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Diterpenoids. XXIX. Nitration of Methyl Dehydroabietate Derivatives[1]

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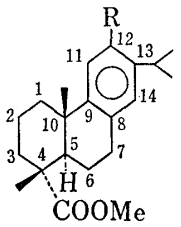
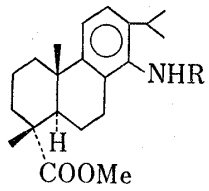
The nitration of methyl dehydroabietate derivatives having a hydroxyl and methoxyl group as in methyl 12-hydroxy-dehydroabietate and methyl 12-methoxy-dehydroabietate gave only 11-substituted compound. However, methyl 12-bromo-dehydroabietate was nitrated in different behavior and gave more complex result.

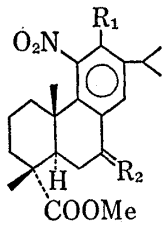
In our preceding work, it was ascertained that a subtle change in the structure exerts a marked influence on the nitration of methyl 7-oxo-dehydroabietate derivatives, and the selective nitration at C-13 (accompanied with deisopropylation) and C-14 in their aromatic C-ring was observed. By extending this investigation, effect of the 12-substituent in methyl dehydroabietate (**1**) itself on nitration was examined in the present study.



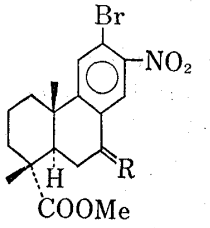
1: R=H
2: R=OH
3: R=OMe
15: R=Br



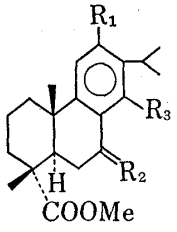
19: R=H
20: R=Ac



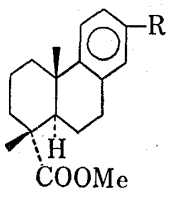
4: R_1=OH, R_2=H_2
5: R_1=OMe, R_2=H_2
6: R_1=OMe, R_2=O



22: R=H_2
23: R=O



12: R_1=Br, R_2=O, R_3=H
13: R_1=OH, R_2=O, R_3=H
14: R_1=OMe, R_2=O, R_3=H
16: R_1=Br, R=H_2, R_3=NO_2
17: R_1=NO_2, R_2=α-OAc, β-H, R_3=H
18: R_1=NO_2, R_2=α-OH, β-H, R_3=H
21: R_1=NO_2, R_2=O, R_3=H



24: R=NH_2
25: R=OH

Chart 1

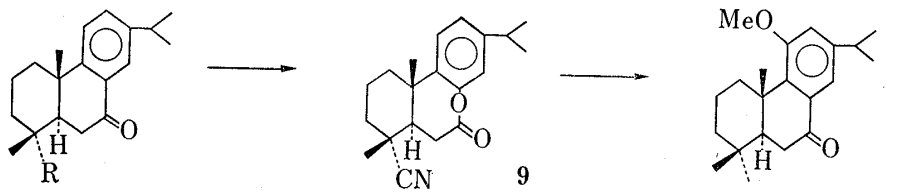
1) A part of the work was published as preliminary communication: Y. Ohtsuka, H. Akita, and A. Tahara, *Chemistry Letter*, **1973**, 229; Part XXVIII: A. Tahara, H. Akita, and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **22**, 1547 (1974).
All melting points were measured on a micro-hot stage and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured (δ) at 100 MHz (*60 MHz) in $CDCl_3$ *vs.* Me_4Si as internal reference. Infrared spectrum (IR) data (KBr disk) indicated maximum absorption as cm^{-1}.

2) Location: *Wako-shi, Saitama.*

Under the same condition (fuming HNO_3(d=1.47)–conc.H_2SO_4) as used for 7-oxo series,[3] 12-hydroxy (**2**)[4] and 12-methoxy ester (**3**)[4] were nitrated and gave only inseparable mixtures. The condition was changed to the milder one (conc.HNO_3(d=1.38)–Ac_2O) and the sole product (**4**) thereby obtained was converted into the corresponding 7-oxo ester (**6**) *via* 12-methoxy compound (**5**). Location of the nitro group in **6** (therefore, 4) was confirmed as C-11 by uncelar magnetie resonance (NMR) spectral observation of a singlet signal due to an aromatic proton (14-H), which appeared in a lower field (8.18) than that of the original deoxo esters (**4**: 6.97 (s) and **5**: 7.01 (s)) by the magnetic effect of 7-oxo group.

