Unconventional Nucleotide Analogues. Part IX.[1] *N*-Substituted 3-(Pyrimidin-1-yl)pyrrolidin-2-ones

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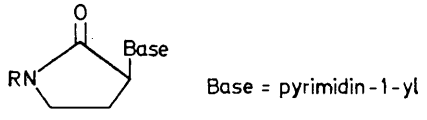
Hilbert–Johnson reaction of the 2,4-diethoxypyrimidines (2a and b) with 2-bromobutyrolactone (3), followed by hydrolysis of the coupling products (4a and b), gave the pyrimidin-1-yl lactones (5a and b). 2-(1,2,3,4-Tetrahydro-2,4-dioxopyrimidin-1-yl)butyrolactone (5a) was converted into the *N*-vinylpyrrolidin-2-one analogue (11) *via* a five-step reaction sequence [(5a) → (7a) → (7b) → (8) → (10c) → (11)]. Polymerisation of the product (11) yielded material (12) (mol. wt. 80,000) which, in aqueous solution, exhibited a pronounced (25%) hypochromicity effect at 263 nm.

NUCLEOSIDES modified with respect to their glycosidic components are of interest as potential substrates for or inhibitors of nucleoside-utilizing enzymes. Amongst related naturally occurring systems, drastic structural departures from the sugar system occur in the nucleoside antibiotics aristeromycin,[2] blasticidin,[3] and eritadenine [4] and in the pyrimidinyl amino-acids willardiine [5] and lathyrine.[6] If the glycosidic residue in a nucleoside is replaced by a molecular unit capable of polymerization or intermolecular condensation, the derived analogue acquires the character of a monomer capable of forming novel nucleic acid models. The syntheses of diverse pyrimidinyl and purinyl amino-acids and their corresponding peptides have been previously reported.[7-9] We have now extended our studies to nucleoside analogues in which the glycosidic system is replaced by a pyrrolidin-2-one derivative. The choice of this heterocyclic system was influenced in particular by two considerations: (*a*) the resemblance of pyrrolidin-2-one to the five-membered ring carbohydrates (ribose or deoxyribose) and (*b*) the known ability of *N*-vinylpyrrolidin-2-one to give water-soluble polymers. We now describe the synthesis of several *N*-substituted 3-(pyrimidin-1-yl)pyrrolidin-2-ones (1) and the preparation and properties of the polymer



(1)

derived from 3-(uracil-1-yl)-*N*-vinylpyrrolidin-2-one (11).[10]

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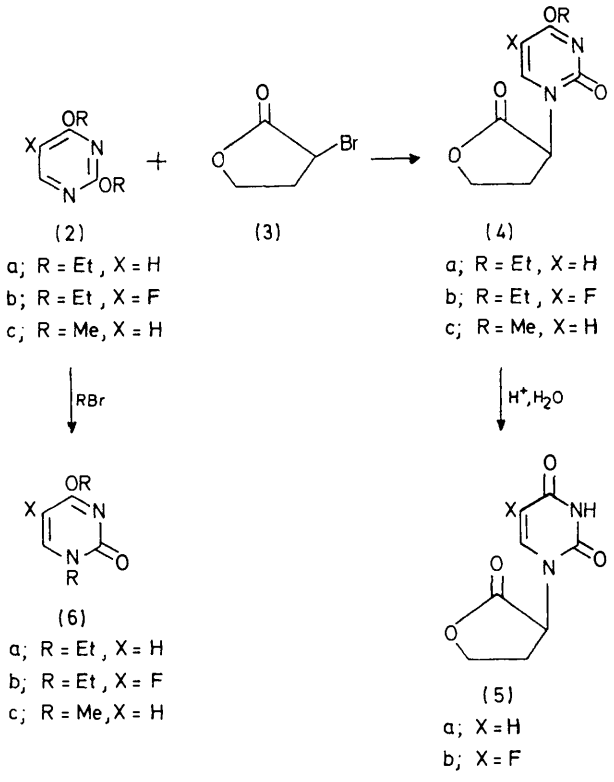
[10] (*a*) Part of this work was presented in the 7th I.U.P.A.C. International Symposium on the Chemistry of Natural Products, Riga, 1970; (*b*) G. J. Koomen, A. P. Kroon, A. P. Goores, and U. K. Pandit, *Synth. Comm.*, 1971, **1**, 41.

