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STUDIES ON SAPONINS AND SAPOGENINS OF GINSENG
THE STRUCTURE OF PANAXATRIOL

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THE presence of more than ten neutral saponins in Ginseng (the root of Panax ginseng C.A. Meyer) has been demonstrated by thin layer chromatography. We designated them tentatively according to the sequence of R_F value from the bottom to the top as ginsenosides R_x (x= a,b,c,d,e,f,g-1,g-2,g-3 and h). Of these compounds, ginsenoside R_f might possibly be a prosapogenin which was formed during the process of isolation by the partial hydrolysis of ginsenosides R_b and R_c.

In the preceding papers[1-4], we reported the structures of panaxadiol (I), a secondary genin, and protopanaxadiol (II), a genuine sapogenin of ginsenosides R_b, R_c, R_d, R_e and R_f.

In the present paper, we propose the structural formula (III) for panaxatriol, $C_{30}H_{52}O_4$, m.p. 238-239°, $[\alpha]_D^{22°}$ + 14.2° ($CHCl_3$), $\nu_{max}^{CHCl_3}$: 3600; 3262cm^{-1} (intramolecularly hydrogen bonded OH), which has been obtained by the acid hydrolysis of ginsenoside R_{g-1}. On acetylation with acetic anhydride and pyridine at room temperature, panaxatriol gave diacetate (IV), $C_{34}H_{56}O_6$, m.p. 268-269°, $[\alpha]_D^{31°}$ +24.9°($CHCl_3$), $\nu_{max}^{CCl_4}$:

3327 (intramolecularly hydrogen bonded OH); 1737 cm^{-1}(OAc).

Oxidation of IV with Jones' reagent yielded a diacetate of monoketonic compound (V), $C_{34}H_{54}O_6$, m.p. 240-241°, $\nu_{max}^{CS_2}$: 1737 (OAc); 1712 cm^{-1}(six-membered ring C=O);no OH band.

Mild oxidation of panaxatriol with chromium trioxide in pyridine afforded a diketonic compound (VI), $C_{30}H_{48}O_4$, m.p. 219-220°, $\nu_{max}^{CCl_4}$: 3327 (intramolecularly hydrogen bonded OH); 1718 cm^{-1}(six-membered ring C=O), which gave monosemicarbazone (VII), $C_{31}H_{51}O_4N_3$, m.p. 254-255°.

The mass-spectrum of panaxatriol showed a base peak at m/e 127 (VIII) as same as that of panaxadiol(I)[4] to indicate the presence of 2,2,6-trimethyltetrahydropyrane ring in its molecule. The n.m.r. spectrum of panaxatriol (in $CDCl_3$) exhibits eight methyl signals,and three of them at τ 8.72, 8.77 and 8.81 can be assigned to three methyls in the tetrahydropyrane ring.[3] The 12β-hydroxyl of panaxadiol (I) is intramolecularly hydrogen bonded ($\nu_{max}^{CCl_4}$:3353; $\nu_{max}^{CHCl_3}$: 3260 cm^{-1})[3] and sterically hindered by the gem-dimethyl of the tetrahydropyrane ring. This hydroxyl showed a resistance against acetylation[4] and mild oxidation. The O.R.D. curve of V revealed a negative Cotton effect which is almost superimposable on those of 3-O-acetyl-12-ketonic compound (IX) derived from dihydroprotopanaxadiol (X) and panaxanolone acetate (XI).[1] On the basis of such findings and from the biogenetical point of view, it has been suggested that panaxatriol is a homologue of panaxadiol (I), having one more hydroxyl. The position and the configuration of the

additional hydroxyl have been proved as follows:

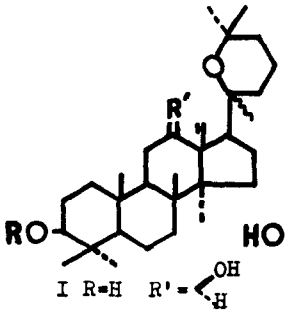
The n.m.r. spectra of panaxatriol and its derivatives indicate the absence of primary alcoholic hydroxyl. The formation of VI and its I.R. spectrum showed that the hydroxyl is secondary and located in a six-membered ring, therefore, the hydroxyl is not involved in ring D.

The U.V. spectrum of VI giving no strong absorption maximum suggested the absence of a 1,2- or 1,3-diketonic system.

Thus the hydroxyl is not located in ring A. Triphenyltetrazolium chloride gave no reaction with VI to indicate the absence of α-ketol system eliminating the possibility of location of the hydroxyl at $C_{(11)}$ in ring C. Consequently, the position of the hydroxyl has been limited to $C_{(6)}$ or $C_{(7)}$ in ring B.

