Purines, Pyrimidines, and Imidazoles. Part 60.[1] Some Oxazolo[3,2-*a*]pyrimidines and a Novel Conversion of a Cyanouracil into a Barbituric Acid Derivative

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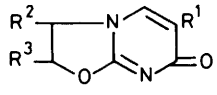
The synthesis of several 6-acetyl(or 6-cyano)-2,3-dihydro-7-oxo-7*H*-oxazolo[3,2-*a*]pyrimidines (**1**) from 5-acetyl(or 5-cyano)-1-[2-hydroxy(or 1-ethyl or 2-phenyl)ethyl]uracils and 5-acetyl(or 5-cyano, or 5-cinnamoyl, or 5-*N*-ethoxycarbonylcarbamoyl)-1-(1-ethyl-2-hydroxyethyl)uracils (**2**) by cyclisation of their toluene-4-sulphonates or methanesulphonates with triethylamine is described. The reaction of 6-cyano-1-(1-ethyl-2-hydroxyethyl)-2,3-dihydro-7-oxo-7*H*-oxazolo[3,2-*a*]pyrimidine (**1e**) with cyclohexylamine produced 5-amino-6-cyclohexyliminomethyl-1-ethyl-2,3-dihydro-7-oxo-7*H*-oxazolo[3,2-*a*]pyrimidine (**6a**) which with hot water gave ammonia and 5-cyclohexylaminomethylene-1-(1-ethyl-2-hydroxyethyl)barbituric acid (**7a**).

Similar reactions occurred with butylamine and benzylamine and with related oxazolopyrimidines, but in contrast compound (**1e**) and morpholine gave the isocytosine (**11**). The structures assigned were confirmed by the synthesis of the acid (**7a**) and of the related 5-cyclohexylaminomethylene-1-methylbarbituric acid and by ^{1}H n.m.r., i.r., u.v., and mass spectroscopy.

In an earlier publication[2] in this series we have recorded the synthesis of some oxazolo[3,2-*a*]pyrimidines (**1**) by the cyclisation of 5-cyano(or 5-acetyl)-1-[2-tosyl(or mesyl)oxyalkyl]uracils (**2**) with triethylamine in acetone solution. We are interested in extending these reactions further since some of the products from the reaction of the cyano-oxazoles with primary amines proved to have modest anti-inflammatory properties. As related compounds including anhydro (cyclic) nucleoside derivatives are known to produce isocytosines with ammonia, we first assumed that the products obtained in these latter reactions were also isocytosine derivatives, but further investigations have shown that this is not the case.

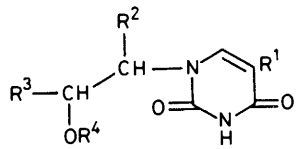
In preliminary experiments the 5-acetyl-1-hydroxyalkyluracils (**2a**) and (**2d**) were prepared by the reaction of α-acetyl-β-ethoxy-*N*-ethoxycarbonylacrylamide (**3a**) with ethanolamine and 2-aminobutan-1-ol by the general method outlined in an earlier publication.[3] The uracils were converted into the tosyloxy [(**2b**), (**2e**)] or mesyloxy [(**2c**)] derivatives and cyclised with triethylamine in acetone solution into the corresponding oxazolo[3,2-*a*]pyrimidines (**1a**) and (**1b**) respectively. When the oxazolopyrimidine (**1a**) was heated in methanol with cyclohexylamine, reaction soon occurred but only to produce a complex mixture of compounds which was not further examined. In hot methanol containing triethylamine, however, compound (**1a**) readily gave in excellent yield a methanol adduct, the properties of which are consistent with the 2-methoxypyrimidinone structure (**4**). Similarly the acetyl derivative (**1a**), on reaction with methanolic hydrogen sulphide and triethylamine, gave the corresponding 2-thiouracil (**5a**) in good yield. The related oxazole (**1b**) behaved in a similar manner. Modification of the 5-acetyl group of the uracil (**2d**) by reaction with benzaldehyde in ethanolic sodium hydroxide readily produced the cinnamoyluracil (**2f**) in high yield and this was converted into the mesyloxy compound (**2g**) which readily gave the corresponding 6-cinnamoyloxazolopyrimidine (**1c**) with triethylamine in acetone solution. The reaction of compound (**1c**) with cyclohexylamine was much slower than that of (**1a**) or (**1b**), but a similar complex mixture of compounds was produced.

The reaction of the carbamate (**3b**) (from malonyl urethane[4] and triethyl orthoformate) with 2-aminobutan-1-ol, produced the uracil (**2h**) which reacted with methanesulphonyl chloride in pyridine to give the mesyloxy compound (**2i**); this readily cyclised to give the oxazolopyrimidine (**1d**) with triethylamine in acetone. However, compound (**1d**) also gave a complex mixture



(**1**)

a; R^1 = COMe, R^2 = R^3 = H
b; R^1 = COMe, R^2 = Et, R^3 = H
c; R^1 = COCH=CHPh, R^2 = Et, R^3 = H
d; R^1 = $CONHCO_2Et$, R^2 = Et, R^3 = H
e; R^1 = CN, R^2 = Et, R^3 = H
f; R^1 = CN, R^2 = H, R^3 = Ph
g; R^1 = CN, R^2 = R^3 = H

