hydride reduction of methyl isopropyl ketone, followed by careful fractionation. The pure acetate,[31] b.p. 124.0–124.5° at 680 mm., $n^{20}D$ 1.3960, was obtained in 68% yield from the alcohol by the acetyl chloride–pyridine method (see below) and careful fractionation of the acetate.

2-Methyl-3-pentanol[32] was prepared from ethylmagnesium bromide and isobutyraldehyde in 67% yield and agreed well with the b.p. and index of refraction reported. Acetylation by the acetyl chloride–pyridine method (see below) afforded the pure acetate (see Table III).

Formation of Acetates.—Two different methods were used for acetylation of the alcohols: (1) acetyl chloride–pyridine method and (2) reaction with isopropenyl acetate using a catalytic amount of acid.[33] The following modification of the acetyl chloride–pyridine method was used: to an equimolar mixture of alcohol and dry pyridine in dry ether (about 250 ml. per mole) was added dropwise with stirring acetyl chloride in ether at a rate to maintain gentle reflux. After the addition was complete, refluxing of the stirred reaction mixture was continued for 30 minutes to 6 hours (depending on the alcohol structure). The acetates were carefully dried over anhydrous calcium sulfate and fractionally distilled through a packed column. The physical constants, yields and analyses of the acetates prepared are given in Table III. The amounts of alcohols used varied from 0.05 to 1.0 mole.

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[32] F. Hovorka, H. P. Lankelma and A. E. Axelrod, THIS JOURNAL, **62**, 187 (1940).

[33] H. J. Hagemeyer, Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Rates of Alkaline Hydrolysis of a Series of Primary and Secondary Alkyl Acetates

BY SHALOM SAREL,[1] LIN TSAI AND MELVIN S. NEWMAN[2]

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The rates of alkaline hydrolysis of a number of branched primary and secondary alkyl acetates in 70% dioxane–water have been measured. The possible utility of the information thus gained in the improvement of condensation reactions is discussed.

We became interested in a study of steric hindrance to ester hydrolysis because of possible applications of knowledge thus gained to improvement of synthetic reactions. There are many examples of the use of bifunctional (or polyfunctional) reagents in which one function is the esterified carboxyl group. The yields of desired products are often reduced by side reactions which stem from undesired condensation reactions involving the ester function.

It seemed likely that such side reactions might be decreased by modifying the ester function to provide a greater degree of steric hindrance. This modification could be effected by choice of the proper alkyl moiety in the ester group. However, the use of too hindered an ester would be unwise as hydrolysis at a later stage might prove too difficult.

A notable example of judicious choice of alkyl moiety in an ester has been provided by the studies on the Stobbe condensation in which[3] the use of *t*-butyl succinate was shown far superior to that of methyl or ethyl succinate. However, it is not known to what extent the polar or steric properties of the *t*-butyl group are responsible for the results. Another example of the utility of *t*-butyl esters is found in the condensation of *t*-butyl acetate with ketones.[4] A study of the effect of the alkyl group in Reformatsky reactions involving alkyl α-bromopropionates has also been made.[5]

In order to provide a background of quantitative data upon which future (or past) work might be analyzed we have chosen to study the alkaline hydrolysis of alkyl acetates as a typical example of a reaction known to proceed by carbonyl addition.[6] An immediate object of this research was to find which primary or secondary alkyl acetates would saponify at rates comparable to that of *t*-butyl acetate. Thus one would have alcohols to substitute for *t*-butyl alcohol in the preparation of esters desired for synthetic work. Such substitutions are often desirable because of the difficulty of preparing certain *t*-butyl esters.

Little attention has been paid to the effect of steric factors in the alkyl moiety of an ester on the rate of alkaline hydrolysis. In a general way it is known that esters of tertiary alcohols are saponified at a slower rate than those of secondary alcohols, and the latter at a slower rate than esters of primary alcohols.[7] However, this rate order is probably determined by polar as well as steric factors in the alkyl portion since the alkoxide ions released during hydrolysis are of widely different base strengths: *e.g.*, primary $RO^- <$ secondary $RO^- <$ tertiary RO^-. Therefore, in order to evaluate steric effects, one should limit comparison of hydrolysis rates to esters of the same class of alcohol.

