and added to a hot solution of 3.0 g. (0.0074 mole) of 1-methyl-4-(α-carbamylbenzyl)-quinolinium iodide in 200 ml. of water. The mixture was boiled for 30 minutes and then filtered to remove the silver chloride and iodide. The filtrate was evaporated to dryness. The residue was triturated with ethanol, giving 1.45 g. (63%) of colorless crystals which decomposed at approximately 177°. This material was used directly for catalytic hydrogenation.

Hydrogenation of 1-Methyl-4-(α-carbamylbenzyl)-quinolinium Chloride.—A solution of 1.0 g. (0.0032 mole) of XVII in 100 ml. of absolute ethanol was hydrogenated during 18 hours at 3–4 atm. and 20° using 0.3 g. of platinum oxide. The catalyst was removed by filtration, and the solution was concentrated to 15 ml. and cooled. The solid which separated was recrystallized from ethanol–ether as colorless prisms, m.p. 325–327°; yield 0.21 g. (21%) of 1-methyl-4-(α-carbamylbenzyl)-decahydroquinoline hydrochloride. Mixtures with the hydrochloride obtained from the hydrogenation of 1-methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline (XIII) gave no depression in melting point. The infrared spectra of the two hydrochlorides (in Nujol mulls) were identical.

The base was liberated from the hydrochloride by solution in water and addition of ammonium hydroxide. The precipitate was recrystallized from hexane as colorless prisms, m.p. 157–162°. The authentic 1-methyl-4-(α-carbamylbenzyl)-decahydroquinoline (XIV) had an infrared spectrum identical with that of the base obtained by catalytic reduction of 1-methyl-4-(α-carbamylbenzyl)-1,2,3,4-tetrahydroquinoline (XIII). Their picrates, both m.p. 225–227°, with decomposition, were also identical.

1-Methyl-4-(α-cyano-α-methylbenzyl)-1,4-dihydroquinoline (Vb).—This compound was made by the same method used for its homolog Va, from equimolar amounts of 1-methylquinolinium iodide (I), α-phenylpropionitrile,[15] and sodium ethoxide in ethanol at 0°. The product was recrystallized from petroleum ether (b.p. 90–110°) as colorless needles, m.p. 132–133°; yield 80%.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 82.92; H, 6.92; N, 10.19.

(15) S. Wideqvist, *Svensk. Kem. Tid.*, **55**, 125 (1943).

When the compound was heated with picric acid in ethanol, a picrate formed which was recrystallized from ethanol, m.p. 169–170°, and was shown to be 1-methylquinolinium picrate (VII).

Methylation of 1-Methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline.—Sodium amide was prepared by adding 1.15 g. (0.05 gram atom) of sodium in small pieces to 75 ml. of liquid ammonia containing a crystal of ferric nitrate. The ammonia was displaced by the dropwise addition of 100 ml. of anhydrous ether. To the suspension of sodium amide at 20° was added 13.0 g. (0.05 mole) of 1-methyl-4-(α-cyanobenzyl)-1,4-dihydroquinoline. The suspension was stirred for 15 minutes, and 7.0 g. (0.05 mole) of methyl iodide in 30 ml. of anhydrous ether was added gradually. After the addition, stirring was continued for 15 minutes. The solid material was collected on a filter and leached with hot petroleum ether (b.p. 90–110°). The combined filtrates were evaporated, and the residue was recrystallized from petroleum ether as colorless needles, m.p. 130.5–131°. Mixtures with compound Vb obtained by condensation of I with α-phenylpropionitrile gave no melting point depression, and the infrared spectra of the two samples were identical.

1-Methyl-4-(α-cyano-*p*-methylbenzyl)-1,4-dihydroquinoline (Vc).—This compound was prepared by the same method as that used for Va and Vb, from equimolar quantities of 1-methylquinolinium iodide (I), *p*-tolylacetonitrile[16] and sodium ethoxide in ethanol at 0°. Recrystallized from petroleum ether, the colorless needles melted at 133–134°; yield 88%.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.27; H, 6.85; N, 10.36.

