309. *Purines, Pyrimidines, and Imidazoles. Part XXI.* Some Uracils and Isocytosines*

By J. H. Dewar and G. Shaw

Addition of ammonia to the oxazolidine (V) has been shown to give either a uracil or an isocytosine according to the reaction conditions; the isocytosine degrades further in water at room temperature. The *C*-formyl derivative of cyanoacetylcyanamide has been prepared and found to react with amines in water to give β-amino-*N*-carbamoyl-α-cyanoacrylamides. The structure of these compounds was confirmed by their reactions and synthesis from cyanoacetylurea.

Preparations of various uracil derivatives from suitable linear precursors and primary amines have been recorded in earlier publications.[1,2] We have been interested in extending these reactions to include analogous syntheses of isocytosines for which there are few satisfactory preparations. At the same time we envisaged an extension of our earlier *N*-terminal assay procedure for proteins [3] to include a possible stepwise degradation of a suitable isocytosine derivative, *e.g.*, (I), which might be expected to cyclise with separation of the terminal amino-acid group; to test the possibility of this we decided to prepare the model compound (I) by our earlier recorded route to isocytosines.[4]

The uracil (II), prepared from the ethoxy-derivative (III) and DL-serine by an improvement of the method used earlier for the preparation of the L-isomer,[3] with glycine ethyl ester and dicyclohexylcarbodi-imide in tetrahydrofuran gave the peptide derivative (IV).

* Part XX, G. Shaw, D. V. Wilson, and (in part) C. P. Green, *J.*, 1964, 2650.

[1] R. K. Ralph and G. Shaw, *J.*, 1956, 1877; M. R. Atkinson, G. Shaw, and D. N. Butler, *J.*, 1956, 4118; M. R. Atkinson, G. Shaw, K. Schaffner, and R. N. Warrener, *J.*, 1956, 3847; G. Shaw and R. N. Warrener, *J.*, 1958, 153, 157.

[2] G. Shaw, *J.*, 1955, 1834.

[3] J. H. Dewar and G. Shaw, *J.*, 1961, 3254.

[4] G. Shaw and R. N. Warrener, *J.*, 1959, 50.

Reaction of this with either toluene-*p*-sulphonyl chloride or methanesulphonyl chloride gave, in each case, the oxazolidine (V). In neither case could the intermediate toluene-*p*-sulphonyl or methanesulphonyl derivatives be isolated although in this type of system it is unusual for such derivatives to cyclise spontaneously, and the behaviour is more reminiscent of that of analogous thio-derivatives.[4] In the present example the leaving activity of the toluene-*p*-sulphonyloxy-group is clearly enhanced by the β-carbonyl group.

The oxazolidine (V) with ammonia gave two isomers depending on the concentration of reactants and the temperature. In strong solution on heating, the product formed was undoubtedly the acetyluracil (VI) with ultraviolet absorption spectra at different pH values typical of such compounds and in particular very similar to those of the analogous compound (IV) (see Table 1). In dilute solution at room temperature the compound formed is

TABLE 1

Ultraviolet absorption spectra of some uracils and isocytosines

Compound	Solvent	$\lambda_{min.}$ (mμ)	$\varepsilon_{min.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
(II)	Water	252—253, 211	2900, 6650	286—287, 231	14,150, 11,750
	pH 2	249—250	2400	283	13,900
	pH 12	260	3650	288	10,550
(IV)	Water	250, 212—213	3000, 8750	283—284, 230	14,200, 12,950
	pH 2	248—249	2700	283—284	14,200
	pH 12	258	4850	285	11,600
(V)	Water	252, 207	4700, 8050	282, 226—227	13,350, 12,550
	pH 2	252	5100	282	13,750
	pH 12	260	5900	285	10,600
(I)	Water	232—233	9050	277—278	19,700
	pH 2	—	—	276—277	20,050
	pH 12	260	5750	285	8950
(VI)	Water	249	4750	280	10,800
	pH 2	248	4500	280	10,550
	pH 12	259	4250	284	8300
(X)	Water	251—252	3250	277—278	7900
	pH 2	250—251	3100	231, 277—278	10,900, 8150
	pH 12	263	4500	240—241, 289	13,900, 9800

