of this magnitude (3–4%) were obtained in checking the osmometer with known materials.

Electrolytic Reduction of Dimer.—A sample of 1-methyl-3-carbamidopyridinium chloride was completely reduced to the dimer at −1.2 v. as described above. The resulting solution was then electrolyzed at −1.8 v., whereupon a 2-electron reduction occurred (measured value: 2.11 electrons/initial molecule of pyridinium salt). The ultraviolet spectrum retained the 298-mμ band observed with the original dimer.

Catalytic Hydrogenation of Dimer.—One millimole of 1-methyl-3-carbamidopyridinium chloride was completely reduced electrolytically to the dimer as described above. About 50 mg. of 10% palladium on charcoal was added to the solution, and hydrogenation was carried out at atmospheric pressure in an apparatus similar to that described by Wiberg.[36] Hydrogen uptake was rapid at first and gradually tapered to a very slow rate. After 5 hr., 0.8 mmole of hydrogen had been consumed and the absorbance at 298 mμ had decreased by 15%. After 59 hr., the absorbance at 298 mμ had decreased by 25% from its initial value, and hydrogen uptake was correct for the complete reduction of one double bond and 25% completion in the reduction of a second one. Thus, in the rapid stage, it appears that a double bond having little involvement with the chromophore is reduced while simultaneously but much more slowly a second reduction process destroys the chromophore.

In another experiment, a sample of the dimer, prepared electrolytically, was further reduced electrolytically as described above, and then subjected to hydrogenation. In this case, there was no rapid initial stage, only a very slow hydrogen uptake, and an absorbance decrease at the same rate as in the later stage of the previous experiment. Thus it appears that, early in the catalytic hydrogenation, the same reduction product is formed as in the electrolytic reduction but that the latter is "cleaner," stopping after one double bond is reduced.

Preparation of 1-Methyl-3-carbamido-1,4-dihydropyridine by Electrolysis on the Second Wave.—Six samples of 1-methyl-3-carbamidopyridinium chloride ranging from 100–960 mg. were reduced in phosphate buffers of pH 7.8–9.2 with the cathode potential controlled at −1.85 v. Both polarographic waves disappeared during the electrolysis. Coulometry showed that the reduction involved 2 electrons (1.93 ± 0.15; the precision is poor because of the high background current at this potential). The ultraviolet spectrum of the starting material (λ_{max} 264 mμ) gave way to one with a band at 360 mμ. In one of the experiments, the reduction product was isolated as follows. With all solutions carefully deoxygenated and kept under an atmosphere of nitrogen, the 200-ml. electrolyzed solution was extracted 20 times with 50-ml. portions of chloroform, and the combined extracts were evaporated *in vacuo*. The yellow, oily residue could not be crystallized, but was simply stored in the cold under nitrogen.[37] A portion of the material was spread in a thin, uniform layer between rock salt plates and its infrared spectrum was recorded. Ultraviolet spectra in aqueous Tris buffer of pH 9 were also obtained. The infrared spectrum of the electrolytic reduction product was identical, band for band including the fingerprint region, with that of authentic 1,4-dihydro compound prepared by dithionite reduction, and both materials exhibited the same λ_{max} values in the ultraviolet.

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(36) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 227.

(37) Failure to obtain a crystalline product does not reflect unfavorably upon the electrolytic preparation; crystallization is often equally difficult with the dithionite product. Crystals have occasionally been obtained after electrolysis by treating the chloroform residue with ethyl acetate [H. Kuhnis, W. Traber, and P. Karrer, *Helv. Chim. Acta*, **40**, 751 (1957)], but often the oil is intractable.[8]

