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STEREOCHEMISTRY OF PROTOPANAXADIOL: ACID CATALYSED EPIMERIZATION OF C-20 HYDROXYL OF BETULAFOLIENETRIOL, PROTOPANAXADIOL, AND THEIR DERIVATIVES

Osamu Tanaka, Masahiro Nagai, Tomihiko Ohsawa,
Nobutoshi Tanaka, and Shoji Shibata
Faculty of Pharmaceutical Sciences, University of Tokyo, Japan

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In our previous communication(1), the absolute configurations of C-20 of dammarenediols-I and -II have been assigned as R and S respectively by the chemical correlation of panaxadiol(I) with (-)-R-cinenic acid. It has been reported that panaxadiol(I) was formed from protopanaxadiol (II)(12β-hydroxydammarenediol-I) by the acid catalysed cyclization of the side chain (2,3,4).

In connection with the study of the Ginseng neutral saponins, the acid catalysed epimerization of C-20 hydroxyl of dammarane type triterpenes having 12β-hydroxyl has been examined. On refluxing with dil. H_2SO_4 in 60%aq.ethanol, betulafolianetriol(III) (3-epi-12β-hydroxydammaranediol-II)(5) was rapidly equilibrated with its C-20 epimer (IV) (3-epi-12β-hydroxydammaranediol-I), m.p. 252-255°, in a small excess of the latter compound (IV). The structure of IV was established by the correlation of this compound with dihydroprotopanaxadiol (V)(12β-hydroxydammaranediol-I) as the 3,12-diketone (VI), m.p. 124-126°.

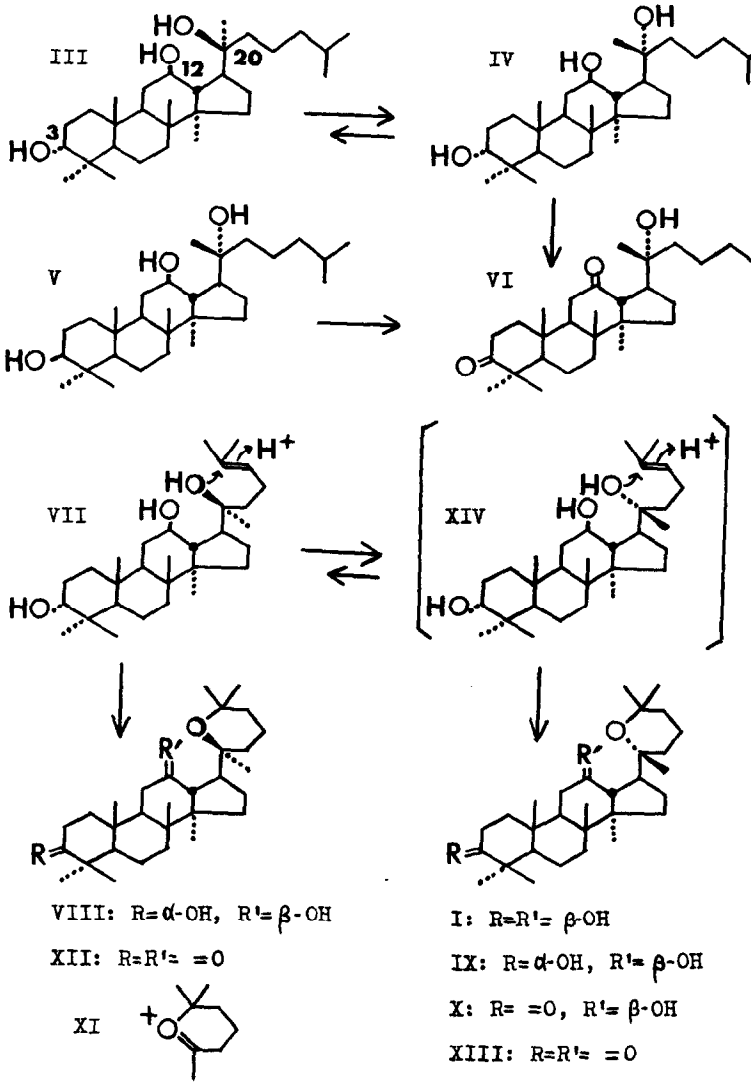
Treatment of betulafolienetriol (VII) (3-epi-12β-hydroxydammarenediol-II), a constituent of the leaves of white birch (5,6), with boiling dil. mineral acid in aq.ethanol afforded a compound (VIII), $C_{30}H_{52}O_3$, m.p. 230-233°(I.R.: $\nu_{max}^{CCl_4}$ 3637 (free OH) and 3355 cm^{-1} (intramolecularly hydrogen bonded OH, concentration-independent)) and a compound (IX), $C_{30}H_{52}O_3$, m.p.