The same nitration (conc.HNO_3 (d=1.38)–Ac_2O) of 12-methoxy ester (**3**) was accompanied by hydrolysis and the resulting mixture consisting of **4** and **5** was inseparable. Thereupon, an improved condition (fuming HNO_3(d=1.52)–Ac_2O) was used to bring the by-product (**4**) to a minimum. 12-Hydroxy-11-nitro ester (**4**: 12% yield) and the starting material (**3**: 8% yield) were isolated in addition to the main product, 12-methoxy-11-nitro ester (**5**: 65% yield).

The selective nitration at C-11 succeeded by the effect of 12-hydroxyl and 12-methoxyl groups as described above. The substitution at C-11 was considered to be important for our synthetic project, but our previous attempt of nitration at C-11 by the electronic effect of 7-oxo group fail and gave 13-(with deisopropylation) and/or 14-substituted compound.[3] An other attempt to synthesize 11-substituted compounds was accomplished by its B-ring cleavage and recyclization (**7**→**8**→**9**→**10**→**11**).[5]



7 : R=COOH
8 : R=CN

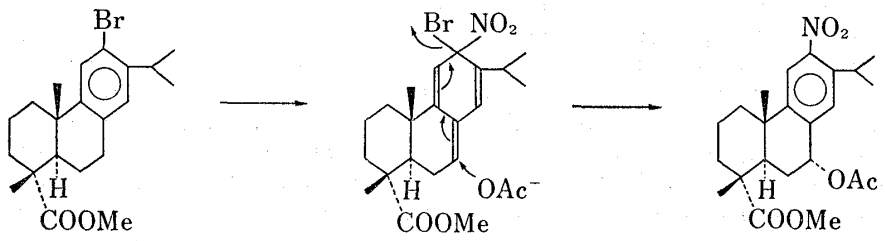
10 : R=CN
11 : R=COOMe

Chart 2

In the previous study on 7-oxo series,[3] 12-bromo-7-oxo ester (**12**) was reacted in the same as the corresponding 12-hydroxy (**13**) and 12-methoxy ester (**14**). However, nitration of 12-bromo ester (**15**)[6] afforded a completely different result from that of 12-hydroxy (**2**) and 12-methoxy ester (**3**). The nitration product (conc.HNO_3(d=1.38)–Ac_2O) was chromatographed to be separated into five fractions: (i) the starting material (**15**: 2% yield), (ii) 12-bromo-14-nitro ester (**16**: 16% yield), (iii) unknown ester containing a bromine atom (6% yield), (iv) 7α-acetoxy-12-nitro ester (**17**: 4% yield), and (v) 7α-hydroxy-12-nitro ester (**18**: 21% yield).[7] The following chemical conversion confirmed their structures. Reduction of **16** gave the authentic 14-amino ester (**19**)[8] (identified as acetamide (**20**)), and oxidation and acetylation of **18** yielded 7-oxo ester (**21**) and **17**, respectively. The α-configuration of 7-acetoxy group in **17** was confirmed by the half bond width value (10 Hz) due to 7-proton and a mechanism of the formation can be considered as shown in Chart 3.

In further examination of the bromide (**15**),[6] a different nitration result was obtained under the condition (fuming HNO_3(d=1.47)–conc.H_2SO_4) used for the 7-oxo series;[3] two

3) A. Tahara, H. Akita, and Y. Ohtsuka, *Chem. Pharm. Bull.* (Tokyo), **22**, 1547 (1974).
4) R.C. Cambie and R.A. Franich, *Aust. J. Chem.*, **24**, 117 (1971); *idem*, *Chem. Commun.*, **1970**, 845.
5) Y. Ohtsuka and A. Tahara, *Chem. Pharm. Bull.* (Tokyo), **21**, 653 (1973).
6) W. Campbell and M. Morgana, *J. Am. Chem. Soc.*, **63**, 1838 (1941).
7) The ester (**18**) would be obtained from **17** by treatment after the nitration. In fact, yield of **17** was increased in a case in which **18** was not found in the products.
8) E. Ochiai and M. Ohta, *Yakugaku Zasshi*, **74**, 203 (1954).



15 17

Chart 3

kinds of nitrated products (**22**: 56% yield) and the known **16** were isolated. The structure of the major (**22**) was proved by chemical conversion to the 7-oxo ester (**23**).[3] The method using **22** (*via* **24**) is most superior for the synthesis of the important intermediate (**25**)[4,9] from dehydroabietic acid (yield of **25**: 74% from **22** and 41% from **15**).

In this report, it was found that the nitration of methyl dehydroabietate derivatives having a hydroxyl and methoxyl group as in **2** and **3** gave only 11-substituted compound. However, 12-bromo ester (**15**) was nitrated in different behavior and gave more complex result.

