product after one recrystallization from methanol–isopropyl alcohol remained constant at 255–256°.

Methyl Ethers of 1-(2-Thienyl)-2-N,N-disubstituted Aminoethanols (IE-G) (Method E).—These compounds, prepared by the method A of a previous publication,[16] are described in Table I.

Reaction of 2-(1-Piperidyl)-ethyl 2-Thienyl Ketone with Grignard Reagents.—An ether solution of cyclohexylmagnesium bromide, prepared from 29.2 g. (1.2 moles) of magnesium turnings and 163.1 g. (1.0 mole) of cyclohexyl bromide, and 0.50 mole of 2-(1-piperidyl)-ethyl 2-thienyl ketone (IIC), prepared without isolation by method C, was refluxed for one hour and then decomposed with 250 ml. of saturated aqueous ammonium chloride solution. The aqueous layer was separated and extracted several times with ether. The organic layer was combined with the ether extracts, dried over anhydrous magnesium sulfate and the ether removed by distillation. Distillation of the residue yielded 58.0 g. of the ketone (IIC) as a yellow oil, b.p. 125–127° (0.30 mm.). Some decomposition apparently occurred during the distillation as difficulty was experienced in maintaining a constant pressure and a considerable amount of tarry non-distillable residue remained in the distillation flask.

Anal. Calcd. for $C_{11}H_{15}NOS$: S, 15.32. Found: S, 15.20.

The hydrochloride, recrystallized to constant melting point from methanol–isopropyl alcohol, melted at 245–247°.

Anal. Calcd. for $C_{11}H_{15}NOS{\cdot}HCl$: Cl, 14.42. Found: Cl, 14.57.

The melting point of the hydrobromide, after one recrystallization from methanol–isopropyl alcohol, was 255–256° and was not depressed by admixture with an authentic sample of the hydrobromide of IIC.

In a similar manner the reaction of methylmagnesium iodide with IIC yielded, in addition to some unreacted aminoketone, a fraction, b.p. 120–140° (0.45 mm.), from which no crystalline salts or esters could be prepared.

Anal. Calcd. for $C_{12}H_{19}NOS$: OH, 7.54. Found: OH, 2.68.

Acknowledgment.—The authors gratefully acknowledge the financial support of this investigation by The Society of the Sigma Xi and Research Corporation and wish to thank the Fine Chemicals Division, Nopco Chemical Co., for the use of their laboratory facilities during part of this work.

BROOKLYN 10, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND LABORATORY FOR NUCLEAR SCIENCE AND ENGINEERING, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Mechanisms of Acid Catalysis. The Kinetics and Mechanisms of the Acid-catalyzed Reactions of Ethyl Diazoacetate with Ethanol and Acetic Acid[1]

BY JOHN D. ROBERTS, CLARE M. REGAN AND INKA ALLEN

RECEIVED JANUARY 4, 1952

The *p*-toluenesulfonic acid-catalyzed reaction of ethyl diazoacetate with ethanol has been found to have different hydrogen isotope and solvent effects from the formally similar reaction with diphenyldiazomethane. Deuterium-exchange experiments have demonstrated that ethyl diazoacetate is involved in a rapid and reversible equilibrium with the corresponding diazonium ion with *p*-toluenesulfonic acid in ethanol, in the absence of strong acid in acetic acid or with acetic acid in benzene. It is concluded that the general-acid and "specific-oxonium" catalyzed reactions of diazo compounds involve different types of mechanisms.

One of the vexing problems in the unraveling of the mechanisms of acid-catalyzed reactions is the question of the ultimate mechanistic difference between general-acid and "specific-oxonium" catalysis. General-acid catalysis, as its name implies, involves catalysis by all effective proton-donating species present in a given medium while, with "specific-oxonium" catalysis, the reaction rate is dependent on the concentration of oxonium ion or, more precisely, on the lyonium-ion activity.[2,3] Although there seems to be little dispute that the rate-determining step in a general-acid catalyzed reaction involves a proton transfer[2] it is fair to say that the rate-determining steps of but few LIAC reactions are known with certainty. The difficulty arises primarily from the fact that experimental distinction between the various alternatives is by no means straightforward and, indeed, there is question as to whether one mechanism or type of mechanism will suffice for different substrates. The most likely possibilities[2] for the rate-determining steps of LIAC reactions are: (1) a rate-determining proton transfer to substrate with the lyonium ion functioning as the only effective general acid[2,4] (*i.e.*, a steep slope for the Brønsted catalysis law plot); (2) a termolecular reaction involving substrate, lyonium ion and solvent (or other suitable nucleophilic agent),[2,5-7] again with lyonium ion as the only effective proton-donating agent; or (3) a rapid reversible proton transfer to substrate followed by a rate-determining non-protolytic reaction.[2b,8] It was the purpose of the present

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[1] Supported in part by the program of research of the United States Atomic Energy Commission.

