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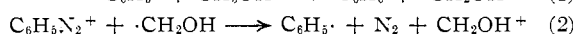
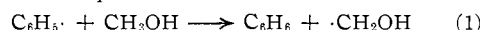
Mechanisms of Diazonium Salt Reactions. VI. The Reactions of Diazonium Salts with Alcohols under Acidic Conditions; Evidence for Hydride Transfer¹BY DELOS F. DETAR AND TAKUO KOSUGE²

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Previous studies of the reactions of diazonium salts with alcohols have shown that the products are either the aryl alkyl ethers formed by replacement of nitrogen by the alkoxy group derived from the alcohol or the reduction products by replacement of nitrogen by hydrogen. The present work is a further survey of this reaction under various conditions intended to minimize the free radical chain steps leading to reduction. A preliminary study of the photoinduced decomposition of diazonium salts has also been made. Surprisingly the products are essentially the same as those formed in the thermal decomposition. This result and other data constitute evidence that reduction may occur by hydride transfer as well as by the free radical chain process.

The thermal decomposition of a diazonium salt in an alcoholic solution yields mixtures of alkyl aryl ethers and reduction products. In ether formation the nitrogen has been replaced by the alkoxy group of the alcohol, while in reduction it has been replaced by hydrogen, the alcohol undergoing concurrent oxidation to an aldehyde or a ketone. These reactions have been known for a long time and received considerable study about sixty years ago, particularly by Hantzsch and by Remsen and their students.^{3,4} In general the yield of reduction product increases at the expense of the ether as the alcohol is changed from methyl to ethyl or higher alkyl or as halogen atoms or nitro groups are substituted into the diazonium salt.

Recently we have applied modern techniques to a detailed study of the reaction of benzenediazonium fluoroborate and bisulfate with methanol.⁵ Under acidic conditions the heterolytic cleavage yielding anisole proceeded in 90–95% yield. In the presence of acetate buffers complex dark reaction mixtures were produced unless oxygen was excluded, and in the absence of oxygen some 90% of benzene was formed along with about 5% of biphenyl. The sensitivity of the homolytic cleavage reaction to oxygen shows that a chain process is involved, and reactions 1 and 2 have been suggested for the chain steps.



The heterolytic cleavage is almost certainly an $\text{S}_{\text{N}}1$ process.^{5–7} Nitro groups, for example, greatly reduce the rate. Furthermore careful studies of reactions in aqueous solutions have shown that the rates are relatively insensitive to the anions present and that products do not correlate with rates as

they would for a direct displacement mechanism.⁷ The free radical reactions in alcoholic solvents are less clear. In addition to homolytic cleavage occurring by the electron transfer step (eq. 2) it is necessary to have some other homolytic cleavage reaction to initiate the chains.

Recently the work of Kelley on the reactions of benzene- and *p*-toluenediazonium salts with ethanol⁸ has become available. Insofar as this work parallels the present study, the agreement is satisfactory as is indicated in the appropriate tables.

The purpose of the present study has been to survey further the reactions of diazonium salts with alcohols. We have been particularly interested in determining the limiting yields of ethers obtained by suppressing the free radical chain reactions, and we also have been interested in the products of the photoinduced decomposition. The work includes (1) a survey of the yields of ether and of reduction product for the reactions of ten diazonium salts with methanol, (2) a systematic study of the effect of oxygen and of added acid as inhibitors of the chain reaction, (3) a brief study of the products and of the kinetics of the reactions of benzenediazonium fluoroborate with several alcohols, and (4) a preliminary study of the effect of ultraviolet light in determining the products.

Product Studies (Various Diazonium Salts in Methanol).—The survey comprised some sixty runs at various concentrations (0.004–0.04 *M*) and temperatures. The ether and the reduction product were co-distilled with methanol and determined spectrophotometrically (ultraviolet).^{5a,9} Previous workers have isolated both these products from the reactions of many of the diazonium salts used in this study. For the present purpose we considered it sufficient to compare the ultraviolet spectra with those of synthetic mixtures since the spectra for both the ether and the reduction product have several characteristic peaks. When the ether was the principal product, agreement was excellent. When the reduction product predominated, the later fractions showed strong absorption that could be attributed to small amounts of the corresponding biaryl. The analytical procedures were tested on known mixtures.

The results of the survey are summarized in Table I. High yields of ethers could be obtained with the diazotized toluidines and anisidines while high yields of reduction products could be obtained

(1) We wish to express our appreciation to the National Science Foundation for the support of this work under grant G-1863.

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(3) Reviews: K. H. Saunders, "The Aromatic Diazo-Compounds and their Technical Application," Longmans, Green and Co., New York, N. Y., 2nd ed., 1949, pp. 66, 268, 306; K. Holzach, "Die aromatischen Diazoverbindungen," Sammlung Chemischer und Chem.-techn. Vorträge, vol. 38, Ferdinand Enke, Stuttgart, 1947, p. 205; N. Kornblum, *Org. Reactions* **2**, 262 (1944).

(4) Cf. A. Hantzsch and B. Jochem, *Ber.*, **34**, 3337 (1901); J. L. Beeson, *Am. Chem. J.*, **16**, 246 (1894); I. Remsen and W. R. Orndorff, *ibid.*, **9**, 387 (1887); F. K. Cameron, *ibid.*, **20**, 229 (1898).

