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STUDIES ON SAPONINS OF GINSENG: THE STRUCTURE OF GINSENOSIDE-Rg_1

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In our previous papers(1,2), it has been reported that the genuine sapogenin of ginsenosides-Rb_1, Rb_2, and Rc, the saponins of Ginseng roots(3), can be represented by 20S-protopanaxadiol(=20-epiprotopanaxadiol)(I)(4), and the partial structure of these saponins can be formulated as II. This communication deals with the structure of ginsenoside-Rg_1(abbrev. Rg_1), another saponin of this crude drug(3).

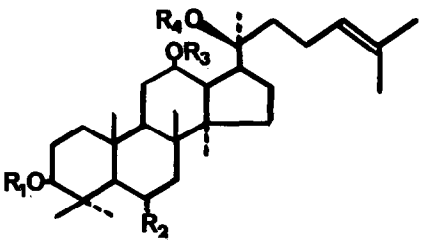
Rg_1, colourless powder, mp 194-196.5°; $[\alpha]_D^{19.5}$+32°(pyridine), has been isolated through its deca-acetate(III), colourless crystals, mp 242-243°; $[\alpha]_D^{24.5}$ +7.0° ($CHCl_3$), $C_{42}H_{72}O_{14}(C_2H_2O)_{10}$, molecular weight: Calcd. 1221.4, found by osmometry 1199.1, IR: no OH band. On hydrolysis with dil.mineral acid in aqueous ethanol, Rg_1 yielded D-glucose and panaxatriol(IV), whose structure has already been proved to be 6α-hydroxy-20R-panaxadiol(4,5,6,7). On the analogy of the study on ginsenosides-Rb_1, Rb_2, and Rc(1), the mild hydrolysis of Rg_1 gave its genuine sapogenin, 20S-protopanaxatriol(=6α-hydroxy-20S-protopanaxadiol)(V)(7).

Repeated methylation of Rg_1 with CH_3I and DMSO-NaH reagent(2,8) gave an amorphous decamethyl ether(VI), IR: no OH band, NMR: signals due to $-OC\underline{H}_3$(singlets) at δ3.23(3H), 3.35(3H), 3.36(6H), 3.51(6H), 3.55(3H), 3.56(3H), 3.62(3H), and 3.63ppm (3H), signals due to $-C\underline{H}=C(C\underline{H}_3)_2$ at δ1.63(3H, singlet), 1.69(3H, singlet), and 5.06 ppm(1H, broad)(9), through an amorphous nonamethyl ether(VII), IR: $\nu_{max}^{CCl_4}$ 3463cm^{-1} (OH), NMR: signals due to $-OC\underline{H}_3$(singlets) at δ3.38(9H), 3.53(6H), 3.59(6H), 3.62

(3H), and 3.65ppm(3H), signals due to $-C\underline{H}=C(C\underline{H}_3)_2$ at δ1.62(3H, singlet), 1.71(3H, singlet), and 5.11ppm(1H, broad); the anomeric proton signals(1H each, doublets) at δ4.24(J=7cps) and 4.39ppm(J=7cps) in the spectrum of VI, and at δ4.27(J=7.5cps) and 4.46ppm(J=7.5cps) in that of VII indicated the β-linkage of the both glucosyl moieties of Rg_1(10). The decamethyl ether(VI) was subjected to methanolysis with HCl in methanol. The gas liquid chromatography of the sugar part of the products revealed the presence of methyl 2,3,4,6-tetra-O-methylglucopyranoside and the absence of methyl tri- or di-O-methylglucopyranoside(2). Accordingly, it is evident that Rg_1 is a β-diglucoside of V and each of its β-glucosyl moieties is combined separately with two of four hydroxyl groups of 20S-protopanaxatriol(V).

