[Contribution from the Laboratory of Organic Chemistry of the State University of Iowa]

FORMATION AND BEHAVIOR OF SOME CARBOARYLOXYAMINOANILINES

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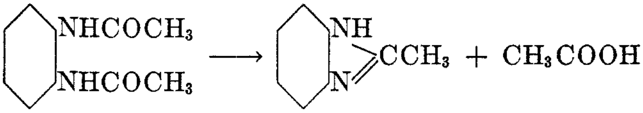
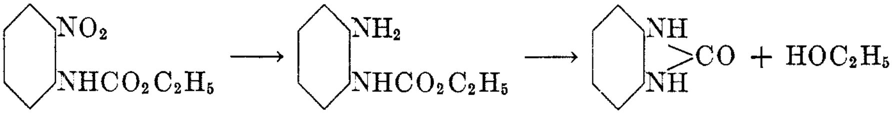
The formation of heterocyclic five-membered rings from certain ortho derivatives of benzene has frequently been observed. Ladenburg (1) found that heating *o*-phenylenediamine with glacial acetic acid and finally distilling the product gave 2-methylbenzimidazole. The intermediate in this case was probably the N,N′-diacetyl derivative of the diamine, because distillation of the latter by Rupe and Porai-Koschitz (2) was found to give the imidazole in quantitative yield. The conditions under which the imidazole is formed directly from the monoacylated compound are indicated by later studies of Phillips (3), of Roeder and Day (4), and of Green and Day (5).



Ring closure may occur with other closely related derivatives of *o*-phenylenediamine. Rudolph (6) reduced 2-carboethoxyaminonitrobenzene to the related aniline and found that when the latter was heated above its melting point it lost the elements of alcohol and was converted into *o*-phenyleneurea. He also noted that the urea may be formed during reduction of the nitro compound if the mixture is not kept cool. The structure of the final product has been established by Hartmann (7) who obtained it by the action of phosgene on the hydrochloride of *o*-phenylenediamine.



These observations and similar ones made by Ladenburg (8), by Groenvik (9) and by Raiford and Inman (10) on derivatives of 2-aminophenol, which also gave heterocyclic compounds, made it of interest to test the behavior of the related carboaryloxyaminoanilines and some of their substitution products. Attempts to obtain these compounds directly from the diamines gave diacyl derivatives, hence it was necessary to prepare first the carbophenoxyaminonitrobenzenes, and then reduce the latter to the desired products. The relations for the para compound are shown in Figure 1.

Although these reactions were carried through with the three nitroanilines, the behavior of derivatives of the ortho compound are of special interest. It was found that reduction of 2-carbophenoxyaminonitrobenzene with stannous chloride and hydrochloric acid gave the related amino compound, which was isolated and for which a satisfactory analysis was obtained. This product was readily soluble in a 10% solution of caustic potash, and acidification of the resulting liquid precipitated a product that melted at 300–303° with apparent decomposition. The identity of this compound was established by comparing it with that obtained from the interaction of *o*-phenylenediamine and phosgene as described by Michler and Zimmermann (11). Analysis of the product here in question indicated that it was *o*-phenyleneurea, now designated as benzimidazolon (12), and first obtained by Hartmann (7), who reported the melting point 307–308°. The *m*- and *p*- carbophenoxyaminoanilines do not give cyclic ureas when treated with alkali under these conditions.

