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Studies on the Constituents of Japanese and Chinese Crude Drugs. XII.[*2] Panaxadiol, A Sapogenin of Ginseng Roots. (2).[*2]

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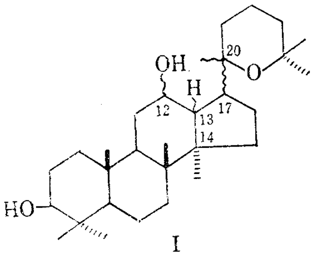
In the preceding paper,[*2] the structure of panaxadiol was elucidated by the formula (I) whose configurations at positions 12, 13, 17 and 20 were not confirmed.



I

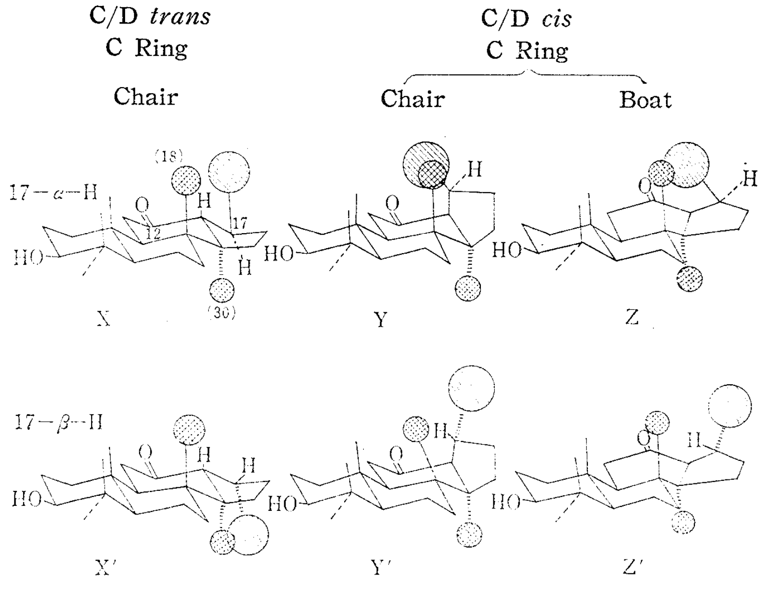
This paper concerns with the determination of configuration and conformation of panaxadiol and some of its derivatives.

On heating with ethanolic alkali, panaxanolone acetate was deacetylated, and the product regenerated the starting acetate on reacetylation. It has therefore been concluded that the initial stereochemical situation of panaxanolone, as well as that of panaxadiol at the C/D ring junction, and trimethyl-tetrahydropyrane ring attached to $C_{(17)}$, is less unstable, since it has been shown that there occurs no inversion at $C_{(13)}$ of panaxanolone by the action of alkali.

Of the possible partial structures (X, Y, Z, X′, Y′ and Z′) of panaxanolone the Dreiding Model showed obvious strong stereochemical hindrance between the trimethyl-tetrahydropyrane ring attached to $C_{(17)}$ and 30-CH_3 in X′, 18-CH_3 in Y, and $C=O_{(12)}$ in Z.[1,2]

If panaxanolone possesses one of those structures, it must be converted into the less hindered $C_{(13)}$-epimer by the C/D ring inversion which would be caused by the action of alkali.

Fig. 1.



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[*2] Part XI. This Bulletin, **11**, 759 (1963).

1) Cf. P. Crabbé, G. Ourisson, T. Takahashi : Tetrahedron, **3**, 279 (1958).

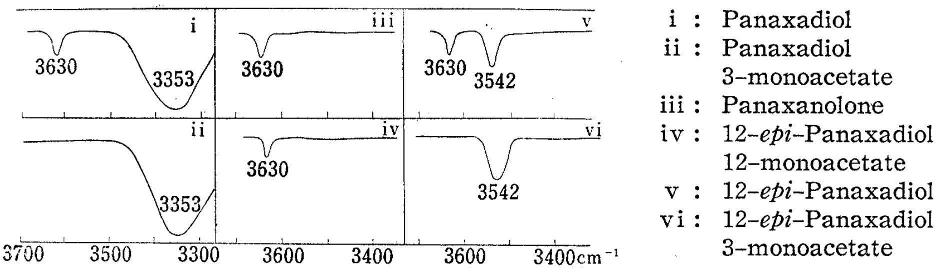
2) Cf. J. F. Biellmann, P. Crabbé, G. Ourisson : *Ibid.*, **3**, 303 (1958).

