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Fused Pyrimidines. II.[1] Synthesis and Oxidation of 3-Aminoisothiazolo[3,4-*d*]pyrimidines

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Reaction of 6-aminouracils (I) with alkyl or aryl isothiocyanates afforded 6-amino-5-substituted thiocarbamoyluracils (II), which were oxidized with bromine or hydrogen peroxide to afford 3-(substituted)aminoisothiazolo[3,4-*d*]pyrimidin-4,6-(5H, 7H)-diones (III). Alkylation of III afforded 3-(N,N-disubstituted)amino derivatives (V). Further oxidation of 1,3-diethyl-3-dimethylamino- or -3-methylaminoisothiazolo[3,4-*d*]pyrimidin-4,6-(5H, 7H)-dione (Vb or IIIb) with hydrogen peroxide afforded 1,3-diethyl-5-alkylcarbamoyl-5-hydroxybarbituric acid (Xa or Xb). Treatment of Xa with Raney nickel afforded 1,3-diethyl-5-dimethylcarbamoylbarbituric acid (XII).

In the previous paper,[1] the authors have reported a novel synthetic method of 3-aminoisothiazolo[3,4-*d*]pyrimidines. This paper deals with another synthetic method and an oxidation reaction of 3-aminoisothiazolo[3,4-*d*]pyrimidines.

Goerdeler and coworkers[3] have reported that phenyl isothiocyanates added to the 4-position of dimedon monoimide and that the oxidation of the adducts afforded benzthiazoles or 4,5,6,7-tetrahydro-2,1-benzisothiazoles depending on the substituents of the phenyl group. We applied this method to 6-aminouracils.

6-Amino-1-benzyluracil (Ia) and ethyl isothiocyanate were heated in pyridine to afford 6-amino-1-benzyl-5-ethylthiocarbamoyluracil (IIa) in good yield. The nuclear magnetic resonance (NMR) spectrum of IIa (absence of a proton at the 5-position) demonstrated that the isothiocyanate added to the 5-position of Ia. This fact is consistent with the findings that alkylation[4] and acylation[5] of 6-aminouracils took place at the 5-position rather than the amino group. Oxidation of IIa with bromine afforded 3-ethylamino-7-benzylisothiazolo-[3,4-*d*]pyrimidin-4,6(5H,7H)-dione (IIIa) in good yield.[6] The structure of IIIa was confirmed by its elemental analysis, ultraviolet (UV) (Fig. 2) and NMR spectra and by the fact that desulfurization with Raney nickel afforded 6-amino-1-benzyl-5-methyluracil (IV). Similar reactions of nine 6-aminouracils (Ib—k) with various alkyl, aryl or benzyl isothiocyanates afforded the corresponding adducts (IIb—k), which were oxidized with bromine or hydrogen peroxide to afford 3-(monosubstituted)aminoisothiazolo[3,4-*d*]pyrimidines (IIIb—k) (Chart 1, Tables I and II). In the above oxidative cyclization, bromine was superior to hydrogen peroxide when the products (III) were soluble in the reaction solvents, because further oxidation of III with hydrogen peroxide resulted in the degradation of the isothiazole ring (described

1) Y. Furukawa, O. Miyashita, and S. Shima, *Chem. Pharm. Bull.* (Tokyo), **24**, 970 (1976).
2) Location: *17–85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka.*
3) J. Goerdeler and U. Kenser, *Chem. Ber.*, **97**, 2209 (1964).
4) W. Pfleiderer, L. Grözinger, and F. Sági, *Chem. Ber.*, **99**, 3524 (1966); H. Ogura, M. Sakaguchi, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 404 (1972); Y. Tamura, T. Sakaguchi, T. Kawasaki, and Y. Kita, *Heterocycles*, **3**, 183 (1975).
5) W. Pfleiderer and G. Strauss, *Ann. Chem.*, **612**, 173 (1958); C.W. Noell and R.K. Robins, *J. Heterocycl. Chem.*, **1**, 34 (1964); H. Bredereck, F. Effenberger, and G. Simchen, *Chem. Ber.*, **97**, 1403 (1964); J.L. Shim, R. Niess, and A.D. Broom, *J. Org. Chem.*, **37**, 578 (1972); F. Yoneda and M. Higuchi, *Bull. Chem. Soc. Japan*, **46**, 3849 (1973).
6) After our experiments had finished, a similar reaction using acyl isothiocyanate was published.[7]
7) R. Niess and H. Eilingsfeld, *Ann. Chem.*, **1974**, 2019.

