795. *Purines, Pyrimidines, and Glyoxalines. Part IV.* Cyanouracils from Amines and Amino-acids.†*

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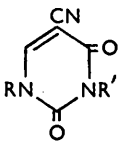
Cyanoethoxyacrylamide derivatives, $CN\cdot C(:CH\cdot OEt)\cdot CO\cdot NR'\cdot CO_2Et$, react with amines and amino-acids, forming 5-cyanouracils. Intermediate aminoacrylamides $CN\cdot C(:CH\cdot NHR)\cdot CO\cdot NR'\cdot CO_2Et$, isolated in a number of cases, cyclised to the cyanouracils when warmed or in alkali.

Derivatives of uracil, substituted at $C_{(5)}$ with such groups as bromo, chloro, nitro, and hydroxy, inhibit the growth of a number of organisms.[1] 5-Bromouracil is incorporated into nucleic acids,[2] and the growth-inhibition of micro-organisms which it causes is reversed by thymine and thymidine.[3,4] 5-Cyanouracils are closely related to thymine, and their potential action as metabolite antagonists is being studied.

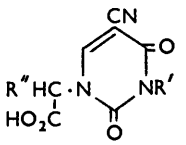
5-Cyanouracil, its 1-methyl derivative, and the anilinoacrylamide (II; R = Ph, R′ = H) have been prepared (cf. Part I) by treating ammonia, methylamine, and aniline respectively with the ethoxyacrylamide (I; R′ = H; referred to below as "the ethoxyacrylamide"). When heated near its melting point the anilinoacrylamide cyclised to 5-cyano-1-phenyluracil. The structure of 5-cyanouracil was shown by hydrolysis and decarboxylation to uracil. This is probably the most convenient method available for the synthesis of *N*-substituted uracils with an unambiguous orientation of substituents. The

(I) $CN\cdot C(:CH\cdot OEt)\cdot CO\cdot NR'\cdot CO_2Et$

(II) $CN\cdot C(:CH\cdot NHR)\cdot CO\cdot NR'\cdot CO_2Et$



(III)



(IV)

reaction has been applied to glycosylamines (cf. Part II). Conditions have now been found for the preparation of 5-cyanouracils and 5-cyano-3-methyluracils from amines, amino-acids, and hydrazines. Intermediate aminoacrylamides have been isolated in a number of cases; these compounds cyclise to uracil derivatives in alkali, and this procedure facilitates the preparation of uracils with heat-sensitive substituents.

With ethylamine, aromatic primary amines, or benzamide the ethoxyacrylamide gave aminoacrylamides (II; R = Et, aryl, or Bz, R′ = H), while with secondary amines it gave acrylamides $CN\cdot C(:CH\cdot NR_2)\cdot CO\cdot NH\cdot CO_2Et$. In the presence of an excess of aliphatic amine 1-alkyl-5-cyanouracils were formed in nearly quantitative yields and aminoacrylamides could not be isolated. An excess of aromatic amine did not promote cyclisation of arylaminoacrylamides; these were, however, converted into pyrimidines by alkali. The *N*-methyl derivative of the ethoxyacrylamide (I; R′ = Me; referred to below as "the

* Parts I—III, *J.*, 1955, 1834; 1956, 1877, 3847.

† Submitted in honour of the seventieth birthday of Sir Ian Heilbron, D.S.O., F.R.S.

[1] See Roblin, *Ann. Rev. Biochem.*, 1954, **23**, 506, 515.

[2] Weygand, Wacker, and Dellweg, *Z. Naturforsch.*, 1952, **7b**, 19.

[3] Weygand, Wacker, and Grisebach, *ibid.*, 1951, **6b**, 177.