Consequently, panaxanolone must have one of the structures X, Y′ or Z′. The formula (X) possesses a C/D *trans*-fused system with 17-α-H, and the formulas (Y′) and (Z′) have a C/D *cis*-fused system and 17-β-H with either chair or boat-form C ring.

As shown in Fig. 2, panaxadiol shows OH infrared absorption bands (in CCl_4 solution) at 3630 and 3353 cm^{-1}, the latter of which is concentration independent. Panaxadiol monoacetate gives only the latter band, while panaxanolone shows a single band at 3630 cm^{-1}. This indicated that the band at 3353 cm^{-1} given by panaxadiol accounted for the hindered $OH_{(12)}$. On the other hand, on reduction with lithium aluminum hydride, panaxanolone acetate was converted into an epimer of panaxadiol, $C_{30}H_{52}O_3$, m.p. 232.5°, $[\alpha]_D$ +18°, which was named 12-*epi*-panaxadiol.

12-*epi*-Panaxadiol gave the infrared absorption at 3630 and 3542 cm^{-1}. The latter concentration independent band was also given by the 3-monoacetate, m.p. 222°, $[\alpha]_D$ +36°, which was prepared by acetylation of 12-*epi*-panaxadiol with acetic anhydride and pyridine under cooling, while the former band of the free hydroxyl was shown by the 12-monoacetate, m.p. 252°, $[\alpha]_D$ +66°, of 12-*epi*-panaxadiol, which was afforded by the partial deacetylation of diacetate with alkali. The diacetate of 12-*epi*-panaxadiol, $C_{34}H_{56}O_5$, m.p. 183°, $[\alpha]_D$ +67°, was prepared by the acetylation in heating.

Fig. 2. OH Stretching Absorption Bands



The IR spectra were measured using Hilger H 800 double beam spectrometer with LiF prism and 1.0～5.0 mm. cells at concentrations of 5/1000*M* or below in CCl_4.

The infrared spectra showed that 12-OH in panaxadiol as well as in 12-*epi*-panaxadiol forms a hydrogen bond with the oxygen of trimethyl-tetrahydropyrane ring[3].

As shown in Fig. 3, in the C/D *trans*-fused system 12-β-OH can form a hydrogen bond with the hydropyrane ring oxygen, whereas *epi*-12α-OH exists far distant from the hydropyrane ring showing that the hydrogen bonding would not be formed. Thus panaxadiol and 12-*epi*-panaxadiol cannot be represented by the C/D *trans*-fused system.

As shown in Fig. 1, if panaxadiol possesses a C/D *cis*-fused system, the hydropyrane ring attached at $C_{(17)}$ would give α-orientation, and hence the formulas (c, d, e, and f) would be considered as representing panaxadiol and its 12-epimer.

Of these structures, the formula (d) (12-α-OH and chair form C ring) would be ruled out, since it could not account for the strong hydrogen bonding between 12-OH and hydropyrane ring oxygen.

The formula (e) having boat C ring which shows a strong stereochemical hindrance between 12-β-OH and 18-CH_3 would not actually be present, and converted readily into the chair C-ring form (c).

The Dreiding Model showed in the *cis* C/D 17β-H system an atomic distance between the oxygen of trimethyl-tetrahydropyrane ring and 12-OH, irrespective to its

