Thiolactam Formation of VIII to IX——A mixture of 200 mg of VIII (1.1 mmole) and 360 mg of P_2S_5 (1.62 mmole) in 8 ml of 1% aq. pyridine was warmed at 100° (bath-temperature) under stirring for 1 hr, then after addition of a further 200 mg of P_2S_5 (0.9 mmole) for another 2 hr. After being cooled, the reaction-mixture was poured in ice-water and extracted with $CHCl_3$–MeOH (3:1). The organic-layer was washed, dried, and evaporated. The residue was dissolved in CH_3COCH_3, decolorized with active-charcoal, and concentrated to give 206 mg of IX (94%).

Conversion of IV to IX——a) A mixture of 50 mg of IV and 55 mg of P_2S_5 in 2 ml of 1% aq. pyridine was warmed at 85° for 1.5 hr under stirring. After cooling the mixture, the precipitate was filtered off and the filtrate was extracted with $CHCl_3$–MeOH (3:1). The organic-layer was washed, dried, and concentrated at reduced pressure. The residue was purified by preparative TLC, (Silica gel GF, solvent-system $CHCl_3$–CH_3COCH_3 (5:1)) to give 14 mg of IV and 10 mg of IX.

b) Hydrogen sulfide was passed into a solution of 30 mg of IV in 1% aq. pyridine heated at 120° for 1 hr under stirring. Solvent was evaporated at reduced pressure and the residue was purified in the same manner as in a) to give 14 mg of IV and 7 mg of IX.

Acknowledgement We are grateful to Dr. K. Takeda, Director of this laboratory for his encouragement. Thanks are also to Dr. M. Narisada and Dr. K. Horiki of this laboratory for helpful discussion and to the members of analytical and physical chemistry sections of this laboratory for elemental analysis, NMR, IR and mass spectra measurements.

[Chem. Pharm. Bull. 19(9)1974—1978(1971)] UDC 547.92.07

Synthesis of a Heterocyclic Ring Steroid[1] Rearrangements of C-nor-steroid

Hiroshi Mitsuhashi and Koji Tomimoto

Faculty of Pharmaceutical Sciences, Hokkaido University[2]

(Received April 16, 1971)

The preparation of steroids containing nitrogen in the ring system has been reported by several workers, but reports concerning the synthesis of 12-aza-[3,4] and 11-aza-steroid[5,6] are limited.

Hecogenin (I) is a readily available substance for the preparation of steroids modified in ring C and such a modification could be the introduction of nitrogen into C-12 or C-11 position in ring C. Hecogenin (I) had been converted into the C-nor-steroid[7,8] and Beckmann rearrangement of the oxime of the C-nor-steroid produced rearrangement products. 3β,20-Diacetoxy-5α-pregnan-12-one (IX) was selected as the starting material for C-nor-steroid in consideration of the modification of azasteroids.

Bismuth trioxide[9] was chosen for the oxidation of 11,12-ketol group in 3β,12β,20-trihydroxy-5α-pregnan-11-one (X) and by its use, a mixture of compounds with C-3 or C-20 hydroxyl groups acetylated were obtained. Since the following step includes alkaline treatment of the mixture, the next reaction was carried out without separation of the acetates.

---

1) A part of this work was presented at the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July 1970.
2) Location: *Kita-12-jo, Nishi-5-Chome, Sapporo, Hokkaido, 60, Japan.*
3) U.K. Pandit and H.O. Huisman, *Tetrahedron Letters*, **1967**, 3901.
4) R.H. Mazur, *J. Am. Chem. Soc.*, **81**, 1454 (1954).
5) J.P. Kutney and I.J. Wattas, *Steroids*, **4**, 595 (1964).
6) J.A. Zderic and J. Iriarte, *J. Org. Chem.*, **27**, 1756 (1962).
7) M. Rajic, T. Rüll and G. Ourisson, *Bull. Soc. Chim. France*, **1961**, 1213.
8) H. Mitsuhashi and Y. Shimizu, *Tetrahedron*, **19**, 1027 (1963).
9) W. Rigby, *J. Chem. Soc.*, **1951**, 793.