261-263°(I.R. in CCl_4: a free and an intramolecularly hydrogen bonded OH bands at the nearly same positions as those of VIII) along with other products.

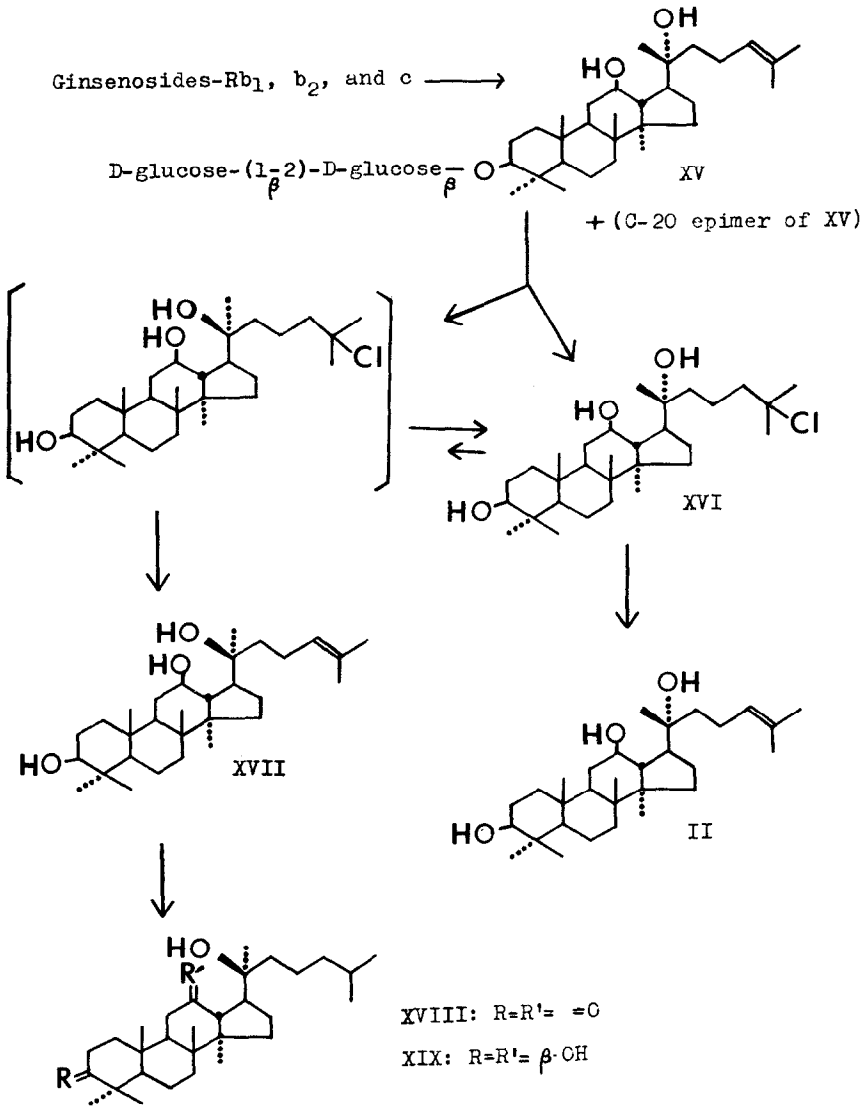
Mild oxidation of IX with chromic acid in pyridine yielded a ketone (X), which was identical with the 3-ketone derived from panaxadiol (I) (1). Consequently, the compound (IX) can be formulated in term of 3-epi-panaxadiol.