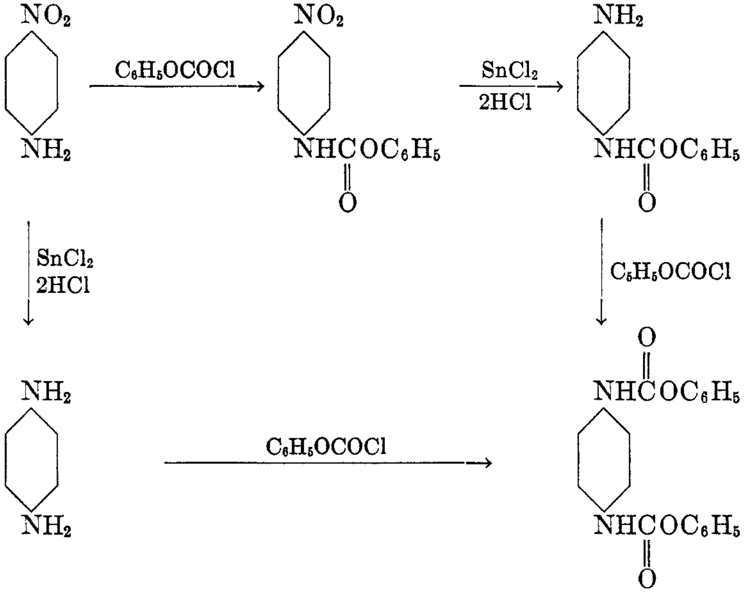


FIGURE 1. FORMATION OF MONO- AND DI-CARBOARYLOXYAMINO DERIVATIVES FROM PHENYLENEDIAMINES

The effect of substituents in the carbophenoxy radical was also tested. Repetition of the above experiment with 2-carbo-(2-chlorophenoxy)aminonitrobenzene was carried through. Reduction with stannous chloride and hydrochloric acid gave an amine hydrochloride that had a melting range of 175–180°. Analysis of the product showed the required amount of halogen and the compound seemed to be stable. Attempts to convert the hydrochloride into the free base by treatment with caustic alkali caused the loss of 2-chlorophenol and the formation of benzimidazolon. Treatment of a water solution of the hydrochloride with ammonium carbonate liberated the amino compound, which was removed by extraction with ether, but attempts to purify it caused the decomposition indicated above. In the ether extract the amino group was acylated by benzoyl chloride and by 2-chlorophenyl chlorocarbonate, as shown in Figure 2.

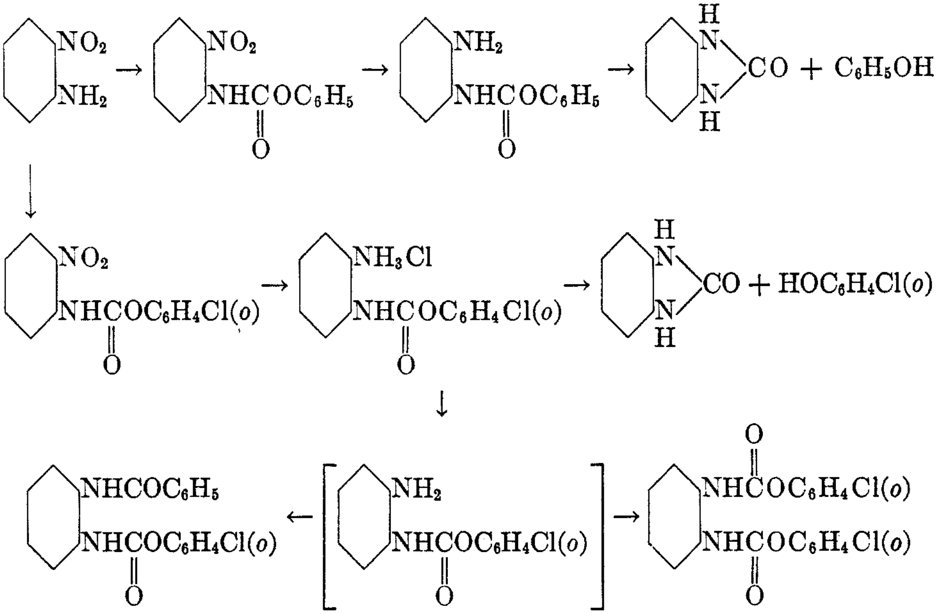


FIGURE 2. FORMATION OF A CYCLIC UREA FROM 2-CARBO-(2-CHLOROPHENOXY)-AMINOANILINE

The isomeric compounds having the substituted carboaryloxy residue in positions 3 and 4 were stable under these conditions.

EXPERIMENTAL

Carbophenoxy derivatives of the isomeric aminonitrobenzenes. Acylation was accomplished by adding gradually and with constant stirring, one molecular proportion of phenyl chlorocarbonate or its substitution product to an ether solution of two molecular proportions of the required nitroaniline, after which the mixture was allowed to stand for two hours. The hydrochloride of the aniline which had formed during this period was removed by filtration, the ether was distilled from the filtrate and the residue was crystallized from a suitable solvent. Analytical date and other properties are given in Table I.

Reduction of the nitro compounds. The general method may be illustrated by the preparation of the hydrochloride of 2-carbo-(2-chlorophenoxy)aminoaniline. Ten and seven-tenths grams of the related nitro compound, dissolved in hot alcohol, was reduced with a mixture of stannous chloride and hydrochloric acid. When the action was complete, the mixture was allowed to cool, and one volume of concentrated hydrochloric acid was added. The hydrochloride that separated was dissolved in the smallest possible amount of warm water, after which one volume of concentrated acid was poured in (13). The solid that was precipitated showed a melting range of 175–180°, and analysis indicated that the product was nearly pure.

Anal. Calc'd for $C_{13}H_{12}Cl_2N_2O_2$: Cl, 23.74, N, 9.36.
Found: Cl, 24.10; N, 9.09

Benzimidazolon. Three grams of 2-carbophenoxyaminoaniline was dissolved in 10% solution of caustic potash, and the resulting liquid was acidified with hydrochloric acid.

