Diterpenoids. XIV. Conformational Studies. II.¹⁾ Preferred Conformation of A/B-*cis* Ring-C Aromatic Tricyclic Diterpenes

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Syntheses of 20-nor tricyclic diterpene derivatives and determination of their structures are described. In the A/B-*cis* ring system, it is revealed by the analysis of proton magnetic resonance, infrared spectrum and reaction that the steroid type conformation of 10-methyl series is preferred to nonsteroid type conformation, conversely, nonsteroid type conformation is preferred in 20-nor derivatives.

In recent years conformational examinations of ring-C aromatic tricyclic diterpene have been appeared in our¹⁾ and other papers³⁾ with the aid of proton magnetic resonance (PMR) spectrum. Especially, much interest has been directed towards the preferred conformation of *cis*-decaline system, which were shown to be influenced by the position, configuration and size of their substituents in the system. Among these investigations it is of interesting example that the preferred conformation assigned to *cis*-10-methyl-2-decalone⁴⁾ itself was revised twice in only few years. These contributions aroused our interest in a study of the preferred conformation of A/B-*cis*-diterpene derivatives. This communication details our initial work⁵⁾ concerning the synthesis of A/B-*cis*-20-nor and -10-methyl tricyclic diterpenes and conformational difference between them including new results.

Synthesis and Structure of 20-Nor-diterpenes and A/B-*cis*-10-Methyl Compounds

It was suggested in our previous paper⁶⁾ that A/B-*trans*- and -*cis*-20-nor compounds were obtained on the way to accomplish a chemical conversion from abietic acid to natural diterpene alkaloids. For the present purpose, the synthesis and structure of 20-nor-diterpene will be described firstly. The hydroxy lactone (I), obtained from abietic acid, was treated in drastic alkaline condition (KOH in aq. ethylene glycol at 200°) to give an oily acidic substance in more than 50% yield together with crystalline keto diacid (II) in about 40% yield. The oily substance was methylated with diazomethane and was shown to be a mixture of two components, V and VI (ratio of 1:1), by gas-liquid chromatography. They were separated into crystals (V), mp 75—77°, and VI, mp 77—79°, by careful column chromatography on neutral alumina. As the elemental analysis data of V and VI conforms to C₁₇H₂₀O₃ and a

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signal due to tertiary methyl group is still observed in their PMR spectra, both V and VI have a common 20-nor keto ester skeleton. Furthermore, the same mixture of V and VI (ratio of 3:1) could be obtained from II by the same procedure as in the case of I. Therefore the

Chart 1

configuration of C₅-H in V and VI sustains β orientation being identical to that of II. The stereochemistry of C₁₀ of V and VI was substantiated with the following observations.

The compound (VI) was hydrogenolized to give deoxo ester (VII), mp 43—44°, which was reduced to the corresponding alcohol (VIII), mp 81—83°, with lithium aluminium hydride in good yield. In our precesing paper⁷⁾ the chemical shift of C₄-methyl in podocarpic acid skeleton was found to show a diamagnetic shift when C₄-carbomethoxy group was converted to C₄-hydroxymethyl group (from 8.73 to 8.96 ppm). The chemical shifts of C₄-methyl group in VII and VIII are exactly identical with those of respective enantio deoxypodocarpic acid derivatives as shown in Table I. So that these observation indicates that VI, VII and VIII should have podocarpic acid type skeleton, *e.g.* the hydrogen at C₁₀ should have α configuration.