[4] Hitchings, Elion, Falco, Russell, Sherwood, and VanderWerff, *J. Biol. Chem.*, 1950, **183**, 1.

ethoxy-*N*-methylacrylamide ") was more reactive, forming 5-cyano-3-methyl-1-phenyluracil when treated with ethanolic aniline. α-Amino-acids in alkaline solution reacted with the ethoxyacrylamides, forming uracil-1-acetic acids (IV; R′ = H or Me).

Cyanouracils are useful derivatives of amines and amino-acids. These compounds may be separated, identified, and estimated by paper chromatography, ion-exchange, and ultraviolet spectrophotometry. The absorption spectra resemble those of uracil derivatives, but the cyano-group causes a slight bathochromic shift.

A cyanouracil derivative of glycylglycine (III; R = CH_2·CO·NH·CH_2·CO_2H, R′ = H) has now been prepared in nearly quantitative yield and without cleavage of the peptide bond. Acid hydrolysis of this bond took place without destruction of the pyrimidine ring, but the nitrile was hydrolysed. Ethoxyacrylamides in which the cyano-group is replaced by acid-stable structures are now being examined as reagents for the *N*-terminal residues of proteins.

Pyrimidines prepared by these methods are being tested as inhibitors of tumour-growth in the Division of Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research.

Experimental

Unless otherwise indicated, compounds were dried over phosphoric oxide at 55°/0·1 mm. before analysis; spectra were measured in M/100-aqueous sodium borate (pH 9·4), and R_F values were determined on Whatman No. 1 paper in a solvent containing propan-2-ol (95%; 68 ml.), hydrochloric acid (10N; 20 ml.), water (12 ml.).

N-*Cyanoacetylurethane*.—Cyanoacetic acid (8·5 g.), urethane (8·9 g.), and phosphoryl chloride (7·6 g.) were heated at 70° (bath). Evolution of hydrogen chloride started after 15 min. and continued for a further 15 min.; then crystallisation took place. The suspension was chilled and diluted with water (35 ml.) before recovery of the *N*-cyanoacetylurethane (12·5 g.), m. p. 166°. The compound crystallised from ethanol as colourless plates (11·7 g., 75%), m. p. and mixed m. p. 168° (cf. Conrad and Schulze [5]).

α-Cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide, m. p. 122°, was prepared from *N*-cyanoacetylurethane (cf. Part I). The compound, recrystallised from ethyl acetate, was obtained in yields of 55—75%.

5-Cyanouracils from Primary Aliphatic Amines.—A suspension of the ethoxyacrylamide (2·0 g.) in a solution of ethylamine (0·85 g.) in water (10 ml.) was warmed for 10 min. The resultant solution was cooled and acidified with hydrochloric acid (10N; 2 ml.); *5-cyano-1-ethyluracil* (1·49 g., 96%), m. p. 208—209°, was precipitated immediately. The compound crystallised from ethanol as colourless prisms, m. p. 209° (R_F = 0·63; ε 8·8 × 10^3, $\lambda_{max.}$ 279 mμ) (Found: C, 51·2; H, 4·3; N, 25·3. $C_7H_7O_2N_3$ requires C, 50·9; H, 4·3; N, 25·45%). Other *5-cyanouracils* prepared in this way from primary amines are shown in Table 1.

TABLE 1. *1-Alkyl-5-cyanouracils* (III; R′ = H).

				Found (%)				Required (%)		
R	M. p.	Yield (%)	R_F [a]	C	H	N	Formula	C	H	N
Pr^n	165° [b]	95	0·75	53·7	4·9	23·4	$C_8H_9O_2N_3$	53·6	5·1	23·45
Pr^i	274	72 [c]	0·68	53·5	4·8	23·5				
Bu^n	190 [d]	98	0·76	55·85	5·6	21·7	$C_9H_{11}O_2N_3$	55·95	5·7	21·75
Bu^s	265	97	0·79	55·7	5·7	21·8				
Bu^i	221	73 [c]	0·80	55·9	5·6	21·7				
n-Pentyl	176	50 [c]	0·84	57·85	6·2	20·4	$C_{10}H_{13}O_2N_3$	58·0	6·3	20·3
i-Pentyl	215	58 [c]	0·86	57·7	6·1	20·5				
Ph·CH_2	234	65 [c]	0·78	63·7	4·1	18·6	$C_{12}H_9O_2N_3$	63·4	4·0	18·5
*cyclo*Hexyl	324	97	—	60·0	5·85	19·2	$C_{11}H_{13}O_2N_3$	60·3	6·0	19·15