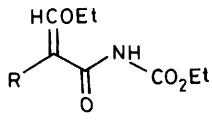


(**2**)

a; R^1 = COMe, R^2 = R^3 = R^4 = H
b; R^1 = COMe, R^2 = R^3 = H, R^4 = tosyl
c; R^1 = COMe, R^2 = R^3 = H, R^4 = mesyl
d; R^1 = COMe, R^2 = Et, R^3 = R^4 = H
e; R^1 = COMe, R^2 = Et, R^3 = H, R^4 = tosyl
f; R^1 = COCH=CHPh, R^2 = Et, R^3 = R^4 = H
g; R^1 = COCH=CHPh, R^2 = Et, R^3 = H, R^4 = mesyl
h; R^1 = $CONHCO_2Et$, R^2 = Et, R^3 = R^4 = H
i; R^1 = $CONHCO_2Et$, R^2 = Et, R^3 = H, R^4 = mesyl
j; R^1 = CN, R^2 = Et, R^3 = R^4 = H
k; R^1 = CN, R^2 = Et, R^3 = H, R^4 = tosyl
l; R^1 = CN, R^2 = R^4 = H, R^3 = Ph
m; R^1 = CN, R^2 = H, R^3 = Ph, R^4 = mesyl

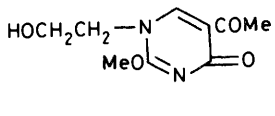
of compounds when heated with cyclohexylamine in methanol or acetonitrile solution.

The reaction of 2-aminobutan-1-ol with a α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (**3c**) gave the cyanouracil (**2j**) which was readily converted into the 6-cyano-oxazolopyrimidine (**1e**) *via* the tosyloxy derivative (**2k**). In contrast to the aforementioned 6-acyloxazolopyrimidine derivatives, the reaction of compound (**1e**) with cyclohexylamine readily gave an excellent yield of a single crystalline product, which was shown to be an adduct with one molecule of amine; similar

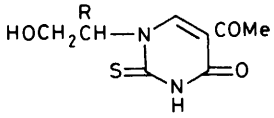


(3)

a; R = COMe
b; R = $CONHCO_2Et$
c; R = CN



(4)



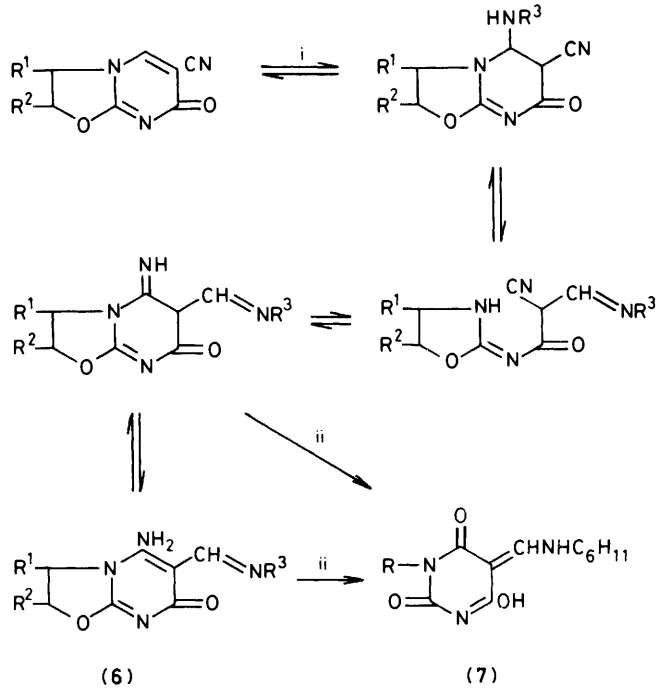
(5)

a; R = H
b; R = Et

adducts were obtained from the 6-cyano compound (**1e**) with n-butylamine and benzylamine. In a similar manner the reaction of α-cyano-β-ethoxy-*N*-ethoxycarbonylacrylamide (**3c**) with 2-amino-1-phenylethan-1-ol produced the uracil (**2l**), the methanesulphonate (**2m**) and the oxazolopyrimidine (**1f**); compound (**1f**) reacted readily with cyclohexylamine to give a 1 : 1 adduct in high yield, and adducts of the oxazolopyrimidine (**1g**) with cyclohexylamine, butylamine, and benzylamine were similarly produced.

It was soon discovered that none of the adducts were isocytosines as their i.r. spectra showed no absorption in the 2 200 cm^{-1} region indicating that there are no cyano groups present. Moreover, when the addition product of compound (**1e**) and cyclohexylamine was heated for 15 min in aqueous acetonitrile, ammonia was evolved and a good yield (75%) of a crystalline compound was isolated, the elemental analysis of which suggested that it had been produced by the addition of two moles of water and the elimination of ammonia; this was confirmed by high resolution mass spectrometry. The analytical and spectroscopic data suggest that the addition product is the oxazolopyrimidine (**6a**) produced by the initial addition of cyclohexylamine to the 5,6-double bond of the oxazolopyrimidine (**1e**), followed by a rearrangement involving opening of the uracil ring system and closure in the manner outlined in the Scheme. Hydrolysis of the resulting amino-oxazolopyrimidine (**6a**) then leads to the barbituric acid derivative (**7a**), whose structure was confirmed by the elemental analysis, the ^1H n.m.r. spectra, and independent synthesis.

