[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

BEHAVIOR OF SOME CARBAMIC ACID DERIVATIVES OF 2-AMINOPHENOL

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By use of substituted carbamyl radicals, Raiford and Alexander (1) introduced another type of acyl group into the study of the migration of acyl radicals from oxygen to nitrogen in 2-aminophenols. A great quantity of previous work had dealt with radicals of the carbonyl (R—C(=O)—), carboalkoxy (R—O—C(=O)—), and sulfonyl (R—S(=O)(=O)—) types.

Raiford and Alexander showed that when methylphenylcarbamyl chloride was brought into reaction with 2-aminophenol in the presence of dimethylaniline, 2-methylphenylcarbamylaminophenol was obtained, but when pyridine was used as hydrogen chloride acceptor, 2-aminophenyl methylphenylcarbamate was isolated in addition to the phenol. They also showed that reduction of 2-nitrophenyl methylphenylcarbamate, as is also the case with 2-nitrophenyl sulfonates (2), did not result in migration of the acyl from oxygen to nitrogen. This is contrary to the result usually obtained when 2-nitrophenyl esters (3) of the R—C(=O)— and R—O—C(=O)— types are reduced. These in general rearrange to the corresponding acylaminophenol. Occasionally benzoxazolone formation has been noted (4).

The present study has extended Raiford and Alexander's work along similar lines using the ethylphenylcarbamyl radical. The reaction of ethylphenylcarbamyl chloride with 2-aminophenol in pyridine gave results similar to those with methylphenylcarbamyl chloride, and similarily no migration was found on reduction of 2-nitrophenyl ethylphenylcarbamate. The course of these reactions with proof of structure of each product is shown in Diagram 1.

Raiford and Alexander further studied the mixed diacyl derivatives of 2-aminophenol in which one of the acyls was always diphenylcarbamyl and the other acetyl or benzoyl. Both radicals were introduced in both possible ways, and in all cases two isomeric diacyl derivatives were obtained, showing no rearrangement on acylation. On hydrolysis each isomer of a given pair lost acetyl or benzoyl, and the corresponding carbamylaminophenol was formed, showing that migration of the diphenylcarbamyl radical must have occurred in one case during the hydrolysis.

