The Synthesis of 6α-Difluoromethyl Steroids[1]

DAVID G. MARTIN AND JOHN E. PIKE

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan

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Certain modifications of the hydrocortisone molecule at C-6, for example the introduction of a 6α-methyl group[2] or a 6α-halogen atom,[2] have resulted in derivatives having valuable therapeutic properties. Recently several 6α-monofluoromethyl steroids[3] and 6α-trifluoromethyl steroids[4] have been synthesized. We now report the preparation of 6α-difluoromethyl corticoids, a study which was facilitated by the availability of a suitable intermediate (I)[3a] for the preparation of a 6-formyl cortical steroid (II), and a mild procedure[5] for the selective replacement of formyl oxygen with fluorine.

Oxidation of the hydroxymethyl derivative I with chromium trioxide in pyridine[6] afforded ketoaldehyde II. Treatment of this aldehyde with a large excess of a reagent comprised of two parts of hydrogen fluoride, ten parts of sulfur tetrafluoride, and one part of tetrahydrofuran afforded a difficultly separable mixture of the desired difluoromethyl derivative IIIa and a product, assigned either the fluoro ether[7] structure IIIb or IIIc, resulting from attack on the bismethylenedioxy grouping.[8] Fortunately the relatively high order of reactivity of the 6-formyl group towards fluorination with sulfur tetrafluoride permitted the use of milder conditions (a lower hydrogen fluoride to sulfur tetrafluoride ratio was employed) which selectively fluorinated the formyl group affording IIIa in over 60% yield. Survival of the bismethylenedioxy group in the presence of the hydrogen fluoride–sulfur tetrafluoride reagent provided another synthetic application for this versatile protective grouping.[9] Reduction of the 6α-difluoromethyl compound (IIIa) with lithium aluminum hydride afforded the diol IV which was oxidized to the monoketone V by the Oppenauer method. Selenium dioxide dehydrogenation,[10] hydrolysis of the bismethylenedioxy protective group and acetylation of the C-21 alcohol function afforded a low yield of 6α-difluoromethylprednisolone 21-acetate (VIII). Removal of the bismethylenedioxy protective group and acetylation prior to the selenium dioxide treatment afforded some improvement in the yield of VIII from V.

(1) Presented in part at the Symposium on Fluorine Containing Compounds of Biological Interest, at the 140th National Meeting of the American Chemical Society, September 6, 1961, Chicago, Ill.

(2) See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 685, 686, and 692, 693.

(3) (a) P. F. Beal, R. W. Jackson, and J. E. Pike, *J. Org. Chem.*, **27**, 1752 (1962); (b) A. L. Nussbaum, M. Kirtley, A. V. Maresco, and E. P. Oliveto, *ibid.*, **26**, 2147 (1961).

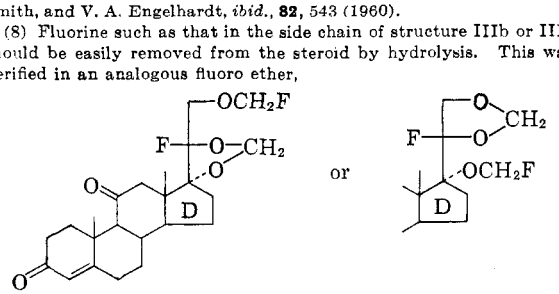
(4) W. O. Godtfredsen, S. African Patent 611049; W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **15**, 1786 (1961).

(5) D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962) and references cited.

(6) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(7) An analogous reaction $(HCHO)_x + SF_4 \longrightarrow CH_2F_2$ (49%) + $FCH_2—O—CH_2F$ (21%) has been reported, W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *ibid.*, **82**, 543 (1960).

(8) Fluorine such as that in the side chain of structure IIIb or IIIc should be easily removed from the steroid by hydrolysis. This was verified in an analogous fluoro ether,



obtained from the bismethylenedioxy derivative of cortisone on fluorination under the same conditions (see Experimental). Hydrolysis of a small analytically pure specimen of this difluoro derivative in aqueous formic acid regenerated cortisone (see Experimental).

