[Chem. Pharm. Bull. 26(7)2007—2013(1978)]

UDC 547.913.6.04 : 542.943.2.04

Diterpenoids. XLVI.[1] Syntheses of Taxodione, Royleanone and Their Analogues

Yasuo Ohtsuka and Akira Tahara (the late)

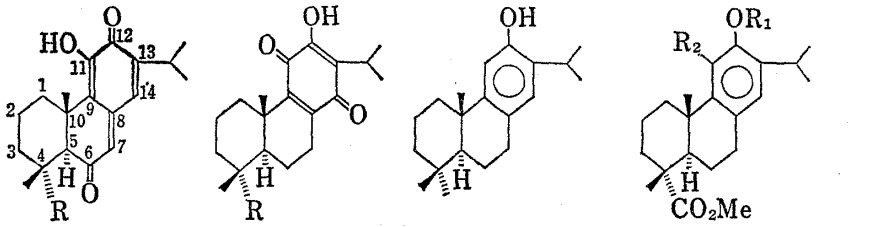
Rikagaku Kenkyusho (The Institute of Physical and Chemical Research)[2]

(Received December 2, 1977)

Using the readily obtainable 11-nitrophenol **5** prepared by selective nitration of the 12-hydroxy ester **4**, syntheses of taxodione (**1**), royleanone (**2**) and their analogues (**7** and **8**) having the methoxy-carbonyl group in place of the 4α-methyl group were accomplished.

Keywords——taxodione; royleanone; methyl 11-nitro-12-hydroxydehydroabietate; DDQ oxidation of 11-hydroxyferruginol; aerial oxidation

Many diterpenes bearing an oxygen function at the 11-position have been isolated[3] and some of them including taxodione (**1**),[4] a tumor-inhibitory diterpenoid quinone methide, and royleanone (**2**)[4c] have already been synthesized. The introduction of an oxygen function to the 11-position of diterpenes is obviously a key step for the synthesis of this type of compounds because that particular position is sterically hindered. For example, ferruginol (**3**) was subjected to diazo-coupling whose method had been originally developed by E. Wenkert, *et al.*[5] or benzoyl peroxide oxidation for the synthesis of taxodione (**1**) by K. Mori, *et al.*[4a] and T. Matsumoto, *et al.*,[4c] respectively.



1: R=Me **2**: R=Me **3** **4**: R_1=R_2=H
7: R=CO_2Me **8**: R=CO_2Me **5**: R_1=H, R_2=NO_2
6: R_1=Me, R_2=NO_2
9: R_1=H, R_2=NH_2

Fig. 1

1) Part XLV: H. Akita, K. Mori and A. Tahara (the late), *Chem. Pharm. Bull.* (Tokyo), **25**, 974 (1977).
2) Location: *Hirosawa, Wako-shi, Saitama, 351, Japan.*
3) *e.g.* O.E. Edwards, G. Feniak and M. Los, *Can. J. Chem.*, **40**, 1540 (1962); T. Kondo, M. Sudo and M. Teshima, *Yakugaku Zasshi*, **82**, 1252 (1962); C.H. Brieskorn, A. Fuchs, J.B. -son Bredenberg, J.D. McChesney and E. Wenkert, *J. Org. Chem.*, **29**, 2293 (1964); E. Wenkert, A. Fuchs and J.D. McChesney, *ibid.*, 30, 2931 (1965); D. Karanatsios, J.S. Scarpa and C.H. Eugster, *Helv. Chim. Acta*, **49**, 1151 (1966); K. Kawazu, M. Inaba and T. Mitsui, *Agric. Biol. Chem.* (Tokyo), **31**, 494, 498 (1967); S.M. Kupchan, A. Karim and C. Marks, *J. Org. Chem.*, **34**, 3912 (1969); P. Ruedi and C.H. Eugster, *Helv. Chim. Acta*, **54**, 1606 (1971); A.H. -J. Wang, I.C. Paul, R. Zelnik, K. Mizuta and D. Lavie, *J. Am. Chem. Soc.*, **95**, 598 (1973); J.M. Lisy, J. Clardy, M. Anchel and S.M. Weinreb, *Chem. Commum.*, **1975**, 406; S.V. Bhat, P.S. Kalyanaranan, H. Hohl, N.J. DeSouza and H.-W. Fehlhaber, *Tetrahedron*, **31**, 1001 (1975).
4) *a*) K. Mori and M. Matsui, *Tetrahedron*, **26**, 3467 (1970); *b*) T. Matsumoto, Y. Tachibana and K. Fukui, *Bull. Chem. Soc. Jpn.*, **44**, 2766 (1971); T. Matsumoto, Y. Ohsuga and K. Fukui, *Chem. Lett.*, **1974**, 279; *c*) T. Matsumoto and S. Harada, *ibid.*, **1976**, 1311; T. Matsumoto, Y. Ohsuga, S. Harada and K. Fukui, *Bull. Chem. Soc. Jpn.*, **50**, 266 (1977); T. Matsumoto, S. Usui and T. Morimoto, *ibid.*, **50**, 1575 (1977).
5) C.H. Brieskorn, A. Fuchs, J.B. -son Bredenberg, J.D. McChesney and E. Wenkert, *J. Org. Chem.*, **29**, 2293 (1964).