(5) (a) D. F. DeTar and M. N. Turetzky, *THIS JOURNAL*, **77**, 1745 (1955); (b) **78**, 3925 (1956); (c) **78**, 3928 (1956).

(6) D. F. DeTar and A. R. Ballentine, *ibid.*, **78**, 3916 (1956).

(7) B. S. Lewis and W. H. Hinds, *ibid.*, **74**, 304 (1952).

(8) A. E. Kelley, Ph. D. Thesis, Purdue University, June, 1956.

(9) D. F. DeTar, *THIS JOURNAL*, **73**, 1446 (1951).

TABLE I
PRODUCTS OF THE THERMAL DECOMPOSITION OF DIAZONIUM SALTS

X in XC ₆ H ₄ N ₂ - HSO ₄	No. of runs	Temp., °C., conditions ^a	Products, %	
			XC ₆ H ₅	XC ₆ H ₄ - OCH ₃
<i>p</i> -CH ₃	2	25-100	4	94
	1	65, N ₂	23	73
<i>m</i> -CH ₃	2	Reflux	6-14	91-84
	1	Reflux	5	95
<i>p</i> -Br	4	100-185	47-67	45-31
	1	65, N ₂	96	2
	5	Reflux	66-84	31-17
<i>m</i> -Br	2	100	30	60
	1	65, N ₂	85	12
<i>o</i> -Br	4	Reflux	18-40	76-53
	2	100, or refl.	97	1
<i>p</i> -NO ₂	4	25-135	66-89	13-5
	3	Reflux	79-83	14-9
<i>m</i> -NO ₂	2	100, or refl.	85	4
<i>o</i> -NO ₂	2	100, or refl.	96	2
<i>p</i> -CH ₃ O	10	65-150	10-29	85-64
	1	65, N ₂	96	4
	9	Reflux	76-99	18-1
<i>m</i> -CH ₃ O	2	100, or refl.	2	94

^a 0.004-0.04 *M* solutions in sealed tube with air atmosphere unless otherwise indicated. Individual runs are reported in the Experimental; in this table runs at various temperatures and concentrations are grouped together since these variables have only a secondary effect.

from the diazotized bromoanilines and nitroanilines. It is clear that the presence of oxygen affects the results, for the outgassed runs under a nitrogen atmosphere gave the highest yields of reduction products, while those carried out in the presence of oxygen gave the most ether. In fact, diazotized *p*-anisidine can be converted either into anisole or into hydroquinone dimethyl ether in high yields, depending on whether oxygen is absent or present. Somewhat variable results were obtained under reflux, but these can be rationalized as involving relatively oxygen-free conditions, for the methanol atmosphere removes much of the oxygen. A consideration of the effect of temperature and of concentration (details are given in the Experimental) indicates that these variables have relatively little influence. The reaction of diazotized *p*-anisidine with methanol was also relatively unaffected by formaldehyde or by formic acid. In a previous study the rate of decomposition of benzenediazonium fluoroborate also was found to be unaffected by formaldehyde.^{5b}

Because of the observed effect of oxygen on the reaction products, it appears that a free radical chain reaction may be of some significance even under acidic conditions. To investigate this point systematically a series of forty runs was carried out as summarized in Table II. A representative series of diazonium bisulfates was allowed to undergo thermal decomposition under conditions considered least favorable for reduction: in the presence of oxygen and of added acid to suppress chain initiation; and under other conditions expected to permit increasing extents of reduction: oxygen atmosphere, no added acid; nitrogen atmosphere and added acid; nitrogen atmosphere, no added acid. Two different temperatures were investigated; *a priori* we expected the higher

TABLE II
PRODUCTS OF THE THERMAL DECOMPOSITION OF BENZENE-DIAZONIUM BISULFATES IN METHANOL^a

Reaction cond.	Time, days	Redn. prod., %	Ether, %	Time, days	Redn. prod., %	Ether, %
Benzenediazonium bisulfate						
		25°			65°	
N ₂	14	18	73	2	11	80
N ₂ , H ⁺	14	19	72	1	13	77
O ₂	14	4	96	1	5	95
O ₂ , H ⁺	14	3	94	1	4	93
<i>p</i> -Toluenediazonium bisulfate						
		25°			65°	
N ₂	14	60	42	1, 3 ^b	20, 23	80, 73
N ₂ , H ⁺	14	65	34	1	27	72
O ₂	14, 5 ^{b,c}	1, 4	98, 90	1	2	96
O ₂ , H ⁺	14	1	97	1	2	(88+)
<i>p</i> -Bromobenzenediazonium bisulfate						
		65°			100°	
N ₂	7, 7 ^b	98, 96	3, 2	5	95	4
N ₂ , H ⁺	7	93	8	5	93	6
O ₂	7	7	70	5	6	73
O ₂ , H ⁺	14	5	73	3	3	76
<i>p</i> -Nitrobenzenediazonium bisulfate						
		65°			100°	
N ₂	14	76	20	7	74	22
N ₂ , H ⁺	14	59	36	7	51	45
O ₂	14	30	32	3	32	33
O ₂ , H ⁺	14	25	49	3	33	40
<i>p</i> -Methoxybenzenediazonium bisulfate						
		65°			100°	
N ₂	7, 21 ^d	96, 99	4, 1	3	67	34
N ₂ , H ⁺	21 ^e	98	1	3	83	13
O ₂	7, 21 ^d	13, 67	79, 11	3	7	84

^a Reaction mixtures contained 200 μmoles of diazonium salt in 25 ml. of methanol. The runs with initially added acid contained 1 mmole of sulfuric acid. All reactions were carried out in sealed ampoules. ^b Second run reported here has been reported already in Table I. ^c Air atmosphere in second run rather than O₂. ^d Second run at 25°; first run already reported in Table I. ^e At 25°.

temperature to favor ether formation since this reaction has an activation energy of about 25-30 kcal. per mole, larger than the probable sums of the energies for a chain process. In general these expectations were borne out.

