[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Rate of the Alkaline Chlorination of Ketones

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Enolization appears to be an intermediate step in the halogenation of ketones, in alkaline as well as in acid solutions.[3] Of the six halogenating agents, iodine, bromine, chlorine, hypoiodite, hypobromite and hypochlorite ions, only the last is insufficiently active to react with the enol of acetone as rapidly as this is formed under the usual conditions of kinetic measurements. Since hypoiodite and hypobromite react rapidly with the enol, and not appreciably with the ketone directly, we ascribe the unique behavior of hypochlorite to a difference of rate rather than of mechanism, and regard the alkaline chlorination of acetone as a reaction of the enol which is slow enough so that this tautomer is present at substantially its equilibrium concentration during the reaction.

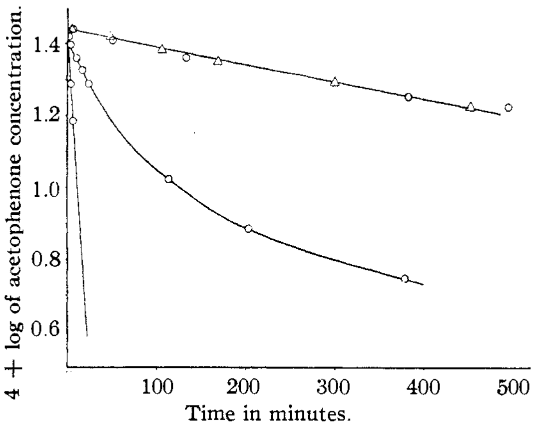

Fig. 1.—Upper curve, △, bromination of acetophenone at *p*H 9; upper curve, ○, chlorination of acetophenone at *p*H 9; middle curve, chlorination of acetophenone at *p*H 11; lower curve, bromination of acetophenone at *p*H 11.

This reaction interests us from several viewpoints. First, it offers a means of closer study of the mechanism of a reaction of an enol. Second, it may offer an approach to the mechanism of other slow reactions involving an enol at equilibrium. Third, its rate is sensitive to changes in structure in a way consistent with our view of the acid–base catalysis of ketone reactions.[3] We have accordingly carried out a kinetic study of the chlorination of acetone, acetophenone and pinacolone over a range of alkalinity up to that of 1 *M* sodium hydroxide, in aqueous solution.

Since in acid solution both chlorine and bromine react with acetophenone at the same rate, a rate depending only upon the concentration of the ketone, it is evident that as the alkalinity is increased there must come a point at which the rates of halogenation by these two halogens diverge, and the rate of chlorination becomes bimolecular and dependent upon the concentration of the chlorine. We have located this point for dilute solutions as between *p*H 9 and 11 at 25°, by studies on solutions originally about 0.003 molar in acetophenone. Figure 1 shows these results graphically, the logarithm of the acetophenone concentration being plotted against time. The upper curve shows the identical rate of chlorination and bromination in a borate buffer of *p*H 9.17; the lower two curves show the disparity between the two rates at *p*H 11.37, and the departure of the chlorination reaction from the unimolecular course. The hypochlorite run shown here as a curve gives a straight line when plotted as a bimolecular reaction. This change is evidently associated with the increasing conversion of chlorine into the form of hypochlorite ion with increasing alkalinity of the solution, and the relative weakness of hypochlorite ion as a chlorinating agent. It is evident that at *p*H 11.37 the ketone is enolizing much more rapidly than the enol is being consumed. This situation is maintained in the more alkaline solutions, for the rate of enolization is increased while the rate of chlorination is up to about 0.03 *M* alkali, still further diminished, by increasing alkalinity of the solution.

For following the change in chlorination rate in very alkaline solutions, the temperature of 35° was chosen because it afforded rates of a convenient magnitude. Since we wished to go up to 1 molar sodium hydroxide, the ionic strength was made uniformly equal to 1.00 in all the runs. This was done as the best way to minimize salt effects in changing from one concentration of

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[2] The greater part of the present work is described in a thesis presented by John R. Vincent for the degree of Master of Science at the University of Minnesota in 1935.

