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ON GENUINE SAPOGENIN OF GINSENG

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PREVIOUSLY we reported the formation of a sapogenin named panaxadiol, $C_{30}H_{52}O_3$, m.p. 250°, $[\alpha]_D^{18.5}$ + 1.0°, from saponin of Ginseng (the roots of Panax ginseng C.A. Meyer), and elucidated its chemical reactions[1] and stereochemistry[2] to propose the structure (I).

It has now been shown by the present study that panaxadiol (I) is not a genuine sapogenin of Ginseng, but an artifact formed during the process of hydrolysis of saponin.

The neutral saponin isolated from Ginseng roots was treated with 0.7% H_2SO_4 in aq. methanol to give a prosapogenin which would be corresponding to Kotake's α-panaxin[3]. On refluxing the prosapogenin with 7% HCl in aq. ethanol panaxadiol was yielded, whereas on treating with conc. HCl at room temperature, an unstable chlorine containing compound,

1 S. Shibata, M. Fujita, H. Itokawa, O. Tanaka and T. Ishii, Tetrahedron Letters No. 10, 419 (1962); M. Fujita, H. Itokawa and S. Shibata, Yakugaku-Zasshi (J. Pharm. Soc. Japan) 82, 1634, 1638 (1962).

2 S. Shibata, O. Tanaka, M. Nagai and T. Ishii, Tetrahedron Letters in press.

3 M. Kotake, Nippon Kagaku-Kaishi (J. Chem. Soc. Japan) 51, 357 (1930).

$C_{30}H_{53}O_3Cl$, m.p. 219-220° (Found: C, 72.49; H, 10.74; Cl, 7.04. Calc. for $C_{30}H_{53}O_3Cl$, C, 72.50; H, 10.69; Cl. 7.14) which was seemed to be identical with the hydrolysate of α-panaxin reported earlier by Kotake[3].

On heating this compound with diethylaniline in xylene, a new compound, protopanaxadiol, $C_{30}H_{52}O_3$, m.p. 236-238°, $[\alpha]_D$ + 20.5°(c: 1.03, $CHCl_3$) (Found: C, 78.36; H, 11.36. Calc. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38) was obtained. The infrared spectrum of protopanaxadiol showed a free OH band at 3600 cm^{-1} ($CHCl_3$), an intramolecular hydrogen bonding OH band at 3340 cm^{-1} ($CHCl_3$) and an end vinyl group band at 1645 and 882 cm^{-1} (KBr).

Protopanaxadiol diacetate, m.p. 125-127°, $[\alpha]_D^{34}$ - 5.6° (c: 1.03, $CHCl_3$) (Found: C, 74.95; H, 10.42. Calc. for $C_{34}H_{56}O_5$: C, 74.95; H, 10.36) gave an intramolecular hydrogen bonding OH band at 3537 cm^{-1} (CCl_4), which indicated that a hindered hydroxyl group was still remained unblocked while two other hydroxyls were acetylated.

On refluxing with dil. HCl for 1.5 hrs., protopanaxadiol was converted into panaxadiol (I), m.p. 250°. Thus the formula (II) would be put forward to represent protopanaxadiol, and the chlorine containing product* would possibly be represented by the formula (III).

The compound (VI), m.p. 208-209°, $[\alpha]_D$ + 22.6° ($CHCl_3$) (Diacetate, m.p. 166-167°, $[\alpha]_D$ + 11.2° ($CHCl_3$))which was derived from alnus-folienediolone by Fischer and Seiler[4] has

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[4] F.G. Fischer and N. Seiler, Liebigs Ann. 644, 162 (1961).

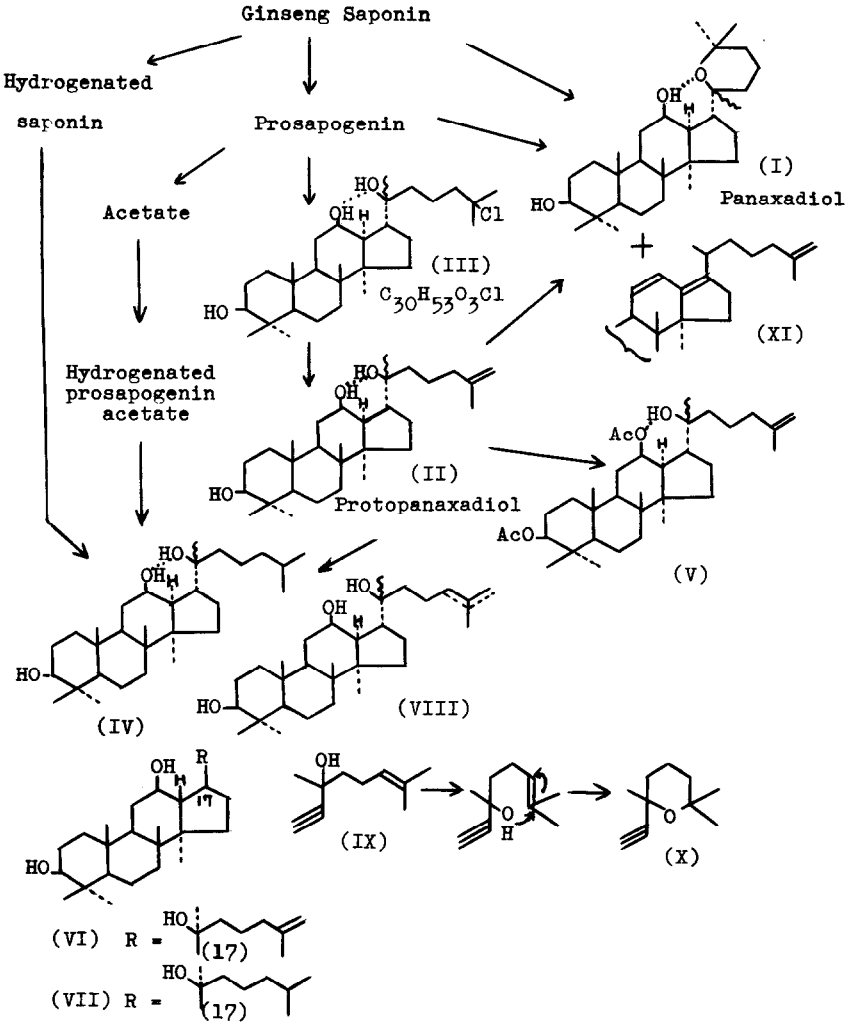
* This compound will be elucidated in detail in the forthcoming report of this series of study.