It has already been reported from this laboratory that a nitration of methyl 12-hydroxydehydroabietate (**4**) took place selectively on the 11-position to give the 11-nitrophenol **5** by treatment with conc. HNO_3(d=1.38) in Ac_2O.[6] Using this readily obtainable compound **5**, syntheses of taxodione (**1**), royleanone (**2**) and their analogues (**7** and **8**) having the methoxycarbonyl group in place of the 4α-methyl group were examined.

Catalytic hydrogenation of the nitrophenol **5** with PtO_2 in isoPrOH afforded the aminophenol **9**, mp 137.5—140.5°, which formed the oxazole derivative **10**, mp 117—119°, by HCO_2H treatment. The above observation showed again that the amino group in the aminophenol **9**, namely the nitro group in **5**, was located at the 11-position. The aminophenol **9** was treated with *aq.* $FeCl_3$ solution in MeOH to give the methoxy 11,12-quinone **11**. Hydrogenolysis of the methoxy quinone **11** with Pd-C in AcOH afforded the catechol derivative **12**, mp 145—146.5°. The spectral data (infrared (IR) and nuclear magnetic resonance (NMR)) of **11** and **12** are consistent with the structures shown in Fig. 2 and since the methoxy group of **11** was eliminated by hydrogenolysis, this group should be located at the benzylic 7-position.

Although peracetic acid oxidation of the 12-methoxy ester (**14**→**15**)[7] and CrO_3 oxidation of the 11-methoxy-12-benzoyloxy compound (**16**→**17**)[5b] have been reported for the prepara-

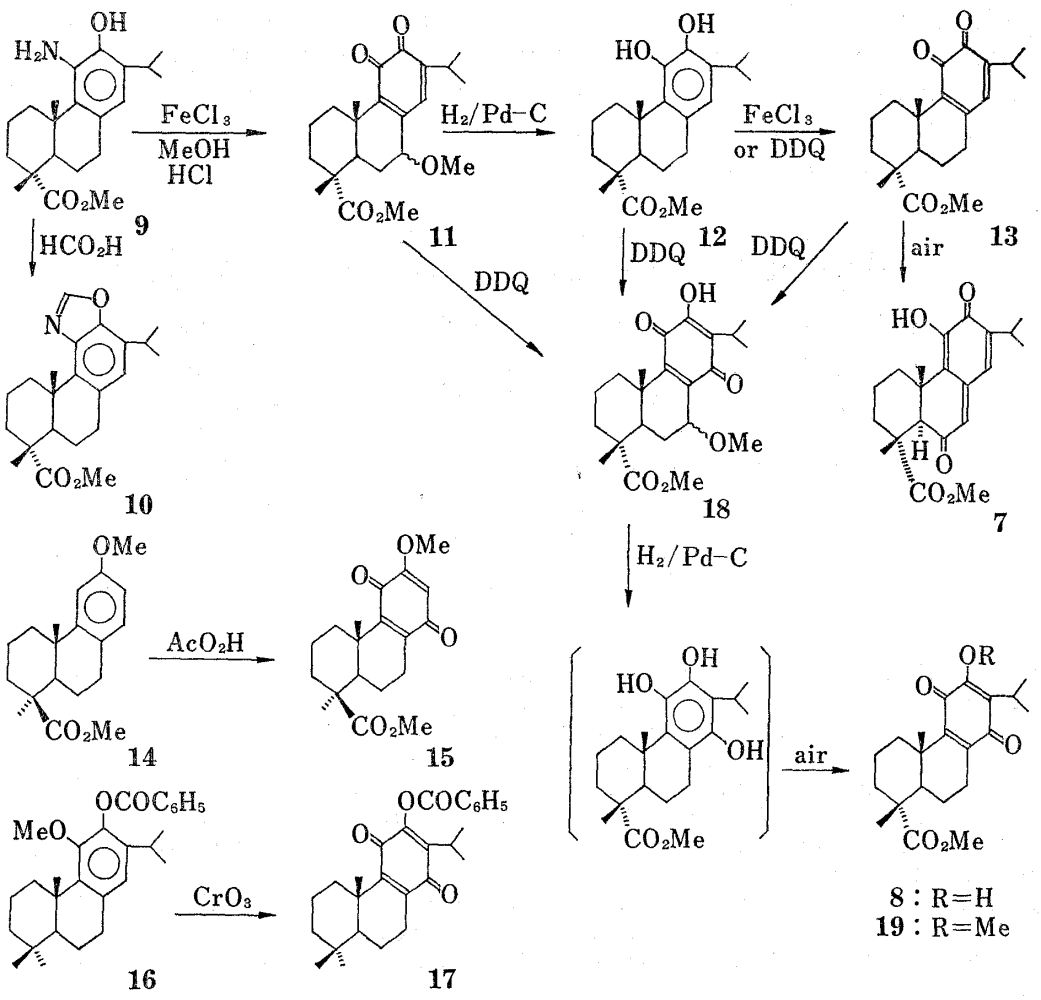


Fig. 2

6) Y. Ohtsuka, H. Akita and A. Tahara, *Chem. Lett.*, **1973**, 229; A. Tahara, H. Akita and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **22**, 1555 (1974).
7) B.R. Davis and W.B. Watkins, *Aust. J. Chem.*, **21**, 1611 (1968).

