3α-Chloro-5α-androstan-17-one (XIII)——Isoandrosterone (XIV, 1.0 g.) was treated with SO_2Cl_2 (1.0 ml.) and pyridine (20 ml.) as described above. Recrystallization from MeOH gave 3α-chloro-5α-androstan-17-one (XIII, 430 mg.) as colorless prisms, m.p. 125~128°, $[\alpha]_D^{25}$ +89° (c=1.50). (reported,[5] m.p. 128°, $[\alpha]_D$ +94°). No melting point depression was observed on admixture with the authentic sample.

We are very grateful to Dr. I. Chuman, Director of this laboratory, for his valuable advices, and to Miss S. Kobayashi for her technical help.

Summary

Some hydroxy-steroids were transformed into the corresponding chloro-steroids with Walden inversion, when treated with sulfuryl chloride in pyridine; testosterone (I), 4-chlorotestosterone (IV), 17β-hydroxy-5α-androstan-3-one (V), 5α-androstane-3β, 17β-diol 3-acetate (VIII), and estradiol 3-benzoate (IX) were introduced to the corresponding 17α-chloro compounds, II, III, VI, VIIa, and X, respectively. From androsterone (XI) and isoandrosterone (XIV) were obtained 3β-chloro-5α-androstan-17-one (XII) and 3α-chloro-5α-androstan-17-one (XIII) respectively.

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221. Hiromu Mori and Kiyoshi Tsuneda : Studies on Steroidal Compounds. X.[1] Preparation of 17β-Chloro Steroids.

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Preparation of 17α-chloro steroids was described in the preceding paper.[1] This paper describes preparation of 17β-chloro compounds and the evidence of α-configuration of chlorine atom at C-17 prepared in the preceding paper.

An elegant new reaction was recently reported by Barton and his coworkers,[2] who described that hydrazones of 17-oxo and 20-oxo steroids were treated with iodine in the presence of triethylamine to give 17-iodo-16-ene and 20-iodo-20-ene compounds respectively. They proposed the mechanism of this reaction as shown in Chart 1. This mechanism contains oxidation process (A→B) and attack of iodine cation. It would be

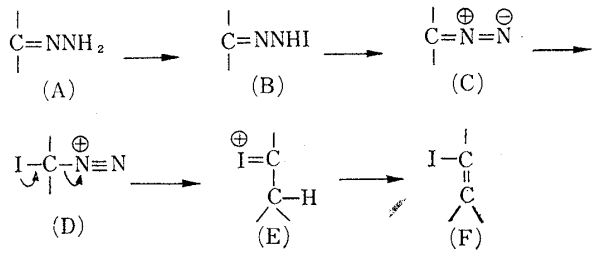

Chart 1.

*1 1604 Shimosakunobe, Kawasaki-shi (森 弘, 常田 清).

1) H. Mori, S. Wada : This Bulletin, **11**, 1409 (1963).
2) D. H. R. Barton, R. E. O'Brien, S. Sternhell : J. Chem. Soc., **1962**, 470.

expected that the reaction of hydrazone with N-halosuccinimide would give the same type of halo compound, because N-halosuccinimide can be used as an oxidation reagent[3] as well as halogenation reagent.[4]

3β-Acetoxy-5α-androstan-17-one (I) was refluxed with 60% hydrazine and ethanol in the presence of triethylamine to give the hydrazone (II) in good yield. The hydrazone (II) was reacted with N-bromosuccinimide or N-chlorosuccinimide in pyridine at room temperature. The reaction proceeded very rapidly with evolving nitrogen gas and IVb and IVa were obtained respectively as expected. The assignment of these compounds as 17-halo-16-ene compounds was based upon the fact that the reduction of IVa and IVb with sodium-ethanol gave the known 5α-androst-16-en-3β-ol (V). The hydrazone was also treated with iodine as the same manner described by Barton and his coworkers to give 17-iodo-16-ene compound (III). III was reduced to V by sodium-ethanol.

