Diterpenoids. XXVII. 1) Synthesis of 11-Methoxy-diterpenoids. (2).

Synthesis of 11-Methoxy-dehydroabietic Acid Derivatives

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7-Oxo-dehydroabietamide (XI) derived from l-abietic acid (III) was converted to methoxycyano acid (XVI) via cyano lactone (XIII) and the intramolecular cyclization of XVI gave the expected 11-methoxy-7-oxo-dehydroabietonitrile (XVII). The cyclized compound (XVII) was converted to some 11-methoxy-dehydroabietic acid derivatives, which could be regarded as potential intermediates for synthesis of natural products having 11-hydroxyabietane skeleton.

11-Methoxy compounds (I and II) can be regarded as potential intermediates for the synthesis of the interesting natural products (e.g. tumor-inhibitor taxodione 3,4 and fish-killing callicarpone 5). So, a synthetic attempt of I and II was made by the chemical conversion of l-abietic acid (III).

In previous paper, 1) the conversion was carried out by the oxidative B-ring cleavage (Baeyer–Villiger oxidation) and successive recyclization of 7-oxo ester (IV and V). As the


All melting points were measured on a micro hot-stage and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured at 60 MHz in CDCl3 (5–10% solution) vs. Me4Si as internal reference. Retention time (tR) of gas–liquid chromatography were detected by using of the column (1.5% OV-17 on Shimalite W (80–100 mesh), 4 mm × 2.0 m) and carrier N2 gas.

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results, IV of podocarpic acid type was converted to the expected 11-methoxy-7-oxo ester (I) via half ester (VI), but V of dehydroabietic acid type was only derived to the undesirable compound (VII) of bicyclo[3,3,1]nonane type via half ester (VIII). The latter observation (V→VII) have been reported by Fukui and co-workers, independently.6)

In the latter case (V→VII), methoxy migration to 6-carboxyl group from 4-methoxy-carbonyl group is occurred via oxonium intermediate (IX) and the resulting 4-carboxyl group is cyclized to C-aromatic ring to give VII. Thus, it was considered that an analogous derivative (e.g. XVI) having 4-modified function would be prevented from the undesirable cyclization and be cyclized to the expected 11-methoxy compound (XVII) as in the case of VI. The result will be reported herein.

7-Oxodehydroabietamide (XI), mp 195–196°C, ν\text{max}^CHCl_3 3500, 3430, 1667 cm\(^{-1}\), prepared (CrO\(_3\)-AcOH aq., room temp.) from dehydroabietamide (X),7) was readily oxidized (CF\(_3\)CO\(_2\)H- Na\(_2\)HPO\(_4\)-CH\(_2\)Cl\(_2\), 5–7°C) to give lactone (XII), ν\text{max} KBr 3540, 3430, 1760, 1675 cm\(^{-1}\). The 4-carbamoyl group of XII was modified to cyano group (XIII), bp 163–164°C (bath temp.)/10\(^{-3}\) mmHg, ν\text{max} 2225, 1760 cm\(^{-1}\). All of these structures (XI, XII and XIII) were ascertained by their above infrared (IR) spectral data.

![Chart 2](image)

Methanolation (MeOH– conc. HCl aq., reflux) and successive methylation (CH\(_2\)N\(_2\)-MeOH, room temp. or Me\(_2\)SO\(_4\)-K\(_2\)CO\(_3\)-acetone, reflux) of XIII gave methoxy cyano ester (XV), bp 136–138°C (bath temp.)/10\(^{-3}\) mmHg, ν\text{max} 2225, 1737 cm\(^{-1}\), via hydroxy cyano ester (XIV), mp 146.5–147.5°C, ν\text{max} 3360, 2225, 1714 cm\(^{-1}\). The resulting ester (XV) was hydrolyzed (10% KOH aq. –MeOH, reflux) to yield methoxy cyano acid (XVI), bp 156–158°C (bath temp.)/3–10\(^{-3}\) mmHg, ν\text{max} 2230, 1690 cm\(^{-1}\), which had the aimed structure. The cyclized nitrile (XVII) was hydrogenolyzed (H\(_2\), 15% Pd–C–AcOH–conc.H\(_2\)SO\(_4\), room temp.) to give methoxy nitrile (XVIII), bp 128–130°C (bath temp.)/10\(^{-3}\) mmHg, ν\text{max} 2235 cm\(^{-1}\), and, on the other way, XVII was hydrolyzed (50% KOH aq. –diethylene glycol, reflux) and successively met hylated

