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## Separation and Determination of Primary, Secondary and Tertiary Alkaryl Amines (Ring-methylated and Nitrogen-methylated Homologs of Aniline)<sup>1,2</sup>

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A method of analysis was needed for mixtures of aniline and its ring-methylated and nitrogen-methylated homologs which would make possible the quantitative separation and determination of the primary, secondary and tertiary amines as groups followed by subsequent recovery of the groups of free amines. The Hinsberg method,<sup>4</sup> to be followed by hydrolysis of the sulfonamides, seemed the most promising for this purpose. A study of the literature, however, indicated that this method does not always proceed in as straightforward a manner as its originator thought. Solonina<sup>5</sup> reported that under some conditions, particularly with certain amines such as aniline and *m*-xylidine, disulfonamides are formed which are insoluble in alkali and so simulate secondary amines; and that some primary amines form monosulfonamides which are insoluble in alkali. Taking cognizance of this work, Hinsberg and Kessler<sup>6</sup> proposed a scheme of quantitative analysis which purported to eliminate these difficulties. Their published analyses, however, indicated frequent departures from quantitative values.

Still another type of side reaction is that of aryl-sulfonyl chlorides with tertiary amines, such as dimethylaniline, to form compounds such as triphenylmethane dyes: *e. g.*, crystal violet; *p,p'*-tetramethyldiaminodiphenylmethane; the aryl-sulfonates of secondary amines, such as the *p*-toluenesulfonate of methylaniline; sulfonic acids such as sulfanilic acid; and sulfones such as 4'-dimethylamino-4-methyldiphenylsulfone.<sup>7</sup>

**Analyses by the Hinsberg Method.**—Howard and Derrick<sup>8</sup> analyzed mixtures of *p*-toluidine, methylaniline and dimethylaniline by the Hinsberg method. They found that the values obtained for the first two amines were high by 1.6 to 4.8% and were low for the third by 21 to 22%.

Some mixtures of amines were analyzed in this

Laboratory by the Hinsberg method.<sup>9,10</sup> Table I gives some recoveries with mixtures of aniline, methylaniline and dimethylaniline, using tosyl chloride and also benzenesulfonyl chloride. The weight of each constituent ranged from 0.45 to 2.6 g.

TABLE I  
DETERMINATION OF AMINES BY THE HINSBERG METHOD

Aniline	Recovery, %	
	Methylaniline	Dimethylaniline
Using Tosyl Chloride		
80	122	..
81	128	..
71	91	134
78	92	143
85	100	113
90	110	81
Using Benzenesulfonyl Chloride		
87	95	94
84	93	115
93	99	92

From these values it would appear that some of the side reactions which have been reported cause erratic results. The consistently low recovery of benzenesulfonanilide is probably caused by incomplete reaction in the aqueous, non-homogeneous reaction mixture, so that some aniline appears with the dimethylaniline. On the other hand, conversion of dimethylaniline to methylaniline may occasionally raise the value of the latter and lower the value of the former.

The method of analysis which follows is presented as an improvement over the methods just discussed.

### Method of Analysis

This method is proposed as a means for the quantitative separation of aniline and its *N*-methylated and ring-methylated homologs into groups of primary, secondary and tertiary amines and the recovery and determination of these groups of amines. The procedure involves the formation of the toluenesulfonamides of the primary and secondary amines, their separation from the unreacted tertiary amines, and their gravimetric determination;

(9) Much of this work was done by Mr. R. M. Giveen.

(10) To a flask containing about 5 g. of the amines and 60 ml. of 5 *N* sodium hydroxide, 10 g. of *p*-toluenesulfonyl chloride (tosyl chloride) were added. The mixture was shaken vigorously and kept cool for several minutes. The excess tosyl chloride was decomposed by heating under reflux for a few minutes and the mixture steam-distilled into hydrochloric acid to remove the tertiary amines. These were determined by potentiometric titration with standard sodium hydroxide after saturation with sodium chloride to ensure a good break at the point of neutralization of the excess acid (Fig. 1). The alkali-insoluble sulfonamides were recovered from the steam-distillation residue by filtration and then dried and weighed. The filtrate was acidified and the acid-insoluble sulfonamides determined in a similar manner. (Purified amines and reagents were used.)

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(2) The authors acknowledge their indebtedness to Dr. H. Z. Lecher for his suggestion of and interest in the problem, and to Dr. A. G. Hill and Mr. F. H. Megson for furnishing mesidine and other samples and for their interest and cooperation.

(3) Deceased.

(4) Hinsberg, *Ber.*, **23**, 2962 (1890).

(5) Solonina, *J. Russ. Phys.-Chem. Soc.*, **29**, 404 (1897); **31**, 640 (1899).

(6) Hinsberg and Kessler, *Ber.*, **38**, 906 (1905).

(7) Michler, *ibid.*, **10**, 1742 (1877); Hassencamp, *ibid.*, **12**, 1275 (1879); Michler and Meyer, *ibid.*, **12**, 1791 (1879); Bergel and Doering, *ibid.*, **61**, 844 (1928); Wahl, *Rev. gen. mat. color.*, **32**, 176 (1928); Doering, Inaugural Dissertation, "Ueber einige Thioether der *N*-Dimethylanilin und ihre Oxydationsprodukte," Freiburg University, 1928.

(8) Howard and Derrick, *This Journal*, **46**, 168 (1924).

the determination of the tertiary amines by a method of extraction from a chlorobenzene solution by means of hydrochloric acid; and the hydrolysis of the sulfonamides of the primary and secondary amines, separately, and the potentiometric titration of these liberated amines in acid solution by means of standard alkali.<sup>11</sup>

**Reaction with *p*-Toluenesulfonyl Chloride.**—About 6 to 7 g. of the sample is weighed into a dry 250-ml. flask from a weighing pipet, 50 ml. of benzene added and the solution cooled in ice. A solution of 20.0 g. of a good grade of *p*-toluenesulfonyl chloride in 25 ml. of dry pyridine (not above room temperature) is added rapidly to the cold benzene solution. The stoppered flask is kept in the ice-bath for thirty minutes with frequent swirling. Keeping the flask in the ice-bath, the stopper is removed and washed with benzene, the benzene being added to the flask. The flask is attached to a reflux condenser through which 10 ml. of water is added in small portions at two to three minute intervals with shaking after each addition, while keeping the flask in ice. The reaction flask is allowed to stand in the ice-bath for thirty minutes with frequent vigorous shaking.

