

ate was prepared as above and recrystallized from methanol to yield white leafy crystals, m. p. 76.7–78° (cor.); lit. m. p.'s: 77°,<sup>52</sup> 77.8°.<sup>53</sup>

Stock acetophenone was twice distilled; b. p. 198–199°. *o*-Hydroxyacetophenone (Eastman White Label) was twice distilled; b. p. 109–110° (32 mm.);  $n_{20}^D$  1.5585. A sample of distilled benzaldehyde, which had been stored over hydroquinone, was twice redistilled (nitrogen atmosphere); b. p. 71.8–72° (21.5 mm.). Stock salicylaldehyde was twice redistilled; b. p. 194°;  $n_{20}^D$  1.5729. Methyl benzoate (Eastman White Label) and stock methyl salicylate were each redistilled twice; b. p.'s: 193–193.5 and 216–217°, respectively. Phenol (Baker and Adamson Reagent) was distilled twice; b. p. 179–180°. Stock  $\alpha$ -naphthol was twice recrystallized (charcoal) from aqueous ethanol and then from water (charcoal); m. p. 94.8–95.3° (cor.). Stock  $\beta$ -naphthol was thrice recrystallized (charcoal) from water; m. p. 120–121.2°.

**Acknowledgments.**—The author takes pleasure in thanking the Atomic Energy Commission for the fellowship on which this work was performed. The author is grateful to Dr. C. S. Marvel for valuable advice throughout the course of the work and for providing every possible laboratory facility. Without the aid of Miss Elizabeth Petersen, who determined and helped interpret most of the spectra, and Mrs. Agatha Johnson, who determined some of the spectra, this work would not have been possible. Thanks also are due Dr. E. D. Amstutz for many helpful discussions.

### Summary

#### 1. An improved apparatus for the cryoscopic

(52) Vieth, *Ann.*, **180**, 305 (1876); Stohmann, Kleber and Langbein, *J. prakt. Chem.*, [N. F.] **40**, 341 (1889).

(53) Lauer, *ref.* 51.

determination of molecular weights in naphthalene solution was used to show that chelated disubstituted naphthalenes exhibit the cryoscopic behavior characteristic of chelated benzene derivatives. This method failed to reveal any differences in the strength of chelation among isomeric 1,2-, 2,1- and 3,2-disubstituted naphthalenes.

2. Infrared spectra were used to show that chelation in 1,2- and 2,1-disubstituted naphthalenes is of about equal strength and considerably greater than in the isomeric 2,3-disubstituted naphthalenes. This result was interpreted as evidence for the proposition that the C<sub>1</sub>–C<sub>2</sub> bond of naphthalene has greater than 50% double bond character and that the C<sub>2</sub>–C<sub>3</sub> bond has less than 50% double bond character.

3. Infrared spectra were used to show that chelation in a given *o*-disubstituted benzene has a strength intermediate between that of the analogous 1,2- (or 2,1-) and 2,3-disubstituted naphthalenes. This result was explained as a consequence of the relative degrees of bond fixation in the parent hydrocarbons.

4. The acid dissociation constants of salicylaldehyde and the three *o*-hydroxynaphthaldehydes were correlated with the degree of conjugation between substituents.

5. The utility of a knowledge of bond fixation in correlating the infrared spectra of certain compounds was demonstrated.

URBANA, ILLINOIS

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## Effect of Structure on Reactivity.<sup>1</sup> III. Aminolysis of Esters with Primary Amines<sup>2</sup>

BY EDWARD McC. ARNETT<sup>3</sup>, JOHN G. MILLER AND ALLAN R. DAY

The first investigations in this series<sup>4</sup> dealt with the ammonolysis of esters. In these studies the influence of alkyl and aryl groups present in the esters and the catalytic effects of various solvent media were measured. While detailed investigation of the ammonolysis reaction is being continued, it has been advantageous to extend the scope of these studies by taking up the aminolysis of esters, a reaction whose kinetics have been studied previously by only a few workers.<sup>5</sup>

This investigation has profited from the studies

(1) From a thesis submitted in April, 1949, by E. McC. Arnett in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Presented at the Philadelphia Meeting of the Division of Organic Chemistry, American Chemical Society, April, 1950.

(3) du Pont Fellow, 1948–1949.

(4) (a) Gordon, Miller and Day, *THIS JOURNAL*, **70**, 1946 (1948); (b) Gordon, Miller and Day, *ibid.*, **71**, 1245 (1949); (c) Gordon, Dissertation, University of Pennsylvania, 1948.

