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Steroids. CCLX.[1] Spectra and Stereochemistry. XV.[1,2] A Survey of Long-Range Proton–Fluorine Coupling in Fluorosteroids

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Nuclear magnetic resonance (n.m.r.) spectral data for numerous fluorosteroids are presented and analyzed together with related data published elsewhere. Long-range coupling between fluorine and angular methyl protons separated by five or more σ-bonds is dependent upon the stereochemical relationship of the coupling atoms. This dependence is expressed in terms of the empirical "converging-vector rule" for which no exceptions have yet been discovered. Several applications of the rule are discussed.

The phenomenon of long-range coupling is well known in n.m.r. spectroscopy. Coupling of protons separated by as many as nine π-bonds has been reported,[4] while for σ-bond systems strong proton–proton coupling has been observed for nuclei four bonds apart.[5] In these latter cases the stereochemical disposition of the coupling nuclei can be critical for such coupling to occur.[5] Fewer cases have been reported of long-range proton–fluorine coupling.[6] Elegant work by Roberts and his collaborators[6b] established that long-range five-bond H–F coupling between the methyl protons and one of the fluorines of 1,1-difluoro-2,2-dichloro-3-phenyl-3-methylcyclobutane is a *cis* interaction unless unusual factors operate.

Independent discovery of long-range coupling of angular methyl protons with fluorine in fluorosteroids[7,8] led us to conduct investigations of the stereochemical requirements[9] and mechanism of this interaction. As a result there was formulated an empirical expression—now termed the "converging-vector rule"—governing the stereochemical requirements for coupling of fluorine with angular methyl protons concerning which a preliminary report has appeared.[9] Applications of this rule were subsequently made to structural problems in fluorosteroid chemistry,[10–13] while the more recent literature has contained other reports of angular methyl proton–fluorine coupling in fluorosteroids.[14–18] Long-range coupling of 6β-fluorine, but not of 6α-fluorine, with the allylic proton at C-4 in 6-fluoro-Δ^4-3-ketosteroids has been observed[19–20] and some mechanistic implications discussed.[19,21] We now present in detail n.m.r. spectral data for numerous fluorosteroids illustrating the extent of long-range angular methyl proton–fluorine coupling and the "converging-vector rule." For the purposes of discussion the compounds examined may be divided into two classes: (a) compounds in which fluorine is attached directly to the steroid nucleus, and (b) steroids in which fluorine is a substituent of a side-chain. Data for these two classes of fluorosteroids are collected in Tables I and II, respectively,[22,23] together with relevant results gleaned from the literature.

A study of Table I reveals that where only four σ-bonds separate fluorine and angular methyl protons, then coupling is sometimes, but not always, observed for α-oriented fluorine (*e.g.*, 17α-F–18-H).[24,25] However, the situation for α-fluoro substituents changes for coupling through five σ-bonds, where not one case has been discovered of a split 18-H or 19-H resonance. This statement is also true where one or two of the carbon atoms in the connecting chain of bonds is sp^2-hybridized. Examination of molecular models[26] of each type of fluorosteroid for which coupling was observed dis-

(1) Steroids. CCLIX: O. Halpern, P. Crabbé, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, in press.

(2) Spectra and Stereochemistry. XIV: A. D. Cross, J. Hrbek, Jr., J. L. Kaul, and F. Santavý, *Collection Czech. Chem. Commun.*, in press.

(3) To whom enquiries should be addressed.

(4) E. I. Snyder and J. D. Roberts, *J. Am. Chem. Soc.*, **84**, 1582 (1962).

(5) For typical examples see, *inter al.*, J. Meinwald and A. Lewis, *ibid.*, **83**, 2769 (1961); K. B. Wiberg, B. R. Lowry and B. J. Nist, *ibid.*, **84**, 1594 (1962); F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); J. Meinwald and Y. C. Meinwald, *J. Am. Chem. Soc.*, **85**, 2514 (1963); A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, *Tetrahedron Letters*, 233 (1964).

(6) For nonsteroids, *inter al.*, (a) D. R. Davis, R. P. Lutz, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 246 (1961); (b) M. Takahashi, D. R. Davis, and J. D. Roberts, *ibid.*, **84**, 2935 (1962); (c) D. F. Evans, S. L. Manatt, and D. D. Elleman, *ibid.*, **85**, 238 (1963); (d) M. S. Newman, R. G. Meutzer, and G. Slomp, *ibid.*, **85**, 4018 (1963).

(7) G. Slomp, private communication.

(8) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 1736 (1962).

(9) A. D. Cross and P. W. Landis, *ibid.*, **84**, 3784 (1962).

(10) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross, *ibid.*, **85**, 1851 (1963).

(11) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *Tetrahedron Letters*, 1249 (1962).

(12) P. G. Holton, A. D. Cross, and A. Bowers, *Steroids*, **2**, 71 (1963).

(13) L. H. Knox, S. Berger, E. Velarde, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).

(14) D. E. Ayer, *Tetrahedron Letters*, 1065 (1962).

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

(16) P. D. Klimstra and R. E. Counsell, *J. Med. Pharm. Chem.*, **5**, 1216 (1962).

(17) C. H. Robinson, N. F. Bruce, and E. P. Oliveto, *J. Org. Chem.*, **28**, 975 (1963).

