Heterocycles from Substituted Amides. VII (1,2). Oxazoles from 2-Isocyanoacetamides

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Certain heretofore unknown tertiary α-isocyanacetanilides **1** are reported for the first time, prepared by methods necessarily different from those employed to prepare the previously cited aliphatic α-isocyanoacetamides **2**. Like **2**, **1** has been shown to readily undergo dialkylation with alkyl halides. Moreover, **1** also gives rise to oxazole and oxazoline derivatives upon reaction with acyl halides and aldehydes, respectively, resembling the similarly activated α-isocyano esters and sulfones. Further, in a demonstrable ring-chain tautomeric equilibration, apparently restricted to tertiary amides, **1** readily cyclizes, providing the only known synthesis of 5-amino-2,4-unsubstituted oxazoles **3**. In other examples 4-chloro and 4-alkyl-5-aminooxazoles are produced. The materials and reactions are characterized, and compared with previous related studies.

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The isocyanide group incorporated in organic molecules has been shown, like the isomeric nitrile moiety, to stabilize an adjacent carbanion charge. Manifestations of this property have been intensively studied with activation solely by this group (3), or in conjunction with ester (3), and sulfonyl (4,5) functions, while recently a brief description of this activation in certain aliphatic isocyanoacetamides **2** has been noted (6).

We would like to report our concurrent investigation of similar isocyanide activation at the *alpha*-carbon of acylanilides. This latter function would be expected to facilitate carbanion formation, but perhaps less than the more negative ester and sulfonyl moieties previously investigated, while more so than the purely aliphatic amides. It consequently became necessary to prepare the requisite 2-isocyanoaccetanilides **1** for the first time (7,8).

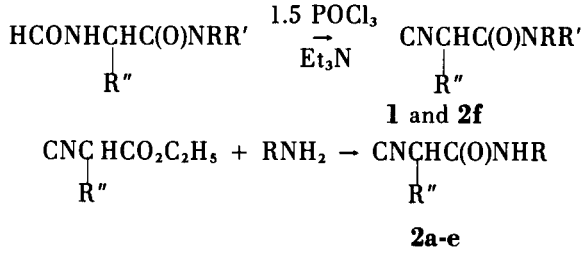
A number of procedures were attempted before conditions were found, fairly optimizing yields of **1**. The compounds so prepared (Scheme 1) are listed in Table 1.

It was found expedient for tertiary amides and anilides to first prepare the 2-aminoacyl amide, either through direct ammonialysis or by Gabriel synthesis from the corresponding 2-chloroacetamide. Formylation could then be accomplished either by direct action of concentrated formic acid or the mixed formic-acetic anhydride reagent. Dehydration of the purified 2-formamidoacetamides was optimized by low temperature dehydration with 1.5 moles of phosphorus oxychloride per mole of amide; lesser amounts left unreacted starting material, while a greater excess of dehydrating agent contributed to resin formation. Although phosgene could be used as the dehydrating agent, it tended to react with isocyanide, thus creating problems with product isolation.

Primary and secondary aliphatic 2-isocyanoacetamides **2**, used in this study (Table 1) were prepared by the previously reported reaction of α-isocyanoacetate esters (9) with the requisite amine (6,10). However, even forcing conditions such as higher temperatures, with the less reactive primary anilines failed to give *sec*-α-isocyanacetanilides by this method.

Unlike certain other organic isocyanides, **1** is characterized by excellent shelf stability. All the materials in Table 1, when properly purified, showed little tendency to darken or decompose on prolonged storage. Further, these isocyanides possess none of the horrendous odor problems associated with many members of this class, including α-isocyanocarboxylic esters.

Scheme 1 (a)



(a) See Table 1 for definition of R, R′ and R″.

