33. *Purines, Pyrimidines, and Glyoxalines. Part VIII.** *New Syntheses of Uracils and Thymines.*

By G. Shaw and R. N. Warrener.

Uracils and thymines have been prepared by the reaction of β-ethoxyacryloyl and β-methoxy-α-methylacryloyl *iso*cyanate respectively with (*a*) ammonia or primary amines (followed by cyclisation of the resulting acylureas) and (*b*) ethanol (followed by reaction of the β-alkoxyacryloylurethanes so formed with primary amino-compounds). The *iso*cyanates were prepared from the acid chlorides and silver cyanate.

Part V[1] of this series described new syntheses of uracil and its 1-substituted derivatives by the reaction of ammonia or a primary amine with propioloylurethane or β-ethoxyacryloylurethane (IV; R = Et, R′ = H). However the preparation of these intermediates was not entirely satisfactory, so we examined alternatives. With a view to extending the reactions to syntheses of 1-substituted thymine derivatives, we studied first the β-alkoxyacryloylurethanes.

In an attempt to prepare the potential thymine precursor (IV; R = R′ = Me) by the reaction of β-methoxy-α-methylacryloyl chloride * (I; R = R′ = Me) with sodiourethane in benzene only the bisurethane derivative, $EtO_2C{\cdot}NH{\cdot}CH{:}CMe{\cdot}CO{\cdot}NH{\cdot}CO_2Et$, was isolated. When sodium β-methoxy-α-methylacrylate was treated with a half molar quantity of thionyl chloride and the product, presumably the anhydride, warmed with urethane, the urethane, $EtO_2C{\cdot}NH{\cdot}CH{:}CMe{\cdot}CO_2H$, was obtained, again by replacement of the methoxy-group.

In Part VII we described syntheses of thiouracils and thiothymines from β-alkoxyacryloyl *iso*thiocyanates and primary amines. We have extended this reaction to analogous oxy-compounds.

β-Methoxy-α-methylacryloyl chloride (I; R = R′ = Me) with silver cyanate in benzene at room temperature readily gave a crystalline compound which, though so reactive as to be unstable, was clearly the *iso*cyanate (IV; R = R′ = Me). In air it immediately gave a solid which rapidly evolved carbon dioxide, leaving a crystalline residue of the *NN*′-diacylurea. Benzoyl *iso*cyanate and water also give some dibenzoylurea although the major product in this case is benzamide.[2] It has been suggested that diacylureas are formed by reaction of excess of acyl *iso*cyanate with the amide first formed: $R{\cdot}CO{\cdot}NH_2 + R{\cdot}CO{\cdot}NCO \longrightarrow (R{\cdot}CO{\cdot}NH)_2CO$. It seems much more likely however that the reaction proceeds *via* a carbamic anhydride: $2R{\cdot}CO{\cdot}NCO + H_2O \longrightarrow (R{\cdot}CO{\cdot}NH{\cdot}CO)_2O \longrightarrow R{\cdot}CO{\cdot}N(CO_2H){\cdot}CO{\cdot}NH{\cdot}CO{\cdot}R \longrightarrow (R{\cdot}CO{\cdot}NH)_2CO + CO_2$.

The *iso*cyanate (II; R = R′ = Me) reacted violently with ammonia, methylamine, aniline, and phenylhydrazine, to give the linear derivatives (III; R = R′ = Me, R″ = H, Me, Ph, or Ph·NH respectively). The acylureas (III; R = R′ = Me, R″ = H, Me, or Ph) were converted into the corresponding thymines (V; R = Me, R′ = H, Me, or Ph) when warmed respectively with aqueous ammonia, methylamine, and sodium hydroxide. The last base with the acylureas (III; R = R′ = Me, R″ = H, Me) also gave a small yield of pyrimidines although reaction conditions were difficult to define and in one case this reaction gave a compound $C_{11}H_{18}O_6N_2$, which was a molecular complex of the urea (III; R = R′ = Me, R″ = H) and β-methoxy-α-methylacrylic acid, since it gave these compounds when sublimed *in vacuo*. The semicarbazide (III; R = R′ = Me, R″ = Ph·NH) when warmed with sodium hydroxide solution gave the triazole (VI; R = R′ = Me, R″ = Ph).

---

* Part VII, preceding paper.

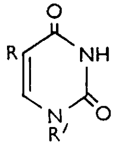
[1] Part V, Atkinson, Maguire, Ralph, Shaw, and Warrener, *J.*, 1957, 2363.