Synthesis of N-*Substituted* 3-(*Pyrimidin*-1-*yl*)*pyrrolidin*-2-*ones*.—Of the potentially available routes to the pyrrolidinone derivatives (1), transformations of the lactones (4) and (5) were investigated. The lactones (4) and (5) were obtained as outlined in Scheme 1. The Hilbert–Johnson reaction [11] of the pyrimidine (2a) with the bromo-lactone (3) gave, under standard conditions, a mixture of the substituted lactone (4a) and the O ⟶ N migration product (6a). Under similar conditions treatment of the dimethoxypyrimidine (2c) with the lactone (3) yielded almost exclusively (6c). In contrast to the behaviour of the two dialkoxypyrimidines towards bromobutyrolactone (3), their reactions with glycosyl halides give normal pyrimidine nucleosides as major products. These results can be best understood by comparing the reactivities of glycosyl halides, the bromolactone (3), and the alkyl halides produced during the course of the Hilbert–Johnson reaction towards nucleophilic attack by dialkoxypyrimidines. Since the lactone (3) is less reactive than a glycosyl halide, the pyrimidinyl ethers (2a and c) can be consumed *via* a competitive reaction with the liberated alkyl halides. In case of (2c), the released methyl bromide reacts very rapidly with the dialkoxypyrimidine, making the competing process [conversion of (2c) into its *N*-methyl isomer (6a)] predominant.

To suppress the competitive reaction, further Hilbert–Johnson reactions were conducted under reduced pressure to remove the volatile alkyl halides.[12] At moderate temperatures (60° at 15 mmHg) and with long reaction times (14 days), the pyrimidines (2a and b) reacted with the lactone (3) to give good yields of compounds (4a and b) [no *N*-alkylpyrimidines (6a and b) were identified in these reactions]; however, reaction of the lactone with (2c) gave a 2 : 3 mixture of (4c) and (6c) (respectively). Mild acidic hydrolysis of compounds (4a and b) gave the uracilyl lactones (5a and b) in excellent yields. The latter compounds exhibited physical characteristics identical with those reported for the products obtained by reaction of uracilyl and 5-fluorouracilyl anions with the bromo-lactone (3).[13] It is generally presumed that the Hilbert–Johnson reaction proceeds at N-1 of the pyrimidine ethers.[14] That this was the case in the formation of compound (5a) was established by the n.m.r. spectrum of the product in scrupulously dried [$^2H_6$]dimethyl sulphoxide, which showed the expected N(3), H-5 coupling [15,16] (2 Hz).

We hoped to convert the uracilyl lactone (5a) into the hydroxyethylpyrrolidinone (10a) *via* aminolysis with 2-aminoethanol followed by cyclization. The first step of this sequence proceeded smoothly, giving the dihydroxy-amide (9) in high yield. However we were unable to cyclize the product, which, under forcing conditions, reverted to aminoethanol and (5a). An alternative sequence utilizing *O*-protected 2-aminoethanol (Scheme 2) was therefore undertaken. Aminolysis of (5a) with 2-benzyloxyethylamine [17] gave the hydroxy-amide (7a), which could be smoothly chlorinated to (7b) with thionyl chloride. Both steps proceeded in high yield. Ring closure [18,19] of (7b) to the crystalline pyrrolidinone (8) was effected with sodium methoxide. Compound (8) showed no amide II band (1540 cm^{-1}) in its i.r. spectrum; the disappearance of this band was utilized for following the ring-closure reaction.