[2] (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chap. VII–IX; (b) R. P. Bell, "Acid–Base Catalysis," Oxford University Press, London, 1941.

[3] The designation, "specific-*oxonium*" catalysis, is undesirable since it is perfectly conceivable that systems can be devised which would exhibit analogous phenomena without involving *oxonium* ions at all. A designation which obviates this difficulty is *lyonium-ion activity-controlled* catalysis or, for short, *LIAC*-catalysis. A concise alternative name, H_0-dependent catalysis, was pointed out to us to be undesirable by Dr. Ernest Grunwald on the grounds that the necessary condition for an H_0-function (*i.e.*, $f_B/f_{BH^\oplus}$ a function of solvent alone) is not satisfied for a number of common solvent systems such as ethanol–water in which acid-catalyzed reactions are often studied.

[4] J. N. Brønsted, *Chem. Revs.*, **5**, 231 (1928).

[5] T. M. Lowry, *J. Chem. Soc.*, 2554 (1927).

[6] C. K. Ingold and C. L. Wilson, *ibid.*, 93 (1934); (b) S. K. Hsü, C. K. Ingold and C. L. Wilson, *ibid.*, 1778 (1935).

[7] C. G. Swain, THIS JOURNAL, **72**, 4578 (1950).

[8] (a) K. J. Pedersen, "Den almindelige Syre- og Basekatalyse," Copenhagen, 1932; *cf.*, R. P. Bell, *Proc. Roy. Soc.* (*London*), **A154**, 414 (1936); (b) it should be clear that a pre-equilibrium involving proton transfers from solvent to substrate will lead to an apparent general acid catalysis when the rate-determining step is reaction between the conjugate acid of the substrate and any bases present. The isotope effects on the acid-catalyzed bromination of acetone, K. F. Bonhoeffer, *Trans. Faraday Soc.*, **34**, 252 (1938), provide strong evidence for an example of the operation of this type of stepwise mechanism.

research to obtain further information as to which of these three mechanisms best correlates the classical LIAC reactions of ethyl diazoacetate (diazoacetic ester) of the type

$$ROH + N_2{=}CHCO_2C_2H_5 \xrightarrow{H^+} ROCH_2CO_2C_2H_5 + N_2$$

These processes are of particular interest since, despite the reported general-acid catalysis in benzene,[9] kinetically termolecular reactions of ethyl diazoacetate involving nucleophilic agents are well known[10] and indirect evidence has been obtained for protolytic pre-equilibria by the variation of the reaction rate with medium composition in mixtures of light and heavy water.[11]

The question of general-acid catalysis of diazoacetic ester reactions will be considered first. Such catalysis was reported by Snethlage[12] for undissociated picric acid in ethanol and disputed by Brønsted[4] and Bell.[2b] Qualitative confirmation of the validity of the objections may be obtained as follows. In the alcoholysis of diphenyldiazomethane, where picric acid serves as a *bona fide* general-acid catalyst,[13] the over-all reaction rate *increases* about 50% in the transition from zero to 0.1 *M* picrate ion and, after allowance for salt effects, it is found that undissociated picric acid has more than 95% of the catalytic effectiveness of ethyloxonium ion.[13] On the other hand, with ethyl diazoacetate, where the salt effects are considerably larger (*cf.* Fig. 1), the rate *decreases* fourfold on going to 0.09 *M* picrate ion.[12] It seems reasonable that undissociated picric acid is not filling a similar function in each reaction. Further evidence is supplied by the similarity in concentration dissociation constant K_c (4.2×10^{-3} mole/l.) at 25° and $\mu = 0.09$ calculated by Bell[2b] from Snethlage's rate data assuming no general-acid catalysis and the measured value of K_c (3.2×10^{-3} mole/l.) obtained at 30° and $\mu = 0.1$.[13]