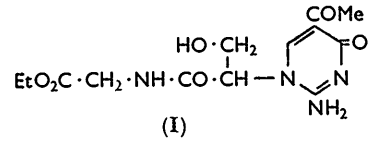
regarded as the isocytosine (I) which would be the normal result of this type of reaction. An aqueous solution of the isocytosine (I) showed a marked change in ultraviolet absorption after a few hours at room temperature and the absorption became constant after about 70 hours. At the same time two ninhydrin-positive spots were detected on paper chromatograms, corresponding to a loss of glycine ethyl ester. The small amount of material available made the isolation of a crystalline product difficult but the relative ease of breakdown of (I) under mild conditions encouraged us to examine the possibility of preparing a simple linear precursor of isocytosines.

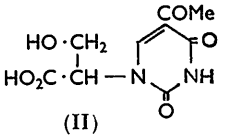
Reaction of ethyl cyanoacetate with sodium cyanamide in dry ethanol gave the sodium salt of cyanoacetylcyanamide (VII). Attempts to convert this into the ethoxymethylene derivative with ethyl orthoformate and acetic anhydride led only to a brown polymeric material. However, formylation of (VII) with ethyl formate and sodium ethoxide in ethanol readily gave the disodium salt (VIII) of the hydroxymethylene derivative which gave a blood red colour with ferric chloride.

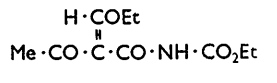
The disodium salt (VIII) with hydrochloric acid followed immediately by aqueous ammonia gave a crystalline precipitate, analysis of which suggested that it was either a monohydrate of the required isocytosine, or an isomer thereof such as a hydrate of the corresponding aminomethylenecyanamide or the aminomethyleneurea (IX; R = H). Similar compounds were obtained by reaction of the disodium salt with several amines or with hydroxylamine or semicarbazide. Attempts to dehydrate these compounds were unsuccessful, and this constant presence of a molecule of water suggested that the compounds were in fact aminomethyleneureas (IX). This was confirmed by the following series of experiments.

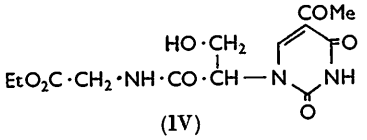
The urea (IX; R = $CH_2 \cdot CH_2OH$) derived from ethanolamine was not identical with

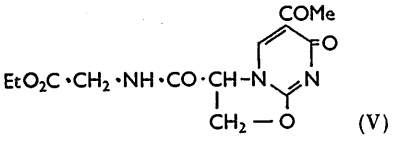
the isocytosine (X) which we had previously prepared by another route.[4] Alkaline hydrolysis of (IX; R = $CH_2{\cdot}CH_2OH$) gave 5-carbamoyluracil which could be hydrolysed with acid to uracil-5-carboxylic acid identical with a sample prepared by acid hydrolysis of 5-cyanouracil. It is noteworthy that little or no 5-carbamoyluracil is obtained by

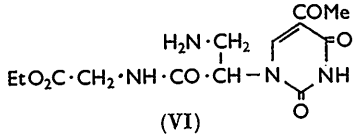

(I)

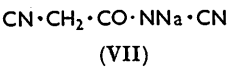

(II)

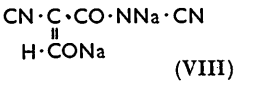

(III)

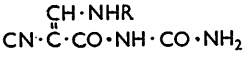

(IV)

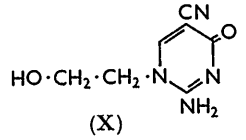

(V)

