[CONTRIBUTION NO. 213 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Identification of Organic Compounds. III. Chlorosulfonic Acid as a Reagent for the Characterization of Aromatic Ethers[1,2]

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The use of chlorosulfonic acid as a tool for the characterization of organic compounds whose application to the identification of aryl halides was reported in the first paper[3] of this series has now been extended to thirty-six aromatic ethers. The principle employed is twofold: first, introduction of one sulfonyl chloride group into each aromatic nucleus by direct treatment with chlorosulfonic acid, and, second, conversion of the resultant sulfonyl chlorides into the corresponding sulfonamides. The sulfonyl chlorides were generally obtained in excellent yields and their conversion to sulfonamides was nearly quantitative. The resultant products crystallize well and possess sharp and characteristic melting points. Data expressing the results of this study are given in Table I.

TABLE I

SULFONAMIDES[a] FROM AROMATIC ETHERS

Original compound	Sulfonamide	Yield, %	M. p. obsd. uncor., °C.
	A. Substituted benzenesulfonamides		
Anisole	*p*-Methoxy-	53	110–111[b]
Phenetole	*p*-Ethoxy-	78	149–150[c]
n-Propyl phenyl ether	*p*-(*n*-Propoxy)-	68	116–117
n-Butyl phenyl ether	*p*-(*n*-Butoxy)-	35	103–104
o-Tolyl methyl ether	3-Methyl-4-methoxy-	84	137[d,e,f]
m-Tolyl methyl ether	2-Methyl-4-methoxy-	69	129–130[g]
p-Tolyl methyl ether	5-Methyl-2-methoxy-	86	182[h]
o-Tolyl ethyl ether	3-Methyl-4-ethoxy-	71	148–149[i]
m-Tolyl ethyl ether	2-Methyl-4-ethoxy-	61	110–111[b]
p-Tolyl ethyl ether	5-Methyl-2-ethoxy-	77	138–138.5[j,f]
n-Propyl *p*-tolyl ether	2-(*n*-Propoxy)-4-methyl-	54	126–127
n-Butyl *o*-tolyl ether	4-(*n*-Butoxy)-5-methyl-	44	95–96
Catechol dimethyl ether	3,4-Dimethoxy-	89	135–136[k]
Resorcinol dimethyl ether	2,4-Dimethoxy-	53	166–167[l]
Hydroquinone dimethyl ether	2,5-Dimethoxy-	53	148[i,m]
Catechol diethyl ether	3,4-Diethoxy-	81	162–163
Resorcinol diethyl ether	2,4-Diethoxy-	59	184–185
Hydroquinone diethyl ether	2,5-Diethoxy-	47	154–155[m]
Pyrogallol trimethyl ether	2,3,4-Trimethoxy-	29	123–124
o-Chloroanisole	3-Chloro-4-methoxy-	85	130–131[n]
p-Chloroanisole	5-Chloro-2-methoxy-	82	150–151[o]
o-Bromoanisole	3-Bromo-4-methoxy-	78	139–140[p]
p-Bromoanisole	5-Bromo-2-methoxy-	81	147–148
p-Fluoroanisole	5-Fluoro-2-methoxy-	86	174–175
o-Chlorophenetole	3-Chloro-4-ethoxy-	73	132–133[q]
p-Chlorophenetole	5-Chloro-2-ethoxy-	71	134–134.5[q]
o-Bromophenetole	3-Bromo-4-ethoxy-	76	134–135[p]
p-Bromophenetole	5-Bromo-2-ethoxy-	68	144–144.5
p-Bromodiphenyl ether	4-(*p*-Bromophenoxy)-	67	130–131[r]
	B. Substituted naphthalene sulfonamides		
α-Naphthyl methyl ether[s]	4-Methoxynaphthalene-	55	156–157[t]
β-Naphthyl methyl ether[s]	7-Methoxynaphthalene-	65	150–151[t]
α-Naphthyl ethyl ether[s]	4-Ethoxynaphthalene-	64	164–165[u]
β-Naphthyl ethyl ether[s]	7-Ethoxynaphthalene-	58	161–163[v]
	C. Miscellaneous Disulfonamides		
Diphenyl ether	Diphenyl ether 4,4'-di-	86	159[w]
Ethylene glycol diphenyl ether	α,β-Diphenoxyethane-4,4′-di-	74	228–229
Trimethylene glycol diphenyl ether	α,γ-Diphenoxypropane-4,4′-di-	44	245–255

