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Revision of Structure of Anhydronellionol Triacetate

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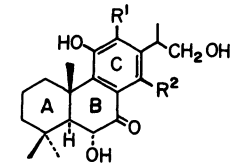
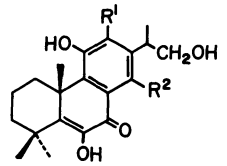
The structure of anhydronellionol triacetate was revised to 11,12,16-triacetoxy-6-hydroxyabieta-5,8,11,13-tetraen-7-one (**18**) by the following syntheses. Acetylation of 16-acetoxyabieta-8,11,13-trien-12-ol, followed by oxidation with chromium trioxide, afforded 12,16-diacetoxyabieta-8,11,13-trien-7-one. This was converted into 6,12,16-triacetoxyabieta-5,8,11,13-tetraen-7-one (**17**) *via* 12,16-diacetoxyabieta-8,11,13-trien-6-one. Oxidation of 11,12,16-triacetoxyabieta-8,11,13-trien-6-one with Jones reagent gave **18**, whose ^{1}H NMR spectrum was in good agreement with that of natural anhydronellionol triacetate. 11,12,16-Triacetoxyabieta-5,8,11,13-tetraen-7-one (**28**) was also synthesized from 11,12,16-triacetoxyabieta-8,11,13-trien-7-one. The ^{1}H NMR spectra of **17** and **28** were different from that of natural anhydronellionol triacetate. Since the revised structure **18** corresponds to dehydronellionol triacetate, the name of anhydronellionol should now be dropped from the list of natural diterpenes.

Recently three tricyclic aromatic diterpenes, nellionol, dehydronellionol, and anhydronellionol, have been isolated from the root bark of *Premna latifolia* Roxb. by Rao *et al.*[1] On the basis of chemical and spectroscopic studies, they deduced the structures of nellionol, dehydronellionol, and anhydronellionol to be 6α,11,14,16-tetrahydroxyabieta-8,11,13-trien-7-one (**1**), 6,11,14,16-tetrahydroxyabieta-5,8,11,13-tetraen-7-one (**2**), and 11, 14,16-trihydroxyabieta-5,8,11,13-tetraen-7-one (**3**), respectively. The isolation of several abietane type diterpenes possessing two oxygen functions in the C-ring have already been reported. In these natural products oxygen functions are usually present at the C-11 and C-12 positions such as cryptojaponol (**4**),[2] fuerstione (**5**),[3] taxodione (**6**),[4] and carnosolone (**7**).[5] However, the proposed structures (**1**, **2**, and **3**) are unique because they possess two oxygen functions at the C-11 and C-14 positions and no oxygen function at the C-12 position. In the previous paper[6] we have reported the revised structures of nellionol and dehydronellionol to be respectively 6α,11,12,16-tetrahydroxyabieta-8,11,13-trien-7-one (**8**) and 6,11,12,16-tetrahydroxyabieta-5,8,11,13-tetraen-7-one (**9**); these possess two oxygen functions in the C-ring at the C-11 and C-12 positions. As an extension of the previous work,[6] we have now examined the published spectral data[1] of natural anhydronellionol triacetate to confirm the validity of the proposed structure **3**. The ^{1}H NMR spectrum of anhydronellionol triacetate showed singlet signals at δ 7.11 and 8.16 which were assigned respectively to the C-6 olefinic proton and the C-12 aromatic proton in the proposed structure (**10**). However, the chemical shift (δ 8.16) of the aromatic proton is different from those (δ 7.04 and 7.09) of the C-12 aromatic protons in methyl 11,14-diacetoxy-7-oxoabieta-8,11,13-trien-18-oate (**11**)[6] and 11,14-diacetoxy-13-(acetoxymethyl) podocarpa-8,11,13-trien-7-one (**12**),[7] but very similar to those (δ 8.15, 8.13, and 8.23) of the C-14 aromatic protons in methyl 11,12-diacetoxy-7-oxoabieta-5,8,11,13-tetraen-20-oate (**13**),[8] 12-acetoxyabieta-5,8,11,13-tetraen-7-one (**14**),[9] and carnosolone diacetate (**15**).[5] These spectral data strongly suggested that the aromatic proton in anhydronellionol triacetate is located at the C-14 position ortho to a carbonyl group. Furthermore the assignment of the signal at δ 7.11 to the C-6 olefinic proton was also unusual, because the olefinic protons in the same moiety of **13** and **14** were observed as singlets at δ 6.57 and 6.50 respectively. On the other hand, the ^{1}H NMR spectrum of **14** showed a singlet signal at δ 7.20 due to the C-11 aromatic proton and that of 6-hydroxyabieta-5,8,11,13-tetraen-7-one (**16**)[10] showed a singlet signal due to an enolic hydroxyl group at δ 7.08. From these spectral analyses, together with consideration of the other spectral data, we deduced a preferable structure of anhydronellionol triacetate to be 6,12,16-triacetoxyabieta-5,8,11,13-tetraen-7-one (**17**) or 11,12,16-triacetoxy-6-hydroxyabieta-5,8,11,13-tetraen-7-one (**18**). To obtain final confirmation of the structure of anhydronellionol triacetate, syntheses of **17** and **18** have been attempted.

