[Chem. Pharm. Bull.
11 (11) 1409 ~ 1413]

UDC 547.92

220. **Hiromu Mori and Shunyo Wada**: Studies on Steroidal Compounds. IX.[1] Preparation of 17α-Chloro Steroids.

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In the preceding paper[1] it was described that 3-oxo-4-ene steroids having no hydroxyl group were converted to the corresponding 4-chloro-3-oxo-4-ene steroids, but 3-oxo-4-ene steroids having hydroxyl group could not be introduced to 4-chloro-3-oxo-4-ene steroids by the same condition. The preparations of two isomeric 17-chloro steroids were reported in communications to the editor in this Bulletin.[2] This paper describes the preparation of 17α-chloro steroids from 17β-hydroxy steroids by means of sulfuryl chloride in pyridine in details.

When testosterone (I) was treated with sulfuryl chloride in pyridine as described in the preceding publification, the compound, m.p. 150~153°(II), which showed positive Beilstein reaction, was obtained. No hydroxy band was observed in infrared spectrum and a strong absorption was recognized at 241 mμ in ultraviolet absorption spectrum. It was considered, therefore, that 3-oxo-4-ene structure was retained and C-17 hydroxyl group was reacted with the reagent. Analysis showed that molecular formula of II was $C_{19}H_{27}OCl$, so that the reaction of I was considered as the replacement of hydroxyl group with chlorine. Westphal[3] reported in 1939 that testosterone (I) was reacted with phosphorus pentachloride to give 17-chloroandrost-4-en-3-one, the melting point of which was the same as that for II. They are considered as the same material, although optical rotation value was not given in the literature. II was further treated with sulfuryl chloride in pyridine to give dichloro compound (III), which showed a strong absorption at 255 mμ in ultraviolet absorption spectrum characteristic for 4-chloro-3-oxo-4-ene structure.[4] This compound was therefore formulated as 4,17-dichloroandrost-4-en-3-one.

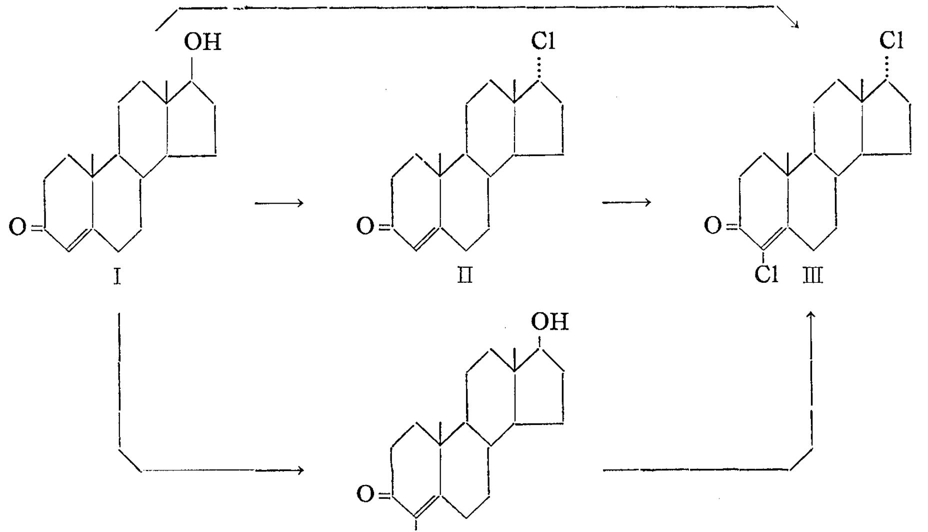

Chart 1.

[*1] 1604 Shimosakunobe, Kawasaki-shi (森 弘, 和田俊洋).

1) H. Mori: This Bulletin, **10**, 429 (1962).

2) H. Mori, S. Wada, K. Tsuneda: *Ibid.*, **11**, 684 (1963).

3) U. Westphal: Ber., **72**, 1233 (1939).

4) D.N. Kirk, D.K. Patel, V. Petrow: J. Chem. Soc., 1184 (1956). B. Camerino, B. Patelli, A. Vercellone: J. Am. Chem. Soc., **78**, 3540 (1956). H.J. Ringold, E. Batres, O. Mancera, G. Rosenkranz: J. Org. Chem., **21**, 1432 (1956).