(5) Glascoe, Kleinberg and Audieth, *ibid.*, **61**, 2387 (1939); *ibid.*, **63**, 2965 (1941); Grunfeld, *Compt. rend.*, **194**, 893 (1932); Vavon and Bourgeois, *ibid.*, **202**, 1446, 1593 (1936).

of ammonolysis. Thus, for example, from the earlier work in this series it was possible to predict a suitable standard medium and a single ester for comparison of the reactivities of the series of primary amines studied.

The results show clearly the effect of both the basicity of the amines and their bulks and shapes, as well as the catalytic activity of hydroxylated compounds.

### Experimental

The experimental procedure was essentially that used in the earlier investigations.<sup>4</sup> The unreacted amine in any reaction system was determined by titration with half-normal hydrochloric acid, back-titration being carried out with half-normal sodium hydroxide with methyl red as indicator. Addition of ethylene glycol or dioxane to the extent of 50% of the volume of the sample titrated, or addition of sodium chloride to a concentration of 2 molar did not affect the end-point. Hydrolysis of the esters or amides during the titration was considered negligible because no change in the end-point color was observed when several of the systems were allowed to stand for long periods after titration and were later heated to boiling.

Loss of amine or ester by evaporation during the preparation and handling of the mixtures was ruled out by repeated assays.

Errors due to reversibility of aminolysis, loss of available amine through reaction with glycol and other factors have been discussed for the special case of ammonolysis<sup>4c</sup> and these possibilities were ruled out. There is little likelihood that other simple amines would show complexities that were not exhibited by ammonia and the fact that the results in general show closer adherence to a strict second order course and less drift than the ammonolytic reactions support this belief. That we are dealing with simple aminolyses is shown rather conclusively by the fact that the reactions approach very exactly to completion as measured by amine content if allowed to run long enough.

The following reagents were used: ethylene glycol, b. p. 72° at 1 mm.,  $n_D$  1.4319 at 20°; 1,4-dioxane, 101.5° at 760 mm., 1.4224 at 20°; methyl acetate, 57.1° at 760 mm., 1.3610 at 20°; ethyl acetate, 77.0° at 760 mm., 1.3728 at 20°; methylamine, -6.7° at 758 mm.; ethylamine, 16.6° at 760 mm.; *n*-propylamine, 49-50° at 761 mm., 1.3901 at 16.6°; isopropylamine, 31.7° at 760 mm., 1.3742 at 20°; *n*-butylamine, 77.8° at 760 mm., 1.4008 at 20°; isobutylamine, 67° at 760 mm., 1.3988 at 17°; *s*-butylamine, 66° at 772 mm., 1.3950 at 16.7°; *t*-butylamine, 45.2° at 760 mm., 1.3794 at 18°; *n*-amylamine, 103° at 760 mm., 1.4118 at 20°;  $\beta$ -phenylethylamine, 56° at 1 mm., 1.5315 at 25°; ethylenediamine, 117.2° at 760 mm., 1.4540 at 26.1°; ethanolamine, 171° at 757 mm., 1.4539 at 20°; allylamine, 56.6° at 756 mm., 1.4194 at 21.8°; benzylamine, 184.5° at 760 mm., 1.5441 at 19.5°.

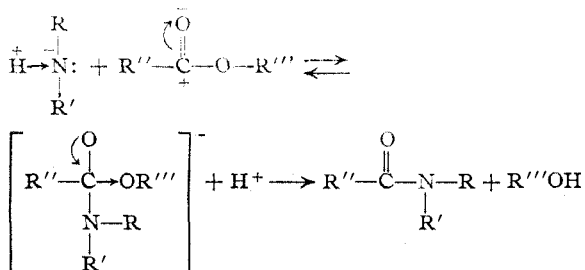
The amines were commercially available with the exception of *t*-butylamine which was prepared by the method of Pearson, Baxter and Carter.<sup>6</sup> Except for methylamine, ethylamine and ammonia, these amines were dried over potassium hydroxide pellets and distilled through an all-glass system. Methylamine was generated by dropping water onto a mixture of sodium hydroxide pellets and methyl ammonium chloride. The gas was dried over potassium hydroxide pellets and finally liquefied in a trap immersed in cellosolve and Dry Ice. Both methylamine and ethylamine were measured out as liquids, using a chilled pipet or buret.

1,4-Dioxane was purified by prolonged refluxing over sodium followed by distillation. Ethylene glycol and the esters used were dried over anhydrous potassium carbonate and distilled under vacuum when necessary to prevent decomposition.

