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Some New Fumaric Acid Derivatives. Preparation of Mixed Fumarates and Thiolfumarates

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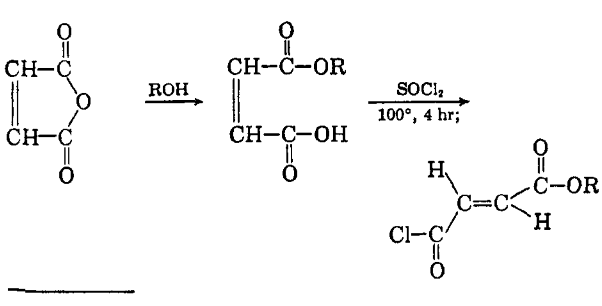
Several new bis-aryl fumarates were prepared by the Schotten-Baumann method. Attempts to modify the chemical and physical properties of these compounds led to the synthesis of certain new alkyl fumaryl chlorides by a convenient method. This involved the reaction of maleic anhydride with an alcohol, followed by treatment with thionyl chloride. The acid chlorides were used as intermediates in the preparation of a variety of mixed fumarate and thiolfumarate esters, and of some new fumaramates.

In the framework of a larger program, we prepared several halogenated bisaryl fumarate esters to investigate their utility in conveying flame retardant properties to copolymers. These compounds were prepared by a Schotten-Baumann reaction utilizing a halogenated phenol and fumaryl chloride.[1,2] The high melting points and slight solubility of these materials in organic liquids led us to attempt to obtain materials with more desirable physical properties by incorporating an alkyl group on one end of the fumarate structure. Such mixed esters do not appear to have been reported in the literature. We are reporting here the preparation of these and related compounds.

A promising approach to the synthesis of such compounds appeared to be the reaction of a phenol with an alkyl half-ester, half-acid chloride of the fumaric acid. A convenient method of preparing ethyl fumaryl chloride in good yield has been reported by Eisner, Elvidge, and Linstead,[3] involving the isomerization of ethyl hydrogen maleate to the fumarate, followed by reaction with thionyl chloride. These workers also prepared methyl fumaryl chloride similarly, though in lower yield. We attempted to apply the method to the preparation of *n*-propyl fumaryl chloride and obtained poor results. This led to an attempt to convert crude *n*-propyl hydrogen maleate (from the alcohol and maleic anhydride) to *n*-propyl fumaryl chloride in one step by refluxing with a small excess of thionyl chloride. The method was very successful, giving an 80% yield of the desired acid chloride which was easily purified by fractional distillation. Table I gives the data on the alkyl fumaryl chlorides prepared in this manner.[4] The lower yield of the *i*-propyl derivative may, in part, have been due to the incomplete esterification of *i*-propyl alcohol by maleic anhydride. This difference in reactivity of maleic anhydride with primary and secondary alcohols has previously been observed by Siegel and Moran.[5,6]



In the course of our work we used these alkyl fumaryl chlorides to prepare a number of alkyl aryl fumarates, the aryl group being a halogenated phenyl group. As expected, the compounds were much lower melting than the bisaryl fumarates, several of them being liquids at room temperature. We also allowed these acid chlorides to react with several primary and secondary amines yielding fumaramates. These were solids with suitable solubility properties for polymerization studies with liquid comonomers.

The acid chlorides were also allowed to react with various mercaptans, yielding mixed thiolfumarates. As expected, these compounds were also considerably lower melting and more soluble than the dithiolfumarates previously reported from these

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(1) For the similar reaction of methacrylyl chloride with thiolphenols, see G. Sumrell, G. E. Ham, and E. D. Hornbaker, *J. Am. Chem. Soc.*, **80**, 2509 (1958).

(2) For the similar preparation of aryl methacrylates, see (a) S. Patai, M. Bentov, and M. E. Reichmann, *J. Am. Chem. Soc.*, **74**, 845 (1952); and (b) G. Sumrell, P. G. Campbell, C. H. Schramm, and G. E. Ham, *J. Am. Chem. Soc.*, **81**, 4310 (1959).

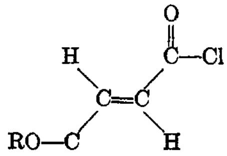
(3) U. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, 1501 (1951).