[3] Bartlett, THIS JOURNAL, **56**, 967 (1934).

sodium hydroxide to another, although the effects of individual ions at such high ionic strengths are to a considerable extent specific. Results bearing on this specificity are reported in the experimental part of this paper. After ascertaining that the chloride ion had no special effect upon the velocity of the reaction, we used potassium chloride in the proper concentration to bring the ionic strength of each reaction solution up to 1.00.

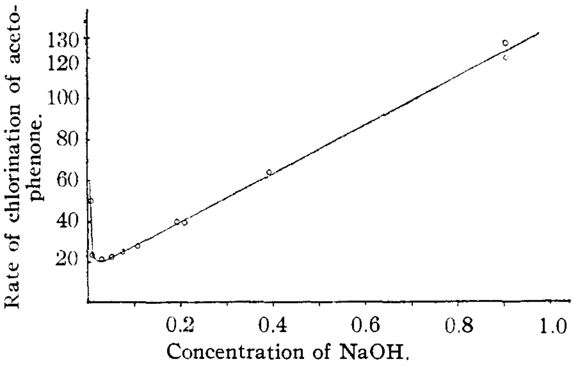

Fig. 2.

The results for the three ketones are shown in Figs. 2, 3, and 4, where the bimolecular velocity constants for the reaction between hypochlorite ion and ketone are plotted against concentration of sodium hydroxide. As the alkalinity is increased above *p*H 11, a minimum velocity of chlorination is soon reached, and beyond this point the rate of chlorination of the ketone becomes again a linear function of the concentration of hydroxyl ion. In sodium hydroxide solutions stronger than 0.05 *M*, the following equations express the dependence of the velocity constant *k* on the hydroxyl-ion concentration *x*

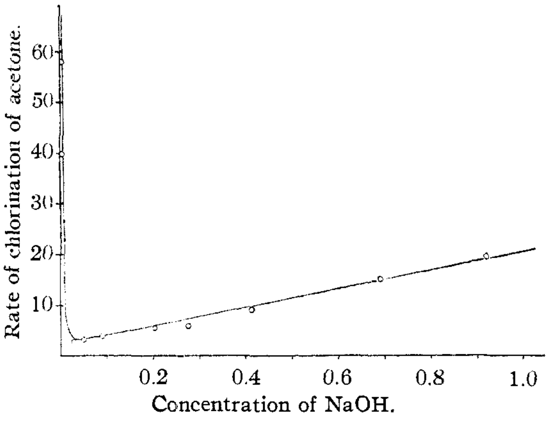

Fig. 3.

$$\left.\begin{array}{lll}\text{Acetophenone} & k = 16.1 + 119.0x \\ \text{Acetone} & k = 1.38 + 19.8x \\ \text{Pinacolone} & k = 0.0 + 2.99x\end{array}\right\} \qquad (1)$$

The decrease in rate of chlorination and the changing to a second order reaction occur in that *p*H region where free hypochlorous acid is disappearing from the solution and giving place to hypochlorite ion. Where the linear relationship obtains between rate of chlorination and hydroxyl-ion concentration, the amount of free hypochlorous acid present is evidently too small to make an appreciable contribution to the rate of chlorination of the enol. The steady *increase* in the rate of chlorination with increasing alkali concentration can scarcely be due to the conversion of the hypochlorite ion into any other form, and must be associated with the *ionization* of the enol. If a ketone KH is in equilibrium with an enol EH

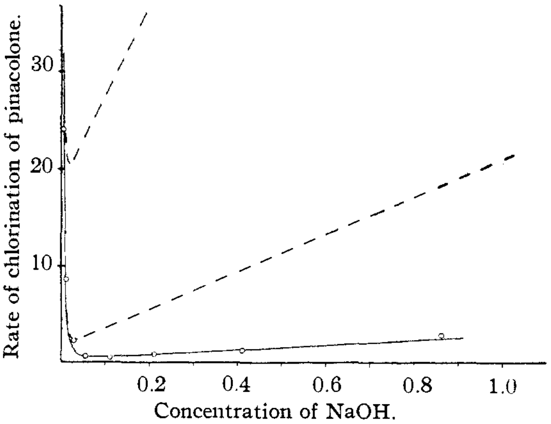

Fig. 4.—The dotted lines are the curves of Figs. 2 and 3, plotted to this scale for the sake of comparison.