When IVa was hydrogenated over 5% palladium-charcoal in ethanol, one equivalent of hydrogen was absorbed and the saturated 17-chloro compound (VII) was obtained. The configuration of chlorine atom at C-17 was considered as β, because it is generally accepted that Δ^{16}-double bond was attacked from back side on hydrogenation;[5] so that

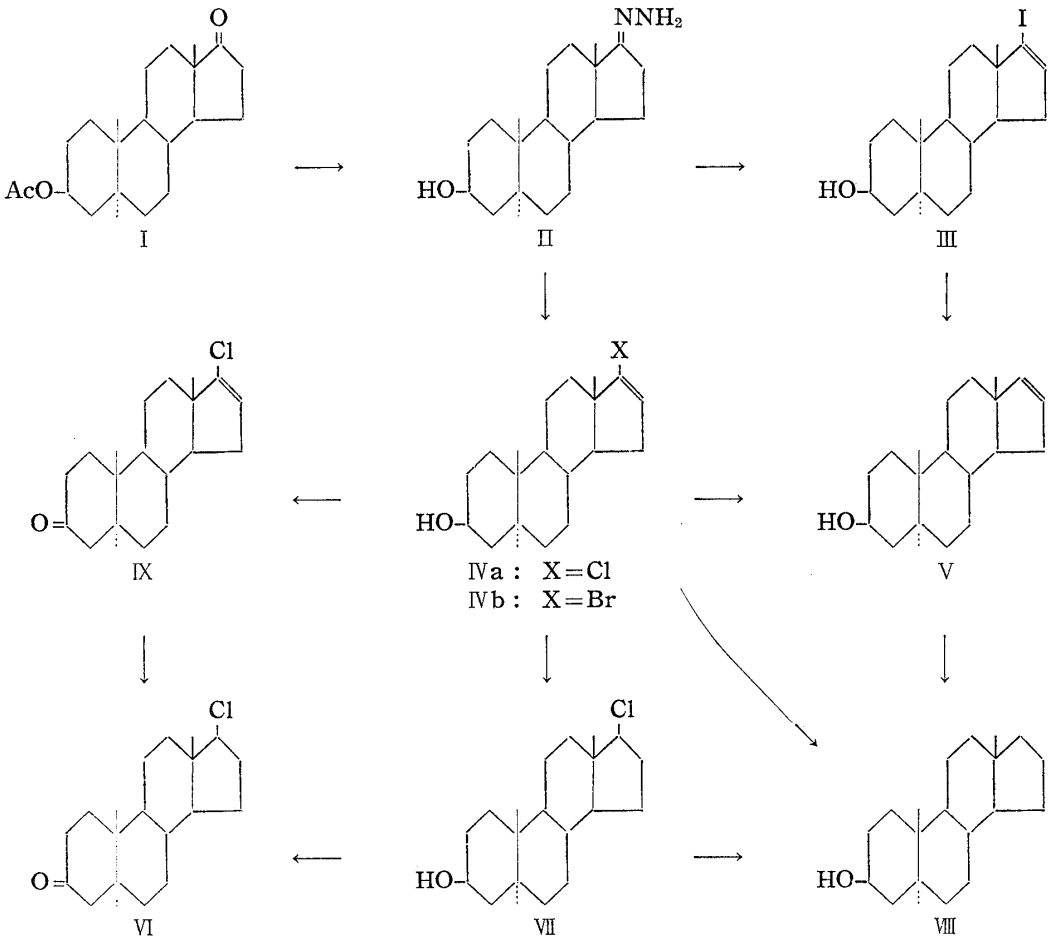

Chart 2.

3) L.F. Fieser, S. Rajagopalan : J. Am. Chem. Soc., **71**, 3938 (1949); *Ibid.*, **73**, 118 (1951).
4) Many publifications in which N-halosuccinimide was used as halogenation reagent can be found in steroid field; for example, Ch. Meystre, A. Wettstein : Experientia, **2**, 408 (1946); H.J. Ringold, E. Batres, A. Bowers, J. Zderic : J. Am. Chem. Soc., **81**, 3485 (1959).
5) R.E. Marker, R.B. Wagner, P.R. Ulshafer, E.L. Wittbecker, D.P.J. Goldsmith, C.H. Ruof : *Ibid.*, **69**, 2167 (1947). D.K. Fukushima, T.F. Gallagher : *Ibid.*, **73**, 196 (1951).

17-chloro compound (VII) could be formulated as 17β-chloro-5α-androstan-3β-ol. The oxidation of VII with chromium trioxide gave the chloro ketone (VI). This ketone was also obtained from 17-chloro compound (IVa) by another route; oxidation of IVa to 17-chloro-5α-androst-16-en-3-one (IX) followed by hydrogenation with 5% palladium-charcoal to the chloro ketone (VI). Now, 17β-chloro-5α-androstan-3β-ol (VII) and 17β-chloro-5α-androstan-3-one (VI) obtained here were not identical with the corresponding 17-chloro compounds, 17-chloro-5α-androstan-3β-ol and 17-chloro-5α-androstan-3-one described in the preceding paper respectively. Thus it could be unequivocally proved that 17-chloro compounds obtained by the reaction of 17β-hydroxy steroids with sulfuryl chloride in pyridine was 17α-chloro isomer. The comparison of molecular rotation difference among two isomers of 17-chloro compounds and 17-nonsubstituted parent compound is shown in Table I. In the case of 17α-isomer the molecular rotation contribution

Table I.