(18) D. E. Ayer, *J. Med. Chem.*, **6**, 608 (1963).

(19) T. A. Wittstruck, S. K. Malhotra, H. J. Ringold, and A. D. Cross, *J. Am. Chem. Soc.*, **85**, 3028 (1963).

(20) K. Tori and K. Kuriyama, *Chem. Ind.* (London), 1525 (1963).

(21) In the following paper the long-range coupling of 6β-fluorine with angular methyl 19-protons is discussed with particular reference to the possible mechanisms of coupling: *J. Am. Chem. Soc.*, **86**, 4011 (1964).

(22) N.m.r. spectra were generally recorded for 5–10% solutions in deuteriochloroform containing tetramethylsilane (TMS) as an internal reference (0 c.p.s.). For a few compounds chloroform or carbon tetrachloride was used as solvent. For these latter results small shifts of the resonance frequencies, ν (quoted in c.p.s. units downfield from TMS and accurate to ± 1 c.p.s.), occur relative to spectra recorded using deuteriochloroform. However, the coupling constants, J (generally accurate to better than ± 0.5 c.p.s.) have a magnitude which is experimentally independent of the solvent employed.

(23) All data recorded by us were obtained on Varian A-60 or HR-60 instruments. Where literature data were obtained using a 40 Mc.p.s. oscillator the reported values have been multiplied by $^3/_2$ for comparative purposes. Literature data for which other reference standards were employed are quoted here relative to TMS by using the following frequency shift values: $\nu_{H_2O} - \nu_{TMS} = 282$ c.p.s., $\nu_{benzene} - \nu_{TMS} = 384$ c.p.s. No attempts were made to allocate signs to coupling constants.

(24) $J_{18H\text{-}12\alpha F} = 2$ c.p.s. was reported for a 12α-fluorosteroid at the International Congress on Hormonal Steroids, Milan, Italy, May, 1962, by P. A. Diassi, J. Fried, R. M. Palmere, and P. A. Principe.

(25) Unfortunately, no fluorosteroids have yet been available for study of coupling of a β-oriented fluorine with angular methyl protons four σ-bonds distant.

(26) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

TABLE I

ANGULAR METHYL PROTON RESONANCE FREQUENCIES AND J_{HF} VALUES FOR FLUOROSTEROIDS IN WHICH FLUORINE IS A RING SUBSTITUENT[22,a]

