35°) to the well-stirred mixture, and the resulting emulsion was heated on a steam bath at 80~95° for 1~6 hr. The reaction mixture gradually turned to a yellow or red solution.

The reaction mixture was then extracted several times with $CHCl_3$ or ethyl ether. The combined extracts were washed with saturated sodium chloride solution and dried over calcium chloride. After removing the solvent, the residue was distilled to give a pure material.

Summary

Reaction of alkyl halides with benzyltrimethylammonium cyanide in water proceeds rapidly and efficiently to result in an improved general method for preparing nitriles. Benzyltrimethylammonium chloride and alkali cyanide can be used instead of benzyltrimethylammonium cyanide. A general procedure is described and many examples are listed. In this reaction, alkali rhodanate can be used in place of alkali cyanide to obtain alkyl rhodanate in a good yield.

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Hiromu Mori: Studies on Steroidal Compounds. VIII. A New Synthesis of 4-Chloro-4-en-3-oxo-steroids.[1]

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4-Chloro-4-en-3-oxo-steroids were first synthesized by Kirk,[2] Camerino,[3] and Ringold[4] in 1956. 4-Chlorotestosterone and its acylates, particularly among these compounds, have high ratio of anabolic-androgenic activity[5] and are excellent anabolic steroids. It has been shown that the treatment of 4-en-3-oxo-steroid (I) with alkaline hydrogen peroxide leads to 4,5-epoxide (II), which on treatment with hydrogen chloride including fission of epoxide and dehydration gives 4-chloro-4-en-3-oxo-steroids (III).[3,4] On the other hand, Kirk has shown that 4-en-3-oxo-steroid (I) is converted into 4-chloro-4-en-3-oxo-steroid (III) by addition of chlorine and dehydrochlorination with pyridine (I→IV→III).[2] In the present paper, another synthetic method for 4-chloro-4-en-3-oxo-steroids (III) will be described.

A better result may be otained, if a mild chlorination reagent such as sulfuryl chloride is used instead of chlorine in the method of Kirk. However, it has recently been reported that the treatment of 4-en-3-oxo-steroid with sulfuryl chloride in benzene leads to 2-chloro-4-en-3-oxo-steroid.[6] On the other hand, it has been shown that 4-en-3-oxo-steroid (I) is converted directly into 4-chloro-4-en-3-oxo-steroid (III) on treatment with chlorine in the presence of pyridine.[2] Chlorination of 4-en-3-oxo-steroid with sulfuryl chloride in pyridine solution was therefore attempted and 4-chloro-4-en-3-oxo-steroid (III) was found to be prepared directly in a high yield. On the first attempt, one equivalent

*1 1604, Shimosakunobe, Kawasaki, Kanagawa-ken (森　弘).

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2) D.N. Kirk, D.K. Patel, V. Petrow: J. Chem. Soc., **1956**, 1184.
3) B. Camerino, B. Patelli, A. Vercellone: J. Am. Chem. Soc., **78**, 3540 (1956).
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5) L.G. Hershberger, E.G. Shipley, R.K. Meyer: Proc. Soc. Exptl. Biol. Med., **83**, 175 (1953).
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volume of sulfuryl chloride was added to a solution of testosterone propionate (Ⅶ) in pyridine and the mixture was stored at room temperature overnihgt. 4-Chlorotestoste rone propionate (Ⅷ) was obtained in 40~50% yield. It was made clear by further experiments that, when excess of sulfuryl chloride (2.0 equivalent to 4-en-3-oxo-steroid) was used, the reaction was completed in 30 minutes and that excess sulfuryl chloride did not react with 4-chloro-4-en-3-oxo-steroid produced. The completion of reaction was recognized by ultraviolet absorption spectrum, by completely disappearance of absorption maximum at 240 mμ and shift of maximal absorption to 254 mμ. When 2.0 equivalent of sulfuryl chloride was added to (Ⅶ) in pyridine and stirred for 30 minutes, (Ⅷ) was obtained in 82.7% yield which was better than any known method.

It is worthy to note that the position of chlorination changes according to the solvent used in the reaction of 4-en-3-oxo-steroid with sulfuryl chloride. The mechanism of this chlorination with sulfuryl chloride might be not that shown by Kirk which is through 4,5-dichloride (Ⅳ).