Accordingly we have measured the rates of alkaline hydrolysis of a series of primary and secondary acetates in 70% dioxane–water at 20 and 30°. The data is listed in Table I together with that for a few esters included for comparative purposes.

Experimental

Solvents and Reagents.—Dioxane was purified by the method described.[8] Sodium hydroxide solution in 70% dioxane was prepared by diluting 1.0 *N* aqueous solution with distilled water so that the total volume was short of 300

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[1] Formerly Shalom Israelashvili.

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[3] G. H. Daub and W. S. Johnson, THIS JOURNAL, **72**, 501 (1950).

[4] C. R. Hauser and W. H. Puterbaugh, *ibid.*, **75**, 1068 (1953).

[5] M. S. Newman and F. J. Evans, Jr., *ibid.*, **77**, 946 (1955).

[6] M. L. Bender, *ibid.*, **73**, 1626 (1951).

[7] For example, the relative rates of hydrolysis of 1-butyl, 2-butyl and *t*-butyl acetates in water at 20° are 3.93, 0.82 and 0.08, respectively; see M. S. Newman "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 220-222.

[8] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 369.

TABLE I

ALKALINE HYDROLYSIS OF ALKYL ACETATES IN 70% DIOXANE–WATER

No.	R in CH_3COOR	$10^3 k$, l./mole/sec. 20°	30°	E_{act}, kcal.	log PZ	$\frac{k_{20°}(CH_3COOC_2H_5)}{k_{20°}(CH_3COOR)}$
			Primary			
1	CH_3-[a]	54				0.65
2	CH_3CH_2-	35	66[b]			1
3	$(CH_3)_3CCH_2CH_2-$	21				1.7
4	$(C_2H_5)(CH_3)CHCH_2-$	12.5	27	13.7	8.5	2.8
5	$(CH_3)_3CCH(CH_3)CH_2-$	10				3.5
6	$(CH_3)_2CHCH(CH_3)CH_2-$	10	24	15.2	9.3	3.5
7	$(CH_3)_3CCH_2-$	8.6	17	12.5	7.2	4.1
8	$(C_2H_5)(CH_3)_2CCH_2-$	6.0	11	11.6	6.4	5.8
9	$(CH_3)_2CHCH(C_2H_5)CH_2-$	5.3	12	14.9	8.8	6.6
10	$(C_2H_5)_2CHCH_2-$	5.1	16	20.0	12.7	6.9
11	$(n\text{-}C_4H_9)(C_2H_5)CHCH_2-$	5.1	12	15.6	9.3	6.9
12	$(C_2H_5)_2(CH_3)CCH_2-$	3.7				9.5
13	$(CH_3)_2CHCH(i\text{-}C_3H_7)CH_2-$	2.5				14
14	$(CH_3)_3CCH(C_2H_5)CH_2-$	1.7	3.6	12.9	6.8	20
15	$(C_2H_5)_3CCH_2-$	1.5	3.4	14.6	8.1	23
			Cycloalkanemethyl			
16	$(CH_2)_2CHCH_2-$	31	63	12.5	7.8	1.1
17	$(CH_2)_3CHCH_2-$	23	49	13.4	8.4	1.5
18	$(CH_2)_4CHCH_2-$	16	36	14.0	8.7	2.2
19	$(CH_2)_5CHCH_2-$	10	23	14.6	8.9	3.5
20	$CH_2{=}CH{-}CH_2-$[a]	62				0.6
			Secondary			
						$\frac{k_{30°}\ CH_3COOCH(CH_3)_2}{k_{30°}\ CH_3COOR}$
21	$(CH_3)_2CH-$		12.4			1
22	$[(CH_3)_2CH](CH_3)CH-$		5.1			2.4
23	$[(CH_3)_2CH](C_2H_5)CH-$		1.0			12.4
24	$[(CH_3)_3C](CH_3)CH-$		0.93			13.3
25	$[(CH_3)_2CHCH_2]_2CH-$		0.56			22
			Tertiary			
26	$(CH_3)_3C-$		0.8			15.5