TABLE I. Chemical Shifts of C₄-Me Group (τ -Value)

VII	8.73	VIII	8.96
XXI	8.73	XXII	8.95

As stated above, then, the configuration of C₁₀-hydrogen in another isomeric keto ester (V) should be β . This assumption was further supported by another experiments. Reduction of V with sodium borohydride gave hydroxy ester (IX), mp 104—106°, IR _{ν_{max}} ^{CCl₄}: 3590, 1738 cm⁻¹, and then IX was hydrolyzed to give an oily hydroxy acid (X). Since X was methylated with diazomethane to give the original (IX), the configuration at C₇ did not change during alkaline hydrolysis. The dehydration reaction of X with acid is so facile that the lactonization of X does not proceed in sufficient yield. But, when methanolic hydrochloric acid solution of X was kept at room temperature, aimed δ -lactone (XII), mp 119—121°, was obtained in about 40% yield together with unsaturated acid (XI). Lithium aluminium hydride reduction of XII gave crystalline diol (XV), mp 205—207°, which was also yielded from IX by the same reduction. In the stereochemical view of the lactone formation, the C₇-O bond in XII must be α orientation and also its A/B ring juncture must be *cis* system (β C₁₀-hydrogen). Accordingly, the C₇-hydroxy group in IX should be α configuration and this fact is consistent with the stereochemical course of sodium borohydride reduction that hydride ion should attack from less hindered β side of molecule (V).

For the present purpose of the conformational study, other derivatives of A/B-*cis*-20-nor compound were furthermore synthesized as follows. Hydroxy ester (IX) was converted to unsaturated ester (XIII), bp 175—177° (2 mmHg), UV $\lambda_{\text{max}}^{\text{EtOH}}$ 263 m μ (ϵ 6900), with methanolic hydrochloric acid, and XIII was shown to be identical with methylated compound derived from unsaturated acid (XI). Saturated ester (XIV) was obtained from V and XIII by catalytic hydrogenolysis (10% Pd-C, AcOH, H₂SO₄) and hydrogenation (10% Pd-C, AcOH) respectively. In consequence of the above observation, it is apparent that there have been no skeletal rearrangement in the above chemical courses.

In accordance with the necessity for the comparative study of the conformation of A/B-*cis*-20-nor compounds, whose structures were characterised as described so far, to that of A/B-*cis*-10-methyl derivatives, 5-isodehydroabiatic acid series were synthesized. Methylation of 5-isodehydroabiatic acid, obtained from dehydroabiatic acid (XVI) by Wenkert's method,^{4a,8)} gave *cis*-10-methyl ester (XVII). Oxidation of XVII with chromic anhydride afforded 7-keto ester (XVIII), mp 100—102°, and reduction of XVIII with sodium borohydride gave hydroxy

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ester (XIX). On treatment with alumina this hydroxy ester (XIX) was readily converted to δ -lactone (XX), mp 166—167°, in quantitative yield.

Conformational Analysis

Since the derivatives of 5-isodehydroabiatic acid are obtained, the conformation of 20-nor and corresponding 10-methyl compounds will be discussed comparatively. Between these two systems definitive differences exist in the spectral and chemical properties as summarized below. (1) Infrared (IR) spectrum (CCl_4 solution) of XIX shows intramolecular hydrogen bonded hydroxy and carbonyl bands (IR ν_{max} : 3520, 1705 cm^{-1}) with free respective absorptions (IR ν_{max} : 3590, 1735 cm^{-1}), while that of IX has only free bands. (2) Though easy and quantitative lactonization of XIX was performed with alumina, IX is stable to alumina, and for the formation of XII hydrochloric acid treatment of hydroxy acid (X) is required involving the risk of dehydration. Such differences are consistent with the idea that carbomethoxy group in XIX is located near to C_7 - α -hydroxy group, while that in IX is not the case. (3) In contrast with the normal chemical shifts of carbomethoxy methyl of 20-nor series, (V, 6.27; IX, 6.27; XIII, 6.32; XIV, 6.32), those of 10-methyl compounds are shielded considerably (XVII, 6.63; XVIII, 7.06; XIX, 6.82). Thus, the ester methyl group in 10-methyl series is concluded to be situated above the plane of aromatic C-ring.