(4) Attempts to extend this method to the preparation of either methyl or ethyl fumaryl chloride gave mixtures which were largely the desired acid chlorides. However, fractional distillation was not successful in removing traces of the dialkyl fumarates and possibly other impurities. Yields of 40 to 50% of product of >90% purity were obtained.

(5) E. F. Siegel and M. K. Moran, *J. Am. Chem. Soc.*, **69**, 1457 (1947).

(6) When this reaction was carried out between *t*-butyl alcohol and maleic anhydride, maleic acid was obtained in 97.8% yield. The maleic anhydride dissolved upon heating on the steam bath with *t*-butyl alcohol, but after three quarters of an hour a vigorous exothermic reaction occurred with gas evolution, and the residual maleic acid solidified. The maleic acid was identified by elemental analysis and melting point determinations. The evolved gas decolorized bromine in carbon tetrachloride was presumably isobutylene. It is possible that this reaction may be of value as a synthetic tool for converting tertiary alcohols to olefins.

TABLE I



ALKYL FUMARYL CHLORIDES

R	B.P.	n_D^{25}	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. Halogen	Found C	Found H	Found Halogen
n-C_3H_7—	99–100/15 mm.	1.4599	80.2	$C_7H_9ClO_3$	47.60	5.14	20.08	47.73	5.26	20.07
i-C_3H_7—	88–90/12 mm.	1.4540	46.8	$C_7H_9ClO_3$	47.60	5.14	20.08	47.68	5.30	20.23
n-C_4H_9—	102–104/9 mm.	1.4610	82.1	$C_8H_{11}ClO_3$	50.40	5.82	18.60	50.55	5.96	18.60
n-C_5H_{11}—	120.5–122/13 mm.	1.4612	83.4	$C_9H_{13}ClO_3$	52.82	6.40	17.33	52.88	6.51	17.17

laboratories.[7,8] Table II lists the properties of the fumaric acid derivatives prepared.

EXPERIMENTAL

Boiling points and melting points are uncorrected. Unless otherwise indicated, distillations were carried out through an 80-cm. Podbielniak-type column.

Starting materials. The phenols, amines, mercaptans, and maleic anhydride were commercial materials and were used without purification. The thionyl chloride was distilled from quinoline before use. Methyl and ethyl fumaryl chloride were prepared essentially as described by Eisner, Elvidge and Linstead.[3]

Bis(4-bromophenyl) fumarate. The preparation of bis-(4-bromophenyl) fumarate illustrates the method used for the remaining bisaryl fumarate esters. One mole of 4-bromophenol was dissolved in 1000 ml. of 5% sodium hydroxide in a 2 l. three necked flask fitted with a dropping funnel, stirrer and thermometer. The solution was maintained at 0° with an acetone-ice bath while 0.5 mole of fumaryl chloride was added dropwise. Stirring was continued for 1 hr. Then the solid was filtered, washed well with water, and air dried. Recrystallization from a mixture of benzene and acetone gave 96.3 g. (44%) of product of m.p. 174–175 (lit.,[9] m.p. 174°).

Bis(2,4-dibromophenyl) fumarate was similarly prepared and recrystallized from benzene-acetone; yield, 110.7 g. (38%), m.p. 215–216°.

Anal. Calcd. for $C_{16}H_8Br_4O_4$: C, 32.91; H, 1.38; Br, 54.75. Found: C, 32.88; H, 1.50; Br, 54.65.

Bis(2,4-dichlorophenyl) fumarate was similarly prepared and recrystallized; yield 87.7 g. (43%), m.p. 186–187.

Anal. Calcd. for $C_{16}H_8Cl_4O_4$: C, 47.32; H, 1.98; Cl, 34.93. Found: C, 47.28; H, 1.97; Cl, 34.71.

Bis(2,4,5-trichlorophenyl) fumarate was similarly prepared and recrystallized; yield, 96.3 g. (40%), m.p. 205–206°.