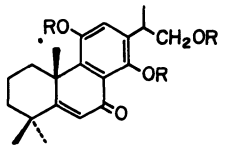
Acetylation of 16-acetoxyabieta-8,11,13-trien-12-ol (**19**)[6,11] with acetic anhydride in pyridine, followed by oxidation of the resulting acetate (**20**: 91%) with chromium trioxide in acetic acid at room temperature, afforded 12,16-diacetoxyabieta-8,11,13-trien-7-one (**21**:



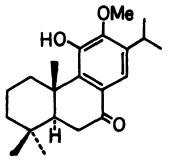
1 R¹=H, R²=OH
8 R¹=OH, R²=H



2 R¹=H, R²=OH
9 R¹=OH, R²=H



3 R=H
10 R=Ac



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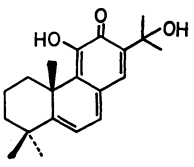

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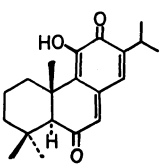
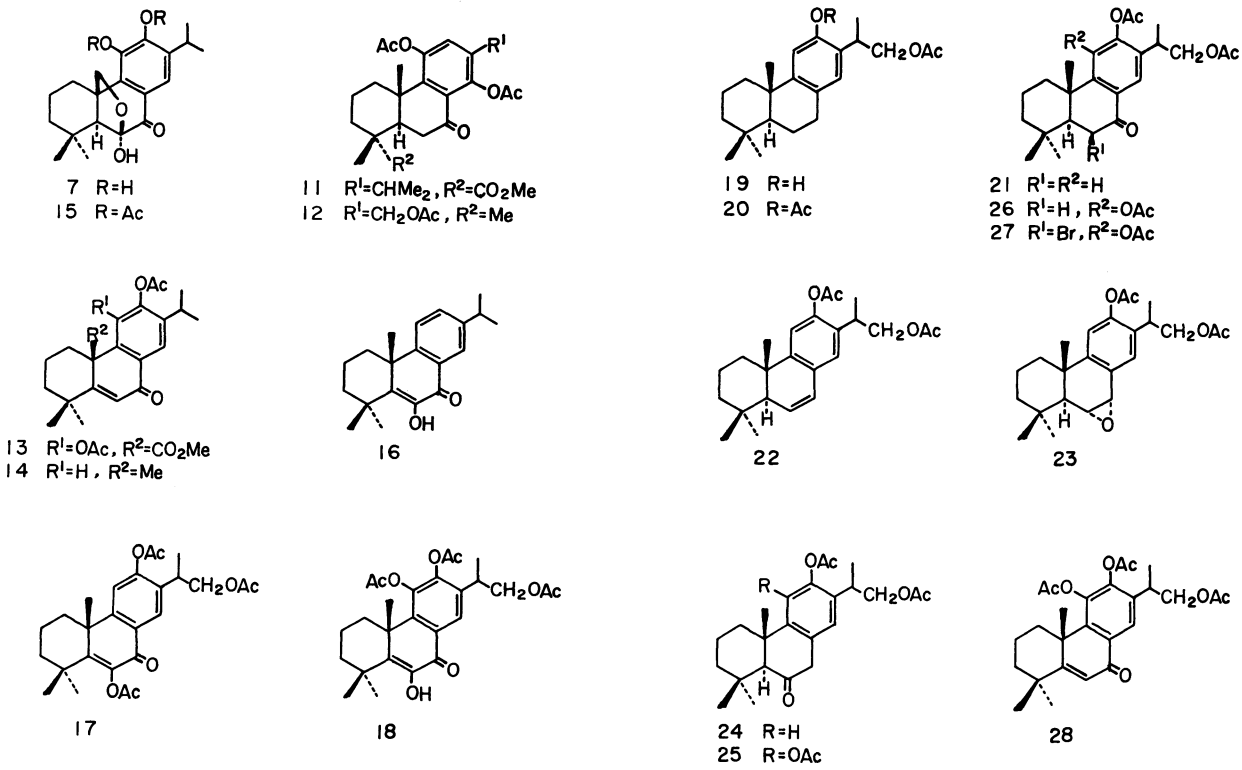


