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Chemical Studies on Breynin A, Breynogenin and Breynolide

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The structure of breynogenin ($C_{22}H_{26}O_9S$), an aglycone of breynin A, was established as III on the basis of chemical and spectral investigations. The structure of isobreynogenin ($C_{22}H_{26}O_9S$), a secondary degradation product from breynin A, was determined as IV. Partial structure for breynin A has been presumed.

In the previous paper,[2] we described the isolation from *Breynia officinalis* Hemsl of new sulfur-containing glycosides, breynins A ($C_{40}H_{56}O_{23}S$) and B ($C_{40}H_{56}O_{24}S$), as well as their hypocholesterolemic activity in rats. This paper reports chemical studies on breynin A and its degradation products, breynogenin, isobreynogenin and breynolide.

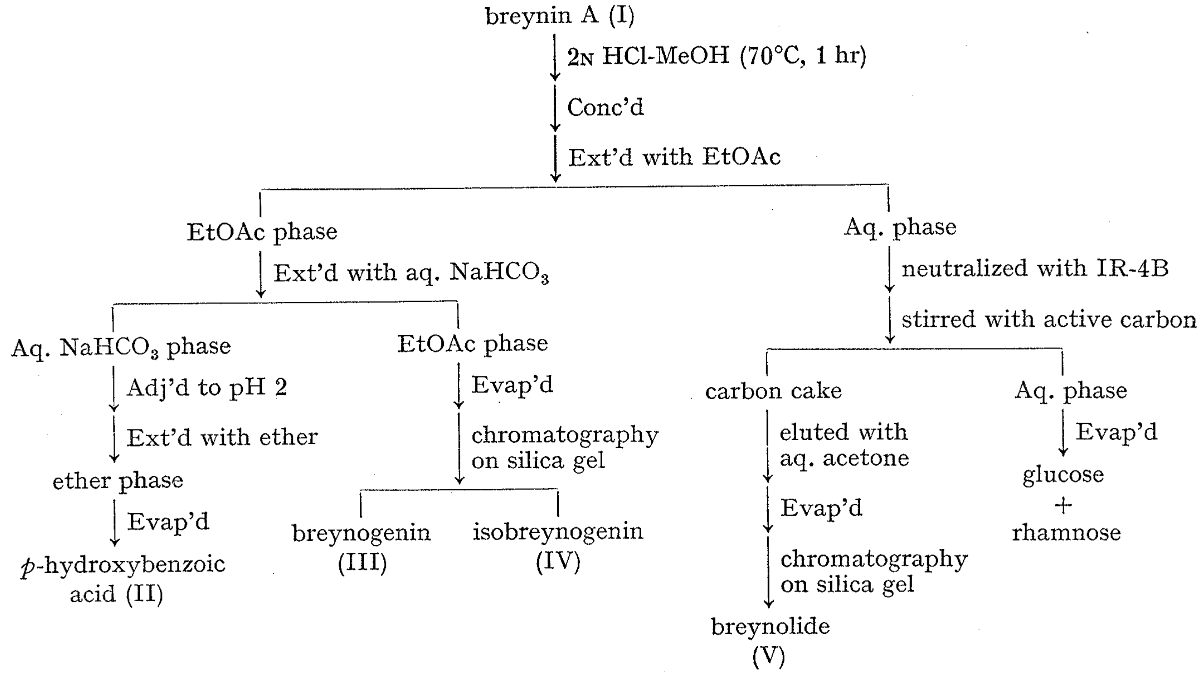

Chart 1. Isolation of Hydrolysis Products from Breynin A

Acid Hydrolysis of Breynin A (I)

Breynin A (I) was hydrolyzed by heating with 2N HCl in methanol for an hour. The hydrolyzate was fractionated as shown in Chart 1 yielding glucose, rhamnose, *p*-hydroxybenzoic acid (II) and the aglycone, breynogenin ($C_{22}H_{26}O_9S$, III), along with its secondary reaction products, isobreynogenin ($C_{22}H_{26}O_9S$, IV) and breynolide ($C_{15}H_{22}O_7S$, V). Further acid hydrolysis of III gave II and V. Breynogenin (III) showed a ultraviolet (UV) spectrum similar to that of I[2] with a maximum at 258 nm in methanol and three maxima at 288, 352

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[2] H. Koshiyama, M. Hatori, H. Ohkuma, F. Sakai, H. Imanishi, M. Ohbayashi, and H. Kawaguchi, *Chem. Pharm. Bull.* (Tokyo), 24, 169 (1976).

and 393 nm in alkaline methanol (Fig. 1). The infrared (IR) spectrum of III (Fig. 2) showed a characteristic high-frequency carbonyl band at 1780 cm^{-1} which was also present in I and V. The IR absorption band of III at 1705, 1680, 1280 and 770 cm^{-1}, the presence of ring proton signals at δ 6.90 and 7.96 in the NMR spectrum of III (Fig. 3) and the lack of the UV absorption maximum at 258 nm in V suggested that III is a *p*-hydroxybenzoyl ester of V.

