Heterocycles from Substituted Amides. VIII (1,2). Oxazole Derivatives from Reaction of Isocyanates with 2-Isocyanoacetamides

John P. Chupp and Kindrick L. Leschinsky*

Monsanto Agricultural Products Company, Research Department, 800 N. Lindbergh Blvd., St. Louis, Missouri 63166

Received December 13, 1979

A facile reaction of 2-isocyanoacetamides **1** with reactive aryl and sulfonyl isocyanates is shown to give 5-amino-2-oxazolecarboxamides **3** in a reaction arising from electrophilic attack of isocyanate with the nucleophilic isocyanide carbon. This reaction, perhaps proceeding through an unstable nitrile ylid intermediate reminiscent of the Cornforth rearrangement, is a first example of ring closure *via* acylation, involving the activated methylene of an organic isocyanide, without recourse to added base. Isomeric 5-amino-4-oxazolecarboxamides **4** are formed when 5-aminooxazoles **2** react with isocyanates. Since **2** has previously been shown to easily form by thermal isomerization of **1**, methods now exist for the preparation of both 5-amino- 2- and 4-oxazolecarboxamides from the single starting material **1**. In contrast, **1** with acyl isocyanates is shown to give a variety of products, including iminooxazolinediones, 5-amino-2-oxazolecarboxamide **3** and 2 (1) pyrazinones (tentatively identified), depending on the structure of the isocyanates.

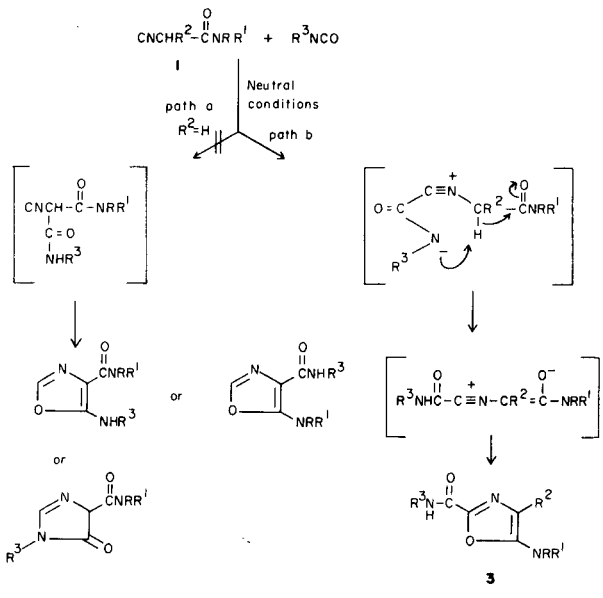
J. Heterocyclic Chem., **17**, 711 (1980).

In a previous report (1), 2-isocyanoacetamides **1** were demonstrated to form 5-aminooxazoles **2** by ring closure of the amide carbonyl on the isocyanide carbon. Moreover, acylation of **1** was shown to give oxazoles *via* ring closure through ketone carbonyl. Consequently, it was thought of interest to carbamylate **1** with isocyanates. In like manner to acylation, it would be expected that the resulting carbamoylation of the *alpha*-carbon would give rise to an unstable intermediate, which could effect ring closure through either one of the more nearly equally reactive amidic carbonyl groups, or alternatively *via* the secondary amidic nitrogen. In this fashion, 5-amino-4-oxazolecarboxamides or 4-imidazolincarboxamide-5-ones would be the respective expected products. Any of these materials would possess an unsubstituted 2-position (formyl proton, R^2 = H, Scheme 1a).

Carbamoylation of labile protic materials by isocyanates often proceeds easily without added base, as these reagents serve as their own proton acceptor. Consequently the isocyanates were initially contacted with **1** under neutral conditions in inert hydrocarbyl solvents. Reaction readily occurred with the sulfonyl isocyanates at room temperature, and with reactive aryl isocyanates in refluxing benzene or toluene, to give fair to good yields of crystalline products. These materials however did not evidence a formyl proton in their nmr spectra, but rather an upfield olefinic proton singlet (R^2 = H).