The Synthesis and Reactions of 2-Isocyanatoacyl Chlorides

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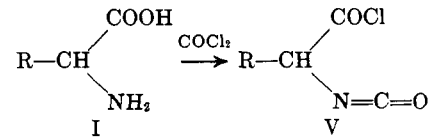
A series of 2-isocyanatoacyl chlorides was prepared by treating glycine, DL-alanine, L-valine, L-leucine, and L-phenylalanine with phosgene in an inert solvent such as dioxane. A reaction mechanism for 2-isocyanatoacyl chloride formation is proposed. The acid chloride group of the 2-isocyanatoacyl chloride is more reactive than the isocyanate group as an electrophile. In the reaction with an equimolar amount of ethanol or water, 2-isocyanatoacetyl chloride gave ethyl 2-isocyanatoacetate or 2,5-oxazolidinedione, respectively. With a molar excess of *p*-phenetidine, it gave 3-(*p*-phenetyl)hydantoin and with a 2 molar or greater excess of amine it gave the corresponding ureidoamide. Treatment with molar quantities of N-methylaniline in the presence of molar quantities of pyridine furnished N-methyl-2-isocyanatoacetanilide.

It has been well established that the reaction of α-amino acids with phosgene gives 2,5-oxazolidinediones in good yield under suitable conditions.[1] However, on prolonged exposure, a tendency to form an oily product instead of the 2,5-oxazolidinedione was noted.[2]

This work was undertaken to elucidate the nature of this oily product. During the course of the investigation, it was shown that the oil contains 2-(N-chloroformylamino)acyl chlorides (IV) and that they are converted to 2-isocyanatoacyl chlorides (V) with evolution of hydrogen chloride when distilled.



I V

a, R = H
b, R = CH_3
c, R = $(CH_3)_2CH$
d, R = $(CH_3)_2CHCH_2$
e, R = $C_6H_5CH_2$

The formation of compounds of type V has briefly been described by Baird, Parry, and Robinson.[3]

When α-amino acids (I) were treated with phosgene in an inert solvent such as dioxane and the oil remaining

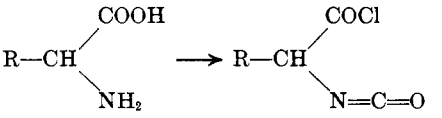
(1) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1961, p. 867.

(2) A. C. Farthing, *J. Chem. Soc.*, 3213 (1950).

(3) W. Baird, E. G. Parry, and S. Robinson, British Patent 646,033 (1950).

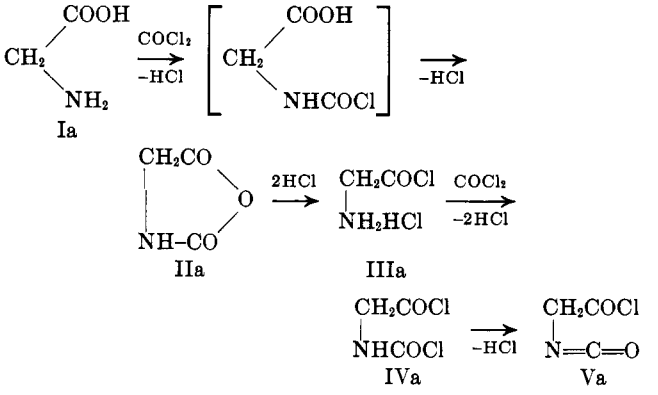
TABLE I

PREPARATION OF 2-ISOCYANATOACYL CHLORIDES (V)



R	Dioxane, ml./ amino acid, g.	Reaction[a] temp., °C.	Reaction[b] time, hr.	HCl pass. time, hr.	Yield, %
H	50	45–50	5	0	0[c]
H	30	45–50	9	0	30[d]
H	20	49	17	2	76
CH_3	25	45	5	0	6
CH_3	15	50–55	5	4	67
$(CH_3)_2CH$	14	45–55	11	0	9[e]
$(CH_3)_2CH$	14	45–50	11	4	75
$(CH_3)_2CH$	14	75–80	11	0	16[e]
$(CH_3)_2CHCH_2$	20	40	17	0	11
$(CH_3)_2CHCH_2$	14	50–55	7	3	76
$C_6H_5CH_2$	14	50–55	5	8	74
$C_6H_5CH_2$	15	60–70	8	4	70