(CH$_2$N$_2$) to give 11-methoxy-7-oxo ester (II),\(^8\) mp 167—169\(^\circ\), \(\nu_{\text{CDCl}_3} 1727, 1690\text{ cm}^{-1}\), accompanied with 7-hydroxy ester (XIX), \(\nu_{\text{CDCl}_3} 3620, 1727\text{ cm}^{-1}\), \(\text{(ca. 7:3 ratio)}\). The latter ester (XIX) was assumed to be 7-epimeric mixture by reason that the methyl signal of the methoxycarbonyl group appeared as two peaks (\(\delta 3.66\) and 3.68, ratio of peak height \(\text{ca.} 1:1\)). However, the epimeric component could not be distinguished by comparison of chemical shifts of the other methyl groups and of gas-chromatographic retention time (\(t_R=4.18\text{ min}: 230\text{\celsius}\)). The epimeric mixture was readily oxidized (Jones reagent\(^9\) -acetone, room temp.) to give the former product (II).

Hydrogenolysis (H$_2$, 15\% Pd-C–AcOEt–HClO$_4$ aq., room temp.) of II gave methyl 11-methoxy-dehydroabietate (XX), bp 115—116\(^\circ\) (bath temp.),/\(5 \times 10^{-3}\) mmHg, \(\nu_{\text{film}} 1726\text{ cm}^{-1}\), which was further reduced (LiAlH$_4$-ether, reflux) to give 11-methoxy alcohol (XXI), mp 86—88\(^\circ\), \(\nu_{\text{CDCl}_3} 3650\text{ cm}^{-1}\).

The structures of the cyclized products (XVII and its derivatives (XVIII, II, XX and XXI)) were confirmed by the following NMR analyses. At first, 11-methoxy position was clearly proved by the coupling constant due to the aromatic 14-proton. The signal of 14-proton (\(\delta 7.63, J=2.0\text{ Hz (meta coupling)}\)) in XVII is obviously observed in a lower magnetic field than that of the other aromatic proton (\(\delta 6.97\)) by the effect of 7-oxo group and it shows the figure of 1,2,3,5-tetrasubstituted benzene type. Thus, the methoxy group is located at 11-position.

Further structural evidence of 11-methoxy compounds was adduced by NMR-comparison between methoxy compounds (XVII, XVIII, II, XX and XXI) and the corresponding demethoxy standards (XXII,
\(^{10}\) XXIII,
\(^{11}\) V, XXIV and XXV\(^\text{12}\)) (see Table I). It is re-

**Table I.** Chemical Shifts of 11-Methoxy- and The Corresponding Demethoxy-compounds

<table>
<thead>
<tr>
<th>7-Oxo-nitriles</th>
<th>Nitriles</th>
<th>7-Oxo-esters</th>
<th>Esters</th>
<th>Alcohols</th>
</tr>
</thead>
<tbody>
<tr>
<td>XVII</td>
<td>XXII</td>
<td>XVIII</td>
<td>XXIII</td>
<td>II</td>
</tr>
<tr>
<td>10-Me</td>
<td>1.36</td>
<td>1.24</td>
<td>1.23</td>
<td>1.17</td>
</tr>
<tr>
<td>4-Me</td>
<td>1.47</td>
<td>1.48</td>
<td>1.40</td>
<td>1.41</td>
</tr>
</tbody>
</table>