These compounds were identified as 5-amino-2-oxazolecarboxamides **3** and arise by attack of the electrophilic isocyanate on the nucleophilic isocyanide (Scheme 1b). α-Methylene proton lability is utilized however, as the resulting nitrogen anion, formed *in situ*, and behaving as a base, can initiate enolization. The nitrile-ylid so formed bears a strong resemblance to the intermediate originally postulated in the Cornforth rearrangement (3,4).

Scheme I



It has more lately been theorized (5,6) that this unstable intermediate probably does not possess a formal charge separation so distinct as represented in Scheme 1b, and perhaps the Cornforth rearrangement is better characterized as proceeding *via* a more concerted pathway. In similar manner, formation of **3** from **1** and isocyanate would not necessarily possess the distinct unstable intermediate shown in Scheme 1b. Nevertheless, drawing a parallel between this reaction and that of the Cornforth rearrangement seems unavoidable (7).

Scheme 1b also illustrates for the first time the successful reaction of an activated methylene isocyanide without prior carbanion generation. Moreover, it is worth noting that, whereas, as shown in the preceding study (1),

0022-152X/80/040711-05$02.25

Table 1

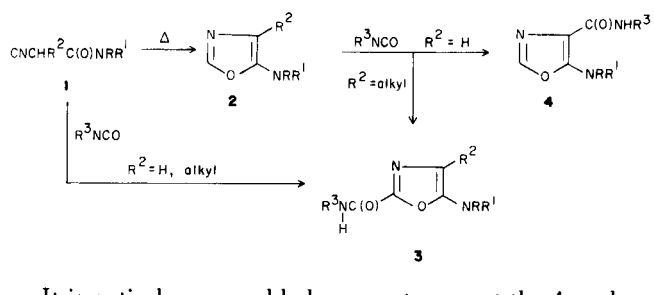
5-Amino-2-oxazolecarboxamides, **3**, and 5-Amino-4-oxazolecarboxamides, **4**

Compound No.	R	R¹	R²	R³	Yield (%)	M.p. °C	Elemental Analyses Calcd. C	H	N	Found C	H	N
3a	C_6H_5	$(CH_3)_2CH$	H	4-$(CH_3)C_6H_4SO_2$-	70	157-158	60.13	5.30	10.52	60.10	5.30	10.43
3b	4-ClC_6H_4	CH_3	H	3,4-$Cl_2C_6H_4$	49	144-145	51.47	3.05	10.59	51.34	3.25	10.41
3c	4-ClC_6H_4	$(CH_3)_2CH$	H	4-$(CH_3)C_6H_4SO_2$	75	130-132	53.27	3.97	10.35	53.21	4.03	10.36
3d	3,4$Cl_2C_6H_3$	$(CH_3)_2CH$	H	4-$(CH_3)C_6H_4SO_2$	64	122-124	51.29	4.09	8.97	51.10	4.06	9.01
3e	$C_6H_5CH_2$	H	H	4$(CH_3)C_6H_4SO_2$	19	145-147	58.21	4.61	11.31	58.22	4.61	11.34
3f	C_6H_5	$(CH_3)_2CH$	H	$(CH_3)_3CC(O)$	61	211	65.63	7.04	12.76	65.66	7.10	12.76
3g	C_6H_5	$(CH_3)_2CH$	CH_3	4$(NO_2)C_6H_4SO_2$	36,50	141-146	54.05	4.54	12.61	53.81	4.67	12.59
4a	C_6H_5	$(CH_3)_2CH$	—	4$(CH_3)C_6H_4SO_2$	73	146-147	60.13	5.30	10.52	60.09	5.30	10.49
4b	-CH-$(CH_2)_4$- (CH₃)		—	4$(CH_3)C_6H_4SO_2$	73	129-131	56.18	5.82	11.56	55.82	5.85	11.44
4c	-CH-$(CH_2)_4$- (CH₃)		—	3,4$(Cl_2)C_6H_3$	58	132-134	54.25	4.84	11.86	54.12	4.89	11.93
4d	C_6H_5	$(CH_3)_2CH$	—	$ClCH_2C(O)$	56	129-130	55.99	5.01	13.06	56.19	4.94	12.72
4e	C_6H_5	$(CH_3)_2CH$	—	$Cl_3CC(O)$	72	143-145	46.12	3.61	10.76	46.23	3.77	10.64
4f	C_6H_5	$(CH_3)_2CH$	—	$(CH_3)_3CC(O)$	30	160-161	65.63	7.04	12.76	65.58	7.08	12.70
4g	C_6H_5	$(CH_3)_2CH$	—	$C_6H_5C(O)$	35	116-119	68.75	5.48	12.03	67.99	5.44	11.72

1 possessing a secondary (N-H) amide linkage resists cyclization to **2**, reaction with isocyanate does give ring closure although in lower yield (see Table 1, **3e**). α-Isocyanoacetates however, remain inert to cyclization in the presence of reactive isocyanates.