Experimental[11]

17,20;20,21-Bismethylenedioxy-6α-formyl-3β-hydroxy-5α-pregnan-11-one Acetate (II).—The 6α-hydroxymethyl compound I[3a] (10.0 g.) was dissolved in pyridine (100 ml.) and oxidized for 18 hr. at room temperature with the chromium trioxide–pyridine complex prepared from chromium trioxide (10.0 g.) and pyridine (100 ml.). Isolation was effected by the addition of benzene–ether (1:1) and water followed by filtration through Supercel. The organic layer was separated and the aqueous layer twice re-extracted with benzene–ether. The combined extracts were washed with sodium bicarbonate solution, water, dried (sodium sulfate), and the solvent removed; toluene (200 ml.) was added and the solvent evaporated to remove residual pyridine. This latter operation was repeated twice. The residue was dissolved in methylene chloride (25 ml.) and chromatographed on Florisil[12] (900 g.). The column was eluted with increasing proportions of acetone in Skellysolve B.[13] Elution with 20% acetone–Skellysolve B gave, after combination of the fractions and crystallization from acetone–Skellysolve B, ketoaldehyde II, 2.48 g., m.p. 212–220°. Crystallization from acetone–Skellysolve B gave a sample, m.p. 205–210°; ν_{max} 2710 (—CHO), 2680, 1720, 1702, 1275 sh, 1260, 1250, 1125, 1105, 1085, 1040, 1010 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}O_8$: C, 65.53; H, 7.61. Found: C, 65.19, 65.33; H, 7.69, 8.14.

17,20;20,21-Bismethylenedioxy-6α-difluoromethyl-3β-hydroxy-5α-pregnan-11-one Acetate (IIIa).—In a 100-ml. stainless steel autoclave a mixture of 0.94 g. of 17,20;20,21-bismethylenedioxy - 6α - formyl - 3β - hydroxy - 5α - pregnan-11-one acetate, 0.05 ml. of water, 0.25 ml. of tetrahydrofuran, 20 ml. of methylene chloride, and 46 g. of sulfur tetrafluoride was agitated for 16 hr. at 15°. After venting the autoclave,[5] its contents were diluted with methylene chloride and washed with excess aqueous potassium bicar-

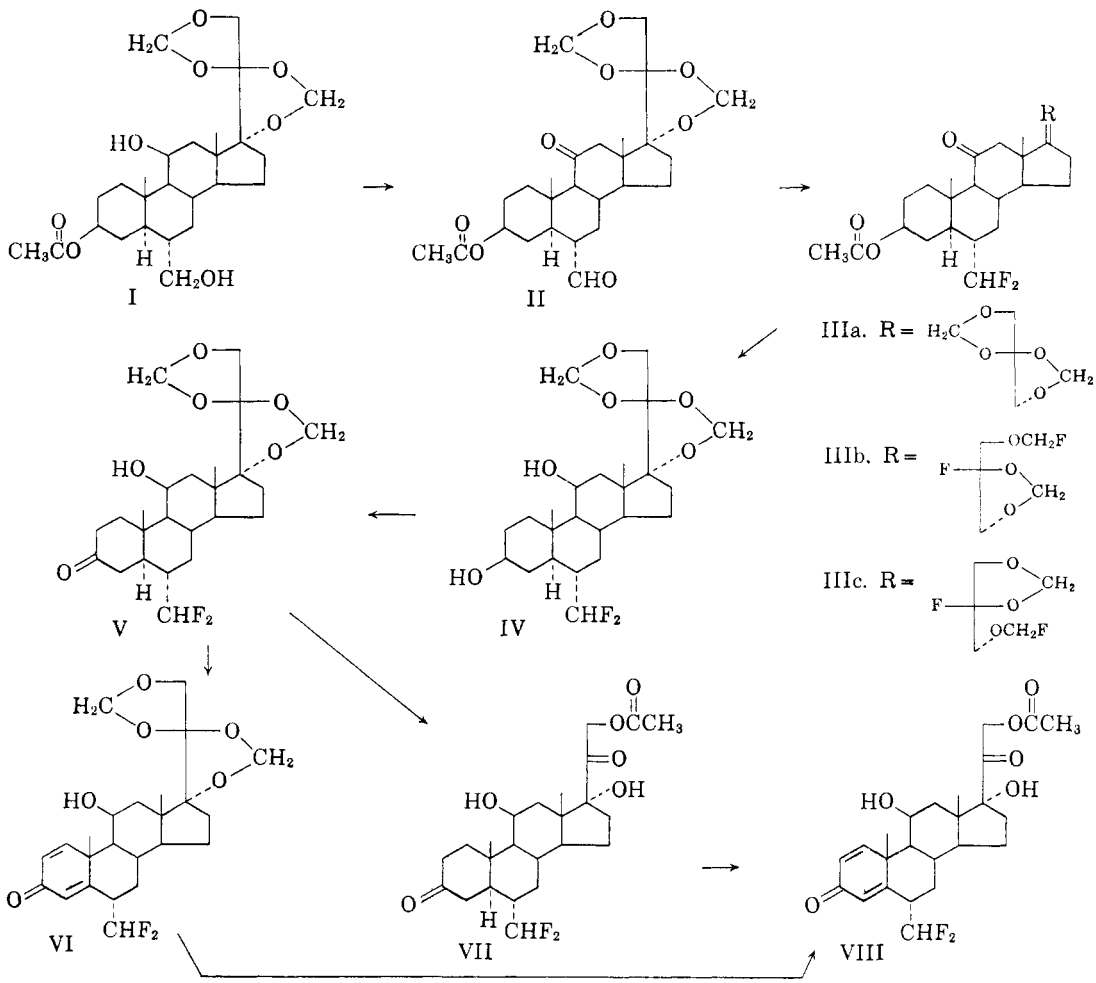
(9) *Cf.* R. E. Beyler, F. Hoffman, L. H. Sarett, and M. Tishler, *J. Org. Chem.*, **26**, 2426 (1961), and prior references.