Anal. Calcd. for $C_{16}H_6Cl_6O_4$: C, 40.46; H, 1.27; Cl, 44.79. Found: C, 40.53; H, 1.32; Cl, 44.62.

n-Propyl fumaryl chloride.[10] A sample of crude n-propyl hydrogen maleate was prepared by warming a mixture of 1 mole each of maleic anhydride and n-propyl alcohol on the steam bath until a syrupy liquid resulted. To this mixture was added dropwise and with stirring 1.25 moles of thionyl chloride. The temperature was maintained below 45° by cooling. After the addition was complete, the mixture was gradually heated to 100° in *ca.* 2 hr., and maintained at this temperature for an additional 4 hr. The dark mixture was fractionally distilled, yielding 141.5 g. (80%) of product at 99–100° (15 mm.), n_D^{25} 1.4599.

The other alkyl fumaryl chlorides (Table I) were prepared by the same procedure.

Methyl 2,4,5-trichlorophenyl fumarate. A mixture of 43.4 g. (0.22 mole) of 2,4,5-trichlorophenol, 10 g. (0.25 mole) of sodium hydroxide and 200 ml. of water was cooled to 0°, and 29.7 g. (0.2 mole) of methyl fumaryl chloride was added dropwise with stirring. The mixture was allowed to stir several hours. The reaction mixture consisted of an upper aqueous phase and a lower solid phase. The solid was filtered, washed with water, and recrystallized from isopropyl alcohol; yield, 18.0 g. (29.9%), m.p. 36–37°. This general procedure was used for the preparation of the remaining alkyl aryl fumarates (Table II).

Ethyl N-morpholinofumarate. The preparation of this compound illustrates the method used to synthesize the fumaramates described in Table II. Morpholine (0.23 mole), dissolved in 200 ml. of ethylene dichloride, was placed in a 500 ml. three necked flask fitted with a stirrer, dropping funnel, and thermometer. The mixture was cooled to 0° and ethyl fumaryl chloride (0.1 mole) was added dropwise. The mixture was allowed to stir overnight. The organic solution was washed with dilute phosphoric acid and then with brine until the washings were neutral. The ethylene dichloride was removed by flash evaporation. The semisolid residue was recrystallized from ligroin–isopropyl alcohol, giving 16.6 g. (78%) of product, m.p. 72.5–73°.

O-Methyl S-methyl thiolfumarate. Methyl mercaptan was bubbled into 100 ml. of ice cold anhydrous 1,2-dimethoxyethane until the weight increased 24 g. (0.5 mole). This solu-

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[7] G. Sumrell, M. Zief, E. J. Huber, C. H. Schramm, and G. E. Ham, *J. Am. Chem. Soc.*, **81**, 4313 (1959).

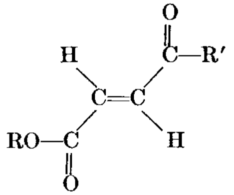
[8] It was pointed out in Reference 7 that the dithiol fumarates with aryl groups in the ester functions were yellow in color. Even di-t-butyl dithiolfumarate and some simpler thiol esters such as pentachlorochlorophenyl thiolacetate and pentachlorophenyl thiolmethacrylate proved to be yellow solids. Similarly, the thiolfumarates described in this paper were yellow in color when an aryl group was in the thiol ester function. However, O-methyl S-t-butyl thiolfumarate, though yellow as a liquid, on cooling formed a colorless crystalline solid which melted at 24°. O-Ethyl S-t-butyl thiolfumarate was a yellow oil which froze to a colorless solid in Dry Ice.

The reason for the yellow color in these compounds, seemingly lacking in chromophoric groups, is speculative. Dr. E. M. Kosower, University of Wisconsin, has suggested in a private communication that the color may be due to inter- or intramolecular charge-transfer transitions. We are at present not able to offer a more suitable explanation.

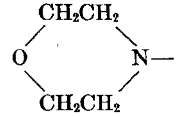
[9] R. Anschütz, *Chem. Ber.*, **60B**, 1320 (1927).

[10] n-Propyl hydrogen fumarate was prepared in 60% yield on a 1 mole scale, following the procedure given in reference 3 for ethyl hydrogen fumarate. This compound was converted to the acid chloride in only 20% yield using phosphorus trichloride. The use of thionyl chloride did not improve the yield. For n-propyl hydrogen fumarate, m.p. 48–49°. *Anal.* Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.16; H, 6.43.

