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THEASAPOGENOL A, THE MAJOR SAPOGENOL OF THE SEEDS SAPONIN OF THEA SINENSIS L.

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In the preceding communication[1], we proposed IIa as the structure of theasapogenol B, a second major sapogenol of the seeds saponin obtained from Thea sinensis L. (Japanese name, "Cha"). In this paper, we describe the structural study on theasapogenol A, the major sapogenol of the above mentioned saponin, which led us to present Ia.

Theasapogenol A (Ia), $C_{30}H_{50}O_6$*, mp. 301-303°, IR (KBr): 3356, 1639 cm^{-1}, $[\alpha]_D$ +14° (c, 0.51; pyridine), gave a tetraacetate (Ib), $C_{38}H_{58}O_{10}$, mp. 225-228°, $[\alpha]_D$ +18° (c, 1.0), and a pentaacetate (Ic), $C_{40}H_{60}O_{11}$, mp. 174-178°, $[\alpha]_D$ +29° (c, 1.0), by a usual acetylation, whereas, under more forced condition, it yielded a hexaacetate (no OH absorption band in the IR spectrum), which reproduced the starting sapogenol on alkaline hydrolysis, thus indicating theasapogenol A is a hexahydroxy-triterpene.

Chromium trioxide-pyridine complex oxidation of the pentaacetate (Ic)

* All the compounds described with the chemical formulae gave satisfactory analytical data. Melting points were taken on the Yanagimoto micromelting point apparatus(a hotstage type) and recorded uncorrected, optical rotations were measured in $CHCl_3$, NMR in $CDCl_3$ (at 100 Mc. and 60 Mc.), unless specified otherwise.

Table 1. NMR data of Ic and IIb (τ-values).

	Ic (100 Mc)	IIb (60 Mc)
	6 Me-, 5 AcO-	7 Me-, 4 AcO-
$-C\underline{H}_2OAc$	6.19 (2H, AB q.), 6.33 (2H, s.)	6.30 (2H, s.)
$>C\underline{H}$-OH(ax.)	5.81 (1H, m, $w_{1/2}$=8.7 cps.)	5.77 (1H, m.)
$>C(3)\underline{H}$-OAc	5.20 (1H, q., J_A=9.6, J_B=6.1)	5.45 (1H, t,-like)
a vinyl proton	4.63 (1H, m.)	4.60 (1H, m.)
	4.48, 4.59 (AB q., J=10 cps.)	4.40, 4.54 (AB q., J=10 cps.)

afforded a monoketone (III), $C_{40}H_{58}O_{11}$, mp. 264-266°, $(\alpha)_D$ -30° (c, 0.62); IR (KBr): 1751, 1245 (OAc), 1725 cm^{-1} (CO), no OH. Accordingly, it would appropriately be pointed that one secondary hydroxyl function in theasapogenol A has an axial orientation, which is supported by the NMR signal of Ic appearing at τ 5.81 with a rather small half-band width (8.7 cps.), assignable to a proton on the hydroxyl bearing carbon atom.

In Table 1, the lower field signals in the NMR spectra of Ic and theasapogenol B tetraacetate[1] (IIb) are given, which manifest that theasapogenol A possesses one more primary carbinol and one less tertiary methyl compared to theasapogenol B. The signals at τ 4.48 and τ 4.59 (AB q., J=10 cps.) of Ic shifted to two doublets centered at τ 6.06 (1H, d., J=10 cps.) and τ 4.82 (1H, d., J=10 cps.) in the tetraacetate (Ib), showing one of the α-glycolic hydroxyls was not acetylated in the latter and also suggesting both hydrogens on the glycolic carbon atoms could be represented as trans diaxial configuration based on their coupling constants. The assignment was furthermore confirmed by a decoupling experiment of the tetraacetate (Ib) at 100 Mc. Thus, an irradiation of 124 cps (w_1=394 cps, w_2=518 cps) at τ 6.06 caused the doublet at τ 4.82 changing into a sharp singlet. Therefore, the α-glycolic hydroxyls of theasapogenol A should be expressed as being trans-diequatorial*. Treatment of the

* The evidence along with the fact (direct linking between theasapogenol A and B) postulated in the later part of this paper affords an additional support for theasapogenol B having a trans-diequatorial glycol at C_{21} and C_{22}.