tion of a quinoid system, several oxidation were studied in the methoxy quinone **11** and the catechol **12** for the direct preparation of taxodione (**7**) or royleanone (**8**) analogues. Treatment of the catechol **12** with $FeCl_3$ under the same conditions as in the case of the oxidation of the aminophenol **9** to the methoxy quinone **11**, afforded not **11** but the 11,12-quinone **13** which was easily obtained also by DDQ (2.2 eq. mol) treatment in dioxane or *tert*-BuOH. Further DDQ (1.06 eq.) oxidation of the quinone **13** in MeOH containing a small amount of conc. HCl gave a mixture of royleanone analogues **8** and **18**. The compound **18**, mp 188—191.5°, was also obtained by DDQ treatment of the methoxy quinone **11** (1.1 eq. of DDQ) and the catechol **12** (3.15 eq.) in high yield under the same conditions as in case of **13**. Hydrogenolysis of **18** with Pd-C in AcOH followed by aerial oxidation in AcOH yielded readily the royleanone analogue **8**, mp 152—153.5°.

On the other hand, aerial oxidation of the quinone **13** in alcohols such as MeOH or isoPrOH afforded directly the taxodione analogue **7** in 14.3% yield. The yield of **7**, however, could not be improved by addition of a sensitizer such as rose bengal and the same treatment of the catechol **12** did not give **7** but led to a recovery of the starting material.

Structures of these taxodione (**7**) and royleanone (**8**) analogues were determined by spectral analysis. The IR spectrum of **7**, 3630 (w), 3340, 1670, 1640 (w) cm^{-1}, supported the presence of a hydroxy-*p*-benzoquinone structure. In NMR spectrum of **7**, the one-proton singlet at δ 3.54 was assigned to a tertiary proton α to a carbonyl group (5-H). The two one-proton singlets at δ 6.24 (7-H) and 6.90 (14-H) were attributed to protons on the quinone methide system. It can be understood that an abnormal downfield shift of 4-methyl signal

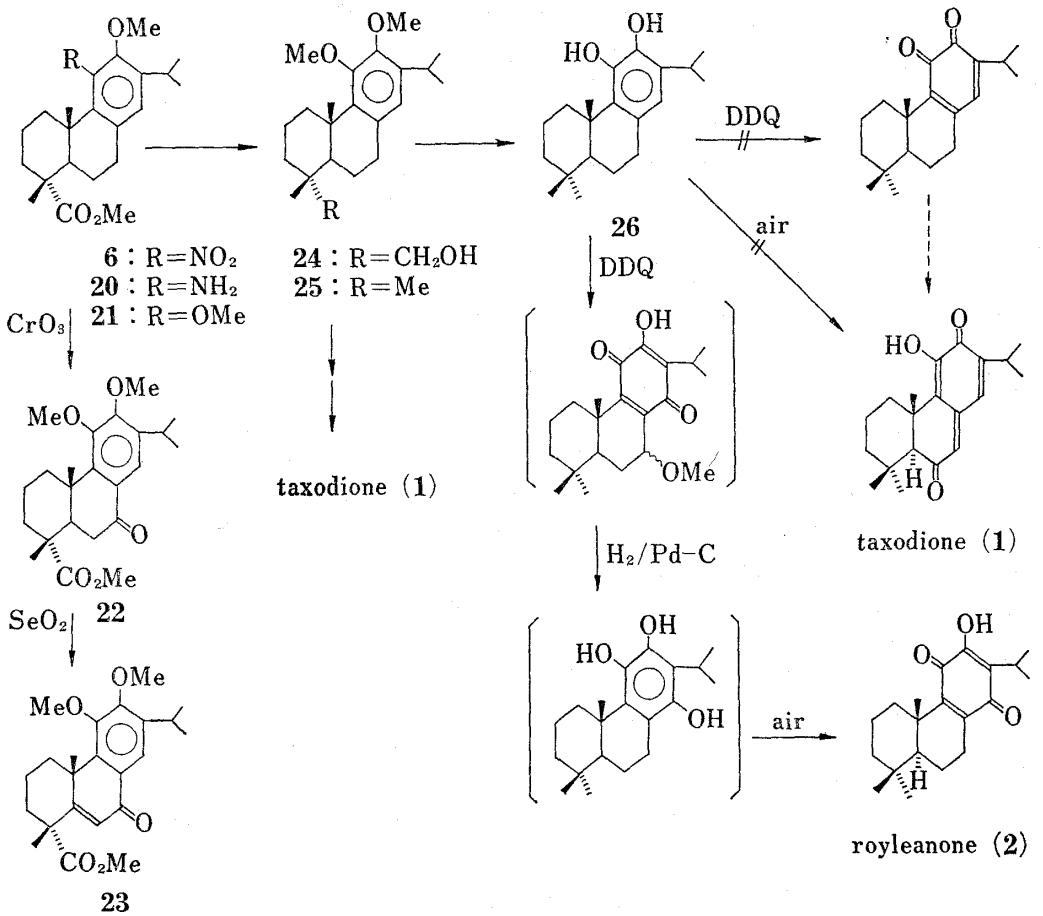


Fig. 3

(δ 1.51) was caused by the effect of the carbonyl group at the 6-position.[8] Except this signal due to 4-methyl group, the NMR signals due to the quinone methide moiety of **7** were almost identical with those of the reported value of taxodione (**1**). Thus, the compound **7** was established to have a taxodione structure.

