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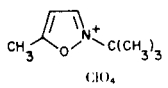
Carboxylic *N,N*-diphenylcarbamic anhydrides have been isolated from the reaction of carboxylate salts with 1-(*N,N*-diphenylcarbamoyl)pyridinium chloride in aqueous or ethanolic solution. These anhydrides have been shown to be stable, crystalline derivatives and to be very reactive in acylation reactions.

A comparison of pyrazinecarboxylic acid derivatives demonstrated these products to be more reactive than cyanomethyl esters or the so-called Woodward's esters, acyloxyacrylamides.

J. Heterocyclic Chem., **16**, 321 (1979).

The search for an acid activating function in the aminopyrazinecarboxylic acids led to the descovery that "active esters" from these acids and *N-t*-butyl-5-methylisoxazolium perchlorate (**1**) were stable, crystalline, and reactive acylating agents (2). Upon closer examination of



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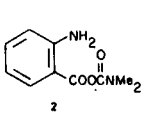
the acyloxyacrylamide structure, *i.e.*, **15a**, it became apparent that these derivatives could be viewed as vinylogs (3) of carboxylic carbamic mixed anhydrides. Because of our interest in carboxyl activation for acylation reactions, an investigation was initiated into this class of mixed anhydride. Although such mixed anhydrides are known, their synthesis and isolation has proved difficult and their subsequent use has been somewhat meager (4,5). A mixed anhydride of this type (**2**) has been isolated from the reaction of triethylammonium anthranilate with two moles of dimethylcarbamoyl chloride-pyridine complex in dioxane (4). However, this material was unstable and could only be stored at temperatures below -10°C. Newman reported the preparation of 2-benzoylbenzoic *N,N*-dimethylcarbamic anhydride (**4**) without comment as to its uniqueness (5). Subsequent to our preliminary publication, Rawlinson reported the isolation of benzoic dimethylcarbamic anhydride (**3**) (6). Carboxylic carbamic anhydrides have also been proposed as intermediates in the high temperature preparation of amides from dialkylcarbamoyl chlorides and alkali carboxylates (7).



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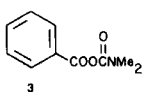

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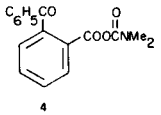

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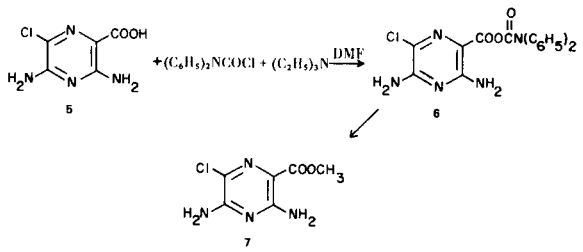
Our goal was to develop a stable, isolable mixed anhydride, and it was felt that the most promising structure would be derived from diphenyl carbamic acid. Previous experiences with 3,5-diamino-6-chloropyrazinecarboxylic acid likewise, dictated its choice as the initial carboxylic acid for derivatization (2). When the triethylamine salt of **5** was allowed to react with an equivalent



of diphenylcarbamoyl chloride in DMF for twenty-four hours, and the solution diluted with water, a crude solid separated that exhibited spectral characteristics of the desired compound (**6**). Initial cautious and careful manipulation was subsequently shown to be unnecessary since the isolated material was not sensitive to air, moisture, light or temperature under normal storage conditions. Strong infrared absorption at 1725 and 1700 cm^{-1} was consistent with the incorporation of the diphenylcarbamoyl moiety into a mixed anhydride function (8). A brief treatment of the material with sodium methoxide in methanol smoothly converted this material into the methyl ester (**7**), confirming the position of attachment of the diphenylcarbamoyl segment. Surprisingly, the anhydride (**6**) could be purified by recrystallization from boiling acetonitrile without appreciable decomposition.