(10) C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(11) Melting points are uncorrected. Rotations were observed at 26° on chloroform solutions. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer from Nujol mulls. Ultraviolet spectra were taken on 95% ethanol solutions using a Cary Model 14 spectrophotometer.

(12) A synthetic magnesia–silica gel manufactured by the Floridin Co., Warren, Pa.

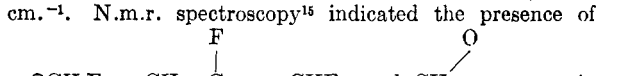
(13) A saturated hydrocarbon fraction, b.p. 60–71°.



bonate. This organic solution was dried (sodium sulfate) and concentrated to dryness. Chromatography on Florisil with increasing percentages of acetone in Skellysolve B gave crystalline material from the 2–5% acetone–Skellysolve B eluates; recrystallization of those fractions melting between 232 and 238° afforded 0.59 g. III (60%), m.p. 233–238°. Further recrystallization from acetone and Skellysolve B gave the analytical sample, m.p. 238–242°; $[\alpha]_D$ ($CHCl_3$) −40°; ν_{max} 1720, 1710, 1280 sh, 1265, 1255, 1133, 1104, 1088, 1045, 1027 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}F_2O_7$: C, 62.63; H, 7.28; F, 7.62. Found: C, 62.38; H, 7.11; F, 7.44.

17,20-Methylenedioxy-20-fluoro-21-fluoromethoxy-6α-difluoromethyl-3β-hydroxy-5α-pregnan-11-one Acetate IIIb or Alternate Structure IIIc.—A mixture of 17,20;20,21-bismethylenedioxy - 6α - formyl - 3β - hydroxy - 5α - pregnan - 11 - one acetate (1.00 g.), 0.75 ml. of water, 3.50 ml. of tetrahydrofuran, 20 ml. of methylene chloride, and 46 g. of sulfur tetrafluoride was agitated overnight at 15°. The crude product was isolated as described above and chromatographed on 50 g. of Florisil without delay. Elution with 2% acetone in Skellysolve B afforded 297 mg. of a partially crystalline gum which was evidently a mixture[14] of IIIa and IIIb (or IIIc). Continued elution with 2% acetone–Skellysolve B and with 3% acetone–Skellysolve B afforded fractions totalling 404 mg. from which crystalline material was obtained by trituration with ether. Combining and recrystallizing these fractions from ether–Skellysolve B gave 269 mg. of a substance melting 173–174° with decomposition. Three recrystallizations from acetone–Skellysolve B afforded the analytical sample, m.p. 183.5–184° with decomposition; $[\alpha]_D$ 0 (micro determination); ν_{max} 1723, 1703, 1253, 1178, 1147, 1130, 1093, 1078, 1035, 1018 cm.$^{-1}$. N.m.r. spectroscopy[15] indicated the presence of



groups in addition to the angular methyl groups and the acetate function.