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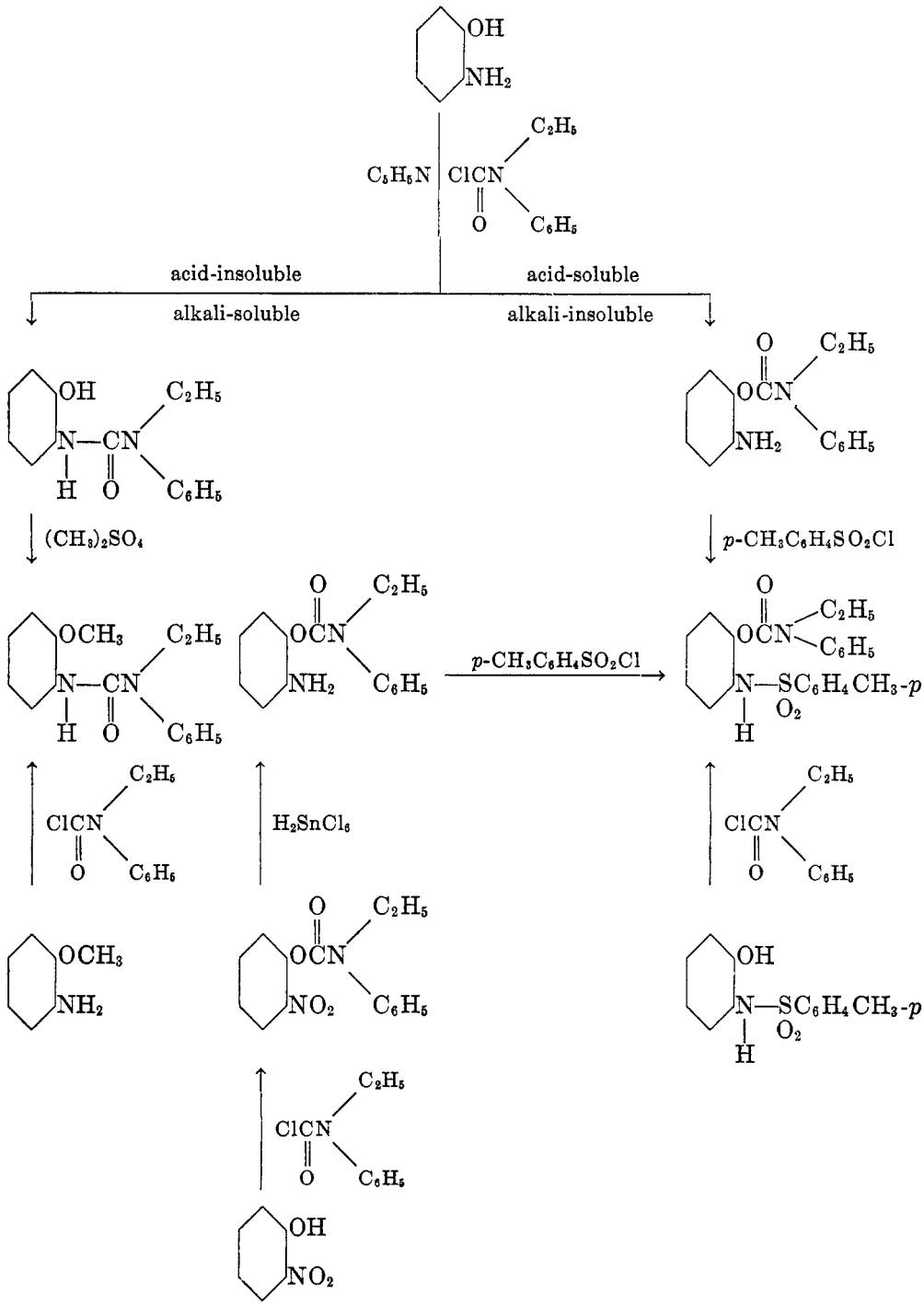
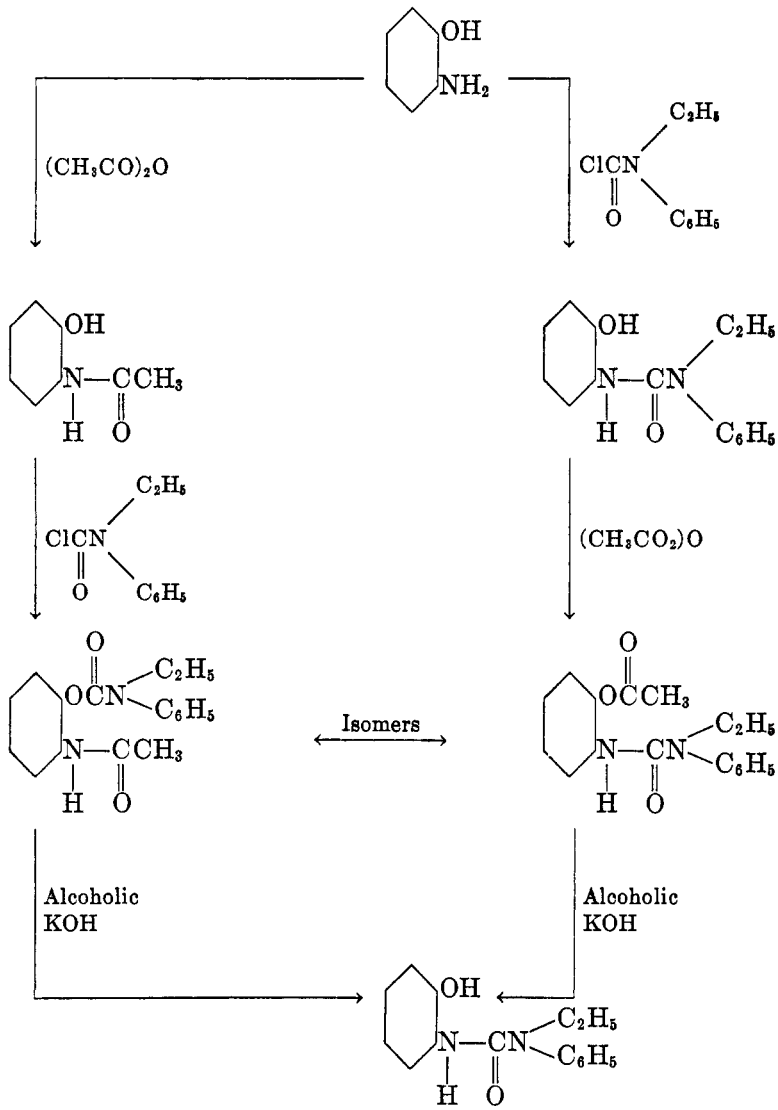
DIAGRAM 1