1-Methyl-4-(α-cyano-*o*-methylbenzyl)-1,4-dihydroquinoline (Vd).—Prepared in like manner from *o*-tolylacetonitrile,[17] compound Vd was recrystallized from ether, colorless prisms, m.p. 96–97°; yield 59%.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.30; H, 6.60; N, 10.23.

(16) A. F. Titley, *J. Chem. Soc.*, 508 (1926).

(17) M. S. Newman, THIS JOURNAL, **62**, 2295 (1940).

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

Some 1-(2-Thienyl)-2-N,N-disubstituted-aminoalkanols and Their Methyl Ethers

BY IRVING ALLAN KAYE, HOWARD C. KLEIN,[1] WILLIAM J. BURLANT AND IRVING C. KOGON

RECEIVED DECEMBER 3, 1951

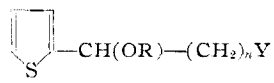
Several 1-(2-thienyl)-2-N,N-disubstituted-aminoethanols were prepared from 2-acetylthiophene without isolation of the bromo- or aminoketone intermediates. Although 1-piperidyl- and 4-morpholinylmethyl 2-thienyl ketones were stable to air and acids, di-*n*-butylaminomethyl 2-thienyl ketone could be prepared only in an inert atmosphere and decomposed in the presence of mineral acids. 1-Piperidylmethyl 2-thienyl ketone was recovered unchanged from a reaction with cyclohexylmagnesium bromide. Three aminoethers were obtained in low yield by the reaction of 2-thienylmagnesium bromide with dialkylaminoacetals.

Since aminoalkoxy and thienyl groups are each found in a number of substances which exhibit marked pharmacological activity, several 1-(2-thienyl)-2-N,N-disubstituted-aminoethanols (IA-D) and their methyl ethers (IE-G), as well as 1-(2-thienyl)-3-(4-morpholinyl)-propanol (IH) were prepared for therapeutic evaluation. Although compounds of this type are covered by a patent,[2] none have been described. A similar group of 3-amino-1,1-di-(2-thienyl)-alkan-1-ols has recently been shown to include some powerful antispasmodic and local anesthetic agents.[3]

(1) Part of this communication is taken from a thesis submitted by H. C. Klein to the Graduate Faculty of Brooklyn College, January, 1949, in partial fulfillment of the requirements for the M.A. Degree.

(2) G. J. Van Zoeren, U. S. Patent 2,367,702 (January 23, 1945).

(3) D. W. Adamson, *J. Chem. Soc.*, 885 (1950).



(IA–H)

(A) Y = diethylamino; R = H; n = 1
(B) Y = di-*n*-butylamino; R = H; n = 1
(C) Y = 1-piperidyl; R = H; n = 1
(D) Y = 4-morpholinyl; R = H; n = 1
(E) Y = diethylamino; R = CH_3; n = 1
(F) Y = di-*n*-propylamino; R = CH_3; n = 1
(G) Y = di-*n*-butylamino; R = CH_3; n = 1
(H) Y = 4-morpholinyl; R = H; n = 2

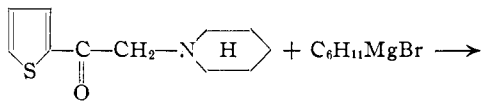
The aminoethanols (IA-D) were prepared by aluminum isopropoxide reduction of the corresponding ketones, which in turn were formed by condensing secondary amines with 2-bromoacetylthiophene. Initial attempts to prepare one of these

$$2\text{-}C_4H_3S\text{—}COCH_2Br + HNRR' \longrightarrow 2\text{-}C_4H_3S\text{—}COCH_2NRR'$$
(IIA–D)