**Separation of Tertiary from Primary and Secondary Amines.**—The reaction mixture is transferred quantitatively by means of water and benzene to a 2-liter balloon flask to which there is then added 100 ml. of 5 *N* sodium hydroxide solution. The mixture is steam-distilled, the distillate being collected under 30 ml. of concd. hydrochloric acid in a 500-ml. flask until the receiver is nearly full, the volume of the distillate being kept at approximately 500 ml. The completeness of removal of amines is tested by collecting additional distillate in normal hydrochloric acid, and making alkaline. The appearance of a turbidity necessitates continued distillation until a negative test is obtained.

The distillate is transferred quantitatively to a separatory funnel and enough concd. hydrochloric acid is added, if necessary, to make the solution acid to congo red paper. After vigorous shaking the lower aqueous layer is drawn off and the benzene layer is washed twice with 50-ml. portions of normal hydrochloric acid, the washings being added to the main aqueous layer (Solution A). The benzene layer, which may contain traces of the sulfonamides of secondary amines, is saved for subsequent treatment (Solution B).

**Separation of Sulfonamides of Primary and Secondary Amines.**—The alkaline residue from the distillation is allowed to stand at room temperature long enough for the oil droplets to settle as a homogeneous phase. The aqueous phase is carefully decanted through an 18.5-cm. wet folded filter paper so that as little of the oil as possible is transferred to the paper. If the filtrate is turbid, it is refiltered until clear. The oil is heated nearly to the boil with 200 ml. of *N* sodium hydroxide, agitated frequently while hot for about five minutes, and then cooled to room temperature by immersing the flask in ice. The aqueous layer is filtered on the previously used paper with the same precautions as before. This procedure is repeated once with 200 ml. of *N* sodium hydroxide and several times with 100-ml. portions until a 25-ml. test portion of the filtrate acquires either no turbidity or only a faint opalescence upon acidification. Finally any oil on the filter paper is washed into the balloon flask with a stream of hot water and the filter paper is saved.

**Determination of Sulfonamides of Primary Amines.**—The combined alkaline filtrates and washings are transferred quantitatively to a separatory funnel and acidified to congo red paper with concd. hydrochloric acid. The liberated sulfonamides are extracted once with 100 ml., and twice with 50-ml. portions of benzene. The combined benzene extracts are dried over anhydrous calcium sulfate and transferred (in portions) quantitatively by

filtration and washing to a tared 250-ml. round, flat-bottom, glass-stoppered flask containing some boiling chips. The benzene is removed as well as possible by distillation in a boiling, saturated-salt-water bath and the residue is dried at 110° first for three hours and then for hourly intervals until the loss in weight after one hour drying is less than 15 mg. (To facilitate the drying, the flask is allowed to rest on its side.) The weight of sulfonamides of primary amines ( $W_p$ ) is obtained by difference.

**Determination of Sulfonamides of Secondary Amines.**—The oil in the balloon flask is transferred by means of solution B to a 500-ml. separatory funnel. The flask is washed several times with benzene and water, and the filter paper is macerated with two or three 50-ml. portions of benzene, the whole being added to the main benzene solution in the separatory funnel. The mixture is shaken, allowed to separate and the aqueous layer removed. The aqueous layer is washed with 35 ml. of benzene which is then added to the main benzene layer in a flask, dried over anhydrous calcium sulfate, filtered (in portions) into a tared 250-ml. round, flat-bottom, glass-stoppered flask containing boiling chips and treated in the same manner as the sulfonamides of the primary amines. The weight of sulfonamides of secondary amines ( $W_s$ ) is obtained by difference.

**Regeneration of Primary and Secondary Amines by Hydrolysis of the Sulfonamides and Titration of the Liberated Amines.**—Five ml. of 1:1 hydrochloric acid per gram of sulfonamides is added to the flasks containing the sulfonamides of the primary and secondary amines, respectively. The flasks are attached to long upright condensers and the mixtures boiled (adding a little concd. hydrochloric acid through the condenser two or three times during the hydrolysis) until the oily layers either dissolve or become crystalline. This usually requires from 75 to 100 hours. (If the oil should crystallize, very little hydrolysis will take place on further heating.) To test for completeness of hydrolysis, dilute a 1-ml. test portion with 10 ml. of water. A turbidity indicates unhydrolyzed sulfonamide in solution and necessitates further boiling. The reaction mixture, including the test portions, is diluted with 10 to 15 volumes of water, transferred quantitatively with small volumes of water and benzene to a separatory funnel and extracted with two 100-ml. portions of benzene to dissolve unaponified sulfonamide. (If separation of unaponified sulfonamide is not desired, the extractions may be omitted.) The combined benzene extracts are extracted with two 35-ml. portions of *N* hydrochloric acid which are added to the main aqueous solution. (Avoid as far as possible including with the acid extract such insoluble solids as appear at this point in greater or lesser quantity, apparently from some reaction of the toluenesulfonic acid.)

The benzene solution is treated with anhydrous calcium sulfate and dried and weighed in the same manner as was described for the sulfonamides previously. The weights of unhydrolyzed sulfonamides of primary amines ( $W_{pu}$ ) and secondary amine ( $W_{su}$ ) are recorded.