[a] Duplicate combustion analyses were carried out on every sulfonamide in Table I. Their results gave values agreeing closely with each other and with the theoretical values. [b] A mixed melting point of *p*-methoxybenzenesulfonamide (m. p. 110–111°) with 2-methyl-4-ethoxybenzenesulfonamide (m. p. 110–111°) was depressed to 99–103°. [c] Recorded m. p. 149°, Schober and Bowers, *Am. Chem. J.*, **25**, 72 (1901). [d] Recorded m. p. 137°, Kolhatkar and Bokil, *J. Indian Chem. Soc.*, **7**, 845 (1930). [e] Bromwell, *Am. Chem. J.*, **19**, 573 (1897). [f] A mixed melting point of 3-methyl-4-methoxybenzenesulfonamide (m. p. 137°) with 5-methyl-2-ethoxybenzenesulfonamide (m. p. 138°) was depressed to 129–131°. [g] Recorded m. p. 129–130°, Haworth and Lapworth, *J. Chem. Soc.*, **123**, 2988 (1923). [h] Recorded m. p. 183°, Stewart, *ibid.*, **121**, 2558 (1922). [i] A mixed melting point of 3-methyl-4-ethoxybenzenesulfonamide (m. p. 148°) with 2,5-dimethoxybenzenesulfonamide (m. p. 148°) was depressed to 141–143°. [j] Recorded m. p. 138–139°, Metcalf, *Am. Chem. J.*, **15**, 307 (1893). [k] Recorded m. p. 136°, Brown and Robinson, *J. Chem. Soc.*, **111**, 953 (1917). [l] Recorded m. p. 166–167°, Suter and Hansen, THIS JOURNAL, **55**, 2082 (1933). [m] A mixed melting point of 2,5-dimethoxybenzenesulfonamide (m. p. 148°) with 2,5-diethoxybenzenesulfonamide (m. p. 154°) was depressed to 142–144°. [n] Recorded m. p. 130° cor., Child, *J. Chem. Soc.*, 718 (1932). [o] Recorded m. p. 154°, Gauntlett and Smiles, *ibid.*, **127**, 2745 (1925). [p] A mixed melting point of 3-bromo-4-methoxybenzenesulfonamide (m. p. 139–140°) with 3-bromo-4-ethoxybenzenesulfonamide (m. p. 134–135°) was depressed to 128–130°. [q] A mixed melting

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[1] This paper is constructed from part of a dissertation submitted by Frederick H. Carten to the Faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1939. Original manuscript received August 23, 1939.

[2] This work was assisted by a grant to one of us (E. H. H.) from the Warren Fund of the American Academy of Arts and Sciences for which grateful acknowledgment is hereby made.

[3] Huntress and Carten, THIS JOURNAL, **62**, 511 (1940).

point of 3-chloro-4-ethoxybenzenesulfonamide (m. p. 132–133°) with 5-chloro-2-ethoxybenzenesulfonamide (m. p. 134–134.5°) was depressed to 129–130°. [r] Recorded m. p. 131–132°, Suter, THIS JOURNAL, **53**, 1115 (1931). [s] With these compounds use of the usual quantity (5.0 g.) of chlorosulfonic acid yielded mainly water-soluble products. Upon reduction of the chlorosulfonic acid to two grams, however, the sulfonamides were obtained readily in the indicated yields. [t] A mixed melting point of 4-methoxynaphthalenesulfonamide-1 (m. p. 156–157°) with 7-methoxynaphthalenesulfonamide (m. p. 150–151°) was depressed to 146–147.5°. [u] Recorded m. p. 167°, Witt and Schneider, *Ber.*, **34**, 3182 (1901). [v] Recorded m. p. 155°, Lapworth, *Chem. News*, **71**, 206 (1895). [w] Recorded m. p. 158–160°, ref. *r*.

