368. *Purines, Pyrimidines, and Glyoxalines. Part II.* New Syntheses of Some Pyrimidine Nucleosides.*

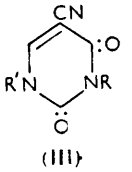
By R. K. Ralph and G. Shaw.

N-Cyanoacetyl-*N*-methylurethane (IV) has been prepared and converted into α-cyano-β-ethoxy-*N*-ethoxycarbonyl-*N*-methylacrylamide (I; R = Me). The latter compound with ammonia gave 5-cyano-3-methyluracil. Reaction of either of the ethoxy-acrylamides (I; R = H and Me) with a number of D-glycosylamines in water or alcohol gave the 5-cyano-1-D-glycopyranosyluracils (III; R = H, R′ = D-ribo-, D-xylo-, D-galacto-, D-gluco-, and 2-deoxy-D-gluco-pyranosyl) and the 3-methyl derivatives (III; R = Me, R′ = D-ribo-, D-xylo-, D-galacto- and D-gluco-pyranosyl) respectively.

It was recorded in Part I* that reaction of α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (I; R = H) with ammonia or with primary amines yields the 1-alkyl(aryl-)-5-cyanouracils (III; R = H, R′ = H, alkyl, or aryl). In these reactions, initially the linear amino-compounds (II; R = H) are formed and were separately isolated in the examples (II; R = H, R′ = Ph and Ph·NH).

$EtO{\cdot}CH{:}C(CN){\cdot}CO{\cdot}NR{\cdot}CO_2Et$
(I)

$R'{\cdot}NH{\cdot}CH{:}C(CN){\cdot}CO{\cdot}NR{\cdot}CO_2Et$
(II)


(III)

$NC{\cdot}CH_2{\cdot}CO{\cdot}NMe{\cdot}CO_2Et$
(IV)

The present work was undertaken in an attempt to widen the scope of these reactions to include the synthesis of 5-cyanouracils with substituents in position 3 (III; R′ = H) and jointly in positions 1 and 3, and at the same time to extend the reactions to include the synthesis of 5-cyano-1-glycosyluracils related to the naturally occurring pyrimidine nucleosides.

* Part I, *J.*, 1955, 1834.

Reaction of *N*-methylurethane with a mixture of cyanoacetic acid and acetic anhydride gave a readily separable mixture of *N*-acetyl- and *N*-cyanoacetyl-*N*-methylurethane (IV). The latter product reacted smoothly with ethyl orthoformate and acetic anhydride, to give an excellent yield of the ethoxy-compound (I; R = Me); the reaction of this with aqueous ammonia gave the pyrimidine (III; R = Me, R′ = H).

The preparation of 1-D-glycosyluracils by this method required D-glycosylamines (1-amino-1-deoxy-sugars or tautomers thereof) as intermediates, and, in particular, for the synthesis of uridine derivatives, 1-D-ribofuranosylamine. The literature records several D-glycosylamines including D-ribosylamine,[1] D-xylosylamine,[2] D-glucosylamine,[3] and D-galactosylamine,[2] generally prepared by reaction of the sugar with dry methanolic ammonia at room temperature for times varying from a few days for ribose, xylose, and galactose to about a month for glucose; in addition Muskat[4] claimed the preparation of D-glucosylamine by dissolving glucose in liquid ammonia, but this reaction was unsuccessful in the hands of Wayne and Adkins.[5]

Reaction of D-ribosylamine with (I; R = H) in aqueous or ethanolic solution[6] at room temperature or with gentle warming gave a solution which failed to give a precipitate with basic lead acetate; however, when the mildly alkaline solution was warmed for a short time and then cooled, an insoluble lead salt appeared. This behaviour suggests the formation of a linear compound (II; R = H, R′ = D-ribosyl) and subsequent cyclisation of this to a pyrimidine nucleoside. The lead salt was suspended in ethanol and decomposed with hydrogen sulphide, to give eventually a 40% yield of 5-cyano-1-D-ribopyranosyluracil (III; R = H, R′ = 1-D-ribopyranosyl). The pyranose nature of the compound was indicated by titration with sodium metaperiodate and the presence of a pyrimidine ring was shown by ultraviolet-absorption measurements. The specific rotation of the compound suggests that it is the β-form. Similarly the nucleosides (III; R = H, R′ = 1-D-xylo-, D-galacto-, D-gluco-, and 2-deoxy-2-D-gluco-pyranosyl) were prepared from the ester (I; R = H) and the corresponding amino-sugar.