The analyses are satisfactory for most of the runs, but are low (recoveries less than 80%) for the *p*-bromobenzenediazonium bisulfate and for the *p*-nitrobenzenediazonium bisulfate runs in the presence of oxygen. Since variation of reaction times did not affect the yields it is likely that other products than ether and bromobenzene or nitrobenzene were formed under these conditions with these compounds. Except for *p*-methoxybenzenediazonium bisulfate the effect of temperature is small, although both benzenediazonium bisulfate and *p*-toluenediazonium bisulfate gave somewhat more reduction product under nitrogen at the lower temperature than at the higher. Except for the *p*-nitrobenzenediazonium bisulfate, initially added sulfuric acid (0.04 *M*) had no effect and even with it the effect was small. Many of these data can thus be averaged for purposes of comparison. For averages of yields of 70% or higher for runs

believed to be comparable, the standard deviation is about 3% (15 D.F.)

We conclude that as the rate of the ionic reaction decreases in the order $H > p\text{-CH}_3 > p\text{-Br}, p\text{-NO}_2 > p\text{-CH}_3\text{O}$ the opportunity for the free radical chain reaction increases and may significantly determine the products unless special steps are taken to suppress the chain reaction.

Reaction of Benzenediazonium Fluoroborate with Various Alcohols.—We began the present study with the reactions of benzenediazonium fluoroborate in various alcohols. Application of the co-distillation technique gave distillates which had the series of peaks characteristic of the ethers and of benzene, but we were puzzled for a while by abnormal peaks at 266 and 260 $m\mu$. Eventually we found that these peaks could be attributed to fluorobenzene (absorption maxima ($\log \epsilon$): 248 (2.52), 254(2.81), 260(2.99), 266(2.97)) for they were absent in runs with the diazonium bisulfate, the reaction of which in methanol gave a pattern corresponding to known benzene-anisole mixtures. Formation of some fluorobenzene is not especially surprising. In alcoholic solutions the diazonium salts are expected to be present primarily as ion pairs or higher aggregates, and the fluoroborate ion concentration is therefore especially high in the neighborhood in which the phenyl "cation" is forming.

The yields reported in Table III are quantitative for methanol, but the analytical procedures were incompletely worked out for the other alcohols and the reported benzene and fluorobenzene yields may well be low. The reactions were carried out under comparable conditions with an air atmosphere, acidity increasing with decomposition of the diazonium salt.

TABLE III

PRODUCTS OF DECOMPOSITION OF BENZENEDIAZONIUM FLUOROBORATE IN ALCOHOLS^a

Alcohol	C ₆ H ₆	Products, % C ₆ H ₅ F	C ₆ H ₅ OR
CH ₃ OH	4	3	93
CH ₃ CH ₂ OH ^b	27	6	66
1-C ₄ H ₉ OH ^b	9	10	57
2-C ₃ H ₇ OH ^b	37	8	43

^a 200 μ moles of benzenediazonium fluoroborate in 50 ml. of alcohol, 3 hours at 50–60°. ^b Biphenyl probably also present since later distillate fractions showed broad background absorption in the 220–260 $m\mu$ region. It should be noted that benzene, fluorobenzene and the ether all have a series of characteristic peaks in the 230–270 $m\mu$ region.

The reaction rates were determined, as previously described, by measuring the increase in nitrogen pressure with time.⁶ With ethanol as solvent the initial rate was some 30% greater than the rate during the last half of the reaction, and in isopropyl alcohol it was still higher and did not become first order until about 70% of the reaction was over. The data for the first-order portions of the reactions are reported in Tables IV and V. It should be noted that at the higher temperatures the time required for equilibration (1–2 min.) permits considerable reaction to occur before readings become significant even for reactions that are first order throughout. For convenience in comparison, the rate at 25.0° has been calculated for