TABLE II



FUMARIC ACID DERIVATIVES

R	R′	B.P. or (M.P.)	n_D^{25}	Yield, %	Formula	Calcd.					Found				
						C	H	Halogen	N	S	C	H	Halogen	N	S
CH_3—	2,4,5-$Cl_3C_6H_2O$—	(90–91)		29.2	$C_{11}H_7Cl_3O_4$	42.68	2.28	34.36			42.68	2.40	34.32		
CH_3—	2,4-$Br_2C_6H_3O$—	(122–123)		49.2	$C_{11}H_8Br_2O_4$	36.29	2.22	43.91			36.49	2.33	43.61		
CH_3—	4-BrC_6H_4O—	(72–73)		68.2	$C_{11}H_9BrO_4$	46.34	3.18	28.03			46.40	3.14	28.20		
CH_3—	CH_3S—	(53–54)		58.5	$C_6H_8O_3S$	44.99	5.03			20.01	44.87	5.12			19.80
CH_3—	$(CH_3)_2CHS$—	60–61/0.5 mm. (−6)	1.5002	57.0	$C_8H_{12}O_3S$	51.07	6.43			17.04	51.20	6.58			17.12
CH_3—	$(CH_3)_3CS$—	69–71/0.5 mm. (24)	1.4948	40.0	$C_9H_{14}O_3S$	53.44	6.98			15.85	53.39	7.00			15.79
CH_3—	Cl_5C_6S—	(157–159)		34.6	$C_{11}H_5Cl_5O_3S$	33.49	1.28	44.94		8.13	33.60	1.37	44.91		7.99
CH_3—	4-ClC_6H_4S—	(82–83)		46.8	$C_{11}H_9ClO_3S$	51.47	3.53	13.81		12.49	51.32	3.70	13.75		12.49
C_2H_5—		(72.5–73)		77.9	$C_{10}H_{15}NO_4$	56.32	7.09		6.57		56.48	7.15		6.64	
C_2H_5—	2,5-$Cl_2C_6H_3NH$—	(121–122)		50.0	$C_{12}H_{11}Cl_2NO_3$	50.02	3.85	24.61	4.86		50.07	3.87	24.59	4.93	
C_2H_5—	2-ClC_6H_4NH—	(103.5–104.5)		45.4	$C_{12}H_{12}ClNO_3$	56.81	4.77	13.98	5.52		56.85	4.89	13.87	5.60	
C_2H_5—	3-ClC_6H_4NH—	(154–154.5)		51.0	$C_{12}H_{12}ClNO_3$	56.81	4.77	13.98	5.52		56.87	4.80	14.00	5.56	
C_2H_5—	2,4,5-$Cl_3C_6H_2O$—	(51.5–53)		76.8	$C_{12}H_9Cl_3O_4$	44.54	2.80	32.87			44.74	2.85	32.70		
C_2H_5—	2,4-$Br_2C_6H_3O$—	(52–53)		46.7	$C_{12}H_{10}Br_2O_4$	38.12	2.67	42.28			38.23	2.78	42.27		
C_2H_5—	4-BrC_6H_4O—	(49–50)		79.3	$C_{12}H_{11}BrO_4$	48.18	3.71	26.72			48.01	3.61	26.74		
C_2H_5—	$(CH_3)_3CS$—	94–96/1 mm.	1.4908	65.5	$C_{10}H_{16}O_3S$	55.53	7.46			14.82	55.67	7.49			14.77
C_2H_5—	Cl_5C_6S—	(134.5–135.5)		39.2	$C_{12}H_7Cl_5O_3S$	35.28	1.73	43.40		7.85	35.26	1.88	43.35		8.09