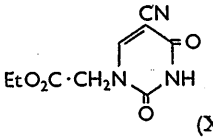

(VI)

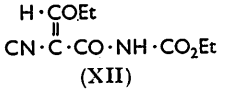

(VII)

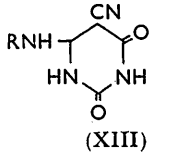

(VIII)

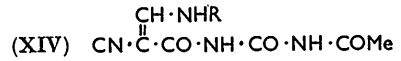

(IX)

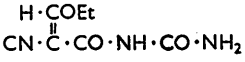

(X)


(XI)


(XII)


(XIII)


(XIV)


(XV)

alkaline hydrolysis of 5-cyanouracil and this suggests that the conversion of the cyano-group into carbamoyl is occurring at a pre-uracil stage. The formation of 5-carbamoyl-uracil by this type of reaction is a useful preparation of the compound. 5-Carbamoyl-uracil was also isolated from the alkaline hydrolysate of the glycine ester derivative (IX; R = $CH_2{\cdot}CO_2Et$) and, in addition, the ureas (IX; R = Ph) and (IX; R = $CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CO_2Me$), derived respectively from aniline and glycylglycine methyl ester, when similarly hydrolysed gave 5-carbamoyluracil which was detected on paper chromatograms. Also, reaction of the ester (IX; R = $CH_2{\cdot}CO_2Et$) with acetic anhydride gave the ethoxycarbonylmethyluracil (XI), identical with an authentic sample prepared from the ethoxy-derivative (XII) and glycine ethyl ester. The mechanism of the base-catalysed cyclisation involves, presumably, the formation of a dihydrouracil (XIII) followed by β-elimination of $R{\cdot}NH_2$. In the case of the acetic anhydride, cyclisation formation of a dihydrouracil would be hindered by prior formation of an acetyl derivative (XIV) which could then cyclise with loss of acetamide. In order to confirm fully the structures proposed for the aminomethyleneureas (IX) we decided to investigate their preparation by an alternative route.

Formylation of cyanoacetylurea with ethyl orthoformate and acetic anhydride gave a mixture of the ethoxymethyleneurea (XV) and the related urethane (XII). The last compound was identical with an authentic specimen prepared from cyanoacetyl urethane, ethyl orthoformate, and acetic anhydride by our earlier recorded method.[2] The ethoxy-methyleneurea (XV) with aniline readily gave the anilinomethylene derivative (IX; R = Ph) identical with the corresponding compound prepared from (VIII) and aniline. The ethoxymethyleneurea (XV), like the corresponding aminomethylene derivatives, with alkali readily gave 5-carbamoyluracil.

Having proved the identity of the aminomethyleneureas it was necessary to confirm if

the cyanamide moiety was indeed present in either the disodium salt (VIII) or the monosodium derivative (VII). The sodium salt of cyanoacetylurea was readily prepared from cyanoacetylurea and sodium ethoxide in dry ethanol in high yield. Infrared-spectral comparison of this substance with the sodium salt (VII) showed that they were not identical. Similarly, formylation of cyanoacetylurea with ethyl formate and sodium ethoxide in ethanol gave a disodium salt not identical with that prepared from cyanoacetylcyanamide. Also, infrared-spectral comparison of cyanide absorption in the 4·6 μ region showed that the cyanamides had, in each case, a much higher absorption than the corresponding ureas. These results appear to confirm conclusively that the structures allotted to the sodium derivatives (VII) and (VIII) are in fact correct, and that the conversion of the cyanamide group into a carbamoyl group occurs during the reaction in aqueous solution with the amino-compounds.