$$\mathrm{KH} \rightleftharpoons \mathrm{EH}$$

then at all *p*H's we have the equilibrium constant

$$K_\mathrm{E} = [\mathrm{EH}]/[\mathrm{KH}]$$

The enol is an acid, whose ionization is governed by the equilibrium constant

$$K_\mathrm{A} = [\mathrm{H}^+][\mathrm{E}^-]/[\mathrm{EH}]$$

The total concentration of all forms of the ketone present is then

$$[\mathrm{KH}] + [\mathrm{EH}] + [\mathrm{E}^-] = [\mathrm{KH}]\left[1 + K_\mathrm{E} + K_\mathrm{E}K_\mathrm{A} \times \frac{1}{[\mathrm{H}^+]}\right] = [\mathrm{KH}]\,[1 + K_\mathrm{E} + (K_\mathrm{E}K_\mathrm{A}/K_w)\,[\mathrm{OH}^-]]$$

where $K_w = [\mathrm{H}^+][\mathrm{OH}^-]$. Even in 1 *M* sodium hydroxide solution there is not enough enol or enol ion present to modify the solubility of acetophenone, so that our values of *k* may be taken as referred to the pure keto form, KH. If k_KH, k_EH, and k_{E^-} are the constants for the rate of reaction of hypochlorite ion with the ketone, enol and enol ion, respectively, then the rate is

$$\frac{-\mathrm{d}[\mathrm{KH}]}{\mathrm{d}t} = k[\mathrm{OCl}^-]\,[\mathrm{KH}] =$$

$$[\mathrm{OCl}^-]\,[\mathrm{KH}]\left[k_{\mathrm{KH}} + k_{\mathrm{EH}}K_{\mathrm{E}} + k_{\mathrm{E}^-}\frac{K_{\mathrm{E}}K_{\mathrm{A}}}{K_w}\,[\mathrm{OH}^-]\right]$$

and

$$k = k_{\mathrm{KH}} + k_{\mathrm{EH}}K_{\mathrm{E}} + k_{\mathrm{E}^-}\,(K_{\mathrm{E}}K_{\mathrm{A}}/K_w)\,[\mathrm{OH}^-] \quad (2)$$

where k is the experimentally determined velocity constant, referred to the ketone form. This is an interpretation of the linear variation of rate with hydroxyl-ion concentration. According to it the constant term in Equation (1) is in each case $(k_{\mathrm{KH}} + k_{\mathrm{EH}}K_{\mathrm{E}^-})$, which is indistinguishable from $k_{\mathrm{EH}}K_{\mathrm{E}^-}$; the slope (coefficient of x) in Equation (1) is equal to $k_{\mathrm{E}^-}(K_{\mathrm{E}}\text{-}K_{\mathrm{A}}/K_w)$, and is a measure of the importance of the enol ion in determining the rate of chlorination. If this slope is greater in one case than in another, it means that either the enol ion is more readily chlorinated or the enol is a stronger acid, in the first case than in the second, or both.

In the closely related case of the chlorination of phenol, Soper and Smith[4] have investigated the participation of undissociated phenol and phenoxide ion. The reaction velocity constant passed through an immeasurably high maximum in the region between pH 7 and 10, decreasing at higher pH and becoming inversely proportional to the hydroxyl-ion concentration. This was explained on the basis of the phenoxide ion and hypochlorous acid being the active reactants. At first sight it might appear that the kinetic maximum found by Soper and Smith and the kinetic minimum found in our case pointed to entirely different courses for the two reactions; but actually two differences in experimental conditions are sufficient to account for this apparent discrepancy. The work on phenol was done with concentrations of sodium hydroxide below 0.1 *M*. If the ratio of the chlorinating efficiencies of hypochlorous acid and hypochlorite ion is somewhat greater for phenol than for enols of simple ketones, then the studies of Soper and Smith were concerned with that region which corresponds to the descending part of our curves, to the left of the minimum, where in our case also the rate is inversely proportional to the hydroxyl-ion concentration. In the second place, if our theory leading to Equation (2) is correct, the keto form functions as a large inert reservoir of material, which maintains constant enol concentration and (with increasing alkalinity) increasing concentration of enol ion. In the case of a phenol, the concentration of ion cannot increase very much above pH 11, where about 90% of all the phenol is in the ionized form; and while we might expect the curve of rate *vs.* hydroxyl-ion concentration to flatten off in strongly alkaline solutions, it would never be expected to rise. It would seem, then, that the chlorination of aliphatic enols and that of phenols are essentially alike, differing only in the magnitude of some of the constants involved.

