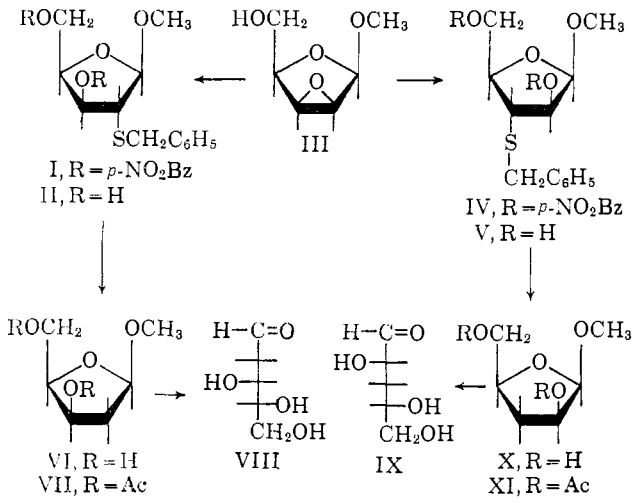

The optical rotation of the mixture of *p*-nitrobenzoates derived from the reaction of sodium benzyl mercaptide and the epoxide (III) indicated that approximately a 60:40 mixture of II and V, respectively, was formed in the ring-opening of III, *as the result of predominant attack at C.2.*

In order to provide chemical proof of structure, the diols (II and IV) were desulfurized with Raney nickel, affording, after acetylation, the acetates VII, isolated as a liquid by preparative gas chromatography,[9] and XI as a solid, m.p. 63–64°. The n.m.r. spectra of the desulfurized compounds were in complete agreement with their assignments as 2-deoxy- and 3-deoxyglycosides, respectively. Thus the C.1 proton signal of the 2-deoxy acetate (VII) appeared as a pair of doublets while that of the 3-deoxyacetate (XI) was found as a well-resolved doublet. These acetates were deacetylated to the deoxyfuranosides (VI and X), and hydrolyzed to the free sugars (VIII and IX). The α-benzylphenylhydrazone of 2-deoxy-D-*threo*-pentose (VIII) agreed in properties with the derivative reported in the literature[10] and the α-benzylphenylhydrazone of 3-deoxy-D-*threo*-pentose (IX), a new sugar, was a crystalline solid, m.p. 86–87°.

Clearly the assumption of invariable predominant opening of a 2,3-anhydrofuranoside at C.3 can lead to an incorrect structure assignment.

Studies are in progress to determine whether the disulfonate esters of II and V will provide a common episulfonium ion intermediate for further transformations.

(9) The desulfurization of II, but not of V, led to appreciable amounts of furfuryl acetate.

(10) F. Weygand and H. Wolz, *Ber.*, **85**, 256 (1952); G. Rembarz, *ibid.*, **95**, 1565 (1962).

LIFE SCIENCES RESEARCH GIOVANNI CASINI[1b]
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RECEIVED NOVEMBER 1, 1962

16-METHYLATED STEROIDS. IV. 6,16α-DIMETHYL-Δ⁶-HYDROCORTISONE AND RELATED COMPOUNDS

Sir:

The unrelenting search for an antiinflammatory steroid with superior therapeutic properties had led to intense synthetic effort during the last decade. It has been shown that a number of substituents on the hydrocortisone molecule, including methyls at C-2,[1] 6[2] and 16,[3,4,5] fluorine at C-6[6], 9[7] and 16[8] and a double bond at C-1[9] have increased the antiinflammatory potency of the parent compound.

We wish to report a number of compounds having a methyl group at C-16 in combination with a Δ⁶-6-methyl group showing pronounced activity, which is retained to a substantial degree by the corresponding 21-desoxy derivatives. Particularly interesting are the [3,2-c]-2′-phenylpyrazole[10] X of 6,16α-dimethyl-Δ⁶-hydrocortisone and the corresponding 21-deoxy derivative XVI which show anti-inflammatory activities in rats of 550 and 350 times hydrocortisone, respectively. Furthermore the [3,2-c]-2′-phenylpyrazole XII of 9α-fluoro-6,16α-dimethyl-Δ⁶-hydrocortisone is by far the most potent corticoid ever reported. This compound is 2000 × hydrocortisone in the rat systemic granuloma assay.