Compound	$\nu_{18\text{-H}}$	$\nu_{19\text{-H}}$	Ref.
17,20;20,21-Bis methylenedioxy-2α-fluorocortisone[b]	50.5	92.1	34
2α-Fluoro-5α-androstane-3,17-dione	[c]	68	16
2β-Fluoro-5α-androstane-3,17-dione	[c]	63, 65	16
		$J_{H,F}$ 2 c.p.s.	
2β-Fluoro-3α-hydroxy-5α-androstan-17-one	[c]	56, 58	16
		$J_{H,F}$ 2 c.p.s.	
3β-Fluoro-16α,17α-methylenepregn-5-en-20-one[d]	56.3	62.5	8
3β-Fluoro-17α-hydroxypregn-5-en-20-one acetate	39.1	62.4	[e]
3β-Fluoropregn-5-en-20-one	38.8	62.2	13[f]
3β-Fluoroandrost-5-en-17-one	53.5	63.7	13, 15
3α-Fluoro-5α-androstan-17-one	51.3	48.7	13
3,3-Difluoro-5α-androstan-17β-ol acetate[d]	45.0	50.1	8
3,3-Difluoro-5α-pregnan-20-one[g]	36	49	36
3,3-Difluoro-5β-pregnan-20-one[g]	37	60	36
3,3,20,20-Tetrafluoro-5α-pregnane[g]	52	52	36
3,3,20,20-Tetrafluoro-5β-pregnane[g]	49	60	36
3β-Fluoro-17α-hydroxypregnan-20-one 5α,6α-epoxide	34.4	64.6	[h]
3β,6β-Difluoro-17α-hydroxypregn-4-en-20-one acetate[d]	39.4	70.6, 72.5	8[h]
		J_{HF} 1.9 c.p.s.	
3β,6β-Difluoro-5α,17α-dihydroxypregnan-20-one 17α-acetate	38.6	65.4, 69.7	[h]
		J_{HF} 4.3	
4-Fluoropregn-4-ene-3,20-dione[d]	38.0	70.6	[i]
4β-Fluoro-5β-cholestan-3-one[k]	41.2	54.5	37
4,4-Difluoro-17β-hydroxyandrost-5-en-3-one acetate[k]	49.7	66.0	37
	(h.b.w. 1.4 c.p.s.)	(h.b.w. 3.2 c.p.s.)	
		J_{HF} *ca.* 1 c.p.s.	
5α-Fluoro-6β-iodoandrostane-3β,17β-diol 17β-acetate	51.1	87.7	[l]
5α-Fluoro-6β-iodo-3β-hydroxypregnan-20-one	40.0	87.0	[l]
5α-Fluoro-6β-iodo-3β-hydroxypregnan-20-one acetate	40.8	88.1	[l]
5α,6α-Difluoro-3β-hydroxypregnan-20-one	37.4	58.5	[f]
5α-Fluoro-3β-hydroxypregnan-20-one acetate	37.0	59.7	[f]
6α-Fluoro-17β-hydroxyandrost-4-en-3-one[g]	47.6	71.7	[m]
6α-Fluoro-17α,21-dihydroxypregn-4-ene-3,20-dione diacetate[g]	45.4	71.8	[n]
6α-Fluoro-17α-hydroxypregn-4-ene-3,20-dione acetate	42.4[g]	75.0[g]	[o]
	41	72	20
6α-Fluoro-17α,21-dihydroxypregn-4-ene-3,11,20-trione 21-acetate[g]	42.0	88.3	[p]
6α-Fluoro-17α,21-dihydroxypregn-4-ene-3,20-dione 21-acetate[g]	45.0	74.4	[n]
6α-Fluoro-16α,17α,21-trihydroxypregn-4-ene-3,20-dione 21-acetate 16α,17α-acetonide	37.8	75.7	[q]
6α-Fluoropregn-4-ene-3,20-dione	42	74	7
6α-Fluoro-17α,21-dihydroxypregn-4-ene-3,20-dione 21-acetate 9β,11β-epoxide	49.3	80.7	[p]
6α-Fluoro-17α-hydroxy-16α-methylpregn-4-ene-3,20-dione acetate	43.9	71.7	[r]
6α-Fluoro-16α,17α,21-trihydroxypregn-4-ene-3,20-dione 16α,21-diacetate	45.9	71.0	[s]
6α-Fluoro-16α,17α,21-trihydroxypregn-4-ene-3,20-dione 21-acetate 16α,17α-acetonide 9β,11β-epoxide	48.9	81.0	[t]
6α-Fluoro-16α,17α,21-trihydroxypregna-4,9-diene-3,20-dione 21-acetate 16α,17α-acetonide	36.9	78.9	[u]
6α-Fluoro-16α,17α,21-trihydroxypregn-4-ene-3,11,20-trione 21-acetate 16α,17α-acetonide	38.0	84.0	[v]
6α-Fluoro-6β-bromomethyl-17α,20;20,21-bismethylenedioxypregnan-3β-ol acetate	49.0	54.0	[w]
6α-Fluoro-11α,17α,21-trihydroxy-16α-methylpregn-4-ene-3,20-dione 11α,21-diacetate	50.1	71.5	[x]
6-Fluoro-16α,17α,21-trihydroxypregna-4,6-diene-3,20-dione 16α,17α-acetonide	40.7	70.4	[y]
6-Fluoro-16α,17α,21-trihydroxypregna-4,6-diene-3,20-dione 21-acetate 16α,17α-acetonide	45.5	70.3	[y]
6-Fluoro-17α,21-dihydroxy-16α-methylpregna-4,6-diene-3,11,20-trione 21-acetate	47.3	81.2	[z]
6-Fluoro-17α-hydroxypregna-4,6-diene-3,20-dione acetate	44.0	70.2	[o]
6α,9α-Difluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione 21-acetate 16α,17α-acetonide	55.3	91.0	[u] [aa]
6β-Fluorosteroids			
9α-Fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione 21-acetate	57	94.5	[bb]
9α-Fluoropregn-4-ene-3,20-dione	41	79	14
9α-Fluoro-17α,21-dihydroxypregn-4-ene-3,20-dione 21-acetate	44	77.5	[cc]
9α-Fluoroandrost-4-ene-3,17-dione	56	80	[cc]
10β-Fluoro-19-norpregna-1,4-diene-3,20-dione	43	...	[dd]
10β-Fluoro-17α-hydroxy-19-norpregna-1,4-diene-3,20-dione	47.6	...	[dd]
10β-Fluoro-17α-hydroxy-19-norpregna-1,4-diene-3,20-dione acetate	43.8	...	[dd]
10β-Fluoroestra-1,4-dien-3,17-dione[d]	57.9	...	[dd]
10β-Fluoro-17α-oxa-D-homoestra-1,4-diene-3,17-dione	83.2	...	[dd]
10β-Fluoro-17β-hydroxyestra-1,4,6-trien-3-one acetate	55.6	...	[dd]

TABLE I (*Continued*)