The singlet (δ 8.78) due to 5-H in the oxazolopyrimidine (**1e**) also appears as a singlet (δ 8.4) in the adduct (**6a**), and neither signal exchanges with D_2O. However, in $(CD_3)_2SO$ the same signal in the acid (**7a**) appears as a doublet [δ 8.23 (*J*, 14 Hz, 1 H, C*H*NH)] which on treatment with D_2O is replaced by a one-proton singlet (δ 8.16); compound (**7a**) also shows two signals [δ 10.2 (1 H, br HOC=N) and 10.6 (1 H, CHN*H*)] each of which exchanged in D_2O. The data suggests that in $(CD_3)_2SO$, compound (**7a**) is best represented as the enol (lactim) form with hydrogen bonding of the hydroxy hydrogen to the basic centre in the 5 position and this is consistent with earlier structural assignments[6,7] of related compounds. In support of this it is noteworthy that when a basic group is absent, as with 1-methylbarbituric[8] acid and 5-benzylidenebarbituric acid,[9] the ^1H n.m.r. spectra show a one-proton singlet and two one-proton singlets, respectively, which exchange with D_2O and are readily assigned to the ring NH protons. The absence of lactim forms in barbituric acid derivatives similar to these compounds has also been noted elsewhere.[10] Interestingly, however, in $CDCl_3$ the



(6)

a; R^1 = Et, R^2 = H, R^3 = C_6H_{11}
b; R^1 = Et, R^2 = H, R^3 = nBu
c; R^1 = Et, R^2 = H, R^3 = CH_2Ph
d; R^1 = R^2 = H, R^3 = nBu
e; R^1 = R^2 = H, R^3 = CH_2Ph
f; R^1 = Me, R^2 = H, R^3 = C_6H_{11}
g; R^1 = Me, R^2 = H, R^3 = nBu
h; R^1 = Me, R^2 = H, R^3 = CH_2Ph
i; R^1 = Ph, R^2 = H, R^3 = C_6H_{11}

(7)

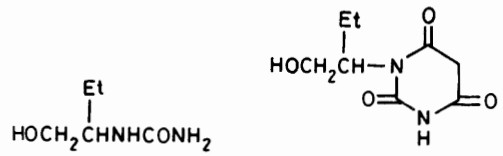
a; R = $CH(Et)CH_2OH$
b; R = Me
c; R = $CH_2CHOHCH_3$
d; R = H

(8)

Scheme. *Reagents:* i, R^3NH_2; ii, H_2O

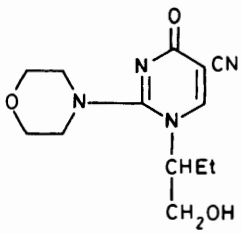
^1H n.m.r. spectrum of compound (**7a**) shows that the doublet noted at δ 8.23 in $(CD_3)_2SO$ is replaced by two doublets [δ 8.15 (J < 2 Hz)] and [δ 8.3 (J < 2 Hz)] each integrating to one proton. With D_2O the two doublets are replaced by a one-proton doublet [δ 8.2 (J < 2 Hz)]. This suggests that in $CDCl_3$ the imino form (**8**) is the major tautomer. The splitting of this signal in the imine (**8**) may result from coupling of the methylidene proton with one of the cyclohexyl protons which are closer in (**8**) than in the amine (**7a**). In the analogous compound (**6a**) the corresponding signal is not split in either $(CD_3)_2SO$ or $CDCl_3$ and this may be due to hydrogen bonding of the methylidene proton with the (non-enolisable) ring carbonyl keeping it away from the cyclohexyl group. Confirmation of these assignments has come from a synthesis of the amine (**7a**) and related compounds. Thus, 5-cyclohexylaminomethylene-1-methylbarbituric acid (**7b**) was prepared by a standard procedure[6,7] from 1-methylbarbituric acid with triethyl orthoformate and cyclohexylamine.

The ^1H n.m.r. spectrum of compound (**7b**) was almost identical with that of (**7a**), the only difference being in the assignment of the *N*-alkyl-substituent protons. In particular, the characteristic one-proton doublet [δ 8.3 (J 14 Hz)] collapsed to a singlet (δ 8.19) in D_2O. The barbituric acid (**7a**) was also synthesised by reaction of the urea (**9**) with diethyl



(9)

(10)



(11)

malonate and sodium ethoxide to produce the triketone (**10**) which, on treatment with triethyl orthoformate followed by cyclohexylamine, gave the methylene compound (**7a**), identical with the compound prepared as outlined above. The urea (**9**) was obtained as a crystalline solid by the reaction of 2-aminobutan-1-ol with silicon tetra-isocyanate[11] and hydrolysis of the intermediate compound with aqueous propan-2-ol.

In a similar manner, 5-cyclohexylaminobarbituric acid (**7d**) was obtained from barbituric acid, triethyl orthoformate, and cyclohexylamine. In this case the ^{1}H n.m.r. spectrum showed a doublet [δ 8.25 (*J* 14 Hz, 1 H, C*H*NH)] which was replaced in D_2O by a one-proton singlet (δ 8.2), and two signals at δ 10.9 (1 H, br HOC=N) and 11.22 (2 H, m, CONHCO and CHNH), each of which exchanged in D_2O.

In contrast to the reaction of the cyano compound (**1e**) with primary amines, the reaction with morpholine produced a 1:1 molecular adduct, the i.r. spectrum of which had an absorption band at 2 238 cm^{-1} characteristic of a cyano group; the spectral properties of the compound suggest that it has the isocytosine structure (**11**). This observation adds weight to the proposed mechanism outlined in the Scheme as such a route would not be available to a secondary amine adduct.

Experimental

Evaporations were carried out with a Buchi rotary evaporator, under a water-pump vacuum with a flask temperature of < 40 °C, unless otherwise stated. U.v. absorption spectra were measured with a Unicam SP 800 spectrophotometer, ^{1}H n.m.r. spectra with a Varian EM390 90 MHz spectrometer (tetramethylsilane as internal standard), and mass spectra with an A.E.I. MS 902 spectrometer. Silica gel $60F_{254}$ 0.25 mm precoated glass plates (Merck) were used for t.l.c. with **A** chloroform–methanol (9:1) or **B** n-butanol–acetic acid–water (12:3:5) as development systems. Ether refers to diethyl ether.