SCHEME 1

Attempts to debenzylate compound (8) with hydrogen bromide in acetic acid gave mixtures of the desired alcohol (10a) and its acetate (10d). Hydrogenolysis over palladium, however, provided pure crystalline alcohol (10a) in almost quantitative yield. Conversion of the *N*-hydroxyethyl-lactam (10a) into the vinylpyrrolidinone (11) presented problems. Efforts at dehydration under a variety of conditions, and attempts to eliminate acids from suitable ester derivatives of (10a), proved unsuccessful. Attempted dehydrohalogenation of the chloride (10b) with a wide variety of bases gave mixtures

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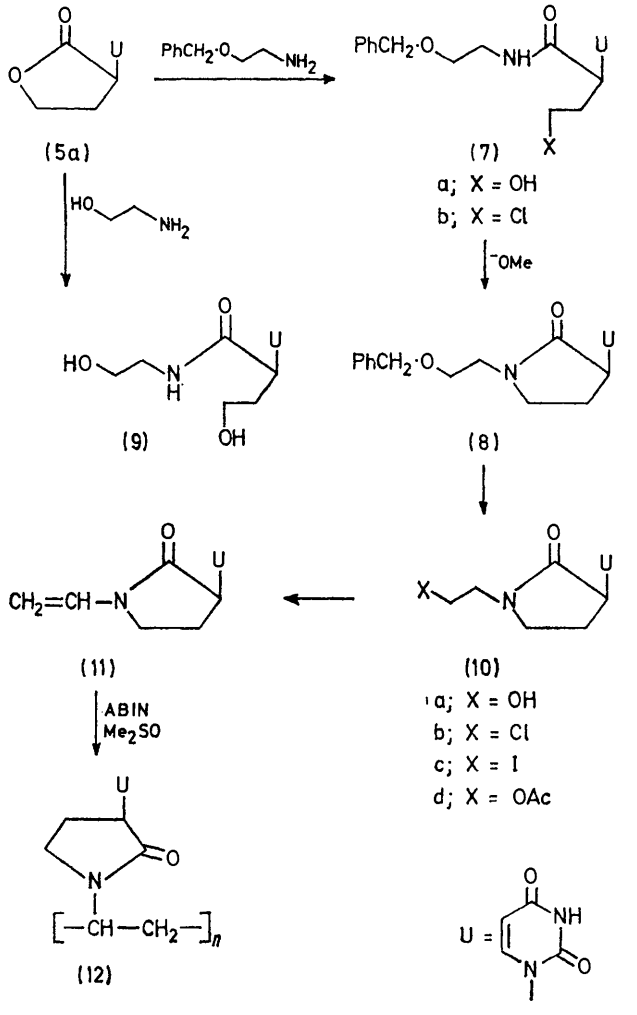
in which small (variable) quantities of (11) could be recognized by n.m.r. spectroscopy. The transformation (10a) → (11) was achieved eventually by conversion into the iodide (10c) (by treatment with triphenoxymethylphosphonium iodide [20]) followed by dehydroiodination with scrupulously purified potassium t-butoxide,



SCHEME 2

in dimethoxyethane, under carefully controlled conditions.

Preparation and Properties of Poly-[3-(uracil-1-yl)-N-vinylpyrrolidin-2-one] (12).—Polymerization of compound (11) was carried out in dimethyl sulphoxide with *NN'*-azobisisobutyronitrile (ABIN) as radical initiator. The reaction was followed by examining the disappearance of the n.m.r. signal due to the vinyl protons. The polymer was purified by repeated precipitation with hydrochloric acid from an ammoniacal solution. After dialysis of the polymer against 0·1M-sodium chloride, its molecular weight was determined by ultracentrifugal measurements. On the basis of an $s_{20\cdot50\%}$ (0·01N-NaOH) value of 2·6 s for the polymer and using Scholtan's relationship[21] ($s=8{\cdot}81\times10^{-16}M^{\frac{1}{2}}$) for poly(vinylpyrrolidinone), an average molecular weight of 80,000 was calculated. Microanalytical data for the polymer (12) indicated that *ca.* 1·9 molecules of water were associated with each monomer unit.

