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Preparation of Steroid Haloformate Esters

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Steroid alcohols are converted to their chloroformate esters by reaction with phosgene in the presence of a base. Replacement of chlorine by fluorine takes place smoothly by treatment with anhydrous thallous fluoride in ethylene glycol dimethyl ether. Significant shifts in the positions of both infrared spectra-carbonyl and carbon-oxygen single bond absorption frequency due to the fluorine are discussed.

Keywords——replacement; steroid chloroformates; steroid fluoroformates; thallous fluoride; IR-carbonyl shift; IR-carbon-oxygen single bond absorption shift.

In the course of investigations on the preparation of fluorinated steroids, various steroidal chloroformate esters have been prepared according to the procedure for alkyl chloroformate.[2,3] Conversion of the obtained chloroformates to the corresponding fluoroformates has been accomplished by treatment with anhydrous thallous fluoride in ethylene glycol dimethyl ether. Attempts by both base and acid catalyzed decompositions[3,4] of these fluoroformate esters to the corresponding fluorinated steroids have been unsuccessful. For the preparation of steroid fluoroformates, anhydrous conditions are essential. Employing wet solvents or reagents gave rise to the dimeric carbonates such as bis-cholestanylcarbonate, $C_{55}H_{94}O_3$, mp 189.5—190.5°, $[\alpha]_D^{25}$ +15.3° (c=1, chloroform), as well as the corresponding steroid alcohol were obtained.

The infrared spectra of both chloroformate and fluoroformate esters show marked shifts in the positions of both carbonyl and carbon-oxygen single bond absorption frequencies. The carbonyl groups of the chloroformates show a band between 1760—1774 cm^{-1}, and the C–O bonds show absorption between 818—836 cm^{-1}. On the other hand, for the fluoroformate a noticeable shift of carbonyl absorption peaks to 1815—1823 cm^{-1} were observed and the carbon-oxygen absorption appeared between 770—780 cm^{-1}.

Experimental

3β-Hydroxy-5α-cholestane 3-Chloroformate (I)——Cholestanol (8 g) was treated with equimolar quantity of quinoline and 2.36 g of phosgene in ether according to the procedure for alkyl chloroformates[2,3] and the product was recrystallized from acetone to give 8.68 g (96%) of I, mp 95.2—96.8°, $[\alpha]_D^{25}$ +25° (c=1, chloroform), ν_{max}^{KBr} cm^{-1}: 1772 (C=O). *Anal.* Calcd. for $C_{28}H_{47}ClO_2$: C, 74.54; H, 10.50; Cl, 7.83. Found: C, 74.43; H, 10.74; Cl, 7.80.

3α-Hydroxy-5α-cholestane 3-Chloroformate (II)——Epicholestanol (1.17 g) was treated in the same manner yielded 1.33 g of the crude chloroformate, mp 70.5—74°, which was recrystallized from acetone gave 1.18 g (37%) of II, mp 75—76°, $[\alpha]_D^{25}$ +26.4° (c=0.5, chloroform), ν_{max}^{KBr} cm^{-1}: 1774 (C=O). *Anal.* Calcd. for $C_{28}H_{47}ClO_2$: C, 74.54; H, 10.50; Cl, 7.83. Found: C, 74.68; H, 10.51; Cl, 8.06.

5-Androstene-3β,17β-diol 17-Benzoate 3-Chloroformate (III)——5-Androstene-3β,17β-diol 17-benzoate (1.97 g) was treated by the same manner to give 2.12 g (93%) of cystals, mp 151—152°, which was recrystallized from acetone, gave 1.89 g of III, mp 152—153°, $[\alpha]_D^{25}$ +1.2° (c=1, chloroform), ν_{max}^{KBr} cm^{-1}: 1760 (C=O), 1715 (C=O). *Anal.* Calcd. for $C_{27}H_{33}ClO_4$: C, 70.96; H, 7.28; Cl, 7.76. Found: C, 70.98; H, 7.46; Cl, 7.88.