Reaction of the glycosylamines with the ester (I; R = Me) proceeded readily in aqueous or ethanolic solution at room temperature, or with warming, to give directly, good yields of the nucleosides (III; R = Me, R′ = 1-D-ribo-, D-xylo-, D-galacto-, and D-gluco-pyranosyl).

Experimental

Absorption max. and $[\alpha]_D$ were measured in H_2O.

The D-glycosylamines were prepared by saturating a methanolic solution or suspension of the sugar with dry ammonia gas and allowing the solution so obtained to stand. Crystalline material was filtered off and used directly.

N-*Cyanoacetyl*-N-*methylurethane*.—A mixture of cyanoacetic acid (43 g.), *N*-methylurethane (52·2 g.), and acetic anhydride (102 g.) was heated on a water-bath for 3 hr., to give a reddish-brown solution, which was cooled and added to water (2 l.). The precipitated oil was extracted with ether (2 × 200 ml.), and the extract washed with water and aqueous sodium hydrogen carbonate until free from acid. The dried extract was evaporated to an oil (45 g.) which was distilled *in vacuo*, to give *N*-acetyl-*N*-methylurethane (20 g.), b. p. 81—83°/21 mm. (Found: C, 49·9; H, 7·75; N, 9·8. Calc. for $C_6H_{11}O_3N$: C, 49·65; H, 7·65; N, 9·65%), and N-*cyanoacetyl*-N-*methylurethane* (22·9 g.), b. p. 133°/1 mm. (Found: C, 49·05; H, 5·85; N, 16·55. $C_7H_{10}O_3N_2$ requires C, 49·4; H, 5·95; N, 16·45%). The latter (0·26 g.) in ethanol (5 ml.) containing aniline (2—3 drops) was boiled for 30 min., cooled, and treated with water to precipitate cyanoacetanilide (0·1 g.), m. p. and mixed m. p. 198°.

α-*Cyano*-β-*ethoxy*-N-*ethoxycarbonyl*-N-*methylacrylamide*.—A mixture of *N*-cyanoacetyl-*N*-methylurethane (13 g.), ethyl orthoformate (13 g.), and acetic anhydride (25 ml.) was boiled under reflux for 1 hr., to give a pale brown solution which was distilled *in vacuo* to afford α-*cyano*-β-*ethoxy*-N-*ethoxycarbonyl*-N-*methylacrylamide* (14·3 g.), b. p. 160°/1 mm. (Found: C, 53·1; H, 6·55; N, 12·05. $C_{10}H_{14}O_4N_2$ requires C, 53·1; H, 6·25; N, 12·3%).

[1] Levene and La Forge, *J. Biol. Chem.*, 1915, **20**, 440.
[2] Lobry de Bruyn and van Leent, *Rec. Trav. chim.*, 1895, **14**, 145.
[3] Irvine, Thomson, and Garrett, *J.*, 1913, **103**, 239; Levene, *J. Biol. Chem.*, 1916, **24**, 60.
[4] Muskat, *J. Amer. Chem. Soc.*, 1934, **56**, 693.
[5] Wayne and Adkins, *ibid.*, 1940, **62**, 3314.
[6] For a note see Ralph and Shaw, *Chem. and Ind.*, 1955, **38**, 1185.