On the basis of the stated observations, the following conclusion is driven.⁹⁾ Namely, the steroid type A/B ring conformation of the 10-methyl series preferred to the nonsteroid type conformation having the unfavorable 1,3-diaxial nonbonding interaction between C_{10} - and C_4 -methyl groups. Conversely, nonsteroid type conformation is preferred in the 20-nor compounds with an angular hydrogen in place of the bulky methyl group at C_{10} . Thus, in the course of lactonization, nonsteroid type conformation of X must change to steroid type, and such reorientation accounts for insufficient yield for lactonization of 20-nor series.

Subsequently, account was taken to make the conformational examination of ring B of 20-nor- and 10-methyl hydroxy esters (IX and XIX). Large vicinal coupling constants between C_7 - β -H and C_6 -H in both (IX) (triplet: J_{obs} , 7.5, 9.0 cps) and XIX (triplet: J_{obs} , 6.8, 7.5 cps) show the orientation of C_7 - β -H in both compounds is *quasi axial*. The preferred conformation of 20-nor and 10-methyl derivatives was confirmed as above to be nonsteroid and steroid type, respectively, and IX and XIX have the same C_7 - α -hydroxy group, so that, B-ring of IX should be half chair and that of XIX should be half boat. Such conformation

TABLE II. Coupling Constants of C_7 - β -H (cps)

Hydroxy esters			Lactones		
	τ	J_{obs}		τ	J_{obs}
XIX	5.34	6.8 triplet	XX	4.82	9.0 (half band width) broad singlet
IX	5.24	7.5 triplet 9.0	XII	4.75	5.3 (half band width) broad singlet

of XIX satisfy the need of diminishing the unfavorable interactions between C_7 -hydroxy and C_4 -carbomethoxy group, and also between C_6 -protons and two methyl groups. This interpretation of the analysis of C_7 - β -H in IX and XIX is further confirmed with another fact that PMR pattern of C_7 - β -H in both the δ -lactones (XII, broad singlet, half band width=5.3

9) On the conformation of tricyclic 2-nor diterpene resin acid analogs, Dr. U.R. Ghatak came to the similar conclusion as reported by us.^{1d)}

cps: XIX, broad singlet, half band width=9.0 cps) being fixed by lactone ring to have chair B ring, shows the equatorial character.

Conclusively, in the case of A/B-*cis* ring C aromatic tricyclic diterpenes, their preferred conformation is dependent on whether angular methyl group is present or not. These observations provide an interesting example of the preferred conformation of A/B-*cis* fused ring system being susceptible to the stereochemical character of nonbonding interactions between substituents.

Experimental¹⁰⁾

Methyl 20-Nor-7-oxo-5-iso-deisopropyldehydroabietate (V) and Methyl 20-Nor-7-oxo-*enantio*-deoxypodocarpate (VI)—i) From 7-Hydroxy Lactone (I): As reported in our previous paper,⁶⁾ alkaline decarboxylation of 7-hydroxy lactone (I) gave crystalline diacid (II) and oily acidic fraction consisting of two stereoisomers of 20-nor-methyl acid III and IV. The oily acidic fraction (131 mg) was methylated with diazomethane to give an oily substance, which was shown to be a mixture consisting of two components in equal amounts by gas-liquid chromatography [t_R =28.7 for VI, 31.8 for V, 1.5% XE-60 on Anakrom (80—100 mesh), 4 mm×1.75 mm, 160°]. The methylated oil was chromatographed for three times on neutral alumina using pet. ether as a solvent to give two fractions. a) The first fraction (50 mg) afforded on crystallization from MeOH-H₂O colorless needles of VI, mp 77—79°. *Anal.* Calcd. for C₁₇H₂₀O₃: C, 74.97; H, 7.40. Found: C, 75.33; H, 7.30. IR $\nu_{\max}^{KBr}$ cm⁻¹: 1720, 1680, 1600. PMR τ : 8.73 (3H, singlet, CH₃). b) The second fraction (50 mg) afforded on distillation at 199—202° (5 mmHg) colorless oil, which crystallized on standing at room temperature. Recrystallization from MeOH-H₂O yielded colorless prisms of V, mp 75—77°. *Anal.* Calcd. for C₁₇H₂₀O₃: C, 74.97; H, 7.40. Found: C, 74.82; H, 6.87. IR $\nu_{\max}^{CCl_4}$ cm⁻¹: 1735, 1685, 1600. PMR τ : 8.58 (3H, singlet, CH₃).

