

pure acid and freshly distilled triethylamine was cooled to 0° in an ice bath. With stirring, an equivalent amount of ethyl chlorocarbonate was slowly added so that the temperature remained near 0°. The mixture was stirred an additional 1.5 hr. during which time it slowly warmed to room temperature. The amine salt was filtered (nearly quantitative yield in every case) and washed with ether. The combined filtrate was washed with sodium bicarbonate solution and water, and after drying over magnesium sulfate was evaporated under vacuum at room temperature. The crystalline mixed anhydrides were recrystallized for analysis from ether-petroleum ether or benzene-petroleum ether.

*Methyl hydrogen decatetraene-dioate* was prepared<sup>12</sup> by the action of methanolic sodium hydroxide on fumagillin and melted at 209–210°; the reported<sup>12</sup> value is 217–218°.

*Methyl hydrogen decatetraene-dioic acid chloride and amide.*

A mixture of 0.50 g. of methyl hydrogen decatetraenedioate, 0.6 g. of phosphorus pentachloride, and 10 cc. of petroleum ether was refluxed for 1.75 hr. The solvent and phosphorus oxychloride were removed under reduced pressure, yielding 0.28 g. of product, m.p. 151–154° with decomposition.

*Anal.* Calcd. for C<sub>11</sub>H<sub>11</sub>ClO<sub>3</sub>: C, 58.28; H, 4.90. Found: C, 58.32; H, 5.05.

Treatment of a chloroform solution of the ester acid chloride above with ammonia gas gave a white precipitate of the corresponding *amide*, m.p. 209–210° after recrystallization from aqueous methanol. This product gave no depression on mixed melting point with the amide prepared by action of ammonia gas on the mixed anhydride VI.

*Anal.* Calcd. for C<sub>11</sub>H<sub>13</sub>NO<sub>3</sub>: C, 63.75; H, 6.32. Found: C, 63.33; H, 6.50.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

## Action of Secondary Amines on Mixed Carboxylic-Carbonic Anhydrides; the Factors Favoring Urethan Formation Instead of Amide Formation<sup>1</sup>

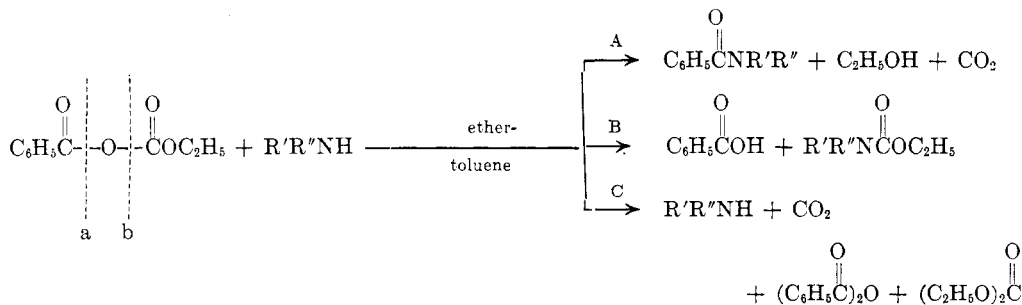
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The action of a series of ten secondary amines on benzoic-carbonic anhydride leads in each case to urethan formation in addition to amide formation, with urethan predominating in most cases. Increasing the steric hindrance around the amino nitrogen increases the ratio of urethan to amide. A series of mixed anhydrides in which the carboxylic acid component was varied was treated with *N*-methylaniline. Pivalic acid and aromatic acids gave more urethan than amide; other acids, without alkyl or aryl substitution on the  $\alpha$ -carbon, gave more amide than urethan. The results are discussed in the light of other work on reactions of unsymmetrical anhydrides.

It has been shown that mixed carboxylic-carbonic anhydrides are very useful for acylation of primary amines to form amides,<sup>1</sup> and for formation of phthalimides from phthalamic acids,<sup>3</sup> as well as for various acylations on carbon.<sup>1,4</sup> We were therefore surprised to find that an attempt to prepare the bisamide from *N*-methylaniline and a phthalic acid derivative gave a very unsatisfactory result. A study of the action of *N*-methylaniline on benzoic-carbonic anhydride showed that the main product was *N*-methyl-*N*-phenylcarbamate, instead of the

expected *N*-methylanilide. The action of a series of representative secondary amines on this mixed anhydride was therefore studied, as well as the action of *N*-methylaniline on a series of mixed anhydrides in which the carboxylic acid component was varied. The results show that secondary amines usually react with mixed carbonic anhydrides to form a mixture of urethan and amide; the former may predominate, depending on the compounds involved. These results may be useful in considering the mixed carbonic anhydrides for synthetic operations.



