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THE STEREOCHEMISTRY OF PROTOPANAXADIOL, A GENUINE SAPOGENIN OF GINSENG

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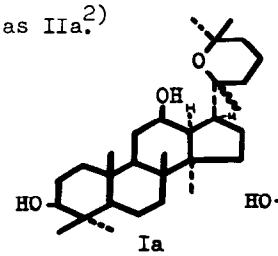
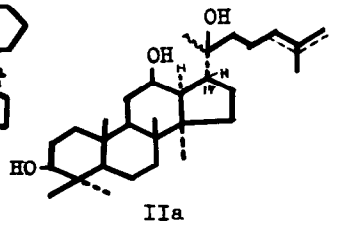
PREVIOUSLY we proposed[1] a structural formula (Ia: C/D cis, 17β-H) for panaxadiol, which was prepared by the acid hydrolysis of one of the neutral saponins of Ginseng, which has now been designated ginsenoside R-b. Thereafter, panaxadiol has been found to be a secondary product formed during the process of the hydrolysis of the saponin, and the genuine sapogenin named protopanaxadiol has been reported to be formulated as IIa.[2]



Ia



IIa

The present study deals with a further stereochemical investigation of the Ginseng sapogenin, which has led us to give a conclusion that the former proposal should be amended to formulate panaxadiol and protopanaxadiol as Ib and IIb (C/D trans 17α-H), respectively.

The stereochemical correlation of dihydroprotopanaxadiol (III)[2] with betulafolianetriol (IV)[3] has now been elucidated.

The 3-O-acetyl 12-keto derivative of III (V) has been prepared by the following steps: The chromic acid oxidation of III afforded a diketone (VI), $C_{30}H_{50}O_3$, m.p. 126°, which was reduced with $LiAlH_4$ to give 12-epi-dihydroprotopanaxadiol (VII), $C_{30}H_{54}O_3$, m.p. 214° (12 α-OH (axial)). The selective acetylation of 3β-hydroxyl of VII with acetic anhydride and pyridine at 4°C yielded 3-monoacetate (VIII), $C_{32}H_{56}O_4$, m.p. 218°, which on oxidation with chromic acid gave V, $C_{32}H_{54}O_4$, m.p. 161°. Since III was regenerated from V by reduction with sodium and isopropyl alcohol, it is evident that no inversion of the skeletal configuration is involved in the above reactions. On the modified Wolff-Kishner reduction (via the hydrazone of V[5]) followed by acetylation, V yielded a compound, $C_{32}H_{56}O_3$, m.p. 146°, $[\alpha]_D$ + 37.6° ($CHCl_3$), which was proved to be identical with dammaranediol-I 3-monoacetate (IX)[6] by a mixed fusion and a comparison of the infrared spectra and the thin layer and gas chromatograms. The optical rotatory dispersion curve of V which gave a negative Cotton effect was almost superimposable with that of the 3β-acetoxy-12-keto derivetive (X), $C_{32}H_{54}O_4$, m.p. 169°, prepared from betulafolianetriol (IV)[4]. As the stereochemical correlation of betulafolianetriol (IV) with dammaranediol-II[6] (XI) has already been established by Fischer and Seiler[3], it can be concluded that dihydroprotopanaxadiol (III) differs from betulafolianetriol (IV) only in the configuration at C-3 and C-20.

Ourisson et al.[7] have already proposed a C/D trans 17α-H structure for the dammarane nucleus. The C/D trans system was proved mainly by the optical rotatory dispersion study[8] of the

17-keto derivative (XIVa) and its C-13 isomer (XVa) prepared from dipterocarpol (XIII) by the process through XIIa-b.

We prepared the 3-deacetoxy derivative of XIVa (XIVb) by the following steps of reactions: The bisdeoxyhexanor-20-keto derivative (XVI)[3] prepared from betulafolianetriol (IV) was subjected to the Baeyer-Villiger oxidation with trifluoroperacetic acid to yield an acetate (XVII), $C_{24}H_{40}O_2$, m.p.135-137°, which was saponified to give 17-hydroxy compound (XVIII), $C_{22}H_{38}O$, m.p. 124-126°. Oxidation of XVIII with Jones' reagent afforded XIVb, $C_{22}H_{36}O$, m.p. 150-151°, which showed a positive Cotton effect in the optical rotatory dispersion curve. This 17-keto compound (XIVb) was readily equilibrated to give a mixture of XIVb and XVb by the treatment with alkali or acid, or by the process of chromatography on neutral alumina.

On recrystallization of the mixture of the C-13 isomers from ethanol, there was obtained the isomerized compound (XVb), $C_{22}H_{36}O$, m.p. 177-181°, which showed a negative Cotton effect.

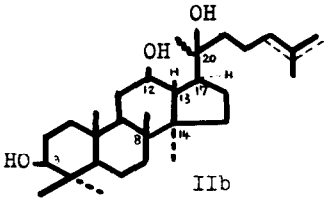
The configuration of the C/D ring fusion of XIVb has also been proved by the N.M.R. spectral shifts of the methyl signals of XIVb and its C-13 isomer (XVb).

Recently , Lehn et al.[9] have reported an extensive N.M.R. study on the methyl group of the various types of triterpenes.