The combined acid solution is treated with 5 *N* sodium hydroxide until it is only slightly acid, cooled in an ice-bath, transferred to a 500-ml. separatory funnel and made strongly alkaline with an excess of 25 ml. of 5 *N* sodium hydroxide. The amines are extracted with three 100-ml. portions of benzene, excluding as much as possible of any insoluble material. The combined benzene extracts are extracted with three 100-ml. portions of *N* hydrochloric acid, again excluding insolubles as much as possible. The acid extracts are transferred to a beaker and treated with 5 *N* sodium hydroxide until the pH measures 1.0 (glass electrode and calomel half cell). The solution is boiled gently for five minutes to remove carbon dioxide, cooled in ice to room temperature and saturated with a small excess of sodium chloride. The solution is titrated with standardized normal sodium hydroxide to pH about 1.8, then pH readings are taken for each addition of 0.2 ml. Readings are continued to pH 3.5. The first inflection (J) occurs in the neighborhood of pH 2.5. The dial of the pH meter is set at pH 6 and *N* sodium hydroxide added until this reading is attained. Readings are now taken for 0.2-ml. additions of alkali up to pH 10. The

(11) The hydrolysis is carried out for the purpose of recovering the free amines for further study. If that is not desired, a simpler method such as a determination of the sulfur content or the nitrogen content of the sulfonamides should furnish adequate data for the calculation of the weight % of amines.

second inflection (*K*) occurs at about pH 7. The inflection points *J* and *K* may be calculated from the pH increments in the usual manner. If  $J_p$  and  $K_p$  are the milliequivalents of alkali consumed at the first and second inflection points, respectively, for the primary amines, and  $J_s$  and  $K_s$  are the corresponding values for the secondary amines, then the number of milliequivalents of regenerated primary amines =  $L_p = K_p - J_p$  and the corresponding value for secondary amine =  $L_s = K_s - J_s$ .

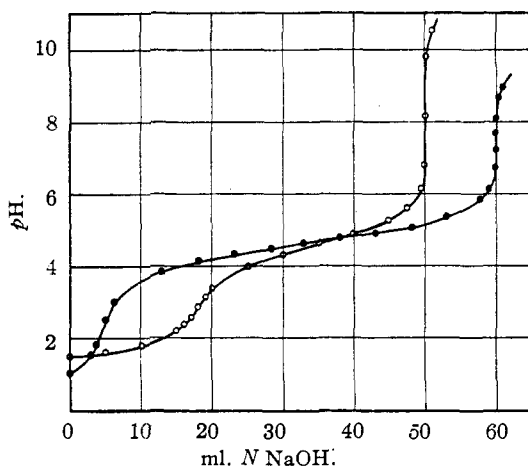


Fig. 1.—Titration of aniline: ● solution (55.2 mmols. aniline) saturated with NaCl; ○ solution (32.1 mmols. aniline) without added NaCl.

**Calculations for Primary and Secondary Amines.**—From the equivalence value of the amines and the weight of sulfonamides the weight % of amines may be calculated. Since the equivalence value  $L_p$  or  $L_s$  is low by the number of milliequivalents of unhydrolyzed sulfonamide, a correction must be applied. This necessitates a knowledge of the identity of the unhydrolyzed sulfonamide. In the work with the mixtures reported in this paper, the unhydrolyzed sulfonamide of the primary amine was shown to be largely *p*-toluenesulfonamide and that of the secondary amine was *p*-toluenesulfonamonomethyl-*p*-toluidide, with molecular weights of 289.4 and 275.4, respectively. The corrections in terms of milliequivalents would then be  $K_p = 1000 W_{pu}/289.4$  and  $K_s = 1000 W_{su}/275.4$ , respectively.

$$\begin{aligned} \% \text{ Primary amines} &= \frac{W_p - (L_p + K_p) 155.186/1000 + (L_p + K_p) 1.008/1000}{\text{Wt. of sample, g.}} \times 100 \\ &= \frac{100 W_p - 15.42 (L_p + 1000 W_{pu}/289.4)}{\text{Wt. of sample, g.}} \end{aligned}$$

$$\begin{aligned} \% \text{ Secondary amines} &= \\ &= \frac{100 W_s - 15.42 (L_s + 1000 W_{su}/275.4)}{\text{Wt. of sample, g.}} \end{aligned}$$

In this derivation  $(L_p + K_p) 155.186/1000$  equals the weight of the residue  $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2$  which is lost by the sulfonamide during hydrolysis and  $(L_p + K_p) 1.008/1000$  equals the weight of hydrogen gained, and similarly for secondary amines.

**Calibration of Apparatus for the Determination of Tertiary Amines.**—An apparatus is used such

as is shown in Fig. 2. The scale is calibrated in terms of weight of chlorobenzene by weighing into it known weights of chlorobenzene, adding 1 ml. of *N* hydrochloric acid, extracting as described under the determination of tertiary amines, and noting the scale reading. For the particular bulb used in this work, the weight of the chlorobenzene ( $W_E$ ) present with the meniscus at any definite scale division (*h*) is given by the expression

$$W_E = 11.754 + 0.369 h \quad (1)$$

#### Determination of Tertiary Amines.

—Solution A containing the tertiary amines is chilled, transferred to a separatory funnel, made alkaline with 5 *N* sodium hydroxide and extracted once with 150 ml., once with 75 ml. and three times with 50-ml. portions of ether. The combined ether extracts are dried over anhydrous calcium sulfate, filtered, and washed quantitatively in portions into a flask which has been tared together with some boiling chips, and the ether removed on a water-bath. The flask, to which 75 ml. of pure chlorobenzene has been added, is wiped clean, connected to an efficient fractionating column and the mixture distilled carefully until the constant boiling point of chlorobenzene is reached (*ca.* 132°) and an additional 10–15 ml. of distillate has collected. The flask and contents are weighed and the weight ( $W_C$ ) of the chlorobenzene solution (C) of amines is obtained by difference (about 10–15 g.).