Ammonia was measured from a tank using a steel needle valve. Isopropylamine was supplied through the kindness of the Shell Chemical Corporation, Inc. Sharples Chemicals, Inc., generously contributed the *n*-amylamine.

## Results and Discussion

The measurements can best be discussed with reference to the scheme showing the mechanism of the reaction



This scheme shows aminolysis in its most general terms; with the R groups taken to represent aryl

(6) Pearson, Baxter and Carter, *THIS JOURNAL*, **70**, 2290 (1948).

or alkyl groups and also hydrogen, it includes all esters from formates to the most complex types and all primary and secondary amines as well as ammonia. Since no water is involved it should be possible to carry out any of the reactions included in the scheme under completely anhydrous conditions. Our results in anhydrous dioxane solution show that this is true and that the aminolyses are catalyzed by hydroxylated substances similar to the ammonolysis reactions. In the absence of a catalyst, *n*-butylamine reacted very slowly with ethyl acetate. It took well over 1000 hours to obtain 10% aminolysis at 25°, three separate experiments giving an average bimolecular rate constant of approximately  $4 \times 10^{-5}$  (l. mole<sup>-1</sup> hour<sup>-1</sup>) under these conditions. With ethyl acetate, *n*-butylamine gave average rate constants of  $4.97 (\pm 0.07) \times 10^{-4}$ ,  $3.95 (\pm 0.28) \times 10^{-3}$ , and  $4.28 (\pm 0.13) \times 10^{-3}$  at 25° in dioxane solution, in the presence of 5 and 15 moles of water per liter and 5 moles of ethylene glycol per liter, respectively.

It may be anticipated from the mechanism shown for the reaction that three factors are of paramount importance in determining the rate. First, the basicity of the amine, *i. e.*, the electron density on the nitrogen, should affect the ease of its attachment to the electrophilic carbonyl carbon atom. We should expect from this that the greater the  $pK_a$  value of the amine, the greater its velocity constant in aminolysis. Second, steric requirements are an obvious factor in the orientation and attachment of the amine to the ester carbonyl carbon atom. Third, the presence of a catalyst is required in view of the low rates otherwise obtained in anhydrous media.

The intermediate complex formed in the initial attachment of amine to ester may either revert to amine and ester, or, if a proton is readily lost from the nitrogen at some stage of the attack, proceed to give amide and alcohol. In the absence of an ionizing medium the former will occur, except in the rare case where another amine molecule might remove the proton. This explains the very low rate of aminolysis of most esters in the absence of water or other hydroxylated compounds, especially the 1,2-glycols, such as ethylene glycol, whose structures are favorable for forming hydrogen bridges with the amino group to aid in the ionization of a proton.<sup>4</sup>

In order to determine the importance of these factors, a series of related primary amines was studied using the same ester, methyl acetate, and the same catalytic medium throughout. The results are shown in Table I which lists the average bimolecular velocity constants, expressed in liter mole<sup>-1</sup> hour<sup>-1</sup>, determined at 25 ± 0.02° in the presence of 5 moles per liter of ethylene glycol as catalyst, dioxane being the solvent diluent. The ester concentration was 1 molar throughout and the amine concentration always approximately 2 molar. The constants showed no appreciable

drift and the standard deviations are listed in this table. In the case of ethylenediamine, *n*-butylamine and *n*-propylamine the values are those of the grand mean and its standard deviation for two or more runs.

TABLE I

BIMOLECULAR VELOCITY CONSTANTS FOR THE AMINOLYSIS OF METHYL ACETATE BY PRIMARY AMINES AND AMMONIA AT 25°

Amine	Av. velocity constant	Standard deviation
Methyl-	$8.53 \times 10^{-2}$	$\pm 0.30 \times 10^{-2}$
Ethylenedi-	$2.38 \times 10^{-2}$	$\pm .04 \times 10^{-2}$
Monoethanol-	$1.16 \times 10^{-2}$	$\pm .03 \times 10^{-2}$
Ethyl-	$1.11 \times 10^{-2}$	$\pm .01 \times 10^{-2}$
<i>n</i> -Butyl-	$1.06 \times 10^{-2}$	$\pm .01 \times 10^{-2}$
<i>n</i> -Amyl-	$9.87 \times 10^{-3}$	$\pm .02 \times 10^{-3}$
<i>n</i> -Propyl-	$8.79 \times 10^{-3}$	$\pm .10 \times 10^{-3}$
Isobutyl-	$4.35 \times 10^{-3}$	$\pm .09 \times 10^{-3}$
$\beta$ -Phenylethyl-	$3.20 \times 10^{-3}$	$\pm .09 \times 10^{-3}$
Allyl-	$2.06 \times 10^{-3}$	$\pm .11 \times 10^{-3}$
Benzyl-	$1.65 \times 10^{-3}$	$\pm .02 \times 10^{-3}$
Ammonia	$1.33 \times 10^{-3}$	$\pm .13 \times 10^{-3}$
Isopropyl-	$4.22 \times 10^{-4}$	$\pm .21 \times 10^{-4}$
<i>s</i> -Butyl-	$2.27 \times 10^{-4}$	$\pm .18 \times 10^{-4}$
<i>t</i> -Butyl-	Immeasurably slow	

