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.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# Some Fluorine and Chlorine Derivatives of Sulfanilamidobenzenesulfonic Acids

BY C. M. SUTER AND ARTHUR W. WESTON[1]

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-

(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).

going replacement with halogen[7] whereas in meta sulfonic acids the sulfo substituent is unaffected.[8]

The sulfonic acids were condensed with *p*-acetaminobenzenesulfonyl chloride in alkaline solution,[2] and the acetyl group removed by alkaline or acid[9] hydrolysis, the latter giving the better results.

The sodium salts of the sulfanilamidobenzenesulfonic acids and also N-sulfanilyl-4-fluoroaniline were tested for their therapeutic action against Streptococcus infections in white mice.[10]

None of the compounds evidenced any therapeutic effect when administered orally in daily doses of 10 mg. per 20 g. mouse for four days, except the N-sulfanilyl-4-fluoroaniline and this was much less effective than sulfanilamide. The sodium sulfonates were further tested against Type I Pneumococcus infections, also in white mice, employing 20 mg. per dose. Doses were administered simultaneously with the inoculation of the organisms, seven hours later and then at 24-hour intervals for a total of six doses in five days.

Here also the results showed an absence of therapeutic effect. Crossley, Northey and Hultquist[2] have shown that the presence of a methyl, ethoxyl or hydroxyl attached to the ring bearing the sulfonic acid group nullifies the therapeutic activity of otherwise active compounds. Fluorine and chlorine are in the same category.

## Experimental

**Materials.**—*p*-Fluoroacetanilide[11] melting[12] at 150–151° and *p*-chloroacetanilide were obtained in 80% yields by acetylation of *p*-fluoroaniline in aqueous solution with acetic anhydride at 50°. The *p*-acetaminobenzenesulfonyl chloride was the crude product obtained in the usual manner.

**4-Fluoro- and 4-Chloroaniline-2-sulfonic Acids.**—A mixture of 10.7 g. (0.07 mole) of *p*-fluoroacetanilide and 7 g. (0.07 mole) of 100% sulfuric acid was heated until the solid melted and kept at this temperature until acetic acid was no longer evolved. The thick paste was then heated in an oil-bath at 170–180° for two hours, cooled and mixed with water. Recrystallization from hot water (Darco) gave 8.6 g. (64%) of white flaky crystals which decomposed above 310°.

*Anal.* Calcd. for $C_6H_6O_3NSF$: neut. equiv., 191.1. Found: neut. equiv., 190.8.

4-Chloroaniline-2-sulfonic acid[4,6] was obtained in a 49% yield by a similar procedure as fine white needles which decomposed above 325°.

*Anal.* Calcd. for $C_6H_6O_3NSCl$: neut. equiv., 207.5. Found: neut. equiv., 206.9, 206.6.

Bromination of 0.5 g. of 4-fluoroaniline-2-sulfonic acid in aqueous solution with excess 5% aqueous bromine gave 0.6 g. of a slightly pink solid which crystallized from dilute acetic acid as white needles melting at 64–65°. A mixture of this with the 2,6-dibromo-4-fluoroaniline obtained from *p*-fluoroaniline, m. p. 63–64°, showed no depression of the melting point.

*Anal.*[13] (Kjeldahl) Calcd. for $C_6H_4NBr_2F$: N, 5.21. Found: N, 5.09.

Bromination of 4-chloroaniline-2-sulfonic acid similarly gave 2,6-dibromo-4-chloroaniline, m. p. 94.5–95.5°. This melting point is about the average of those given in the literature for this compound.[14]

**4-Fluoro- and 4-Chloroaniline-3-sulfonic Acids.**—A mixture of 10.7 g. (0.07 mole) of 4-fluoroacetanilide and 65 ml. of 15% oleum was heated to 130° where frothing occurred and the temperature rose to 145°. After fifteen minutes at 140–145° the mixture was allowed to cool, poured on ice and the solid crystallized from hot water using decolorizing carbon. The yield of fine white needles was 8.4 g. (63%). These decomposed above 310°.

*Anal.* Calcd. for $C_6H_6O_3NSF$: neut. equiv., 191.1. Found: neut. equiv., 190.7.

4-Chloroaniline-3-sulfonic acid was obtained in 30–34% yield. It crystallized in white needles which decomposed above 310°.

*Anal.* Calcd. for $C_6H_6O_3NSCl$: neut. equiv., 207.5. Found: neut. equiv., 206.6.