Although the introduction of a double bond between C-6 and C-7 causes a reduction of the glucocorticoid activity of hydrocortisone by a factor of two,[11] this is not observed with 16α-methylated steroids.[12] For example the antiinflammatory activity of 9α-fluoro-16α-methyl-1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione 21-acetate (Δ⁶-dexamethasone), I, m.p. 204–209°; $\alpha^{23}D$ +55° ($CHCl_3$): ultraviolet λ_{max}^{MeOH} 219, 248, 298 mμ, ε 13,000, 9,850, 11.500; (*Anal.* Found: C, 66.21; H, 6.73), prepared in low yield from dexamethasone[13] II by chloranil dehydrogenation[14] was approximately equal to the parent compound. A similar result was obtained with 9α-fluoro-16α-methyl-4,6-pregnadiene-11β,-17α,21-triol-3,20-dione 21-acetate III, m.p. 235–241°: $\alpha^{25}D$ +112° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 281 mμ, ε 27,100; (*Anal.* Found: C, 66.56; H, 7.33), prepared from 16α-methylhydrocortisone *via* chloranil dehydrogenation[14] at C-6 followed by dehydration at C-11[13] and elaboration of the C-ring fluorohydrin system.[7,15]

Combination of the Δ⁶-function with a C-6 methyl group afforded a number of surprisingly active antiinflammatory agents.

Reaction of 6α,16α-dimethyl-17α,20,20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one[16] with chloranil[14] afforded the C-6 unsaturated derivative IV, m.p. (dec.) 294–295°; $\alpha^{25}D$ +35° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 290 mμ, ε 22,900; (*Anal.* Found: C, 69.95; H, 8.03), which after reaction with 60% formic acid[17] and acetylation at C-21 afforded 6,16α-dimethyl-4,6-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate, V, m.p. 208–210°; $\alpha^{26}D$ +180° ($CHCl_3$); ultraviolet λ_{max}^{MeOH}

(1) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).

(2) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956).

(3) G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff and L. H. Sarett, *ibid.*, **80**, 3160 (1958).

(4) D. Taub, R. D. Hoffsommer, H. L. Slates and N. L. Wendler, *ibid.*, **80**, 4435 (1958).

(5) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 4428 (1958).

(6) A. Bowers and H. J. Ringold, *ibid.*, **80**, 4423 (1958).

(7) J. Fried and E. F. Sabo, *ibid.*, **76**, 1455 (1954); **79**, 1130 (1957).

(8) B. J. Magerlein, R. D. Birkenmeyer and F. Kagan, *ibid.*, **82**, 1252 (1960).

(9) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(10) R. Hirschmann, N. G. Steinberg, P. Buchschacher, J. H. Fried, G. J. Kent and M. Tishler, *J. Am. Chem. Soc.*, **85**, 120 (1963); *cf.* R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts and A. Arnold, *ibid.*, **81**, 1513 (1959).

(11) S. Tolksdorf, M. L. Battin, J. W. Cassidy, R. M. MacLeod, F. H. Warren and P. L. Perlman, *Proc. Soc. Exptl. Biol. Med.*, **92**, 207 (1956).

(12) This was first established with 16α-methyl-4,6-pregnadiene-11β,17α,-21-triol-3,20-dione acetate. Unpublished results of J. Korntved, D. R. Hoff and G. E. Arth of these laboratories.

(13) G. E. Arth, J. H. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958).

(14) E. J. Agnello and G. D. Laubach, *ibid.*, **79**, 1257 (1957).

(15) R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *ibid.*, **78**, 4956 (1956).

(16) M. Sletzinger and W. Gaines, to be published.

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

289 mμ, ε 23,100; (*Anal.* Found: C, 69.56; H, 7.80).