reported\(^{13}\) that the 10-methyl group of abietane series having a 11-methoxy group is suffered by paramagnetic effect (\(\text{ca.} 0.1—0.2\) ppm) by the 11-methoxy group. In our case, NMR signals due to 4-methyl groups were not shifted, but those due to 10-methyl groups (XVII: \(\delta 1.36\); XVIII: \(\delta 1.23\); II: \(\delta 1.39\) or 1.33; XX: \(\delta 1.30\) or 1.27; XXI: \(\delta 1.33\)) were shifted \(\text{ca.} 0.15—0.05\) ppm to lower magnetic field than those of the corresponding demethoxy standards (XXII: \(\delta 1.24\); XXIII: \(\delta 1.17\); V: \(\delta 1.24\); XXIV: \(\delta 1.22\); XXV: \(\delta 1.22\)), respectively. The above NMR data are consistent with the conclusion that these compounds (XVII, XVIII, II, XX and XXI) have 11-methoxy group of abietane skeleton.

In conclusion, the aimed 11-methoxy-dehydroabietic acid derivatives (XVII, XVIII, II, XX and XXI) were synthesized by use of 4-modified acid (XVI). It is properly considered that the other derivatives having 4-function modified from 4-methoxycarbonyl group are

\(^8\) Fukui and co-workers\(^9\) reported that this compound (II) was obtained from half acid (VIII) in only 4\% yield by successive treatment with PCl$_5$ and SnCl$_4$ in benzene. NMR spectrum of the compound is almost the same as ours, but the melting point (114—115\(^\circ\)) is different.


\(^{10}\) This compound (XXII) was prepared by oxidation (CrO$_3$-AcOH aq., room temp.) of XXIII\(^\text{11}\) as described in experimental.


cyclized as was expected. The 11-methoxy compounds obtained (e.g. II) are suitable for synthesis of taxodione and the others, and the conversion is now attempted.

**Experimental**

**Oxidation of Dehydroabietamide (X) to 7-Oxo-dehydroabietamide (XI)** — A solution of CrO₃ (11.0 g) in 80% AcOH aq. (250 ml) was dropwise added to a solution of dehydroabietamide (X) (10.0 g) in AcOH (500 ml) at room temperature with stirring and the mixture was continued to stir for 24 hr at room temperature. The mixture was stirred for 1 hr more at room temperature after an addition of MeOH (10 ml), and was evaporated under reduced pressure. The ether extract of the resulting residue was washed with sat. Na₂CO₃ aq., sat. NaCl aq., and dried over Na₂SO₄. The solvent was removed to give crystals which were recrystallized from CHCl₃-petr. ether to a pale blue powder (XI) (9.07 g). The powder was pure enough for the further experiment and was recrystallized from CHCl₃-petr. ether to give colorless fine prisms, mp 195—196°. Anal. Calcd. for C₄₀H₄₆O₄: C, 73.91; H, 8.74; N, 4.18. Found: C, 73.68; H, 8.60; N, 4.13. IR v max cm⁻¹: 3360, 2225, 1714. NMR δ: 1.20 (d, 6H, J = 6.5 Hz; -CH(CH₃)₂), 1.35 (s, 3H; 4-CH₃), 2.31 (d, 2H, J = 6.0 Hz; -CH-CH₂-CO₂CH₃), 3.93 (s, 3H; OCH₃).

