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Studies on the Constituents of Asclepiadaceae Plants. XLVII.[1] Acyl Migration of Polyoxypregnane Derivatives

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A chemical acyl migration equilibrium between 12β-hydroxyl and 20-hydroxyl groups was found to depend on the C-17 and C-20 configurations in C/D-*cis*-polyoxypregnane derivatives. In the case of 20*S* derivatives with a 17α-side chain, the equilibrium mixture was separated to afford 12β-ester compound and 20*S*-ester compound. On the other hand, separation of the equilibrium mixture of the 20*R* compound with a 17α-side chain was difficult, since the 20-ester compound changed to an equilibrium mixture at room temperature. In both 20*S* and 20*R* compounds having a 17β-side chain, acyl migration was not observed, and the starting material were recovered.

Keywords——Asclepiadaceae plants; C/D-*cis* polyoxypregnane; acyl migration; 20*S*-17α side chain; 20*R*-17α side chain; 20*S*-17β side chain; 20*R*-17β side chain

Acyl migration of an ester group is often observed in the chemistry of natural products.[3] In the C/D-*cis*-polyoxypregnane derivatives, for instance, C-12 to C-20 hydroxyl group migration was first reported through structural studies of gagaminin.[4] In our preceding paper, the migration of hydroxyl groups from C-12 to C-20 and *vice versa* was reported to occur effectively under basic conditions.[5] The present paper deals with the configurational specificities at C-17 and C-20 in the acyl migration of C/D-*cis*-polyoxypregnane derivatives from *Cynanchum caudatum* Max. (Asclepiadaceae).

During the course of studies on this migration, acetyl and cinnamoyl groups were used as the acyl group in order to examine the effect of bulkiness on the steric course of the reaction.

Compounds Having a 17α-Side Chain

Studies of the acyl migration were carried out using sarcostin and ikemagenol derivatives having a C-17 side chain; the configuration of these compounds at C-20 had been determined as *S*.[6] The reaction was carried out described in the preceding work.[5] Treatment of 3,12-diacetylsarcostin (III) with sodium hydride in dimethylformamide (DMF) gave an equilibrium mixture of 3,12-diacetate (III) and 3,20-diacetate (IV). These compounds, III and IV, were isolated in a ratio of 1 : 2. In the case of penupogenin[7] (V), the reaction gave a mixture of 12-cinnamate (V) and 20-cinnamate (VI), in a 1 : 2 ratio as above.[5]

These reactions gave 20*S*-esters irrespective of the bulkiness of the acyl groups. Therefore, it appeared that the preference was due to the hydrogen bonding between the C-17β hydroxyl and C-20*S* ester groups, in comparison with the case of ikemagenol derivatives, as described below.

1) Part XLVI: S. Terada and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **27**, 2304 (1979).
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3) J. Wagner, H. Hoffman, and I. Low, *Arch. Pharm.*, **304**, 804 (1971); T. Konishi, A. Tada, J. Shoji, R. Kasai, and O. Tanaka, *Chem. Pharm. Bull.* (Tokyo), **26**, 668 (1978).
4) T. Yamagishi, K. Hayashi, and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2289 (1972).
5) H. Bando and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **26**, 2128 (1978).
6) K. Hayashi and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **23**, 1845 (1975).
7) T. Sasaki, K. Hayashi, and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 628 (1972).

The reaction of ikemagenol derivatives was carried out using 3,12-diacetylikemagenol (VII) and 12-cinnamoylikemagenol[5] (IX). Under the same reaction conditions, 3,12-diacetylikemagenol (VII) gave the expected mixture, which was separated by preparative thin-layer chromatography (TLC) into the 3,12-diacetate (VII) and 3,20-diacetate (VIII) in a 1:1 ratio. The 12-cinnamate (IX) also gave same result.[5] Accordingly, it appears that ikemagenol derivatives are not affected by the bulkiness of the acyl group or by the hydrogen bonding mentioned above.

