[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE GEORGIA INSTITUTE OF TECHNOLOGY]

The Effect of Halogen Atoms on the Reactivity of Other Halogen Atoms in the Same Molecule. V. The SN2 Reactivity of Methylene Halides[1]

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RECEIVED NOVEMBER 2, 1954

The effect of the various halogens as α-substituents, on reactivity by the SN2 mechanism, has been studied by determining the rate constants for the reactions of FCH_2Br, $ClCH_2Br$, CH_2Br_2, C_2H_5Br, CH_2Cl_2 and ICH_2Cl with sodium iodide in acetone and also for the reaction of each of these halides, in addition to CH_2I_2, CH_3I and CH_3Br, with sodium methoxide in methanol. It is found that the SN2 reactivity of the halides studied varies with the nature of the α-substituent as follows: H > F > Cl > I, Br.

Introduction

There are a number of reports which show that the ease of displacement of a halogen atom in an alkyl halide by the bimolecular nucleophilic substitution (SN2)[2] mechanism may be decreased by the replacement of an α-hydrogen atom by another halogen atom. Petrenko-Kritschenko and coworkers have studied the reactivity of a number of organic polyhalides toward several reagents.[3] They have determined the extent of reaction after a given time under a given set of conditions but, in general, have not determined the kinetic form of the reaction nor its rate constant. Products were isolated in very few cases and many of the reactions were heterogeneous. In a number of cases, however, reactions were carried out in a homogeneous medium and many of these probably proceeded by the SN2 mechanism. Some of the nucleophilic reagents were potassium hydroxide, sodium ethoxide, piperidine and potassium thiocyanate. Most of the following pairs of compounds were tested toward several of these reagents and in each case relative reactivities were found as shown: $CH_3X > CH_2X_2$ (X = Cl, Br, I); $XCH_2CO_2H > X_2CHCO_2H$ (X = Cl, Br); $C_6H_5CH_2Cl > C_6H_5CHCl_2$; $CH_3CH_2X > CH_3CHX_2$ (X = Cl, Br, I). The reactivities of haloforms and carbon tetrahalides have been omitted since these probably do not react by the SN2 mechanism.[4] Backer and van Mels[5] have reported several instances in which α,α-dihalocarboxylic acid anions are less reactive toward potassium sulfite than are the corresponding monohalides. Toward the same nucleophilic reagent, potassium chlorobromoacetate was found to be more reactive than potassium dibromoacetate, showing that α-bromine atoms decrease SN2 reactivity more than α-chlorine atoms in this case.[5] Davies, Evans and Hulbert found that toward trimethylamine in 90% acetone, methylene chloride is only about one-fifth as reactive as ethyl chloride but more than twice as reactive as ethylene chloride (all at 55°) and methylene bromide is slightly less reactive than ethylene bromide and only about one-tenth as reactive as trimethylene bromide (all at 35°).[6] McKay reported that methylene iodide is about one-tenth as reactive as ethyl iodide toward radioactive iodide ions in ethanol at 60°.[7]

Except for the work of Backer and van Mels on chlorobromoacetic acid and dibromoacetic acid no data appear to exist permitting a direct comparison of the relative effects of the various halogens, as α-substituents, on SN2 reactivity (although some indirect comparisons may be made). In fact, no kinetic study at all appears to have been made on any compound with an α-fluorine as a substituent. Since the halogen substituents, being monatomic, are relatively simple (*e.g.*, many of the complexities due to internal rotation and its hindrance are absent) and since they have received considerable study in physical organic chemistry, both as substituents and otherwise, we felt it desirable to carry out such an investigation.

We have studied the effect of α-halogen substituents by investigating methylene halides since the SN2 reactivity of these compounds is greater than that of most available geminal dihalides and since competing olefin-forming elimination reactions and reactions by the SN1 (carbonium ion) mechanism[2] are very unlikely. We have studied the reactions with iodide ion in acetone, a reagent whose reactivity toward a wide variety of alkyl halides has been examined. To get some idea of the extent to which the relative reactivities of the methylene halides may vary with the nucleophilic reagent and solvent used, we have also studied the reaction with sodium methoxide in methanol.