TABLE IV

RATE OF DECOMPOSITION OF BENZENEDIAZONIUM FLUOROBORATE IN ALCOHOLS

Alcohol	Temp., °C.	$k \times 10^4, \text{sec.}^{-1}$		Prev. work	Reaction range ^c	N ₂ , %	
		Obsd.	Calcd. ^a				
CH ₃ OH	20.0	...	0.41	0.43 ¹⁰			
	25.0	...	0.91	.96 ^{3c}			
					.98 ^{5c}		
	30.0	1.98	1.96	2.05 ¹⁰	5–92	88	
	35.2	4.2	4.16	...	15–99	98	
	40.0	8.5	8.5	8.70 ¹⁰	20–99	92	
	44.8	17	16.5	...	25–96 ^d	90	
	49.4	30	30.5	...	45–93	82	
	C ₂ H ₅ OH	20.0	...	0.376	0.43 ¹⁰		
		25.15	...	1.09	1.72 ^b		
30		...	1.75	2.05 ¹⁰			
30		...	1.75	2.03 ^b			
35.2		3.9	3.75	...	25–97 ^d	84	
40.0		7.4	7.4	8.36 ¹⁰	40–93	83	
44.8		14	14.3	...	40–99	88	
49.4		26.5	26.5	...	40–97	85	
55.0		55	53.2	...	70–99	89	
59.8		97	100	...	55–91	93	
2-C ₃ H ₇ OH	30.0	...	2.12	2.64 ¹⁰			
	35.2	4.2	4.28	...	75–90 ^e	77	
	40.0	8.2	8.0	11.0 ¹⁰	68–87 ^e	72	
	44.8	15	14.8	...	80–93 ^e	66	
	49.4	27	28	...	65–90 ^e	67	
	59.8	85	82	...	65–98	90	
	CH ₃ OH ^f	29.9	0.20	0.207	...	2–99 ^d	88
40.0		1.1	1.03	...		85	
40.0		...	1.03	0.92 ^g			
50.0		3.75	3.74	...	14–83 ^d	83	

^a Calcd. from Arrhenius equations, Table V. ^b Kelley's values⁸ multiplied by 2.3. ^c Analytical expression for first-order equation fits the p -values with a standard deviation of 0.3 mm. or less over at least this range of reaction, except where otherwise noted; total pressure increase about 200 mm. ^d Std. dev. 0.4 mm. ^e First 65% of reaction not first order; k -values estimated by Roseveare calculation over the range stated. ^f p -Toluenediazonium fluoroborate. ^g p -Toluenediazonium chloride in ethanol; Kelley's value⁸ multiplied by 2.3.

TABLE V

ARRHENIUS PARAMETERS FOR DECOMPOSITION OF BENZENEDIAZONIUM FLUOROBORATE IN ALCOHOLS

Alcohol	$\log A^a$	$10^{-3} E$	$100^b \ln k$	$k_{25} \times 10^{-4} \text{sec.}^{-1}$ (calcd.)	Note
CH ₃ OH	15.9	27.4			d
CH ₃ OH	16.0	27.4			e
C ₂ H ₅ OH	15.8 ± 0.2	27.199 ± 0.3	2.6	8.2	c
C ₂ H ₅ OH	16.1	27.5			d
2-C ₃ H ₇ OH	14.415 ± 0.4	25.095 ± 0.5	3.7	10.6	c
2-C ₃ H ₇ OH	14.0	24.6			d
H ₂ O	15.516 ± 0.04	27.098 ± 0.05	0.48	4.56	f
H ₂ O	12.7	23.4			d
CH ₃ OH ^g	15.439 ± 0.4	27.887 ± 0.5	4	1.01	c
H ₂ O ^g	15.981 ± 0.04	29.188 ± 0.06	0.51	0.39	f

^a Sec.-1. ^b Percentage precision with which observed rate constant agrees with that calculated from the Arrhenius expression: $\log k = \log A - E/(2.30259 \times 1.98773T)$. The parameters were computed by averaging the $\log k$ and the $1/T$ values. ^c This work. ^d Waring and Abrams, diazonium chloride.¹¹ ^e Pray, diazonium chloride.^{5b} ^f DeTar and Ballentine.⁶ ^g p -Toluenediazonium fluoroborate.

all reactions. It can be seen that the rates in the three alcohols are all within about 10% of each

other. Pray¹⁰ reports similar rates in *n*-propyl, *n*-butyl and isobutyl alcohols. The present rate data agree satisfactorily with those previously reported,^{8,10,11} although our rates in isopropyl alcohol refer to the later first-order portion of the reaction and are somewhat lower than those of other workers. If these rates pertain to the heterolytic cleavage of the diazonium salt to give ethers, then the insensitivity of the rates to the relatively small variation in alcohol structures is understandable, particularly when compared with the corresponding insensitivity of the rates in aqueous solution to ionic environment.⁶ The fast initial rates may be due therefore to the chain reaction forming benzene which is of some consequence until the acidity of the solution has increased sufficiently to suppress it.⁵ The factor of two difference between the rates in alcohols and in water is in the direction expected for a reaction involving some charge dispersion in the transition state.

Photodecomposition.—In studying the effect of ultraviolet light on the reaction of diazonium salts with methanol we expected that the radiation might either accelerate the initiation of the free radical chain process or else that it might exclusively promote the heterolytic decomposition. In order to ensure that photoinduced decomposition had occurred, we measured the reaction rates crudely.

As can be seen from the results summarized in Table VI radiation had very little effect on the products even though essentially all of the reaction was photoinduced under the conditions used. In this connection it is of interest that thermal and photochemical decomposition of diazo oxides has also been reported to lead to similar reaction mixtures.¹² Apparently thermal and photoactivation of the diazonium salts lead to essentially the same type of decomposition.

