Communications to the Editor

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Acetyl Shengmanol, a Possible Parental Triterpene Acetate of Cimigenol and Cimigol from *Cimicifuga japonica*

A new triterpene glycoside (I) named acetyl shengmanol xyloside, mp 280—281°, $[\alpha]_D^{27}$ −23.7°, which was isolated from the underground part of *Gimicifga japonica*, yielded an amorphous aglycone (XII) on enzymatic hydrolysis. The peracetate of I afforded mainly 25-*O*-methylcimigenol (IV) along with cimigenol (V) and isodahurinol (VI) on acidic hydrolysis, while I gave cimigol xyloside (III), mp 297—299°, on alkaline treatment. The degradation of I with *meta*-periodate–cyclohexylamine gave an aldehyde–carboxylic acid, methyl ester of which has structure (IX).

From chemical and spectral evidence, the structure of acetyl shengmanol (XII) was proposed to be (23*R*, 24*S*)-24,25-epoxy-3β,15ξ-dihydroxy-23-acetoxy-9,19-cyclolanost-16-one. I is so unstable that it is readily convertible to cimigol xyloside (III) on alkaline treatment and to cimigenol (V) during acid hydrolysis. XII seems to be a precursor of cimigenol and cimigol in *C. japonica*. The mechanism of transformation of XII to V and VII was discussed.

Previously, we reported the isolation of a new triterpene glycoside (I), mp 280—281°, $[\alpha]_D^{27}$ −23.7° (CH_2Cl_2–CH_3OH (1 : 1)) from the underground part of *Cimicifuga japonica* (Thunb.) Sprengel (Ranunculaceae).[1] It is an acetate, now named acetyl shengmanol xyloside (IR ν_{max}^{KBr} cm^{-1}: 1735, 1230, NMR (d_5-pyridine) δ_H[2]: 2.05 (3H, s)). Acetylation of acetyl shengmanol xyloside (I) with acetic anhydride–pyridine afforded a peracetate (II), $C_{45}H_{66}O_{14}\cdot H_2O$, mp 188—189°, $[\alpha]_D^{20}$ −35.7° ($CHCl_3$), (NMR (d_5-pyridine) δ_H: 1.95 (3H, s), 2.02 (6H, s), 2.10 (3H, s), 2.17 (3H, s), Mass Spectrum *m/e*: 830 (M^+), 639 (M^+-2CH_3COOH- $\overset{O}{\overset{/\backslash}{CH}}-C(CH_3)_2$).[3] On treatment with sodium ethoxide in ethanol or with 2.5% methanolic (or ethanolic) potassium hydroxide, both I and II afforded a glycoside (III), mp 297—299°. The peracetate (II) was hydrolysed with 5% sulfuric acid in 50% aqueous methanol, yielding mainly 25-*O*-methylcimigenol (IV), mp 228—230°, along with cimigenol (V) and isodahurinol (VI), as the aglycone, and xylose as its sugar part.

We have previously reported a hydrolytic procedure for glycosides with sodium *meta*-periodate–cyclohexylamine.[4] This procedure was applied to hydrolysis of the glycoside (III) to give cimigol (VII),[5] mp 280—282°, $[\alpha]_D^{29}$ +114.7° (CH_2Cl_2–CH_3OH (1 : 1)), thus indicating that III is cimigol xyloside. The procedure was also applied to hydrolysis of acetyl shengmanol xyloside (I) to give an aldehyde–carboxylic acid (VIII). Alkaline treatment[6] and subsequent methylation of the acid (VIII) afforded a methyl ester (IX), mp 161—163°, $[\alpha]_D^{29}$ +44.8° (CH_2Cl_2–CH_3OH (1 : 1)), Mass Spectrum *m/e*: 518 ($C_{31}H_{50}O_6$), while alkaline treatment in a shorter period and subsequent methylation of VIII afforded a monoacetylated IX (X). IX and X yielded a same diacetate (XI), $C_{35}H_{54}O_8$, mp 176—177°, $[\alpha]_D^{34}$ +24.0° ($CHCl_3$), which no longer showed hydroxyl absorption in its infrared (IR) spectrum. The nuclear magnetic resonance (NMR) spectrum of the methyl ester (IX) showed a doublet due to the aldehyde carbon at δ_C[2] 206.7 as well as a singlet due to the ester carbon at δ_C 174.1.