Reactions of Breynogenin (III) (Chart 2)

Treatment of III with acetic anhydride in pyridine at 0° gave triacetylbreynogenin (VI, $C_{28}H_{32}O_{12}S$), while the tetraacetate (VII, $C_{30}H_{34}O_{13}S$) was obtained by acetylation at 70°. The acetylation of VI at 70° also afforded VII. In the comparative nuclear magnetic resonance (NMR) analysis of III, VI and VII, two methine signals of III (δ 3.99 and 4.31) appeared at lower field (δ 5.00—5.31) in both VI and VII. Of the four O-acetyl signals in the NMR spectrum of VII, the chemical shifts for three was in the region of δ 1.92—2.12 and the other at δ 2.35. These data indicated that the four acetylation sites of III involved two secondary, one tertiary and one phenolic hydroxyl group. A one-proton multiplet at δ 5.33 in the NMR spectrum of III was assigned to the methine group bearing the *p*-hydroxybenzoyl ester moiety since the signal was shifted in the NMR spectrum of V.

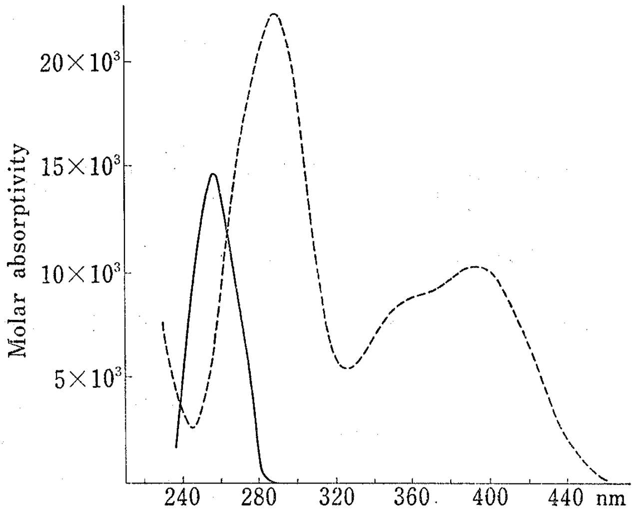

Fig. 1. UV Spectrum of Breynogenin (III)
——:MeOH, ----:1/10N NaOH-50% MeOH

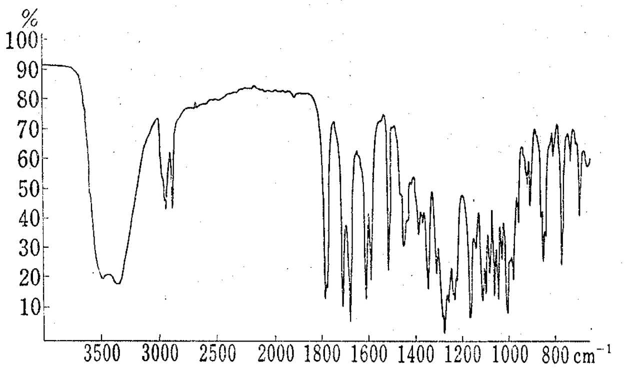

Fig. 2. IR Spectrum of Breynogenin (III) (in KBr pellet)

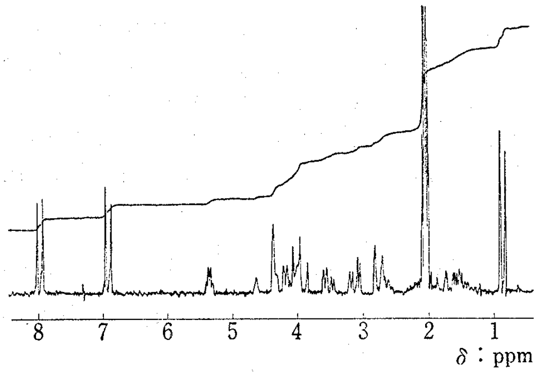

Fig. 3. NMR Spectrum of Breynogenin (III) (100 Mc, acetone-d_6)