For elcidating the structure **8**, the methylation was carried out and under the usual conditions for methylation of phenols, the methoxy ester **19**, mp 139—141.5°, was obtained. In IR spectra, the carbonyl frequencies, $\nu_{max}^{CCl_4}$ 1670 (w), 1635 cm^{-1}, due to the hydrogen-bonded *p*-quinone moiety of **8**, is shifted to the higher, $\nu_{max}^{CCl_4}$ 1665 cm^{-1}, by the methylation to **19** and no proton signal is present in the aromatic region in NMR spectra of **8** and **19**. The above spectral data are consistent with the conclusion that the compound **8** has desired royleanone structure as shown in Fig. 2.

On the basis of the above model experiments, syntheses of taxodione (**1**) and royleanone (**2**) were carried out by using a similar technique starting from the catechol derivative **26** which was prepared from the nitro ester **6**.

Reduction of the nitro ester **6** with tin in MeOH–conc. HCl gave the amino ester **20**, mp 143—145°, in high yield, which was transformed to the dimethoxy ester **21**, mp 84.5—86.5°, in 60.5% yield *via* diazonium salt ($NaNO_2$–MeOH–conc.H_2SO_4). Successive oxidation of the dimethoxy ester **21** with CrO_3 in aq. AcOH and SeO_2 in AcOH afforded readily the Δ^5-7-oxo ester **23**, mp 101.5—102.5° *via* the 7-oxo ester **22**, mp 95—97°.

Treatment of the dimethoxy ester **21** with $LiAlH_4$ in ether gave the alcohol **24**, bp 128° (bath temp.) (6×10^{-3} mmHg), in 90% yield. Oxidation of **24** with CrO_3–pyridine complex in CH_2Cl_2 followed by a modified Hang-Minllon reduction gave 11,12-dimethoxyabieta-8,11, 13-triene (**25**), mp 88.5—90°, in 55% yield. The physical data (mp, IR and NMR) of this product are identical with those of the desired compound **25** reported by Mori[4a] and Wenkert.[5] The dimethoxy compound **25** was hydrolyzed with BBr_3 in CH_2Cl_2 to afford the corresponding catechol derivative **26** as an oil in a quantitative yield. The physical properties (IR, NMR and *Rf* of thin-layer chromatography (TLC)) of the product were identical with those of **26** prepared *via* nitration of ferruginol (**3**) by Akita in our laboratory.[9]

It is known that substituents such as a hydroxy or a methoxy group at the 11-position cause a downfield shift (*ca.* 0.1—0.2 ppm) in the NMR signal of the 10-methyl group in abietane series.[5,10] A similar phenomenon is also observed in the 11,12-dimethoxy and dihydroxy compounds **12**, **21**, **22**, **23**, **24**, **25** and **26** (0.1—0.17 ppm).

The catechol derivative **26** was treated with DDQ under the same conditions as in the case of the catechol **12**. DDQ oxidation (3.1 eq. mol) of **26** in MeOH containing a small amount of conc. HCl gave a methoxy quinone which was subjected to hydrogenolysis with Pd-C in AcOH followed by aerial oxidation in AcOH to afford yellow crystals in 59% yield. The spectral data (IR and NMR) and mp, 181—183°, of the product were identical with those of royleanone (**2**).[3,4c] On the other hand, DDQ (2 eq.) oxidation of **26** in dioxane, however, did not give a quinone but led to a recovery of the starting material contrary to an easy oxidation of **12**. Although taxodione (**1**) could not be obtained from the catechol **26**, the transformation of the dimethoxy compound **25** to **1** has already been accomplished by Mori.[4a] Therefore, the synthesis of **25** means that taxodione (**1**) was synthesized from the 11-nitrophenol **5**.

In conclusion, taxodione (**1**), royleanone (**2**) and their analogues (**7** and **8**) having the methoxycarbonyl group in place of the 4α-methyl group were synthesized from *l*-abietic acid *via* the 11-nitrophenol **5**. The 11-nitro compounds appear to be useful intermediates in the synthesis of diterpenoid quinones bearing an oxygen function at the 11-position.

8) R.C. Cambie and R.A. Franich, *Aust. J. Chem.*, **24**, 571 (1971).
9) The alternative preparation of the compound **26** will be described in the successive paper.
10) Y. Ohtsuka and A. Tahara, *Chem. Pharm. Bull.* (Tokyo), **21**, 643, 653 (1973).

Experimental

All melting points were measured on a micro hot-stage and are uncorrected. NMR spectra were measured at 60 MHz in $CDCl_3$ (5—10% solution) *vs.* Me_4Si as internal reference except for the compound **25**. High resolution mass spectra were taken with JMS-01SG spectrometer.

Methylation of Methyl 11-Nitro-12-hydroxydehydroabietate (5) to 6 in a Preparative Scale——The methylation of **5** to **6** was previously carried out by use of CH_2N_2 as described in lit. 6 and that with Me_2SO_4 was reported herein. A mixture of the nitrophenol **5**[11] (7.964 g), Me_2SO_4 (12.6 ml) and $KHCO_3$ (79.0 g) in acetone (760 ml) was refluxed for 16 hr with stirring and filtered. After addition of water to the filtrate, the organic solvent was evaporated. The ethereal extract was washed with water and dried (Na_2SO_4). Removal of the solvent gave crystals (7.832 g) which was recrystallized from ether–petr. ether to colorless needles **6** (5.400 g), mp 148—149°. The physical properties (IR, NMR and mp) are identical with those of the product (**6**) obtained by methylation of **5** with CH_2N_2.