1) N. Sakurai, M. Nagai, and T. Inoue, *Yakugaku Zasshi*, **95**, 1354 (1975).
2) NMR spectra were recorded using Me_4Si as internal standard. The chemical shifts are given in δ_H values (ppm) and in δ_C values (ppm) for proton and carbon respectively.
3) D. Lavie, M.K. Jain, and I. Kirson, *Tetrahedron Letters*, **1966**, 2049; C.W.L. Bevan and D.E.U. Ekong, *J. Chem. Soc.* (*C*), **1967**, 820.
4) M. Nagai, N. Sakurai, T. Inoue, and K. Kawai, *Yakugaku Zasshi*, **95**, 1350 (1975).
5) G. Kusano and T. Takemoto, *Yakugaku Zasshi*, **95**, 1133 (1975).
6) This alkaline treatment was carried out in order to convert a formate of VIII into VIII. See ref. 4).

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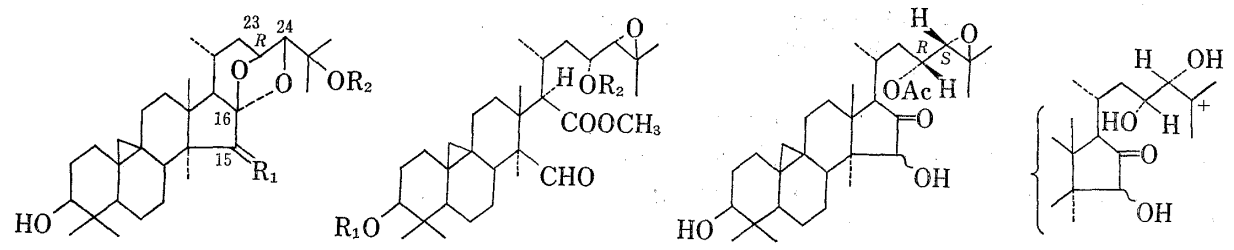
The α-carbon to the aldehyde function has no proton on it, since the aldehydic proton of the methyl ester (IX) was observed as a singlet at δ_H 9.43 in its NMR spectrum. The proton chemical shifts of the methyl ester (IX), the monoacetate (X) and the diacetate (XI) are summarized in Table I. In the nuclear magnetic double resonance experiments, the doublet at δ_H 2.76 of XI varied to a singlet on irradiation at δ_H 4.86, and the sextet at δ_H 4.86 to a quartet on irradiation at δ_H 2.76. The multiplet at δ_H 4.58 in XI is apparently ascribable to 3-H, and the other secondary carbinol carbon, the proton on which was observed as a sextet at δ_H 4.86, is adjacent to two carbons bearing at least three protons on them. From these findings, the oxygen atoms of the aglycone of I is considered to link to C-3,15,16,23,24 and 25 of 9,19-cyclolanostane skeleton, and the presence of 15-hydroxy-16-oxo- and 24,25-epoxy structures in I is presumed. The existence of a ketonic function at C-16 of I accounts for a strong negative Cotton effect, $[\theta]_{316}-1.86\times10^4$, in its circular dichroism (CD) curve.[7]

Table I. The Proton Chemical Shifts of IX, X and XI

	C-3-H	C-23-H	C-24-H	Methyl groups attached at C-25
IX	3.24m	~3.5m	2.68 d (J=7.2)	1.26 s (3H), 1.41 s (3H)
X	3.26m	4.83m	2.74 d (J=7.2)	1.29 s (6H)
XI	4.58m	4.86 (sextet)	2.76 d (J=7.2)	1.31 s (6H)

In order to obtain the genuine aglycone of I, enzymatic hydrolysis using crude hesperidinase[8] was applied to the xyloside. The aglycone, acetyl shengmanol (XII) was isolated as an amorphous substance, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600—3400 (OH), 1738 (shoulder), 1730, 1235 (ketone and acetate); NMR (CCl_4) δ_H: 2.07 (s, CH_3COO–), 2.65 (1H, d, J=8.4 Hz, 24-H), 3.22 (1H, m, 3-H), 3.88 (1H, br. s, 15-H), 4.90 (1H, m, 23-H); Mass Spectrum m/e: 530 (M^+), 470 (M^+-CH_3COOH); CD $[\theta]_{316}-1.11\times10^4$. Acetyl shengmanol (XII) afforded cimigol (VII) when treated with alkali, and the diacetate (XI) when subjected to periodate oxidation followed by methylation and acetylation.

