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Studies on C-Nor-D-homosteroids. X.[1] Conversion of Normal Steroids to C-Nor-D-homosteroids

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The rearrangement of 3β,20β-dihydroxy-5α-pregnan-12-one derivatives to C-nor-D-homosteroid was studied by several methods, and a few new methods were devised.

C-Nor-D-homo rearrangement of normal steroids has been tried in several laboratories,[3-10] but there are not very much hope that these results may used as a raw material in this field because of the low yield of this rearrangement. In this paper, we describe recent studies which contain a few of new methods for C-nor-D-homo rearrangement of normal steroids.

Hecogenin (I) was degraded to 3β,20β-dihydroxy-5α-pregnan-12-one (II) in several steps. Cyanohydrin (III) was prepared with KCN in $CHCl_3$, MeOH, and AcOH, and it was acetylated with Ac_2O in pyridine at room temperature to give IV. III and IV were degraded to II and V by heating. The dehydration of IV with $SOCl_2$ in pyridine afforded an endocyclic olefin (VI), mp 103°, ν_{max}^{Nujol} cm^{-1}: 2250, 1730, and exocyclic olefin (VII), mp 203—205°, ν_{max}^{Nujol} cm^{-1}: 2250, 1730, 1650, 910, in 90% yield. Attempted reduction of VII with $LiAlH_4$ in refluxing tetrahydrofuran gave a small amount of VIII, mp 196—198°, and a basic substance (IX). More moderate condition of reduction in refluxing ether afforded only IX. Acetylation of IX with Ac_2O in pyridine yielded a triacetate (X), $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1730, 1660, 1550, 1240. Heating of VII with alkali at 190° in an autoclave afforded an acidic substance (XI), mp 219—220°, which was converted to the methyl ester (XII). The double bond at 13—18 migrated to 13—17 during this treatment.

Several attempts at decarboxylation of XI to prepare the known compound (VIII) by treatment with alkali and acid failed. Reduction of VI and VII with EtONa in boiling toluene geve VIII in 50—60% yield identical with the compound[3] prepared from tosylhydrazone of II. Moreover these results support the structure of VIII from the reduction mechanism.

Both the Oppenauer oxidation and CrO_3-pyridine oxidation of VIII gave a diketone[8] (XIII) which was so resistant to migration of the double bond to α,β-unsaturated ketone (XIV) that an intractable mixture was obtained under several conditions. A/B-*cis* diketone[10] (XV) is stable to alkali but converted to XVI with acid, and deconjugation of XVI to XVII occurred with alkali. Mitsuhashi, *et al.*[11] reported some reactions A/B-*trans* series, XVIII