U.v. spectra of the polymer in 0·1M-NaCl and 0·1M-NaOH solutions were taken; the extinctions at 263 nm were compared with extinctions at the same wavelength for similar solutions of *N*-2-hydroxyethyl-3-(uracil-1-yl)-pyrrolidin-2-one (10a). The results are shown in the Table. In neutral solution the polymer exhibits a

Extinction values at 263 nm

Solvent	Polymer (12)	Monomer (10a) [a]
0·1M-NaCl	7700 [b]	10,600
0·1M-NaOH	7100 [b]	7700

[a] The chromophore of (10a) may be assumed to represent a monomer unit. [b] Values calculated per monomer unit after correction for associated water.

hypochromicity of 25%. Since the polymer is prepared from racemic monomeric units, a stereochemically organized structure (helices) would not be expected. However, the high hypochromicity value observed indicates that a strong base–base interaction is present in the polymer. In fact, comparison with hypochromicity effects in poly-U (8%) [22] leads to the conclusion that the freedom of relative displacement and rotation of the uracil units in the polymer chain in compound (12) is severely restricted. Poly(vinyluracil), a system which contains even more closely spaced uracil units, exhibits a 40% decrease in the absorption maximum at 263 nm.[23] The lowering of hypochromicity in basic solution (0·1M-NaOH) is consistent with the fact that under these conditions the uracil residues in the polymer are largely negatively charged. The charges decrease the interaction of the aromatic units by disturbing base-stacking along the chain. A similar phenomenon has been observed in spectroscopic models of dinucleotide analogues.[24]

Cytostatic Activities.—Compound (4b) inhibited the growth of 3T3 and BHK-21 cells ($E.D._{50}\pm100$ μg ml^{-1}). Under similar conditions compounds (5b) and (10a) were inactive. The difference in activity between (4b) and (5b) is being further investigated. An inhibitory effect in KB-cells was also found for compounds (4a) and (4b) ($E.D._{50}$ 140 and 83 μg ml^{-1}, respectively). In the L-1210 murine leukemia test system, no significant effect (increase in survival time >25%) was observed for compounds (4a), (4b), (5a), (5b), (8), (10a), and (10d). The compounds, however, were non-toxic in doses up to 400 mg kg^{-1}.

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EXPERIMENTAL

I.r. spectra were recorded on a Unicam SP 200 instrument and u.v. spectra on a Cary 14 recording spectrophotometer. N.m.r. spectra were obtained with a Varian A 60 or HA 100 spectrometer, with tetramethylsilane as internal standard. Determination of molecular weights was carried out with an M.S.E. Analytical Ultracentrifuge at 20 °C and 50,000 rev. min^{-1}. The sedimentation was observed *via* direct measurement of the u.v. extinction at 260 nm.

Reaction of 2,4-*Dimethoxypyrimidine* (2c) *with* 2-*Bromobutyrolactone* (3).—(*A*) A mixture of the pyrimidine (2c) (4·2 g, 0·03 mol) and the lactone (3) (4·9 g, 0·03 mol) was heated to 60° with stirring for 20 h. After cooling, the precipitate (6c) (2·9 g, 64%) was washed with ether; m.p. 135—138°, $\nu_{max.}$ ($CHCl_3$) 1650 (C=O) and 1320 cm^{-1} ($COCH_3$), δ ($CDCl_3$) 3·5 (s, NMe), 3·9 (s, OMe), 5·9 (d, *J* 7 Hz, 5-H), and 7·7 (d, *J* 7 Hz, 6-H). Hydrolysis of the product (1·0 g) by heating to evaporation with dil. hydrochloric acid (10 ml) gave 1-methyluracil (0·6 g, 66%), m.p. 237·5—238·5° (from ethanol).

(*B*) A stirred mixture of the pyrimidine (2c) (7·0 g, 0·05 mol) and the lactone (3) (4·1 g, 0·025 mol) was heated to 50° under water-pump vacuum during 72 h. After cooling, addition of ether gave a white solid (2·4 g) which consisted of a 3 : 2 mixture of compounds (6c) and (4c) (n.m.r.). Dissolution of the mixture in methanol, slow addition of ether, and cooling gave 2-(1,2-*dihydro*-4-*methoxy*-2-*oxopyrimidin*-1-*yl*)*butyrolactone* (4c), m.p. 160—163° (ethyl acetate), $\nu_{max.}$ ($CHCl_3$) 1780 (C=O lactone), 1670 (C=O amide), and 1330 cm^{-1} (C-OMe), δ ($CDCl_3$) 3·9 (s, OMe), 5·0 (t, 2-H), 5·9 (d, *J* 7 Hz, 5′-H), and 7·2 (d, *J* 7 Hz, 6′-H) (Found: C, 51·7; H, 5·0; N, 13·0. $C_9H_{10}N_2O_4$ requires C, 51·4; H, 4·8; N, 13·35%).

