Unconventional Nucleotide Analogues. Part XIV.[1] (2*S*,4*S*)-2-Hydroxymethyl- and 2-Carboxy-4-(pyrimidin-1-yl)pyrrolidines

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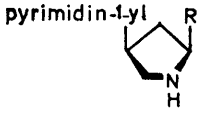
The syntheses of (4*S*)-4-uracilyl-, 4-thyminyl-, and 4-cytosinyl-L-prolinol and (4*S*)-4-uracilyl- and 4-thyminyl-L-proline are described. The uracil derivatives (12a) and (13e) inhibit the growth of BHK cells.

In connection with our interest in non-saccharidal nucleoside and nucleotide analogues we now report the synthesis and biological evaluation of 4-(pyrimidin-1-yl)pyrrolidine derivatives (1a and b). The corresponding purine analogues are described in Part XIII.

In principle, the analogues (1a and b) might be synthesized by either direct coupling between pyrimidine and pyrrolidine derivatives or *via* a *de novo* construction of the pyrimidine upon a suitable pyrrolidine derivative. The direct formation of a pyrimidine glycosidic linkage



(1) a; R = CH_2OH b; R = CO_2H

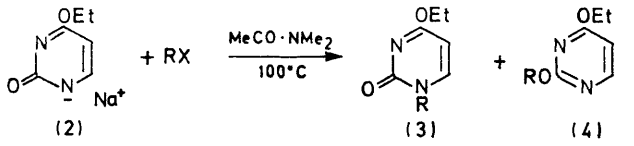
is generally carried out by alkylation of pyrimidinyl anions or pyrimidinyl ethers (Hilbert–Johnson reaction) with protected glycosyl halides.[2]

[1] Part XIII. F. M. Kaspersen and U. K. Pandit, *J.C.S. Perkin I*, 1975, 1617.

[2] J. Pliml and M. Prystas, *Adv. Heterocyclic Chem.*, 1967, **8**, 115.

Preliminary experiments showed that reaction between 2,4-dialkoxypyrimidines and methyl *trans*-4-bromo-*N*-tosylpyrolinate or the corresponding 4-tosylate led to the formation of C-4 epimeric mixtures of the coupling products, albeit in unacceptably low yields. In the case of the tosylate the predominant reaction involved an ethyl tosylate-catalysed rearrangement of diethoxypyrimidine. The success of the Hilbert–Johnson reaction is dependent upon a higher reactivity of the alkylating reagent as compared with the electrophile generated as a result of the reaction itself.[3]

The accessibility of the sodium salt of 4-*O*-ethyluracil (2)[4] (Scheme 1) led us to consider the nucleophilic substitution of proline derivatives (halides or sulphonate esters) by the corresponding pyrimidinyl anion. However, in order to choose a derivative that would be most responsive to the aforementioned nucleophilic substitution reaction and, to optimise the reaction conditions, a study of the nucleophilic reaction of (2) with selected electrophiles was undertaken (Scheme 1).†



R = benzyl, n-pentyl, or cyclopentyl
X = Cl, Br, or OTs

SCHEME 1

When the reaction was carried out in dimethylacetamide both *N*- and *O*-alkylated products [(3) and (4)] were obtained in each case. The total yields of the substitution products and the percentages of *N*- and *O*-alkylation are given in the Table. Ratios of *N*- to *O*-alkylation for the reactions with benzyl derivatives are based upon the amounts of isolated products; those for the reactions with n-pentyl and cyclopentyl systems are derived from the n.m.r. spectra of the mixtures. The Table indicates that, in general, reaction of (2) with primary halides and tosylates results in predominant *N*-alkylation, whereas that with secondary halides and tosylates gives predominant *O*-alkylation and in a lower overall yield.

Reaction of 4-*O*-ethyluracil anion (2) with alkylating agents (RX) (in dimethylacetamide at 100 °C; 20 h)

R	X	Substitution products (%)	Substitution at N (%)	Substitution at O (%)
$PhCH_2$	Cl	85	96	4
	Br	90	97	3
	OTs	81	89	11
n-Pentyl	Br	90	82	18
	OTs	95	62	38
Cyclopentyl	Cl	3 *	33	66
	Br	67	36	64
	OTs	75	30	70

* Incomplete reaction.

