was added over a 25-min period. The brown mixture was poured into 100 ml of water, and the two layers were thoroughly mixed and separated. The aqueous layer was extracted with 40 ml of benzene. The yellow benzene solutions were combined, washed with water, dried over sodium sulfate, and concentrated to a volume of about 50 ml. Addition of 150 ml of cyclohexane and concentration of the solution gave 0.02 g (2%) of nitrile II, mp 274–278°. The mother liquor was chromatographed through a column of neutral alumina. Elution with a 1:1 mixture of benzene and cyclohexane and evaporation of the solvent *in vacuo* gave 0.54 g (66%) of unchanged hydrocarbon (Ia), mp 179–183°. Elution with benzene gave a material which was recrystallized from a mixture of chloroform and ethanol to give 0.16 g (18%) of nitrile Ib, mp 190–193°. The identification of each compound was confirmed by comparison of its infrared spectrum with that of an authentic sample.

Reaction of Nitrile II with Sodium Cyanide in Dimethylformamide Followed by Treatment with Oxygen. Preparation of Nitrile Ib.—A mixture of 0.50 g (0.010 mole) of sodium cyanide and 20 ml of dimethylformamide was stirred at room temperature with nitrogen bubbling into the liquid in a 50-ml, three-necked, round-bottomed flask equipped with a magnetic stirrer, a calcium sulfate drying tube, and a gas inlet tube extending into the liquid. After 20 min 0.44 g (0.001 mole) of nitrile II was added. The mixture became intensely green within 1 min and was stirred under nitrogen for 3 hr. Oxygen was passed into the flask and the mixture became yellow-brown in about 45 min. Nitrogen was again bubbled into the liquid while it was being stirred at room temperature. After 45 min the red-orange mixture was poured into 100 ml of water, 20 ml of 10% sodium hydroxide solution was added, and the mixture was extracted twice with 100-ml portions of benzene. The yellow benzene extracts were combined, washed with 5% sodium hydroxide solution and with water, dried over sodium sulfate, and concentrated to a volume of about 15 ml. Addition of 30 ml of cyclohexane and concentration of the solution was followed by chromatography of the solution through a column of neutral alumina. Elution with benzene, evaporation of the solvent *in vacuo*, and recrystallization of the orange residue from ethanol gave 0.21 g (49%) of nitrile Ib, mp 190–194°. The product was identified by comparison of its infrared spectrum with that of an authentic sample.

Distillation of the Solvent from a Mixture of Hydrocarbon Ia and Sodium Cyanide in Dimethylformamide.—A mixture of 0.16 g (0.0004 mole) of hydrocarbon Ia, 0.002 g (0.0004 mole) of sodium cyanide, and 4 ml of dimethylformamide was placed in a 10-ml, round-bottomed flask. The flask was evacuated by means of a vacuum pump and allowed to stand at room temperature. The mixture became intensely green within 15 min. After 5 hr at room temperature, the solvent was removed under reduced pressure by heating the mixture to about 85° (oil-bath temperature). The green color disappeared when the solvent had been distilled. The yellow-orange residue was washed with benzene, the benzene was evaporated, and the residue was recrystallized from cyclohexane to give 0.06 g (38%) of unchanged hydrocarbon (Ia), mp 182–84°, identified by comparison of its infrared spectrum with that of an authentic sample.

Nuclear Magnetic Resonance Spectroscopy.—The nmr spectra were recorded with a Varian Associates Model A-60 nmr spectrometer and, in the case of nitrile II, with a Varian Associates Model A-56/60A analytical nmr spectrometer, using tetramethylsilane as an internal standard. Chemical shifts are expressed in parts per million as shielding values (τ), defined by Tiers.[22]

(22) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1959).

Reactions of Isocyanates with Cyanohydrins. The Synthesis of 2,4-Oxazolidinediones and 1,3-Disubstituted Parabanic Acids

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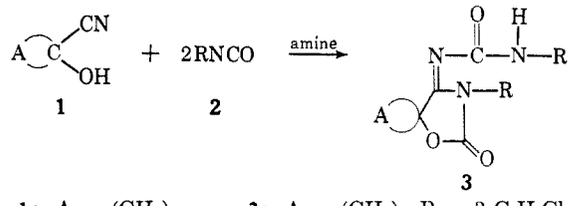
Isocyanates react with cyanohydrins to form substituted 4-carbamoylimino-2-oxazolidinones which hydrolyze to 2,4-oxazolidinediones. Acetone cyanohydrin reacts with 3-chlorophenyl isocyanate to form two products: 3-(3-chlorophenyl)-4-(3-chlorophenylcarbamoylimino)-5,5-dimethyl-2-oxazolidinone and 1,3-di(3-chlorophenyl)-4-imino-2,5-imidazolidinedione. The latter product arises from the reaction of the isocyanate with hydrogen cyanide which is formed when the cyanohydrin dissociates. Reaction conditions necessary to produce either product in high yield with the exclusion of the other are reported. Acid hydrolysis of the 4-imino-2,5-imidazolidinediones produces 1,3-disubstituted parabanic acids.

Many methods are available for the synthesis of 2,4-oxazolidinediones.[2-7] 3-Substituted 2,4-oxazolidinediones have been prepared by the reaction of N-substituted carbamates with α-chloroacetyl chlorides[6] and by cyclization of the urethans formed by the reaction of α-hydroxy esters with isocyanates.[7]

It has now been found that cyanohydrins can be used for the synthesis of 2,4-oxazolidinediones without first converting them into the corresponding α-hydroxy esters. This paper describes the base-catalyzed reaction of isocyanates with cyanohydrins to form labile 1-cyanoalkyl carbamates which immediately cyclize to 3-substituted 4-imino-2-oxazolidinones. These products then react with 1 additional mole of isocyanate to form stable 3-substituted 4-carbamoylimino-2-oxazolidinones which readily hydrolyze in the presence of acid to form the corresponding 3-substituted 2,4-oxazolidinediones quantitatively.