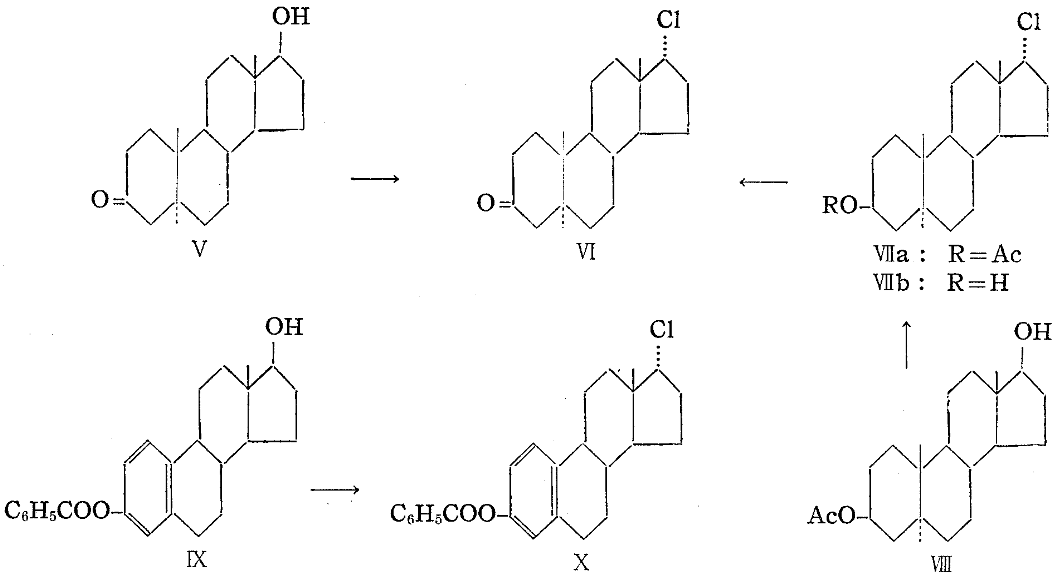

Chart 2.

III was also obtained from 4-chlorotestosterone (VI) by the same treatment, or from testosterone (I) by the reaction with a large excess of sulfuryl chloride in pyridine.

The same replacement of 17β-hydroxyl group in 17β-hydroxy-5α-androstan-3-one (V), 5α-androstan-3β,17β-diol 3-acetate (VIII) and estradiol 3-benzoate (IX) by chlorine gave the corresponding 17-chloro compounds, VI, VIIa, and X. The melting point and optical rotation of 17-chloroestra-1,3,5(10)-trien-3-ol benzoate reported by Westphal[3] were the same as those of X, and so that they seemed to be identical. VI was also obtained from VIIa by two steps; VIIa was transformed into VIIb by hydrolysis, which on oxidation by Jones reagent gave VI.

No report could be found in literature on 17-chloro steroids having no substituent at C-16 except Westphal's paper, and the configuration of chlorine atom at C-17 has not been determined. In order to examine the nature of the displacement of hydroxyl group by chlorine with sulfuryl chloride in pyridine, and to determine the configuration of chlorine atom at C-17, the reactions of androsterone (XI) and isoandrosterone (XIV) were carried out, because the configuration of C-3 chlorine atom in this series has been

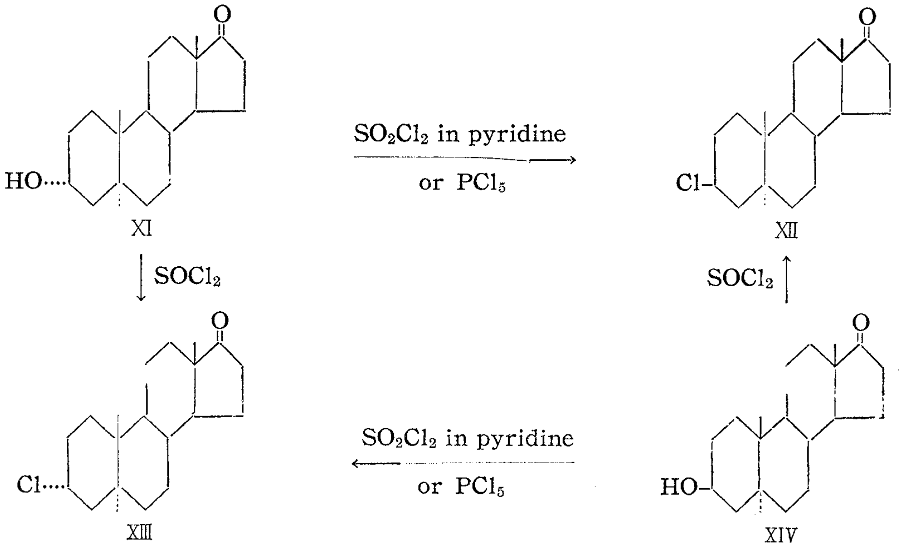

Chart 3.

