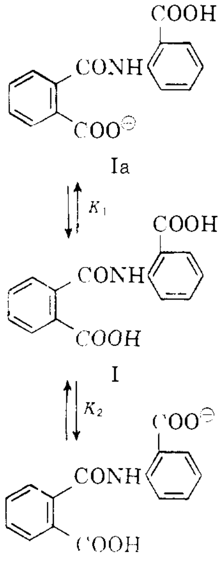
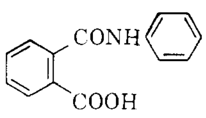
where k_1, k_2 and k_3 are the contributions made to the observed rate constant (k_{obs}) by species Ia, Ib and I, respectively, k_4 is the contribution from the hydrogen ion catalyzed reaction of species I, while K_1 and K_2 are the acid dissociation constants of the carboxyls on the phthalic and anthranilic acid residue, respectively.



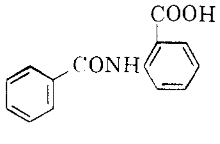
Ia

I

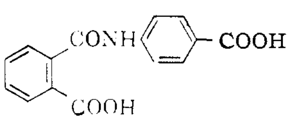
Ib



II



III



IV

In contrast, compound II has a pH-reactivity profile analogous to phthalamic acid,[2] *i.e.*, the solvolysis rate is proportional to the fraction of neighboring carboxyl which is un-ionized.

Compound III was unreactive under the conditions investigated. These data suggest that of the two singly ionized forms of I, Ib is the reactive species. With this assumption, the rate enhancement produced by the second ionized carboxyl is about 80-fold, similar to that found in the ester studies by Morawetz and Oreskes.[1]

To separate clearly the neighboring group effect and the electronic effects caused by the ionization of the carboxyl on the anthranilic acid residue, species IV also was investigated. Because of the change in electronic effects with the ionization of the *p*-carboxyl group equation (1) should also be used in analyzing the pH-dependence of the solvolysis rate of IV. A summary of the results obtained from the kinetic data is given in Table I.

TABLE I

Compound	10^4K_1	10^4K_2	10^4k_2 (sec.$^{-1}$)	10^4k_3 (sec.$^{-1}$)	10^4k_4 (l.-mole.$^{-1}$-sec.$^{-1}$)
I	5.5	1.8	124^a	1.5	18.1
IV	2.4	0.6	1.6^a	0.53	
II	2.4			2.6	7.2

^{a} Assuming $k_1 \ll k_2$.

By comparing the values of k_3 it is seen that the inactivating effect of the carboxyl is larger in the *p* than in the *o* position. Similarly, an electronic effect must contribute to the enhancement of the reactivity of Ib over that of I. A factor of 1.8 may be estimated as an upper limit of this effect by comparing k_3 for species I and II. An additional increase in the reactivity of Ib by a factor of at least 40 must then be attributed to neighboring carboxylate group participation.

Acknowledgment.—Support of this study by the Office of Naval Research and National Institute of Health is gratefully acknowledged.

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RECEIVED JULY 16, 1962

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[2] M. L. Bender, Y.-L. Chow and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).

STEROIDS. CCXXVI.[1a] SPECTRA AND STEREOCHEMISTRY. PART IV.[1b] SPATIAL REQUIREMENTS FOR LONG-RANGE SPIN–SPIN COUPLING BETWEEN FLUORINE AND STEROID ANGULAR METHYL PROTONS

Sir:

We recently reported examples of resolvable long-range spin–spin coupling between the protons of the steroid 10β-methyl group (19-H), and fluorine separated by five or six σ bonds from the methyl protons and situated on the same side of the molecule.[2] Roberts and his co-workers earlier had observed long-range H–F coupling in fluorinated ethane derivatives,[3] and very recently established that long-range five-bond H–F coupling between the methyl group and one of the fluorines of 1,1-difluoro-2,2-dichloro-3-phenyl-3-methylcyclobutane is likely to be a *cis*-interaction.[4] We have now examined more than 100 fluorosteroids and report here certain generalities, as well as new examples of long-range coupling with the 18-protons. A conclusion drawn from the earlier work was that a *cis* stereochemical relationship of proton and fluorine is preferred for long-range coupling.[2] However, existence of favorable stereochemistry is not always accompanied by long-range coupling. Thus, none of the 10β-fluoro-19-norsteroids[5] examined showed splitting of the 18-H singlet due to coupling, nor has any example appeared so far of 3β-F–19-H coupling.[2,6,7] In keeping with expectations no long-range coupling of the 18-H or 19-H with fluorine was detected in