Certain rough estimates of these constants can be made. We find by titration of a large amount of acetophenone solution that K_{E^-} must be less than 10^{-4}. For the other hypohalites, and presumably also for hypochlorite, $k_{\mathrm{EH}}K_{\mathrm{E}^-}$ is at least 100 times k_{KH}. Hypohalite ions therefore react with these enols at least 10^6 times as rapidly as with the keto forms. K_{A} for a simple enol may be expected to be of the same order of magnitude as that of phenol (about 10^{-10}) and surely not less than that of a saturated alcohol (about 10^{-15}). When pH equals pK_{A}, the enol and enol ion are present at equal concentrations; therefore if K_{A} is 10^{-10} for the three enols in question, then for acetophenone k_{EH} is 1350 times as great as k_{E^-}, and for acetone k_{EH} is 700 times as great as k_{E^-}, while the value of k_{EH} for pinacolone was not obtained with sufficient accuracy to make the corresponding estimate. Evidently if the simple enols are acids weaker than 10^{-13}, then their ions may be even more readily chlorinated than the undissociated enols. This seems possible but our data do not suffice to prove it.

Studies of enolization[5] and of ester hydrolysis[6] have shown that the effect of structure upon reactivity appears more clearly in the relative susceptibilities of compounds of a series to basic and to acidic catalysis than in the rates of reaction under any identical set of conditions. Compounds which differ but slightly in their rates of reaction under identical conditions of acid catalysis may show large differences when compared in this way. The sequence of groups, phenyl, methyl, tertiary butyl, represents a passage from a weakly electron attracting group to a weakly electron repelling group. The methyl ketones containing these groups enolize with an acid catalyst at rates varying not more than threefold from one

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[4] Soper and Smith, *J. Chem. Soc.*, 1582 (1926).

[5] Hughes, Watson and Yates, *J. Chem. Soc.*, 3318 (1931); Watson and Yates, *ibid.*, 1207 (1932).

[6] Skrabal and Rückert, *Monatsh.*, **50**, 369 (1928); S. Goldschmidt in ed. Freudenberg, "Stereochemie," Verlag Franz Deuticke, Vienna, 1932, p. 485; Ingold and co-workers, *J. Chem. Soc.*, 1032, 1039 (1930); 2035, 2043 (1931).

another, as shown by the following results of Dawson and Ark:[7] rate of enolization at 25° in 40% alcohol 0.2 N in H_2SO_4: acetophenone, 108; acetone, 288; pinacolone, 132. Both the quantities $k_{EH}K_E$- and k_E-K_B-K_A vary by at least fortyfold on passage from acetophenone to pinacolone, these quantities being greatest in the compound with the most strongly electron attracting group.

Experimental

The samples of the three ketones that were used in the experiments had the following boiling points: acetone, 56°, acetophenone, 196–197.5°, and pinacolone, 104–105°. The runs were carried out at 35 ± 0.05°. Suitable amounts of sodium hydroxide solution, 1.00 N potassium chloride solution, and an alkaline chlorine solution whose ionic strength was made equal to 1 with potassium chloride and which, though it remained almost constant, was standardized before each run, were pipetted into glass stoppered Erlenmeyer flasks. Then an amount of ketone solution providing a slight excess was pipetted in, to start the reaction. For measuring the time a stop watch accurate to 0.01 minute was used. Samples were pipetted from the reaction flask into a solution containing at least a fivefold excess of acetic acid. An excess of solid sodium iodide was immediately added. (If the sodium iodide was added to the acetic acid before the sample, the results were not reproducible.) The iodine was then titrated with standard thiosulfate solution. A typical run with acetophenone follows. The volumes of solutions used in cc. were: KCl, 375; NaOH, 3; Cl_2, 4; $C_6H_5COCH_3$, 25; samples, 50.