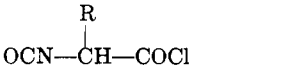
[a] Phosgenation temperature. [b] Total phosgenation time. [c] 2,5-Oxazolidinedione was obtained in 89% yield. [d] 2,5-Oxazolidinedione was obtained in 16% yield. [e] Distillation residue was mainly valine peptide (it showed strong biuret reaction).



to be small, because at a high temperature such as 110 or 200° acid chloride is formed by phosgenation of carboxylic acid[4] but not at 50–60° as described below. The ring-opening reaction was confirmed by the fact that IIa gave 2-aminoacetylchloride hydrochloride (IIIa) with evolution of carbon dioxide on treating it with hydrogen chloride in ether. Furthermore, the above mechanism is supported by following facts: (1) Va was prepared from IIa, phosgene, and hydrogen chloride; (2) butyryl chloride was not obtained from butyric acid and phosgene under the conditions given in Table I.

TABLE II

PROPERTIES OF 2-ISOCYANATOACYL CHLORIDES



R	Starting amino acids	B.p., °C. (mm.)	$[\alpha]_D$,[a] deg.	Calcd., % C	H	Cl	N	Found, % C	H	Cl	N
H	Glycine	64–64.5 (31)				29.70				29.82	
CH_3	DL-Alanine	67–68 (47)				26.55				26.80	
$(CH_3)_2CH$	L-Valine	87.5–88 (39)	+52.1	44.59	4.99			44.23	4.92		
$(CH_3)_2CHCH_2$	L-Leucine	101–102 (39)	+39.5				7.98				7.76
$C_6H_5CH_2$	L-Phenylalanine	101–102 (1)	−31.7	57.29	3.85		6.68	57.37	3.97		6.86

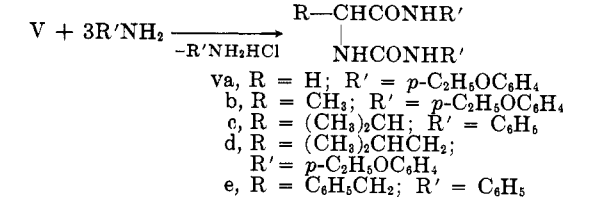
[a] Observed in benzene at 21°.

after removal of the 2,5-oxazolidinediones (II) was distilled, V was obtained in less than 30% yield, and the reaction temperature had little effect on the yield. On the other hand, addition of hydrogen chloride to the reaction mixture considerably increased the yield of V to 67–76% (Table I).

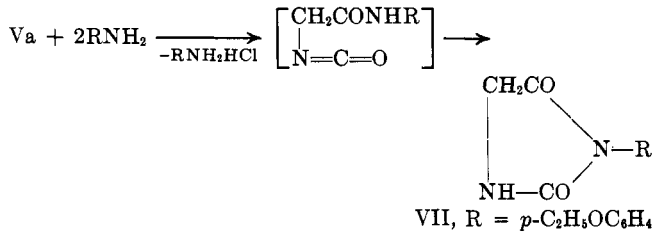
Compounds of type V were characterized by elementary analyses and infrared spectra; their properties are given in Table II. As is evident, high optical activity was observed with the V derived from optically active α-amino acids.

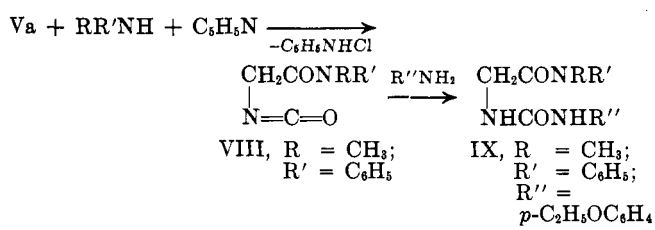
Because of the remarkable effect of hydrogen chloride and the small effect of reaction temperature on the yield of V, the following mechanism can be reasonably advanced for the formation of V (2-isocyanatoacetyl chloride is exemplified as V, and suffix "a" is given to the compounds of its series). This mechanism proposes that the acid chloride of Va is not directly formed by reaction between the carboxyl group and phosgene, but through a ring-opening reaction of 2,5-oxazolidinedione (IIa) with hydrogen chloride. If the acid chloride were formed by a reaction of the carboxyl group with phosgene, the effect of reaction temperature would be expected to be large and that of hydrogen chloride