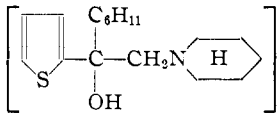
$$\xrightarrow{Al[OCH(CH_3)_2]_3} IA\text{–}D$$
(–NRR′ = Y in IA–D)

aminoketones (IIB) gave largely intractable tars. This is not surprising since many thiophene compounds are unstable in air, in acids, or at high temperatures[4,5] and some aminoalkylketonic side chains, when attached to certain aryl[6–10] or heterocyclic[6,8] nuclei, are readily cleaved by air[6] or alkali.[7] The preparation was easily effected, however, when repeated in a nitrogen atmosphere (method A). The ketone, on reduction in an inert atmosphere (method B), yielded the more stable (to air and acids) aminoalcohol (IB). This product was obtained more conveniently, and in about the same over-all yield, from 2-acetylthiophene without isolating the bromo or aminoketone intermediates (method C). Compounds IA-D were synthesized in this fashion.

Since some 1,1-disubstituted-3-(1-piperidyl)-propanols have been described as possessing pronounced antispasmodic activity,[3,11] an attempt was made to prepare the structurally-similar 3-(1-piperidyl)-1-cyclohexyl-1-(2-thienyl)-ethanol (III) by the reaction of cyclohexylmagnesium bromide with 1-piperidylmethyl 2-thienyl ketone (IIC). The latter (IIC), prepared by method C



IIC



III (not isolated)

and employed in this reaction as a concentrate of the crude substance, was not purified since its air-instability was inferred from the behavior of the di-*n*-butylaminoketone analog (IIB). The stable base isolated from the reaction, however, gave the correct analysis for the starting aminoketone (IIC). Its identity was confirmed by the fact that its hydrobromide showed no depression in melting point when admixed with product obtained by a modification of method A. This unexpected stability of the piperidyl ketone, and the morpholinyl ketone which was prepared similarly, toward acids and oxygen has its counterpart in the behavior of the corresponding aminoalcohols and ethers in the presence of mineral acids. Both the piperidyl- and morpholinylalcohols (IC and D) formed crystalline hydrohalide salts with ease whereas the diethyl- and di-*n*-butylaminoalcohols and ethers (IA, B, E and G) underwent decomposition in acidic media, forming purple solutions. This experience has been paralleled by Mathieson and Newberry,[12] who obtained uncrystallizable oils which rapidly decomposed in the presence of hydrochloric acid, in condensing ω-bromo-(5 or 4)-nitro-(2 or 4)-methoxyacetophenone with diethylamine or di-*n*-butylamine. With piperidine and morpholine, on the contrary, crystalline hydrobromides were easily prepared.[12]

Although the homologous Mannich base, 2-(1-piperidyl)-ethyl 2-thienyl ketone, on reaction with 2-thienylmagnesium bromide, has been reported to give the aminoalcohol in 31% yield,[3] none of the expected product (III) could be isolated from the reaction of IIC with cyclohexylmagnesium bromide. With methylmagnesium iodide there was obtained, in addition to some unreacted aminoketone (IIC), an oil which distilled over a wide range. Although analysis revealed a low hydroxyl content, no pure substance could be isolated from this fraction.

Aluminum isopropoxide reduction of 2-(4-morpholinyl)-ethyl 2-thienyl ketone gave the desired product (IH) in 53% yield. This is apparently the first time that a Mannich base derived from a 2-acythiophene[13,14] has been reduced to an aminoalcohol.

The ethers (IE-G) were prepared by the reaction of 2-thienylmagnesium bromide with dimethyl dialkylaminoacetals.[15,16] An alternate procedure, which gave good yields of alkyl ethers of basically-

$$2\text{-}C_4H_3S\text{—}MgBr + (CH_3O)_2CHCH_2Y \longrightarrow I(E\text{–}G) + CH_3OMgBr$$

substituted 2-amino-1-phenylethanols,[15] could not be used since the requisite intermediate, the methyl ether of 2-bromo-1-(2-thienyl)-ethanol, proved too sensitive to heat, air, acids and alkalies. The inferior yields of these thiophene aminoethers may be attributed to a similar instability.