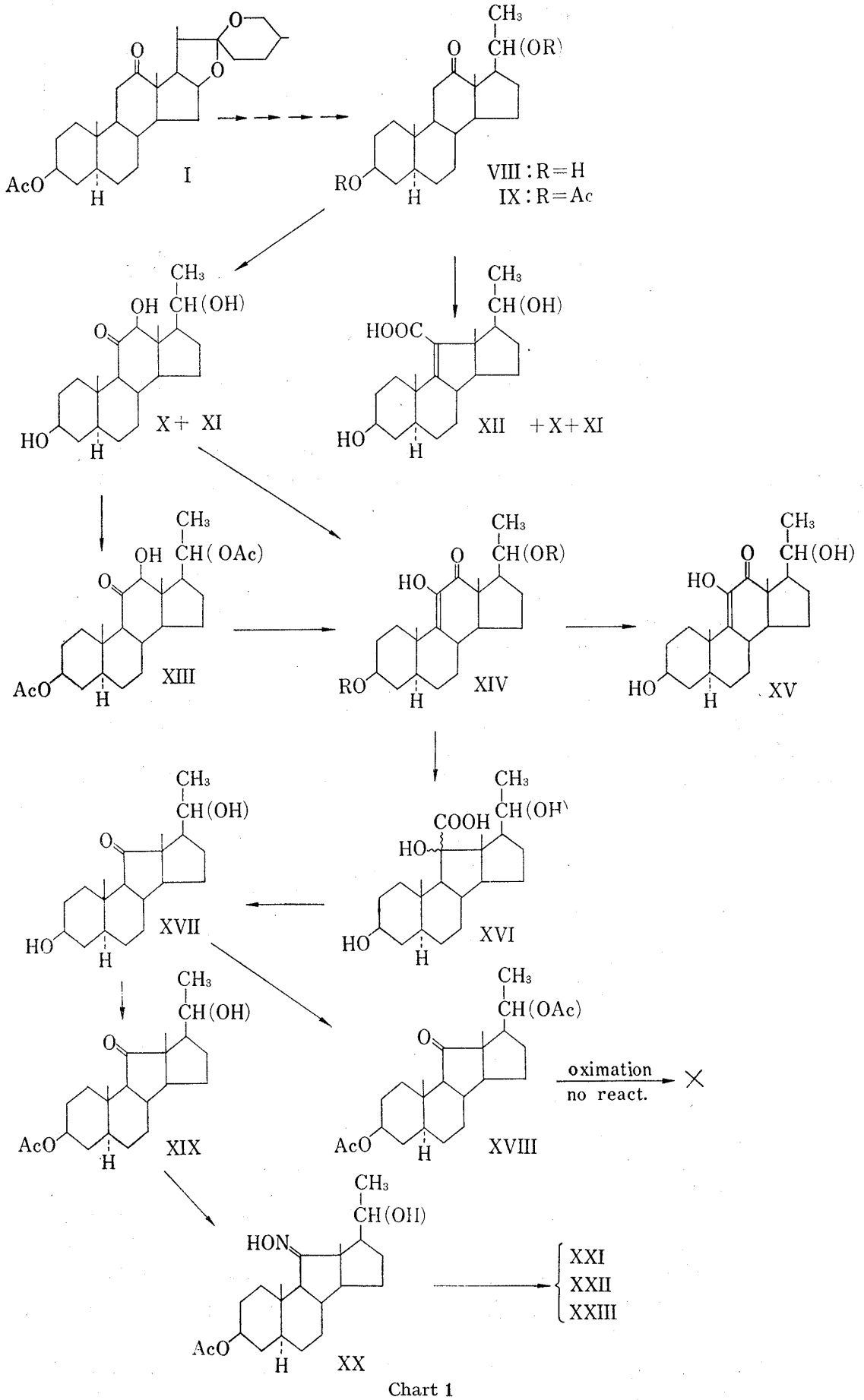


Chart 1

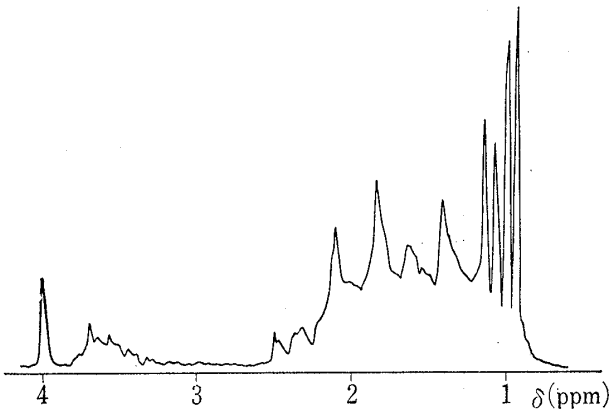


Fig. 1. NMR Spectrum of 3β,20-Dihydroxy-C-nor-5α-pregnan-11-one (XVII) (in $CDCl_3$)

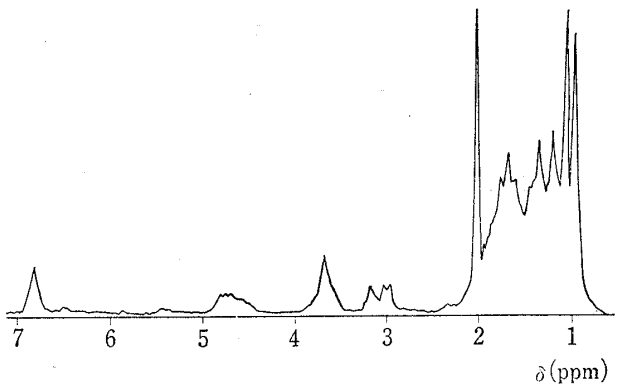
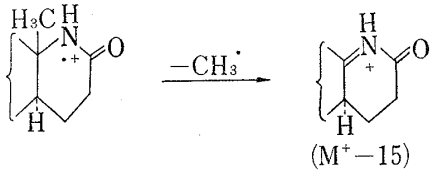


Fig. 2. NMR Spectrum of 3β-Acetoxy-20-hydroxy-12-aza-5α-pregnan-11-one (in $CDCl_3$)

The other series of oxidation of 3β,20-diacetoxy-12β-hydroxy-pregnan-11-one (XIII) led to 3β,20-diacetoxy-11-hydroxy-pregn-9-en-12-one (XIV) in a good yield. The conversion of α-diketone (XIV) by the benzylic acid rearrangement yielded the α-hydroxycarboxylic acid (XVI). Further treatment of XVI with lead tetraacetate gave 3β,20-dihydroxy-C-nor-pregnan-11-one (XVII). The physical constants (infrared (IR) spectrum, mass spectrum, and nuclear magnetic resonance (NMR) spectra) of the product (XVII) clearly correspond to its structure (Fig. 1). In the IR spectrum of XVII, the absorption at 1704 cm^{-1} is in a longer wave length region for a five-membered ring ketone but this might be due to hydrogen bonding with C-20 hydroxyl group.

XVII was then treated with acetic anhydride in pyridine and a diacetate (XVIII) was obtained. It was thought that protection of hydroxyl function with an acetyl group would be convenient for later Beckmann rearrangement. Several attempts of oxime formation of XVIII did not materialize because of the presence of 20-acetoxy group, so attention was turned to the use of 3β-acetoxy-20-hydroxy-C-nor-pregnan-11-one (XIX) as a starting material for the oxime formation. Treatment of the oxime (XX) with tosyl chloride in pyridine yielded a mixture of three kinds of lactam (XXI, XXII, and XXIII). The structure of 12-aza compound (XXII) was established by mass and NMR spectra.

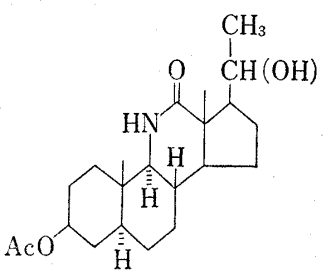
The assignment of the structure of steroid lactam at D ring was made on the basis of the peak of M^+-15, observed by Budzikiewicz.[10] In a mass spectrum of a lactam nitrogen atom attached to C-13 shows very strong M^+-15 ion peak. On the other hand, the lactam CONHR group attached to C-13 produces very weak M^+-15.