2-(4-*Ethoxy*-1,2-*dihydro*-2-*oxopyrimidin*-1-*yl*)*butyrolactone* (4a).—A mixture of the pyrimidine (2a) (6·7 g, 0·04 mol) and the lactone (3) (3·3 g, 0·02 mol) was heated with stirring at 60° under water-pump vacuum. After 120 h addition of ether gave *compound* (4a) as a white solid (2·1 g). Heating the filtrate for 120 h gave another 0·7 g. Repetition of the procedure gave an additional 0·4 g (total 3·2 g, 70%); m.p. 164—166° (water or ethanol), $\nu_{max.}$ ($CHCl_3$) 1780 (C=O lactone), 1660 (C=O amide), and 1310 cm^{-1} (C-OEt), δ ($CDCl_3$) 1·31 (t, Me), 4·97 (t, 2-H), 5·9 (d, *J* 7 Hz, 5′-H), and 7·65 (d, *J* 7 Hz, 6′-H) (Found: C, 53·5; H, 5·5; N, 12·5. $C_{10}H_{12}N_2O_4$ requires C, 53·55; H, 5·4; N, 12·5%).

2-(4-*Ethoxy*-5-*fluoro*-1,2-*dihydro*-2-*oxopyrimidin*-1-*yl*)-*butyrolactone* (4b).—A mixture of the pyrimidine (2b) (5·6 g) and the lactone (3) (5·5 g, 1·1 equiv.) was stirred at 65° under vacuum for 16 days. The resulting solid was dissolved in boiling chloroform; di-isopropyl ether was added and the solution was cooled, whereupon the *product* (4b) (4·5 g, 62%), m.p. 145—151°, precipitated; $\nu_{max.}$ ($CHCl_3$) 1780 (C=O lactone), 1690 (C=O amide), and 1350 cm^{-1} (C-OEt), δ ($CDCl_3$) 1·4 (t, Me), 5·0 (t, 2-H), and 7·6 (d, *J* 6 Hz, 6′-H) (Found: C, 49·2; H, 4·6; F, 8·0; N, 11·7. $C_{10}H_{11}FN_2O_4$ requires C, 49·6; H, 4·6; F, 7·85; N, 11·55%).

2-(1,2,3,4-*Tetrahydro*-2,4-*dioxopyrimidin*-1-*yl*)*butyrolactone* (5a).—The ethyl ether (4a) (19·2 g) was dissolved in hot water (150 ml). After addition of conc. hydrochloric acid (10 ml) the solution was stirred for 4 h. The precipitate (12 g, 72%) was collected. Evaporating the mother liquor and addition of ethanol gave an additional 4·2 g of the *uracil* (5a) (total yield 96%), m.p. 240—242° (water), $\nu_{max.}$ (KBr) 3500 (NH), 1750 (C=O lactone), and 1660—1700 cm^{-1} (uracil C=O) (1310 absent), τ [$(CD_3)_2SO$] 5·13 (t, 2-H), 5·66 (d, *J* 8 Hz, 5′-H), 7·66 (d, *J* 8 Hz, 6′-H), and 11·45br (s, NH) (Found: C, 48·8; H, 4·3; N, 14·0. $C_8H_8N_2O_4$ requires C, 49·0; H, 4·1; N, 14·3%).

2-(5-*Fluoro*-1,2,3,4-*tetrahydro*-2,4-*dioxopyrimidin*-1-*yl*)-*butyrolactone* (5b).—By a procedure like that described for (5a), the ether (4b) (2·9 g) gave the *uracil* (5b) (1·7 g, 70%), m.p. 230—232° (water), $\nu_{max.}$ (KBr) 3500 (NH), 1760 (C=O lactone), 1710, and 1670 cm^{-1} (uracil C=O), δ [$(CD_3)_2SO$] 5·15 (t, 2-H), 8·2 (d, *J* 6 Hz, 6′-H), and 12·0br (s, NH) (Found: C, 44·9; H, 3·3; F, 8·8; N, 13·0. $C_8H_7FN_2O_4$ requires C, 44·85; H, 3·3; F, 8·85; N, 13·1%).