General Methods.—Uracils, tosyl(or mesyl)oxyalkyuracils, and the derived oxazolo[3,2-*a*]pyrimidines were prepared by the following general methods.

Uracils. A mixture of α-acetyl(or α-cyano or α-ethoxycarbonylcarbamoyl)-β-ethoxy-*N*-ethoxycarbonylacrylamide (0.02 mol), a primary alkanolamine (0.02 mol), and water (20 ml) was heated on a steam-bath for 5—10 min. The cooled solution was acidified with 10M-hydrochloric acid and the precipitate collected. 5-*Acetyl*-1-(1-*ethyl*-2-*hydroxyethyl*)*uracil* (**2d**) (72%) crystallised from ethanol as needles, m.p. 203—204 °C (Found: C, 53.05; H, 6.2; N, 12.55%; M^+, 226. $C_{10}H_{14}N_2O_4$ requires C, 53.1; H, 6.25; N, 12.4%; *M*, 226); $\lambda_{max.}$(EtOH) 231 and 287 nm; when heated with benzaldehyde and sodium hydroxide in aqueous ethanol for 5 min it produced, on acidification, 5-*cinnamoyl*-1-(1-*ethyl*-2-*hydroxyethyl*)*uracil* (**2f**) (96%) as needles (from methanol), m.p. 250 °C (Found: C, 65.1; H, 5.45; N, 8.95%; M^+, 314. $C_{17}H_{18}N_2O_4$ requires C, 64.95; H, 5.8; N, 8.9%; *M*, 314); $\lambda_{max.}$(EtOH) 231 and 324 nm; 5-*ethoxycarbonylcarbamoyl*-1-(1-*ethyl*-2-*hydroxyethyl*)*uracil* (**2h**) (76%), as needles (from methanol), m.p. 228—229 °C (Found: C, 48.15; H, 5.85; N, 14.05%; M^+, 299. $C_{12}H_{17}N_3O_6$ requires C, 48.15; H, 5.7; N, 14.05%; *M*, 299), $\lambda_{max.}$(EtOH) 227 and 287 nm; 5-*cyano*-1-(1-*ethyl*-2-*hydroxyethyl*)*uracil* (**2j**) (95%), as needles (from aqueous ethanol), m.p. 231—233 °C (Found: C, 51.4; H, 5.35; N, 20.15%; M^+, 209. $C_9H_{11}N_3O_3$ requires C, 51.65; H, 5.3; N, 20.1%; *M*, 209), $\lambda_{max.}$(pH 1) 221, 278; $\lambda_{max.}$(pH 7) 220, 280; $\lambda_{max.}$(pH 12) 218, 280 nm; 5-*cyano*-1-(2-*hydroxy*-2-*phenylethyl*)*uracil* (**2l**) (93%) as needles (from aqueous ethanol), m.p. 250 °C (Found: C, 60.4; H, 4.3; N, 16.05%; M^+, 257. $C_{13}H_{11}N_3O_3$ requires C, 60.7; H, 4.3; N, 16.35%; *M*, 257).

Tosyl(or mesyl)oxyalkyluracils.—A suspension of the 1-hydroxyalkyluracil (0.01 mol) in dry pyridine (10 ml) was shaken with toluene-4-sulphonyl (or methanesulphonyl) chloride (0.012 mol) and the resultant solution set aside overnight at room temperature then poured into cold water (50 ml) and the solid precipitate collected. The following were thus prepared 5-*Acetyl*-1-(2-*tosyloxyethyl*)*uracil* (**2b**) (58%) separated from ethanol as needles, m.p. 165—167 °C (Found: C, 51.25; H, 4.35; N, 7.85. $C_{15}H_{16}N_2O_6S$ requires C, 51.15; H, 4.55; N, 7.95%); $\lambda_{max.}$(EtOH) 227 and 285 nm. 5-*Acetyl*-1-(2-*mesyloxyethyl*)*uracil* (**2c**) (72%), as needles (from ethanol), m.p. 135—137 °C (Found: C, 39.25; H, 4.35; N, 10.1. $C_9H_{12}N_2O_6S$ requires C, 39.25; H, 4.4; N, 10.15%); $\lambda_{max.}$(EtOH) 225 and 280 nm. 5-*Acetyl*-1-(1-*ethyl*-2-*tosyloxyethyl*)*uracil* (**2e**) (77%) as needles (from ethanol), m.p. 165—167 °C (Found: C, 53.85; H, 5.35; N, 7.35%; M^+, 380. $C_{17}H_{20}N_2O_6S$ requires C, 53.7; H, 5.3; N, 7.35%; *M*, 380); $\lambda_{max.}$(EtOH) 229 and 283 nm. 5-*Cinnamoyl*-1-(1-*ethyl*-2-*mesyloxyethyl*)*uracil* (**2g**) (76%) as needles (from methanol), m.p. 167—168 °C (Found: C, 54.7; H, 5.05; N, 7.25. $C_{18}H_{20}N_2O_6S$ requires C, 55.1; H, 5.15; N, 7.15%); $\lambda_{max.}$(EtOH) 234 and 322 nm. 5-*Ethoxycarbonylcarbamoyl*-1-(1-*ethyl*-2-*mesyloxyethyl*)*uracil* (**2i**) (84%) (Found: C, 41.5; H, 5.25; N, 11.15; S, 8.35. $C_{13}H_{19}N_3O_8S$ requires C, 41.35; H, 5.10; N, 11.15; S, 8.50%); $\lambda_{max.}$(EtOH) 220 and 280 nm. 5-*Cyano*-1-(1-*ethyl*-2-*tosyloxyethyl*)*uracil* (**2k**) (72%) as needles (from ethanol), m.p. 172 °C (Found: C, 52.8; H, 4.8; N, 11.45%; M^+, 363. $C_{16}H_{17}N_3O_5S$ requires C, 52.9; H, 4.7; N, 11.55%; *M*, 363).