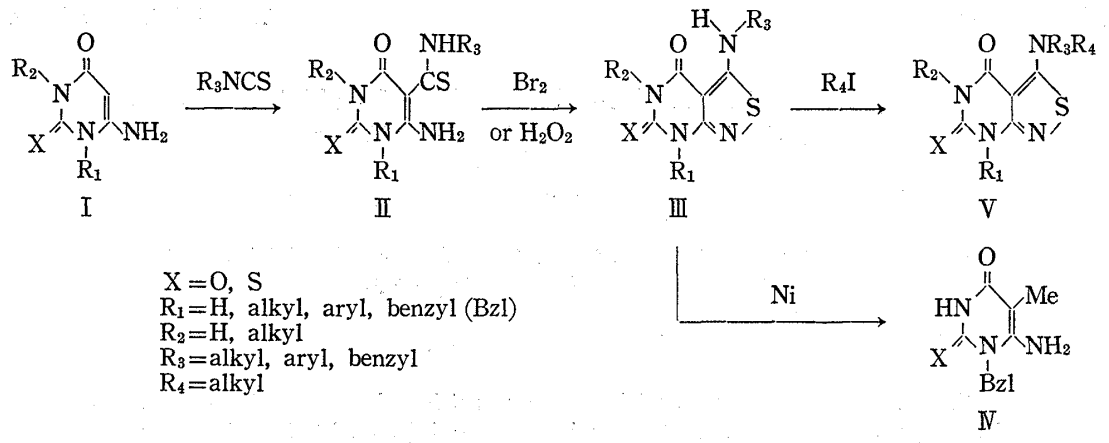


Chart 1

TABLE I. 6-Amino-5-substituted Thiocarbamoyluracils (II, X=O)

Series	R_1[a]	R_2	R_3	mp (°C) (Solvent)[b]	UV λ_{max}^{EtOH} (nm)	Formula[c]	NMR (d_6-DMSO) δ (ppm)	Yield (%)
a	Bzl	H	Et	287(C)	259 300	$C_{14}H_{16}O_2N_4S$	1.43 (3H, t), 3.8 (2H, m) 5.4 (2H, s), 7.5 (5H, s), 7.3, 10.6, 11.4, 12.6 (1H)	92
b	Et	Et	Me	185—190(E)	259 300	$C_{10}H_{16}O_2N_4S$		66
c	H	H	Et	>300(M)	259 300	$C_7H_{10}O_2N_4S$	1.33 (3H, t), 3.6 (2H, q), 4.5, 11.3, 12.4 (1H)	77
d	Me	H	*p*-Cl-Ph	>300(C)	260 312	$C_{12}H_{11}O_2N_4SCl$	3.46 (3H, s), 7.6 (4H, s) 8.66, 14.4 (1H,) 11.3 (2H)	89
e	*p*-Cl-Ph	H	Et	>300(C)	259 298	$C_{13}H_{13}O_2N_4SCl$	1.07 (3H, t), 3.45 (2H, q) 7.1—7.7 (4H, m), 11.15, 12.4 (1H)	62
f	$MeOCH_2$-CH_2–	H	Ph	235(E)	261 309	$C_{14}H_{16}O_3N_4S$	3.17 (3H, s), 3.46, 4.08 (2H, m), 7.0—7.6 (5H, m), 10.6, 11.2, 14.1 (1H)	69
g	Et	Et	*p*-OH-Ph	233—234(E)	260 308	$C_{15}H_{18}O_3N_4S$	0.7—1.4 (6H, m), 3.5—4.3 (4H, m), 6.4—7.4 (4H), 9.36, 13.86 (1H), 10.6 (2H)	66
h	Ph	H	Me	265—275(B)	258 298	$C_{12}H_{12}O_2N_4S$		79
i	iBu	H	Bzl	228—229(E)	258 301	$C_{16}H_{20}O_2N_4S$		63
j	Et	Et	*p*-Cl-Ph	201—203(E)	260 312	$C_{15}H_{17}O_2N_4SCl$		64
k	*p*-MeOPh	H	Et	290—295(C)	258 298	$C_{14}H_{16}O_3N_4S$		93

a) Me, methyl; Et, ethyl; Ph, phenyl; iBu, iso-butyl; Bzl, benzyl
b) recrystallization solvent: A, aq. ethanol; B, butanol; C, methylcellosolve; D, dioxane; E, ethanol; F, ether; M, methanol
c) Satisfactory elemental analyses (C, H, N, S, Cl) were obtained for all compounds of Table I—IV.

later). In case of dimedon imide, addition of alkyl isothiocyanate did not take place and benzthiazole ring was formed from the dimedon imide-phenyl isothiocyanate adducts when electronegative substituents were not attached to the phenyl group.[3] In contrast, addition of not only aryl isothiocyanate but also alkyl and benzyl isothiocyanate to I took place in high yield and the cyclization of the adducts proceeded to isothiazole exclusively even when the hydroxyl group was attached to the phenyl group (IIIg), though two side products having one or two bromine in the phenyl group (IIIg′, g″) were obtained.