The dry calibrated bulb, fitted with a cork stopper, is weighed accurately ( $W_B$ ). Through a funnel sufficient of Solution C is introduced to come to the top of the scale. The bulb and contents are weighed and the weight of Solution C ( $W_Q$ ) is obtained by difference.

To the bulb there is added 15 ml. of *N* hydrochloric acid. The contents of the stoppered bulb are mixed thoroughly for about five minutes. The apparatus is supported in a notched cork in the centrifuge cup and centrifuged. In order to join the thin film of chlorobenzene which may be floating on top of the aqueous layer, the latter is drawn off by a capillary tube as completely as possible without disturbing the chlorobenzene–water interface and the bulb is centrifuged as before. The entire bulb is immersed in a thermostat at  $25.0 \pm 0.2^\circ$  for thirty minutes and the scale reading *h* at the top of the meniscus at the chlorobenzene–water interface is read.

The extractions are repeated with fresh 15-ml. portions of *N* hydrochloric acid until constant differences are observed in the value of *h*, usually after about three or four extractions. This constant difference is caused by a slight solubility of chlorobenzene in *N* hydrochloric acid. If, during the extractions, the level of the interface should fall below the scale, an additional weighed quantity ( $W_X$ ) of pure chlorobenzene may be added from a weight pipet to raise the level sufficiently. Sometimes it is difficult to obtain a satisfactory dome-shaped meniscus at the interface even with a scrupulously clean glass surface. (Level or even concave menisci may be obtained.) Sometimes this may be corrected by tapping or swirling; at other times it is necessary to chill the bulb and solution in ice

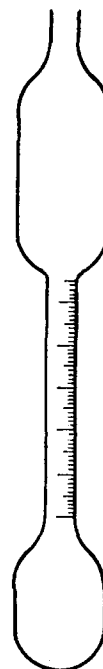


Fig. 2.—Extraction bulb for determining tertiary amines (one-half actual size).

TABLE II

Source and assay of individual amines Amine	Assay	Composition of 6 mixtures analyzed					
		1	2	3	4	5	6
		Primary amines (% of whole mixture)					
Aniline <sup>a</sup>	100.0 <sup>b</sup>	16.36	15.06	17.82	13.67	6.50	4.54
Mesidine <sup>c</sup>	99.8 <sup>d</sup>	11.86	14.83	10.43	14.03	11.75	3.54
<i>o</i> -Toluidine <sup>e</sup>	99.7 <sup>d</sup>	4.77	4.54	4.78	4.33	5.74	2.85
<i>p</i> -Toluidine <sup>f</sup>	100.0 <sup>d</sup>	10.20	9.02	10.59	13.10	7.68	2.40
4-Amino-1,3-dimethyl-benzene <sup>g</sup>	<sup>h</sup>	14.40	11.07	10.99	11.42	7.97	3.06
Impurity in dimethyl- <i>p</i> -toluidine <sup>i</sup>	<sup>j</sup>	0.01	0.01	0.01	0.01	.....	0.03
Total %		57.60	54.53	54.62	56.56	39.64	16.42
Total Weight		3.7935	3.6749	3.6591	3.8618	2.5907	1.0933
		Secondary amines (% of whole mixture)					
Methylaniline <sup>g</sup>	100.1 <sup>d</sup>	10.99	14.93	15.88	14.12	27.25	19.78
	100.4 <sup>b</sup>						
Methyl- <i>o</i> -toluidine <sup>g</sup>	99.6 <sup>d</sup>	7.75	6.76	7.04	5.95	14.96	18.99
Methyl- <i>p</i> -toluidine <sup>g</sup>	100.1 <sup>d</sup>	6.98	7.02	7.38	7.62	14.32	17.57
Impurity in 4-amino-1,3-dimethylbenzene <sup>i</sup>	<sup>h</sup>	0.05	0.03	0.04	0.03	0.03	0.25
Impurity in dimethyl- <i>p</i> -toluidine <sup>i</sup>	<sup>j</sup>	0.06	0.09	0.09	0.07	0.03	0.01
Total %		25.83	28.83	30.43	27.79	56.59	56.60
Total Weight		1.7009	1.9427	2.0385	1.8974	3.6982	3.7681
		Tertiary amines (% of whole mixture)					
Dimethylaniline <sup>i</sup>	100.4 <sup>b,h</sup>	11.79	9.87	8.03	10.52	1.65	9.13
Dimethyl- <i>p</i> -toluidine <sup>g</sup>	97.0 <sup>b,h</sup>	4.37	6.46	6.61	4.80	1.89	17.76
Impurity in 4-amino-1,3-dimethylbenzene <sup>i</sup>	<sup>h</sup>	0.41	0.31	0.31	0.33	0.23	0.09
Total %		16.57	16.64	14.95	15.65	3.77	26.98
Total Weight		1.0915	1.1213	1.0013	1.0681	0.2461	1.7969

<sup>a</sup> Twice refracted commercial grade. <sup>b</sup> Determined by potentiometric titration in excess acid with *N* sodium hydroxide in solution saturated with sodium chloride. <sup>c</sup> Furnished by Dr. A. G. Hill of the Calco Chemical Division Research Department. <sup>d</sup> Determined by titration with 0.1 *N* sodium nitrite in the presence of sodium bromide at 0-5°. <sup>e</sup> By hydrolysis of aceto-*o*-toluidide (m. p. constant at 111-111.5° (cor.)) and distillation of recovered amine. <sup>f</sup> Recrystallization to a constant melting point of 43.6-44.0° (cor.). <sup>g</sup> Eastman Kodak Co. Organic Chemical, highest grade. <sup>h</sup> Analysis of 1.7248 g. by the method of this paper gave 3.752 g. of sulfonamides of primary amines, 0.0122 g. of sulfonamides of secondary amines, and 0.047 g. of tertiary amines. <sup>i</sup> These impurities were assumed to be of the same molecular weight as the main constituent. <sup>j</sup> Analysis of 0.8730 g. by the method of this paper gave 0.0027 g. of sulfonamides of primary amines, 0.0244 g. of sulfonamides of secondary amines and 0.824 g. of tertiary amines. Some oil could be extracted from an acid solution of the sample by means of ether. <sup>k</sup> One gram gave no sulfonamides of primary amines, only 10 mg. of sulfonamides of secondary amines, and 101.0% tertiary amines. <sup>l</sup> Commercial grade.