(1) Previous papers in this field: (a) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957); (b) D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958). Reference 1b contains adequate references to the earlier literature.

(2) Monsanto Fellow, 1956–1957.

(3) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).





(4) J. A. Price and D. S. Tarbell, *Org. Syntheses*, **37**, 20 (1957).

The possible reactions between a secondary amine and benzoic-carbonic anhydride are indicated above.<sup>5</sup>

Path A involves attack of the amine nitrogen on the carboxylic carbonyl, with splitting at "a" to give the amide. In path B, the carbonate carbonyl is attacked by the amine, and the bond at "b" is broken, resulting in urethan formation and regeneration of benzoic acid. Path C corresponds to no reaction with the amine, but instead, disproportionation of the mixed anhydride leads to benzoic anhydride, diethyl carbonate, and carbon dioxide.

A series of secondary amines was allowed to react with the anhydride under standard conditions, the products were separated and purified by ordinary methods, and percentage yields were determined. The results are shown in Table I. All of the products obtained corresponded to those expected from paths A, B, and C.

TABLE I  
REACTIONS OF SECONDARY AMINES WITH BENZOIC-CARBONIC ANHYDRIDE

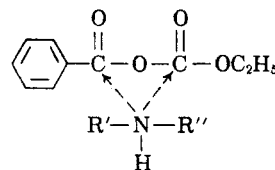
Amine	Products				%A/ %B
	% A (Amide)	% B (Ure- than) (Acid)	% C (Unre- acted amine)		
(CH <sub>3</sub> ) <sub>2</sub> NH	28 <sup>a</sup>	19 <sup>a</sup>	43	— <sup>b</sup>	Ca. 1.0
(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH	29	49	58	—	0.59
(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> NH	4	44	40 <sup>c</sup>	40 <sup>c</sup>	0.09
 NH	50	34	39	—	1.5
 NH CH <sub>3</sub>	15	67	67	10	0.22
 NH CH <sub>3</sub>	16	66	68	4	0.24
 NH CH <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	9	63	54	24	0.14
C <sub>2</sub> H <sub>5</sub> OOCCH <sub>2</sub> NH   CH <sub>3</sub>	9.5	72	80	—	0.13
(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> NH	4	0 (1)	0 (1)	86	4

<sup>a</sup> These yields are lower than the actual amount of material generated in the reaction. Losses were due to the relatively high volatility and water solubility of these compounds. <sup>b</sup> The dash (—) signifies that the yield was small and could not be conveniently determined. <sup>c</sup> Isolated as diisopropylamine benzoate.

A brief inspection of the results in Table I indicates that the reaction of secondary amines with benzoic-carbonic anhydride is not generally a good method for the preparation of amides. The particularly low yield of the amide derived from ethyl sarcosinate would perhaps indicate that the procedure is also inapplicable to the preparation of

(5) W. H. Davies, *J. Chem. Soc.*, 1357 (1951), observed formation of a carbamate from aniline and the anhydride of *O*-carboxysalicylic acid.

*N*-substituted peptide linkages, although mixed anhydrides other than benzoic-carbonic anhydride may give better yields. Nevertheless, most amino acids have bulky residues on the  $\alpha$ -carbon atom and, since such substitution seems to hinder amide formation markedly, the general usefulness of the method is questionable. By analogy with the mechanisms proposed for nucleophilic attack on carboxylic anhydrides,<sup>6,7</sup> it is assumed that there is involved in these reactions a rate-determining nucleophilic attack of the amine nitrogen on one of the carbonyl carbons of the mixed carbonic anhy-



dride. Competition for the amine nitrogen is thereby established between the two carbonyl carbon atoms. Since paths A and B are not reversible and the products of each are not interconvertible, the relative amounts of products formed from the two cannot be thermodynamically controlled but rather must be kinetically controlled. Thus, the amide to urethan ratio (A/B), as given in Table I, is a measure of the relative rates of attack of the amine on one or the other of the two carbonyl carbon atoms.