Table II gives the relative reaction rates calculated from Table I, and also lists the aqueous  $pK_a$  values of the amines. The values in this table

TABLE II

RELATIVE REACTION RATES FOR THE AMINOLYSIS OF METHYL ACETATE BY PRIMARY AMINES AND AMMONIA AT 25° AND THE  $pK_a$  VALUES FOR THE AMINES

Amine	Relative $k$ , %	$pK_a$
Methylamine	100.00	10.64
Ethylenediamine	27.9	10.06 <sup>a</sup>
Monoethanolamine	13.6	9.44
Ethylamine	13.0	10.67
<i>n</i> -Butylamine	12.4	10.61
<i>n</i> -Amylamine	11.6	10.70
<i>n</i> -Propylamine	10.3	10.58
Isobutylamine	5.10	10.42
$\beta$ -Phenylethylamine	3.75	9.83
Allylamine	2.42	
Benzylamine	1.93	9.34
Ammonia	1.56	9.27
Isopropylamine	0.495	10.63
<i>s</i> -Butylamine	0.267	10.56
<i>t</i> -Butylamine	Immeasurably slow	10.45

<sup>a</sup> Calculated from the work of Britton and Williams (*J. Chem. Soc.*, 796 (1935)). The other values are quoted from the results of Hall and Sprinkle (*THIS JOURNAL*, **54**, 3469 (1932)).

show that any discussion based on the  $pK_a$  values must also consider the steric effects. This is not surprising in view of such studies as those of Brown and his co-workers<sup>7</sup> which have shown definitely that interpretations based on the use of dissociation constant data must include careful

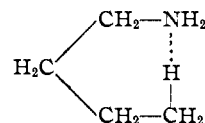
(7) See for example, Brown and Taylor, *THIS JOURNAL*, **66**, 846 (1944); **69**, 1332 (1947).

consideration of the steric requirements of the amine and the acid with which it is to react.

Using the same ester, as we descend the series of amines in Table II, not only is the charge on the amine nitrogen being slightly increased by addition of electron releasing groups but these same groups are becoming increasingly bulky. Among those amines of very similar  $pK_a$  values, the least bulky amine will have the greatest rate of reaction, but if the basicity is low even smallness will not compensate for the lower electrostatic attraction between the nitrogen of the amine and the ester carbonyl carbon.

It should be noted that methyl acetate is an ideal choice of ester for this study. Its simplicity of structure minimizes its contribution to the steric effects and, in addition, it shows only 1% hydrolysis in 700 hours in the titrimetric procedure followed in these studies.<sup>4c</sup>

Methylamine is the most active of the amines listed, which is in accord with its relatively high basicity and molecular size. The velocity constant for ethylenediamine is approximately twice that of ethylamine and reflects the condition that statistically the probability for it to form an amide is twice as great. The unexpectedly high rate for ethanolamine, considering its low basicity, must be the result of the autocatalytic effect produced by adding two more moles per liter of hydroxyl groups in the form of the hydroxy amine. Ethylamine offers the first evidence of the steric factor overcoming an increase in basicity. The appearance of *n*-butylamine as the next amine in the series appeared unusual at first.<sup>8</sup> It is believed that the activity of this amine can be explained in terms of a hydrogen bond between the delta carbon atom and the amine nitrogen.



Such a bond would reduce the negative charge on the nitrogen atom, but at the same time would be expected to diminish steric hindrance and thus overcome the effect of reduced basicity.

Most of the remaining amines in the series fall in a logical order if both base strengths and steric effects are considered. The position of ammonia may be somewhat surprising. This position, however, follows consistently from what has been said above. The low reactivity of ammonia can be traced directly to the relatively small negative charge on its nitrogen atom and shows why the basicity factor has been given a position of primary importance in the mechanism. Since the nitrogen in ammonia is completely unshielded, as compared to the other amines, its slow reaction

(8) Inversion of values for *n*-propyl, *n*-butyl and *n*-amyl derivatives has been observed before. Dippy (*Chem. Revs.*, **25**, 151 (1939)) explained the fact that *n*-butyric acid is a stronger acid than propionic acid by assuming hydrogen bonding between the gamma methylene group and the carbonyl oxygen atom.

rate can only be due to a much smaller attraction for electrophilic centers.