Transformation of acetyl shengmanol (XII), the aglycone of the xyloside (I), to cimigenol (V) and to cimigol (VII) could be rationalized as follows. The acid-catalized opening of the 24,25-epoxide seems to proceed through a carbonium ion intermediate shown as ion a in



IV: $R_1=\langle^{H}_{OH}$, R_2=CH_3, 24S

V: $R_1=\langle^{H}_{OH}$, R_2=H, 24S

VII: $R_1=\langle^{OH}_{H}$, R_2=H, 24R

IX: $R_1=R_2$=H

X: R_1=H, R_2=$COCH_3$

XI: $R_1=R_2$=$COCH_3$

XII

ion a

Chart 1

7) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill, New York, 1960, Chapter IV.
8) H. Kohda and O. Tanaka, *Yakugaku Zasshi*, **95**, 246 (1975).

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Chart 1, with retention of the configuration at C-24. The resulted alcohol forms 24*S* ketal derivatives such as 25-*O*-methylcimigenol (IV) and cimigenol (V) during the acid hydrolysis of I. On the other hand, when I was treated with alkali, deacetylation and subsequent hemiketal formation between 16-keto group and 23-alcohol occur first and then the hemiketal hydroxyl at C-16 attacks C-24 of the epoxide with inversion of its configuration. This reaction mechanism explains the formation of 24*R*-ketal derivative such as cimigol xyloside (III) from I on alkaline treatment.

Based on the above described evidence and discussion, we propose the structure (XII) (23*R*, 24*S*) for acetyl shengmanol. It seems noteworthy that acetyl shengmanol xyloside (I) is unstable even in the separation procedures from the plant material, and that I is readily convertible to cimigol xyloside (III) on alkaline treatment, and to cimigenol (V) during its acid hydrolysis. We consider that acetyl shengmanol (XII) is a precursor of cimigenol (V) and cimigol (VII) in *Cimicifuga japonica.*

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Studies on the Structure Activity Relationship of Adrenergic β-Mimetic Benzylamine Derivatives. II.[1] 1-Alkylamino-2-phenyl-1,2,3,4-tetrahydronaphthalenes

The synthesis and adrenergic activity of stereoisomeric 1-methylamino- and 1-isopropylamino-2-(3,4,5-trimethoxyphenyl)-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalenes (IIa,b and IIIa,b), rigid structures related to the benzylamine derivatives (I), are presented. These compounds were found to possess direct β-stimulating activity both in the isolated tracheal and right atrial preparations of the guinea pigs. The structure-activity relationship in this series is described.

In the previous paper,[1] appropriately substituted benzylamine derivatives (I), fragmented derivatives of trimetoquinol (TMQ), were reported to be directly acting β-mimetics. In this series of compounds (I), the spatial arrangement of the nitrogen atom, the catechol and the trimethoxyphenyl group, which are necessary to manifest the β-mimetic actions, is flexible, while in TMQ the spatial relationship between the nitrogen atom and the catechol group is fixed.

In continuation of our study on the steric requirements for the manifestation of the β-mimetic actions, *cis*- and *trans*-isomers of 1-methylamino- and 1-isopropylamino-2-(3,4,5-trimethoxyphenyl)-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (IIa, b and IIIa, b), conformationally more rigid compounds than the benzylamine derivatives (I), were synthesized and tested for their β-mimetic actions.

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1) Y. Iwasawa, M. Ohashi, S. Yamamura, S. Saito, and A. Kiyomoto, *Japan, J. Pharmacol.*, **26**, 133 (1976).

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