Verification for Scheme 1b is found upon reacting 2,4-unsubstituted 5-aminooxazoles **2** with isocyanates (Scheme 2). In these instances the 4-position is preferred over that of the 2-position for substitution, to give 5-amino-oxazolecarboxamides **4**. In previous studies, reaction of 5-aminooxazoles with isocyanates had necessarily given substitution at the 4-position, as all examples examined possessed a 2-substituent other than hydrogen (8). On the other hand, as shown in Scheme 2, when the 4-position is occupied ($R^2 = CH_3$), substitution can and does give the 2-substituted material **3**, identical with the oxazole arising from reaction of **1** with isocyanate. The former sequence appears to proceed more slowly and require greater energy input than the latter "Cornforth"-type pathway shown in Sheme 1b.

Scheme 2



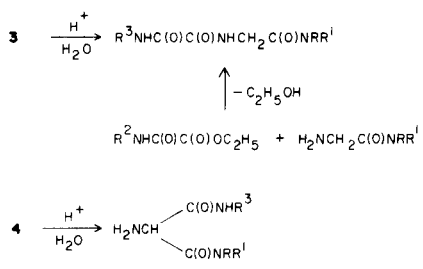
It is entirely reasonable however to expect the 4- rather than 2-position to be more activated towards electrophilic substitution, as the former bears a more formal analogy to the electron rich *beta*-carbon found in 1-enamines. Nevertheless, the 2-position must also be activated to some extent by electron enrichment from the 5-amino group, to allow substitution at this position when the 4-position is blocked. Other pathways such as the Diels-Alder mechanism suggested for isothiocyanate substitution at the 5-position in 2-aminooxazoles (9) seems less tenable.

The sequences as shown in Schemes 1b and 2 thus reveal convenient methods for preparing either 5-amino-2- or -4-oxazolecarboxamides from identical starting isocyanide **1**. Examples of both **3** and **4** with pertinent physical properties prepared from these procedures are listed in Table 1.

The nmr spectra serves nicely to delineate between the isomers **3** and **4**. The 2-proton (formyl) in **4** appears downfield at *ca.* δ 7.2, often distinguishable as a sharp singlet even though amidst aromatic protons. On the other hand, the 4-proton in **3** has been considerably shifted (*ca.* 1 ppm) upfield and appears as a single absorption near δ 5.8, having lost much of the hetero-aromatic character of its parent **2** by virtue of ring substitution by carboxamide. The latter moiety withdraws electrons, reducing the ring currents and attenuating the deshielding effects of the heteroaromatic system. This same type of effect has been previously observed in the thiophene system (10).

In addition to the structural confirmation given by the spectral data, and the identical oxazole **3g**, formed from both oxazole and isocyanide (Scheme 2), advantage was taken of the usually easy hydrolytic cleavage of oxazoles. As described in the Experimental Section, such treatment gives predictable rise to *bis*-amides (Scheme 3).

Scheme 3

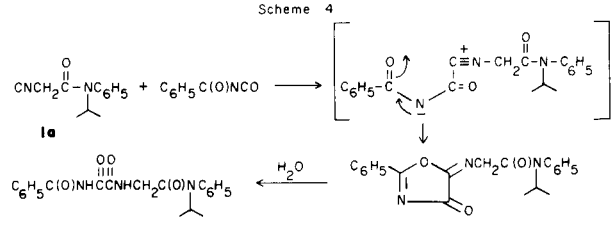


It appears that for optimum yields, and to minimize side reactions, the isocyanates employed in Schemes 1 and 2 should be fairly reactive. Both sulfonyl and negatively substituted aryl isocyanates fit this criteria. Acyl isocyanates, easily derived from the parent amide (11), are also very reactive, comparable to sulfonyl isocyanates. Moreover, certain of these compounds had previously been found to react with simple, non-enolizable organic isocyanides to give iminooxazolinediones (12,13). It therefore became of interest to contrast the different reaction modes of several of these isocyanates with **1**.