[a] The previously described compounds with R = H and R = Me (cf. Part I) had R_F = 0·32 and 0·43; the latter had ε 8·3 × 10^3, $\lambda_{max.}$ 278 mμ. [b] ε 8·9 × 10^3, $\lambda_{max.}$ 280 mμ. [c] Yield of thrice recrystallised analytical material. [d] ε 9·6 × 10^3, $\lambda_{max.}$ 280 mμ.

Aminoacrylamides from Amines and the Ethoxyacrylamide.—(a) *Reaction with ethylamine*. The ethoxyacrylamide (1·25 g.) in ethanol (20 ml.) was mixed at 0—5° with a solution of ethylamine (0·26 g.) in aqueous ethanol (95%; 4 ml.). The solution was cooled to −50°, *α-cyano-N-ethoxycarbonyl-β-ethylaminoacrylamide* (0·90 g., 72%) crystallising as colourless needles, m. p.

[5] Conrad and Schulze, *Ber.*, 1909, **42**, 734.

144° (Found : C, 51·3; H, 6·4; N, 19·9. $C_9H_{13}O_3N_3$ requires C, 51·2; H, 6·2; N, 19·9%). The compound could be recrystallised from warm acetone without decomposition, but when its solution in ethanol was boiled 5-cyano-1-ethyluracil was formed.

(b) *Reaction with aromatic and heterocyclic amines.* Solutions of the ethoxyacrylamide (5·0 g.) in ethanol (50 ml.), and sulphanilamide (4·1 g.) in ethanol (50 ml.), were mixed and warmed until no more solid separated. The resultant suspension was stored at 5° overnight, and *α-cyano-N-ethoxycarbonyl-β-p-sulphamoylanilinoacrylamide* (6·2 g., 78%) was collected (m. p. 213—214°). The compound crystallised from ethanol as colourless needles, m. p. 214° (Found : C, 46·2; H, 4·4; N, 16·55. $C_{13}H_{14}O_5N_4S$ requires C, 46·15; H, 4·2; N, 16·6%). Other *aminoacrylamides*, prepared similarly, are shown in Table 2.

(c) *Reaction with secondary amines.* The ethoxyacrylamide (0·5 g.) in ethanol (15 ml.) was warmed for 15 min. with ethanolic dimethylamine (33% w/v; 0·33 ml.). *α-Cyano-β-dimethylamino-N-ethoxycarbonylacrylamide* (0·10 g., 20%), m. p. 142° crystallised from the cooled solution, and a further portion (0·13 g., 27%), m. p. 142°, was recovered after concentration of the solution. Crystallisation from acetone did not raise the m. p. (ε 24·2 × 10^3, $\lambda_{max.}$ 296 mμ) (Found : C, 51·3; H, 6·2; N, 19·9. $C_9H_{13}O_3N_3$ requires C, 51·2; H, 6·2; N, 19·9%).

The ethoxyacrylamide (1·0 g.) and diethylamine (0·35 g.) similarly gave *α-cyano-β-diethylamino-N-ethoxycarbonylacrylamide* (0·73 g., 65%), which, crystallised from acetone at −50°, had m. p. 90° (Found : C, 55·4; H, 7·2; N, 17·35. $C_{11}H_{17}O_3N_3$ requires C, 55·2; H, 7·2; N, 17·55%).