Experimental

Nitration of Methyl 12-Hydroxy-dehydroabietate (2) to 12-Hydroxy-11-nitro-dehydroabietate (4)——12-Hydroxy ester (**2**)[4] (1.5 g) in Ac_2O (15 ml) was nitrated with conc.HNO_3 (d=1.38)–Ac_2O (1: 10) (4.95 ml) under stirring at −4——5° and it was stirring under salt–ice cooling for 30 min. After the mixture was poured into ice-water, it was alkalified by Na_2CO_3 and extracted with ether. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give light brown caramel (1.69 g), which was crystallized from petr. ether–ether to give pale yellow prisms (1.17 g; 68.7% yield). Residue resulted by evaporation of the mother liquid, was chromatographed on silicic acid–celite (1: 1) (25 g) to isolate pale yellow caramel (0.48 g) in petr. ether–ether (14: 1) elution. The caramel was crystallized to give prisms (0.29 g; 17% yield). The crystals (1.46 g) combined, mp 166—170°, were recrystallized from petr. ether–ether to give pale yellow prisms (**4**), mp 167.5—170.5°. *Anal.* Calcd. for $C_{21}H_{29}O_5N$: C, 67.18; H, 7.79; N, 3.74. Found: C, 67.16; H, 7.81; N, 3.55. IR (CCl_4): 3520, 1727. NMR: 1.22 (d, 6H, J=7 Hz; iso-C_3H_7), 1.27 (s, 3H; 4-Me), 1.48 (s, 3H; 10-Me), 3.66 (s, 3H; 4-COOMe), 6.07 (s, 1H; 12-OH), 6.97 (s, 1H; 14-H).

Methyl 12-Methoxy-11-nitro-dehydroabietate (5)——Methylation (CH_2N_2) and then recrystallization from MeOH–H_2O of 12-hydroxy-11-nitro ester (**4**) (60 mg) gave colorless needles (37 mg), mp 148—149°. *Anal.* Calcd. for $C_{22}H_{31}O_5N$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.81; H, 7.97; N, 3.57. IR: 1720, 1530, 1385. NMR: 1.22 (d, 6H, J=6.5 Hz; iso-C_3H_7), 1.26 (s, 3H; 4-Me), 1.38 (s, 3H; 10-Me), 3.67 (s, 3H; 4-COOMe), 3.76 (s, 3H; 12-OMe), 7.01 (s, 1H; 10-Me).

Methyl 12-Methoxy-11-nitro-7-oxo-dehydroabietate (6)——The ester (**5**) (240 mg) in AcOH (16 ml) was oxidized with CrO_3 (330 mg) in 80% AcOH aq. (8 ml) and it was stirring at room temperature for 15 hr. After MeOH (5 ml) was added and then was stirring for 1 more hr, residue resulted by removal of the solvent was extracted with ether and the extract was washed with sat. Na_2CO_3 aq., sat. NaCl aq. and was dried over Na_2SO_4. The resulting crystals (215 mg) was chromatographed on silica gel (25 g) and crystals isolated in petr. ether–ether (9: 1) elution were recrystallized from MeOH–H_2O to give yellow prisms (**6**) (157 mg), mp 132—134°. *Anal.* Calcd. for $C_{22}H_{29}O_6N$: C, 65.49; H, 7.25; N, 3.47. Found: C, 65.24; H, 7.15; N, 3.48. IR: 1718, 1692, 1597, 1536. NMR: 1.28 (d, 6H, J=7 Hz; iso-C_3H_7), 1.33 (s, 3H; 4-Me), 1.45 (s, 3H; 10-Me), 3.67 (s, 3H; 4-COOMe), 3.85 (s, 3H; 12-OMe), 8.18 (s, 1H; 14-H).

Nitration of Methyl 12-Methoxy-dehydroabietate (3) to Methyl 12-Hydroxy-11-nitro (4) and Methyl 12-Methoxy-11-nitro-dehydroabietate (5)——12-Methoxy ester (**3**)[4] (743 mg) in Ac_2O (7.5 ml) was nitrated with f.HNO_3 (d=1.52)–Ac_2O (1: 10) (2.5 ml) at −2—0° and it was stirring for 14 min. An oil resulted by treatment as in the case of **2**, was chromatographed on silica gel (45 g) to separate the oily fractions, the starting material (**3**) (62 mg; 8% yield) (identification by IR and NMR), **5** (543 mg; 65% yield) and **4** (95 mg; 12% yield), successively. Recrystallization of the latter faction (**5**) and **4** gave the sample for comparison (identification by IR and NMR).