**Oxidation and Successive Dehydration of 7-Oxo-dehydroabietamide (XI) via Lactone (XII)** — A peracid solution prepared from (CF₃CO)₂O (11.1 ml) and 90% H₂O₂ (11.1 ml) in CH₂Cl₂ (111 ml) by usual method, was dropwise added to a mixture of oxo amide (XI) (4.50 g) and Na₂HPO₄ (13.0 g) in CH₂Cl₂ (111 ml) at 5—7° with vigorous stirring. The mixture was continued to stir for 30 min at 5—7° and then, it was diluted with cold water. The organic layer was washed with sat. Na₂CO₃ aq., sat. NaCl aq., and dried over Na₂SO₄. The solvent was evaporated to give a pale yellow powder which was chromatographed on silica gel (20 g) to give a colorless cil (XV) (355 mg) in petr.ether-ether (9:1) elution and crystals (50 mg) was evaporated under reduced pressure. The ether extract was washed with sat. Na₂CO₃ aq., sat. NaCl aq., and dried over Na₂SO₄. The solvent was removed to give crystals which were recrystallized from CHCl₃-petr. ether to give colorless fine prisms, mp 195—196°. Anal. Calcd. for C₂₁H₂₉O₃N: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.15; H, 8.46; N, 4.20. IR v max cm⁻¹: 3540, 3430, 1760, 1675. NMR δ: 1.22 (d, 6H, J = 7.0 Hz; -CH(CH₃)₂), 1.47 (s, 3H), 1.50 (s, 3H), 6.11 (br, 2H; CONH₂).

**Phosphorus pentachloride (1.00 g) was added to a solution of lactone (XII) (1.670 g) in CCl₄ (50 ml) and, then, it was refluxed for 1 hr. The solvent was evaporated and the resulting residue was washed with sat. Na₂CO₃ aq., sat. NaCl aq., and dried over Na₂SO₄. The solvent was removed to give a pale yellow powder (280 mg), which was purified by chromatography on silica gel (40 g) in petr. ether—ether (4:1) elution to give a colorless oil (XIII) (522 mg), bp 163—164° (bath temp.)/10⁻³ mmHg. Anal. Calcd. for C₂₀H₂₅O₂N: C, 77.13; H, 8.09; N, 4.50. Found: C, 76.87; H, 8.01; N, 4.57. IR v max cm⁻¹: 3360, 2225, 1760. NMR δ: 1.24 (d, 6H, J = 6.5 Hz; -CH(CH₃)₂), 1.47 (s, 3H), 10-CH₃), 1.61 (s, 3H; 4-CH₃), tₖ = 6.70 min (240°).

**Methanolation of Cyano Lactone (XIII) to Hydroxy Cyano Ester (XIV)** — A mixture of lactone (XIII) (800 mg) in MeOH (80 ml)—conc. HCl aq. (1.5 ml) was refluxed for 10 min. The solvent was removed under reduced pressure and the resulting residue was extracted with ether. The extract was washed with sat. Na₂CO₃ aq., sat. NaCl aq., and dried over Na₂SO₄. The solvent was evaporated to give crystals (XIV) (837 mg) which were recrystallized from CH₂Cl₂ (111 ml) at 5—7° with vigorous stirring. The mixture was continued to stir for 30 min at 5—7° and then, it was diluted with cold water. The organic layer was washed with sat. Na₂CO₃ aq., sat. NaCl aq., and dried over Na₂SO₄. The solvent was removed to give a pale yellow powder (780 mg), which was purified by chromatography on silica gel (40 g) in petr.ether—ether (4:1) elution to give a colorless oil (XV) (431 mg), which was identified with methoxy cyano ester(XV) by comparison of IR spectrum and tₖ.

**Methylation of Hydroxy Cyano Ester (XIV) to Methoxy Cyano Ester (XV)** — Methylation with CH₃J—MeOH: Hydroxy cyano ester (XIV) (400 mg) in MeOH (20 ml) was methylated as usual with CH₃J—ether. The solvent was removed under reduced pressure and the resulting oil was purified by chromatography on silica gel (20 g) to give a colorless oil (XV) (355 mg) in petr. ether—ether (4:1) elution and crystals (50 mg) in petr. ether—ether (4:1) elution. The latter crystals (50 mg) were identified with the starting hydroxy cyano ester (XIV) by comparison of IR spectrum (CCl₄) and tₖ.

**Hydrolysis of Methoxy Cyano Ester (XV) to Methoxy Cyano Acid (XVI)** — A mixture of hydroxy cyano ester (XV) (775 mg) in 10% KOH aq. (30 ml) was refluxed for 60 min with stirring and, then, it was removed to the half volume under reduced pressure. The resulting mixture was washed with...
ether and acidified with dil. HCl aq. The ether extract was washed with sat. NaCl aq. and dried over Na$_2$SO$_4$.