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2) Location: *a) N-12, W-6, Kita-ku, Sapporo, Hokkaido, 060, Japan; b) 1-1-8 Azusawa, Itabashi-ku, Tokyo, 174, Japan.*
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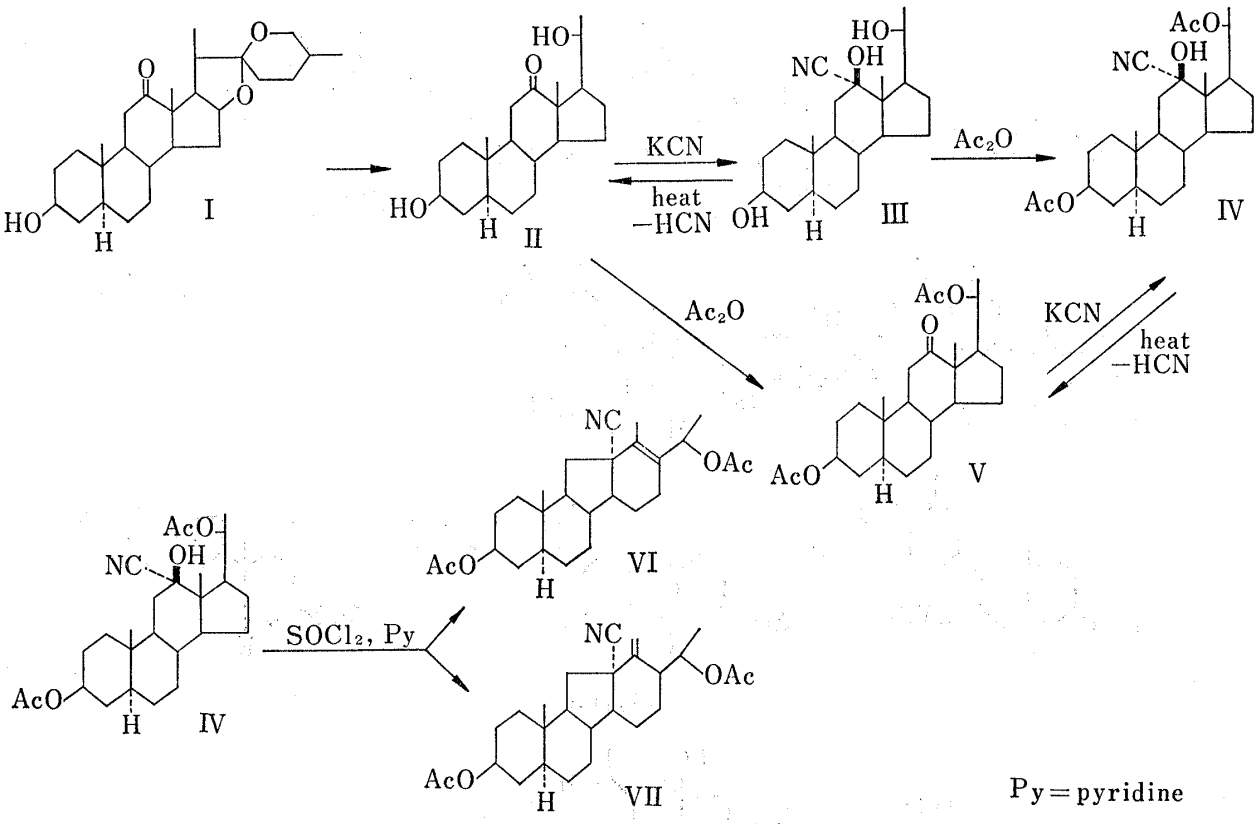

Chart 1

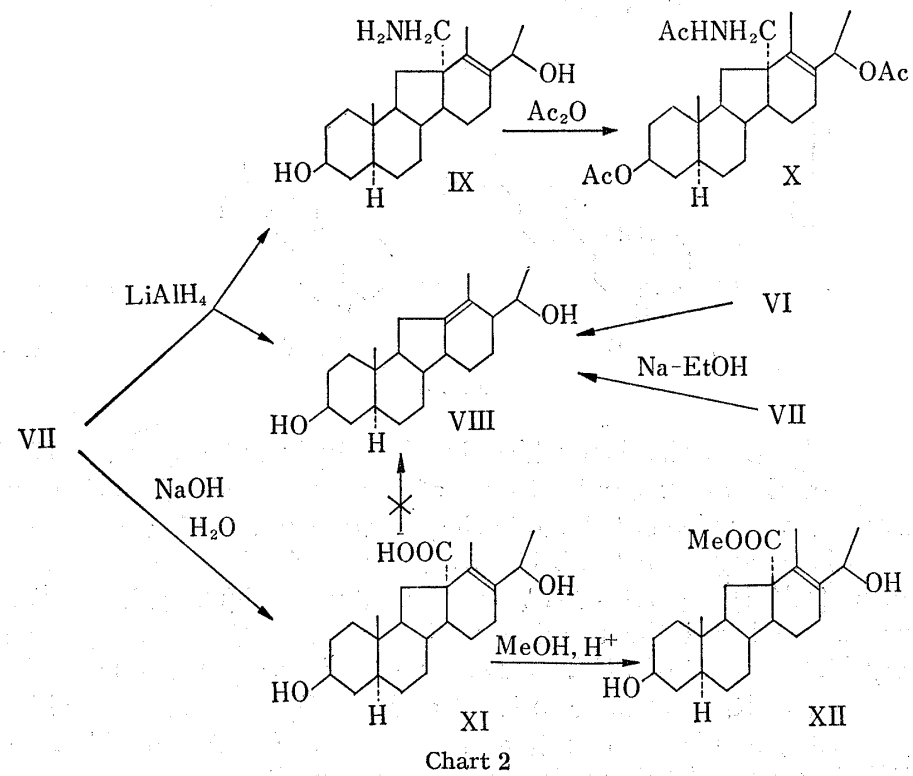

Chart 2

to XIX. These results indicate that XIII-type structure in the steroids with C-nor-D-homo skeleton is thermodynamically more stable than α,β-unsaturated ketone-type structure (XIV).