Under the condition (conc.HNO_3 (d=1.38)–Ac_2O) as in the case of **2**, the hydrolized product (**4**) was increased to give an inseparable mixture.

9) A.W. Burgsthaler and L.R. Worden, *J. Am. Chem. Soc.*, **86**, 96 (1964).

Nitration of Methyl 12-Bromo-dehydroabietate (15)——The ester (**15**)[6] (5 g) in Ac_2O (200 ml) was nitrated with conc.HNO_3 (d=1.38)–Ac_2O (1: 2) (30 ml) at room temperature and it was stirring for 1 hr. An oil (5.9 g) resulted by treatment in the case of **2**, was chromatographed on alumina (200 g) to separate the five fractions successively: (i) The starting material (**15**) (149.5 mg; 2% yield) (identification by IR, gas–liquid chromatography (GLC)) in petr. ether–ether (49: 1), (ii) **16** (890 mg; 16% yield) (identification[10] by mixed mp, IR, GLC, NMR), (iii) unknown compound (348 mg; 6% yield) in petr. ether–ether (19: 1) elution (iv) **17** (207 mg; 4% yield) in petr. ether–ether (4: 1—1: 1) and (v) **18** (802 mg; 21% yield) in ether elution.

The third fraction (iii) was crystallized from MeOH to give colorless needles, mp 170—174.5°. The compound is unstable to decompose. *Anal.* Calcd. for $C_{21}H_{28}O_4NBr$: C, 57.53; H, 6.39; N, 3.20. Found: C, 57.96; H, 6.48; N, 3.13. IR: 1725, 1362, 1528. NMR: 1.20, 1.28 (s, 3H each; 4- and 10-Me), 1.28 (d, 6H; iso-C_3H_7), 3.74 (s, 1H; 4-COOMe), 5.61 (m, 1H), 7.60, 7.42 (s, 1H each). The forth fraction (iv) was crystallized from MeOH to give colorless powder (**17**) (54 mg), mp 180.5—182°. *Anal.* Calcd. for $C_{23}H_{31}O_6N$: C, 66.16; H, 7.48; N, 3.36. Found: C, 66.36; H, 7.45; N, 3.07. IR: 1732, 1728, 1532, 1352, 1242. NMR:1.21, 1.23, 1.28, 1.30 (s, 3H each; 4-, 10- and iso-C_3H_7), 2.10 (s, 3H; 7-OAc), 3.66 (s, 3H; 4-COOMe), 5.94(m,1H, Wl/2=10 Hz; 7-H), 7.34, 7.64 (s, 1H each; arom. H). The fifth fraction (v) was crystallized from petr. ether–ether to give colorless powder (**18**) (649.5 mg), mp 143—144.5°. *Anal.* Calcd. for $C_{21}H_{29}O_5N$: C, 67.18; H, 7.79; N, 3.73. Found: C, 66.47; H, 7.68; N, 3.62. IR: 3540, 1722, 1518, 1360. NMR: 1.18—1.32 (unsolved pattern, 12H; 4-, 10- and iso-C_3H_7), 3.69 (s, 3H; 4-COOMe), 4.80 (br. s, 1H, Wl/2=10 Hz; 7-H), 7.34—7.66 (m, 2H; arom. H).

Acetylation of Methyl 7α-Hydroxy-12-nitro-dehydroabietate (18) to 17——The ester (**18**) (50 mg) was acetylated with Ac_2O (1 ml)–pyridine (5 ml) as usual. The resulting oil (56.5 mg) was crystallized from MeOH to give colorless prisms (**17**) (19 mg) (identification by mixed mp, IR, GLC).

Oxidation of Methyl 7α-Hydroxy-12-nitro-dehydroabietate (18) to 21——The ester (**18**) (50 mg) in AcOH (3.5 ml) was oxidized with CrO_3 (70 mg)–80% AcOH (1.8 ml) as usual. The resulting oil (54.5 mg) was purified by the preparative thin-layer chromatography (silica gel, petr. ether–ether (1: 1)) to isolate crystals (30 mg), which were recrystallized from MeOH to give pale yellow plates (**21**) (18.5 mg)[3] (identification by mixed mp, IR).