The hexamethylenetetramine salt of 2-bromoacetylthiophene,[17] compounds IA and IB, and the hydrobromide of ID were ineffective in retarding the growth of Sarcoma 180 in mice.[18a] Fresh solutions of the methiodide of IC showed no curariform activity whereas solutions which had been left at 5°

(4) F. Kipnis, H. Soloway and J. Ornfelt, THIS JOURNAL, **71**, 10 (1949).

(5) F. F. Blicke and F. Leonard, *ibid.*, **68**, 1934 (1946).

(6) D. R. U. Golding and W. H. McNeely, *ibid.*, **68**, 1847 (1946), observed that phenyl di-*n*-butylamino ketone absorbed oxygen readily, forming benzoic acid and di-*n*-butylamine.

(7) P. Rabe and W. Schneider, *Ber.*, **41**, 872 (1908).

(8) T. L. Jacobs, S. Winstein, J. W. Ralls, J. H. Robson, R. B. Henderson, R. I. Akawie, F. W. Florsheim, D. Seymour and C. A. Seil, *J. Org. Chem.*, **11**, 21 (1946).

(9) E. L. May and E. Mosettig, *ibid.*, **11**, 105 (1946).

(10) J. B. Wright and R. C. Elderfield, *ibid.*, **11**, 111 (1946).

(11) J. J. Denton, H. P. Schedl, W. B. Neier and V. A. Lawson, THIS JOURNAL, **71**, 2054 (1949).

(12) D. W. Mathieson and G. Newberry, *J. Chem. Soc.*, 1133 (1949).

(13) F. F. Blicke and J. H. Burckhalter, THIS JOURNAL, **64**, 451 (1942).

(14) R. S. Harradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1939); *C. A.*, **33**, 5855 (1939).

(15) I. A. Kaye and I. C. Kogon, *ibid.*, **73**, 4893 (1951).

(16) W. Beck, I. A. Kaye, I. C. Kogon, H. C. Klein and W. J. Burlant, *J. Org. Chem.*, **16**, 1434 (1951).

(17) Very dilute aqueous solutions of several similar salts have been found to have an effect of the same order of magnitude as nitrogen mustard in inhibiting the respiration of rabbit bone marrow cells in serum: C. T. Bahner, M. D. Pickens, D. Pickens and W. K. Easley, THIS JOURNAL, **72**, 2266 (1950); C. T. Bahner, W. K. Easley, M. D. Pickens, H. D. Lyons, L. L. Norton, B. G. Walden and G. E. Biggerstaff, *ibid.*, **73**, 3499 (1951).

(18) The authors are grateful to (a) Dr. C. Chester Stock of the Sloan-Kettering Institute for Cancer Research and (b) Dr. Irwin H. Slater of the School of Medicine and Dentistry at the University of Rochester for this information.

TABLE I

AMINOKETONES, ALCOHOLS AND ETHERS, 2-C_4H_3S-CO-CH_2-Y AND 2-C_4H_3S-CH(OR)-$(CH_2)_n$Y

Compd.	B.p., °C.	Mm.	M.p., °C.	Method	Yield, %	Formula	Nitrogen, % Calcd.	Found
IA	124	4	154–155.5[a,b]	C	60	$C_{10}H_{17}NOS$	7.03	6.87
IB	155	4	121–122[c]	C	59	$C_{14}H_{25}NOS$	5.48	5.56
IC	154–156	7	81–82[d]	C	64	$C_{11}H_{17}NOS$	6.63	6.55
ID	[e]		100–102[f]	C	61	$C_{10}H_{15}NO_2S$	6.57	6.53
IE	122–123	20	116–117[a]	E	18	$C_{11}H_{19}NOS\cdot CH_3I$	40.56[g]	40.63[g]
							6.24[h]	6.33[h]
IF	65–70	0.02	114–115[i]	E	40	$C_{13}H_{23}NOS$	5.80	5.75
IG	140–144	4	[j]	E	17	$C_{15}H_{27}NOS$	5.20	5.03
IH	120	0.03	77–77.5[k]	A	53	$C_{11}H_{17}NO_2S$	6.16	6.19
IIB	140–145	4	[l]	A	75	$C_{14}H_{23}NOS$	5.53	5.48
IIC	125–127	0.3	255–256[l]	D	67	$C_{11}H_{15}NOS\cdot HBr$[l]	4.83	4.83
IID			236–238[m]	D	84	$C_{10}H_{13}NO_2S\cdot HCl$	14.33[n]	14.43[n]
[o]			208–209[p]	D	57	$C_{13}H_{13}NOS\cdot HCl$	13.23[n]	13.24[n]