OH
NH2
C5H5N
ClCN
C2H5
C6H5
O
acid-insoluble
alkali-soluble
acid-soluble
alkali-insoluble
OCH3
(CH3)2SO4
H2SnCl6
p-CH3C6H4SO2Cl
NO2
p-CH3C6H4CH3-p
SO2

Ehrich (5) reported the same results using the acetyl and methylphenylcarbamyl radicals with 2-aminophenol.

In the present work further studies were made of mixed diacyl derivatives of 2-aminophenol. The ethylphenylcarbamyl, the diphenylcarbamyl, and the

DIAGRAM 2



4,4′-dibromodiphenylcarbamyl radicals were tested with various acyls of the R—C(=O)— type, and the ethylphenylcarbamyl radical was tested against the diphenylcarbamyl group. In all cases two isomers were formed, which on hy-

drolysis gave the same 2-carbamylaminophenol and the same acid, indicating that a rearrangement had occurred in one case. When the ethylphenylcarbamyl and the diphenylcarbamyl radicals were tested against each other, hydrolysis of the two diacyls yielded only 2-diphenylcarbamylaminophenol and a mixture of compounds that were not separated. These diacyls hydrolyze slowly as compared to the diacyls containing one R—C(=O)— radical. The general picture is shown in Diagram 2. Tables I, II, and III give the properties of these diacyls and a summary of the rearrangements.

No explanation can be given why the carbamyl radical on oxygen was able to displace the R—C(=O)— radical from nitrogen on hydrolysis of a mixed diacyl. Contrary to work by Raiford and Greider (6) and others (7, 8) but in line with other findings (9, 10), the weight of the acyl is not a prime factor in determining the position of the radical since identical results were obtained when the acyl was lighter (acetyl) or heavier (3-bromobenzoyl) than ethylphenylcarbamyl.

Since no data are available on the dissociation constants of the carbamic acids, any attempt to correlate migration of an acyl from oxygen to nitrogen and displacement of an acyl on nitrogen with the dissociation constants of the corresponding acids cannot be made. As the carbamic acids are somewhat similar in structure to the amino acids which are very weak acids because of inner neutralization, one may assume that the substituted carbamic acids are weaker acids than the RCOOH acids used in this study. If this is true, then acidity is not a prime factor since the less acidic acyl was repeatedly found on nitrogen. Earlier work (11) has shown that when the two acyls were both derived from carboxylic acids, the heavier and more acidic of a given pair was found on nitrogen. The very acidic R—S(=O)(=O)— group (2, 11), however, has failed to migrate from oxygen to nitrogen.

EXPERIMENTAL

Reaction between ethylphenylcarbamyl chloride and 2-aminophenol. A solution of 12.8 g. of ethylphenylcarbamyl chloride, m.p. 49–50°,[2] prepared according to the method used by Raiford and Alexander (1) for the preparation of methylphenylcarbamyl chloride, in 20 ml. of pyridine was added to a solution of 7.7 g. of 2-aminophenol, m.p. 174–175°, Eastman Kodak product crystallized from dioxane, in 20 ml. of pyridine. The solution was heated on the steam-bath for five minutes and allowed to stand twenty-four hours. On pouring the solution into 10% hydrochloric acid, a solid, I, separated and was filtered. A gum, II, formed when the filtrate was made alkaline.