5-Cyano-3-methyluracil.—The foregoing acrylamide (0·63 g.) was shaken with aqueous ammonia (10 ml.; 3%), a clear solution being soon obtained. This was acidified with hydrochloric acid, cooled and set aside. The precipitated *5-cyano-3-methyluracil* (0·25 g.) crystallised from water as needles, m. p. 223° (Found: C, 47·8; H, 3·2; N, 27·65. $C_6H_5O_2N_3$ requires C, 47·7; H, 3·35; N, 27·8%).

5-Cyano-3-methyl-1-D-xylopyranosyluracil.—(*a*) A solution of the ethoxy-acrylamide (1·28 g.) in ethanol (10 ml.) was treated with D-xylosylamine (0·84 g.). The suspension was warmed and shaken, a clear solution being soon obtained. This was evaporated to about half volume and cooled; after a short time a jelly containing a few crystals separated; when rubbed, the gel rapidly crystallised. The solid was washed with a little ethanol and ether; *5-cyano-3-methyl-1-D-xylopyranosyluracil monohydrate* (0·8 g.) separated from ethanol as needles, m. p. 120° (decomp. to a glass, then m. p. 200°), $[\alpha]_D^{20}$ −17·2° (*c* 4·08) (Found: C, 44·3; H, 5·0; N, 14·15° $C_{11}H_{13}O_6N_3,H_2O$ requires C, 43·85; H, 5·0; N, 13·95%). Absorption max. at 273 (ε 11,580) and <215 mμ (ε > 10,100). A further quantity (0·25 g.) of the xyloside was recovered from the filtrate. In 24 hr. at 20° the substance consumed 2·04 mols. of 0·0841N-sodium metaperiodate and liberated 0·85 mol. of formic acid. (*b*) The ethoxy-acrylamide (0·48 g.) was covered with water (1 ml.), and D-xylosylamine (0·31 g.) was added. The mixture was shaken; after about 5 min. a clear very pale yellow solution was obtained. This was kept over phosphoric oxide to give finally a syrup which when stirred with ethanol and ether gave a crystalline solid (0·35 g.), m. p. and mixed m. p. 120° (decomp. to a glass; m. p. 200°).

5-Cyano-3-methyl-1-D-ribopyranosyluracil.—The ethoxy-acrylamide (1·15 g.) in ethanol (20 ml.) was treated with D-ribosylamine (0·74 g.); the mixture was gently warmed and shaken to give a clear solution; this was evaporated to *ca.* 5 ml. and cooled. A small portion was treated with ether, to precipitate a gum which when kept with a little ethanol gave crystals. The main solution, when seeded, rapidly crystallised. *5-Cyano-3-methyl-1-D-ribopyranosyluracil* (0·55 g.) separated from ethanol as needles, m. p. 223°, $[\alpha]_D^{20}$ −16·91° (*c* 2·36) (Found: C, 46·15; H, 4·55; N, 14·55. $C_{11}H_{13}O_6N_3$ requires C, 46·65; H, 4·65; N, 14·85%); a further quantity (0·53 g.) was obtained by treating the ethanol solution with ether. Absorption max. at 273 (ε 5780) and <215 mμ (ε > 5300). In 24 hr. at 20° the substance consumed 1·78 mols. of 0·0841N-sodium metaperiodate and liberated 1·2 mols. of formic acid.

5-Cyano-3-methyl-1-D-galactopyranosyluracil.—D-Galactosylamine (1·5 g.) was added to a solution of the ethoxy-acrylamide (1·9 g.) in ethanol (10 ml.); the suspension was warmed for a short time to give a clear solution which when cooled gave a crystalline precipitate; *5-cyano-3-methyl-1-D-galactopyranosyluracil* (1·78 g.) separated from ethanol as prisms, m. p. 240° (decomp.), $[\alpha]_D^{20}$ +42·2° (*c* 4·26) (Found: C, 45·95; H, 4·7; N, 13·5. $C_{12}H_{15}O_7N_3$ requires C, 46·0; H, 4·85; N, 13·4%). Absorption max. at 273 (ε 11,580) and <215 mμ (ε >10,300). In 24 hr. at 20° the substance consumed 2·3 mols. of 0·0826N-sodium metaperiodate and liberated 1·1 mols. of formic acid.