Attempts were made to prepare mixed anhydrides from other pyrazinecarboxylic acids, aromatic acids, and aliphatic acids by this procedure. No success was obtained in this venture, for reasons as yet unexplained. In an attempted condensation between **5** and dimethylcarbamoyl chloride, no reaction was observed at 0° (tlc). As the temperature was allowed to warm to 25° a new material was detected, which on isolation and purification was identified as the amide **8**.

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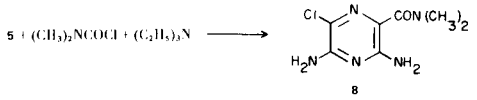

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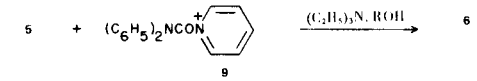
In an investigation of *N,N*-disubstituted carbamoyl chlorides, Johnson and Rumon found that the pyridinium salts, derived from carbamoyl chlorides and pyridine, were soluble in, and *stable to*, hydroxylic solvents such as *t*-butanol, ethanol, methanol, and water (9). These authors likewise demonstrated that 1-(*N,N*-dimethylcarbamoyl)pyridinium chloride undergoes S_N2 type nucleophilic substitution reactions in contrast to dimethylcarbamoyl chloride, which reacts by an S_N1 process (10). We thus explored the use of 1-(*N,N*-diphenylcarbamoyl)-pyridinium chloride (**9**) in the preparation of (**6**).



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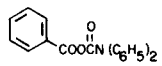
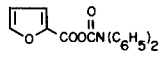
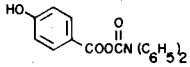
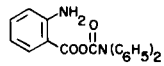
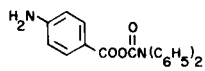
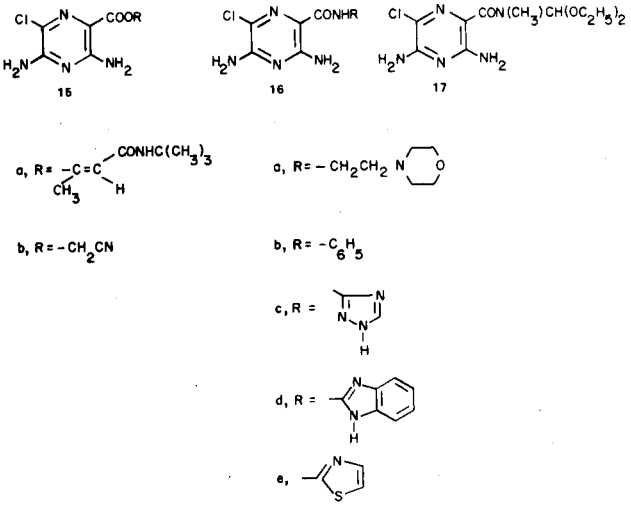
Addition of an aqueous solution of **5** as its triethylamine salt, to an aqueous solution of **9** produced an immediate precipitate of **6**. When the condensation was performed in ethanol solution, a 65% yield of **6** precipitated within one-half hour.

Application of the pyridinium salt (**9**), in aqueous solution, to a variety of carboxylic acids produced the mixed anhydrides listed in Table 1. These are all stable crystalline solids that react rapidly with benzyl amine in THF solution (25°) to form the corresponding amide. The anhydride of anthranilic acid reported here seems superior to the dimethyl analog in ease of synthesis and stability (4). Similarly, there appear to be no urea by-products from employment of **6**, whereas the use of isatoic anhydride is complicated by such side reactions (11).

Table I

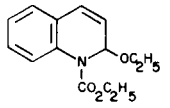
10		1760, 1725
11		1780, 1725
12		1755, 1700
13		1750, 1680
14		1755, 1700