Chromic acid oxidation of XX in AcOH gave XXI, mp 208—210°, ν_{max}^{Nujol} cm^{-1}: 2260, 1710, 1700, which showed no selective ultraviolet (UV) absorption. Previously, same results were reported in the case of MnO_2 and CrO_3 oxidation of VIII.[8] These kinds of oxidation are

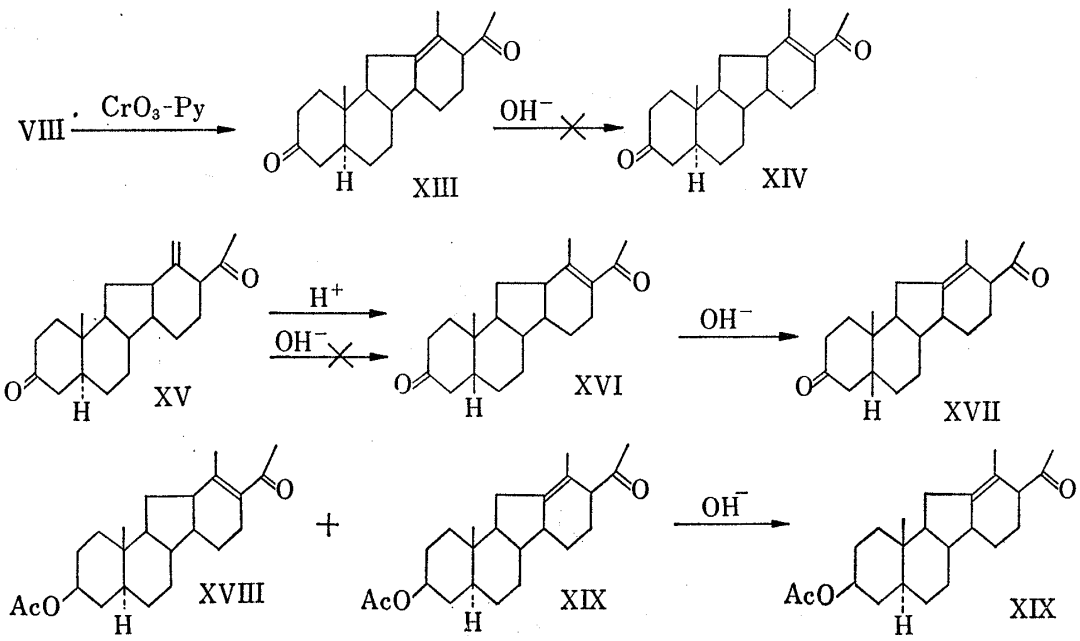

Chart 3

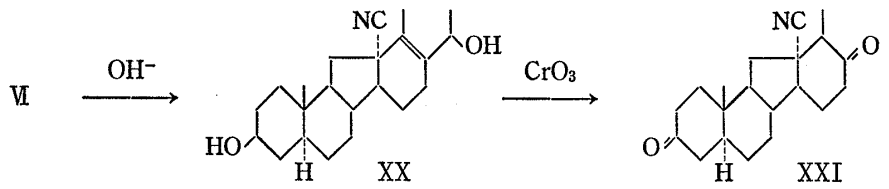

Chart 4

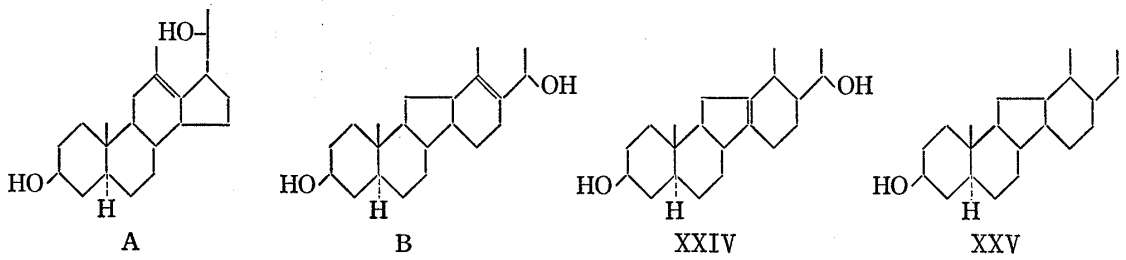

Chart 5

expected to occur by a mechanism which involves hydroxylation at C-17 followed by oxidative cleavage of C 17—20 bond. In an attempt to obtain C-nor-D-homosteroids by these new reactions, we carried out the following experiments. It is considered necessary to create a more positive charge near the C-12 with electron withdrawing groups.

12-Hydrazone (XXII), mp 170—177°, was treated with $Pb(OAc)_4$ in CH_2Cl_2. Evolution of N_2 gas was observed and the reaction product showed the same spot on thin-layer chromatography (TLC) as that of VIII. However, it had a vinyl methyl signal in its nuclear magnetic resonance (NMR) spectrum at δ 1.79 (singlet, 3H), besides 19 methyl (δ 0.79, singlet, 6H), 21 methyl (δ 1.30, doublet J=6 cps), and 21 methyl (δ 1.32, doublet, J=6 cps).

These NMR data proved this product to be a composite of two compounds, VIII and XXIII. Several attempts to separate this product by preparative TLC were unsuccessful, but a part was crystallized from MeOH to give VIII and XXIII, mp 215—216°. XXIII is either a methyl-migrated compound (A) or a $\Delta^{13(17)}$-C-nor-D-homo compound (B).

Catalytic hydrogenation of a mixture of VIII and XXIII over PtO_2 as a catalyst in AcOH and EtOH gave a relatively small amount of XXIV and XXV.[9] This result suggests that