The presence of the trimethyl-tetrahydropyrane ring in the compound (VIII) was demonstrated by the mass spectrum (base peak: m/e 127, ion XI) and the n.m.r. spectrum (tertiary methyl signals at τ 8.72(6H) and 8.77(3H) in $CDCl_3$) on the analogy of panaxadiol (I) (2,3). The diketone (XII), $C_{30}H_{48}O_3$, m.p. 180-182°(I.R.: $\nu_{max}^{CS_2}$ 1718cm^{-1} (six membered ring ketone) and no OH band) prepared from VIII exhibited an o.r.d. curve being similar to that of the 3,12-diketone (XIII), m.p. 248-249°, derived from panaxadiol (I). On the basis of these evidences, the structure of VIII can be assigned as 3,20-epi-panaxadiol.

It has been found that the above epimerization of C-20 hydroxyl of III occurs more slowly by the action of p-toluenesulfonic acid in chloroform. Betulafolienetriol (VII) was treated with this reagent at room temperature, and the reaction process was followed by the thin layer chromatography in comparison with the epimerization reaction of betulafolianetriol (III) under the same condition. In the early stage of the former reaction (within 4 hours), only 3,20-epi-panaxadiol (VIII) was formed and 3-epi-panaxadiol (IX) began to appear almost simultaneously as the C-20 epimer (IV) of III appeared in the mixture of the latter reaction. This observation proved that 3,20-epi-panaxadiol (VIII) was formed directly from VII by the acid catalysed cyclization of the side chain, and that 3-epi-panaxadiol (IX) was formed from VII through the epimerized compound (XIV), though XIV has not been isolated as yet (see Chart 1). Therefore, it is evident that VIII retains the same configuration of C-20 as that of betulafolienetriol (VII) (dammarenediol-II type), then the configuration of C-20 of panaxadiol (I) is same as that of protopanaxadiol (II) (dammarenediol-I type).



The same type of the epimerization reaction would also be expected in case of the acid hydrolysis of the Ginseng neutral saponins, ginsenosides-Rb_1, Rb_2, and Rc. These saponins afforded the same prosapogenin (XV), m.p. 260-262° by the mild hydrolysis with hot aq.acetic acid as reported previously (7). This prosapogenin (XV) yielded only protopanaxadiol (II) by the



oxidation with periodate and the subsequent alkaline treatment (8). Accordingly, the genuine sapogenin of this prosapogenin (XV) should be represented by II. Since the epimerization of C-20 hydroxyl of betulafolianetriol (III) also takes place by the action of hot aq.acetic acid , the C-20 epimer of XV is expected to be formed along with XV on the above partial hydrolysis of the saponins. This epimer of XV would be removed during the

process of the purification of XV. From the ether-less soluble part of the hydrolysate of the prosapogenin (XV) with conc.HCl at room temperature, the chloride (XVI) (9) was obtained, which gave protopanaxadiol (II) by dehydrochlorination with potassium tert.butoxide (3,10). The ether-soluble part of the above hydrolysate was subjected to the dehydrochlorination and the crude product was purified by chromatography to give 20-epi-protopanaxadiol (XVII), $C_{30}H_{52}O_3$, m.p. 197-200°. The structure of XVII was proved by derivation of XVII to the 3,12-diketone (XVIII) (4,5) of betulafolianetriol (III) through 20-epi-dihydroprotopanaxadiol (XIX), $C_{30}H_{54}O_3$, m.p. 214-215°. The isolation of the C-20 epimer of the chloride (XVI) has not been achieved due to its unstability to the column chromatography on silica gel or alumina (3). The respective isolation of the C-20 epimers of panaxadiol (I) and dihydroprotopanaxadiol (V) from the crude hydrolysate of the saponins or from the crude hydrolysate of the hydrogenated saponins with dil.mineral acid are under progress.

The absolute configuration of C-20 of the genuine sapogenin (protopanaxadiol(II) or its C-20 epimer (XVII)) of ginsenosides-Rb_1, Rb_2, and Rc is also being studied.

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10) By the action of diethylaniline or silica gel, the chloride (XVI) gave a mixture of protopanaxadiol (II)(isopropylidene type double bond) and isoprotopanaxadiol (isopropenyl type double bond) (3), while the dehydrochlorination of XVI with potassium tert.butoxide afforded mostly II. The details will be reported elsewhere.