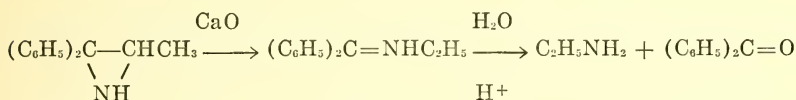


Derivatives of the Lower Aliphatic Amines

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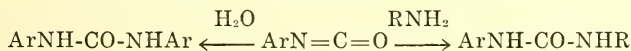
In previous work in this Laboratory, low molecular-weight amines have frequently been obtained as hydrolysis products of more complex compounds; thus when 2,2-diphenyl-3-methylethylenimine is heated with calcium oxide, and the product hydrolyzed with dilute acid, ethylamine is formed(1):



In some cases, considerable difficulty has been experienced in identifying these amines, because they have been formed in dilute aqueous solution, from which it is difficult to isolate them, and because most of the common amine reagents give oily or low-melting solids with the low molecular weight amines, and these derivatives are not sufficiently characteristic for identification purposes. The object of the present work was, therefore, to seek a reagent which would give more suitable derivatives.

Such a reagent would have to have certain characteristics. It must not react with water, and it must be capable of reacting with amines in low concentrations (5-10%). The reaction must proceed in high yields, and the products must be essentially insoluble in water, and of fairly high melting point. While many reagents have been proposed for derivatizing amines, many of them have not been investigated with the lower aliphatic amines, and of those that have been so studied, none of them meets all the above requirements.

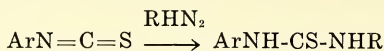
The aryl isocyanates are widely used to derivatize amines. They do react readily with most primary and secondary amines, and give good crystalline derivatives, but since they also react very rapidly with water, they are not satisfactory for our purpose:



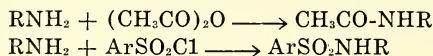
The aryl acid azides proposed by Sah (2) are unsatisfactory for the same reason.

The aryl isothiocyanates, like their oxygen analogs, react well with most amines, and since they do not react readily with water, the presence of some moisture is not a disadvantage. Although the phenyl- and o-tolylisothiocyanates tend to give oily derivatives with the lower aliphatic amines, this difficulty can be overcome by the use of p-methoxyphenyl (3) or alpha-naphthyl-isothiocyanates.(4) We have found, however, that these reagents cannot be used with dilute aqueous

solutions of amines (5-10%) because they are insoluble in water, and the reaction is too slow to be useful.



A reaction that has been of much value in derivatizing primary and secondary amines is the one with acid anhydrides or acid chlorides to form substituted amides:



In many cases this reaction can be carried out by the Schotten-Baumann technique, in aqueous solution, in the presence of an inorganic base to take up the acid formed in the reaction. Most of the acid anhydrides and acid chlorides commonly used for this purpose have certain disadvantages when applied to the lower aliphatic amines. Acetic anhydride, benzoyl chloride, benzene- and p-toluenesulfonyl chlorides give oily derivatives with these amines. 2,4-Dinitrobenzenesulfonyl chloride has been used by Billman (5) with aliphatic amines; the derivatives have good melting points, and can be formed in concentrated aqueous solution (30%), but not very well in more dilute solutions (5-10%). p-Acetaminobenzenesulfonyl chloride has been found by Magini (6) to react readily with some of the lower aliphatic amines in aqueous solution, to give derivatives of good melting points; this reagent probably merits further study. Reichstein (7) has used 3,5-dinitrobenzoyl chloride to derivatize amines, but he gives no experimental details.

Other reagents have been proposed, but it appeared to us that the best reagent would probably be an aromatic acid chloride or an arylsulfonyl chloride with a nuclear substituent, such as nitro, to raise the melting point of the derivatives. Such a reagent could probably be used with the standard Schotten-Baumann technique. Accordingly, we have investigated the reaction of 3,5-dinitrobenzoyl chloride, *para*-nitro- and *meta*-nitro-benzenesulfonyl chlorides and beta-naphthalenesulfonyl chloride with all the aliphatic primary and secondary amines up to amyl. The amines were used in 5% aqueous solution, and were shaken for $\frac{3}{4}$ —1½ hours with the reagent, in the presence of enough potassium hydroxide to keep the reaction mixture basic to litmus.

The results obtained with 3,5-dinitrobenzoyl chloride were very disappointing. Even on prolonged shaking of the reactants, apparently but little derivative was formed, for recrystallization of the water-insoluble material from alcohol gave, in every case, a large amount of ethyl 3,5-dinitrobenzoate, formed by esterification of the unused reagent, and little or no amide.

The best results were obtained with *para*-nitrobenzenesulfonyl chloride. This reagent gave good yields of crystalline products with practically all the amines tried, and the melting points of the derivatives were sufficiently high, and sufficiently far apart to be characteristic of each amine.