Anal. Calcd. for $C_{26}H_{36}F_4O_6$: C, 59.99; H, 6.97; F, 14.60; mol. wt., 520.55. Found: C, 59.42; H, 7.07; F, 14.33; mol. wt.,[16] 519.5.

17,20;20,21-Bismethylenedioxy-6α-difluoromethyl-5α-pregnane-3β,11β-diol (IV).—A solution of 17,20;20,21-bismethylenedioxy-6α-difluoromethyl-3β-hydroxy - 5α - pregnan-11-one acetate (0.86 g.; m.p. 237.5–240°; and 0.59 g.; m.p. 233–238°; total weight 1.45 g.) in benzene (20

(14) Repeat chromatography of these fractions yielded 88 mg. of 111a.m.p. 227–236°, as the only crystalline product. However, the observation that crystalline IIIb or IIIc was not obtained from this repeat chromatography was not surprising since the fluoro ether derivative was not very stable except as a pure crystalline solid.

(15) N.m.r. spectra were determined in deuterochloroform on a Varian DP-60 spectrometer at 60 Mc. and calibrated against internal tetramethylsilane by audio-frequency–side band interpolations. The authors are grateful to Dr. G. Slomp and Mr. F. A. MacKellar of these laboratories for the determination and interpretation of these spectra. These spectra will be included in a forthcoming publication by them.

(16) The authors are indebted to Dr. John W. Shell of these laboratories for the molecular weight determination by the method of X-ray diffraction (J. W. Shell, *J. Pharm. Sci.*, **51**, in press.)

(17) R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

ml.) and ether (10 ml.) was added dropwise to a stirred suspension of lithium aluminum hydride (2.0 g.) in ether (40 ml.) and benzene (80 ml.) under nitrogen. The reduction was allowed to proceed at room temperature for 1.5 hr. Isolation was effected by the successive addition of ethyl acetate and water. Filtration of the inorganic salts with the aid of Supercel, and evaporation of the solvent gave a crystalline residue. Recrystallization from acetone–Skellysolve B gave 990 mg., m.p. 186–188°. Further crystallization from acetone–Skellysolve B gave 17,20;20,21-bismethylenedioxy-6α-difluoromethyl-5α-pregnane-3β,11β-diol, m.p. 186–188°; ν_{max} 3500, 3250, 1198, 1173, 1130, 1100–1080, 1065, 1048, 1030, 1023, 1007, 990 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}F_2O_6$: C, 62.88; H, 7.86; F, 8.3. Found: C, 62.95; H, 7.99; F, 8.2.

17,20;20,21-Bismethylenedioxy-6α-difluoromethyl-11β-hydroxy-5α-pregnan-3-one (V).—17,20;20,21-Bismethylenedioxy-6α-difluoromethyl-5α-pregnane-3β,11β-diol (0.625 g., m.p. 186–188°) was stirred and refluxed for 1 hr. in toluene (100 ml.) and cyclohexanone (30 ml.) while removing water as its toluene azeotrope. Aluminum *t*-butoxide (1.3 g.) was added and the solution heated under reflux for 18 hr. The mixture was then cooled and washed successively with Rochelle salt solution, dilute hydrochloric acid, water, and finally dried (sodium sulfate). Removal of the solvent gave an oil which was dissolved in methylene chloride (10 ml.) and chromatographed on Florisil (50 g.). Elution with increasing proportions of acetone in Skellysolve B gave crystalline material from the 10 to 20% acetone–Skellysolve B eluates. Crystallization from acetone–Skellysolve B gave 0.391 g., m.p. 184–188°. Further crystallization from the same solvent gave 17,20;20,21-bismethylenedioxy-6α-difluoromethyl-11β-hydroxy-5α-pregnan-3-one, acetone solvate, m.p. 189–190°; ν_{max} 3510, 1712, 1135, 1100, 1090, 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}F_2O_6 \cdot C_3H_6O$: C, 63.02; H, 7.78; F, 7.39. Found: C, 63.18; H, 7.62; F, 7.74.

