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Diterpenoids. XXXIV.[1] Stereochemistry on the Rearranged Compound (Benzilic Acid Rearrangement) of Methyl 6,7-Dioxo-5α,10α-podocarpa-8,11,13-trien-15-oate[2,3]

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Stereochemistry of the hydroxy diacid (III), which was obtained by the benzilic acid rearrangement of the dioxo ester (II) derived from *l*-abietic acid (I), was determined uneqivocally. Moreover, the rearranged compounds (III and IX) were concluded to have a nonsteroidal form.

Chemical conversion of *l*-abietic acid (I), a major component of pine rosin, to biologically active compounds has been carried out in our laboratory. Synthesis of gibberellin was also attempted by the use of *l*-abietic acid (I) as the starting material. In this synthesis, the first important step was the skeletal rearrangement of a hydrophenanthrene skeleton of the acid (I) into a hydrofluorene skeleton of gibberellin. In 1961, this problem was independently solved both by a British group[5] and our group.[6] Namely, the dioxo ester (II) derived from the acid (I) was converted into the hydroxy diacid (III) using the benzilic acid rearrangement.

Discussion on the stereochemistry of the rearranged acid (III) was made by the British group, who reported that heating of III with acetic anhydride under reflux gave a mixture of Δ^5-anhydride (V) and acetoxy anhydride (IV'), which on alkaline hydrolysis gave the same product (VII). Acetoxy anhydride was estimated to have the structure (IV') by its ability to form an anhydride ring in which 5-hydrogen atom and 6-acetoxy group were *trans* and near coplaner, and from the ready *trans*-elimination between 5-hydrogen atom and 6-acetoxy group. Based on this fact, they concluded that the original diacid had the structure (III) among the four possible stereoisomers due to asymmetric 5- and 6-carbon centers. Moreover, they reported with respect to the comformation of the rearranged acid (III) that 4-carboxylic acid and 10-methyl group are equatorial, and 5-hydrogen atom is axial. In contrast, our recent examination of the molecular model suggested the difficulty of the anhydride (IV') to be formed and stereochemistry of the acid (III) is still open to discussion.

The purpose of the work reported here is to determine the stereochemistry of the acid (III) unequivocally.

In the same way as reported by Grove, *et al.*,[5] III was acetylated with acetic anhydride under reflux to give Δ^5-anhydride (V), mp 207—209° (decomp.), IR ν_{max}^{KBr} cm^{-1}: 1792, 1757. NMR τ: 8.62, 8.38 (4- and 10-Me), and acetoxy anhydride (IV), mp 161—163°, IR ν_{max}^{KBr} cm^{-1}: 1811, 1761, 1735, 1235. NMR τ: 9.33 (4-Me), 8.63 (10-Me), 7.93 (6-OAc), 7.35 (5α-H). They were assumed to correspond to Grove's anhydrides (V, mp 208—209° (decomp,), and IV',

1) Part XXXIII: A. Tahara, Y. Harigaya, and M. Onda, *Chem. Pharm. Bull.* (Tokyo), **23**, 1996 (1975).
2) A part of the work was published as a preliminary communication: A. Tahara, T. Nakata, Y. Ohtsuka, and S. Takada, *Chem. Pharm. Bull.* (Tokyo), **19**, 2653 (1971). Dr. Akira Tahara passed away suddenly on January 2, 1975.
3) The hydrofluorene compounds were obtained from *l*-abietic acid in this work and the usual numbering for diterpenes was used for the hydrofluorene derivatives.
4) Location: *a*) *Wako-shi, Saitama*; *b*) *Honkomagome, Bunkyo-ku, Tokyo.*
5) J.F. Grove and B.J. Riley, *J. Chem. Soc.*, **1961**, 1105.
6) A. Tahara, *Chem. Pharm. Bull.* (Tokyo), **9**, 252 (1961); A. Tahara and O. Hoshino, *ibid.*, **9**, 655 (1961).