Table I shows a sharp decrease in the A/B ratios as methyl groups are added to the  $\alpha$ -carbons of the amines in the series dimethyl-, diethyl-, diisopropyl-amine. A similar decrease is observed in the piperidine-2-methylpiperidine pair, and the *N*-methylaniline - *N*-ethyl-2-methylaniline pair. The rate of reaction according to path A is being diminished more than that according to path B. This is most plausibly attributed to the steric effect of increasing substitution around the nitrogen, and not to changes in the intrinsic nucleophilicity of the nitrogen. Path B would be expected to be less sensitive to changes in steric requirements than path A. It is known that increasing substitution in alcohols diminishes the rate of acylation by acid chlorides.<sup>8</sup>

Furthermore, Hall has recently shown<sup>9</sup> the rate of acylation of amines by ethyl chlorocarbonate to be very sensitive to increasing substitution around the amino nitrogen; the relative rates of reaction of piperidine, 2-methylpiperidine, *s*-butyl-amine and *t*-butylamine with this acylating agent are approximately 10<sup>4</sup>, 10<sup>2</sup>, 10, and 1. It has been

(6) A. R. Emery and V. Gold, *J. Chem. Soc.*, 1456 (1950).

(7) D. B. Denney and M. A. Greenbaum, *J. Am. Chem. Soc.*, 79, 3701 (1957).

(8) J. F. Norris and A. A. Ashdown, *J. Am. Chem. Soc.*, 47, 837 (1925); J. F. Norris and F. Cortese, *J. Am. Chem. Soc.*, 49, 2640 (1927).

(9) H. K. Hall, Jr., *J. Am. Chem. Soc.*, 79, 5439 (1957).

shown that the catalytic effect of tertiary amines on the hydrolysis of acetic anhydride is diminished by increasing substitution on the  $\alpha$ -carbon of the amines.<sup>10</sup>

The behavior of diphenylamine does not follow the above pattern; it reacts only slightly, but gives exclusively amide and no urethan. This is possibly connected with its low basicity.

In order to gain some insight into the effect of changes in the carboxylic portion of the mixed anhydride in these reactions, *N*-methylaniline was treated with a series of carboxylic-carbonic anhydrides in which the carboxylic group was varied in size and conjugation. The same standard conditions and methods of product separation were employed as in the study just described, and the results are given in Table II.

TABLE II  
REACTIONS OF *N*-METHYLANILINE WITH CARBOXYLIC-CARBONIC ANHYDRIDES

$$\text{RCOOCOOC}_2\text{H}_5 + \text{C}_6\text{H}_5\text{N}-\underset{\text{CH}_3}{\text{H}} \xrightarrow{\text{ether}} \text{Products}$$

R—	Products				
	% A (Amide)	(Ure- than)	% B (Acid)	(Unre- acted amine)	%A/ %B
<i>iso</i> -C <sub>4</sub> H <sub>9</sub> —	64	0 (<1)	0 (<1)	12	>64
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> —	75	8.4	15	5	8.9
C <sub>6</sub> H <sub>5</sub> CH=CH—	63	17	20	5	3.7
CH <sub>3</sub> (CH=CH) <sub>2</sub> —	49	20	29	4	2.5
<i>tert</i> -C <sub>4</sub> H <sub>9</sub>	0 (<1)	32	1 <sup>b</sup>	65	<0.03
C <sub>6</sub> H <sub>5</sub> —	16	66	68	5	0.24
<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	29	39	38	11	0.74
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> —	8 <sup>a</sup>	47	58	41	0.17

<sup>a</sup> Not isolated. <sup>b</sup> Generated pivalic acid reacted with mixed anhydride to give 88% of pivalic anhydride.

It is immediately evident that good yields of *N*-methylanilides can indeed be obtained with certain carboxylic-carbonic anhydrides. Others, however, such as pivalic- and benzoic-carbonic anhydrides give mainly the urethan. In the first four cases listed the degree of extended conjugation is varied widely and yet the yields of amides change very slightly. On the other hand, a change in the extent of  $\alpha$ -substitution, such as that in going from isovaleric- to pivalic-carbonic anhydride, effects an absolute reversal of reaction course. Seemingly, then, the degree of conjugated unsaturation is of relatively little importance as compared with the degree of substitution of the  $\alpha$ -carbon atom in the carboxylate grouping. On the basis of the results given in Tables I and II it can thus be concluded that this method is most probably suitable for the preparation of tertiary amides if the secondary amine does not contain a high degree of steric bulk

about the nitrogen atom and if the  $\alpha$ -carbon of the carboxylate grouping is not highly branched.

A comparison of the results with hydrocinnamic, cinnamic, and sorbic anhydrides shows that conjugation decreases the reactivity of the carbonyl carbon, relative to the carbonate carbonyl. This is in agreement with observations<sup>11</sup> which show that  $\alpha,\beta$ -unsaturated esters are hydrolyzed by base at a somewhat slower rate than the corresponding saturated esters.