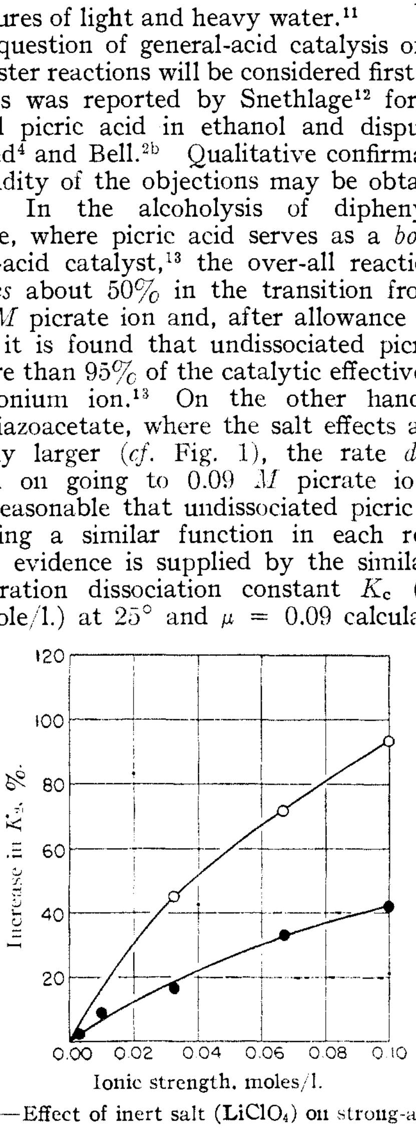

Fig. 1.—Effect of inert salt ($LiClO_4$) on strong-acid catalyzed reactions in absolute ethanol: O, ethyl diazoacetate, 0.00503 *M* *p*-toluenesulfonic acid; ●, diphenyldiazomethane, 0.000334 *M* *p*-toluenesulfonic acid (data from Roberts and Watanabe[13]). The ordinate values represent the percentage change of k_2 over value at $\mu = 0$.

The reality of the "general-acid catalysis" reported for benzene solutions[9] may well depend on definitions of terms. We believe it is reasonable to expect that there can be reactions of the LIAC type in the formal absence of lyonium ions through operation of a pre-equilibrium between acid and substrate followed by a rate-determining nonprotolytic reaction. Consequently, we hesitate to class reactions which are clearly LIAC in amphoteric solvents, as being general-acid catalyzed, solely on the basis of the presence of an aprotic solvent, in the absence of proof for a fundamental change of mechanism in aprotic solvents. This point will be considered again later.

Considerable evidence has now been obtained for differences in the rate-determining steps of the formally similar alcoholyses of diphenyldiazomethane and ethyl diazoacetate. The reactions of the former substance, which show unmistakable general-acid catalysis,[13,14] were found to have quite different solvent and hydrogen isotope effects from ethyl diazoacetate reactions. Thus, while additions of 28.6% (by volume) of nitrobenzene, chloroform or benzene to the ethanol solvent *increase* the rate of the *p*-toluenesulfonic acid-catalyzed reaction of diphenyldiazomethane with ethanol by 23–70% (*cf.* Table I), similar solvent changes *decrease* by 35–43% the rate of ethanolysis of ethyl diazoacetate. The effects of water on the rates are in the same direction but of rather different magnitudes. Thus, on going to 0.50 *M* water the rate of the diphenyldiazomethane reaction drops about 50%[13] while that of ethyl diazoacetate is reduced about sixfold as shown in Fig. 2. As