6



65%). The ketone **21** was reduced with sodium borohydride in methanol and the resulting mixture of epimeric 7-hydroxy compounds was immediately subjected to dehydration with dilute hydrochloric acid in refluxing methanol. Under these conditions, the acetoxyl groups were hydrolyzed. Therefore, the crude product was acetylated with acetic anhydride in pyridine to give 12,16-diacetoxyabieta-6,8,11,13-tetraene (**22**). This was treated with *m*-chloroperbenzoic acid in dichloromethane at room temperature. The resulting crude epoxide (**23**) was refluxed with dilute hydrochloric acid in methanol and then acetylated[12] with acetic anhydride in pyridine to afford 12,16-diacetoxyabieta-8,11,13-trien-6-one (**24**: 48% from **21**). The structure of **24** was supported by its ^{1}H NMR spectrum which showed singlet signals at δ 2.39 (1H) due to the $C_{5\alpha}$ proton and at δ 3.61 (2H) due to the C-7 methylene protons. Oxidation of **24** with Jones reagent at room temperature, followed by treatment with anhydrous sodium acetate in refluxing acetic anhydride, afforded the desired **17** (55%). The ^{1}H NMR spectrum of synthetic **17** showed singlet signals due to three acetoxyl groups at δ 2.01 (3H) and 2.36 (6H), and due to two aromatic protons at δ 7.21 (1H) and 8.08 (1H). However, the spectrum of **17** was different from that of natural anhydronellionol triacetate.

Subsequently, 11,12,16-triacetoxyabieta-8,11,13-trien-6-one (**25**)[6,11] was oxidized with Jones reagent and the resulting crude product purified by column chromatography on silica gel to give the desired **18** (49%). The ^{1}H NMR spectrum of synthetic **18** showed singlet signals due to three acetoxyl groups at δ 2.01 (3H), 2.32 (3H), and 2.35 (3H), due to an enolic hydroxyl group at δ 7.05 (1H), and due to an aromatic proton at δ 8.15 (1H). The spectrum of **18** was in good agreement with that of natural anhydronellionol triacetate.

For comparison, 11,12,16-triacetoxyabieta-5,8,11,13-tetraen-7-one (**28**) was also synthesized as follows. Bromination of 11,12,16-triacetoxyabieta-8,11,13-trien-7-one (**26**)[6,11] with pyridinium tribromide in a mixture of chloroform and ethanol (2 : 1) at room temperature produced 11,12,16-triacetoxy-6β-bromoabieta-8,11,13-trien-7-one (**27**). The β-configuration of the bromine atom in **27** was supported by its ^{1}H NMR spectrum, which showed a signal due to the C-10 methyl group in low field (δ 1.75), owing to the 1,3-diaxial interaction between the bromine atom and the C-10 methyl group. Dehydrobromination of the crude bromide **27** with 1,5 diazabicyclo[4.3.0]non-5-ene in refluxing benzene, followed by acetylation,[12] afforded **28** (37% from **26**). The ^{1}H NMR spectrum of **28** showed signals due to the C-6 olefinic proton at δ 6.53 (1H) and due to an aromatic proton at δ 8.13 (1H), which were different from those of natural anhydronellionol triacetate.