Compound	$\nu_{19\text{-H}}$	$\nu_{19\text{-H}}$	Ref.
11β-Fluoro-pregn-4-ene-3,20-dione	47, 50 J_{HF} 3 c.p.s.	80, 83 J_{HF} 3 c.p.s.	14
11β-Fluoro-9α-chloropregna-1,4-diene-3,20-dione[ee]	49.5, 52.2 J_{HF} 2.7	91.9, 97.2 J_{HF} 5.3	ff
12α-Fluorosteroids			24
13α-Fluoro-17β-methyl-18-norandrost-4-en-3-one	...	70.5	13
15β-Fluoropregn-4-ene-3,11,20-trione	49, 50 J_{HF} 1 c.p.s.	87	18
15β-Fluoropregna-4,17(20)-diene-3,11-dione 21-carboxylic acid methyl ester	76, 77 J_{HF} 1 c.p.s.	87.5	18
16α-Fluoro-3β-hydroxyandrost-5-en-17-one acetate[gg]	56.2 (h.b.w. 0.6 c.p.s.)	63.1 (h.b.w. 0.6 c.p.s.)	43
16α-Fluoro-11β,21-dihydroxypregna-1,4,17(20)-*trans*-trien-3-one 21-acetate	65	[c]	41
16β-Fluoro-3-hydroxyestra-1,3,5(10)-trien-17-one 3-methyl ether	61.9 (h.b.w. 0.8–1 c.p.s.) J_{HF} *ca.* 0.5 c.p.s.	...	43
16,16-Difluoro-3-hydroxyestra-1,3,5(10)-trien-17-one 3-methyl ether	66, 67 J_{HF} 1 c.p.s.[hh]		43
	64, 65 J_{HF} 1 c.p.s.	...	17
16,16-Difluoro-3-hydroxy-1-methylestra-1,3,5(10)-trien-17-one 3-methyl ether	68, 69 J_{HF} 1	...	9
17α-Fluoroandrost-4-en-3-one	38.8, 40.9 J_{HF} 2.1 c.p.s.	70.6	13
17α-Fluoroestra-1,3,5(10)-trien-3-ol methyl ether	40.8, 42.6 J_{HF} 1.8 c.p.s.	...	13
17α-Fluoro-21-hydroxy-5β-pregnan-3,11,20-trione acetate[ii]	41.4 (broadened singlet, J_{HF} *ca.* 1 c.p.s.)	73.9	9, [kk]
17α-Fluoro-3α,21-dihydroxy-5β-pregnan-11,20-dione diacetate[ii]	36.0 (broadened singlet, J_{HF} *ca.* 1 c.p.s.)	69.6	9, [kk]
17α,21,21-Trifluoro-3β-hydroxypregn-5-en-20-one 3-acetate	48 J_{HF} 1–2 c.p.s.	64	7

[a] Except where indicated otherwise spectra were taken for deuteriochloroform solutions[22]: half-band widths (h.b.w.) of singlets are quoted where relevant. [b] Sample kindly provided by Dr. H. Kissman. [c] Data not reported in the literature. [d] N.m.r. data for carbon tetrachloride solution. [e] O. Halpern, J. A. Edwards, and J. A. Zderic, *Chem. Ind.* (London), 1571 (1962). [f] A. Bowers, P. G. Holton, E. Denot, M. C. Loza, and R. Urquiza, *J. Am. Chem. Soc.*, **84**, 1050 (1962). [g] Data for chloroform solution. [h] J. A. Edwards and A. Bowers, unpublished results. [i] R. Joly and J. Warnant, *Bull. soc. chim. France*, 569 (1961). [k] Sample kindly donated by Prof. E. V. Jensen. [l] A. Bowers, E. Denot, and R. Becerra, *J. Am. Chem. Soc.*, **82**, 4007 (1960). [m] A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958). [n] A. Bowers, L. Cuéllar Ibáñez, and H. J. Ringold, *ibid.*, **7**, 138 (1959). [o] A. Bowers, L. Cuéllar Ibáñez, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5991 (1959). [p] A. Bowers, E. Denot, M. Blanca Sánchez, and H. J. Ringold, *Tetrahedron*, **7**, 153 (1959). [q] J. S. Mills, A. Bowers, C. Casas Campillo, C. Djerassi, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 1264 (1959). [r] J. A. Edwards, A. Zaffaroni, H. J. Ringold, and C. Djerassi, *Proc. Chem. Soc.*, 87 (1959). [s] J. S. Mills and A. Bowers, U. S. Patent 3,014,938. [t] Prepared by addition of hypobromous acid addition to the corresponding $\Delta^{9(11)}$-derivative[u] followed by methoxide treatment and acetylation; J. S. Mills and A. Bowers, unpublished results. [u] J. S. Mills, A. Bowers, C. Djerassi, and H. J. Ringold, *J. Am. Chem. Soc.*, **82**, 3399 (1960). [v] Prepared by chromic acid oxidation of the corresponding 11β-alcohol[q]; J. S. Mills and A. Bowers, unpublished results. [w] Spectrum kindly run by Dr. L. F. Johnson, Varian Associates at 60 and 100 Mc.p.s.; J. A. Edwards and A. Bowers, unpublished results.[40] [z] C. Djerassi and H. J. Ringold, U. S. Patent 2,983,737. [y] R. Villotti, R. Grezemkovsky, and A. Bowers, submitted for publication. [z] O. Halpern, unpublished results. [aa] See following paper. [bb] J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958). [cc] C. G. Bergstrom, R. T. Nicholson, and R. M. Dodson, *J. Org. Chem.*, **28**, 2633 (1963). [dd] J. S. Mills, J. Barrera, E. Olivares, and H. Garcia, *J. Am. Chem. Soc.*, **82**, 5882 (1960). [ee] Sample kindly provided by Dr. E. P. Oliveto. [ff] H. Reimann, E. P. Oliveto, R. Neri, M. Eisler, and P. Perlman, *J. Am. Chem. Soc.*, **82**, 2308 (1960). [gg] Sample kindly supplied by Dr. A. H. Goldkamp. [hh] Data of Dr. A. H. Goldkamp. [ii] Sample kindly provided by Dr. A. L. Herzog. [kk] A. L. Herzog, M. J. Gentles, H. M. Marshall, and E. B. Hershberg, *J. Am. Chem. Soc.*, **82**, 3691 (1960).