[2] Billeter, *Ber.*, 1903, **36**, 3218; Arcus and Prydal, *J.*, 1954, 4018.

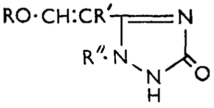
The *iso*cyanate (II; R = R′ = Me) with ethanol gave the acylurethane (IV; R = R′ = Me) in excellent yield. This with ammonia, methylamine, and aniline readily afforded the thymines (V; R = Me, R′ = H, Me, Ph) respectively. An intermediate acylurea (III; R = R′ = Me, R″ = Ph) was obtained from the reaction of the urethane with aniline.

(I) $RO{\cdot}CH{:}CR'{\cdot}COCl$ $RO{\cdot}CH{:}CR'{\cdot}CO{\cdot}NCO$ (II)

(III) $RO{\cdot}CH{:}CR'{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NHR''$ $RO{\cdot}CH{:}CR'{\cdot}CO{\cdot}NH{\cdot}CO_2Et$ (IV)



(V)



(VI)

In a similar manner, β-ethoxyacryloyl chloride (I; R = Et, R′ = H) reacted readily with silver cyanate in benzene solution. The resulting solution of the acyl *iso*cyanate (II; R = Et, R′ = H) with ammonia, methylamine, aniline, and phenylhydrazine gave the linear derivatives (III; R = Et, R′ = H, R″ = H, Me, Ph, or Ph·NH respectively). The acylureas (III; R = Et, R′ = H, R″ = H, Me, or Ph) were cyclised to the corresponding uracils (V; R = H, R′ = H, Me, Ph) when treated with dilute alkali or sublimed *in vacuo*.

1-Methyluracil (V; R = H, R′ = Me) was also obtained directly by reaction of β-ethoxyacryloyl chloride with methylurea in boiling benzene containing a trace of sulphuric acid.

The last-mentioned *iso*cyanate with ethanol readily gave the acylurethane (IV; R = Et, R′ = H) which we prepared previously from ethyl β-ethoxyacrylate and sodiourethane.[1] The conversion of the urethane into uracil and its derivatives was also described in Part V;[1] however an intermediate linear derivative has now been obtained from the urethane and aniline and this proved to have the structure $Ph{\cdot}NH{\cdot}CH{:}CH{\cdot}CO{\cdot}NH{\cdot}CO_2Et$ where replacement of the β-alkoxy-group has occurred, as in reaction of the α-cyano-derivative (IV; R = Et, R′ = CN) with aniline[3] but differing from the reaction of the α-methyl compound (IV; R = R′ = Me) described above. It appears that, in compounds of type (IV), increasing nucleophilic character of the α-substituent decreases reactivity of the β-alkoxy-group (at least towards nucleophiles), corresponding to a decrease in the polarisation of the αβ-double bond.

EXPERIMENTAL

Compounds were dried (P_2O_5) for analysis at 56°/0·1—0·5 mm.

Reaction of β-Methoxy-α-methylacryloyl Chloride with Urethane.—A solution of urethane (4·65 g.) in dry ether (20 ml.) was boiled with a suspension of sodium powder (1·08 g.) in dry ether (100 ml.) for 10 hr., reaction then appearing to be complete. The resulting suspension of sodiourethane was treated with β-methoxy-α-methylacryloyl chloride (Part VII) (6·2 g.) in ether (20 ml.) and, after a vigorous reaction had subsided, the mixture was boiled for 3 hr., kept overnight, and filtered. The filtrate was evaporated to an oil which was distilled *in vacuo*. A viscous distillate was obtained with a wide boiling range (112—143°/0·5 mm.); this partly crystallised and, recrystallised from ethanol, gave N-*ethoxycarbonyl*-β-(N-*ethoxycarbonylamino*)-α-*methylacrylamide* (0·1 g.) as needles, m. p. 172—174° (Found: C, 49·25; H, 6·3; N, 11·65. $C_{10}H_{16}O_5N_2$ requires C, 49·2; H, 6·6; N, 11·45%).