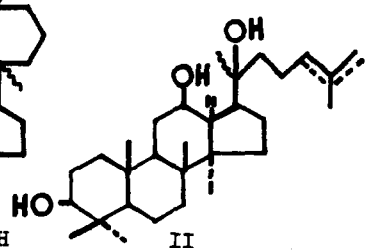
The Huang-Minlon reduction of VI under the ordinary condition[5], resulted elimination of one ketone at $C_{(3)}$ to afford a monoketonic compound (XII), $C_{30}H_{50}O_3$, m.p. 198-199°, $\nu_{max}^{CCl_4}$:3327 (intramolecularly hydrogen bonded OH); 1713 cm^{-1} (six-membered ring C=O), which gave AB-type doublet signals at τ 7.40 and 8.20 (1 H each, J= 12 c.p.s.) and a singlet at 7.91 (1H) in the n.m.r. spectrum (in $CDCl_3$). These proton signals disappeared when XII was deuterised (using $NaOCH_3$ in CH_3OD-D_2O) to indicate the three reactive hydrogen atoms would exist at the α,α'-positions of the carbonyl to form a $-\overset{|}{C}-\underset{H}{\overset{|}{C}}-\underset{O}{\overset{||}{C}}-\underset{H}{\overset{|}{C}}-$ system. Such a system can only be represented by the 6-position in ring B.*

The above evidence was supported by the facts that the carbonyl in the 6-position of zeorinone (XIII) and zeorini-

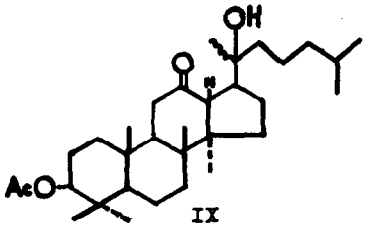


I R=H R'= OH

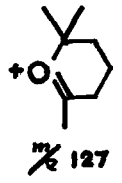
XI R=Ac R'= O



II

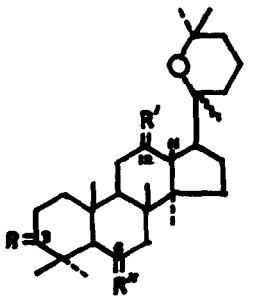


IX



m/e 127

VIII



III R=R'= OH R''= H

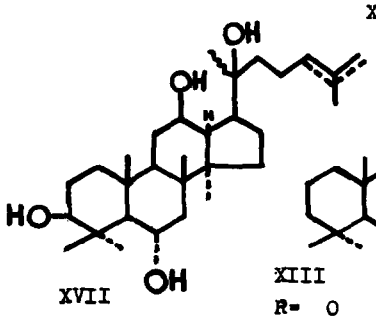
IV R= OAc R'= OH R''= H

V R= OAc R'= O R''= H

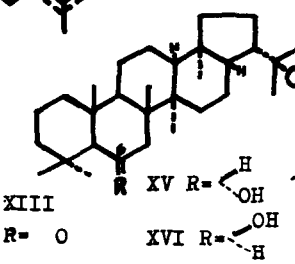
VI R=R''= O R'= OH

VII R= :N-NHCONH$_2$ R'= OH R''= O

XII R= H R'= OH R''= O



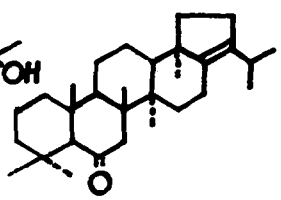
XVII



XIII R= O

XV R= H OH

XVI R= OH H



XIV

none (XIV) is also strongly hindered to show a resistance to ketonic reagents and the Wolff-Kishner reduction[6].

The O.R.D. curves of these compounds gave a similar negative Cotton effect[7] as that given by XII.

The configuration of 6-hydroxyl of panaxatriol has been regarded as α (equatorial), since the 6α(equatorial)hydroxyl of zeorin (XV) is readily acetylated, whereas the 6β (axial) hydroxyl of epi-zeorin (XVI) showed a resistance to acetylation. The above evidences lead to the structure(III) for panaxatriol, which would arise secondarily during the acid hydrolysis of ginsenoside R_{g-1} in regard to the occurrence of panaxadiol (I) from ginsenoside R_b. The genuine sapogenin of ginsenoside R_{g-1} would be represented by protopanaxatriol (XVII).

Ginsenoside R_g fraction would correspond to panaxoside A reported by Kochetkov and his co-workers[8], though the direct comparison has not been made.

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* The intramolecularly hydrogen bonded 12-β-hydroxyl in panaxadiol (I) showed a signal at τ 3.75 (1H, singlet) in the n.m.r. spectrum (in $CDCl_3$), which disappeared by the addition of acid. The n.m.r. spectra of panaxatriol, IV, VI, and XII showed the same type of signal.

Note: After the completion of this mauscript, we have been aware of the appearance of a report on Ginseng saponins and sapogenins published by G.B. Elyakov, L.I. Strigina, N.I. Uvarova, V.E. Vaskovsky, A.K. Dzizenko, and N.K. Kochetkov (Tetrahedron Letters,No.48, 3591 (1964)), who obtained a sapogenin from panaxosides A,B, and C, and named it panaxatriol, $C_{30}H_{49}O(OH)_3$,m.p. 225-227°,$[\alpha]_D$: + 18.18°. The fundamental carbon skeleton of panaxatriol was proved by Russian workers as same as that of panaxadiol, and the position of third hydroxyl was assigned to be located at $C_{(23)}$ in the tetrahydropyrane ring.

However, we could not agree to such a conclusion for the location of third hydroxyl in panaxatriol by the reasons elucidated in the present paper(e.g. panaxatriol gave a base peak at m/e 127 (VIII) in the mass-spectrum) and some additional evidences (e.g. the lower shift of n.m.r. signals of the gem-dimethyl in ring A of panaxatriol and its derivatives in comparison with those of panaxadiol), if the compound obtained by Russian workers is identical with our panaxatriol.