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GLYCOSIDES FROM GINSENG ROOTS

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A few years ago we started to investigate in our laboratories active principles of Ginseng roots, one of the most interesting curatives of the Chinese medicine. The investigation resulted in isolating a number of individual glycosides. Recently we published a communication on isolation of two neutral glycosides - panaxosides A and B from a methanol root extract (1). By means of partition chromotography on silica gel or alumina in water saturated tolyene-butanol, with continuous gradient (100:0→0:100), we have isolated from the methanol Ginseng extract besides panaxosides A and B also other panaxosides, that were named according to their increasing polarity - C, D, E, and F. Constants and composition of carbohydrate parts of the glycosides are given in Table 1.

TABLE 1

Panaxoside	M.p.	$[\alpha]_D^{20}$ CH_3OH	M.w.[x]	Found: C	Found: H	Monose
A	176-8°	+30° c 7.6	-	60.92	8.78	Gl(3)
B	182-5°	-12.2° c 3.27	-	61.88	8.98	Gl(2)Rm(1)
C	185-7°	-4.3° c 2.76	1031 1064	58.53	8.94	Gl(3)Rm(1)
D	157-60°	+29° c 4.82	1178	58.27	8.86	Gl(4-5)
E	185-7°	+21.5° c 4.18	1222 1230	58.23	8.88	Gl(4)Ar(1)
F	185-7°	+20.6° c 5.34	1388 1424	56.07	8.48	Gl(6)

We were able to obtain a crystalline and chromotographically homogenous acetate only for the panaxoside A, m.p. 242-46°, $[\alpha]_D^{20}$ 0° (c:3.7, $CHCl_3$); (Found: C, 60.87, 60.55; H, 7.35, 7.47).

Methylation of the panaxoside A and subsequent hydrolysis of a permethyl derivative resulted in 2, 3, 4, 6-tetra-O-methyl-D-glucose and 2, 3-di-O-methyl-D-glucose, the ratio being 2:1. Thus it has been demonstrated that the panaxoside A is not a bioside, as it was previously supposed(1) but a trioside having a branched carbohydrate chain.

An attempt to get aglicones of panaxosides A-F by means of hydrolysis with mineral acids in water solutions was unsuccessful, resulting in products of destruction and partial hydrolysis of genines. Hydrolysis of panaxosides with mineral acids in methanol, e.g. 20% HCl in methanol (65°),

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[x] Defined by the method of isothermal distillation.

results in complex mixtures of substances that appear to be products of modification of genuine genine formed during the process of hydrolysis.

Neutral panaxosides A, B, and C in that case yield an equilibrious mixture of quite identical substances (A_I-A_6). Hydrolysis of panaxosides D, E, F in the same conditions results also in analogous mixtures of substances (F_I-F_5), differing from A_I-A_6. It should be noted that substances A_I-A_6 under no conditions turn into substances F_I-F_5; which proves that Ginseng glycosides divide according to their genines into two groups - panaxosides A, B, and C, and panaxosides D, E, and F.

Most of the above products of hydrolysis were isolated in individual crystalline state by means of chromotography on alumina and silica gel (of the chloroform-methanol and chloroform-ethyl-acetate respectively). Corresponding data are given in Table 2.

TABLE 2

Subst.	M.p.	$[\alpha]_D^{20}$	Found: C	H	H_{act}	OCH_3	Brutto-formula
A_I	252-54°	+30° c 1.8	71.27 71.05	10.96 10.75		0.00	$C_{30}H_{52}O_6$
A_2 x	253-54°	+30.5° c 3.14	71.51 71.62	11.34 11.40		4.82 5.40	$C_{31}H_{54}O_6$
A_5	159-163°	+34.02° c 1.94	73.66 73.40	11.15 10.97	0.63	10.15 10.20	$C_{32}H_{58}O_5$
A_6 xx	225-27°	+18.18° c 1.98	75.35 75.24	11.19 11.05	0.64	0.00	$C_{30}H_{52}O_4$

x Acetate, m.p. 162.5-163.5°, $[\alpha]_D^{20}$ + 15.50 (c:2.06, $CHCl_3$); (Found: C, 70.48; H, 9.73; $C_{33}H_{56}O_7$. Calc. for: C, 70.17; H, 9.99)

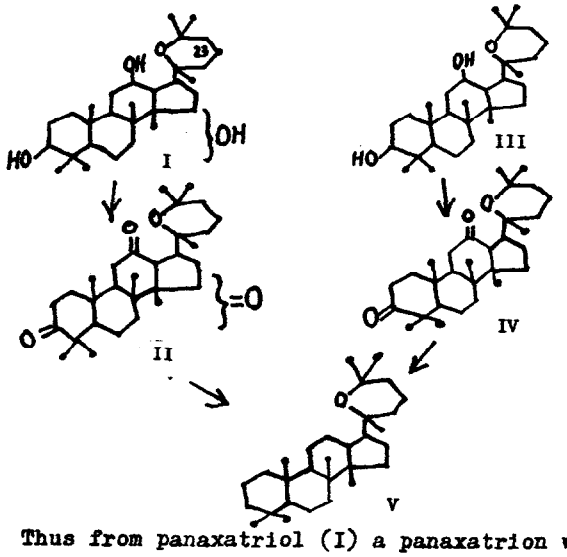
xx Acetate, m.p. 287-289°, $[\alpha]_D^{20}$ + 33.9° (c:2.12, $CHCl_3$); (Found: C, 72.86; H, 10.42; $C_{34}H_{56}O_6$. Calc. for: C, 72.81; H, 10.06).