ii) From 7-Oxo Diacid (II): A solution of II (53 mg) and KOH (60 mg) in diethyleneglycol (4 ml)-H₂O (5 drops) was refluxed for 25 min. After cooling the reaction mixture was diluted with water, acidified with hydrochloric acid and extracted with ether. The ethereal solution was washed with water, dried and the solvent was removed. Treatment of the residue with diazomethane gave an oil (41 mg), whose gas-liquid chromatogram using the same condition as in (i), showed that the oil contained only V and VI.

Methyl 20-Nor-*enantio*deoxypodocarpate (VII)—To the acetic acid solution of VI (40 mg) containing sulfuric acid (3 drops), 10% Pd-C (70 mg) was added, and the mixture was shaken under an atmosphere of hydrogen until the absorption of hydrogen was ceased. Then, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with water, extracted with ether and then ethereal solution was washed with water, dried and the solvent was removed. The obtained crude crystals (32 mg) was recrystallized from MeOH-H₂O to yield prisms (VII), mp 43—45°. *Anal.* Calcd. for C₁₇H₂₂O₂: C, 79.03; H, 8.58. Found: C, 79.30; H, 8.93. IR $\nu_{\max}^{KBr}$ cm⁻¹: 1715. PMR τ : 8.73 (3H, singlet, CH₃).

20-Nor-*enantio*deoxypodocarpol (VIII)—To a solution of VII (42 mg) in ether (10 ml), LiAlH₄ (50 mg) was added and the solution was stood for 11 hr at room temperature. The reaction mixture was treated in usual way to give crude crystals (40 mg), which was crystallized from MeOH-H₂O to give colorless needles of VIII, mp 81—83°. *Anal.* Calcd. for C₁₆H₂₂O: C, 83.43; H, 9.63. Found: C, 83.75; H, 9.58. IR $\nu_{\max}^{KBr}$ cm⁻¹: 3300. PMR τ : 8.96 (3H, singlet, CH₃).

Methyl 20-Nor-7 α -hydroxy-5-iso-deisopropyldehydroabietate (IX)—To a solution of V (93 mg) in MeOH (4 ml) was added NaBH₃ (100 mg). The mixture was stirred at room temperature for 3 hr to give crude solid (78 mg) on usual treatment. The solid was chromatographed on neutral alumina to separate crystals (78 mg) using pet. ether-ether (10:1) as a solvent. The obtained crystals on recrystallization from MeOH-H₂O yielded needles of IX, mp 104—106°. *Anal.* Calcd. for C₁₇H₂₂O₃: C, 74.42; H, 8.08. Found: C, 74.47; H, 7.88. IR $\nu_{\max}^{CCl_4}$ cm⁻¹: 3590 (free OH), 1738 (free C=O). PMR τ : 8.63 (3H, singlet, CH₃), 6.27 (3H, singlet, COOCH₃).

20-Nor-7 α -hydroxy-5-iso-deisopropyldehydroabietic Acid (X)—A solution of IX (20 mg) and KOH (100 mg) in diethyleneglycol (5 ml) containing H₂O (2 drops) was refluxed for 2 hr. The reaction mixture was treated in the usual way to give acidic oil (X) (18 mg), which was treated with diazomethane to give crystals, whose physical constants [mixed mp, gas-liquid chromatography, t_R =4.8, 1.5% SE-30 on Shimalite

10) Proton magnetic resonance spectra were taken in deuteriochloroform solution containing tetramethylsilane as an internal standard on Japan Electron Optics Lab. C-60 NMR Spectrometer operating at 60 Mc. Infrared spectra were obtained on Hitachi Perkin Elmer spectrophotometers, Model 521. Gas-liquid chromatogram were recorded on Shimadzu gaschromatography, Model 1-C. All melting and boiling points were uncorrected.