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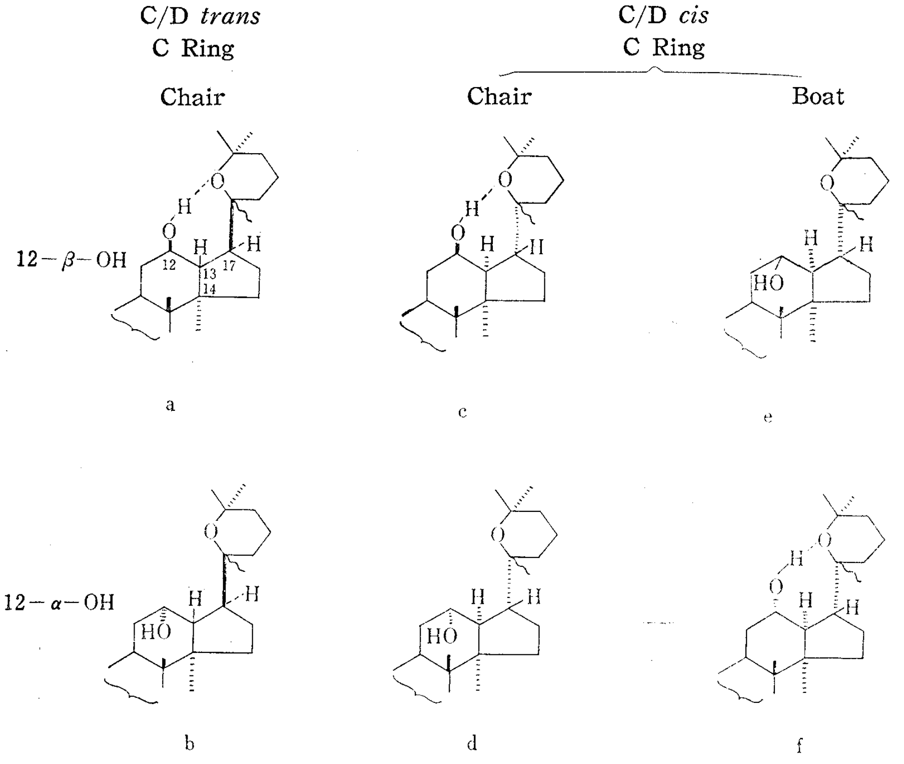
[3] Cf. L.P. Kuhn : J. Am. Chem. Soc., **74**, 2492 (1952); A.R.H. Cole, *et al.* : J. Chem. Soc., **1959**, 1224 and references there cited; D.H.R. Barton, G.W. Kirby : *Ibid.*, **1962**, 806; Proc. Chem. Soc., **1960**, 392; G. Buchi, *et al.* : J. Chem. Soc., **1961**, 2843.

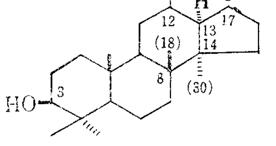
Fig. 3.



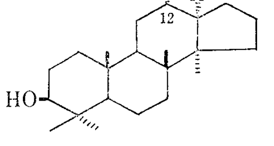
α- or β-orientation, close enough to form a hydrogen bond when the α-OH exists in the boat C-ring (formula f) and the β-OH in the chair C-ring (formula c). Moreover, the atomic distance is much closer in the case of 12-β-OH (formula c) than 12-α-OH (formula f), then the stronger hydrogen bonding and steric hindrance would exist in the former case.

The carbonyl at the 12-position of panaxanolone acetate (IV: R=Ac) would result a repulsion with the oxygen of trimethyltetrahydropyrane ring. Thus the attack of lithium aluminum hydride would happen from the β-side to form α-12-OH in 12-*epi*-panaxadiol.

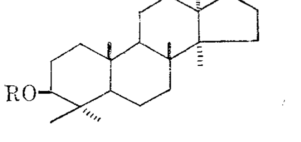
Accordingly, panaxadiol which showed a strong resistance for acetylation of 12-OH must be represented by the formula (II) (*cis* C (chair)/D 12β-OH, 17β-H system) and the 12-epimer by the formula (III) (*cis* C(boat)/D 12α-OH, 17β-H system). It would be noted that panaxadiol is the first example of naturally occurring *cis* C/D 13α-H tetracyclic triterpene. The study on the orientation at $C_{(20)}$ is under progress.



II : panaxadiol



III : 12-*epi*-panaxadiol



IV : panaxanolone (R=H)

Experimental

Treatment of Panaxanolone Acetate (IV : R=Ac) with Caustic Alkali——1) A solution of panaxanolone acetate (300 mg.) and NaOH (2.4 g.) in EtOH (30 cc.) was refluxed on a water bath for 1 hr. The reaction mixture was diluted with H_2O and the precipitate formed was taken up in Et_2O. The ethereal solution was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOAc to give panaxanolone (IV) as colorless needles, m.p. 215~217°. *Anal.* Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found : C, 78.57; H, 11.05. IR : $\nu_{max}^{CS_2}$ 1716 cm^{-1}.

2) A mixture of panaxanolone acetate (IV : R=Ac) and 8% ethanolic NaOH solution was heated under reflux for 2 hr. The reaction mixture was treated as mentioned above, and the product was subjected to acetylation with Ac_2O in pyridine affording colorless needles (from MeOH), m.p. 183~184°, $[\alpha]_D^{17.7}$ +52°(c=0.91, $CHCl_3$). The identity of this compound and panaxanolone acetate (IV : R=Ac) was confirmed by a mixed fusion, and the comparison of IR spectrum with an authentic sample.