Although III was inert to catalytic hydrogenation over Pd/C, the $NaBH_4$ reduction of III gave dihydrobreynogenin (VIII, $C_{22}H_{28}O_9S$) whose IR spectrum no longer showed the characteristic carbonyl band of III at 1780 cm^{-1}. The NMR spectrum of VIII in acetone-d_6 suggested the presence of five hydroxyl group signals at δ 4.03, 4.17, 4.60, 5.26 and 9.05 which disappeared upon addition of D_2O. Furthermore the $LiAlH_4$ reduction of III afforded *p*-hydroxybenzyl alcohol and dihydrobreynolide (IX, $C_{15}H_{24}O_7S$) which was also obtained by the treatment of VIII with $LiAlH_4$. These results excluded the possibility of the high-frequency (1780 cm^{-1}) carbonyl function being a γ-lactone, an enol ester or a ketone in a four-membered ring but suggested the possible presence of a tetrahydrofuranone ring in III.

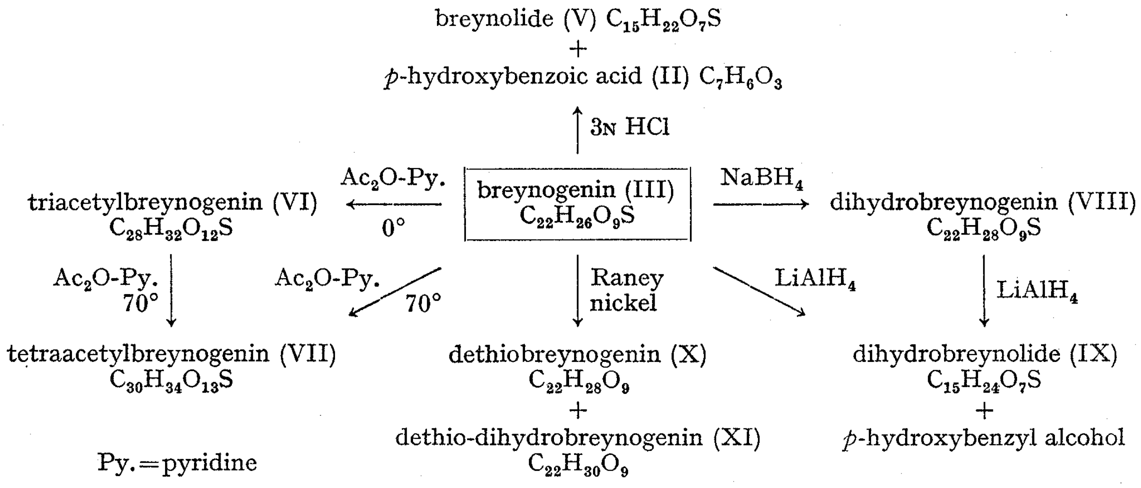

Chart 2. Reaction of Breynogenin (III)

Treatment of III with Raney nickel in boiling ethanol gave two desulfurized products, X ($C_{22}H_{28}O_9$) and XI ($C_{22}H_{30}O_9$). The IR absorption band at 1780 cm^{-1} remained in X but disappeared in XI, suggesting that a simultaneous desulfurization and carbonyl reduction took place in XI. The sulfur atom in III should be present as a sulfide or sulfoxide linkage since the possibility of thiol was excluded because of the lack of an SH band in the IR spectrum of III as well as the absence of a thioacetyl signal in the NMR spectrum of VII. The NMR spectrum of X showed a newly-formed doublet methyl signal at δ 0.87 and an increase of two protons in the 1.2—2.0 ppm region. These data along with a positive haloform reaction of X suggested a partial structure $\rangle CH{-}S{-}CH_2{-}\underset{|}{C}H{-}OH$ in III neighboring the sulfur atom. Chart 2 summarizes the above reactions of III, and Fig. 4 shows the partial structures involved in III, which are deduced from the information above.