(80—100 mesh), 4 mm $\times$ 1.75 m, 155°, and IR (CCl₄ solution)] were identical to those of the original ester (IX).

Lactonization of 7-Hydroxy Acid (X)—A solution of X (53 mg) and hydrochloric acid (1 ml) in MeOH (5 ml) was kept at room temperature for 2 days. Then the mixture was concentrated under reduced pressure without heating. To the residue was added H₂O, and the mixture was extracted with ether. Etheral solution was washed with 10% KOH solution and with H₂O, dried and concentrated to dryness. The obtained crude solid (20 mg) was chromatographed on neutral alumina using pet. ether as a solvent to yield crystals (13 mg), which gave colorless needles (XII), mp 119—121°, by recrystallization from MeOH-H₂O. Mass-Spect. Calcd. for C₁₆H₁₈O₂: 242.13068. Found: 242.1323. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 1740. PMR τ : 8.59 (3H, singlet, CH₃). Alkaline layer was acidified with hydrochloric acid under cooling and the mixture was extracted with ether. The etheral solution was washed with H₂O, dried and the solvent was removed to give oil (31 mg). The obtained oil was treated with diazomethane to give an oily substance, whose IR spectrum (CCl₄ solution) was identical to that of standard (XIII).

Methyl 20-Nor-4⁶-5-iso-deisopropyldehydroabietate (XIII)—i) From 7-Hydroxy Ester (IX): A solution of IX (20 mg) in MeOH (10 ml) containing 20% hydrochloric acid (5 drops) was refluxed for 2 hr. The mixture was concentrated, diluted with H₂O and then extracted with ether. The etheral solution was washed with H₂O, dried and the solvent was removed. Obtained oil (20 mg) was chromatographed on neutral alumina using pet. ether as a solvent to elute (XIII) (17 mg), bp 175—178° (bath temperature, 2 mmHg). Anal. Calcd. for C₁₇H₂₀O₃: C, 79.65; H, 7.86. Found: C, 79.68; H, 7.80. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 1735. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (ϵ): 263 (6900). PMR τ : 8.64 (3H, singlet, CH₃), 6.32 (3H, singlet, COOCH₃).

ii) From 7-Hydroxy Acid (X): A solution of X (15 mg) in MeOH (10 ml) containing 15% hydrochloric acid (3 ml) was refluxed for 1 hr. The reaction mixture was treated in usual way to give an acidic oil, which was methylated with diazomethane. The obtained oil (13 mg) was identified with standard (XIII) by IR (CCl₄ solution).

Methyl 20-Nor-5-iso-deisopropyldehydroabietate (XIV)—i) From Unsaturated Ester (XIII): A mixture of XIII (15 mg), 10% Pd-C (30 mg) and acetic acid (3 ml) was shaken under hydrogen at atmospheric pressure. After uptake of hydrogen ceased, the catalyst was filtered off and the solvent was removed under reduced pressure to give oil (13 mg). The crude oily substance was chromatographed on neutral alumina using pet. ether as a solvent to yield an oil (XIV), bp 168—171° (bath temperature, 1 mmHg). Anal. Calcd. for C₁₇H₂₂O₂: C, 79.03; H, 8.58. Found: C, 79.01; H, 8.66. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 1735. PMR τ : 8.64 (3H, singlet, CH₃), 6.32 (3H, singlet, COOCH₃).

ii) From 7-Oxo Ester (V): A mixture of V (13 mg), 10% Pd (20 mg) and acetic acid (5 ml), containing sulfuric acid (3 drops) was shaken under hydrogen at atmospheric pressure. After the uptake of hydrogen ceased, 10% aq. NaOH (2 ml) was added to the mixture and the solvent was removed under reduced pressure. Water was added to the residue, and this was extracted with ether. The etheral solution was washed with H₂O, dried and concentrated to dryness to give oil (11 mg), which was identified with standard XIV by IR (CCl₄ solution).

