

Phenylcarbamic Acid Anhydrides; a New Class of Compounds

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Anhydrides of *N*-aryl-*N*-methylcarbamic acids (carbanilic acids), a class of compounds not previously described in the literature, have been prepared from the corresponding carbamoyl chlorides by refluxing the compound with a mixture of sodium hydroxide and sodium hydride in dry toluene or xylene. Depending on the substitution pattern of the aromatic ring and the reaction temperature, *N*-methylanilines and/or *N,N'*-diaryl-*N,N'*-dimethylureas were formed as by-products in various amounts.

The reaction seems to involve formation of a sodium salt of the carbamic acid which then reacts with the carbamoyl chloride to form an anhydride. This is evidenced by the isolation of *N*-(2-chloro-6-methylphenyl)-*N*-methylcarbamic acid sodium salt from the reaction mixture, and its further reaction with *N*-(4-methoxyphenyl)-*N*-methylcarbamoyl chloride (4) to the mixed carbanilic acid anhydride 13.

In a preliminary communication¹ we have recently described the first discovery of a stable carbanilic acid anhydride (compound 7, Table 1) formed as a by-product when a carbamoyl chloride and a sodium alcoholate were allowed to react in toluene. We have now further investigated the synthesis and mechanism of formation of this new class of compounds.

Carbamic acids are under normal conditions very unstable compounds that easily undergo decarboxylation. Olah and Calin² have presented evidence for the existence of protonated carbamic acids at -60° in acidic solvents, but even in these solutions the acids decompose at higher temperatures.³ The acyl chlorides, amides, esters, and salts of carbamic acids, however, are stable compounds.

A well-known synthetic procedure for carboxylic acid anhydrides involves the reaction between an acyl chloride and a free acid or its salt and similar reactions to carbamic acid anhydrides would seem to be feasible. However, such stable anhydrides have apparently not been described in the literature though such compounds have been suggested as possible intermediates in the formation of *N,N'*-disubstituted ureas from the reaction of water with

arylisocyanates.⁴⁻⁵ These anhydrides have been described as unstable compounds which decompose to ureas by loss of CO₂ at or below room temperature. Mixed anhydrides between carboxylic acids and carbamic acids are readily formed from equimolar mixtures of isocyanates and carboxylic acids.⁶⁻⁸ Stronger acids like trichloroacetic or cyanoacetic acids form mixed anhydrides which decompose spontaneously into amides and CO₂, while mixed anhydrides of weaker aliphatic or aromatic acids decompose at elevated temperatures into disubstituted ureas, carboxylic acid anhydrides and CO₂.^{7,8} Wittman *et al.*⁹ have recently described a stable mixed anhydride formed from malonic acid and chlorosulphonylisocyanate. A well-known stable mixed anhydride is oxazolidindione which can be prepared from an α -amino acid and phosgene¹⁰ through an intramolecular condensation; it is used in the preparation of poly α -amino acids.¹¹

We have now been able to synthesize a series of stable crystalline carbanilic acid anhydrides using a method apparently involving the sodium salt of the carbanilic acid as an intermediate.

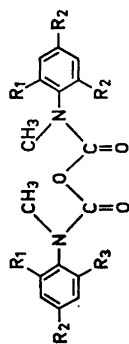
SYNTHETIC PROCEDURES AND RESULTS

The anhydrides were all prepared from *N*-aryl-*N*-methylcarbamoyl chlorides. These starting materials have been synthesized by reacting the appropriate aniline with ethyl chloroformate and then reducing the urethane formed with LiAlH₄ in dry tetrahydrofuran to the *N*-methylaniline. This was then treated with phosgene to yield the carbamoyl chloride. To synthesize the anhydrides, a suspension of sodium hydride and sodium hydroxide was prepared by adding one equivalent of water to three equivalents of sodium hydride in dry toluene. Two equivalents of the carbamoyl chloride were then added and the mixture was refluxed for 18–20 h. The anhydrides obtained are presented in Table 1.

