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Chemical Studies on the Oriental Plant Drugs. XXII.[1] Some New Constituents of Licorice Root. (2).[2] Glycyrol, 5-O-Methylglycyrol and Isoglycyrol

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From the root of licorice (*Glycyrrhiza* spp., Leguminosae) three new coumestan derivatives, named glycyrol, 5-O-methylglycyrol and isoglycyrol, have been isolated, whose structures have been established to be Ia, IIa and IIIa, respectively. Betulic acid was also obtained.

From the sodium carbonate-soluble fraction of methanol extracts of licorice root, a colourless crystalline substance, mp 243.5—245°, $C_{21}H_{18}O_6$, named glycyrol (Ia), was obtained.

On the other hand, from the later part of the elution of silica gel column chromatography of the fraction D from which the first naturally occurring isoflavan, licoricidin,[2] was separated, two fluorescent substances named isoglycyrol (IIIa), mp 298—300° (decomp.), $C_{21}H_{18}O_6$, and 5-O-methylglycyrol (IIa), mp 259—260.5°, $C_{22}H_{20}O_6$, were isolated.

Table I. The UV and IR Spectra of Glycyrol (Ia), 5-O-Methyl-glycyrol (IIa) and Isoglycyrol (IIIa)

	Glycyrol	5-O-Methylglycyrol	Isoglycyrol
UV λ_{max}^{EtOH} mμ (log ε)	227 (4.49)	229 (4.50)	224 (4.38 sh).
	244 (4.36)	247 (4.35 sh.)	248 (4.34)
	256 (4.26 infl.)	264 (4.14 infl.)	256 (4.27 infl.)
	347 (4.42)	346 (4.38)	348 (4.40)
	356 (4.38 infl.)	362 (4.32 infl.)	356 (4.36 infl.)
IR ν_{max}^{KBr} cm^{-1}	3440	3240	3250
	3370	1697 (δ-lactone)	1705 (δ-lactone)
	1717 (δ-lactone)	1625 (sh.)	1625
	1632	1612	1588
	1614	1583	1504
	1595	1554	
	1514	1504	

The infrared (IR) absorption at 1705 cm^{-1} in isoglycyrol (IIIa), and 1717 cm^{-1} in glycyrol (Ia) indicated the presence of δ-lactone system in their molecules. 5-O-Methylglycyrol (IIa) was identified with the product which was prepared from glycyrol (Ia) on the partial methylation. The ultraviolet (UV) spectra of these three natural products (Table I) resembled those of medicagol[4] (VI), erosnin[5] (VII) and psoralidin[6] dimethyl ether (VIIIb) suggesting that the three new compounds would be coumestan derivatives (Fig. 1).