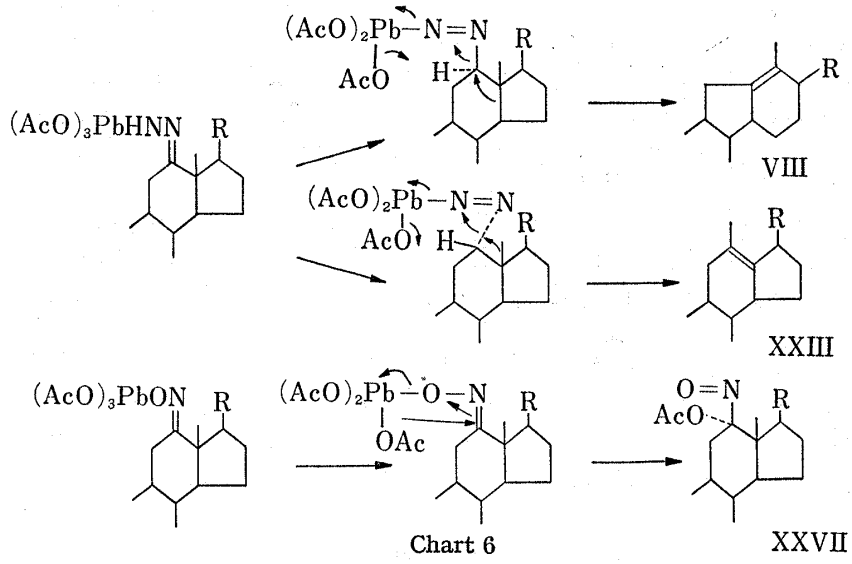

Chart 6

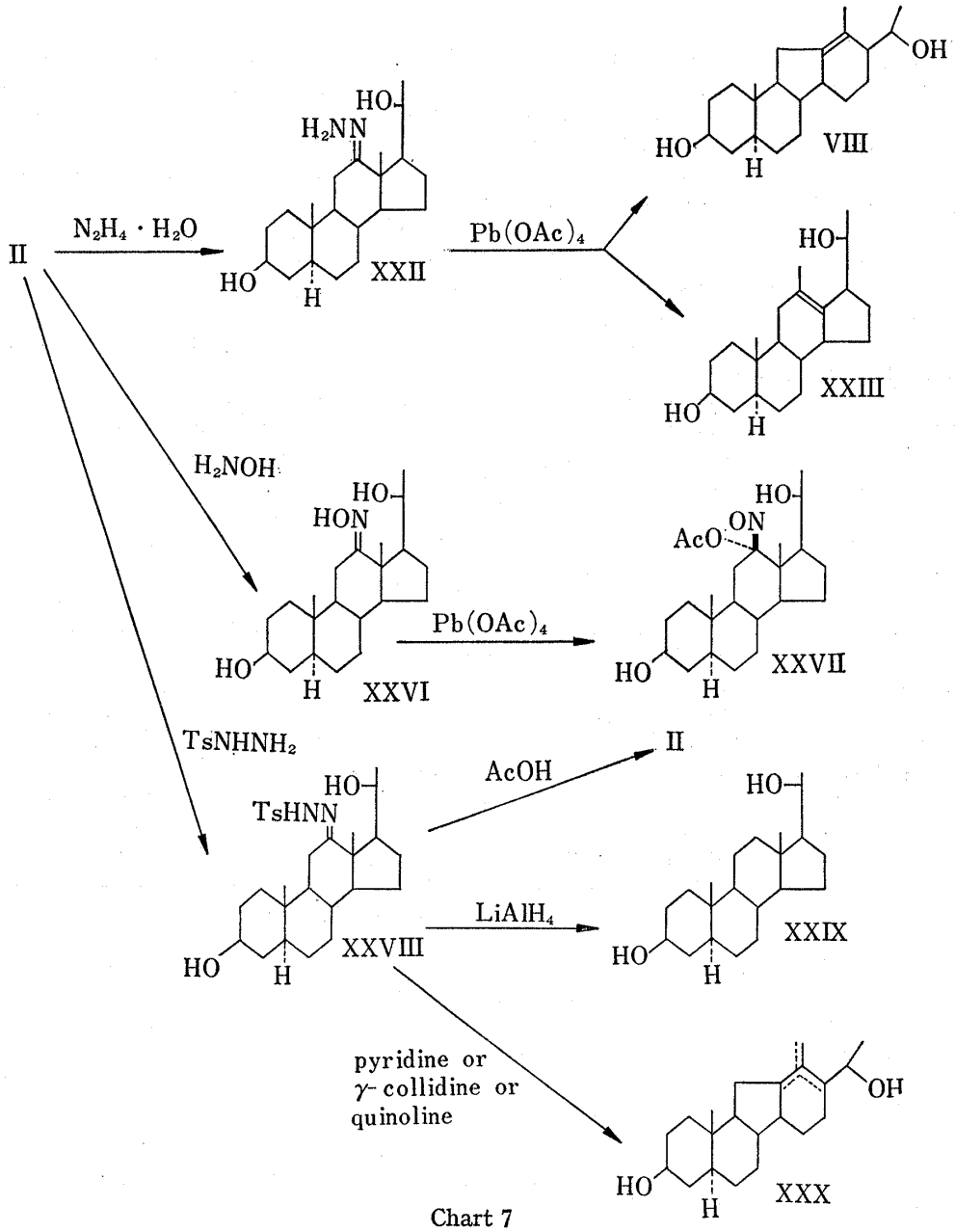

Chart 7

XXIII has a structure (A). 12-Oxime (XXVI) was treated with $Pb(OAc)_4$ in CH_2Cl_2 and the reaction products were separated by preparative TLC using Silica gel HF_{254} nach Stahl (Merck). The main product (XXVII), mp 98—105°, colored blue was considered to be a nitroso compound. Its NMR spectrum shows that 18-methyl (δ 0.17) shifts to a high field by magnetic anisotropic effect of 12β-NO group. The above reactions can be illustrated by a mechanism which goes through the intermediate as shown in the following scheme.[12]

The tosylhydrazone (XXVIII) was refluxed in AcOH overnight but the starting material was recovered. The reduction of XXVIII with $LiAlH_4$ in tetrahydrofuran gave quantitatively 5α-pregnan-3β,20β-diol (XXIX), mp 194—196°. Neither refluxing with potassium *t*-butoxide in *t*-butanol nor heating at 80° with sodium ethylene glycolate in ethylene glycol gave any rearranged product, but heating at 135° under the above condition and refluxing in quinoline, γ-collidine, or pyridine yielded C-nor-D-homo compound (XXX). We must conclude from the above experimental studies that C-nor-D-homo rearrangement of XXVIII was achieved by pyrolysis and there is no effect of a strong base.