The acyl migration in the compound with 20*R* configuration was studied using epiikemagenol derivatives, as sarcostin and ikemagenol derivatives have a 20*S* configuration. The sodium borohydride reduction of I afforded A, mp 222—228°, and B, mp 209—215°, in a 3:1 ratio. On the other hand, the Meerwein–Ponndorf reduction of I afforded A and B in a 2:3 ratio. Since A was identical with ikemagenol[5] (XIa) in optical rotation and mp, and the mixed mp (219—229°) showed no depression, B was determined to be 20-epiikemagenol (XIb). The configuration at C-20 was assigned as *R* in the 20-epi isomer. Acetylation of XIb gave the 3-acetate (XII), 3,20-diacetate (XIV), and 3,12,20-triacetate (XV). The diacetate (XIV), dissolved in chloroform-d for PMR spectral measurement, gave an equilibrium mixture containing two components after being allowed to stand for 10 hr or so at room temperature. One of the two components was assigned as the 3,20-diacetate (XIV), and the other could be assigned as the 3,12-diacetate (XIII) from the PMR spectrum of the resulting mixture. The PMR spectrum of the mixture showed two acetyl groups at δ 2.03 (6H, s), 12β-hydroxyl methine at δ 3.64 (1/2H, d.d, J=11 Hz, 4 Hz), 20-hydroxyl methine at δ 3.95 (1/2H, m), 3β-acetoxyl methine at δ 4.63 (1H, m), 12β-acetoxyl methine at δ 4.72 (1/2H, d.d, J=10 Hz, 5 Hz), and 20-acetoxyl methine at δ 5.20 (1/2H, m). Accordingly, this was a mixture of the 3,12-diacetate (XIII) and 3,20-diacetate (XIV) in a 1:1 ratio. This indicates that the migration reaction was easier than in ikemagenol and sarcostin derivatives. This acyl migration is the first reported example in pregnane derivatives with 20*R* configuration. Cinnamoylation of XII gave 3-acetyl-20-cinnamoylepiikemagenol (XVI), whose PMR spectrum showed an acetyl group at δ 2.03 (3H, s), 12β-hydroxyl methine at δ 3.68 (1H, d.d, J=11 Hz, 4 Hz), 3β-acetoxyl methine at δ 4.59 (1H, m), and 20-cinnamoyloxy methine at δ 5.39, with an overlapping signal of C-6 hydrogen (2H, total). This compound also showed two spots on TLC after standing for 2 days. The PMR spectrum of the resulting mixture was very similar to that of XVI. The mixture was separated by preparative TLC into two components. The major one was 3-acetyl-20-cinnamoylepiikemagenol (XVI) and the minor one was found to be 3-acetyl-12-cinnamoylepiikemagenol (XVII) from its PMR spectrum, which showed an acetyl group at δ 2.04 (3H, s), 20-hydroxyl methine at δ 3.96 (1H, m), 3β-acetoxyl methine at δ 4.69 (1H, m), and 12β-cinnamoyloxy methine at δ 4.90 (1H, d.d, J=11 Hz, 5 Hz). The isolated major and minor components also changed to mixture containing 20-cinnamate (XVI) and 12-cinnamate (XVII) after standing for 2 days at room temperature as chloroform-d solutions for PMR spectral measurements. In the equilibrium mixture, XVII and XVI were in a 1:3 ratio judging from their intensities in a thin-layer chromatoscanner spectrum using an ultraviolet monitor. These findings showed that the acyl migration occurred more easily in epiikemagenol derivatives than in ikemagenol derivatives. The ratio of components in the equilibrium mixture from epiikemagenol derivatives was found to vary with the bulkiness of the acyl group. The difference in ease of acyl migration between ikemagenol and epiikemagenol derivatives may be explained by the formation of an intermediate of ortho ester type, as follows (Fig. 1). In the ikemagenol derivatives with 20*S* configuration, the

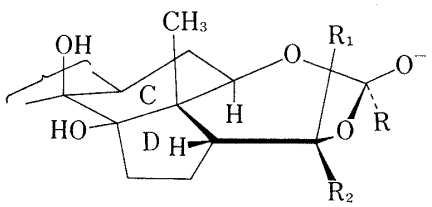
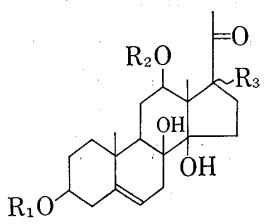
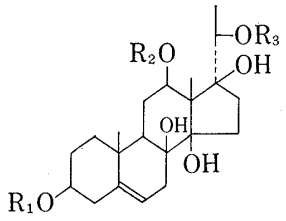


Fig. 1. C/D-Ring Moiety of an *ortho* Ester Intermediate

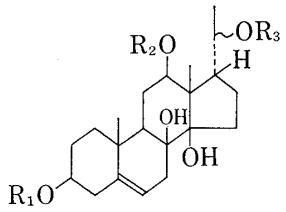
20*S* derivatives: R_1=CH_3, R_2=H.
20*R* derivatives: R_1=H, R_2=CH_3.