1) Part XXI: M. Kaneda, E. Morishita, and S. Shibata, *Chem. Pharm. Bull.* (Tokyo), **17**, 665 (1969).
2) Part (1): S. Shibata and T. Saitoh, *Chem. Pharm. Bull.* (Tokyo), **16**, 1932 (1968).
3) Location: *Hongo, Tokyo.*
4) A.L. Livingston, S.C. Witt, R.E. Lundin, and E.M. Bickoff, *J. Org. Chem.*, **30**, 2353 (1965).
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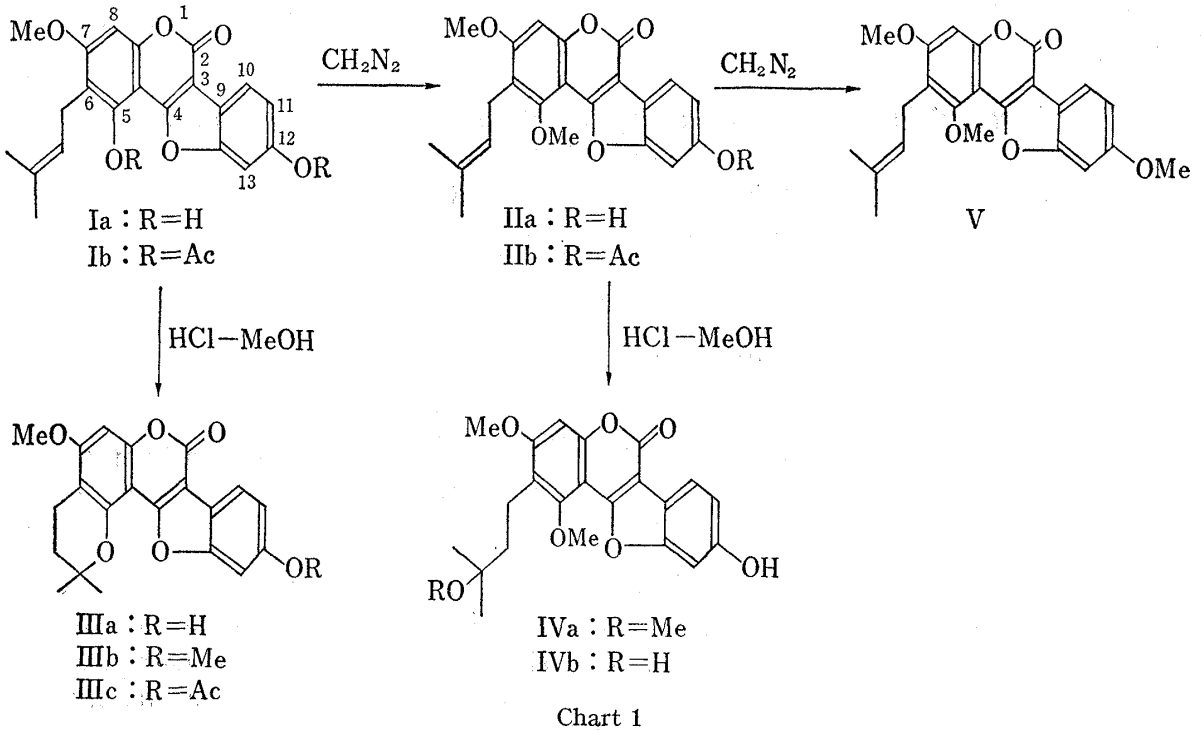
6) H.N. Khastgir, P.C. Duttagupta, and P. Sengupta, *Tetrahedron*, **14**, 275 (1961).



Ia : R=H
Ib : R=Ac
IIa : R=H
IIb : R=Ac
V
IIIa : R=H
IIIb : R=Me
IIIc : R=Ac
IVa : R=Me
IVb : R=H

Chart 1

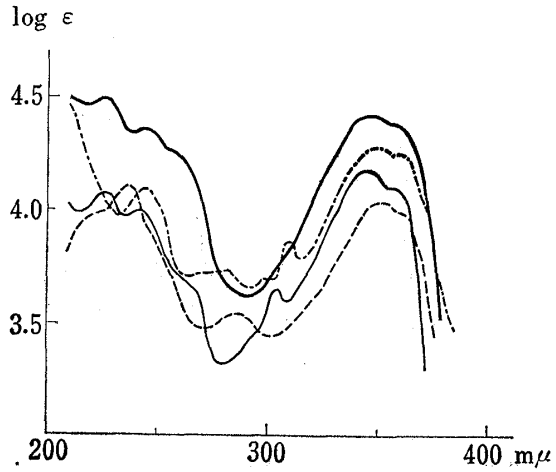


Fig. 1. The UV Spectra of Glycyrol (Ia) (——), Medicagol (VI) (— — —), Erosnin (VII) (- - - - -) and Psoralidin Dimethyl Ether (VIIIb) (— · —) in Ethanol

The nuclear magnetic resonance (NMR) spectrum (Table II) showed that glycyrol (Ia) possesses one isopentenyl group, one methoxyl and four aromatic protons, and the presence of two hydroxyls were proved by the formation of diacetate. The presence of 2,2-dimethylchroman ring system in isoglycyrol (IIIa) was proved by the NMR spectrum, and by the fact that the isopentenyl side chain of glycyrol (Ia) was cyclized with the neighbouring hydroxyl to form isoglycyrol (IIIa). On the other hand, 5-O-methylglycyrol (IIa) possesses one isopentenyl group, two methoxyls, four aromatic protons and one hydroxyl group which was confirmed by acetylation.

One methoxyl and four aromatic protons in isoglycyrol (IIIa) were shown by the NMR spectrum, while one hydroxyl was proved by acetylation to form monoacetate.

The location of substituents in the coumestan nucleus of glycyrol (Ia) was discussed by the NMR spectrum of glycyrol diacetate (Ib) (Fig. 2).