closed that in all cases the coupling nuclei tended to be spatially close together. The desirability of proximity of nuclei for long-range coupling suggested that coupling by transmission of spin-state knowledge across space by orbital overlap was a possibility, but did not provide proof of such a mechanism.[8,9] An alternative interpretation was that a particularly favorable set of bond angles obtained in these cases permitting exchange of spin-state knowledge through the bonding electrons of the intervening chain of bonds. No decision has yet been arrived at concerning the main coupling mechanism.[21] However, the limiting stereochemical requirements for long-range proton–fluorine coupling could be stated in terms of an empirical expression which we term the "converging-vector rule." This rule states that "*long-range coupling between angular methyl protons and fluorine five or more σ-bonds apart may occur only when a vector directed along the C–F bond, and originating at the carbon atom, converges upon and intersects a vector drawn along an angular methyl C–H bond in the direction of the proton, and originating at the methyl carbon.*" Insofar as the methyl group is rotating, the C–H vector sweeps a cone the nodal surface of which is intersected by the C–F vector. It seems plausible that modification of the phrasing of the rule may well permit its extension to other fluorinated alicycles. Before discussing the detailed results (Tables I and II) in terms of the rule a number of points need to be emphasized.

TABLE II

ANGULAR METHYL PROTON RESONANCE FREQUENCIES AND J_{HF} VALUES FOR FLUOROSTEROIDS IN WHICH FLUORINE IS A SIDE-CHAIN RING SUBSTITUENT[22,a]

Compound	ν_{18-H}	ν_{19-H}	Ref.
5β,6β-Difluoromethylene-3β-hydroxypregn-16-en-20-one acetate	53.7	64.6, 66.9 J_{HF} 2.3 c.p.s.	10
16-Fluoromethylene-17α-hydroxypregn-4-ene-3,20-dione	43	73	44
16-Fluoromethyl-17α-hydroxypregna-4,15-diene-3,20-dione	47	73	44
16-Fluoromethylpregn-4-ene-3,20-dione 16α,17α-epoxide	63.6	72.6	44
2-Difluoromethylandrost-2-en-17β-ol[b]	43.7	43.7	47
2-Difluoromethylandrost-2-en-17-one[c]	49.8	45.2	[d]
2-Difluoromethylandrost 2-en-17β-ol acetate[c]	48.2	44.5	47
20,20-Difluoro-5β-pregnan-3α-ol acetate	50 triplet J_{HF} 2 c.p.s.	58	15

[a] Except where indicated to the contrary spectra were recorded using deuteriochloroform solutions. [b] Data for chloroform solution. [c] Data for carbon tetrachloride solution. [d] J. C. Orr, unpublished results.

First, the rule is advanced on the basis of experimental results and has received no mathematical treatment. Second, the rule does *not* state that wherever the stereochemical prerequisites for coupling obtain then coupling will occur. The rule defines solely a certain requirement for coupling, but other factors too must be satisfied. For example, angular methyl protons and fluorine which are separated by a lengthy intervening chain, or are far apart spatially, are not expected to couple since the number of bonds, or distance between the nuclei, is too great for strong coupling to operate.[27] Thus, there is no observable splitting of the 18-H resonance in 10β-fluorosteroids (seven connecting σ-bonds).[30,31] It is axiomatic that where *both* coupling nuclei are components of groups capable of rotation about a single bond then coupling will be observed only if the coupling nuclei maintain the favorable stereochemical relationship for most of the time. This infers a slower than normal rate of rotation. That a nucleus requires a finite time to "see" a second nucleus in a particular stereochemical position is well known from temperature studies on alicyclic derivatives where the separation of resonances and coupling constants corresponding to different conformers disappears with increasing rate of conformation interchange. Therefore no long-range H–F coupling is expected between rapidly rotating methyl and fluorinated methyl groups. This point will be a subject of further consideration (*vide infra*). It is gratifying to note that several predictions made on the basis of the converging-vector rule[32] have since been confirmed experimentally. As an example there may be cited the verification[14] of the predicted coupling of 11β-fluorine with both 18- and 19-protons.[32]

(27) The magnitude of coupling between two nuclei diminishes rapidly as the number of intervening bonds increases.[28,29]

(28) *Cf.* J. D. Roberts, "Nuclear Magnetic Resonance," McGraw–Hill Book Co., Inc., New York, N. Y., 1959, Chapter 3.

(29) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, Chapter 6.

(30) There may be a weak long-range 10β-F–18-H coupling but, if there is, it is too small to be detected by the equipment at our disposal.

(31) Attempts were made to obtain a well-resolved ^{19}F n.m.r. spectrum in a few fluorosteroids, but without success. It seems highly probable that extensive coupling of the fluorine with numerous protons, other than those of the angular methyls, operates.

(32) See ref. 9, footnote 15.

(a) **Steroids with Fluorine as a Ring Substituent.**—Although no 1-fluorosteroids were available, both 2α- and 2β-fluoro derivatives have been studied with significant results. Klimstra and Counsell[16] have described the synthesis of 2α- and 2β-fluoro-5α-androstane-3,17-diones. They detected a split 19-H resonance only for the 2β-fluorosteroid and conjectured that the apparent splitting might be due to long-range coupling or to the presence in solution of two conformational isomers. Allinger and co-workers[33] subsequently demonstrated from optical rotatory dispersion, n.m.r., and dipole moment evidence that the 10β-methyl-2β-fluorine 1,3-diaxial repulsion probably distorts the C–F bond by *ca.* 10° away from the methyl. It seems improbable that such a relatively minor deformation could lead to two conformers of roughly equal stability which would be needed to give rise to two 19-H resonances of equal intensity. Moreover, the rate of interconversion of the two conformers would need to be slow to permit individual resonances to appear. A distinctly more plausible explanation of the 19-H resonance doublet lies in a long-range 2β-F–19-H coupling, as anticipated.[32] The converging-vector rule also supports the assignment of a 2α-orientation for the fluorine atom in 17,20;20,21-bismethylenedioxy-2α-fluorocortisone[34] for which no long-range 19-H–2-F coupling is observed. For similar reasons coupling of only the 2β-fluorine in 2,2,9α-trifluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione 16α,17α-acetonide[35] with the 19-proton is expected. Lack of material prevented verification of this point.