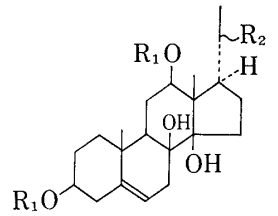
I: $R_1=R_2=H$, $R_3=\beta$-H
IIa: $R_1=R_2=H$, $R_3=\alpha$-H
IIb: $R_1=R_2=Ac$, $R_3=\alpha$-H



III: $R_1=R_2=Ac$, $R_3=H$
IV: $R_1=R_3=Ac$, $R_2=H$
V: $R_1=R_3=H$, $R_2=Cin$
VI: $R_1=R_2=H$, $R_3=Cin$



VII: $R_1=R_2=Ac$, $R_3=H$ (20*S*)
VIII: $R_1=R_3=Ac$, $R_2=H$ (20*S*)
IX: $R_1=R_3=H$, $R_2=Cin$ (20*S*)
X: $R_1=R_2=H$, $R_3=Cin$ (20*S*)
XIa: $R_1=R_2=R_3=H$ (20*S*)
XIb: $R_1=R_2=R_3=H$ (20*R*)
XII: $R_1=Ac$, $R_2=R_3=H$ (20*R*)
XIII: $R_1=R_2=Ac$, $R_3=H$ (20*R*)
XIV: $R_1=R_3=Ac$, $R_2=H$ (20*R*)
XV: $R_1=R_2=R_3=Ac$ (20*R*)
XVI: $R_1=Ac$, $R_2=H$, $R_3=Cin$ (20*R*)
XVII: $R_1=Ac$, $R_2=Cin$, $R_3=H$ (20*R*)



XVIII: $R_1=Ac$, $R_2=OH$ (20*R*)
XIX: $R_1=Ac$, $R_2=OH$ (20*S*)

Chart 1. $Ac=CH_3CO-$, $Cin=C_6H_5-CH=CH-CO-$

two methyl groups at C-18 and C-21 are in a 1,3-diaxial position. In the epiikemagenol derivatives with 20*R* configuration, the methyl group at C-20 is equatorial. Therefore, the acyl migration might be expected to more easily in compounds with 20*R* configuration than in those with 20*S* configuration.

Compounds Having a 17β-Side Chain

Reduction of 3,12-diacetylisolineolon (IIb) with sodium borohydride gave two compounds, XVIII and XIX. XVIII was identical with an authentic sample of 3,12-diacetyldihydroisolineolon[6] having R configuration at C-20, as regards mp and mixed mp. Therefore, XIX was assigned as 3,12-diacetyl-20-epidihydroisolineolon from its PMR spectrum, which showed two acetyl groups at δ 2.03 (3H, s), and 2.07 (3H, s), 20-hydroxyl methine at δ 3.97 (1H, q, $J=6$ Hz), 12β-acetoxyl methine at δ 4.59 (1H, d.d, $J=11$ Hz, 4 Hz), and 3β-acetoxyl methine at δ 4.60 (1H, m). Since XVIII has a 20*R* configuration, the configuration at C-20 in XIX was assigned as *S*. Neither XVIII nor XIX gave the corresponding migrated compounds upon treatments with sodium hydride. These findings support the view that the 12β-ester group is sterically distant from the 20-hydroxyl group in these compounds.

Table I. The Ratios of 12-Ester to 20-Ester in the Equilibrium Mixture

	Sarcostin der.	Ikemagenol der.	Epiikemagenol der.
Acetate	1 : 2	1 : 1	1 : 1
Cinnamate	1 : 2	1 : 1	1 : 3

Experimental

Melting points were determined using a Yanaco micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 spectrometer. PMR spectra were recorded on a JEOL FX-100 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Hitachi RMU-7 mass spectrometer. Optical rotations were taken with a Jasco DIP-4 digital polarimeter. Preparative TLC was carried out using silica gel (HF 254, type 60, Merck). The TLC chromatoscanner was a Shimadzu CS-900 unit.