One of the aromatic protons of glycyrol (Ia) gave a doublet signal in the noticeably low field (δ 8.02), which might be attributed to $C_{(10)}$–H by the deshielding effect of carbonyl at $C_{(2)}$.[4] Another aromatic proton (δ 7.11) showing *ortho*-coupling (J=8.5 cps) with the above proton should be $C_{(11)}$–H. The proton signal at δ 7.46 which showed a meta coupling with $C_{(11)}$–H must be $C_{(13)}$–H.

A hydroxyl should be present at $C_{(12)}$, and the remaining one must be located at $C_{(5)}$ or $C_{(7)}$ which would be explained reasonably from the biogenetical view point. It was reported that the λ_{max} of the UV spectrum of coumestan having a hydroxyl group at $C_{(7)}$ position

TABLE II. Nuclear Magnetic Resonance Spectral Data of Glycyrol and the Other Related Compounds

	8-H	10-H	11-H	13-H	Methoxyl	Acetate methyl	γ,γ-Dimethylallyl			2,2-Dimethylchroman			Solvent
							$-CH_2-$	$-CH=C$	$C=C(Me)_2$	$-CH_2-$ (benzyl)	$-CH_2-$	$-O-C(Me)_2-$	
Glycyrol (Ia)	6.78	7.70 (d, J=9.0)	6.95 (q, J=9.0 and 2.5)	7.17 (d, J=2.5)	3.94		3.36 (d, J=7)	5.20 (t, J=7)	1.68 1.78				a
Glycyrol dimethyl ether (V) (=5-O-methylgycyrol monomethyl ether)	6.77	7.92 (d, J=9.0)	7.01 (q, J=9.0 and 2.5)	7.17 (d, J=2.5)	3.90 3.90 3.99		3.42 (d, J=7)	5.18 (t, J=7)	1.69 1.82				b
Glycyrol diacetate (Ib)	6.98	8.02 (d, J=8.5)	7.11 (q, J=8.5 and 2.5)	7.46 (d, J=2.5)	3.98	2.31 2.33	3.33	5.04	1.68 1.76				b
5-O-Methylglycyrol (IIa)	6.92	7.68 (d, J=9.0)	6.96 (q, J=9.0 and 2.5)	7.15 (d, J=2.5)	3.89 3.89		3.29** (d, J=7)	5.13 (t, J=7)	1.65 1.74				a
5-O-Methylglycyrol monoacetate (IIb)*	6.84	8.16 (d, J=8.7)	7.26 (q, J=8.7 and 2.0)	7.55 (d, J=2.0)	3.93 3.98	2.35	3.46 (d, J=7)	5.20 (t, J=7)	1.70 1.82				b
Compound A (IVa)*	6.99	7.84 (d, J=8.7)	7.44 (q, J=8.7 and 2.0)	7.24 (d, J=2.0)	3.25 3.99 4.02					(2.74	1.69	1.22 1.22)	c
Isoglycyrol (IIIa)*	6.67	7.74 (d, J=8.7)	6.97 (q, J=8.7 and 2.0)	7.38 (d, J=2.0)	3.96					2.80 (t, J=7)	1.81 (t, J=7)	1.34 1.34	a
Isoglycyrol monomethyl ether (IIIb)	6.66	7.89 (d, J=8.7)	6.97 (q, J=8.7 and 2.0)	7.15 (d, J=2.0)	3.88 4.01					2.86 (t, J=7)	1.85 (t, J=7)	1.38 1.38	b
Isoglycyrol monoacetate (IIIc)	6.70	8.05 (d, J=8.7)	7.15 (q, J=8.7 and 2.0)	7.48 (d, J=2.0)	4.00	2.37				2.87 (t, J=7)	1.87 (t, J=7)	1.39 1.39	b

The spectra were determined in d_6-DMSO (a), $CDCl_3$ (b), and d_6-DMSO–d_6-acetone (1:3) solution (c) with tetramethyl silane as an internal standard at 60 Mc/sec except * marked compounds at 100 Mc/sec.

Unless otherwise indicated, all signals are singlets. In other cases d=doublet, t=triplet, q=quartet and the coupling constants J are given in c/s. Chemical shifts are on the δ scale.