Oxazolo[3,2-a]*pyrimidines.*—A suspension of the 4-tolylsulphonyl- (or methylsulphonyl-)oxyalkyluracil (1.5—2.0 g) in acetone (50—75 ml) with triethylamine (4—6 ml) was heated under reflux for 2 h. The solution was evaporated to about half volume and the precipitated crystalline solid collected. The following compounds were thus prepared. 6-*Acetyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolopyrimidine* (**1a**) (96%) crystallised from methanol as needles or from acetone as plates, m.p. 188—190 °C (Found: C, 53.0; H, 4.5; N, 15.25%; M^+, 180. $C_8H_8N_2O_3$ requires C, 53.35; H, 4.45; N, 15.55%; *M*, 180); a suspension of compound (**1a**) (0.5 g) in methanol (10 ml) containing cyclohexylamine (0.35 g) was boiled under reflux for 1 h. The bright yellow solution was evaporated to an orange gum, t.l.c. examination of which (systems A and B) showed the presence of seven almost equally intense u.v. absorbing compounds. It was not examined further. 6-*Acetyl*-3-*ethyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolo*[3,2-a]*pyrimidine* (**1b**) (82%) as needles (from methanol), m.p. 143—145 °C. (Found: C, 57.75; H, 5.85; N, 13.35%; M^+, 208. $C_{10}H_{12}N_2O_3$ requires C, 57.7; H, 5.8; N, 13.45%; *M*, 208) (with cyclohexylamine a complex mixture was produced). 5-*Cinnamoyl*-3-*ethyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolo*[3,2-a]-

pyrimidine (**1c**) (66%) as needles (from methanol), m.p. 250 °C (Found: C, 69.25; H, 5.4; N, 9.65%; M^+, 296. $C_{17}H_{16}N_2O_3$ requires C, 68.9; H, 5.45; N, 9.45% *M*, 296). 6-*Ethoxycarbonylcarbamoyl*-3-*ethyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolo*[3,2-a]*pyrimidine* (**1d**) (54%) as needles (from methanol), m.p. 178—179 °C (Found: C, 51.25; H, 5.25; N, 15.1%; M^+, 281. $C_{12}H_{15}N_3O_5$ requires C, 51.25; H, 5.4; N, 14.95%; *M*, 281). 6-*Cyano*-3-*ethyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolo*[3,2-a]*pyrimidine* (**1e**) (40%) as needles (from methanol), m.p. 196—198 °C (Found: C, 56.35; H, 4.85; N, 22.1%; M^+, 191. $C_9H_9N_3O_2$ requires C, 56.55; H, 4.75; N, 22.0%; *M*, 191); δ [$(CD_3)_2SO$] 0.88 (3 H, t, CH_3), 1.70—2.0 (2 H, m, $MeCH_2$), 4.44—4.85 (3 H, m, $CHCH_2O$), and 8.78 (1 H, s). 6-*Cyano*-2,3-*dihydro*-7-*oxo*-2-*phenyl*-7H-*oxazolo*[3,2-a]*pyrimidine* (**1f**) (29%) as plates (from methanol), m.p. 208—210 °C (Found: C, 65.65; H, 3.95; N, 17.65%; M^+, 239. $C_{13}H_9N_3O_2$ requires C, 65.5; H, 3.8; N, 17.55%; *M*, 239).

5-*Acetyl*-1,4-*dihydro*-1-(2-*hydroxyethyl*)-2-*methoxypyrimidin*-4-(1H)-*one* (**4**).—A suspension of the 6-acetyl-7-oxo-oxazolo[3,2-*a*]pyrimidine (**1a**) (0.25 g) in dry methanol (10 ml) with triethylamine (3 ml) was heated under reflux for 30 min. The solution was cooled when a solid separated. The *pyrimidinone* (**4**) (0.2 g) recrystallised from methanol as needles, m.p. 154—156 °C (Found: C, 50.7; H, 5.7; N, 13.2%; M^+, 212. $C_9H_{12}N_2O_4$ requires C, 50.95; H, 5.7; N, 13.2%; *M*, 212); $\lambda_{max.}$ (EtOH) 237 and 282 nm.

5-*Acetyl*-1-(2-*hydroxyethyl*)-2-*thiouracil* (**5a**).—A suspension of compound (**1a**) (2.0 g) in methanol (50 ml) containing triethylamine (8 ml) was saturated with hydrogen sulphide then set aside at room temperature with occasional shaking until a clear yellow solution was obtained (*ca.* 3 h); this was then evaporated to a yellow solid. 5-*Acetyl*-1-(2-*hydroxyethyl*)-2-*thiouracil* (1.5 g) recrystallised from methanol as needles, m.p. 229—231 °C (Found: C, 44.9; H, 4.55; N, 13.10%; M^+, 214. $C_8H_{10}N_2O_3S$ requires C, 44.85; H, 4.7; N, 13.1%; *M*, 214). Similarly 5-*acetyl*-1-(1-*ethyl*-2-*hydroxyethyl*)-2-*thiouracil* (**5b**) (0.9 g) crystallised from methanol as needles, m.p. 214—216 °C (Found: C, 49.35; H, 5.65; N, 11.6; S, 13.0%; M^+, 242. $C_{10}H_{14}N_2O_3S$ requires C, 49.6; H, 5.8; N, 11.55; S, 13.2%; *M*, 242).