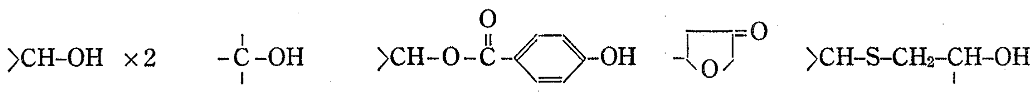

Fig. 4. Partial Structures of Breynogenin (III)

Structure of Breynogenin (III)

Because of the seeming difficulty in determining the complete structure of III only by the chemical and spectral means, and X-ray crystallographic study was undertaken by Sasaki and Hirata,[3] who determined the structure of breynolide (V) as shown in Fig. 5. As described above, III is a p-hydroxybenzoyl ester of V, and therefore the determination of the site of esterification should establish the total structure of III.

The NMR spectrum of III in dimethylsulfoxide (DMSO-d_6) showed signals for three alcoholic hydroxy groups. One of them with a singlet at δ 5.88, appeared to be a tertiary hydroxy group, indicating that the C-7 hydroxy group (see Fig. 5 for numbering) is unsubstituted in III. The desulfurization experiment on III described above suggested a partial structure of $\rangle CH{-}S{-}CH_2{-}\underset{|}{C}H{-}OH$ in III which indicated that the C-3 hydroxy group in the tetrahydrothiophene ring is free. As described later in the analysis of the NMR spectrum of III, the signal at δ 3.99 is assigned to the methine proton at position-6 which bears a secondary hydroxy group. Acetylation of III gave VI or VII in which a downfield shift (δ 5.00—5.31) of the C-6 methine signal was apparent, excluding the C-6 hydroxy group as the esterification site in III. Thus, the C-11 hydroxy group in the group in the tetrahydropyranyl ring must be esterified by the p-hydroxybenzoic acid. Other support for this assignment was obtained from the mass spectra of III and V. As shown in Fig. 6, both compounds gave

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[3] K. Sasaki and Y. Hirata, *Tetrahedron Letters*, **1973**, 2439.

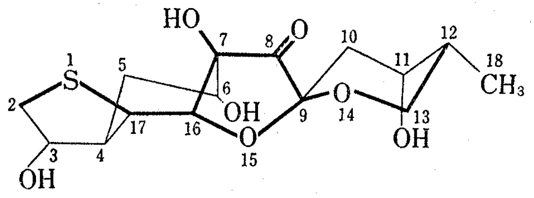

Fig. 5. Structure of Breynolide (V)

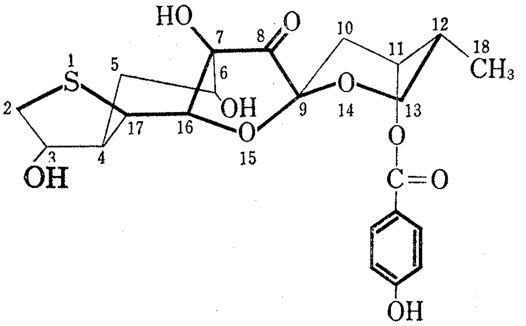

Fig. 7. Structure of Breynogenin (III)

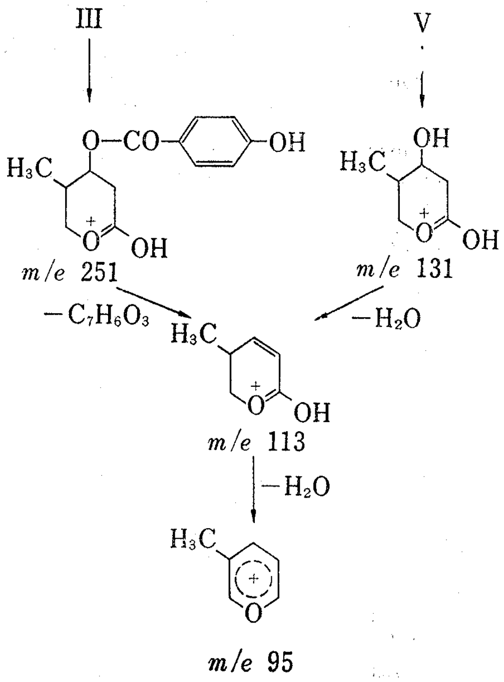

Fig. 6. Fragmentation of Breynogenin (III) and Breynolide (V) in Mass Spectroscopy

significant peaks assignable to the tetrahydropyranyl fragments with an *m/e* difference of 120 corresponding to the *p*-hydroxybenzoyl moiety.