### Summary

1. The rates of reaction of a series of primary aliphatic amines with methyl acetate, in the presence of ethylene glycol, have been determined.

2. The order of activity found for the series is: methylamine > ethylenediamine > ethanolamine > ethylamine > *n*-butylamine > *n*-amylamine > *n*-propylamine > isobutylamine >  $\beta$ -phenylethylamine > allylamine > benzylamine > ammonia > isopropylamine > *s*-butylamine > *t*-butylamine.

3. These results are discussed from the standpoints of the basicities and steric bulks of the amines.

PHILADELPHIA, PA. RECEIVED FEBRUARY 25, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TOLEDO]

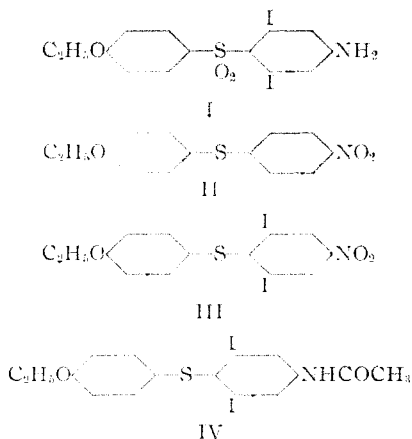
## Oxidation of a Di-*o*-substituted Diphenyl Sulfide

BY PAUL BLOCK, JR., AND JEAN L. BALMAT<sup>1</sup>

In an attempt to prepare a thyroxine-like molecule in which the oxygen atom linking the two benzene rings of thyroxine would be replaced by the sulfone grouping, the substituted 2,6-diiododiphenyl sulfone (I) has been synthesized, and the effect of iodine atoms ortho to the sulfide linkage on the oxidation of sulfide to sulfoxide and sulfone has been investigated. The hope of converting such an oxidized molecule to a thyroxine analog by standard procedures<sup>2</sup> has not yet been realized.

For comparison of their behavior toward oxidizing agents, and as an aid in proof of structure, the uniodinated 4'-ethoxy-4-nitrodiphenyl sulfide<sup>3</sup> (II) and its 2-monoiodo derivative (X) were oxidized. The uniodinated compound readily yielded both a sulfoxide and a sulfone under the usual conditions for such oxidations. One molar-equivalent of hy-

drogen peroxide in acetic acid at 25° caused the sulfoxide to form, whereas excess hydrogen peroxide at 25° or at 90° gave the sulfone. While no attempt was made to obtain the sulfoxide of the monoiodinated diphenyl sulfide (X), this compound also readily yielded the sulfone.



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(1) From a thesis by J. L. Balmat submitted in partial fulfillment of the requirements for the degree of Master of Science, 1948.

(2) C. R. Harrington, *Biochem. J.*, **21**, 169 (1927).

(3) G. H. Law and T. B. Johnson, *This Journal*, **52**, 3625 (1930).

drogen peroxide in acetic acid at 25° caused the sulfoxide to form, whereas excess hydrogen peroxide at 25° or at 90° gave the sulfone. While no attempt was made to obtain the sulfoxide of the monoiodinated diphenyl sulfide (X), this compound also readily yielded the sulfone.

Oxidation of the sulfide (III) to the sulfone (XIII) in one step could be effected by potassium permanganate in boiling acetic acid, but except in very dilute solution the oxidation was accompanied by formation of more or less of a partially deiodinated substance. This deiodination also occurred when the sulfoxide was prepared (under the optimum conditions for its formation) in hot acetic acid with hydrogen peroxide, and the reaction subsequently cooled and treated with potassium permanganate.

Oxidation of the compound in which the nitro group had been reduced and acetylated, 4'-ethoxy-2,6-diiodo-4-acetamidodiphenyl sulfide (IV), also did not proceed at 25°, and, as in the case of the nitro compound (III), could not be carried beyond the sulfoxide stage by hydrogen peroxide in acetic acid at higher temperatures. However, in the case of (IV), no conditions were found which gave rise to the desired sulfone, although a partially deiodinated product was occasionally isolated in small yield. This sulfone could be synthesized, however, by acetylation of the amine (I).

(4) S. L. Bass and T. B. Johnson, *ibid.*, **52**, 1146 (1930).