Experimental

Apparatus.—The measurement and control of temperature was carried out as described previously.[8]

Materials.—All of the organic halides used, except methyl bromide, were fractionated under nitrogen (CH_2I_2 and $BrCH_2I$ at reduced pressure) before use. Matheson C.P. methyl bromide was used from the cylinder without further purification. Chloroiodomethane and bromoiodomethane were prepared from methylene chloride and bromide by the action of sodium iodide in acetone. Fluorobromomethane was prepared from silver fluoroacetate and bromine by the method of Haszeldine.[9] The other halides were the best grades available commercially.

Acetone was dried over calcium oxide and potassium per-

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[1] For part IV of this series see J. Hine and W. H. Brader, Jr., THIS JOURNAL, **77**, 361 (1955).

[2] For the significance of the terms SN2 and SN1 see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chap. VII.

[3] P. Petrenko-Kritschenko, D. Talmud, B. Talmud, W. Butmy-de-Katzman and A. Gandelman, *Z. physik. Chem.*, **116**, 313 (1925); P. Petrenko-Kritschenko and V. Opotsky, *Ber.*, **59B**, 2131 (1926); P. Petrenko-Kritschenko, A. Rawikowitsch, V. Opotsky, E. Putjata and M. Diakowa, *ibid.*, **61B**, 845 (1928); P. Petrenko-Kritschenko, V. Opotsky, M. Diakowa and A. Losowog, *ibid.*, **62B**, 581 (1929).

[4] J. Hine, THIS JOURNAL, **72**, 2438 (1950); J. Hine and A. M. Dowell, Jr., *ibid.*, **76**, 2688 (1954).

[5] H. J. Backer and W. H. van Mels, *Rec. trav. chim.*, **49**, 177 (1930).

[6] W. C. Davies, E. B. Evans and F. L. Hulbert, *J. Chem. Soc.*, 412 (1939).

[7] H. A. C. McKay, THIS JOURNAL, **65**, 702 (1943).

[8] J. Hine and W. H. Brader, Jr., *ibid.*, **75**, 3964 (1953).

[9] R. N. Haszeldine, *J. Chem. Soc.*, 4259 (1952).

manganate by the method of Conant and Kirner[10] although it was known that the material obtained thus is about 0.15 *M* in water.[11] The drying method is evidently reasonably reproducible since we were able to obtain the same rate constants with different batches of solvent. Furthermore, since other workers have also used acetone containing about this much water, our data may be compared with theirs better than if we had used more completely anhydrous material, which is also rather difficult to work with because of its hygroscopic character. Methanol was dried with magnesium by the method described by Fieser.[12] The sodium iodide and potassium iodate were reagent grade chemicals vacuum dried at 100°. Carbonate-free sodium hydroxide solutions were used in titrations.

Kinetic Runs.—Runs near the boiling point of the solvent or halide being used were made by sealing a thin-walled ampoule containing a weighed amount of the organic halide, a few glass beads, and a known volume of a standard solution of the nucleophilic reagent into a small glass tube. This tube was allowed to reach thermal equilibrium in the constant temperature bath and was then shaken to break the ampoule and start the reaction. The reaction with iodide in acetone was stopped by breaking the sealed tube into ice-cold hydrochloric acid, and the unreacted iodide ion was titrated with potassium iodate.[10,13] In this titration the iodide is first oxidized to iodine and then to iodine chloride. The end-point is the disappearance of iodine from the few milliliters of carbon tetrachloride used as an indicator. Since Senior, Hetrick and Miller have reported that acetone interferes with the end-point when chloroform is used as an indicator,[14] we have made tests and have shown that this is not the case when carbon tetrachloride is used. The reaction with sodium methoxide in methanol was stopped by breaking the tube into a known volume (excess) of standard hydrochloric acid and back-titrating to the rosolic acid end-point, except in the case of fluorobromomethane where the reaction mixture was added to 5 ml. of methanol at −80° and the unreacted sodium methoxide titrated to the brom phenol blue end-point with methanolic *p*-toluenesulfonic acid.

TABLE I

REACTION OF $ClCH_2Br$ WITH NaI IN ACETONE AT 20.3°

$[ClCH_2Br]_0 = 0.286\ M$, $[NaI]_0 = 0.0385\ M$.