Alkylation of III with methyl or ethyl iodide afforded 3-(N,N-disubstituted)amino derivatives (V), one of which (Vb) was reported in the previous paper (Table IV). When R_2 of III

TABLE II. 3-(Substd.)aminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H,7H)-diones (III)

Series	R_1[a]	R_2	R_3	mp (°C) (Solvent)[b]	UV λ_{max}^{EtOH} (nm)	Formula[c]	NMR (d_6-DMSO) δ (ppm)	Yield (%)
a	Bzl	H	Et	269(E)	229, 269, 292	$C_{14}H_{14}O_2N_4S$	1.40 (3H, t), 3.35 (2H, m), 5.3 (2H, s), 7.46 (5H, s), 8.2, 10.9 (1H)	93
b	Et	Et	Me	156—158(M)	233, 269, 291	$C_{10}H_{14}O_2N_4S$	1.13, 1.22 (3H, t), 2.92 (3H, d), 3.84, 3.96 (2H, q), 8.3 (1H)	86
c	H	H	Et	>300(M)	231, 268, 290	$C_7H_8O_2N_4S$	1.34 (3H, t), 3.55 (2H, m), 8.26, 10.77, 11.37 (1H)	90
d	Me	H	*p*-Cl-Ph	>300(C)	234, 284, 327	$C_{12}H_9O_2N_4SCl$	3.32 (3H, s), 7.1—7.55 (4H) 9.8, 10.8 (1H)[d]	70
e	*p*-Cl-Ph	H	Et	280—281(E)	230, 268, 292	$C_{13}H_{11}O_2N_4SCl$	1.04 (3H, t), 3.0 (2H, q), 7—7.7 (4H, m), 8.2, 11.0 (1H)	62
f	$MeOCH_2CH_2$	H	Ph	210—212(C)	232, 281, 324	$C_{14}H_{14}O_3N_4S$	3.22 (3H, s), 3.57, 4.08 (2H, t), 7—7.5 (5H, m), 10.02, 11.17 (1H)	73
g	Et	Et	*p*-OH-Ph	269—270(M)	232, 281, 334	$C_{15}H_{16}O_3N_4S$	1.10, 1.15 (3H, t), 3.83 (4H, m), 6.6—7.3 (4H), 9.54, 9.74 (1H)	23
g′	Et	Et	*p*-OH-Ph, Br	191—193(C)	236(s), 282, 332	$C_{15}H_{15}O_3N_4SBr$	1.25, 1.3 (3H, t), 3.96 (4H, m), 7—7.6 (3H, m), 9.86, 10.43 (1H)	27
g″	Et	Et	*p*-OH-Ph, Br_2	244—246(C)	234(s), 283, 321	$C_{15}H_{14}O_3N_4SBr_2$	1.0—1.5 (6H, m), 3.5—4.2 (4H, m), 7.55 (2H, s), 10.1 (2H)	12
h	Ph	H	Me	>300(C)	230, 268, 290	$C_{12}H_{10}O_2N_4S$		95
i	iBu	H	Bzl	215—217	228, 271, 290(s)	$C_{16}H_{18}O_2N_4S$		95[e]
j	Et	Et	*p*-Cl-Ph	182—185	235, 284, 328	$C_{15}H_{15}O_2N_4SCl$		90[e]
k	*p*-MeOPh	H	Et	290—295	227, 268, 293	$C_{14}H_{14}O_3N_4S$		95[e]

a), *b*), *c*) See Table I.
d) NMR spectrum was taken on a Hitachi HA-100 spectrometer (100 Mc) at 110°.
e) Method ii), see Experimental.