Experimental

DL-5-*Acetyluracil*-1-(α-*hydroymethyl*)*acetic Acid* (II).—α-Acetyl-β-ethoxy-*N*-ethoxycarbonylacrylamide [3] (23 g.) was added to a solution of DL-serine (11 g.) in 2N-sodium hydroxide (110 ml.) and the mixture heated on a steam-bath for 15 min. then cooled and acidified with 10N-hydrochloric acid (25 ml.). The solution was evaporated *in vacuo* to 100 ml., cooled, and saturated with ether to give a crystalline precipitate of the *uracil* (25·3 g.), m. p. 204° (Found: C, 41·8; H, 4·35; N, 10·9. $C_9H_{10}N_2O_6,H_2O$ requires C, 41·55; H, 4·65; N, 10·75%). The L-isomer has m. p. 216°.

DL-5-*Acetyluracil*-1-(α-*hydroxymethyl*-N-*ethoxycarbonylmethyl*)*acetamide* (IV).—To a solution of the foregoing uracil (5·2 g.) in tetrahydrofuran (100 ml.) and water (3 ml.) was added glycine ethyl ester (3 g.) followed by addition, with cooling, of a solution of dicyclohexylcarbodi-imide (4·2 g.) in tetrahydrofuran (10 ml.) over 30 min. with shaking. The mixture was set aside at room temperature overnight then treated with acetic acid (2 ml.) and the precipitated *NN'*-dicyclohexylurea (m. p. and mixed m. p. 232°) collected and washed with tetrahydrofuran (10 ml.). The filtrate was evaporated to dryness *in vacuo* and the residue extracted with nitromethane in three portions (total volume 60 ml.) to leave a further quantity of the urea. The solution was evaporated to a clear gum, and a solution of this in ethyl acetate was washed with saturated aqueous sodium hydrogen carbonate (10 ml.) and water (10 ml.). Careful addition of light petroleum (b. p. 40—60°) to the dried solution then gave a crystalline precipitate. The *acetyluracil* (5·3 g.) recrystallised from acetone–light petroleum as needles, m. p. 164° (Found: C, 47·85; H, 5·2; N, 12·8. $C_{13}H_{17}N_3O_7$ requires C, 47·7; H, 5·25; N, 12·85%).

DL-6-*Acetyl*-3-*ethoxycarbonylmethylaminocarbonyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolo*[3,2-a]*pyrimidine* (V).—To a solution of the foregoing acetyluracil (4·4 g.) in anhydrous pyridine (15 ml.) was added redistilled methanesulphonyl chloride (2 ml.). The mixture was set aside at room temperature overnight, filtered, treated with water (2 ml.) and, after 5 min. evaporated *in vacuo* to a gum. This with warm water (25 ml.) gave a clear solution which was extracted continuously with ethyl acetate for 3 hr. Evaporation of the extract *in vacuo* left a gum which dissolved in a small volume of hot nitromethane; the cooled solution gave a crystalline precipitate. The *oxazolopyrimidine* (0·73 g.) recrystallised from nitromethane as rods, m. p. 163—164° (Found: C, 50·4; H, 4·85; N, 13·4. $C_{13}H_{15}N_3O_6$ requires C, 50·5; H, 4·9; N, 13·6%). A mixed m. p. with the starting material was strongly depressed. The same compound was also obtained when toluene-*p*-sulphonyl chloride replaced methanesulphonyl chloride in the reaction; in neither case could an intermediate sulphonate be detected.

5-*Acetylisocytosine*-1-(α-*hydroxymethyl*-N-*ethoxycarbonylmethyl*)*acetamide*.—The foregoing oxazolopyrimidine (0·2 g.) in ethanol (75 ml.) was set aside at room temperature for 3 hr. with saturated ethanolic ammonia (30 ml.). The solution was evaporated *in vacuo* to a small volume to give a crystalline precipitate. The *isocytosine* (0·1 g.) separated from ethanol as rods, m. p. 181° (Found: C, 47·85; H, 5·7; N, 17·4. $C_{13}H_{18}N_4O_6$ requires C, 47·9; H, 5·55; N, 17·2%).