before placing the bulb in the thermostat. This latter method is almost infallible.<sup>12</sup>

**Calculations.**—Let  $f$  = the solubility correction factor of chlorobenzene in *N* hydrochloric acid. This is the fraction of a division by which the volume decreases when chlorobenzene is treated with 15 ml. of *N* hydrochloric acid (for the bulb in question it was 0.02). Let  $n$  = the number of 15-ml. portions of *N* hydrochloric acid used; and let  $h$  = the first reading at which constant differences are obtained. Then  $h(\text{cor.}) = h + f \times n$ . Substitute  $h(\text{cor.})$  in equation (1) and solve for  $W_E$ . Then  $W_Q - W_E = W_D$  = weight of tertiary amine in the weight,  $W_Q$ , of the chlorobenzene solution. If additional chlorobenzene has been added, the equation would become  $W_Q + W_X - W_E = W_D$ . The % tertiary amines in the original sample is

$$\frac{W_Q \times W_D}{W_Q \times \text{wt. of sample (g.)}} \times 100$$

(12) If both methods should fail, a correction could be calculated for the change in volume caused by a level or concave, rather than a convex, interface. For one bulb it has been calculated that the error, for a level meniscus, might be as much as 26 mg. of chlorobenzene.

## Results

The mixtures of amines which were used to test the method, and information concerning the source and purity of the individual components of the mixtures, are given in Table II. Six mixtures are reported. The percentage of each individual amine and the total percentage of each group in each of the six mixtures is given under the column for that mixture; for example, mixture 1 had 57.60% primary amines, 25.83% secondary amines and 16.57% tertiary amines.

Table III gives the % of each class of amines present and found, and the absolute errors in terms of % amines.

**Accuracy.**—From the errors given in Table III the standard (root mean square) deviation of a single value from the true value has been calculated. It is  $\pm 1.6\%$  (absolute) for primary amines,  $\pm 2.3\%$  (absolute) for secondary amines and  $\pm 0.3\%$  (absolute) for tertiary amines. [If the tertiary amines are considered to have a mean systematic error of  $-0.2\%$ , then the standard deviation from the value corrected by this figure would be  $\pm 0.2\%$  (absolute)].

TABLE III

Mixture no.	Amines		Error % Found - % Present
	% Present	% Found	
Primary amines			
1	57.6	56.7	-0.9
2	54.5	53.0	-1.5
3	54.6	54.6	0.0
4	56.6	57.8	1.2
5	39.6	36.6	-3.0
6	16.4	15.4	-1.0
Secondary amines			
1	25.8	25.3	-0.5
2	28.8	27.7	-1.1
3	30.4	32.6	2.2
4	27.8	29.1	1.3
5	56.6	60.5	3.9
6	56.6	54.3	-2.3
Tertiary amines			
1	16.6	(Determination lost)	
2	16.6	16.3	-0.3
3	15.0	14.4	-0.6
4	15.6	15.6	0.0
5	3.8	3.7	-0.1
6	27.0	27.0	0.0

### Discussion

**Study of Optimum Conditions for Reaction with Arylsulfonyl Chlorides and for Decomposition of Excess Chloride.**—From the values in Table I it appears that the Hinsberg method is erratic, possibly because the reaction is carried out in two phases, and that a more complete and reproducible reaction might be brought about in a homogeneous solution. Hickinbottom<sup>13</sup> had found that certain alkylated anilines which reacted sluggishly with arylsulfonyl chlorides underwent reaction satisfactorily in pyridine. Table IV shows the extent of recovery of the sulfonamides which were isolated from some individual amines, and their quality, as indicated by their melting points, when the reaction was carried out in pyridine with tosyl chloride.

TABLE IV  
RECOVERY OF SULFONAMIDES AFTER REACTION IN  
PYRIDINE

Amine	Recovery of sulfonamide, %	M. p. of sulfonamide, °C. (cor.)	
		Found	Reported <sup>a</sup>
Aniline	99.3, 99.2	100.5-103.5	103
<i>p</i> -Toluidine	99.0	110.4-118.5	117
Mixed xylidines	98.8	.....	..
Methylaniline	98.5	88.3- 92.4	94

<sup>a</sup> Shriner and Fuson "Identification of Organic Compounds", 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, pp. 193, 196.

The method was then extended to some mixtures of single primary, secondary and tertiary amines. Table V gives the results with two such mixtures. The recoveries of the primary and secondary amines are based on weights of sulfon-

(13) Hickinbottom, *J. Chem. Soc.*, 946 (1933).

amides; that of the tertiary amines on potentiometric titration in acidified sodium chloride solution.<sup>14</sup>

TABLE V

### RECOVERY OF AMINES IN SIMPLE MIXTURES

Amine	% of Mixture			Error (% Absolute) (% Found) - (% Present)
	Present	Found	Found	
Mixture 1				
<i>p</i> -Toluidine	28.2	30.6	28.6	av. 29.6
Methylaniline	56.2	56.4	54.4	av. 55.4
Dimethylaniline	15.6	14.6	14.4	av. 14.5
Total	100.0	101.6	97.4	99.5
Mixture 2				
<i>p</i> -Toluidine	59.8	58.6	64.6	av. 61.6
Methylaniline	33.5	32.9	33.6	av. 33.3
Dimethyl- <i>p</i> -toluidine	6.7	6.2	7.1	av. 6.7
Total	100.0	97.7	105.3	101.6