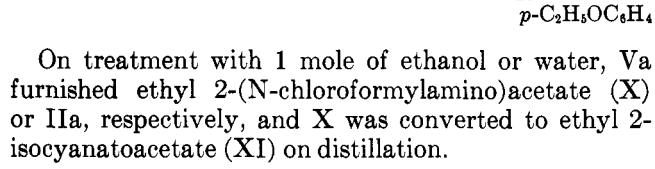
2-Isocyanatoacyl chlorides (V) have two different reactive functions, –COCl and –NCO, and react with nucleophilic reagents. With a primary amine, Va, for example, gave two different products depending upon the molar ratio of the reactants used. With 3 moles of *p*-phenetidine, Va gave 2-(*p*-phenetylureido)acet-*p*-phenetidide (VIa) in quantitative yield, and, with 2 moles of the amine, Va gave 3-(*p*-phenetyl)-hydantoin (VII). When treated with 1 mole of N-methylaniline in the presence of 1 mole of pyridine, Va gave N-methyl-2-isocyanatoacetanilide (VIII). The reactions are summarized as follows.



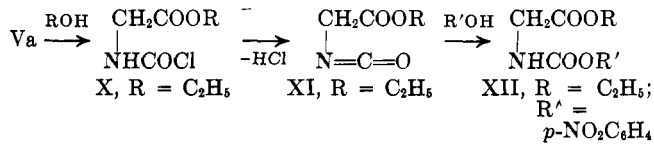
(4) T. Kempf, *J. prakt. Chem.*, **1**, 402 (1870); A. Hochstetter, German Patent, 283,896 (1915).

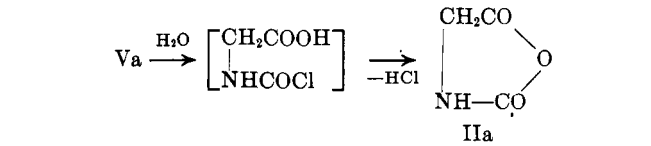






On treatment with 1 mole of ethanol or water, Va furnished ethyl 2-(N-chloroformylamino)acetate (X) or IIa, respectively, and X was converted to ethyl 2-isocyanatoacetate (XI) on distillation.





All of these experiments clearly demonstrate that the acid chloride group of Va is more reactive than the isocyanate group as an electrophile. It seems reasonable to conclude that the other 2-isocyanatoacyl chlorides (V) also have the same reactivity as that of Va.

Table III shows the physical properties and elementary analyses of derivatives from V.

Experimental

2,5-Oxazolidinedione (IIa).—Into a suspension of 15 g. of finely ground glycine in 750 ml. of dry dioxane, phosgene was introduced in a thin stream at 45–50° with efficient agitation. A clear solution was obtained after 5 hr. The solution was filtered to remove unreacted glycine (1.7 g.), and the dioxane was then removed under reduced pressure at a temperature below 40°, access to moisture being prevented. To the residue was added 100 ml. of dry ether, and the crystals of 2,5-oxazolidinedione (IIa) were filtered off and dried over P_2O_5 in a vacuum desiccatar. The crude product so obtained, 16 g. (89%), was recrystallized from ethyl acetate–petroleum ether to yield 14.3 g. (77.2%) of pure material which showed no melting point because of polymerization.

Anal. Calcd. for $C_3H_3NO_3$: N, 13.86. Found: N, 13.69.

Isopropyl N-Carbisopropoxyglycinate.—Sixteen grams of finely ground glycine was treated with phosgene for 8 hr. in 750 ml. of dry dioxane by the above procedure. The solution was concentrated under reducted pressure. The residue consisting of white crystals and violet oil was filtered with the aid of 50 ml. of dry ether, and the collected 2,5-oxazolidinedione was recrystallized from ethyl acetate–petroleum ether, 10.2 g. (47.4%). To the filtrate was added an excess of 2-propanol and the mixture was allowed to stand at room temperature. After 3 days the solvents and excess 2-propanol were removed by distillation under reduced pressure, and the residue was distilled to yield isopropyl N-carbisopropoxyglycinate, 6.3 g. (14.6%), b.p. 94–94.2° (2 mm.) or 110° (5 mm.).