When a benzene solution of equimolar quantities of 1-cyanocyclopentanol (**1a**) and 3-chlorophenyl isocyanate (**2a**) was heated in the presence of DABCO (triethylenediamine), a 42% yield of 3-(3-chloro-



1 2 3

1a, A = $(CH_2)_4$ **3a**, A = $(CH_2)_4$; R = 3-C_6H_4Cl
b, A = $(CH_2)_5$ **b**, A = $(CH_2)_4$; R = C_6H_5
2a, R = 3-C_6H_4Cl **c**, A = $(CH_2)_5$; R = C_6H_5
b, R = C_6H_5

(1) (a) Esso Research and Engineering Co., Baytown, Texas. (b) Spencer Chemical Co. is now named Gulf Research and Development Co., Kansas City Division.

(2) J. W. Clark-Lewis, *Chem. Rev.*, **58**, 63 (1958).

(3) K. Gulbins, M. Roth, and K. Hamann, *Angew. Chem.*, **73**, 434 (1961).

(4) J. W. Cornforth, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 411.

(5) E. Schmidt and W. Carl, *Ann.*, **639**, 24 (1961).

(6) M. Pianka and D. J. Polton, *J. Chem. Soc.*, 983 (1960).

(7) R. F. Rekker, A. C. Faber, D. H. E. Tom, H. Verleur, and W. Th. Nauta, *Rec. Trav. Chim.*, **70**, 113 (1951).

phenyl)-4-(3-chlorophenylcarbamoylimino)-1-oxa-3-azaspiro[4.4]nonan-2-one (**3a**) was obtained. The yield was increased to 86% when 2 moles of **2a** was mixed with 1 mole of the cyanohydrin. The yield of **3a** was also affected by the tertiary amine which was used for a catalyst (Table I). Although DABCO

TABLE I

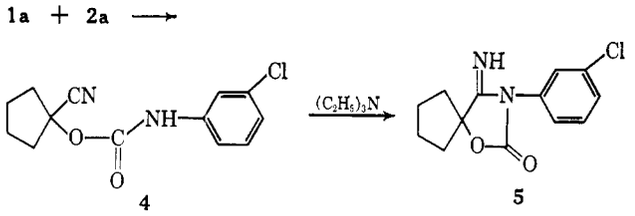
THE INFLUENCE OF VAROUS AMINE CATALYSTS ON THE YIELD OF **3a**[a]

Amine	Conditions	Yield, %[b]
DABCO	Reflux for 3 hr	86
Triethylamine	Exothermic reaction	81
4-Methylmorpholine	Reflux for 3 hr	74
Pyridine	Reflux for 3 hr	49

[a] Molar ratio of **1** and **2a** was 1:2; the solvent was benzene. [b] Based on **1**.

produced the highest yield of **3a**, the reaction was more vigorous when it was catalyzed by triethylamine as evidenced by an immediate exothermic reaction which was essentially complete after 20 min.

In the absence of a tertiary amine, **3a** was not formed even after heating a benzene solution of **1a** and **2a** at reflux temperature for 6 hr or after heating a mixture of the reagents at 60° for 12 hr in the absence of a solvent. However, when a mixture of **1a** and **2a** in a molar ratio of 2:1, respectively, remained at room temperature in the dark for 14 days, the carbamate **4** was formed. It was assigned the structure of 1-

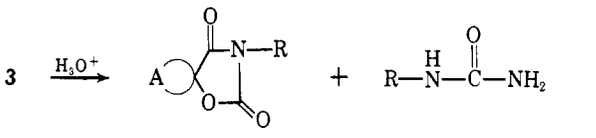


4 5

cyanocyclopentyl-N-(3-chlorophenyl) carbamate on the basis of its infrared spectrum. All attempts to purify **4** by recrystallization failed; new bands always appeared in the infrared spectrum at 5.58 and 5.96 μ with a concomitant decrease in intensity of the nitrile band at 4.43 μ. The addition of triethylamine to a benzene solution of **4** catalyzed the intramolecular N–H addition to the cyano triple bond so that 3-(3-chlorophenyl)-4-imino-1-oxa-3-azaspiro[4.4]nonan-2-one (**5**) was formed quantitatively. This reaction is akin to that of tertiary ethynyl alcohols with isocyanates; the propynylcarbanilates which are formed cyclize readily to 4-methylene-2-oxazolidinones.[8,9] The infrared spectrum of **5** was considerably different from that of **4** and showed absorption maxima characteristic of an imino N–H, a carbonyl, and an exocyclic C=NH.[10] No absorption bands characteristic of the nitrile and amide groups were present.

The reaction of **5** with 1 mole of **2a** in the presence of triethylamine gave a product which had a melting point and infrared spectrum identical with those of **3a**. Thus, all of the intermediates which would be expected to be formed in the one-step synthesis of **3a** by the reaction of **1a** with **2a** were isolated and identified.

The acid hydrolysis of **3a** gave 3-(3-chlorophenyl)-1-oxa-3-azaspiro[4.4]nonan-2,4-dione (**6a**) and 3-chlorophenylurea (**7a**). The absorption maxima in the infrared spectrum of **6a** (Table II) corresponded well to those reported for another series of 2,4-oxazolidinediones.[6] The fact that **6a** was also obtained in a



6 7

6a, A = $(CH_2)_4$; R = 3-C_6H_4Cl **7a**, R = 3-C_6H_4Cl
b, A = $(CH_2)_4$; R = C_6H_5 **b**, R = C_6H_5 (not isolated)
c, A = $(CH_2)_5$; R = C_6H_5

quantitative yield by the acid hydrolysis of **5** confirmed the assumption that **3a** and **5** had the same heterocyclic ring structure.