TABLE I

ACYL DERIVATIVES OF AMINONITROBENZENES

COMPOSITION AND POSITION OF SUBSTITUENT	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C	FORMULA	ANALYSES			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
2-Carbophenoxy-	73	Ligroin (65–67°)	Pale yellow needles	98–99	$C_{13}H_{10}N_2O_4$	—	—	10.85	11.01
2-Carbo-(2-chlorophenoxy)-	55	Alcohol	Pale yellow needles	113–115	$C_{13}H_9ClN_2O_4$	12.13	11.91	—	—
3-Carbophenoxy-	92	Toluene	Cream needles	123–124	$C_{13}H_{10}N_2O_4$	—	—	10.85	11.07
3-Carbo-(2-chlorophenoxy)-	76	Toluene	Colorless leaflets	136–137	$C_{13}H_9ClN_2O_4$	12.13	11.87	—	—
3-Carbophenoxy-4-methyl-	34[a]	Chloroform-ligroin	Colorless square prisms	128–130	$C_{14}H_{12}N_2O_4$	—	—	10.29	9.92
4-Carbophenoxy-	83	Toluene	Colorless needles	165–166	$C_{13}H_{10}N_2O_4$	—	—	10.85	10.90
4-Carbo-(2-chlorophenoxy)-	80	Toluene	Colorless needles	154–155	$C_{13}H_9ClN_2O_4$	12.13	11.70	—	—

[a] Refers to purified product. Starting material to the extent of 28% was recovered.

TABLE II

CARBOPHENOXYAMINOANILINES

COMPOSITION AND POSITION OF SUBSTITUENT	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C	FORMULA	ANALYSIS NITROGEN	
						Calc'd	Found
2-Carbophenoxy-	50	Alcohol	Pink needles	157–158 (decomp.)	$C_{13}H_{12}N_2O_2$	12.28	12.18
3-Carbophenoxy-	82	Alcohol	Colorless leaflets	178–179	$C_{13}H_{12}N_2O_2$	12.28	12.28
3-Carbo-(2-chlorophenoxy)-	32	Alcohol	Colorless leaflets	160 (decomp.)	$C_{13}H_{11}ClN_2O_2$	10.66	10.53
4-Carbophenoxy-	61	Toluene	Brown powder	134–135	$C_{13}H_{12}N_2O_2$	12.28	12.48
4-Carbo-(2-chlorophenoxy)-[a]	43	[b]	Pink powder	140 (decomp.)	$C_{13}H_{11}ClN_2O_2$	10.66	10.76

[a] The hydrochloride of this compound was isolated in colorless shining leaflets. *Anal.* Calc'd for $C_{13}H_{12}Cl_2N_2O_2$: N, 9.36. Found N, 9.28.

[b] No suitable solvent was found.

TABLE III

Dicarbophenoxydiaminobenzene and Substitution Products

COMPOSITION AND POSITION OF SUBSTITUENT	YIELD, %[a]	SOLVENT	CRYSTAL FORM	M.P., °C	FORMULA	ANALYSES			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
1,2-Dicarbophenoxy-	60	Alcohol	Colorless needles	189–190	$C_{20}H_{16}N_2O_4$	—	—	8.04	8.20
1,2-Di-(2-chloro-carbophenoxy)-	61	Dilute acetic acid	Colorless needles	170[b]	$C_{20}H_{14}Cl_2N_2O_4$	17.02	16.91	6.71	6.70
1,3-Dicarbophenoxy-	54	Dilute acetic acid	Colorless needles	163–165	$C_{20}H_{16}N_2O_4$	—	—	8.04	8.04
1,3-Di-(2-chloro-carbophenoxy)-	60	Acetic acid	Colorless leaflets	201–202	$C_{20}H_{14}Cl_2N_2O_4$	17.02	16.97	6.71	6.92
1,4-Dicarbophenoxy-	72	Alcohol	Pale brown leaflets	238–239	$C_{20}H_{16}N_2O_4$	—	—	8.04	8.06
1,4-Di-(2-chloro-carbophenoxy)-	67	Acetic acid	Colorless needles	223–224	$C_{20}H_{14}Cl_2N_2O_4$	17.02	17.08	6.71	6.63

[a] These figures represent purified materials.

[b] The product softened at 140°.