While an interpretation of the results of the reaction with benzyl derivatives is complicated by the rapid transformation of the *O*- into the corresponding *N*-substitution product,‡ the change in *N*- *versus* *O*-alkylation can, in principle, be rationalized in terms of the hard–soft acid–base (HSAB) theory of reactivity.[5] Since considerations of electronegativity require the oxygen end of the anion (2) to be a harder base, an increase in hardness of the electrophilic centre (acid) (as a result of a change in the structure of the alkyl radical or the leaving group) would be expected to lead to an increased proportion of *O*-alkylation.[6] Consistent with these ideas, it is observed (Table) that a transition from a primary (n-pentyl) to a secondary (cyclopentyl) electrophile, or from a primary halide to a primary tosylate, is accompanied by an enhancement in *O*-substitution. The similar *N*- to *O*-alkylation ratios for the cyclopentyl derivatives (X = Cl, Br, or OTs) may be explained on the assumption that the significance of the leaving group decreases with the increase in intrinsic ' hardness ' of the alkyl radical.§

In the light of the aforementioned results and in view of the fact that the glycosyl unit in pyrimidine *O*-glycosides is known to undergo a ready O ⟶ N migration,[7] the anion (2a) was treated with the tosylates (5a and b) (Scheme 2). The substitution of the pyrrolidine *O*-tosylates (5a and b) proceeded in a lower overall yield than that of cyclopentyl tosylate. Presumably approach of the nucleophile to the electrophilic centre is sterically hindered by the *N*-substituent. An increase in total substitution in going from the *N*-tosyl (5a) to the *N*-acetyl (5b) derivative (decrease in bulk) supports this idea. The course of the reaction with compounds (5a and b) corresponded to overwhelming *O*-alkylation (6a and b). The small amounts of *N*-alkylation products (7a and b) were identified by their i.r. spectra. Contrary to expectation, the intramolecular O ⟶ N transfer of the pyrrolidine unit in (6a and b) could not be achieved. However, compounds (6a and b) reacted with ethyl iodide to yield the corresponding *N*-ethyl derivatives. The latter reaction confirms the

† A referee has called our attention to the following papers in which *N*- and *O*-alkylations of pyrimidine derivatives have been compared: (*a*) G. C. Hopkins, J. P. Jonak, H. Tieckelmann, and H. J. Minnemayer, *J. Org. Chem.*, 1966, **31**, 3269; (*b*) D. M. Brown and C. M. Taylor, *J.C.S. Perkin I*, 1972, 2385.

‡ The *O*-benzyl derivative was shown to be convertible into the *N*-benzyl derivative under the reaction conditions, *i.e.* in the presence of a benzyl halide.

§ An alternative explanation should also be considered. In the series cyclopentyl chloride, bromide, and tosylate, increasing contribution from an S_N1 reaction can complicate the picture. The influences of the leaving group and the change in mechanism may become mutually compensatory.

[3] G. J. Koomen and U. K. Pandit, *J.C.S. Perkin I*, 1973, 1930; see also D. W. Visser, I. Goodman, and K. Dittmer, *J. Amer. Chem. Soc.*, 1948, **70**, 1926.

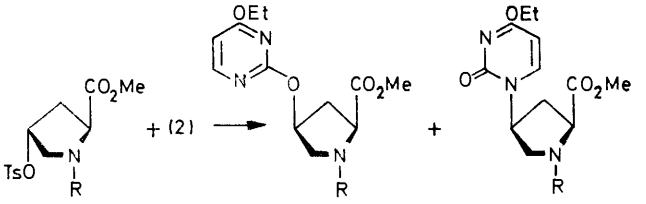
[4] (*a*) G. E. Hilbert and E. F. Jansen, *J. Amer. Chem. Soc.*, 1935, **57**, 552; (*b*) H. Plaut in ' Organic Sulfur Compounds,' vol. I, ed. N. Kharasch, Pergamon, New York, 1961, p. 521.

[5] R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, 1967, **89**, 182.

[6] (*a*) W. J. le Noble and H. F. Morris, *J. Org. Chem.*, 1969, **34**, 1969; (*b*) W. J. le Noble and J. E. Puerta, *Tetrahedron Letters*, 1966, 1087; (*c*) G. Brieger and W. M. Pelletier, *ibid.*, 1965, 3555.