TABLE VI
EFFECT OF ULTRAVIOLET LIGHT ON REACTION OF DIAZONIUM BISULFATES WITH METHANOL, *p*-XC₆H₄N₂H₂SO₄

X	Half-time, min. ^a	Temp., °C.	Products, %	
			XC ₆ H ₅	XC ₆ H ₄ - OCH ₃
H	D 60	31	5	95
H	U 20	35
CH ₃	D 350	33	4	91
CH ₃	U 40	38	12	85
NO ₂	D 300	35	80	13
NO ₂	U 10	38	82	4
CH ₃ O	D ^b	30	56	12
CH ₃ O	U 35	43	31	57

^a D signifies reaction in flask painted with Glyptal varnish and covered with aluminum foil; U signifies flask exposed to light from Hanovia utility model mercury vapor lamp at 15 cm. in a 500-ml. flask of Corning No. 7910 glass (ultraviolet transparent Vycor); 2.2 mmoles of diazonium salt in 200 ml. methanol, air atmosphere. The half-times are only crude approximations since the flask was not agitated and the temperature was not controlled. They are, however, sufficiently good to show whether the irradiated solution decomposed significantly faster than the dark reaction. ^b Some diazonium salt remained after 50 days; rate not measured.

Discussion.—The product studies reported in Tables I and II, the kinetic results and previous

(10) H. A. Pray, *J. Phys. Chem.*, **30**, 1477 (1926).

(11) C. E. Waring and J. R. Abrams, *THIS JOURNAL*, **63**, 2757 (1941).

(12) Cf. P. Yates and E. W. Robb, *ibid.*, **79**, 5760 (1957).

work⁵ indicate that there must be at least two reaction paths for the thermal decomposition of the diazonium salt: (1) an ionic decomposition forming the ether and (2) a free radical chain process forming reduction product. The chain process is retarded by oxygen, and we are inclined to believe that it may in fact have been suppressed almost completely since the presence of additional acid and change of temperature have only minor effects on the products. We need then to account at the very least for the formation of nitrobenzene if the chain reaction has been suppressed, and for the photochemical results. It is, of course, conceivable that these reduction products arise from some non-chain free radical process. We wish to suggest, however, that they arise instead by a hydride transfer process (eq. 3) analogous to those dis-



cussed by Bartlett and McCollum.¹³ The following considerations lend support to this suggestion: (1) The formation of free radicals from a diazonium ion is energetically unfavorable since either an ionized nitrogen molecule (N₂⁺) or an ionized solvent molecule (ROH⁺) must result. Furthermore these solutions contain no obvious nucleophilic species that might make a good covalent diazo compound as a way around this difficulty. (2) The efficiency of the proposed ionic reduction is related in a plausible way to the structure of the diazonium ion on the assumption that hydride transfer requires a more energetic carbonium ion than does ether formation. Thus the presence of strong electron-attracting groups should favor reduction by enhancing the electron deficiency of the carbonium ion. A halogen substituent should lead to more reduction than a hydrogen or an alkyl group, and a nitro group to still more. A group in the *o*-position should be more effective than one in the *p*-position; the results reported in Tables I and II follow just this pattern. (3) It seems reasonable to expect that photoactivation will enhance either a heterolytic cleavage or a homolytic cleavage. It would be surprising, however, to have two such different processes so balanced as to be equally favored upon receipt of the large energy of the light quanta. The formation of appreciable ether indicates that at least some of the photodecomposition occurs by heterolytic cleavage, and it seems reasonable to postulate that all of the cleavage is ionic, even that leading to reduction products.

We therefore conclude that heterolytic decomposition of a diazonium salt leads to both the ether and to the reduction product, with the ether often predominating. The free radical chain reaction leads primarily to reduction product along with small amounts of such products as the biaryl.⁵ The free radical chain reaction is favored by bases such as sodium acetate and by the absence of oxygen. It can be suppressed in favor of the heterolytic reaction by carrying out the thermal decomposition in the presence of strong acids and in an oxygen atmosphere. Heterolytic cleavage also

(13) P. D. Bartlett and J. D. McCollum, *ibid.*, **78**, 1441 (1956).

occurs during photoinduced decomposition of the ion.

Recently Meerwein has obtained very good evidence of hydride transfer in the reaction of 2,4,6-trichlorobenzenediazonium fluoroborate with 2-phenyl-1,3-dioxolane (ethylene glycol acetal of benzaldehyde) to give a 55% yield of trichlorobenzene and an 80% yield of 2-phenyl-1,3-dioxolanium fluoroborate.¹⁴ This paper also summarizes the very interesting work of the Marburg group on the reaction of diazonium salts with ethers.¹⁵

Acknowledgment.—This work was greatly facilitated by a grant from Research Corporation toward the purchase of a Cary model 14 recording spectrophotometer.

Experimental

Reagents.—Most of the compounds were commercially available. Hydroquinone dimethyl ether was prepared by Miss M. A. Barber by alkylation of the monomethyl ether with dimethyl sulfate. *m*-Bromoanisole was obtained from *m*-anisidine by reaction of the diazonium salt with methanol. The compounds were redistilled or recrystallized, and the physical constants agreed with those reported. The ethers were all subjected to an additional purification by chromatography on silica gel to remove phenolic impurities. This step was checked with the infrared spectra in the 3- μ region. The alcohols were redistilled through a 15–20 plate column. The procedure for preparation of the diazonium bisulfates has been described.⁶ These were purified by dissolving in glacial acetic acid and adding acetone. In some cases ether also had to be added to give a suitable recovery.