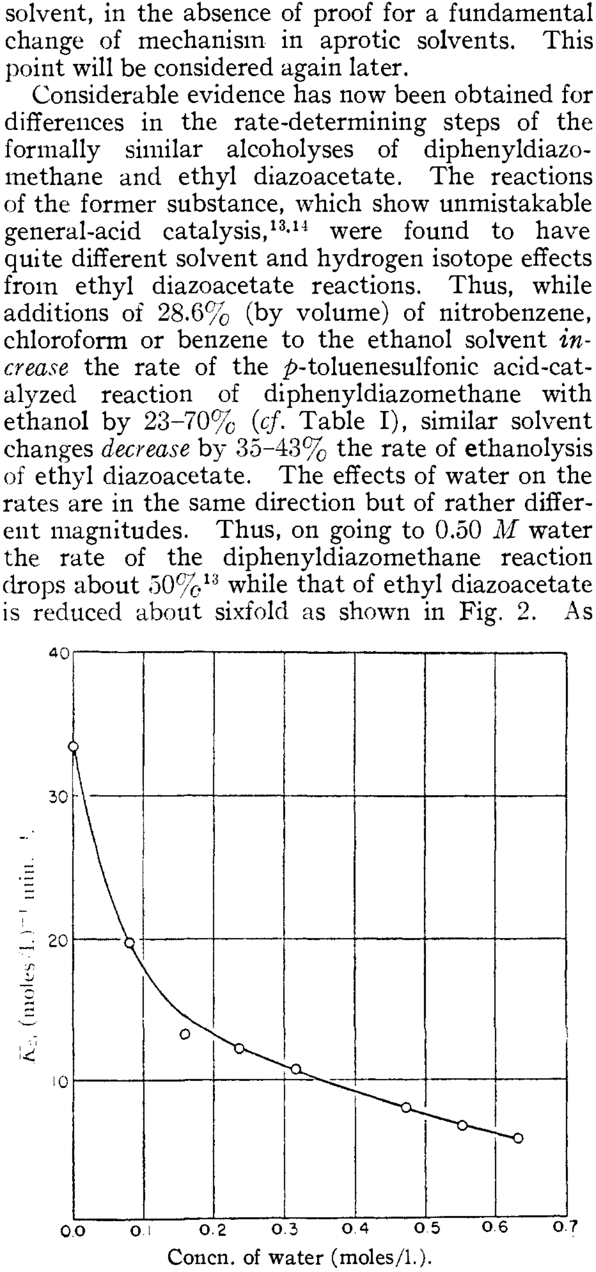

Fig. 2.—Effect of water on rate of 0.00636 *M* *p*-toluenesulfonic acid-catalyzed reaction of ethyl diazoacetate with ethanol.

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[9] J. N. Brønsted and R. P. Bell, THIS JOURNAL, **53**, 2478 (1931).

[10] (a) G. Bredig and P. F. Ripley, *Ber.*, **40**, 4015 (1907); (b) H. Lachs, *Z. physik. Chem.*, **73**, 291 (1910).

[11] P. Gross, H. Steiner and H. Suess, *Trans. Faraday Soc.*, **32**, 883 (1936).

[12] H. C. S. Snethlage, *Z. Elektrochem.*, **18**, 539 (1912).

[13] J. D. Roberts and W. Watanabe, THIS JOURNAL, **72**, 4869 (1950).

[14] (a) J. D. Roberts, R. E. McMahon and W. Watanabe, *ibid.*, **73**, 760 (1951); (b) **73**, 2521 (1951).

was pointed out previously,[13] the influence of water on the former reaction is due to conversion of an effective general-acid catalyst, ethyloxonium ion, to a less effective one, hydronium ion. With ethyl diazoacetate, the change in rate is due to reduction of the protonating power of the medium.[15] The effects of neutral salt on the strong-acid catalyzed reactions of the two diazo compounds in ethanol are in the same direction but the effect on the reaction of ethyl diazoacetate is substantially larger (*cf.* Fig. 1). Replacement of the O–H groups of the solvent by O–D groups uniformly and markedly decreases the rates of diphenyldiazomethane reactions while with ethyl diazoacetate substantial accelerations are observed (*cf.* Table II). While the difference in isotope effects cannot be regarded as an absolute indication of differences in reaction mechanism, the enhancement of rate with ethyl diazoacetate indicates the operation of a substrate–catalyst equilibrium before the rate-determining step.[8b,11,16]

TABLE I

RATES OF REACTION OF DIPHENYLDIAZOMETHANE AND ETHYL DIAZOACETATE IN ABSOLUTE ETHANOL AT 30.0°

p-Toluenesulfonic acid, mole/l.	Diazo compound, mole/l.	Solvent diluent	k_2 (moles/l.)$^{-1}$ min.$^{-1}$
0.000251	0.00230 DDM[a]	....	243
.000251	.00230 DDM	Benzene[b]	298
.000251	.00230 DDM	Chloroform[c]	412
.000251	.00230 DDM	Nitrobenzene[d]	412
.00836	.01574 EDA[e]	....	31.5
.00836	.01574 EDA	Benzene[b]	20.6
.00836	.01574 EDA	Chloroform[c]	17.6
.00836	.01574 EDA	Acetone[f]	17.8

[a] DDM, diphenyldiazomethane. [b] Solvent was 28.6% benzene–71.4% ethanol (by volume). [c] Solvent was 28.6% chloroform–71.4% ethanol (by volume). [d] Solvent was 28.6% nitrobenzene–71.4% ethanol (by volume). [e] EDA, ethyl diazoacetate. [f] Solvent was 28.6% acetone–71.4% ethanol (by volume).

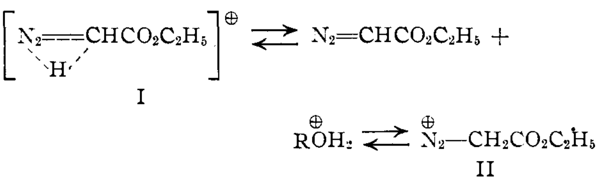
TABLE II

HYDROGEN ISOTOPE EFFECTS ON THE REACTIONS OF DIPHENYLDIAZOMETHANE AND ETHYL DIAZOACETATE IN VARIOUS SOLVENTS

Diazo compound	Acid	Solvent	Temp., °C.	k_H/k_D	Investigation
DDM[a]	TsOH[b]	82.5% C_2H_5OH–17.5% H_2O	30.0	1.45[c]	Ref. 13
DDM	BzOH[d]	82.5% C_2H_5OH–17.5% H_2O	30.0	1.61[c]	Ref. 14a
DDM	BzOH	C_2H_5OH	30.0	3.62[e]	This research
EDA[f]	TsOH	C_2H_5OH	30.0	0.55[e]	This research
EDA	H_2SO_4	H_2O	0.0	0.47[g]	Ref. 11