C_2H_5—	4-ClC_6H_4S—	(47–48.5)		50.6	$C_{12}H_{11}ClO_3S$	53.23	4.10	13.10		11.84	53.41	4.26	13.11		11.89
n-C_3H_7—	$(C_6H_5)_2N$—	(85.5–86.5)		41.9	$C_{19}H_{19}NO_3$	73.76	6.19		4.53		73.73	6.13		4.49	
n-C_3H_7—	2,4,5-$Cl_3C_6H_2O$—	(34.5–36.2)		67.6	$C_{13}H_{11}Cl_3O_4$	46.25	3.29	31.51			46.45	3.35	31.51		
n-C_3H_7—	2,4-$Br_2C_6H_3O$—	208–210/0.5 mm.	1.5593	77.3	$C_{13}H_{12}Br_2O_4$	39.82	3.09	40.77			39.97	3.30	40.77		
n-C_3H_7—	4-BrC_6H_4O—	(42–43)		80.5	$C_{13}H_{13}BrO_4$	49.86	4.18	25.52			49.97	4.16	25.40		
n-C_3H_7—	$(CH_3)_3CS$—	86/0.4 mm.	1.4875	62.1	$C_{11}H_{18}O_3S$	57.36	7.88			13.92	57.29	7.85			13.83
n-C_3H_7—	4-ClC_6H_4S—	(43–44.5)		43.5	$C_{13}H_{13}ClO_3S$	54.83	4.60	12.45		11.26	54.87	4.64	12.41		11.17
i-C_3H_7—	4-BrC_6H_4O—	(40–41)		62.5	$C_{13}H_{13}BrO_4$	49.86	4.18	25.52			49.90	4.28	25.60		
n-C_4H_9—	2,4-$Br_2C_6H_3O$—	184/0.7 mm.	1.5526	66.9	$C_{14}H_{14}Br_2O_4$	41.40	3.48	39.36			41.60	3.49	39.42		
n-C_4H_9—	4-BrC_6H_4O—	(32–33.5)		81.2	$C_{14}H_{15}BrO_4$	51.39	4.62	24.43			51.35	4.60	24.30		
n-C_4H_9—	$(CH_3)_3CS$—	109–110/0.8 mm.	1.4860	67.7	$C_{12}H_{20}O_3S$	58.98	8.25			13.12	59.03	8.37			13.03
n-C_4H_9—	4-ClC_6H_4S—	163–166/0.4 mm. (41)	1.5560	35.6	$C_{14}H_{15}ClO_3S$	56.28	5.06	11.87		10.73	56.29	4.97	11.97		10.75
n-C_5H_{11}—	2,4,5-$Cl_3C_6H_2O$—	181–183/0.6 mm.	1.5336	73.2	$C_{15}H_{15}Cl_3O_4$	49.27	4.14	29.09			49.42	4.15	29.25		
n-C_5H_{11}—	2,4-$Br_2C_6H_3O$—	(29–30)		69.7	$C_{15}H_{16}Br_2O_4$	42.88	3.84	38.05			42.85	3.85	38.20		
n-C_5H_{11}—	4-BrC_6H_4O—	158/0.2 mm.	1.5283	62.4	$C_{15}H_{17}BrO_4$	52.80	5.02	23.42			53.04	4.93	23.68		
n-C_5H_{11}—	$(CH_3)_3CS$—	113/0.5 mm.	1.4854	55.0	$C_{13}H_{22}O_3S$	60.43	8.56			12.41	60.33	8.46			12.45
n-C_5H_{11}—	4-ClC_6H_4S—	(36–37)		44.5	$C_{15}H_{17}ClO_3S$	57.59	5.48	11.34		10.25	57.63	5.30	11.33		10.35

