Phytochemistry, 1971, Vol. 10, pp. 1647 to 1651. Pergamon Press. Printed in England.

DERIVATIVES OF NORDEHYDROABIETANE FROM PINE BARK

JOHN W. ROWE and BHIMSEN A. NAGASAMPAGI*
Forest Products Laboratory,† Forest Service, U.S. Department of Agriculture, Madison,
Wisconsin 53705, U.S.A.
and
ALBERT W. BURGSTAHLER and JON W. FITZSIMMONS‡
Department of Chemistry, University of Kansas, Lawrence, Kansas 66044, U.S.A.

(Received 14 October 1970)

Abstract—18- And **19-norabieta-8,11,13-trien-4-ol** and **18-hydroxy-8,11,13-abietatrien-7-one** have been isolated from jack pine (*Pinus banksiana* Lamb.) and their constitution confirmed by synthesis. Three 19-norabietatetraenes have been detected in western white pine (*Pinus monticola* Dougl.).

INTRODUCTION

IN THE course of our investigations of the nonpolar extractives of pine bark,[1,2] we have encountered several new derivatives of nordehydroabietane which evidently arise from an oxidative free-radical decarboxylation of dehydroabietic acid analogous to that observed with lead tetra-acetate.[3] Since woody plants synthesize lignin through a nonspecific free-radical oxidation, these nordehydroabietanes may be true *in vivo* products.[4]

RESULTS AND DISCUSSION

We initially isolated **18-norabieta-8,11,13-trien-4-ol**[5] **(Ia)** from jack pine (*Pinus banksiana* Lamb.) bark and characterized it as the 3,5-dinitrobenzoate. Later we were able to make direct spectral and GLC comparisons of the free alcohol with authentic samples of **Ia** prepared both by ourselves and by others.[6–8] A new synthesis of **Ia** was developed involving lithium aluminum hydride (LAH) reduction of the 4α,19-epoxide derived from **19-norabieta-4(18),8,11,13-tetraene (IIa)**, thus providing confirmatory proof of the 4α-ol configuration. Previous routes[6–8] to **Ia** have led to conflicting NMR spectral assignments of the C-4 and C-10 methyl signals, but by using lithium aluminum deuteride to obtain the 19-monodeuterated analog **(Ib)**, we were able to prove, in agreement with Huffman,[8] that the

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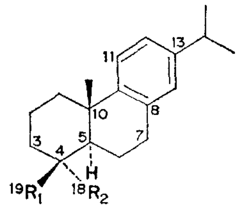
- * Wisconsin Section of the American Chemical Society postdoctoral fellow.
- † Maintained in cooperation with the University of Wisconsin.
- ‡ From M.S. Thesis of J.W.F., University of Kansas, August 1970.

[1] C. L. BOWER and J. W. ROWE, *Phytochem.* 6, 151 (1967).
[2] J. W. ROWE, C. L. BOWER, and E. R. WAGNER, *Phytochem.* 8, 235 (1969).
[3] J. W. HUFFMAN and P. G. ARAPAKOS, *J. Org. Chem.* 30, 1604 (1965).
[4] However, R. C. A. ROTTLÄNDER, *Tetrahedron Letters* 4127 (1969), reports oxidative free radical decarboxylation of dehydroabietic acid on irradiation.
[5] This nomenclature is based on *The Common and Systematic Nomenclature of Cyclic Diterpenes*, 3rd rev., October 1968, with addenda and corrigenda of February 1969, available from the Forest Products Laboratory, Madison, Wis. 53705, U.S.A.
[6] R. N. SEELYE and W. B. WATKINS, *Tetrahedron* 25, 447 (1969).
[7] C. R. BENNETT, R. C. CAMBIE, R. A. FRANICH and T. J. FULLERTON, *Australian J. Chem.* 22, 1711 (1969).
[8] J. W. HUFFMAN, *J. Org. Chem.* 35, 478 (1970).

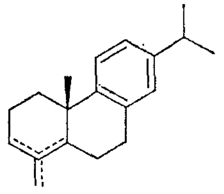
chemical shift value of the C-4 methyl group lies 0·05 ppm downfield from that of the C-10 methyl group and not vice versa[6,7]

In further studies on jack pine, we later isolated 19-norabieta-8,11,13-trien-4-ol (Ic) in one-fourth the yield of the 4α-ol (Ia). Since appreciable amounts of Ia were undoubtedly lost during attempted acetylation (which we have since found leads to extensive dehydration), the natural occurrence of these two norabietatrienols parallels the 13 : 1 ratio of 4α-ol to 4β-ol we observe in the lead tetra-acetate decarboxylation of dihydropimaric acid.