By a similar treatment, testosterone acetate (Va), progesterone (Vb), cholest-4-en-3-one (Vc), and androst-4-ene-3,17-dione (X) were converted into the corresponding 4-chloro-4-en-3-oxo compounds (VIa, VIb, VIc, and XI). (XI) was also prepared by the oxidation of 4-chlorotestosterone (IX), obtained by the saponification of its propionate with

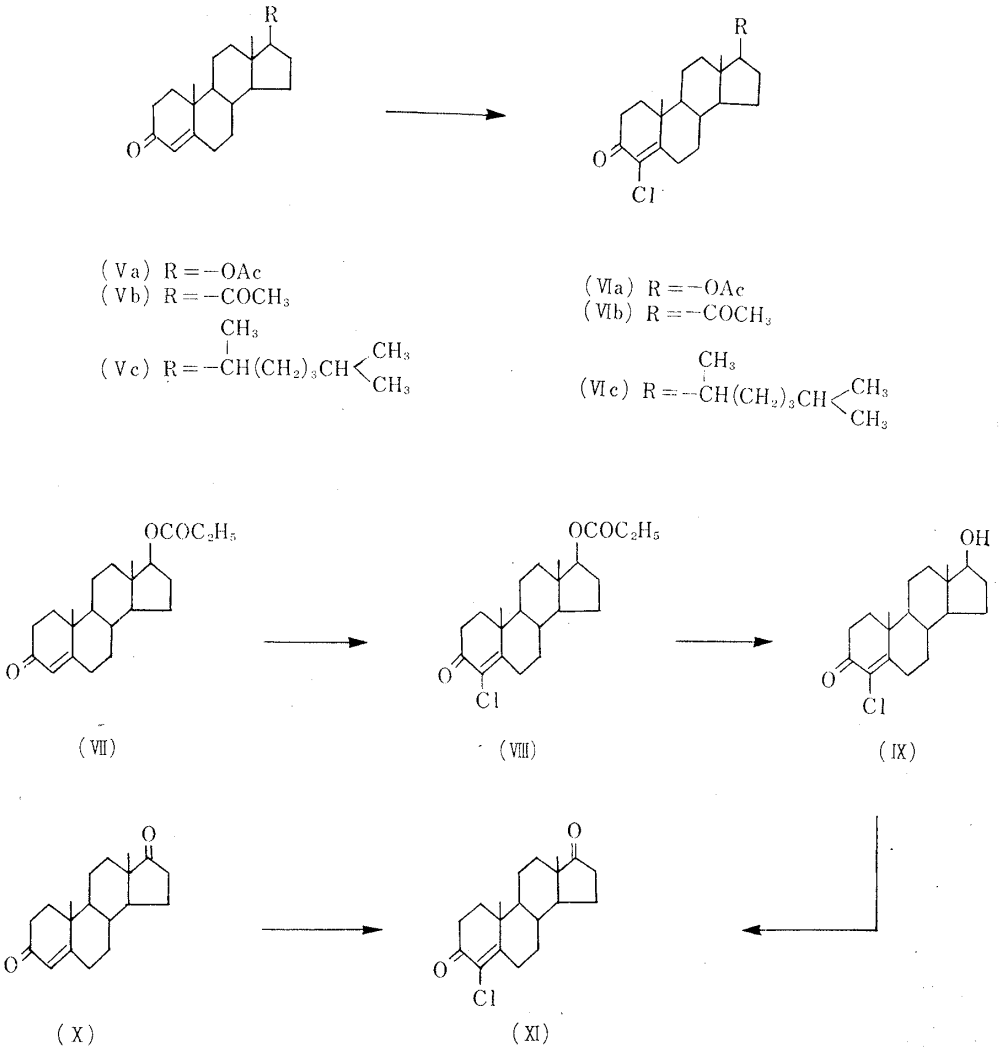

Chart 1

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hydrochloric acid, with chromium trioxide in acetic acid or with chromium trioxide-pyridine complex. 4-En-3-oxo-steroids having a hydroxyl group such as testosterone, methyltestosterone, and 17α-hydroxyprogesterone, could not be converted into 4-chloro-4-en-3-oxo-steroids by this method.