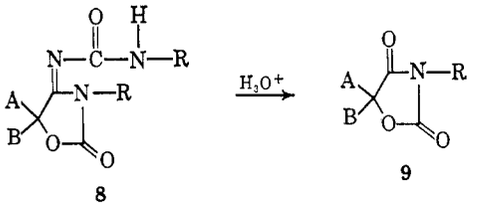
TABLE II

THE INFRARED SPECTRA OF 2,4-OXAZOLIDINEDIONES (μ)

Compd	2-C=O	4-C=O
6a	5.50	5.72
6b	5.50	5.72
6c	5.52	5.75
9a	5.51	5.78
9b	5.50	5.75
9d	5.50	5.76
9e	5.50	5.80
9f	5.54	5.76
9g	5.50	5.78

Phenyl isocyanate (**2b**) reacted with **1a** in the same way as **2a** to form the corresponding 3-phenyl-4-phenylcarbamoylimino-1-oxa-3-azaspiro[4.4]nonan-2-one (**3b**). Acid hydrolysis of the product gave 3-phenyl-1-oxa-3-azaspiro[4.4]nonan-2,4-dione (**6b**).

In addition to **1a** other cyanohydrins reacted with isocyanates to form derivatives of 4-carbamoylimino-2-oxazolidinone which readily hydrolyze to the corresponding 2,4-oxazolidinediones. 1-Cyanocyclohexanol (**1b**) reacted with **2b** to form 3-phenyl-4-phenylcarbamoylimino-1-oxa-3-azaspiro[4.5]decan-2-one (**3c**) which hydrolyzed to form 3-phenyl-1-oxa-3-azaspiro[4.5]decane-2,4-dione (**6c**). Similarly, the 4-carbamoylimino-2-oxazolidinones **8** were synthesized by the reactions of the appropriate isocyanates with the cyanohydrins of formaldehyde, acetone, benzaldehyde, and 2,4-dichlorobenzaldehyde. The corresponding 2,4-oxazolidinediones **9** were readily formed by the acid hydrolysis of **8**.



8 9

a, A = B = H; R = 3-C_6H_4Cl
b, A = B = H; R = C_6H_5
c, A = B = H; R = 2,5-$C_6H_3(CH_3)Cl$
d, A = B = H; R = 2,5-$C_6H_3(CH_3)_2$
e, A = B = CH_3; R = 3-C_6H_4Cl
f, A = C_6H_5; B = H; R = CH_3
g, A = 2,4-$C_6H_3Cl_2$; B = H; R = C_6H_5

(8) R. Sisido, K. Hukoka, N. Tuda, and H. Nozaki, *J. Org. Chem.*, **27**, 2663 (1962).
(9) P. J. Stoffel and A. J. Speziale, *ibid.*, **28**, 2814 (1963).
(10) M. E. Baguley and J. A. Elvidge, *J. Chem. Soc.*, 709 (1957).

TABLE III
THE INFRARED SPECTRA OF 4-CARBAMOYLIMINO-2-OXAZOLIDINONES (μ)

Compd	N—H	2-C=O[a]	Amide C=O	Exocyclic C=N[b]
3a	3.00	5.60	5.80,[c] 5.86	5.95
3b	2.95	5.55	5.92	6.02
3c	3.01	5.58	5.82	5.92
8a	3.01	5.52	5.95,[c] 6.00	6.10
8c	3.01	5.49	5.93,[c] 5.98	6.08
8e	2.99	5.58	5.80,[c] 5.86	5.94

[a] See footnote 11. [b] See footnote 10. [c] Shoulder on main band.

The infrared spectra of the purified 4-carbamoylimino-2-oxazolidinones exhibited absorption maxima at wavelengths which were characteristic of their assigned structures (Table III). The absorption band at 5.49–5.60 μ agreed well with the cyclic carbamate carbonyl frequency at 1746–1810 cm^{-1} (5.52–5.73 μ) which was reported for a series of 2-oxazolidinones.[11]

The infrared spectra of all of the 2,4-oxazolidinediones (**6** and **9**) exhibited absorption maxima at 5.49–5.54 (2-C=O) and 5.72–5.80 μ (4-C=O) (Table II). These agree with the assignments made for the carbonyl groups in another series of 2,4-oxazolidinediones.[6]

Confirmatory evidence that the correct structural assignments were made was provided by the synthesis of two 2,4-oxazolidinediones (**9b** and **9f**) which had been previously reported. In addition, the melting point and infrared spectrum of **9d** and **9e** were identical with those of authentic 3-(2,5-dimethylphenyl)-2,4-oxazolidinedione and 3-(3-chlorophenyl)-5,5-dimethyl-2,4-oxazolidinedione,[12] respectively.

The course of the reaction of **2a** with acetone cyanohydrin was dependent upon the solvent and tertiary amine used as a catalyst. In benzene solution two products were formed when DABCO was the catalyst. First, the expected 3-(3-chlorophenyl)-4-(3-chlorophenylcarbamoylimino)-5,5-dimethyl-2-oxazolidinone (**8e**) separated from the reaction solution in a yield of less than 12%.

A second product (**10a**) was isolated from the filtrate of **8e**. It melted 36° higher than **8e**, and, on the basis of elemental analysis, had the formula $C_{15}H_9Cl_2N_3O_2$. This formula implies that it resulted from the reaction of 2 moles of **2a** with 1 mole of hydrogen cyanide. This was confirmed when an identical product was formed by the reaction of **2a** with anhydrous hydrogen cyanide. On the basis of this and other data to be presented later **10a** was assigned the structure of 1,3-di(3-chlorophenyl)-4-imino-2,5-imidazolidinedione.

When the reaction of **2a** with acetone cyanohydrin in benzene was catalyzed with triethylamine, **10a** was the exclusive product (60% yield). Apparently the reaction conditions were conducive for the dissociation of the cyanohydrin with consequent liberation of hydrogen cyanide. Since the isocyanate would probably react more readily with hydrogen cyanide than with the tertiary hydroxyl group of the cyanohydrin, the dissociation of the latter would be driven to completion.