β-(N-*Ethoxycarbonylamino*)-α-*methylacrylic Acid*.—Thionyl chloride (1·5 ml.) was shaken with a suspension of finely ground dry sodium β-methoxy-α-methylacrylate (5·1 g.) in dry ether (50 ml.) for 10 min., then kept overnight. The mixture was filtered, the filtrate was evaporated to an oil which was heated on a water-bath with urethane (1·9 g.) in ether (20 ml.) for 1 hr., and the resulting oil cooled. β-(N-*Ethoxycarbonylamino*)-α-*methylacrylic acid* (2·3 g.) separated and

---

[3] Shaw *J.*, 1955, 1834.

recrystallised from ethanol or ethyl acetate as needles, m. p. 193—194° (decomp.) (Found: C, 48·3; H, 6·55; N, 7·8. $C_7H_{11}O_4N$ requires C, 48·55; H, 6·4; N, 8·1%), soluble in solutions of sodium hydrogen carbonate or ammonia and recovered therefrom on acidification.

Reaction of β-*Methoxy*-α-*methylacryloyl Chloride with Silver Cyanate.*—Silver cyanate (dried *in vacuo* over P_2O_5 at 100°) (16 g.) was shaken with the acid chloride (10·5 g.) in benzene (50 ml.), heat being evolved. The whole was then boiled for 30 min. (alternatively shaken for 3 hr. at room temperature). The supernatant liquid was rapidly decanted from silver salts, and the latter were washed by stirring them with benzene and again decanting the liquor. The solvent was removed, and the residue distilled *in vacuo* with rigorous exclusion of moisture; β-*methoxy*-α-methylacryloyl *iso*cyanate (5·65 g.) boiled at 57°/0·5 mm., crystallised in ice, and remelted at about room temperature. The intense reactivity of this substance towards atmospheric moisture precluded its being weighed for analysis without special apparatus. For most purposes the benzene solution obtained above may be used directly.

NN′-*Di*-(β-*methoxy*-α-*methylacryloyl*)*urea.*—When the foregoing *iso*cyanate was exposed to air an immediate vigorous reaction occurred, giving a solid which rapidly liberated carbon dioxide to leave crystalline NN′-*di*-(β-*methoxy*-α-*methylacryloyl*)*urea* which separated from ethyl acetate or water as needles, m. p. 186° (Found: C, 51·5; H, 6·1; N, 11·15. $C_{11}H_{16}O_5N_2$ requires C, 51·55; H, 6·3; N, 10·95%).

N-*Ethoxycarbonyl*-β-*methoxy*-α-*methylacrylamide.*—A suspension of dry silver cyanate (12 g.) in benzene (50 ml.) containing β-methoxy-α-methylacryloyl chloride (6 g.) was boiled for 30 min., then treated with dry ethanol (5 ml.), cooled, and filtered. The filtrate was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated *in vacuo* to a syrup which crystallised when rubbed with light petroleum (b. p. 40—60°). N-*Ethoxycarbonyl*-β-*methoxy*-α-*methylacrylamide* (6 g.) separated from chloroform–light petroleum (b. p. 60—80°) as prisms, m. p. 103°, which partly sublimed when dried for analysis (Found: C, 51·55; H, 7·05; N, 7·55. $C_8H_{13}O_4N$ requires C, 51·35; H, 7·0; N, 7·5%).

Thymine.—(*a*) β-Methoxy-α-methylacryloyl *iso*cyanate and methanolic ammonia reacted violently. β-*Methoxy*-α-*methylacryloylurea* separated immediately; it recrystallised from ethanol as prisms, m. p. 147° (Found: C, 45·8; H, 6·1; N, 17·7. $C_6H_{10}O_3N_2$ requires C, 45·6; H, 6·4; N, 17·7%). The urea (0·25 g.) was heated on a water-bath with 15N-ammonia for 30 min. until the solvent had almost evaporated. The residue was treated with a little water, cooled, and acidified, affording thymine (0·1 g.), m. p. and mixed m. p. 310° (decomp.) (Found: C, 47·5; H, 4·95; N, 22·1. Calc. for $C_5H_6O_2N_2$: C, 47·6; H, 4·8; N, 22·2%). The urea (0·5 g.) soon dissolved in 2N-sodium hydroxide (5 ml.). After a few minutes the solution was acidified to give a precipitate of a *compound* (0·28 g.) which crystallised from water as needles, m. p. 122° (Found: C, 48·25; H, 6·5; N, 10·1. $C_{11}H_{18}O_6N_2$ requires C, 48·2; H, 6·6; N, 10·2%); when sublimed at 120°/0·1 mm. this gave two zones of crystalline material; the more volatile was β-methoxy-α-methylacrylic acid, m. p. and mixed m. p. 106°, and the second was β-methoxy-α-methylacryloylurea, m. p. and mixed m. p. 145°.