6α-Difluoromethylprednisolone-B.M.D. (VI).—A mixture of 17,20;20,21-bismethylenedioxy-6α-difluoromethyl-11β-hydroxy-5α-pregnan-3-one (284 mg., m.p. 184–188°) and selenium dioxide (400 mg.) in *t*-butyl alcohol (20 ml.) and acetic acid (0.1 ml.) was heated to reflux for 20 hr. Further selenium dioxide (400 mg.) was then added and the reflux period continued for another 24 hr. After cooling, the insoluble material was removed by filtration through Celite; the filtrate was then evaporated to dryness in a nitrogen stream, and the residue extracted with ethyl acetate. These extracts were washed successively with sodium bicarbonate solution, freshly prepared ice-cold ammonium sulfide solution, dilute aqueous ammonia, dilute hydrochloric acid, sodium bicarbonate solution, and water. After drying over sodium sulfate the solvent was removed *in vacuo* to give an oil which was dissolved in methylene chloride (10 ml.) and chromatographed on Florisil (25 g.). Elution with increasing proportions of acetone in Skellysolve B gave crystalline material from the 20% acetone–Skellysolve B to give 6α-difluoromethylprednisolone-B.M.D., 64 mg., m.p. 248–252°. Further crystallization from acetone–Skellysolve B gave material, m.p. 263–265°; ν_{max} 3370, 1660, 1608, 1182, 1125, 1102, 1082, 1062, 1053, 1038, 1026, 1005 cm.$^{-1}$; λ_{max} 242 mμ (ε 15,550).

Anal. Calcd. for $C_{24}H_{30}F_2O_6$: C, 63.72; H, 6.64; F, 8.41. Found: C, 63.67; H, 6.73; F, 8.43.

6α-Difluoromethylprednisolone 21-Acetate (VIII). Procedure A.—6α-Difluoromethylprednisolone-B.M.D. (480 mg.) was suspended in 20 ml. of 65% aqueous formic acid and the mixture heated in a nitrogen stream on a steam bath for 15 min. The solution was then cooled and poured onto ice water; the organic material was extracted with ethyl acetate. The combined extracts were washed successively with water, sodium bicarbonate solution, water and then dried (sodium sulfate). Removal of the solvent gave an oil which was dissolved in pyridine (35 ml.) and acetic anhydride (5 ml.). After standing 18 hr. at room temperature this mixture was poured onto ice:sodium bicarbonate solution and the organic material extracted with ethyl acetate. The combined extracts were washed with dilute hydrochloric acid, sodium bicarbonate solution, water and dried (sodium sulfate). Removal of the solvent gave an oil which was dissolved in methylene chloride and chromatographed on Florisil (40 g.). Elution with increasing proportions of acetone in Skellysolve B gave crystalline material from the 20–30% acetone–Skellysolve B eluates. Crystallization from acetone–Skellysolve B gave 25 mg., m.p. 210–214° (positive triphenyltetrazolium chloride test). Further crystallization from acetone–Skellysolve B gave 6α-difluoromethylprednisolone 21-acetate, acetone solvate, m.p. 212–215°; ν_{max} 3520, 3240, 1750, 1722, 1650, 1610, 1600, 1260, 1250, 1230, 1180, 1125, 1055, 1040 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{30}F_2O_6 \cdot C_3H_6O$: C, 63.52; H, 7.06; F, 7.45. Found: C, 63.59; H, 6.92; F, 7.19, 7.49.

6α-Difluoromethyl-4,5α-dihydrohydrocortisone 21-Acetate (VII).—17,20;20,21-Bismethylenedioxy-6α-difluoromethyl-11β-hydroxy-5α-pregnan-3-one (250 mg.) was heated on a steam bath in 10 ml. of 65% formic acid in a nitrogen stream for 10 min. Isolation was then effected by cooling and then pouring the reaction mixture onto ice-water, and extracting the organic material with methylene chloride. The combined extracts were washed with dilute sodium bicarbonate solution, water and dried (sodium sulfate). After evaporation of the solvent the residue was dissolved in pyridine (10 ml.) and acetic anhydride (5 ml.). After standing 18 hr. at room temperature, the reaction mixture was poured onto ice–water and extracted with methylene chloride. These extracts were washed with dilute hydrochloric acid, sodium bicarbonate solution, water and dried (sodium sulfate). Evaporation of the solvent gave an oil which was dissolved in methylene chloride (10 ml.) and chromatographed on Florisil (25 g.). Elution with increasing proportions of acetone in Skellysolve B gave crystalline material from the 20–30% acetone–Skellysolve B eluates. These were combined and crystallized from acetone–Skellysolve B to give 86 mg., m.p. 189–192° (positive triphenyltetrazolium chloride test). Further crystallization from acetone–Skellysolve B gave m.p. 192–195°; ν_{max} 3620, 3420, 1755, 1725, 1704, 1277, 1237, 1202, 1125, 1090, 1063, 1050, 1020, 1002 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}F_2O_6 \cdot C_3H_6O$: C, 63.00; H, 7.78; F, 7.39. Found: C, 62.45; H, 7.78; F, 7.64.