Anal. Calcd. for $C_9H_{17}NO_4$: C, 53.19; H, 8.34; N, 6.89. Found: C, 53.13; H, 8.42; N, 6.92.

TABLE III.—PHYSICAL PROPERTIES AND ELEMENTARY ANALYSES OF DERIVATIVES FROM 2-ISOCYANATOACYL CHLORIDES

Compd.	R	R′	R″	M.p. or b.p. (mm.), °C.	Yield, %	Recrystn. solvents	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
RCHCONR′R″ NHCONR′R″	H	H	*p*-$C_6H_4OC_2H_5$	242.5	94.2	Pyridine	63.85	6.44	11.77	63.73	6.59	11.95
	CH_3	H	*p*-$C_6H_4OC_2H_5$	244	95.7	Pyridine–dioxane (1:3)			11.31			11.62
	$(CH_3)_2CH$	H	C_6H_5	256–257	97.0	Ethanol			13.50			13.80
	$(CH_3)_2CHCH_2$	H	*p*-$C_6H_4OC_2H_5$	214	96.5	Ethanol–water (2:1)			10.16			9.93
	$C_6H_5CH_2$	H	C_6H_5	220–221	97.2	Acetone–water (2:1)	73.51	5.94	11.69	73.91	5.94	11.57
CH_2CO NR / NH–CO	*p*-$C_6H_4OC_2H_5$			198	90.0	Benzene	59.99	5.49	12.72	59.79	5.52	12.80
CH_2CONRR' NHCONHR″	CH_3	C_6H_5	*p*-$C_6H_4OC_2H_5$	153	90.0	Benzene			12.83			13.00
CH_2CONRR' N=C=O	CH_3	C_6H_5		57–58	70.4		63.15	5.30	14.73	63.07	5.50	14.49
CH_2COOR N=C=O	C_2H_5			67–68 (13)	88.7				10.77			10.68
CH_2COOR NHCOOR′	C_2H_5	*p*-$C_6H_4NO_2$		97–97.5	97.5	Toluene			10.44			10.59
CH_2CO O / NH–CO	$(CH_3)_2CH$	$(CH_3)_2CH$		94 (2)			53.19	8.34	6.89	53.13	8.42	6.92
					100[a]	AcOEt–petr. ether			13.86			13.72

[a] Yield of the product before recrystallization.

2-Isocyanatoacetyl Chloride (Va) from Glycine and Phosgene.—Into a suspension of 25 g. of finely ground glycine in 750 ml. of dry dioxane, phosgene was introduced in a thin stream at 45–50° with stirring. After 6 hr., the mixture became almost clear. The reaction was further continued for another 3 hr. The solution obtained was filtered to remove a small amount of insoluble solid and concentrated under reduced pressure at a temperature below 50°. The residue consisting of white crystals and violet oil was filtered with the aid of 50 ml. of ether. The crystals of 2,5-oxazolidinedione (IIa) were collected and washed with dry ether and dried over P_2O_5 in a vacuum desiccator. They weighed 5.5 g. (16%). The filtrate was distilled to yield 12 g. (30%) of an irritating colorless liquid, 2-isocyanatoacetyl chloride (Va), b.p. 64–64.5° (31 mm.). The compound showed characteristic absorption peaks at 2250 (N=C=O) and 1800 cm.$^{-1}$ (C=O of COCl).

Anal. Calcd. for $C_3H_2ClNO_2$: Cl, 29.70. Found: Cl, 29.82.

Other 2-isocyanatoacyl chlorides (V) were also prepared from the corresponding α-amino acids and phosgene by the similar procedure described above. The results are given in Table I.