(d) *Reaction with benzamide.* The acrylamide (1·0 g.) and benzamide (0·57 g.) were heated for 30 min. at 160° (bath). *β-Benzamido-α-cyano-N-ethoxycarbonylacrylamide*, which was obtained on cooling, crystallised from acetone as needles (0·66 g., 59%), m. p. 158° (Found : C, 58·5; H, 4·8; N, 14·85. $C_{14}H_{13}O_4N_3$ requires C, 58·5; H, 4·6; N, 14·6%).

TABLE 2. *Substituted β-amino-α-cyano-N-ethoxycarbonylacrylamides* (II).

R	M. p.	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
p-C_6H_4·NO_2	198°	92	51·3	3·7	18·65	$C_{13}H_{12}O_5N_4$	51·3	4·0	18·4
p-C_6H_4·CO_2H ...	220	92	55·2	4·3	13·65	$C_{14}H_{13}O_5N_3$	55·45	4·3	13·9
2-Naphthyl	156	82	66·0	5·1	13·3	$C_{17}H_{15}O_3N_3$	66·0	4·9	13·6
2-Pyridyl	256	81	55·0	4·9	21·9	$C_{12}H_{12}O_3N_4$	55·4	4·65	21·5
3-Pyridyl	160[a]	81	55·4	4·8	21·65				

[a] Decomposes and immediately resolidifies above the m. p.

Cyclisation of Aminoacrylamides to Substituted Uracils.—A suspension of β-anilino-α-cyano-*N*-ethoxycarbonylacrylamide (cf. Part I) (0·2 g.) in aqueous sodium hydroxide (N; 5 ml.) was warmed at 80° to produce a clear solution, which was cooled and acidified with hydrochloric acid. 5-Cyano-1-phenyluracil (0·12 g.) was precipitated and crystallised from ethanol as colourless plates, m. p. and mixed m. p. 290° (cf. Part I).

When α-cyano-*N*-ethoxycarbonyl-β-phenylhydrazinoacrylamide (cf. Part I) (0·25 g.) was treated with alkali, as in the case of the anilinoacrylamide, 1-anilino-5-cyanouracil (0·15 g.), m. p. and mixed m. p. 334° (cf. Part I), was obtained.

α-Cyano-*N*-ethoxycarbonyl-β-*p*-nitroanilinoacrylamide (0·50 g.) was boiled with aqueous sodium hydroxide (2N; 10 ml.) for 30 min. The red solution was cooled and acidified with hydrochloric acid (10N; 2·1 ml.), *1-p-nitrophenyluracil-5-carboxyamide* (0·27 g., 60%) being precipitated (m. p. 327—328°). When recrystallised from water the product had m. p. 328° (Found, in material dried for 3 hr. at 100°/0·1 mm. : C, 47·8; H, 3·0; N, 20·1. $C_{11}H_8O_5N_4$ requires C, 47·8; H, 2·9; N, 20·3%).

Reaction of the Ethoxyacrylamide with Hydrazine.—Hydrazine hydrate (60% w/v; 0·4 ml.) was added to the ethoxyacrylamide (1·0 g.) in hot ethanol (10 ml.), and the solution was boiled for 5 min. A mixture of compounds (0·65 g.) crystallised from the cooled solution, and was separated into two approximately equal fractions by crystallisation from ethanol. The less soluble compound, which was identified as *1-amino-5-cyanouracil*, crystallised from ethanol as pale yellow plates, m. p. 288° (Found : C, 39·5; H, 2·7; N, 37·0. $C_5H_4O_2N_4$ requires C, 39·5; H, 2·65; N, 36·8%). The more soluble *hydrazinium salt* crystallised from ethanol as cream needles which darkened on exposure to air. The salt had m. p. 142°, but resolidified above the m. p. and then did not melt below 360° (Found : C, 32·9; H, 5·0; N, 45·6. $C_5H_8O_2N_6$ requires C, 32·6; H, 4·4; N, 45·6%).