Time, sec.	$[NaI]_t$	10^5k, l. mole^{-1} sec.$^{-1}$	Time, sec.	$[NaI]_t$	10^5k, l. mole^{-1} sec.$^{-1}$
0	0.0385	..	22,680	0.0238	7.63
3,840	.0356	7.17	34,260	.0196	7.16
10,560	.0312	7.06	81,600	.0076	7.47
15,180	.0281	7.40		Av.	7.32 ± 0.19

Reactions at lower temperatures were carried out in volumetric flasks, samples being withdrawn by pipet at various times.

All of the iodide-containing reaction mixtures were protected from the light by the use of opaque or "low-actinic" reaction vessels and/or a constant temperature water-bath to which a large amount of black ink had been added. Most of these reactions were also carried out under nitrogen.

Results

For the reactions with sodium iodide in acetone, rate constants were calculated from the integrated second-order rate equation

$$k = \frac{2.303}{t(a - b)} \log \frac{b(a - x)}{a(b - x)} \qquad (1)$$

where $a = [RX]_0$, $b = [NaI]_0$, $x = \Delta[RX]_t$, and t = time (sec.). In these reactions only the replacement of the first halogen atom was studied, the organic halide being used in excess. The calculated rate constants showed no marked trend as the reaction proceeded, except in the cases of ethyl bromide and bromoiodomethane. The data from a typical run may be seen in Table I. The average values (and average deviations) of the rate constants for all except the two compounds mentioned are listed in Table II. The rate constants for methylene bromide and chloride have been divided by two to obtain the rate constants per bromine or chlorine. In addition to our data, those of Evans and Hamann[15] on methyl bromide has been included for the purpose of comparison. Also listed are heats and entropies of activation calculated from the absolute rate equation[16]

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

TABLE II

KINETIC CONSTANTS FOR REACTIONS WITH IODIDE ION IN ACETONE

Halide	10^5k(l. mole^{-1} sec.$^{-1}$) 20.3°	36°	50°	$\Delta H^{\ddagger}$, kcal.	$\Delta S^{\ddagger}$, e.u.
CH_3Br[a]	22,900[b]	276[c]		15.9 ± 1.0	−7.2 ± 3
CH_3CH_2Br	120 ± 20[d]	14 ± 2[d,e]	1700 ± 200[d]	16.4 ± 2.0	−16.0 ± 6
FCH_2Br	64 ± 10		1350 ± 18	18.8 ± 1.2	−9.1 ± 4
$ClCH_2Br$	7.32 ± 0.19	47.3 ± 0.5	218 ± 5	20.9 ± 0.5	−6.2 ± 2
$BrCH_2Br$[f]	2.03 ± 0.08	16.0 ± 0.4	69 ± 1	21.7 ± 1.2	−6.0 ± 4
ICH_2Br	5 ± 0.6[d]		100 ± 20[d]	18.4 ± 2.5	−15.5 ± 7
$ClCH_2Cl$[f]		0.842 ± 0.02[g]	0.211 ± 0.003	29.0 ± 1.0	+5.0 ± 3
ICH_2Cl			0.155 ± 0.005		

[a] From data of ref. 15c. [b] At 20.0°. [c] At −19.6°. [d] Estimated by extrapolation to zero time. [e] At 0.0°. [f] The observed rate constants have been divided by two to get the rate constants per bromine (or chlorine) shown. [g] At 60.0°.

For ethyl bromide, rate constants calculated from equation 1 fell sharply as the reaction proceeded. Dostrovsky and Hughes made a similar observation for the reaction with both sodium and potassium iodide at 64° and attributed the fall to reversibility.[17] They obtained rate constants for the reaction with lithium iodide at 0 and 20°, but the data for the individual points are not given. The lithium iodide reaction, in which the metal bromide formed does *not* precipitate, was said to be only about 10% complete at equilibrium at 64° under the conditions used. The fall in our rate constants appears to be partly, but not entirely, due to reversibility. We have calculated rate

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[10] J. B. Conant and W. R. Kirner, THIS JOURNAL, **46**, 232 (1924).