The reactivity of the carboxyl carbonyl in the benzoic anhydride is increased by the presence of the electron-withdrawing *p*-nitro group, and is decreased by the electron-donating *p*-methoxyl group. These effects on the reactivity are similar to those shown by electron-donating and -withdrawing groups on the rate of alkaline hydrolysis of esters of substituted benzoic acids,<sup>12</sup> and may be taken as support for the assumption that in the present reactions, as in the alkaline hydrolysis of esters, the rate-determining step is the attack of the nucleophile on the carbonyl carbon atom.

It is apparent that in general the rates of reaction by paths A and B are of the same order of magnitude; path A can be slowed down markedly by changes in both the environment of the carboxyl carbonyl group and the nature of the attacking nucleophile. The retardation is doubtless due mainly to steric effects.

#### EXPERIMENTAL<sup>13</sup>

*Reactions of secondary amines with benzoic-carbonic anhydride.* A solution of 12.2 g. (0.1 mole) of benzoic acid and 10.1 g. (0.1 mole) of dry triethylamine in 150 cc. of dry toluene and 50 cc. of dry ether was cooled to  $-5$  to  $0^\circ$  in an ice salt bath. With stirring, 10.8 g. (0.1 mole) of ethyl chlorocarbonate was added from a Dry Ice-cooled addition funnel at such a rate that the temperature did not exceed  $0^\circ$ . The mixture was stirred for 0.5 hr. at this temperature. The secondary amine (0.1 mole) was then added from the Dry Ice-cooled addition funnel (solid amines were dissolved in ether) and the mixture stirred another 0.5 hr. at  $0^\circ$ . After warming to room temperature overnight, the triethylamine hydrochloride was filtered, washed several times with ether and dried. An essentially quantitative yield (95–99%) was obtained in each case.

The filtrate was in general washed with dilute hydrochloric acid, then with saturated sodium bicarbonate solution, and finally with water. Acidification of the bicarbonate solution yielded the benzoic acid, which was collected and weighed. The organic solution was dried and distilled under reduced pressure. The benzamides and carbamates obtained in this way, which were known compounds, were found to agree satisfactorily in physical properties with those reported in the literature. The infrared spectra were determined in some cases, and the carbonyl frequencies agreed with the expected values. The reactions yielding new compounds are described below.

(11) P. Heinänen, *Ann. Acad. Sci. Fennicae, Ser. A, II*, No. 9 (1943); *Chem. Abstr.*, **40**, 3672 (1946).

(12) C. K. Ingold and W. S. Nathan, *J. Chem. Soc.*, **222** (1936); E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, **1801** (1938).

(13) See footnote 14 of reference 1b.

(10) V. Gold and E. G. Jefferson, *J. Chem. Soc.*, **1409** (1953).

*Diisopropylamine.* The precipitated triethylamine hydrochloride was filtered at 0°, after which the diisopropylamine was added to the filtrate and the reaction mixture stirred 0.5 hr. at the low temperature. After warming to room temperature overnight, the solution had deposited 8.9 g. (40%) of diisopropylamine benzoate, m.p. 132–154°. (Recrystallization of this material from ethanol-ether did not change the melting point behavior, which was also exhibited by an authentic sample prepared by addition of diisopropylamine to benzoic acid in ether.) Washing the reaction filtrate with dilute acid and base gave no isolable unreacted amine or regenerated benzoic acid. Fractional distillation of the neutral material yielded 7.65 g. (44%) of ethyl *N,N*-diisopropylcarbamate, b.p. 83–87.5°/20 mm.,  $n_D^{20}$  1.4294.

*Anal.* Calcd. for  $C_9H_{19}NO_2$ : C, 62.39; H, 11.05. Found: C, 62.72; H, 11.02.

Further distillation produced 1.0 g. of *N,N*-diisopropylbenzamide, b.p. 164–174°/20 mm., which partially solidified on standing. After several recrystallizations from ligroin it had m.p. 69–71° (0.8 g., 4%).

*Anal.* Calcd. for  $C_{13}H_{19}NO$ : C, 76.05; H, 9.33. Found: C, 76.29; H, 9.63.

Further distillation afforded 4.1 g. (36%) of benzoic anhydride.