Turning to 3-fluorosteroids, no 19-H–F coupling is detectable for either 3α- and 3β-monofluoro[13] or 3,3-difluoro derivatives[15,36] when fluorine is absent elsewhere in the molecule. This is true for both 5α-H and 5β-H steroids. Failure of fluorine to couple with 19-H is in accord with the converging-vector rule for all of these orientations. Where coupling is observed for 3β,6β-difluorosteroids it is significant that the 19-H resonance is a doublet and therefore is coupled to only one fluorine. Since every other 6β-fluorosteroid studied shows 19-H–6β-F coupling, it may be concluded that in 3β,6β-difluoro derivatives 6β-, and not 3β-, fluorine is coupling with the 19-protons. 3,3,20,20-Tetrafluorosteroids[36] are considered further in discussion of side-chain fluorinated derivatives (*vide infra*).

4-Fluorosteroids provided another test of the converging vector rule. As expected, neither a 4-fluoro-4-en-3-one nor a 4β-fluoro-5β-steroid[37] showed a split 19-H resonance. However, the 19-H resonance of 4,4-difluoro-17β-hydroxyandrost-5-en-3-one[37] was a "singlet," the half-band width of which was more than double that measured for the 18-H resonance singlet in the same spectrum.[38] There is little doubt therefore that 19-H–4β-F coupling, J_{HF} *ca.* 1 c.p.s., is in fact occurring in this compound, in full agreement with prediction.[32]

Data for four 5α-fluorosteroids are assembled for

(33) N. L. Allinger, M. A. DaRooge, M. A. Miller, and B. Weagell, *J. Org. Chem.*, **28**, 780 (1963).

(34) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2312 (1960).

(35) H. M. Kissman, A. S. Hoffman, J. F. Poletto, and M. J. Weiss, *J. Med. Chem.*, **5**, 950 (1962).

(36) J. Tadanier and W. Cole, *J. Org. Chem.*, **26**, 2436 (1961).

(37) S. Nakanishi, R. L. Morgan, and E. V. Jensen, *Chem. Ind.* (London), 1136 (1960).

(38) Usually half-band widths of 18-H and 19-H resonances are of almost equal magnitude when neither proton shows long-range coupling.

completeness. As only four σ-bonds separate the 5α-fluorine and 19-protons, the vector rule cannot be applied. No coupling is observed. One of these four compounds is a 5α,6α-difluorosteroid. As with the many other 6α-fluorosteroids listed in Table I there is no evidence of either splitting or broadening of the 19-H resonance. The absence of detectable coupling concurs with expectations.[9] Similarly, no coupling is predicted or observed for 6-fluoro-4,6-dien-3-ones. 7α-Fluoroestradiol and its diacetate have been described recently,[39] but the n.m.r. data provided did not include the 18-H frequency and multiplicity. A singlet 3-proton resonance is expected.

Clearly the converging vector rule offers a simple method for differentiating between 6α- and 6β-fluorine substituents, especially since the splitting due to 19-H–6β-F coupling is frequently substantial.[21,40]

9α-Fluorosteroids are analogous to the 5α-fluoro compounds discussed above and merit no further consideration. 10β-Fluorosteroids, though meeting stereochemical requirements for long-range 10β-F–18-H coupling, show a singlet 18-H resonance for reasons outlined earlier.

In agreement with Ayer's findings,[14] and as predicted,[32] the only 11β-fluorosteroid available for study manifested doublets for both 18-H and 19-H resonances. The significance of the wide difference in $J_{19H-11\beta F}$ values for the two derivatives listed in Table I is discussed elsewhere.[21] 12α-Fluorosteroids[24] are not encompassed by the converging-vector rule and 13α-fluoro compounds[13] do not couple with the 10β-methyl protons. Ayer has described the preparation of 15β-fluoropregnanes and, again as predicted,[32] found long-range 15β-F–18-H coupling.[18]

In an earlier communication we noted coupling of 16β-fluorine, but not 16α-fluorine, with 18-protons.[9] In the interim further n.m.r. data (see Table I) on 16-fluorinated steroids have been published,[17,41] all supporting the original observations as well as being compatible with the converging-vector rule.[42]

17-Fluorosteroids are not subject to limiting stereochemical requirements for coupling, the fluorine being only four σ-bonds from the 18-protons (*vide supra*). Resonance frequencies for such compounds complete the table of n.m.r. data on steroids bearing fluorine as a ring substituent.