The solvent was evaporated to give the colorless oil (XVI) (684 mg), which was pure enough for the further experiment. A part of an oil (120 mg) was chromatographed on silica gel—Celite (1:1) (10 g) in petr. ether—ether (4:1) elution to give a colorless oil (XVI) (108 mg), bp 165—183° (bath temp.),10$^{-4}$ mmHg. *Anal.* Calcd. for C$_{22}$H$_{32}$O$_3$: C, 76.70; H, 9.36. Found: C, 76.91; H, 9.42.

Cyclization of Methoxy Cyano (XVI) to 11-Methoxy-7-oxo-dehydroabietonitrile (XVII) — A solution of methoxy cyano acid (XVI) (440 mg) in (CF$_2$CO$_2$)O (3.6 ml)—CF$_2$CO$_2$H (1.8 ml) was left for standing for 3 hr at room temperature. The reaction mixture was poured into ice and extracted with ether. The ether extract was washed 10% KOH aq., then, sat. NaCl aq., and was dried over Na$_2$SO$_4$ (neutral part). The alkaline layer was acidified and extracted with ether. The extract was washed with sat. NaCl aq. and dried over Na$_2$SO$_4$ (acidic part). Both solvents were evaporated respectively to give a colorless oil (349 mg) as the neutral part and a pale yellow powder (57 mg) as the acidic part. The latter acidic powder (57 mg) was identified with the starting methoxy cyano acid (XVI) by comparison of IR spectrum (CCl$_4$). The former neutral oil (349 mg), whose gas chromatogram showed it was almost single product (t$_R$ = 2.80 min; 240°), was chromatographed on silica gel (30 g in petr. ether—ether (4:1) elution to give a colorless oil (XVII) (280 mg), bp 156—158° (bath temp.)/3 × 10$^{-3}$ mmHg. *Anal.* Calcd. for C$_{21}$H$_{27}$O$_2$N: C, 77.50; H, 8.36; N, 4.50. Found: C, 81.03; H, 9.27; N, 4.39. IR $\nu_{max}$ cm$^{-1}$: 2235. *NMR*: δ (6H, J = 7.0 Hz; -CH(CH$_3$)$_2$), 1.28 (s,3H; 4-CH$_3$), 1.33 (s,3H; 10-CH$_3$), 3.66 (s,3H; OCH$_3$), ca. 8.5s (br, CO$_2$H).

Hydrolysis and Successive Methylation of 11-Methoxy-7-oxo-dehydroabietonitrile (XVII) to Methyl 11-Methoxy-7-oxo-dehydroabietonitrile (XIX) — A solution of methoxy oxo nitrile (XVII) (280 mg) in conc. H$_2$SO$_4$ (5 drops)—AcOH (70 ml) was stirred in the presence of 15% Pd-C (560 mg) under an atmospheric hydrogen pressure at room temperature. After hydrogen absorption was ceased, the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The ether extract of the resulting residue was washed with sat. Na$_2$CO$_3$ aq., sat. NaCl aq. and dried over Na$_2$SO$_4$. The solvent was evaporated to give a powder, which was methylated as usual with CH$_2$N$_2$—ether to yield a pale yellow oil (118 mg). The oil was purified by chromatography on silica gel (15 g) to give colorless crystals (II) (71 mg) in petr. ether—ether (9:1) elution and a colorless oil (18.5 mg) and it was identified with 11-methoxy-7-oxo ester (II) by comparison of IR spectrum (CCl$_4$) and t$_R$.