2-Isocyanatoisovaleryl Chloride (Vc) from L-Valine, Phosgene, and Hydrogen Chloride.—Into a suspension of 15 g. of finely ground L-valine in 210 ml. of dry dioxane, a slow stream of phosgene was introduced at 45–50° with stirring. A clear solution was obtained after 1.5 hr. Treatment with phosgene was then stopped, and hydrogen chloride was introduced at 5–10° for 4 hr. After the solution stood overnight, a stream of phosgene was introduced again at 45–50° for 9 hr., and the reaction mixture was allowed to stand at room temperature. After 2 days, the solution was concentrated under reduced pressure and the residual oil was dissolved in 30 ml. of dry benzene. The solution was distilled under atmospheric pressure in order to remove hydrogen chloride together with benzene, and, finally, the residue was distilled to yield 15.5 g. (75.0%) of 2-isocyanatoisovaleryl chloride (Vc), b.p. 87.5–88° (39 mm.). The compound showed characteristic absorption peaks at 2250 (N=C=O) and 1795 cm.$^{-1}$ (C=O of COCl) and $[\alpha]^{21}D$ +52.1°.

Anal. Calcd. for $C_6H_8ClNO_2$: C, 44.59; H, 4.99. Found: C, 44.23; H, 4.92.

Other 2-isocyanatoacyl chlorides (V) were also prepared from the corresponding α-amino acids, phosgene, and hydrogen chloride by the similar procedure described above. The results are given in Table I.

2-Isocyanatoacetyl Chloride (Va) from 2,5-Oxazolidinedione (IIa), Hydrogen Chloride, and Phosgene.—Into a solution of 10 g. of 2,5-oxazolidinedione (IIa) in 300 ml. of dry dioxane, phosgene and then hydrogen chloride were introduced at 10° with stirring for 1 hr. each. The solution was then maintained at 50° and treated with phosgene for 7 hr. After 2 days, the solution was concentrated under reduced pressure, and the residual brown liquid was distilled to yield 10.5 g. (89.0%) of 2-isocyanatoacetyl chloride, b.p. 54.5–56.5° (22 mm.)

2-Aminoacetyl Chloride Hydrochloride (IIIa).—To 300 ml. of dry ether saturated with hydrogen chloride was added 4.0 g. of finely ground 2,5-oxazolidinedione (IIa). The mixture was stirred efficiently at room temperature for 5 hr. and allowed to stand for 2 days. Crystals of 2-aminoacetyl chloride hydrochloride (IIIa) formed were collected by filtration and washed with dry ether followed by petroleum ether, and dried over P_2O_5 in a vacuum desiccator: 5.1 g. (100%), m.p. 97° dec.

Anal. Calcd. for $C_2H_5Cl_2NO$: N, 10.79. Found: N, 10.68.

2-(*p*-Phenetylureido)acet-*p*-phenetidide (VIa).—To a solution of 8.25 g. (0.06 mole) of *p*-phenetidine in 160 ml. of ether, a solution of 2.39 g. (0.02 mole) of 2-isocyanatoacetyl chloride (Va) in 40 ml. of ether was added dropwise at room temperature with stirring. White crystals were immediately precipitated. After filtration, they were washed with water to remove *p*-phenetidine hydrochloride. Recrystallization of residual solid from pyridine gave pure product, 4.14 g. (94.2%), m.p. 242.5°.

Anal. Calcd. for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.44; N, 11.77. Found: C, 63.73; H, 6.59; N, 11.95.

Other ureidoamides (VIb–e) listed in Table III were also prepared similarly from corresponding 2-isocyanatoacyl chlorides (Vb–e) and amines.

3-(*p*-Phenetyl)hydantoin (VII).—To a solution of 2.400 g. (0.02 mole) of 2-isocyanatoacetyl chloride (Va) in 100 ml. of toluene, a solution of 5.504 g. (0.04 mole) of *p*-phenetidine in 50 ml. of toluene was added dropwise at 10° with stirring. White crystals were immediately precipitated. After 1 day, the reaction mixture was heated at reflux with stirring for 1 hr., and the solid, obtained after removal of toluene under reduced pressure, was washed with water to remove *p*-phenetidine hydrochloride. Recrystallization of crude product from benzene gave 3.98 g. (90.0%) of pure 3-(*p*-phenetyl)hydantoin, m.p. 198°. The infrared spectrum showed peaks at 1780 and 1710 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.79; H, 5.52; N, 12.80.