The NMR spectrum of III indicated that the C-11 methine proton of III has the same equatorial conformation as was found with V, suggesting an S_N1-type elimination of the *p*-hydroxybenzoyl group during the acid hydrolysis of III. Thus the structure of III has been determined as shown in Fig. 7. In order to assign each of the proton signals in the NMR spectrum of III, the spin-decoupling experiments were carried out. The results are summarized and shown in Table I. This and the other NMR data described above led to a complete assignment of the protons of III as shown in Table II.

TABLE I. Spin-decoupling of Breynogenin (III) (100 MHz, in acetone-d_6)

Decoupled proton	Irradiated at (δ, ppm)			
	2.1—2.2 C_{10}-α,βH C_{12}–H	2.7 C_4–H	3.99 C_6–H	5.33 C_{11}–H
C_{12}–CH_3 (d, $J=7$)	singlet	—	—	—
C_{10}-α,βH (d-d, $J=13.5$, 3.5)	—	—	—	doublet ($J=13.5$)
C_5-αH (d-d-d, $J=13$, 4.5, 4.5)	—	deformed	deformed	—
C_5-βH (d-d-d, $J=13$, 13, 2)	—	deformed	deformed	—
C_{17}-H (d, $J=5$)	—	singlet	—	—
C_{11}-H (d-d-d, $J=3.5$, 3.5, 3.5)	singlet	—	—	—
C_{13}-αH (d-d, $J=11$, 4.5)	doublet ($J=11$)	—	—	—
C_{13}-βH (d-d, $J=11$, 11)	doublet ($J=11$)	—	—	—
C_3-H (m)	—	deformed	—	—

Table II. Proton Chemical Shifts of Breynogenin (III)

Protons	Chemical shift (δ, ppm)			Multiplicity	Coupling constant[a] (Hz)
	Acetone-d_6	DMSO-d_6	Pyridine-d_5		
C_{18}-methyl	0.85	0.75	0.85	d	$J_{12}=7$
C_5-αH	1.48	1.27	1.75	d-d-d	$J_{5\beta}=13,\ J_6=J_4=4.5$
C_5-βH	1.71	1.46	2.21	d-d-d	$J_{5\alpha}=J_4=13,\ J_6=2$
C_{10}-α,βH	2.1	1.92	2.50	d-d	$J_{10\alpha-10\beta}=13.5,$ $J_{10\alpha-11}=J_{10\beta-11}=3.5$
C_{12}-H	2.2	2.08	2.10	m	$J_{11}=3.5$
C_4-H	2.70		3.40	m	$J_{17}=5$
C_2-αH	3.12	3.00	3.34	d-d	$J_{2\beta}=11,\ J_3=4$
C_2-βH	2.75	2.62	3.10	d	$J_{2\alpha}=11$
C_{13}-αH	3.94	3.79	4.08	d-d	$J_{13\beta}=J_{12}=11$
C_{13}-βH	3.51	3.50	3.58	d-d	$J_{13\alpha}=11,\ J_{12}=4.5$
C_6-H	3.99	3.79	4.64	m	
C_{17}-H	4.16	3.93	4.93	d	$J_4=5$
C_3-H	4.31	4.14	4.64	m	$J_{2\alpha}=4$
C_{16}-H	4.35	4.17	5.12	s	
C_{11}-H	5.33	5.25	5.62	d-d-d	$J_{10\alpha}=J_{10\beta}=J_{12}=3.5$
Aromatic H (m, m′)	6.90	6.89	7.27	d	$J_o=8.5$
Aromatic H (o, o′)	7.96	7.90	8.38	d	$J_m=8.5$
C_3-OH		4.94 (or 4.98)			
C_6-OH		4.98 (or 4.94)			
C_7-OH		5.88			
Phenolic OH		11.35			

[a] J-suffix identifies the coupling proton only.

Structure of Isobreynogenin (IV)

Isobreynogenin (IV) was isolated from the hydrolyzate of I and differentiated from III by silica gel thin-layer chromatography (TLC). It analyzed for $C_{22}H_{26}O_9S$, the same formula as III, and gave a mass peak at m/e 328 corresponding to M^+-138 (p-hydroxybenzoic acid). The UV and IR spectra of IV were very similar to those of III, while differences were seen in the NMR spectra. The C-18 methyl signal at δ 0.85 (acetone-d_6) of III shifted to δ 1.12 in IV, and the equatorial methine proton at C-11 of III (m, δ 5.24—5.60) appeared in IV as a quintet-like signal in the region of δ 5.18—5.60 with a large coupling constant, suggesting an axial conformation of the C-11 proton in IV.