5-*Acetyluracil*-1-(α-*aminomethyl*-N-*ethoxycarbonylmethyl*)*acetamide*.—The foregoing oxazolopyrimidine (0·5 g.) in ethanol (1·5 ml.) was heated on a steam-bath with saturated ethanolic ammonia (4 ml.) for 5 min. The clear solution soon deposited a solid. The *acetyluracil* (0·39 g.) was washed with warm ethanol and recrystallised from ethanol as thick hexagonal plates, m. p. 189° (decomp.) (Found: C, 48·0; H, 5·9; N, 17·0. $C_{13}H_{18}N_4O_6$ requires C, 47·9; H, 5·55; N, 17·2%).

5-*Acetyl*-2-N-*benzylisocytosine*-1-(α-*hydroxymethyl*-N-*ethoxycarbonylmethyl*)*acetamide*.—The

oxazolopyrimidine (0·074 g.) in methanol (2 ml.) containing benzylamine (3 drops) was set aside at room temperature, when a crystalline precipitate soon separated. The *benzylisocytosine* (0·035 g.) recrystallised from methanol as needles, m. p. 167° (Found: C, 57·65; H, 5·95; N, 13·75. $C_{20}H_{24}N_4O_6$ requires C, 57·7; H, 5·8; N, 13·45%).

Decomposition of 5-Acetylisocytosine-1-(α-hydroxymethyl-N-ethoxycarbonylmethyl)acetamide.—The isocytosine (0·19 g.) in cold water (750 ml.) was set aside for 80 hr., when the ultraviolet absorption spectrum of the solution had become constant with values $\lambda_{min.}$ 210 mμ, $\lambda_{max.}$ 227 mμ, $\lambda_{min.}$ 251 mμ, $\lambda_{max.}$ 282 mμ, compared with $\lambda_{min.}$ 232 mμ and $\lambda_{max.}$ 277 mμ for the original solution. Evaporation of the solution *in vacuo* gave a gum which, when chromatographed on paper in the system butanol–acetic acid–water (12 : 3 : 5), showed a major absorbing spot (R_F 0·84), a minor absorbing spot (R_F 0·58), and two ninhydrin-positive spots (R_F 0·29 and 0·54). The gum was extracted with hot ethanol, and the solution after filtration, treated with ether to give a solid precipitate. This was redissolved in moist acetone, the mixture filtered, the filtrate evaporated, and the residue again extracted with hot ethanol. Evaporation of the ethanol gave an amorphous solid which gave only one ultraviolet-absorbing spot (R_F 0·84) in the above solvent system (Found: C, 50·0; H, 5·3; N, 13·4%).

Cyanoacetylcyanamide.—To a solution of cyanamide (4·2 g.) in ethanol (100 ml.) was added a solution from sodium (2·3 g.) and ethanol (50 ml.), then after a few minutes ethyl cyanoacetate (11·8 g.), and the mixture was heated on a steam-bath for 10 min. Evaporation of the solution *in vacuo* to about 60 ml. gave a crystalline precipitate. The *sodium salt of cyanoacetylcyanamide* (11·5 g.) recrystallised from a large volume of ethanol as laths, which retained water (Found: C, 32·9; H, 2·9; N, 29·8. $C_4H_2N_3ONa,\frac{3}{4}H_2O$ requires C, 33·2; H, 2·4; N, 29·05%).

α,N-*Dicyano-β-hydroxyacrylamide.*—To a suspension of the foregoing sodio derivative (12·1 g.) in ethanol (50 ml.) were added successively a solution from sodium (2·14 g.) in ethanol (100 ml.), and ethyl formate (9 ml.). The mixture was boiled under reflux for 50 min. during which time the starting material slowly dissolved and was replaced by a solid precipitate of the product. The *dicyanide disodium salt* (13 g.) gave a blood-red colour with ferric chloride (Found: C, 27·1; H, 2·35; N, 17·2. $C_5HN_3Na_2O_2,2H_2O$ requires C, 27·65; H, 2·3; N, 19·35%). The product was probably contaminated with a little of the monosodium derivative.