With a convenient and efficient synthesis of these mixed anhydrides, it was of interest to compare the reactivity of such derivatives with other active ester reagents. Our previous results in the pyrazine series (2) led us to employ a variety of derivatives of **5** in a general comparison of reactivities. We had previously demonstrated the superiority of **15a** over the methyl ester, phenyl ester, thiol esters, and *N*-hydroxysuccinimide ester of **5** in acylation reactions. The cyanomethyl ester (**15b**)



was prepared and a qualitative comparison was made with **15a, 15b, 6,** and **7**. Solutions of these compounds in DMF, when warmed (90°) with *N*-(2-aminoethyl)morpholine produced the following results. The ester (**15a**) and the anhydride (**6**) were completely converted into amide (**16a**) in less than two hours, whereas **15b** produced only a 20% yield of amide (80% recovered ester) and **7** was unreactive. Upon further comparison of **15a** and **6**, it was found that each reacted completely (tlc) to form **16a** in THF solution (25°) within the course of an hour. The secondary amine, *N*-methylaminoacetaldehyde diethylacetal, completely converted **6** to amide **17** in four hours (25°, THF), whereas no reaction was observed with **15a** (tlc). Refluxing **15a** with this amine (THF) however, did produce **17** in equivalent yield. Aniline reacted completely with **6** (25°, THF, 24 hours), whereas no observable change was apparent with **15a** under identical conditions (12). The difference in reactivity between **15a** and **6** was most dramatically displayed when each was mixed with 3-amino-1,2,4-triazole in THF. The anhydride (**6**) produced **16c** (80%) after twenty-four hours reflux, whereas **15a** gave no observable reaction under identical conditions. Furthermore, **15a** failed to react with the aminotriazole under any conditions employed. Similar results were obtained when 2-aminobenzimidazole and 2-aminothiazole were employed with **15a** and **6** (13).

Having established the greater reactivity of **6** over other active esters in this series, it was of interest to compare **6** with other mixed anhydrides. We investigated the generation of oxygen containing mixed anhydrides but obtained only high melting, intractable solids from **5**. EEDQ (**18**) has been employed as an acid activating reagent and reportedly generates a mixed anhydride moiety as the acylating species (14). This compound was compared with **6** in the coupling reaction between **5** and aniline. An 84% yield of anilide (**16b**) was obtained. This compares favorably to the results with **6**.



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A recent report describes the generation of a series of benzoic *N*-alkyldithiocarbamic anhydrides (15). Although the compounds reported therein were crystalline solids, they were unstable to heat and light. A more serious disadvantage of the thio analogs is that they must be prepared from another activated carboxyl derivative. The mixed anhydrides reported here are generated from the carboxylic acid itself under mild, slightly alkaline conditions.

With regard to the criteria set forth earlier (2), **6** is the most satisfactory of the acylating derivatives synthesized in the pyrazine series. As indicated above, it is extremely reactive, soluble in common solvents, stable, undergoes virtually no side reactions, and the by-product, diphenylamine, is conveniently removed by washing the product with an organic solvent. Also, in this respect, the diphenyl derivative is preferred over a dialkylamino analog since the liberated amine is a weaker base and dosen't undergo acylation reactions under the conditions.

Since mixed anhydrides of this type are prepared, isolated, and stored under normal laboratory conditions with essentially no special precautions, they should be of particular advantage where it is difficult or impossible to prepare other carboxyl activated derivatives.

EXPERIMENTAL (16)

Cyanomethyl 3,5-Diamino-6-chloropyrazinecarboxylate (**15b**).

Chloroacetonitrile (0.90 mole) was added to a solution of **5** (1.90 g., 0.01 mole) and triethylamine (1.5 ml.) in DMF (20 ml.). After twenty four hours of stirring, this mixture was diluted with cold water (100 ml.) and the solid was filtered giving 2.08 g., m.p. 276-279° dec. Recrystallization from warm DMF by the addition of hot ethanol followed by cooling gave 1.64 g., m.p. 281-283° dec.

Anal. Calcd. for $C_7H_6ClN_5O_2$: C, 36.93; H, 2.66; N, 30.77. Found: C, 37.15; H, 2.67; N, 30.65.

N,N-Diphenylcarbamic 3,5-diamino-6-chloropyrazinecarboxylic anhydride (**6**).

