

and washed with ether. The salt thus obtained was recrystallized from boiling absolute ethanol containing a small amount of dry hydrogen chloride. The solution was finally cooled and filtered and the product washed with ether and dried at 110°.

*Method (B).* Ten grams (0.059 mole) of 1-methyl-4-chloropyrazolo[3,4-*d*]pyrimidine<sup>4</sup> was added to twice the molar amount (0.119 mole) of the amine dissolved in 150 ml. of absolute ethanol. The solution was heated on the steam bath until the volume had been reduced to approximately 50 ml. (6 hr.). The desired 1-methyl-4-(substituted amino)pyrazolo[3,4-*d*]pyrimidine crystallized upon cooling. The compound was further purified by recrystallization from ethanol.

*General method of preparation of 4-(Substituted amino)pyrazolo[3,4-*d*]pyrimidines listed in Table II. Method (A).* Eight grams of 4-chloropyrazolo[3,4-*d*]pyrimidine<sup>3</sup> (0.053 mole) was added to an equal molar amount of a solution of the amine dissolved in 200 ml. of absolute ethanol. The mixture was heated on the steam bath for 2 hr., boiled with charcoal for 5 min., and filtered. Dry hydrogen chloride was passed into the cooled filtrate for 20 min. and the solution allowed to stand overnight and finally filtered. The crude product was washed with ether and recrystallized from boiling absolute ethanol which contained a small amount of dry hydrogen chloride. The hydrochloride salt was filtered, washed with dry ether, and dried at 110°.

*Method (B).* Eight grams (0.053 mole) of 4-chloropyrazolo[3,4-*d*]pyrimidine<sup>3</sup> was added to twice the molar amount (0.106 mole) of the amine, and the ethanolic solution was reduced to 50 ml. by heating on the steam bath. Then 100 ml. of distilled water was added and the solution cooled. The crude product was filtered and purified by recrystallization from a methanol-water solution.

*Method (C).* This method was the same as Method B except that the ethanolic reaction mixture was heated for 2 hr. on the steam bath and then allowed to cool. The product either crystallized during the reaction period or appeared on cooling the solution overnight. The product was filtered and recrystallized from ethanol.

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## The $S_N2$ Reactivity of $\beta$ -Fluoroethyl Iodides<sup>1</sup>

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It has been shown earlier that  $\beta$ -fluorine, chlorine, and bromine substituents all decrease  $S_N2$  reactivity,<sup>2</sup> at least in the reactions of ethyl bromides with sodium thiophenoxide in methanol.<sup>3</sup> We have now studied the effect of one, two, and three  $\beta$ -fluorine substituents on the reactivity of ethyl iodide under the same conditions.

(1) Part VIII in the series "The Effect of Halogen Atoms on the Reactivity of Other Halogen Atoms in the Same Molecule." This work was supported in part by the U. S. Atomic Energy Commission.

(2) For the meaning of the term  $S_N2$ , see J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1956, chap. 5.

(3) J. Hine and W. H. Brader, Jr., *J. Am. Chem. Soc.*, **75**, 3964 (1953).

## EXPERIMENTAL

*Reagents.* Reagent ethyl iodide (Matheson,  $n_D^{25}$  1.5098) was used as received while the 1,1-difluoro-2-iodoethane and 1,1,1-trifluoro-2-iodoethane purchased were fractionally distilled. Each of the latter compounds had been made by the Columbia Organic Chemicals Co., Columbia, S. C., by the action of sodium iodide on the appropriate *p*-toluenesulfonate.<sup>4</sup> For the difluoroethyl iodide, we found b.p. 86.8–87.1° (740 mm.),  $n_D^{25}$  1.4577,  $d_4^{25}$  2.1840, in comparison with previous reports of b.p. 89.5°,  $n_D^{25}$  1.46807,<sup>5</sup>  $d_4^{25}$  2.24328,<sup>5</sup>  $d_4^{25}$  2.2259.<sup>6</sup> For the trifluoroethyl iodide, b.p. 53.5–54.0° (732 mm.),  $n_D^{25}$  1.3981 (reported,<sup>4</sup> b.p. 55.0°,  $n_D^{25}$  1.3981).