fully established. The substitution in androsterone (XI) with sulfuryl chloride in pyridine gave 3β-chloro-5α-androstan-17-one (XII), while the same reaction of isoandrosterone (XIV) afforded 3α-chloro-5α-androstan-17-one (XIII). It is well-known that the substitution of 3-hydroxyl group with chlorine in 5α-steroid with thionyl chloride gave 3-chloro compound with retention of C-3 configuration, whereas the reaction with phosphorus pentachloride gave 3-chloro compound with Walden inversion.[5] Therefore the chlorination reagent, sulfuryl chloride-pyridine is similar as phosphorus pentachloride rather than thionyl chloride, as far as inversion and retention of configuration is concerned. The assignment of the configuration of chlorine atom at C-17 as α seems more suitable from this observation. Moreover molecular rotation difference supports also this assignment. M_D value was reduced by the introduction of chlorine atom at C-17 by this method comparing with parent hydrocarbon. It is generally observed that α-substitution of hydroxyl or acetoxy group at C-17 causes decreases of M_D value, while β-substitution of the same group increases M_D value.[6] These observations seems to support the assignment of the configuration, but cannot be said to be unequivocal evidences. More unequivocal evidence of the assignment will be given in the following publification.

The mechanism of the replacement by this reagent seems to be S_{N_2} reaction mechanism, because the replacement of hydroxyl group with chlorine was accompanied with Walden inversion. Acetolysis of 17β-tosyloxy compound (XV) was reported by Elks and Shoppee.[7] The reaction products are 16-ene (XVII) and the replacement product, 17-methyl-13(17)-ene compound (XVIII), accompanied a small amount of 17α-acetoxy compound (XVI). This fact suggests that S_{N_1} reaction at C-17 position is very complicated. In the above-mentioned replacement reaction by sulfuryl chloride such products could not be obtained. S_{N_2} mechanism seems to be suitable one also from this observation. It is of interest to note that this combination of reagents (sulfuryl chloride-pyridine) can be used as general chlorination reagent of hydroxyl group in steroids, because sulfuryl chloride is considered as the chlorination reagent of active hydrogen atom.[8]

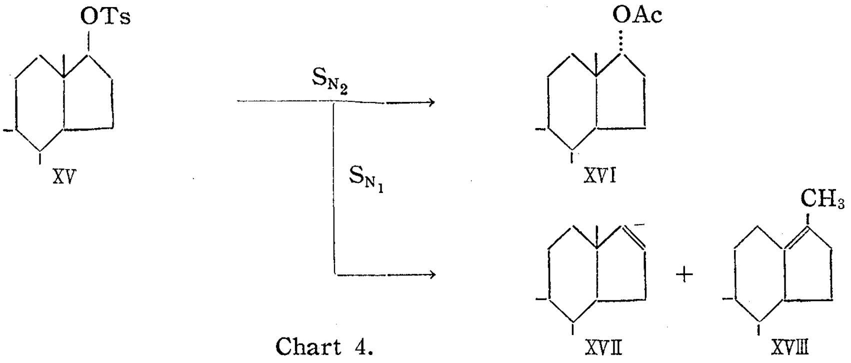

Chart 4.

Experimental[*2]

17α-Chloroandrost-4-en-3-one (II)——SO_2Cl_2 (2.5 ml.) was added dropwise to a ice-cold solution of testosterone (I, 5.0 g.) in dry pyridine (50 ml.) with stirring, and the solution was stirred for 1 hr. at

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

5) R.E. Marker: J. Am. Chem. Soc., **57**, 1755 (1935). R.E. Marker, F.C. Whitmore, O. Kamm: *Ibid.*, **57**, 2358 (1935).

6) L.F. Fieser, M. Fieser: "Steroids," p. 179 (1959), Reinhold Publishing Corp. (New York).

