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165. Shunsaku Noguchi, Masayuki Imanishi, and Katsura Morita : Steroid [16,17-*c*]isoxazoline.*1

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The biological activity of the steroids produced by fusion of a pyrazol ring to 2,3-positions of androstanes and 19-norandrostanes was first announced by Clinton, *et al.*[1] Syntheses of similar compounds involving isoxazole,[2] thiazol,[3] pyrimidine,[2] triazol,[4] pyrrole,[5] indole,[5] quinoline,[6] oxazine,[7] and pyridine[8] moieties were thereafter reported by other groups. In this connection, we have already reported the synthesis of steroid-[16,17-*c*]pyrazoles by the reaction of 16,20-dioxosteroids with hydrazine hydrate.[9] The present paper deals with the synthesis of steroid[16,17-*c*]isoxazolines from 20α-hydroxy-16-oxosteroids.

A selective oxidation of 16β,20α-dihydroxysteroids to 20α-hydroxy-16-oxosteroids was described in the previous paper.[10] Thus 3β,20α-dihydroxy-5α-pregnan-16-one 3-acetate (IIa) was obtained from 5α-pregnane-3β,16β,20α-triol 3-acetate (Ia), and 3β,20α-dihydroxypregn-5-en-16-one 3-acetate (IIb) from pregn-5-ene-3β,16β,20α-diol 3-acetate (Ib), respectively.

IIa was treated with hydroxylamine to give the 16-oxime (IIIa). When IIIa was treated with tosyl chloride or acetic anhydride in pyridine, that is, under the conditions of the Beckmann rearrangement, a crystalline product was obtained in good yield. The product was positive for Kraut-Dragendorff reagent[11] and the elementary analysis was in agreement with the formula $C_{23}H_{35}O_3N$. After hydrolysis with potassium bicarbonate, the resulting 3β-hydroxy compound showed no carbonyl band in the infrared spectrum. Eventually the nuclear magnetic resonance spectrum (Fig. 1) led us to the assignment of 3β-acetoxy-5'-methyl-5α-androstano[16,17-*c*]-isoxazoline (IVa) to the reaction product.

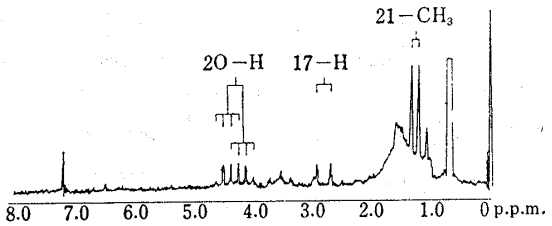

Fig. 1. 60-Mc. Nuclear Magnetic Resonance Spectrum of Va in Deuteriochloroform with Tetramethylsilane (TMS) Internal Standard at 0°

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Furthermore, from the nuclear magnetic resonance spectrum of Va (Fig. 1) it was deduced that the hydrogens at C-17 and C-20 should be *trans*, because the coupling constant ($J_{17H,20H}=12$ c.p.s.) was reasonably large. This also implied that the cyclization took place with retention of the original configuration at C-20. The most plausible explanation for the cyclization process from IIIa to IVa would therefore be as shown in Chart 2, wherein the starting oxime (IIIa) would provably be an *anti*-form. If the cyclization had taken place from the *syn* oxime isomer as shown in Chart 3, the resulting isoxazoline