A

Diphenylcarbamoyl chloride (33.8 g., 0.146 mole) was added to a solution of **5** (27.6 g., 0.146 mole) and triethylamine (20.5 ml., 0.146 mole) in DMF (300 ml.). The solution was stirred for twenty four hours and poured into cold water (1500 ml.). The precipitated solid was filtered and suspended in acetonitrile (100 ml.) to remove unreacted carbamoyl chloride. Filtration and drying gave 20 g., m.p. 202-206° (resolidification). Repeated recrystallization from acetonitrile produced a material melting at 228-230° dec; ir (potassium bromide): 1725, 1700 cm^{-1} (-CO-O-CON<).

Anal. Calcd. for $C_{18}H_{14}ClN_5O_3$: C, 56.33; H, 3.68; N, 18.25. Found: C, 56.13; H, 3.43; N, 18.40.

B.

(*N,N*-Diphenylcarbamoyl)pyridinium chloride (17) (3.11 g., 0.01 mole) in water (25 ml.) was added rapidly to a stirred solution of **5** (1.90 g., 0.01 mole) and triethylamine (0.01 ml.) in water (25 ml.). After one hour the precipitated solid was filtered and washed with acetonitrile to yield 2.20 g. of light yellow powder. The ir (potassium bromide) of this sample was superimposable with the analytical sample above, although some melting and resolidification occurred in the region 170-180°.

C.

The procedure in B was followed using ethanol (50 ml.) rather than water (it was necessary to use four equivalents of triethylamine to solubilize the acid). After one hour, 2.5 g., was filtered. This material was satisfactory for further studies without additional purification.

Reaction of *N,N*-Diphenylcarbamic 3,5-diamino-6-chloropyrazinecarboxylic Anhydride (**6**) with sodium Methoxide.

The anhydride **6** (0.17 g., 0.5 mmole) was added to a solution of sodium methoxide (0.05 g., 1.0 mmole) in methanol (2 ml.). The resulting mixture was warmed for a few minutes then allowed to cool. The solid that crystallized was identical in all respects with a known sample of **7** (18).

Preparation of Anhydrides Listed in Table I.

N,N-Diphenylcarbamic Benzoic Anhydride (**10**).

To a stirred solution of **9** (1.24 g., 4 mmoles) in water (5 ml.) was added a solution of triethylamine (0.6 ml., 4 mmoles) and benzoic acid (0.488 g., 4 mmoles) in water (5 ml.). A cream-colored solid separated immediately. The mixture was stirred for 1 hour, filtered, the solid washed with water and dried (80%), 1.2 g., m.p. 115-120°. Recrystallization from cyclohexane gave white hard crystals, m.p. 124-125°.

Anal. Calcd. for $C_{20}H_{15}NO_3$ (317.33): C, 75.69; H, 4.76; N, 4.41. Found: C, 75.59; H, 4.74; N, 4.47.

N,N-Diphenylcarbamic Furoic Anhydride (**11**).

This compound was synthesized as above using **9** (6.35 g., 0.02 mole) in water (25 ml.) and (3.0 ml, 0.02 mole) and furoic acid (2.24 g., 0.02 mole) in water (25 ml.), 5.46 g., m.p. 90-105°. Recrystallization from 1-chlorobutane gave white needles, m.p. 116-118°.

Anal. Calcd. for $C_{18}H_{13}NO_4$ (307.29): C, 70.35; H, 4.26; N, 4.56. Found: C, 70.70; H, 4.34; N, 4.53.

N,N-Diphenylcarbamic *p*-Hydroxybenzoic Anhydride (**12**).

This compound was synthesized as described above, using **9** (1.24 g., 4 mmoles) in water (5 ml.) and a solution of *p*-hydroxybenzoic acid (0.55 g., 4 mmoles) and triethylamine (0.6 ml., 4 mmoles) in water (5 ml.) at 0-5°. The precipitated solid was collected after 10 minutes and washed with cold 1-chlorobutane, 0.31 g. (23%), m.p. 143-146° dec., with effervescence. The compound recrystallized from benzene had m.p. 170-172°, dec., with effervescence when heated rapidly, otherwise it did not melt below 280°.

Anal. Calcd. for $C_{20}H_{15}NO_4$ (333.33): C, 72.06; H, 4.54; N, 4.20. Found: C, 71.91; H, 4.60; N, 4.05.