Benzoyl isocyanate apparently gives an iminooxazolinedione, of a type mentioned above, upon reaction with **1** (Scheme 4). The highly crystalline, sharply melting product possesses an ir absorption for ring carbonyl at 5.6 μ, while amide carbonyl and imino absorptions are recorded at 6.0 μ and 6.2 μ, respectively. In addition, nmr shows slightly unequal singlets for the *alpha*-methylene group at δ 4.3 and δ 4.6, distinctly different from the absorption for the methylene in starting **1a**. This observation would suggest the material reverts to *syn* and *anti* isomers in solution. Finally, mild hydrolysis in aqueous alcohol yields a compound identified by spectra and analysis as an oxamide derivative.

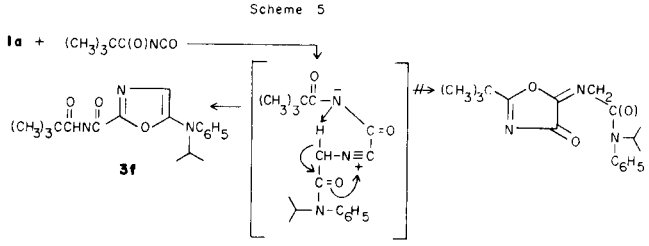
Pivaloyl isocyanate appears to react with **1** in a fashion identical to sulfonyl and aryl isocyanates, forming a 5-amino-2-oxazolecarboxamide **3f** (Scheme 5). As is apparent here, the Cornforth-type intermediate (nitrile ylid) can either ring close through the acyl carbonyl to form iminooxazoleinedione or the amide carbonyl to give oxazole. In contrast to benzoyl isocyanate, perhaps the acyl

Scheme 4



oxygen is too hindered by the adjacent *t*-butyl group to take part in the reaction. Structure verification is offered by the ir absorption at 3 μ for N-H and the typical 4-oxazole proton (**3**) singlet at δ 5.4.

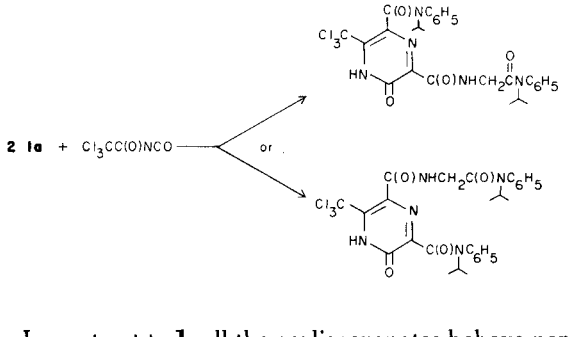
Scheme 5



Two molar equivalents of **1a** reacted with trichloroacetyl isocyanate to give pure crystalline adduct. Nmr indicated an *alpha*-methylene group appearing as a doublet at δ 3.63, and the presence respectively, of two different pairs of $CH(CH_3)_2$, two isopropyl methine heptets and two separate downfield amide protons. A partial wash with deuterium oxide succeeded in wholly removing the N-H farther downfield, while only partly removing the more upfield N-H; in this way the latter proton was shown to be coupled to the *alpha*-methylene because it was only partially resolved to a singlet by this procedure.

On the basis of the above results, and satisfying mechanistic considerations (which however, will not be detailed here), the alternate structures given in Scheme 6 are isomeric 2(1) pyrazinones (14). Both of these materials contain two amide protons of differing lability, and one *alpha*-methylene, coupled to the predictably less mobile proton. Both structures have four amide carbonyls and one imino group, enough functions to satisfy the multiple ir absorptions found in the 6 μ region.

Scheme 6



In contrast to **1**, all the acylisocyanates behave normally in reaction with **2**, giving **4** in good yields (Table 1).

EXPERIMENTAL

Representative procedures only for the preparation of **3** and **4** (Table 1) from **1** and **2** will be given. Complete hydrolysis studies will be detailed as will reactions between **1** and acyl isocyanates.

N-(4-Toluenesulfonyl)-5-(*N*-isopropylanilino)-2-oxazolecarboxamide (**3a**).