In order to suppress the dissociation of acetone cyanohydrin, its base-catalyzed reaction with **2a** was done in acetone. Compound **8e** was then formed in high yields (81–85%). The reaction which was catalyzed by DABCO had to be heated whereas the one which was catalyzed by triethylamine was exothermic. In the triethylamine-catalyzed reaction a small quantity of **10a** was also formed while **8e** was the only product isolated from the reaction which was catalyzed with DABCO.

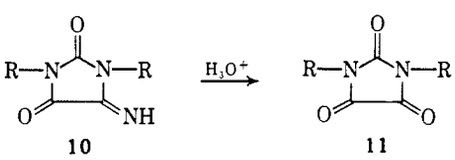
In 1905 Dieckmann and Kämmerer[13] reported that hydrogen cyanide reacted with 2 moles of **2b** in the presence of basic catalysts to form 1,3-diphenyl-4-imino-2,5-imidazolidinedione. Acid hydrolysis of the product gave 1,3-diphenylparabanic acid.

The base-catalyzed reaction of **2b** with acetone cyanohydrin in benzene was exothermic and gave a partially crystalline gum (**10b**) which was not further purified. It had an infrared spectrum similar to that of **10a** (Table IV) and had absorption maxima which were consistent

TABLE IV
THE INFRARED SPECTRA OF 1,3-DISUBSTITUTED 4-IMINO-2,5-IMIDAZOLIDINEDIONES (μ)

Compd	N—H	2-C=O	5-C=O	Exocyclic C=N
10a	3.04	5.58	5.72	5.98
10b	3.03	5.55	5.75	6.09
10c	3.02	5.56	5.76	5.95
10d	3.05	5.58	5.72	5.96
10e	3.02	5.50	5.75	5.92
10f	3.06	5.55, 5.61	5.75	5.95, 6.00

with the structure of a 1,3-disubstituted 4-imino-2,5-imidazolidinedione. As reported by Dieckmann and Kämmerer, the acid hydrolysis of **10b** produced 1,3-diphenylparabanic acid (**11b**).



10 11

a, R = 3-C_6H_4Cl
b, R = C_6H_5
c, R = 2-$C_6H_4CH_3$
d, R = 3,4-$C_6H_3Cl_2$
e, R = $CH_2CO_2C_2H_5$
f, R = CH_3
g, R = C_2H_5

2-Tolyl isocyanate, 3,4-dichlorophenyl isocyanate, ethyl isocyanatoacetate, and methyl isocyanate reacted similarly with acetone cyanohydrin in benzene solution to give 1,3-disubstituted 4-imino-2,5-imidazolidinediones **10c**, **10d**, **10e**, and **10f**, respectively. The reactions were exothermic and complete within a few minutes. Since the reactions proceeded rapidly to the final products, no intermediate cyanoformamides were isolated. The products exhibited similar infrared spectra (Table IV) and had elemental analyses consistent with the structural assignments (Table V).

Although many aryl isocyanates were found to react with the cyanohydrins **1a** and **1b** to form derivatives of 4-imino-2-oxazolidinone (**3**), 2-tolyl isocyanate and alkyl isocyanates did not. Alkyl isocyanates are known to be less reactive than aryl isocyanates, and the reactivity of aryl isocyanates is decreased by sub-

(11) S. Pinchas, and E. Ben-Ishai, *J. Am. Chem. Soc.*, **79**, 4099 (1957).

(12) Dr. L. V. Phillips kindly provided the author with the insrared spectrum of an authentic sample of 3-(3-chlorophenyl)-5,5-dimethyl-2,4-oxazolidinedione which he nad synthesized from ethyl α-hydroxyisobutyrate and 3-chlorophenyl isocyanate.

(13) W. Dieckmann and H. Kämmerer, *Ber.*, **38**, 2977 (1905).