Experimental

The melting points reported in this paper are uncorrected. They were determined on a standard rod form 360° melting point thermometer in a copper melting point block of the Berl and Kullmann type. Observation of the sample was facilitated by means of a small twenty-five power microscope permanently attached to the apparatus.

The purification of all materials used in this work was the same as stated in our earlier paper. The chlorosulfonylation procedure was identical with Procedure I of the earlier paper. Since with the ethers the intermediate sulfonyl chlorides were sometimes difficult to purify, their chloroform solution (resulting from Procedure I) was treated directly with dry powdered ammonium carbonate (2.0 g.) and the mixture evaporated to dryness. After washing the dry residue with several 10-cc. portions of cold distilled water (to remove ammonium chloride), the crude sulfonamide was recrystallized from dilute alcohol. If desired the sulfonamides may be purified by solution in 6 *N* alkali and reprecipitation with acid (removal of traces of sulfonamides).

The color usually observed during the reaction of chlorosulfonic acid with aromatic ethers varies from pale yellow to brown. In a few cases, however, other colors were noted which appear to have diagnostic value. A red color was observed in three cases, *viz.*, *o*-tolyl methyl ether, *o*-tolyl *n*-butyl ether and trimethylene glycol diphenyl ether. A blue color was observed in one case, *viz.*, *p*-methoxybiphenyl. Shades of green were noted with eight compounds, *viz.*, *o*- and *p*-chloroanisole, *o*- and *p*-chlorophenetole, α- and β-naphthyl methyl ether, and α- and β-naphthyl ethyl ether.

Satisfactory monochlorosulfonylation could not be obtained with six other compounds which were studied, *viz.*, *o*- and *p*-methoxybiphenyl, methyl and ethyl benzyl ether, diphenylene oxide, and 4,4'-dibromodiphenyl ether.

Summary

1. A method for the identification of aromatic ethers by chlorosulfonylation with chlorosulfonic acid has been shown to yield excellent results.

2. Of forty-two aromatic ethers examined, thirty-six yield monosulfonyl chlorides readily converted to characteristic sulfonamides.

3. Eighteen previously unreported sulfonamides prepared in the course of this work have been characterized and structures tentatively assigned.

CAMBRIDGE, MASS. RECEIVED JANUARY 23, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Some Fluorine and Chlorine Derivatives of Sulfanilamidobenzenesulfonic Acids

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Recently it has been reported that the three isomeric sulfanilamidobenzenesulfonic acids[2] have a marked therapeutic effect against β-hemolytic streptococcus infections in mice, the ortho compound being superior to sulfanilamide. In an extension of the investigation on fluorine derivatives of aromatic medicinals in progress in this Laboratory,[3] several fluorine and chlorine derivatives of sulfanilamidobenzenesulfonic acid have been prepared.

4-Fluoroaniline-2-sulfonic acid was obtained readily by sulfonation of *p*-fluoroacetanilide with 100% sulfuric acid, whereas *p*-fluoroaniline remains unchanged under the same conditions. When 15% oleum was employed as the sulfonating agent the anilide gave the isomeric 3-sulfonic acid. 4-Chloroacetanilide behaved in similar fashion.[4] This convenient method for obtaining the isomeric 4-haloanilinesulfonic acids was developed by Kreis[5] for the case of *p*-bromoacetanilide. Both acids have been obtained[6] by direct sulfonation of *p*-chloroaniline with 15% oleum. The structures of the sulfonic acids were determined by bromination in aqueous solution, sulfonic acid groups ortho to amino groups under-

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[1] Sharp and Dohme Fellow, 1938–1939.

[2] Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2220 (1938). References to previous literature on sulfanilamide are listed here.

[3] Suter, Lawson and Smith, THIS JOURNAL, **61**, 161 (1939); Suter and Weston, *ibid.*, **61**, 2317, 2556 (1939).

[4] Scott and Cohen, *J. Chem. Soc.*, **123**, 3190 (1923); see also Paal, *Ber.*, **34**, 2753 (1901).

[5] Kreis, *Ann.*, **286**, 381 (1895).

[6] Claus and Mann, *Ann.*, **265**, 93 (1891); see also Fischer, *Ber.*, **24**, 3196 (1891); Armstrong, *ibid.*, **25R**, 752 (1892).