[a] Methiodide, recrystallized from isopropyl alcohol. [b] *Anal.* Calcd. for $C_{10}H_{17}NOS\cdot CH_3I$: I, 37.18. Found: I, 36.80. [c] Oxalate, recrystallized from methanol–isopropyl alcohol. *Anal.* Calcd. for $C_{14}H_{25}NOS\cdot H_2C_2O_4$: $C_2O_4^=$, 25.48. Found: $C_2O_4^=$, 25.30. [d] Recrystallized from hexane. The hydrobromide melted at 173° (dec.) after recrystallization from methanol–isopropyl alcohol. *Anal.* Calcd. for $C_{11}H_{17}NOS\cdot HBr$: Br, 27.35. Found: Br, 27.46. [e] This product was not distilled but crystallized from hexane–chloroform, m.p. 96–99°. [f] Recrystallized from isopropyl alcohol–hexane. The hydrobromide melted at 178° (dec.) after recrystallization from methanol–isopropyl alcohol. *Anal.* Calcd. for $C_{10}H_{15}NO_2S\cdot HBr$: Br, 27.17. Found: Br, 27.46. [g] Carbon analysis. [h] Hydrogen analysis. [i] Hydrochloride, recrystallized from acetone. *Anal.* Calcd. for $C_{13}H_{23}NOS\cdot HCl$: N, 5.05. Found: N, 5.01. [j] Solid derivatives of this compound could not be prepared. [k] The distillate crystallized on rubbing with isopropyl alcohol–hexane, m.p. 71–73°. This was recrystallized twice from hexane. [l] Hydrobromide, recrystallized from methanol–isopropyl alcohol. *Anal.* Calcd.: S, 11.04. Found: S, 11.05. [m] Hydrochloride, recrystallized from methanol–acetone. [n] Chloride analysis. [o] Benzylaminomethyl 2-thienyl ketone. [p] Hydrochloride recrystallized from methanol-isopropyl alcohol.

for several weeks did show an activity which was too small to warrant further investigation.[18b] The compound appeared to offer no protection in mice against electric shock, Metrazol or strychnine.[18b]

Experimental[19]

2-Bromoacetylthiophene.[4]—The bromoketone, a strong lachrymator and skin irritant, was obtained in 74–82% yield by brominating 2-acetylthiophene[20] in chloroform, in the presence of calcium carbonate,[21] or in ether[8] at room temperature. The product, collected at 127–130° (7 mm.), $n^{29}D$ 1.6168, d^{29}_4 1.6657, was a viscous liquid which darkened progressively on standing until an infusible black mass was finally formed. In ether solution (2 *M*) at 5° it showed no signs of deterioration even after many months and is best preserved in such a manner.

Hexamethylenetetramine Salt of 2-Bromoacetylthiophene.—This compound was prepared by a slight modification of a recently published procedure,[22] m.p. 154–156°. After one recrystallization from methanol, the substance melted at 155–156°. Keskin, Mason and Nord[22] found that their product melted at 148–149°.

Anal. Calcd. for $C_{12}H_{17}BrN_4OS$: Br, 23.02. Found: Br, 22.86.