[a] Diphenyldiazomethane. [b] *p*-Toluenesulfonic acid. [c] Deuterated solvent had 38% of O–H bonds replaced by O–D bonds. [d] Benzoic acid. [e] Deuterated solvent was C_2H_5OD. [f] Ethyl diazoacetate. [g] Deuterated solvent was D_2O.

A substrate–catalyst pre-equilibrium with ethyl diazoacetate might be expected to involve either (1) a more or less loosely protonated species with the proton associated with the diazo group (I) or (2) a *bona fide* diazonium ion (II).[17] The bonding of the proton in I might be formulated as



I

II

postulated by Dewar.[18] An essential difference between I and II is that with II, but not I, the α-hydrogen of the ester and the added proton are fully equivalent. Formation of II was conclusively demonstrated by the finding that ethyl diazoacetate reacts with C_2H_5OD in the presence of a strong acid to yield a deuterated ethyl ethoxyacetate with the extent of deuteration depending on the ratio of C_2H_5OD to ethyl diazoacetate (see Table III). If II (or the equivalent) were not in equilibrium with the diazoacetate only *one* deuterium atom should be present in each molecule of ethyl ethoxyacetate formed, irrespective of the C_2H_5OD–ethyl diazoacetate ratio. The excess deuteration was shown not to be due to exchange of the product with solvent by control experiments.

The demonstration of an equilibrium step involving II does not prove beyond doubt that II is an intermediate in the formation of final product since conceivably II might be formed in a side reaction. However, there seems little question that II is a reasonable intermediate since it has strongly electrophilic carbon and should be readily susceptible to attack by nucleophilic agents to yield the observed products.[2a]

TABLE III

DEUTERIUM ANALYSES OF PRODUCTS FROM REACTIONS OF ETHYL DIAZOACETATE WITH DEUTERATED SOLVENTS

Solvent	Molal ratio, solvent to ethyl diazoacetate	Atom % D Calcd.[a]	Atom % D Found[b]
C_2H_5OD[c]	0.87	7.7	7.7
C_2H_5OD[c]	1.74	10.6	9.8
C_2H_5OD[c]	8.7	14.9	13.9
CH_3CO_2D[d]	1.09	9.8	10.0
CH_3CO_2D[d]	2.16	13.0	12.5
CH_3CO_2D[d]	20.0	19.1	16.4
CH_3CO_2D–C_6H_6[d]	1.79[c]	12.8	10.6
CH_3CO_2D–C_6H_6[d]	20.9[e]	19.2	15.8

[a] Calculated assuming complete equilibration between α-hydrogen of ethyl diazoacetate and O–H hydrogens of the solvents (equilibrium constants for H and D were assumed to be equal). [b] Determined by combustion and analysis of the resulting water by the "falling-drop" procedure. [c] Product was ethyl ethoxyacetate. [d] Product was ethyl acetoxyacetate. [e] Ratio of CH_3CO_2D to ethyl diazoacetate.

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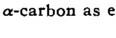
(15) E. A. Braude and E. S. Stern, *J. Chem. Soc.*, 1982 (1948).

(16) W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **34**, 245 (1938). See, however, H. Gilman, G. E. Dunn and G. S. Hammond, THIS JOURNAL, **73**, 4499 (1951).

(17) Other protonated species might be written such as



$N_2{=}CH\overset{\overset{OH^{\oplus}}{\|}}{C}OC_2H_5$ but the proton in these would not appear to facilitate the rate-determining attack of a nucleophilic agent at the α-carbon as effectively as in I or II.

(18) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, p. 17.