	M	ΔM_D[a]
5α-Androstan-3β-ol	0[7]	
17α-Chloro-5α-androstan-3β-ol	−115	−115
17β-Chloro-5α-androstan-3β-ol	+ 16	+ 16
5α-Androstan-3-one	+ 69[8]	
17α-Chloro-5α-androstan-3-one	− 71	−140
17β-Chloro-5α-androstan-3-one	+117	+ 48

a) $\Delta M_D = M_D(17\text{-Cl}) - M_D(17\text{-H})$

[$\Delta M_D = M_D(17\text{-Cl}) - M_D(17\text{-H})$] was negative, while that for 17β-isomer was positive. The same relation is observed in the case of 17-hydroxy and 17-acetoxy compounds.[6] This fact supports that the assignment of the configuration of chlorine atom at C-17 is right.

17-Bromo-16-ene (IVb) and 17-iodo-16-ene (III) were hydrogenated over 5% palladium-charcoal. In the case of IVb, 5α-androstan-3β-ol (VIII) was obtained, while the starting material was recovered on catalytic hydrogenation of III. It is of interest to point out the difference of catalytic hydrogenation of 17-halo-16-ene compounds. When the bromo compound (IVb) was catalytically hydrogenated, the first reduction product, perhaps 17β-bromo-5α-androstan-3β-ol, would be further hydrogenated to VIII for the more easily spliting property of bromine atom than chlorine atom. In the case of III, it is considered to be the reason why hydrogenation was not occurred that the substituent, iodine atom is so bulky that the catalyst cannot approach to the molecule near enough to hydrogenation. VIII was also obtained by catalytic hydrogenation of V over 5% palladium-charcoal or sodium-ethanol reduction of VII.

Biologically, it may be stated that the substitution of hydroxyl group with chlorine essentially destroys androgenic and myotropic actitivity of parent androgen. Neither androgenic nor myotropic activity were observed in biological test of 17α-chloroandrost-4-en-3-one and 17β-chloro-5α-androstan-3-one.

Experimental*2

3β-Hydroxy-5α-androstan-17-one Hydrazone (II)——A solution of 3β-acetoxy-5α-androstan-17-one (I, 2.0 g.) in EtOH (12 ml.), triethylamine (6.0 ml.) and 60% $NH_2NH_2H_2O$ (9.0 ml.) was refluxed for 1.25 hr., and poured into H_2O. Precipitates were collected by filtration and washed with H_2O. Recrystallization from MeOH-H_2O gave the hydrazone (II, 1.6 g.), m.p. 183~187° as colorless plates. The material was not analytically pure, but sufficiently pure for further transformation.

*2 All melting points are uncorrected, and all optical rotations are measured in chloroform solution.

6) L. F. Fieser, M. Fieser: "Steroids," p. 179 (1959). Reinhold Publishing Corp. (New York).
7) L. Ruzicka, V. Prelog, P. Meister: Helv. Chim. Acta, 28, 1651 (1945).
8) V. Prelog, L. Ruzicka, P. Meister, P. Wieland: *Ibid.*, 28, 618 (1945).

17-Iodo-5α-androst-16-en-3β-ol (III)——The hydrazone (II, 5.0 g.) was treated with I_2 as the same way described by Barton, *et al.*[2] The product was recrystallized several times from MeOH-H_2O to give 17-iodo-5α-androst-16-en-3β-ol (III) as colorless needles, m.p. 146~148°, $[\alpha]_D^{20}$ +22°(c=1.56). IR: $\nu_{max}^{CS_2}$ 3650 cm^{-1}(-OH). *Anal.* Calcd. for $C_{19}H_{29}OI$: C, 57.00; H, 7.30. Found: C, 56.38; H, 7.45.