As indicated in Scheme 1, the anhydrides are apparently formed from one molecule of carbamoyl chloride and one molecule of sodium carbamate. All the reactions were carried out under standardized conditions. The data presented in Table 1 therefore indicate that the yields of the anhydrides are dependent on the aromatic substitution pattern. A reaction time of 18–20 h seems to be optimal under the conditions used. Shorter reaction times (<10h) diminished the yield, probably because several of the reactants are solids in the reaction mixture and therefore react only very slowly. Longer reaction times (>30 h) also diminished the yield, *N*-methylanilines and ureas being the main products. Reaction between the formed anhydride and the remaining sodium hydroxide may account for the anilines and ureas formed when very long reaction times were used (Path 3; Scheme 1).

The reaction has been studied at different temperatures in xylene and toluene and the same yields were obtained in the two solvents at the same temperature. In most cases a reaction temperature of about 110° (refluxing toluene) gave better yields than other temperature. At room temperature, no reaction took place. At 70°, no anhydride could be isolated, but detectable amounts (TLC) of *N*-methylanilines were formed. This seems to indicate that the carbamoyl chloride reacts with NaOH at this temperature but the further

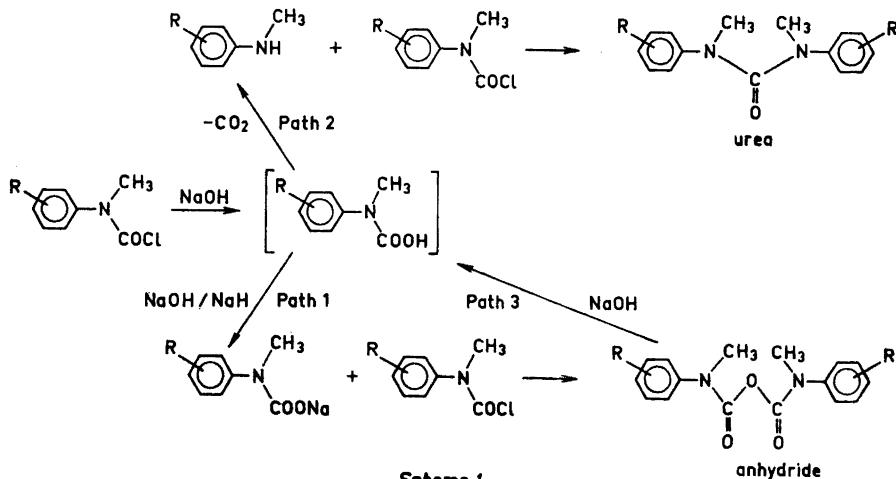
Table 1. Physical and analytical data of the carbamic acid anhydrides.



Compound	R ₁	R ₂	R ₃	Yield %	M.p. °C	IR KBr-disc. (cm ⁻¹)	Formula	Calc. %			Found %		
								C	H	N	C	H	N
7	CH ₃	H	Cl	41 ^a	163-164	1710 1760	C ₁₈ H ₁₈ Cl ₂ N ₂ O ₃	56.9	4.76	7.35	57.1	4.82	7.35
8	CH ₃	H	CH ₃	57	173.5-174.5	1710 1760	C ₂₀ H ₂₄ N ₂ O ₃	70.6	7.11	8.23	70.3	7.26	8.15
9	CH ₃	H	H	15	92-93.5	1705 1755	C ₁₈ H ₂₀ N ₂ O ₃	69.9	6.45	8.97	70.0	6.42	9.16
10	H	OCH ₃	H	14	114.5-115.5	1705 1760	C ₁₈ H ₂₀ N ₂ O ₅	62.8	5.85	8.14	62.6	5.91	8.01
11	H	H	H	13	68.5-70	1705 1755	C ₁₈ H ₁₆ N ₂ O ₃	67.6	5.67	9.86	67.5	5.61	9.92
12	H	Cl	H	3	140.5-142	1695 1755	C ₁₈ H ₁₄ Cl ₂ N ₂ O ₃	54.4	3.99	7.93	54.3	4.46	8.01

^a In refluxing xylene; 18 % yield in refluxing toluene. The other anhydrides were all prepared in refluxing toluene.