The 2-fluoroethyl iodide used was prepared from 2-fluoroethyl bromide<sup>7</sup> by the action of sodium iodide in acetone. A solution of 30.6 g. (0.24 mole) of 1-bromo-2-fluoroethane and 40 g. (0.29 mole) of sodium iodide in 200 ml. of acetone was refluxed for 4 hr. and then most of the acetone was removed by fractional distillation. When the residue was cool, 60 ml. of water was added, the two resultant layers were separated, and the aqueous layer was extracted with methylene chloride. This extract was combined with the organic layer and fractionated to give 2.6 g., b.p. 94.5–96.5°, 29.6 g., b.p. 96.5–97.0°, and after the addition of a still base (bromobenzene), 6.4 g., b.p. 95.8–96.5° (all at 741 mm.). The total yield was thus 92% and for the middle fraction,  $n_D^{25}$  1.5010,  $d_4^{25}$  2.136, molar refractivity<sup>8</sup> calcd. 24.24, found 24.00. Henne and Renoll report that 1-fluoro-2-iodoethane boils at 98–102° but give no other properties.<sup>10</sup>

The methanol and thiophenol used and the methods of preparing sodium thiophenoxide solutions and titrating for thiophenol have been described previously.<sup>3</sup>

*Kinetic runs.* The kinetic runs were carried out as described previously<sup>3,11</sup> except that unpainted long-necked Erlenmeyer flasks were used as reaction vessels, 5 ml. of acetic acid was added to stop the reaction and the thiophenol was then titrated in the reaction flask.

*Reaction products.* Some of the residual solutions from the reaction of trifluoroethyl iodide with sodium thiophenoxide were combined and the methanol removed by heating to 90°. The remaining material was then added to 20 ml. of water and 30 ml. of ether. The ether was evaporated and the residue fractionally distilled in vacuum giving principally a colorless liquid, b.p. 62–63° (5.5 mm.),  $n_D^{20}$  1.4906,  $d_4^{20}$  1.2582, molar refractivity<sup>8</sup> calcd. for  $C_6H_5SCH_2CF_3$  43.47, found 44.21. Analogous treatment of residues from the difluoroethyl iodide reaction gave a product, b.p. 87–89° (7 mm.),  $n_D^{20}$  1.5350,  $d_4^{20}$  1.1977, molar refractivity<sup>8</sup> calcd. for  $C_6H_5SCH_2CHF_2$  43.47, found 45.28.

*Calculations.* Rate constants were calculated for each point by use of the integrated form of the second order rate equation

$$k = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$$

where  $a = [RI]_0$ ,  $b = [C_6H_5SNa]_0$ ,  $x = b - [C_6H_5SNa]_t$ ,  $t$  = time (sec.). This equation is derived with the assumption that only one halogen atom (the iodine) is replaced, in

(4) G. V. D. Tiers, H. A. Brown, and T. S. Reid, *J. Am. Chem. Soc.*, **75**, 5978 (1953).

(5) F. Swarts, *Bull. Acad. roy. Belg.*, 383 (1901); *Chem. Zentr.*, II, 804 (1901).

(6) V. Desreux, *Bull. Soc. chim. Belg.*, **44**, 249 (1935).

(7) F. W. Hoffmann, *J. Org. Chem.*, **14**, 105 (1949).

(8) The atomic refraction constant for fluorine varies from 0.95 to 1.24.<sup>9</sup> We have used an average value, 1.10.

(9) Cf. A. V. Grosse and G. H. Cady, *Ind. Eng. Chem.*, **39**, 367 (1947).

(10) A. L. Henne and M. W. Renoll, *J. Am. Chem. Soc.*, **58**, 889 (1936).