(*b*) *N*-Ethoxycarbonyl-β-methoxy-α-methylacrylamide (1 g.) was heated on a water-bath with 15N-ammonia (10 ml.) for 20 min.; crystals separated as the solution evaporated. The mixture was cooled and acidified with hydrochloric acid, and the precipitated thymine collected. This recrystallised from water as needles (0·28 g.), m. p. and mixed m. p. 308° (decomp.).

1-*Methylthymine.*—(*a*) *N*-Ethoxycarbonyl-β-methoxy-α-methylacrylamide (1 g.) was warmed with 25% aqueous methylamine (2 ml.) on a water-bath for 20 min. Crystals remained. These were dissolved in 2N-sodium hydroxide (3 ml.). Acidification precipitated 1-methylthymine (0·33 g.) which recrystallised from water as needles, m. p. 281° (Johnson and Clapp[4] give m. p. 280—282°) (Found: C, 51·6; H, 5·65; N, 20·0. Calc. for $C_6H_8O_2N_2$: C, 51·4; H, 5·75; N, 20·0%).

(*b*) β-Methoxy-α-methylacryloyl *iso*cyanate and an excess of methanolic methylamine gave a precipitate of N-(β-*methoxy*-α-*methylacryloyl*)-N′-*methylurea* which separated from ethanol as needles, m. p. 127° (Found: C, 48·95; H, 6·95; N, 16·45. $C_7H_{12}O_3N_2$ requires C, 48·85; H, 7·05; N, 16·25%). The urea (0·36 g.) was dissolved in 2N-sodium hydroxide (5 ml.); acidification precipitated unchanged urea (0·16 g.). The urea (0·25 g.) was warmed with aqueous methylamine (5 ml.) for 20 min. and the solution acidified and kept overnight, giving a precipitate of 1-methylthymine (0·08 g.), m. p. and mixed m. p. 280° (Found: C, 51·4; H, 5·55; N, 19·95%).

---

[4] Johnson and Clapp, *J. Biol. Chem.*, 1908, **5**, 56.

1-*Phenylthymine*.—(*a*) The foregoing *iso*cyanate was added to an ethereal solution of aniline. N-(β-*Methoxy*-α-*methylacryloyl*)-N′-*phenylurea*, which separated, formed needles, m. p. 144°, from ethanol (Found: C, 61·5; H, 5·95; N, 12·15. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·00 N, 11·95%). The phenylurea (0·41 g.) was warmed with 2N-sodium hydroxide (5 ml.) with shaking until a clear solution was obtained. This was cooled and acidified, affording 1-*phenylthymine* (0·27 g.) which recrystallised from water as needles, m. p. 199° (Found: C, 65·25; H, 5·0; N, 13·9. $C_{11}H_{10}O_2N_2$ requires C, 65·35; H, 5·0; N, 13·85%). (*b*) *N*-Ethoxycarbonyl-β-methoxy-α-methylacrylamide (1 g.) and aniline (0·6 g.) were heated together on a water-bath for 1 hr., then kept overnight, and the residual oil treated with ether to precipitate *N*-(β-methoxy-α-methylacryloyl)-*N*′-phenylurea (0·2 g.), m. p. and mixed m. p. 143—144°, which with alkali gave 1-phenylthymine.

2 : 3-*Dihydro*-5-(β-*methoxy*-α-*methylvinyl*)-1-*phenyl*-1 : 2 : 4-*triazol*-3-*one*.—β-Methoxy-α-methylacryloyl *iso*cyanate when added to ethereal phenylhydrazine afforded a precipitate of N^1-(β-*methoxy*-α-*methylacryloyl*)-N^3-*phenylsemicarbazide* which separated from ethanol as prisms, m. p. 193° (Found: C, 57·95; H, 5·95; N, 16·95. $C_{12}H_{15}O_3N_3$ requires C, 57·8; H, 6·05; N, 16·85%). The semicarbazide (0·52 g.) was warmed with 2N-sodium hydroxide (10 ml.) with shaking until a clear red solution was obtained. Acidification precipitated a gum which solidified when rubbed with ethanol; the *triazolone* (0·42 g.) crystallised from ethanol as needles, m. p. 195—197° (Found: C, 62·55; H, 5·55; N, 18·45. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·65; N, 18·15%).