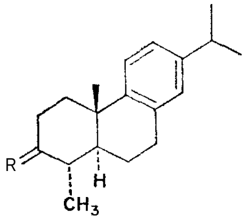
Synthesis of Ic was achieved by treatment of 19-norabieta-3,8,11,13-tetraene (IIb) with *N*-bromoacetamide in aq. acetone followed by reduction with LAH of the intermediate bromohydrin (presumably 3α-bromo-19-norabieta-8,11,13-trien-4-ol, resulting from *trans*-diaxial addition of HOBr to the double bond). Attempts to obtain the corresponding 3β,4β-epoxide by reaction of the crude bromohydrin with alkali were unsuccessful. The NMR spectrum of Ic shows the expected C-10 angular methyl resonance at τ 8·75, deshielded by the 4β-hydroxyl group, and the normal C-4 methyl signal at 8·82.



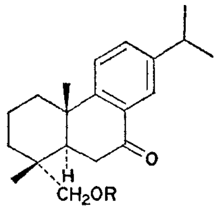
(Ia) $R_1 = CH_3$; $R_2 = OH$
(Ib) $R_1 = CH_2D$; $R_2 = OH$
(Ic) $R_1 = OH$; $R_2 = CH_3$



(IIa) 4 (18)-ene (5αH)
(IIb) 3-ene (5αH)
(IIc) 4-ene



(IIIa) R = $\overset{H}{HO}$
(IIIb) R = O



(IVa) R = H
(IVb) $R = COCH_3$

In considering possible alternative routes to Ic it was thought that epoxidation of IIb might yield some of the desired 3β,4β-epoxide. However, as reported recently by Cambie and Franich,[9] the product of this reaction is essentially only the 3α,4α-epoxide. In agreement with these authors, its reduction by LAH was found to proceed principally by axial attack" at C-4 to yield 19-norabieta-8,11,13-trien-3α-ol (IIIa). Oxidation of IIIa under non-epimerizing conditions afforded the corresponding ketone (IIIb) which Huffman[8] has also prepared, but by a different route.

Since both epimeric norabietatrien-4-ols are found in jack pine bark, it is reasonable to expect that the three related 19-norabietatetraenes, IIa, IIb, and IIc should also be present.

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[9] R. C. CAMBIE and R. A. FRANICH, *Australian J. Chem.* **23**, 93 (1970).

[10] Similar diaxial opening has been found with 3α,4α-epoxy-12-methoxy-18-norpodocarpa-8,11,13-triene by R. C. CAMBIE and W. A. DENNY, *Australian J. Chem.* **22**, 1699 (1969).

Unfortunately, the terpene hydrocarbon fraction had already been sent to Dr. L. Westfelt at the Swedish Forest Products Laboratory and was no longer available to us. He detected pimaradiene, isopimaradiene, and δ-cadinene in this fraction by GLC.

However, we have been investigating the terpene hydrocarbon fraction of the benzene extract of western white pine (*Pinus monticola* Dougl.) bark. We find that all three isomeric 19-norabietatetraenes IIa, IIb, and IIc are present and have isolated the major isomer, the 4(18),8,11,13-tetraene (IIa), which is the isomer that predominates in the lead tetra-acetate decarboxylation of dehydroabietic acid.

From jack pine bark we also isolated a new natural dehydroabietane derivative, 7-oxodehydroabietol (18-hydroxy-8,11,13-abietatrien-7-one) (IVa), as the acetate IVb. Although the free alcohol is known as a synthetic product,[11] the acetate has not been previously reported. The proof of structure was therefore completed by a simple synthesis of IVb via chromic acid oxidation of 8,11,13-abietatrien-18-yl acetate.