Selenium dioxide dehydrogenation[18] of V afforded 6,16α - dimethyl - 1,4,6 - pregnatriene - 11β,17α,21-triol-3,20-dione 21-acetate VI, m.p. 179–183°; $\alpha^{24}D$ +94° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 228, 248, 304 mμ, ε 14,100, 9,200, 10,800; (*Anal.* Found: C, 69.54; H, 7.73). Mesyl chloride–pyridine dehydration[13] yielded 6,16α-dimethyl-1,4,6,9(11)-pregnatetraene-17α, 21-diol-3,20-dione 21-acetate, m.p. 208–216°; $\alpha^{23}D$ −148° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 230, 253, 308 mμ, ε 15,000, 9,000, 10,500; (*Anal.* Found: C, 73.28; H, 7.60). Elaboration of the C-ring fluorohydrin system[7,15] afforded 9α-fluoro-6,16α-dimethyl-1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione 21-acetate VII, m.p. 240–247°; $\alpha^{23}D$ +42° (acetone); ultraviolet λ_{max}^{MeOH} 225, 245, 302 mμ, ε 14,400, 9,800, 10,600; (*Anal.* Found: C, 67.02; H, 6.58).

Introduction of the 9α-fluorine into IV[7,13,15] as above afforded 9α-fluoro-6,16α-dimethyl-17α,20,20,21-bismethylenedioxy-4,6-pregnadiene-11β-ol-3-one (VIII, m.p. *dec.* 279–283°; $\alpha^{25}D$ −19° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 288 mμ, ε 23,200; (*Anal.* Found: C, 67.06; H, 7.22), which after reaction with 60% aqueous formic acid[17] afforded 9α-fluoro-6,16α-dimethyl-4,6-pregnadiene-11β,17α,21-triol-3,20-dione IX, m.p. dec. 247–254°; $\alpha^{25}D$ +44° (pyridine); ultraviolet λ_{max}^{MeOH} 288 mμ, ε 24,400; (*Anal.* Found: C, 67.52; H, 7.51).

The interesting biological results obtained with 16α-methylhydrocortisone-(3,2-c)-2′-phenylpyrazole[10] suggested the preparation of the corresponding compounds in the 6,16α-dimethyl-Δ⁶-hydrocortisone series.

Formylation of IV with ethyl formate and sodium hydride afforded 2-hydroxymethylene-17α,20,20,21-bismethylenedioxy - 6,16α - dimethyl - 4,6 - pregnadiene-11β-ol-3-one, m.p. 198–205°; $\alpha^{25}D$ −197° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 295 mμ, ε 15,100: (*Anal.* Found: C, 68.12; H, 7.32). Reaction of the hydroxymethylene compound with phenylhydrazine yielded 17α,20,20,21 - bismethylenedioxy - 6,16α - dimethyl-4,6-pregnadiene-11β-ol-[3,2-c]-2′-phenylpyrazole, m.p. 258–262°; $\alpha^{24}D$ −123° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 283, 315 mμ, ε 17,200, 20,800; (*Anal.* Found: C, 72.22; H, 7.08; N, 5.11). Hydrolysis of the bismethylenedioxy protecting group with 60% aqueous formic acid,[17] then acetylation, afforded 6,16α-dimethyl - 4,6 - pregnadiene - 11β,17α,21 - triol - 20-one[3,2-c]-2′-phenylpyrazole 21-acetate X, double m.p. 160–165° and 229–230°; $\alpha^{23}D$ +14° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 283, 315 mμ, ε 15,700, 19,000; (*Anal.* Found: C, 72.55; H, 7.28).

Similarly the reaction of the 2-hydroxymethylene compound with *p*-fluorophenylhydrazine and hydrolysis of the bismethylenedioxy protecting group afforded 6,16α - dimethyl - 4,6 - pregnadiene - 11β,17α,21 - triol-20-one[3,2-c]-2′-*p*-fluorophenylpyrazole XI, m.p. 197–203°; $\alpha^{25}D$ −26° (acetone); ultraviolet λ_{max}^{MeOH} 280, 313 mμ, ε 15,800, 19,300; (*Anal.* Found: C, 71.29; H, 7.16).

