Reaction of Phosphorus Pentachloride with Aromatic Esters of Fluorocarbon Acids

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Phosphorus pentachloride has been used for a long time to replace the carbonyl group in ketones and aldehydes with chlorine. However, Kirsanov and Molosnova[2] have reported this reaction for the carbonyl group of an ester. We wish to report the reaction of phosphorus pentachloride with the carbonyl group of two phenyl esters of fluorocarbon acids to form dichloro ethers.

The reaction was carried out by heating the reactants for a considerable length of time near the reflux temperature of the esters. The reaction was attempted with phenyl trifluoroacetate, phenyl pentafluoropropionate, and higher homologs[3]; however, only the first two reacted to replace the carbonyl, yielding 2,2,2-trifluoro-1,1-dichloro-ethyl phenyl ether and 3,3,3,2,2-pentafluoro-1,1-dichloropropyl phenyl ether, respectively.

These ethers were very stable to acids and alkanolic caustic solutions. Refluxing the ethers with sodium in ethyl ether yielded sodium phenoxide together with sodium chloride and sodium fluoride.

The sulfonyl chlorides were prepared and treated with ethylene diamine to form 1,2-disulfonamides. The sulfonation occurred in the *para* position as determined *via* infrared. The absorption bands for the *para* substitutes are at 5.25, 5.65, and 16.06 μ, as determined on a Baird-Atomic Model 4-55 instrument.

EXPERIMENTAL

2,2,2-Trifluoro-1,1-dichloroethyl phenyl ether. A mixture of 28.3 g. (0.15 mole) of phenyl trifluoroacetate and 33.3 g. (0.16 mole) of phosphorus pentachloride was heated to 140° for 72 hr. Anhydrous acetone was added to decompose the unchanged phosphorus pentachloride and the mixture fractionated. Upon removal of phosphorus oxychloride the residue was neutralized with 10% sodium carbonate solution and steam distilled. Following separation and drying the organic layer, fractionation yielded 9.6 g. of unchanged ester and 15.8 g. (64.5%) of 2,2,2-trifluoro-1,1-dichloroethyl phenyl ether, b.p. 181–182°; n_D^{30} 1.4564; d_D^{30} 1.392.

Anal. Calcd. for $C_8H_5Cl_2F_3O$: C, 39.21; H, 2.06; Cl, 28.93. Found[4]: C, 39.18; H, 2.00; Cl, 29.00.

3,3,3,2,2-Pentafluoro-1,1-dichloropropyl phenyl ether. Phosphorus pentachloride and phenyl propforate were treated using the above procedure at 150° to give in 31.2% yield, 3,3,3,2,2-pentafluoro-1,1-dichloropropyl phenyl ether, b.p. 192–193°; n_D^{30} 1.4492; d_D^{30} 1.466.

Anal. Calcd. for $C_9H_5Cl_2F_5O$: C, 36.63; H, 1.71; Cl, 24.04. Found[5]: C, 36.55; H, 1.65; Cl, 24.05.

1,2-Di(p-2,2,2-trifluoro-1,1-dichloroethylphenylsulfonamido)-ethane. The sulfonyl chloride of 2,2,2-trifluoro-1,1-dichloroethyl phenyl ether was prepared by the method of Huntress and Carten,[6] and treated with ethylene diamine. After recrystallization from alcohol, the 1,2-di(*p*-2,2,2-trifluoro-1,1-dichloroethylphenylsulfonamido)-ethane melted at 192–193°.

Anal.[5] Calcd. for $C_{18}H_{28}Cl_4F_6N_2O_6S_2$: C, 31.40; H, 4.10; Cl, 20.60; S, 9.31. Found: C, 31.26; H, 3.98, Cl, 21.27; S, 9.17.

1,2-Di(p-3,3,3,2,2-pentafluoro-1,1-dichloropropylphenylsulfonamido)-ethane. The sulfonyl chloride of 3,3,3,2,2-pentafluoro-1,1-dichloropropyl phenyl ether was prepared and treated with ethylene diamine as above to yield 1,2 di-(*p* - 3,3,3,2,2 - pentafluoro - 1,1 - dichloropropylphenylsulfonamido)ethane, m.p. 182–183°.

Anal.[5] Calcd. for $C_{20}H_{28}Cl_4F_{10}N_2O_6S_2$: C, 27.42; H, 3.57; Cl 18.06; S, 8.16. Found: C, 27.34; H, 3.31; Cl, 18.28; S, 8.42

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Steroids. CLXXIII.[1] Unsaturated Derivatives of C_{22} Steroidal Lactones

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In recent years a very important group of steroids with sodiuretic properties has been synthesized by Cella *et al.*[2] These aldosterone antagonists are characterized by a 17-spiro-lactone side chain. Other sodiuretic steroids, 16-hydroxy derivatives of the pregnane series, have been isolated from hog adrenals.[3]

In order to investigate the possibility that other steroidal lactones similar to the spirolactones might have the same physiological activity, we decided to synthesize a few unsaturated keto lactones derived from the well known C_{22} lactones obtained by oxidation of tigogenin and sarsasapogenin. The tigogenin lactone has recently been synthesized by Sondheimer *et al.*[4]

