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THE STEREOCHEMISTRY OF PANAXADIOL

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PREVIOUSLY we proposed the structure of panaxadiol[1], a sapogenin of Ginseng roots (Panax ginseng C.A. Mey.) as being a tetracyclic triterpene of dammarane series having a trimethyltetrahydropyrane ring at $C_{(17)}$ instead of the ordinary C_8-side chain.

The nuclear magnetic resonance spectrum of panaxadiol (in chloroform) shows the presence of eight methyl groups which is consistent with the structure proposed: singlets at τ : 8.71, 8.76, 8.80 corresponding to $H_3C-\overset{|}{\underset{|}{C}}-O-\overset{|}{C}\begin{matrix}CH_3\\CH_3\end{matrix}$ [2]; singlet at τ : 9.20 and overlapping singlets of double magnitude at τ : 9.00 and 9.10 corresponding to the other five methyl groups.

On treatment with boiling ethanolic alkali, panaxanolone was recovered from its acetate showing that no inversion of the C/D ring junction occurred by the action of alkali. This would suggest the less unstable stereochemical situation of panaxanolone at the C/D

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[1] Shibata, Fujita, Itokawa, Tanaka and Ishii, Tetrahedron Letters No. 10, 419 (1962).

[2] Carman, Tetrahedron 18, 285 (1962); Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, London, 1959, p.54.

ring junction with respect to the trimethyltetrahydropyrane ring attached to $C_{(17)}$.

Of the possible stereochemical structures of panaxanolone (trans C/D 17 α-H, and 17 β-H; cis C/D 17 α-H and 17 β-H) the Dreiding Model showed that the trans C/D 17 β-H and the cis C/D 17 α-H systems are improbable, since a strong steric hindrance is expected between the trimethyltetrahydropyrane ring attached to $C_{(17)}$ and 30-CH_3 in the former, and 18-CH_3 in the latter system, respectively[3,4], where a steric inversion at $C_{(13)}$ into the less-hindered structure by the action of alkali would occur.

The reduction of panaxanolone acetate with $LiAlH_4$ yielded 12-epipanaxadiol, m.p. 232.5°, $[\alpha]_D$ + 18° (c:1.00, $CHCl_3$) (Found: C, 78.3; H, 11.3. $C_{30}H_{52}O_3$ requires C, 78.2; H, 11.4%), which afforded stepwise 3-monoacetate, m.p.222°, $[\alpha]_D$ + 36° (c: 1.05, $CHCl_3$) (Found: C, 76.9; H, 10.9. $C_{32}H_{54}O_4$ requires C, 76.4; H, 10.8%) and 3.12-diacetate, m.p. 183°, $[\alpha]_D$ + 67° (c:1.00, $CHCl_3$) (Found: C, 74.9; H, 10.3. $C_{34}H_{56}O_5$ requires C, 75.0; H, 10.4%), while panaxadiol yielded only 3-monoacetate. On partial deacetylation of 3.12-diacetate of 12-epipanaxadiol, 12-monoacetate, m.p. 252°, $[\alpha]_D$ + 66° (c:0.76, $CHCl_3$) (Found: C, 76.6; H, 10.7. $C_{32}H_{54}O_4$ requires C, 76.4; H, 10.8%) was formed. This would suggest that 12-OH of panaxadiol is more strongly hindered than that of its 12-epimer. Panaxadiol and 12-epi-panaxadiol gave two separated OH bands in the infrared spectra. The OH band of lower frequencies, which is "concentration independent",

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[3] Cf. Crabbé, Ourisson and Takahashi, Tetrahedron 3, 279 (1958).

[4] Cf. Biellmann, Crabbé and Ourisson, Tetrahedron 3, 303 (1958).

disappears in 12-monoacetate of 12-epipanaxadiol (see Table 1). This would indicate that the 12-OH, irrespective of the orientation α or β, must form an intramolecular hydrogen bond[5] more or less strongly with the oxygen of trimethyltetrahydropyrane ring.

TABLE 1

ν OH Absorption (cm^{-1}) in CCl_4 (Dilution < M/500) using LiF prism

Panaxadiol	3630	3353
3-Monoacetate	----	3353
12-Epipanaxadiol	3630	3542
3-Monoacetate	----	3542
12-Monoacetate	3630	----
Panaxanolone	3630	----

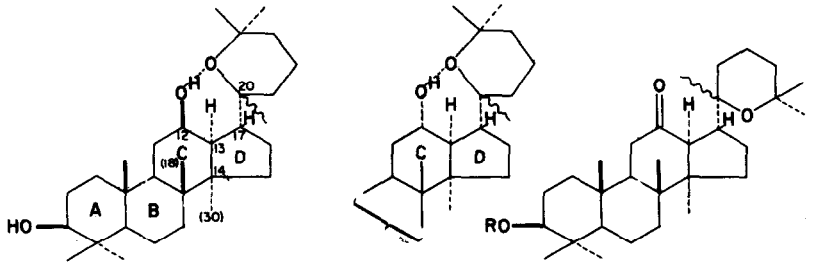
Of the possible stereochemical structures for panaxadiol and 12-epipanaxadiol which could be derived from the remaining probable formulae for panaxanolone (trans C/D 17 α-H; cis C/D 17 β-H), trans C/D 17 α-H system appeared unlikely, since the atomic distance between 12-OH and the oxygen of the trimethyltetrahydropyrane ring in this system showed that the hydrogen bonding can only form when the hydroxyl is in the β-orientation and not in the α-orientation.

The Dreiding Model showed in the cis C/D 17 β-H system an atomic distance between the oxygen of trimethyltetrahydropyrane ring and 12-OH, irrespective to its α or β-orientation, close enough to form a hydrogen bond when the α-OH exists in the boat C-ring and the β-

[5] Cf. Kuhn, J. Amer. Chem. Soc. 74, 2492 (1952); Cole et al., J., 1224 (1959) and references there cited; Barton and Kirby, J., 806 (1962); Proc. Chem. Soc. 392 (1960); Büchi et al., J., 2843 (1961).

OH in the chair C-ring. Moreover, the atomic distance is much closer in the case of 12-β OH than 12 α-OH, then the stronger hydrogen bonding and steric hindrance would exist in the former case.

The carbonyl at the 12-position of panaxanolone acetate (III R:Ac) would result in a repulsion with the oxygen of trimethyltetrahydropyrane ring. Thus the attack of $LiAlH_4$ would happen from the β-side to form α-12 OH in 12-epipanaxadiol.



(I) (II) (III)

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

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