Hydrogenolysis of 11-Methoxy-7-oxo-dehydroabietonitrile (XVII) to 11-Methoxy-dehydroabietonitrile (XVIII) — A solution of methoxy oxo nitrile (XVII) (280 mg) in conc. H$_2$SO$_4$ (5 drops)—AcOH (70 ml) was refluxed for 12 hr with stirring and, then, acidified with dil. HCl aq. The ether extract was washed with H$_2$O and extracted with 10% KOH aq. The alkaline extract was acidified and extracted with ether. The ether extract was washed with sat. NaCl aq. and dried over Na$_2$SO$_4$. The solvent was evaporated to give a colorless oil (349 mg), whose gas chromatogram showed it was almost single product (t$_R$ = 8.20 min; 240°), and it was identified with the starting methoxy cyano acid (XVI) by comparison of IR spectrum (CCl$_4$). The former neutral oil (349 mg), whose gas chromatogram showed it was almost single product (t$_R$ = 8.20 min; 240°), was chromatographed on silica gel (30 g in petr. ether—ether (4:1) elution to give a colorless oil (XVIII) (280 mg), bp 128—130° (bath temp.)/10$^{-4}$ mmHg. *Anal.* Calcd. for C$_{21}$H$_{29}$O$_3$N: C, 73.43; H, 8.51; N, 4.08. Found: C, 73.14; H, 8.49; N, 4.08. IR $\nu_{max}$ cm$^{-1}$: 1727; NMR a: 1.23 (d, 6H, J = 7.0 Hz; -CH(CH$_3$)$_2$), 1.33 (s,3H; 10-CH$_3$), 2.28 (d, 6H, J = 6.0 Hz; -CH$_2$-CH$_2$-CO$_2$H), 3.87 (s,3H; OCH$_3$), ca. 8.16 (br, CO$_2$H).
Reduction of Methyl 11-Methoxy-dehydroabietate (XX) to 11-Methoxy-dehydroabietanol (XXI)—A mixture of methoxy ester (XX) (63 mg) and LiAlH₄ (50 mg) in ether (10 ml) was refluxed for 5 hr with stirring and dil. HCl aq. was added to the reaction mixture. The organic layer was washed with sat. NaCl aq. and dried over Na₂SO₄. The solvent was evaporated to give a colorless oil (55 mg) and it was chromatographed on silica gel (10 g) in petr. ether—ether (9:1) elution to give colorless crystals (XXI) (53 mg), which were recrystallized from petr. ether—ether to colorless fine needles (20 mg), mp 86—88°. Anal. Calcd. for C₂₁H₃₂O₂: C, 79.70; H, 10.19. Found: C, 80.07; H, 10.63. IR vₐ₅ cm⁻¹: 3650. NMR δ: 0.88 (s, 3H; 4-CH₃), 1.22 (d, 6H, J=7.0 Hz; -CH(CH₃)₂), 1.33 (s, 3H; 10-CH₃), 3.15 (d, 1H, J=10.5 Hz; CH₂OH), 3.48 (d, 1H, J=10.5 Hz; CH₃OH), 3.78 (s, 3H; 11-OCH₃), 6.63 (s, 2H; 12- and 14-H).

Oxidation of Dehydroabietonitrile (XXIII) to 7-Oxo-dehydroabietonitrile (XXII)—Nitrile (XXIII) (150 mg) in AcOH (10.5 ml) was treated with CrO₃ (210 mg)—80% AcOH aq. (5.25 ml) as in the case of amide (X). The resulting oil (127 mg) was chromatographed on silica gel (15 g) in petr. ether—ether (4:1) elution to give a colorless oil (XXII) (74 mg), bp 109—110° (bath temp.)/10⁻³ mmHg. Anal. Calcd. for C₂₀H₂₅ON: C, 81.31; H, 8.35; N, 4.74. Found: C, 80.91; H, 8.26; N, 4.70. IR vₐ₅ cm⁻¹: 2230, 1685. NMR δ: 1.24 (d, 6H, J=6.5 Hz; -CH(CH₃)₂), 1.24 (s, 3H; 11-CH₃), 1.48 (s, 3H; 4-CH₃), 7.93 (d, 1H, J=2.0 Hz; 14-H). tᵣₐ₅=3.50 min (250°).

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