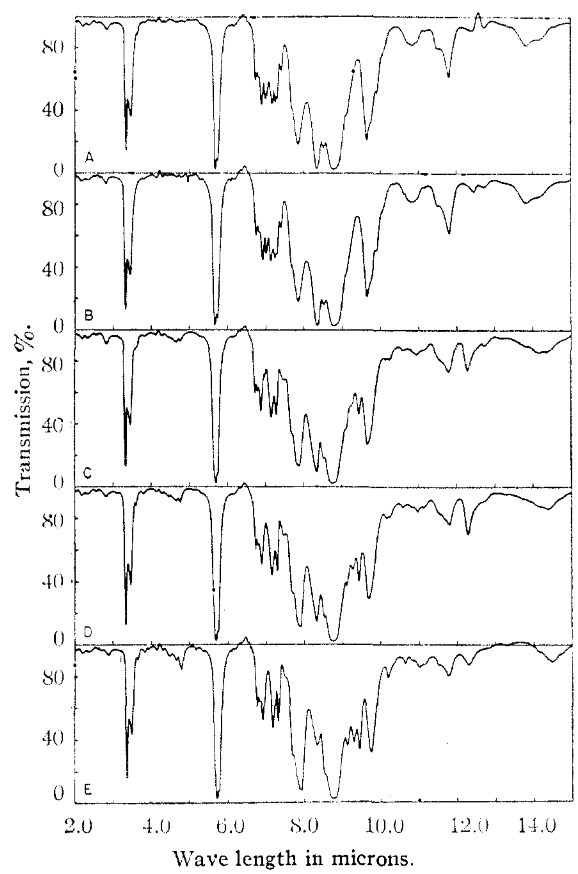


Fig. 3.—Infrared spectra of deuterated ethyl ethoxyacetates. Baird spectrograph with NaCl prism, solutions of 50 mg. of compounds in 0.50 ml. of carbon disulfide except in the regions 4.2–5.0 and 6.2–7.4 μ where carbon tetrachloride was the solvent: A, ethyl ethoxyacetate from C_2H_5OH and ethyl diazoacetate; B, ethyl ethoxyacetate recovered from treatment with C_2H_5OD in presence of HBF_4 catalyst after several days at room temperature; C, ethyl ethoxyacetate from 1:0.87 molal ratio of C_2H_5OD to ethyl diazoacetate; D, 1.74:1 molal ratio; E, 8.7:1 molal ratio.

Ethyl diazoacetate reacts quite slowly with glacial acetic acid at room temperature and qualitative experiments showed that the rate is no more affected by addition of acetate ion than by addition of neutral salt. The situation here corresponds closely to that which obtains in the reaction of α-diazoacetophenone with acetic acid[19] and the product, ethyl acetoxyacetate, can be formed either by a direct reaction of acetic acid with the diazo ester similar to that postulated for diphenyldiazomethane and benzoic acid[14] or a stepwise process involving a rate-determining attack of acetate ion on II (or I). Evidence for the latter mechanism (Eq. 1) was obtained by using CH_3CO_2D as solvent and it was found that the amount of deuterium in

$$N_2{=}CHCO_2C_2H_5 + HOAc \xrightleftharpoons{\text{fast}} \text{II (or I)} + \overset{-}{O}Ac \xrightarrow{\text{slow}} AcOCH_2CO_2C_2H_5 + N_2 \quad (1)$$

the product was dependent on the CH_3CO_2D–ethyl diazoacetate ratio as would be expected for a pre-equilibrium forming II (see Table III).

Similar indications of pre-equilibria were found in the reaction of ethyl diazoacetate with acetic acid in benzene and, as before, the degree of introduction of deuterium with CH_3CO_2D as the reactive species depended markedly on the CH_3CO_2D–ethyl diazoacetate ratio. As a result, doubt is cast on the classification of reactions of ethyl diazoacetate with carboxylic acids in aprotic solvents as "general-acid catalyzed"[9] so far as the classification implies that the slow steps of the reactions are proton additions. These reactions in aprotic solvents are well formulated by Hammett.[2a]