When *meta*-nitrobenzenesulfonyl chloride was used, good yields of crystalline derivatives were obtained in most cases. The products tended to melt lower than those from the *para*- isomer, however, and the melting points were closer together, making these derivatives less suitable for characterization purposes. With beta-naphthalenesulfonyl chloride, the results were much poorer. The yields were very low, so that it was necessary to use relatively large quantities of amine and reagent to get enough derivative for purification. The melting points of the derivatives lay between those from *meta*- and *para*-nitrobenzenesulfonyl chloride, and in several cases, oils were formed. The derivatives from these acid chlorides are recorded in Table I.

It is of interest to note that we were unable to obtain a satisfactory derivative from di-isopropylamine and from di-*sec*-butylamine with any of the reagents used. In every case, the product was very high melting, and analyzed for the potassium salt of the sulfonic acid. Apparently, in these two molecules, the steric effect of the large, branched chain groups, is sufficient to make attack on the nitrogen atom difficult. In other reactions, also, these amines are relatively inert.

Experimental Part

Reagents: The 3,5-dinitrobenzoyl chloride and the three sulfonyl chlorides were obtained from the Eastman Kodak Company, and were used without purification. Most of the amines were also obtained from Eastman Kodak; a few were student preparations.

para-Nitrobenzenesulfonamides.—These were prepared as follows: A 5% solution of the amine (15 ml.) was added to one equivalent of the reagent, suspended in 5 ml. of a 10% potassium hydroxide solution. The reaction mixture was shaken mechanically for forty-five minutes, the basicity of the solution being checked from time to time. When secondary amines were used, the insoluble product was collected, washed with water and recrystallized twice from 95% alcohol. When primary amines were used, the basic reaction mixture was filtered, and the filtrate acidified with hydrochloric acid. The precipitate so obtained was collected, washed with water and recrystallized twice from 95% alcohol.

meta-Nitrobenzenesulfonamides.—These were prepared in the same way, except that the reaction time was increased to seventy-five minutes.

beta-Naphthalenesulfonamides.—The same general procedure was used, except that 20 ml. of the amine solution and 10 ml. of 10% potassium hydroxide were used, and the mixture was shaken for one and one-half hours.

A representative number of the sulfonamides was analyzed for nitrogen; in every case the observed value was in good agreement with the theoretical value. (We wish to thank Mr. Charles Beazeley of the Microtech Laboratory, Skokie, Illinois, for carrying out these analyses.)

TABLE I.—Melting Points of Sulfonamides.

Amine Used	Arylsulfonyl chloride Used		
	p-Nitrobenzene-	m-Nitrobenzene	beta-Napthalene
Methyl	110-111°C	117-118°C	105-106°C
Dimethyl	92-93	73-74	oil
Ethyl	105-106	77-78	81-82
Diethyl	134-135	65-66	83-84 ^a
n-Propyl	84-85 ^b	59-60	73-74
iso-Propyl	114-115	64-65	100-101
Di-n-propyl-	86-87 ^c	59-60 ^d	oil
Di-iso-propyl	340 with dec. ^e	320 with dec. ^e	oil
n-Butyl	81-82	55-56 ^f	54-55
sec-Butyl	114-115	58-59	101-102
iso-Butyl	94-95	84-85	84-85
tert-Butyl	104-105	99-100	
Di-n-butyl	55-56	59-60 ^g	66-67
Di-sec-butyl	320 dec. ^e	320 dec. ^e	no product
Di-iso-butyl	91-92 ^h	87-88	81-82 ⁱ

(a) Calculated N, 5.31%, found, 5.02%. (b) Calc'd N, 11.47%, found, 11.05%. (c) Calc'd N, 9.78%, found, 9.43%. (d) Calc'd N, 9.78%, found, 9.62%. (e) Calc'd for K salt of sulfonic acid, N, 5.8%, found, 5.41, 5.75, 5.35, 5.64. (f) Calc'd N, 10.84, found, 10.77%. (g) Calc'd N, 8.91, found, 8.53. (h) Calc'd N, 8.91, found, 8.78%. (i) Calc'd N, 4.38%, found, 4.10%.

Summary

Methods of derivatizing dilute aqueous solutions of the low molecular weight aliphatic amines have been investigated. The best results were obtained with *para*-nitrobenzenesulfonyl chloride; *meta*-nitrobenzenesulfonyl chloride was fairly satisfactory. The yields from beta-napthalenesulfonyl chloride were very low, and no satisfactory derivatives could be obtained under the conditions used with 3,5-dinitrobenzoyl chloride. Several new sulfonamides have been prepared and their melting points tabulated.

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