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The starting material was the keto lactone I (16β-hydroxy-3-oxo-5α-pregnane-20-carboxylic acid lactone) obtained from tigogenin.[5] Bromination with two molar equivalents of bromine in acetic acid led to a mixture of the dibromo and tribromo ketones, (II) and (III). The separation of the tribromo compound III (in varying yields) was achieved by direct crystallization of the crude reaction mixture. The dibromo compound II could then be isolated by purification of the mother liquors. The use of three molar equivalents of bromine led again to a mixture of the two products, containing a larger proportion of the tribromo ketone. Based on analogy with the bromination of cholestanone,[6] we have assigned the 2,4-dibromo structure to compound II and the 2,2,4-tribromo structure to compound III.[7] This assignment of structure was further supported as follows. Dehydrobromination of II with *sym*-collidine resulted in the formation of the $\Delta^{1,4}$-dienone (V). On the other hand, treatment of compound III with concentrated hydrobromic acid in acetic acid–methylene chloride solution afforded (by loss of bromine) a new dibromo ketone (IV), showing a more negative rotation than compound II. Compound IV could be dehydrobrominated with *sym*-collidine to the same $\Delta^{1,4}$-dienone (V) as compound II. Thus, the two dibromo ketones differ only in the steric configuration of one or both of the bromine atoms.

The differences in molecular rotation of the dibromo ketones (II) and (IV) in relation to the nonhalogenated keto lactone (I) suggest that the bromine atoms are in the 2α,4α-configuration in compound II and the 2α,4β-configuration in compound IV (Table I). The strongly negative contribution of the 4β-bromo grouping has been established in the androstane[8] and cholestane[9] series.

TABLE I

Compound	$[\alpha]_D^{20}$	$[\phi]$	$\Delta[\phi]$
I	−22.8°	−78.4°	—
II	−42.8°	−214.9°	−136.5°
III	+33.9°	+197.0°	+275.4°
IV	−96.9°	−503.7°	−425.3°
Cholestanone	+41.0°	+158.3°	—
2α,4α-Dibromocholestanone	−3.0°	−16.3°	−174.6°
2,2,4-Tribromocholestanone	+60°	+373.2°	+214.9°

The optical rotatory dispersion curves of II and IV corroborate the assigned structures. Whereas the curve of the 2α,4α-dibromoketone (II) does not differ significantly from the one of the nonhalogenated ketolactone (I), the curve of the 2α,4β-dibromo ketone (IV) shows a strongly negative Cotton effect. Djerassi *et al.*[10] have reported a similar finding in the case of 2α,4α-dibromocholestanone and 2α,4β-dibromofriedelin. The negative Cotton effect of the 4β-bromo compounds is attributed to the axial configuration of the 4-bromo grouping, while the equatorial bromine atoms do not cause a significant change in the optical rotatory dispersion in comparison to the parent compound.[11]

The steric configuration of the 4-bromine atom in the tribromo ketone (III) is less easy to establish. Crowne *et al.*[7] have reported that the base-catalyzed bromination of 2,2-dibromocholestanone leads to the formation of 2,2,4β-tribromo-cholestanone; treatment of the latter compound with hydrobromic acid under certain conditions affords 2α,4α-dibromocholestanone, whereas more energetic conditions give rise to an unidentified dibromocholestanone with a more negative rotation, possibly the 2α,4β-dibromo ketone. The stability of the axial bromo grouping at C-4 in the presence of hydrobromic acid is rather surprising in view of the findings of Fajkos[8] and Malunowics,[9] who prepared

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(10) C. Djerassi, J. Osiecki, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, 80, 1216 (1958).
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the 4β-bromo ketones in the androstane and cholestane series and reported their ready rearrangement to the 4α-bromo compounds under acidic conditions. The stability of the 2α,4β-dibromo ketone (IV) may be explained by the fact that enolization of the dibromo ketone does not occur as easily as in the case of a monobromo ketone. Possibly, for the same reason the 2α,4α-dibromo ketone (II) is also stable under the same conditions and is not rearranged to the 2α,4β-isomer. The optical rotatory dispersion curve of compound III shows a strong positive Cotton effect. This can be attributed to the presence of one β-oriented bromine in the 2-position.[11]

The infrared spectrum of the keto lactone (I) exhibits a strong band at 1716 cm.$^{-1}$ due to the carbonyl group and at 1775 cm.$^{-1}$, characteristic of the lactone ring.[12] The spectrum of the 2α,4α-dibromo ketone (II) contains only a single maximum at 1775 cm.$^{-1}$ due to the strong positive shift of the two equatorial bromine atoms, which causes the merger of the maximum of the keto group with the maximum of the lactone group.[13] The spectrum of the 2α,4β-isomer (IV) shows the strong maximum of the lactone group at 1775 cm.$^{-1}$ and a band of low intensity at 1720 cm.$^{-1}$ The tribromo ketone (III) exhibits only a maximum at 1775 cm.$^{-1}$ as expected.