Material **1a** was reacted under carbanion forming conditions with reagents that had previously been shown to react successfully with ethyl 2-isocyanoacetate (3) and certain aliphatic 2-isocyanoamides (6). Thus methyl iodide was shown to give the dimethyl derivative of **1a**, and after hydrolysis, the 2-formamido derivative of *N*-isopropyl-2-methylpropionanilide (Scheme 2a). *p*-Nitrobenzaldehyde reacted with **1a**, from which both the *cis* and *trans* forms of4-(*N*-isopropylcarbaniloyl)-5-(*p*-nitrophenyl)-4,5-oxazoline could be isolated (Scheme 2b). Upon acylation of **1a** with acetyl chloride, ring closure took place through the

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Table 1

2-Isocyanoacylanilides **1** and Amides **2**

Compound No.	R	R′	R″	Yield (%)	M.p. (°C)	Formula	Elemental Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1a	C_6H_5	$(CH_3)_2CH$	H	60	80-82	$C_{12}H_{14}N_2O$	71.26	6.98	13.85	71.33	7.03	13.80
1b	4-ClC_6H_4	CH_3	H	88	102-104	$C_{10}H_9ClN_2O$	57.56	4.35	13.43	57.40	4.60	13.29
1c	3,4-$Cl_2C_6H_3$	$(CH_3)_2CH$	H	88	89-91	$C_{12}H_{12}Cl_2N_2O$	53.15	4.46	10.33	53.28	4.53	10.22
1d	C_6H_5	C_2H_5	H	72	52-54	$C_{11}H_{12}N_2O$	70.19	6.43	14.88	70.21	6.44	14.90
1e	C_6H_5	$(CH_3)_2CH$	CH_3	85	47-50	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.14	7.47	12.85
2a (a)	H		H	36	119-121	$C_3H_4N_2O$	42.86	4.80 (c)	33.32	42.54	5.35	33.21
2b	CH_3		H	78	82-84	$C_4H_6N_2O$	48.97	6.16	28.56	48.85	6.17	28.69
2c (b)	$C_6H_5CH_2$		H	85	122-124	$C_{10}H_{10}N_2O$	68.95	5.79	16.08	68.84	5.86	16.02
2d	$(CH_3)_2CH$		H	61	68-71	$C_6H_{10}N_2O$	57.12	7.99	22.21	57.01	8.04	22.11
2e	$C_6H_5CH_2$		CH_3	77	68-70	$C_{11}H_{12}N_2O$	70.19	6.43	14.88	70.00	6.46	14.78
2f	-CH(CH$_3$)-(CH$_2$)$_4$-		H	16	53-55	$C_9H_{14}N_2O$	65.03	8.49	16.85	64.94	8.15	17.06

(a) See reference 10, m.p. 121-122. (b) See reference 6, m.p. 120-122. (c) Repeated analyses did not result in better data for this hygroscopic compound.

Table 2

5-Aminooxazoles **3**

Compound No.	R	R′	R″	Yield (%)	B.p. °C mm	Formula	Elemental Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3a	C_6H_5	$(CH_3)_2CH$	H	60	90-94 (0.4)	$C_{12}H_{14}N_2O$	71.26	6.98	13.85	71.20	7.27	13.42
3b	4-ClC_6H_4	CH_3	H	50	112-113 (0.1)	$C_{10}H_9ClN_2O$	57.56	4.35	13.43	57.55	4.39	13.39
3c	3,4-$Cl_2C_6H_3$	$(CH_3)_2CH$	H	70	125 (0.025)	$C_{12}H_{12}Cl_2N_2O$	53.15	4.46	10.33	52.95	4.48	10.40
3d	-CH(CH$_3$)-(CH$_2$)$_4$-		H	50	75 (0.1)	$C_9H_{14}N_2O$	65.03	8.49	16.85	64.85	8.52	16.91
3e	C_6H_5	C_2H_5	H	45	89-91 (0.025)	$C_{11}H_{12}N_2O$	70.19	6.43	14.88	69.98	6.50	14.80
3f	C_6H_5	$(CH_3)_2CH$	CH_3	71	90-96 (0.03)	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.09	7.46	12.85
3g	C_6H_5	$(CH_3)_2CH$	Cl	44	102-107 (0.1)	$C_{12}H_{13}ClN_2O$	60.89	(14.98)(a)	11.84	60.79	(14.47)(a)	11.67

(a)Chlorine analysis.

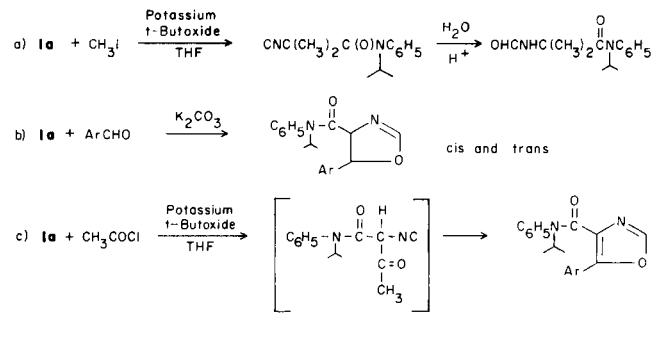
isocyanide group and ketonic oxygen, forming 4-(*N*-isopropylcarbaniloyl)-5-methyl oxazole (Scheme 2c).

