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Studies on Organic Fluorine Compounds. XVI.[1] Stereochemistry in Fluorination of Sterols with Phenylfluorophosphoranes[2]

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Stereochemistry of the fluorination of an alcohol with phenyltetrafluorophosphorane was investigated in the case of steroidal alcohols. 5α-Cholestan-3β-ol and 3α-ol gave 3α- and 3β-fluoro-5α-cholestane, respectively, which suggests that the fluorination proceeded through S_N2 mechanism; while, cholesterol and 3β-acetoxy-5-bromo-5α-cholestane-6β-ol gave fluoro compounds with retention of configuration, which shows that a neighboring group may have participated in stabilizing the carbonium intermediate in special cases. Diphenyltrifluorophosphorane gave similar results.

We reported that triphenyldifluorophosphorane[4] and diphenyltrifluorophosphorane (I)[5] convert primary and secondary alcohols to the corresponding alkyl fluorides in high yields, while phenyltetrafluorophosphorane (II) gives a small amount of the corresponding fluorides along with olefins and isomeric alkyl fluorides secondarily produced by addition of hydrogen fluoride to the olefins.[6] Paths for the reactions of the latter phosphorane (II) with amyl alcohol are shown in Chart 1.

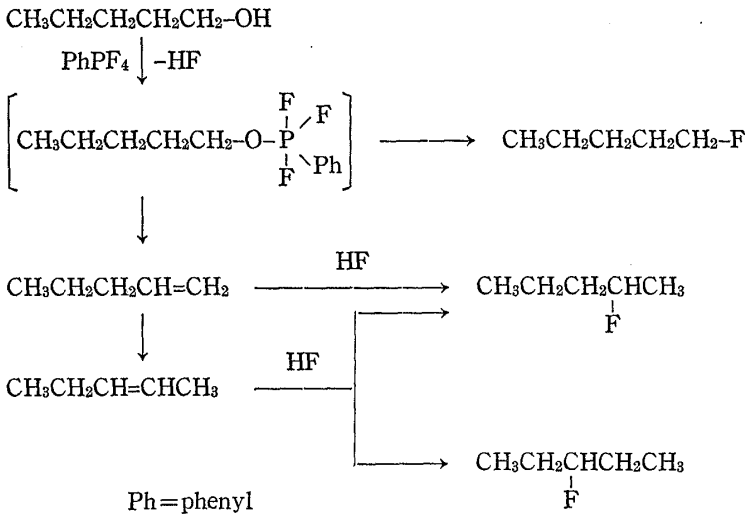

Chart 1

The reason for production of olefins was speculated (Chart 2, eq. 1), and the mechanism for production of alkyl fluoride was postulated as S_Ni (eq. 2) in our earlier paper.[6] On the other hand, Riess, *et al.*[7] reported the fluorination of trimethylsilylated alcohols with II and

1) Part XV: C. Kaneko, S. Hayashi, and Y. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 2147 (1974).
2) Presented mainly at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1973.
3) Location: *Kitashinjuku 3-chome, Shinjuku-ku, Tokyo.*
4) Y. Kobayashi and C. Akashi, *Chem. Pharm. Bull.* (Tokyo), **16**, 1009 (1968).
5) Y. Kobayashi, C. Akashi, and K. Morinaga, *Chem. Pharm. Bull.* (Tokyo), **16**, 1784 (1968).
6) Y. Kobayashi, I. Kumadaki, A. Ohsawa, and M. Honda, *Chem. Pharm. Bull.* (Tokyo), **21**, 867 (1973).
7) D.U. Robert, G.N. Flatau, A. Cambon, and J.G. Riess, *Tetrahedron*, **29**, 1877 (1973).