Reaction of the Disodium Salt with Ammonia and Amines.—(*a*) To a slurry of the disodium salt (1·08 g.) in water (2 ml.) was added 5N-hydrochloric acid (2 ml.) followed by aqueous ammonia (2 ml.; *d* 0·88). *β-Amino-N-carbamoyl-α-cyanoacrylamide* (0·4 g.) separated from the cooled solution and recrystallised from methanol containing a little water as rosettes of needles, m. p. 220° (decomp.) (Found: C, 34·6; H, 4·75; N, 33·2. $C_5H_6N_4O_2,H_2O$ requires C, 34·9; H, 4·7; N, 32·55%). (*b*) Methylamine similarly gave *N-carbamoyl-α-cyano-β-methylaminoacrylamide* which crystallised from water as pale yellow rods, m. p. 206° (decomp.) (Found: C, 41·7; H, 4·65; N, 32·4. $C_6H_8N_4O_2,\frac{1}{4}H_2O$ requires C, 41·7; H, 4·95; N, 32·45%). (*c*) Aniline gave *β-anilino-N-carbamoyl-α-cyanoacrylamide* as pale yellow needles (from water) m. p. 188—190° (decomp.) (Found: C, 57·2; H, 4·5; N, 25·75. $C_{11}H_{10}N_4O_2$ requires C, 57·4; H, 4·35; N, 24·35%). (*d*) Benzylamine gave *β-benzylamino-N-carbamoyl-α-cyanoacrylamide* as pale yellow elongated rods (from water), m. p. 153—155° (Found: C, 58·85; H, 5·25; N, 22·7. $C_{12}H_{12}N_4O_2$ requires C, 59·0; H, 4·95; N, 22·95%). (*e*) Cyclohexylamine gave *N-carbamoyl-α-cyano-β-cyclohexylaminoacrylamide* as pale yellow plates (from water) m. p. >300° (Found: C, 52·5; H, 7·05; N, 22·8. $C_{11}H_{16}N_4O_2,\frac{3}{4}H_2O$ requires C, 52·9; H, 7·05; N, 22·45%). (*f*) Hydroxylamine gave *N-carbamoyl-α-cyano-β-hydroxyaminoacrylamide* as needles (from water), m. p. 300° (Found: C, 35·7; H, 3·35; N, 33·6. $C_5H_6N_4O_3$ requires C, 35·3; H, 3·55; N, 32·95%). (*g*) Semicarbazide hydrochloride and the disodium salt gave *N-carbamoyl-α-cyano-β-semicarbazidoacrylamide* which separated from the reaction mixture as rosettes of needles, m. p. >300° (Found: C, 34·25; H, 4·25; N, 38·9. $C_6H_8N_6O_3$ requires C, 33·95; H, 3·8; N, 38·7%). The compound dissolved in boiling water and the clear hot solution soon gave a precipitate of elongated needles of an isomer which would not redissolve in large volumes of hot water; it had m. p. >300° (Found: C, 33·5; H, 3·7; N, 39·9%). The compounds had different infrared spectra. (*h*) The disodium salt and glycine ethyl ester hydrochloride gave *N-carbamoyl-α-cyano-β-ethoxycarbonylmethylaminoacrylamide* which separated from water as pale yellow diamond-shaped plates, m. p. 179° (decomp.) (Found: C, 45·3; H, 5·15; N, 22·9. $C_9H_{12}N_4O_4$ requires C, 45·0; H, 5·05; N, 23·35%). (*i*) The disodium salt and glycylglycine methyl ester hydrochloride in water gave *N-carbamoyl-α-cyano-β-[N-(methoxycarbonylmethyl)carbamoylmethylamino]acrylamide* which separated from 90% aqueous acetone as pale yellow rosettes of

needles, m. p. 188—189° (Found: C, 42·3; H, 4·7; N, 24·65. $C_{10}H_{13}N_5O_5$ requires C, 42·4; H, 4·65; N, 24·75%). (*j*) Ethanolamine gave N-*carbamoyl*-α-*cyano*-β-2-*hydroxyethylacrylamide* which crystallised from water as pale yellow needles, m. p. 190° (decomp.) (Found: C, 42·5; H, 5·1; N, 28·7. $C_7H_{10}N_4O_3$ requires C, 42·45; H, 5·1; N, 28·3%).