(11) J. Hine, S. J. Ehrenson, and W. H. Brader, *J. Am. Chem. Soc.*, **78**, 2282 (1956).

agreement with earlier observations<sup>3</sup> and the known unreactivity of alkyl fluorides. Data on a typical run are shown in Table I and in Table II are summarized all of the rate constants and average deviations obtained and also the heats and entropies of activation calculated from the equation.<sup>12</sup>

$$k = \frac{kT}{h} e^{-\frac{\Delta H^\ddagger}{RT}} e^{-\frac{\Delta S^\ddagger}{R}}$$

The deviations listed on the  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  values are those obtained by using the lower temperature rate constant plus its average deviation and the higher temperature rate constant minus its average deviation.

TABLE I

REACTION OF 2,2,2-TRIFLUOROETHYL IODIDE WITH SODIUM THIOPHENOXIDE IN METHANOL AT 40.0°<sup>a</sup>

Time, Sec.	Iodine, <sup>b</sup> 0.05078M, Ml.	10 <sup>3</sup> k, L. Mole <sup>-1</sup> Sec. <sup>-1</sup>
0	17.53	
56,580	16.41	1.63
141,480	14.85	1.70
249,660	13.15	1.75
357,360	12.06	1.65
487,440	10.68	1.68
665,820	9.12	1.72
859,920	8.02	1.68
1,178,580	6.51	1.66
		Av. 1.68 ± 0.03

<sup>a</sup> [CF<sub>3</sub>CH<sub>2</sub>I]<sub>0</sub> = 0.07358M. <sup>b</sup> Per 30.39 ml. sample.

TABLE II

KINETIC DATA FOR REACTIONS WITH SODIUM THIOPHENOXIDE IN METHANOL

	10 <sup>3</sup> k (L. Mole <sup>-1</sup> Sec. <sup>-1</sup> )			$\Delta H^\ddagger$ , Kcal./Mole	$\Delta S^\ddagger$ , E.U.
	0°	20°	40°		
CH <sub>3</sub> CH <sub>2</sub> I	408 ± 5	2600 ± 30		14.2 ± 0.2	-16.5 ± 0.8
FCH <sub>2</sub> CH <sub>2</sub> I	15.1 ± 0.1	166 ± 2		18.5 ± 0.2	-8.0 ± 0.6
F <sub>2</sub> CHCH <sub>2</sub> I	611 ± 6 <sup>a</sup>	7.34 <sup>b</sup>	77.0 ± 0.4	20.8 ± 0.2	-6.4 ± 0.5
F <sub>3</sub> CCH <sub>2</sub> I	14.0 ± 0.2 <sup>a</sup>	0.149 <sup>b</sup>	1.67 ± 0.03	21.4 ± 0.4	-12.1 ± 1.2

<sup>a</sup> At 60°. <sup>b</sup> Extrapolated from data at 40° and 60°.

## RESULTS AND DISCUSSION

Table II shows that the continued introduction of  $\beta$ -fluorine atoms causes a continued decrease in S<sub>N</sub>2 reactivity. In Fig. 1 a plot of log  $k/k_0$  (where  $k$  is the rate constant for the compound in question and  $k_0$  is that for the unsubstituted ethyl halide) vs. the number of  $\beta$ -fluorine substituents does not deviate greatly from linearity. The deactivating influence of the fluorine atoms may be practically entirely polar with the observed curvature of the plot being due to a saturation effect.<sup>13</sup> It seems more probable that the curvature is due more to a steric effect, however. Since steric effects tend to increase quite sharply with increasing crowding once they have become at all important, the curvature shown by the plot for the fluorine compounds seems too small to arise from a major steric effect. For pur-

(12) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N.Y., 1941, p. 14.

