

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Hydrolysis of Substituted Benzenesulfonanilides. III. Acid Hydrolysis

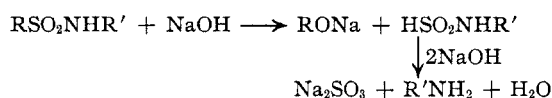
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The alkaline hydrolysis of aryl sulfonanilides was found to be a useful method for recovering the amines only in those cases in which a nitro group is situated in a position ortho or para to the sulfone group.¹ This procedure necessitated the preparation and use of *o*- or *p*-nitrobenzenesulfonchloride in the initial separation.

Surprisingly enough, it has now been found that many benzenesulfonamides may be hydrolyzed by refluxing with 25% hydrochloric acid. This simple substitution of hydrochloric acid² for various concentrations of sulfuric and phosphoric acids used by previous investigators^{1,3} has raised the yields of amine recovered from 0–40% to 90–95%. A study of this hydrochloric acid hydrolysis of various substituted sulfonanilides has been carried out in order to determine the influence of groups *o*-, *m*- and *p*- to the sulfone group. All the possible products of the reaction were determined and the results are summarized in Table I.

yielded results which are complementary to those obtained by the use of alkalis. Here the yields are very low in the case of the *o*- and *p*-nitrobenzenesulfonanilides but surprisingly good in all the other cases.

The acid hydrolysis involves a splitting between sulfur and nitrogen which is in contrast to that observed in the case of an alkaline cleavage which occurred according to the equations:



The preliminary split in the latter case appears to be between the carbon and sulfur atoms in order to explain why the ortho and para nitrobenzenesulfonanilides undergo hydrolysis whereas those sulfonanilides with other groups (methyl or bromine) ortho or para do not cleave with alkali. The evidence that the acid hydrolysis takes place according to the following equations

TABLE I
HYDROCHLORIC ACID HYDROLYSIS OF SUBSTITUTED BENZENESULFONANILIDES

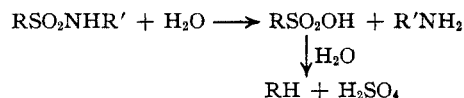
No.	Compound	Time for hydrolysis, hr.	Yield of hydrocarbon, %	Yield of amine, %	Yield of sulfonic acid, %	Unhydrolyzed, %
1	C ₆ H ₅ SO ₂ NHC ₆ H ₅	36	None	91	82	None
2	C ₆ H ₅ SO ₂ NCH ₃ C ₆ H ₅	12	None	94	78	None
3	4-CH ₃ C ₆ H ₄ SO ₂ NHC ₆ H ₅	32	None	90	76	None
4	4-CH ₃ C ₆ H ₄ SO ₂ NCH ₃ C ₆ H ₅	12	None	93	80	None
5	2,4-(CH ₃) ₂ C ₆ H ₃ SO ₂ NHC ₆ H ₅	30	9.4	90	56	None
6	2,4-(CH ₃) ₂ C ₆ H ₃ SO ₂ NCH ₃ C ₆ H ₅	10	11.3	91	70	None
7	2,4,6-(CH ₃) ₃ C ₆ H ₂ SO ₂ NHC ₆ H ₅	28	89.0	92	None	None
8	2,4,6-(CH ₃) ₃ C ₆ H ₂ SO ₂ NCH ₃ C ₆ H ₅	12	92.0	95	None	None
9	2-NO ₂ C ₆ H ₄ SO ₂ NHC ₆ H ₅	36	None	None	None	99
10	2-NO ₂ C ₆ H ₄ SO ₂ NCH ₃ C ₆ H ₅	36	None	17	6	71
11	3-NO ₂ C ₆ H ₄ SO ₂ NHC ₆ H ₅	36	None	None	None	96
12	3-NO ₂ C ₆ H ₄ SO ₂ NCH ₃ C ₆ H ₅	36	None	87	64	6
13	4-NO ₂ C ₆ H ₄ SO ₂ NHC ₆ H ₅	36	None	None	None	98
14	4-NO ₂ C ₆ H ₄ SO ₂ NCH ₃ C ₆ H ₅	36	None	31	20	61

¹ The general conclusion from consideration of the data in Table I is that this acid hydrolysis

(1) (a) Schreiber and Shriner, *THIS JOURNAL*, **56**, 114 (1934); (b) Pezold, Schreiber and Shriner, *ibid.*, **56**, 696 (1934).

(2) The use of hydrochloric acid at high temperatures and in sealed tubes has been described previously but the yields are low, the amounts which can be thus hydrolyzed are limited and the procedure is time-consuming and inconvenient. Johnson and Ambler, *THIS JOURNAL*, **36**, 373 (1914); Schotten and Schlömann, *Ber.*, **24**, 3687 (1891).

(3) Schroeter and Eisleb, *Ann.*, **367**, 101 (1909); Witt and Uermenyi, *Ber.*, **46**, 296 (1913); Marvel, Helfrick and Belsley, *THIS JOURNAL*, **51**, 1272 (1929).



is the fact that benzene- and *p*-toluenesulfonanilides hydrolyzed to the amine and the aryl sulfonic acid, the xylene sulfonanilides produced the amine, the sulfonic acid and a little *m*-xylene, whereas the mesitylene sulfonanilides hydrolyzed to the amine sulfuric acid and mesitylene only.