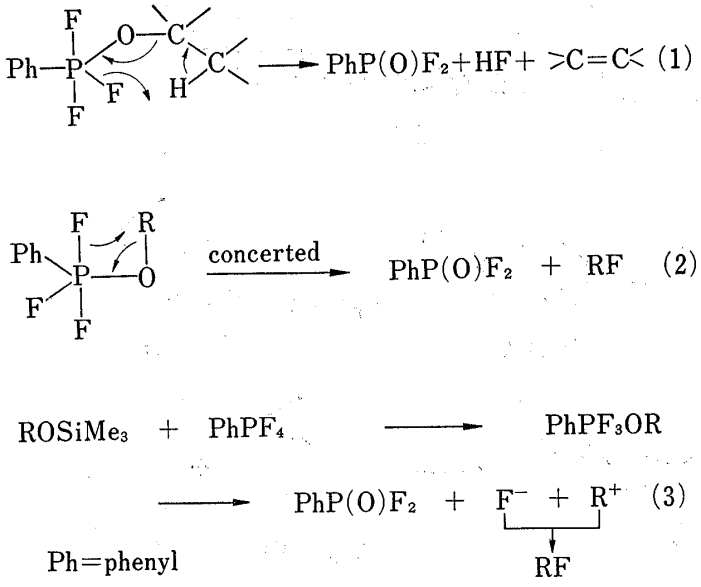

Chart 2

proposed S_N1 mechanism from the easiness of fluorination (eq. 3). However, since both authors did not try fluorination of any optically active alcohols, the possibility of the S_N2 mechanism should still be considered. On the other hand, since fluorine compounds behave quite peculiarly compared with other halogeno compounds, it is very important to examine the reaction mechanism.

In this study, we tried to clarify the stereochemistry in the fluorination of optically active cholesterol derivatives to elucidate the reaction mechanism. First, 5α-cholestan-3β-ol (III) was made to react with II in carbon tetrachloride at 20° and the products were separated by silica gel column chromatography to give 3α-fluoro-5α-cholestane (IV), 5α-cholest-2-ene (V), and 5α-cholestan-3β-yl phenylfluorophosphonate (VI). IV must have been produced by the attack of fluoride anion to C-3 of the fluorophosphoroxy intermediate from α-side; V may have been produced by elimination reaction through a cyclic intermediate or a carbonium ion; VI was produced by partial hydrolysis of the intermediate (Chart 3). But none of 3β-fluoro-5α-cholestane (VII) was produced. 5α-Cholestan-3α-ol (VIII) was treated as in the case of III to give VII and V, but none of IV. In this case, the fluoride ion attacked from the side opposite to the fluorophosphoroxy group, too, but *trans*-elimination mechanism may have participated in the production of V. These results show that fluorination proceeded with complete inversion of configuration at C-3. $E1$ mechanism could be suggested for production of the olefin, but no racemization at C-3 was observed. This shows that no free carbonium ion at least exists in the course of fluorination of these alcohols. The reaction condition used by Riess, *et al.* is slightly different from ours, but they proposed alkoxyphosphorane as an intermediate, as we did in our mechanism. If their S_N1 mechanism were correct, III and VIII should give a mixture of IV and VII in almost the same ratio.

Under our reaction condition, cholesterol (IX) gave cholesteryl fluoride (X), mp 92—94°[8] and dicholesteryl ether (XI), with complete retention of configuration at C-3. Further, 3α,5-cyclo-5α-cholestan-6β-ol (XII) gave X and XI in almost the same ratio as with IX. These results suggest that X and XI were produced through the same carbonium intermediate (XIII) from IX and XII (Chart 3). Further, XI was converted to X when treated with II at 80°. This fact shows that an ether which gives an especially stable carbonium ion can be fluorinated with II.

The above examples show that olefinic double bond participated in stabilizing the carbonium intermediate as a neighboring group. To confirm the neighboring-group participation in another case, fluorination of 3β-acetoxy-5-bromo-5α-cholestan-6β-ol (XIV) was examined under the same reaction condition to give 3β-acetoxy-5-bromo-6β-fluoro-5α-cholestane (XV) and 5-bromo-6β-fluoro-5α-cholestan-3β-ol (XVI). Compound (XV) was hydrolyzed to XVI in alcoholic potassium hydroxide. This result shows that configuration at C-6 was retained by the participation of 5α-bromine as a neighboring group (Chart 3).

8) C.W. Shoppee and G.H.R. Summers, *J. Chem. Soc.*, **1957**, 4813.