6α-Difluoromethylprednisolone 21-Acetate (VIII). Procedure B.—6α-Difluoromethyl-4,5α-dihydrohydrocortisone 21-acetate (307 mg.) and selenium dioxide (400 mg.) in *t*-butyl alcohol (25 ml.) and acetic acid (1.5 ml.) were heated to reflux for 18 hr. At the end of this time further selenium dioxide (400 mg.) was added and the reflux period extended for another 24 hr. Isolation was effected exactly as described for the corresponding bismethylenedioxy compound. The residual oil was chromatographed on Florisil (25 g.) and crystalline material was obtained from the 20–30% acetone–Skellysolve B to give 24 mg., m.p. 217–220°. A mixed melting point with the previously prepared sample of 6α-difluoromethylprednisolone 21-acetate was not depressed.

Sulfur Tetrafluoride Fluorination of Cortisone B.M.D.—A mixture of cortisone B.M.D.[17] (1.00 g.), 0.75 ml. of water, 3.50 ml. of tetrahydrofuran, 20 ml. of methylene chloride, and 46 g. of sulfur tetrafluoride was agitated overnight at 20°. Volatile materials were evaporated[5] and a solution of the crude product in methylene chloride was washed with 10% potassium bicarbonate solution, dried (sodium sulfate), and concentrated to dryness under reduced pressure at room temperature leaving an amber gum which was chromatographed on 80 g. of Florisil without delay.[18] The polarity of the solvent was gradually and

(18) When allowed to stand as a crude gum the fluoro ether slowly decomposed. A sample of this gum, after standing 1 month, had turned black and etched the flask containing it; chromatography of this black residue afforded a small amount of recovered cortisone B.M.D. as the only crystalline product.

continuously increased from 3–10% acetone in Skellysolve B over 8 l. The first eluates contained negligible amounts of material. When the solvent consisted of approximately 6% acetone–Skellysolve B, gummy fractions totalling 227 mg. were eluted. Chromatography on paper[19] indicated that these fractions contained cortisone B.M.D. and the fluoro ether described below along with a variety of more polar materials presumably arising from degradation of the fluoroether. The first gummy fractions were followed by oils (380 mg.) which were crystallized from acetone–Skellysolve B affording 234 mg., m.p. 147° dec. A sample was recrystallized from the same solvents for analysis, m.p. 149.5–151° (dec.); $[\alpha]_D$ +104°; ν_{max} 1708, 1670, 1615, 1280, 1227, 1205, 1180, 1150, 1123, 1110, 1012, 1006, 993, 970 cm.$^{-1}$. N.m.r. spectroscopy indicated the presence of $-OCH_2F$, $-CH_2-\overset{F}{\underset{|}{C}}-$, and $CH_2\begin{smallmatrix}O\\/\\\backslash\\O\end{smallmatrix}$ groups as well as the angular methyl groups.

Anal. Calcd. for $C_{23}H_{30}F_2O_5$: C, 65.08; H, 7.12; F, 8.95. Found: C, 65.19; H, 7.06; F, 9.09.

Hydrolysis of the Fluoro Ether from Cortisone B.M.D.—A solution of 11 mg. of the fluoro ether described above, m.p. 149.5–151°, in 8 ml. of 60% formic acid which had been previously purged with nitrogen was heated for 16 min. on the steam bath while bubbling nitrogen through the solution. The solution was cautiously poured into excess 10% potassium bicarbonate and extracted with three portions of methylene chloride. The extracts were dried (sodium sulfate) and concentrated to dryness leaving 9 mg. residue. This residue was dissolved in 5 ml. of methanol (previously purged with nitrogen), treated with 2 ml. of aqueous 1% potassium bicarbonate (previously purged with nitrogen), and stirred under nitrogen for 48 hr. After the potassium bicarbonate had been neutralized with acetic acid, the solution was concentrated to dryness under reduced pressure and the organic material isolated by extraction with methylene chloride and a small volume of acetone. The extracts held 8 mg. of gummy residue. Attempts at crystallization were not successful but paper chromatographic analysis[19] indicated that the major constituent of this residue moved with cortisone in two different systems (formamide stationary phase developed with 1:1 benzene–chloroform and the Bush B_5[20]).