Solid I was dissolved in potassium hydroxide, filtered through charcoal, and then precipitated by saturation with carbon dioxide. Two crystallizations from ethyl acetate gave 5 g. (28%) of large tan rectangular crystals, m.p. 167–168°.

Anal. Calc'd for $C_{15}H_{16}N_2O_2$: N, 10.94. Found: N, 11.18.

All attempts to crystallize II were negative, and the compound was characterized by the preparation of its toluenesulfonamide derivative.

[2] Michler (12) reported 52°.

TABLE I

DIACYL DERIVATIVES OF 2-AMINOPHENOL CONTAINING THE ETHYLPHENYLCARBAMYL RADICAL

POSITION OF ACYL	PURIFICATION SOLVENTS[a]	M.P. °C[b]	YIELD %[b]	CRYSTAL FORM	FORMULA	ANAL. FOR N		ACYL ON N AFTER HYDROLYSIS
						Calc'd	Found	
N-Acetyl[c]	Ethyl acetate, ligroin (65–70°); methyl alcohol	104.5–105.5	35	Pink needles	$C_{17}H_{18}N_2O_3$	9.40	9.49	Ethylphenyl-carbamyl
O-Acetyl[d]	Ethyl acetate, ligroin (65–70°); ethyl acetate; ligroin (86–100°)	89.5–90.5	27	Colorless needles	$C_{17}H_{18}N_2O_3$	9.40	9.36	Ethylphenyl-carbamyl
N-Benzoyl[c]	Ligroin (86–100°); 50% ethanol; 95% ethanol	98–98.5	50	Shiny white needles	$C_{22}H_{20}N_2O_3$	7.78	7.89	Ethylphenyl-carbamyl
O-Benzoyl[d]	Ethyl acetate, ligroin (65–70°); carbon tetrachloride	111–111.5	56	Colorless short thick rods	$C_{22}H_{20}N_2O_3$	7.78	7.91	Ethylphenyl-carbamyl
N-3-Bromo-benzoyl[e]	Ethanol	134–134.5	70	Colorless fluffy needles	$C_{22}H_{19}BrN_2O_3$	6.38	6.50	Ethylphenyl-carbamyl
O-3-Bromo-benzoyl[e]	Ligroin (65–70°); ethanol	90–90.5	45	White glistening crystals	$C_{22}H_{19}BrN_2O_3$	6.38	6.54	Ethylphenyl-carbamyl
N-4-Nitro-benzoyl[e]	Ethanol; 75% acetic acid	152.5–153[f]	74	Colorless needles	$C_{22}H_{19}N_3O_5$	10.37	10.34	Ethylphenyl-carbamyl
O-4-Nitro-benzoyl[e]	Ethanol; 90% acetic acid; ethyl acetate, ligroin (65–70°)	155.5[f]	40	Pale yellow needles	$C_{22}H_{19}N_3O_5$	10.37	10.57	Ethylphenyl-carbamyl

[a] Comma between two solvents indicates mixture.
[b] These values represent the final purified materials.
[c] Prepared in pyridine and dioxane.
[d] Prepared in pyridine.
[e] Prepared in pyridine and chloroform.
[f] A mixed melting point of these isomers was 135–140°.