2-Isocyano-*N*-isopropylacetanilide (1), **1a**, (2.02 g., 0.01 mole) was dissolved in benzene and 2.0 g. (0.01 mole) of *p*-toluenesulfonyl isocyanate was added. There was an immediate color change (to yellow) and the ir showed considerable isocyanate and isocyanide disappearance. After a half-hour at room temperature, the reaction was essentially com-

plete. The nmr of the benzene solution in the non-aromatic region showed a "clean" spectra, indicating essentially quantitative conversion to **3a**. The sticky, non-crystalline residue after solvent removal was dissolved in ether. Upon cooling and scratching, 2.8 g. of yellow crystals resulted, m.p. 153-155°. Recrystallization from isopropanol gave white crystals; ir (chloroform): 3.05 μ (N-H), 5.85 μ (C=O); nmr (deuteriochloroform): δ 1.2 (d, 6, J = 7 Hz, $(CH_3)_2CH$), 2.4 (s, 3, $ArCH_3$), 4.3 (heptet, 1, J = 7 Hz, $(CH_3)_2CH$), 5.8 (s, 1, =CH), 7-7.4 and 7.95-8.2 (multiplets, 9, ArH), 8.8 (broad, 1, N-H).

3',4'-Dichloro-5-(*N*-methyl-4-chloroanilino)-2-oxazolecarboxanilide (**3b**).

4'-Chloro-2-isocyano-*N*-methylacetanilide (1) (1.0 g., 0.005 mole) and 0.94 g. of 3,4-dichlorophenyl isocyanate (0.005 mole) were heated at reflux in benzene for 24 hours. A small amount of isocyanate (ir) remained. The solvent was removed, and the residue triturated with ether to yield 0.95 g. of crystals. Further purification was accomplished by recrystallization from isopropanol; ir (chloroform): 3.1 μ (N-H), 5.92 μ (C=O); nmr (deuteriochloroform): δ 3.4 (s, 3, NCH_3), 6.37 (s, 1, =CH), 7.8 (m, 7, ArH), 8.3 (broad, 1, N-H).

5-(Benzylamino)-*N*-(4-toluenesulfonyl)-2-oxazolecarboxamide (**3e**).

N-Benzyl-2-isocyanoacetamide (1) (1.75 g., 0.01 mole) was added to methylene chloride and 2.0 g. (0.01 mole) of *p*-toluenesulfonyl isocyanate was added, causing an exothermic reaction. Ir examination of the mixture shortly thereafter indicated only a small amount of isocyanide remaining. The mixture was allowed to stand at room temperature for 1.5 hours. The material was filtered to remove a small amount of insolubles, then the solvent removed to give a sticky, semi-solid residue. This was recrystallized from methanol, then acetonitrile, to give 0.7 g. of crystals; ir (chloroform): 2.98 (N-H), 5.9 μ (C=O); nmr (deuteriochloroform): δ 2.4 (s, 3, $ArCH_3$), 4.21 (d, 2, J = 6 Hz, CH_2NH), 6.0 (s, 1, =CH), 7.2-8.0 (m, 11, ArH and NH).

N-(4-Nitrobenzenesulfonyl)-5-(*N*-isopropylanilino)-4-methyl-2-oxazolecarboxamide (**3g**).

2-Isocyano-*N*-isopropylpropionanilide (1) (2.16 g., 0.01 mole) was dissolved in 50 ml. of benzene and 2.28 g. (0.01 mole) of *p*-nitrobenzenesulfonyl isocyanate was added, causing a mild exotherm. After four hours the reaction was complete as indicated by absence of both isocyanide and isocyanate (ir 4.7 and 4.4 μ, respectively). The material was filtered, solvent removed from the filtrate, and the residue eluted through a silicic acid column with chloroform-ethanol (95:5). The compound so obtained was recrystallized from isopropanol to give 1.6 g. of product ir (chloroform): 3.0 μ (N-H), 5.85 μ (C=O), nmr (deuteriochloroform): δ 1.2 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 1.8 (s, 3, $C=CCH_3$), 4.3 (heptet, 1, J = 7 Hz, $CH(CH_3)_2$), 6.8-7.3 (m, 6, ArH and NH), 8.4 (s, 4, ArH).