EXPERIMENTAL

Jack Pine Bark

The hexane-soluble neutral terpenoids (43·9 g) of jack pine bark were chromatographed as described previously.[1,2] Light petroleum–benzene (4 : 1) and (1 : 1) eluted 4·57 g from which Ic (0·01% of the benzene extract) was obtained.[12] Light petroleum–benzene (1 : 1) and benzene then eluted 7·74 g from which Ia (0·04% of the benzene extract) was obtained.[13] Benzene–Et$_2$O then eluted 5·93 g from which 7-oxodehydroabietol (IVa) (0·005% of the benzene extract) was obtained.[14]

18-*Norabieta*-8,11,13-*trien*-4-*ol* (*Ia*)

The eluate of 7·74 g was acetylated (Ac$_2$O-pyridine), treated with urea to remove residual wax alcohols, and distilled to remove triterpenes, b.p. (0·1 mm) 124–208°. The 4·12 g of distillate were chromatographed on 508 g of silica. Benzene–Et$_2$O eluted 271 mg of colorless oil which appeared by GLC (SE-30, DEGS) to be essentially a single compound; IR (CCl$_4$) ν_{max} 3614 cm^{-1} (unacetylated tertiary alcohol). The NMR and IR spectra were identical to synthetic Ia, but showed the presence of impurities. The natural and the synthetic samples had identical retention times on GLC of the alcohols (SE-30) and of the TMS ethers (DEGS).

The crude material was treated with a 10-fold excess of 3,5-dinitrobenzoyl chloride in pyridine to yield 378 mg of a red solid, which was absorbed on 143 g of SiO$_2$ in a multibore column. Light petroleum–benzene mixtures eluted 94 mg of an oil which appeared to be the dehydration product. Pure benzene eluted 70 mg of white crystals, which were crystallized from CH$_2$Cl$_2$–CH$_3$OH and CH$_2$Cl$_2$–hexane to constant melting point for analysis: m.p. 154·5–155·5° cor., $[\alpha]_D^{21°}$ −13° (c 1·0, CHCl$_3$). (Found: C, 67·15; H, 6·5; N, 6·05. C$_{26}$H$_{30}$N$_2$O$_6$ required: C, 66·9; H, 6·5; N, 6·0%.)

The NMR spectrum (CDCl$_3$) showed three aromatic protons at τ 0·3 for the dinitrobenzoate group and three aromatic protons at 2·9 with a dehydroabietate type pattern, a broad multiplet centered at 7·0 for three benzylic protons, two tertiary methyls at 8·25 (C-4) and 8·72 (C-10), and an isopropyl doublet at 8·74 (J = 6·5 Hz). The IR spectrum was rich in aromatic bands and showed the expected bands for a 3,5-*dinitrobenzoate ester* (1721, 732 and 721 cm^{-1}) but no hydroxyl.

19-*Norabieta*-8,11,13-*trien*-4-ol (*Ic*)

The eluate of 4·57 g was treated with Girard T reagent to remove the carbonyl components. The non-carbonyl fraction was again treated with the reagent, and the combined carbonyl fractions were further purified by treatment with the reagent. These operations yielded 1·09 g of carbonyl and 2·85 g of noncarbonyl

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[11] L. A. Subluskey, U.S. Patent 2,750,370 (June 12, 1956); *Chem. Abs.* **51**, 1277 g (1957).

[12] This fraction was also found to contain 4-stigmasten-3-one, 4-campesten-3-one, 3,5-stigmastadien-7-one, 3,5-campestadien-7-one, 21β-methoxy-14-serraten-3-one, diepiserratenediol 3-methyl ether, (+)-epimanool, *cis*- and *trans*-pinosylvin dimethyl ether (unpublished results).

[13] This fraction was also found to contain dehydroabietol, pimarol, isopimarol, oleyl alcohol, *cis*-9-docosen-1-ol,13-ethoxy-8(17),14-labdadien-19-ol (artifact), and 18-norpimara-8(14),15-dien-4-ol (unpublished results).

[14] This fraction was also found to contain diepiserrantenediol, episerratenediol, 15,16-dinor-19-hydroxy-8-(17)-labden-13-one, 8(17),*E*-13-labdadien-15-ol, isopimarol, and 15-ethoxy-8(17),13-labdadien-19-ol (artifact) (unpublished results).