mp 163—165°) by comparison with their physical constants. However, contrary to Grove's report, the acetoxy anhydride (IV: Grove's formula IV′) was not recovered by alkaline hydrolysis (1N KOH, room temp.)[7] but was converted to a new hydroxy diacid (VI), mp 143.5—144.5°, $C_{17}H_{20}O_5 \cdot H_2O$, in company with VII. The hydroxy diacid (VI) and its diester (X), oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3526, 1721. NMR (CCl_4) τ: 6.34, 6.31 (COOMe), 6.63 (5α-H), 5.97 (OH), are considered to be stereoisomer of the hydroxy diacid (III) and its diester (IX), mp 98—100°, IR ν_{max}^{KBr} cm^{-1}: 3494, 1721. NMR (CCl_4) τ: 6.35, 6.17 (COOMe), 6.58 (5α-H), 6.47 (OH), by comparison of their infrared (IR) and nuclear magnetic resonance (NMR) spectra.

Therefore, the structure of both isomeric diacids (III and VI) was re-examined from the following experiments.

i) The new diacid (VI) was oxidized with chromium trioxide in acetic acid to give authentic 6-keto acid[8] (VIII), already obtained from the isomer[5,6] (III). Thus, it is evident that the hydroxyl group in VI was situated at the same 6-position as that in III.

ii) Catalytic hydrogenolysis of the corresponding methyl esters (IX and X) over 10% palladium-charcoal in acetic acid containing conc. sulfuric acid similarly gave a mixture of XI and XII in a ratio of 3: 1 and 1: 3, respectively. The structure of the resulting diesters (XI and XII) was reported to have *cis*-A/B ring junction in our previous paper,[9] so that the hydroxy diesters (IX and X) should have the same *cis*-A/B ring junction.

As a result of these experiments, the two hydroxy diacids (III and VI) were proved to be stereoisomers with respect to the 6-hydroxy group alone, and both having a *cis*-A/B ring junction.

iii) Successively, stereochemistry of III and VI was investigated. Mild acetylation of VI in acetic anhydride at room temperature readily gave the acetoxy anhydride (IV: Grove's formula IV′), while that of III only gave an acetate (XIII), oil, $C_{23}H_{26}O_8$, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1825, 1752, 1713. NMR τ: 7.88, 7.74, 7.70 (OAc), whose hydrolysis (1N KOH, room temp.) gave III and VII. Furthermore, more drastic acetylation of III and VI in acetic anhydride under reflux gave a mixture of IV and V, respectively.

It may be concluded from the above experimental results that the inversion occurred in the formation of acetoxy anhydride (IV) from the acid (III) under a drastic condition. The mechanism of this inversion is not obvious.

Considering the molecular model, it is evident that the formation of acetoxy anhydride (IV) is easy and that of IV′ is not. The above consideration is further supported to be correct by another experiment[9] reported previously. Namely, in the anhydride formation of *cis*-A/B diacids (XIV and XV), the anhydride (XVI) with the same configuration as that of IV can be obtained, while the anhydride (XVII) with the same configuration as that of IV′ cannot. Furthermore, the fact that the 4-methyl signal of the anhydride (IV) (τ: 9.33) is observed at an abnormally higher magnetic field is reasonably explained by assuming that the methyl group suffers the diamagnetic effect of the aromatic ring as shown in the structure (IV-A), and its value is in good agreement with that of 4β-methyl group of the anhydride (XVI) (τ: 9.36).

In view of the all these results, the structure (IV) must be assumed for the acetoxy anhydride with a *cis*-A/B ring junction and the formula (IV′) reported by Grove, *et al.* can be ruled out. Accordingly, the new diacid (VI) should have the same configuration as that of the acetoxy anhydride (IV), while the diacid obtained by benzilic acid rearrangement should have the structure (III) as a result of a unique epimerization occurring at C-6 during the

7) The hydrolysis reported by Grove, *et al.* was carried out under alkaline condition (0.1N NaOH, room temp.) and only the starting material was recovered. Our re-examination under the same condition gave Δ^5-diacid (VII).