tetraacetate (Ib) with $POCl_3$-pyridine at reflux gave rise to an anhydro-tetra-acetate (IVa), $C_{38}H_{56}O_9$ (M^+ 656), mp. 188-193°. As it is apparent by the NMR data comparison (Table 2), the newly formed ether linkage in IVa is strongly suggested occurring between C_{16} and C_{21}, similarly as in anhydro-theasapogenol B triacetate (IVb). Two singlets at τ 4.70 (C_{22}-H) and τ 6.39 (C_{21}-H) are in good accord with the dihedral angle of both hydrogens found nearly 90° by a Dreiding model inspection. If the substituent at C_{22} were in β-orientation, two hydrogens at C_{21} and C_{22} should be obtained as a pair of doublets in the NMR spectrum.

Table 2. NMR data of IVa and IVb (τ-values).

	IVa	IVb
C_{16}-H	5.74 (1H, m.)	5.71 (1H, m.)
AcO-C_{22}-H	4.70 (1H, s.)	4.71 (1H, s.)
C_{21}-H	6.39 (1H, s.)	6.39 (1H, s.)

The mass spectrum of IVa showed peaks at m/e 307 (a) and m/e 348 (b), remarkable to a Δ^{12}-pentacyclic triterpene by its retro Diels-Alder type fragmentation[2]. The fragment (a) indicates rings A and B carry two acetoxyl functions, one of them is certainly referred to 3β-OAc analogously as in the case of theasapogenol B, and the other would be at C-23 (an equatorial primary carbinol acetate, estimated by the methylene chemical shift at τ 6.19 in Ic)[3], which appears to correspond to the additional OH in theasapogenol A compared to B. The following evidence moreover substantiates the location of a primary carbinol.

On treating theasapogenol A with acetone and p-TsOH, two diacetonides (main products) and a monoacetonide (Va), $C_{33}H_{54}O_6$, mp. 299-301°; $[\alpha]_D$ +27° (c, 1.0; dioxane) were obtained. The acetylation of the latter yielded a mono-acetonide-triacetate (Vb), $C_{39}H_{60}O_9$, mp. 234-235.5°; $[\alpha]_D$ +15° (c, 1.0). The NMR signals ascribable to C_3-α-proton (τ5.20) and C_{23}-methylene protons (τ6.19) of Ic have now been shifted to the higher field at τ ca. 6.5 (1H, m.), and

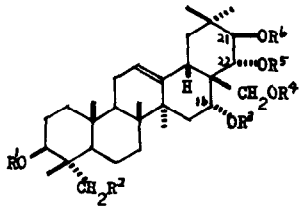
τ 6.46 (2H, br. s.) respectively in Vb, thus indicating both of these hydroxyls are involved to form an acetonide bonding.

Finally, the definite proof of the structural relation between theasapogenol A and B was obtained by converting the former through reductive elimination of the C_{23}-hydroxyl group to the latter.

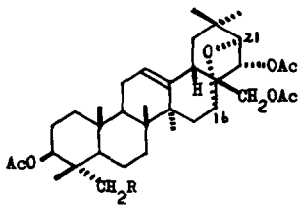
Thus, a mixture of two monotrityl derivatives of theasapogenol A, produced by the usual trityl ether formation, was treated on heating with Ac_2O and pyridine giving C_{23}-trityl and C_{28}-trityl pentaacetates, the separation of both was attained by preparative TLC. The more polar component was defined as a C_{28}-trityl pentaacetate by direct comparison with a compound derived from the monoacetonide (Va) via successive tritylation (affording Vc), deacetonidation, and acetylation. The desired C_{23}-trityl pentaacetate, less polar one, was then treated with aqueous acetic acid, followed by CrO_3-pyridine complex oxidation resulting a ketonic mixture (recognized 2 spots close together on TLC). The major product showed an IR band at 1708 cm^{-1} (CCl_4)(six membered ring carbonyl) and a positive Zimmermann color test, reminiscent of the C_3-carbonyl existence. The compound was presumably arised by an acetyl migration[4] from 3β to 23 on the detritylation. The minor one, exhibiting an IR band at 2720 cm^{-1} (CCl_4) characteristic to an aldehydic ν C-H, was subjected to the Huang-Minlon reduction yielding theasapogenol B (identified by mixed mp., IR in KBr, and TLC) as expected.

Therefore, the structure of theasapogenol A is now best represented by Ia.

