,14-Dihydroxymethyltetrahydroabietol triacetate (5)—was also obtained as a colorless viscous liquid.

Anal. Calcd for $C_{28}H_{46}O_6$: C, 70.28; H, 9.69; sapon equiv, 159.6. Found: C, 70.21; H, 9.62; sapon equiv, 161.

12-Hydroxymethylabietic Acid.[4]—Levopimaric acid–formaldehyde adduct (66 g, 0.2 mole) in 95% ethanol (100 cc) on standing at 20° for 15 hr with 6 *N* HCl (10 cc) and dilution with water gave an oil which solidified on standing overnight. Recrystallization from methanol gave the **acid** in 82% yield: mp 167–168°; λ_{max} 242 mμ (ε 25,000); $[\alpha]^{24}D$ +48°.

7,12,14-Trihydroxymethylabietol Tetraacetate.—12-Hydroxymethylabietic acid (64 g, 0.192 mole) and paraformaldehyde (12.6 g, 0.42 mole) in glacial acetic acid (300 cc) were refluxed 18 hr, and then the excess acetic acid was removed *in vacuo* and the residue taken up in ether. The solution was washed with aqueous $NaHCO_3$ solution and water, dried, and concentrated *in vacuo* to give a low melting solid (80 g): λ_{max} 253 mμ; neut equiv 491. Hydrolysis of this product (20 g) with KOH (15 g) in ethanol (70 cc) and water (70 cc) by refluxing for 3 hr followed by reduction with lithium aluminum hydride (5.0 g) in ether (150 cc) under reflux for 3 hr afforded a colorless solid (12 g). Acetylation with excess acetic anhydride under reflux for 2 hr gave a viscous liquid (15 g) which on glpc at 320° showed the presence of three major components: t = 4.2 (12-hydroxymethylabietol diacetate), t = 6.8 and 7.0 (triacetates), and t = 9.6 min (tetracetate).

Chromatography of the mixture (10 g) over Fisher neutral alumina (150 g) and elution with *n*-hexane–ether (4:1) gave 12-hydroxymethylabietol diacetate (3.6 g) (infrared and ultraviolet spectra identical with an authentic sample[4]) and elution with hexane–ether (3:2) gave a mixture of triacetates (4.2 g), sapon equiv 159 (calcd: 158.2). After a forerun of a mixture of components (1.0 g), elution with ether gave the **tetraacetate** (0.4 g): mp 144–145° (from aqueous EtOH); λ_{max} 252 mμ (ε 10,700); glpc showed a major component (~95%), t = 9.6 min, with impurities having lower retention times.

Anal. Calcd for $C_{31}H_{46}O_8$: C, 68.08; H, 8.48. Found: C, 68.12; H, 8.50.

Methyl 12-Acetoxymethylabietate (8).—12-Hydroxymethylabietic acid (20 g) in ether (100 cc) was treated with excess ethereal diazomethane at room temperature. Concentration *in vacuo* gave **methyl 12-hydroxymethylabietate** (20 g): ν_{max} 3350 (OH), 1730 cm^{-1} (ester C=O); λ_{max} 234, 241.5 (ε 23,800) and 250 mμ. Acetylation of the above ester (20 g) with acetic anhydride (20 cc) under reflux 2 hr gave **8** as a viscous liquid (18.2 g, 78%): bp 225–228° (2 mm); ν_{max} 1730 (ester C=O), 1720 (acetate C=O) and 825 cm^{-1} (C=CH); λ_{max} 235, 242 (ε 21,000) and 250 mμ; nmr signals appeared at 0.98, 1.09, 1.01, 1.12 (two doublets, isopropyl group, J = 7.0 cps), 0.80 (C-10 Me), 1.21 (C-4 Me), 1.98 (acetate Me), 3.57 (ester Me), 5.32 (broadened doublet, J = 4 cps, H-7), and 5.78 ppm (singlet, H-14).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.23; H, 9.28. Found: C, 74.05; H, 9.55.

Reaction of Methyl 12-Acetoxymethylabietate with Paraformaldehyde.—Methyl 12-acetoxymethylabietate (3.0 g, 0.0077 mole) was refluxed 24 hr with paraformaldehyde (0.6 g, 0.02 mole) in glacial acetic acid (20 cc) and acetic anhydride (2 cc), then concentrated *in vacuo*. The residue was poured into ice water, the pH adjusted to 8.0, and the mixture ether extracted. The extracts were washed with cold 5% aqueous NaOH solution and water and dried. Removal of solvent gave a viscous liquid (3.8 g): λ_{max} 243 and 250 mμ; glpc at 320° showed components with t = 4.5 (methyl dehydroabietate, λ_{max} 268 and 276 mμ), t = 6.2 (starting material), and t = 8.5 and 8.7 min.