8) M. Ohta, *Chem. Pharm. Bull.* (Tokyo), **5**, 256 (1957).

9) A. Tahara and Y. Ohtsuka, *J. Chem. Soc.* (Perkin I), **1972**, 320.

anhydride ring formation (III→IV). The assigned structures are further supported by the observable tendency of dehydration (*trans*-elimination, III>VI); drastic acetylation of III and VI in acetic anhydride under reflux gave an unsaturated anhydride (V) and an acetoxy anhydride (IV) in a ratio of 1.4: 1 and 1: 2.2, respectively.

Grove, *et al.* regarded the conformation of the rearranged acid (III) as a steroidal form. If the acid (III) has a steroidal form (III-A), the chemical shift of 4β-methyl group sohuld be observed at a higher magnetic field by the diamagnetic effect of the aromatic ring, similar to the acetoxy anhydride (IV) (τ: 9.33) and the anhydride (XVI) (τ: 9.36) which have a steroidal form, but 4β-methyl group of the corresponding diester (IX) (τ: 8.80) does not appear at a higher magnetic field. Accordingly, it is considered that the benzilic acid rearranged compounds (III and IX) have a nonsteroidal form as in the *cis*-A/B diester (XI), NMR τ: 8.82 (4β-Me), which was previously reported[9] to have a nonsteroidal form.