(13) Cf. J. Hine, N. W. Burske, M. Hine, and P. B. Langford, *J. Am. Chem. Soc.*, **79**, 1406 (1957).

poses of comparison, a plot of the data on the reactivity of increasingly  $\beta$ -methylated ethyl bromides toward iodide ion at 25°<sup>14</sup> is also given in Fig. 1. The influence of the three  $\beta$ -methyl groups of neopentyl halides is rather generally agreed to be steric in character<sup>15,16</sup> and is seen in the Figure to be only slightly larger than that of three  $\beta$ -fluorine atoms. The curvature of the line for the  $\beta$ -methyl compounds is far more pronounced than that for the fluoro compounds. It thus seems likely that the effect of the fluoro atoms is largely polar. This conclusion is supported by the fact that fluorine atoms are nearer in size to hydrogen atoms than to methyl groups. The covalent radius plus the van der Waals radius for hydrogen, fluorine, and methyl are 1.50, 1.99, and 2.77 Å., respectively.<sup>17</sup> The steric effect of  $\beta$ -fluorine should therefore be far less than half that of  $\beta$ -methyl. According to Ingold and coworkers the deactivating influence of  $\alpha$ -methyl groups (compared to  $\alpha$ -hydrogen) is partly steric and partly polar.<sup>16</sup> We believe that the data on the S<sub>N</sub>2 reactivity of alkyl halides is explained more simply by the assumption that electron-donating groups increase and electron-withdrawing groups decrease S<sub>N</sub>2 reactivity. This explains the present and earlier<sup>3</sup> data on the effect of  $\beta$ -halogen substituents and helps explain the effect

of  $\alpha$ -halogen substituents.<sup>18</sup> It has been pointed out previously that no complete explanation has been given for the available data on S<sub>N</sub>2 reactivities.<sup>19</sup> The generalizations that correctly predict one set of data seem to fail when applied to another. The data remaining unexplained usually include some of the following: Some S<sub>N</sub>2 reactions of benzyl halides are speeded by both electron-withdrawing and electron-donating substituents.<sup>19</sup> The reactivity of  $\beta$ -

(14) L. Fowden, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 3187 (1955).

(15) P. D. Bartlett and L. J. Rosen, *J. Am. Chem. Soc.*, **64**, 543 (1942).

(16) I. Dostrovsky, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 173 (1946); P. B. D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold, and J. D. H. Mackie, *J. Chem. Soc.*, 3200 (1955).

(17) L. Pauling, *Nature of the Chemical Bond*, 2nd ed., Cornell University Press, Ithaca, New York, 1945, pp. 164, 189.

(18) J. Hine, C. H. Thomas, and S. J. Ehrenson, *J. Am. Chem. Soc.*, **77**, 3886 (1955); J. Hine, S. J. Ehrenson, and W. H. Brader, Jr., **78**, 2282 (1956).

(19) Ref. 2, sec. 6-3b.

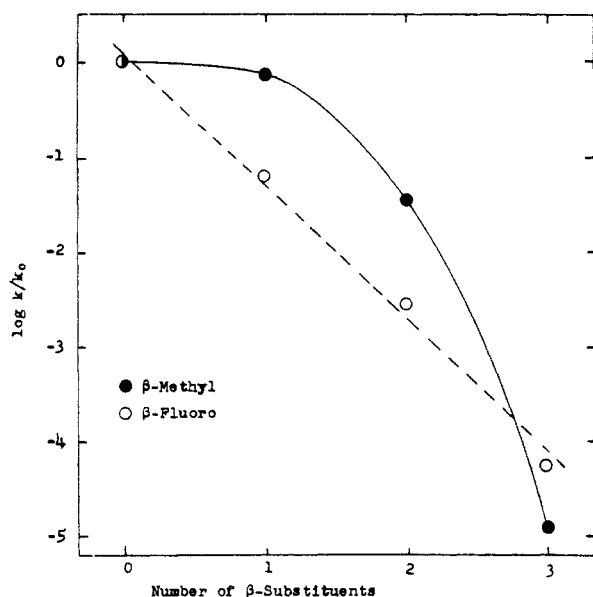


Fig. 1. Plot of  $\log(k/k_0)$  for  $S_N2$  reactions of ethyl iodides vs. the number of  $\beta$ -fluorine or  $\beta$ -methyl substituents

phenylethyl chlorides toward iodide in acetone is increased by both *p*-methoxy and *p*-nitro groups.<sup>19</sup> Both  $\alpha$ - and  $\beta$ -halogen substituents decrease  $S_N2$  reactivity to an extent that is proportional to neither their polar nor steric factors alone.<sup>19</sup>  $\alpha$ -Haloketones (and also  $\gamma$ -chlorobutyrophenone<sup>20</sup>) are quite reactive.<sup>19</sup> In the  $\beta$ -position alkoxy groups deactivate and in the  $\alpha$ -position they activate.<sup>19,21</sup> Benzyl and allyl halides are often more reactive than the corresponding methyl halides.<sup>19</sup>