Separation by preparative glpc afforded 0.6 g of **methyl 7,12-diacetoxymethylabietate (9)**: ν_{max} 1730 (ester C=O), 1725 and 1245 (acetate C=O), 828 cm^{-1} (C=CH); λ_{max} 244 (ε 14,900) and 250 mμ; glpc, t = 8.7 min; nmr signals at 1.22 and 1.12 (isopropyl group, J = 6.5 cps), 0.79 (C-10 Me), 1.15 (C-4 Me), 1.96 (acetate Me), 3.57 (ester Me), 1.90 (C-7 acetate $-CH_2-$), and 6.07 ppm (singlet, H-14).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75; sapon equiv, 153.5. Found: C, 70.59; H, 8.89; sapon equiv, 156.

Methyl 12,14-diacetoxymethylabietate (10) (0.2 g) was also obtained: λ_{max} 244 and 250 mμ; nmr signals appeared at 6.07 (singlet, H-14) and 5.33 ppm (broadened doublet, H-7); glpc showed the fraction to be contaminated with ~30% of the 7,12-diacetoxy compound.

Hydrogenation of Methyl 7,12-Diacetoxymethylabietate (9).—Ester **9** (0.2 g, 0.00043 mole) in ethanol (20 cc) was hydrogenated under pressure (30 psi) in the presence of prereduced Adams platinum oxide catalyst (0.05 g). The hydrogenation was stopped after the absorption of 10 cc of hydrogen. Filtration and concentration *in vacuo* gave a colorless viscous liquid (0.2 g) which on glpc at 320° showed the presence of two major components, t = 8.9 and 8.7 min (unreduced **9**) (ratio of 3:1).

Preparative glpc gave **methy l7,12-diacetoxymethylabiet-7,8-enoate (11)**: nmr signals appeared at 0.94 and 1.05 (isopropyl group, J = 6.5 cps), 0.81 (C-10 Me), 1.18 (C-4 Me), 3.60 (ester Me), 1.96 (acetate Me), 1.92 (C-7 acetate $-CH_2-$), and a quartet centered at 3.89 ppm (C-12 acetate).

Anal. Calcd for $C_{27}H_{42}O_6$: C, 69.63; H, 9.09. Found: C, 69.59; H, 9.02.

Reaction of 12-Hydroxymethylabiet-7,8-enoic Acid with Paraformaldehyde.—12-Hydroxymethylabiet-7,8-enoic acid (10 g), paraformaldehyde (2 g), and glacial acetic acid (80 cc) were refluxed 36 hr and excess acetic acid was removed *in vacuo*. Usual work-up, addition of excess ethereal diazomethane, and concentration *in vacuo* gave a pale yellow viscous liquid (11.7 g). Glpc showed the presence of two major components at t = 3.7 and 3.8 with three minor components at t = 6.5–8.4 min.

The above mixture (7 g) was chromatographed over Alcoa alumina (50 g). Elution with *n*-hexane–ether (9:1) gave unresolved components with retention times t = 3.7 and 3.8 (**mixture A**, 6 g) followed by components with t = 6.5–8.4 min (**mixture B**, 1.0 g).

Rechromatography of mixture A on Alcoa alumina (50 g) and elution with *n*-hexane afforded **methyl 12-acetoxymethylabiet-7,8-enoate** (3.6 g): nmr signals appeared at 0.87 and 0.96 (isopropyl group, J = 6.5 cps), 0.78 (C-10 Me), 1.16 (C-4 Me), 1.95 (acetate Me), 3.57 (ester Me), and a broadened doublet at 5.33 ppm (H-7, J = 4.0 cps).[5] After eluting with hexane–ether (19:1, 150 cc), further elution with hexane–ether (9:1) gave a crystalline solid (2.0 g) which on recrystallization from aqueous EtOH gave colorless needles, mp 118–119°, identified as **methyl 12,14-methyleneoxyabiet-8,9-enoate** (**14**) (see later).

Rechromatography of mixture B (1 g) over Alcoa alumina (40 g) and elution with hexane (200 cc), hexane–ether (19:1, 200 cc), and hexane–ether (9:1, 200 cc) failed to give any material. Elution with hexane–ether (4:1) gave unresolved components with glpc retention times t = 7.5 and t = 8.4 min. Preparative glpc (T = 300°) gave a component with t = 7.5 min as a viscous liquid and was identified as **methyl 7,12-diacetoxymethylabiet-7,8-enoate** (**11**), identical (infrared and nmr spectra) with that obtained from the hydrogenation of **9** (*vide infra*).

The second component with t = 8.4 min was obtained as a pale yellow viscous liquid (0.15 g), λ_{max} 245 mμ ($E^{1\%}_{1.cm}$ 350), identified as **methyl 7-acetoxymethyl-12-methylabietate** (**13**): nmr signals at 0.93 and 1.03 (isopropyl group, J = 7.0 cps), 0.80 (C-10 Me), 1.18 (C-4 Me), 1.97 (acetate Me), 1.92 (C-7 acetate $-CH_2-$ singlet), 3.56 (ester Me), and a singlet at 5.93 ppm (H-14).