Bromination of an aqueous solution containing 0.5 g. of the 4-fluoroaniline-3-sulfonic acid gave no precipitate. Evaporation of the solution to dryness gave a solid which was very soluble in water and alcohol but crystallized from concentrated hydrochloric acid. It was not obtained in a high state of purity. The basic properties of the amine group are here so completely lost that internal salt (dipolar ion) formation does not occur.

*Anal.* Calcd. for $C_6H_4O_3SNBr_2F$: neut. equiv., 349. Found: neut. equiv., 342.

Bromination of the 4-chloroaniline-3-sulfonic acid likewise gave no precipitate, confirming its structure. The anhydrous bromosulfonic acid was hygroscopic but the nature of the resulting hydrate was not determined. The compound crystallized as fine white needles which decomposed above 310°.

*Anal.* Calcd. for $C_6H_4O_3NSClBr_2$: neut. equiv., 365.5. Found: neut. equiv., 370, 372.

**N-Sulfanilyl-4-fluoroaniline.**—To a well-stirred mixture of 8.9 g. (0.08 mole) of *p*-fluoroaniline, 1.6 g. (0.015 mole)

(7) Limpricht, *Ann.*, **181**, 193 (1876); *Ber.*, **9**, 474 (1876).

(8) The two sulfonating agents lead to different products even though acetic acid is lost in both reactions. One explanation for this is that when the theoretical amount of 100% sulfuric acid is employed the first-formed phenylaminosulfonic acid rearranges when heated to 170–180°, while with the excess oleum the phenylaminosulfonic acid is sulfonated by the excess reagent. This is substantiated by the fact that *p*-fluoroaniline sulfate remains unchanged at 170–180° as already mentioned.

(9) Kolloff, THIS JOURNAL, **60**, 950 (1938); Bauer, *ibid.*, **61**, 613 (1939).

(10) We are much indebted to Dr. Maurice L. Moore and Mr. G. W. Webster of the Technical Division of Sharp and Dohme for these tests.

(11) Schiemann and Pillarsky, *Ber.*, **62B**, 3041 (1929).

(12) All melting points are corrected.

(13) Analysis by Mr. E. Washburn of this Laboratory.

(14) Chattaway and Orton, *J. Chem. Soc.*, **79**, 825 (1901); Zincke, Heuser and Möller, *Ann.*, **333**, 338 (1904); Reed and Orton, *J. Chem. Soc.*, **91**, 1552 (1907); Gilbert, THIS JOURNAL, **48**, 2242 (1926).

of sodium carbonate and 60 ml. of water, was added simultaneously and gradually 18.7 g. (0.08 mole) of *p*-acetaminobenzenesulfonyl chloride and enough 30% sodium hydroxide to maintain a *p*H of about 10. Stirring was continued for thirty minutes after the additions were complete and then 8 g. of solid sodium hydroxide was added and the mixture refluxed for ninety minutes. Exact neutralization gave 10 g. (47%) of the anilide which after crystallization from dilute methanol melted at 163–164°. Considerable unchanged *p*-fluoroaniline was recovered.

*Anal.* (Kjeldahl) Calcd. for $C_{12}H_{11}O_2SN_2F$: N, 10.53. Found: N, 10.8.

**Sulfanilamidofluoro- and -chlorobenzenesulfonic Acids.**—*p*-Acetaminobenzenesulfonyl chloride was condensed with the aminosulfonic acids essentially according to the procedure of Crossley, Northey and Hultquist,[2] and the sulfanilamido compounds were isolated as the free acids. The sodium salts of these were very soluble in water. The yields and analyses are summarized in Table I.

TABLE I

| Compound, -benzenesulfonic acid | Yield,[a] % | Decompn. temp., °C. | Neutral eq.[b] Calcd. | Found |
|---|---|---|---|---|
| 2-Sulfanilamido-5-fluoro- | 14[c] | 285 | 346 | 343 |
| 5-Sulfanilamido-2-fluoro- | 42 | 260 | 346[d] | 345 |
| 2-Sulfanilamido-5-chloro- | 20[c] | 300 | 380.5[e] | 383 |
| 5-Sulfanilamido-2-chloro- | 57 | 310 | 362.5 | 360 |

[a] These percentages do not take into account unreacted starting materials which were recovered. [b] The indicator used was methyl red–methylene blue. [c] The low yields were partly due to the low solubilities of the original sodium sulfonates. [d] This compound crystallized as the monohydrate. *Anal.* Calcd. for $C_{12}H_{11}O_5N_2S_2F\cdot H_2O$: neut. equiv., 364. Found: neut. equiv., 361.2. [e] This compound crystallized as the monohydrate. *Anal.* Calcd. for $C_{12}H_{11}O_5N_2S_2Cl\cdot H_2O$: $H_2O$, 4.72. Found: $H_2O$, 4.89. The dry material absorbed water rapidly when exposed to the air.