Drastic Nitration of Methyl 12-Bromo-dehydroabietate (15) to Methyl 12-Bromo-14-nitro-dehydroabietate (16) and Methyl 12-Bromo-13-nitro-dehydrodeisopropylabietate (22)——12-Bromo ester (**15**)[6] (5 g) was nitrated with f.HNO_3 (d=1.47) (30 ml)–conc.H_2SO_4 (1.5 ml) as in the case of **2**. The resulting oil (4.45 g) was chromatographed on alumina (270 g) to separate two oily fractions, (948 mg; 17% yield) in petr. ether–ether (9: 1) and (2.83 g; 56% yield) in the same solvents (4: 1—1: 1), successively. The former was crystallized from MeOH to give pale yellow needles (**16**) (778.5 mg) mp 164.5—167°. *Anal.* Calcd. for $C_{21}H_{28}O_4NBr$: C, 57.53; H, 6.39; N, 3.20; Br, 18.26. Found: C, 57.84; H, 6.39; N, 3.20; Br; 17.95. NMR: 1.33 (d, 6H, J=6 Hz; iso-C_3H_7), 1.21, 1.26 (s, 3H each; 4- and 10-Me), 3.66 (s, 3H; 4-COOMe), 7.54 (s, 1H; arom. H), IR: 1726, 1532, 1250. The latter fraction was crystallized from MeOH to give colorless prisms (**22**) (1.8 g), mp 131.5—132°. *Anal.* Calcd. for $C_{18}H_{22}O_4NBr$: C, 54.55; H, 5.56; N, 3.54; Br, 20.20. Found: C, 54.39; H, 5.54; N, 3.43; Br, 20.51. IR: 1720, 1535, 1252. NMR: 1.23, 1.30 (s, 3H each; 4- and 10-Me), 3.70 (s, 3H; 4-COOMe), 7.58, 7.59 (s, 1H each; 11 and 14-H).

Catalytic Reduction of Methyl 12-Bromo-14-nitro-dehydroabietate (16) to 19——The ester (**16**) (600 mg) was hydrogenated in AcOH (50 ml)–conc.H_2SO_4 (0.5 ml) with 10% Pd–C (1 g) under H_2-atmosphere (3 kg/cm^2). After the catalyst was filtered off, residue resulted by evaporated of the filtrate was alkalized with 10% Na_2CO_3 aq. and was extracted with ether. The extract was washed with sat. NaCl aq., dried over Na_2SO_4 and removal of the solvent gave an oil (460.5 mg), which was chromatographed on alumina (50 times) to give oil (270 mg) in petr. ether–ether (4: 1) elution. Rechromatography of the oil on alumina (100 times) gave oil (**19**)[8] (190.5 mg) petr. ether–ether (9: 1) elution.

A part (47 mg) of the oil (**19**) was acetylated with Ac_2O (1 ml)–pyridine (5 ml) as usual. The resulting oily acetate (71.5 mg) was purified by preparative thin-layer chromatography (silica gel, $CHCl_3$) and then was recrystallized from petr. ether–ether to give colorless needles (**20**) (19.5 mg), mp 184.5—185.5° (identification by mixed mp and IR).

Oxidation of Methyl 12-Bromo-13-nitro-dehydrodeisopropylabietate (22) to 23——The ester (**22**) (100 mg) in AcOH (7 ml) was oxidized with CrO_3 (140 mg) in AcOH (2.8 ml)–H_2O (0.8 ml) at room temperature as usual. The resulting oil (95 mg) was chromatographed on silica gel (50 g) to separate a homogeneous oil (71 mg) in petr. ether–ether (9: 1) elution and then was crystallized from petr. ether–ether to give colorless plates (**23**)[3] (43.5 mg), mp 153—158° (identification by mixed mp and IR).

Methyl 12-Bromo-13-nitro-dehydrodeisopropylabietate (22) to Methyl 13-Hydroxy-dehydrodeisopropylabietate (25) *via* 24——The ester (**22**) (894 mg) was hydrogenated in AcOEt (60 ml)–conc.H_2SO_4 (1 ml) with 10% Pd-C (2 g) under H_2-atmosphere (3 kg/cm^2). The mixture was treated as in the case of **16**. The resulting oil (**24**) (677 mg) was reacted in pyridine (12 ml) with $NaNO_2$ (1.8 g)—80% H_2SO_4 (40 ml) accordingly

10) A structure of the compound (**16**) will be confirmed as described later in this report.

to the Ohta' method.[11] 13-Hydroxy ester (**25**) (413.5 mg) obtained was recrystallized from MeOH to mp 147.5—150° (126.5 mg) (identification by mixed mp and IR).

Overall yield of **25** was 74% from **22** and 41% from **15**.

Acknowledgement The authors are indebted to Mr. Yoshiteru Tōjō for his valuable assistant. Financial support from the Ministry of Education (Grant-in-Aid for Scientific Research, No. 67031 (1972)) are gratefully acknowledged.

11) M. Ohta, *Yakugaku Zasshi*, **77**, 924 (1957).