The reaction of the above reagents with the carbanion derived from 2-isocyanoacetanilides are thus entirely in accord with previous literature (3-5, 11-13) regarding the interaction of such alkylating and acylating reagents with carbanions derived from ethyl 2-isocyano acetate and sulfonylmethyl isocyanides.

Oxazole formation in Scheme 2c proceeds through the ketonic oxygen, probably *via* the enol (or enolate anion). It is noteworthy that the amidic oxygen does not take part in the ring closure. This is consistent with the facile conversion of certain ketonic isocyanides to oxazoles. Although phenacyl isocyanide can be isolated, even simple recrystallization causes it to convert quantitatively to the isomeric 5-phenyloxazole (14).

On the other hand, *alpha*-isocyanoesters cyclize with considerably more reluctance; ethyl 2-isocyanoacetate giving 5-ethoxyoxazole in only 5% yield (9). This result is also in accord with the spontaneous ring closure observed with ethyl 2-acyl-2-isocyanoacetates where closure occurs exclusively through the ketonic oxygen to give oxazole-4-carboxylate (12). Further, in the material 2-isocyano-2-(ethoxycarbonyl) *N,N*-dimethyl acetamide, where the isocyano group can optionally ring close on either an ester or aliphatic amide carbonyl, only the former occurs on distillation to form 5-ethoxy-4-(dimethylcarbamoyl)oxazole

Scheme 2



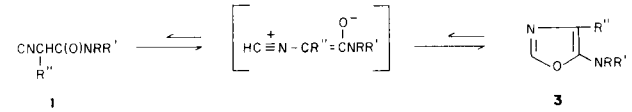
(15). Finally, certain aliphatic sec-2-isocyanoacetamides (*i.e.* **2c**) have recently been shown to undergo ring-closure under base alkylating conditions to imidazolinones (6).

To date then, no ring-closure of an isocyanide through an amidic carbonyl has been observed; indeed data from the above observations and references would indicate this type of carbonyl to be resistant to such transformations.

It therefore was of interest to study the ring-closure properties of tertiary isocyanoacetamides such as newly derived **1** as well as **2f**. Although these materials are stable at room temperature, and can be easily purified by recrystallization, surprisingly, **1** cannot be successfully distilled without formation of the isomeric 5-aminooxazoles, **3**.

The ring closure to oxazoles (Scheme 3), as typified by **1a-3a** appears to be a genuine case of ring-chain tautomerism, including a demonstrable equilibrium between the pair. Thus on heating **1a** to 130°, isomerization is quickly (one-half hour) effected. However, as measured by the nmr of the sample, the *alpha*-methylene singlet attributable to **1a** remains (2.2%), slightly upfield from the isopropyl methine proton of **3a**. Conversely, on heating **3a** at 130° the same *alpha* methylene singlet reappears, with **1a** again present to the extent of 2.5 percent. In confirmation of this, a small isocyanide band at 4.7 μ also reappears.

Scheme 3



1 3

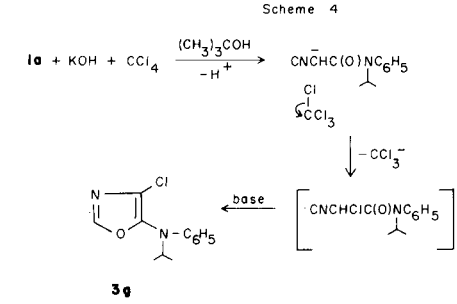
The nitrilium intermediate postulated from the equilibrium in Scheme 3 can be considered a nitrile ylid (of HCN), a structure heretofore postulated for cyclizations to substituted oxazoles (16), including the Cornforth rearrangement (17,18). In succeeding papers (see also reference 8), additional novel substituted oxazole syntheses from 2-isocyanoacylamides will be shown to occur, presumably through similar nitrilium intermediates.