From the present study, the proposed structure[1] of natural anhydronellionol triacetate must be revised to **18**, which corresponds to dehydronellionol 11,12,16-triacetate.[6] Therefore, the name of anhydronellionol should now be dropped from the list of natural diterpenes.

Experimental

The IR spectra were measured in chloroform, and the ^{1}H NMR spectra in deuterochloroform at 60 MHz, with tetramethylsilane as an internal standard, unless otherwise stated. The chemical shifts are reported in terms of δ values; s: singlet, d: doublet, bd: broad doublet, m: multiplet. Column chromatography was performed using Merck silica gel.

*12,16-Diacetoxyabieta-8,11,13-triene (**20**).* A solution of

16-acetoxyabieta-8,11,13-trien-12-ol (**19**)[6,11] (678 mg) and acetic anhydride (1.5 ml) in pyridine (2.0 ml) was heated at 75—85 °C for 2 h. After the usual work-up, the crude product was chromatographed on silica gel (20 g), using ether–benzene (3 : 97) as the eluent, to give **20** (690 mg: 91%). IR: 1750, 1730 cm^{-1}; ^1H NMR (CCl_4): δ=0.95 (6H, s, $-C(CH_3)_2$), 1.18 (3H, d, J=7 Hz, C_{15}–CH_3), 1.19 (3H, s, C_{10}–CH_3), 1.95 (3H, s, C_{16}–$OCOCH_3$), 2.24 (3H, s, C_{12}–$OCOCH_3$), 3.97 (d, J=7 Hz) and 4.01 (d, J=7 Hz) (2H, $-CH_2OCOCH_3$), 6.78 (1H, s) and 6.85 (1H, s) (C_{11}–H and C_{14}–H).

*12,16-Diacetoxyabieta-8,11,13-trien-7-one (**21**).* Anhydrous chromium trioxide (416 mg) was added to a solution of **20** (913 mg) in acetic acid (10 ml) with cooling in an ice–water bath. The mixture was stirred at this temperature for 15 min and then at room temperature for 22 h. The mixture was diluted with water and extracted with ether. The ether extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (40 g), using ether–benzene (4 : 96) as the eluent, to give the starting **20** (103 mg: 11%). Further elution with ether–benzene (7 : 93) gave **21** (615 mg: 65%). IR: 1750, 1730, 1673, 1607 cm^{-1}; ^1H NMR: δ=0.95 (3H, s) and 1.02 (3H, s) ($-C(CH_3)_2$), 1.26 (3H, d, J=7 Hz, C_{15}–CH_3), 1.27 (3H, s, C_{10}–CH_3), 2.04 (3H, s, C_{16}–$OCOCH_3$), 2.38 (3H, s, C_{12}–$OCOCH_3$), 4.13 (2H, d, J=7 Hz, $-CH_2OCOCH_3$), 7.07 (1H, s, C_{11}–H), 8.03 (1H, s, C_{14}–H).

*12,16-Diacetoxyabieta-8,11,13-trien-6-one (**24**).* A mixture of **21** (767 mg) and sodium borohydride (150 mg) in methanol (10 ml) was stirred at 0—5 °C for 30 min and then at room temperature for 1 h. The mixture was acidified with dilute hydrochloric acid (10%: 2.0 ml), refluxed for 1 h, and evaporated *in vacuo*. The residue was extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residual oil was acetylated with acetic anhydride (2.0 ml) in pyridine (2.0 ml) at 75—85 °C for 2 h to give the crude 12,16-diacetoxyabieta-6,8,11,13-tetraene (**22**) (743 mg) which was used without purification in the next reaction.

