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The Structure and Internal Acyl Migration of Gagaminin

Recently, Nomura, *et al.* isolated the diester of sarcostin with a cinnamic acid and a nicotinic acid from *Metaplexis japonica* Makino,1) *Marsdenia condurango* Reich.,2) and *Marsdenia tomentosa* Decne.3) The determination of the location of diester linkages in polyoxy pregnane is usually rather difficult, so the exact structure has not been decided till present. We newly isolated the same diester from *Cynanchum caudatum* Max. and determination of the structure of this diester, which was named gagaminin,4) is described here.

Gagaminin (I) has the following physical constants, $C_{36}H_{43}O_8N$, mp 166—170°, $[\alpha]_D^{20}$ $+143.8°$ ($c=0.7$, $CHCl_3$). Its nuclear magnetic resonance (NMR) spectrum5) shows the signal for C-12α H at δ 4.82 (double-doublet, $J=5$ and 9 Hz), for C-20 H at δ 4.88 (quartet, $J=6$ Hz), and for C-21-methyl at δ 1.31 (doublet, $J=6$ Hz), suggesting the location of each acid at either the C-20 or C-12β of sarcostin (II).6)

Acetylation of gagaminin with Ac_2O–pyridine gave an amorphous, $C_{38}H_{45}O_9N$, monoacetate (V), IR $\nu_{max}^{CHCl_3}$ 1720, 1710, 1640, 1595, 1580 cm^{-1}, mass spectrum, *m/e* 659 (M^+), 599 (M^+-60), 511 (M^+-cinnamic acid). Oxidation of gagaminin with lead tetraacetate in acetic acid for 4 hr gave an amorphous, $C_{36}H_{39}O_8N$, 8,14-*seco*-gagaminin (VIII), IR $\nu_{max}^{CHCl_3}$ 1740 (5-membered ring ketone), 1720, 1715 cm^{-1}; mass spectrum, *m/e* 615 (M^+), 467 (M^+-cinnamic acid), NMR δ 0.73 (C-18-methyl), 1.40 (C-19-methyl), 1.40 as a doublet (C-21-methyl), 3.5 as a multiplet (C-3α H).

Gagaminin on mild alkaline hydrolysis (K_2CO_3 in MeOH) formed monoester-I (III), monoester-II (IV), and II. Reduction of gagaminin with $LiAlH_4$ (one equivalent) in tetrahydrofuran gave only the monoester-II (IV), mp 145—150°, $[\alpha]_D^{20}$ $+6.83°$ ($c=1$, $CHCl_3$), $C_{30}H_{40}O_7$, whose physical constants were in good agreement with those of penupogenin.7) The identity was established by direct comparison with the authentic sample. The monoester-I (III), mp 154—158°, $C_{30}H_{40}O_7$, exhibits the signals for C-20 H at δ 5.31 (quartet, $J=6$ Hz) and for C-21-methyl at δ 1.31 (doublet, $J=6$ Hz), and for cinnamoyl at δ 6.42 (doublet, $J=16$ Hz), 7.66 (doublet, $J=16$ Hz), and 7.2—7.6 (multiplet) in its NMR spectrum,

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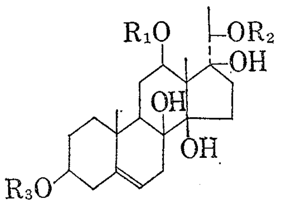
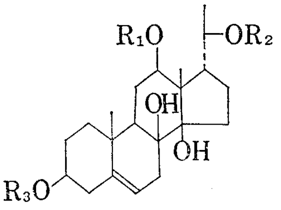
2) K. Hayashi and H. Mitsuhashi, Abstr. Papers, 90th Annu. Meet. of Pharmaceutical Society of Japan, II, 1970, p. 215.
3) T. Sasaki, K. Hayashi, and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), in preparation.
4) T. Yamagishi, K. Hayashi, and H. Mitsuhashi, Abst. Papers, 92nd Annu. Meet. of Pharmaceutical Society of Japan, II, 1972, p. 174.
5) The NMR spectra were determined in $CDCl_3$ solution on a PS-100 (JEOL) instrument, using tetramethylsilane as an internal standard.
6) Y. Shimizu and H. Mitsuhashi, *Tetrahedron*, **24**, 4143 (1968); J.E. Bridgeman, P.C. Cherry, A.S. Cleggy, J.M. Evans, Sir Ewart R.H. Jones, A. Kasal, V. Kumar, G.D. Meakins, Y. Morisawa (Mrs), E.E. Richards, and P.D. Woodgate, *J. Chem. Soc.* (*C*), **1970**, 252.
7) T. Sasaki, K. Hayashi, and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 628 (1972).

