ally until a permanent precipitate began to form. This, a high-melting impurity, was removed by filtration. The filtrate was diluted further with ether, and the desired product separated. Occasionally it was necessary to repeat this process several times to obtain a constant, sharply-melting product.

Summary

Ten new diethylaminoethyl 4-alkoxybenzilates have been prepared in the form of hydrochlorides and screened for antispasmodic potency. None possesses greater activity than diethylaminoethyl benzilate itself; the n-amoxy derivative is approximately as active as the latter, and has half its acute toxicity.

These and nine additional new diethylaminoethyl benzilate hydrochlorides containing various nuclear ether substituents have also been screened for local anesthetic potency. The n-hexyloxy derivative is the most active of the series.

Eighteen new benzilic acids, eighteen new benzils and eleven new desoxybenzoins were prepared as intermediates.

Relative Chloromethylation Rates of Some Aromatic Compounds[1]

BY H. HARRY SZMANT AND JOSEPH DUDEK

Apparently the only extensive study of relative chloromethylation rates of aromatic compounds is that of Vavon, Bolle and Calin[2]; the conclusions of that study are the only ones quoted in authoritative reviews of the chloromethylation reaction.[3] In this paper we wish to point out certain errors in the results of Vavon and co-workers, and to present what we believe to be more nearly correct relative chloromethylation rates of certain compounds studied by these authors. The rates for a few compounds not previously studied are also reported.

The chloromethylation reaction (I) is accompanied by several competitive reactions (II–IV). The situation may be illustrated with the chloromethylation of benzene.

$$C_6H_6 + CH_2O + HCl \longrightarrow C_6H_5CH_2Cl + H_2O \quad (I)$$

$$C_6H_5CH_2Cl + C_6H_6 \longrightarrow C_6H_5CH_2C_6H_5 + HCl \quad (II)$$

$$2C_6H_5CH_2Cl \longrightarrow$$
$$C_6H_5CH_2C_6H_4CH_2Cl + HCl, \text{ etc.} \quad (III)$$

$$C_6H_5CH_2Cl + C_6H_5CH_2C_6H_5 \longrightarrow$$
$$C_6H_5CH_2C_6H_4CH_2C_6H_5 + HCl, \text{ etc.} \quad (IV)$$
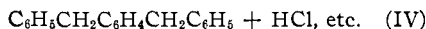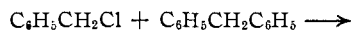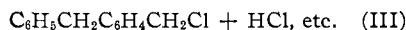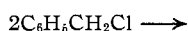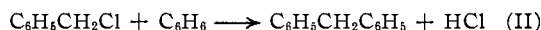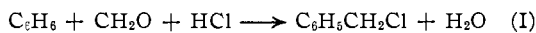
The course of the chloromethylation reaction can be followed by determining ionic chlorine at certain time intervals. However, the various side reactions liberate ionic chlorine from the initial chloromethylated product; hence to evaluate the chloromethylation rate, one must determine the rate of loss of chloride during the initial period of the reaction before the initial chloromethylation product has accumulated. In arriving at the relative chloromethylation rates in this study we have arbitrarily chosen to compare the time intervals required for the loss of ten per cent. of the initial ionic chlorine. In most of the cases studied, a linear relationship between the

rate of chloride loss and elapsed time persisted to the point chosen for the comparison. In a few cases where the curve tended to bend ahead of time, the initial slope was extrapolated to the point chosen for the comparison. The relative chloromethylation rates obtained in this study are listed in Table I, together with the values obtained by Vavon and co-workers. Typical graphs showing per cent. loss of ionic chlorine with time are given in Figs. 1 and 2.

TABLE I

RELATIVE RATES OF CHLOROMETHYLATION

	Compound	$t10\%^a$	Relative rate[b]	Relative rate[c] of Vavon and co-workers
1	Benzene	9.2	1.0	1
2	Toluene	3.0	3.1	3
3	n-Butylbenzene	3.2	2.9	..
4	t-Butylbenzene	3.3	2.8	..
5	p-Xylene	5.7	1.6	2
6	Mesitylene	0.7	13	600
7	Diphenylmethane	12	0.77	..
8	Bromobenzene	19	0.48	..
9	Diphenyl sulfide	10.5	0.88	..
10	Diphenyl ether	6.1	1.5	100
11	Anisole	0.4	23	1334
12	p-Methyl cresyl ether	1.25	7.4	1200

[a] Time (in minutes) required for a 10% decrease in initial chloride concentration. [b] Relative rate ($t10\%$ of benzene)/($t10\%$ of compound). [c] Relative rates reported in ref. 2.

Experimental

All chloromethylation experiments were carried out by allowing 0.1 mole of the aromatic starting material, 0.11 mole of paraformaldehyde and 9 ml. of concd. hydrochloric acid (equivalent to 0.11 mole hydrogen chloride) to react in 125 ml. of glacial acetic acid. In order to avoid any reaction at temperatures other than the desired one, all the formaldehyde, hydrochloric acid and 100 ml. of the acetic acid were heated with stirring in the reaction flask until the desired temperature (85°) was reached, and then (at zero time) the preheated mixture of the compound under study was added in 25 ml. of acetic acid. Samples (2 ml.) were withdrawn from the reaction mixture at desired intervals

(1) Presented at the San Francisco meeting of the American Chemical Society. March. 1949.