7) J. Elks, C.W. Shoppee: J. Chem. Soc., **1953**, 241.

8) L.F. Fieser: "Experiments in Organic Chemistry" third edition, p. 344 (1955), D.C. Heath and Company (Boston).

10~25°, and poured into ice-cold 5% HCl. The resulting precipitates were collected by filtration, washed with 10% HCl and H_2O, and dried. Recrystallization from Me_2CO gave 17α-chloroandrost-4-en-3-one (II, 2.6 g.) as colorless needles. m.p. 150~153°, $[\alpha]_D^{20}$ +32°(c=1.42). (reported,2) m.p. 148°). It showed positive Beilstein reaction and melting point depression on admixture with testosterone. UV: λ_{max}^{EtOH} 241 mμ (ε 15,210). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1675, 1618 (3-oxo-4-ene). *Anal.* Calcd. for $C_{19}H_{27}OCl$: C, 74.36; H, 8.87. Found: C, 74.23; H, 8.90.

4,17α-Dichloroandrost-4-en-3-one (III)——a) From II: 17α-Chloroandrost-4-en-3-one (II, 2.0 g.) was treated with SO_2Cl_2 (1.0 ml.) and pyridine (18 ml.) as described above. Recrystallization from Me_2CO-H_2O gave 4,17α-dichloroandrost-4-en-3-one (III, 1.3 g.), m.p. 144~147°. Further recrystallization from the same solvent gave an analytical sample as colorless needles. m.p. 152~153°, $[\alpha]_D^{20}$ +84° (c=1.00). UV: λ_{max}^{EtOH} 255 mμ (ε 17,210). *Anal.* Calcd. for $C_{19}H_{26}OCl_2$: C, 66.86; H, 7.68. Found: C, 66.78; H, 7.64.

b) From 4-chlorotestosterone (IV): 4-Chlorotestosterone (IV, 2.0 g.) was treated with SO_2Cl_2 (1.0 ml.) and pyridine (20 ml.) as described above. Recrystallization from Me_2CO-H_2O gave IV (1.1 g.), m.p. 147~151°, which was identical with the compound obtained above in all respects.

c) From testosterone (I): Testosterone (I, 0.5 g.) was treated with SO_2Cl_2 (0.5 ml.) and pyridine (5.0 ml.) as described above. The identical compound, m.p. 148~151° was obtained.

17α-Chloro-5α-androstan-3-one (VI)——a) From 17β-hydroxy-5α-androstan-3-one (V): V (1.0 g.) was treated with SO_2Cl_2 (1.0 ml.) and pyridine (20 ml.) as described above. The solution was poured into H_2O and the product was extracted with Et_2O. Ethereal layer was washed with 5% Na_2CO_3, 10% HCl and H_2O, dried over Na_2SO_4, and passed through a Florisil column. The column was washed with another portion of Et_2O. The combined Et_2O solution was condensed to dryness *in vacuo*. The residue was recrystallized from Me_2CO to give 17α-chloro-5α-androstan-3-one (V, 220 mg.), m.p. 179~183°. An analytical sample was obtained by recrystallization from the same solvent as colorless needles, m.p. 180~183°, $[\alpha]_D^{27}$ −23°(c=2.49). IR: $\nu_{max}^{CS_2}$ 1720 cm^{-1}(C=O). *Anal.* Calcd. for $C_{19}H_{29}OCl$: C, 73.88; H, 9.46. Found: C, 73.72; H, 9.44.

b) From 17α-chloro-5α-androstan-3β-ol (VIIb): 8*N* CrO_3 solution (in H_2SO_4-H_2O)9) was added to an ice-cold solution of VIIb (0.2 g.) in EtOH free Me_2CO (10 ml.) with stirring. After storage at 0° for 5 min., the resulting suspension was poured into H_2O. The precipitates were collected by filtration, washed with H_2O and dried. Recrystallization from Me_2CO geve VI (110 mg.) as colorless needles, m.p. 180~183°. No melting point depression was observed on admixture with the sample obtained above.