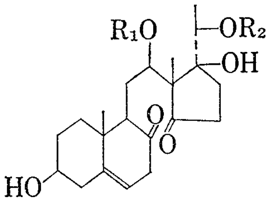
and the cinnamoyl absorption bands at 216, 222, and 276 nm in its ultraviolet (UV) spectrum. Moreover, the mass spectral data, showing a peak at *m/e* 337 (M^+-CH_3CHO-cinnamoyl) but no peak at *m/e* 467 (M^+-CH_3CHOH), indicate that the cinnamoyl group is attached to the C-20 oxygen of sarcostin. Treatment of IV with K_2CO_3 in boiling toluene for 3 hr afforded III (yield, 34%). III also gave IV under the same condition. These results suggested that IV was converted into III by base-catalyzed internal acyl migration, and the structure of gagaminin is assigned as formula I.



I: R_1=cinnamoyl, R_2=nicotinoyl, R_3=H
II: R_1=R_2=R_3=H
III: R_1=R_3=H, R_2=cinnamoyl
IV: R_1=cinnamoyl, R_2=R_3=H
V: R_1=cinnamoyl, R_2=nicotynoyl, R_3=acetyl



VIa: R_1=R_3=benzoyl, R_2=H
VIb: R_1=H, R_2=R_3=benzoyl
VIIa: R_1=ikemaoyl, R_2=R_3=H
VIIb: R_1=R_3=H, R_2=ikemaoyl



VIII: R_1=cinnamoyl, R_2=nicotinoyl

This kind of acyl migration also occurred under acidic condition (2% MeOH–HCl), and was reversible. On the basis of these results, it was deduced that the acyl group transferred from the C-12β to the C-20-hydroxyl group through the orthoester intermediate. The effective reaction conditions and the mechanism of this type of acyl migration in C/D *cis*-pregnane derivatives were studied. 12-O-Ikemaoyl-20-dihydrolineolon (VIIa), mp 213—217°, $C_{28}H_{44}O_6$, which was prepared from cynanchogenin,[8] was treated with a small quantity of KOH in *tert*-BuOH for 7 min at 70°, to give 20-O-ikemaoyl-20-dihydrolineolon (VIIb) (yield, 28%) and the starting material. 3,12-O-Dibenzoyl-20-dihydrolineolon (VIa), mp 144—147°, $C_{35}H_{42}O_7$, derived from lineolon,[8] was converted into 3,20-dibenzoyl-20-dihydrolineolon (VIb) (yield, 30%) as the migration product by the same treatment for 4 min. Because of dehydration during the reaction, the yield of the migration under an acidic condition was lower than that under a basic condition. Since the solvolysis predominated over intramolecular acyl migration, the yield was lower in water and methanol than in higher alcohols such as *tert*-BuOH and in aprotic solvent like toluene.

The reactivity of acyl groups in the migraion decreases in the order of cinnamoyl, benzoyl, and ikemaoyl. Since the distance between the carbonyl carbon and the C-20-OH is very near in 17β-H–12β-acyloxy-20-hydroxy-(C/D-)*cis*-pregnane derivatives, the migration easily occurrs in spite of the seven membered intermediate. Although internal acyl migration was reported in triterpene and cortisone by many workers,[9] migration from C-12β to C-20-OH is the first example.