** was overlapped with the signal of H_2O.

underwent a bathochromic shift in the presence of sodium acetate.[7] The UV spectrum of glycyrol (Ia), however, gave no shift of the absorption band by the addition of sodium acetate. This result suggested that a methoxyl group of glycyrol (Ia) would be located at $C_{(7)}$ position.

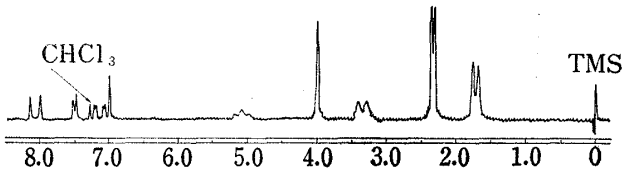
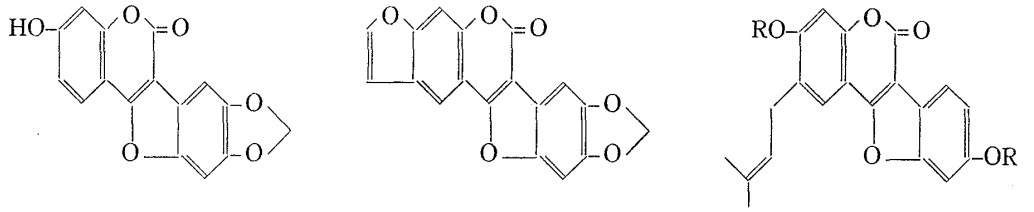


Fig. 2. The NMR Spectrum of Glycyrol Diacetate (Ib) (60 Mc/sec in $CDCl_3$, δ Value)



VI VII VIIIa : R=H VIIIb : R=Me

Chart 2

Consequently, one of two hydroxyls would be located at $C_{(5)}$ position, and then the isopentenyl group at $C_{(6)}$ position, because the acid-catalyzed cyclization occured to form a chroman ring.

Furthermore the Gibbs test[8] was positive (the absorption appeared at 691 mμ) to prove the location of another hydroxyl group at $C_{(12)}$.

The structure of 5-O-methylglycyrol (IIa) was confirmed by the following experimental results. (1) It was identified with the product which was obtained from the partial methylation of glycyrol (Ia). The methylation would be predominantly occured at the hydroxyl group of $C_{(5)}$ position, because it was more acidic than that of $C_{(12)}$. (2) In the NMR spectrum of 5-O-methylglycyrol (IIa), only the chemical shift of a singlet aromatic proton differed from that of glycyrol (Ia), whereas the signals of the other three aromatic protons appeared at almost the same position as those of glycyrol. (3) On treatment of methanolic hydrochloric acid, 5-O-methylglycyrol (IIa) gives compound A (IVa) and B (IVb) by the addition of methanol and water, respectively, whereas glycyrol (Ia) underwent isomerization to isoglycyrol (IIIa) under the formation of chroman ring by the same reagent. The NMR and Mass spectra of compound A indicated the structure (IVa). Compound B could not be examined fully due to shortage of the material, but the structure would be represented by IVb in comparison of its Mass and UV spectra with those of compound A.

These results indicated that the structures of glycyrol, 5-O-methylglycyrol and isoglycyrol must be represented by Ia, IIa and IIIa, respectively.

Isoglycyrol might be the first example of the compound having a 2,2-dimethylchroman ring isolated from the higher plants.

The coumestans so far known in nature are wedelolactone,[9] norwedelolactone,[9] coumestrol,[10] erosnin,[5] psoralidin,[6] trifoliol,[7b] medicagol,[4] 4'-methylcoumestrol,[11] lucernol,[12] sativol,[12] 7-hydroxy-11,12-dimethoxycoumestan.[7c]

And also betulic acid was first isolated from the root of licorice.

7) *a*) L. Jurd, *J. Org. Chem.*, **24**, 1786 (1959); *b*) A.L. Livingston, E.M. Bickoff, R.E. Lundin, and L. Jurd, *Tetrahedron*, **20**, 1963 (1964); *c*) R.R. Spencer, B.E. Knuckles, and E.M. Bickoff, *J. Org. Chem.*, **31**, 988 (1966).
8) H.D. Gibbs, *J. Biol. Chem.*, **72**, 649 (1927); F.E. King, T.J. King, and L.C. Manning, *J. Chem. Soc.*, **1957**, 563.
9) T.R. Govindachari, K. Nagarayan, B.R. Pai, and P.C. Parthasarathy, *J. Chem. Soc.*, **1957**, 545.
10) E.M. Bickoff, R.L. Lyman, A.L. Livingston, and A.N. Booth, *J. Am. Chem. Soc.*, **80**, 3969 (1958).
11) A.L. Livingston, E.M. Bickoff, S.C. Witt, R.I. Lundin, and R.R. Spencer, *J. Agric. Food. Chem.*, **13**, 597 (1965).