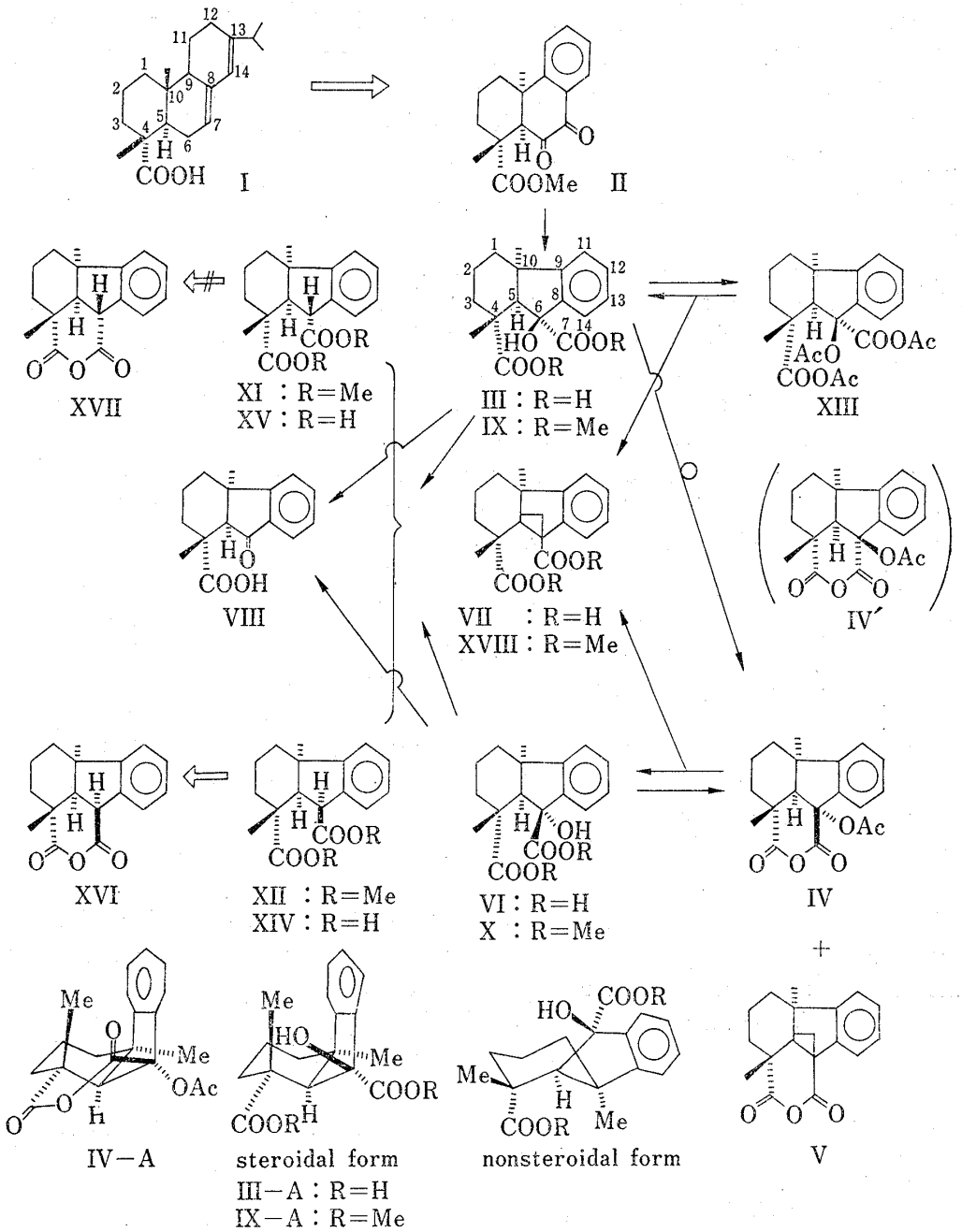

Chart 1

In conclusion, the acetoxy anhydride (IV'), Grove's important compound for the elucidation of hydroxy diacid (III), should be revised to formula (IV). However, the acid (III) in question was correctly assigned by chance, because an interesting epimerization at C-6 had fortunately occurred during the acetylation of III to IV. Moreover, the rearranged compounds (III and IX) were concluded to have a nonsteroidal form.

Experimental

All melting points were measured on a micro hot-stage and uncorrected. Nuclear magnetic resonance (NMR) spectra were measured at 60 MHz in $CDCl_3$ *vs.* Me_4Si as internal reference. Retention times (t_R) of gas–liquid chromatography (GLC) were detected by using of the column (1.5% OV-17 on Shimalite W (80—100 mesh), 4 mm × 2.0 m) and carrier N_2 gas.

Reaction of 1,2,3,4,5α,10-Hexahydro-6β-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylic Acid (III) with Acetic Anhydride——A solution of 6β-hydroxy diacid (III) (15 g) in acetic anhydride (300 ml) was refluxed for 30 min. The solvent was removed under reduced pressure to give crude crystals. The crystals were recrystallized from acetone to give colorless needles (V) (8.159 g), mp 207—209°, and from acetone–petr. ether to give colorless prisms (IV) (2.835 g), mp 161—163°. Mp and IR spectrum of the needles (V) were identical with those of Δ^5-anhydride[5] (V) reported by Grove, *et al.* *Anal.* Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.70; H, 5.60. IR ν_{max}^{KBr} cm^{-1}: 1792, 1757. NMR τ: 8.62 (s, 3H, Me), 8.38 (s, 3H, Me). Mp and IR spectrum of the prisms (IV) were identical with those of acetoxy anhydride[5] (IV') reported by Grove, *et al.* *Anal.* Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.27; H, 6.41. IR ν_{max}^{KBr} cm^{-1}: 1811, 1761, 1737, 1235. NMR τ: 9.33 (s, 3H; 4-Me), 8.63 (s, 3H; 10-Me), 7.93 (s, 3H, OAc), 7.35 (s, 1H; 5α-H).