## Summary

The isomeric 4-fluoroaniline- and 4-chloroanilinesulfonic acids have been prepared. The sulfanilamidohalobenzenesulfonic acids prepared from these did not exhibit therapeutic action against Streptococcus and Type I Pneumococcus infections in white mice. N-Sulfanilyl-4-fluoroaniline showed a slight effect against Streptococcus infections.

EVANSTON, ILLINOIS RECEIVED DECEMBER 16, 1939

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF COLORADO]

# A Series of 2-Methyl-5-alkyl-4,6-dihydroxypyrimidines

BY LIVINGSTON P. FERRIS II* AND ANTHONY R. RONZIO

E. L. Pinner[1] prepared 2-phenyl-4,6-dihydroxypyrimidine by the condensation of benzamidine with malonic ester. Dox and Yoder[2] continued this investigation obtaining more members of the same series. At this time they pointed out that the condensation using aliphatic amidines had not been tried. Remfry[3] discovered a reaction in which malonamide condensed with substituted malonic esters to give pyrimidines, identical in structure to those which theoretically should form if aliphatic amidines successfully condensed with substituted malonic esters.

We have investigated this reaction using acetamidine and substituted malonic esters in the presence of sodium alcoholate and have found that the expected pyrimidines are formed. The first six members of the series have been prepared for the purpose of a pharmacological study. Absorption spectra data were taken for the first member of the series.

(*) Now at Colorado Experiment Station, Ft. Collins, Colo.

(1) E. L. Pinner, *Ber.*, **41**, 3517 (1908).

(2) A. W. Dox and L. Yoder, THIS JOURNAL, **44**, 361 (1922).

(3) F. G. P. Remfry, *J. Chem. Soc.*, **99**, 610 (1911).

## Experimental Part

Acetamidine hydrochloride, one-eighth mole, and either the redistilled malonic ester or the redistilled monoalkyl substituted malonic ester, one-twentieth mole, were added in the order given, to about 150 cc. of absolute alcohol in which had been dissolved 3.3 g. of sodium (slight excess over one-eighth mole). After standing for two to three days, the solution was exactly neutralized with concentrated hydrochloric acid. Enough water to dissolve the precipitated sodium chloride was then added. The un-

TABLE I

2-METHYL-5-ALKYL-4,6-DIHYDROXYPYRIMIDINES

| 5 Occupied by | Yield, % | Empirical formula | % C Calcd. | % C Found | % H Calcd. | % H Found | % N Calcd. | % N Found |
|---|---|---|---|---|---|---|---|---|
| H | 43 | $C_5H_6N_2O_2$ | 47.62 | 47.61 | 4.79 | 5.07 | 22.22 | 22.22 |
| | | | | 47.64 | | 4.99 | | 22.14 |
| Methyl | 18 | $C_6H_8N_2O_2$ | 51.42 | 51.45 | 5.75 | 6.08 | 19.99 | 20.00 |
| | | | | 51.40 | | 6.03 | | 19.90 |
| Ethyl | 15 | $C_7H_{10}N_2O_2$ | 54.53 | 54.52 | 6.54 | 6.62 | 18.17 | 18.09 |
| | | | | 54.49 | | 6.72 | | 18.28 |
| *n*-Propyl[a] | 22 | $C_8H_{12}N_2O_2$ | 57.13 | 57.17 | 7.19 | 7.29 | 16.66 | 16.79 |
| | | | | 57.21 | | 7.33 | | 16.73 |
| *n*-Butyl | 33 | $C_9H_{14}N_2O_2$ | 59.32 | 59.52 | 7.74 | 7.80 | 15.38 | 15.32 |
| | | | | 59.51 | | 7.86 | | 15.49 |
| *n*-Amyl | 26 | $C_{10}H_{16}N_2O_2$ | 61.20 | 61.28 | 8.22 | 8.40 | 14.28 | 14.32 |
| | | | | 61.30 | | 8.32 | | 14.33 |

[a] First prepared by Remfry, ref. 3.