Experimental

All melting points were measured on a Kofler block and are uncorrected. For homogeneity tests and identification, TLC using Silica gel HF_{254} nach Stahl (Merck) and aluminium oxide G (Merck) were used. The NMR spectra were taken on either Nihon Denshi JNMC-60 or Hitachi H-60 instrument working at 60 Mc. The infrared (IR) spectra were taken in Shimadzu IR spectrometer type IR. The UV spectra were measured on a Shimadzu Self-Recording UV Spectrophotometer RS-27. Compounds II, XXVIII, XIII, XV, and XVI were prepared from hecogenin (I) by the methods previously described.[3,10]

Cyanohydrin (III)——To a solution of II (5 g) in $CHCl_3$ (40 ml), MeOH (60 ml) and AcOH (14 ml), KCN (14.5 g) was gradually added during 20 min under ice-cooling and the mixture was stirred for 8 hr at room temperature. After addition of H_2O and $CHCl_3$, the organic layer was washed with water and dried (Na_2SO_4). Removal of the solvent yielded crystals which were recrystallized from AcOEt to give 4.2 g of III, mp 194° (236°), ν_{max}^{Nujol} cm^{-1}: 3400 (broad), 2250. *Anal.* Calcd. for $C_{22}H_{35}O_3N$: C, 73.09; H, 9.76; N, 3.87. Found: C, 73.12; H, 9.74; N, 3.76.

Diacetate (IV)——i) III was dissolved in 20 ml pyridine, to which was added Ac_2O (10 ml), and the mixture was allowed to stand at room temperature for 24 hr and H_2O added. Recrystallization of the product from AcOEt gave IV, mp 184—185°; ν_{max}^{Nujol} cm^{-1}: 3420, 2250, 1723, 1710, 1275, 1243. *Anal.* Calcd. for $C_{26}H_{39}O_5N$: C, 70.08; H, 8.82; N, 3.14. Found: C, 70.19; H, 8.75; N, 2.96.

ii) II was refluxed in a mixture of Ac_2O and pyridine for 16 hr. After pouring into ice-water, the mixture was extracted with ether and treated as usual to give V, mp 139—140°. The diacetate (V) was converted to IV under the same condition as above.

Dehydration of IV——To a solution of IV (2.0 g) in pyridine (18.5 ml), $SOCl_2$ (1 g) was added under ice-cooling and the mixture was allowed to stand at room temperature overnight. After pouring into ice-water, the mixture was extracted with ether and treated according to the usual procedures. Evaporation of the solvent deposited crystals whose recrystallization from MeOH gave VI (0.403 g, 21%), mp 163°, ν_{max}^{Nujol} cm^{-1}: 2250, 1730, 1250, and VII (1.29 g, 67%) mp 201°. ν_{max}^{Nujol} cm^{-1}: 2250, 1730, 1650, 1250, 910. *Anal.* Calcd. for $C_{26}H_{37}O_4$ (VI): C, 73.03; H, 8.71; N, 8.28. Found: C, 82.82; H, 8.52; N, 3.31. *Anal.* Calcd. for $C_{26}H_{37}O_4N$ (VII): C, 73.03; H, 8.71; N, 3.28. Found: C, 72.91; H, 8.71; N, 2.93.

$LiAlH_4$ Reduction of VII——i) VII (500 mg) was dissolved in dry tetrahydrofuran and added to a suspension of $LiAlH_4$ (1 g) in dry tetrahydrofuran. After refluxing with stirring for 6 hr, H_2O was added. The mixture was extracted with CH_2Cl_2, the organic layer was washed with H_2O, and dried (Na_2SO_4). Evaporation of the solvent gave a colorless oil (385 mg) which was a mixture of VIII and IX (TLC on Silica gel HF_{254}). The mixture was separated by TLC using Silica gel HF_{254} to VIII (25 mg), mp 195—197°, and IX (308 mg), non-crystalline.