17-Bromo-5α-androst-16-en-3β-ol (IVb)——A solution of N-bromosuccinimide (3.0 g.) in dry pyridine (30 ml.) was added dropwise to a cold solution of the hydrazone (II, 2.0 g.) in dry pyridine (40 ml.) with stirring. N_2 gas was evolved during the reaction and the reaction was completed only for 3~5 min. The solution was poured into H_2O, and the product was extracted with Et_2O. After washing with 10% HCl, 5% Na_2CO_3 and H_2O, and drying over Na_2SO_4, Et_2O was evaporated to give a crystalline material. It was chromatographed on Florisil, and the material eluated with Et_2O was recrystallized from Me_2CO-H_2O to give 17-bromo-5α-androst-16-en-3β-ol (IVb, 1.1 g.), m.p. 127~129°. A further recrystallization from the same solvent gave an analytical sample as colorless needles, m.p. 127~129°, $[\alpha]_D^{20}$ +28°(c=1.08). IR: $\nu_{max}^{CS_2}$ 3635 cm^{-1}(-OH). *Anal.* Calcd. for $C_{19}H_{29}OBr$: C, 64.58; H, 8.27. Found: C, 63.76; H, 8.53.

17-Chloro-5α-androst-16-en-3β-ol (IVa)——The hydrazone (II, 5.0 g.) was treated with N-chlorosuccinimide (7.5 g.) as the similar method described above. Recrystallization from MeOH-H_2O gave 17-chloro-5α-androst-16-en-3β-ol (VIa, 2.6 g.), m.p. 127~129°. Further recrystallization from benzene gave an analytical sample as colorless needles, m.p. 127~129°, $[\alpha]_D^{20}$ +13°(c=1.17). IR: $\nu_{max}^{CS_2}$ 3650 cm^{-1} (-OH). *Anal.* Calcd. for $C_{19}H_{29}OCl$: C, 73.88; H, 9.46. Found: C, 73.70; H, 9.61.

5α-Androst-16-en-3β-ol (V)——a) From 17-Iodo-5α-androst-16-en-3β-ol (III): Na (2.7 g.) was added to a hot solution of 17-iodo-5α-androst-16-en-3β-ol (III, 250 mg.) in EtOH (20 ml.) and the solution was refluxed until all Na was dissolved completely. After addition of H_2O the product was extracted with Et_2O and the ethereal solution was washed well with H_2O and dried over Na_2SO_4. After evaporation of the solvent, the residue was recrystallized from MeOH-H_2O to give 5α-androst-16-en-3β-ol (V, 110 mg.) as colorless needles, which showed negative Beilstein reaction and no depression on admixture with the authentic sample, m.p. 124~126°(reported,[9] m.p. 127°, $[\alpha]_D$ +11°). IR: $\nu_{max}^{CS_2}$ 3620 cm^{-1}(-OH).

b) From 17-bromo-5α-andorst-16-en-3β-ol (IVb): 17-Bromo-5α-androst-16-en-3β-ol (IVb, 300 mg.) was treated with Na as the same way described above. Colorless needles (120 mg.), m.p. 124~126.5° was obtained.

c) From 17-chloro-5α-androst-16-en-3β-ol (IVa): 17-Chloro-5α-androst-16-en-3β-ol (IVa, 300 mg.) was treated with Na as the same way described above. Colorless needles (180 mg.), m.p. 123.5~126°, identical with the sample obtained above, was obtained.

17β-Chloro-5α-androstan-3β-ol (VII)——A solution of 17-chloro-5α-androst-16-en-3β-ol (IVa, 1.0 g.) in EtOH (30 ml.) was hydrogenated with 5% Pd-C (300 mg.) for 2 hr. After removal of the catalyst by filtration, the solvent was evaporated *in vacuo*. The residue was recrystallized from MeOH-H_2O to give 17β-chloro-5α-androstan-3β-ol (VII, 800 mg.), m.p. 95~97°. Several recrystallizations from the same solvent gave an analytical sample as colorless needles, m.p. 123~125°, $[\alpha]_D^{20}$ +5°(c=1.10). IR: $\nu_{max}^{CS_2}$ 3650 cm^{-1}(-OH). *Anal.* Calcd. for $C_{19}H_{31}OCl \cdot H_2O$: C, 72.34; H, 10.06. Found: C, 72.22; H, 10.38.

17-Chloro-5α-androst-16-en-3-one (IX)——8*N* CrO_3 solution (Jones reagent, 0.5 ml.) was added dropwise to an ice-cold solution of 17-chloro-5α-androst-16-en-3β-ol (IVa, 500 mg.) in EtOH free Me_2CO (20 ml.) with stirring and the resulting suspension was stirred for 5 min., and poured into H_2O. The product was extracted with Et_2O, and the ethereal solution was washed with H_2O, and dried over Na_2SO_4. Evaporation of the solvent gave white crystals, m.p. 141~145°, which was chromatographed on alumina. The material eluated with hexane-benzene (9:1) was recrystallized from MeOH to give 17-chloro-5α-androst-16-en-3-one as colorless needles, m.p. 147~149°, $[\alpha]_D^{20}$ +49°(c=1.05). IR: $\nu_{max}^{CS_2}$ 1707 cm^{-1}(C=O). *Anal.* Calcd. for $C_{19}H_{27}OCl$: C, 74.36; H, 8.87. Found: C, 74.25; H, 8.91.

