

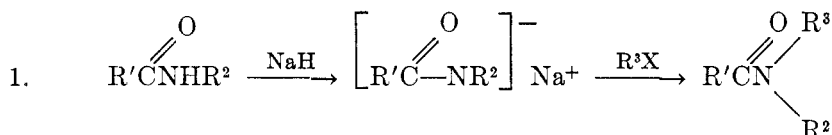
## THE USE OF SODIUM HYDRIDE IN THE ALKYLATION OF N-SUBSTITUTED AMIDES

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In connection with experiments under way in this laboratory the preparation of certain N,N-di-substituted amides was necessary. A number of examples are recorded in the literature in which compounds of this type have been prepared by the alkylation of an alkali salt of the appropriate N-substituted amide or sulfonamide (1-8). The salts have usually been prepared by the reaction of the N-substituted amide with either metallic sodium, (1, 7, 8) or with alcoholic or aqueous alkali as in the case of the sulfonamides (3, 5, 6) and some formamides (2).

The use of sodium offers the advantage of the reaction being carried out in a non-hydrolytic solvent. It was thought that the employment of sodium hydride would also offer this advantage and at the same time would be safer and easier to handle than the metal. With this in mind the preparation of a number of N,N-disubstituted amides by the general reaction shown in Equation 1 was undertaken. The results are summarized in Table I.



From the table it can be seen that when R' and R<sup>3</sup> were methyl and R<sup>2</sup> was aryl yields of 70-89% were obtained. Similar experiments in which R<sup>2</sup> was *p*-nitrophenyl failed to give any N-methyl-*p*-nitroacetanilide. This failure was apparently one in which the sodium hydride did not react with the amide because after six hours refluxing of the two in xylene the amide was recovered unchanged merely by cooling the reaction mixture.

To study the effect of changes in R<sup>3</sup> on the yield acetanilide was chosen as the starting material. From the table it can be seen that when R<sup>3</sup> was primary, allyl, or secondary the yields were 79%, 73%, and 53% respectively. When *tert*-butyl bromide was used as the halide none of the desired amide was obtained. The decrease resulting as one goes from primary to secondary to tertiary is to be expected and is in accord with well known similar effects in the Gabriel synthesis.

Only one example was tried in which both R' and R<sup>2</sup> were phenyl and in that case with R<sup>3</sup> methyl a 62% yield of N-methylbenzanilide was obtained.

When the reaction was run on benzenesulfonamide with R<sup>3</sup> as methyl only about 50% of impure product was obtained and 40% of the starting material was recovered. Similarly the reaction failed with phthalimide as starting material and R<sup>3</sup> as methyl, there being obtained a little impure substance which was not further purified and no attempt was made to recover any phthalimide. In

both of these cases the expected alkali salt seemed to form fairly readily but failed to react with the halide to any appreciable extent.

TABLE I  
ALKYLATION EXPERIMENTS

R'	R <sup>2</sup>	R <sup>2</sup> X	PRODUCT	YIELD, %	M.P. OR B.P., °C.	LIT. VALUE
Methyl	Phenyl	Methyl iodide	N-Methylacetanilide	89	98.5-101	101-102 <sup>a</sup>
Methyl	$\alpha$ -Naphthyl	Methyl iodide	N-Acetyl-N-methyl- $\alpha$ -naphthylamine	82	95-97	95 <sup>b</sup>
Methyl	<i>p</i> -Chlorophenyl	Methyl iodide	N-Methyl- <i>p</i> -chloroacetanilide	72	92-93	92 <sup>c</sup>
Methyl	<i>o</i> -Anisyl	Methyl iodide	N-Acetyl-N-methyl- <i>o</i> -anisidine	79	52-54	51-53 <sup>e</sup>
Methyl	<i>p</i> -Anisyl	Methyl iodide	N-Acetyl-N-methyl- <i>p</i> -anisidine	81	57-59	57-58 <sup>d</sup>
Methyl	<i>p</i> -Phenylazo-phenyl	Methyl iodide	N-Acetyl-N-methyl- <i>p</i> -aminoazobenzene	72	92-94.5 <sup>f</sup>	
Methyl	Phenyl	Butyl bromide	N-Butylacetanilide	79	121-125/4	273-275 <sup>g</sup> /718
Methyl	Phenyl	Isopropyl bromide	N-Isopropylacetanilide	53	40-43	(39 <sup>h</sup> )
Methyl	Phenyl	Allyl bromide	N-Allylacetanilide	73	99-103 <sup>i</sup> /2	
Phenyl	Phenyl	Methyl iodide	N-Methylbenzanilide	62	58-59	63 <sup>j, k</sup>
Methyl	Methyl	Methyl iodide	N,N-Dimethylacetamide	69	164-167	165-175 <sup>l</sup>
Methyl	Butyl	Butyl bromide	N,N-Dibutylacetamide	73	241-244	243-245 <sup>m</sup>