When III in hot methanol-d_4 was treated with a drop of conc. HCl, the NMR spectrum of the mixture showed two doublet methyl signals at δ 0.85 and 1.12 with nearly the same intensity. An identical NMR spectrum was obtained with IV after the same treatment, suggesting that III and IV were in equilibrium under acidic conditions. From the information obtained above, the structure shown in Fig. 8 is proposed for IV.

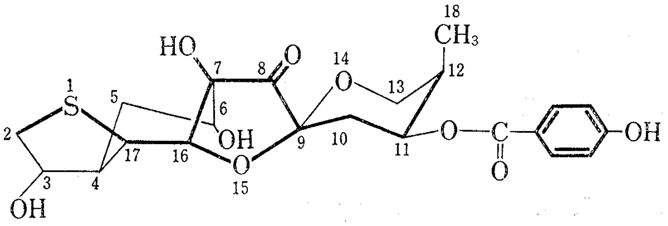

Fig. 8. Structure of Isobreynogenin (IV)

Structure of Breynin A (I)

The NMR spectrum of I[2] shows much greater similarity to that of III than that of IV, indicating that the aglycone structure of I has the same conformation as III but not IV, and that IV was a secondary degradation product during the acid hydrolysis. The site(s) and type of the glycosidic linkages in I have not yet been established. However, since the proton signal for the tertiary hydroxy group at C-7 is present in the NMR spectrum of I, either one or both of the two secondary hydroxy groups at C-3 and C-6 must have the sugar moieties in I.

Experimental

Isolation of Breynogenin (III), Isobreynogenin (IV) and Breynolide (V)——Breynin A (I, 9 g) was heated under reflux with 2 N HCl (60 ml) and MeOH (20 ml) for 1 hr. The reaction mixture was concentrated and extracted with EtOAc. The EtOAc extract was stirred with aqueous $NaHCO_3$ solution. The aqueous bicarbonate layer was separated and treated as shown in Chart 1 to give colorless needles of II which was identified as *p*-hydroxybenzoic acid by UV and IR spectra. The residue obtained after evaporation of the EtOAc layer was chromatographed on a silica gel column which was developed with a mixture of benzene and a increasing proportion of EtOAc. Elution with benzene–EtOAc (6: 4) afforded isobreynogenin (IV) as a white powder (406 mg). *Anal.* Calcd. for $C_{22}H_{26}O_9S$: C, 56.63; H, 5.63; S, 6.87. Found: C, 56.57; H, 6.30; S, 6.90. IR ν_{max}^{KBr} cm^{-1}: 3400, 1780, 1705, 1690, 1610, 1590, 1515, 1280, 770. UV λ_{max}^{MeOH} nm (log ε): 260 (4.18), $\lambda_{max}^{MeOH-NaOH}$: 289 (4.25), 348 (3.94). NMR (in DMSO–d_6) δ: 1.12 (3H, d), 5.38 (1H, m), 6.77 (2H, d), 7.82 (2H, d). Mass Spectrum *m/e*: 328 (M^+-138), 138 (*p*-hydroxybenzoic acid).

Further elution with benzene–EtOAc (5: 5) gave breynogenin (III) as colorless needles (from EtOAc, 584 mg), mp 260—262°, $[\alpha]_D^{22}$ +52° (c=0.5, MeOH). *Anal.* Calcd. for $C_{22}H_{26}O_9S$: C, 56.63; H, 5.63; S, 6.87. Found: C, 56.77; H, 5.48; S, 6.90. IR ν_{max}^{KBr} cm^{-1}: 3500, 3300, 1780, 1705, 1680, 1602, 1585, 1280, 980, 905, 850, 770. UV λ_{max}^{MeOH} nm (log ε): 258 (4.16), $\lambda_{max}^{MeOH-NaOH}$: 288 (4.24), 352 (3.93), 393 (4.01). NMR (in acetone-d_6) δ: 0.85 (3H, d), 1.48 (1H, m), 1.71 (1H, m), 2.1 (2H, d—d), 2.2 (1H, m), 2.7 (1H, m), 2.75 (1H, d), 3.12 (1H, d—d), 3.51 (1H, d—d), 3.94 (1H, t), 3.99 (1H, m), 4.16 (1H, d), 4.31 (1H, m), 4.35 (1H, s), 5.33 (1H, m), 6.90 (2H, d), 7.96 (2H, d). Mass Spectrum *m/e*: 448 (M^+–H_2O), 328 (M^+-138), 138 (*p*-hydroxybenzoic acid).