Table 2 compiles the oxazoles, **3**, derived from isomerization of *t*-2-isocyanoacetanilides **1** and amide **2f**. Materials with *alpha*-alkyl substituents such as **1e** give exceptionally high yields of oxazole under fairly mild cyclization conditions. This is consistent with the favorable effect such substituents have in promoting the cyclization of *alpha*-isocyano esters (9).

Attempts to successfully isomerize certain of the secondary 2-isocyanoacetamides under neutral or basic conditions were abortive, decomposition taking place on prolonged heating. From our results it would appear that the spontaneous cyclization observed upon benzyl bromide alkylation of **2c** (6) must proceed, greatly facilitated by geminal *alpha*-substitution.

In attempting to chlorinate the labile 2-position in **1a** under base conditions, an interesting cyclization to the heretofore unreported 4-chloro-5-aminooxazole **3g** took place. The chlorination utilized carbon tetrachloride as the halogenating agent (Scheme 4), a system previously used with success to initiate chlorination of activated methylene sulfones and ketones under carbanion generating conditions (19). Apparently the *alpha*-chlorinated isocyanide spontaneously enolizes to the chloroamino oxazole. The oxazole **3a** is apparently not appreciably pre-formed, and then chlorinated, as the latter gave much reduced yields of **3g** upon treatment under identical conditions with carbon tetrachloride.

Scheme 4



3g

The 5-amino-2,4-unsubstituted oxazoles **3a-e**, prepared for the first time, are characterized by two oxazole protons, both appearing as singlets in the nmr. The 2-proton in **3a** is downfield at δ 7.8, while the 4-proton absorption is found at δ 6.7. These absorptions are fairly consistent with the 2- and 4-nuclear protons in oxazole itself (20) and other derivatives (21). The greater than usual upfield shift of the 4- proton can be attributed to its decided *beta*-enamine orientation, a phenomonen heretofore observed in some aminothiophenes (22).

Oxazoles **3** are further characterized by lack of N-H or OH infrared absorption bands, but consistent strong absorption for the OC=N stretching frequency at 1610 cm^{-1}, somewhat higher than the usual oxazole frequency between 1555 and 1585 cm^{-1} (21), but in agreement with certain other 5-aminooxazoles (23,18).

Ultraviolet absorption (ethanol) of the 2,4-unsubstituted-5-aminooxazoles as represented by the 5-anilino derivative **3a** (238 mμ, ϵ max = 14,100) and the 5-piperidino compound **3d** (258 mμ, ϵ max = 5700) were little different from the oxazole additionally substituted by a 5-methyl **3f** (242 mμ, ϵ max = 14,600) or 5-chloro **2g** (237 mμ, ϵ max = 13,100). The parent isocyanides **1**, possess no absorption in this region.

Mass spectra as represented by **3a** is in accord with the assigned structure: the parent ion (202) is very strong, while principal fragments are derived from cleavages of the 4-(*N*-isopropylanilino) substituent, with 4-anilinooxazole (160) the base peak, and simple oxazole (68) readily apparent.

Finally, facile hydrolysis of **3** in four percent hydrochloric acid solution afforded the expected acylic hydration products, namely 2-formamidoacetanilides. These materials are consistent with products derived from acid hydrolysis of other 5-aminooxazoles (24).

EXPERIMENTAL

The spectra obtained were recorded from a Perkin-Elmer Infracord (ir), Varian T-60 NMR spectrometer, Beckman DK-2A (uv), and CEC 21-04 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, and Atlantic Microlab, Inc., Atlanta, Georgia.

Representative procedures for the preparation of **1, 2** and **3** (Tables 1 and 2) are detailed below, as well as methods used for the basic alkylation, and acylation of **1a**.

2-Isocyano-*N*-isopropylacetanilide (**1a**).

2-Chloro-*N*-isopropylacetanilide (1.0 mole, 212 g.) was charged to a 3 liter autoclave and *ca* 500 ml. ethanol was added. The autoclave was sealed and cooled by dry-ice, a lecture bottle of ammonia attached, and 190 g. ammonia charged to the autoclave. The contents were then shaken for two days at room temperature, excess ammonia vented, and the contents vacuum treated to remove alcohol. The residue was treated with 500 ml. of 25% caustic, and the resulting oil layer was distilled. The main fraction, as 2-amino-*N*-isopropylacetanilide, was collected, b.p. 125-135° (0.15 mm), weighing 100.6 g. and representing a 55% yield.