5-*Amino*-6-*cyclohexyliminomethyl*-3-*ethyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolo*[3,2-a]*pyrimidine* (**6a**).—Compound (**1e**) (2.0 g) was suspended in methanol (50 ml) containing cyclohexylamine (1.2 g) and the mixture was refluxed for 2 h. The clear solution was cooled and evaporated to an orange gum; this was dissolved in a little methanol and ether was added until turbidity was achieved. A white solid (1.9 g) slowly separated. The *oxazolopyrimidine* recrystallised from methanol–ether as needles, m.p. 175—177 °C (Found: C, 61.7; H, 7.75; N, 19.1%; M^+, 290. $C_{15}H_{22}N_4O_2$ requires C, 62.05; H, 7.65; N, 19.30%; *M*, 290); δ[$(CD_3)_2SO$] 0.8 (3 H, t, CH_3), 1.01—2.1 (12 H, m, C_6H_{10} and $MeCH_2$), 3.12 (1 H, m, $CHCH_2CH_2$), 3.25 (2 H, s, NH_2 exch. with D_2O), 4.5—4.8 (3 H, m, CH_2O, $CHEt$), and 8.4 (1 H, s, CH=N); δ($CDCl_3$) 0.98 (3 H, t, CH_3), 1.1—2.1 (12 H, m, C_6H_{10} and $MeCH_2$), 3.26 (2 H, br, NH_2 exch. with D_2O with difficulty), 4.3—4.8 (3 H, m, CH_2O, $CHEt$), and 8.4 (H, s, CH=N).

In a similar manner were prepared 5-*amino*-6-*butyliminomethyl*-3-*ethyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolo*[2,3-a]*pyrimidine* (**6b**) as needles from methanol (40%), m.p. 222—224 °C (decomp.) (Found: C, 59.1; H, 7.45; N, 21.45%; M^+, 264. $C_{13}H_{20}N_4O_2$ requires C, 59.1; H, 7.65; N, 21.2%; *M*, 264) and 5-*amino*-6-*benzyliminomethyl*-3-*ethyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolo*[3,2-a]*pyrimidine* (**6e**) (80%) as needles (from aqueous methanol), m.p. 170 °C (Found: C, 64.6; H, 6.15; N, 18.85%; M^+, 298. $C_{16}H_{18}N_4O_2$ requires C, 64.4; H, 6.1; N, 18.8%; *M*, 298).

From 6-cyano-2,3-dihydro-7-oxo-7*H*-oxazolo[3,2-*a*]pyrimidine with n-butylamine was obtained 5-*amino*-6-*n-butyliminomethyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolo*[3,2-a]*pyrimidine* (**6d**) (55%) as needles (from methanol–ether), m.p. 217—218 °C (Found: C, 56.1; H, 7.1; N, 23.8% M^+, 236. $C_{11}H_{16}N_4O_2$ requires C, 55.95; H, 6.8; N, 23.75%; *M*, 236) and with benzylamine was obtained 5-*amino*-6-*benzyliminomethyl*-2,3-*dihydro*-7-*oxo*-7H-*oxazolo*[3,2-a]*pyrimidine* (**6e**) (30%) as needles (from methanol), m.p. 200—202 °C (Found: C, 61.9; H, 5.25; N, 20.8%; M^+, 270. $C_{14}H_{14}N_4O_2$ requires C, 62.2; H, 5.2; N, 20.75%; *M*, 270). From 6-cyano-2-methyl-2,3-dihydro-7-oxo-7*H*-oxazolo[3,2-*a*]pyrimidine and cyclohexylamine was obtained 5-*amino*-6-*cyclohexyliminomethyl*-2,3-*dihydro*-2-*methyl*-7-*oxo*-7H-*oxazolidono*[3,2-a]*pyrimidine* (**6f**) (75%) as needles (from ethanol–ethyl acetate), m.p. 232—234 °C (Found: C, 60.55; H, 7.05; N, 20.1%; M^+, 276. $C_{14}H_{20}N_4O_2$ requires C, 60.85; H, 7.30; N, 20.3%; *M*, 276), from n-butylamine was obtained 5-*amino*-6-*butyliminomethyl*-2,3-*dihydro*-2-*methyl*-7-*oxo*-7H-*oxazolo*[3,2-a]*pyrimidine* (**6g**) (50%) as needles (from methanol), m.p. 214—216 °C (Found: C, 57.9; H, 7.15; N, 22.3%; M^+, 250. $C_{12}N_{18}N_4O_2$ requires C, 57.6; H, 7.2; N, 22.4%; *M*, 250), and from benzylamine was obtained 5-*amino*-6-*benzyliminomethyl*-2,3-*dihydro*-2-*methyl*-7-*oxo*-7H-*oxazolo*[3,2-a]-*pyrimidine* (**6h**) (45%) as needles (from methanol), m.p. 212—213 °C (Found: C, 63.0; H, 5.9; N, 19.75%; M^+, 284. $C_{15}H_{16}N_4O_2$ requires C, 63.4; H, 5.65; N, 19.7%; *M*, 284).