Product Study Runs.—The reactions were carried out under reflux in a 250-ml. flask or in a sealed tube of about 100-ml. capacity. The oxygen-free reaction mixtures were prepared on a vacuum train. Experiments utilizing an oxygen atmosphere also were done on the vacuum train.

Product Analyses.^{8a,9}—The reaction mixture was transferred to a 250-ml. round-bottomed flask which was attached by a ground joint to a special head containing a sealed-in dropping funnel and sealed-on condenser with drawn-down adapter which fitted well into the volumetric flasks used as receivers. After the alcohol had distilled, the distilling flask was heated in an oil-bath to 5° above the b.p. of the alcohol, and 50 to 100 ml. of the alcohol was dropped in slowly to sweep over the reaction products. Generally four fractions were collected such that most of the reduction product was in the first and second fractions.

(14) H. Meerwein, H. Allendorfer, P. Beekmann, F. Kunert, H. Morschel, F. Pawellek and K. Wunderlich, *Angew. Chem.*, **70**, 211 (1958).

(15) NOTE ADDED IN PROOF.—Since submitting this manuscript we have learned of the work of William Lee, Jack G. Calvert and Earl Malmberg of Ohio State University on the photochemical reaction of the *p*-nitrobenzenediazonium chloride stannous chloride complex and other salts with ethanol at 0°. With their kind permission we can report that their product yields as determined chromatographically correspond closely with ours as far as the ether and the reduction product are concerned. They have, however, gone further and have identified a number of other interesting products such as α -*p*-nitrophenylethanol, which are indicative of free radical intermediates ($O_2NC_6H_4 + CH_3CHOH \rightarrow O_2NC_6H_4CH(OH)CH_3$). Furthermore, they have shown that in fairly dilute solution in ethanol a slight excess of iodine suppresses the formation of nitrobenzene, yielding an equivalent amount of *p*-nitroiodobenzene instead, while the yield of *p*-nitrophenetol is essentially unchanged. A chain reaction is excluded by their finding of a quantum yield of approximately one. They tentatively interpret these results in terms of a photodecomposition of the diazonium salt partly by an ionic but mainly by a free radical process. We agree that this conclusion is in accord with their data and with ours. The formation of a *p*-nitrophenyl radical from a *p*-nitrobenzenediazonium ion requires an electron-donor, and it now appears to be necessary to postulate seriously an electron-transfer reaction leading to an ionized methanol molecule. A decision as to whether hydride transfer plays a significant role in any of the alcohol reactions or whether the electron transfer step is a general mechanism must await further experimental work.

Ultraviolet spectra of appropriately diluted samples were taken with a Cary model 14 ultraviolet spectrophotometer. Concentrations were calculated using at least two wave lengths per component. The procedures were standardized using known mixtures.

Representative mixtures were carried through the complete distillation procedure: the numbers refer, respectively, to sample taken (mg.) and amount recovered (mg.): (1) benzene, 2.70, 1.80; anisole, 17.6, 17.9; (2) toluene, 7.95, 7.82; *p*-methylanisole, 15.1, 15.2; (3) bromobenzene, 5.0, 5.0; *p*-bromoanisole, 27.7, 27.5; (4) anisole, 17.4, 17.5; hydroquinone dimethyl ether, 3.4, 3.5; (5) nitrobenzene, 10.0, 10.2; *p*-nitroanisole, 13.0, 12.8; (6) benzene, 6.0, 5.7; phenetole, 12.6, 12.5; (7) benzene, 14.9, 14.1; phenyl 2-propyl ether 20.5, 20.4; (8) benzene 7.5, 6.8; phenyl 1-butyl ether 10.7, 10.4.

These various synthetic mixtures also were analyzed (but were not taken through the distillation step): (9) benzene, 4.24, 3.92; anisole, 3.67, 3.63; (10) benzene, 0.81, 0.71; anisole, 5.16, 5.16; fluorobenzene, 0.83, 0.74; (11) benzene, 2.80, 2.25; phenetole, 5.01, 4.98; (12) benzene, 2.80, 2.22; phenetole, 5.01, 4.98; fluorobenzene, 0.46, 0.42; (13) benzene, 4.90, 5.06; phenyl 2-propyl ether, 5.33, 5.30; (14) benzene, 4.90, 4.81; phenyl 2-propyl ether, 5.33, 5.23; fluorobenzene, 0.94, 0.95; (15) benzene, 4.30, 1.79; phenyl 1-butyl ether, 4.85, 4.88; (16) benzene, 4.30, 2.85; phenyl 1-butyl ether, 4.85, 4.95; fluorobenzene, 1.34, 1.18.

Product Identification.—Previous workers^{3,16,17} have isolated the ethers and the reduction products in preparative scale runs: e.g., anisole, *p*-methylanisole, *p*-bromoanisole and *p*-nitroanisole. In addition, the ultraviolet spectra had the characteristic shape of the expected products, and many fractions had the spectra of nearly pure reduction product or ether.

Kinetics.—The rates were determined in the apparatus previously described.⁴ The data were examined graphically and by the methods of computation previously used.¹⁸ Dr. Julius English developed a program for the IBM 650 computer for obtaining the adjusted parameters for the first order equation $p = a + be^{ct}$. The data for all runs in Table IV except those with superscript "e" were evaluated on the 650 computer.