The aqueous layer obtained after the EtOAc-extraction of the acid hydrolyzate of I was neutralized with Amberlite IR-4B (OH^-) and stirred with activated carbon for 2 hr. After filtration, the carbon cake was eluted with aqueous acetone, the solvent evaporated and the residue chromatographed on silica gel. Elution with EtOAc gave colorless needles (157 mg) of breynolide (V), mp 241—243°. *Anal.* Calcd. for $C_{15}H_{22}O_7S$: C, 52.01; H, 6.40; S, 9.26. Found: C, 52.06; H, 6.40; S, 9.26. IR ν_{max}^{KBr} cm^{-1}: 3500, 3350, 1780, 1390, 1050, 1010, 860. UV λ_{max}^{MeOH} nm (log ε): no max, $\lambda_{max}^{MeOH-NaOH}$: 349 (3.85). NMR (in DMSO–d_6) δ: 0.84 (3H, d), 1.29 (1H, m), 1.49 (1H, m), 1.68 (2H, d), 2.55 (1H, d), 2.93 (1H, d—d), 3.43 (1H, m), 3.5—4.0 (3H, m), 4.1 (1H, s), 4.2 (1H, m) 4.85 (2H, d), 5.55 (1H, s). Mass Spectrum *m/e*: 346 (M^+–H_2O).

The filtrate after the above carbon absorption was evaporated, and the residue was examined by PPC (isoamyl alcohol–pyridine–H_2O=1: 1: 1), TLC (silica gel plate, *n*–BuOH–acetone–AcOH–H_2O=4: 5: 1: 1) and, after trimethylsilylation of the sample, by GLC. D-glucose and L-rhamnose were identified.

Triacetyl Breynogenin (VI)——III (100 mg) was acetylated with Ac_2O (2 ml) and pyridine (2 ml) overnight at 0°. The reaction mixture was diluted with ice-water and extracted with EtOAc. After removal of the solvent, the residue was subjected to silica gel column chromatography. Elution with benzene–EtOAc (9: 1) gave triacetate VI (77 mg) as a white powder, mp 93—95°. *Anal.* Calcd. for $C_{28}H_{32}O_{12}S$: C, 56.74; H, 5.45; S, 5.41. Found: C, 57.50; H, 5.88; S, 4.83. IR ν_{max}^{KBr} cm^{-1}: 3450, 1780, 1745, 1720, 1602, 1505. UV λ_{max}^{MeOH} nm (log ε): 236 (4.31), $\lambda_{max}^{MeOH-NaOH}$: 300 (4.45), 354 (3.90). NMR (in $CDCl_3$) δ: 0.95 (3H, d), 1.94 (3H, s), 1.96 (3H, s), 2.30 (3H, s), 4.94—5.25 (3H, m). Mass Spectrum *m/e*: 574 (M^+–H_2O).

Tetraacetyl Breynogenin (VII)——III (50 mg) was acetylated with Ac_2O (2 ml) and pyridine (2 ml) at 70—80° for 5 hr. The reaction product was precipitated by an addition of ice-water and purified by silica gel column chromatography. Elution with *n*–hexane–benzene (1: 1) gave the tetraacetate VII (23 mg) as an amorphous white powder, mp 96—98°. *Anal.* Calcd. for $C_{30}H_{34}O_{13}S$: C, 56.77; H, 5.40; S, 5.05. Found: C, 57.15; H, 5.60; S, 4.95. IR ν_{max}^{KBr} cm^{-1}: 1782, 1750, 1715, 1600, 1500. UV λ_{max}^{MeOH} nm (log ε): 236 (4.17), $\lambda_{max}^{MeOH-NaOH}$: 299.5 (4.36), 352 (3.76). NMR (in $CDCl_3$) δ: 0.96 (3H, d), 1.92 (3H, s), 1.98 (3H, s), 2.42 (3H, s), 2.35 (3H, s), 5.0—5.31 (3H, m), 7.07 (2H, d). 8.02 (2H, d). Mass Spectrum *m/e*: 394 (M^+-240, loss of *p*-acetoxybenzoic acid + acetic acid).

VI (30 mg) was acetylated with Ac_2O (2 ml) and pyridine (2 ml) at 70—80° for 5 hr. The reaction product was treated in the same manner as above to give 20 mg of VII.