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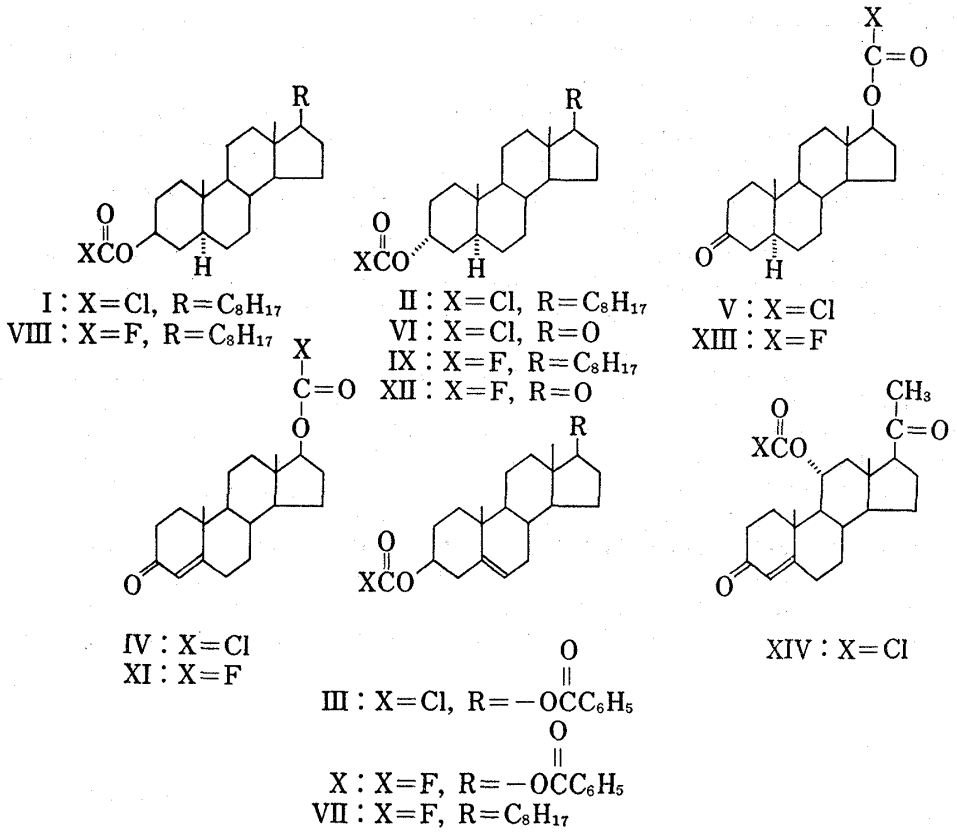

17β-Hydroxy-4-androsten-3-one 17-Chloroformate (IV)——Testosterone (2.88 g) was treated by the same procedures to give 3.39 g (97%) of the chloroformate, mp 136—140°, which was recrystallized from acetone to give 2.96 g of IV, mp 140—141°. The reported[5] melting point is 139—140°. $[\alpha]_D^{25}$ +126.7° (c=1, chloroform), ν_{max}^{KBr} cm^{-1}: 1766 (C=O). *Anal.* Calcd. for $C_{20}H_{29}ClO_3$: C, 68.46; H, 7.76; Cl, 10.11. Found: C, 68.68; H, 7.88, Cl, 10.11.

17β-Hydroxy-5α-androstan-3-one 17-Chloroformate (V)——Dihydrotestosterone (872 mg) gave V, mp 151—152° (from acetone), $[\alpha]_D^{25}$ +46.9° (c=1, chloroform), ν_{max}^{KBr} cm^{-1}: 1770 (C=O). *Anal.* Calcd. for $C_{20}H_{29}ClO_3$: C, 68.07; H, 8.28; Cl, 10.05. Found: C, 68.03; H, 8.32; Cl, 10.10.