The Δ^4-unsaturated keto lactone (VI) could be prepared easily from the 2α,4α-dibromo compound (II) by the method of Rosenkranz *et al.*[14] The 2-iodo-Δ^4-ketone obtained from II by treatment with sodium iodide was not characterized and without further purification was dehalogenated with chromous chloride to VI.

Compound V was tested in a sodiuretic assay, but no significant activity could be detected.

EXPERIMENTAL[15]

Bromination of the keto lactone (I). A solution of 4.62 g. (2 molar equiv.) of bromine in 46 cc. of glacial acetic acid was added to a stirred suspension of 5 g. of the keto lactone (I)[5] in 200 cc. of glacial acetic acid, after the bromination had been initiated by addition of a few drops of hydrobromic acid in acetic acid. At the end of the addition of bromine a clear solution was formed, from which after a few minutes a white crystalline product started to precipitate. Stirring was continued for another 15 min. after which time the precipitation of the tribromo ketone (III) was complete. The latter was filtered, washed with methanol, and dried at room temperature; yield 4.8 g., m.p. 190° dec., $[\alpha]_D^{20}$ + 33.9°. The analytical sample was prepared by crystallization form methylene chloride–methanol.

Anal. Calcd. for $C_{22}H_{29}O_3Br_3$: C, 45.46; H, 5.03; Br, 41.25. Found: C, 46.04; H, 5.49; Br, 40.61.

The mother liquors of the bromination were poured into water, and the precipitated solid material was filtered and crystallized from methylene chloride–methanol. The resulting dibromo ketone (II) (2.1 g.) showed a m.p. of 202° dec., the analytical sample, which was prepared after several crystallizations from methylene chloride–methanol, melted at 208° dec., $[\alpha]_D^{20}$ −42.8°.

Anal. Calcd. for $C_{22}H_{30}O_3Br_2$: C, 52.63; H, 6.02; Br, 31.82. Found: C, 52.21; H, 5.84; Br, 32.71.

Treatment of the tribromo ketone (III) *with hydrogen bromide.* A solution of 1 g. of the tribromo ketone (III) in 10 cc. of methylene chloride was treated with 5 cc. of glacial acetic acid saturated with hydrogen bromide. The reaction mixture was left to stand overnight, after which it was poured into water. The methylene chloride layer was separated and washed with sodium bicarbonate solution and then with water. The solution was dried and evaporated, and the residue was crystallized from methanol. The resulting dibromo ketone (IV), 690 mg., showed a m.p. of 183° dec.; the analytical sample was obtained from methylene chloride–methanol and exhibited m.p. 190° dec., $[\alpha]_D^{20}$ −96.9°.

Anal. Calcd. for $C_{22}H_{30}O_3Br_2$: C, 52.63; H, 6.02; Br, 31.82. Found: C, 51.46; H, 5.96; Br, 32.62.

16β-Hydroxy-3-oxo-$\Delta^{1,4}$-pregnadiene-20-carboxylic acid lactone (V). A suspension of 6 g. of the dibromo ketone (II) in 20 cc. of *sym*-collidine was heated under reflux for 30 min. After being cooled, the reaction product was poured into a mixture of 2*N* hydrochloric acid and ice. The solid precipitate was extracted with ethyl acetate, and the organic extract was washed with dilute hydrochloric acid and then dried over anhydrous sodium sulfate. The dark solution was decolorized with activated charcoal and evaporated to dryness. The residue on crystallization from ether yielded 2.5 g. of the $\Delta^{1,4}$-dienone (V), m.p. 252–254°. The analytical sample was crystallized from methanol, m.p. 254–255°, $[\alpha]_D^{20}$ −17.2°; $\lambda_{max}^{CH_3OH}$ 244 mμ, log ε 4.21.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.46; H, 8.26.

The same compound could be obtained from the isomeric dibromo ketone (IV) after treatment with *sym*-collodine in the manner described above.

16β-Hydroxy-3-oxo-Δ^4-pregnene-20-carboxylic acid lactone (VI). Sodium iodide (4.0 g.) was added to a solution of 5.5 g. of the dibromo ketone (II) in 200 cc. of acetone. The solution was refluxed for 4 hr., during which time iodine was liberated and sodium bromide precipitated. The reaction mixture was poured into a solution of sodium thiosulfate. The precipitated iodo ketone was extracted with methylene chloride, the solution was washed with water, dried, and evaporated to dryness. The residue was taken up in 100 cc. of acetone and treated with 50 cc. of a chromous chloride solution (1.2 *N*)[14] at room temperature under nitrogen. After being allowed to stand for 1 hr., the mixture was poured into water, and the organic material was extracted with methylene chloride. The extract was washed with water, dried, and evaporated. The residue was then crystallized several times from methanol. After separation of some of the less soluble saturated ketone, 1 g. of the Δ^4-3-ketone (VI) was obtained in pure form. The analytical sample showed a m.p. of 210–212°, $[\alpha]_D^{20}$ +49.6, $\lambda_{max}^{CH_3OH}$ 241 mμ, log ε 4.22.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.57; H, 9.26.

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