5-Cyano-3-methyl-1-D-glucopyranosyluracil.—D-Glucosylamine (1·25 g.), warmed with the ethoxy-acrylamide (1·62 g.) in ethanol (10 ml.) for a few min., gave a clear solution; this after 1 hr. was treated with ether, to precipitate a semi-solid gum. The solvent was decanted, the gum dissolved in ethanol (20 ml.), and the solution kept at 0° for a few hr. A crystalline precipitate was obtained; *5-cyano-3-methyl-1-D-glucopyranosyluracil monohydrate* (1·1 g.) crystallised from ethanol as prisms, m. p. 204° (after sintering at 135—140°), $[\alpha]_D^{20}$ +13·4° (*c* 4·10) (Found: C, 43·65; H, 5·15; N, 12·55. $C_{12}H_{15}O_7N_3,H_2O$ requires C, 43·5; H, 5·15; N, 12·7%). Absorption max. at 273 (ε 7800) and <215 mμ (ε > 10,300). In 24 hr. at 20° the substance consumed 1·91 mols. of 0·0826N-sodium metaperiodate and liberated 1·17 mols. of formic acid.

5-Cyano-1-D-ribopyranosyluracil.—A solution of D-ribosylamine (1·41 g.) in water (30 ml.) was added to one of α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (2 g.) in warm ethanol (30 ml.) and kept at room temperature for 1 hr. The solution was evaporated to dryness and the resulting gum dissolved in water (10 ml.) and treated with a solution of basic lead acetate; there was no immediate precipitate but when the solution was warmed on the steam-bath for a few minutes and then cooled a thick solid precipitate was obtained. The lead salt was filtered off, washed with a little ice water, suspended in ethanol, and decomposed with hydrogen sulphide. After removal of lead sulphide, the colourless solution was evaporated to a small volume and cooled. A crystalline precipitate was obtained. *5-Cyano-1-D-ribopyranosyluracil* (0·96 g.) separated from ethanol as needles, m. p. 231°, $[\alpha]_D^{20}$ −22·85° (*c* 7·26) (Found: C, 44·4; H, 4·1; N, 15·5. $C_{10}H_{11}O_6N_3$ requires C, 44·6; H, 4·1; N, 15·6%). Absorption max. at 274 (ε 6270) and <215 mμ (ε > 5500). In 24 hr. at 20° the substance consumed 2·1 mols. of 0·0841N-sodium metaperiodate and liberated 1·23 mols. of formic acid.

5-Cyano-1-D-galactopyranosyluracil.—D-Galactosylamine (1·75 g.) was added to α-cyano-β-ethoxycarbonylacrylamide (2·12 g.) in ethanol (15 ml.). The solution was warmed and shaken until clear. Addition of basic lead acetate to the alcoholic solution precipitated a solid. This was filtered off, washed with water, dispersed in ethanol, and decomposed with hydrogen sulphide. Lead sulphide was filtered off, and the colourless filtrate evaporated to a small volume, and set aside. A crystalline precipitate soon appeared; *5-cyano-1-D-galactopyranosyluracil* (0·6 g.) separated from ethanol as needles, m. p. 254°, $[\alpha]_D^{20}$ +50·2° (*c* 2·39) (Found: C, 43·9; H, 4·25; N, 13·95. $C_{11}H_{13}O_7N_3$ requires C, 44·15; H 4·4; N, 14·05%). Absorption max. at 274 (ε 4700) and <215 mμ (ε > 4650). In 24 hr. at 20° the substance consumed 2·0 mols. of 0·0826N-sodium metaperiodate and liberated 1·0 mol. of formic acid.