TABLE V
ANALYSES, MELTING POINTS, AND YIELDS OF PRODUCTS

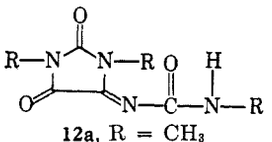
Product	Yield, %	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Chlorine, % Calcd	Chlorine, % Found
3a	86.3	178.5[a]	$C_{20}H_{17}Cl_2N_3O_3$	57.43	57.30	4.10	4.04	10.05	9.81	16.95	16.93
3b	100	158–159[b]	$C_{20}H_{19}N_3O_3$	68.75	68.89	5.48	5.66	12.03	11.79		
3c	50	174–175[c]	$C_{21}H_{21}N_3O_3$	69.40	69.24	5.82	5.92	11.56	11.40		
6a	98	134–135[c]	$C_{13}H_{12}ClNO_3$	58.77	58.50	4.55	4.55	5.27	5.14	13.34	13.27
6b	80	129.0–130.5[c]	$C_{13}H_{13}NO_3$	67.52	67.84	5.67	5.70	6.05	5.97		
6c	98	140–141[c]	$C_{14}H_{15}NO_3$	68.55	68.79	6.16	6.17	5.71	5.50		
8a	66	131.5–132.5[a]	$C_{16}H_{11}Cl_2N_3O_3$	52.76	52.79	3.04	3.15	11.54	11.43	19.47	19.37
8c	25	142.5–143.0[a]	$C_{18}H_{15}Cl_2N_3O_3$	55.12	55.12	3.85	4.08	10.71	10.54	18.08	18.02
8e	85	163–164[d]	$C_{18}H_{15}N_3Cl_2O_3$	55.12	55.28	3.85	4.03	10.71	10.42	18.08	18.00
9a	90	126–127[c]	$C_9H_6ClNO_3$	51.08	51.02	2.86	3.05	6.62	6.51	16.75	16.98
9b	65	122–123[c]	$C_9H_7NO_3$	61.02	60.89	3.98	4.11	7.90	7.93		
9d[e]	54	94–95[c]	$C_{11}H_{11}NO_3$	64.68	64.20	5.40	5.62	6.82	6.87		
9e[f]	96	95–96[c]									
9f		111–112[c,g]									
9g		147–148[c]	$C_{15}H_8Cl_2NO_3$	56.10	56.07	2.51	2.77	4.36	4.20	22.08	22.04
10a	60	200–201[h]	$C_{15}H_9Cl_2N_3O_2$	53.91	53.81	2.71	2.58	12.57	12.43	21.22	21.34
10c	77	173–174[d]	$C_{17}H_{15}N_3O_2$	69.69	69.66	5.15	5.46	14.33	14.10		
10d	80	217–217.5[a]	$C_{15}H_7Cl_4N_3O_2$	44.70	44.73	1.75	1.32	10.43	10.33	35.19	35.17
10e	94	82–83[i]	$C_{11}H_{15}N_3O_6$	46.31	46.21	5.30	5.30	14.73	14.70		
10f	74	119–120[a]	$C_5H_7N_3O_2$	42.55	42.67	4.99	4.64	29.78	29.80		
11a	98	255–256[j]	$C_{15}H_8Cl_2N_2O_3$	53.80	53.75	2.85	2.70	8.23	8.36	20.98	21.16
11b	77	206–207[c,k]									
11c	92	207–208[c,l]	$C_{17}H_{14}N_2O_3$	69.37	69.21	4.79	4.84	9.52	9.74		
11e	69	121[c]	$C_{11}H_{14}N_2O_7$	46.15	46.29	4.93	4.94	9.79	9.73		
11f	68	152–153[c,m]	$C_8H_6N_2O_3$	42.25	42.25	4.25	4.26	19.71	19.41		
11g	96	49–51[c,n]	$C_7H_{10}N_2O_3$	49.40	49.46	5.92	5.86	16.47	16.04		
12a	27	222[d]	$C_7H_{10}N_4O_3$	42.42	42.23	5.09	5.11	28.27	28.54		
12b	70.5	67–69[i]	$C_{10}H_{16}N_4O_3$	49.99	49.83	6.71	6.51	23.32	23.86		
13a	37	155–155.5[d]	$C_{15}H_{11}Cl_2N_3O_2$	53.59	53.20	3.30	3.40	12.50	12.68	21.09	21.34
13b	93	79–80.5[d]	$C_5H_9N_3O_2$	41.95	41.88	6.33	6.28	29.36	29.16		
14a	95	191[d]	$C_{12}H_{14}N_4O_3$	54.95	54.92	5.38	5.44	21.36	21.44		
14b	96	196.5–197.5[d]	$C_{12}H_{13}ClN_4O_3$	48.57	48.77	4.42	4.47	18.88	18.50	11.94	11.80
14c	91	191–193[d]	$C_{12}H_{13}ClN_4O_3$	48.57	48.47	4.42	4.44	18.88	18.40	11.95	11.93

[a] Recrystallized from benzene. [b] Recrystallized from 1-propanol. [c] Recrystallized from ethanol. [d] Recrystallized from benzene–hexane. [e] The product was identical with an authentic sample which was made from ethyl glycolate. [f] See footnote 12. [g] Reference in footnote 7 reported a melting point of 111°. [h] Recrystallized from benzene–ethanol. [i] Recrystallized from hexane. [j] Recrystallized from ethyl acetate–benzene. [k] C. W. Whitehead and J. Traverso [*J. Am. Chem. Soc.*, **80**, 962 (1958)] reported a melting point of 204°; Th. Figee [*Rec. Trav. Chim.*, **34**, 289 (1915)] reported a melting point of 206–207°. [l] F. Berger [*Ber.*, **12**, 1854 (1879)] reported a melting point of 202–203°. [m] H. Biltz and H. Rakett [*ibid.*, **61**, 1409 (1928)] reported a melting point of 154°. [n] H. Biltz and E. Topp [*ibid.*, **46**, 1387 (1913)] reported a melting point of 49–51°.

stituents *ortho* to the isocyanate group.[14] Their reactivities are apparently so low that they cannot react with the tertiary hydroxyl group of cyanohydrins. However, they do react with the hydrogen cyanide formed by dissociation of the cyanohydrins and form the substituted 4-imino-2,5-imidazolidinediones **10c**, **e**, and **f**.

Compounds **10a–c**, **e**, and **f** were all hydrolyzed to the corresponding 1,3-disubstituted parabanic acids **11a–c**, **e**, and **f**, respectively.

The reactions of ethyl isocyanate with **1a**, **1b**, and acetone cyanohydrin always proceeded beyond the 1,3-diethyl-4-imino-2,5-imidazolidinedione stage to the formation of 1,3-diethyl-4-ethylcarbamoylimino-2,5-imidazolidinedione (**12b**). Since the same product was formed from all three cyanohydrins it was obvious that reaction occurred with the hydrogen cyanide liberated by their dissociation.

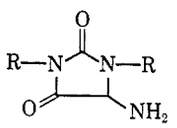


12a, R = CH_3
b, R = C_2H_5

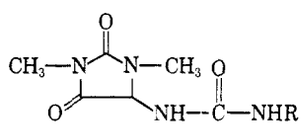
Surprisingly, the reaction of methyl isocyanate with hydrogen cyanide liberated from a cyanohydrin always stopped with the formation of **10f**. However, extensive refluxing of a benzene solution containing 3 moles of methyl isocyanate and 1 mole of the cyanohydrin produced a low yield of **12a**. It was also synthesized by the reaction of methyl isocyanate with **10f**.

The infrared spectra of **12a** and **12b** differed from those of **10a–f** chiefly in the carbonyl region. In addition to the band characteristic of the exocyclic C=N bond (6.05 μ), three carbonyl bands appeared at 5.59, 5.74, and 5.92 μ.

Hydrogenation of **10a** and **10f** over palladium–charcoal gave the expected 4-amino-1,3-disubstituted 2,5-imidazolidinediones, **13a** and **13b**, respectively.