[7] See, for example, (*a*) T. Ukita, M. Hayatsu, and Y. Tumita, *Chem. and Pharm. Bull. (Japan)*, 1963, **11**, 1068; (*b*) T. Nishimura and B. Shimizu, *ibid.*, 1965, **13**, 803; (*c*) J. J. Fox, N. Yung, T. Wempen, and I. L. Doerr, *J. Amer. Chem. Soc.*, 1957, **79**, 5060.

spectral evidence (see Experimental section) for the *O*-alkyl structures of (6a and b). The larger *O*- to



(5) a; R=Ts
b; R=Ac

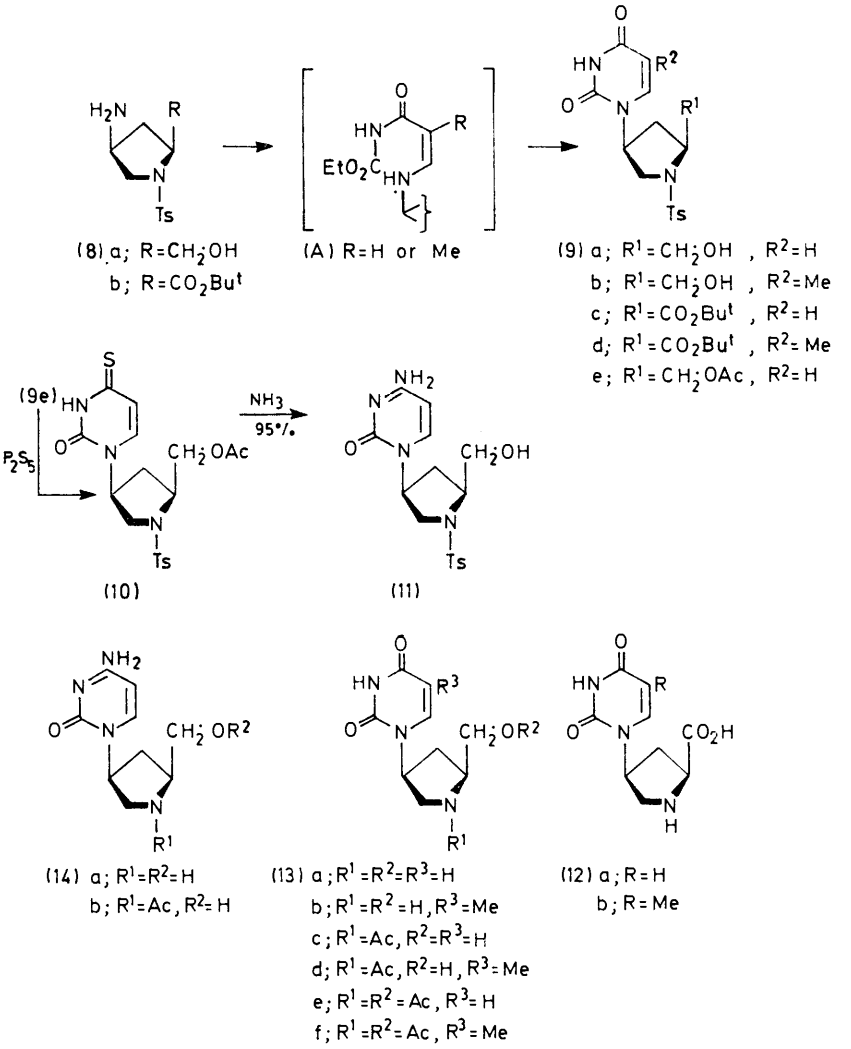
(6) a; R=Ts (25%)
b; R=Ac (50%)

(7) a; R=Ts (3%)
b; R=Ac (7%)

SCHEME 2

N-alkylation ratio for the tosylates (5a and b) in comparison with cyclopentyl tosylate may again be attributed to steric factors. The relatively exposed oxygen end of the ambient anion (2) is the favoured (nucleophilic) centre for S_N2 attack on the sterically shielded (*N*-substituent) C-4 of the pyrrolidine ring in (5a and b).

In the light of the difficulties encountered in the synthesis of the desired analogues *via* a substitution reaction of a proline derivative, attention was directed to the construction of the nucleoside base upon a suitably substituted aminopyrrolidine. The amino-derivatives (8a and b) [1] are ideally suited for this purpose. Elaboration of the amino-group in (8a and b) by utilizing ethyl *N*-(3-ethoxyacryloyl)carbamate and ethyl *N*-(3-methoxy-2-methylacryloyl)carbamate as the base precursors (Shaw procedure; [8] ethanol as solvent) led to the uracil and thymine derivatives (9a—d). Spectral analysis ($\lambda_{max.}$ at 300 nm) of the reaction mixture indicated that both the uracil and thymine systems are produced *via* the non-cyclic intermediates of type (A). This is noteworthy in the context of the question as to whether the thymine precursor is formed *via* a Michael