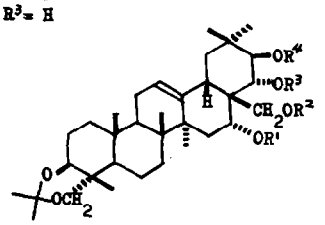
As was cited already in the preceding paper[1], the respective identities of anhydrotheasapogenol B with barringtogenol D and theasapogenol B (IIa) with barringtogenol C (= aescinidin), would bring forward the inconsistency of the structures of barringtogenol D, barringtogenol C (= aescinidin), aescigenin, protoaescigenin, and isoaescigenin, hitherto proposed as VIa[6], VIIa[5,10], VIb[7], VIIb[8], and VIIc[9], respectively, concerning to the C_{22}-hydroxyl or the



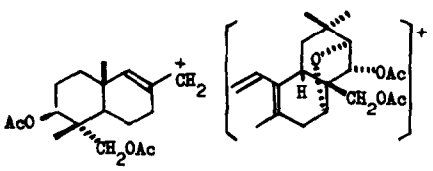
Ia: R^1 R^3 R^4 R^5 R^6= H, R^2= OH
theasapogenol A
b: R^1 R^4 R^5= Ac, R^2= OAc, R^3 R^6= H
c: R^1 R^4 R^5 R^6= Ac, R^2= OAc, R^3= H
IIa: R^1 R^2 R^3 R^4 R^5 R^6= H
theasapogenol B
b: R^1 R^4 R^5 R^6= Ac, R^2 R^3= H
III : R^1 R^4 R^5 R^6= Ac, R^2= OAc
CO at C-16



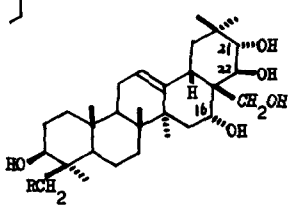
IVa: R = OAc
b: R = H



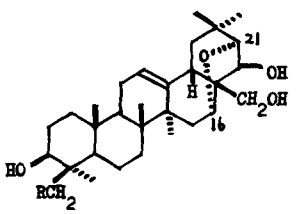
Va: R^1 R^2 R^3 R^4= H
b: R^2 R^3 R^4= Ac, R^1= H
c: R^1 R^3 R^4= H, R^2= Tr



(a) m/e 307 (b) m/e 348



VIIa: R = H
barringtogenol C
(= aescinidin)
b: R = OH
protoaescigenin
c: R = OH, Δ^{15}
isoaescigenin
(without OH at C-16)



VIa: R = H barringtogenol D
b: R = OH aescigenin

α-glycol configuration in ring E*. The result leading to the structure Ia for theasapogenol A having C_{21}β-OH and C_{22}α-OH configurations (trans diequatorial) seems to be an additional evidence for supporting the structure of theasapogenol B (IIa).

It has now become an important requisite to study further on the theasapogenols together with the above mentioned compounds in the sense of hydroxyl configurations in ring E, which will be discussed in more detail in a future paper.

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REFERENCES

1) I. Yosioka, T. Nishimura, A. Matsuda, I. Kitagawa: Tetrahedron Letters, (preceding paper).
2) H. Budzikiewicz, J.M. Wilson, C. Djerassi: J.Am.Chem.Soc., 85 3688(1963).
3) A. Gaudemer, J. Polonsky, E. Wenkert: Bull.soc.chim. Fr., 1964 407; M. Shamma, R. E. Glick, R. C. Mumma: J.Org.Chem., 27 4512(1962).
4) T. Kubota, F. Tonami, H. Hinoh: Tetrahedron Letters, 1966 701.
5) A.K. Barua, P. Chakrabarti: Tetrahedron, 21 381 (1965).
6) S.K. Chakraborti, A.K. Barua: Tetrahedron, 19 1727 (1963).
7) G. Cainelli, A. Melera, D. Arigoni, O. Jeger: Helv.Chim.Acta, 40 2390(1957).
8) R. Kuhn, I.Loew: Liebig's Ann., 669 183 (1963).
9) J.B. Thomson: Tetrahedron, 22 351 (1966).
10) R. Tschesche, G. Wulff: Tetrahedron Letters, 1965 1569.

* These compounds, whose structures were determined in the close relations, have been believed to have the C_{21}α-OH and C_{22}β-OH orientations (trans diaxial)(VIIa, b, and c) or the C_{21}-O-C_{16} ether linkage with the C_{22}β-OH configuration (VIa or b).