N-Methyl-2-isocyanatoacetanilide (VIII).—To a solution of 1.20 g. (0.01 mole) of 2-isocyanatoacetyl chloride in 50 ml. of ether, a solution of 1.07 g. (0.01 mole) of N-methylaniline and 0.79 g. (0.01 mole) of pyridine in 30 ml. of ether was added dropwise at 10° with stirring. Pyridine hydrochloride was immediately precipitated. After filtration of the precipitates, the filtrate was evaporated under reduced pressure. The residual white crystals were dried in a vacuum desiccator. The product, m.p. 57–58°, 1.36 g. (70.4%), showed characteristic absorption peaks at 2250 (N=C=O) and 1670 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.07; H, 5.50; N, 14.49.

N-Methyl-2-(*p*-phenetylureido)acetanilide (IX).—With excess *p*-phenetidine, 0.56 g. of N-methyl-2-isocyanatoacetanilide (VIII) was treated in ether. The crude product obtained was washed with ether, and recrystallization from benzene gave pure product, m.p. 153°, 0.86 g. (90.0%).

Anal. Calcd. for $C_{18}H_{21}N_3O_3$: N, 12.79. Found: N, 13.00.

Ethyl 2-Isocyanatoacetate (XI).—To a solution of 4.5942 g. of 2-isocyanatoacetyl chloride (Va) in 20 ml. of ether, a solution of 1.7682 g. (equimole) of ethanol in 50 ml. of ether was added dropwise at room temperature with stirring. After 1 day, removal of ether under reduced pressure gave an oily product, ethyl 2-(N-chloroformylamino)acetate (X), showing peaks at 3350 (N—H), 1770 (C=O of carbamic acid chloride), and 1745 cm.$^{-1}$ (C=O of ester). Distillation gave 3.0 g. (88.7%) of ethyl 2-isocyanatoacetate (XI), b.p. 67.5–68.5° (13 mm.), with evolution of hydrogen chloride. The infrared spectrum showed strong peaks at 2250 (N=C=O) and 1745 cm.$^{-1}$ (C=O of ester).

Anal. Calcd. for $C_5H_7NO_3$: N, 10.77. Found: N, 10.68.

Ethyl 2-(Carbo-*p*-nitrophenoxyamino)acetate (XII).—To a solution of 3.9 g. of *p*-nitrophenol and 3.5 g. of ethyl 2-isocyanatoacetate (XI) in 50 ml. of ether was added a trace of triethylamine as a catalyst. The mixture was allowed to stand at room temperature. After 1 month, the crystals formed were collected by filtration and a second crop was obtained by evaporation of the filtrate. The combined crude product was washed with water and recrystallized from toluene, affording the pure product, 7.1 g. (97.5%), m.p. 97–97.5°.

Anal. Calcd. for $C_{11}H_{12}N_2O_6$: N, 10.44. Found: N, 10.59.

2,5-Oxazolidinedione (IIa) from 2-Isocyanatoacetyl Chloride (Va) and Water.—To a solution of 4.5942 g. of 2-isocyanatoacetyl chloride (Va) in 150 ml. of ether, 20 ml. of dioxane containing 0.6920 g. (equimole) of water was added dropwise at room temperature with stirring. After the reaction mixture was allowed to stand for a day, 3.8 g. (100%) of crude product was obtained by evaporating the solvents under reduced pressure. Pure product, 2,5-oxazolidinedione (IIa), was obtained by recrystallization from ethyl acetate–petroleum ether. The infrared spectrum showed strong peaks at 3250 (N—H), 1855 (unsym. C=O), and 1780 cm.$^{-1}$ (sym. C=O).

Anal. Calcd. for $C_3H_3NO_3$: N, 13.86. Found: N, 13.72.

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