On catalytic hydrogenation and subsequent saponification, III afforded dihydroginsenoside-Rg_1, which was methylated repeatedly with CH_3I and DMSO-NaH reagent(2,8) to give a decamethyl ether(VIII) of dihydroginsenoside-Rg_1, IR: no OH band, NMR: no signals attributable to $-C\underline{H}=C(C\underline{H}_3)_2$. Hydrolysis of VIII with conc. HCl at room temperature and chromatographic separation of the products gave a di-O-methyl-20ξ-dihydroprotopanaxatriol(IX), mp 180-182°; $[\alpha]_D^{11}$ +19.3°($CHCl_3$), $C_{32}H_{58}O_4$, IR: $\nu_{max}^{CCl_4}$ 3620(free OH) and 3380cm^{-1}(concentration independent, bonded OH). The locations of two methoxyl groups of IX (at C-3 and C-12) were elucidated by the following evidences. On oxidation with Jones' reagent, IX yielded a ketone(X), mp 155-156°; $[\alpha]_D^{14}$ -6.2°($CHCl_3$), $C_{32}H_{56}O_4$. It has been found that the 20-hydroxyl group of the 20-hydroxy-12-keto derivatives(XI) of dammarane type triterpenes is mostly(in case of C-20R series) or partly(in case of C-20S series) hydrogen bonded with the 12-ketone exhibiting a bonded OH band near 3450cm^{-1} and a bonded C=O band at 1695cm^{-1} in the IR spectra in CCl_4(11), whereas, the IR spectra of the 20-hydroxy-12β-methoxy derivatives(XII) in CCl_4 show a strong band near 3380cm^{-1} due to the 20-hydroxyl group hydrogen bonded with the 12-methoxyl group(2). The IR spectrum of X in CCl_4 showed a carbonyl band at 1713cm^{-1} and a strong OH band at 3380 cm^{-1}(concentration independent) indicating the presence of the partial structure

XII in its molecule. The negative Zimmermann test(12) of X and a negative Cotton effect of the ORD curve of X in methanol(13) excluded the possibility of the 3-ketone. The shape of the ORD curve of X(trough 326mμ, λ.306mμ, peak 285mμ) resembles that of the 6-keto derivative(XIII) prepared from IV(5) being clearly different from that of 3β-acetoxy-20R-dammaran-12-one(trough 303mμ, λ.295mμ, peak 260mμ). Further, the NMR signals of X characteristic to active methylene and methine

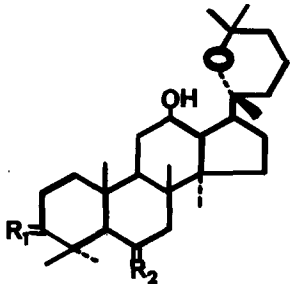


I: $R_1=R_2=R_3=R_4=H$

II: $R_1=$ βglucosyl-(2-1β)glucosyl or -(βglucosyl-(2-1β)glucosyl)-sugar, $R_2=H$, $R_3=H$ or sugar, $R_4=H$ or sugar

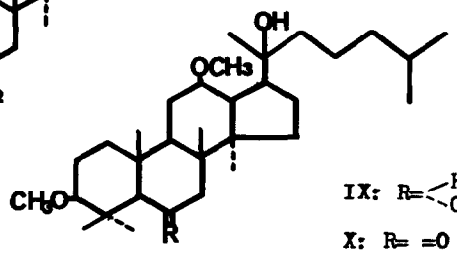
V: $R_1=R_3=R_4=H$, $R_2=OH$

XIV: $R_1=R_3=H$, $R_2=$ -Oβglucosyl, $R_4=$ βglucosyl



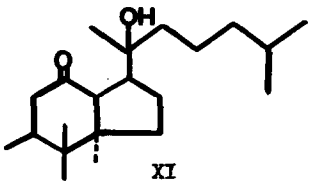
IV: $R_1=$  , $R_2=$ 

XIII: $R_1=$, $R_2=$ =O

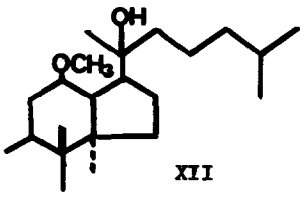


IX: R=

X: R= =O



XI



XII

protons are observed at the similar positions with the similar coupling patterns (doublets(1H each, J=11cps) at δ1.87 and 2.60ppm and a singlet(1H) at δ2.11ppm) to those of XIII(5).

Consequently, it follows now that Rg_1 should be formulated as 6,20-di-O-β-D-glucosyl-20S-protopanaxatriol(XIV). The presence of an O-glucosyl group at C-20 was also supported by the absence of an OH band in the IR spectra of III and VI in

spite of the resistance of the 20-hydroxyl group of dammarane type triterpenes to acetylation and methylation(2). Rg_1 is the first example of the saponin with the dammarane type sapogenin whose structure has been fully established.

Elyakov et al. have also reported the isolation of several saponins from Ginseng roots cultivated in the Far Eastern region of USSR and designated them panaxosides A-F(6a). On acid hydrolysis, panaxoside A afforded IV and D-glucose and they proposed the partial structure XV for this saponin(14). The respective comparisons of the physical constants and Rf values of the thin layer chromatograms of Rg_1 and III with those of panaxoside A and its acetate as well as the comparison of the X-ray powder pattern of III with that of panaxoside A acetate strongly suggest the identity of both the substances, though their assignment of the structure(XV) is inconsistent with our present conclusion.

D-glucose —1-6— D-glucose-genin
D-glucose —1-4—
XV

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