[11] A. R. Olson, L. D. Frashier and F. J. Spieth, *J. Phys. Chem.*, **55**, 860 (1951).

[12] L. F. Fieser, "Experiments in Organic Chemistry," Part II, 2nd Ed., D. C. Heath and Co., Boston, Mass., 1941, p. 359.

[13] L. W. Andrews, THIS JOURNAL, **25**, 736 (1903).

[14] K. L. Senior, R. R. Hetrick and J. G. Miller, *ibid.*, **66**, 1987 (1944).

[15] A. G. Evans and S. D. Hamann, *Trans. Faraday Soc.*, **47** 25 (1951).

[16] 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.

[17] I. Dostrovsky and E. D. Hughes, *J. Chem. Soc.*, 161 (1946).

constants by use of an equation derived on the assumption that the reaction was reversible but homogeneous, and another equation which assumed that the sodium bromide precipitated very early in the reaction with its concentration in solution remaining constant thereafter. The fall in these rate constants, especially those calculated from the second equation (whose assumptions are probably nearer the truth), was less than in those calculated from equation 1, but it was still considerable. We have checked the purity of our reagents and used both sodium and potassium iodide. Runs have also been made independently by three different investigators,[18] but we still have found no explanation for our results. The rate constants listed for ethyl bromide in Table II were obtained by extrapolating our data to zero time. The values at 0 and 20° are higher than those of Dostrovsky and Hughes, perhaps because of the greater tendency of lithium iodide to exist as an ion-pair. Our rate constants may be extrapolated to 64° to yield a value in reasonable agreement with the data these workers obtained using sodium and potassium iodide.

The rate constants obtained in the reaction of bromoiodomethane with sodium iodide in acetone also fell as the reaction proceeded. Because of the greater sensitivity of this compound to air and light and the possibility of the reaction of the sodium bromide formed with *both* the organic reactant and product, this case may be more complicated than that of ethyl bromide. Therefore, without studying the reaction in great detail, we obtained rate constants by extrapolation to zero time.

For these rate constants estimated by extrapolation and for the heats and entropies of activation for all of the reactions we have attempted to consider all relevant factors in an estimate of the deviation sufficient to bring the reliability of our data to the 95% probability level. These deviations are listed in Tables II and IV.

Since alkyl bromides have been found to be from 550 to 1500 times as reactive toward iodide ion in acetone as the corresponding alkyl chlorides[19] which are in turn much more reactive than alkyl fluorides,[22] it will be assumed in the cases of FCH_2Br and $ClCH_2Br$ that the reaction is essentially entirely that of the bromine atom. The rate constants listed for ICH_2Cl and ICH_2Br are for the reactions of the chlorine and bromine atoms, respectively, since the replacement of iodine is not experimentally observable in the present case.

In the reaction between sodium methoxide and a methylene halide the primary product should be a halomethyl ether. If the further reaction of this primary product is negligible under the conditions used, rate constants may be calculated from an equation of the type of (1). On the other hand if the primary product is so reactive that no appreciable concentration of it ever accumulates, equation 2 is applicable.

$$k = \frac{2.303}{t(2a - b)} \log \frac{b(a - x)}{a(b - 2x)} \qquad (2)$$

where $a = [CH_2X_2]_0$, $b = [NaOMe]_0$, and $x = \Delta[CH_2X_2]_t$ so that k is expressed in l. (moles of $CH_2X_2)^{-1}$ sec.$^{-1}$ Equation 2 was used for all of the methylene halides except fluorobromomethane. Data on chloroiodomethane, the member of this group for which accumulation of the intermediate would appear to be most likely, are shown in Table III.

TABLE III

REACTION OF $ClCH_2I$ WITH NaOMe IN MeOH AT 50°

Time, sec.	$[ClCH_2I]_t$	$[NaOMe]_t$	10^5k, l. mole^{-1} sec.$^{-1}$
7,740	0.2622	0.2180[a]	4.30
11,940	.2619	.1972[a]	4.57
23,400	.2639	.1524[a]	4.80
33,540	.2628	.1342[a]	4.28
37,140	.2524	.1276[a]	4.42
69,240	.2693	.0739[b]	4.27
81,420	.2743	.0605[b]	4.23
		Av.	4.41 ± 0.16

[a] $[NaOMe]_0$ = 0.2578. [b] $[NaOMe]_0$ = 0.2573.