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Isolation of Hexahydrocurcumin, Dihydrogingerol and Two Additional Pungent Principles from Ginger

Curcumin has attracted special attention from a biosynthetic point of view,[1,2] meanwhile gingerol has also been the subject of many investigations.[3] In our study on the pungent principles of ginger[4] we have now isolated the four new compounds (**1**, **3**, **6**, and **7**); the first of these closely relates to curcumin, while the latter three to gingerol.

The ethyl acetate soluble fraction obtained from acetone extract of Japanese commercial ginger, was successively chromatographed on silica gel column using benzene–acetone mixtures as the eluent. Compounds (**1** and **3**) were isolated from fractions more polar than gingerol (**5**), whereas **6** and **7** from crude gingerol fraction.[4]

Compound (**1**),[5] $C_{21}H_{26}O_6$, mp 90—91° (benzene), $[\alpha]_D^{24}$ +9.0°, Mass Spectrum *m/e*: 374 (M^+), IR ν_{max}^{KBr} cm^{-1}: 3380 (OH); 1705 (ketone); 1610 and 1510 (benzene ring), was obtained in 0.002% yield based on the fresh material. The compound gives a positive ferric chloride test. The NMR spectrum of **1** displays six aromatic proton signals, forming finely overlapped two, 1,2,4-substitution patterns of benzene ring (2H each at δ 6.79 d, J=8 Hz; 6.64 d, J=2 Hz; 6.6 dd, J=8 and 2 Hz), 6H singlet (3.80, $2\times C\underline{H}_3O$), overlapped multiplets (near 2.7, total 8H, four methylene groups), 2H multiplet (near 1.7, methylene) and 1H quintet (J=6 Hz) at 4.01 ppm. A broad 2H singlet also appears at 5.67 ppm; the signal diminished promptly on addition of D_2O.

Compound (**1**) upon treatment with acetic anhydride and pyridine afforded the diacetate (**2**) of anhydro derivative; the NMR spectrum of the latter shows one of the newly formed olefinic protons at 6.03 ppm as a doublet (J=17 Hz). The spectrum also exhibits 6H singlet at 2.28 due to acetyls, 6H singlet at 3.72 due to methoxyls, broad overlapped multiplets between 2.6 to 2.8 (total 8H, four methylenes) besides six aromatic and one olefinic proton

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[1] T.A. Geissman and D.H. Grout, "Organic Chemistry of Secondary Plant Metabolism," Freeman, Cooper and Company, San Fransisco, 1969, p. 169.

[2] P.J. Roughley and D.A. Whiting, *Tetrahedron Letters*, **1971**, 3741.

[3] For a histrory of studies on gingerol, see D.W. Connel and M.D. Sutherland, *Aust. J. Chem.*, **22**, 1033 (1969); They skillfully determined the absolute configuration of gingerol.

[4] We have already reported on the isolation of crystalline gingerol (**5**), mp 29—31°, $[\alpha]_D^{24}$ +25.1°; whose structure and purity were demonstrated by nuclear magnetic resonance (NMR) spectroscopy, mass spectrum and gas–liquid chromatography (GLC), trimethylsilylation method, QF-1 column). *Cf.* M. Miyamoto, M. Shinohara, and T. Murata, presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1968, Abstract Papers, p. 231. We also suggested the presence of two minor compounds (**6** and **7**) in ginger by mass spectrum and GLC of a crude gingerol fraction; the two shogaols corresponding to **6** and **7** were detected and identified with synthetic specimens, respectively, by GLC.

[5] All melting points were measured on Kofler block and uncorrected. The specific rotations were taken on $CHCl_3$ solutions, c=1.0%. The NMR spectra were recorded with a Varian HA-100 spectrometer and calibrated against internal tetramethylsilane. Chemical shifts are expressed in ppm (δ): s, singlet; d, doublet; t, triplet; m, multiplet.