Starting with VIII, formylation, phenylpyrazole formation and hydrolysis of the bismethylenedioxy protecting groups afforded 9α-fluoro-6,16α-dimethyl-4,6-pregnadiene - 11β,17α,21 - triol - 3,20 - dione - [3,2 - c]-2′-phenylpyrazole XII, m.p. dec. 241–245°; $\alpha^{24}D$ −46° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 283, 314 mμ, ε 17,700, 20,900; (*Anal.* Found: C, 71.34; H, 6.60).

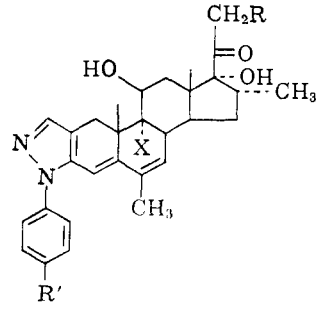
The preparation of a number of 21-desoxy derivatives in this series appeared to be of interest since Liddle and Fox[19] have reported that a group of 21-desoxy steroids used in human subjects showed a separation of anti-inflammatory and adrenal suppressing activity as compared to their eosinopenic and hyperglycemic activities.

The 21-desoxy derivative of compound I was prepared by hydrolysis of the 21-acetate, formation of the C-21-mesylate, replacement of the mesylate with iodide and reduction of the C-21-iodide with sodium bisulfite[20] to yield 9α-fluoro-16α-methyl-1,4,6-pregnatriene-11β,17α-diol-3,20-dione XIII, m.p. 245–250°; $\alpha^{24}D$ +17° (acetone); ultraviolet λ_{max}^{MeOH} 220, 248, 298 mμ, ε 12,000, 9,000, 11,600; (*Anal.* Found: C, 70.25; H, 7.55). A similar sequence starting with III afforded 9α-fluoro-16α-methyl-4,6-pregnadiene-11β,17α-diol-3,20-dione XIV, m.p. 255–265°; $\alpha^{24}D$ +59° (acetone); ultraviolet λ_{max}^{MeOH} 281 mμ, ε 26,400; (*Anal.* Found; C, 71.15, H, 8.06); compound V afforded 6,16α-dimethyl-4,6-pregnadiene-11β,17α-diol-3,20-dione XV, m.p. 228–238°; $\alpha^{24}D$ +117° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 290 mμ, ε 24,400; (*Anal.* Found: C, 73.93; H, 8.37); compound X afforded 6,16α-dimethyl-4,6-pregnadiene-11β,17α-diol-20-one-[3,2-c]-2′-phenylpyrazole XVI, m.p. 219–222°; $\alpha^{24}D$ −70° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 281, 315 mμ, ε 17,100, 20,800; (*Anal.* Found: C, 75.95; H, 7.57); compound XI afforded 6,16α - dimethyl - 4,6 - pregnadiene - 11β,17α - diol-20-one-[3,2-c]-2′-*p*-fluorophenylpyrazole XVII, m.p. 209–214°; $\alpha^{24}D$ −51° ($CHCl_3$); ultraviolet λ_{max}^{MeOH} 281, 312 mμ, ε 15,900, 19,800; (*Anal.* Found; C, 73.67; H, 7.17).

Table I lists the anti-inflammatory activities[21] of the

TABLE I

Compound	Systemic granuloma	Compound	Systemic granuloma	Compound	Systemic granuloma
I	150	VII	121	XIII	20
II	162	IX	50	XIV	2
III	29	X[23]	551	XV	18
V	40	XI	600	XVI	348
VI	71[22]	XII	2000	XVII	464



O
‖
X, R = OCCH₃; R′ = H; X = H
XI, R = OH; R′ = F; X = H
XII, R = OH; R′ = H; X = F
XVI, R = H; R′ = H; X = H
XVII R = H; R′ = F; X = H

(18) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **38**, 734 (1956).