Methyl 11-Amino-12-hydroxydehydroabietate (9)——A mixture of the nitrophenol **5** (1.000 g) and PtO_2 (60 mg) in isoPrOH (50 ml) was stirred for 24 hr at room temperature under a hydrogen atmosphere. The filtrate of the reaction mixture was evaporated under reduced pressure and the resulting crystals (980 mg) were recrystallized from ether–petr. ether to afford colorless fine needles **9** (842 mg), mp 137.5—140.5°. *Anal.* Calcd. for $C_{21}H_{31}NO_3$: C, 73.00; H, 9.05; N, 4.05. Found: C, 72.80; H, 9.03; N, 3.97. IR ν_{max}^{KBr} cm^{-1}: 3490 (sh), 3395, 1698, 1617. NMR δ: 1.20 (6H, d, J=7 Hz, $CH\underline{Me}_2$), 1.27 (6H, s. 4- and 10-Me), 3.66 (3H, s, CO_2Me), 6.54 (1H, s, 14-H).

Treatment of Methyl 11-Amino-12-hydroxydehydroabietate (9) with Formic Acid——A mixture of the aminophenol **9** (200 mg) and 98% HCO_2H (6 ml) was refluxed for 2 hr and the solvent was removed to dryness under reduced pressure. The resulting oil was chromatographed on SiO_2 (15 g) to give crystals **10** (100 mg) by elution with ether–petr. ether (9: 1). Recrystallization of the product from petr. ether gave colorless needles (72 mg), mp 117—119°. *Anal.* Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.58; H, 8.15; N, 3.74. IR ν_{max}^{KBr} cm^{-1}: 1723. NMR δ: 1.32 (3H s, 4-Me), 1.34 (6H, d, J=7.5 Hz, $CH\underline{Me}_2$), 1.46 (3H, s, 10-Me), 3.71 (3H, s, CO_2Me), 6.93 (1H, s, 14-H), 8.05 (1H, s, oxazole-H).

Oxidation of Methyl 11-Amino-12-hydroxydehydroabietate (9)——To a solution of the aminophenol **9** (300 mg) in MeOH (15 ml), a solution of $FeCl_3$ (450 mg) in 0.5 N HCl aq. (11 ml) was added dropwise and the mixture was stirred for 45 min at room temperature. After dilution with water, the mixture was extracted with $CHCl_3$ and the extract washed with water and dried (Na_2SO_4). Removal of the solvent gave the methoxy quinone **11** (313 mg) as a dark green solid which was used for the next reaction without further purification. MS *m/e*: 374 (M^+; $C_{22}H_{30}O_5$). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1722, 1680 (w), 1660. NMR δ: 1.09 (6H, d, J= 6.5 Hz, $CH\underline{Me}_2$), 1.21 and 1.23 (3H each s, 4- and 10-Me), 3.43 (3H, s, 7-OMe), 3.68 (4H, s, CO_2Me and 7-H), 6.64 (1H, s, 14-H).

Methyl 11,12-Dihydroxydehydroabietate (12)——A mixture of the quinone **11** (345 mg) and 10% Pd-C (35 mg) in AcOH (18 ml) was stirred for 1 hr at room temperature under a hydrogen atmosphere. The filtrate of the reaction mixture was evaporated under reduced pressure. The resulting crude crystals (315 mg) was purified by chromatography on silicic acid–Celite (1: 1 w/w). Elution with petr. ether–ether (9: 1) followed by removal of the solvent gave the crystalline dihydroxy ester **12** (247 mg) which was recrystallized from ether–petr. ether to afford colorless prisms (163 mg), mp 145—146.5°. *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.96; H, 8.43. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640, 3555, 1723. NMR δ; 1.21 (6H, d, J=6 Hz, $CH\underline{Me}_2$), 1.26 (3H, s, 4-Me), 1.33 (3H, s, 10-Me), 3.66 (3H, s, CO_2Me), 6.43 (1H, br, 14-H).

Oxidation of Methyl 11,12-Dihydroxydehydroabietate (12) to the Quinone 13— i) Oxidation with DDQ: The dihydroxy ester **12** (100 mg) was treated for 16 hr at room temperature with DDQ (145 mg; 2.20 eq. mol) in dioxane or *tert*-BuOH (5 ml), diluted with water and extracted with ether. The extract was washed with sat. aq. $NaHCO_3$, water and dried (Na_2SO_4). Removal of the solvent gave the quinone **13** (96 mg) as a dark green solid, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725, 1675, 1655, NMR δ: 1.08 (6H, d, J=6 Hz, $CH\underline{Me}_2$), 1.23 (6H, s, 4- and 10-Me), 3.66 (3H, s, CO_2Me), 6.40 (1H, s, 14-H), which was used for the next experiment without purification.

ii) Oxidation with $FeCl_3$: To a solution of **12** (50 mg) in MeOH (2.5 ml) was added dropwise a solution of $FeCl_3$ (75 mg) in 0.5 N HCl aq. (2 ml) and the mixture was stirred for 45 min at room temperature. The work-up was as described for the oxidation of **9**. The IR and NMR spectra of the product (50 mg) were identical with those of the quinone **13** obtained by DDQ oxidation.