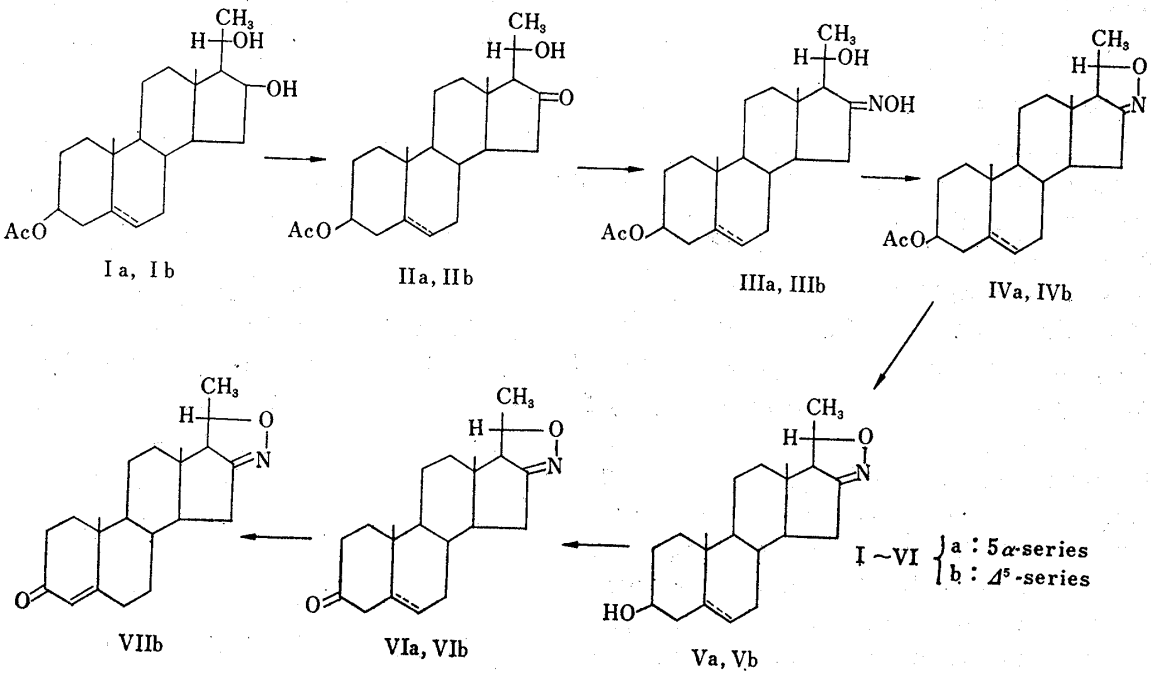

Chart 1.

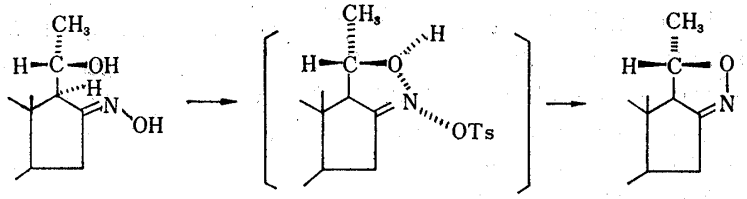

Chart 2.

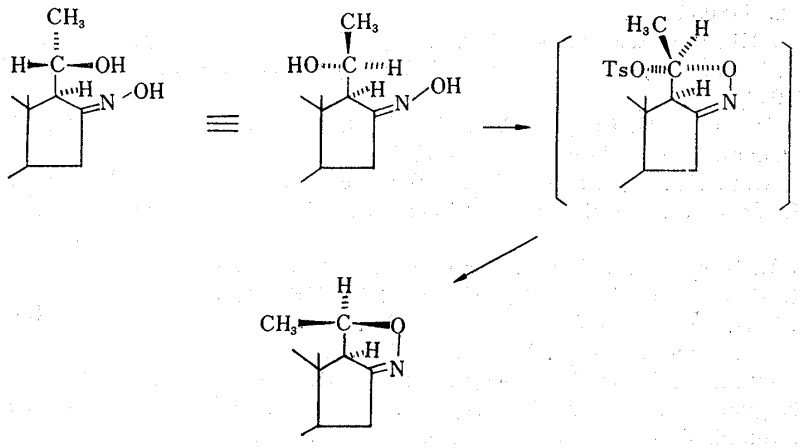

Chart 3.

would have the reverse configuration at C-20, which is quite unfavorable on the basis of the nuclear magnetic resonance spectrum of the product.

Similarly, Δ^5-unsaturated compound (IIb) was converted to the corresponding isoxazoline compound (Vb) by treatment of the intermediate 16-oxime derivative (IIIb) with tosyl chloride in pyridine followed by hydrolysis. Va and Vb were oxidized with CrO_3-H_2SO_4 reagent[12] to afford the corresponding 3-oxo-compounds (VIa and VIb), respectively.