<sup>a</sup>Hepp, ref. (1). <sup>b</sup>Norton and Livermore, *Ber.*, **20**, 2272 (1887). <sup>c</sup>Chattaway and Orton, *J. Chem. Soc.*, 465 (1901). <sup>d</sup>Thielepape, ref. (8). <sup>e</sup>Ingold and Ingold, *J. Chem. Soc.*, 1310 (1926). <sup>f</sup>*Anal.* Calc'd for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>O: C, 71.1; H, 5.9; N, 16.6. Found: C, 71.3; H, 6.2; N, 16.6. <sup>g</sup>Kahn, *Ber.*, **18**, 3365 (1885). <sup>h</sup>Pictet and Crepieux, ref. (2). <sup>i</sup>*Anal.* Calc'd for C<sub>11</sub>H<sub>13</sub>NO: C, 75.4; H, 7.4; N, 8.0. Found: C, 75.1; H, 7.6, N, 8.1. <sup>j</sup>Hess, *Ber.*, **18**, 685 (1885). <sup>k</sup>The melting point 58-59° was also obtained for the same compound prepared by benzoylating N-methylaniline. <sup>l</sup>Mitchell and Reid, *J. Am. Chem. Soc.*, **53**, 1879 (1931). <sup>m</sup>Dermer and Fernelius, *Z. anorg. u. allgem. Chem.*, **221**, 83 (1934).

In the two instances where R<sup>2</sup> was alkyl instead of aryl the yield of N,N-dialkylamide was somewhat lower.

Of the compounds prepared only N-allylacetanilide and N-acetyl-N-methyl-

*p*-aminoazobenzene<sup>1</sup> were new. The first was characterized by analysis and hydrolysis to *N*-allylaniline which was identified as the monoxalate (9). The *N*-acetyl-*N*-methyl-*p*-aminoazobenzene was analyzed and hydrolyzed to the known *N*-methyl-*p*-aminoazobenzene (10).

In the preparation of *N*-methylacetanilide from acetanilide, sodium hydride, and methyl iodide, either ligroin (b.p. 90–120°) or benzene could be used with equal success as a solvent, but when sodium hydride and *N*-acetyl- $\alpha$ -naphthylamine were refluxed twenty-four hours in benzene no apparent reaction occurred. However, if xylene was used as the solvent a good yield of the desired compound was obtained by alkylation of the intermediate sodio derivative. As a result of this observation xylene was used as the solvent in the remaining experiments except for those run on methylacetamide and phthalimide. Benzene was used as a solvent for the former because of the proximity of the boiling point of the product to that of xylene and phenetole was used for phthalimide because of the slight solubility of the latter in xylene.

In the experiment using acetanilide two hours refluxing was sufficient to bring about complete formation of the sodium salt but in the case of some of the other compounds, e.g. *N*-acetyl-*o*-anisidine, overnight refluxing led to improved yields.

#### EXPERIMENTAL<sup>2, 3, 4, 5.</sup>

Since all of the reactions were carried out in similar ways, complete directions will be given only for the preparation of *N*-acetyl-*N*-methyl-*p*-anisidine.