13a, R = 3-C_6H_4Cl
b, R = CH_3



14a, R = C_6H_5
b, R = 3-C_6H_4Cl
c, R = 4-C_6H_4Cl

(14) J. H. Saunders and K. C. Frisch, "Polyurethanes. Chemistry and Technology. I. Chemistry," Interscience Publishers, Inc., New York, N. Y., 1962, p 64.

Compound **13b** reacted with **2a**, **2b**, and 4-chlorophenyl isocyanate to form the expected 1,3-dimethyl-4-ureido-2,5-imidazolidinediones **14a–c**.

Experimental Section[15]

3-Aryl-4-arylcarbamoylimino-2-oxazolidinones. Procedure A (3a, 3b, 3c, 8a, 8c, and 8e).—To a solution of a cyanohydrin (0.1 mole) and an aryl isocyanate (0.2 mole) in benzene (100 ml) was added the amine catalyst (0.1–0.5 g). If necessary it was heated under reflux for 3 hr. Evaporation of 50–75% of the solvent left a residue which solidified when cool. The solid product was recrystallized from an appropriate solvent.

Procedure B (3a).—To a solution of **5** (1.32 g, 0.005 mole) in benzene (20 ml) was added **2a** (0.76 g, 0.005 mole) and triethylamine (0.1 ml). After remaining at room temperature overnight the solution was diluted with hexane. The solid product (1.8 g, 86% yield), mp 178–179°, was identical with the product **3a** synthesized in part A as shown by a comparison of their infrared spectra. Also there was no depression of the melting point when a mixture of the two was melted.

1-Cyanocyclopentyl N-(3-Chlorophenyl)carbamate (4).—Compound **1a** (22.2 g, 0.2 mole) and **2a** (15.3 g, 0.1 mole) were mixed and stored at room temperature while protected from moisture and light for 14 days. The unreacted starting materials were removed by warming the product to 50–55° (0.1 mm). The viscous residue solidified when hexane was added. The product, mp 60–65°, weighed 20.6 g (78% yield). The infrared spectrum indicated that it was the desired product: λ_{max} 3.02 (N—H), 4.43 (C≡N), 5.78 (shoulder), 5.85 (C=O), and 6.55 μ (CONH). Attempts to recrystallize the product from benzene–hexane, ethanol, and ethyl acetate–hexane always converted some of the material into the cyclized product (**5**) described below. A pure sample could not be obtained for analysis.

3-(3-Chlorophenyl)-4-imino-1-oxa-3-azaspiro[4.4]nonan-2-one (5).—To a solution of **4** (10 g) in benzene (35 ml) was added 1 ml of triethylamine. A very mild exothermic reaction occurred; the temperature increased less than 5°. The solution was diluted with 100 ml of hexane and left at room temperature for 2 days. Concentration at reduced pressure gave 10 g (100% yield) of product, mp 109–111°. Recrystallization from benzene–hexane raised the melting point to 110.5–112.0°. The infrared spectrum showed λ_{max} 3.01 (=N—H), 5.58 (C=O), and 5.96 μ (exocyclic C=NH).[10]

Anal. Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.98; H, 4.95; Cl, 13.39; N, 10.59. Found: C, 59.10; H, 5.33; Cl, 13.20; N, 10.35.

3-Substituted 2,4-Oxazolidinediones. Procedure A (6a, 6b, 6c, 9a, and 9e).—To a solution of a 3-aryl-4-arylcarbamoylimino-2-oxazolidinone (**3a**, **3b**, **3c**, **8a**, or **8e**, respectively) (0.005–0.024 mole) in ethyl alcohol (50–400 ml) was added concentrated hydrochloric acid (25 ml). After heating on a steam bath for 1–3 hr the solution was poured over crushed ice. The solid product was usually purified by recrystallization from ethyl alcohol.

Procedure B (9b, 9d, 9f, and 9g).—The 3-substituted 4-carbamoylimino-2-oxazolidinone formed from the reaction of an isocyanate with a cyanohydrin by the general procedure described above was not purified. Instead, the crude product which remained after evaporation of the benzene was then hydrolyzed directly with acid in ethyl alcohol by procedure A above.

Procedure C (6a).—To a solution of 3-(3-chlorophenyl)-4-imino-1-oxa-3-azaspiro[4.4]nonan-2-one (**5**, 0.15 g) in ethyl alcohol (6 ml) and water (2 ml) was added 3 drops of concentrated hydrochloric acid. After 30 min at room temperature a crystalline product had formed and was collected. Its infrared spectrum was identical with that of **6a** which was prepared by method A. The yield of the product, mp 131–132°, was 87% (0.13 g).

Products from the Hydrolysis of 3a.—Compound **3a** (10 g, 0.024 mole) was hydrolyzed under the conditions reported above for the synthesis of **6a** by procedure A. A 98% yield (6.3 g) of **6a** was obtained.

The filtrate from the above reaction was concentrated at reduced pressure to a volume of about 50 ml. Upon cooling, a crystalline product (3.1 g, 75.7% yield), mp 151–153°, was isolated and identified as 3-chlorophenylurea (**7a**). Recrystallization raised the melting point to 156–157°. The infrared spectrum (λ_{max} 2.95, 2.98, 3.10, 6.10, 6.21, 6.31, and 6.55 μ) was identical with that of an authentic specimen of 3-chlorophenylurea which had been prepared from **2a** and dry ammonia in benzene.[16]

Anal. Calcd for $C_7H_7N_2ClO$: Cl, 20.78; N, 16.43. Found: Cl, 20.51; N, 16.10.

Synthesis of 9d from Ethyl Glycolate.—Ethyl glycolate (10.4 g, 0.1 mole), 2,5-dimethylphenyl isocyanate (14.7 g, 0.1 mole), and DABCO (0.1 g) were dissolved in benzene (100 ml) and heated at reflux temperature for 24 hr. Upon cooling, 23.5 g (93.6% yield) of **ethoxycarbonylmethyl-N-(2,5-dimethylphenyl) carbamate**, mp 84.5–86°, crystallized out of solution. Recrystallization from ethanol–water gave an analytical sample: mp 94–95°; λ_{max} 3.02, 5.77, and 5.90 μ.