fractions. The noncarbonyl fraction was chromatographed on 500 g of silica. Benzene eluted 386 mg of yellow oil which consisted of a mixture of three diterpenes by GLC. The mixture was separated by preparative GLC on EGiP and SE-52. The smallest component (21 ma) was distilled. b.p. (0·035 mm) 150”. $[\alpha]_D^{21°}$ $+36°$ (c 0·8, $CHCl_3$), and had IR and NMR spectra identical with those of the synthetic sample of Ic, $\nu_{max}^{CCl_4}$ 3615 cm^{-1} (tertiary OH). The high resolution mass spectrum was run by Professor Ralph C. Dougherty at Florida State University. It showed a strong molecular ion at 272.2133 corresponding to $C_{19}H_{28}O$ (theor. 272.2140). Also significantly strong were the peaks corresponding to the loss of the 10—$CH_3\cdot$, H_2O, or both at *m/e* 257,254, and 239. The *m/e* 239 fragment then further degraded by loss of the isopropyl group as propene to give an ion at *m/e* 197 or by loss of butadiene representing C-2, C-3, C-4, and C-18 to give an ion at *m/e* 185. This fragmentation is in agreement with the reported data on the mass spectra of aromatic diterpenes.[15]

7-Oxodehydroabietyl Acetate (IVb)

The eluate of 5.93 g was crystallized from hexane and MeOH to remove triterpenes, acetylated, and distilled to yield 3.485 g of oil, b.p. (0·2 mm) 158-248”. This was chromatographed on 250 g of SiO_2. Elution with benzene yielded 583 mg of oil, GLC (SE-30) of which showed a major and a minor component. The minor component (34 mg) was isolated by preparative-scale GLC. The NMR, IR and UV spectra correspond to those of a synthetic sample of 7-oxodehydroabietyl acetate (IVb).

Western White Pine Bark—19-Norabietatetraenes

The benzene extract of western white pink bark[16] was processed as usual to yield the nonsaponifiable fraction (14.9% of the benzene extract). Chromatography on alumina yielded 3·5 g of hydrocarbons” (0·4 % of the benzene extract) which were rechromatographed on 260 g of 40 % $AgNO_3$ on Woelm alumina. Light petroleum-benzene (95 : 5) eluted 32 mg of a mixture of hydrocarbons, a minor one of which (0.0002 % of the benzene extract) had the identical retention time on GLC (SE-30, DEGS) and an identical *R*, on argentian TLC as synthetic 19-norabieta-4,8,11,13-tetraene (IIc).

The same solvent later removed 38 mg of a mixture of hydrocarbons, one of which (0·001% of the benzene extract) had the identical retention time on GLC (SE-30, DEGS) and an identical R_f on argentian TLC as synthetic 19-norabieta-3,8,11,13-tetraene (IIb).

Light petroleum-benzene 3 : 1 eluted 74 mg of 54% pure hydrocarbon (0·004 % of the benzene extract) with aretention time on GLC (SE-30, DEGS) that was identical to that of synthetic 19-norabieta-4(18),8,11,-13-tetraene (Ila). This was purified by preparative GLC (DEGS) and distillation, b.p. (0·02 mm) 90–95°, $[\alpha]_D^{19°}$ $+225°$ (c 0·9, $CHCl_3$) (reported: $+195·5°$,[18] 152°).[7] It gave a single peak on GLC and a single spot on argentian TLC identical to the synthetic hydrocarbon. Their IR and NMR spectra were superimposable.

Synthesis of Reference Compounds

Preparative separation of the 19-norabieta-3, -4, and -4(18),8,11,13-tetraenes (Ha, IIb, and IIc) formed in the lead tetra-acetate decarboxylation[4,7,8] of dehydroabietic acid[19] was readily achieved by chromatography on 20 % silver nitrate-alumina activated overnight at 140”. From 4·2 g of the tetraene mixture adsorbed on a 50 x 2-cm column, 0·81 g of the 4-ene (IIc), 1·65 g of the 3-ene (IIb), and 1·68 g of the 4(18)-ene (Ha) were obtained by successive elution with light petroleum, light petroleum-Et_2O (3: 1), and Et_2O, respectively. The spectral properties of each isomer were in substantial agreement with those reported.[7,8]