12-epi-Panaxadiol (III)——To a suspension of $LiAlH_4$ (4 g.) in Et_2O (150 cc.) was added an ethereal solution of panaxanolone acetate (IV : R=Ac) (2.1 g.), and the mixture was refluxed for 30 min. The excess reagent was decomposed by addition of H_2O and dil. H_2SO_4 under ice cooling. After treatment in the usual way, the product[*3] was recrystallized from EtOAc to give 12-*epi*-panaxadiol (III) as colorless needles, m.p. 230~232.5°, $[\alpha]_D^{20}$ +18°(c=1.00, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38. Found : C, 78.30; H, 11.33.

12-*epi*-Panaxadiol Diacetate——A solution of 12-epi-panaxadiol (III) (1.7 g.) in a mixture of pyridine (60 cc.) and Ac_2O (28 cc.) was allowed to stand at 100~110° for 4.5 hr. After treating the reaction mixture by the usual way, the product was recrystallized from MeOH yielding the diacetate as colorless needles, m.p. 181~183°, $[\alpha]_D^{20}$ +67°(c=1.00, $CHCl_3$). *Anal.* Calcd. for $C_{34}H_{56}O_5$: C, 74.95; H, 10.36. Found : C, 74.90; H, 10.26. IR : $\nu_{max}^{CS_2}$ 1740 cm^{-1}(acetyl). OH band was not observed.

Partial Hydrolysis of 12-*epi*-Panaxadiol Diacetate (Formation of 12-*epi*-Panaxadiol 12-Monoacetate)——A solution of 12-*epi*-panaxadiol diacetate (700 mg.) in 5% methanolic KOH solution (60 cc.) was refluxed for 1.25 hr. The solution was diluted with H_2O and the resulting precipitate was taken up in Et_2O. The ethereal solution was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to dryness. Recrystallization of the residue from EtOAc gave 12-*epi*-panaxadiol 12-monoacetate in colorless prisms, m.p. 250.5~252°, $[\alpha]_D^{20}$ +66°(c=0.76, $CHCl_3$). *Anal.* Calcd. for $C_{32}H_{54}O_4$: C, 76.44; H, 10.83. Found : C, 76.61; H, 10.72. IR : $\nu_{max}^{CHCl_3}$ 1729 cm^{-1}(acetyl).

To a suspension of $LiAlH_4$ (0.68 g.) in Et_2O (20 cc.) was added a solution of 12-*epi*-panaxadiol 12-monoacetate (300 mg.) in Et_2O (23 cc.) and the reaction mixture was refluxed for 1 hr. The product, colorless needles, m.p. 230.5~232°, recrystallized from EtOAc was proved to be identical with 12-*epi*-panaxadiol (III) by a mixed fusion.

Partial Acetylation of 12-*epi*-Panaxadiol (III) (Formation of 12-*epi*-Panaxadiol 3-Monoacetate)——A solution of 12-*epi*-panaxadiol (III) (100 mg.) in a mixture of pyridine (3.5 cc.) and Ac_2O (1.8 cc.) was kept at 2° for 44 hr. The product was recrystallized from MeOH giving colorless plates, 12-*epi*-panaxadiol 3-monoacetate, m.p. 220~222°, $[\alpha]_D^{20}$ +36°(c=1.05, $CHCl_3$). *Anal.* Calcd. for $C_{32}H_{54}O_4$: C, 76.44; H, 10.83. Found : C, 76.89; H, 10.88.IR : $\nu_{max}^{CS_2}$ 1740 cm^{-1}(acetyl).

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Summary

The treatment of panaxanolone acetate with caustic alkali showed that it possesses a less-hindered stereochemical structure. The Dreiding Model suggested three possible less-hindered structures for panaxanolone which included *trans* C/D 17α-H system (X), *cis* C/D 17β-H system both chair (Y′) and boat (Z′) C-ring (Fig. 1). The infrared spectral analysis showed that the hydroxyl at the 12-position of panaxadiol (12β-OH) as well as that of 12-*epi*-panaxadiol (12α-OH) are hydrogen-bonded with the oxygen of trimethyltetrahydropyrane ring attached at $C_{(17)}$. Moreover, the atomic distance between 12-OH and tetrahydropyrane ring oxygen is shown by the Dreiding Model as being much closer in the case of 12β-OH than 12α-OH, which is proved by the resistance of panaxadiol against acetylation at 12-OH.

This can only be explained by the stereochemical system of *cis* C (chair)/D, 12β-OH, 17β-H for panaxadiol (II), and *cis* C (boat)/D, 12α-OH, 17β-H for 12-*epi*-panaxadiol (III).

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[*3] The absence of panaxadiol (II) in the crude product of this reaction was proved by the thin layer chromatography on silica gel using $CHCl_3$-Et_2O mixture (2:1) as moving phase (T. Sakaguchi).