Mixtures of the same ten amines, which have been described in Table II and which later gave the values shown in Table III by the method finally adopted, were then analyzed by the same preliminary method<sup>14</sup> as had been used for Mixtures 1 and 2 in Table V. However, the latter experiments were probably better controlled for it was found with the mixtures of ten amines that low values were obtained for tertiary amines (from 6 to 88% recovery) and higher values for secondary amines (from 94 to 124% recovery). Some experiments (see Table VI) indicated that the difficulty lay, at least partially, in the erratic degradation of dimethyl-*p*-toluidine to secondary amines. This could be largely remedied by carrying out the tosylation in a pyridine-benzene

TABLE VI

### EFFECT OF COOLING AND DILUTION WITH BENZENE ON TOSYLATION OF TERTIARY AMINES

Conditions of tosylation	Amine taken, g.	Tertiary amine recovered, %	Sulfonamide of secondary amine found, g.
Dimethylaniline			
80°—no benzene	0.9727	101	0.027
25°—no benzene	0.9460	101	0.014
Dimethyl- <i>p</i> -toluidine <sup>a</sup>			
80°—no benzene	0.8234	18	1.5430 <sup>b</sup>
25°—no benzene	0.7012	63	0.4711
5°—no benzene	1.0303	89	.0631
5° + benzene	0.8468	97	.0521
25° + benzene	0.9879	100	.0279

<sup>a</sup> The dimethyl-*p*-toluidine used contained about 3% of a neutral oil; the weight of amine taken has been corrected for this. <sup>b</sup> From this sulfonamide an amine was regenerated from which there was obtained a sulfonamide of only a secondary amine.

(14) The analyses were carried out essentially as described in the section on Method of Analysis except for some differences introduced because at the time this work was done the method had not been completely worked out. The differences were as follows: (1) The tosylation was carried out in pyridine in an ice-bath without dilution with benzene; (2) excess tosyl chloride was decomposed with sodium carbonate with no control of the temperature; (3) the alkaline mixture of sulfonamides was extracted with benzene; and (4) the sulfonamides were dried at 50° under vacuum for three hours, a procedure which had been shown to give complete recovery of sulfonamides.

solution in the cold; and in order to maintain a reduced temperature, the decomposition of the excess tosyl chloride was accomplished by the slow addition of water to the reaction mixture with cooling. (This is similar to the behavior reported for acetylsulfanilyl chloride.<sup>14a</sup>) These changes were incorporated in the method as finally adopted.

**Separation of Sulfonamides of Primary Amines from Sulfonamides of Secondary Amines.**—In procedures used preliminary to the development of the finished method of analysis, sulfonamides of secondary amines were separated from the alkaline solution of the sulfonamides of primary amines by extraction of the former with benzene. It was soon found, however, that *p*-toluenesulfonmesidide responded abnormally to this treatment. Using the same procedure whereby *p*-toluenesulfonanilide was caused to remain completely behind in alkaline solution, *p*-toluenesulfonmesidide was extracted to the extent of about 90%, thus appearing as sulfonamide of a secondary amine. That the sulfonamide, both in the alkaline solution and in the benzene extract, was that of mesidine was indicated by similar melting ranges for each and by comparison under the microscope. The optical and crystalline characteristics of each were identical.<sup>15</sup> The sulfonamide of 2,6-dimethylaniline also exhibited similar behavior, 70% being extracted from alkaline solution by benzene. Evidently the acid dissociation of these sulfonamides is so weak that there is considerable un-ionized, benzene-soluble, free sulfonamide present even in a highly alkaline medium.

To overcome the difficulty caused by this behavior the method of separating sulfonamides of secondary from those of primary amines was altered so that the latter were extracted from the former with normal sodium hydroxide (this concentration appeared to be most suitable) without the use of an organic solvent. This modification was also incorporated in the method as finally adopted.

**Hydrolysis of Separated Sulfonamides.**—In order to obtain the primary and secondary amines in the free state for further study and at the same time get data from which to calculate weight percentage, it was necessary to find a suitable method of hydrolysis. Hinsberg<sup>4</sup> originally hydrolyzed the sulfonamides by means of concentrated hydrochloric acid in a sealed tube at 150–160°. A number of workers have reported using sulfuric acid under varying conditions of time, temperature and dilution, but all agree that

there is more or less difficulty under these conditions, caused by sulfonation and the formation of sulfones.<sup>16</sup> Johnson and Ambler<sup>17</sup> found no advantage in the use of sulfuric acid over that of hydrochloric acid, and recommended the latter. Schreiber and Shriner<sup>18</sup> recommended refluxing with 25% hydrochloric acid.

The authors found that when *p*-toluenesulfonanilide was treated with 80% sulfuric acid at temperatures of from 135–160° (for a period of time sufficient to get complete solution in one case and for an additional twenty-five-minute period in some other experiments) only 50 to 58% of the theoretical amount of aniline was recovered after making the reaction mixture alkaline, extracting with benzene, extracting the amine into acid and titrating with standard bromide-bromate solution. Under comparable conditions, recoveries of about 97% of the free amine were obtained in experiments with *p*-toluenesulfonmethylanilide, as determined by titration with standard sodium nitrite in the presence of added sodium bromide. Hydrolysis by prolonged boiling under reflux with 1:1 hydrochloric acid yielded practically quantitative recovery with both compounds.<sup>19</sup> However, when the hydrolysis with hydrochloric acid was applied to *p*-toluenesulfonmesidide, only 1.1% hydrolysis was attained after seventy hours' refluxing. Yet in admixture with *p*-toluenesulfonanilide the hydrolysis of the *p*-toluenesulfonmesidide went considerably farther, as shown by Table VII.