Ultraviolet absorption spectra of several of these acrylamides are recorded in Table 2.

TABLE 2

Ultraviolet absorption spectra of some β-amino-*N*-carbamoyl-α-cyanoacrylamides $CN{\cdot}C(:CHNHR){\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH_2$

R	Solvent	$\lambda_{min.}$ (mμ)	$\varepsilon_{min.}$	$\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
H	Water	242	1100	278	11,300
Me	Water	249	1000	292	16,600
Me	0·1N-HCl	252	1650	291	19,550
Me	0·1N-NaOH	255	3200	284	11,450
Ph	Water	257—258	1950	326	25,300
CH_2Ph	Water	252	2050	294	28,100
C_6H_{11}	Water	240—241	2200	278	15,050
CH_2CO_2Et	Water	244	700	290	24,350
CH_2CO_2Et	pH 2·5	244	1000	290	24,350
CH_2CO_2Et	pH 11·5	253	3150	291—292	19,300
OH	Water	247—248	9450	266—267, 241	15,200, 9750

Reaction of some β-*Amino*-N-*carbamoyl*-α-*cyanoacrylamides with Sodium Hydroxide.*—A portion of *N*-carbamoyl-α-cyano-β-2′-hydroxyethylacrylamide was boiled with dilute sodium hydroxide for a few minutes then the clear solution was cooled and acidified to precipitate 5-carbamoyluracil as boats, m. p. >300° (Found: C, 38·8; H, 3·5; N, 26·95. Calc. for $C_5H_5N_3O_3$: C, 38·7; H, 3·25; N, 27·1%). The same compound was also isolated from a similar hydrolysis of *N*-carbamoyl-α-cyano-β-ethoxycarbonylmethylaminoacrylamide. In addition, paper chromatography, in butan-1-ol–acetic acid–water (4 : 1 : 5), of the alkaline hydrolysates of β-anilino-*N*-carbamoyl-α-cyanoacrylamide and *N*-carbamoyl-α-cyano-β-[*N*-(methoxycarbonylmethyl)carbamoylmethylamino]acrylamide showed the presence of 5-carbamoyluracil, R_F 0·51. The structure of the carbamoyluracil was confirmed by hydrolysis with 6N-hydrochloric acid for 5 hr. and evaporation of the solution to give uracil-5-carboxylic acid, m. p. 288° (decomp.), identical (mixed m. p. and infrared spectrum) with an authentic specimen prepared by acid hydrolysis of 5-cyanouracil.

Ethyl 5-*Cyanouracil*-1-*acetate* (XI).—(*a*) A small amount of *N*-carbamoyl-α-cyano-β-ethoxycarbonylmethylaminoacrylamide was heated on a water-bath for 5 min. with acetic anhydride. The solution was then evaporated *in vacuo* to a crystalline solid. The *uracil* recrystallised from ethyl acetate–light petroleum (b. p. 40—60°) as plates, m. p. 137—141° (Found: C, 48·3; H, 4·15; N, 18·35. $C_9H_9N_3O_4$ requires C, 48·4; H, 4·05; N, 18·85%).

(*b*) To a solution of glycine ethyl ester hydrochloride (0·7 g.) in water (1 ml.) was added N-sodium hydroxide (4·5 ml.) and α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (0·5 g.). The mixture was heated on a water-bath for 10 min., cooled, and acidified to precipitate 5-cyano-1-ethoxycarbonylmethyluracil (0·5 g.). The compound was identical (m. p., mixed m. p., and infrared spectrum) with the substance formed under (*a*).