2-Amino-*N*-isopropylacetanilide (0.4 mole, 76.8 g.) was mixed with 97% formic acid, and the mixture heated at 125° for two hours. The mixture was cooled to 110° and toluene added. The temperature was raised to reflux and held for 24 hours, causing water and excess formic acid to be removed *via* an azeotrope. The solvent was removed and the residue was recrystallized from benzene to give 75.6 g. of 2-formamido-*N*-isopropylacetanilide, m.p. 144-146°, as white solid (86% yield). This material was identical with that obtained by acid hydrolysis of **3a**.

2-Formamido-*N*-isopropylacetanilide (0.25 mole, 55.0 g.) was placed in a 2 liter, 4-neck-flask. Triethylamine (1.25 moles, 126 g.) and 400 ml. of methylene chloride were then added. The resulting clear solution was cooled to −10°, and the dropwise addition of phosphorus oxychloride (0.375 mole, 57.5 g.) was performed. After the addition was complete, the ir showed a strong isocyanide absorption. The temperature was lowered to −10° and continuous addition of sodium carbonate solution (1 mole, 106 g.) was commenced, maintaining the temperature at 0° or lower. After addition, more water was added, and the mixture allowed to stir at room temperature for thirty minutes. The organic layer was separated, it being found expedient to filter this phase through powdered magnesium sulfate to avoid an appreciable "rag" layer. The filtrate was then washed with salt water, and again filtered through magnesium sulfate. After drying over the same reagent, the material was vacuum treated to remove solvent. The residue was recrystallized from ether to give 30.9 g. of white crystals, 61% yield (**1a**). The residue from the ether filtrate was distilled to give 4.9 g. of 5-(*N*-isopropylanilino)oxazole **3a**.

4'-Chloro-2-isocyano-*N*-methylacetanilide (**1b**).

2,4'-Dichloro-*N*-methylacetanilide (0.5 mole, 109 g.) was added all at once to a hot slurry of 101.8 g. (0.55 mole) of potassium phthalimide in 500 ml. of DMF. The mixture was heated to 60-75° and maintained at that temperature for two hours. The material was allowed to stir at room temperature overnight. One liter of water was added, the mixture cooled to 6° filtered, and the residue air-dried to give 163.7 g. (100% yield) of *N*-[*N*-(*p*-chlorophenyl)-*N*-methylcarbamoylmethyl]phthalimide. This material (0.46 mole, 151 g.) was slurried with 1.25 liter ethanol and 23.2 g. (0.69 mole) 95% hydrazine added. The temperature was raised to reflux and more ethanol added to enable stirring of the slurry. After two hours, the material was vacuum treated to remove solvent, and the residue (92.4 g.) was treated with one liter of 2*N* hydrochloric acid and filtered. The material was vacuum treated to remove water, and the residue treated with *ca.* 250 ml. of 25% caustic. Ether was added, the layers separated, and the organic phase was dried over magnesium sulfate. After solvent removal, 68.3 g. of the residue was distilled to give 48.8 g. of 2-amino-4'-chloro-*N*-methylacetanilide. This material (0.248 mole, 47 g.) was mixed with 23 g. (0.476 mole) of concentrated formic acid and toluene was added. The material was refluxed for 36 hours, allowed to cool, and the product allowed to crystallize from the toluene solution. A total of 46.5 g. (83% yield) of 2-formamido-4'-chloro-*N*-methylacetanilide, m.p. 148-150° was obtained.

The formamido compound was dehydrated by dissolving 22.6 g. (0.1 mole) in 300 ml. of methylene chloride with 50.5 g. of triethyl amine. After the temperature was lowered to −10°, phosphorus oxychloride (0.15 mole, 23 g.) in methylene chloride was added dropwise. Immediately upon addition the ir revealed an isocyanide band at 4.7 ν with no N-H and only one carbonyl absorption (no formamide). A solution of sodium carbonate (0.4 mole, 42.4 g. in 500 ml. of water) was added, and the whole mixture, with stirring, allowed to warm to 20°. The layers were separated, and the organic layer filtered through magnesium sulfate, washed with water, and again filtered through magnesium sulfate. After drying over the same reagent, the solvent was removed and the solid residue recrystallized from carbon tetrachloride to give 18.3 g. (88% yield). Further purification for analytical analyses was performed by recrystallization from methanol.

2-Isocyano-*N*-isopropylpropionanilide (**1e**).