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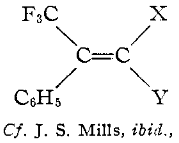
[1] (a) Steroids. CCXXV, J. S. Matthews, *Anal. Chem.*, in press; (b) Part III, A. D. Cross, *J. Am. Chem. Soc.*, **84**, 3206 (1962).

[2] A. D. Cross and P. W. Landis, *ibid.*, **84**, 1736 (1962).

[3] D. R. Davis, R. P. Lutz and J. D. Roberts, *ibid.*, **83**, 247 (1961).

[4] M. Takahashi, D. R. Davis and J. D. Roberts, *ibid.*, **84**, 2935 (1962). We are indebted to Prof. Roberts for informing us of these results prior to publication. It is also of interest to note that S. Andreades, *ibid.*, **84**, 864 (1962), has found long-range fluorine–fluorine coupling in (i) to be much stronger when the fluoromethyl groups are *cis* (iA) than when they are *trans* (iB).



A, X = CF_3, Y = F
B, X = F, Y = CF_3

[5] *Cf.* J. S. Mills, *ibid.*, **81**, 5515 (1959); J. S. Mills, J. Barrera, E. Olivares and H. Garcia, *ibid.*, **82**, 5882 (1960).

[6] Steroids are from the Syntex collection, with two exceptions. A full list of compounds examined, together with pertinent data, will appear in our full paper.

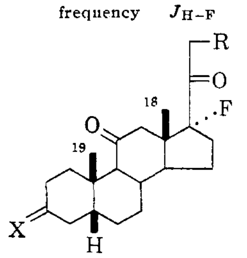
[7] J. Tadanier and W. Cole, *J. Org. Chem.*, **26**, 2436 (1962), very recently reported the n.m.r. spectra of two 3,3-difluorosteroids and two 3,3,20,20-tetrafluorosteroids but made no reference to any observable long-range coupling of fluorine with angular methyl protons.

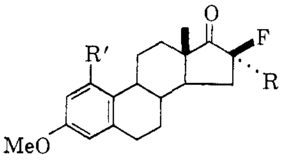
fluorosteroids where the fluorine has a 5α- or 6α-orientation. 4-Fluoro-Δ^4-3-ketones, 6α-trifluoromethyl-Δ^4-3-ketones and 6-fluoro-$\Delta^{4,6}$-diene-3-ones likewise showed unsplit angular methyl 3-proton singlets. Conversely, *every one of 33* 6β-fluorosteroids examined had a split 19-H absorption.[8] Two 17α-fluoropregnanes, I and II,[9] both showed long-range coupling between the 17α-fluorine and 18-protons[10] (Table I). This result, a recent report that 18-methyl protons long-range couple with 12α-fluorine (J, 2c./s.)[11], and further work on 17-fluorosteroids in the Syntex Laboratories[12] suggests that when the coupling is taking place through only four σ bonds the angular methyl protons may show coupling with α-fluorine substituents.[13] However, no coupling of 19-H with either 5α-F or 9α-F has been observed. An empirical limiting stereochemical requirement for proton–fluorine long-range coupling through five or more bonds in fluorosteroids may now be advanced on the basis of the accumulated results. *Long-range coupling between angular methyl protons and fluorine 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.*[14,15] This expression uniquely encompasses all our results.

16,16-Difluoroestrone methyl ether (III)[16] and its 1-methyl analog IV[17] both show a split angular methyl proton resonance absorption and from an examination of molecular models it is apparent that it is the 16β-F which is involved in the H–F spin-spin coupling. 16β-Fluoro-1-methylestrone methyl ether (V)[17] shows a similar splitting.