The formation of the hydrocarbon is evidently a secondary reaction since it is well known that mesitylene sulfonic acid is readily hydrolyzed by boiling with 15% hydrochloric acid.⁴ It was also shown that *m*-xylene sulfonic acid was partially hydrolyzed to *m*-xylene and sulfuric acid under the conditions of the above hydrolysis.

From the data in Table I it is interesting to note that the sulfonyl derivatives of secondary amines (Nos. 2, 4, 6, 8) hydrolyze in about one-third the time required for the sulfonyl derivatives of primary amines (Nos. 1, 3, 5, 7). In the case of the nitro substituted sulfonyl derivatives of primary amines (Nos. 9, 11, 13) no appreciable hydrolysis took place in thirty-six hours, the nitro sulfon-anilides being recovered unchanged in 96–99% yields.

A rather surprising result, shown in the above table, is to be found in a consideration of the hydrolyses of Compounds 10, 12 and 14. It seems that an ortho or para nitro group inhibits acid hydrolysis whereas Compound 12, containing a meta nitro group, hydrolyzes to only slightly less extent than the unsubstituted benzenesulfon-methylanilide (Compound 2). This effect of the nitro group on acid hydrolysis ($m > p > o$) is exactly the opposite to that which it exerted on the alkaline hydrolysis where the observed order was $o > p > m$.

Experimental

The aryl sulfonchlorides, anilides and methylanilides used in the present study have been previously described⁵ except those derived from *m*-xylene. *m*-Xylene sulfonyl chloride⁶ has been made by the action of phosphorus pentachloride on the sodium *m*-xylene sulfonate but the following direct preparation is more convenient.

2,4-Dimethylbenzenesulfonchloride.—Three hundred grams of *m*-xylene was cooled to -5° , to which was added one kilogram of chlorosulfonic acid at such a rate that the temperature never exceeded 0° . The reaction mixture was then carefully poured onto crushed ice, which caused the sulfonchloride to separate as a white oil, and it was then extracted with ether, dried with anhydrous magnesium sulfate, and vacuum distilled. The sulfonchloride boils at $163\text{--}165^{\circ}$ (15 mm.). If cooled to -35° , the sulfonchloride can be crystallized, m. p. 34° , yield 384 g. or 67%.

Preparation of Sulfonanilides and N-Methylsulfon-anilides.—The general method followed consisted in adding the powdered or liquid sulfonchloride slowly to a 5% aqueous sodium hydroxide solution containing a slight

excess of the amine, with vigorous stirring. The solutions were then made strongly acid, precipitating the amides which were filtered, washed well with water and recrystallized from alcohol.

2,4-Dimethylbenzenesulfon-anilide.—Colorless crystals, m. p. $109\text{--}110^{\circ}$. *Anal.* Calcd. for $C_{14}H_{16}O_2NS$: N, 5.36. Found: N, 5.58.

2,4-Dimethylbenzenesulfonmethylanilide.—As colorless crystals, m. p. 55° . *Anal.* Calcd. for $C_{15}H_{17}O_2NS$: N, 5.09. Found: N, 5.31.

The General Procedure for Hydrolysis.—A 25-g. sample of each of the sulfonamides was treated with 125 cc. of 25% hydrochloric acid and refluxed until completion of hydrolysis, which was indicated by solution of the sulfonamide in most cases. In cases where a hydrocarbon was produced by the hydrolysis, samples were run for various intervals of time until complete hydrolysis was produced. A solution of 25% hydrochloric acid was found to be the most convenient since weaker concentrations took a much longer time for complete hydrolysis and stronger concentrations produced troublesome foaming. After the completion of hydrolysis, the solutions were steam distilled to remove any hydrocarbon then made alkaline with sodium hydroxide and steam distilled again to remove the aniline or methylaniline. The remaining liquid was filtered and evaporated nearly to dryness. The precipitated salt was extracted several times with hot alcohol to obtain the sodium sulfonates. The essential data have been summarized in Table I.

Hydrolysis of 2,4-Dimethylbenzenesulfonic Acid.—Twenty-five grams of 2,4-dimethylbenzenesulfonchloride was hydrolyzed completely by refluxing with an aqueous solution of sodium carbonate. The solution was then exactly neutralized and sufficient hydrochloric acid added to make the concentration up to 25%. This solution was refluxed for thirty-six hours and then extracted with ether to remove the xylene. The yield was 5 g. or 39%.

Summary

1. Benzenesulfon-anilides and methyl substituted benzenesulfon-anilides are readily hydrolyzed by refluxing with 25% hydrochloric acid, producing the amine in 90–95% yields. The other products depend on the number of methyl groups in the ring. Benzene and toluene sulfon-anilides give the sulfonic acid only, mesitylene sulfon-anilides produce mesitylene and sulfuric acid whereas the intermediate *m*-xylene sulfon-anilides produced *m*-xylene sulfonic acid and some *m*-xylene.

2. The sulfonamides of secondary amines hydrolyze in about one-third the time required for the sulfonamide of a primary amine.

3. The presence of ortho and para nitro groups inhibits acid hydrolysis. The influence of the nitro group in various positions is $m > p > o$, which is just the opposite to that found in alkaline hydrolysis, $o > p > m$.

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(4) Gilman, "Organic Syntheses," John Wiley and Sons, New York, Coll. Vol. I, p. 337, 1932.

(5) See Ref. 1. The melting point of *p*-nitrobenzenesulfon-anilide was erroneously reported as $135\text{--}136^{\circ}$. It should melt at $169\text{--}170^{\circ}$.

(6) Jacobsen, *Ber.*, 11, 17 (1878).