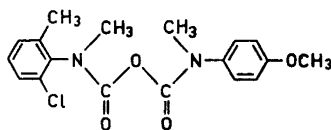
reaction to the anhydride does not occur and the *N*-methylaniline is formed by Path 2, Scheme 1. At a temperature of about 140° (refluxing xylene),



N-methylanilines and ureas were the main products except in the synthesis of *N*-(2-chloro-6-methylphenyl)-*N*-methylcarbamamic acid anhydride (7), which was formed in good yield under these conditions.

The anhydrides were identified by their IR-spectra and elementary analysis (Table 1) and by alkaline hydrolysis,¹ which gave the corresponding *N*-methylanilines as the only products. In the IR-spectra, three characteristic bands appear. The carbonyl absorption region shows two strong bands around 1700 cm⁻¹ separated by approximately 50 cm⁻¹. A similar pattern is exhibited by carboxylic acid anhydrides, which normally show two bands between 1850 and 1710 cm⁻¹ usually separated by about 60 cm⁻¹.¹² Another IR-band of medium intensity, characteristic of carbanilic acid anhydrides, appears at 970–950 cm⁻¹. The carbonyl chlorides have no significant absorption between 1000 and 900 cm⁻¹ and the *N*-methylanilines and ureas formed as by-products have a weak absorption at or below 940 cm⁻¹.

When *N*-(2-chloro-6-methylphenyl)-*N*-methylcarbamoyl chloride (1) was reacted with the sodium hydride/sodium hydroxide suspension in refluxing toluene, a white precipitate identified as the sodium salt of *N*-(2-chloro-6-methylphenyl)-*N*-methylcarbamamic acid was formed. When this was reacted with one equivalent of *N*-(4-methoxyphenyl)-*N*-methylcarbamoyl chloride (4) in refluxing xylene, a white crystalline compound, m.p. 58.5–60°, was formed. Spectral data and the elementary analysis are consistent with the structure 13 for this compound, a mixed carbanilic acid anhydride formed from the starting materials as indicated in Scheme 1. Formation of 13 strongly suggests that the other prepared anhydrides are formed by the same mechanism.



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DISCUSSION OF THE RESULTS

The data presented in Table 1 show that the yield in the synthesis is dependent on the aromatic substitution pattern. Thus the highest yields are obtained when the aromatic ring has two substituents *ortho* to the nitrogen (7 and 8). When the ring carries a *para* substituent, lower yields are obtained if the group is electron withdrawing (*cf.* -H and -Cl, compounds 11 and 12). These data indicate that the aromatic substitution may effect the reaction in two different ways, namely by a steric and an inductive effect.

The most likely reactions in the synthesis and decomposition of the anhydrides are depicted in Scheme 1. The first step in their formation is conversion of the acyl chloride to the carbanilic acid under the influence of sodium hydroxide. That sodium hydroxide is necessary for the reaction is shown by the observation that no anhydride is formed in a refluxing toluene mixture of sodium hydride and carbamoyl chloride if moisture is carefully excluded. When only sodium hydroxide was used as base, the yield of the anhydride was considerably lowered probably because of water formation in the reaction. Although, the presence of the free carbanilic acid has not been demonstrated it is a logical reaction intermediate (Scheme 1) and it is likely that the influence of the aromatic substituents is most important in the free carbanilic acid molecule before this has reacted to the more stable sodium salt. The presence of the carbanilic acid sodium salt as a reaction intermediate is shown by the isolation of the salt of *N*-(2-chloro-6-methylphenyl)-carbamic acid and its further conversion to the mixed anhydride 13. The formation of the *N*-methylanilines and ureas as by-products probably takes place as indicated by Path 2 in Scheme 1. The same products are also slowly formed from the anhydride as shown by Path 3, Scheme 1. Our study is so far limited to *N*-aryl-*N*-methylcarbamic acid anhydrides. These compounds are all stable even at elevated temperatures and they melt without decomposition. They remain unchanged in the atmosphere for months and react only reluctantly with methanol. Studies on the synthesis of other carbamic acid anhydrides and their behavior in various reactions are in progress.