It was found that when a methanolic fluorobromomethane reaction mixture was added to aqueous acid to stop the reaction and then titrated with aqueous alkali, the end-points slowly drifted. It was further found that rate constants calculated from equation 2 increased with time. Thus it appears that fluorodimethyl ether was accumulating in the reaction mixture and being hydrolyzed when water was added. The reaction was therefore stopped by freezing in cold methanol and was titrated with methanolic acid. The resultant data then gave satisfactory rate constants when an equation of the type of (1) was used. This equation also was used, of course, for the monohalides studied.

Kinetic data for the reactions with sodium methoxide are listed in Table IV. Because of the generally observed greater reactivity of bromides and iodides (compare $ClCH_2I$, $ClCH_2Br$, and CH_2Cl_2 in Table IV), it is assumed that the reaction of FCH_2Br and $ClCH_2Br$ is solely a replacement of the bromine atom while that of $ClCH_2I$ involves only iodine replacement in the rate-controlling step. Although iodides are usually more reactive than the corresponding bromides in nucleophilic displacement reactions at saturated carbon, this is not invariably the case, and indeed one exception may be seen in Table IV (CH_3I and CH_3Br).[23] An estimate of the relative extent to which bromine and iodine atoms are replaced in the initial attack of methoxide ions on $BrCH_2I$ is therefore very difficult especially since we are comparing the reactivity of *bromomethyl* iodide not with that of the corresponding bromide but with *iodomethyl* bromide.

The rate constants for CH_2I_2 and $BrCH_2I$ at 20° drifted downward somewhat, perhaps due to the photolysis and/or oxidation of these rather sensi-

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(18) We are indebted to Dr. W. H. Brader, Jr., for having made several runs using a conductimetric method.

(19) From the data of Table II and refs. 15, 20 and 21.

(20) J. B. Conant, W. R. Kirner and R. E. Hussey, THIS JOURNAL, **47**, 488 (1925).

(21) P. D. Bartlett and L. J. Rosen, *ibid.*, **64**, 543 (1942).

(22) From the data of ref. 20 and of W. T. Miller, Jr., and J. Bernstein, *ibid.*, **70**, 3600 (1948), *p*-nitrobenzyl chloride may be estimated to be about 500 times as reactive as the fluoride.

(23) For other exceptions see H. Böhme, H. Fischer and R. Frank, *Ann.*, **563**, 54 (1949); D. N. Glew and E. A. Moelwyn-Hughes, *Proc. Roy. Soc. (London)*, **A211**, 254 (1952).

TABLE IV

KINETIC CONSTANTS FOR REACTIONS WITH SODIUM METHOXIDE IN METHANOL

Halide	10^5k (l. mole^{-1} sec.$^{-1}$) 20.3°	50°	$\Delta H^{\ddagger}$, kcal.	$\Delta S^{\ddagger}$, e.u.
CH_3I	14.9 ± 0.2	433 ± 9	20.8 ± 0.4	−5.2 ± 2
$ClCH_2I$	0.0863 ± .004	4.41 ± 0.16	24.4 ± 0.7	−3.1 ± 2
$BrCH_2I$	.031 ± .003[d]	1.02 ± .03	21.6 ± 1.0	−14.7 ± 4
ICH_2I[a]	.010 ± .002[d]	0.536 ± .007	24.7 ± 2.0	−6.4 ± 7
CH_3Br	17.1 ± .6	472 ± 24	20.5 ± 0.7	−5.9 ± 2
CH_3CH_2Br	1.33 ± .02	47.2 ± 1.6	22.0 ± 0.6	−5.9 ± 2
FCH_2Br	7.37 ± .14	225 ± 11	21.1 ± 0.7	−5.6 ± 2
$ClCH_2Br$[b]	0.0418 ± .001	2.36 ± 0.03	25.0 ± 0.4	−2.5 ± 2
$BrCH_2Br$[a,c]	0.00616 ± .0002	0.370 ± .02	25.4 ± 0.7	−4.9 ± 2
$ClCH_2Cl$[a]		0.0284 ± .001		

[a] The observed rate constants have been divided by two to get the rate constants per iodine (or per bromine or chlorine) shown. [b] At 36°, 10^5k = 0.378 ± 0.002. [c] At 36°, 10^5k = 0.0613 ± 0.002. [d] Estimated by extrapolation to zero time.

tive compounds during the several weeks required for a kinetic run at this temperature. The values given in Table IV were therefore obtained by extrapolation to zero time.