(8) a; R=CH_2OH
b; R=CO_2Bu^t

(A) R=H or Me

(9) a; R^1=CH_2OH, R^2=H
b; R^1=CH_2OH, R^2=Me
c; R^1=CO_2Bu^t, R^2=H
d; R^1=CO_2Bu^t, R^2=Me
e; R^1=CH_2OAc, R^2=H

(10)

(11)

(14) a; R^1=R^2=H
b; R^1=Ac, R^2=H

(13) a; R^1=R^2=R^3=H
b; R^1=R^2=H, R^3=Me
c; R^1=Ac, R^2=R^3=H
d; R^1=Ac, R^2=H, R^3=Me
e; R^1=R^2=Ac, R^3=H
f; R^1=R^2=Ac, R^3=Me

(12) a; R=H
b; R=Me

SCHEME 3

addition or an acylation reaction involving the amino-group and ethyl *N*-(3-methoxy-2-methylacryloyl)carb-

[8] (*a*) G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 1958, 157; (*b*) M. R. Atkinson, M. H. Maguire, R. K. Ralph, G. Shaw, and R. N. Warrener, *ibid.*, 1957, 2363.

amate. Conversion of (9a) into the corresponding cytosine derivative (11) was achieved by the sequence (9a) ⟶ (9e) ⟶ (10) ⟶ (11). Detosylation of (9c and d) (HBr–HOAc) yielded, after basification, the amino-acids (12a) (80%) and (12b) (70%). A similar detosylation of (9a and b) and (11) resulted in mixtures of the amino-alcohols (13a and b) and (14a), and the corresponding *N*-acyl derivatives (13c and d) and (14b), respectively. The hygroscopic uracil and thymine derivatives (13a—d) were converted into the corresponding diacetates (13e and f) with acetic anhydride (Scheme 3).

Biological Results.—Compounds (12a) and (13e) inhibited the growth of BHK cells [(12a) 35%; (13e) 40% at 10 μg ml^{-1}].

EXPERIMENTAL

For instrumentation see Part XIII.

Reactions of the Sodium Salt of 4-O-*Ethyluracil with Various Electrophiles.*—The electrophile (1 mmol) was added to a suspension of the sodium salt of 4-*O*-ethyluracil (2) (1.1 equiv.) in dimethylacetamide (5 ml). After stirring at 100 °C [for (5a) and (5b) 96 h] the solvent was distilled off *in vacuo* and the residue put on a silica gel column. The isomers were eluted together from the column with chloroform and separated by preparative t.l.c. [SiO_2 (2 mm); $CHCl_3$]. The R_F values were not reproducible and varied with the moisture content of the silica plates. The yields presented in the Table and the *N*- to *O*-alkylation ratios are based upon amounts of individual isomers isolated. The *N*-substituted derivatives (3) (R = benzyl, pentyl, or cyclopentyl) were obtained as crystalline products; however, they were isolated in amounts which did not permit the preparation of analytically pure samples.

2-*O*-Benzyl-4-*O*-ethyluracil (4; R = benzyl) was a liquid, $\nu_{max.}$ ($CHCl_3$) 1 585 and 1 575 (pyrimidine) and 1 280 cm^{-1} (OEt); δ ($CDCl_3$) 1.35 and 4.39 (t and q, OEt), 5.40 (s, PhCH_2), 6.33 (d, *J* 5.5 Hz, pyrimidine), 7.20—7.60 (m, Ph), and 7.18 (d, *J* 5.5 Hz, pyrimidine).

4-*O*-Ethyl-2-*O*-pentyluracil (4; R = pentyl) was a liquid, $\nu_{max.}$ ($CHCl_3$) 1 575 (pyrimidine) and 1 285 cm^{-1} (OEt); δ ($CDCl_3$) 0.7—2.1 (m, pentyl), 1.39 (t, OEt), 4.40 (t, pentyl), 4.49 (q, OEt), and 6.45 and 8.35 (2d, pyrimidine).

2-*O*-Cyclopentyl-4-*O*-ethyluracil (4; R = cyclopentyl) was a liquid, $\nu_{max.}$ ($CHCl_3$) 1 590 and 1 570 (pyrimidine) and 1 285 cm^{-1} (OEt); δ ($CDCl_3$) 1.36 (t, OEt), 1.5—2.1 (m, cyclopentyl), 4.40 (q, OEt), 5.38 (m, cyclopentyl), and 6.28 and 8.15 (2d, *J* 5.5 Hz, pyrimidine).