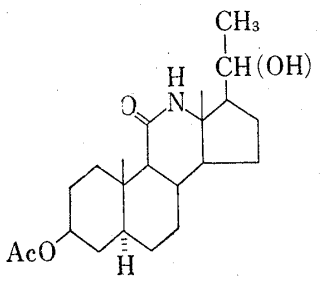
If we assumed this observation can extend to C-ring lactam, the mass spectrum of XXII indicate very clear M^+-15 as strong as base peak. In the NMR spectrum of 3β-acetoxy-20-hydroxy-12-aza-5α-pregnan-11-one (XXII), determined in deuteriochloroform solution, the signal of C-18 methyl moved to a higher field (0.97 ppm) due to an isotropic effect of C-11 carbonyl group (Fig. 2). On the other hand in 3β-acetoxy-20-hydroxy-11-aza-5α-pregnan-12-one (XXI), the signal for C-18 methyl appeared 1.2—1.3 ppm as expected for R-NH-CO-$\dot{C}$-CH_3 and XXI also indicates weak M^+-15 peak in mass spectrum. The other compound

10) H. Budzikiewicz, F. Compernolle, K. Cauwenberghe, K. Schulze, H. Wolf and G. Quinkert, *Tetrahedron*, **24**, 6797 (1968).

(XXIII) on the basis of its IR and NMR spectra, was readily recognized as the amide in which the formation of one double bond was assumed from the signal of 5.88 ppm (=CH-) and absorption at 3070 cm^{-1} of IR spectrum. The structure with one double bond added to XXI is considered, but the nature of this compound (XXIII) is still in doubt.



XXI



XXII

Chart 2

Experimental[11]

3β,20-Dihydroxy-5α-pregnan-12-one (VIII)——Hecogenin (I) was selected as the starting material and series of reactions, ψ-hecogenin (II)→ψ-hecogenin acetate (III)→3β-acetoxy-5α-pregn-16-en-12,20-dione (IV)→3β-acetoxy-5α-pregn-12,20-dione (V)→3β-acetoxy-12,12-ethylendioxy-5α-pregn-20-one (VI), and reduction of VI led to 3β,20-dihydroxy-12,12-ethylendioxy-5α-pregnane (VII).

VII (0.7 g) was dissolved in 20 ml of 90% AcOH, the solvent was evaporated *in vacuo*, and the residue was crystallized from CH_2Cl_2–AcOEt to prisms, yield I→VIII, 20%.

VIII (2 g) was dissolved in a mixture of equal amounts of pyridine and Ac_2O (15 ml), and heated under reflux for 2 hr. The cooled reaction mixture was poured into ice–water and the product was collected by filtration. Crystallization from MeOH gave IX as small prisms, mp 211—212°, yield, quantitative.

3β,12β,20-Trihydroxy-5α-pregnan-11-one (X)——IX (2.5 g) was dissolved in benzene (30 ml) and brominated with bromine (1 g) in benzene (10 ml). The first few drops of the bromine solution were discolored, the rest was added after 5 min, and the mixture was kept at room temperature for 2 hr. The benzene solution was washed with Na_2CO_3 solution and water, dried, and evaporated to dryness under reduced pressure.

Above obtained 3β-acetoxy-20-hydroxy-11α-bromo-5α-pregnan-12-one was dissolved in *tert*-BuOH (30 ml) and 7% NaOH solution (30 ml). The two-phase solution was refluxed for 6 hr. The initially appeared crystals disappeared on prolonged boiling. After addition of water, the product was extracted with $CHCl_3$ and the $CHCl_3$ extract was evaporated to dryness. Crystallization of X from MeOH gave prisms (1117 mg), mp 201—204°, yield, 54%. IR ν_{max}^{Nujol} cm^{-1}: 3445, 3360, 3200, 1720, 1150, 1045. NMR (in $CDCl_3$) δ: 0.52 (s, 3H), 1.07 (s, 3H), 1.12 (d, J=6 cps, 3H), 2.31 (s, 1H), 2.46 (d, J=5 cps, 1H), 3.52 (m, 2H).