Reduction of Lineolon (I)——a) $NaBH_4$ (310 mg) was added to a solution of 720 mg of I dissolved in 30 ml of MeOH, and the mixture was stirred at room temperature. After 1 hr the solution was neutralized with 5% HCl, and extracted with $CHCl_3$. The organic layer was worked up as usual and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by preparative TLC to afford 370 mg of ikemagenol[5] (XIa) and 120 mg of epiikemagenol (XIb).

b) Aluminium isopropoxide (2.4 g) was added to a solution of 770 mg of I dissolved in 60 ml of iso-PrOH and the solution was refluxed. During refluxing, the resulting acetone was removed through an air condenser, and small amounts of iso-PrOH were occasionally added to the solution. After 13 hr, 150 ml of 5% HCl was added to the resulting mixture and the mixture was stirred for 10 min. The solution was extracted with $CHCl_3$. The organic layer was worked up as usual for purification by preparative TLC to afford 205 mg of ikemagenol (XIa) and 290 mg of 20-epiikemagenol (XIb), mp 207—215°, $[\alpha]_D$ +30° (c=0.1, MeOH). PMR (δ) pyridine: 1.35 (3H, d, J=6 Hz), 1.47 (3H, s), 1.70 (3H, s), 3.88 (1H, m), 4.05 (1H, d.d, J=11 Hz, 4 Hz), 4.53 (1H, q, J=6 Hz), 5.40 (1H, m).

Acetylation of 20-Epiikemagenol (XIb)——Acetic anhydride (387 mg) was added to a solution of 280 mg of XIb dissolved in 2 ml of pyridine, and the solution was stirred for 3 days at room temperature. When the starting material had disappeared from the solution, the mixture was poured into ice-water and extracted with $CHCl_3$. The organic layer was worked up as usual for purification by preparative TLC to afford 185 mg of 3-acetate (XII), 5 mg of 3,20-diacetate (XIV), and 40 mg of 3,12,20-triacetate (XV). 3-Acetate: From AcOEt as needles, mp 258—259°, *Anal.* Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.73; H, 8.98. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3440, 1720, 1250, 1190. PMR (δ) $CDCl_3$: 1.12 (3H, s), 1.19 (3H s), 1.23 (3H, d, J=6 Hz), 2.04 (3H, s), 3.68 (1H, d.d, J=11 Hz, 4 Hz), 4.16 (1H, q, J=6 Hz), 4.60 (1H, m), 5.39 (1H, m). 3,20-Diacetate: oil, PMR (δ) $CDCl_3$: 1.14 (3H, s), 1.17 (3H, s), 1.26 (3H, d, J=6 Hz), 2.02 (3H, s), 2.06 (3H, s), 3.64 (1H, d.d, J=11 Hz, 4 Hz), 5.19 (1H, m), 5.38 (1H, m). Equilibrium mixture of 3,12-diacetate (XIII) and 3,20-diacetate (XIV): A solution of compound (XIV) dissolved in $CDCl_3$ for PMR spectral measurement gave a mixture of XIII and XIV after standing for 10 hr at room temperature. PMR (δ) $CDCl_3$: 1.13—1.19 (6H, broad s), 1.24—1.30 (3H, m), 2.03 (6H, s), 3.64 (1/2H, d.d, J=11 Hz, 4 Hz), 3.95 (1/2H, m), 4.63 (1H, m), 4.72 (1/2H, d.d, J=11 Hz, 5 Hz), 5.20 (1/2H, m), 5.39 (1H, m). 3,12,20-Triacetate (XV): From AcOEt as needles, mp 232—234°, *Anal.* Calcd. for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19. Found: C, 65.96; H, 8.13. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1725, 1260. PMR (δ) $CDCl_3$: 1.14 (3H, s), 1.23 (3H, d, J=6 Hz), 1.24 (3H, s), 1.95 (3H, s), 2.00 (3H, s), 2.04 (3H, s), 4.63 (1H, m), 4.76 (1H, d.d, J=10 Hz, 5 Hz), 4.98 (1H, d, q, J=3 Hz, 6 Hz), 5.39 (1H, broad s).