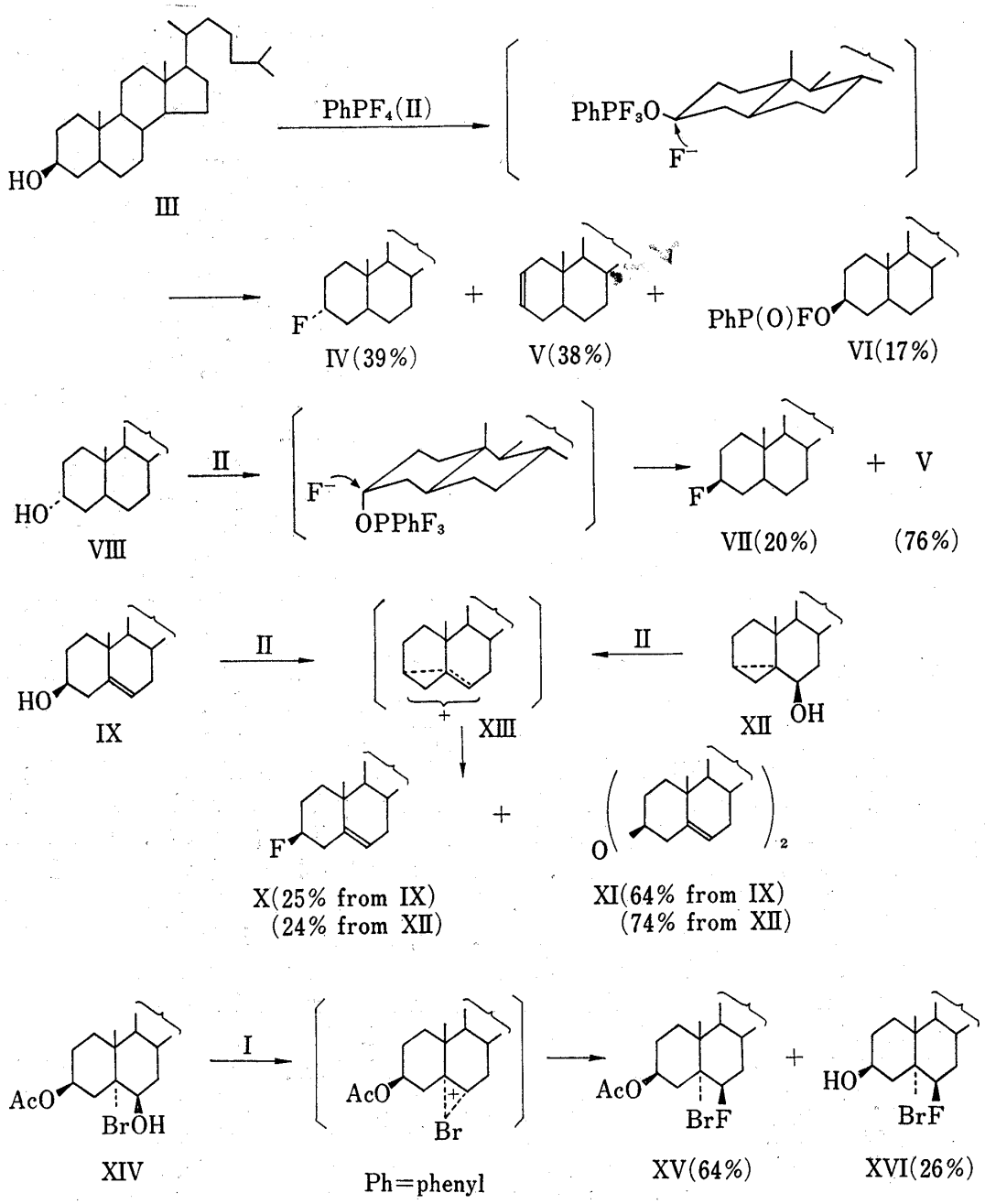

Chart 3

Next, reaction of these alcohols with diphenyltrifluorophosphorane (I) was examined. In the cases of 5α-cholestan-3β-ol (III) and cholesterol (IX), the results were almost the same as with phenyltetrafluorophosphorane (II), while 5α-cholestan-3α-ol (VIII), where the surrounding of hydroxyl group is extremely crowded, gave only 5α-cholest-2-ene (V) as an identified product. This shows that olefin formation is preferred to fluorination, which may be due to the bulkiness of I. In other words, *E*1 mechanism is more accelerated than S_N2 mechanism. These results suggest that mechanisms of fluorination with I and II are identical, but olefin formation depends on the bulkiness of phosphorane.