TABLE IV

MIXED DIACYL DERIVATIVES OF PHENYLENEDIAMINES

RELATIVE POSITIONS OF SUBSTITUENTS	ACYLS	YIELD, %[a]	SOLVENT	CRYSTAL FORM	M.P., °C	FORMULA	ANALYSES NITROGEN	
							Calc'd	Found
1,2-	Acetyl and carbophenoxy-	13	Ether[b]	Colorless powder	143–144	$C_{15}H_{14}N_2O_3$	10.37	10.19
	Benzoyl and carbophenoxy-	60	Alcohol	Colorless scales	146–148	$C_{20}H_{16}N_2O_3$	8.43	8.32
	Acetyl and carbo-(2-chlorophenoxy)-	85	[c]	Colorless leaflets	125–126	$C_{15}H_{13}ClN_2O_3$	9.19	9.41
	Benzoyl and carbo-(2-chlorophenoxy)-	80	[c]	Colorless powder	145–147	$C_{20}H_{15}ClN_2O_3$	7.64	7.82
1,3-	Acetyl and carbophenoxy-	41	Dilute alcohol	Colorless needles	144–146	$C_{15}H_{14}N_2O_3$	10.37	10.30
	Benzoyl and carbophenoxy-	60	Alcohol	Colorless fluffy masses	157–158	$C_{20}H_{16}N_2O_3$	8.43	8.55
	Acetyl and carbo-(2-chlorophenoxy)-	52	Dilute alcohol	Colorless needles	175–176	$C_{15}H_{13}ClN_2O_3$	9.19	9.42
	Benzoyl and carbo-(2-chlorophenoxy)-	28	Ether[b]	Gray powder	170–171	$C_{20}H_{15}ClN_2O_3$	7.64	7.52
1,4	Acetyl and carbophenoxy-	85	Dilute dioxane	Colorless powder	175–176	$C_{15}H_{14}N_2O_3$	10.37	10.35
	Benzoyl and carbophenoxy-	50	Alcohol	Pink leaflets	223	$C_{20}H_{16}N_2O_3$	8.43	8.43
	Acetyl and carbo-(2-chlorophenoxy)-	56	Dilute alcohol	Colorless leaflets	182–183	$C_{15}H_{13}ClN_2O_3$	9.19	9.23
	Benzoyl and carbo-(2-chlorophenoxy)-	60	Dilute alcohol	Colorless needles	195–196	$C_{20}H_{15}ClN_2O_3$	7.64	7.69

[a] These figures represent purified material.

[b] Ether was used to remove foreign matter.

[c] The product obtained by evaporation of ether was analyzed without further purification.

The precipitate that separated was crystallized from alcohol and was obtained as colorless plates that melted with apparent decomposition at 300–303°. The same product was obtained by the action of alkali solution on the hydrochloride of 2-carbo-(2-chlorophenoxy)-aminoaniline, in an attempt to secure the free amine, and also by the action of phosgene on a chloroform solution of *o*-phenylenediamine.

Anal. Calc'd for $C_7H_6N_2O$: N, 20.89. Found: N, 20.58.

Other carbophenoxyaminoanilines were prepared, and in most instances their salts were purified as indicated above. When it was not possible to free them from tin salts in the way specified, a solution of the salt was treated with hydrogen sulfide. In either case the solution of the amine hydrochloride was decomposed with ammonium carbonate solution in order to obtain the free bases, and these were purified by crystallization from suitable solvents. Analytical date and other properties are shown in Table II.

The carboaryloxyaminoanilines listed in Table II were further characterized by conversion into simple and mixed diacyl derivatives. The dicarbophenoxy compounds were obtained by treatment of one molecular proportion of the above-described monoacyl derivatives, in ether solution and in the presence of an equivalent amount of dimethylaniline, with one molecular proportion of the required acid chloride. When the free aniline was not available and it was necessary to use the hydrochloride, the latter was dissolved in water, the solution was mixed with ammonium carbonate, and the free base formed was extracted with ether. The resulting extract was then treated with the required acid chloride. The products were isolated and purified in the same general way as that described for the monoacyl derivatives tested above. The compounds thus were identical with those formed when the required phenylenediamines were treated directly with two molecular proportions of the necessary acylating agent. Analytical data and other properties of these substances are recorded in Table III.

To obtain the mixed diacyl derivatives the necessary acid chloride was added to an ether solution of the required amino compound in the presence of dimethylaniline to combine with the hydrogen chloride eliminated, the mixture was stirred for fifteen minutes, extracted with dilute hydrochloric acid, washed, dried over anhydrous sodium sulfate, and the ether distilled. The products were crystallized from suitable solvents. Data are given in Table IV.

SUMMARY

The carbophenoxyaminonitrobenzenes have been prepared and reduced to the related anilines, and the latter have been characterized. Heating the ortho aniline above its melting point causes the elimination of phenol and the formation of a cyclic urea. The presence of a "negative" substituent in the carbophenoxy radical makes the aniline less stable. It was possible to isolate the hydrochloride of 2-carbo-(2-chlorophenoxy)aminoaniline, but attempts to obtain the free aniline by treatment of the salt with an alkali caused elimination of 2-chlorophenol and the formation of the related cyclic urea. The isomers having the carbophenoxy radical in positions 3 and 4 are more stable.

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