5-Cyanouracils from the Ethoxyacrylamide and α-Amino-acids.—The ethoxyacrylamide (5·0 g.)

was shaken with a solution of glycine (1·8 g.) in aqueous sodium hydroxide (2N; 12 ml.). When most of the ethoxyacrylamide had dissolved (15 min.) a second portion of sodium hydroxide (10N; 2·4 ml.) was added, and the resultant solution was warmed for 5 min. Addition of hydrochloric acid to the cooled mixture precipitated *5-cyanouracil-1-acetic acid* (3·9 g., 85%) which crystallised from water as needles, m. p. 233° (decomp.), R_F 0·44 (Found: C, 43·35; H, 2·6; N, 21·7. $C_7H_5O_4N_3$ requires C, 43·1; H, 2·6; N, 21·5%).

When an alkaline solution, obtained as above from the same amounts of reactants but without the second equivalent of alkali, was diluted with ethanol (20 ml.) and ether (30 ml.) *sodium 5-cyanouracil-1-acetate monohydrate* (5·2 g., 93%) crystallised, having m. p. >300° (Found: C, 35·7; H, 2·5. $C_7H_4O_4N_3Na,H_2O$ requires C, 35·75; H, 2·5%).

Other *5-cyanouracil-1-acetic acids* prepared by the former procedure are described in Table 3. Compounds which did not crystallise from the acidified reaction mixture were isolated by

TABLE 3. *5-Cyanouracil-1-acetic acids* (IV; R′ = H).

No.	R	Generating acid	R_F	Yield (%)	M. p.[c]
1	Me[a,b]	DL-Alanine	0·58	94	202°
2	Pr^n	DL-Norvaline	0·80	93	176
3	Pr^i	DL-Valine	0·77	56	254
4	Bu^n	DL-Norleucine	0·80	99	196
5	Bu^s	DL-Isoleucine	0·81	92	198
6	Bu^i[d,e]	L-Leucine	0·80	73	206
7	*n*-Pentyl	DL-α-Amino-*n*-octanoic acid	0·88	90	137
8	$HO\cdot CH_2\cdot CH_2$[a]	DL-Serine	0·44	91	168
9	$MeS\cdot[CH_2]_2\cdot CH_2$[a]	DL-Methionine	0·69	51	161
10	$HO_2C\cdot CH_2$[f,g]	DL-Aspartic acid	0·53	52	218
11	$H_2N\cdot CO\cdot CH_2$	DL-Asparagine	0·23	81	189
12	,,	L- ,,	—	92	198
13	$HO_2C\cdot CH_2\cdot CH_2$[f,g]	DL-Glutamic acid	0·50	42	193
14	,,[h]	L- ,,	—	—	191
15	$Ph\cdot CH_2$[i,k]	DL-Phenylalanine	0·80	64	186
16	$p\text{-}HO\cdot C_6H_4\cdot CH_2$[j]	L-Tyrosine	0·74	96	234

	Found (%)				Required (%)		
No.	C	H	N	Formula	C	H	N
1	45·9	3·5	20·1	$C_8H_7O_4N_3$	45·9	3·4	20·1
2	50·8	4·65	17·45	$C_{10}H_{11}O_4N_3$	50·6	4·7	17·7
3	50·25	4·45	17·5				
4	52·8	5·1	16·9	$C_{11}H_{13}O_4N_3$	52·6	5·2	16·7
5	52·75	5·0	16·7				
6	52·8	5·25	16·9				
7	55·7	6·0	14·9	$C_{13}H_{17}O_4N_3$	55·9	6·1	15·05
8	41·35	3·4	18·0	$C_8H_7O_5N_3,\frac{1}{2}H_2O$	41·0	3·4	17·95
9	44·4	3·9	15·2	$C_{10}H_{11}O_4N_3S$	44·6	4·1	15·6
10	42·6	3·0	16·7	$C_9H_7O_6N_3$	42·7	2·8	16·6
11	43·05	3·05	22·1	$C_9H_8O_5N_4$	42·9	3·2	22·2
12	42·7	3·0	22·3				
13	44·9	3·75	15·7	$C_{10}H_9O_6N_3$	44·95	3·4	15·7
14	44·7	3·6	15·7				
15	58·9	3·7	14·8	$C_{14}H_{11}O_4N_3$	58·9	3·9	14·7
16	56·1	3·8	13·4	$C_{14}H_{11}O_5N_3$	55·8	3·7	13·95