2-Chloro-*N*-isopropylpropionanilide (135 g., 0.6 mole) was added at 60° to a slurry of 122 g. (0.66 mole) of potassium phthalimide. The mixture was heated at reflux for 16 hours, treated with 1500 ml. of ice-water and the precipitate filtered and air-dried to give 170 g. (85% yield) of *N*-isopropyl-2-(1-phthalimido)propionanilide. Recrystallization from methanol gave white crystals, m.p. 169-171°. This material (161 g., 0.48 mole) was slurried in ethanol at *ca.* 50° and 23 g. (0.72 mole) of hydrazine was added. The mixture was refluxed for eight hours, then cooled and filtered. After evaporation of the ethanol from the filtrate, the residue (89.1 g., 88% yield) crystallized as 2-amino-*N*-isopropylpropionanilide. All of this material was converted to the 2-formamido compound by refluxing with 80 g. (1.73 mole), 97% formic acid. After two hours, 200 ml. of toluene was added, and water with excess formic acid removed by azeotrope. Upon cooling, crystals formed, which were combined with the crystals obtained on solvent removal and trituration with ether. Total yield of 2-formamido-*N*-isopropylpropionanilide was 80.7 g. (81%). Recrystallization afforded white crystals, m.p. 129-132.

N-Isopropyl-2-formamidopropionanilide (23.4 g., 0.1 mole) was dissolved in 200 ml. of methylene chloride and 50 g. of triethylamine, and the resulting solution was cooled to −10°. Phosphorus oxychloride (23 g., 0.15 mole) was added dropwise, not permitting the mixture to exceed −5°. After the addition, 250 ml. of 15% sodium carbonate solution was added, keeping the temperature below 20°. The layers were separated and the organic portion washed with 100 ml. of 5% sodium chloride solution, then dried over magnesium sulfate. After removing the drying agent and solvent, the oily residue was taken up in methylcyclohexane to produce 18.3 g. (85%) of crystalline 2-isocyano-*N*-isopropylpropionanilide.

N-Isopropyl-2-isocyanoacetamide (**2d**).

Ethyl 2-isocyanoacetate (9) (0.03 mole, 3.4 g.) was mixed with 1.8 g. (0.03 mole) of isopropyl amine. The mixture was allowed to stand overnite at room temperature, when the ester carbonyl was still detected (ir). To insure complete reaction, 0.9 g. of isopropyl amine was added. After five hours the material was vacuum treated to remove ethanol and excess amine. The solid residue was recrystallized from ether to give 2.3 g.

5-(2-Methylpiperidino)oxazole (**3d**).

Material **2f** was heated at a pot temperature of 90-95°, with **3d** being collected pure as a distillate at b.p. 75° (0.4 mm).

5-(*N*-Isopropyl-3,4-dichloroanilino)oxazole (**3c**).

The isocyanide **1c** (0.0184 mole, 5.0 g.) was heated under vacuum with distillation of 3.5 g. of oxazole **3c** at b.p. 125 (0.025 mm).

5-*N*-(Isopropylanilino)-4-methyloxazole (**3f**).

The isocyanide **1e** (10.0 g., .0462 mole) was heated for 15 minutes at *ca.* 130°. Ir showed no isocyanide (4.5 μ) after this time. The dark oil was then distilled, to give a 7.1 g. yield, b.p. 90-96° (0.03 mm).

Equilibration of 2-Isocyano-*N*-isopropylacetanilide **1a** and 5-(*N*-Isopropylanilino)oxazole (**3a**).

Material **1a** when heated in the absence of solvent at 130° converted 97% to 5-(*N*-isopropylanilino)oxazole **3a**. Conversely, pure distilled oxazole **3a** [b.p. 86-90° (0.02 mm)] was converted to 3% 2-isocyano-*N*-isopropylacetanilide (**1a**) at 140°. This was qualitatively evidenced from the reappearance of the isocyanide ir absorption at 4.7 μ. Quantitatively, expansion of the *N*-isopropyl methyne nmr absorption revealed the upfield *alpha*-isocyanomethylene singlet at *ca.* δ 3.9, calculated at 3% concentration.

4-Chloro-5(*N*-isopropylanilino)oxazole (**3g**).