EXPERIMENTAL

General comments. Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. Microanalyses were performed in the laboratories of Dr. A. Bernhardt, Mülheim, Germany. Infrared absorption spectra were measured on a Perkin-Elmer 237 spectrophotometer and the nuclear magnetic resonance spectra were measured with a Varian Associates A 60 instrument. Chemical shifts are expressed in τ units relative to tetramethylsilane. Thin layer chromatography was

performed using silica gel G plates of 0.3 mm thickness. The plates were activated by heating at 130° for 1.5 h and stored in a dry cabinet until used. Chloroform was used as solvent in the chromatography and the spots were detected after treatment with iodine vapor. *N*-(2-Chloro-6-methylphenyl)-*N*-methylcarbamoyl chloride (1) was prepared as described.¹

N-(2,6-Dimethylphenyl)-*N*-methylcarbamoyl chloride (2). Ethyl 2,6-dimethylphenylcarbamate (87 g, 0.45 mole), prepared from 2,6-dimethylaniline and ethyl chloroformate as described by Dahlbom and Österberg,¹⁸ was reduced with LiAlH₄ (34.1 g, 0.90 mole) in dry tetrahydrofuran (700 ml). After refluxing and stirring overnight, the reaction mixture was worked up in the usual way yielding *N*-methyl-2,6-dimethylaniline as a colourless oil (58 g, 98 %), b.p. 55° (2 mm), n_D^{21} 1.5375. (Lit.¹⁴ 99° (22 mm), $n_D^{15.5}$ 1.5400).

N-Methyl-2,6-dimethylaniline (21.2 g, 0.16 mole) was treated with a solution of phosgene (62.5 g, 0.63 mole) in 500 ml of benzene at 0°. The solution was slowly allowed to reach room temperature and was then refluxed with stirring for 4 h. After evaporation of the solvent, a white crystalline product was obtained (24.2 g, 78 %), m.p. 78–79° (from ligroin). (Found: C 60.6; H 6.26; N 7.02. Calc. for C₁₀H₁₁ClNO: C 60.8; H 6.12; N 7.09). ν_{\max} (KBr) 1725 cm⁻¹ (C=O).

N-(2-Methylphenyl)-*N*-methylcarbamoyl chloride (3) was similarly obtained in 88 % yield, m.p. 60–61°. (Lit.¹⁵ 62°).

N-(4-Methoxyphenyl)-*N*-methylcarbamoyl chloride (4) was prepared from phosgene and *N*-methyl-4-methoxyaniline¹⁶ (obtained in 76 % yield by the method described above) in 71 % yield, m.p. 44–45° (from ligroin), ν_{\max} (KBr) 1740 cm⁻¹ (C=O). Lit.¹⁷ b.p. 166–169° (17 mm).

N-Methyl-*N*-phenylcarbamoyl chloride (5) was similarly obtained in 88 % yield, m.p. 85–87°. (Lit.¹⁸ 88°).

N-(4-Chlorophenyl)-*N*-methylcarbamoyl chloride (6) was prepared from phosgene and *N*-methyl-4-chloroaniline¹⁹ (obtained in 88 % yield by the method described above) in 69 % yield, m.p. 64–66° (from ligroin). (Lit.²⁰ 59–63°).

Preparation of carbanilic acid anhydrides. Sodium hydride (0.021 mole) in dry toluene (75 ml) was mixed with water (0.007 mole). This was then heated to reflux, *N*-methylcarbamoyl chloride (0.014 mole) was added and the mixture was refluxed and stirred for 18–20 h. After cooling, the precipitate was filtered off and washed with dry toluene. The filtrate was evaporated *in vacuo* affording an oily residue which was dissolved in toluene/light petroleum. Upon cooling, a solid material precipitated, from which the anhydride was isolated by repeated crystallization from toluene/light petroleum (1:30). Unreacted carbamoyl chloride remained in solution and it was recovered after evaporation of the solvent. The *N*-methylaniline formed was not isolated but was identified by chromatography with an authentic sample.