5-*Amino*-6-*cyclohexyliminomethyl*-2,3-*dihydro*-2-*phenyl*-7-*oxo*-7H-*oxazolo*[3,2-a]*pyrimidine* (**6i**).—Compound (**1f**) (2.0 g) was suspended in methanol (50 ml) containing cyclohexylamine (0.95 g) and the mixture refluxed for 2 h. The clear solution was cooled and evaporated to half volume when crystals slowly separated. The *oxazolopyrimidine* (**6i**) (1.1 g) crystallised from a large volume of methanol as small prisms, m.p. 202—203 °C (Found: C, 67.1; H, 6.6; N, 16.55%; M^+, 338 $C_{19}H_{22}N_4O_2$ requires C, 67.45; H, 6.55; N, 16.55%; *M*, 338).

5-*Cyclohexylaminomethylene*-1-(1-*ethyl*-2-*hydroxyethyl*)-*barbituric Acid* (**7a**).—(*a*) A suspension of 5-amino-6-cyclohexyliminomethyl-3-ethyl-2,3-dihydro-7-oxo-7*H*-oxazolo-[3,2-*a*]pyrimidine (0.5 g) in water (20 ml) containing acetonitrile (2 drops) was heated on a water-bath for 30 min. The resulting clear solution was evaporated to a solid. The *barbituric acid derivative* (0.2 g) recrystallised from water as rods, m.p. 163—164 °C (Found: C, 58.15; H, 7.5; N, 13.65%; M^+ 309. $C_{15}H_{23}O_3O_4$ requires C, 58.25; H, 7.50; N, 13.6%; *M*, 309); *m/z* 309.167 68 (*M*), 278.152 77 ($M - CH_2OH$); $\lambda_{max.}$(pH 1) 228, 288; $\lambda_{max.}$(pH 7) 228, 287; $\lambda_{max.}$(pH 12) 230, 307 nm; δ[$(CD_3)_2SO$] 0.76 (3 H, t, CH_3), 1.03—2.10 (12 H, m, C_6H_{10} and $MeCH_2$), 3.26—4.0 (3 H, m, CH_2OH and $CHCH_2CH_2$), 4.47—4.86 (2 H, m, $CHCH_2OH$, one proton exch. with D_2O), 8.23 [(1 H, d, *CH*NH); after treatment with D_2O δ 8.16 (1 H, s)], 10.2 [(1 H, br, C(OH)=N) exch. with D_2O], 10.6 (1 H, m, CHN*H*, exch. with D_2O); δ($CDCl_3$) 0.9 (3 H, t, CH_3), 1.15—2.15 (12 H, m, C_6H_{10} and $MeCH_2$), 3.3 (1 H, br), 3.5—4.2 (3 H, m, CH_2OH and $CHCH_2CH_2$), 4.7—5.1 (2 H, m, $CHCH_2OH$, one proton exch. with D_2O), 8.15 (1 H, d, $J < 2.0$ Hz, *CH*CH=N), and 8.3 (1 H, d $J < 2.0$ Hz, CH*CH*=N); with D_2O the latter two signals occur at δ 8.2 (1 H, d, $J < 2.0$ Hz, CH=N) and 10.3 [1 H, br, C(OH)=N, exch. with D_2O].

(*b*) A solution of 2-aminobutan-1-ol (2.745 g) in dried benzene (18 ml) was added dropwise to a solution of silicon tetraisocyanate[11] (5.382 g) in benzene (48 ml). The mixture was heated under reflux for 30 min, then evaporated to dryness. Aqueous propan-2-ol (50 ml; 9:1 Pr^iOH–H_2O) was added to the residue and the mixture refluxed for 40 min, then filtered hot through Celite and washed with acetone, and the combined filtrates evaporated to a white solid. The N-(1-*ethyl*-2-

hydroxyethyl)urea (**9**) (6.4 g, 87%), m.p. 40 °C, was dried over P_2O_5 during 4 days (Found: C, 45.2; H, 9.35; N, 21.0%; M^+, 132. $C_5H_{12}N_2O_2$ requires C, 45.45; H, 9.15; N, 21.2%; *M*, 132); δ [$(CD_3)_2SO$] 0.82 (3 H, t, CH_3), 1.05—1.67 (2 H, m, CH_3CH_2), 3.03—3.53 (2 H, m, CH_2OH), 4.6 (1 H, br, OH exch. with D_2O), 5.38 (2 H, s, NH_2 exch. with D_2O with difficulty), and 5.73 (1 H, d, NH exch. with D_2O with difficulty).

A solution of the urea (2.25 g), diethyl malonate (2.8 g), and sodium (0.4 g) in ethanol (15 ml) was boiled under reflux for 4 h then evaporated to dryness. The residue was dissolved in the minimum amount of water, acidified carefully with hydrochloric acid, and cooled to give a solid precipitate; *1-(1-ethyl-2-hydroxyethyl)barbituric acid* (0.25 g) had m.p. > 200 °C (Found: C, 47.7; H, 6.2; N, 14.4. $C_8H_{12}N_2O_4$ requires C, 48.0; H, 6.0; N, 14.0%). The barbituric acid (0.2 g) with triethyl orthoformate (0.3 g) and DMF (1.5 ml) was heated at 50 °C during 2 h and the mixture treated with cyclohexylamine (0.1 g) heated to reflux for 3 h, then evaporated to dryness under reduced pressure. The residue with water gave a solid precipitate. The barbituric acid derivative crystallised from water as rods, m.p. and mixed m.p. 164 °C.