[a] The rate of hydrolysis of ethyl acetate in water at 20° is 8.5×10^{-2} l./mole/sec.; H. Olsson, *Z. physik. Chem.*, **133**, 233 (1928). The rate of hydrolysis of ethyl acetate in 70% dioxane–water at 20° determined in this Laboratory is $3.5 \times 10^{-}$ l./mole/sec. Hence $k_{CH_3COOOC_2H_5(H_2O)}/k_{CH_3COOOC_2H_5(70\%\ \text{dioxane–water})}$ is 2.4. This ratio is used to estimate the rate constants given for methyl and allyl acetates, using Olsson's rate constants in water at 20°. H. Olsson, *et al.*, *Z. physik. Chem.*, **118**, 99 (1925). [b] This rate constant was obtained by extrapolation of the data of P. M. Nair and S. V. Anantakrishnan, *Proc. Indian Acad. Sci.*, **32A**, 187 (1950).

ml. This solution was placed in a 1-l. volumetric flask to which 700 ml. of purified dioxane had been added. The volumetric flask was then filled to the mark with distilled water. All solvents and reagents prepared were kept under nitrogen in Pyrex glass containers and the contents were forced out of the containers with nitrogen as needed. Double distilled water was used in the preparation of all solutions required for kinetic runs. All transfers of basic solutions were made under nitrogen.

Hydrochloric acid solutions were titrated against standard sodium hydroxide solutions. Sodium hydroxide solutions used in back titration were prepared by diluting a saturated carbonate-free solution. These solutions were protected from atmospheric carbon dioxide by Ascarite (soda lime) absorption tubes.

The preparation and properties of the alkyl acetates are described in the accompanying paper.[9]

Kinetic Studies.—All hydrolysis experiments were carried out in Pyrex glass under nitrogen. Solutions for runs were prepared by weighing the desired amount of ester into a 200-ml. volumetric flask to which was added 100 ml. of 70% dioxane. To this, at the reaction temperature, was added 100 ml. of sodium hydroxide solution in 70% dioxane of such a strength that the final concentration of hydroxide ion was between 1.5 to approximately two times that of the ester.

The extent of reaction was determined from the loss of base during the reaction, by withdrawing aliquots at regular intervals and running into excess standard hydrochloric acid. The excess acid was then back-titrated with sodium hydroxide solution using phenolphthalein as indicator. Duplicate runs for each ester were carried out. The reaction temperature was controlled to approximately ±0.03°. The concentration of esters was between 0.006 to 0.01 N and that of sodium hydroxide 0.013 to 0.018 N. Blank runs were carried out without ester to determine the decrease in hydroxide ion concentration with time. Under nitrogen at 20 and 30° the loss of base during the reaction period was negligible. Pipets, volumetric flasks and microburet were calibrated. Rate constants were calculated by the following expression which was derived from the integrated form of the second-order rate equation[10] where T_0 is the volume of standard acid required

$$k = 2.303/t\ T_\infty \times \log \frac{T_t(T_0 - T_\infty)}{T_0(T_t - T_\infty)} \times v/N$$

to neutralize the hydroxide at the beginning of the experiment, T_t is the volume after t min., and T_∞ that equivalent to the excess alkali remaining when all the ester had been saponified, v is the volume of reaction mixture in ml. removed for each titration and N is the normality of the acid used. Results of a typical run are shown in Table II.

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[9] S. Sarel and M. S. Newman, THIS JOURNAL, **78**, 5416 (1956).

[10] S. Glasstone, "Textbook of Physical Chemistry," the Macmillan Co., New York, N. Y., 1946, p. 1058.