N,N-Diphenylcarbamic Anthranilic Anhydride (**13**).

This compound was synthesized as described above, using **9** (6.22 g., 0.02 mole) in water (15 ml.) and a solution of anthranilic acid (2.74 g., 0.02 mole) and triethylamine (3.0 ml., 0.02 mole) in water (10 ml.). An additional 25 ml. of water and 100 ml. of 2-propanol were added and the solid that separated was collected giving 4.05 g., m.p. 117-127°. Repeated recrystallization from 1-chlorobutane gave m.p. 133-135°.

Anal. Calcd. for $C_{20}H_{16}N_2O_3$ (332.34): C, 72.28; H, 4.85; N, 8.43. Found: C, 72.20; H, 4.86; N, 8.35.

N,N-Diphenylcarbamic *p*-Aminobenzoic Anhydride (**14**).

This compound was synthesized as described above, using **9** (9.33 g., 0.03 mole) in water (50 ml.) and a solution of *p*-aminobenzoic acid (4.12 g., 0.03 mole) and triethylamine (4.5 ml., 0.03 mole) in water (25 ml.) at 0-5°. After 0.5 hour the yellowish solid was collected, washed with cold water and cold 2-propanol giving 8.77 g., m.p. > 190°. This material was extracted with hot benzene (800 ml.) and concentrated to a volume of 400 ml. Filtration yielded 6.9 g., m.p. 181-184° dec. with effervesence.

Anal. Calcd. for $C_{20}H_{16}N_2O_3$ (332.34): C, 72.28; H, 4.85; N, 8.43. Found: C, 72.46; H, 4.96; N, 8.28.

Comparison of Mixed Anhydride (**6**) with Other Acylating Species.

A. *N*-(2-Aminoethyl)morpholine.

(1) A mixture of **7** (2.02 g., 0.01 mole), *N*-(2-aminoethyl)-morpholine (1.50 ml.) and DMF (20 ml.) was warmed on the steam bath for two hours. Dilution with water (100 ml.) led to the recovery of **7** (> 90%). No indication of amide formation was found by *tlc.*

(2) A solution of **15b** (2.3 g., 0.01 mole) and *N*-(2-aminoethyl)morpholine (1.50 ml.) in DMF (30 ml.) was warmed on the steam bath for two hours. Addition of water (100 ml.) led to the recovery of 1.5 g. of **15b**. Evaporation of the filtrate produced 0.6 g. of amide (**16a**), m.p. 170-176°.

(3) *N*-(2-aminoethyl)morpholine (0.5 ml.) was added to a solution of **15a** (0.95 g., 2.5 mmoles) in THF (30 ml.). After one hour (25°), tlc examination indicated complete conversion to the amide (**16a**).

(4) *N*-(2-aminoethyl)morpholine (0.5 ml.) was added to a solution of **6** (0.95 g., 2.5 mmoles) in THF (30 ml.). After one hour (25°), tlc examination indicated complete conversion to the amide (**16a**).

B. *N*-Methylaminoacetaldehyde Diethyl Acetal.

(1) A solution of *N*-methylaminoacetaldehyde diethyl acetal (2.94 g., 0.02 mole) and **15a** (3.27 g., 0.01 mole) in THF (100 ml.) was stirred at 25° for 4 hours. A tlc probe (silica gel, chloroform: methanol, 9:1) indicated no reaction. The solution was heated to reflux for 18 hours. Tlc examination showed no detectable amount of **15a**. The solvent was evaporated and the residual oil was triturated with 1-chlorobutane to give 2.31 g., (73%) of yellow solid (**17**), m.p. 117-119°.

Anal. Calcd. for $C_{12}H_{20}ClN_5O_3$ (317.78): C, 45.35; H, 6.34; N, 22.04. Found: C, 45.34; H, 6.29; N, 22.09.

(2) A solution of **6** (5.0 g., 0.013 mole) and *N*-methylaminoacetaldehyde diethyl acetal (3.82 g., 0.026 mole) in THF (250 ml.) was stirred at 25° for 4 hours. Tlc indicated complete conversion of **6** to **17**.