was hydrogen, it was alkylated in short time whereas alkylation of the amino group of the 3-position required longer reaction time, so that the selective alkylation on the N-5 position was possible (Table III). 6-Amino-1,3-diethyl-2-thiouracil (Is) was allowed to react in a similar manner to afford 3-methylamino- and 3-dimethylamino-1,3-diethylisothiazolo[3,4-*d*]-pyrimidin-4(5H)-one-6(7H)-thione (IIIs and Vs), the latter being obtained in only small yield by the reaction of Is with dimethylformamide (DMF)–thionyl chloride.[1]

Reaction of 6-amino-1-ethyl- or -1-phenylpyrimidin-4(1H)-one[8] (VIIa, b) with *p*-chlorophenyl isothiocyanate afforded 6-amino-5-(*p*-chlorophenyl)thiocarbamoyl-1-ethyl- or -1-phenylpyrimidin-4(1H)-one (VIIIa, b), but the oxidation of VIII with bromine or hydrogen peroxide did not give the expected isothiazolo[3,4-*d*]pyrimidines (IX) (Chart 2).

8) The NMR spectra of VIIa, b (presence of two protons corresponding to hydroxyl and imino groups, see Experimental) suggest that the compounds exist as the tautomeric forms (VII′), but the above nomenclature was adopted for convenience.

Table III. 3-(Substd.)aminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H,7H)-diones (III)

Series	R_1[a]	R_2	R_3	mp (°C) (Solvent)[b]	UV λ_{max}^{EtOH} (nm)	Formula[c]	NMR (d_6-DMSO) δ (ppm)	Yield (%)
l	Bzl	Me	Et	96—98(A)	235, 271, 303	$C_{15}H_{16}O_2N_4S$	1.34 (3H, m), 3.36 (3H, s), 3.8 (2H, q), 5.26 (2H, s), 7.2—7.6 (5H), 8 (1H)	86
m	*p*-Cl-Ph	Et	Et	231(E)	232, 269, 294	$C_{15}H_{15}O_2N_4SCl$	1.15, 1.37 (3H, t), 3.25, 4.05 (2H, q), 7.2—7.7 (4H)	92
n	Ph	Me	Me	>300(D)	231, 268, 292	$C_{13}H_{12}O_2N_4S$		87

a), b), c) See Table I.

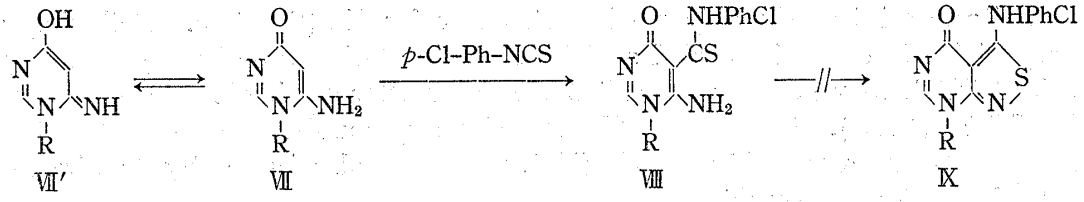
Table IV. 3-(N,N-Disubstd.)aminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H,7H)-diones (V)

Series	R_1[a]	R_2	R_3	R_4	mp (°C) (Solvent)[b]	UV λ_{max}^{EtOH} (nm)	Formula[c]	NMR ($CDCl_3$) δ (ppm)	Yield[d] (%)
a	Bzl	Me	Et	Me	117(E)	239, 277, 309	$C_{16}H_{18}O_2N_4S$	1.26 (3H, t), 3.15, 3.35 (3H, s), 3.8 (2H, q), 5.26 (2H, s), 7.0—7.6 (5H)	91 (IIIa)
b	Et	Et	Me	Me	90—91(M)	235, 278, 308	$C_{11}H_{16}O_2N_4S$	1.1—1.55 (6H), 3.36 (6H, s), 4.3—5.0 (4H)	85 (IIIb)
d	Me	Me	*p*-Cl-Ph	Me	150—151(A)	213, 283, 325	$C_{14}H_{13}O_2N_4SCl$	3.27, 3.5, 3.66 (3H, s), 7.0—7.5 (4H)	92 (IIId)
e	*p*-Cl-Ph	Et	Et	Et	127—128(F)	234, 275, 311	$C_{19}H_{24}O_2N_4SCl$	1.0—1.5 (9H), 3.5—4.3 (6H), 7.1—7.7 (4H)	60 (IIIe)
f	$MeOCH_2CH_2$	Me	Ph	Me	122(M)	212, 283, 324	$C_{16}H_{18}O_2N_4S$	3.35, 3.40 (3H, s), 3.5—4.0 (5H), 4.4 (2H, m), 7.0—7.7 (5H)	70 (IIIf)
h	Ph	Me	Me	Me	155—156(E)	230, 276, 308	$C_{14}H_{14}O_2N_4S$	3.0—3.6 (9H), 7.44 (5H, s)	68 (IIIh)
i	iBu	Me	Bzl	Me	121—123(E)	234, 274, 303	$C_{18}H_{22}O_2N_4S$	1.05 (6H, d), 2.1—2.7 (1H, m), 3.2 (3H, s), 3.48 (3H, s), 4.0 (2H, m), 5.2 (2H, s), 7.4 (5H)	78 (IIIi)