Alkaline Hydrolysis of 1,2,3,4,5α,10-Hexahydro-6α-acetoxy-4β,10α-dimethylfluorene-4α,6β-dicarboxylic Anhydride (IV)——Acetoxy anhydride (IV) (2.0 g) in 1N KOH (300 ml) was stirred at room temperature for 3 days. The cooled solution was acidified with conc. HCl and extracted with ether. The ether extract was washed with sat. NaCl aq. and dried over Na_2SO_4. The solvent was evaporated to give crude crystals, which were recrystallized from MeOH–H_2O to give colorless needles (VII) (1.126 g), mp 201—202°; the compound was identical (mp and IR spectrum) with Δ^5-diacid[5] (VII) synthesized *via* Grove's route. Furthermore, the mother solution was added with H_2O to give colorless scales (VI) (269 mg), mp 143.5—144.5°. *Anal.* Calcd. for $C_{17}H_{20}O_5 \cdot H_2O$: C, 63.34; H, 6.88. Found: C, 63.64; H, 6.84. IR ν_{max}^{KBr} cm^{-1}: 1741, 1717, 1694, 1671.

Dimethyl 1,2,3,4,5α,10-Hexahydro-6α-hydroxy-4β,10α-dimethylfluorene-4α,6β-dicarboxylate (X)——6α-Hydroxy diacid (VI) was methylated as usual with CH_2N_2–ether to give colorless oil (X), bp 145—150° (bath temp.)/10^{-3} mmHg, quantitatively. *Anal.* Calcd. for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.72; H, 6.97. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3526, 1721. NMR (CCl_4) τ: 8.78 (s, 3H; Me), 8.73 (s, 3H; Me), 6.63 (s, 1H; 5α-H), 6.34 (s, 3H; COOMe), 6.31 (s, 3H; COOMe), 5.97 (s, 1H; OH). GLC (220°): t_R=4.0 min. *cf*) 6β-Hydroxy diester (IX), colorless needles, mp 98—100°. IR ν_{max}^{KBr} cm^{-1}: 3494, 1721. NMR (CCl_4) τ: 8.80 (s, 6H; 2×Me), 6.58 (s, 1H; 5α-H), 6.47 (s, 1H; OH), 6.35 (s, 3H; COOMe), 6.17 (s, 3H; COOMe). GLC (220°): t_R=3.55 min.

Oxidation of 1,2,3,4,5α,10-Hexahydro-6α-hydroxy-4β,10α-dimethylfluorene-4α,6β-dicarboxylic Acid (VI) with Chromium Trioxide——A solution of anhydrous CrO_3 (20 mg) in AcOH–H_2O (3: 1) (1 ml) was added dropwise with stirring under ice-cooling to a solution of 6α-hydroxy diacid (VI) (10 mg) in AcOH (10 ml), and the mixture was heated at 30° for 2 hr, then was set aside at room temperature for 2 days. The reaction mixture was diluted with H_2O, and extracted with ether. The ether extract was dried over Na_2SO_4 and evaporated to give oil, which was crystallized with petr. ether to give crystals (VIII) (5.5 mg), mp 122—124°; the compound was identical (mp mixed mp and IR spectrum) with the authentic 6-keto acid[8] (VIII).

Catalytic Hydrogenolysis of Dimethyl 1,2,3,4,5α,10-Hexahydro-6β-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylate (IX)——A solution of 6β-hydroxy diester (IX) (250 mg) in AcOH (75 ml) was shaken in the presence of 10% Pd-C (500 mg) and conc. H_2SO_4 (5 drops) under a hydrogen atmosphere at room temperature for 16 hr. The catalyst was filtered off and about half volume of the filtrate was evaporated. The residual solution was diluted with H_2O and extracted with ether. The ether extract was washed with sat. Na_2CO_3aq., H_2O and dried over Na_2SO_4. The solvent was evaporated to give oil, which still contained about one-third volume of the starting material (IX). The oil was again treated under the above same condition. After 20 hr, the reaction mixture was worked up to give oil (226 mg); the oil was identical with a mixture of *cis*-A/B diester[9] (XI) and (XII) in a ratio of 3: 1 by NMR spectrum.