Discussion

It is seen that as α-substituents all four halogens (compared to hydrogen) decrease the reactivity by the SN2 mechanism in both of the reactions studied. This decrease in reactivity is least for fluorine where it is in one case less and in the other case somewhat more than that produced by a methyl group. The decrease is more for chlorine and most for iodine and bromine. In a number of cases the differences in heats of activation clearly contribute to the differences in reactivity. In most cases the differences in entropies of activation are no larger than our sometimes considerable experimental error. Therefore in few cases can we be sure that an entropy difference contributes to the difference in reactivity. The data presented herein will be discussed further in a subsequent, more general article on the effect of structure on SN2 reactivity.

Acknowledgments.—The authors would like to express their gratitude to the Research Corporation of New York for the grant of a fellowship to C. H. T. and to the National Science Foundation for a fellowship to S. J. E., and for other support which has made this work possible; and to the Dow Chemical Company for samples of methylene bromide and bromochloromethane.

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, TENNESSEE A. & I. STATE UNIVERSITY]

Grignard Reagents and Unsaturated Ethers. V.[1] Mode of Cleavage of α- and γ-Substituted Allyl Ethers by Grignard Reagents[2]

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RECEIVED DECEMBER 15, 1954

An investigation to ascertain the influence of structural and electrical factors upon the mode of cleavage of substituted allyl ethers by Grignard reagents has been undertaken. For this investigation several α- and γ-substituted allyl ethers of type: R-CH=CH-CHR′-O-R″, where R is CH_3 and C_6H_5, R′ is H, *n*- and *t*-C_4H_9 and $C_6H_5CH_2$, and R″ is *n*- and *t*-C_4H_9 and $C_6H_5CH_2$-CH_2 were synthesized and characterized, and their reaction with Grignard reagents observed. Results from our present study indicate that aryl and alkyl (lower than *n*-heptyl) Grignard reagents cleave substituted allyl ethers by a 1,2-addition mechanism; while *n*-heptyl- and *n*-octylmagnesium bromides cleaved both mono and disubstituted allyl ethers by a 1,4-addition mechanism.

The second paper in this series showed that Grignard reagents cleave allyl ethers to yield olefinic hydrocarbons and saturated alcohols.[3] The hydrocarbon products, except one, were accounted for by assuming that the Grignard reagents cleaved the ethers by a 1,2-addition mechanism. However, the observation that *n*-heptylmagnesium bromide reacted with *n*-butyl 3-phenylallyl ether to yield 3-phenyl-1-decene suggested further study of the reaction of Grignard reagents with substituted allyl ethers. Hence, to explore the hypothesis that the nature of the Grignard reagent and of substituents at the α- and γ-positions in the allylic system would be expected to influence the mode of cleavage of the ether by the reagent, we have expanded our investigation. For laboratory study, allyl ethers substituted at the α- and γ-positions with substituents suspected of imparting electrical[4] or sterically hindered effects, or both, were synthesized and their behavior toward various Grignard reagents studied. We have found that in reactions involving *n*-heptylmagnesium bromide structural variation of the allyl ether affects the mode of cleavage of the ether

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(1) For the fourth paper, see C. M. Hill, R. M. Prigmore and G. J. Moore, THIS JOURNAL, **77**, 352 (1955).

(2) This research was supported by the United States Air Force, through the Office of Scientific Research of the Air Research and Development Command.

(3) C. M. Hill, L. Haynes, D. E. Simmons and M. E. Hill, THIS JOURNAL, **75**, 5408 (1953).

(4) M. S. Kharasch and A. L. Flenner, *ibid.*, **54**, 678 (1932).