C. Aniline.

Compound **15a** (0.48 g., 1.3 mmoles) and **6** (0.48 g., 1.3 moles) were each dissolved in THF (20 ml.). To each solution was added aniline (0.5 ml.) and the resulting solutions were stirred at 25°. After 24 hours, **15a** showed little or no reaction (tlc, silica gel, chloroform: methanol, 9:1), whereas **6** was essentially completely converted to **16b**. After 48 hours, **15a** (0.42 g., 88%) was recovered and **16b** (0.25 g., 74%) was isolated from the reaction with **6**.

N-(1,2,4-triazol-3-yl)-3,5-diamino-6-chloropyrazinecarboxamide (**16c**).

3-Amino-1,2,4-triazole (1.68 g., 0.02 mole) was added to a solution of **6** (3.84 g., 0.01 mole) in THF (150 ml.) and the resulting mixture heated to reflux for 24 hours. The yellow solid (2.0 g., 80%) that was collected after cooling did not melt below 300°. Purification was effected by dissolution in warm DMF (30 ml.), filtration, and addition of warm water (250 ml.) giving 1.7 g. (no observed change in melting); ir (potassium bromide): 3330 (broad), 1680, 1655, 1615 cm^{-1}.

Anal. Calcd. for $C_7H_7ClN_8O$ (254.66): C, 33.01; H, 2.77; N, 44.01. Found: C, 33.02; H, 2.95; N, 43.85.

N-(2-Benzimidazolyl)-3,5-diamino-6-chloropyrazinecarboxamide (**16d**).

Following the procedure for **16c** and using 2-aminobenzimadazole (1.33 g., 0.01 mole), 3.4 g. of yellow solid, m.p. 162-172°, was obtained. Recrystallization from acetonitrile gave 2.5 g. (82%), m.p. 169-172° dec after drying.

Anal. Calcd. for $C_{12}H_{10}ClN_7O$ (303.71): C, 47.45; H, 3.32; N, 32.29. Found: 47.44; H, 3.60; N, 32.34.

N-(2-Thiazolyl)-3,5-diamino-6-chloropyrazinecarboxamide (**16e**).

A mixture of **6** (3.83 g., 0.01 mole), 2-aminothiazole (2.0 g., 0.02 mole) and THF (150 ml.) was heated to reflux for 2 hours, then allowed to stir overnight. Removal of the solvent *in vacuo* and addition of ethanol to the residue gave 2.5 g., (90%) of dark yellow solid, m.p. 220-228° dec. Recrystallization from 2-propanol produced a material with m.p. 236-239°; ir (potassium bromide): 3330 (broad), 1660 cm^{-1}.

Anal. Calcd. for $C_8H_7ClN_6OS$ (270.71): C, 35.49; H, 2.61; N, 31.05. Found: C, 35.53; H, 2.71; N, 30.85.

A similar experiment using **15a** in place of **6** produced no observable reaction in each case.

N-Phenyl-3,5-diamino-6-chloropyrazinecarboxamide (**16b**) from **5** and EEDQ (**18**).

EEDQ (14) (2.47 g., 0.01 mole) was added to a solution of aniline (5 ml.) and **5** (1.9 g., 0.01 mole) in DMSO (30 ml.). After 24 hours, the reaction mixture was poured into water (150 ml.) and the solid was collected. Extraction of this material with dilute aqueous ammonia provided 0.55 g. of recovered **5**. The residue (1.58 g., 84% based on recovered acid) was identical in all respects with a known sample of **16b**. (2).

Acknowledgement.

The authors would like to express their sincere gratitude to Dr. Edward J. Gragoe of these laboratories for many helpful discussions during the course of this work.

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(12) Aniline does react with **10a** in refluxing *n*-amyl alcohol to produce **16b** in low yield, see reference 2.

(13) Structures are assigned to the *exo*-position since very active acylating agents usually undergo reaction at that site. In addition, ring acylated products undergo rearrangement to *exo*-derivatives on heating. No such rearrangement was observed.

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