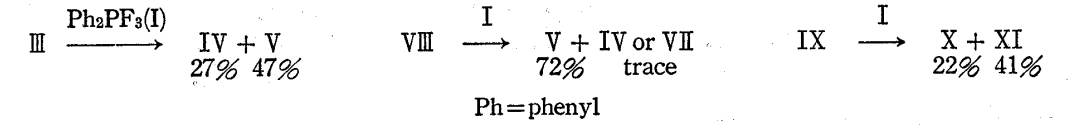

Chart 4

Therefore, we conclude that the relevant fluorination would generally proceed with inversion of configuration, but in some special cases the configuration is retained or the rearranged product is obtained.

Experimental

Reaction of 5α-Cholestan-3β-ol (III) with Phenyltetrafluorophosphorane (II)——A solution of II (1300 mg) and III (300 mg) in CCl_4 (5 ml) was shaken at 20° for 2 hr in a stainless-steel reaction tube. The reaction mixture was poured into an ice-cooled $NaHCO_3$ solution and extracted with ether. The ether layer was washed with sat. NaCl and dried over Na_2SO_4. The residue obtained after evaporation of ether was separated by silica gel column. The first effluent with *n*-hexane gave colorless needles (V) (from acetone), mp 71°, 109 mg (38%). This was identified with the authentic sample[9] by mixture melting point.

The second effluent with *n*-hexane gave colorless needles (IV) (from acetone), mp 103°, 117 mg (39%); Mass Spectrum *m/e*: 390 (M^+); High Mass Spectrum, Calcd. for $C_{27}H_{47}F$: 390.367; Found: 390.366; NMR (in $CDCl_3$) δ: 4.79 (1H, broad d, J_{HF}=47.5 Hz, 3β-H). *Anal.* Calcd. for $C_{27}H_{47}F$: C, 83.01; H, 12.13. Found: C, 83.45; H, 12.43.

The third effluent with benzene gave a thick oil (VI), 68 mg (16.6%); Mass Spectrum *m/e*: 530 (M^+); NMR (in $CDCl_3$) δ: 4.60 (1H, broad, 3α-H), 7.55 (3H, m, ar-H), 7.84 (2H, m, ar-H). ^{19}F-NMR (in $CDCl_3$) δ (from $C_6H_5CF_3$): 1.75 (1F, d, J_{PF}=1095.6 Hz).

Reaction of 5α-Cholestan-3α-ol (VIII) with II——A solution of II (1013 mg) and VIII (202 mg) in CCl_4 (5 ml) was treated as in the case of 3β-ol (III). The first effluent with *n*-hexane gave colorless needles (V) (from acetone), mp 72°, 147 mg (76.3%), which was identified with the authentic sample by mixture melting point.

The second effluent with *n*-hexane gave white needles (VII) (from acetone), mp 82°, 41.5 mg (20.4%); Mass Spectrum *m/e*: 390 (M^+); NMR (in $CDCl_3$) δ: 4.71 (1H, broad d, J_{HF}=46.0 Hz, 3α-H). This was identified with the authentic sample[10] by mixture melting point.

Reaction of Cholesterol (IX) with II——A solution of II (1600 mg) and IX (1000 mg) in CCl_4 (6 ml) was shaken in a stainless-steel reaction tube at 25° for 4 hr and the reaction mixture was worked up as in the case of III. The first effluent with *n*-hexane gave a colorless needles (X) (from acetone), mp 92—94°, 254.9 mg (25%); NMR (in $CDCl_3$) δ: 4.54 (1H, broad d, J_{HF}=50 Hz, 3α-H), 5.35 (1H, m, 6-H). This was identified with the authentic sample[8] by mixture melting point.

The second effluent with *n*-hexane–benzene (1: 1) gave colorless needles (XI) (from ether), mp 196°, 627.1 mg (64%); Mass Spectrum *m/e* 754 (M^+); NMR (in $CDCl_3$) δ: 3.23 (2H, broad, 3α-H), 5.29 (2H, m, 6-H). This was identified with the authentic sample[10] by mixture melting point.

Reaction of 3α,5-Cyclo-5α-cholestan-6β-ol (XII) with II——A solution of II (940 mg) and XII (100 mg) in CCl_4 (4 ml) was shaken in a stainless-steel reaction tube at 25° for 2 hr and at 60° for another 2 hr. The reaction mixture was worked up as in the case of III.