17β-Chloro-5α-androstan-3-one (VI)——a) From 17β-chloro-5α-androstan-3β-ol (VII): 8*N* CrO_3 solution (Jones reagent, 0.5 ml.) was added dropwise to an ice-cold solution of 17β-chloro-5α-androstan-3β-ol (VII, 500 mg.) in EtOH free Me_2CO (20 ml.) and the resulting suspension was stirred for 5 min. and poured into H_2O. Precipitates were collected by filtration, washed with H_2O and dried. Recrystallization from MeOH gave 17β-chloro-5α-androstan-3-one (VI, 410 mg.), m.p. 117~119.5°. Further recrystallization from MeOH gave an analytical sample as colorless needles, m.p. 120~121°, $[\alpha]_D^{20}$ +38°(c=1.32). IR: $\nu_{max}^{CS_2}$ 1720 cm^{-1}(C=O). *Anal.* Calcd. for $C_{19}H_{29}OCl$: C, 73.88; H, 9.41. Found: C, 73.68; H, 9.46.

b) From 17-chloro-5α-androst-16-en-3-one (IX): 17-Chloro-5α-androst-16-en-3-one (IX, 100 mg.) in EtOH (10 ml.) was hydrogenated with 5% Pd-C (50 mg.) at room temperature and atmospheric pressure. The absorption of H_2 was completed for 1.5 hr. After removal of the catalyst by filtration, solvent was evaporated and the residue was recrystallized from MeOH-H_2O to give 17β-chloro-5α-androstan-3-one, m.p. 117~119°, as colorless needles, which was identical with the sample obtained above in all respects.

9) V. Prelog, L. Ruzicka, P. Wieland: Helv. Chim. Acta, **27**, 66 (1944).

5α-Androstan-3β-ol (VIII)——a) From 17β-chloro-5α-androstan-3β-ol (VII): Na (7.0 g.) was added to a hot solution of 17β-chloro-5α-androstan-3β-ol (VII, 700 mg.) in EtOH (62 ml.) and the mixture was refluxed until all Na was dissolved. The resulting solution was poured into H_2O, and the product was extracted with Et_2O. The ethereal solution was washed with H_2O, and dried over Na_2SO_4. The solvent was evaporated and the residue was recrystallized from MeOH-H_2O to give 5α-androstan-3β-ol (VIII, 530 mg.), m.p. 148~150°, $[\alpha]_D^{20}$ +1° as colorless needles, which showed no melting point depression on admixture with an authentic sample. (reported,[7] m.p. 152°, $[\alpha]_D$ 0°).

b) From 5α-androst-16-en-3β-ol (V): VIII, m.p. 149~151° was obtained by catalytic hydrogenation of 5α-androst-16-en-3β-ol with 5% Pd-C in EtOH at room temperature and at atmospheric pressure.

c) From 17-bromo-5α-androst-16-en-3β-ol (IVb): A solution of 17-bromo-5α-androst-16-en-3β-ol (IVb, 300 mg.) in EtOH (10 ml.) was hydrogenated with 5% Pd-C (100 mg.) at room temperature and atmospheric pressure. The absorption of H_2 was completed within 2 hr. After removal of the catalyst by filtration, the solution was diluted with H_2O and the product was extracted with Et_2O. Ethereal extract was washed with 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. The solvent was evaporated, and the residue was recrystallized from MeOH-H_2O to give 5α-androstan-3β-ol (VIII, 180 mg.), m.p. 141~143°. Further recrystallization from the same solvent gave colorless needles, m.p. 149~151°, identical with the sample obtained above.

We are very grateful to Dr. I. Chuman, Director of this laboratory, and Dr. S. Wada for their valuable advices.

Summary

17β-Chloro-5α-androstan-3β-ol (VII) and 17β-chloro-5α-androstan-3-one (VI) were prepared. 3β-Hydroxy-5α-androstan-17-one hydrazone (II) was treated with N-chlorosuccinimide in pyridine to give 17-chloro-5α-androst-16-en-3β-ol (IVa), which on hydrogenation with 5% palladium charcoal afforded VII. The chromium trioxide oxidation of VII gave VI. Some observations concerning 17-bromo and 17-iodo compounds (IVb and III) were also written.

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