A mixture of the crude tetraene **22** (743 mg) and *m*-chloroperbenzoic acid (590 mg) in dichloromethane (10 ml) was stirred at 0—5 °C for 1 h and then at room temperature for 14 h. The mixture was diluted with ether and washed successively with aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. The ether solution was dried over sodium sulfate and evaporated *in vacuo* to give a crude epoxide (**23**) (871 mg) which was used without purification in the next reaction.

A mixture of the crude epoxide **23** (871 mg) and dilute hydrochloric acid (10%: 2.0 ml) in methanol (10 ml) was refluxed for 1 h. The mixture was evaporated *in vacuo*, diluted with water, and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to give an oil (784 mg). This was acetylated with acetic anhydride (2.0 ml) in pyridine (2.0 ml) at 75—85 °C for 2 h. After the usual work-up, the crude product was purified by column chromatography on silica gel (40 g), using ether–benzene (3 : 97) as the eluent, to give **24** (368 mg: 48% from **21**). IR: 1750sh, 1732, 1710 cm^{-1}; ^1H NMR: δ=1.09 (3H, s), 1.18 (3H, s), and 1.34 (3H, s) ($-C(CH_3)_2$ and C_{10}–CH_3), 1.23 (3H, d, J=7 Hz, C_{15}–CH_3), 2.05 (3H, s, C_{16}–$OCOCH_3$), 2.36 (3H, s, C_{12}–$OCOCH_3$), 2.39 (1H, s, $C_{5\alpha}$–H), 3.61 (2H, s, $-COCH_2-$), 4.12 (2H, d, J=7 Hz, $-CH_2OCOCH_3$), 7.01 (2H, s, C_{11}–H and C_{14}–H).

*6,12,16-Triacetoxyabieta-5,8,11,13-tetraen-7-one (**17**).* A solution of **24** (368 mg) in acetone (8.0 ml) was oxidized with Jones reagent [2.5 M (1 M=1 mol dm^{-3}): 1.2 ml] at 0—5 °C for 10 min and then at room temperature for 2.5 h. The mixture was diluted with water and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give a crude 6,7-dioxo compound. This was immediately refluxed with acetic anhydride (15 ml) in the presence of anhydrous sodium acetate (900 mg) for 2.5 h with stirring. The mixture was diluted with water and benzene, evaporated *in vacuo* to remove the excess acetic anhydride, and extracted with ether. The ether extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (20 g), using ether–benzene (5 : 95) as the eluent, to give **17** (229 mg: 55%). IR: 1760, 1735sh, 1660, 1615 cm^{-1}; ^1H NMR (90 MHz): δ=1.27 (d, J=7 Hz) and 1.30 (d, J=7 Hz) (3H, C_{15}–CH_3), 1.33 (3H, s) and 1.40 (3H, s) ($-C(CH_3)_2$), 1.59 (3H, s, C_{10}–CH_3), 2.01 (3H, s, C_{16}–$OCOCH_3$), 2.36 (6H, s, C_6 –$OCOCH_3$ and C_{12}–$OCOCH_3$), 4.04—4.18 (2H, m, $-CH_2$–$OCOCH_3$), 7.21 (1H, s, C_{11}–H), 8.08 (1H, s, C_{14}–H). The ^1H NMR spectrum of **17** was different from that of natural anhydronellionol triacetate. Found: C, 68.12; H, 7.17%. Calcd for $C_{26}H_{32}O_7$: C, 68.40; H, 7.07%.