An over-all picture of long-range proton–fluorine coupling in fluorosteroids demonstrating the close agreement of predicted and observed couplings is presented in Table III. As other fluoro analogs become available it will become possible to subject the converging vector rule to even closer scrutiny. In Table III 5β- as well as 5α-hydrogen stereochemistry is considered for 2-, 3-, and 4-fluorosteroids. For 14β-steroids only 15- and 16-fluoro substituents are tabulated. Otherwise, all compounds refer to the normal 5α,14α-steroid stereochemistry except where double bonds eliminate

(39) M. Neeman and Y. Osawa, *Tetrahedron Letters*, 1987 (1963).

(40) A further illustration of the utility of this method in stereochemical problems will appear shortly: J. A. Edwards, A. D. Cross, and A. Bowers, forthcoming publication.

(41) F. Kagan, B. J. Magerlein, and R. D. Birkenmeyer, *J. Org. Chem.*, **28**, 3477 (1963).

(42) We wish to acknowledge a most useful exchange of correspondence with Dr. A. H. Goldkamp, G. D. Searle and Co., who also generously provided n.m.r. data for 16-fluorosteroids[43] for inclusion in this present paper.

(43) *Cf.* A. H. Goldkamp, *J. Med. Pharm. Chem.*, **5**, 1176 (1962).

TABLE III

COMPARISON OF OBSERVED AND PREDICTED SPLITTINGS OF ANGULAR METHYL PROTON RESONANCES IN FLUOROSTEROIDS[a]

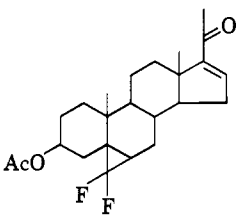
	18-H		19-H	
Fluorine substituent	Obsd.	Predicted	Obsd.	Predicted
2α-F, 5α-H	s	s	s	s
2β-F, 5α-H	s	s[c]	d	d
2α-F, 5β-H	[b]	s	[b]	s
2β-F, 5β-H	[b]	s	[b]	s
3α-F, 5α-H	s	s	s	s
3α-F, 5β-H	[b]	s	[b]	s
3,3-DiF, 5α-H or 5β-H	s	s	s	s
3β-F, Δ^5	s	s	s	s
3β-F, 5β-H	[b]	s	[b]	s
4-F, Δ^4-3-one	s	s	s	s
4,4-DiF, Δ^5-3-one	s	s[c]	[d]	[d]
4α-F, 5α-H or 5β-H	[b]	s	[b]	s
4β-F, 5α-H	[b]	s[c]	[b]	d
4β-F, 5β-H	s	s	s	s
5α-F	s	s	s	[e]
6α-F	s	s	s	s
6β-F	s	s[c]	d	d
6-F, Δ^6	s	s	s	s
7α- or 7β-F	s	s	s	s
8β-F	[b]	d	[b]	d
9α-F	s	s	s	[e]
10β-F	s	s[c]	..	..
11α-F	[b]	s	[b]	s
11β-F	d	d	d	d
12α-F	d	[e]	s	s
12β-F	[b]	[e]	[b]	s
13α-F	..	..	s	s
14α-F or 14β-F	[b]	[e]	[b]	s
15α-F, 14α-H or 14β-H	[b]	s	[b]	s
15β-H, 14α-H	d	d	s	s[c]
15β-F, 14β-H	[b]	s	[b]	s
16α-F, 14α-H	s	s	s	s
16α-F, 14β-H	[b]	s	[b]	s
16β-F, 14α-H	d	d	s	s[c]
16β-F, 14β-H	[b]	s	[b]	s
17α-F, 14α-H	d	[e]	s	s
17α-F, 14β-H	[b]	[e]	[b]	s
17β-F, 14α-H or 14β-H	[b]	[e]	[b]	s[c]

[a] s = singlet, d = doublet. [b] No fluorosteroid with this stereochemistry has yet become available for study. [c] Stereochemical requirements met but intervening carbon chain too long. [d] Distinctly broadened singlet indicative of unresolved splitting. [e] Converging-vector rule not applicable since only four σ-bonds separate F and angular methyl H.

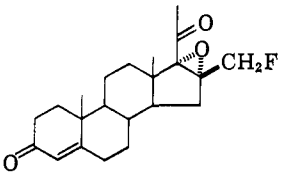
one or more asymmetric centers. It may be noted that although for the unknown 15β-fluoro-14β-steroids no long-range 18-H–15β-F coupling is predicted, such coupling might occur if nonbonded interactions on the α-face of the molecule force ring C to adopt a boat conformation. The converging vector rule can therefore provide a sensitive indicator of stereochemical change.

(b) **Steroids with Fluorine as a Side-Chain Substituent.**—Fluorosteroids which fall into this classification are divisible further into two structural types. The first of these resembles the ring-substituted fluorosteroids in that the fluorinated side-chain is rigidly attached to the quadricyclic carbon skeleton. A detailed discussion has already been presented elsewhere of sixteen such compounds all containing a fused difluorocyclopropane ring.[10] The converging-vector rule was found to be generally applicable. Of particular interest are 5β,6β-difluoromethylene derivatives (*e.g.*, I) for which the rule predicts that only *one* of the two fluorines should couple with the 19-protons. A doublet reso-

nance for the latter is observed.[10] Three 16-fluoromethylene derivatives of progesterone have been synthesized.[44] Examination of molecular models[26] suggests



I

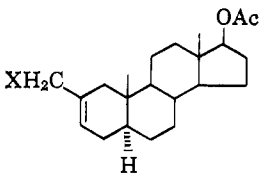


II

that whether the fluorine is *cis* or *trans* relative to the C-17 side-chain no long-range 18-H–F coupling is to be expected. Singlet 18-proton resonance was observed for all three compounds.