Experimental[13]

Isolation of Glycyrol (Ia)——The fraction E was chromatographed on calcium hydrogen phosphate. Elution with ether gave a number of fractions which were chromatographed again on silica gel yielded glycyrol, a fluorescent substance, and isoliquiritigenin. By the infrared spectrum and thin-layer chromatography, isoliquiritigenin was identified with authentic sample which was derived from liquiritin on the hydrolysis with acid and base.

Glycyrol was recrystallized from ethanol to give colourless needles (yield 0.001%). mp 243.5—245°, UVλ_{max} (EtOH–AcONa); unchanged. Gibbs' test; positive (691 mμ). *Anal.* Calcd. for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 68.91; H, 5.07.

Glycyrol Diacetate (Ib)——A mixture of glycyrol (Ia) (100 mg), acetic anhydride (1 ml) and pyridine (1 ml) was kept at room temperature overnight, and then poured into ice water. The solid was collected and recrystallization from methanol gave glycyrol diacetate (80 mg) as colourless needles, mp 195—196°. UV λ_{max}^{EtOH}mμ (log ε): 204 (4.63), 228 (4.56), 236 (4.49 infl.), 259 (3.99 sh.), 290 (3.90 infl.), 317 (4.32 sh.), 329 (4.42), 344 (4.32). IR ν_{max}^{KBr}cm^{-1}: 1775 (sh.), 1752, 1624, 1589, 1559, 1493, 1362, 1198; $\nu_{max}^{CHCl_3}$ cm^{-1}: 1768 (sh.), 1752 (sh.), 1747, 1624, 1588, 1495, 1366, 1191. Mass spectrum: *m/e* 450 (25.7%), 408 (29.1), 366 (base peak), 348 (4.2), 335 (8.4), 321 (4.2), 311 (44.2), 296 (10.1), 295 (9.3), 279 (8.0), 267 (5.9), 253 (2.9), 69 (9.3). *Anal.* Calcd. for $C_{25}H_{22}O_8$: C, 66.66; H, 4.92. Found: C, 66.59; H, 4.99. mol. wt. 450 (Mass).

Glycyrol Monomethyl Ether (IIa) and Dimethyl Ether (V)——To a solution of glycyrol (Ia) (90 mg) in methanol was added a solution of diazomethane in ether at room temperature. After standing for 30 min the solvent was removed under diminished pressure. Silica gel chromatography of the solid gave glycyrol monomethyl ether (IIa) (16 mg) and glycyrol dimethyl ether (V) (56 mg).

Glycyrol Monomethyl Ether (IIa): mp 260—262° (from acetone), was identified with 5-O-methylglycyrol (IIa) by the infrared spectrum and thin-layer chromatography.

Glycyrol Dimethyl Ether (V): mp 206.5—207.5° (from acetone), UV λ_{max}^{EtOH} mμ (log ε): 209 (4.55), 230 (4.53), 243 (4.39), 254 (4.25), 263 (4.13), 344 (4.43), 357 (4.36). IR λ_{max}^{KBr} cm^{-1}: 1750, 1615, 1595, 1505, 1372, 1274, 1118, 1008, 835, 810; $\lambda_{max}^{CCl_4}$ cm^{-1}: 1748, 1620, 1595, 1504. *Anal.* Calcd. for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62. Found: C, 70.13; H, 5.58.

Acid-catalized Cyclization of Glycyrol (Ia) (Formation of Isoglycyrol (IIIa))——A mixture of glycyrol (25 mg), methanol (20 ml) and conc. hydrochloric acid (5.6 ml) was refluxed for 2 hr and allowed to stand overnight at room temperature. A crystalline material was recrystallized from acetone to yield a product (17 mg) which was identified with isoglycyrol (IIIa) by the infrared spectrum and thin-layer chromatography.