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.98; H, 6.57; N, 5.73.

The above carbamate (10 g) was heated 3 hr at 160–180°. Recrystallization from ethanol–water gave 4 g of **9d**, mp 94–95°; mixture with the product formed by method A did not depress the melting point. Also the infrared spectrum was identical with the spectrum of the compound prepared by procedure A above.

2,4-Dichloromandelonitrile.—An ether solution of 2,4-dichlorobenzaldehyde (100 g, 0.57 mole) was mixed thoroughly with a solution of sodium cyanide (49 g, 1.0 mole) in 300 ml of water. The mixture was cooled to 0° and ice-cold, concentrated hydrochloric acid (100 ml) was added dropwise. It was stirred for 30 min after the addition was completed. The ether layer was separated and the aqueous phase was extracted with two 200-ml portions of ether. The combined ether phases were washed with water, dried over anhydrous sodium sulfate, and evaporated. The crude residue solidified upon trituration with hexane. The yield was quantitative, mp 103–106°. An analytical sample melted at 117–118°.

Anal. Calcd for $C_8H_5Cl_2NO$: C, 47.56; H, 2.49; Cl, 35.09; N, 6.93. Found: C, 47.59; H, 2.56; Cl, 35.01; N, 6.83.

Reaction of 3-Chlorophenyl Isocyanate with Acetone Cyanohyrin. Procedure A. Using DABCO in Benzene Solution.—Acetone cyanohydrin (8.5 g, 0.1 mole) and **2a** (30.6 g, 0.2 mole) were dissolved in benzene (100 ml) and heated for 3 hr at reflux temperature in the presence of DABCO (0.1 g). The reaction solution was allowed to remain at room temperature for 36 hr during which time 4.6 g (11.7% yield) of 3-(3-chlorophenyl)-4-(3-chlorophenylcarbamoylimino)-5,5-dimethyl-2-oxazolidinedione (**8e**) separated from solution. It melted at 162–165°. Recrystallization from benzene–hexane raised the melting point to 163–164°. The infrared spectrum showed λ_{max} 2.99, 5.58, 5.80 (shoulder), 5.86, and 5.94 μ.

Concentration of the filtrate to half-volume and dilution with hexane gave a yellow gum which, when stirred with anhydrous ethyl alcohol, solidified to a pale yellow material (4.5 g, 14% yield), mp 188–194°. Recrystallization from benzene–ethanol gave an analytical sample of 1,3-di(3-chlorophenyl)-4-imino-1,3-imidazolidine-2,5-dione (**10a**): mp 200–201°; λ_{max} 3.04, 5,58, 5.72, and 5.98 μ.

Procedure B. Using DABCO in Acetone Solution.—The same quantities of reagents used in part A were dissolved in acetone (100 ml). DABCO (0.1 g) was added, and the solution was heated at reflux temperature for 3 hr. Evaporation of the solvent left a solid residue which was taken up in hot benzene, diluted with hexane, and cooled. The solid product (32 g, 81.8% yield), mp 152–154°, exhibited an infrared spectrum identical with that of **8e** synthesized in part A. Recrystallization raised the melting point to 160–162°.

Procedure C. Using Triethylamine in Acetone Solution.—The same quantities of reagents and acetone used in part B were mixed together. Then triethylamine (1 ml) was added. Heat was evolved, and the solution began to boil within a few minutes. No additional heat was required. Upon cooling, **10a** (1.6 g), mp 195–199°, crystallized from solution. The filtrate was evaporated to an oil (35 g, 85% yield) which soon solidified to crude **8e**, mp 142–144°. It was recrystallized from benzene to

(15) The melting points were determined with a Mel-Temp apparatus and are uncorrected; the infrared spectra were determined as Nujol mulls with a Perkin-Elmer grating infrared spectrophotometer, Model 237. Unless otherwise noted, the analysis of each product is recorded in Table V.

(16) The crude product isolated from the reaction of **2a** with a benzene solution of anhydrous ammonia melted at 142–143°; however, recrystallization from benzene raised the melting point to 156–157°. The melting point was not depressed on admixture with **7a**.

give 20 g of product, mp 160–162°, which had an infrared spectrum identical with that of **8e** described in part A.

1,3-Disubstituted 4-Imino-1,3-imidazolidine-2,5-dione. Procedure A (from Acetone Cyanohydrin) (10a, 10d, 10e, and 10f).—To a solution of acetone cyanohydrin (0.1 mole), an isocyanate (0.2 mole), and benzene (100 ml) was added triethylamine (0.5 ml). When an aryl isocyanate was used, an exothermic reaction began immediately after adding the catalyst, and the reaction was complete within 30 min. However, when alkyl isocyanates were used, heating at reflux temperature for 3–5 hr was required to complete the reaction. If the products did not crystallize out of the cooled reaction solution, they were isolated by evaporation of the solvent. The crude products were evaporated from benzene, ethanol, or hexane, or a combination of them.

Procedure B (from 1-Cyanocyclopentanol, 1a) (10c and 10f).—To a solution of **1a** (0.1 mole) and an isocyanate (0.2 mole) in benzene (50–100 ml) was added triethylamine (0.5–1 ml) to catalyze the reaction. If an exothermic reaction ensued, it was allowed to proceed without additional heat. Otherwise, the reaction solution was heated at reflux temperature for 3 hr. The products were isolated and purified by the same techniques used for the products formed from acetone cyanohydrin.