TABLE II

HYDROLYSIS OF CYCLOHEXANEMETHYL ACETATE IN 70% DIOXANE SOLUTION AT 20°

Acid = 0.0244 N; v = 25.00

t, min.	T_t	$T_t - T_\infty$	k, l. mole^{-1} min.$^{-1}$
0	15.25 (T_0)	10.29	...
40	12.55	7.59	0.565
129	9.59	4.63	.572
170	8.79	3.83	.532
225	7.96	3.00	.535
278	7.45	2.49	.522
352	6.75	1.79	.548
48 hr.	4.96 (T_∞)	...	...
		Average	.546

Discussion

From Table I it can be seen that 2,2-diethyl-1-butyl acetate, no. 15, is the primary acetate which is hydrolyzed at the slowest rate, about 1/23 as fast as that of ethyl acetate. Although we were unable to compare the rate of 2,2-diethyl-1-butyl acetate, no. 15, with that of t-butyl acetate, no. 26, at 20° because of the slow rate of hydrolysis of the latter at 20°, comparison at 30° showed that no. 26 is hydrolyzed about 1/4 as rapidly as no. 15. Perhaps more highly branched primary alkyl acetates than no. 15 would be hydrolyzed at a rate equal to or slower than that of t-butyl acetate, no. 26, but in view of the difficulty of preparation, it is doubtful that such an alkyl moiety would prove useful for any synthetic purpose. In view of the moderate hindrance to hydrolysis shown by esters no. 10 and 11 and the ready availability of 2-ethyl-1-butyl and 2-ethyl-1-hexyl alcohols,[11] the use of these two alkyl groups may be advisable where moderate steric hindrance seems indicated in the alkyl portion of the ester function.

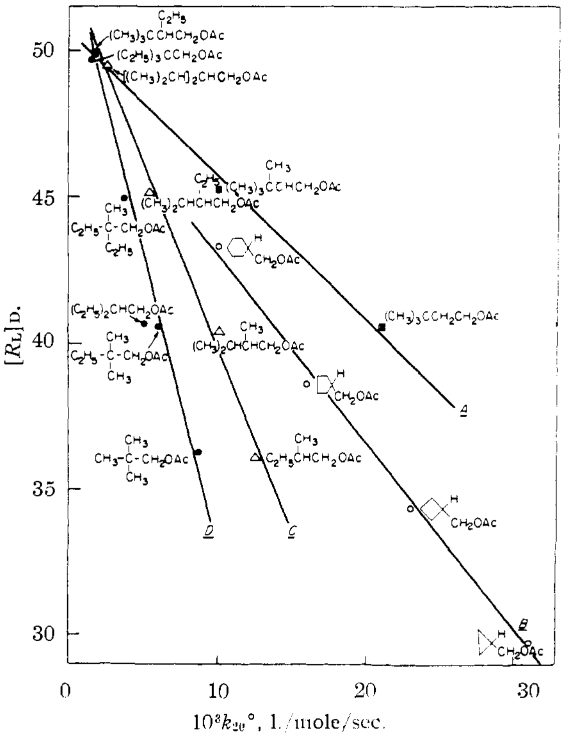

Fig. 1.—Plot of molecular refractivity, $[R_L]$D, against rate of hydrolysis at 20° in 70% dioxane.

In the secondary alkyl series, ethylisopropylcarbinyl acetate, no. 23, and methyl t-butylcarbinyl acetate, no. 24, are hydrolyzed slightly faster than is t-butyl acetate, no. 26, whereas diisobutylcarbinyl acetate, no. 25, is hydrolyzed slightly slower. Thus it is seen that a variety of secondary alkyl groups will afford esters which undergo carbonyl addition reactions at about the same rate at which the corresponding t-butyl esters will. Hence, in line with the agruments put forth in the introduction to this paper, these alkyl moieties may prove useful in synthetic operations. Of these the diisobutylcarbinyl esters seem most attractive because of the ready availability of diisobutylcarbinol.

When the specific second-order rate constants in 70% dioxane-water at 20° for all the primary acetates are plotted against the molecular refraction,[8] see Fig. 1, some interesting relationships may be seen. In general the higher the molecular refractivity of an ester, the slower its rate of hydrolysis. Esters having the same number of carbon atoms (excluding the cycloalkyl series) have about the same molecular refractivity. Within each series of isomers the rate of hydrolysis is slower the closer the branching occurs to the ester group.