Synthesis of the Taxodine Analogue, Methyl 6,12-Dioxo-11-hydroxyabieta-7,9(11),13-trien-19-oate (7)——A solution of the quinone **13** (400 mg) in MeOH or isoPrOH (40 ml) was stirred for 5 hr (or 26 hr in case of isoPrOH solution) at room temperature and the solvent was removed under reduced pressure. The residue was chromatographed on silicic acid–Celite (1: 1 w/w) (50 g) to give a reddish brown solid **7** (68 mg) (elution with petr. ether–ether (9: 1)). *Anal.* (by high-resolution mass spectrometry) Calcd. for $C_{21}H_{28}O_5$: *m/e*;

11) The melting point of the nitrophenol **5**, mp 167.5—170.5°, reported in lit. 6 should be corrected to mp 175—182°.

358.1780. Found: *m/e*; 358.1783. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630 (w), 3340, 1725, 1670 (w), 1625, 1617. NMR δ: 1.19 (6H, d, J=6.6 Hz, CH<u>Me</u>$_2$), 1.32 (3H, s, 10-Me), 1.51 (3H, s, 4-Me), 3.54 (1H, s, 5-H), 3.66 (3H, s, CO_2Me), 6.24 (1H, s, 7-H), 6.90 (1H, s, 14-H).

Methyl 7*e*-Methoxy-11,14-dioxo-12-hydroxyabieta-8,12-dien-19-oate (18)——i) The dihydroxy ester **12** (100 mg) was treated for 15 hr at room temperature with DDQ (207 mg; 3.15 eq. mol) in MeOH (10 ml) containing conc. HCl *aq.* (3 drops) and diluted with water. The work-up was as described for the preparation of **13** and the yellow crystalline product (81 mg) obtained was recrystallized from MeOH to give yellow needles **18** (65 mg), mp 188—191.5° (dec.). *Anal.* Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74; O, 24.59. Found: C, 67.50; H, 7.60; O, 24.67. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400, 1727, 1674 (w), 1642. NMR δ: *ca.* 1.18 and *ca.* 1.21 (3H each, d, J= undistinguishable, CH<u>Me</u>$_2$), 1.24 (6H, s, 4- and 10-Me), 3.40 (3H, s, 7-OMe), 3.70 (3H, s, CO_2Me), *ca.* 4.28 (1H, t, J=2.8 Hz, 7-H), 7.18 (1H, s, OH).

ii) The same treatment of a mixture of the quinone **13** (80 mg) and DDQ (56 mg; 1.06 eq.) in MeOH (8 ml) containing conc. HCl *aq.* (2 drops) as in case of **12** gave a yellow solid (81 mg) which was chromatographed on SiO_2 (8 g) to afford a yellow solid (12 mg) as a less polar fraction and yellow crystals (43 mg) as a polar fraction by elution with petr. ether–ether (19: 1 and 9: 1, respectively). The former solid (12 mg) and the latter (43 mg) were identical (IR, NMR and Rf of TLC) with royleanone analogues **8** as described below and **18**, respectively.

iii) The quinone **11** (90 mg) was treated for 15 hr at room temperature with DDQ (65 mg; 1.1 eq.) and *p*-TsOH (10 mg) in MeOH (9 ml). The work-up was as described for the preparation of **13** and recrystallization of the resulting crystals (108 mg) from MeOH gave yellow needles (64 mg), mp 188—191°, whose physical data (IR, NMR and *Rf* of TLC) were identical with those of **18**.

Synthesis of the Royleanone Analogue, Methyl 11,14-Dioxo-12-hydroxy-abieta-8,12-dien-19-oate (8)——A mixture of **18** (51 mg) and 10% Pd-C (25 mg) in AcOH (5 ml) was stirred at room temperature under a hydrogen atmosphere. After adsorption of hydrogen had been stopped, the filtrate was refluxed for 20 min under the bubbling of air. Removal of the solvent under reduced pressure gave yellow crystals (44 mg), which were recrystallized from ether–petr. ether to form yellow needles **8**, mp 152—153.5°. *Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.95; H, 7.64. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3390, 1725, 1670 (w), 1635. NMR δ: 1.20 (6H, d, J=6 Hz, CH<u>Me</u>$_2$), 1.27 (6H, s, 4- and 10-Me), 3.68 (3H, s, CO_2Me).

Methylation of 8 to 19——A mixture of **8** (210 mg), K_2CO_3 (10.5 g) and Me_2SO_4 (2 ml) in acetone (42 ml) was refluxed for 10 hr with stirring and diluted with water. The organic solvent was removed under reduced pressure and the ethereal extract of the residue was washed with water and dried (Na_2SO_4). After removal of the solvent, the obtaining crystals (258 mg) were recrystallized from *aq.* MeOH to afford yellow prisms **19** (190 mg), mp 139—141.5°. *Anal.* Calcd. for $C_{22}H_{30}C_5$: C, 70.56; H, 8.08. Found: C, 70.48; H, 7.96. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1727, 1655, 1640, 1597. NMR δ: 1.16 and 1.18 (3H each, d, J=6.5 Hz, CH<u>Me</u>$_2$), 1.23 (3H, s, 4-Me), 1.32 (3H, s, 10-Me), 3.66 (3H, s, CO_2Me), 3.88 (3H, s, 12-OMe).