Di-*n*-butylaminomethyl 2-Thienyl Ketone (IIB) (Method A).—To a solution of 51.7 g. (0.4 mole) of redistilled di-*n*-butylamine dissolved in 200 ml. of anhydrous ether, 41.0 g. (0.2 mole) of 2-bromoacetylthiophene was added dropwise over a one-half hour period. The reaction mixture, maintained under 10° in a nitrogen atmosphere during the addition, was then left overnight at 0–5°. The glistening, pearly plates of di-*n*-butylamine hydrobromide which had precipitated were separated by filtration and washed with ether until colorless. After drying in an oven overnight, the salt weighed 41.8 g., m.p. 295–297°. The ether was removed from the filtrate *in vacuo* and the residue distilled at reduced pressure using a fine stream of nitrogen to prevent bumping during the distillation. The product, collected at 140–145° (4 mm.), weighed 38.0 g. (75%), $n^{29}D$ 1.5221, d^{29}_4 1.0102. Attempts to form salts yielded only purple-colored oils.

1-(2-Thienyl)-2-di-*n*-butylaminoethanol (IB) (Method B).—A solution of 16.2 g. (0.0795 mole) of aluminum isopropoxide in an equal weight of toluene was added to a solution of 20.1 g. (0.0795 mole) of IIB in 250 ml. of isopropyl alcohol which had been dried over calcium hydride. The solution was distilled slowly through a 38-cm. Vigreux column until acetone was no longer detected in the distillate.[23] The volume of the reaction mixture was kept constant during the distillation by the dropwise addition of isopropyl alcohol. Most of the solvent was then removed *in vacuo* and the dark residue was treated with *ca.* 275 ml. of 10% aqueous sodium hydroxide solution. The mixture was extracted several times with ether. The combined ether extracts were washed twice with a saturated aqueous sodium chloride solution and dried over anhydrous potassium carbonate. After removing the drying agent and ether, the product was distilled *in vacuo*. The fraction distilling at 125–130° (2 mm.) weighed 15.1 g. (74%), $n^{29}D$ 1.5082, d^{29}_4 0.9861. The yield dropped to 54% when the aminoketone was simply refluxed with a considerable excess of aluminum isopropoxide without removing the acetone formed in the reaction.[24]

Preparation of 1-(2-Thienyl)-2-N,N-disubstituted-aminoethanols (IA-D) from 2-Acetylthiophene without Isolation of Intermediates (Method C).—The procedure described in a previous publication[16] was followed; results are summarized in Table I. The yields given in the table are over-all yields based on the amount of 2-acetylthiophene used in the initial bromination reaction.

1-Piperidylmethyl 2-Thienyl Ketone Hydrobromide (Method D).—From a solution of 23.4 g. (0.275 mole) of piperidine in 300 ml. of ether containing 0.1375 mole of crude 2-bromoacetylthiophene[16] there was obtained, after standing overnight at 5°, a precipitate of piperidine hydrobromide weighing 20.5 g. Upon the addition of an ethanolic solution of hydrogen bromide followed by 100 ml. of isopropyl ether to the filtrate, a brown precipitate appeared which was separated and washed with cold isopropyl alcohol. The white crystalline salt weighed 26.7 g. (67%) after drying *in vacuo* at 60°, m.p. 252–253°. The melting point of the

(19) All melting points are corrected; boiling points are not.

(20) Prepared by the method of H. D. Hartough and A. I. Kosak, THIS JOURNAL, **68**, 2639 (1946), b.p. 90–92° (10 mm.). Their yield was duplicated even though equivalent amounts of reactants (10 moles) were employed.

(21) C. M. Suter and A. W. Ruddy, *ibid.*, **66**, 747 (1944).

(22) H. Keskin, C. D. Mason and F. F. Nord, *J. Org. Chem.*, **16**, 1333 (1951).

(23) A. L. Wilds, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, chapter 5.

(24) S. Winstein, T. L. Jacobs, R. B. Henderson and W. H. Florsheim, *J. Org. Chem.*, **11**, 150 (1946).

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,[15] 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

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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

(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.