5-Cyano-1-D-glucopyranosyluracil.—A suspension of D-glucosylamine (1·79 g.) in ethanol (20 ml.) containing α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (2·12 g.) was shaken and warmed gently, to give, after a short time, a clear solution. This was evaporated to dryness and the residual gum dissolved in water, and to the solution was added basic lead acetate until no further precipitate was obtained. The lead salt was filtered off, washed with water and ethanol, and decomposed in ethanol with hydrogen sulphide. Lead sulphide was filtered off and the colourless filtrate evaporated to a small volume and set aside overnight; a crystalline precipitate separated. *5-Cyano-1-D-glucopyranosyluracil* (0·61 g.) recrystallised from ethanol as needles, m. p. 240°, $[\alpha]_D^{20}$ +44·2° (*c* 1·81) (Found: C, 44·35; H, 4·4; N, 14·0%). Absorption max. at 274 (ε 9450) and <215 mμ (ε > 9200). In 24 hr. at 20° the substance consumed 1·9 mols. of 0·0826N-sodium metaperiodate and liberated 0·87 mol. of formic acid.

5-Cyano-1-D-xylopyranosyluracil.—(*A*) D-Xylosylamine (1·49 g.) was shaken with α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (2·12 g.) in ethanol (20 ml.) until a solution was obtained. This was evaporated to a gum which was dissolved in water. Addition of basic lead acetate gave a precipitate which was filtered off, washed with water, and decomposed in ethanol with hydrogen sulphide. The solution was filtered from lead sulphide, evaporated to a small volume, and set aside, to give a crystalline precipitate; *5-cyano-1-D-xylopyranosyluracil* (0·41 g.) recrystallised from ethanol as needles, m. p. 247°, $[\alpha]_D^{20}$ −25·1° (*c* 2·38) (Found: C, 44·45; H, 4·05; N, 15·3%). Absorption max. at 273 (ε 11,090) and <215 mμ (ε > 10,650). In 24 hr. at 20° the substance consumed 1·86 mols. of 0·0826N-sodium metaperiodate and liberated 0·99 mol. of formic acid. (*B*) A finely powdered mixture of D-xylosylamine (0·5 g.) and α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (0·74 g.) was heated at 110° (bath) for 5 min. A clear melt was obtained which was cooled, dissolved in water, and worked up as under (*A*), to give the xyloside (0·1 g.), m. p. and mixed m. p. 247°. (*C*) D-Xylosylamine (1·49 g.) and the acrylamide (2·12 g.) were allowed to react in ethanol as in (*A*). The solution was treated with methanolic ammonia, to precipitate a colourless solid (presumably an ammonium salt). Crystallisation of this from ethanol gave however the xyloside (0·5 g.), m. p. and mixed m. p. 245°, $[\alpha]_D^{20}$ −24·9° (*c* 2·0) (Found: C, 44·65; H, 4·15; N, 15·5%).

5-Cyano-1-2-deoxy-D-glucopyranosyluracil.—To a solution of 2-amino-2-deoxy-D-glucose hydrochloride (1 g.) in water (5 ml.) and 2N-sodium hydroxide (2·34 ml.) was added a solution of α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (0·98 g.) in ethanol (10 ml.). The solution was warmed on a water-bath for 15 min., cooled, and treated with a solution of basic lead acetate, a solid precipitate being obtained. The lead salt was washed with water and ethanol and decomposed as a suspension in ethanol with hydrogen sulphide. Lead sulphide was removed and the filtrate evaporated to a small volume and cooled. The *pyrimidine monohydrate* (0·3 g.) crystallised from ethanol as plates, m. p. 218°, $[\alpha]_D^{20}$ +67·6° (*c* 2·07) (Found: C, 42·0; H, 4·65; N, 12·65. $C_{11}H_{13}O_7N_3,H_2O$ requires C, 41·65; H, 4·75; N, 13·25%). Absorption max. at 274 (ε 13,600) and <215 mμ (ε > 10,700). In 24 hr. at 20° the substance consumed 4·05 mols. of 0·0895N-sodium metaperiodate and liberated 2·9 mols. of formic acid.

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