TABLE II

DIACYL DERIVATIVES OF 2-AMINOPHENOL CONTAINING THE DIPHENYLCARBAMYL RADICAL

POSITION OF ACYL	PURIFICATION SOLVENTS[a]	M.P. °C[b]	YIELD %[b]	CRYSTAL FORM	FORMULA	ANAL. FOR N		ACYL ON N AFTER HYDROLYSIS
						Calc'd	Found	
N-3-Bromobenzoyl[c]	Ethanol, ethyl acetate, dioxane; benzene; benzene; dioxane	157.5–158[d]	64	White tetragonals	$C_{26}H_{19}BrN_2O_3$	5.75	5.73	Diphenylcarbamyl
O-3-Bromobenzoyl[e]	Ethyl acetate, dioxane; acetic acid	159–159.5[d]	60	White squares	$C_{26}H_{19}BrN_2O_3$	5.75	5.82	Diphenylcarbamyl
N-4-Nitrobenzoyl[e]	Ethanol; 80% acetic acid	179.5–180.5	86	Yellow needles	$C_{26}H_{19}N_3O_5$	9.27	9.17	Diphenylcarbamyl
O-4-Nitrobenzoyl[f]	Chloroform	195.5–196.5	67	Yellow plates	$C_{26}H_{19}N_3O_5$	9.27	9.23	Diphenylcarbamyl
N-Ethylphenylcarbamyl[f]	50–50 *n*-Butanol, ethanol	174–174.5	67	White rods	$C_{28}H_{25}N_3O_3$	9.32	9.21	Diphenylcarbamyl[g]
O-Ethylphenylcarbamyl[f]	Methanol[h]	123	66	Colorless square plates	$C_{28}H_{25}N_3O_3$	9.32	9.35	Diphenylcarbamyl[g]

[a] Comma between two solvents indicates mixture.
[b] These values represent the final purified materials.
[c] Prepared in pyridine and dioxane.
[d] A mixed melting point of these isomers was 145–146°.
[e] Prepared in pyridine and chloroform.
[f] Prepared in pyridine.
[g] Difficult to hydrolyze. Only small yields of 2-diphenylcarbamylaminophenol obtained.
[h] Some unchanged diphenylcarbamylaminophenol (10%) was recovered from the methanol mother liquors.

TABLE III

DIACYL DERIVATIVES OF 2-AMINOPHENOL CONTAINING THE 4,4′-DIBROMODIPHENYLCARBAMYL RADICAL

POSITION OF ACYL	PURIFICATION SOLVENTS[a]	M.P. °C[b]	YIELD %[b]	CRYSTAL FORM	FORMULA	ANAL.		ACYL ON N AFTER HYDROLYSIS
						Calc'd	Found	
N-Acetyl[c]	Ether; ethanol	158–159	46	Colorless crystals	$C_{21}H_{16}Br_2N_2O_3$	Bromine 31.72	31.87	4,4′-Dibromodiphenylcarbamyl
O-Acetyl[d]	Ethyl acetate, ligroin (65–70°); ethanol	146.5–147	73	Colorless needles	$C_{21}H_{16}Br_2N_2O_3$	Nitrogen 5.51	5.47	4,4′-Dibromodiphenylcarbamyl
N-Benzoyl[e]	Ethyl acetate; benzene, dioxane	170–170.5	74	Powdery	$C_{26}H_{18}Br_2N_2O_3$	Bromine 28.24	28.25	4,4′-Dibromodiphenylcarbamyl
O-Benzoyl[c]	Chloroform, ethyl acetate	193	32	Diamonds	$C_{26}H_{18}Br_2N_2O_3$	Nitrogen 4.95	4.78	4,4′-Dibromodiphenylcarbamyl

[a] Comma between two solvents indicates mixture.
[b] These values represent the final purified materials.
[c] Prepared in dioxane and pyridine.
[d] Prepared in benzene.
[e] Prepared in pyridine and chloroform.

2-(4-Toluenesulfonylamino)phenyl ethylphenylcarbamate, III. (*a*). *From ethylphenylcarbamyl chloride and 2-(4-toluenesulfonylamino)phenol.* A solution of 6.5 g. of ethylphenylcarbamyl chloride in 15 ml. of chloroform was added to a suspension of 9.2 g. of 2-(4-toluenesulfonylamino)phenol (13) in 10 ml. of pyridine and 5 ml. of chloroform. The mixture was refluxed for forty-five minutes. The next day the chloroform was steam distilled, and the residue on acidification with dilute hydrochloric acid gave a gum which was solidified by mixing with 200 g. of sodium sulfate. The resulting solid after washing with water was recrystallized twice from ethanol, once from benzene, once from a benzene-ligroin (86–100°) mixture to give 6 g. (42%) of colorless shining needles, m.p. 119–120°.