Experimental*2

4-Chlorotestosterone Propionate (VIII)——Testosterone propionate (VII) (10.0 g.) was dissolved in dry pyridine (100 cc.). To the solution, while kept in agitation at 20~25°, freshly distilled SO_2Cl_2 (7.8 g., 2.0 equiv. to (VII)) was added dropwise over a period of 5 min. Stirring was continued for an additional 30 min. The reaction mixture was poured into water and extracted with Et_2O. After washing with 10% HCl, 5% Na_2CO_3, and water, and drying over Na_2SO_4, Et_2O was evaporated. The residue was a crystalline material of m.p. 148~155°, which was recrystallized from MeOH to (VIII), m.p. 155~159°. Yield, 9.1 g. (82.7%). Further recrystallization from MeOH gave white needles, m.p. 162~164°, $[\alpha]_D^{22}$ +102° (c=1.00, dioxane). UV : λ_{max}^{MeOH} 254 mμ (log ε 4.17) (reported[2] m.p. 164°, $[\alpha]_D^{22}$ +114° (c=0.4, $CHCl_3$); UV $\lambda_{max}^{iso\text{-}PrOH}$ 254 mμ (log ε 4.12)). No depression of the melting point was observed with the authentic sample.

4-Chlorotestosterone Acetate (VIa)——To a solution of testosterone acetate (Va) (10.0 g.) in dry pyridine (100 cc.), SO_2Cl_2 (8.2 g., 2.0 equiv. to (Va)) was added dropwise at 15° over a period of 5 min. Stirring was continued for an additional 55 min. The reaction mixture was poured into 3% HCl, the precipitate was collected, washed with 10% HCl, 5% Na_2CO_3, and water, dried, and crystallized from Me_2CO to (VIa), m.p. 222~224°. Yield, 9.8 g. (87.6%). Further recrystallization gave white needles, m.p. 228~230.5°. $[\alpha]_D^{19}$ +121° (c=1.00, dioxane), UV : λ_{max}^{MeOH} 255 mμ (log ε 4.17) (reported[3] m.p. 228~230°, $[\alpha]_D$ +118°; UV : λ_{max} 255 mμ (log ε 4.12).

4-Chlorotestosterone (IX)——A solution of 4-chlorotestosterone propionate (VIII) (1.0 g.) in MeOH (20 cc.) and 10% HCl (2.0 cc.) was refluxed for 3 hr, and poured into water. The precipitate was collected, washed with water, dried, and crystallized from Me_2CO to (IX), m.p. 181~183°. Yield, 0.67 g. (78.6%). Further recrystallization from Me_2CO gave white needles, m.p. 187.5~189.5°. $[\alpha]_D^{15}$ +129° (c=1.00, dioxane). UV : λ_{max}^{MeOH} 255 mμ (log ε 4.17) (reported[4] m.p. 188~190°; $[\alpha]_D$ +148° ($CHCl_3$); UV : λ_{max}^{EtOH} 256 mμ (log ε 4.13)).

4-Chloroprogesterone (VIb)——To a solution of progesterone (Vb) (1.0 g.) in dry pyridine (10 cc.), SO_2Cl_2 (0.86 g., 2.0 equiv. to (Vb)) was added dropwise at 15~20° and stirring was continued for 30 min. The reaction mixture was poured into 3% HCl, the precipitate was collected, washed with 10% HCl, 5% Na_2CO_3, and water, dried, and crystallized from MeOH to (VIb), m.p. 202~206°. Yield, 0.82 g. (73.9%). Further recrystallization from MeOH gave white prisms, m.p. 216.5~219°. $[\alpha]_D^{27}$ +201° (c=1.00, dioxane), UV : λ_{max}^{MeOH} 255 mμ (log ε 4.17) (reported[2] m.p. 218~220.5°, $[\alpha]_D^{25}$ +198° (c=0.569, $CHCl_3$); UV $\lambda_{max}^{iso\text{-}PrOH}$ 255 mμ (log ε 4.12)).