tion was mixed with 74.4 g. (0.5 mole) of methyl fumaryl chloride in a 500 ml. three necked flask equipped with stirrer, dropping funnel, and thermometer. The temperature was maintained at 0–5° by cooling with an acetone ice bath while 40 ml. of pyridine was added dropwise with stirring. After 0.5 hr. of additional stirring, 200 ml. of water was added. The mixture was cooled back to 0° and filtered. The brown solid was washed thoroughly with water and air dried; crude yield, 57 g. (71%), m.p. 50–53°. Recrystallization from a mixture of 120 ml. of isopropyl alcohol and 120 ml. of water gave 47 g. of long colorless blades, m.p. 53–54°, unchanged by further recrystallization.

O-Methyl S-isopropyl thiolfumarate was prepared in a similar manner. However, the crude product separated as an oily lower phase. This was extracted into 50 ml. of chloroform, washed with water, and dried over sodium sulfate. The material was then purified by fractional distillation.

O-Methyl S-t-butyl thiolfumarate. The synthesis of this compound describes the method used for the preparation of the remaining thiolfumarates. A solution of 36 g. (0.4 mole) of *t*-butyl mercaptan in 400 ml. of 5% aqueous sodium hydroxide was maintained at 10–15° by cooling while 59.5 g. (0.4 mole) of methyl fumaryl chloride was added dropwise with stirring. An oil separated to the bottom when stirring was stopped. The mixture was stirred for 3 hr. with cooling to −5° in an unsuccessful attempt to induce crystallization. Then the oil was extracted into 50 ml. of chloroform, washed with water, and dried over sodium sulfate. Fractional distillation gave 32 g. (40%) of light yellow product at 69–71° (0.5 mm.), n_D^{25} 1.4948. When this material was chilled at 0° for several hours, it crystallized to colorless blades which melted at 24°.

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PHILLIPSBURG, N. J.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, TENNESSEE EASTMAN CO., DIVISION OF EASTMAN KODAK CO.]

Chemistry of Dimethylketene Dimer. I. Catalytic Hydrogenation and Ring Cleavage by Alcohols

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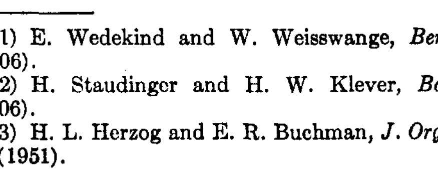
The hydrogenation of dimethylketene dimer (I) was investigated to find the optimum conditions for preparation of the corresponding glycol III. Excellent yields were obtained with a ruthenium catalyst. Hydrogenation over Raney nickel was often accompanied by formation of by-products. In a methanolic medium, some of the dimer was cleaved to form methyl 2,2,4-trimethyl-3-oxovalerate (VI). This reaction, when catalyzed by bases, was generally applicable to other alcohols and to phenols and mercaptans. Another by-product was identified as 1-hydroxy-2,2,4-trimethyl-3-pentanone (V), which presumably was formed by ring opening of the intermediate ketol II and subsequent hydrogenation of the acyclic keto aldehyde IV formed by this cleavage. The glycol III was separated into isomers melting at 148° and 163°, which were characterized by infrared and NMR spectra as the *trans* and *cis* isomers, respectively.

Tetramethyl-1,3-cyclobutanedione (I) was first prepared by Wedekind and Weisswange[1] by the dehydrohalogenation of isobutyryl chloride with triethylamine. At about this same time, Staudinger and Klever[2] succeeded in preparing dimethylketene from bromisobutyryl bromide and zinc, and it was recognized that this compound spontaneously formed a dimer which was identical with I.



The structure of dimethyketene dimer as a cyclic 1,3-diketone has been well established by the formation of typical carbonyl derivatives,[1,3] the Beckmann rearrangement of oximes,[4] the Wolff-Kishner reduction of the disemicarbazone,[3] and electron diffraction studies.[5] An unsuccessful attempt was made to obtain the corresponding glycol, 2,2,4,4-tetramethyl-1,3-cyclobutanediol (III), by reduction of I with sodium amalgam.[6] Catalytic hydrogenation under relatively mild conditions produced the intermediate ketol, 3-hydroxy-2,2,4,4-tetramethylcyclobutanone (II). Gross[7] first carried out this reduction over platinum oxide catalyst[8] in equipment similar to the Adams-Voorhees apparatus,[9] but Miller[4] obtained better results (80% yield) with Raney nickel under 5–6 atm. pressure of hydrogen. More drastic conditions, up to 150° and 100 atm. over Raney nickel, were used by Miller to force the hydrogenation to the glycol III.

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(6) E. Wedekind and M. Miller, *Ber.*, **44**, 3285 (1911).

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(8) R. Adams, V. Voorhees, and R. L. Shriner, *Org. Syntheses*, Coll. Vol. I, 463 (1941).

(9) R. Adams and V. Voorhees, *Org. Syntheses*, Coll. Vol. I, 61 (1941).