18-*Norabieta*-8,11,13-*trien*-4-*ol (la)*

Epoxidation of 0·1 g (0·4 mmol) of the 4(18)-ene (IIa) in 10 ml of $CHCl_3$ at 25” by 2 ml of 1·8 M perphthalic acid in Et_2O was nearly complete after 1 hr provided the Et_2O was evaporated from the mixture after the oxidizing agent was added. For reduction, the resulting (crude) 4α,19-epoxy-18-norabieta-8,11,13-triene[9] was dissolved, in 15 ml of dry Et_2O and stirred at 25” for 24 hr with 0·5 g of fresh $LiAlH_4$. Chromatography of the neutral product on 15 g of silica gel and elution with light petroleum–Et_2O (4: 1) gave 17 mg of olefinic material and then 80 mg of 18-norabieta-8,11,13-trien-4-ol (la), which crystallized on standing. Recrystallization from light petroleum at -70” afforded 70 mg (65 % yield) of analytically pure Ia as small white spores: m.p. *89-91”* (lit. m.p. 91·5–92·5°,[6] 89–90°,[7] 90-91”[8]); $[a]_D$ $+45°$ (c 2·0, $CHCl_3$) (lit.’ $+12°$); IR $\nu_{max}^{CCl_4}$ 3614 and 3460 cm-’ (-O-H); NMR (CCl_4) τ 8.91 (C-10 Me), 8.85 (C-4 Me), and 8·80 (i-Pr

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[15] C. R. ENZELL and I. WAHLBERG, *Acta Chem. Scand. 23, 871 (1969).*

[16] W. C. NICKLES and J. W. ROWE, ***Forest Products J. 12, 374*** (1962).

[17] This fraction was also found to contain (—)-calamenene, cadalene, (+)-dehydroabietane, (—)-6,8,11,13-abietatetraene, (—)-sandaracopimaradiene, and (—)-isopimaradiene (unpublished results).

[18] H. H. ZEISS and W. B. MARTIN, ***J. Am. Chem. Soc. 75, 5935 (1953).***

[19] Prepared from dehydroabietonitrile and purified through the methyl ester [cf. A. W. BURGSTAHLER and L. R. WORDEN, ***J. Am. Chem, Soc. 86, 96*** (1964)].

doublet, J = 6·5 Hz).[20] (Found: C, 84·0; H, 10·6. Calc. for $C_{19}H_{28}O$: C, 83.8; H, 10·4%.) Spectral and mixture m.p. comparison showed this material to be identical with a sample of Ia prepared by $LiAlH_4$ reduction of 1 8-norabieta-8,11,13-trien-4-yl acetate isolated from the lead tetra-acetate decarboxylation reaction.

Similar reduction of 0·1 g of the 4α,19-epoxide with 0·2 g of $LiAlD_4$ in 15 ml of dry Et_2O afforded 80 mg of 18-norabieta-8,11,13-trien-4-ol-19d (IIb): m.p. 88–90°; IR $\nu_{max}^{CCl_4}$ 3614 and 3455 cm^{-1} (-O-H); 2180 cm^{-1} (C-D); NMR τ 8.91 (3H, C-10 Me), 8.86 (2H, C-4 —CH_2D), and 8·80 (6H, i-Pr doublet, J = 6·5 Hz).

19-Norabieta-8,11,13-trien-4-ol (Zc)

To a solution of 0·70 g of N-bromoacetamide and 0·63 g of NaOAc in 20 ml H_2O was added a solution of 0·254 g (1·0 mmol) of 19-norabieta-3,8,11,13-tetraene (IIb) in 50 ml of acetone. The mixture was stirred overnight at 25” and then evaporated under reduced pressure until most of the acetone was removed. An additional 10 ml H_2O were added, and the mixture was extracted with Et_2O. The extract was dried (molecular sieves) and evaporated under reduced pressure to give crude 3α-bromo-19-norabieta-8,11,13-trien-4β-ol as a yellow oil which could not be crystallized. The oil was dissolved in 30 ml of dry Et_2O and stirred for 24 hr at 25” with 1·0 g of $LiAlH_4$. Chromatography of the neutral product on 17g of silica gel furnished 0·15 of recovered IIb by elution with light petroleum and then 50 mg of 19-norabieta-8,11,13-trien-4-ol (Ic) by elution with light petroleum–Et_2O (5: 1). Further elution afforded only bromine-containing material. On standing, Ic slowly crystallized, and on recrystallization from light petroleum at -70” had m.p. 65-67”: $[\alpha]_D$ +50° (c 2.0, $CHCl_3$); NMR τ 8.82 (C-4 Me), 1.19 (i-Pr doublet, J = 6·5 Hz), and 8·75 (deshielded C-10 Me). On TLC on silica gel with cyclohexane–EtOAc 9: 1, Ic showed R_f 0·59 compared to R_f 0·38 for Ia and Ib. The mass spectrum had a parent peak of m/e 272 ($C_{19}H_{28}O$ = 272).