The material **3g** prepared as described above was identical with the compound obtained from 5-(*N*-isopropylanilino)-4-methyloxazole (1) and *p*-nitrobenzenesulfonyl isocyanate. Equimolar amounts (0.005 mole) of these two reactants were allowed to stand in benzene at room temperature 12 hours. This time it was found necessary to effect complete reaction (monitoring isocyanate, ir: 4.4 μ) by heating. After filtering, solvent was removed from the filtrate and the residue recrystallized from 2-propanol to give 1.1 g. of **3g**.

5-(*N*-Isopropylanilino)-*N*-(4-toluenesulfonyl)-4-oxazolecarboxamide (**4a**).

5-(*N*-Isopropylanilino)oxazole (1) (2.02 g., 0.01 mole), was placed in benzene and an equimolar amount of *p*-toluenesulfonyl isocyanate was added. Monitoring by ir revealed complete reaction after one-half hour. Removal of benzene gave crystals which were further recrystallized from isopropanol to give a 2.9 g. yield; ir (chloroform): 2.95 μ (N-H), 5.85 μ (C=O); nmr (deuteriochloroform): δ 1.2 (d, J = 7 Hz, $CH(CH_3)_2$), 2.45 (s, 3, $ArCH_3$), 5.03 (heptet, 1, J = 7 Hz, $NCH(CH_3)_2$), 6.9-8.2 (m, 9, ArH), 7.15 (s, 1, =CH), 8.75 (broad, 1, N-H).

3',4'-Dichloro-5-(2-methyl-1-piperidino)-4-oxazolecarboxanilide (**4c**).

5-(2-Methyl-1-piperidino)oxazole (1) (1.66 g., 0.01 mole), was dissolved in 60 ml. of toluene with 1.88 g. (0.01 mole) of 3,4-dichlorophenyl isocyanate and the temperature raised to reflux. After six hours the material was cooled, solvent removed, and the residue was recrystallized from 2-propanol to give 1.1 g. of product. Further purification could be effected by a second recrystallization from methylcyclohexane; ir (chloroform): 3.0 μ (N-H), 6.0 μ (C=O); nmr (deuteriochloroform): δ 1.1-2.1 (m, 9, $(CH_2)_3CH_3$), 2.9-4.6 (m, 3, $CHNCH_2$), 7.5 (s, 1, N=CH), 7.2-7.9 (m, 3, ArH), 8.8 (broad, 1, N-H).

N-Pivaloyl-5-(*N*-isopropylanilino)-4-oxazolecarboxamide (**4f**).

5-(*N*-Isopropylanilino)oxazole (2.02 g., 0.01 mole) was dissolved in benzene and an equimolar amount of pivaloyl isocyanate added. After it was apparent by ir monitoring that the reaction was slow at room temperature, the mixture was heated at reflux for *ca.* 18 hours; even after this time some isocyanate remained. After solvent was removed, the residue was triturated with ether, then recrystallized from isopropanol to give 1.0 g. of crystals, ir (chloroform): 2.9 μ (N-H), 5.8 μ (C=O); nmr (deuteriochloroform): δ 1.2-1.4 (s, d, 15, $C(CH_3)_3$, $CH(CH_3)_2$), 5.2 (heptet, 1, $CH(CH_3)_2$), 7.0-7.5 (m, 6, ArH, =CH), 10.0 (broad, 1, N-H).

2-Phenyl-5-(*N*-isopropylcarbaniloylmethylimino)-2-oxazoline-4,5-dione.

2-Isocyano-*N*-isopropylacetanilide (2.02 g., 0.01 mole), was placed in 50 ml. of carbon tetrachloride with 1.5 g. of benzoyl isocyanate (0.01 mole). A crystalline product (2.9 g.), 84% yield deposited from solution, m.p. 118-120°. Recrystallization from ethyl acetate gave m.p. 124-125°; ir (chloroform): no N-H, 5.6 μ (C=O), 6.0 μ (amide C=O), 6.2 μ (C=N), 6.4 μ (C=N); nmr (deuteriochloroform): δ 1.1 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 4.25 (s, 1.1, syn or anti $=NCH_2CO$), 4.60 (s, 0.9, anti or syn $=NCH_2CO$), 5.0 (heptet, 1, J = 7 Hz, $CH(CH_3)_2$), 7.03-8.4 (m, 10, ArH).

Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.72; H, 5.48; N, 12.03. Found: C, 68.11; H, 5.29; N, 11.78.

Repeated analyses did not result in better data for this mositure sensitive compound.

Reaction Product from 2-Isocyano-*N*-isopropylacetanilide and Trichloroacetyl Isocyanate.

2-Isocyano-*N*-isopropylacetanilide (2.02 g., 0.01 mole) was mixed with an equimolar amount of trichloroacetyl isocyanate in 75 ml. of benzene. Monitoring by ir indicated that all of the isocyanide had reacted, while about half of the isocyanate remained. Consequently a second molar equivalent of isocyanide was added. After several hours standing at room temperature, the reaction mixture was vacuum treated to remove solvent and the residue recrystallized from 2-propanol to give 49% yield of product. Three recrystallizations from 2-propanol only raised the m.p. from 153-155° to 154-156°; ir (chloroform): 2.9 μ (N-H), 5.7-6.0 μ (multiple C=O), 6.2 (C=N); nmr (deuteriochloroform): δ 1.1 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 1.28 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 3.64 (d, 2, J = 4.5 Hz, $NHCH_2$), 4.2 (heptet, 1, J = 7 Hz, $CH(CH_3)_2$), 4.95 (heptet, 1, J = 7 Hz, $CH(CH_3)_2$), 6.65-7.6 (m, 10, ArH), 8.15 (broad, 1, N-H), 8.9 (s, 1, N-H).

Anal. Calcd. for $C_{27}H_{28}Cl_3N_5O_4$: C, 54.69; H, 4.76; N, 11.81; Cl, 17.94. Found: C, 54.78; H, 4.76; N, 11.89; Cl, 17.88.

Hydrolysis of 2-Phenyl-5-(*N*-isopropylcarbaniloylmethylimino)-2-oxazolin-4,5-dione.

The title compound (1.0 g.) was placed in 50 ml. of 25% aqueous 2-propanol containing several drops of concentrated hydrochloric acid. The mixture was refluxed for one-half hour, solvent removed, and the remaining residue air-dried, then recrystallized from 2-propanol to give 0.6 g. of *N*-(*N*-isopropylcarbanoloylmethyl)-*N'*-benzoyloxalamide, m.p. 184-185°; ir (chloroform): 2.95 μ (N-H), 5.6 (C=O), 5.9 (C=O), 6.0-6.1 (C=O); nmr (deuteriochloroform): δ 1.10 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 3.65 (d, 2, J = 4.5 Hz, $NHCH_2$), 4.95 (heptet, 1, J = 7 Hz, $CH(CH_3)_2$), 7.8 (m, 10, ArH), 8.25 (broad, 1, NH), 10.3 (broad, 1, N-H).

Anal. Calcd. for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.09; H, 5.77; N, 11.27.

Hydrolysis of **3a**.

One gram of **3a** was placed in 100 ml. of glyme and *ca.* 30 ml. of 12% hydrochloric acid added. More glyme was then added to make the mixture more nearly homogeneous. After standing at room temperature for 24 hours, the solvent was removed and the residue taken up in 2-propanol, then recrystallized to give product. It was necessary to vacuum dry the material at the temperature of refluxing chlorobenzene to remove the last vestiges of 2-propanol. The product, *N*-(*N*-isopropylcarbaniloylmethyl)-*N'*-(4-toluenesulfonyl)oxamide, possessed m.p. 156-157°; ir (chloroform): 3.0 μ (N-H), 5.8 and 5.95 (C=O); nmr (deuteriochloroform): δ 1.0 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 2.4 (s, 3, $ArCH_3$), 3.58 (d, 2, J = 5 Hz, $NHCH_2$), 4.9 (heptet, 1, J = 7 Hz, $CH(CH_3)_2$), 6.95-8.2 (m, 10, Ar*H* and N-*H*), 9.8 (broad, 1, N-*H*).

Anal. Calcd. for $C_{20}H_{23}N_3O_5S$: C, 57.54; H, 5.55; N, 10.07. Found: C, 57.68; H, 5.74; N, 10.09.

Hydrolysis of **3b**.