3α-Hydroxy-5α-androstan-17-one 3-Chloroformate (VI)——Androsterone (872 mg) gave 1.04 g (98%) of the chloroformate, mp 124—126°, which was recrystallized from ether to give 1.01 g (96%) of VI, mp 125—126°, $[\alpha]_D^{25}$ +86.0° (c=0.5, chloroform), ν_{max}^{KBr} cm^{-1}: 1760 (C=O). *Anal.* Calcd. for $C_{20}H_{29}ClO_3$: C, 68.07; H, 8.28; Cl, 10.05. Found: C, 68.13; H, 8.35; Cl, 10.06.

3β-Hydroxy-5-cholestene 3-Fluoroformate (VII)——A solution of commercial 3β-hydroxy-5-cholestene 3-chloroformate (5 g) in 10 ml of dry ethylene glycol dimethyl ether was stirred at 50° with 3.35 g of anhydrous thallous fluoride powder for 12 hr. Then anhydrous ether was added, after a separation of inorganic material, ethereal solution was evaporated to dryness *in vacuo*, and the crystals obtained were first recrystallized from *n*-hexane and then from *n*-pentane. There was obtained 4.2 g (28%) of VII, mp 114—115°, $[\alpha]_D^{25}$ −39.9° (c=0.5, chloroform), ν_{max}^{KBr} cm^{-1}: 1823 (C=O). *Anal.* Calcd. for $C_{28}H_{45}FO_2$: C, 77.72; H, 10.48; F, 4.39. Found: C, 77.71; H, 10.51; F, 4.42.

3β-Hydroxy-5α-cholestane 3-Fluoroformate (VIII)——I (10 g) in 50 ml of ethylene glycol dimethyl ether was stirred with 5.36 g of anhydrous thallous fluoride at 70° for 13 hr , then inorganic material was removed by a filtration. Evaporation of the solvent resulted in 9.45 g of crude solid, mp 85—89°, which was recrystallized from *n*-hexane–acetone to give 6.95 g (72%) of VIII, mp 101—102.5°, $[\alpha]_D^{25}$ +18.1° (c=0.5, chloroform), ν_{max}^{KBr} cm^{-1}: 1823 (C=O). *Anal.* Calcd. for $C_{28}H_{47}FO_2$: C, 77.36; H, 10.89; F, 4.37. Found: C, 77.26; H, 10.92; F, 4.36

3α-Hydroxy-5α-cholestane 3-Fluoroformate (IX)——A solution of II (902 mg) in 30 ml of ethylene glycol dimethyl ether was treated with 2 g of anhydrous thallous fluoride powder for 14 hr at room temperature, followed by a heating at 50° for an additional 5 hr. After removal of inorganic material, solvent was removed *in vacuo* to give crude product of 846 mg, mp 94—97°. Recrystallization from acetone yielded 680 mg (78%) of IX, mp 104—105°, $[\alpha]_D^{25}$ +19.1° (c=1, chloroform), ν_{max}^{KBr} cm^{-1}: 1815 (C=O). *Anal.* Calcd. for $C_{28}H_{47}FO_2$: C, 77.36; H, 10.89; F, 4.37. Found: C, 77.47: H, 10.93; F, 4.42.

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5-Androstene-3β,17β-diol 3-Fluoroformate 17-Benzoate (X)——A mixture of III (919 mg) in 30 ml of ethylene glycol dimethyl ether and 2 g of anhydrous thallous fluoride powder was treated for 14 hr at room temperature, followed by an additional heating at 50° for 5 hr. There was obtained 793 mg (90%) of crude product, mp 131—132°, which was recrystallized from *n*-hexane and acetone to give 661 mg (75%) of X, mp 130—132°, $[\alpha]_D^{25}$ −13.1° (*c*=1, chloroform), ν_{max}^{KBr} cm^{-1}: 1815 (C=O). *Anal.* Calcd. for $C_{27}H_{33}FO_4$: C, 73.60; H, 7.55; F, 4.31. Found: C, 73.85; H, 7.63; F, 5.02.