$[Cl] = 0.2151\ N$

Min.	$S_2O_3^=$, cc.	$[OCl^-]$ in mole/liter	$[C_6H_5COCH_3]$ in mole/liter	$\log_{10} [C_6H_5COCH_3]/[OCl^-]$
0	..	0.001057	0.001738	0.2248
1.18	3.30	.000660	.001614	.3858
6.16	2.78	.000556	.001568	.4760
15.95	2.00	.000400	.001526	.5815
24.95	1.42	.000284	.001488	.7192
35.09	1.05	.000210	.001460	.8590
49.73	0.61	.000122	.001442	.9946
59.90	.43	.000086	.001431	1.0987

(NaOH) = 0.00997–0.01089. Slope = 0.01398. k = 23.07.

The values of $[OCl^-]$ were calculated from the amounts of thiosulfate solution used in the titrations. Since three equivalents of hypochlorite are required to convert one mole of acetone to chloroform

$$[C_6H_5COCH_3]_0 - 1/3\,[OCl^-]_0 = [C_6H_5COCH_3]_\infty$$

Then

$$[C_6H_5COCH_3]_\infty + 1/3\,[OCl^-] = [C_6H_5COCH_3]$$

The bimolecular constants were determined by the equation

$$kt = \frac{2.3}{[C_6H_5COCH_3]} \log_{10} \frac{1/3[OCl^-] + [C_6H_5COCH_3]_\infty}{[OCl^-]} + C$$

$\log_{10} [C_6H_5COCH_3]/[OCl^-]$ was plotted against time, and the values of k were obtained from the equation

$$\text{slope} = k[C_6H_5COCH_3]_\infty/2.3$$

Distribution Experiments.—To investigate the possibility of an appreciable degree of enolate formation by acetophenone in concentrated alkali solutions, the distribution coefficients of acetophenone between benzene and two aqueous solutions were determined. The first aqueous solution was 1 M in potassium chloride, the second was 1 M in sodium hydroxide. In each case 5 cc. of a benzene solution 0.8455 M in acetophenone was vigorously shaken at 22° with 20 cc. of the aqueous solution. Five cc. portions of the latter were then analyzed for acetophenone by titration with a solution of sodium hypoiodite of known strength. The distribution ratio of acetophenone between the benzene and aqueous layers was 217 for the potassium chloride solution and 279 for the sodium hydroxide solution. It is clear that specific salting out effects of the individual ions are larger in amount than any effect of enolate formation, which would produce a difference in the opposite direction from that observed.

Maximal Degree of Enolization of Acetophenone.—One hundred cc. of 0.0303 M aqueous acetophenone, 10 cc. of a 0.5 M phosphate buffer of pH 7 and 5 cc. of 0.01 M iodine solution, after standing for two minutes at 25°, consumed 4.51 cc. of standard thiosulfate solution. The same quantity of iodine alone consumed 4.57 cc. of the thiosulfate solution. This indicates that the degree of enolization of acetophenone under these conditions does not exceed 0.02%. Under these conditions the rate of consumption of iodine in two minutes is of the same order of magnitude as the difference between the test run and the blank. An extension of this method to still larger amounts of ketone does not appear a promising way of measuring its extremely small degree of enolization.

Summary

1. The rate of the chloroform reaction has been measured over a range of alkalinity up to 1 M aqueous sodium hydroxide for acetophenone, acetone and pinacolone.

2. The reaction is bimolecular in solutions of pH greater than 11. The reaction velocity passes

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[7] Dawson and Ark, *J. Chem. Soc.*, **99**, 1740 (1911).

through a minimum and in solutions more alkaline than 0.3 M sodium hydroxide the velocity constant is a linear function of the hydroxyl-ion concentration.

3. The results are interpreted in terms of a mechanism involving chlorination of enol and enolate ion by hypochlorous acid and hypochlorite ion.

4. The rates of reaction increase in the order pinacolone, acetone, acetophenone; both the rate of this reaction and the dependence of the rate on the hydroxyl-ion concentration vary much more with the structure of the ketone than does the rate of enolization in an acid medium.

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Arsenated Phenoxyethanols

BY MELVIN R. STEVINSON[1] AND CLIFF S. HAMILTON

Several arsenated phenylglycol ethers have been reported in the literature[2] and some of these, notably β-2-amino-4-arsonophenoxyethanol, possess rather remarkable trypanocidal action. The present investigation deals with a series of arsenated phenoxyethanols formed by condensing propylene chlorohydrin with 4-hydroxyphenylarsonic acid in alkaline solution.