The remaining side-chain fluorinated compounds available for study all differed from those considered above in that the fluorine is a substituent of a side-chain capable of rotation about a single bond. The absence of long-range proton–fluorine coupling in several chlorofluoroacetate esters has been noted elsewhere.[13] As mentioned earlier (*vide supra*) coupling is to be expected in these cases only when the rate of rotation of the fluorinated side-chain is slow and a favorable steric relation of the fluorine and angular methyl protons is preferred. Measurements of spin-spin coupling at different temperatures appeared to lend itself to a study of the phenomenon by virtue of increased or decreased rotation about a single bond of the connecting chain of atoms. Three 16β-fluoromethylprogesterone 16α,17α-epoxide derivatives all showed singlet 18-proton resonances[44]; n.m.r. spectra for one of these compounds (II)[45] have been recorded at different temperatures. No change in the 18-proton resonance was observed, but the protons of the fluoromethyl group showed a decreased chemical shift difference in accordance with a more rapid rate of rotation at high temperatures.[46]

Similarly, a singlet 19-proton resonance was observed for several 2,2-difluoromethyl-Δ^2-steroids (see Table II), again indicative of a fairly rapid rate of rotation about the carbon–carbon single bond. In view of these findings it was deemed necessary to re-examine the earlier statement that long-range F–19-H coupling occurs for 2-fluoromethyl-5α-androst-2-en-17β-ol acetate.[8] Although the sample had the behavior of a pure specimen in physical analysis, the method of preparation[47] did not exclude the possibility that the sample was a 50:50 mixture of the 2-fluoromethyl-Δ^2 and 2-methylene-3ζ-fluoro isomers. That this possibility was indeed the case was revealed by a high-resolution n.m.r. study at 100 Mc.p.s.[48] from which it was apparent that the resonance pattern for protons on carbon bearing fluorine was inexplicable solely on the basis of a 2-fluoromethyl-Δ^2 structure. Conversion of 2-hydroxymethyl-5α-androst-2-en-17β-ol 17-acetate (IIIa) to the 2-fluoromethyl analog IIIb was then carried out by treatment with the fluoramine IV.[13,14,18] At the second attempt



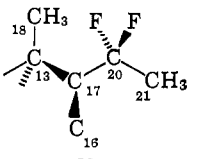
IIIa, X = OH
b, X = F

Et_2NCF_2CHClF
IV

there resulted a mixture of the 2-fluoromethyl derivative IIIb and the 2-methylene-3ζ-fluoro isomer in which the proton resonance for 19-H was no longer a symmetrical pair of peaks but was indicative of a *ca.* 70:30 mixture.[49] The anomaly was therefore resolved.

For 17α,21,21-trifluoro-3β-hydroxypregn-5-en-20-one acetate (see Table I) the 18-proton resonance is a doublet. In all other cases examined 17α-fluorine couples with the 18-proton with J_{HF} *ca.* 2 c.p.s. Accordingly, it is considered that such coupling operates also in the above 17α,21,21-trifluorosteroid and, from the 18-proton resonance pattern, it may be concluded that neither fluorine at C-21 couples measurably.

The n.m.r. data analyzed above for steroids with a fluorinated side chain capable of rotation suggest that long-range coupling in these cases is a rarity. One example has been reported. Although Tadanier and Cole[36] quoted the 18-proton resonance frequencies of two 3,3,20,20-tetrafluorosteroids with no mention of long-range coupling (see Table I), Martin and Kagan[15] found a triplet, J_{HF} 2 c.p.s., for the 18-proton resonance of 20,20-difluoro-5β-pregnan-3α-ol acetate. This indicates that in this compound *both* fluorines couple to an equal extent with the 18-protons and, moreover, suggests that a definite restriction of rotation about the C_{17}–C_{20} bond operates. A study of models[26] does indeed show that when the C-20 atom is sp^3-hybridized and the 17β side chain is a 1,1-difluoroethyl group, then a side-chain configuration as in V is heavily favored. This is because for other side-chain configurations either one of the fluorines approaches the 18-protons or an even more serious interaction develops between the protons at C-21 and those at the 12β-, 18-, or 16β-positions. Furthermore, for this most-favored configuration the converging vector rule predicts that *both* fluorines should couple with the 18-protons as is indeed observed.



V

(44) F. Werder, K. Brückner, K. H. Bork, H. Metz, B. Hampel, and H. J. Mannhardt, *Ber.*, **95**, 2110 (1962).

(45) Generously made available to us by Dr. Brückner and Hochenegger; n.m.r. spectra at 100 Mc.p.s. were recorded through the kind cooperation of Dr. E. A. Pier, Varian Associates.

(46) Low temperature studies are still in progress.

(47) J. A. Edwards, P. G. Holton, J. C. Orr, L. C. Ibanez, E. Necoechea, A. de la Roz, E. Segovia, R. Urquiza, and A. Bowers, *J. Med. Chem.*, **6**, 174 (1963).

(48) Obtained through the courtesy of Dr. E. A. Pier, Varian Associates.

(49) L. H. Knox, unpublished results.