Catalytic Hydrogenolysis of Dimethyl 1,2,3,4,5,α10-Hexahydro-6α-hydroxy-4β,10α-dimethylfluorene-4α,6β-dicarboxylate (X)——A solution of 6α-hydroxy diester (X) (53 mg) in AcOH (15 ml) was shaken in the presence of 10% Pd-C (100 mg) and conc. H_2SO_4 (1 drop) under a hydrogen atmosphere at room temperature for 16 hr. The reaction mixture was further added with 10% Pd-C (50 mg) and shaken for 20 hr, then worked up as in the case of 6β-hydroxy diester (IX) to give oil (54 mg); the oil was identical with a mixture of *cis*-A/B diesters[9] (XI) and (XII) in a ratio of 1: 3 by NMR spectrum.

Reaction of 1,2,3,4,5α,10-Hexahydro-6β-hydroxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylic Acid (III) with Acetic Anhydride (Room Temperature)——A solution of 6β-hydroxy diacid (III) (30 mg) in acetic anhydride (6 ml) was set aside at room temperature for 9 hr. The solvent was removed under reduced pressure to give colorless oil (XIII) (42 mg). *Anal.* Calcd. for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 63.99; H, 6.33. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1825, 1752, 1713. NMR τ: 8.62 (s, 3H; Me), 8.45 (s, 3H; Me), 7.88 (s, 3H; OAc), 7.74 (s, 3H; OAc), 7.70 (s, 3H; OAc), 6.66 (s, 1H; 5α-H).

Reaction of 1,2,3,4,5α,10-Hexahydro-6α-hydroxy-4β,10α-dimethylfluorene-4α,6β-dicarboxylic Acid (VI) with Acetic Anhydride (Room Temperature)——A solution of 6α-hydroxy diacid (VI) (30 mg) in acetic anhydride (6 ml) was set aside at room temperature for 9 hr. The solvent was removed under reduced pressure to give crystals (IV) (34 mg), which were recrystallized from acetone to give colorless prisms (IV), mp 161—163°; the compound was identical (mp, mixed mp, IR and NMR spectra) with acetoxy anhydride (IV) obtained from 6β-hydroxy diacid (III) with acetic anhydride under reflux.

Alkaline Hydrolysis of 1,2,3,4,5α,10-Hexahydro-6β-acetoxy-4β,10α-dimethylfluorene-4α,6α-dicarboxylic Diacetic Anhydride (XIII) and 1,2,3,4,5α,10-Hexahydro-6α-acetoxy-4β,10α-dimethylfluorene-4α,6β-dicarboxylic Anhydride (IV)——Anhydride (XIII) (22 mg) in 1N KOH (3 ml) was stirred overnight at room temperature. The cooled solution was acidified with conc. HCl and extracted with ether. The ether extract was washed with sat. NaCl aq. and dried over Na_2SO_4. The solvent was evaporated to give a mixture of diacids (III) and (VII), which was methylated with CH_2N_2–ether to give a mixture of diesters (IX) and (XVIII) in a ratio of 1: 3 by NMR spectrum.

6α-Acetoxy anhydride (IV) (22 mg) was treated as the same way in the above case to give a mixture of diacids (VI) and (VII), which was methylated with CH_2N_2–ether to a mixture of diesters (X) and (XVIII) in a ratio of 1: 1 by NMR spectrum.

Reaction of 1,2,3,4,5α,10-Hexahydro-6β-hydroxy-4α,10β-dimethylfluorene-4α,6α-dicarboxylic Acid (III) and 1,2,3,4,5α,10-Hexahydro-6α-Hydroxy-4β,10α-dimethylfluorene-4α,6β-dicarboxylic Acid (VI) with Acetic Anhydride (Reflux)——A solution of 6β-hydroxy diacid (III) (150 mg) in acetic anhydride (3 ml) was refluxed for 30 min. The solvent was evaporated under reduced pressure to give a mixture of anhydrides (V) and (IV) (125 mg) in a ratio of 1.4: 1 by NMR spectrum.

6α-Hydroxy diacid (VI) (25 mg) was treated as the same way in the above case to give a mixture of anhydrides (V) and (IV) (27 mg) in a ratio of 1: 2.2 by NMR spectrum.

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