17β-Hydroxy-4-androsten-3-one 17-Fluoroformate (XI)——A solution of IV (1.05 g) in 30 ml of ethylene glycol dimethyl ether and 2 g of anhydrous thallous fluoride powder were treated by the same manner as in the case of epicholestanyl fluoroformate preparation, gave 903 mg (90%) of crude solid, which was recrystallized from ether resulted in 686 mg (66%) of pure XI, mp 99—100°, $[\alpha]_D^{25}$ +82.3° (*c*=0.5, chloroform), ν_{max}^{KBr} cm^{-1}: 1817 (C=O). *Anal.* Calcd. for $C_{20}H_{27}FO_3$: C, 71.83; H, 8.14; F, 5.68. Found: C, 71.87; H, 8.03; F, 5.59.

3α-Hydroxy-5α-androstan-17-one 3-Fluoroformate (XII)——A solution of VI (706 mg) in 30 ml of ethylene glycol dimethyl ether was treated with 2 g of anhydrous thallous fluoride powder for 14 hr at room temperature which was followed by a heating at 50° for 5 additional hours. After working up in the same manner as for IX, 639 mg (95%) of crude product, mp 88—97°, was obtained. Recrystallization from ether resulted in 442 mg (66%) of XII, mp 113—114°, $[\alpha]_D^{25}$ +69.2° (*c*=0.5, chloroform), ν_{max}^{KBr} cm^{-1}: 1816 (C=O). *Anal.* Calcd. for $C_{20}H_{29}FO_3$: C, 71.39; H, 8.69; F, 5.65. Found: C, 71.28; H, 8.64; F, 5.63.

11α-Hydroxy-4-pregnene-3,20-dione 11-Chloroformate (XIV)——11α-Hydroxyprogesterone (6.63 g) was treated in the same manner as for I, gave 7.64 g (97%) of crude XIV, mp 65—98°. Recrystallization from acetone resulted in 3.82 g (49%) of pure XIV, mp 97—98°, ν_{max}^{KBr} cm^{-1}: 1765, 1700, 1666, 1614, 1164, and 818. *Anal.* Calcd. for $C_{22}H_{29}ClO_4$: C, 67.25; H, 7.44; Cl, 9.02. Found: C, 67.23; H, 7.41; Cl, 9.06.

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Effect of Simultaneous Administration of Drugs on Absorption and Excretion. VIII.[1] Effect of Plasma-Protein Binding Displacement on the Intestinal Absorption of Sulfonamides in Rabbits

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Effect of plasma-protein binding displacement on the intestinal absorption of sulfonamides in rabbits was investigated by using salicylic acid and phenylbutazone as displacing drugs. Salicylic acid and phenylbutazone significantly reduced the *in situ* intestinal absorption of sulfadimethoxine that showed high binding to plasma proteins. These two displacing drugs also enhanced the *in situ* intestinal exsorption of sulfadimethoxine. However, salicylic acid and phenylbutazone showed no significant effect in the transport of sulfadimethoxine from mucosal to serosal side solution through the intestinal membrane or the uptake of sulfadimethoxine by the intestinal preparation *in vitro*. In addition, salicylic acid and phenylbutazone did not affect the *in situ* intestinal absorption and exsorption of sulfanilamide that showed little binding to plasma proteins. From these results, it is concluded that the displacement of one drug from its plasma-protein binding sites by another drug is an important determinant affecting drug absorption.

Keywords——intestinal absorption; plasma-protein binding; sulfonamides; salicylic acid; phenylbutazone; displacement; rabbit

It has been known that the intestinal absorption of drugs is influenced by factors related to the physiological conditions of experimental animals such as gastric emptying and intestinal

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