Dihydrobreynogenin (VIII)——III (150 mg) in EtOH (20 ml) was stirred with $NaBH_4$ (150 mg) for 3 hr at room temperature and then heated at 70° for 30 min. The reaction mixture was diluted with water and extracted by EtOAc. The solvent was evaporated and the residue chromatographed on silica gel column. Elution with EtOAc gave VIII (50 mg) as colorless needles, mp 230°. *Anal.* Calcd. for $C_{22}H_{28}O_9S$: C, 54.08; H, 6.61; S, 6.56. Found: C, 54.55; H, 6.47; S, 6.16. IR ν_{max}^{KBr} cm^{-1}: 3480, 3328, 1707, 1675, 1602, 1585, 1510, 1280, 1000, 850, 770. UV λ_{max}^{MeOH} nm (log ε): 258 (4.04), $\lambda_{max}^{MeOH-NaOH}$: 300 (4.23). NMR (in acetone-d_6) δ: 0.75 (3H, d), 4.03, 4.17, 4.60, 5.26, 9.05 (OH × 5), 5.20 (1H, m), 6.82 (2H, d), 7.93 (2H, d). Mass Spectrum *m/e*: 450 (M^+–H_2O), 396 (M^+–$3H_2O$), 330 (M^+-138), 138 (*p*-hydroxybenzoic acid).

Dihydrobreynolide (IX)——III (200 mg) in anhydrous tetrahydrofuran (THF) was stirred with $LiAlH_4$ (300 mg) at 70° for 3 hr. Excess reagent was decomposed by H_2O. The reaction mixture was washed with EtOAc, evaporated *in vacuo*, and the residue extracted with hot methanol. The methanolic extract was chromatographed on silica gel column. Elution with EtOAc gave IX (66 mg) as colorless needles (from benzene–EtOAc). High Mass Spectrum: Calcd. for $C_{15}H_{24}O_7S$: 348.421. Found: 348.124. IR ν_{max}^{KBr} cm^{-1}: 3400, 1020—1000. UV λ_{max}^{MeOH} nm (log ε): no max, $\lambda_{max}^{MeOH-NaOH}$: no max. NMR (in DMSO-$d_6$) δ: 0.85 (3H, d).

The EtOAc washing in the above experiment was evaporated and the residue afforded colorless crystal, which were identified as *p*-hydroxybenzyl alcohol by IR and TLC.

VIII (60 mg) in THF (10 ml) was reduced with $LiAlH_4$ (200 mg). The products were separated in the same way as described above to give 34 mg of IX.

Dethiobreynogenin (X) and Dethio-dihydrobreynogenin (XI)——III (200 mg) in EtOH (30 ml) was heated with excess amount of Raney Ni at 80—90° for 20 hr. The reaction mixture was filtered, the solvent evaporated and the residue subjected to silica gel column chromatography. Elution with benzene–EtOAc (6: 4) gave white powder X (51 mg), mp 125°. *Anal.* Calcd. for $C_{22}H_{28}O_9$: C, 60.54; H, 6.47. Found: C, 60.38; H, 6.58. IR ν_{max}^{KBr} cm^{-1}: 3400, 1770—1680, 1602, 1590, 1510, 1280, 850, 770. UV λ_{max}^{MeOH} nm (log ε): 258 (4.29), $\lambda_{max}^{MeOH-NaOH}$: 299 (4.42), 350 (3.89). NMR (in DMSO-d_6) δ: 0.75 (3H, d), 0.87 (3H, d), 1.2—2.0 (4H, m), 5.03 (1H, m), 6.74 (2H, d), 7.90 (2H, d). Mass Spectrum *m/e*: 298 (M^+-138), 138 (*p*-hydroxybenzoic acid).

Further elution with EtOAc gave white powder XI (21 mg), mp 112—113°. Mass Spectrum Calcd. for $C_{22}H_{30}O_9$: 438.472. Found: 438.188. IR ν_{max}^{KBr} cm^{-1}: 3400, 1690, 1610, 1520, 1280, 1000, 850, 770. UV λ_{max}^{MeOH} nm (log ε): 259 (4.01), $\lambda_{max}^{MeOH-NaOH}$: 300 (4.17). NMR (in DMSO-d_6) δ: 0.85 (3H, d), 0.95 (3H, d), 5.1 (1H, m), 6.70 (2H, d), 7.80 (2H, d). Mass Spectrum *m/e*: 438 (M^+), 300 (M^+-138).

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