N-(2-Chloro-6-methylphenyl)-*N*-methylcarbamic acid anhydride (7) was obtained in 18 % yield by this procedure and in 41 % yield in refluxing xylene. In this solvent (b.p. ~140°) large amounts of *N*-methyl-2-chloro-6-methylaniline were formed whereas in toluene (b.p. ~110°) only traces were detected. Similarly, no *N*-methyl-2,6-dimethylaniline was detected in the synthesis of 8 when toluene was the solvent.

From the synthesis of *N*-(4-methoxyphenyl)-*N*-methylcarbamic acid anhydride (10) *N,N'*-bis-(4-methoxyphenyl)-*N,N'*-dimethylurea was isolated in 45 % yield, m.p. 83–84.5° (from ligroin). (Found: C 67.9; H 6.82; N 9.41. Calc. for C₁₇H₂₀N₂O₃: C 68.0; H 6.71; N 9.33). ν_{\max} (KBr) 1635 cm⁻¹ (C=O). Similarly, the synthesis of *N*-methyl-*N*-phenylcarbamic acid anhydride (11) gave *N,N'*-dimethyl-*N,N'*-diphenylurea in 12 % yield, m.p. 120–121° (from ligroin). (Lit.¹⁸ 121°) and large amounts of *N*-methylaniline. Also in the synthesis of *N*-(4-chlorophenyl)-*N*-methylcarbamic acid anhydride (12) large amounts of *N*-methyl-4-chloroaniline were formed.

Preparation of carbanilic acid anhydride using NaOH as base. *N*-(2,6-Dimethylphenyl)-*N*-methylcarbamoyl chloride (2) (0.014 mole) and NaOH (0.007 mole) was refluxed and stirred in dry toluene (75 ml) for 18 h. Working up as described above, the anhydride 7 was isolated in 9 % yield. Large amounts of *N*-methyl-2,6-dimethylaniline were detected on TLC.

N-(2-Chloro-6-methylphenyl)-*N*-methyl-*N'*-(4-methoxyphenyl)-*N'*-methylcarbamic acid anhydride (mixed carbanilic acid anhydride) (13). *N*-(2-Chloro-6-methylphenyl)-*N*-methylcarbamoyl chloride (0.014 mole) was reacted with the sodium hydroxide/sodium hydride mixture in refluxing toluene for 20 h as described above. The white precipitate formed

was filtered off and the anhydride 7 was isolated from the filtrate in 18 % yield. The IR-spectrum of the precipitate shows bands at 2970–2850 cm^{-1} (C–H stretch) and a strong band at 1565 cm^{-1} (salt of a carboxylic acid¹²). When the precipitate was dissolved in 1 M HCl and the solution was made alkaline and extracted with ether, only one product was obtained (TLC) identified as *N*-methyl-2-chloro-6-methylaniline by co-chromatography and spectral comparison with authentic material. These data are consistent with the formulation of the precipitate as the sodium salt of *N*-(2-chloro-6-methylphenyl)-*N*-methylcarbamic acid, possibly contaminated with NaH, NaCl, and NaOH. This salt (0.5 g, 0.002 mole) and carbamoyl chloride (4) (0.4 g, 0.002 mole) in dry xylene (25 ml) was refluxed under stirring for 2 h. After evaporation of the solvent, 0.7 g of an oily residue was obtained. This was dissolved in ether/light petroleum (1:10) and kept at -20° overnight, by when a white crystalline compound (0.07 g) had precipitated, m.p. 58.5–60°. (Found: C 59.7; H 5.53; N 7.91. Calc. for $\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}_4$: C 59.6; H 5.28; N 7.72). ν_{max} (KBr) 1765, 1700 and 950 cm^{-1} (carbanilic acid anhydride). The NMR-spectrum shows singlets at τ 6.20, (3 H, $-\text{OCH}_3$), 6.85 (6 H, $-\text{NCH}_3$) and 8.00 (3 H, ArCH_3). These data are consistent with structure 13, a mixed carbanilic acid anhydride.

Acknowledgement. We are most grateful to Professor Richard Dahlbom for many valuable and stimulating suggestions during this work. *Apotekarsocieteten* is acknowledged for a grant to one of us (HS).

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Received September 16, 1969.