a), b), c) See Table I.
d) Starting materials were shown in parentheses.

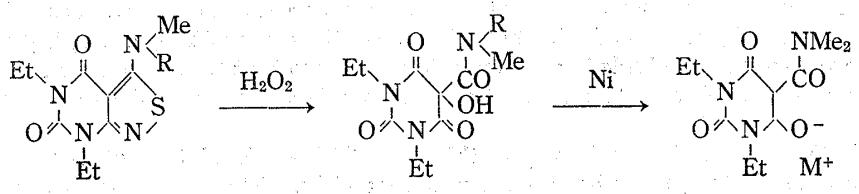
In an attempt to synthesize the sulfones of III and V, Vb was treated with hydrogen peroxide in acetic acid at room temperature to afford a compound (Xa) which contained no sulfur. The molecular formula of Xa was determined as $C_{11}H_{17}O_5N_3$ on the basis of its elemental analysis and mass spectrum (M^+=271), and its NMR spectrum demonstrated one proton at δ 7.32 (disappeared on addition of D_2O) as well as two methyl and two ethyl protons. These data suggested four possible structures (A, B, C and D) for Xa. The IR spectrum (Nujol) of Xa showed no band of N-oxide (950—970 cm^{-1}) and the UV spectrum of Xa (λ_{max}^{MeOH} 230 nm) was quite different from that [λ_{max}^{EtOH} 234 (s), 336 nm] of a known compound[9] (XI) which has a conjugated system similar to that of A. Compound Xa was resistant to catalytic reduction over Raney nickel and to reduction with zinc–acetic acid at reflux temperature. These results excluded the three structures (A, B and C) and left D [1,3-diethyl-5-dimethylcarbamoyl-5-

9) M. Sekiya and C. Yanaihara, *Chem. Pharm. Bull.* (Tokyo), **17**, 747 (1969).



a series: R=Et
b series: R=Ph Ph=phenyl

Chart 2



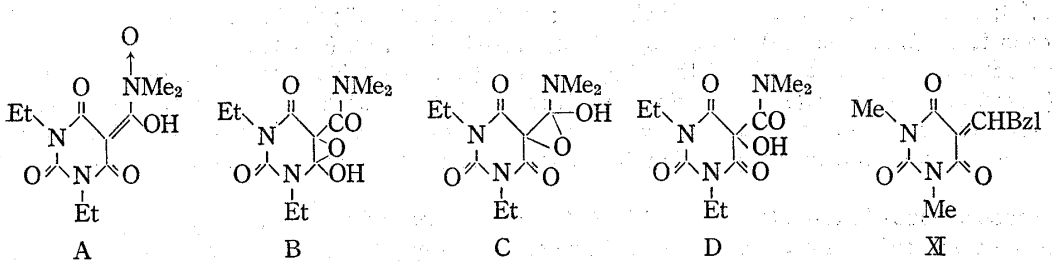


Chart 3

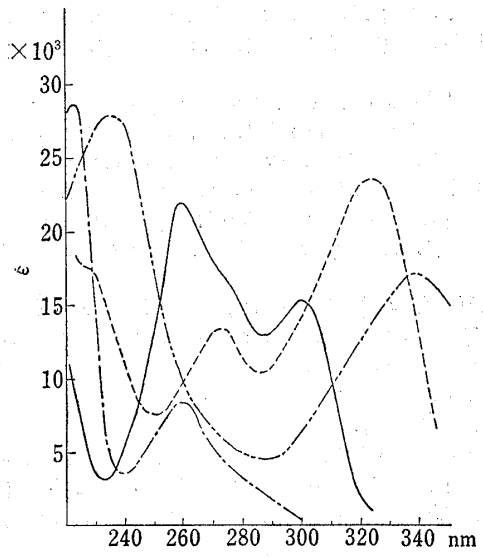


Fig. 1. UV Spectra of Some Typical Derivatives of Pyrimidine (Solvent: EtOH for IIs, VIIa; 10% Methylcellosolve in EtOH for IIa, VIIIa)