*N*-Acetyl-*N*-methyl-*p*-anisidine. Into a dry three-necked round-bottomed flask, equipped with stirrer, reflux condenser, and addition funnel there was introduced 1.4 g. of sodium hydride and 50 ml. of xylene which had been dried over sodium. There was then added 8.3 g. of *N*-acetyl-*p*-anisidine in 200 ml. of boiling xylene and the mixture was refluxed with stirring for twenty hours, under an atmosphere of nitrogen, during which time the white sodium salt precipitated.

After the reaction had been allowed to cool the reflux condenser was replaced by a Dry Ice-acetone condenser; 20 g. of methyl iodide was added and the reaction mixture was refluxed eight hours more. The hot mixture was filtered; the residue was washed with 50 ml. of dry benzene and the washings added to the original filtrate. Stripping of the solvent followed by distillation yielded 8.0 g. of material, b.p. 137–140° at 3.5 mm., m.p. 50–56°. One recrystallization from ligroin (b.p. 90–120°) gave 7.3 g. (80%) of *N*-acetyl-*N*-methyl-*p*-anisidine, m.p. 57–59°.

*N*-Allylaniline. *N*-Allylacetanilide (9.5 g.) was refluxed in 50 ml. of 3 *N* hydrochloric acid for two hours. Isolation of the product in the usual manner gave 5.4 g. of *N*-allyl-

<sup>1</sup> Berju, *Ber.*, **17**, 1400 (1884), reported the preparation of this compound and gave m.p. 139°. However, the starting material he used, supposedly *N*-methyl-*p*-aminoazobenzene, had m.p. 180° and in view of the discrepancy between this and the accepted value [88–88.5° (10)] the product obtained by its acetylation could not have been the reported *N*-acetyl-*N*-methyl-*p*-aminoazobenzene.

<sup>2</sup> All melting points corrected.

<sup>3</sup> Analysis by R. J. Koegel of this laboratory.

<sup>4</sup> The yields in these experiments are not necessarily optimum since conditions for the reactions were not studied sufficiently to make a statement on that point.

<sup>5</sup> We are indebted to the Electrochemicals Department of E. I. du Pont de Neumours Co. for the sodium hydride used in these experiments.

aniline, b.p. 70–80°/2 mm., and 1.2 g. of N-allylacetanilide was recovered. Redistillation of the N-allylaniline yielded 4.7 g. (63%), b.p. 62–65°/1.2 mm.

*N-Allylaniline oxalate.* N-Allylaniline (1.75 g.) in 25 ml. of ether was added to 1.3 g. of oxalic acid dihydrate in 100 ml. of ether. The salt began to separate immediately and after one hour the solution was filtered giving 1.6 g. (60%) of the oxalate, m.p. 120–122°, [lit. (9) 120°]. Concentration of the mother liquors yielded another 0.4 g., m.p. 115–118°.

*Anal.* Calc'd for  $C_{11}H_{13}NO_4$ : C, 59.2; H, 5.8.

Found: C, 59.1, 59.3; H, 5.7, 6.0.

*N-Methyl-p-aminoazobenzene.* Two g. of N-acetyl-N-methyl-p-aminoazobenzene was refluxed six hours in a mixture of 35 ml. of alcohol and 30 ml. of 6 N hydrochloric acid. The solution was made alkaline, cooled, and the resulting precipitate collected by filtration. This was twice recrystallized from ligroin (b.p. 90–120°) to give 1.53 g. (92%) of N-methyl-p-aminoazobenzene, m.p. 86.4–88.6° [lit. (10) 88.0–88.5°].

#### SUMMARY

A number of N,N-dialkyl amides have been prepared by the action of sodium hydride and an alkyl halide on an N-alkyl amide.

Two new substituted amides, N-allylacetanilide and N-acetyl-N-methyl-p-aminoazobenzene were prepared and characterized during the course of the experiments.

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