[a] Recryst. from ethyl acetate–light petroleum (b. p. 40—60°). [b] Treatment of an ethanolic suspension of the lead salt with hydrogen sulphide afforded the *ethyl ester*, m. p. 112° (Found: C, 50·7; H, 5·0; N, 17·7. $C_{10}H_{11}O_4N_3$ requires C, 50·6; H, 4·7; N, 17·7%). [c] With decomp. [d] The *monohydrate* had m. p. 181°, $[\alpha]_D^{17}$ −50·4° (*c* 1·19 in H_2O) (Found: C, 48·7; H, 5·2; N, 15·6. $C_{11}H_{13}O_4N_3,H_2O$ requires C, 49·1; H, 5·6; N, 15·6%). [e] $[\alpha]_D^{19}$ −48·8° (*c* 0·98 in H_2O). [f] Isolated from the aqueous solution by continuous extraction with ethyl acetate. [g] Purified for analysis by displacement from a Deacidite FF column. [h] Analytical material was isolated directly from the reaction mixture by ion-exchange. [i] Dried for 3 hr. at 78°/1 mm. [j] $[\alpha]_D^{16\cdot6}$ −169° (*c* 2·37 in H_2O). [k] Dried material was recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), then from water.

continuous extraction with ethyl acetate or by anion-exchange. Except where indicated, the compounds are racemic mixtures.

Reaction of the Ethoxyacrylamide with Lysine.—DL-Lysine monohydrochloride (1·87 g.) was dissolved in aqueous sodium hydroxide (1·8N; 11·4 ml.), and sufficient ethoxyacrylamide was added (4·4 g.) to form cyanouracil substituents at both amino-groups. After the addition of

more sodium hydroxide (1·8N; 11·4 ml.) the *product* was isolated in the usual way. This compound crystallised from water as the hemihydrate (2·8 g., 68%), m. p. 218—220° with sintering at 160—170° (Found: C, 48·6; H, 3·8; N, 21·5. $C_{16}H_{14}O_6N_6,\frac{1}{2}H_2O$ requires C, 48·6; H, 3·8; N, 21·3%). Treatment of the lead salt in ethanol with hydrogen sulphide gave the *ethyl ester*, m. p. 263° (Found: C, 52·2; H, 4·5; N, 20·3. $C_{18}H_{18}O_6N_6$ requires C, 52·2; H, 4·4; N, 20·3%).

Reaction of the Ethoxyacrylamide with β-Amino-α-methylpropionic Acid.—The ethoxyacrylamide (5·0 g.) and the DL-amino-acid (2·43 g.) were treated with alkali, and the mixture acidified; *5-cyanouracil-1-(α-methylpropionic acid)* (5·20 g., 99%) was precipitated and collected (m. p. 273—274°). The compound crystallised from water as colourless needles, m. p. 275° (Found: C, 48·2; H, 3·9; N, 19·1. $C_9H_9O_4N_3$ requires C, 48·4; H, 4·1; N, 18·8%).