Methyl 11-Amino-12-methoxydehydroabietete (20)——After a mixture of the nitrophenol **6** (1.833 g) and tin (5.40 g) in MeOH (50 ml)–conc. HCl aq. (21.6 ml) was refluxed for 12 hr with stirring, the reaction mixture was poured into ice, alkalized with KOH and extracted with ether. The ethereal extract was washed with water and dried (Na_2SO_4). The solvent was removed to give crystals (1.442 g), which were recrystallized from MeOH to afford colorless needles **20** (1.154 g), mp 143—145°. *Anal.* Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.23; H, 9.17; N, 3.89. IR ν_{max}^{KBr} cm^{-1}: 3473, 3367, 1717. NMR δ: 1.14 (6H, d, J=7 Hz, CH<u>Me</u>$_2$), 1.26 (3H, s, 4-Me), 1.33 (3H, s, 10-Me), 3.61 and 3.65 (3H each, s, CO_2Me and 12-OMe), 6.26 (1H, s, 14-H).

Methyl 11,12-Dimethoxydehydroabietate (21)——To a solution of the aminophenol **20** (697 mg) in MeOH (146 ml) containing conc. H_2SO_4 (4.4 ml) was added portionwise $NaNO_2$ (473 mg) at −5—0° with stirring and the ice-salt bath was took off. The reaction mixture was stirred until the temerature reached room temperature (22°) and then refluxed for 30 min. After the solvent had been removed under reduced pressure, the residue was diluted with water and extracted with ether. The ethereal extract was washed with sat. *aq.* Na_2CO_3, sat. *aq.* NaCl and dried (Na_2SO_4). Removal of the solvent gave a pale yellow oil (674 mg). Chromatography of the oil on SiO_2 (30 g) by elution with petr. ether–ether (29: 1) gave crystals (423 mg) which were recrystallized from *aq.* MeOH to afford colorless needles **21** (275 mg), mp 84.5—86.5°. *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.82; H, 9.04. IR ν_{max}^{KBr} cm^{-1}: 1725. NMR δ: 1.14 and 1.19 (3H each, d, J=7 Hz, CH<u>Me</u>$_2$), 1.27 (3H, s, 4-Me), 1.33 (3H, s, 10-Me), 3.68 (3H, s, CO_2Me), 3.77 and 3.87 (3H each, s, 11- and 12-OMe), 6.66 (1H, s, 14-H).

Methyl 11,12-Dimethoxy-7-oxodehydroabietate (22)——A solution of CrO_3 (350 mg) in 80% *aq.* AcOH (16.4 ml) was added dropwise to a solution of the dimethoxy ester **21** (278 mg) in AcOH (16.6 ml) with stirring and the reaction mixture was stirred for 2.5 hr at room temperature. After addition of MeOH (5.2 ml), the mixture was stirred for an additional 1 hr at room temperature and evaporated under reduced pressure. The ethereal extract of the resulting residue was washed with sat. *aq.* Na_2CO_3, sat. *aq.* NaCl and dried (Na_2SO_4). The solvent was removed to give crystals which were chromatographed on Florisil (16 g). Elution with petr. ether–ether (9: 1) gave crystals which were recrystallized from ether–petr. ether to afford colorless prisms **22** (228 mg), mp 95—97°. *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.84;

H, 7.97. IR ν_{max}^{KBr} cm^{-1}: 1725, 1682. NMR δ: 1.20 and 1.23 (3H each, d, J=7 Hz, CH<u>Me</u>$_2$), 1.33 (3H, s, 4-Me), 1.41 (3H, s, 10-Me), 3.68 (3H, s, CO_2Me), 3.87 (6H, s, 11- and 12-OMe), 7.82 (1H, s, 14-H).

Dehydrogenation of Methyl 11,12-Dimethoxy-7-oxodehydroabietate (22) to 23 with SeO_2——A mixture of the dimethoxy ester **22** (660 mg) and SeO_2 (400 mg) in AcOH (16.5 ml) was refluxed for 1 hr with stirring, filtered and evaporated under reduced pressure. The etheral extract of the residue was washed with sat. *aq*. Na_2CO_3, sat. *aq*. NaCl and dried (Na_2SO_4). The solvent was evaporated to dryness to give a yellow oil (647 mg). The oil was purified by chromatography on Florisil (32 g) using petr. ether–ether (4: 1) for elution to give crystals (525 mg). Recrystallization from aq. MeOH yielded colorless prisms **23** (483 mg), mp 101.5—102.5°. *Anal.* Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.76; H, 7.57. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735, 1660. NMRδ: 1.25 and 1.29 (3H each, d, J=7 Hz, CH<u>Me</u>$_2$), 1.63 (6H, s, 4- and 10-Me), 3.75 (3H, s, CO_2Me), 3.85 and 3.93 (3H each, s, 11- and 12-OMe), 6.21 (1H, s, 6-H), 7.95 (1H, s, 14-H).