6-Cyclohexylaminomethylene-1-(2-hydroxypropyl)barbituric Acid (**7c**).—A suspension of 5-amino-6-cyclohexyliminomethyl-2,3-dihydro-2-methyl-7-oxo-7*H*-oxazolo[3,2-*a*]pyrimidine (**6f**) (0.5 g) in water (20 ml) and acetonitrile (2 drops) was heated on a steam-bath for 30 min, then evaporated to a solid. The *barbituric acid* (0.3 g) crystallised from water as rods, m.p. 210—212 °C (Found: C, 51.8; H, 6.25; N, 16.75%; *M*, 295. $C_{14}H_{21}N_3O_4$ requires C, 51.95; H, 6.3; N, 16.55%; *M*, 295); $\lambda_{max.}$ (pH 1) 234, 290; $\lambda_{max.}$(pH 7) 234, 290; $\lambda_{max.}$(pH 12) 229, 302 nm; δ [$(CD_3)_2SO$] 4.7 (1 H, d, OH, exch. with D_2O), 8.3 [1 H, d, *J* 14 Hz, C*H*NH; with D_2O, δ 8.23 (1 H, s)], 9.9 [1 H, br, C(OH)=N, exch. with D_2O], and 10.2 (1 H, m, CHN*H* exch. with D_2O).

5-Cyclohexylaminomethylene-1-methylbarbituric Acid (**7b**).—1-Methylbarbituric acid[9] (3 g) and triethyl orthoformate (3.15 g) in DMF (15 ml) were stirred at 30 °C for 1 h then heated with cyclohexylamine (2.16 g) at 120—130 °C for 3 h. The solution was cooled to give a yellow solid precipitate. The *barbituric acid* (**7b**) (3.85 g) recrystallised from ethanol as needles, m.p. 200—204 °C (Found: C, 57.35; H, 6.75; N, 16.9%; M^+, 251. $C_{12}H_{17}N_3O_3$ requires C, 57.35; H, 6.85; N, 16.75%; *M*, 251); δ [$(CD_3)_2SO$] 1.0—2.03 (10 H, m, C_6H_{10}), 3.06, (3 H, s, CH_3), 3.4—3.76 (1 H, m, C*H*CH_2), 8.3 [1 H, d, C*H*NH; after treatment with D_2O, δ 8.19 (1 H, s)], 10.25 [1 H, br, C(OH)=N exch. with D_2O], and 10.9 (1 H, m, CHN*H*, exch. with D_2O).

5-Cyclohexylaminobarbituric Acid (**7d**).—Barbituric acid (3 g) and triethyl orthoformate (3.41 g) in dry DMF (15 ml) were stirred at 30 °C for 1 h then heated with cyclohexylamine (2.32 g) at 120—130 °C for 3 h. The mixture was cooled to produce a yellow precipitate. The *barbituric acid* crystallised from n-butanol as cream needles, m.p. 276—278 °C (Found: C, 55.85; H, 6.4; N, 17.6%; M^+, 237. $C_{11}H_{15}N_3O_3$ requires C, 55.7; H, 6.35; N, 17.7%; *M*, 237); δ[$(CD_3)_2SO$] 8.25 [1 H, d, C*H*NH; with D_2O, δ 8.2, (1 H, s)] 10.9 [1 H, br, C(OH)=N, exch. with D_2O], and 11.22 (2 H, m, CONH and CHN*H*, exch. with D_2O).

Ethyl N-[β-Ethoxy-α-(N-ethoxycarbonylcarbamoyl)acryloyl]carbamate (**3b**).—A mixture of malonic acid (10.4 g) and ethyl carbamate (17.8 g) were heated together to 70 °C. Acetic anhydride (20.4 g) was added and the mixture maintained at 70 °C for 3 h to produce a viscous solution. This was cooled and diluted with benzene to precipitate *N,N'*-(ethoxycarbonyl)-malonamide (11.1 g, 45%), m.p. 125 °C (lit.,[5] m.p. 124 °C). The malonamide (4.7 g) triethyl orthoformate (3.2 ml), and acetic anhydride (5 ml) were refluxed together for 1 h. The mixture solidified on cooling. *Ethyl N-[β-ethoxy-α-(N-ethoxycarbonylcarbamoyl)acryloyl]carbamate* (4.53 g, 76%) recrystallised from benzene as needles, m.p. 120 °C (Found C, 47.8; H, 6.1; N, 9.1%; M^+, 302. $C_{12}H_{18}N_2O_7$ requires C, 47.7; H, 6.0; N, 9.25%; *M*, 302).

5-Cyano-1-(1-ethyl-2-hydroxyethyl)-2-morpholinopyrimidin-4-(1H)-one (**11**).—A suspension of compound (**1e**) (1.5 g) in acetonitrile (20 ml) and morpholine (0.74 g) was boiled under reflux for 11 h then cooled to give a solid precipitate. The *pyrimidinone* (1.12 g) crystallised from acetonitrile as fine needles, m.p. 228—230 °C (Found: C, 55.9; H, 6.8; N, 20.5%; *M*, 278. $C_{13}H_{18}N_4O_3$ requires C, 56.1; H, 6.5; N, 20.15%; *M*, 278); $\nu_{max.}$ 2 238 cm^{-1} (CN); δ[$(CD_3)_2SO$] 0.8 (3 H, t, CH_3), 2.25—2.95 (6 H, m, CH_2NCH_2, *ax*-CHOCH), 3.4—3.63 (4 H, m, CH_2OH, *eq*-CHOCH), 4.2 (1 H, d, CH_2OH, exch. with D_2O), 4.42—4.86 (1 H, m, CH_2CH), and 8.68 (1 H, s, 6-H).

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