Reactions of Benzenediazonium Bisulfates with Methanol.—The diazonium salt (200 μ moles except where otherwise indicated) was dissolved in methanol and sealed in a glass ampoule (except for reactions under reflux). The reaction data are summarized in the following sequence: ml. of methanol, reaction temp. (R. = reflux), reaction time (d. = days, h. = hours), the yield of reduction product ArH, and the yield of ether ArOCH₃. The gas phase was air except where indicated; N₂ signifies that the reaction mixture was outgassed on a vacuum train before pressuring with high purity nitrogen and O₂ signifies an oxygen atmosphere. The runs described here are summarized in Table I. All pertinent information for the runs in Table II is given in that table and is not repeated here.

From *p*-CH₃C₆H₄N₂HSO₄: 10 ml., 25°, 5 d., 4, 90; 10 ml., 100°, 3 h., 3, 97; 25 ml., 65° (N₂), 3 d., 23, 73; 50 ml., R., 5 h., 14, 84; 10 ml., R., 5 h., 6, 91.

From *m*-CH₃C₆H₄N₂HSO₄: 50 ml., R., 10 h., 5, 95.
From *p*-BrC₆H₄N₂HSO₄: 10 ml., 100°, 1 d., 55, 36; 10 ml. (400 μ moles), 100°, 1 d., 67, 31; 10 ml., 150°, 1 d., 47, 45; 10 ml., 185°, 1 d., 56, 37; 25 ml., 65° (N₂), 7 d., 96, 2; 50 ml., R., 7 d., 70, 31; 50 ml., R., 7 d., 66, 24; 50 ml. (400 μ moles), R., 7 d., 80, 17; 50 ml. (600 μ moles), R., 7 d., 84, 18; 25 ml. (400 μ moles), R., 7 d., 82, 20.

From *m*-BrC₆H₄N₂HSO₄: 10 ml., 100°, 1 d., 31, 59; 10 ml. (400 μ moles), 100°, 1 d., 30, 60; 25 ml., 65° (N₂), 7 d., 85, 12; 50 ml., R., 5 d., 18, 76; 50 ml. (400 μ moles), R., 7 d., 30, 62; 50 ml. (600 μ moles), R., 7 d., 35, 62; 25 ml. (400 μ moles), R., 7 d., 40, 53.

From *o*-BrC₆H₄N₂HSO₄: 10 ml., 100°, 1 d., 94, 1; 50 ml., R., 7 d., 100, 1.

From *p*-O₂NC₆H₄N₂HSO₄: 10 ml., 25°, 30 d., 66, 13; 10 ml., 100°, 1 d., 86, 5; 10 ml., 100°, 1 d., 89, 5; 10 ml., 135°, 1 d., 85, 6; 50 ml., R., 1 d., 79, 11; 50 ml., R., 7 d., 83, 14; 10 ml., R., 7 d., 81, 9.

From *m*-O₂NC₆H₄N₂HSO₄: 10 ml., 100°, 1 d., 84, 4; 50 ml., R., 7 d., 86, 4.

(16) G. Alleman, *Am. Chem. J.*, **31**, 24 (1904).

(17) G. F. Weida, *ibid.*, **19**, 547 (1897).

(18) D. F. DeTar, *This Journal*, **78**, 3911 (1956).

From *o*-O₂NC₆H₄N₂H₂SO₄: 10 ml., 100°, 1 d., 99, 2; 50 ml., R., 7 d., 94, 2.

From *p*-CH₃OC₆H₄N₂H₂SO₄: 20 ml., 65° (O₂), 7 d., 13, 79; 10 ml., 65°, 7 d., 14, 79; 20 ml., 65°, 7 d., 21, 69; 20 ml., 65°, 7 d., 26, 70; 30 ml., 65°, 7 d., 24, 66; 40 ml., 65°, 7 d., 25, 68; 50 ml., 65°, 7 d., 29, 64; 50 ml. (100 μ moles), 65°, 7 d., 28, 65; 10 ml., 100°, 20 h., 12, 84; 10 ml., 150°, 20 h., 10, 85; 20 ml., 65° (N₂), 7 d., 96, 4; 50 ml., R., 5 d., 94, 4, 50 ml., R., 3 d., 92, 5; 50 ml., R.,

7 d., 99, 1; 50 ml., R., 7 d., 89, 12; 50 ml., R., 7 d., 93, 8; 50 ml., R-O₂, 7 d., 64, 32; 50 ml. (0.5 ml. of formalin), R., 7 d., 76, 18; 50 ml. (3 ml. of formalin), R., 7 d., 80, 14; 50 ml. (85 mg. of HCOOH), R., 7 d., 97, 6; 50 ml. (400 μ moles), R., 7 d., 60, 38; 50 ml., R., 7 d., 83, 13.

From *m*-CH₃OC₆H₄N₂H₂SO₄: 10 ml., 100°, 1 d., 2, 94; 50 ml., R., 2 d., 2, 94.

COLUMBIA, S. C.