ii) A solution of VII (500 mg) dissolved in dry ether (90 ml) and dry tetrahydrofuran (20 ml) was added to a suspension of $LiAlH_4$ (1 g) in dry ether. After refluxing for 2 hr H_2O was added. The mixture was extracted with 3% HCl solution, NH_4OH added to alkali reaction and extracted with CH_2Cl_2. Treatment by the usual procedure gave IX (245 mg) as a colorless oil. Acetylation of IX (71 mg) with Ac_2O (1 ml) in pyridine (2 ml) by heating on a water-bath for 1 hr gave X (53 mg) as an oily substance which was purified by preparative TLC using Silica gel HF_{254}. ν_{max}^{Nujol} cm^{-1}: 3300, 1730, 1660, 1550, 1240. *Anal.* Calcd. for

12) D.C. Iffland and G.X. Criner, *Chem. Ind.* (London), **1956**, 176; D.C. Iffland, L. Salisbury, and W.R. Schafer, *J. Am. Chem. Soc.*, **83**, 747 (1961).

$C_{28}H_{43}O_6N$: C, 68.68; H, 8.85; N, 2.86. Found: C, 68.91; H, 8.78; N, 2.83.

Hydrolysis of VII——i) VII (1 g) was dissolved in MeOH, 20% NaOH was added and the mixture was heated at 190° for 3 hr in an autoclave. After evaporation of MeOH, the solution was acidified with 10% HCl, and a precipitate formed was separated by filtration, washed several times with H_2O, and recrystallized from MeOH to XI (0.45 g, 54%), mp 219—220°. ν_{max}^{Nujol} cm^{-1}: 3380, 2640, 1700. *Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.34. Found: C, 72.98; H, 9.34.

ii) The acid (XI) (100 mg) was refluxed for 3 hr in MeOH (18 ml) containing 40% H_2SO_4 (12 ml). After H_2O was added, MeOH was evaporated *in vacuo* and extracted with ether. The ether layer was washed with H_2O and dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from ether–hexane to XII (65 mg), mp 114—117°. ν_{max}^{Nujol} cm^{-1}: 3300, 1730, 1245.

iii) The carboxylic acid (XI) was treated with pyridine or AcOH with refluxing. In both cases the starting material was recovered quantitatively.

EtONa Reduction of VI and VII——A solution of VI (1 g) dissolved in dry toluene (30 ml) and abs. EtOH (15 ml) was dropped into a suspension of dry toluene containing fused Na metal (15 g) during 30 min under reflux. After cooling to 50° with stirring, 95% EtOH was added, followed by H_2O, and extracted with ether. The organic layer was washed with H_2O and dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from MeOH to VIII (415 mg), mp 196—198°. VI was converted to VIII under the same condition as above.

CrO_3 Oxidation of XX——i) VI (200 mg) was hydrolyzed by refluxing with 5% MeOH–KOH for 2.5 hr on a water-bath. To this solution, when cooled H_2O was added and MeOH removed *in vacuo*. After extraction with ether, the ether solution was washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was crystallized from iso-Pr_2O and recrystallized from benzene to 170 mg of XX, mp 84—85°. *Anal.* Calcd. for $C_{22}H_{33}O_2N$: C, 76.92; H, 9.68; N, 4.08. Found: C, 76.74; H, 9.77; N, 3.95.

ii) A solution of XX (100 mg) dissolved in 90% AcOH (2 ml) was added to a solution of CrO_3 (65 mg) in 90% AcOH (2 ml). After standing 21 hr at room temperature, the reaction mixture was extracted with ether, the extract was washed consecutively with H_2O, $NaHCO_3$ solution, and H_2O, and dried (Na_2SO_4). After evaporation, crystals that separated were recrystallized from EtOH to 50 mg of XXI, mp 208—210°. ν_{max}^{Nujol} cm^{-1}: 2260, 1710, 1700. *Anal.* Calcd. for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68. Found: C, 76.56; H, 8.56.