Isolation of 5-O-Methylglycyrol (IIa), Isoglycyrol (IIIa) and Betulic Acid——Although two fluorescent substances in fraction D have very near the *Rf* values on silica gel thin-layer chromatography using benzene and ether (4:1) as the solvent, these could be separated each other using the column chromatography on silicic acid. The former fraction is a mixture of two compounds, as revealed by thin-layer chromatography of its acetylated products. With further chromatography on silica gel of this mixture, 5-O-methylglycyrol (IIa) and betulic acid were obtained. The latter eluted fraction gave isoglycyrol (IIIa).

5-O-Methylglycyrol (IIa): mp 259—260.5°, colourless needles (from acetone) (yield 0.0001%). UV $\lambda_{max}^{EtOH-NaOAc}$; unchanged. Mass spectrum: *m/e* 380 (M, bace peak), 365 (35.0%), 349 (20.7), 335 (19.4), 334 (23.0), 323 (13.0), 312 (19.1), 295 (14.9), 281 (4.9), 267 (10.7), 69 (11.7). *Anal.* Cacld. for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.56; H, 5.32. mol. wt. 380 (Mass).

5-O-Methylglycyrol Monoacetate (IIb)——The monoacetate was prepared in the usual manner with acetic anhydride and pyridine to give colourless needles. mp 178—180° (from acetone). UV λ_{max}^{EtOH} mμ (log ε): 232 (4.44), 239 (4.36 sh.), 252 (4.08 sh.), 260 (3.90 sh.), 274 (3.53 infl.), 289 (3.35 sh.), 3.01 (3.79 infl.), 310 (4.08 infl.), 326 (4.38 infl.), 336 (4.52), 351 (4.44). IR ν_{max}^{KBr} cm^{-1}: 2943, 1748, 1622, 1596, 1558, 1487, 1368, 1217; $\nu_{max}^{CHCl_3}$ cm^{-1}: 2945, 1742, 1621, 1599, 1562, 1486, 1368, 1194. *Anal.* Calcd. for $C_{24}H_{22}O_7$: C, 68.24; H, 5.25. Found: C, 68.08; H, 5.25.

5-O-Methylglycyrol Monomethyl Ether (V)——To a solution of 5-O-methylglycyrol (15 mg) in methanol (2 ml) and ether (20 ml) was added an excess of etherial diazomethane, and the mixture was allowed to stand at room temperature for 24 hr. Excess of diazomethane was decomposed with a few drops of acetic acid, and the solvent was removed. The solid was crystallized from acetone to give pale yellow needles (10 mg), mp 206.5—207.5°; identified with glycyrol dimethyl ether (V) by IR spectrum and thin-layer chromatography.

Compound A (IVa) and B (IVb)——A mixture of 5-O-methylglycyrol (IIa) (15 mg), methanol (20 ml) and conc. hydrochloric acid (6 ml) was refluxed for 3 hr. After standing at room temperature overnight, the crude solid was collected and washed with water. The column chromatography on silica gel using methylene chloride and acetone (9:1) gave two products and recovered material.

12) R.R. Spencer, E.M. Bickoff, R.E. Lundin, and B.B. Knuckles, *J. Agric. Food. Chem.*, **14**, 162 (1966).
13) All melting points were uncorrected.

The major product (compound A) (IVa) was recrystallized from acetone to give colourless needles (7 mg). mp 266—268°, UV λ_{max}^{EtOH} mμ (log ε): 208.5 (4.39), 228 (4.33), 246 (4.22), 262 (4.02 infl.), 345.5 (4.27), 356 (4.21). IR ν_{max}^{KBr} cm^{-1}: 3150, 2950, 2830, 1694, 1613, 1593, 1555, 1500. Mass spectrum[14]: *m/e* 412 (98.1%), 380 (base peak, M–CH_3OH), 365 (32.1), 349 (15.2), 340 (9.4), 334 (9.3), 325 (60.4), 310 (21.8), 295 (11.4), 267 (17.5), 149 (13.4). *Anal.* Calcd. for $C_{23}H_{24}O_7 \cdot 1/2\ H_2O$: C, 65.55; H, 5.98. Found: C, 65.55; H, 5.68. mol. wt. for $C_{23}H_{24}O_7$: 412 (Mass).