20-Nor-7 α -hydroxy-5-iso-deisopropyldehydroabietol (XV)—i) From 7-Hydroxy Ester (IX): A solution of IX (25 mg) and LiAlH₄ (450 mg) in ether (10 ml) was refluxed for 8 hr with stirring. The mixture was treated in the usual way to give crystals (21 mg), whose recrystallization from ether yielded colorless prisms (XV), mp 205—207°. Anal. Calcd. for C₁₆H₂₂O₂: C, 78.01; H, 9.00. Found: C, 78.16; H, 8.81. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3420, 3360. t_R = 12.6 [2.0% OV-17 on Shimalite (80—100 mesh), 4 mm $\times$ 1.8 m, 180°], 11.8 [2.0% OV-1 on Gaschrom P (80—100 mesh), 4 mm $\times$ 1.8 m, 190°].

ii) From γ -Lactone (XII): The diol (XV) was obtained from γ -lactone (XII) in the same way as in (i). The product was identified with standard XV by IR and gas-liquid chromatography.

Methyl 7-Oxo-5-iso-dehydroabietate (XVIII)—A solution of (XVII) (33 mg)⁸⁾ and chromic anhydride (15 mg) in acetic anhydride (1.5 ml) was kept at room temperature for 24 hr, and to the reaction mixture was added MeOH (1 ml). The solution was concentrated under reduced pressure to dryness, and to the residue H₂O was added. The aq. solution was extracted with ether, and etheral solution was washed with H₂O, dried and the solvent was removed. The obtained crude solid (28 mg) was chromatographed on neutral alumina using pet. ether-ether (10:1) as a solvent to give crystals (21 mg), whose recrystallization from MeOH-H₂O gave colorless needles (XVIII), mp 100—102°. Anal. Calcd. for C₂₁H₂₈O₃: C, 76.79; H, 8.59. Found: C, 76.90; H, 8.27. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1730, 1675, 1610. PMR τ : 8.73 (3H, singlet, CH₃), 8.71 (3H, singlet, CH₃), 7.06 (3H, singlet, COOCH₃).

Methyl 7 α -Hydroxy-5-iso-dehydroabietate (XIX) and γ -Lactone (XX)—To a solution of XVIII (16 mg) in MeOH (4 ml) was added NaBH₄ (20 mg), and the reaction mixture was stirred at room temperature for 30 min. On usual workup oil (14 mg) was obtained. This oil has following physical constants. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 3590 (free OH), 3520 (hydrogen bonded OH), 1735 (free C=O), 1705 (hydrogen bonded C=O). The wave numbers and relative intensities of these absorptions were not affected by dilution (0.0333 $\rightarrow$ 0.0026 mole/liter) showing the existence of intramolecular hydrogen bonding between 7 α -hydroxy and carbomethoxy carbonyl group. PMR τ : 8.68 (3H, singlet, CH₃), 8.74 (3H, singlet, CH₃), 6.82 (3H, singlet, COOCH₃). This hydroxy ester (XIX) was readily converted to γ -lactone (XX) by chromatography on neutral alumina. Thus, XIX obtained above was chromatographed on neutral alumina using pet. ether-ether (20:1) as a

solvent to give crystals (11 mg), whose IR spectrum (CCl_4 solution) was different from that of XIX. This crystalline substance on recrystallization from $\text{MeOH-H}_2\text{O}$ yielded colorless needles (XX), mp 166—167°. *Anal.* Calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_2$: C, 80.49; H, 8.78. Found: C, 80.46; H, 8.80. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1715. PMR τ : (3H, singlet, CH_3), 8.72 (3H, singlet, CH_3).

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