4-Chlorocholest-4-en-3-one (VIc)——To a solution of cholest-4-en-3-one (Vc) (2.0 g.), SO_2Cl_2 (1.4 g., 2.0 equiv. to (Vc)) was added dropwise at 15~20° and stirring was continued for 30 min. The reaction mixture was poured into water and extracted with Et_2O. After washing with 10% HCl, 5% Na_2CO_3, and water, and drying over Na_2SO_4, Et_2O was evaporated. The residue was recrystallized from Et_2O-hexane mixture to (VIc), m.p. 112~121°. Yield, 1.44 g. (65.9%). It was chromatographed on alumina and benzene eluate afforded pure (VIc) as white needles, m.p. 124~126.5°, $[\alpha]_D^{22}$ +100° (c=1.00, dioxane). UV : λ_{max}^{MeOH} 255 mμ (log ε 4.27) (reported[2] m.p. 126~127°, $[\alpha]_D^{20}$ +106° (c=0.492, $CHCl_3$); UV : $\lambda_{max}^{iso\text{-}PrOH}$ 256 mμ (log ε 4.15)).

4-Chloroandrost-4-ene-3,17-dione (XI)——a) From androst-4-ene-3,17-dione (X): To a solution of androst-4-ene-3,17-dione (X) (1.0 g.) in dry pyridine (10 cc.), SO_2Cl_2 (1.0 g., 2.0 equiv. to (X)) was added dropwise at 15~20° and stirring was continued for 30 min. The reaction mixture was poured into water and extracted with Et_2O. After washing with 10% HCl, 5% Na_2CO_3, and water, and drying over Na_2SO_4, Et_2O was evaporated. Recrystallization from MeOH gave (XI), m.p. 172~178°. Yield, 0.80 g. (71.4%). Further recrystallization from MeOH gave white needles, m.p. 183~185.5°. $[\alpha]_D^{23}$ +199° (c=1.00, dioxane). UV : λ_{max}^{MeOH} 254 mμ (log ε 4.14) (reported[2] m.p. 180~182°; $[\alpha]_D^{24}$ +206° (c=0.42, $CHCl_3$); UV : $\lambda_{max}^{iso\text{-}PrOH}$ 254~255 mμ (log ε 4.19)).

b) From 4-chlorotestosterone (IX): i) By oxidation with CrO_3 in AcOH : To a solution of 4-chlorotestosterone (IX) (0.5 g.) in AcOH (25 cc.), a solution of CrO_3 (0.14 g.) in water (1.25 cc.) was added and stored at room temperature for 4 hr. The reaction mixture was poured into water, the precipitate was collected, washed with 5% Na_2CO_3 and water, dried, and crystallized from MeOH to (XI), m.p. 180~183°. Yield, 0.39 g. (78.6%). No depression of melting point was observed on admixture with the sample obtained as above.

*2 All melting points are uncorrected.

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ii) By oxidation with CrO_3-pyridine complex : 4-Chlorotestosterone (IX) (0.5 g.) was dissolved in pyridine (10 cc.) and the solution was added dropwise to ice-cold CrO_3-pyridine complex prepared from CrO_3 (0.5 g.) and pyridine (10 cc.) and the mixture was stored at room temperature overnight. The reaction mixture was poured into water, the precipitate was collected, washed with 10% HCl and water, dried, and crystallized from MeOH to (XI), m.p. 180~183°. Yield, 0.33 g. (66.5%). No depression of the melting point was observed on admixture with the sample obtained as above.

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Summary

4-En-3-oxo-steroid is converted into 4-chloro-4-en-3-oxo-steroid by treatment with sulfuryl chloride in pyridine. Testosterone acetate (Va), testosterone propionate (VII), progesterone (Vb), cholest-4-en-3-one (Vc), and androst-4-ene-3,17-dione (X) are also converted respectively into the corresponding 4-chloro-4-en-3-oxo-steroids, (VIa) (87.6%), (VIII) (82.7%), (VIb) (73.9%), (VIc) (65.9%), and (XI) (71.4%). (XI) was also obtained from 4-chlorotestosterone (IX) by oxidation with chromium trioxide in acetic acid or chromium trioxide-pyridine complex. (IX) was prepared by the saponification of (VIII) with hydrochloric acid.

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