The effluent with *n*-hexane gave 143 mg (24%) of X, mp 93—94° (from acetone). The effluent with *n*-hexane–benzene (1: 1) gave 433 mg (74%) of XI, mp 195—196° (from *n*-hexane).

Reaction of Dicholesteryl Ether (XI) with II——A solution of II (824 mg) and XI (83 mg) in CCl_4 (1.5 ml) was shaken in a stainless-steel tube at 80° for 4 hr. The reaction mixture was treated as in the case of III. The effluent with *n*-hexane gave 38.1 mg (45%) of X, mp 92—93° (from acetone), which was identified with the authentic sample by mixture melting point. The effluent with *n*-hexane–benzene (1: 1) gave 15.3 mg of X (18%), mp 196—197°.

Reaction of 3β-Acetoxy-5-bromo-5α-cholestan-6β-ol (XIV) with II——A solution of II (1392 mg) and XIV (650 mg) in CCl_4 (6 ml) was shaken in a stainless-steel tube at 20° for 3 hr. The reaction mixture was worked up as in the case of III. The effluent with benzene gave colorless needles (XV) (from MeOH), mp 112.5°. 416.3 mg (64%); Mass Spectrum *m/e*: 526 (M^+); High Mass Spectrum, Calcd. for $C_{29}H_{48}O_2BrF$: 526.283; Found: 526.282; NMR (in $CDCl_3$) δ: 4.80 (1H, broad d, J_{HF}=50 Hz, 6α-H); ^{19}F-NMR (in $CDCl_3$) δ (from $C_6H_5CF_3$) 102.8 (m).

The effluent with benzene–acetone (1: 1) gave colorless needles (XVI) (from MeOH), mp 142°, 157.0 mg (26%); Mass Spectrum *m/e*: 484 (M^+); NMR (in $CDCl_3$) δ: 4.31 (1H, broad, 3α-H), 4.80 (1H broad d, J_{HF}= 50 Hz, 6α-H). *Anal.* Calcd. for $C_{27}H_{46}OBrF$: C, 66.78; H, 9.55; F, 3.71. Found: C, 66.71; H, 9.15; F, 4.28.

Hydrolysis of XV to XVI——XV (35 mg) was dissolved in 5% methanolic KOH (10 ml) and refluxed for 0.5 hr. The reaction mixture was cooled in ice-bath, neutralized with dil. HCl, and extracted with ether. The ether layer was dried over Na_2SO_4. After evaporation of ether, the residue was recrystallized from MeOH to give colorless needles, mp 141°, 22 mg (68%). This was identified with XVI obtained in the foregoing experiment by mixture melting point.

9) G.H. Douglas, P.S. Ellington, G.D. Meaking, and R. Swindells, *J. Chem. Soc.*, **1959**, 1720.
10) J.H. Beynon, I.M. Heilbron, and F.S. Spring, *J. Chem. Soc.*, **1936**, 907.

Reaction of 5α-Cholestan-3β-ol (III) with Diphenyltrifluorophosphorane (I)——A solution of I (523.8 mg) and III (76.2 mg) in CCl_4 (3 ml) was shaken at 80° for 5 hr and the mixture was treated as in the case of the reaction of III with II. V (34.2 mg) and IV (26.7 mg) were obtained.

Reaction of 5α-Cholestan-3α-ol (VIII) with I——A solution of I (399.0 mg) and VIII (70.2 mg) in CCl_4 (3 ml) was shaken at 80° for 5 hr and the mixture was treated as in the case of the reaction of VIII with II. V (48.2 mg) was obtained. Further, a trace of 3-fluoro-5α-cholestane was detected by thin-layer chromatography but configuration of fluorine was not determined.

Reaction of Cholesterol (IX) with I——A solution of I (450 mg) and IX (340 mg) in CCl_4 (3 ml) was shaken at 80° for 4 hr and the mixture was treated as in the case of the reaction of IX with II. X (73.6 mg) and XI (137 mg) were obtained.

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Added in Proof (January 20, 1975) After this paper was submitted, we received Dr. H. Koop's dissertation from Professor R. Schmutzler. He fluorinated trimethylsilylcholesterol with I and II without solvent and obtained α- and β-fluoro compounds, respectively. He proposed S_Ni mechanism for both cases, but it seems sterically unfavorable for the former case and our S_N1 mechanism cannot be ruled out for the latter case.