1-Benzyl-4-*O*-ethyluracil (3; R = benzyl) was crystalline material, $\nu_{max.}$ ($CHCl_3$) 1 600 and 1 640 (pyrimidine) and 1 310 cm^{-1} (OEt); δ ($CDCl_3$) 1.33 (t, OEt), 4.40 (q, OEt), 5.01 (s, PhCH_2), 5.81 (d, *J* 7.5 Hz, pyrimidine), 7.31 (s, Ph), and 7.48 (d, *J* 7.5 Hz, pyrimidine).

4-*O*-Ethyl-1-pentyluracil (3; R = pentyl) was crystalline material, $\nu_{max.}$ ($CHCl_3$) 1 660 and 1 640 (pyrimidine) and 1 310 cm^{-1} (OEt); δ ($CDCl_3$) 0.7—2.1 (m, pentyl), 1.36 (t, OEt), 3.92 (t, pentyl), 4.52 (q, OEt), 5.95 (d, *J* 7.5 Hz, pyrimidine), and 7.59 (d, *J* 7.5 Hz, pyrimidine).

1-Cyclopentyl-4-*O*-ethyluracil (3; R = cyclopentyl) was crystalline material, $\nu_{max.}$ ($CHCl_3$) 1 660 and 1 635 (pyrimidine) and 1 315 cm^{-1} (OEt); δ ($CDCl_3$) 1.33 (t, OEt), 1.40—2.35 (m, cyclopentyl), 4.45 (q, OEt), 4.95—5.25 (m, cyclopentyl), and 5.85 and 7.44 (2d, *J* 7.5 Hz, pyrimidine).

cis-4-(4-O-*Ethyluracil-2-yl*)-N-*tosyl*-L-*proline methyl ester* (6a) had m.p. 100.5—102.5°, $\nu_{max.}$ ($CHCl_3$) 1 745 (C=O), 1 595 and 1 575 (pyrimidine), 1 285 (OEt), and 1 160 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 257.5 (ε 6 800) and 228 nm (15 900); δ ($CDCl_3$) 1.35 (t, OEt), 2.42 (m and s, Me and 3-H), 3.45—3.65 and 3.80—4.05 (m, 5-H), 3.70 (s, Me), 4.34 (q, OEt), 4.57 (m, 2-H), 5.31 (m, 4-H), 6.33 (d, *J* 5.5 Hz, pyrimidine), 7.55 (2d, Ph), and 8.11 (d, *J* 5.5 Hz, pyrimidine) (Found: C, 53.9; H, 5.6; N, 10.1; S, 7.6. $C_{19}H_{23}N_3O_6S$ requires C, 54.15; H, 5.5; N, 9.95; S, 7.6%).

N-Acetyl-*cis*-4-(4-*O*-ethyluracil-2-yl)-L-proline methyl ester (6b) was an oil, $\nu_{max.}$ ($CHCl_3$) 1 740 (C=O), 1 645 (NAc), 1 580 and 1 565 (pyrimidine), and 1 280 cm^{-1} (OEt); δ ($CDCl_3$) 1.37 (t, OEt), 2.04 and 2.10 (2s, NAc), 2.30—2.80 (m, 3-H), 3.72 and 3.79 (2s, Me), 3.55—4.10 (m, 5-H), 4.36 (q, OEt), 4.68 (m, 2-H), 5.2—5.6 (m, 4-H), 6.31 and 6.34 (2d, *J* 5.5 Hz, pyrimidine), and 8.05br (d, *J* 5.5 Hz, pyrimidine).

cis-4-(*Uracil-1-yl*)-N-*tosyl*-L-*prolinol* (9a).—A solution of ethyl *N*-(3-ethoxyacryloyl)carbamate (190 mg) and *cis*-4-amino-*N*-tosyl-L-prolinol (8a) (270 mg) in ethanol (1 ml) was stirred for 5 h at 70 °C. After addition of 2N-sodium hydroxide (0.5 ml) the mixture was stirred at this temperature for another hour and, after cooling, adjusted to pH 8 with acetic acid and poured into brine (10 ml). The *product* was extracted with chloroform and after drying ($MgSO_4$) the extract was chromatographed on a silica gel column; yield 245 mg (65%); m.p. 209—211.5°: $\nu_{max.}$ (KBr) 3 500 (NH), 1 680 (pyrimidine), and 1 160 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 264.5 nm (ε 10 600); δ ($CDCl_3$) 2.00—2.50 (m, 3-H), 2.49 (s, Me), 3.35—4.25 (m, 2-H, 5-H, and CH_2O), 4.65 (m, 4-H), 5.76 (2d, *J* 2 and 8 Hz, pyrimidine), 7.58 (2d, Ph), 7.52 (d, *J* 8 Hz, pyrimidine), and 8.18br (NH) (Found: C, 52.5; H, 5.2; N, 11.4. $C_{16}H_{19}N_3O_5S$ requires C, 52.6; H, 5.25; N, 11.5%).