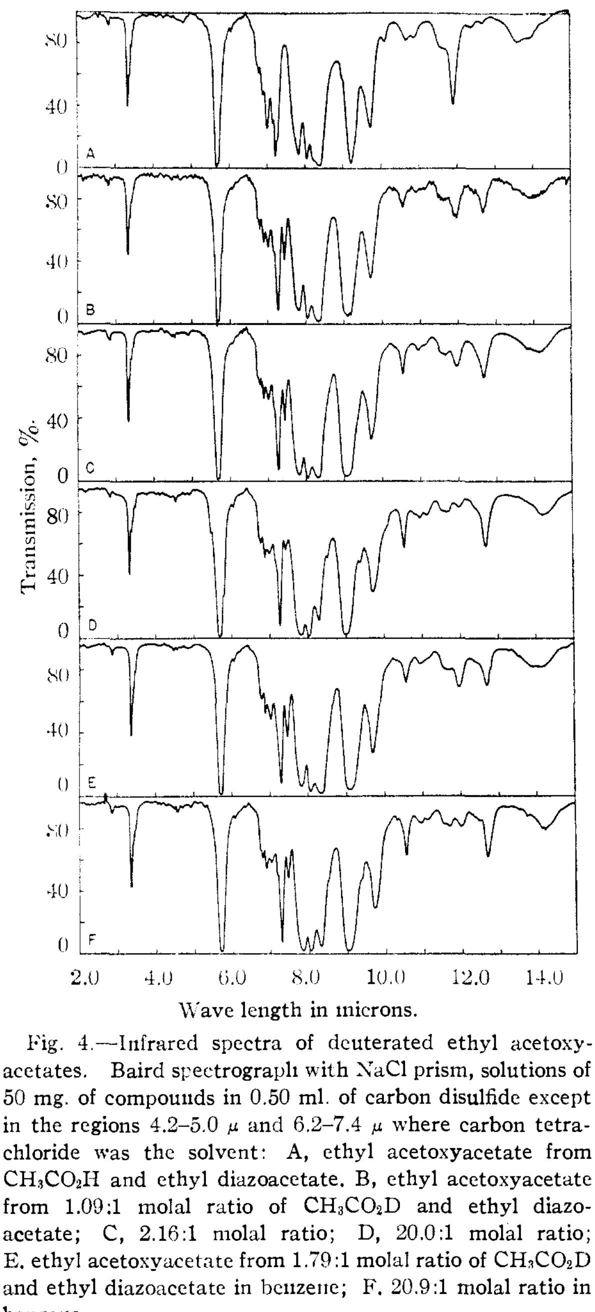


Fig. 4.—Infrared spectra of deuterated ethyl acetoxyacetates. Baird spectrograph with NaCl prism, solutions of 50 mg. of compounds in 0.50 ml. of carbon disulfide except in the regions 4.2–5.0 μ and 6.2–7.4 μ where carbon tetrachloride was the solvent: A, ethyl acetoxyacetate from CH_3CO_2H and ethyl diazoacetate. B, ethyl acetoxyacetate from 1.09:1 molal ratio of CH_3CO_2D and ethyl diazoacetate; C, 2.16:1 molal ratio; D, 20.0:1 molal ratio; E, ethyl acetoxyacetate from 1.79:1 molal ratio of CH_3CO_2D and ethyl diazoacetate in benzene; F, 20.9:1 molal ratio in benzene.

Acknowledgment.—We are indebted to Mr. David B. Kellom for the deuterium analyses reported in Table III.

Experimental

Rate Measurements.—The spectrophotometric apparatus and techniques used for following the rates of diphenyl-

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(19) J. F. Lane and R. L. Feller, This Journal, **73**, 4230 (1951).

diazomethane reactions have been described earlier in detail.[13,14] The same methods were found to be considerably more convenient than the classical gasometric procedures for following the rates of ethyl diazoacetate reactions. With this substance (prepared by the usual method[20] and distilled under reduced pressure before use) the change in concentration was followed by the change in optical density at 375 mμ (ε 15.7 in absolute ethanol).

Deuterated Solvents. A. Deuteroethanol (C_2H_5OD).—The following procedure is ideal for the preparation of C_2H_5OD with maximum deuterium utilization but suffers from the relative inaccessibility of the starting material, ethyl orthocarbonate. A mixture of 140 g. (0.73 mole) of freshly distilled ethyl orthocarbonate,[21] 12.7 ml. (0.70 mole) of 99.75% deuterium oxide (Norsk Hydro) and one drop of concd. sulfuric acid was placed in a flask attached to a short Vigreux column and refluxed gently until it became homogeneous. The material with b.p. 78–82° (79 g.) was then collected and refractionated through a carefully-dried 50-cm. column packed with 2-mm. stainless-steel helices. The product had b.p. 78.5–79°, n^{25}D 1.3583, and showed only very weak hydroxyl (O–H) and carbonyl absorption in the infrared. A saponification equivalent analysis indicated the presence of 1% or less of ethyl carbonate. The paraffin oil method of Robertson[22] indicated the presence of 0.5% of heavy water in the deuteroethanol.

Anal. Calcd. for C_2H_5OD: C, 51.03: H (total), 14.99. Found: C, 51.04; H (total) 14.88.

B. Deuteroacetic Acid (CH_3CO_2D).—Deuterium oxide (99.75%, 6.0 g., 0.30 mole) was refluxed for an hour with 35 g. (0.34 mole) of freshly distilled acetic anhydride. The mixture was fractionated and yielded 40 g. of CH_3CO_2D, b.p. 116–117°, n^{25}D 1.3686–1.3689.