All the above substances during the process of hydrolysis (20% HCl in methanol, 65°) transform readily into each other, each of them producing under the treatment all the substances from A_I to A_6. As shown in the table, substances A_I-A_6 differ from each other in number of oxygen functions (of hydroxyl and methoxyl groups) and probably originate from genuine genine in the course of process of hydration-dehydration.

The same is demonstrated during hydrolysis of panaxosides of the D-F group, but not one of the substances thus produced is identical to a single one of analogous products of the A-C group. The main substance, isolated from the hydrolysates of the D-F group proved to be the panaxadiol, the structure of which has recently been established by Shibata et al (2). Among products from the A-C panaxosides, however, there was no trace of panaxadiol. The main substance in that case was a substance A_6, $C_{30}H_{49}O(OH)_3$. Its composition is similar to that of panaxadiol, but differs from it in that it has one hydroxyl group more. We named it a panaxatriol. Its IR-spectrum ($CHBr_3$) contains absorption bands at 3600 cm^{-1} and 3280 cm^{-1}. The last band corresponds to hydroxyl linked by an intramolecular hydrogen bonding with ethereal oxygen which testifies to the presence of hydroxyl in the 12-position. It is indeed reasonable to suppose that the second hydroxyl, by analogy with panaxadiol, is in 3-position; preliminary data on NMR-spectra of panaxadiol and panaxatriol are shown as analogous (3).

Panaxatriol was converted by means of oxidation of CrO_3 in acetone, followed by elimination of carbonyl functions,

according to Barton (4, cf. 5):



Thus from panaxatriol (I) a panaxatrion was formed (II), m.p. 236.5-238°, $[\alpha]_D^{20}$ 0° (c:2.47, $CHCl_3$); (Found: C, 76.96, 76.74: H, 9.83, 9.72; Calc. for: $C_{30}H_{46}O_4$: C, 76.53; H, 9,85). IR($CHCl_3$): 1712 cm^{-1} (C = O in 6-member cycle). Reduction of II and IV (the latter being the product of oxidation of panaxadiol) in both cases results in the same substance V, m.p. 118-120°, identical by IR-spectra (KBr), having no absorption bands OH- and C=O-groups (Fig. 1).

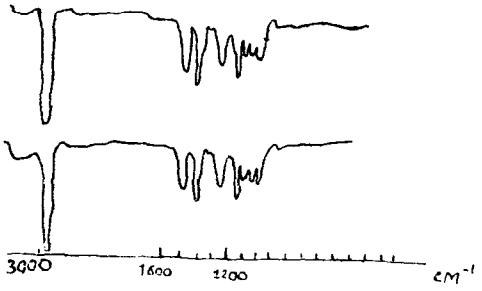


Figure 1.

The II gets reduced to the V much less easily than the IV to V, and during the process, besides the V some unknown ketone (IR-spectrum 1710 cm^{-1}) is formed.

All the above data show that panaxosides of the A-C and D-F groups have got aglicons possessing analogous skeleton; it is probably similar to that proposed by Shibata et al.(6) for the "genuine sapogenin" of Ginseng glycosides. Analytical data for the panaxoside A and its acetate prove that genine contains no more than two hydroxyl groups, while its UV-spectrum - that there is a conjugate bond system (λ = 217 $m\mu$, ε = 96000). One may suppose therefore that substances derived during hydrolysis of both groups of glycosides originate in the process of hydration (or addition of methanol) of conjugate double bonds.

Presence of the third hydroxyl in the panaxatriol is to be explained by hydration of one of the double bands of genuine genine. In order to define its position we have established position of the third OH-group in panaxatriol by means of investigation of NMR-spectrum of the II. In the spectrum there is an unsplit signal (2,3 p.p.m.), corresponding to four protons of two methylene groupings next to carbonyl groups. The C-23 of trimethyl-tetrahydropyran cycle is the only position in molecule of panaxatriol that fulfils the condition.

It follows therefore that the third hydroxyl group of panaxatriol is to be found at C-23,and evidently is the result of hydration of double bonding in a side chain of genuine genine. Thus the genuine genine of panaxosides A-C

differs from the genine of panaxosides D-F by having one additional double bond in the chain of aglicon . Determination of the position of these double bonds is now in progress.

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