When α-methyl-β-4-arsonophenoxyethanol was nitrated at 0° for approximately twenty minutes with one molecular portion of nitric acid (sp. gr. 1.49–1.50) the corresponding nitrate was obtained. If the reaction was carried out with two molecular proportions of nitric acid at the same temperature and for three hours the nitro ester resulted.

α-Methyl-β-2-nitro-4-arsonophenoxyethyl nitrate was hydrolyzed by refluxing with 3 N hydrochloric acid or 3 N sulfuric acid to yield α-methyl-β-2-nitro-4-arsonophenoxyethanol and this was reduced catalytically to the amine. From 4-β-hydroxy-*n*-propoxyphenylarsonic acid the corresponding oxide was prepared by reduction with sulfurous acid, employing hydriodic acid as a catalyst.

Several arseno derivatives were obtained from the corresponding arsonic acids by reduction with hypophosphorous acid.

Experimental

α-Methyl-β-4-arsonophenoxyethanol and its Sodium Salt.—A solution of 218 g. of 4-hydroxyphenylarsonic acid in 750 cc. of 6 N sodium hydroxide was cooled to 20° and 170 cc. (2 mol. eq.) of propylene chlorohydrin was added cautiously. The mixture was refluxed gently as long as two separate layers could be observed; time, eight to ten hours. The solution was then poured into a beaker surrounded by ice and the arsonic acid was precipitated by the addition of 12 N hydrochloric acid until the mixture was distinctly acid to Congo red paper. The acid was purified by recrystallization from water.

When the acid was dissolved in enough 2 N sodium hydroxide to yield a solution neutral to litmus paper and was filtered into absolute ethanol, the monosodium salt separated as small granular crystals.

α-Methyl-β-2-nitro-4-arsonophenoxyethyl Nitrate.—α-Methyl-β-4-arsonophenoxyethanol (40 g.) was stirred with 80 cc. of nitric acid (sp. gr. 1.50) for three hours at 0°. The product was precipitated by pouring into cold water.

α-Methyl-β-2-nitro-4-arsonophenoxyethanol.—α-Methyl-β-2-nitro-4-arsonophenoxyethyl nitrate (40 g.) was hydrolyzed by refluxing for two hours with 144 cc. of 3 N sulfuric acid. During this time the ester passed into solution and brown fumes of oxides of nitrogen were evolved. By filtering the hot solution and cooling it to 0°, α-methyl-β-2-nitro-4-arsonophenoxyethanol was obtained as a pale yellow, crystalline product. It was purified by recrystallization from water.

α-Methyl-β-2-amino-4-arsonophenoxyethanol and its Acetyl Derivative and Sodium and Potassium Salts.—To a suspension of 32 g. (0.10 mole) of very pure α-methyl-β-2-nitro-4-arsonophenoxyethanol in 200 cc. of water was added 50 cc. of 2 N sodium hydroxide and 10 g. of Raney[3] nickel catalyst. The container was placed on a shaking apparatus and hydrogen gas was introduced under a pressure of 2 atm. Shaking was begun and continued until the solution became colorless and the pressure gage indicated the addition of the required amount of hydrogen. The mixture was filtered free of catalyst and placed in a cooled flask. Sufficient 6 N hydrochloric acid was added to make the solution neutral to Congo red paper, and the flask was stoppered and set away in a refrigerator. Overnight the amino derivative crystallized as slender needles. If further purification was necessary, it was recrystallized from 200 cc. of water. The product was quite sensitive to air oxidation, especially in warm aqueous solutions. When the amine was dried for two and one-half hours at 70° in a vacuum oven, it was obtained anhydrous. Upon standing in contact with air at room temperature it formed the monohydrate. Drying the product for prolonged

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[1] Parke, Davis and Company Fellow.

[2] Benda and Sievers, German Patent 552,267 (1932); L. Cassella and Co., British Patent 373,071 (1932); Sweet and Hamilton, THIS JOURNAL, **56**, 2409 (1934).

[3] Covert and Adkins, *ibid.*, **54**, 4116 (1932).