(2) Vavon. Bolle and Calin. Bull. soc. chim., 6, 1025 (1939).

(3) Fuson and McKeever, in "Organic Reactions." John Wiley and Sons. Inc.. New York. N. Y.. 1942. Vol. I, p. 66.
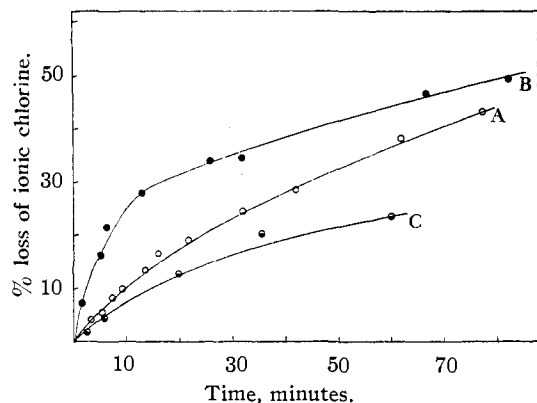
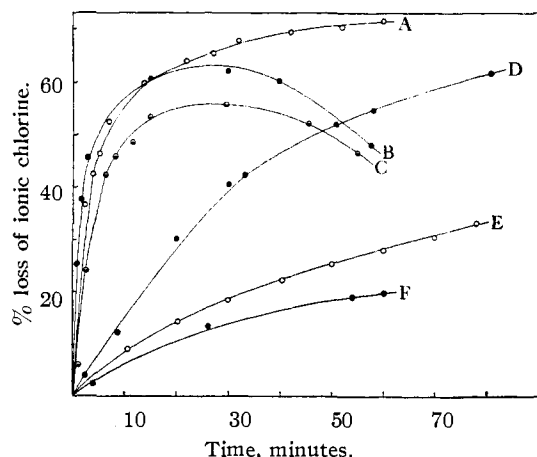Fig. 1.—Chloromethylation curves at 85°: A, benzene; B, toluene; C, diphenylmethane.

Fig. 2.—Chloromethylation curves at 85°: A, mesitylene; B, anisole; C, p-methyl cresyl ether; D, diphenyl ether; E, diphenyl sulfide; F, bromobenzene.

(two to ten minutes, depending on the rate) and introduced into separatory funnels containing 50 ml. of carbon tetrachloride and 25 ml. of water. The contents of the separatory funnel were shaken for approximately thirty seconds, the two layers were allowed to separate, and the lower layer containing the chloromethylation product, starting material, and carbon tetrachloride was drained off. The chloride ion concentration of the aqueous layer was determined in the separatory funnel by means of the conventional Volhard method.[4] The chloride concentration of the reaction mixture was calculated from the relative volumes of the reaction mixture and the sample. The initial chloride concentration was determined in the same fashion by withdrawing a sample of the mixture before the addition of the compound to be chloromethylated. The results of each experiment are plotted as per cent. chloride lost from the reaction mixture against time.

Several possible sources of error resulting from the experimental procedure may be considered. The volume of the reaction mixture at any given time was calculated from the final volume, and possible changes in volume resulting from changes in the composition of the reaction mixture were ignored. This error was minimized, however, by the use of a relatively large volume of solvent. Furthermore, it may be assumed that the changes occurring in the volume of the reaction mixture during the course of the chloromethylation are similar in all the experiments and thus do

(4) Caldwell and Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935).

not affect seriously the *relative* results. In order to check the reliability of the extraction method employed in the analysis, a mixture of the freshly distilled benzyl chloride (0.1 mole), 125 ml. of acetic acid and 9 ml. of water (in place of the hydrochloric acid) was analyzed for chloride ion. The amount of chloride ion was found to be 1–2% of the chloride ion concentration in the chloromethylation experiments. Since the critical part of the chloromethylation reaction is the initial stage during which there is relatively little chloromethylated product, it is believed that the hydrolysis of the product during the extraction does not affect seriously the results obtained.