TABLE VII  
HYDROLYSIS OF MIXTURES OF *p*-TOLUENESULFONANILIDE AND *p*-TOLUENESULFONMESIDIDE

Mixture of 16.18 millimoles of <i>p</i> -toluenesulfonanilide and 3.46 millimoles of <i>p</i> -toluenesulfonmesidide	
Unhydrolyzed sulfonamide, mmols. as mesidine	Time of hydrolysis, hrs.
0.32	29
1.54	47
1.93	41
1.56	41

The lack of correlation of these values with the time of hydrolysis probably indicates variability in the conditions of contact between the acid and the insoluble sulfonamide. The mixture of the two sulfonamides is an oil, whereas the sulfonmesidide, when present alone, remains crystalline during the boiling. Other factors, however, such as, possibly, the extent of a slight solubility in the acid, must also be of importance, since even the sulfonamides of a mixture of isomeric xylydines which were liquid during the hydrolysis required very lengthy refluxing for complete hydrolysis. Table VIII gives the results of some hydrolyses of

(14a) Seaman, Norton, Woods and Massad, *Ind. Eng. Chem., Anal. Ed.*, **16**, 517 (1944).

(15) We are indebted to Dr. C. Maresh and Mr. R. R. Krammes for the following data. *p*-Toluenesulfonmesidide crystallizes from alcohol in the form of prisms and elongated hexagons, which exhibit both parallel and oblique extinction, are biaxial negative in optical character, and have an alpha refractive index of 1.569 ± 0.005° and a beta refractive index of 1.677 ± 0.005° (with sodium light).

(16) Schroeter and Eisleb, *Ann.*, **367**, 157 (1909); Witt and Uermenyi, *Ber.*, **46**, 296 (1913); Witt and Truttwin, *ibid.*, **47**, 2786 (1914); Halberkann, *ibid.*, **54**, 1833 (1921); **55**, 3074 (1922).

(17) Johnson and Ambler, *This Journal*, **36**, 372 (1914).

(18) Schreiber and Shriner, *ibid.*, **56**, 114, 1618 (1934).

(19) Some of this work was done by Mr. R. T. Foley.

primary amine sulfonamides with 1:1 hydrochloric acid. Even though the data are not exhaustive, there is sufficient information to indicate the differences which may be expected between different sulfonamides. It would appear that there is greater difficulty of hydrolysis as the number of methyl groups on the ring increases.

TABLE VIII

<i>p</i> -Toluene-sulfonamide of	Sulfonamide, g.	Time of hydrolysis, hr.	Sulfonamide hydrolyzed, %
Aniline	5.0	16	99
<i>o</i> -Toluidine	4.0	67	100
Mixed xylidines	7.9	110	98
2,6-Dimethylaniline	2.0	120	33
Mesidine	5.0	70	1

When synthetic mixtures of a number of sulfonamides of primary amines were subjected to hydrolysis (see Table II for the composition of these mixtures) the unhydrolyzed residue, which was always crystalline, consisted largely, if not wholly, of *p*-toluenesulfonmesidide. With several synthetic mixtures of sulfonamides of secondary amines (see Table II) the hydrolysis was also incomplete; the crystalline residues, which melted at about 170°, probably consisted of the sulfonamide of methyl-*p*-toluidine.

A few experiments were made with a mixture of equal parts (by volume) of glacial acetic acid and concentrated hydrochloric acid as hydrolyzing agent. This appeared promising since boiling for twenty-four hours caused 83% hydrolysis, and for thirty-eight hours 92% hydrolysis of *p*-toluenesulfonmesidide. As far as could be ascertained no acetylation occurred during the hydrolysis.

The method which was finally adopted involved heating the sulfonamides of primary and secondary amines separately under reflux with 1:1 hydrochloric acid, diluting with water, extracting unhydrolyzed sulfonamides with benzene, releasing the amines from the aqueous solution with alkali, extracting again with benzene, transferring the liberated amines to dilute acid and titrating with standard alkali.

**Acidimetric Titration of Liberated Primary and Secondary Amines.**—The titration is carried out with a glass electrode and a calomel half-cell, using a meter indicating *pH* readings directly. It is necessary to saturate the acid solution of the amines with sodium chloride in order to obtain a sharp break in the curve at the point where the excess mineral acid has been neutralized. Figure 1 shows the curves for aniline with and without the addition of sodium chloride. Similar curves were obtained for most of the bases which are reported here. Table IX gives the values found when some single amines were dissolved in hydrochloric acid and titrated in the manner described.

When a mixture of aniline, *p*-toluidine, methylaniline and dimethylaniline which was equivalent

TABLE IX  
POTENTIOMETRIC TITRATION OF AMINES

Amine	Wt. pres., g.	Titra., ml. <i>N</i> NaOH	% Found
Aniline	2.912	31.33	100.2
<i>p</i> -Toluidine	4.717	43.69	99.2
Mixed xylidines	5.565	45.80	99.7
Methylaniline	4.251	39.86	100.5

to 44.14 millimoles was titrated with *N* NaOH, a titration of 44.05 ml. was obtained, or 99.8% recovery. With some mixtures of aniline, *p*-toluidine, and mixed xylidines, titration values of 99.7, 100.2, 100.6, and 100.0% were obtained.<sup>20</sup>

In order to make certain that the presence of toluenesulfonic acid produced in the hydrolysis did not cause any error in the titration, a solution of 3.521 g. of aniline and 7.000 g. of *p*-toluenesulfonic acid (monohydrate) was titrated by the method described. A titration of 37.68 ml. of *N* NaOH, corresponding to 99.7% of the expected value for aniline, was obtained.

**Determination of Tertiary Amines.**—In the recovery and determination of tertiary amines the first problem is the separation from pyridine. This is also a tertiary amine and steam distills over with the tertiaries from the sample into the hydrochloric acid and is then extracted (at least partially) when the distillate is made alkaline and extracted with ether. The problem was solved satisfactorily by adding chlorobenzene (b.p. 132.1°) to the ether extract of the tertiary amines and distilling through a fractionating column. The ether (b.p. 34.6°) and the pyridine (b.p. 115.3°) distil over with some chlorobenzene, thus effectively separating them from the tertiary amines, the lowest possible boiling point of which would be considerably above that of chlorobenzene. The tertiary amines thus remain behind dissolved in the residual chlorobenzene.