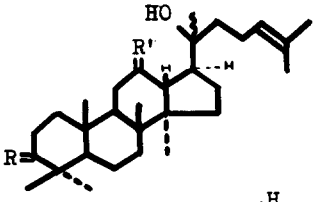
Referring their works, the methyl signals of XIVb have been assigned as follows: τ 8.96 (singlet, 3H): C-8 Me; τ 9.12(singlet, 3H): C-14 Me; τ 9.15 (singlet, 6H) and 9.20 (singlet, 3H): A-ring methyls (in $CDCl_3$). It has been reported[9,10] that the signal of the angular methyl at 3a-position of the cis-hexahydro-1-hydrindanone derivative appears in markedly lower field than that of the trans isomer.

In comparison with the methyl signals of XIVb, the chemical shifts of the methyl signals of the isomerized compound (XVb) (singlets, τ 8.75 (3H), 9.17 (3H), 9.24 (6H), and 9.27 (3H) (in $CDCl_3$)) are in accordance with the formulation of this compound (XVb) as a C/D cis-fused structure. The lowest methyl signal at τ 8.75 can be assigned for the angular methyl at C-14. Three out of four other methyl signals of XVb are observed in the higher field than those of XIVb. This would be explained by the anisotropic effect of 17-ketone to C-8, C-10 and C-4(axial) methyls in XVb. Accordingly, XIVb must have a C/D trans-fused configuration, and it can be concluded that protopanaxadiol should have the C/D trans 17α-H configuration (IIb).

Prior to the isolation of protopanaxadiol, we proposed a C/D cis-fused 17β-H structure (Ia) for panaxadiol on the basis of the presence of an intramolecular hydrogen bonding between 12α OH and oxygen of trimethyltetrahydropyrane ring in 12-epi-panaxadiol (XIX), which was prepared from panaxadiol through panaxanolone acetate (XX).[1, 11] On oxidation with chromic acid, 12-epi-panaxadiol 3-monoacetate (XXI) afforded XX, which on reduction with sodium and isopropyl alcohol gave panaxadiol along with XIX. Therefore, it is apparent that no stereochemical inversion of the nucleus took place during the process of preparation of XIX from panaxadiol. The optical rotatory dispersion curve of XX giving a negative Cotton effect is quite similar to those of V and X. Consequently, panaxadiol also should have the C/D trans-fused 17α-H structure (Ib). The intramolecular hydrogen bonding observed in XIX would be due to an unexpected distortion of the molecule.

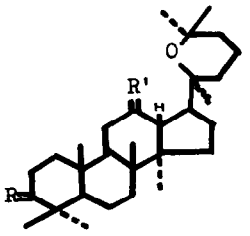


IIb



XIII R= O R'= $\overset{H}{\underset{H}{}}$

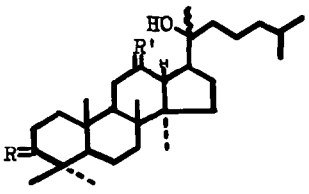
XXII R= $\overset{H}{\underset{OH}{}}$ R'= $\overset{OH}{\underset{H}{}}$



Ib R= $\overset{OH}{\underset{H}{}}$ R'= $\overset{OH}{\underset{H}{}}$

XIX R= $\overset{OH}{\underset{H}{}}$ R'= $\overset{H}{\underset{OH}{}}$

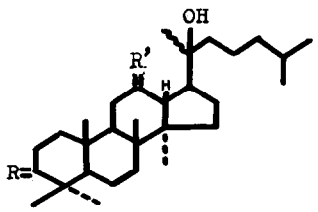
XX R= $\overset{OAc}{\underset{H}{}}$ R'= O



IV R= $\overset{H}{\underset{OH}{}}$ R'= $\overset{OH}{\underset{H}{}}$

X R= $\overset{OAc}{\underset{H}{}}$ R'= O

XI R= $\overset{OH}{\underset{H}{}}$ R'= $\overset{H}{\underset{H}{}}$



III R= $\overset{OH}{\underset{H}{}}$ R'= $\overset{OH}{\underset{H}{}}$

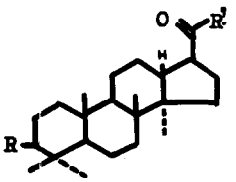
V R= $\overset{OAc}{\underset{H}{}}$ R'= O

VI R= R'= O

VII R= $\overset{OH}{\underset{H}{}}$ R'= $\overset{H}{\underset{OH}{}}$

VIII R= $\overset{OAc}{\underset{H}{}}$ R'= $\overset{H}{\underset{OH}{}}$

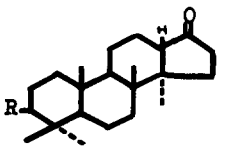
IX R= $\overset{OAc}{\underset{H}{}}$ R'= $\overset{H}{\underset{H}{}}$



XIIa R= OAc R'= CH_3

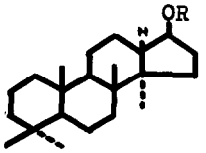
XIIb R= OAc R'=

XVI R= H R'= CH_3



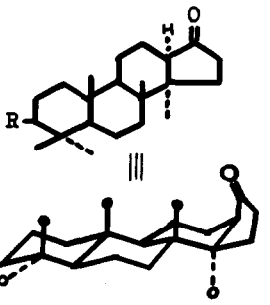
XIVa R= OAc

XIVb R=H



XVII R= Ac

XVIII R= H



XVa R= OAc

XVb R= H

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