Reaction of Cyanoacetylurea with Ethyl Orthoformate and Acetic Anhydride.—A mixture of cyanoacetylurea (44 g.), ethyl orthoformate (80 ml.), and acetic anhydride (150 ml.) was boiled under reflux for 40 min. The cooled solution gave a crystalline precipitate. N-*Carbamoyl*-α-*cyano*-β-*ethoxyacrylamide* (14 g.) recrystallised from acetic acid–ether or from ethyl acetate as rods, m. p. 169—170° (Found: C, 46·25; H, 4·65; N, 22·95. $C_7H_9N_3O_3$ requires C, 45·9; H, 4·95; N, 22·95%). The filtrate from the above reaction was evaporated *in vacuo* to about one third the volume to give a precipitate of α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (25·5 g.) which recrystallised from benzene as rods, m. p. 118° (Found: C, 50·75; H, 5·6; N, 13·35. Calc. for $C_9H_{12}N_2O_4$: C, 50·95; H, 5·7; N, 13·2%). The compound was identical with an authentic specimen prepared from cyanoacetylurethane, ethyl orthoformate, and acetic anhydride.[2]

The foregoing *N*-carbamoyl-α-cyano-β-ethoxyacrylamide (1 g.) was heated on a water-bath with water (1·5 ml.) and aniline (0·55 ml.) for 5 min. The cooled solution gave a crystalline precipitate. β-Anilino-*N*-carbamoyl-α-cyanoacrylamide (0·43 g.) separated from ethanol as needles, m. p. 189—190° (decomp.) (Found: C, 57·4; H, 4·3; N, 24·2%), identical (mixed m. p.

and infrared spectrum) with the compound prepared earlier from the disodium salt and aniline. *N*-Carbamoyl-α-cyano-β-ethoxyacrylamide when warmed for a short time with dilute sodium hydroxide solution gave, after acidification, 5-carbamoyluracil, m. p. >300°.

Sodium Salt of Cyanoacetylurea.—To a slurry of cyanoacetylurea (1·27 g.) in ethanol (50 ml.) was added a solution from sodium (0·23 g.) and ethanol (10 ml.). The clear solution rapidly gave a solid precipitate (1·3 g.) of the sodium salt (Found: C, 31·9; H, 2·95; N, 27·8. $C_4H_4N_3NaO_2$ requires C, 32·2; H, 2·7; N, 28·2%).

Disodium Salt of N-*Carbamoyl-α-cyano-β-hydroxyacrylamide.*—A solution from sodium (0·1 g.) in ethanol (5 ml.) was added to a mixture of cyanoacetylurea (0·5 g.) in ethanol (50 ml.). The mixture was heated on a water-bath until a clear solution was obtained (10 min.), then ethyl formate (0·25 ml.) and a solution from sodium (0·1 g.) and ethanol (5 ml.) were added and the mixture heated for a further 90 min. The cooled solution gave a precipitate of the *disodium salt* (0·3 g.) (Found: C, 29·8; H, 1·85; N, 20·6. $C_5H_3N_3Na_2O_3$ requires C, 30·15; H, 1·5; N, 21·1%).

Infrared spectra of the foregoing mono- and di-sodium salts showed that they were not identical with the corresponding compounds derived from cyanoacetylcyanamide. Also, comparison of the relative intensities of CN absorption in the 4·6 μ region showed that in each case the cyanamide-derived salt had the much higher intensity.

We thank the Medical Research Council for financial assistance.

INSTITUTE OF TECHNOLOGY, BRADFORD 7.

[Present address (J. H. D.): DEPARTMENT OF CLINICAL CHEMISTRY, KING'S COLLEGE, NEWCASTLE UPON TYNE.]

[*Received, July 21st*, 1964.]