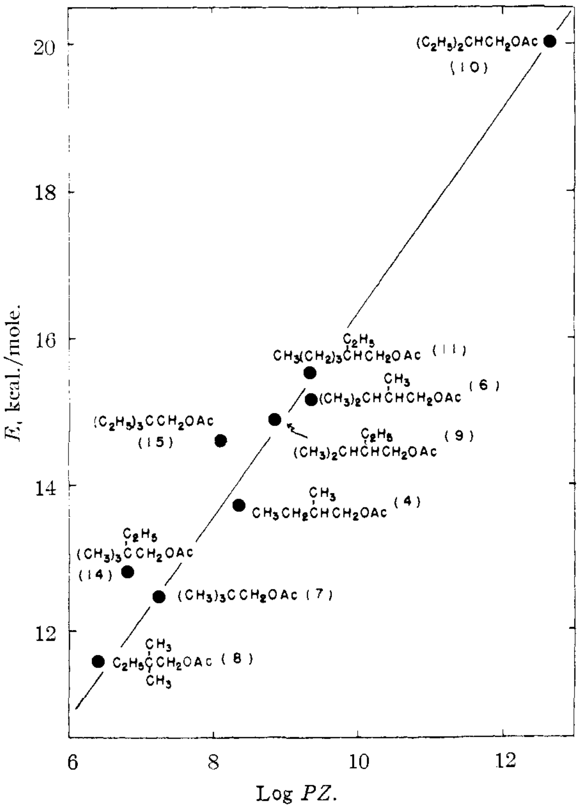

Fig. 2.—Plot of energy reactivations $vs.$ log PZ for hydrolysis of primary alkyl acetates.

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[11] We acknowledge with thanks gifts of samples of 2-ethyl-1-butanol, 2-ethyl-1-hexanol and diisobutylcarbinol by the Carbide and Carbon Chemical Corporation.

For example, compare the isomeric acetates having in all 8 carbons ($[R_L]_D$ 40.5) and 9 carbons ($[R_L]_D$ 45).

For certain types of esters straight lines may be drawn. For example, line A results from esters of type $(CH_3)_3CCHRCH_2OCOCH_3$ in which R varies regularly from ethyl (no. 14) to methyl (no. 6) to hydrogen (no. 3). Line B results from esters of type RCH_2OCOCH_3 where R varies from cyclohexyl (no. 19) to cyclopentyl (no. 18) to cyclobutyl (no. 17) to cyclopropyl analog (no. 16). Line C results for esters of type $(CH_3)_2CHCHRCH_2OCOCH_3$ where R varies from isopropyl (no. 13) to ethyl (no. 9) to methyl (no. 5). Ester no. 4 also falls on this line. Line D results for esters of type $(R)_3CCH_2OCOCH_3$ where the R groups vary from triethyl (no. 15) to diethyl, methyl (no. 12) to ethyl, dimethyl (no. 10) to trimethyl (no. 7).

It is interesting to note that with the series of acetates of the branched primary alcohols a plot of their activation energies and log *PZ* values (Fig. 2) gives a linear relationship for all the members except $(C_2H_5)_3CCH_2OAc$ (no. 15) and $(CH_3)_3CCH(C_2H_5)CH_2OAc$ (no. 14), which are hydrolyzed most slowly in the series and their points lie above and to the left of the isokinetic line. This is in accord with the discontinuous effect of steric hindrance as pointed out by Leffler.[12]

(12) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).

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[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, THE FACULTY OF ENGINEERING, KYOTO UNIVERSITY]

Kinetics of the Chloromethylation of Mesitylene in Aqueous Acetic Acid

BY YOSHIRO OGATA AND MASAYA OKANO

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The rate of the chloromethylation of mesitylene in acetic acid containing 10 volume % water was measured at 60° by estimating the consumed formaldehyde iodometrically and the consumed chloride ion. The rate of the disappearance of formaldehyde was found to be expressed as k_F[mesitylene] [formaldehyde], where a linear relationship with approximate unit slope (−0.96) was observed between log k_F and the Hammett acidity function (H_0). It was also confirmed that mesitylcarbinol and mesitylmethyl chloride are in mobile equilibrium under the experimental conditions. These results are consistent with a mechanism which involves a rate-determining attack of protonated formaldehyde on mesitylene followed by the rapid reversible formation of the chloromethyl compound.