Discussion

Inspection of Table I reveals that the results obtained in the present study are not in agreement with those of Vavon and co-workers in the cases of compounds which tend to chloromethylate very readily (as compared with benzene). These discrepancies may be accounted for, at first glance, by the fact that the reagent used by Vavon was chloromethyl ether rather than a mixture of paraformaldehyde and hydrochloric acid. Otherwise, both studies employed the same solvent, and used essentially the same method of analysis. While the absolute chloromethylation rates are, no doubt, affected by the difference in the reagent, we believe that the discrepancies in the relative rates are explained by the method by which the previous workers arrived at the relative chloromethylation rates. They chose as a point of comparison the time required for the loss of 30% of ionic chlorine at a temperature of 65°. However, in order to obtain convenient time intervals their experiments were carried out in a temperature range of 15–100°, and the time intervals required for 30% loss of ionic chlorine were then converted to time intervals corresponding to a temperature of 65°, by methods not indicated in the publication. It seems reasonable to assume that such calculations are not valid since the activation energies of the various reactions (I–IV) are not known, and since the temperature coefficients of these reactions are not necessarily the same. This view is supported by the fact that satisfactory agreement between the two sets of results is found only in the case of compounds which Vavon and co-workers studied at the same temperature. Compounds 1, 2 and 5 were all studied at 100° and since this set includes benzene, the rates obtained for these compounds agree with those of the present study. Compounds 6, 10, 11 and 12 were studied at 65° and while the relative rates reported differ from ours by a great margin, the relative rates *within* this set of compounds are in closer agreement with our results. This is brought out clearly by comparing Vavon's relative rates with ours, taking the rate of diphenyl ether[5] as unity. His relative rates then become for mesitylene, anisole and p-methylcresyl ether: 6, 13.3 and

(5) Additional information on the temperature coefficients of the various reactions occurring during the chloromethylation process will be presented in a forthcoming publication dealing with the chloromethylation of diphenyl sulfide.

12, as compared with our rates of 8.7, 15 and 4.9, respectively.

While the exact mechanism of chloromethylation of aromatic compounds is not known, and probably depends on the nature of the chloromethylation reagent which is employed, it can be safely assumed that the chloromethylation reaction falls into the broad class of substitution reactions brought about by electrophilic reagents.[6] Thus, the relative chloromethylation rates are in accord with those to be expected from the usual effect of substituent groups on the reactivity of the benzene ring in other substitution reactions involving an electrophilic reagent.

The initial slope of the curves depicting the change in ionic chlorine with time is directly related to the rate of chloromethylation; the actual shape of the curves, on the other hand, depends on the extent to which the competing reactions interfere with the principal chloromethylation process. Work is in progress to determine how the competing reactions are related to the chemical structure of the compound being chloromethylated. The effect of the competitive reactions on the shape of the chloromethylation curve is clearly demonstrated in the comparison of anisole and mesitylene (Fig. 2). Both compounds are very reactive in the principal chloromethylation reaction, but the initial chloromethylated product of anisole undergoes further reactions which restore ionic chlorine to the mixture. Since chloromethylmesitylene is capable of undergoing further substitution reactions[7] the lack of side-reactions in this case may be due to the relative inertness of chloromethylmesitylene as an aralkylating agent.

Acknowledgment.—The authors wish to express their appreciation to Mr. Joseph Anzenberger for his technical assistance in several of the experiments, and to Drs. T. H. Dunkelberger and O. Gawron for their interest in this work and helpful suggestions. Dr. Gawron originally suggested the kinetic approach to the chloromethylation study of diphenyl sulfide.

Summary

The relative chloromethylation rates of twelve aromatic compounds have been determined. The relative rates of six compounds have been critically compared with those previously reported, and the discrepancies between the new and old rates have been explained. The relative order of the chloromethylation rates was found to be in general agreement with that expected from the effect of the substituent on the substitution reactions of benzene involving an electrophilic reagent.

(6) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 90.

(7) Excellent yields of the dichloromethylated mesitylene can be obtained (ref. 3, p. 76).

The Catalytic Hydrogenation of Terpenes

BY HILTON A. SMITH, JOHN F. FUZEK AND HENRY T. MERIWETHER

Introduction

While a number of studies dealing with the catalytic hydrogenation of terpenes have been reported, few investigations have been concerned with the kinetics of this process. Furthermore, much of the work has been done with mixtures of terpenes, rather than with pure compounds. The present work was undertaken in order to study the kinetics of the catalytic hydrogenation of certain terpenes which could be obtained in a reasonably pure state.

Experimental

Dipentene, terpinolene, α- and β-pinenes and camphene were all furnished in relatively pure form by the Hercules Powder Company of Wilmington, Delaware. Four of these terpenes were fractionated before use through an eight-foot Vigreux column in an atmosphere of carbon dioxide. The other, β-pinene, was fractionated in the same column under vacuum. Constant boiling cuts were obtained for each material. d-Limonene was purchased from the Eastman Kodak Company, and carefully fractionated in an atmosphere of carbon dioxide. The constant boiling fraction used had an optical rotation $\alpha^{20}D$ of 104°. Head temperatures and refractive indices of the terpenes used are given in Table I.

Tank hydrogen[1] was used without further purification. Methanol and acetic acid, which were used as solvents, were prepared by fractionation of du Pont methanol or C. P. glacial acetic acid in a five-foot helix-packed still. Sodium oleate and palmitic acid were Merck U.S.P. and Eastman Kodak Co. best grade materials, and were used without further purification. The nickel catalyst was prepared from Raney alloy and the platinum catalyst from platinic chloride in the standard manner.[2,3] The nickel was stored under ethanol.

(1) Purchased from the National Cylinder Gas Co. of Chattanooga, Tenn.

(2) Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(3) Adams, Voorhees and Shriner, "Organic Syntheses," Coll. Vol. I, 463 (1944).