TABLE I

LONG-RANGE H–F SPIN-SPIN COUPLING[a]





	18-H resonance frequency	J_{H-F}	Minimum no. of bonds connecting coupling nuclei	Ref.
I, R = OAc, X = O	41.4	0.8	4	9
II, R = H; X $\begin{smallmatrix}\cdot\cdot H\\ \diagdown OAc\end{smallmatrix}$	36.0	0.8	4	9
III, R = F, R' = H	66.7	*ca.* 1.5	5	16
IV, R = F, R' = Me	68.3	*ca.* 1.0	5	17
V, R = H, R' = Me	59.0	*ca.* 0.5	5	17

[a] Chemical shifts, δ, are expressed as c./s. from the tetramethylsilane reference, and coupling constants, J, as c./s. Accuracies are of the order of ±1 c./s. for δ, and ±0.3 c./s. for J.

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[8] Nuclear magnetic resonance (n.m.r.) spectra were determined with deuteriochloroform solutions containing tetramethylsilane as an internal reference. Measurements were taken on Varian-A-60 or HR-60 spectrometers, all spectra from the former being calibrated, *via* a reference sample, against the higher resolution instrument. The latter was equipped for calibration by the standard side-band technique. A. D. C. thanks Prof. A. Sandoval and the Universidad Nacional Autónoma de México for time on the A-60 instrument.

[9] These two compounds were kindly supplied by Dr. H. Herzog of the Schering Corporation to whom we express our thanks.

[10] Strong coupling occurs also between the 17α-F and 21-protons in these two compounds.

[11] Reported by P. A. Diassi, J. Fried, R. M. Palmere and P. A. Principe at the International Congress on Hormonal Steroids, Milan, May, 1962.

[12] L. H. Knox, S. Berger, D. Cuadriello, E. Velarde and A. D. Cross, *Tetrahedron Letters*, submitted for publication.

[13] Strong coupling of 18-H or 19-H with β-fluorine through four σ bonds is expected to occur, though so far no examples have been available for study.

[14] This expression is derived solely by examination of our experimental findings. No mathematical analysis has been attempted. We are indebted to a Referee who suggested the possibility of such an empirical relation.

[15] From this relation it is possible to predict that coupling may be observable between 18-H and 15β-F, 19-H and 2β-F and 4β-F, but not 19-H and 7β-F. *Both* 18- and 19- angular methyl proton absorptions may be split by either the 11β-F or 8β-F. Except for the possibility that 1α-F and 14α-F substituents may couple with 19-H and 18-H, respectively, no strong coupling of other α-fluorines with these protons is expected. When the number of bounds separating the fluorine and angular methyl protons is large (*e.g.*, 10β-F steroids) coupling may be so small as to be unobservable, even though steric requirements are met.

[16] C. H. Robinson, N. F. Bruce, E. P. Oliveto, S. Tolksdorf, M. Steinberg and P. L. Perlman, *J. Am. Chem. Soc.*, **82**, 5256 (1960).

[17] P. Crabbé, M. J. Durazo and A. Bowers, manuscript in preparation.

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THE CONFORMATION OF *cis,cis*-MUCONIC ACID

Sir:

As part of a research program[1] on the solid-state photochemistry of unsaturated acids and the dependence of the reaction on the crystal structure of the reacting species we are investigating the behavior toward ultraviolet of solid *cis,cis*- and *trans,trans*-muconic acids. The crystallographic constants of the two acids are: *cis*-isomer: a = 9.55 Å., b = 8.89 Å., c = 3.84 Å., β = 99.9°; space group $P2_1/a$; n = 2; d_{calcd} = 1.48 g./cm.^{3}; molecular symmetry $\bar{1}$. *trans*-isomer: a = 6.98 Å., b = 3.76 Å., c = 7.01 Å., α = 123.2°, β = 88.5°, γ = 101.7°; space group $P\bar{1}$ (or P1); n = 1; d_{calcd} = 1.38 g./cm.^{3}; molecular symmetry $\bar{1}$ (or 1).

In keeping with our results on other systems that parallel contact of >C=C< groups of 4 Å. or less permits photochemical reaction,[1] we find that both acids are light sensitive; the products of their photo-reactions are currently being investigated.

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[1] See, *e.g.*, Sadeh and Schmidt, *J. Am. Chem. Soc.*, **84**, in press.