19-Norabieta-8,11,13-trien-3α-ol (IIIa)

The 3α,4α-epoxide prepared by the action of perphthalic acid in $CHCl_3$ on 0·5 g of 19-norabieta-3,8,11,13-tetraene (IIb) was dissolved in 20 ml of dry Et_2O and refluxed for 4 hr with 1·0 g of $LiAlH_4$ in 30 ml of 1,2-dimethoxyethane. Chromatography of the neutral product on 25 g of silica gel afforded, by elution with light petroleum–Et_2O 5 : 1, 0·40 g of 19-norabieta-8,11,13-trien-3α-ol (IIIa) as a viscous oil: $[\alpha]_D$ +61° (c 2·0, $CHCl_3$) (lit.[9] +60°); IR $\nu_{max}^{CCl_4}$ 3675 and 3450 cm^{-1} (-O-H); NMR τ 9·10 (C-4 Me doublet, J = 5 Hz), 8.99 (C-10 Me), and 8.81 (i-Pr doublet, J = 6·5 Hz).

19-Norabieta-8,11,13-trien-3-one (IIIb)

Oxidation of 75 mg of IIIa with Kiliani's reagent according to the procedure of Huffman[8] gave 50 mg of 19-norabieta-8,11,13-trien-3-one (IIIb) with spectral properties as recorded.[8,9] The 2,4-dinitrophenylhydrazone after crystallization from EtOH had m.p. and mixed m.p. 154-155” (lit.” 154-155”).

7-Oxodehydroabietyl Acetate (IVb)

The oily acetate of 8,11,13-abietatrien-18-ol, prepared by reaction of the alcohol with Ac_2O in pyridine at 25” for 6 hr, was oxidized by a procedure similar to that reported for the oxidation of methyl dehydroabietate to the 7-keto derivative.[21] To a solution of 0·50 g of the acetate in 5 ml HOAc was added 6.25 g of a 10% CrO_3 in 80% HOAc. After standing at 25” for 18 hr the mixture was diluted with saturated NaCl and extracted with Et_2O. The combined Et_2O layers were washed with 5 % $NaHCO_3$, then with H_2O, and dried (Na_2SO_4). Evaporation gave a yellow oil which was chromatographed on 45 g of neutral alumina (Woelm, activity grade II). Elution with light petroleum–Et_2O (4: 1) gave a light yellow oil which crystallized on standing. Recrystallization from light petroleum furnished 0·30 g (58%) of *7-oxoabieta-8,11,13-trien-18-yl acetate* (IVb) as colorless prisms: m.p. 62–64° $[\alpha]_D$ +18° (c 2·0, $CHCl_3$); UV λ_{max}^{EtOH} 207 (ε 27,000), 253 (10,800), and 303 nm (2040); IR $\nu_{max}^{CCl_4}$ 1740 (C==O, acetate), 1685 (C=O, 7-keto group), and 1235 cm^{-1} (C-O); NMR τ 9·03 (3H, C-4 Me), 8.78 (6H, i-Pr doublet, J = 6·5 Hz), 8.76 (3H, C-10 Me), 8·08 (3H, acetate), 7.46 (2H, C-6 CH_2 doublet, J = 9 Hz), and 6.28 (2H, C-18 CH_2OAc, AB-quartet, J = 11 Hz). (Found: C, 77·0; H, 8.7. $C_{22}H_{30}O_3$ required: C, 77.2; H, 8·8%.)

Acknowledgements—We are grateful for the invaluable help of Jan K. Toda and Carol L. Bower, Forest Products Laboratory, in the isolation of some of the natural products from jack pine bark. We thank R. C. Cambie, University of Auckland, New Zealand, for a sample of IIa and W. B. Watkins, Oxford, United Kingdom, and J. W. Huffman, Clemson University, South Carolina, U.S.A., for copies of the spectra of Ia. Added thanks are given J. W. Huffman for a sample of Ia and for the mixed melting point determination of the 2,4-DNP of IIIb.

la and IVa have also been found to comprise 0·05% each of the benzene extract of western white pine bark.

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[20] Because these chemical shift values were determined in CCl_4 solution they differ slightly from those recorded in Refs. 6 and 8, which were measured in $CDCl_3$.

[21] E. Wenkert and B. G. Jackson, *J. Am.* Chem. *Soc.* 80,211 (1958).