Purification of 5-Cyanouracil-1-acetic Acids by Anion-exchange.—When solutions of the acids were applied to multiple columns of Deacidite FF (acetate form) following the procedure reported by Anet and Reynolds,[6] acetate was displaced and the pyrimidines were retained by the resin. Hydrochloric acid displaced the pyrimidines, which were isolated analytically pure by evaporation of appropriate fractions of effluent. Thus 5-cyanouracil-1-acetic acid was isolated directly from the reaction mixture, obtained in the usual way, after acidification with acetic acid (Found: C, 43·1; H, 2·7; N, 21·4%). Other examples of compounds purified in this way are included in Table 3. The pyrimidines were located in the effluent from the column by measurement of ultraviolet absorption or optical rotation. In all cases the resin in contact with the pyrimidine showed a light band which facilitated location of the compound.

5-Cyano-3-methyluracils.—α-Cyano-β-ethoxy-*N*-ethoxycarbonyl-*N*-methylacrylamide, b. p. 138°/0·4 mm., was prepared from *N*-cyanoacetyl-*N*-methylurethane (cf. Part II).

The ethoxy-*N*-methylacrylamide (1·0 g.) was added to a solution of ethylamine (0·40 g.) in ethanol (6 ml.). The mixture was heated on a steam-bath until solution was complete and the volume was reduced to 2 ml. On cooling, *5-cyano-1-ethyl-3-methyluracil* (0·67 g., 85%) was precipitated, and crystallised from ethanol as colourless needles, m. p. 133° (Found: C, 53·6; H, 5·3; N, 23·45. $C_8H_9O_2N_3$ requires C, 53·6; H, 5·1; N, 23·45%). Other 5-cyano-3-methyluracils prepared in the same way are described in Table 4.

TABLE 4. *5-Cyano-3-methyluracils* (III; R′ = Me).

				Found (%)			Required (%)		
R	Yield (%)	M. p.	Formula	C	H	N	C	H	N
Me	40	156°	$C_7H_7O_2N_3$	50·9	4·15	25·6	50·9	4·3	25·45
Ph	83	235	$C_{12}H_9O_2N_3$	63·4	4·1	18·3	63·4	4·0	18·5
p-$HO_2C{\cdot}C_6H_4$ [a]	[c]	278	$C_{13}H_9O_4N_3$	57·85	3·5	15·75	57·6	3·3	15·5
$HO_2C{\cdot}CH_2$ [b] ...	[c]	110	$C_8H_7O_4N_3,H_2O$	42·5	4·1	18·7	42·3	4·0	18·5
2-Pyridyl	64	204	$C_{11}H_8O_2N_4$	58·1	3·6	24·3	57·9	3·5	24·55
3- ,, ...	64	167		58·05	3·7	24·45			
H_2N	60	128	$C_6H_6O_2N_4$	43·5	3·7	33·45	43·4	3·6	33·7
Ph·NH	78	210	$C_{12}H_{10}O_2N_4$	59·2	3·95	23·35	59·5	4·2	23·1

[a] Formed from the non-cyclic aminoacrylamide (see below) by the usual treatment with alkali. [b] Sodium hydroxide was added, as with the examples in Table 3. [c] Prepared on a small scale.

Aminoacrylamides from the Ethoxy-N-methylacrylamide.—A mixture of the ethoxy-*N*-methylacrylamide (1·0 g.) and *p*-aminobenzoic acid (0·74 g.) in ethanol (20 ml.) was warmed for 10 min. *β-p-Carboxyanilino-α-cyano-N-ethoxycarbonyl-N-methylacrylamide* (1·1 g., 80%) separated and, recrystallised from acetone, had m. p. 254° (decomp.) (Found: C, 56·9; H, 5·05; N, 13·4. $C_{15}H_{15}O_5N_3$ requires C, 56·8; H, 4·8; N, 13·2%).