$Pb(OAc)_4$ Oxidation of XXII——i) XXII, mp 170—172° was prepared by treating II with $H_2NNH_2 \cdot H_2O$ in EtOH. To a solution of XXII (330 mg) in dry CH_2Cl_2 (4 ml), a solution of $Pb(OAc)_4$ (500 mg) in dry CH_2Cl_2 (3 ml) was added during 5 min under ice-cooling. Immediately the evolution of N_2 gas was observed. The mixture was stirred for 15 min and stirred a further 15 min at room temperature. H_2O was added, the precipitate was filtered off, and the precipitate was extracted with CH_2Cl_2. The organic layer was washed consecutively with H_2O, $NaHCO_3$ solution and H_2O and dried (Na_2SO_4). After evaporation of the solvent, a part of the residual oil (300 mg) crystallized from CH_2Cl_2, and further recrystallized from EtOAc to VIII and XXIII of mp 215—216°. *Anal.* Calcd. for $C_{21}H_{36}O_2N_2$ XXII: C, 72.37; H, 10.41; N, 8.04. Found: C, 72.29; H, 10.39; N, 7.83.

$Pb(OAc)_4$ Oxidation of XXVI——i) XXVI, mp 182—185°, was prepared by heating II with H_2N–OH·HCl in EtOH and pyridine. To a solution of XXVI (350 mg) in CH_2Cl_2 (3ml) and AcOH (2 ml) a solution of $Pb(OAc)_4$ (500 ml) in CH_2Cl_2 (3 ml) was added during 10 min under ice-cooling. The solution gradually became blue. The mixture was stirred for 30 min at room temperature. H_2O was added, the precipitate was filtered off, and the precipitate was extracted with CH_2Cl_2. The organic layer was washed consecutively with H_2O, $NaHCO_3$ solution, and H_2O, and dried (Na_2SO_4). After evaporation of the solvent, the residual oil (353 mg) was separated by preparative TLC using Silica gel HF_{254}. A part (120 mg) of the main product was crystallized from EtOAc to XXVII, mp 98—105°, NMR (in $CDCl_3$) δ: 0.17 (18-Me, s), 0.79 (19-Me, s), 1.14 (21-Me, d, J=6 cps), 2.33 (acetyl). *Anal.* Calcd. for $C_{23}H_{37}O_5N$: C, 67.87; H, 9.15; N, 3.44. Found: C, 66.37; H, 9.07; N, 3.11.

Attempted Solvolysis of Tosylhydrazone (XXVIII)——i) XXVIII (200 mg) was refluxed in AcOH overnight. After addition of H_2O, crystals that separated were recrystallized from MeOH to give a compound (86 mg) which was identical with II.[3]

ii) To a solution of XXVIII (200 mg) in dry tetrahydrofuran (10 ml) $LiAlH_4$ (300 mg) was added. After refluxing with stirring overnight, the mixture was extracted with AcOEt, the organic layer was washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent gave crystals, recrystallized from MeOH to XXIX (78 mg), mp 194—195°, identical with the authentic sample. *Anal.* Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.57; H, 11.06.

iii) The tosylhydrazone XXVIII (300 mg) was dissolved in a solution prepared by dissolving 60% NaH (600 mg) in ethylene glycol (20 ml) and heated at 80° for 6 hr. XXVIII (110 mg) was dissolved in a solution prepared by dissolving K (100 mg) in *t*-BuOH (10 ml) and refluxed for 14 hr. In both cases, the starting material was recovered in quantitatively.

iv) A solution of XXVIII (200 mg) dissolved in quinoline (5 ml) was heated in N_2 stream. The N_2 gas evolution started at 237° and the solution was kept at this temperature for 10 min. When cooled, the reaction mixture was poured into cold HCl solution and extracted with CH_2Cl_2 which was washed with H_2O and dried (Na_2SO_4). After evaporation of the solvent, the residue was separated by TLC using Silica gel

HF_{254} to give VIII (32 mg), mp 195—197°, and an oily substance which was a mixture of VIII, rearranged exomethylene compound, and others.

v) A solution of XXVIII (200 mg) dissolved in γ-collidine (5 ml) was refluxed for 2 hr in N_2 stream. The reaction mixture was treated as above and the product was separated by TLC using Silica gel HF_{254} to give VIII (13 mg), mp 196—197°, and the same mixture as above.

vi) A solution of XXVIII (200 mg) dissolved in pyridine (5 ml) was refluxed for 5 hr in N_2 stream and treated as above to give VIII (11 mg), mp 194—196°, and others which consisted of the same components.

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