[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE¹]

Aminoketones. I. The Preparation of α -Aminoketones from Di-*t*-butyl Acetamidomalonate²

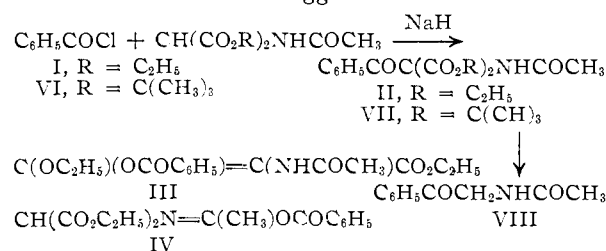
BY ANTHONY W. SCHRECKER AND MARY M. TRAIL

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Benzoylation of diethyl sodioacetamidomalonate yields the C-acyl derivative (II), and not an O-acyl compound as had been postulated. Acid-catalyzed cleavage of di-*t*-butyl acylacetamidomalonates provides acetamidoketones, which can be hydrolyzed to 1-amino-2-alkanone hydrochlorides.

As part of a program dealing with the preparation of amino acid antimetabolites to be tested for potential effect against experimental tumors, the synthesis of certain α -aminoketone derivatives of the general structure RCOCH₂NHR' appeared of interest. Some compounds of this type, such as δ -aminolevulinic acid,³ have been shown to be involved in biochemical pathways, while others have been employed in the synthesis of antibiotics.⁴

In a search for improved methods of preparing such compounds, the acylation and subsequent decarboxylation of N-acylaminomalonic esters has been investigated. The only known acyl derivative of this type, namely, diethyl benzoylacetamidomalonate, was prepared several years ago^{5,6} by treating the sodio derivative of diethyl acetamidomalonate (I) with benzoyl chloride. The product could not, however, be made to undergo ketone cleavage. Treatment with bicarbonate led to reversal of the acylation reaction,⁶ catalytic hydrogenation yielded I and benzaldehyde,⁵ and no carbonyl derivatives could be obtained.⁵ This led the previous investigators to believe that the compound was not the C-acyl derivative II, but an O-acyl derivative. Dalglish⁵ favored structure III, while Viscontini and Adank⁶ suggested formula IV.



(1) National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

(2) Presented in part before the Medicinal Chemistry Division of the American Chemical Society in San Francisco, Calif., April 14, 1958; cf. Abstracts of Papers, **133**, 7M (1958).

(3) (a) A. Neuberger and J. J. Scott, *Nature*, **172**, 1093 (1953); (b) *J. Chem. Soc.*, 1820 (1954); (c) D. Shemin and C. S. Russell, *THIS JOURNAL*, **76**, 4873 (1953).

(4) L. M. Long and H. D. Troutman, *ibid.*, **71**, 2469, 2473 (1949).

(5) C. E. Dalglish, *J. Chem. Soc.*, 90 (1949).

(6) M. Viscontini and K. Adank, *Helv. Chim. Acta*, **35**, 1342 (1952).

An attempt to degrade this benzoyl derivative to α -aminoacetophenone by heating with 6 *N* hydrochloric acid was unsuccessful: benzoic acid and glycine hydrochloride were obtained instead. However, this does not prove that the compound was an O-acyl derivative. Indeed, as Bowman⁷ has shown, only unsubstituted diethyl acylmalonates can be hydrolyzed and decarboxylated to ketones. With compounds of the type R'COCR''(CO₂R)₂ (V) (R = Et, R' = alkyl or aryl, R'' = alkyl), cleavage of the acyl-carbon bond occurs preferentially.⁷

Methods have been developed in recent years which do permit converting esters of this type to ketones. Bowman has shown that the dibenzyl esters (V, R = C₆H₅CH₂) can be hydrogenolyzed and decarboxylated,⁸ and that the bis-tetrahydropyranyl esters (V, R = $\overline{\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}-}$) can be pyrolyzed,⁹ while Fonken and Johnson,¹⁰ and also Puterbaugh, Swamer and Hauser,¹¹ have made use of the facile acid-catalyzed cleavage of the di-*t*-butyl esters (V, R = CMe₃). Application of such a procedure to the preparation and degradation of an appropriate ester of benzoylacetamidomalonic acid appeared desirable not only in order to prove whether C- or O-benzoylation had taken place, but also for the development of a general method of synthesizing aminoketones of the type shown in the introductory paragraph.

The present report deals with the application of the *t*-butyl ester method.¹² Commercially available¹³ diethyl acetamidomalonate (I) was saponified to the free acid, which was converted to the di-*t*-butyl ester VI by the method of McCloskey.^{10,14}

(7) R. E. Bowman, *J. Chem. Soc.*, 322 (1950); cf. H. G. Walker and C. R. Hauser, *THIS JOURNAL*, **68**, 1386 (1946).

(8) R. E. Bowman, *J. Chem. Soc.*, 325 (1950).

(9) R. E. Bowman and W. D. Fordham, *ibid.*, 3945 (1952).

(10) G. S. Fonken and W. S. Johnson, *THIS JOURNAL*, **74**, 831 (1952).

(11) W. H. Puterbaugh, F. W. Swamer and C. R. Hauser, *ibid.*, **74**, 3438 (1952).

(12) Hydrogenolysis of dibenzyl benzoylacetamidomalonate failed to yield α -acetamidoacetophenone (see Experimental). Attempts to prepare bis-(tetrahydropyranyl) acetamidomalonate by Bowman's method⁹ failed.

(13) Matheson, Coleman and Bell, Norwood (Cincinnati), Ohio.

(14) A. L. McCloskey, G. S. Fonken, R. W. Kluiber and W. S. Johnson, *Org. Syntheses*, **34**, 26 (1954).