Reduction of Methyl 11,12-Dimethoxydehydroabietate (21) to 24——A mixture of the dimethoxy ester **21** (300 mg) and $LiAlH_4$ (120 mg) in ether (60 ml) was stirred overnight and an excess of $LiAlH_4$ was decomposed with dil. *aq*. HCl. The usual work-up gave a colorless hard oil (280 mg) which was purified by chromatography on SiO_2 (25 g) using petr. ether–ether (4: 1) for elution to afford a colorless oil **24** (271 mg), bp 128° (bath temp.) (6×10^{-3} mmHg). *Anal.* Calcd, for $C_{22}H_{24}O_3$: C, 76.26; H, 9.89. Found: C, 75.98; H, 9.94. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3660. NMR δ: 0.88 (3H, s, 4-Me), 1.17 and 1.19 (3H each, d, J=6.5 Hz, CH<u>Me</u>$_2$), 1.33 (3H, s, 10-Me), 3.18 and 3.51 (1H each, d, J=11 Hz, C<u>H</u>$_2$OH), 3.75 and 3.84 (3H each, s, 11- and 12-OMe), 6.65 (1H, s, 14-H).

Conversion of 24 into 11,12-Dimethoxyabita-8,11,13-triene (25)——A solution of the dimethoxy alcohol **24** (280 mg) in CH_2Cl_2 (4 ml) was treated for 1 hr at room temperature with CrO_3–pyridine complex prepared from CrO_3 (1.00 g), pyridine (1.70 ml) and CH_2Cl_2 (17 ml) at room temperature (30 min). The reaction mixture was filtered through a short column of alkaline Al_2O_3 (10 g) and washed with ether–CH_2Cl_2. Evaporation of the solvent gave a pale yellow oil (240 mg), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2690, 1727.

To a mixture of hydrazine hydrate (4 ml) and diethylene glycol (5 ml) was added dropwise a solution of the oil (240 mg) obtained above in ether (4 ml). The temperature was maintained at 100° during the addition of the substrate and then 120° for 1 hr. After addition of KOH (2.5 g), the temperature was raised to 210° to remove water during the period and maintained at 210° for 1 hr. The reaction mixture was cooled to room temperature, diluted with water and extracted with ether. The extract was washed with water, dried and evaporated to give an oil (208 mg). Chromatography of the oil on neutral Al_2O_3 (the activity grade II) using petr. ether for elution gave crystals (142 mg). Recrystallization from MeOH afforded colorless needles **25** (109 mg), mp 88.5—90° (lit. 86—87°,[4a] 89—90.5°[5]). *Anal.* Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.83; H, 10.57. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1385, 1318, 1295. NMRδ (100 MHz): 0.93 and 0.95 (3H each, s, 4α- and 4β-Me), 1.18 and 1.21 (3H each, d, J=7 Hz, CH<u>Me</u>$_2$), 1.30 (3H, s, 10-Me), 3.76 and 3.85 (3H each, s, 11- and 12-OMe), 6.63 (1H, s, 14-H).

Hydrolysis of 11,12-Dimethoxyabieta-8,11,13-triene (25) to 26——A solution of **25** (500 mg) in CH_2Cl_2 (2 ml) was treated for 10 min with a solution of BBr_3 (2 ml) and CH_2Cl_2 (3 ml) in dry ice-acetone bath and allowed to stand for 30 min at room temperature. The mixture was poured into ice and extracted with ether. The extract was washed with sat. *aq*. Na_2CO_3, water and dried ($MgSO_4$). Removal of the solvent gave a gum **26** (456 mg) which was used for the next experiment without further purification. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 3520.

Conversion of 11,12-Dihydroxyabieta-8,11,13-triene (26) into Royleanone (2)——A solution of **26** (170 mg) in MeOH (17 ml) containing conc. HCl *aq*. (4 drops) was treated for 15 hr at room temperature with DDQ (400 mg; 3.1 eq. mol) and diluted with water. The ethereal extract of the reaction mixture was washed with sat. *aq*. $NaHCO_3$, water and dried ($MgSO_4$). Removal of the solvent gave a gum (160 mg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3375, 1675 (w), 1645, 1603 (w). NMR δ: 3.39 (3H, s, OMe). The product obtained was subjected to hydrogenolysis in AcOH (20 ml) in the presence of 10% Pd-C (200 mg) under a hydrogen atmosphere. After absorption of hydrogen had been stopped, the filtrate was refluxed for 20 min while air was being bubbled and evaporated to dryness under reduced pressure. The ethereal extract of the resulting residue was washed with sat. *aq*. $NaHCO_3$, water and dried ($MgSO_4$). The crystalline product obtained was purified by preparative TLC on SiO_2 (petr. ether–ether, 4: 1) to yield orange crystals (110 mg). Recrystallization from MeOH gave pale yellow needles (royleanone, **2**), mp 181—183° (lit. 181.5—183°,[3] 179—181°[4]). *Anal.* Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.01; H, 8.89. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3375, 1675 (w), 1640, 1602 (w). NMR δ: 0.89 and 0.92 (3H each, s, 4α- and 4β-Me), 1.19 (6H, d, J=7 Hz, CH<u>Me</u>$_2$), 1.24 (3H, s, 10-Me).

Acknowledgement Financial support from the Ministry of Education, Science and Culture (Grant-in-Aid for Scientific Research No. 877359 (1973)) are gratefully acknowledged.