Reaction of β-*Ethoxyacryloyl Chloride with Silver Cyanate*.—The acid chloride (10·2 g.) in benzene (50 ml.) was treated with silver cyanate (14 g.); the mixture became hot. It was shaken for 3 hr. and the supernatant solution used in the following reactions.

Uracil. The *iso*cyanate solution was added to an excess of ethereal ammonia: a violent reaction occurred, and a precipitate was formed. The mixture was evaporated to dryness and the residue of β-*ethoxyacryloylurea* crystallised from methanol as needles, m. p. 198° (Found: C, 45·7; H, 6·4; N, 17·6. $C_6H_{10}O_3N_2$ requires C, 45·55; H, 6·35; N, 17·7%). The urea (0·25 g.) was warmed with 2N-sodium hydroxide (4 ml.) for a few minutes to give a clear solution which was then acidified and continuously extracted with ethyl acetate for 3 hr. Evaporation of the solvent gave uracil (0·1 g.), m. p. and mixed m. p. 315°.

1-*Methyluracil*. (*a*) The *iso*cyanate solution was added to ethanolic methylamine, and the solution then evaporated *in vacuo* to give a crystalline residue; N-(β-*ethoxyacryloyl*)-N′-*methylurea* separated from ethanol as plates, m. p. 152° (Found: C, 49·0; H, 6·85; N, 16·1. $C_7H_{12}O_3N_2$ requires C, 48·85; H, 7·05; N, 16·25%). The methylurea (0·25 g.) was heated on a water-bath with aqueous methylamine (5 ml.). The residue was stirred with dilute hydrochloric acid and the precipitated 1-methyluracil (0·065 g.) collected; it had m. p. and mixed m. p. 229—230°. (*b*) A small quantity of the methylurea, sublimed at 150°/0·1 mm., gave a crystalline sublimate which separated from water and had m. p. 230°, not depressed by 1-methyluracil. (*c*) β-Ethoxyacryloyl chloride (1·1 g.) and methylurea were heated in benzene (50 ml.) containing a trace of sulphuric acid under reflux for 3 hr. The solution was decanted from a small residue, evaporated to a small volume, and cooled, to give a precipitate of 1-methyluracil (0·4 g.), m. p. and mixed m. p. 230°.

1-*Phenyluracil*. The *iso*cyanate solution was added to aniline in ether, and the resulting precipitate collected. N-β-*Ethoxyacryloyl*-N′-*phenylurea* crystallised from ethanol as plates, m. p. 183° (Found: C, 61·45; H, 6·0; N, 11·95. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 11·95%). The phenylurea (0·165 g.) was heated on a water bath with 2N-sodium hydroxide (3 ml.) and ethanol (3 ml.) for 1 hr. The cooled solution was acidified, affording a precipitate of 1-phenyluracil [1] (0·104 g.), m. p. and mixed m. p. 247°.

N^1-*Ethoxyacryloyl*-N^3-*phenylsemicarbazide*.—The *iso*cyanate solution was added to a solution of phenylhydrazine in ether; a precipitate of the *semicarbazide* was formed which recrystallised from ethanol as plates, m. p. 176—177° (Found: C, 57·95; H, 6·1; N, 16·4%).

β-*Ethoxy*-N-*ethoxycarbonylacrylamide*.—β-Ethoxyacryloyl chloride (3·6 g.) and silver cyanate (5 g.) were boiled in benzene (20 ml.) for 30 min. The cooled solution was treated with dry ethanol (4 ml.), then washed with sodium hydrogen carbonate solution and water, dried, and evaporated to an oil which crystallised when stirred with light petroleum. β-Ethoxy-*N*-ethoxycarbonylacrylamide [1] (1·8 g.) had m. p. and mixed m. p. 84°.

β-*Anilino*-N-*ethoxycarbonylacrylamide*.—The foregoing acrylamide (0·25 g.) and aniline (0·15 g.) were heated together on a water-bath for 1 hr. The cooled product crystallised under ether. β-Anilino-*N*-ethoxycarbonylacrylamide [1] (0·15 g.) crystallised from light petroleum as prisms, m. p. and mixed m. p. 147°.

We thank the N.S.W. State Cancer Council for a research grant, and Dr. E. Challen for the microanalyses.

N.S.W. UNIVERSITY OF TECHNOLOGY,
SYDNEY, N.S.W., AUSTRALIA.

[*Received, June 28th*, 1957.]