cis-4-(*Thymin-1-yl*)-N-*tosyl*-L-*prolinol* (9b).—This was synthesized by reaction of *cis*-4-amino-*N*-tosyl-L-prolinol (8a) with *N*-(3-methoxy-2-methylacryloyl)carbamate in ethanol at 70 °C during 16 h. After 1 h treatment at the same temperature with sodium hydroxide the *compound* was isolated as described for (9a); yield 40% (hygroscopic, crystalline); $\nu_{max.}$ (KBr) 1 675 (pyrimidine) and 1 160 cm^{-1} (SO_2); $\lambda_{max.}$ (MeOH) 269 (ε 11 000) and 228 nm (12 200); δ ($CDCl_3$) 1.84br (s, Me), 1.95—2.65 (m, 3-H), 2.42 (s, Me), 3.15—4.25 (m, 2-H, 5-H, and CH_2O), 4.60 (m, 4-H), 7.38br (s, pyrimidine), 7.56 (2d, Ph), and 10.0 (s, NH); $[\alpha]_D^{24}$ +89.5° (*c* 1.5 in $CHCl_3$) (Found: C, 53.7; H, 5.6; N, 10.9. $C_{17}H_{25}N_3O_5S$ requires C, 53.8; H, 5.6; N, 11.1%).

N-*Tosyl*-cis-4-(*uracil-1-yl*)-L-*proline t-Butyl Ester* (9c).—This *compound* was synthesized from *cis*-4-amino-*N*-tosyl-L-proline t-butyl ester (8b) as described for (9a); yield 350 mg (62%); m.p. 167—171°; $\nu_{max.}$ (KBr) 1 680 (pyrimidine) and 1 160 cm^{-1} (SO_2); $\lambda_{max.}$ (MeOH) 264.5 (ε 11 800) and 229.5 nm (14 400); δ [$(CD_3)_2SO$] 1.44 (s, Bu^t), 1.95—2.80 (m, 3-H), 2.43 (s, Me), 3.46 (m, 5-H), 4.01 (m, 2-H), 4.63 (m, 4-H), 5.59 (2d, *J* 1 and 8 Hz, pyrimidine), 7.61 (2d, Ph), 7.67 (d, *J* 8 Hz, pyrimidine), and 11.28br (NH) (Found: C, 55.0; H, 5.7; N, 9.8. $C_{20}H_{25}N_3O_6S$ requires C, 55.15; H, 5.8; N, 9.65%).

cis-4-(*Thymin-1-yl*)-N-*tosyl*-L-*proline t-Butyl Ester* (9d).—This *compound* was synthesized from (8b) as described for (9e); yield 24%, m.p. 208—210°, $\nu_{max.}$ (KBr) 3 330 (NH), 1 675 (pyrimidine), and 1 160 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 269 (ε 10 800) and 227 nm (15 400); δ [$(CD_3)_2SO$] 1.43 (s, Bu^t), 1.73 (s, CH_3), 1.90—2.65 (m, 3-H), 2.41 (s, CH_3),

3.47 (m, 5-H), 4.08 (m, 2-H), 4.61 (m, 4-H), 7.49 (s, pyrimidine), 7.60 (2d, Ph), and 11.24br (s, NH) (Found: C, 56.1; H, 6.1; N, 9.5. $C_{21}H_{27}N_3O_6S$ requires C, 56.1; H, 6.05; N, 9.35%).

N-*Tosyl*-cis-4-(*uracil*-1-*yl*)-L-*prolinol Acetate* (9e).—To a solution of *N*-tosyl-*cis*-4-(uracil-1-yl)-L-prolinol (9a) (700 mg) and acetic anhydride (5 ml) in 1,2-dimethoxyethane (25 ml), potassium carbonate (500 mg) was added. After 3 h stirring the precipitate was filtered off and the *residue* from the filtrate chromatographed on a silica gel column; yield 500 mg (64%), m.p. 108—110°; $\nu_{max.}$ (KBr) 3 500 (NH), 1 745 (OAc), 1 700 (pyrimidine), and 1 160 cm^{-1} (SO_2); δ [$(CD_3)_2SO$] 2.05 (s, Me), 1.90—2.60 (m, 3-H), 2.46 (s, Me), 3.30—4.00 (m, 2-H and 5-H), 4.05—4.50 (m, 4-H and CH_2O), 5.64 (d, *J* 8 Hz, pyrimidine), 7.64 (2d, Ph), 7.68 (d, *J* 8 Hz, pyrimidine), and 10.25br (s, NH).