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.78; H, 9.54. Found: C, 74.56; H, 9.43.

Methyl 12,14-Methyleneoxyabiet-8,9-enoate (**14**).—A mixture of paraformaldehyde (0.45 g), glacial acetic acid (5 cc), and concentrated sulfuric acid (2 drops) was heated to 50° with stirring, then methyl 12-hydroxymethylabiet-7,8-enoate (3.5 g, 0.01 mole) in acetic acid (5 cc) was added. After heating at 90° for 4 hr, the mixture was poured into water and ether extracted. The extracts were washed with aqueous $NaHCO_3$ solution and water and then dried ($MgSO_4$). Removal of solvent and recrystallization from aqueous EtOH gave **14** (2.7 g, 74%) as colorless needles: mp 118–119°; $[\alpha]^{23}D$ +70° (c 1.21); ν_{max} 1725 cm^{-1} (ester C=O), no OH, acetate C=O or C=C bands; nmr signals ($CDCl_3$) appeared at 0.75, 0.86, 0.81 and 0.92 (isopropyl group, J = 6.0 cps), 1.02 (C-10 Me), 1.21 (C-4 Me), and 3.66 (ester Me).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.61; H, 10.07. Found: C, 76.49; H, 10.01.

Reduction of 14.—Ester **14** (1.8 g) was refluxed 2 hr with lithium aluminum hydride (1.0 g) in ether (100 cc). Addition of water and dilute HCl (1:1) followed by ether extraction gave 1.5 g (88%) of a colorless solid: mp 220–221°; ν_{max} 3400 (OH), no C=O bands; nmr signals (pyridine) appeared at 0.78 and 0.89 (isopropyl group), 0.91 (C-10 Me), 1.09 (C-4 Me), and a quartet centered at 3.48 ppm (J = 10 cps, $-CH_2OH$).

Anal. Calcd for $C_{22}H_{36}O_2$: C, 78.90; H, 11.63. Found: C, 79.26; H, 10.92.

Acetylation of the above alcohol by refluxing 1 hr with acetic anhydride gave the corresponding acetate as a colorless viscous liquid.

Anal. Calcd for $C_{24}H_{38}O_3$: C, 77.15; H, 9.99. Found: C, 77.11; H, 9.92.

12,14-Methyleneoxyabiet-8,9-enoic acid.—Ester **14** (1.8 g) was refluxed 24 hr with KOH (3 g) in water (20 cc) and ethanol (20 cc). Sodium dihydrogen phosphate (10 g) in water (40 cc) was added, the mixture was ether extracted, and the extracts were washed with water until neutral. After drying, concentration *in vacuo* gave the **acid** as a colorless solid (1.2 g), mp 225–227° (from aqueous EtOH), $[\alpha]^{24}D$ +56° (c 1.2).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.23; H, 9.89; neut equiv, 336. Found: C, 76.18; H, 10.08; neut equiv, 346.

Registry No.—Abietic acid, 514-10-3; paraformaldehyde, 110-88-3; **1b**, 14969-87-0; **2b**, 14909-58-1; **3**, 15038-62-7; **4**, 14909-59-2; 7,14-dihydroxymethylabietic acid, 14909-60-5; 7-hydroxymethylabietic acid, 14909-61-6; **5**, 14909-62-7; **6**, 14909-63-8; **7**, 14909-64-9; 7,12,14-trihydroxymethylabietol tetraacetate, 14909-65-0; methyl 12-hydroxymethylabietate, 14909-66-1: **8**, 14909-72-2; **9**, 14909-68-3, **10**, 14909-69-4, **11**, 14909-70-7; methyl 12-acetoxymethylabiet-7,8-enoate, 15076-91-2; **13**, 14969-84-7; **14**, 14969-85-8; alcohol of mp 220–221°, 14909-71-8; 12,14-methyleneoxyabiet-8,9-enoic acid, 14909-72-9.

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Studies in the Ganglioside Series. I. Synthesis of 4-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-D-galactopyranose[1]

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The synthesis of the 1 → 4 disaccharide XIII is reported. A new stable and reactive bromide (III) has been employed in the Koenigs–Knorr reaction. Condensation of III with 2-*O*-acetyl-1,6-anhydro-β-D-galactopyranose (VI) also led to the 1 → 3 isomer which suffered cleavage under the influence of mild alkali. The diacetyl derivative VII could be obtained by selective acetylation of VI.

In the ganglioside molecule *N*-acetylgalactosamine is connected with galactose by a 1 → 4 β linkage.[2-4] The synthesis of glycosides of this type poses a special problem owing to the unstable nature of the acylated amino sugar bromides employed in the Koenigs–Knorr reaction. Thus, Micheel[5] has shown that 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide easily transforms into the amine hydrobromide by an N → O acyl migration *via* the oxazoline. Other bromides in which the amine function was protected by the

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