With sulphanilamide (2·0 g.) the ethoxy-*N*-methylacrylamide (2·6 g.) gave *β-p-sulphamoylanilino-α-cyano-N-ethoxycarbonyl-N-methylacrylamide* (3·4 g., 84%), m. p. 140° (decomp.) (Found: C, 47·6; H, 4·4; N, 15·75. $C_{14}H_{16}O_5N_4S$ requires C, 47·7; H, 4·6; N, 15·9%)

Hydrolysis of the 5-Cyano-group.—(a) *Alkaline hydrolysis.* 5-Cyanouracil-1-acetic acid (1·95 g.) was heated at 85—95° for 2 hr. with aqueous sodium hydroxide (2·5N; 25 ml.). Addition of hydrochloric acid (10N; 7 ml.) to the cooled solution precipitated a product (1·15 g.), m. p. 267° after softening from 254°. Repeated recrystallisation from ethanol and from water gave *5-carbamoyluracil-1-acetic acid monohydrate* as colourless needles, m. p. 275° (decomp.) (Found: C, 36·6; H, 4·4; N, 17·9. $C_7H_7O_5N_3,H_2O$ requires C, 36·4; H, 3·9; N, 18·2%).

(b) *Acid hydrolysis.* 5-Cyanouracil-1-acetic acid (3·6 g.) was boiled under reflux with

[6] Anet and Reynolds, *Austral. J. Chem.*, 1955, **8**, 267.

hydrochloric acid (6N; 75 ml.) for 8 hr. The solution was concentrated to 15 ml. and *5-carboxyuracil-1-acetic acid* (1·1 g.) crystallised [m. p. 247° (decomp.)]. This material crystallised from water as colourless plates, m. p. 275° (decomp.; softens above 250°) (Found: C, 39·4; H, 3·0; N, 13·35. $C_7H_6O_6N_2$ requires C, 39·3; H, 2·9; N, 13·1%).

When 5-cyano-1-α-carboxyphenethyluracil (50 mg.) was similarly hydrolysed with hydrochloric acid (6N; 2 ml.), the *5-carboxylic acid* crystallised, and when washed with water (5 ml.) had m. p. 222° (decomp.) (Found: C, 55·3; H, 4·0; N, 9·25. $C_{14}H_{12}O_6N_2$ requires C, 55·3; H, 4·0; N, 9·2%).

Identification of the N-Terminal Residue in a Peptide.—Glycylglycine (3·1 g.) was converted into *5-cyanouracil-1-(N-carboxymethylacetamide)* (III; R = $HO_2C{\cdot}CH_2{\cdot}NH{\cdot}CO{\cdot}CH_2$, R′ = H) by treatment with the ethoxyacrylamide (5·0 g.) in a reaction similar to that used for the compounds described in Table 3. The cyanouracil derivative crystallised from water as colourless plates (5·3 g., 90%), m. p. 251—253° (decomp.; darkens above 200°) (Found: C, 42·6; H, 3·3; N, 22·3. $C_9H_8O_5N_4$ requires C, 42·9; H, 3·2; N, 22·2%).

Samples (*ca.* 10 mg.) of the 5-cyanouracils derived from glycylglycine and from glycine were boiled under reflux in hydrochloric acid (6N; 2 ml.) for 8 hr. and then evaporated to dryness. Paper chromatograms were run under the conditions described above. Both hydrolysates showed single spots (R_F 0·75, 0·77) which absorbed ultraviolet light and corresponded to 5-carboxyuracil-1-acetic acid. The hydrolysate of the cyanouracil from glycylglycine also showed a spot (R_F 0·44) which reacted with ninhydrin and corresponded to glycine.

Paper Chromatography of Derivatives formed from Ammonia, Methylamine, and Dimethylamine.—The pyrimidines formed from ammonia and methylamine, and the dimethylaminoacrylamide formed from dimethylamine on treatment with the ethoxyacrylamide, were separated by chromatography on Whatman No. 1 paper in a solvent of water (100 ml.)–propan-2-ol (95%; 5 ml.)–ammonium sulphate (5 g.). The compounds were detected as discrete ultraviolet-absorbing spots (R_F values 0·76, 0·85, and 0·93 respectively).

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