Anal. Calc'd for $C_{22}H_{22}N_2O_4S$: N, 6.82. Found: N, 6.86.

(*b*). *From II and 4-toluenesulfonyl chloride.* As stated above II was not crystallized. Hence the following procedure for its identification was followed. After removal of I from the filtrate, the basic material, II, was liberated by the addition of strong ammonia water. The alkaline solution was extracted with two 30-ml. portions of chloroform, extracts combined, washed with water, and dried over sodium sulfate. To the dried chloroform solution were added 7 ml. of pyridine and 7.6 g. of 4-toluenesulfonyl chloride. The resulting solution was allowed to stand for two hours, was heated to reflux for one minute, and when cool, was poured into 300 ml. of dilute hydrochloric acid. The chloroform was steam distilled. The residual gum after separation was solidified by covering with ethanol. The solid was crystallized twice from ethanol to give 2 g. of small shining colorless needles, m.p. 119–120°. The mixed melting point with the compound prepared in (*a*) was 119–120°.

Anal. Calc'd for $C_{22}H_{22}N_2O_4S$: N, 6.82. Found: N, 6.85.

2-Ethylphenylcarbamylaminophenyl methyl ether, IV. (*a*). *From 2-anisidine and ethylphenylcarbamyl chloride.* To 6.3 g. of freshly distilled 2-anisidine in 20 ml. of chloroform was added 4 g. of ethylphenylcarbamyl chloride dissolved in 10 ml. of chloroform. The solution was refluxed forty-five minutes. The next day the chloroform was extracted with 50 ml. of 4% hydrochloric acid, then worked with 50 ml. of 1% sodium carbonate solution, and finally washed with water. After removal of the solvent by the water-pump, a solid remained which after two crystallizations from ethanol yielded 2.5 g. (42%) of shiny white needles, m.p. 76–77°.

Anal. Calc'd for $C_{16}H_{18}N_2O_2$: N, 10.38. Found: N, 10.30.

(*b*). *From dimethyl sulfate and I.* To a stirred solution of 5.12 g. of I in 50 ml. of 8% sodium hydroxide solution maintained at room temperature was added dropwise 2.6 g. of dimethyl sulfate in ten minutes. After cooling to room temperature the resulting precipitate was filtered, washed alkali-free with water, dried, and crystallized twice from ethanol to yield 3.2 g. (59%) of long white needles, m.p. 76–77°. The mixed melting point with the compound prepared in (*a*) was 76–77°.

Anal. Calc'd for $C_{16}H_{18}N_2O_2$: N, 10.38. Found: N, 10.32.

2-Nitrophenyl ethylphenylcarbamate V. A solution of 10.98 g. of ethylphenylcarbamyl chloride in 5 ml. of pyridine was added to 8.5 g. of 2-nitrophenol, m.p. 45–46°, in 11 ml. of pyridine. The next day the reaction was heated on the water-bath for ten minutes. When cool, it was poured into dilute hydrochloric acid. The oil which formed soon solidified and was purified by extraction with 300 ml. of ligroin (65–70°). The ligroin solution deposited 16 g. (84%) of yellow rods, m.p. 74–75°. Recrystallization from ethanol did not change the melting point.

Anal. Calc'd for $C_{15}H_{14}N_2O_4$: N, 9.79. Found: N, 9.87.

Reduction of V. In several attempts to isolate 2-aminophenyl ethylphenylcarbamate, II, from the reduction of V, no solid amine was obtained, but isolation of the 4-toluenesulfonamide, III, as described below, shows that the amine was formed in the reduction experiments.