been regarded as being a stereoisomer of protopanaxadiol (II). This has been confirmed by the dihydro-compound (dammarane-3β,12β,20β-triol) (VII)[4], m.p. 208-210°, $[\alpha]_D$ + 20°, which has been shown to be different from the dihydroprotopanaxadiol (IV), m.p. 246-248°, $[\alpha]_D^{27}$ + 22.9° (c: 1.00, $CHCl_3$) (Found: C, 78.15; H, 11.68. Calc. for $C_{30}H_{54}O_3$: C, 77.86; H, 11.76) by the comparison of melting points and infrared spectra. The Ginseng saponin was hydrogenated catalytically in a mixture of methanol, ethanol and acetic acid using Pt-black as the catalyst, and then hydrolysed by refluxing with dil. HCl to give dihydroprotopanaxadiol (IV). In the same way, the acetylated prosapogenin was subjected to hydrogenation followed by hydrolysis as above to yield dihydroprotopanaxadiol. Panaxadiol (I) was recovered unchanged on catalytic reduction under the same condition and on treating with conc. HCl at room temperature.

It has now been concluded that during the process of hydrolysis of Ginseng saponin or prosapogenin heating with dil. HCl, the trimethyl-tetrahydropyrane ring of panaxadiol (I) was formed secondarily by the ring closure of the open side chain of the genuine sapogenin moiety which possesses a hydroxyl at $C_{(20)}$ and a double bond at $C_{(24)}$ or $C_{(25)}$.

As there is a possibility of migration of double bond in the side chain on mild treatment with acids[5], the position of double bond in genuine sapogenin has not conclusively been established, which at present would be formulated

[5] J.A. Henry, D.S. Irvine and F.S. Spring, J. Chem. Soc. 1607 (1955); L.F. Fieser and M. Fieser, Steroids 392. Reinhold Publ. Co., New York (1959).



as (VIII). An analogous ring closure by the action of acid on the system involving hydroxyl and double bond can be seen

in dehydrolinalool (IX)[6] and some other examples[7].

An oily substance which was obtained as a by-product of panaxadiol formation in the hydrolysis of saponin and prosapogenin of Ginseng on boiling with dil. HCl would be shown by the partial formula (XI) as it gave the UV maxima at 248, 256 and 265 mμ (in EtOH)[8]. This compound has also been derived both from panaxadiol (I) and protopanaxadiol (II) on refluxing with dil. HCl, thus it is also regarded as an artifact.

Recently some studies on the chemical constituents of Ginseng have been reported in some relation with the pharmacological action.

Hörhammer et al.[9] showed by thin-layer chromatography the presence of oleanolic acid and three other unknown sapogenins in the hydrolysate of Panax saponin. Wagner-Jauregg et al.[10] obtained a sapogenin, panaxol, m.p. 238-239°, which seems obviously as being identical with panaxadiol (I), though they proposed a different molecular formula, $C_{29}H_{50}O_3$.

Kochetkov and his coworkers[11] isolated two glycosides,

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6 H. Rupe and G. Lang, Helv. Chim. Acta 12, 1133 (1929).

7 H.N. Khastgir et al., Tetrahedron 14, 275 (1961); P. Yates, G.H. Stout, J. Am. Chem. Soc. 80, 1691 (1958); M.L. Wolfram et al., J. Am. Chem. Soc. 68, 406 (1946).

8 F.G. Fischer and N. Seiler, Liebigs Ann. 626, 185 (1959).

9 L. Hörhammer, H. Wagner and B. Lay, Pharm. Ztg. 106, 1307 (1961).

10 Th. Wagner-Jauregg and M. Roth, Pharm. Acta Helv. 37, 352 (1962)

11 G.B. Eliakov, L.I. Strieina, A. Ya. Charlin and N.K. Kochetkov, Izvest. Acad. Nauk, U.S.S.R. 1125 (1962).

panaxosides A and B, from Ginseng giving molecular formulae, $C_{35}H_{58}O_{12}\cdot H_2O$ and $C_{35}H_{60}O_{12}$, respectively. Panaxgenin B which was isolated from the hydrolysate of Ginseng saponin mixture has been regarded as being identical with panaxadiol (I)[12].

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[12] N.K. Kochetkov, Private communication, Oct. 13, 1962.