(19) G. W. Liddle and M. Fox, "Inflammation and Diseases of Connective Tissue," edited by L. C. Mills and J. H. Moyer, W. B. Saunders Co., Philadelphia, Pa., 1961, p. 302.

(20) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *J. Am. Chem. Soc.*, **77**, 4181 (1955).

(21) Modification of the method of R. Meier, W. Schuler and P. Desaulles, *Experientia*, **6**, 469 (1950). Intact male Holtzman rats (*ca.* 125 g.) are dosed orally each day for one week.

(22) It is interesting to note that the double bond isomer of VI, 6-methylene-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate (unpublished results of J. H. Fried and A. N. Nutile of this laboratory), was about 1.2 × hydrocortisone in the systemic granuloma assay.

(23) Dr. E. W. Boland has informed us that compound X (administered orally) has been found to be approximately 75 × hydrocortisone in the suppression of rheumatoid arthritis in man.

reported compounds. No evidence of sodium retention was obtained for this series of compounds.

FUNDAMENTAL RESEARCH
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RELATIVE SIGNS OF FLUORINE-19–FLUORINE-19 AND HYDROGEN-1–FLUORINE-19 N.M.R. COUPLING CONSTANTS[1]

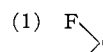
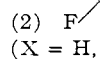
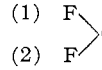
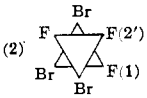
Sir:

The importance of the relative signs of n.m.r. coupling constants has only recently been realized in the analyses of high resolution n.m.r. spectra. The use of double resonance techniques for the determination of the relative signs of coupling constants is rather more attractive than the previously exploited long and tedious iterative high-resolution approach. In this communication we wish to give the results of some double resonance studies which have given the relative signs of several important types of F^{19}–F^{19} and H^1–F^{19} coupling constants.

In Table I are summarized results from F^{19}–F^{19} double resonance studies on a number of fluorocarbon

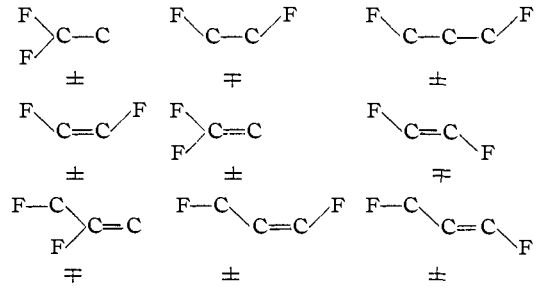
TABLE I

RELATIVE SIGNS OF F^{19}–F^{19} COUPLING CONSTANTS

k_2		Ref.
(1)  (3)	$J_{12} \pm, J_{13} \pm, J_{23} \mp$	a,b,c
(2) 		
(X = H, CF_3, Cl, Br, I)		
(1)  (3)	$J_{12} \pm, J_{13} \pm, J_{23} \mp$	a,c
(2) (4)	$J_{14} \pm, J_{24} \pm, J_{34} \mp$	
$CF_2BrCFClBr$ (2,2′) (1)	$J_{12} \mp, J_{12'} \mp, J_{22'} \pm$	
$CF_2ClCFClI$ (2,2′) (1)	$J_{12} \mp, J_{12'} \mp, J_{22'} \pm$	
$CF_2BrCFBrH$ (2,2′) (1)	$J_{12} \mp, J_{12'} \mp, J_{22'} \pm$	
(2) 	$J_{12} \mp, J_{12'} \mp, J_{22'} \pm$	c,a
$CF_3CF_2CF_2Br$ (3) (2) (1)	$J_{12} \mp, J_{23} \mp, J_{13} \pm$	
$CF_3CF_2CF_2I$ (3) (2) (1)	$J_{12} \mp, J_{23} \mp, J_{13} \pm$	
$CF_3CFClCFCl_2$ (3) (2) (1)	$J_{12} \mp, J_{23} \mp, J_{13} \pm$	
$CF_3CClICF_2Cl$ (3) (1,1′)	$J_{13} \pm, J_{1'3} \pm, J_{11'} \pm$	