Acknowledgment.—The authors are grateful to M. A. Rebenstorf and D. T. Kloosterman for running the sulfur tetrafluoride fluorinations and J. L. Johnson and W. A. Struck and associates for spectral and analytical determinations.

(19) The authors are grateful for Mr. L. M. Reineke of these laboratories for the paper chromatographic analyses.

(20) L. M. Reineke, *Anal. Chem.*, **28**, 1853 (1956).

The Radical Addition of Hydrogen Bromide to Hexafluoropropene

F. W. STACEY AND J. F. HARRIS, JR.

Contribution No. 792 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company Inc., Wilmington, Delaware

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In an earlier publication,[1] we have shown that free radical additions of thiols to trifluoroethylene and to hexafluoropropene are bidirectional. In view of these results and the fact that hydrogen bromide adds to trifluoroethylene to give both possible adducts,[2] the report[3] that radical addition of hydrogen bromide to hexafluoropropene gives only the single isomer, CF_3CFHCF_2Br, seemed questionable. We have now determined unequivocally that *both* isomers are formed in the X-ray- and ultraviolet-initiated reactions of hydrogen bromide with hexafluoropropene.

$$CF_3CF{=}CF_2 + HBr \longrightarrow \underset{\text{I}}{CF_3CFHCF_2Br} + \underset{\text{II}}{CF_3CFBrCF_2H}$$

The reactions were carried out at room temperature using equimolar amounts of reactants, and the products were analyzed by gas chromatography and nuclear magnetic resonance spectroscopy. The adducts, I and II, were found in a ratio of 58:42 for the X-ray-initiated reaction and 62:38 for the ultraviolet-initiated reaction, when determined by proton n.m.r. analysis. Gas chromatographic analysis of the products from the X-ray reaction showed a ratio of 57:43 for the two isomers, in excellent agreement with the values calculated from the n.m.r. spectrum.

In the absence of irradiation, no reaction occurs between hydrogen bromide and hexafluoropropene under the conditions used here.

Experimental

X-Ray-initiated Addition of Hydrogen Bromide to Hexafluoropropene.—A mixture of 15 g. (0.1 mole) of hexafluoropropene and 8 g. (0.1 mole) of anhydrous hydrogen bromide in a 100-ml. stainless steel reaction vessel at 25–35° was irradiated with X-rays for 5 hr. at an average dose rate of approximately 30,000 rads/min. The reaction vessel was then cooled to −10° and the volatile material removed slowly. The liquid residue (16.5 g.) was distilled through a small spinning-band column to give 12 g. (52% yield) of 1:1 adduct boiling at 34°/760 mm.

Anal. Calcd. for C_3HBrF_6: Br, 34.63; F, 49.35. Found: Br, 34.82; F, 49.16.

The proton n.m.r. spectrum of this product indicated the presence of the isomers I and II in a ratio of 58:42. The spectrum of a portion of the crude reaction product gave a similar result indicating that no fractionation of isomers occurred during distillation.

Examination of a portion of the distilled product by gas chromatography (6-ft × 1/4 in. o.d. column packed with 20% ethyl ester of "KelF" acid No. 8114[4] on "Columnpak"[4]; helium flow rate, 62.5 ml./min.; temp., 0°) showed the presence of two principal constituents with elution times of 18.6 min. and 21.3 min. in the ratio of 43:57, together with some nine minor ones totaling about 2.5% of the sample. The principal constituents were separated for identification by preparative-scale gas chromatography.

(1) John F. Harris, Jr., and F. W. Stacey, *J. Am. Chem. Soc.* **83**, 840 (1961).

(2) R. N. Haszeldine, *J. Chem. Soc.*, 2800 (1957), obtained 58% $BrCHFCHF_2$ and 42% $BrCF_2CH_2F$ in an ultraviolet-initiated reaction of hydrogen bromide with trifluoroethylene. With X-ray irradiation, we have obtained the same products in a nearly identical ratio of 57:43.

(3) R. N. Haszeldine, *ibid.*, 3559 (*1953*).

(4) "KelF" acid no. 8114 was obtained from Minnesota Mining and Manufacturing Co. "Columnpak" was obtained from Fisher Scientific Co.