17α-Chloro-5α-androstan-3β-ol Acetate (VIIa)——5α-Androstane-3β,17β-diol 3-acetate (VIII, 500 mg.) was treated with SO_2Cl_2 (0.25 ml.) and pyridine (10 ml.) as described above. The solution was poured into H_2O and the product was extracted with Et_2O. Ethereal layer was washed with 10% HCl, 5% Na_2CO_3 and H_2O, dried over Na_2SO_4, and passed through a Florisil column. The column was washed with another portion of Et_2O and the combined solution was evaporated to dryness *in vacuo*. The residue was recrystallized from Me_2CO-MeOH to give 3β-acetoxy-17α-chloro-5α-androstan-3-one (VIIa, 210 mg.), m.p. 99~102°. Further recrystallization from the same solvent gave an analytical sample as colorless leaflets, m.p. 102~104°, $[\alpha]_D^{20}$ +27°(c=0.66). IR: $\nu_{max}^{CS_2}$ 1740 cm^{-1} (C=O). *Anal.* Calcd. for $C_{21}H_{33}O_2Cl$: C, 71.46; H, 9.43. Found: C, 71.43; H, 9.62.

17α-Chloro-5α-androstan-3β-ol (VIIb)——A solution of 17α-chloro-5α-androstan-3β-ol acetate (VIIa, 650 mg.) in MeOH (10 ml.) and 10% HCl (1.0 ml.) was refluxed for 3 hr., and poured into H_2O. The product was extracted with Et_2O and ethereal layer was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent gave white powder, which on recrystallization from MeOH gave 17α-chloro-5α-androstan-3β-ol (VIIb, 300 ml.) as colorless needles, m.p. 186~188°, $[\alpha]_D^{20}$ −37°(c=1.34). *Anal.* Calcd. for $C_{19}H_{31}OCl$: C, 73.40; H, 10.05. Found: C, 73.57; H, 10.11.

17α-Chloroestra-1,3,5(10)-trien-3-ol Benzoate (X)——Estradiol 3-benzoate (IX, 1.0 g.) was treated with SO_2Cl_2 (1.0 ml.) and pyridine (20 ml.) as described above. The solution was poured into H_2O, and the product was extracted with Et_2O. Ethereal layer was washed with 10% HCl, 5% Na_2CO_3 and H_2O, and dried over Na_2SO_4. After evaporation of the solvent, the residue was recrystallized from Me_2CO-MeOH to give 17α-chloroestra-1,3,5(10)-trien-3-ol benzoate (X, 530 mg.), m.p. 146~155.5°. Further recrystallization from the same solvent gave an analytical sample as colorless cubes, m.p. 156~158°, $[\alpha]_D^{27}$ +16°, IR: $\nu_{max}^{CS_2}$ 1745 cm^{-1}(C=O). (reported,2) m.p. 158°, $[\alpha]_D$ +16.6°). *Anal.* Calcd. for $C_{25}H_{27}O_2Cl$: C, 76.03; H, 6.89. Found: C, 76.05; H, 6.83.

3β-Chloro-5α-androstan-17-one (XII)——Androsterone (XI, 1.0 g.) was treated with SO_2Cl_2 (1.0 ml.) and pyridine (20 ml.) as described above. Recrystallization from Me_2CO-hexane gave 3β-chloro-5α-androstan-17-one (XII, 300 mg.) as colorless needles, m.p. 166~173°, $[\alpha]_D^{25}$ +86° (c=1.68). (reported,5) m.p. 172~173°, $[\alpha]_D$ +92°). No melting point depression was observed on admixture with the authentic sample.

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9) A solution of CrO_3 (26.72 g.) in H_2SO_4 (23 ml.) diluted with H_2O to a volume of 100 ml. was used.

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.

(Received July 8, 1963)

[Chem. Phram. Bull.
11 (11) 1413 ~ 1417]

UDC 547.92

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

(*Research Laboratory, Teikoku Hormone Mfg. Co., Ltd.*[*1])

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

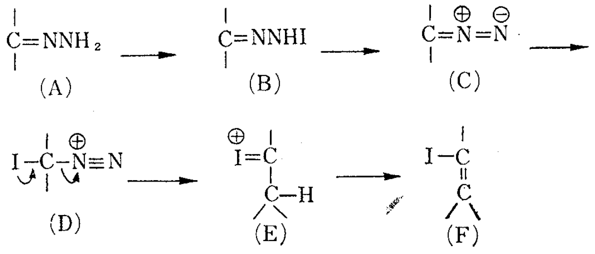

Chart 1.

[*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.