3β,20-Diacetoxy-11-hydroxy-pregn-9-en-12-one (XIV)——1) The ketol (X) (1.4 g) was heated in AcOH (40 ml) with Bi_2O_3 (2 g) under reflux for 30 hr. The solution gradually became dark. The mixture was kept at room temperature for over night, water was added, and the product was extracted with benzene. The benzene solution was treated as usual and evaporated to dryness. Crystallization of the reaction product from MeOH–H_2O gave 1.11 g of a crystalline mixture which was treated with 3% K_2CO_3 in MeOH at room temperature and gave 3β,11,20-trihydroxy-5α-pregn-9-en-12-one (XV). Crystallization from MeOH–H_2O gave needles, mp 189—193°. Yield 940 mg (68%). From the mother liquor, 3β,20-diacetoxy-11-hydroxy-5α-pregn-9-en-12-one (XIV) was separated as rods, mp 198—200°. IR ν_{max}^{Nujol} cm^{-1}: 3363, 1720, 1683, 1614, 1260, 1118. NMR (in $CDCl_3$) δ: 0.91 (s, 3H), 1.12, 1.14, 1.21 (6H), 2.00 (s, 3H), 2.08 (s, 3H), 2.25 (m, 1H), 4.76 (m, 2H).

2) The ketol (X) was heated with a mixture of AcOH and Ac_2O for 1 hr on a water-bath. After pouring into ice–water, the mixture was extracted with $CHCl_3$, XIII was treated according to the usual procedures, and gave 3β,20-diacetoxy-12-hydroxy-5α-pregnan-11-one (XIII) in quantitative yield. XIII was oxidized under the same condition as (1) and gave α-diketone (XIV) in a good yield.

3β,11,12-Trihydroxy-11-carboxy-C-nor-5α-pregnane (XVI)——XIV (1 g) was dissolved in methylcellosolve (60 ml), and a mixture of BaO (5 g) in H_2O (20 ml) was added. The mixture was heated under reflux for 24 hr, then poured into a large amount of aqueous HCl solution, and extracted with $CHCl_3$. The $CHCl_3$ layer was treated in the usual manner. After evaporation of the solvent, the residue was crystal-

11) Satisfactory analytical results were obtained for all compounds described in this paper.

lized from MeOH–H_2O to needles, mp 210—212°. Yield, 71%. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3335, 3200—2700, 1710, 1100.

3β,20-Dihydroxy-C-nor-5α-pregnan-11-one (XVII)——The above acid (XVI) (400 mg) was dissolved in AcOH and $(AcO)_4Pb$ (530 mg) was added. The mixture was kept overnight at room temperature, $(AcO)_4$-Pb (140 mg) was further added, and kept for 3 hr. After addition of diethylene glycol (3 ml), the mixture was evaporated to 1/4 the original volume under reduced pressure. The mixture was poured into ice–water and extracted with benzene. The benzene layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent deposited a crystalline mass, which recrystallized from CH_2Cl_2–AcOEt to plates, mp 170—171°, yield 281 mg (80%). IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH), 1704 (C=O). Mass Spectrum *m/e*: 320 (M^+), its NMR spectrum (in $CDCl_3$) is shown Fig. 1.

3β,20-Diacetoxy-C-nor-5α-pregnan-11-one (XVIII)——The above C-nor compound (300 mg) was warmed with pyridine (5 ml) and Ac_2O (2 ml) on a waterbath for 2 hr. The cooled solution was poured into ice–water and extracted with benzene. The benzene extract was evaporated to dryness under a reduced pressure. The residue chromatographed on alumina, gave a colorless oily substance which behaved as a pure substance on thin–layer chromatography (TLC). IR ν_{max}^{Nujol} cm^{-1}: 1732, 1724, 1251, 1117.

3β-Acetoxy-20-hydroxy-C-nor-pregnan-11-one (XIX)——Compound XVII (300 mg) was dissolved in a mixture of pyridine (4 ml) and Ac_2O (2 ml), and left at 15° for 2 hr. The solution was diluted with EtOH (4 ml) and the solvent was evaporated under a reduced pressure. EtOH was added to the residue and evaporated to dryness to remove pyridine, and the residue was recrystallized from ether–hexane to needles, mp 172—175°; yield, 69%.