N-(2-*Benzyloxyethyl*)-2-(1,2,3,4-*tetrahydro*-2,4-*dioxopyrimidin*-1-*yl*)-4-*hydroxybutyramide* (7a).—A solution of the lactone (5a) (11·7 g, 0·06 mol) and 2-benzyloxyethylamine [17] (10·5 g, 0·07 mol) in methanol was refluxed for 4 h, then evaporated. The residual oil was dissolved in water and washed three times with ether. The water layer was evaporated to dryness and the residue dissolved in hot ethanol. Upon cooling, the *amide* (7a) crystallized (6·1 g). Evaporating the mother liquor gave another 12·2 g of (7a) as a colourless oil which, according to spectral data, corresponded in purity to the crystalline product (total yield 88%); m.p. 124—125·5° (ethanol), $\nu_{max.}$ (KBr) 3400 (OH, NH), 1700, 1670 (3 C=O), and 1550 cm^{-1} (amide II), δ [$(CD_3)_2SO$] 4·45 (s, $PhCH_2$), 4·6 (t, OH), 5·2 (m, 2-H), 5·6 (d, *J* 8 Hz, 5′-H), 7·7 (d, *J* 8 Hz, 6′-H), 8·3 (t, NH), and 13·2 (s, 3′-H) (Found: C, 58·6; H, 6·3; N, 12·1. $C_{17}H_{21}N_3O_5$ requires C, 58·8; H, 6·1; N, 12·1%).

N-(2-*Benzyloxyethyl*)-4-*chloro*-2-(1,2,3,4-*tetrahydro*-2,4-*dioxopyrimidin*-1-*yl*)*butyramide* (7b).—Thionyl chloride (20 ml) was added dropwise to a solution of the amide (7a) (11·2 g) in chloroform with cooling (ice-bath). The solution was stirred overnight at room temperature, refluxed for 5 min, and evaporated to dryness. The resulting oil was dissolved in refluxing ethanol. Upon cooling the *chloride* (7b) (8·3 g, 72%) crystallized; m.p. 138—139° (ethanol), $\nu_{max.}$ ($CHCl_3$) 3300 (NH), 1700—1660 (3 C=O), and 1540 cm^{-1} (amide II), δ ($CDCl_3$) 4·55 (s, $PhCH_2$), 5·45 (t, 2-H), 5·7 (d, *J* 7 Hz, 5′-H), 7·2 (d, Ph), 7·55 (d, *J* 7 Hz, 6′-H), 7·65 (t, NH), and 10·0 (s, 3′-H) (Found: C, 55·8; H, 5·6; Cl, 9·9; N, 11·5. $C_{17}H_{20}ClN_3O_4$ requires C, 55·8; H, 5·5; Cl, 9·7; N, 11·5%).

N-(2-*Benzyloxyethyl*)-3-(1,2,3,4-*tetrahydro*-2,4-*dioxopyrimidin*-1-*yl*)*pyrrolidin*-2-*one* (8).—To sodium (6·9 g, 0·3 mol) dissolved in methanol (300 ml) was added the chloride (7b) (10·0 g, 0·03 mol). After 3 h refluxing the sodium chloride formed was filtered off and the filtrate was evaporated to dryness. The residue was taken up in water and the solution neutralized with hydrochloric acid. The water layer was extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated and the residue was dissolved in boiling benzene. Cooling solution gave the *pyrrolidinone* (8) as white crystals (7·6 g, 85%), m.p. 119—121° (benzene), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1690 (3 C=O), and 1100 cm^{-1} (C–O–C) (no amide II), δ [$(CD_3)_2SO$] 4·5 (s, $PhCH_2$) 4·95 (t, 3-H), 5·55 (d, 5′-H), 7·35 (s, Ph), 7·45 (d, 6′-H), and 11·3 (s, 3′-H) (Found: C, 62·1; H, 5·9; N, 12·6. $C_{17}H_{19}N_3O_4$ requires C, 62·0; H, 5·8; N, 12·75%).