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(21) P. Ballinger, P. B. D. de la Mare, G. Kohnstam, and B. M. Prestt, *J. Chem. Soc.*, 3641 (1955).

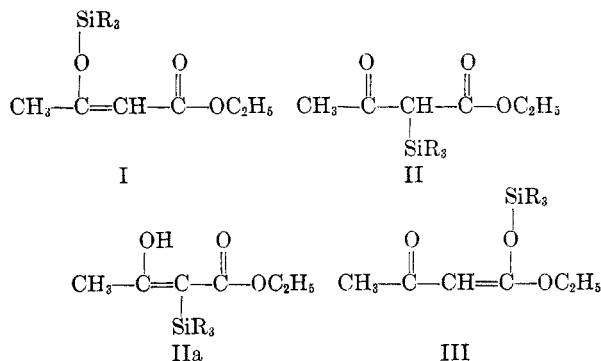
### Structures of Silyl Derivatives of Ethyl Acetoacetate

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The triethylsilyl derivative of ethylacetoacetate was first prepared in 1946 by Gilman and Clark.<sup>1</sup> On the basis of chemical reactions these workers proposed a structure of the type I below with the triethylsilyl group attached to the oxygen of the carbonyl group. However, others have pointed out that the chemical reactions shown by the substance might also be observed if the compound had the C-

(1) H. Gilman and R. N. Clark, *J. Am. Chem. Soc.*, **69**, 967 (1947).



silylated structure of type II<sup>2</sup>; and recently Hurwitz, de Benneville, and Yoncoskie have obtained the trimethylsilyl derivative of ethylacetoacetate and implied that it has the type II structure.<sup>3</sup>

We have prepared the trimethylsilyl and dimethylsilyl derivatives of ethylacetoacetate, and determined their infrared spectra in the sodium chloride region. These spectra are very similar. In the 1500–1800  $\text{cm}^{-1}$  region, the trimethylsilyl compound has strong bands at 1714 and 1630  $\text{cm}^{-1}$ , while in the dimethylsilyl derivative these bands appear at 1712 and 1630  $\text{cm}^{-1}$ . The higher frequency band is in the right range either for a *conjugated* ester or for a *nonconjugated* ketone carbonyl absorption.<sup>4</sup> The 1630  $\text{cm}^{-1}$  band, as in our earlier work with silyl acetylacetonates,<sup>5</sup> is attributed to carbon-carbon double bond absorption, with its position shifted and intensified by conjugation and by substitution with an electronegative (siloxy) group.<sup>6</sup> The C-silylated structure II for these compounds should show only nonconjugated ketone and ester carbonyl absorption, and hence can be eliminated from consideration. It is true that the enol form of the C-silylated structure, IIa, would have absorption in the 1500–1800  $\text{cm}^{-1}$  region similar to that observed; but this structure can be eliminated since the compounds in question do not contain a hydroxylic hydrogen atom. The alternate O-silylated structure III contains a conjugated ketonic carbonyl group, and therefore should absorb near 1670  $\text{cm}^{-1}$  as enol ethers of acetylacetonate do.<sup>5</sup> Thus, the only structure compatible both with physical and chemical properties and with the observed infrared spectra is the  $\beta$ -silyloxyacetate structure I originally proposed by Gilman. An O-silylated structure is further substantiated by the fact that the compounds have strong bands near 1000  $\text{cm}^{-1}$ , attributable to Si—O vibrations.

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