IR ν_{max}^{Nujol} cm^{-1}: 3449, 1732, 1709, 1250, 1028. NMR δ (in $CDCl_3$): 0.88 (s, 3H), 0.95 (s, 3H), 1.11 (d, J=6 cps, 3H), 1.99 (s, 3H), 2.41 (m, 1H), 3.60 (m, 1H), 4.68 (m, 1H).

3β-Acetoxy-20-hydroxy-C-nor-5α-pregnan-11-one Oxime (XX)——Above semi acetate (XIX) (250 mg) was dissolved in pyridine and $NH_2OH \cdot HCl$ (125 mg) was added. The solution was heated at reflux for 5 hr, diluted with H_2O, and extracted with $CHCl_3$. The extract treated by the usual procedure, gave an amorphous product, which failed to crystallize but displayed a single spot on TLC and uniform NMR spectrum. Yield, 226 mg.

Beckmann Rearrangement of 3β-Acetoxy-20-hydroxy-C-nor-5α-pregnan-11-one Oxime——To a solution of XX (200 mg) in pyridine (3 ml) was added tosyl chloride (120 mg) under ice-cooling. The mixture was allowed to stand at 0° for 24 hr. After addition of a few drops of H_2O, the mixture was heated at 100° for 2 hr. After addition of dilute HCl, the mixture was extracted with $CHCl_3$. The organic layer was washed with water and dried (Na_2SO_4).

Removal of the solvent gave a residue. This residue was separated by preparative TLC (silica gel, HF_{254}, ether) into Fraction A (XXI and XXII, 48 mg), Fraction B (XXIII, 10 mg), and the starting material (60 mg).

Fraction A was crystallized from Et_2O, and gave XXII (12-aza compound) mp 248—253° (28 mg). *Anal.* Calcd. for $C_{22}H_{35}O_4N$: C, 69.99; H, 9.35; N, 3.71. Found: C, 69.92; H, 9.59; N, 3.90. IR ν_{max}^{direct} cm^{-1}: 3360, 3300 (NH, OH), 1730 (C=O), 1635 (C=O), 1245 (C-O). Mass Spectrum *m/e*: 377 (M^+). Its NMR spectrum (in $CDCl_3$) is shown in Fig. 2. The signals at δ 6.82 and 3.66 were decreased respectively about 1 proton by addition of D_2O.

The mother liquor was treated with preparative TLC and gave an oily substance (XXI). IR ν_{max}^{direct} cm^{-1}: 3360, 3300 (OH), 1730 (C=O, acetyl), 1635 (C=O, amide), 1245 (C-O). Mass Spectrum *m/e*: 377 (M^+), 362 (M^+-15, weak). NMR (in $CDCl_3$) δ: 1.04 (s, 3H), 1.14 (d, J=6 cps, 3H), 1.29 (s, 3H), 1.99 (s, 3H), 2.50 (m, 1H), 3.70 (m, 1H), 4.78 (m, 1H), 6.69 (br. s, 1H). The signal at δ 6.69 is disappeared upon addition of D_2O. These physical constants correspond to 11- aza compound (XXI).

Fraction B (XXIII), mp 168—174°. IR ν_{max}^{direct} cm^{-1}: 3360, 3250, 3060, 1740, 1640, 1250, 1125, 900, 738. Mass Spectrum *m/e*: 362. NMR (in $CDCl_3$) δ: 1.08 (s, 3H), 1.13 (d, J=6 cps, 3H), 1.39 (s, 3H), 1.99 (s, 3H), 2.30 (m, 3–4H), 3.78 (m, 1H), 4.90 (m, 1H), 5.88 (br. s, 1H), 7.16 (br. d, J=7 cps, 1H). The signal of δ 7.16 is disappeared upon addition of D_2O.

Acknowledgement The authors express their thanks to Dr. K. Takeda, Director of the Shionogi Research Laboratory, for the supply of the starting material, to Miss H. Fujisawa for NMR spectral measurement, and to Miss Y. Imai for the mass spectrum. Elemental analyses were carried out by Miss H. Kakizaki, M. Sato and A. Maeda, to whom the authors' thanks are due.