*11,12,16-Triacetoxy-6-hydroxyabieta-5,8,11,13-tetraen-7-one (Dehydronellionol 11,12,16-Triacetate) (**18**).* A solution of 11,12,16-triacetoxyabieta-8,11,13-trien-6-one (**25**)[6,11] (71 mg) in acetone (2.0 ml) was oxidized with Jones reagent (2.5 M: 0.1 ml) at 0—5 °C for 10 min and then at room temperature for 2 h. The mixture was diluted with water and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (7.0 g), using ether–benzene (3 : 97) as the eluent, to give **18** (36 mg: 49%). IR: 3405, 1775, 1730, 1631, 1605 cm^{-1}; ^1H NMR (90 MHz): δ=1.30 (d, J=7 Hz) and 1.32 (d, J=7 Hz) (3H, C_{15}–CH_3), 1.46 (3H, s) and 1.48 (3H, s) ($-C(CH_3)_2$), 1.59 (3H, s, C_{10}–CH_3), 2.01 (3H, s, C_{16}–$OCOCH_3$), 2.32 (3H, s) and 2.35 (3H, s) (C_{11} –$OCOCH_3$ and C_{12}–$OCOCH_3$), 4.10 (d, J=7 Hz) and 4.13 (d, J=7 Hz) (2H, $-CH_2OCOCH_3$), 7.05 (1H, s, –OH), 8.15 (1H, s, C_{14}–H). The ^1H NMR spectrum of **18** was compatible with that of natural anhydronellionol triacetate, except for the signals due to the corresponding C-15 epimer.

*11,12,16-Triacetoxy-6β-bromoabieta-8,11,13-trien-7-one (**27**).* A mixture of 11,12,16-triacetoxyabieta-8,11,13-trien-7-one (**26**)[6,11] (68 mg) and 80% pyridinium tribromide (120 mg) in chloroform (1.0 ml) and ethanol (0.5 ml) was stirred at room temperature for 2 h. The mixture was diluted with water and extracted with ether. The ether extract was washed successively with water, aqueous sodium thiosulfate, and brine. The dried solution was evaporated *in vacuo* to give a crude bromide (**27**) (87 mg). ^1H NMR (CCl_4): δ=1.42 (6H, s, $-C(CH_3)_2$), 1.75 (3H, s, C_{10}–CH_3), 1.98 (3H, s, C_{16}–$OCOCH_3$), 2.39 (6H, s, C_{11}–$OCOCH_3$ and C_{12}–$OCOCH_3$), 4.80 (1H, bd, J=2.5 Hz, $W_{1/2}$=4 Hz, $C_{6\alpha}$–H), 8.05 (1H, s, C_{14}–H).

*11,12,16-Triacetoxyabieta-5,8,11,13-tetraen-7-one (**28**).* A mixture of the crude bromide **27** (87 mg) and 1,5-diazabicyclo-[4.3.0]non-5-ene (0.1 ml) in dry benzene (2.0 ml) was refluxed for 2 h in a stream of nitrogen. The mixture was cooled, acidified with dilute hydrochloric acid, and extracted with ether. The ether extract was washed with aqueous sodium thiosulfate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was immediately acetylated[12] with acetic anhydride (0.5 ml) in pyridine (0.5 ml) at room temperature for 20 h. After the usual work-up, the crude product was chromatographed on silica gel (7.0 g), using ether–benzene (3 : 97) as the eluent, to give **26** (18 mg: 26%). Further elution with ether–benzene (5 : 95) afforded **28** (25 mg: 37% from **26**). IR: 1772, 1727, 1650, 1605 cm^{-1}; ^1H

NMR (90 MHz): $\delta = 1.30$ (3H, s) and 1.38 (3H, s) ($-\dot{C}(CH_3)_2$), 1.31 (3H, d, $J=7$ Hz, C_{15}–CH_3), 1.59 (3H, s, C_{10}–CH_3), 2.01 (s) and 2.02 (s) (3H, C_{16}–$OCOCH_3$), 2.33 (3H, s) and 2.34 (3H, s) (C_{11}–$OCOCH_3$ and C_{12}–$OCOCH_3$), 3.25 (1H, m, C_{15}–H), 4.09 (d, $J=7$ Hz) and 4.12 (d, $J=7$ Hz) (2H, $-CH_2OCOCH_3$), 6.53 (1H, s, C_6–H), 8.13 (1H, s, C_{14}–H). The ^{1}H NMR spectrum of **28** was different from that of natural anhydronellionol triacetate.

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11) The compound was a mixture of the corresponding C-15 epimers.
12) Under these conditions, the acetoxyl groups were hydrolyzed.