[a] D. F. Evans, *Mol. Phys.*, **5**, 183 (1962). [b] D. D. Elleman and S. L. Manatt, *J. Chem. Phys.*, **36**, 1945 (1962). [c] D. D. Elleman and S. L. Manatt, presented at Third Conference on Experimental Aspects of N.M.R. Spectroscopy, Mellon Institute, Pittsburgh, Penna., March 2, 1962. [d] S. L. Manatt and D. D. Elleman, *J. Am. Chem. Soc.*, **84**, 1305 (1962).

compounds. Some of these results have been previously reported by us.[2,3,4] Four different halogen substituted 1,1,2-trifluoroethanes, which due to asymmetry show ABX n.m.r. spin systems,[5] were studied. It was determined that the vicinal and geminal coupling constants have different signs in the three ethane derivatives studied at room temperature and the one which was frozen into its separate conformers.[4] From the four halogen substituted fluoropropanes studied it was found that the vicinal coupling has a sign different from the geminal and 1,3-couplings. From the data presented above the relative sign relationships between the most commonly encountered F^{19}–F^{19} n.m.r. coupling constants can be tabulated

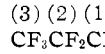
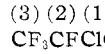


The one assumption involved in this correlation is that the  coupling constant has the same sign as that of the  coupling. This may be a reasonable assumption on grounds that these coupling constants are all fairly large in magnitude (ranging from about 28–224 c.p.s.) and that the contributions to these two types of geminal couplings may be similar. The fact that the F—C—C—F coupling has the same sign as that of the F—C—CF=C coupling with this assumption is interesting and suggests that the contributions to these two types of vicinal coupling may also be similar. Appropriate compounds to test this assumption are in preparation.

Table II summarizes some results for H^1–F^{19} couplings obtained either by H^1–H^1 or F^{19}–F^{19} decoupling.

TABLE II

RELATIVE SIGNS OF H^1–F^{19} COUPLING CONSTANTS

CH_3CH_2F[a], CH_3CHF_2, CF_3CFH_2, CF_3CF_2H, $CF_2BrCFBrH$, $CF_3CF_2CF_2H$, $CF_2HCF_2CFH_2$	J  J 
(1)  (3)[b,c]	$J_{14} \pm, J_{24} \mp, J_{34} \pm$
(2)  (4)	

[a] A similar assignment of the relative signs of the H^1–F^{19} couplings in this molecule also has been obtained from high-resolution analyses at two frequencies by S. L. Stafford and J. D. Baldeschwieler, *J. Am. Chem. Soc.*, **83**, 4473 (1961). [b] D. F. Evans, *Mol. Phys.*, **5**, 183 (1962). [c] D. D. Elleman and S. L. Manatt, presented at Third Conference on Experimental Aspects of N.M.R. Spectroscopy, Mellon Institute, Pittsburgh, Penn., March 2, 1962.

It was found that the  and  couplings are of the same sign in every case regardless of the substituents present.

Banwell and Sheppard recently have reported the relative signs between all the coupling constants in vinyl fluoride[6] and Beaudet and Baldeschwieler[7] have

(1) Presented in part at the Symposium on High-Resolution N.M.R. Spectroscopy, University of Colorado, Boulder, Colorado, July 3, 1962.
(2) D. F. Evans, *Mol. Phys.*, **5**, 183 (1962).
(3) D. D. Elleman and S. L. Manatt, *J. Chem. Phys.*, **36**, 1945 (1962).
(4) S. L. Manatt and D. D. Elleman, *J. Am. Chem. Soc.*, **84**, 1305 (1962).
(5) See for example P. M. Nair and J. D. Roberts, *ibid.*, **79**, 4565 (1957).
(6) C. N. Banwell and N. Sheppard, *Proc. Roy. Soc.* (London), **A263**, 136 (1961).
(7) R. A. Beaudet and J. D. Baldeschwieler, *J. Mol. Spectroscopy*, **9**, 30 (1962); private communication from R. A. Beaudet.