Although many studies of chloromethylation from the synthetic standpoint have been carried out,[1] few data are available for the establishment of the reaction mechanism. The previous reports[2] on the relative rate measurements for the chloromethylation of aromatic hydrocarbons showed that the reaction appeared to involve an electrophilic attack on the aromatic nucleus. It seems to mean that the attacking species in the rate-determining step is either $\overset{+}{C}H_2Cl$ or $\overset{+}{C}H_2OH$. But there is no evidence to decide which is the more probable one. The present report provides information concerning the kinetics and mechanism of the chloromethylation of mesitylene with hydrogen chloride and formaldehyde in 90 volume % aqueous acetic acid.

Experimental

Materials.—Mesitylene was prepared by the cyclization of acetone[3] and purified by duplicate rectifications, b.p. 163–164°. 2,4,6-Trimethylbenzyl chloride (mesitylmethyl chloride) was synthesized by the condensation of mesitylene with monochloromethyl ether in glacial acetic acid,[4] and crystallized from ether, m.p. 37–38°. 2,4,6-Trimethylbenzyl acetate was obtained by treating the chloride with silver acetate,[5] b.p. 146° (24 mm.). 2,4,6-Trimethylbenzyl alcohol (mesitylcarbinol) was prepared by the saponification of the corresponding acetate,[5] and recrystallized from aqueous ethanol, m.p. 88–89°. Glacial acetic acid was of the best grade available, and was used without further purification.

Rate Measurements.—Forty cc. of glacial acetic acid, 24 cc. of 2 *M* hydrogen chloride in acetic acid and 8 cc. of 2 *M* aqueous formaldehyde solution were mixed in a flask, and thermostated at 60°. To the mixture was added from a calibrated pipet 8 cc. of 2 *M* mesitylene in acetic acid maintained previously at the same temperature. At regular time intervals, 3-cc. aliquots were pipetted out into *ca.* 50 cc. of distilled water. Potassium hydroxide solution was added until the solution became alkaline, and the amount of unreacted formaldehyde was determined by iodometry.[6,7] Other 5-cc. aliquots were poured into *ca.* 50 cc. of carbon tetrachloride.[8] The mixture was transferred to a separatory funnel and extracted twice with *ca.* 50 cc. portions of distilled water. The amount of consumed chloride ion was estimated according to the Volhard method.[9] The rate measurement of the chloride ion consumption had to be restricted only to the early stages of the reaction in order to obtain reliable data. The discrepancy seems to depend on the use of a large excess of hydrogen chloride and its vaporization during the reaction.

Measurements of the Acidity Function H_0.—To obtain information on the effective acidity, the indicator ratios (c_B/c_{BH^+}) at 412 mμ for each reaction mixture were determined spectrophotometrically using *o*-nitroaniline (pK_a −0.17)[10] as an indicator.[11] Thus the values of H_0 were calculated by means of the equation[12] where c_B is concentra-

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(1) *Cf.* R. C. Fuson and C. H. McKeever, *Org. Reactions*, **1**, 63 (1942).

(2) G. Vavon, J. Bolle and J. Calin, *Bull. soc. chim. France*, [5] **6**, 1025 (1939); H. H. Szmant and J. Dudek, THIS JOURNAL, **71**, 3763 (1949).

(3) R. Adams and R. W. Hufferd, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 341.

(4) G. Vavon and J. Bolle, *Compt. rend.*, **204**, 1826 (1937).

(5) W. Th. Nauta and J. W. Pienske, *Rec. trav. chim.*, **55**, 1000 (1936).

(6) J. F. Walker, "Formaldehyde," 2nd Ed., Reinhold Publ. Corp., New York, N. Y., 1953, p. 385.

(7) It was also ascertained that loss of formaldehyde due to the polymerization was negligible in this solvent.

(8) Since the chloromethylated compound is readily hydrolyzed, the preliminary removal of the compound by the extraction with carbon tetrachloride is necessary.

(9) J. R. Caldwell and H. V. Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935).

(10) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 266.

(11) For the example, see D. S. Noyce and P. Castelfranco, THIS JOURNAL, **73**, 4482 (1951).

(12) Reference 10, p. 268.