Cinnamoylation of 3-O-Acetyl-20-Epiikemagenol (XII)——Cinnamoyl chloride (36 mg) was added to a solution of 50 mg of XII dissolved in 1 ml of pyridine, and the solution was stirred for 5 hr at 60°. When the starting material had disappeared, the solution was poured into ice-water. The resulting mixture was extracted with $CHCl_3$ and the organic layer was worked up as usual for purification by preparative TLC to afford the 20-cinnamate (XVI), as an amorphous solid. PMR (δ) $CDCl_3$: 1.17 (3H, s), 1.18 (3H, s), 1.35 (3H, d, J=6 Hz), 2.03 (3H, s), 3.68 (1H, d.d, J=11 Hz, 5 Hz), 4.59 (1H, m), 5.39 (2H, m), 6.40 (1H, d, J=16 Hz), 7.30—7.50 (5H, m), 7.62 (1H, d, J=16 Hz). 12-Cinnamate (XVII): A solution of XVI dissolved in $CDCl_3$ for PMR spectral measurement was allowed to stand for 2 days to yield an equilibrium mixture of XVI and XVII. PMR (δ) $CDCl_3$: 1.17 (3H, s), 1.18 (3H, s), 1.35 (3H, d, J=6 Hz), 2.04 (3H, s), 3.96 (1H, m), 4.69 (1H, m), 4.90 (1H, d.d, J=11 Hz, 5 Hz), 5.38 (1H, m), 6.40 (1H, d, J=16 Hz), 7.30—7.50 (5H, m), 7.62 (1H, d, J=16 Hz).

Reduction of 3,12-di-O-Acetylisolineolon with $NaBH_4$——$NaBH_4$ (50 mg) was added to a solution of 190 mg of 3,12-diacetylisolineolon dissolved in 2 ml of MeOH, and the solution was stirred at room temperature. After 20 min, the solution was neutralized with 5% HCl, and a small amount of water was added. The resulting mixture was extracted with $CHCl_3$. The organic layer was worked up as usual for purification by preparative TLC to afford 120 mg of 3,12-diacetyl-20*R*-dihydroisolineolon (XVIII) and 55 mg of 3,12-diacetyl-20*S*-dihydroisolineolon (XIX). 3,12-Diacetyl-20*R*-dihydroisolineolon (XVIII): mp 216—220°, $[\alpha]_D$ +11° (c=0.12, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 3350, 1730, 1260—1200. PMR (δ) $CDCl_3$: 1.19 (3H, s), 1.25 (3H, d, J=6 Hz), 1.41 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 3.82 (1H, m), 4.59 (1H, d.d, J=11 Hz, 4 Hz), 4.60 (1H, m), 5.40 (1H, m). 3,12-Diacetyl-20*S*-dihydroisolineolon (XIX): mp 105°, $[\alpha]_D$ +25° (c=0.09, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3350, 1725, 1260—1200. PMR (δ) $CDCl_3$: 1.13 (3H, d, J=6 Hz), 1.20 (3H, s), 1.26 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 3.97 (1H, q, J=6 Hz), 4.59 (1H, d.d, J=11 Hz, 4 Hz), 4.60 (1H, m), 5.40 (1H, m).

Acyl Migration of 3,20-di-O-Acetylsarcostin (IV)——NaH (4 mg) was added to a solution of 36 mg of IV dissolved in 0.5 ml of DMF under cooling with ice-water. After 15 min, the solution was acidified with 5% HCl in MeOH and a small amount of water was added. The resulting solution was extracted with $CHCl_3$ and the organic layer was worked up as usual for purification by preparative TLC to afford 7 mg of III, mp 156—159°, and 15 mg of IV, mp 230—235°. Each compound was identical with an authentic sample. The mixed mp of III and the authentic sample was 154—158°, and that of IV was 227—235°.

Acyl Migration of 3,12-di-O-Acetylikemagenol (VII)——VII (47 mg) was reacted in the same manner as IV. The reaction mixture gave 16 mg of VII and 15 mg of VIII on purification by preparative TLC. 3,20-Diacetylikemagenol (VIII): mp 185—185.5°, $[\alpha]_D$ +53° (c=0.09, MeOH). *Anal.* Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.68; H, 8.53. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1720, 1260—1200. PMR (δ) $CDCl_3$: 1.18 (3H, s), 1.21 (3H, d, J=6 Hz), 1.27 (3H, s), 2.04 (6H, s), 3.63 (1H, d.d, J=11 Hz, 5 Hz), 4.62 (1H, m), 5.14 (1H, d.q, J=10 Hz, 6 Hz), 5.37 (1H, m).

Acyl Migration of 3,12-di-O-Acetyldihydroisolineolon (XVIII)——XVIII (33 mg) was reacted in the same manner, and only the starting material was recovered. XIX gave the same result.