Material **3b** (0.6 g.) was placed in 150 ml. of glyme with 50 ml. of 12% hydrochloric acid. The material was stirred overnite at room temperature, then volatiles removed under vacuum. The solid residue was recrystallized from nitromethane, m.p. 221-222°. The mixture m.p. was not depressed, and the ir and nmr were identical with authentic *N*-(*N*-methyl-4-chlorocarbaniloylmethyl)-*N'*-(3,4-dichlorophenyl)oxamide, whose authentic preparation is described below; ir (Nujol): 3.0 μ (N-H), 5.9-6.05 μ (C=O); nmr (DMSO-d_6): δ 3.8 (d, 2, J = 5 Hz, $NHCH_2$), 7.3-8.2 (m, 7, Ar*H*), 8.83 (broad, t, 1, CH_2NH), 10.92 (broad, 1, N-*H*).

Anal. Calcd. for $C_{17}H_{14}Cl_3N_3O_3$: C, 49.24; H, 3.40; N, 10.13. Found: C, 49.22; H, 3.46; N, 10.09.

N-(*N*-methyl-4-chlorocarbaniloylmethyl)-*N'*-(3,4-dichlorophenyl)oxamide.

Ethyl 3',4'-dichlorophenyloxamate (2.6 g., 0.01 mole) was mixed with 2.0 g. of 2-amino-*N*-methyl-*p*-chloroacetanilide (1) (0.01 mole) in acetonitrile, and the solution refluxed for 18 hours. The cooled contents was filtered, and the residue recrystallized from nitromethane to give crystals, m.p. 220-221°, and otherwsie entirely identical with the hydrolysis product from **3b**.

Hydrolysis of **4c**.

Material **4c** (1.0 g.) was placed in a solution of 50 ml. of glyme with 10 ml. of 10% hydrochloric acid and allowed to stand overnite at room temperature. The volatiles were removed under vacuum, and the residue dissolved in water, warming being necessary to dissolve the last part of the crude hydrochloride salt. A solution of 5% sodium hydroxide was added, and the precipitated free base filtered and air-dried, to give 2-amino-3',4'-dichloro-2-(2-methylpiperidinocarbonyl)-acetanilide, slightly contaminated by water; nmr (deuteriochloroform): δ 1.15 and 1.25 (2d, 3, J = 7 Hz, achiral-CH_3), 1.65 (m, 6), -CH_2-C), 2.4 (broad, 2, NH_2), 3.0-5.0 (m, 4, C*H*, and $CHNCH_2$), 8.1-7.8 (m, 3, Ar*H*), 9.7-10.1 (broad, 1, N*H*). Picrate, m.p. 199-201° dec.

REFERENCES AND NOTES

(1) Part VII, J. P. Chupp, and K. L. Leschinsky, *J. Heterocyclic Chem.*, **17**, 705 (1980).

(2) Presented in part at the 178th National ACS Meeting, Washington, D.C., Sept. 9-14, 1979 ORGN 44.

(3) J. W. Cornforth, in "The Chemistry of Penicillin", Princeton University Press, Princeton, N.J., 1959.

(4) M. J. S. Dewar, "Electronic Theory of Organic Chemistry", Oxford University Press, 1959.

(5) M. J. S. Dewar, P. A. Spanninger and I. J. Turchi, *J. Chem. Soc., Chem. Commun.*, 925 (1973).

(6) M. J. S. Dewar and I. J. Turchi, *J. Am. Chem. Soc.*, **96**, 6148 (1974).

(7) A similar pathway to 5-(alkylthio)oxazoles from **1** and certain sulfenamides has recently been suggested, J. P. Chupp, J. J. D'Amico, and K. L. Leschinsky, *J. Org. Chem.*, **43**, 3553 (1978).

(8) D. Clerin, and J. P. Fleury, *Bull. Soc. Chim. France*, 3134 (1973).

(9) G. Crank, *Tetrahedron Letters*, 4537 (1974).

(10) J. P. Chupp, *J. Heterocyclic Chem.*, **7**, 285 (1970).

(11) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 1805 (1963).

(12) R. Neidlein, *Chem. Ber.*, **97**, 3476 (1964).

(13) J. Goerdeler and H. Schenk, *Chem. Ber.*, **98**, 3831 (1965).

(14) Attempts at structural confirmation of this or homologous materials by x-ray crystallography were unsuccessful.