Next it is necessary to determine the weight of tertiary amines in the chlorobenzene. Mere extraction with acid and titration would give an equivalent value not a weight. Extraction of the free bases after making the aqueous solution alkaline and finally weighing the bases caused too much loss. A method was first worked out which involved precipitating the hydrochlorides of the tertiary amines by means of hydrogen chloride gas, washing with petroleum ether, drying, weighing and titrating with alkali to determine the free and combined hydrochloric acid. This method proved to have a number of defects such as the variable hydrochloric acid content of the precipitate and the progressive loss of amine when drying the hydrochlorides at 110°, probably because of the presence of moisture which was difficult to exclude on account of the hygroscopic nature of the hydrochlorides. The method reported was finally adopted as being most satisfactory.

(20) Most of this work was done by Mr. E. A. Massad.

Using this method a known weight of dimethylaniline was determined to the extent of 100.3% and a mixture of dimethylaniline and dimethyl-*p*-toluidine to the extent of 99.2%.

### Summary

1. A method of separation, determination and subsequent isolation of primary, secondary and tertiary amines in a mixture of ring- and nitrogen-methylated aromatic amines was developed using a modified Hinsberg reaction with a mixture of pyridine and benzene as the solvent. On synthetic mixtures containing five primary, three secondary and two tertiary amines the method has an accuracy expressed as a standard deviation (absolute per cent.) of  $\pm 1.6\%$  for the primary amines,  $\pm 2.3\%$  for the secondary amines and  $\pm 0.3\%$  for the tertiary amines.

2. The Hinsberg method, when applied to the amines in question in an aqueous medium in the

usual manner, involves side reactions and lack of complete reaction which vitiate it as a quantitative method. With synthetic mixtures of amines such as were used in this work, low values were obtained for primary amines, high values for tertiary amines and erratic values for secondary amines.

3. Increasing methylation of the ring for the primary amines in question results in sulfonamides which are of decreasing acidity, as indicated by the tendency to hydrolyze in alkaline solution to yield benzene-extractable sulfonamides, and from which it is increasingly difficult to regenerate the amines with hydrochloric acid.

4. Solutions of the amines in excess acid may be titrated potentiometrically and a fairly sharp "break" obtained at the point of neutralization of the excess acid provided the solution has previously been saturated with sodium chloride.

BOUND BROOK, N. J.

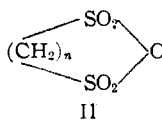
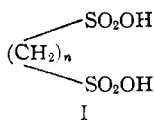
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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

## Ethane-1,2- and Propane-1,3-disulfonic Acids and Anhydrides

By S. M. McELVAIN, ARTHUR JELINEK<sup>1</sup> AND KURT RORIG

In connection with some other work in this Laboratory, it became necessary to prepare ethane-1,2-disulfonic acid (I,  $n = 2$ ). This acid has previously been obtained in a number of ways, either by direct preparation or as an oxidation product isolated in the characterization of other substances.<sup>2</sup> The melting point of the acid has been variously reported as 104,<sup>3</sup> 100<sup>4</sup> and 97°.<sup>5</sup>



The most direct method of preparation of this acid involves its isolation from the sodium salt which may be obtained in high (*ca.* 90%) yields from the Strecker reaction with ethylene bromide and sodium sulfite.<sup>6</sup> This method was used in the work now reported and the free acid was isolated from the sodium salt by first converting this salt to the barium salt and then decomposing the latter with sulfuric acid.

The acid obtained in this manner is a light gray powder which melts, after drying at 40° at 1 mm. for five hours or at 140° at atmospheric pressure

for four hours, at 111–112°. This acid, however, has a neutral equivalent corresponding to the dihydrate; on short exposure to air it absorbs sufficient moisture to lower the melting point well below 100°. When this hydrated acid is further dried at 145° and 1 mm. pressure for six hours, the anhydrous acid with the correct neutral equivalent and sulfur content is obtained. The anhydrous acid melts sharply at 172–174°; in contrast to the hydrated acid it is somewhat soluble in anhydrous ether and quite soluble in dioxane. Unless special precautions are taken in handling or storing the anhydrous acid, it absorbs sufficient moisture from the air to lower the melting point considerably.

When the molten, anhydrous acid is heated in a sublimation apparatus at 190–200° and 1 mm. pressure, the cyclic anhydride (II,  $n = 2$ ) slowly condenses in the cooled portion of the apparatus. Further evaporations and condensations of this condensate give the pure anhydride which melts at 145–146°. Approximately 20% of the original acid remains as a charred residue from the initial evaporation. This is probably the result of formation of a non-volatile, intermolecular anhydride. Ethane-1,2-disulfonic anhydride (II,  $n = 2$ ) rapidly absorbs moisture from the air and dissolves readily in cold water.

Ethanedisulfonyl chloride is probably the most thoroughly investigated derivative of ethanedisulfonic acid. It is readily prepared by the action of phosphorus pentachloride on the sodium salt of the acid. Köhler<sup>4</sup> was the first to observe that this acid chloride reacted with water and alcohols to

(1) Wisconsin Alumni Research Foundation Research Assistant, 1941–1944.

(2) Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 167.

(3) Miolati, *Ann.*, **262**, 61 (1891).

(4) Köhler, *Am. Chem. J.*, **19**, 728 (1897).

(5) Zuffanti and Hendrickson, *THIS JOURNAL*, **63**, 2999 (1941).

(6) Refs. 4 and 5; cf. also Bender, *Ann.*, **148**, 96 (1868), James, *J. Chem. Soc.*, **43**, 44 (1883), and Autenrieth and Rudolf, *Ber.*, **34**, 3473 (1901).