Reaction of Ethyl Diazoacetate with Deuteroethanol.—Mixtures of ethyl diazoacetate and C_2H_5OD in molal ratios of 1:0.87, 1:1.74 and 1:8.7 were cooled in an ice-bath and a trace of concd. fluoboric acid added. Other acids such as hydrochloric, sulfuric, perchloric or *p*-toluenesulfonic acid were ineffective at the lower ratios since they appeared to react irreversibly with the diazo ester. The mixtures were allowed to stand overnight at room temperature, the excess alcohol was removed under reduced pressure and the residual ethyl ethoxyacetate fractionated (b.p. 50°, 10 mm.) through a semimicro column.[23] The mixtures were compared as to deuterium content by their infrared spectra (Fig. 3) and combustion analysis (Table III).

The infrared spectrum of the recovered ethyl ethoxyacetate obtained from a mixture of ethyl ethoxyacetate and deuteroethanol which was allowed to stand for several days in the presence of fluoboric acid is included in Fig. 3.

Reaction of Ethyl Diazoacetate with Deuteroacetic Acid.—The procedure was similar to that used for the deuteroethanol experiments except that no catalyst was used and the reactions were so slow that some heating was required. The products had b.p. 62° (10 mm.) after fractionation through a semi-micro column.[23] The infrared spectra of the products are given in Fig. 4 and the results of the combustion analyses are presented in Table III.

The reactions in benzene (90% by volume) were carried out similarly. The rates were slow and the mixtures were refluxed from 24–40 hr. The infrared spectra of the products are given in Fig. 4 and it is seen that there is no significant difference between the materials obtained in the presence or absence of benzene.

CAMBRIDGE 39, MASSACHUSETTS

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[20] E. B. Womack and A. B. Nelson, *Org. Syntheses*, **24**, 56 (1944).

[21] We are indebted to Dr. Robert E. McMahon for this material which was prepared by a modification of the method of H. Tieckelmann and H. W. Post, *J. Org. Chem.*, **13**, 265 (1948). The procedure will be published in detail elsewhere.

[22] G. R. Robertson, "Laboratory Practice of Organic Chemistry," 2nd Ed., The Macmillan Co., New York, N. Y., 1943, p. 177. We assume here that deuteroethanol and deuterium oxide behave the same as ordinary ethanol and water toward paraffin oil.

[23] C. W. Gould, G. Holzman and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

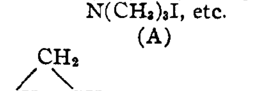
Synthetic Curare Substitutes from Stilbazoline Bis-quaternary Ammonium Salts

BY ARTHUR P. PHILLIPS

RECEIVED FEBRUARY 15, 1952

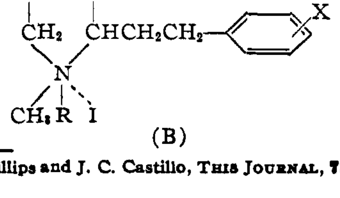
The structure of the alkyl groups attached to the nitrogens in 1,4′-bis-quaternary ammonium salts of 2- and 4-stilbazolines has been varied systematically, and the relationship between structure and curare-like activity has been examined. In the 4-stilbazolines the nature of the alkyls is critical and the completely methylated compound (I) represents maximum activity. Replacement of two methyl groups (one from each nitrogen) by ethyls (or higher alkyls) gives products devoid of curare-like activity, while a single ethyl at either nitrogen results in considerably diminished activity. In the 2-stilbazolines increasing alkyl group size does not diminish the antagonistic activity which these substances have in reversing the myoneural block of I or decamethylene-1,10-bis-trimethylammonium bromide (Syncurine).

An earlier paper[1] reported the discovery of powerful curare-like and related activities in certain 4- and 2-stilbazoline quaternary ammonium salts such as (A) and (B)



R = CH_3, C_2H_5, C_3H_7, C_4H_9
X = H, Cl, OH, OCH_3
$N(CH_3)_3I$, etc.

(A)



(B)

The 4-isomers (A) had a stronger curare-like potency, attaining a maximum in the bis-quaternary ammonium salt I (A, R = CH_3; X = $N(CH_3)_3I$). Reversal of the block of neuromuscular transmission in the cat, produced by these 4-isomers (best by I), was achieved by the 2-stilbazoline salts (B above) which showed only vestigial curariform activity, apparent only at much higher dosages than those required to produce reversal. Again in the latter series maximum activity, as an antagonist to the curare-like action of its 4-isomer, was found in the bis-quaternary ammonium salt X (B, R = CH_3, X = $N(CH_3)_3I$).

The effect of variation of the size of alkyl groups on the quaternary nitrogens on activity has been studied and the results are given in this work.

The compounds were made in the same general fashion as described earlier.[1] Condensation of 4-dimethylamino- and 4-diethylaminobenzaldehyde

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[1] A. P. Phillips and J. C. Castillo, THIS JOURNAL, **73**, 3949 (1951).