As by-product, *cis*-4-(3-acetyluracil-1-yl)-*N*-tosyl-L-prolinol acetate (130 mg, 15%) was isolated.

cis-4-(4-*Thiouracil*-1-*yl*)-N-*tosyl*-L-*prolinol Acetate* (10).—A solution of *N*-tosyl-*cis*-4-(uracil-1-yl)-L-prolinol acetate (9e) (820 mg) and phosphorus pentasulphide (1 300 mg) in dry pyrimidine (10 ml) was refluxed for 1.5 h under nitrogen. The mixture was evaporated and the residue chromatographed on a silica gel column, to give pale yellow *crystals* (520 mg, 61%), m.p. 149—152°; $\nu_{max.}$ ($CHCl_3$) 3 360 (NH), 1 730 (OAc), 1 605 (C=C), and 1 160 cm^{-1} (SO_2); $\lambda_{max.}$ (EtOH) 333 (ε 22 300) and 232 nm (13 500); δ ($CDCl_3$) 1.75—2.50 (m, 3-H), 2.06 (s, Me), 2.48 (s, Me), 3.61 (m, 5-H), 3.55—3.95 (m, 2-H), 4.37 (m, CH_2O), 4.56 (m, 4-H), 6.43 (2d, *J* 8 and 1 Hz, pyrimidine), 7.27 (2d, Ph), and 10.05—10.35br (d, NH) (Found: C, 50.9; H, 4.9; N, 10.1; S, 15.0. $C_{18}H_{21}N_3O_5S$ requires C, 51.05; H, 4.9; N, 9.9; S, 15.15%).

cis-4-(*Cytosin*-1-*yl*)-N-*tosyl*-L-*prolinol* (11).—*cis*-4-(4-Thiouracil-1-yl)-*N*-tosyl-L-prolinol acetate (600 mg) was dissolved in methanol (50 ml) saturated with ammonia at 0 °C. After being heated at 100 °C for 24 h in a Carius tube, the solution was evaporated and the residue chromatographed on a silica gel column; yield 500 mg (96%), m.p. 227—300° (from chloroform); $\nu_{max.}$ (KBr) 3 350 (NH_2) 1 640 (pyrimidine) and 1 155 cm^{-1} (SO_2); $\lambda_{max.}$ (MeOH) 274 (ε 8 500) and 232 nm (13 000); δ [$(CD_3)_2SO$] 1.90—2.40 (m, 3-H), 2.46 (s, Me), 3.30—3.90 (m, 2-H, 5-H, and CH_2O), 4.32 (m, 4-H), 4.9br (s, OH), 5.74 (d, *J* 7 Hz, pyrimidine), 7.08br (NH_2), 7.60 (d, *J* 7 Hz, pyrimidine), and 7.63 (2d, Ph).

Detosylation of the (*Pyrimidin*-1-*yl*)*pyrrolidines* (9a—d) *and* (11).—This was carried out by the method of Weisblat *et al.*[9] as described by Andreatta.[10] In the case of the uracilyl and thyminyl-L-prolinol derivatives the mixture of the amino- and *N*-acetyl products was converted into the diacetyl derivative by reaction with acetic anhydride in 1,2-dimethoxyethane containing potassium carbonate. The cytosinyl products were isolated by chromatography over silica gel.

cis-4-(*Uracil*-1-*yl*)-L-*proline* (12a) had m.p. 268—275° (decomp.); $\nu_{max.}$ (KBr) 2 200—2 800 (salt bands), 1 685 (pyrimidine), and 1 620—1 585 cm^{-1} (C=C and CO_2^-); $\lambda_{max.}$ (H_2O) 265 nm (ε 8 900); δ (D_2O) 2.20—2.60 and 2.75—3.15 (m, 3-H), 3.75 (m, 5-H), 4.24 (m, 2-H), 4.80—5.20 (m, 4-H), 5.83 (d, *J* 8 Hz, pyrimidine), and 7.64 (d, *J* 8 Hz, pyrimidine), $[\alpha]_D^{23}$ −57.5° (*c* 1 in H_2O); o.r.d. (H_2O) ϕ_{277} −5 700 (min.), ϕ_{262} 0 (Found: C, 48.1; H, 4.9. $C_9H_{11}N_3O_4$ requires C, 48.0; H, 4.9%).