The minor product (compound B) (IVb) was recrystallized from acetone to give colourless needles. mp 261—262.5°, UV λ_{max}^{EtOH} mμ (log ε): 207.5 (4.45), 227 (4.37), 246 (4.24), 262 (4.01 infl.), 345 (4.30), 357 (4.24 sh.). IR ν_{max}^{KBr}cm^{-1}: 3370, 2970, 1706, 1616, 1597, 1560, 1500. Mass spectrum: *m/e* 398 (M, base peak), 380 (89.2%, M–H_2O), 365 (60.8), 349 (27.7), 339 (23.0), 334 (16.6), 325 (96.9), 310 (73.1), 295 (35.4), 281 (17.0), 253 (13.5), 211 (18.9), 163 (21.0), 155 (30.5), 59 (45). mol. wt. 398 (Mass).

Isoglycyrol (IIIa)——mp 298—300°, colourless needles (from acetone) (yield 0.002%). *Anal.* Calcd. for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 68,81; H, 4.98.

Isoglycyrol Monoacetate (IIIc)——The monoacetate was prepared in the usual manner with acetic anhydride and pyridine to give colourless needles; mp 175—176° and 197—197.5° (double melting) (from methanol), UV λ_{max}^{EtOH} mμ (log ε): 207 (4.50), 221 (4.44), 226 (4.42 infl.), 242 (4.31), 254 (4.15, sh.), 262 (4.06, infl.), 274 (3.86, infl.), 288 (3.66), 312 (4.05, infl.), 339 (4.47), 353 (4.42). IR ν_{max}^{KBr} cm^{-1}: 1761, 1740, 1624, 1590, 1557, 1406, 1365, 1217, 1203; $\nu_{max}^{CCl_4}$ cm^{-1}: 1751, 1629, 1592, 1409, 1365, 1198. *Anal.* Calcd. for $C_{23}H_{20}O_7$: C, 67.64; H, 4.94. Found: C, 67.78; H, 4.91.

Isoglycyrol Monomethyl Ether (IIIb)——Isoglycyrol (IIIa) (200 mg) was methylated in the usual manner with dimethyl sulphate (1 ml) and anhyd. potassium carbonate (1.5 g) in acetone (20 ml), pale yellow needles (168 mg) (from acetone), mp 222.5—224°. UV λ_{max}^{EtOH} mμ (log ε): 208 (4.49), 225 (4.33), 247 (4.29), 256 (4.19), 264 (4.12), 347 (4.35), 357 (4.29). IR ν_{max}^{KBr} cm^{-1}: 2960, 1742, 1626, 1590, 1558, 1504; $\nu_{max}^{CHCl_3}$ cm^{-1}: 3050, 2980, 2940, 1734, 1626, 1592, 1557, 1505. *Anal.* Calcd. for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.63; H, 5.21.

Betulic Acid (=Betulinic Acid)——Colourless needles (from methanol), mp 300° (lit, 320—321°), identical with authentic sample by IR spectrum and thin-layer chromatography. IR ν_{max}^{KBr} cm^{-1}: 3420, 2940, 1698, 1457, 1384, 1254, 1193, 1114.

3-O-Acetylbetulic Acid——Betulic acid (100 mg) was acetylated in the usual manner with acetic anhydride (2 ml) and pyridine (2 ml). The crude solid on crystallization from acetone afforded 3-O-acetylbetulic acid (91 mg) which was identified with authentic sample by IR spectrum and thin-layer chromatography. mp 280—282° (lit. 295°). IR ν_{max}^{KBr}cm^{-1}: 2945, 1739, 1693, 1642, 1460, 1368, 1244. *Anal.* Calcd. for $C_{32}H_{50}O_4$: C, 77.06; H, 10.11. Found: C, 77.02; H, 9.98.

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The pharmacological studies have been carried out in correlation with our chemical investigation by Prof. K. Takagi (Univ. of Tokyo) and his collaborators, to whom we are deeply indebted.

14) High resolution mass spectrum: *m/e* 412.153 ($C_{23}H_{24}O_7$, Calcd.; 412.152), 380.125 ($C_{22}H_{20}O_6$, Calcd.; 380.126), 365.103 ($C_{21}H_{17}O_6$, Calcd.; 365.103).