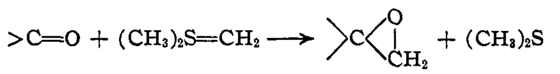
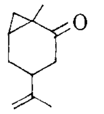
cause of the marked thermal instability of II. In contrast to the oxosulfonium ylide I which can be stored in tetrahydrofuran solution (under nitrogen) for several days at 25° without appreciable decomposition, the sulfonium ylide II decomposes with a half life of a few minutes at room temperature.[5] At 0° or below the stability of II is much greater, and since the process of ylide formation appears to be instantaneous, it is possible to conduct subsequent reactions without significant loss of the reagent by the immediate addition of the appropriate substrate with continued cooling.

The ylide II reacts with a wide variety of aldehydes and ketones by overall methylene transfer to form oxiranes, a process observed previously in many instances with the oxosulfonium ylide I. After a standard reaction time of 10 minutes at 0° and 30–60 minutes for warming to room temperature, the carbonyl compounds studied were consumed completely using 1.1 to 1.2 equivalents of ylide. Thus several compounds were converted to the corresponding oxiranes by selective addition of methylene to the carbonyl group: benzophenone

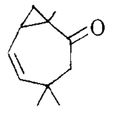


$$>C{=}O + (CH_3)_2S{=}CH_2 \longrightarrow >C\overset{O}{\underset{CH_2}{|}} + (CH_3)_2S$$

(84% yield), benzaldehyde (75%), cycloheptanone (97%), carvone (89%), eucarvone (93%), benzalacetophenone (87%) and pulegone (90%).[6] The only case studied in which the ketone→epoxide conversion was not observed with II was desoxybenzoin (enolate formation). However, an important difference between I and II can be discerned, *viz.*, that the sulfonium ylide selectively affords oxiranes even in the case of α,β-unsaturated carbonyl compounds which behave as Michael receptors with the oxosulfonium ylide. Thus, in contrast with the above results these ketones interact with I to form cyclopropanes: benzalacetophenone (95%),[1] carvone (81% to III) and eucarvone (88% to IV).[7]



III



IV

As expected from relative stabilities of I and II and from data on rates of base-catalyzed hydrogen–deuterium exchange for the corresponding conjugate acids,[8,9] the sulfonium ylide is a far more powerful methylene transfer agent than the oxosulfonium ylide. Thus, the reaction of 5 equivalents of II with 1,1-diphenylethylene effects 60% conversion to 1,1-diphenylcyclopropane, whereas there is no methylene transfer from I under the same conditions. Neither ylide reacts with tolane or *trans*-stilbene. The sulfonium ylide II converts benzalaniline to 1,2-diphenylazirane readily (91% yield) at low temperatures; the oxosulfonium ylide I reacts more slowly and gives a mixture of 1,2-diphenylazirane and acetophenone anil (ratio *ca.* 2:1).

The extension of this investigation to the transfer of substituted methylenes will be discussed in subsequent publications. It is already apparent that this approach presents new opportunities in organic synthesis because of the variegated uses of oxiranes and the many different sulfonium ylides potentially available; the complementary relationship to other reagents for methylene transfer[1,10,11,12] is clear.

This work was supported generously by a grant from the National Institutes of Health.

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[5] This interesting decomposition, which proceeds with the copious evolution of ethylene, will be described in greater detail in due course.

[6] Acceptable elemental analyses have been obtained for all new compounds reported herein along with sufficient physical data (infrared, ultraviolet and nuclear magnetic resonance spectra) to define structure. Previously known compounds were identified by comparison with authentic material.

[7] It is of note that the hydrogenation of IV with palladium-charcoal in methanol produces both 2,2,6,6-tetramethylcycloheptanone and 3,3,8-trimethylcyclooctanone (ratio 3:1).

[8] S. G. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958).

[9] W. von E. Doering and A. K. Hoffman, *J. Am. Chem. Soc.*, **77**, 521 (1955).

[10] H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959).

[11] U. Schöllkopf and A. Lerch, *Angew. Chem.*, **73**, 27 (1961).

[12] *Cf.* also W. Kirmse, *ibid.*, **73**, 161 (1961).

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RECEIVED AUGUST 31, 1962

INTRAMOLECULAR BIFUNCTIONAL CATALYSIS OF AMIDE HYDROLYSIS

Sir:

In a previous communication from this laboratory[1] it was shown that a phenyl ester is highly activated if it is placed between two carboxyl groups, one of which is ionized. With an ester of this type the solvolysis rate has the bell-shaped pH dependence characteristic of many enzyme catalyzed reactions, and is a maximum at a pH corresponding to the maximum concentration of the singly ionized species. We have now demonstrated a similar effect with compound I whose pH-reactivity profile is shown in Fig. 1.

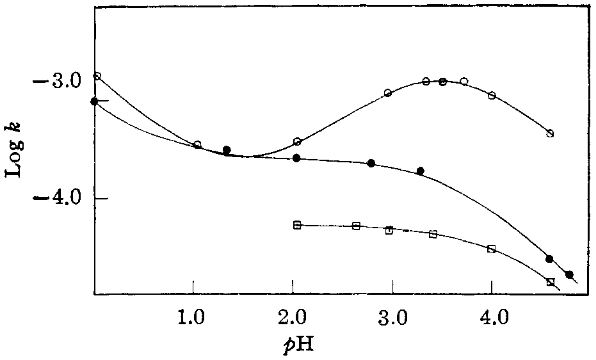

Fig. 1.—Hydrolysis of (I), *o*-carboxyphthalanilic acid, ⊙; (II), phthalanilic acid, ●; and (IV), *p*-carboxyphthalanilic acid, ⊡; at 25.8°; full drawn lines calculated using the constants in Table I.

It may be shown that the change of the *pseudo-first* order rate constant with hydrogen ion activity a_H should be given by

$$k_{obs} = \frac{(k_1K_1 + k_2K_2)a_H + k_3(a_H)^2}{(a_H + K_1)(a_H + K_2)} + k_4a_H \quad (1)$$

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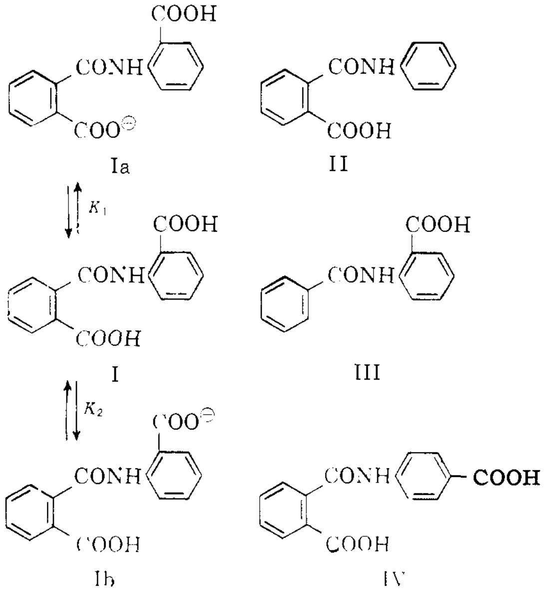
[1] H. Morawetz and I. Oreskes, *J. Am. Chem. Soc.*, **80**, 2591 (1958).

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 II I III Ib 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.

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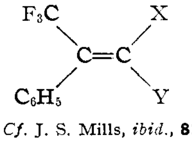
[1] (a) Steroids. CCXXV, J. S. Matthews, *Anal. Chem.*, in press; (b) Part III, A. D. Cross, *J. Am. Chem. Soc.*, **84**, 3206 (1962).

[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.