cis-4-(*Thymin*-1-*yl*)-L-*proline* (12b) had m.p. 275—285° (decomp.); $\nu_{max.}$ (KBr) 2 800—2 200 (salt bands), 1 675 (pyrimidine), and 1 595 cm^{-1} (CO_2^-); $\lambda_{max.}$ (H_2O) 267.5 nm (ε 7 500); δ (D_2O) 1.88br (s, Me), 2.15—2.55 and 2.70—3.10 (m, 3-H), 3.73 (m, 5-H), 4.24 (m, 2-H), 4.80—5.10 (m, 4-H), and 7.48br (s, pyrimidine); o.r.d. (H_2O) ϕ_{286} −3 700 (min.), ϕ_{268} 0 (Found: C, 50.0; H, 5.5; N, 17.4. $C_{10}H_{13}N_3O_4$ requires C, 50.2; H, 5.5; N, 17.55%).

N-*Acetyl*-cis-4-(*uracil*-1-*yl*)-L-*prolinol acetate* (13e) had m.p. 139.5—141.5°; $\nu_{max.}$ (KBr) 1 725 (OAc) and 1 675 cm^{-1} (pyrimidine); $\lambda_{max.}$ (dioxan) 264.5 nm (ε 8 600); δ [$(CD_3)_2SO$] 2.00 and 2.05 (s, 2 × Me), 2.25—2.75 (m, 3-H), 3.20—4.45 (m, 2-H, 5-H, and CH_2O), 4.65—5.00 (m, 4-H), 5.63 (d, *J* 8 Hz, pyrimidine), 7.73 (d, *J* 8 Hz, pyrimidine), and 11.05—11.45 (s, NH) (Found: C, 52.7; H, 5.8; N, 14.2. $C_{13}H_{17}N_3O_5$ requires C, 52.8; H, 5.8; N, 14.25%).

N-*Acetyl*-cis-4-(*thymin*-1-*yl*)-L-*prolinol acetate* (13f) was a slightly hygroscopic solid, $\nu_{max.}$ (KBr) 3 380 (NH), 1 735 (OAc), 1 685 (pyrimidine), and 1 645 cm^{-1} (NAc); $\lambda_{max.}$ (dioxan) 269 nm (ε 7 400); δ [$(CD_3)_2SO$] 1.78br (s, Me), 1.95 and 2.02 (2s, 2 × Me), 2.10—2.50 (m, 3-H), 3.30—4.40 (m, 2-H, 5-H, and CH_2O), 4.65—5.00 (m, 4-H), 7.58br (s, pyrimidine), and 11.26br (s, NH); o.r.d. (dioxan) ϕ_{275} +900 (max.), ϕ_{265} 0 (Found: C, 54.3; H, 6.3; N, 13.7. $C_{14}H_{19}N_3O_5$ requires C, 54.35; H, 6.2; N, 13.6%).

cis-4-(Cytosin-1-yl)-L-prolinol (14a) was yellow crystalline material, $\nu_{max.}$ (KBr) 3 340 and 3 180 (NH and NH_2) and 1 635 cm^{-1} (pyrimidine); δ ([CD_3]$_2$SO) 5.71 and 7.78 (2d, *J* 7.5 Hz, pyrimidine) and 6.95br (s, NH_2).

N-*Acetyl*-cis-4-(*cytosin*-1-*yl*)-L-*prolinol* (14b) had m.p. 110—125°; $\nu_{max.}$ (KBr) 3 310 and 3 370 (NH_2) and 1 640—1 595 cm^{-1} (pyrimidine and NAc); $\lambda_{max.}$ (EtOH) 276 nm (ε 7 900); δ [$(CD_3)_2SO$] (at 108 °C) 1.99 (s, Me), 2.0—2.5 (m, 3-H), 3.20—3.40 (2-H, 5-H, and CH_2O), 4.87 (m, 4-H), 5.78 (d, *J* 7.5 Hz, pyrimidine), 6.40—6.90 (s, NH_2), and 7.61 (d, *J* 7.5 Hz, pyrimidine); o.r.d. (EtOH) ϕ_{338} +300 (max.), ϕ_{312} 0, ϕ_{289} −1 300 (min.), ϕ_{277} 0, ϕ_{265} +2 600 (max.) (Found: C, 52.2; H, 6.4; N, 22.3. $C_{11}H_{16}N_4O_3$ requires C, 52.35; H, 6.4; N, 22.2%).

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