Material **1a** (5 g., 0.0247 mole) was dissolved in a mixture of 50 ml. of carbon tetrachloride and 50 ml. of *t*-butyl alcohol. To this stirred mixture was added 20 g. of powdered potassium hydroxide and the whole stirred at ambient temperature overnight. Water was added with stirring, and the organic phase extracted with methylene chloride. The organic layer was washed once again with water, then dried over magnesium sulfate. After filtering and removing the solvent, an oil was obtained, which gave on distillation, 2.6 g. of colorless distillate, b.p. 102-105° (0.15 mm). Assay on a glc column (10 ft. chromasorb, (210-220°) gave 97% **2g** with 3% unchlorinated oxazole, **2a**; ir (film): no NH or C=O absorption, 6.08, 6.25 μ (oxazole and/or C=N); nmr (carbon tetrachloride): δ 1.2 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 4.2 (heptet, 1, J = 7 Hz, $CH(CH_3)_2$), 6.5-7.4 (multiplets, 4, Ar*H*), 7.52 (s, 1, 2-oxazole - C*H*).

N-Isopropyl-2-formamido-2-methylpropionanilide.

2-Isocyano-*N*-isopropylacetanilide (4.05 g., 0.02 mole) in 10 ml. of tetrahydrofuran (THF) was added dropwise to 0.10 mole of potassium *t*-butoxide (4.5 g.) in 25 ml. of THF at −60°. Then, 0.042 mole of methyl iodide (6.0 g.) in 10 ml. of THF was added at −60° to −50°. The mixture was allowed to warm to room temperature, the solvent was removed, and the residue taken up in methylene chloride, washed with water, and dried over magnesium sufate. After vacuum removal of the solvent, the residue was treated with ether, filtered, and the filtrate was evaporated to give 2-isocyano-2-methylpropionanilide (ir and nmr). A minor contaminate as discerned by nmr appeared to be 4-methyl-5-(*N*-isopropylanilino)oxazole (**3f**), arising from cyclization of traces of 2-isocyano-*N*-isopropylpropionanilide (**1f**). Derivatization of the dialkylated material was accomplished by room temperature hydrolysis of the isocyanide to the formamide with 7% hydrochloric acid. Trituration with hexane gave the analytical sample, m.p. 152-153°; ir (chloroform): 3400 cm^{-1} (NH), 1690 (C=O) nmr (deuteriochloroform): δ 1.03 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 1.45 (s, 6, $C(CH_3)_2$), 4.92 (heptet, 1, J = 7 Hz, $CH(CH_3)_2$), 6.4 (broad, 1, NH), 7-7.5 (multiplets, 5, Ar*H*), 7.8 [d, 1, J = 2 Hz, *H*C(O)].

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.64; H, 8.09; N, 11.26.

cis- and *trans*-4-(*N*-Isopropylcarbanilоyl)-5-(*p*-nitrophenyl)-4,5-oxazoline.

2-Isocyano-*N*-isopropylacetanilide (**1a**) (0.01 mole, 2.02 g.) was placed in methanol containing 1.4 g. of dissolved potassium carbonate and 1.5 g. of *p*-nitrobenzaldehyde. The reaction appeared to be slightly exothermic. The material was permitted to stand several hours, methanol removed under vacuum, then chloroform added. The solution was washed with water, dried over magnesium carbonate, then the solvent was evaporated to give a solid. Recrystallization from isopropyl gave two fractions: m.p. 110° (*cis*) and m.p. 185-190° (*trans*); nmr (deuteriochloroform): *trans* δ 0.7 and 0.9 (two doublets, 6, J = 7 Hz, AB type $(CH_3)CH$), 4.6 (heptet, 1, J = 7 Hz, $(CH_3)_2CH$), 4.9 (two doublets, 1, J = 9 Hz, J = 0.5 Hz, 4-oxazolidine proton), 5.35 (d, 1, J = 9 Hz, 5-oxazolidine proton), 6.8-8.4 (multiplets, 10, Ar*H* and 2-oxazolidine proton); nmr (deuteriochloroform): *cis* δ 1.2 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 4.2 (two doublets 1, J = 7 Hz, (and again by J = 0.5 Hz), 4-oxazolidine proton), 5.0 (heptet, 1, J = 7 Hz, $CH(CH_3)_2$), 6.05 (d, 1, J = 7 Hz, 5-oxazolidine proton), 6.8-8.4 (multiplets, 10, Ar*H* and 2-oxazolidine proton).

Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: *cis* C, 64.32; H, 5.48; N, 11.97; *trans* N, 11.47.

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