Treatment of VIb with alkali finally gave 5′-methylandrost-4-eno[16,17-*c*]isoxazolin-3-one (VIIb), which showed an α,β-unsaturated carbonyl absorption band in the ultraviolet spectrum.

Experimental*3

3β,20α-Dihydroxy-5α-pregnan-16-one 3-Acetate 16-Oxime (IIIa)——To a suspension of 5.0 g. of 3β,20α-dihydroxy-5α-pregnan-16-one 3-acetate[10] (IIa) in 75 ml. of pyridine and 750 ml. of 95% EtOH was added 2.5 g. of $NH_2OH \cdot HCl$ and the mixture was heated under reflux on a steam bath for 3 hr., during this period crystals of IIIa separated. After cooling, the crystalline product was collected, washed with H_2O and then with MeOH to give 4.2 g. of IIIa, which was recrystallized from CH_2Cl_2-Me_2CO, m.p. 273° (decomp.). *Anal.* Calcd. for $C_{23}H_{37}O_4N$: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.67; H, 9.37; N, 3.56.

3β,20α-Dihydroxypregn-5-en-16-one 3-Acetate 16-Oxime (IIIb)——Oximation of 5.0 g. of 3β,20α-dihydroxypregn-5-en-16-one 3-acetate[10] (IIb), according to the procedure for the preparation of IIIa from IIa, and recrystallization of the resulting product from CH_2Cl_2-Me_2CO afforded 4.2 g. of IIIb, m.p. 260° (decomp.). *Anal.* Calcd. for $C_{23}H_{35}O_4N$: C, 70.92; H, 9.06; N, 3.60. Found: C, 70.98; H, 9.11; N, 3.90.

3β-Acetoxy-5′-methyl-5α-androstano[16,17-*c*]isoxazoline (IVa)——a) To a solution of 1.0 g. of IIIa in 20 ml. of pyridine was added 1.0 g. of TsCl and the mixture was allowed to stand overnight at room temperature. The reaction mixture was poured onto ice and the resulting precipitates were collected and washed with H_2O to give 0.9 g. of crude IVa, m.p. 175~180°. Recrystallization from CH_2Cl_2-hexane raised the melting point to 185°. *Anal.* Calcd. for $C_{23}H_{35}O_3N$: C, 73.95; H, 9.45; N, 3.75. Found: C, 74.00; H, 9.13; N, 3.81.

b) Treatment of IIIa with Ac_2O in pyridine also gave IVa, but the yield was much lower compared with the procedure (a).

3β-Acetoxy-5′-methylandrost-5-eno[16,17-*c*]isoxazoline (IVb)——Treatment of 1.0 g. of IIIb with TsCl in pyridine, according to the procedure (a) for the preparation of IVa from IIIa, gave 0.85 g. of crude IVb, m.p. 165~172°. Recrystallization from CH_2Cl_2-MeOH gave an analytical sample of IVb, m.p. 180~182°. *Anal.* Calcd. for $C_{23}H_{33}O_3N$: C, 74.30; H, 8.95; N, 3.77. Found: C, 74.41; H, 8.95; N, 4.17.

5′-Methyl-5α-androstano[16,17-*c*]isoxazolin-3β-ol (Va)——To a solution of 1.0 g. of IVa in 100 ml. of MeOH was added 20 ml. of 5% aq. K_2CO_3 and the mixture was refluxed on a steam bath for 30 min. After cooling, the reaction mixture was diluted with H_2O and the resulting precipiates were collected and washed with H_2O to give 0.7 g. of crude Va. Recrystallization from CH_2Cl_2-AcOEt gave an analytical sample of Va, m.p. 208~209°. *Anal.* Calcd. for $C_{21}H_{33}O_2N$: C, 76.09; H, 10.03; N, 4.23. Found: C, 76.21; H, 10.01; N, 4.29.

5′-Methylandrost-5-eno[16,17-*c*]isoxazolin-3β-ol (Vb)——Hydrolysis of 1.0 g. of IVb with K_2CO_3, as described above, gave 0.7 g. of crude Vb. Recrystallization from CH_2Cl_2-AcOEt gave an analytical sample of Vb, m.p. 184~186°. *Anal.* Calcd. for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.35; H, 9.52; N, 4.44.