*2-Methylpiperidine.* Extraction of the filtered reaction solution with dilute hydrochloric acid gave about 1 g. (10%) of unreacted 2-methylpiperidine. Extraction with sodium bicarbonate solution yielded 8.15 g. (67%) of regenerated benzoic acid, m.p. 121–123°. Drying and removal of the solvent from the remaining neutral solution afforded a colorless liquid, which upon distillation produced 11.5 g. (67%) of the colorless liquid *N*-carbethoxy-2-methylpiperidine, b.p. 53–57°/0.3 mm.,  $n_D^{25}$  1.4561 to 1.4579.

*Anal.* Calcd. for  $C_9H_{17}NO_2$ : C, 63.13; H, 10.00. Found: C, 62.45; H, 9.83.

Further distillation of the residue gave rise to 3.7 g. of a viscous liquid, b.p. 127–134°/0.3 mm., which did not crystallize. Chromatography on acid-washed alumina and elution with 50% ether-ligroin gave a total of 3.0 g. (15%) of colorless prisms of *N*-benzoyl-2-methylpiperidine, m.p. 45.5–48°. <sup>14</sup>

*Ethyl sarcosinate.* Washing of the filtered reaction solution with dilute hydrochloric acid yielded only a trace (1%) of unreacted amine. Sodium bicarbonate extraction gave 6.5 g. (80% from 0.067 mole of reactants) of benzoic acid. Fractionation of the dried, neutral solution afforded 9.1 g. (72%) of product, b.p. 118–122° (20 mm.),  $n_D^{27}$  1.4290 to 1.4295.

(14) H. Bunzel, *Ber.*, 22, 1054 (1889), reports a m.p. 44–45°.

*Anal.* Calcd. for  $C_8H_{15}NO_4$ : C, 50.78; H, 7.99. Found: C, 51.01; H, 8.47.

The residue of the above distillation was redistilled at a lower pressure to give 1.4 g. (9.5%) of ethyl *N*-benzoylsarcosinate, as a viscous oil, b.p. 130–137° (0.5 mm.) which slowly crystallized on standing (m.p. 37.5–40.5°).

*Anal.* Calcd. for  $C_{12}H_{15}NO_3$ : C, 65.14; H, 6.83. Found: C, 64.88; H, 6.94.

*Reactions of N-methylaniline with carboxylic-carbonic anhydrides.* A solution of 0.1 mole of the pure acid and 10.1 g. (0.1 mole) of freshly distilled triethylamine in 200–300 cc. of dry ether or toluene was cooled to –5 to 0° in an ice salt bath. To this stirred solution was added 10.8 g. (0.1 mole) of ethyl chlorocarbonate from an addition tube cooled with Dry Ice. The mixture was stirred 0.5 hr. after the addition was complete. Freshly distilled *N*-methylaniline (10.7 g., 0.1 mole) was then added from the cooled addition tube, and after another 0.5 hr. stirring at 0°, the mixture was allowed to warm to room temperature overnight. The precipitated triethylamine hydrochloride was filtered, washed, and dried, and weighed 12.5–13.5 g. (91–97%). The filtrate was washed three times with dilute hydrochloric acid, five times with saturated sodium bicarbonate solution and once with water. Addition of sodium hydroxide to the acid washes precipitated the unreacted amine. Acidification of the basic washes yielded the regenerated acids which were filtered and dried in the cases of the solid acids or extracted with ether in the cases of the liquid acids. Their identification was established by melting points or infrared spectra. The neutral solution was dried, and after removal of the solvent, was in most cases fractionally distilled. The products formed, the amides, ethyl *N*-methyl-*N*-phenylcarbamate and the symmetrical acid anhydrides, if present, were identified by their boiling point, refractive index, or melting point, and by their infrared spectra. In order to save space the details of separation and identification are omitted.

*Sorbic-carbonic anhydride.* Upon standing a few minutes, the neutral yellow oil as above, (20.5 g.) deposited 7.3 g. of colorless needles, which were recrystallized from ligroin, m.p. 87.7–88.7°. Cooling of the mother liquors in ligroin gave another 2.6 g. (total yield, 49%). The analytical sample was recrystallized from hexane and had m.p. 87–88°.

*Anal.* Calcd. for  $C_{13}H_{15}NO$ : C, 77.58; H, 7.51. Found: C, 77.54; H, 7.76.

Distillation of the mother liquors yielded 3.5 g. (20%) of ethyl *N*-methyl-*N*-phenylcarbamate, b.p. 136–139° (20 mm.),  $n_D^{20}$  1.5125 to 1.5143.

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