A solution of 17 g. of stannous chloride dihydrate in 17 ml. of concentrated hydrochloric acid was added slowly to a boiling solution of 5.72 g. of V in 15 ml. of ethanol. The liquid was refluxed for fifteen minutes, and after cooling was diluted with water until a white cloud formed. Two extractions with 50-ml. portions of ether removed the cloudiness. The

aqueous solution was made alkaline with sodium hydroxide at 10° and then extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and decanted into a dry flask. Then a solution of 4.5 g. of 4-toluenesulfonyl chloride in 10 ml. of pyridine was added. The next day dilute hydrochloric acid was added, and the ether boiled off. A yellow oil formed which soon solidified to 1.8 g. of solid, m.p. 92–100°. Two crystallizations from ethanol gave 1.0 g. of shiny white needles m.p. 118–119°. The mixed melting point with III (*a*) was 118–119°.

Anal. Calc'd for $C_{22}H_{22}N_2O_4S$: N, 6.82. Found: N, 6.93.

Mono acylaminophenols. The following mono acylaminophenols were prepared according to methods previously reported: 2-acetylaminophenol (14), m.p. 207–208°, 2-benzoylaminophenol (15), m.p. 168°, 2-(3-bromobenzoylamino)phenol (16), m.p. 178.5–179°, 2-(4-nitrobenzoylamino)phenol (17), m.p. 202–203°, 2-(4,4′-dibromodiphenylcarbamylamino) phenol (15), m.p. 219–220°, 2-diphenylcarbamylaminophenol (1), m.p. 190–191°.

Diacyl derivatives of 2-aminophenol. The diacyl derivatives of 2-aminophenol except one were prepared by the same general method. The preparations are summarized in Tables I, II, III. The appropriate phenol was suspended or dissolved in a solvent consisting of pyridine either alone or combined with dioxane or chloroform. One mole of the acylating agent in one of the above solvents was added. Unless heat was evolved, the resulting mixture was heated on a boiling water-bath. The time of heating depended on the activity of the acylating agent. The reaction was allowed to stand overnight when it was again heated for not more than thirty minutes, cooled to room temperature, and poured with stirring into iced hydrochloric acid. The solid which separated was purified by crystallization from various solvents until a sharp melting point was obtained.

2-(4,4′-Dibromodiphenylcarbamylamino)phenyl acetate. This compound was prepared using Kaufman's (18) method of acylation. Seven g. of 2-(4,4′-dibromodiphenylcarbamylamino)phenol was refluxed with 30 ml. of benzene and 16 ml. of acetic anhydride for forty-five minutes. The next day the benzene and acetic acid were removed by steam distillation and hydrolysis in one step. The solid was purified by crystallization from various solvents. These solvents and other data on this compound are given in Table III.

Hydrolysis of diacyl derivatives. A small sample (0.8–1.5 g.) of the diacyl derivative was placed in 15 ml. of absolute ethanol containing two mole equivalents of potassium hydroxide. The mixture was heated on a water-bath for three minutes, cooled, and poured into 100 ml. of water. An excess of hydrochloric acid was added, and the mixture was made alkaline with sodium carbonate to remove the organic acid formed. The phenol was filtered, purified if necessary, and identified by mixed melting point with an authentic specimen. The yields were almost quantitative. The alkaline filtrate was acidified, and the resulting acid was identified by mixed melting point.

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SUMMARY

The reaction between ethylphenylcarbamyl chloride and 2-aminophenol in pyridine has been shown to yield 2-ethylphenylcarbamylaminophenol and 2-aminophenyl ethylphenylcarbamate. The structures of both compounds were proved.

The reduction of 2-nitrophenyl ethylphenylcarbamate gave 2-aminophenyl ethylphenylcarbamate.

A number of new mixed diacyl derivatives of 2-aminophenol in which one acyl was of the $R-\overset{|}{C}=O$ type and the other was the $RR'N\overset{|}{C}=O$ type have been described. Both isomeric compounds for a given pair of acyls were prepared. Hydrolysis of each isomer yielded the 2-carbamylaminophenol and a carboxylic acid.

Hydrolysis of the two isomeric diacyl derivatives of 2-aminophenol containing the ethylphenylcarbamyl and diphenylcarbamyl radicals resulted in identification of only one product, 2-diphenylcarbamylaminophenol.

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