N-(2-*Acetoxyethyl*)-3-(1,2,3,4-*tetrahydro*-2,4-*dioxopyrimidin*-1-*yl*)*pyrrolidin*-2-*one* (10d).—The ether (8) (1·0 g) was dissolved in 4N-hydrogen bromide–acetic acid (8 ml). After 3 h of stirring and addition of ether a waxy solid was formed [according to n.m.r. a mixture of alcohol (10a) and its acetate]. The precipitate was purified by repeated addition and decantation of ether and finally dissolution in

acetic anhydride containing a few drops of pyridine. After stirring overnight, evaporation gave the pure *acetate* (0·7 g, 82%), m.p. 137—139° (ethyl acetate), $\nu_{max.}$ ($CHCl_3$) 3400 (NH) and 1680—1730 cm^{-1} (4 C=O), δ [$(CD_3)_2SO$] 2·0 (s, Me), 4·4 (t, AcO·CH_2), 4·95 (t, 3-H), 5·6 (d, 5′-H), 7·5 (d, 6′-H), and 11·3 (s, 3′-H) (Found: C, 51·2; H, 5·5; N, 14·8. $C_{12}H_{15}N_3O_5$ requires C, 51·25; H, 5·4; N, 14·95%).

N-(2-*Hydroxyethyl*)-3-(1,2,3,4-*tetrahydro*-2,4-*dioxopyrimidin*-1-*yl*)*pyrrolidin*-2-*one* (10a).—(*A*) The protected compound (8) (7·6 g) was treated with 4N-hydrogen bromide–acetic acid (30 ml) at room temperature (3 h). The resulting mixture of (10a) and its acetate (see before) was dissolved in methanol (50 ml) and refluxed overnight. After cooling, pure (10a) crystallized (4·7 g, 86%).

(*B*) To palladium–charcoal (10%; 1·5 g) (pre-hydrogenated), suspended in acetic acid, was added the benzyl ether (8) (10·0 g). Catalytic reduction was carried out at room temperature and atmospheric pressure for 40 h. After filtration and evaporation the resulting oil was treated with chloroform, whereupon the *alcohol* (10a) (7·1 g, 98%) crystallized; m.p. 202—203° (methanol), $\nu_{max.}$ (KBr) 3200—3400 (OH, NH), 1710, 1690, 1670 (3 C=O), and 1070 cm^{-1} (C–OH), δ [$(CD_3)_2SO$] 5·0 (t, 2-H), 5·56 (2d, *J* 8 and 2 Hz, 5′-H), 7·49 (d, *J* 8 Hz, 6′-H), and 11·3 (s, 3′-H) (Found: C, 50·5; H, 5·6; N, 17·4. $C_{10}H_{13}N_3O_4$ requires C, 50·2; H, 5·5; N, 17·55%).

N-(2-*Iodoethyl*)-3-(1,2,3,4-*tetrahydro*-2,4-*dioxopyrimidin*-1-*yl*)*pyrrolidin*-2-*one* (10c).—To a solution of the alcohol (10a) (6·0 g, 0·025 mol) in dry dimethylformamide (25 ml) was added slowly a solution of freshly prepared triphenoxymethylphosphonium iodide [18] (22·09 g, 0·05 mol) in dry dimethylformamide (25 ml). After 3 h at room temperature methanol (20 ml) was added to decompose the excess of the reagent. After 1 h stirring the solution was evaporated to dryness and the residue taken up in chloroform and washed with sodium hydrogen carbonate (5%), sodium thiosulphate (10%), and water. The chloroform layer was dried (Na_2SO_4) and evaporated. The residue, recrystallized from acetone, gave the *iodide* (10c) (6·8 g, 78%), m.p. 168—170° (ethanol), $\nu_{max.}$ (KBr) 3400 (NH), 1690, and 1670 cm^{-1} (3 C=O), δ [$(CD_3)_2SO$] 5·0 (t, 3-H), 5·6 (2d, *J* 8 and 2 Hz, 5′-H), 7·5 (d, *J* 8 Hz, 6′-H), and 11·3 (s, NH) (Found: C, 34·5; H, 3·3; I, 36·5; N, 12·0. $C_{10}H_{12}IN_3O_3$ requires C, 34·4; H, 3·45; I, 36·35; N, 12·05%).