5′-Methyl-5α-androstano[16,17-*c*]isoxazolin-3-one (VIa)——To a solution of 1.0 g. of Va in 100 ml. of Me_2CO was added 1.1 ml. of 8*N* CrO_3-H_2SO_4 solution.[12] After 2 min., the excess of CrO_3 was decomposed with MeOH. The resulting green solution was diluted with H_2O and concentrated *in vacuo* until crystalline product separates. The product was collected and washed with H_2O to give 0.9 g. of crude VIa, m.p. 155~163°. Recrystallization from Et_2O gave an analytical sample of VIa, m.p. 165~167°. *Anal.* Calcd. for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.52; H, 9.61; N, 4.88.

5′-Methylandrost-5-eno[16,17-*c*]isoxazolin-3-one (VIb)——To a solution of 1.0 g. of 100 ml. of Me_2CO was added 1.2 ml. of 8*N* CrO_3-H_2SO_4 solution. N_2 gas was bubbled through all the reaction solutions before and during the oxidation. After 2 min., the reaction mixture was diluted with H_2O and the resulting precipitates were collected and washed with H_2O to give 0.7 g. of crude VIb, m.p. 158~161°, which was used for the subsequent reaction without further purification.

*3 All melting points are uncorrected.

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5′-Methylandrost-4-eno[16,17-*c*]isoxazolin-3-one (VIIb)——To a solution of 1.0 g. of crude Ⅵb (m.p. 158~161°) in 50 ml. of MeOH was added 5 ml. of 10% aq. K_2CO_3 and the mixture was heated under reflux on a steam bath for 20 min. After cooling, the reaction solution was diluted with H_2O and the resulting precipitates were collected and washed with H_2O to give 0.8 g. of crude Ⅶb, m.p. 154~156°. Recrystallization from CH_2Cl_2-hexane gave an analytical sample of Ⅶb, m.p. 159~162°, UV : λ_{max}^{EtOH} 239 mμ (ε 16,000). *Anal.* Calcd. for $C_{21}H_{29}O_2N$: C, 77.02; H, 8.93; N, 4.28. Found : C, 77.18; H, 8.98; N, 4.41.

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Summary

5′-Methyl-5α-androstano[16,17-*c*]isoxazolin-3β-ol (Va) and 5′-methylandrost-5-eno[16,17-*c*]isoxazolin-3β-ol (Vb), were obtained by treatment of 3β,20α-dihydroxy-5α-pregnan-16-one 3-acetate 16-oxime (Ⅲa) or 3β,20α-dihydroxypregn-5-en-16-one 3-acetate 16-oxime (Ⅲb) with tosyl chloride in pyridine followed by alkaline hydrolysis. Oxidation of Va and Vb gave the corresponding 3-oxo-compounds, Ⅵa and Ⅵb. Ⅵb was further isomerized to 5′-methylandrost-4-eno[16,17-*c*]isoxazolin-3-one (Ⅶb).

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166. Keiji Sekiguchi, Keiji Ito, Eiji Owada,*1 and Keihei Ueno*2 : Studies on the Method of Size Reduction of Medicinal Compounds. II.*3 Size Reduction of Griseofulvin by Solvation and Desolvation Method using Chloroform (2).*4

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It was recently found that when griseofulvin was administered orally, its blood level was increased in proportion to the logarithm of the specific surface of the drug particles.[1] Thus, the same therapeutic effect as achieved with larger crystals was demonstrated with lesser dose of finely powdered preparation of griseofulvin.[2] In the preceding paper, the authors reported that the particle size of the antibiotics could be reduced to a degree of several microns, if ordinary crystals of the drug were treated with chloroform or its vapor and were subsequently dried by heating in vacuum. On the basis of this simple phenomenon, a new method of size reduction of griseofulvin was successfully established on an industrial scale.

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*2 3-31, Shimo, Kita-ku, Tokyo (上野桂平).
*3 Part Ⅰ : Yakuzaigaku, **23**, 284 (1963).
*4 Partly presented at the Hokkaido Branch Meeting of Pharmaceutical Society of Japan, June 22nd, 1963.

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2) J. Pettit : Brit. J. Derm., **74**, 62 (1962).