Procedure C (from Hydrogen Cyanide) (10a).—Benzene (100 ml) was cooled to 10° and hydrogen cyanide (generated from 0.5 mole of sodium cyanide) was bubbled into it. After the addition of triethylamine (0.5 ml) the solution was added dropwise to a solution of **2a** (15.3 g, 0.1 mole) in benzene (25 ml). The resulting solid product was collected by filtration. It weighed 8 g (48% yield) and melted at 200–201°. The infrared spectrum was identical with that of the product (**10e**) prepared by method A.

1,3-Disubstituted Parabanic Acids. Procedure A (11a, 11c, 11e, and 11f).—To a hot solution of 1,3-disubstituted 4-imino-1,3-imidazolidine-2,5-dione (**10a**, **10c**, **10e**, or **10f**, respectively) (0.002–0.04 mole) in ethyl alcohol (100–200 ml) was added concentrated hydrochloric acid (25–50 ml). After slowly cooling to room temperature, the colorless product crystallized from solution. It was collected, dried, and recrystallized from an appropriate solvent. The infrared spectra of the products showed the following carbonyl absorption peaks: **11a**, 5.77 μ; **11c**, 5.75 μ; **11e**, 5.58 and 5.78 μ; and **11f**, 5.65 and 5.80 μ.

Procedure B (11b and 11e).—The intermediate 1,3-disubstituted 4-imino-1,3-imidazolidine-2,5-dione was prepared by any one of the procedures described above. Then the crude product was dissolved in ethanol, hydrolyzed with hydrochloric acid, and purified by the method described in procedure A. The infrared spectrum of **11b** showed absorption at 5.76 μ (C=O).

Procedure C (11g).—The 1,3-disubstituted 4-substituted carbamoylimino-1,3-imidazolidine-2,5-dione (**12b**) was hydrolyzed by the same general method used in procedure A. The infrared spectrum showed absorption maxima at 5.68 and 5.85 μ.

1,3-Dialkyl-4-alkylcarbamoylimino-1,3-imidazolidine-2,5-dione. Procedure A (12a and 12b).—To a solution of an alkylisocyanate (0.2–0.3 mole) and the cyanohydrin (0.1 mole) of acetone, cyclopentanone, or cyclohexanone in benzene (100 ml) was added triethylamine (0.5–1 ml). The solution was heated at reflux temperature for 3–16 hr. Evaporation of the solvent left a residue from which pure product was obtained by recrystallization.

Procedure B (12a).—A solution of **10f** (14.1 g, 0.1 mole), methyl isocyanate (5.7 g, 0.1 mole), benzene (100 ml), acetone (25 ml), and triethylamine (1 ml) was heated at reflux temperature overnight. The product (2.5 g, 12.6% yield) separated from the cooled solution. It had an infrared spectrum which was identical with that of **12a** synthesized by procedure A.

1,3-Disubstituted 4-Amino-2,5-imidazolidinedione (13a and 13b).—The imino compound **10a** or **10f**, respectively (0.01–0.03 mole), was dissolved in ethyl acetate (200 ml) and hydrogenated in the presence of 5% palladium on charcoal (0.5–1 g) in a Parr pressure reaction apparatus at 60 psig for 2 hr at room temperature. After removal of the catalyst and evaporation of the solvent, the residual product was recrystallized from a mixture of benzene and hexane. The infrared spectra of the products exhibited the following absorption maxima: **13a**, 2.92, 2.99, 5.64, and 5.81 μ; **13b**, 2.95, 3.01, 5.60, and 5.85 μ.

1,3-Dimethyl-4-arylureido-2,5-imidazolidinedione (14a, 14b, and 14c).—To a stirred solution of **13b** (0.02 mole) and an aryl isocyanate (0.02 mole) in benzene (50 ml) was added DABCO (0.1 g). An exothermic reaction began immediately. After stirring for 30 min, hexane was added, and the solution was cooled. The products (91–96% yield) were collected and recrystallized from a mixture of benzene and hexane. The infrared spectra of the products exhibited the following absorption maxima: **14a**, 2.96, 2.98, 5.62, and 5.95 μ; **14b**, 2.98, 3.02, 5.63, and 5.92 μ; **14c**, 2.92, 3.01, 5.66, 5.82, and 6.05 μ.

The Reaction of 3-Unsubstituted N-Arylisoxazolium Salts with Carboxylic Acid Anions

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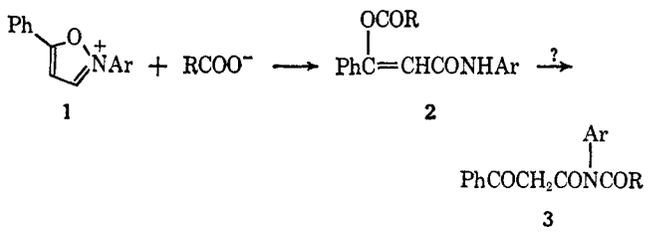
Examination of the reaction of the N,5-diphenylisoxazolium cation with triethylammonium acetate has revealed that 3-unsubstituted N-arylisoxazolium salts are not suitable for use in peptide synthesis, because of ready base-catalyzed rearrangement of the derived enol ester acylating agents.

As part of an investigation[2] of the isoxazolium salt method of peptide synthesis,[3-5] we have studied the use of N-arylisoxazolium salts (**1**) for converting carboxylic acids to reactive enol esters (**2**). Isoxazolium salts bearing an N-aryl substituent were of interest, because they were expected to give enol ester acylating agents **2** which would be resistant to a side reaction encountered with the N-alkyl compounds. In previous work it was shown[3] that N-methyl enol esters were subject to intramolecular rearrangement to ketoimides. It was hoped that the formation of ketoimides (**3**) from enol esters of the type **2** would be relatively slow as a result of the operation of steric and electronic factors, associated with the presence of the N-aryl substituent, which would bring about a diminution of the effective nucleophilicity of the nitrogen atom.



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The method for synthesis of N-arylisoxazolium salts, reported in an earlier communication,[6] involves con-

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(5) D. S. Kemp and R. B. Woodward, *ibid.*, **21**, 3019 (1965).

(6) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **31**, 2039 (1966).