3-(1,2,3,4-*Tetrahydro*-2,4-*dioxopyrimidin*-1-*yl*)-N-*vinylpyrrolidin*-2-*one* (11).—To a solution of the iodide (10c) (500 mg) in dimethoxyethane (150 ml; dried by distillation over calcium hydride) was added a solution of 3·5 equiv. of potassium t-butoxide (sublimed) in dry dimethoxyethane. After 4 h stirring the suspension was diluted with water and the pH adjusted to 8. Evaporation at room temperature gave a red solution (3—5 ml; pH 11—12). After addition of a few drops of conc. hydrochloric acid the product crystallized on cooling (210 mg, 66%), m.p. 222—224° (water), $\nu_{max.}$ (KBr) 3500 (NH), 1760, 1700 (3 C=O), and 1630 cm^{-1} (C=C), δ [$(CD_3)_2SO$] 4·52 (d, *J* 9 Hz, =CH), 4·57 (d, *J* 16 Hz, =CH), 5·08 (t, 3-H), 5·60 (d, *J* 8 Hz, 5′-H), 6·94 (2d, *J* 16 and 9 Hz, =CH), and 7·60 (d, *J* 8 Hz, 6′-H) (Found: C, 54·0; H, 5·1; N, 18·8. $C_{10}H_{11}N_3O_3$ requires C, 54·3; H, 5·0; N, 19·0%).

N-(2-*Chloroethyl*)-3-(1,2,3,4-*tetrahydro*-2,4-*dioxopyrimidin*-1-*yl*)*pyrrolidin*-2-*one* (10b).—The alcohol (10a) (200 mg) was dissolved in purified thionyl chloride (5 ml). Next day the excess of the reagent was evaporated off. Addition of dimethoxyethane to the residue gave the *chloride* (90%), m.p. 208—213° (acetic acid), $\nu_{max.}$ (KBr) 1710 and 1690—1670 cm^{-1} (3 C=O) δ [$(CD_3)_2SO$] 5·0 (t, 3-H), 5·6 (d, *J* 8 Hz, 5′-H), and 7·5 (d, *J* 8 Hz, 6′-H) (Found: C, 46·6; H, 4·6; Cl, 13·6; N, 16·3. $C_{10}H_{12}ClN_3O_3$ requires C, 46·6; H, 4·7; Cl, 13·75; N, 16·3%).

Poly-[3-(*uracil*-1-*yl*)-N-*vinylpyrrolidin*-2-*one*] (12).—A solution of the monomer (11) (70 mg) and azobisisobutyronitrile (2 mg) in [$^2H_6$]dimethyl sulphoxide (0·5 ml) was heated to 60° in an n.m.r. tube under nitrogen. After one night the n.m.r. spectrum of the viscous solution did not exhibit any vinyl signals. Solvent was partly removed at 60° and 0·1 mmHg. The resulting solid was dissolved in ammonia, reprecipitated by addition of hydrochloric acid, and washed with water. This procedure was repeated several times. After drying (P_2O_5; 0·1 mmHg) the *polymer* still contained 1·9 molecules of water per monomer unit (Found: C, 47·0; H, 5·5; N, 16·8. $C_{10}H_{11}N_3O_3,1{\cdot}9H_2O$ requires C, 47·0; H, 5·85; N, 16·45%). For the determination of the molecular weight the polymer was dissolved in 0·01N-NaOH and 0·1M-NaCl. The solution was rotated in an M.S.E. analytical ultracentrifuge at 20° and 50,000 rev. min^{-1}. The sedimentation was measured from the displacement of the boundary at half height. Utilizing Lamms [25] formula [$s = (1/\omega^2)(\mathrm{d} \ln r/\mathrm{d}t)$ where ω = angular velocity of the cell in radians s^{-1}, r = distance from boundary to axis of rotation, t = time in seconds] an $s_{20\cdot50\%}$ value of 2·6 s was calculated (corrected for viscosity of the solution). Since partial specific volume and diffusion coefficient of this polymer are not known, the *s* value was related to the molecular weight by comparing with a structurally related polymer. From Scholtan's formula [21] for polyvinylpyrrolidinone ($s = 8{\cdot}81 \times 10^{-16}M^{\frac{1}{2}}$) an average molecular weight of 80,000 was calculated.

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