------: IIs, —··— VIIIa, ——: IIa, ·—·—: VIIa

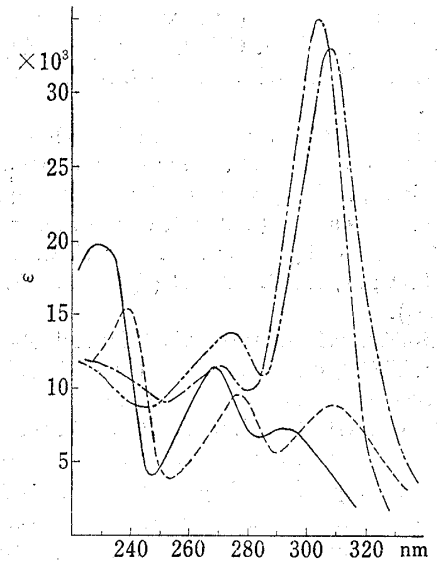


Fig. 2. UV Spectra of Some Typical Derivatives of Isothiazolo[3,4-*d*]-pyrimidine (Solvent: EtOH for IIIs, IVs; 10% Methylcellosolve in EtOH for IIIa, Va)

—·—: Vs, ·—·—: IIIs, ------: Va, ——: IIIa

hydroxybarbituric acid] as the only possible structure for Xa (Chart 3). Refluxing of Xa with Raney nickel in ethanol afforded a nickel salt of 1,3-diethyl-5-dimethylcarbamoylbarbituric acid[10] (XII), whose ammonium salt was isolated after passing it through a column of Amberlite CG-50 (NH_4^+). Compound IIIb was similarly oxidized to afford 1,3-diethyl-5-methylcarbamoyl-5-hydroxybarbituric acid (Xb), which was also formed by the direct oxidation of IIb with hydrogen peroxide.

Experimental[12]

6-Amino-5-substituted Thiocarbamoyluracil (II)——Mixtures of Ia—k (20 mmoles) and isothiocyanates (40—60 mmoles) in pyridine or DMF (only in the cases of Ic, k) (100 ml) were stirred at 140—150° (bath temp.) for 3—16 hr. The mixtures were evaporated to dryness *in vacuo* and the residues either recrystallized (in the cases of IIa, c, d, h, k) or washed with hot ethanol (in the cases of IIb, e, f, g, i, j) to afford IIa—k. The latter samples were sparingly soluble in most organic solvents so that they were used for the next reaction without further purification. For analyses, a part of each sample was recrystallized from solvents shown in Table I.

6-Amino-1,3-diethyl-5-methylthiocarbamoyl-2-thiouracil (IIs)——A mixture of Is (8 g, 40 mmoles) and MeNCS (8 ml) in pyridine (200 ml) was stirred under reflux for 24 hr. The mixture was evaporated to dryness *in vacuo* and the residue recrystallized from MeOH–H_2O (2: 1, v/v, 150 ml) and then from MeOH to afford yellow needles (3 g, 28%), mp 190—193°; UV λ_{max}^{EtOH} nm: 273, 323 (Fig. 1). *Anal.* Calcd. for $C_{10}H_{16}ON_4S_2$: C, 44.10; H, 5.93; N, 20.55; S, 23.53. Found: C, 44.22; H, 6.01; N, 20.07; S, 23.30. NMR (d_6-DMSO) δ: 1.20, 1.30 (3H, each t, CH_3), 3.08 (3H, d, J=5 Hz, NCH_3), 4.2—4.9 [4H, m, $(CH_2)_2$].

3-(Monosubstituted)aminoisothiazolo[3,4-*d*]pyrimidines (III)——i) To suspensions of IIa—h (20 mmoles) in AcOEt (50 ml) was added Br_2 (1.5 ml) and the mixtures were stirred at room temperature for 3—10 hr. The mixtures were evaporated to dryness *in vacuo* and bromine was removed well from the residues by repeated addition of toluene followed by evaporation *in vacuo*. The residues were recrystallized to afford IIIa—h (Table II).

ii) To suspensions of IIi—k (10 mmoles) in AcOH (25 ml) was added 30% H_2O_2 (8 ml) and the mixtures stirred at room temperature for 3 hr. The insoluble crystals were collected and washed well with EtOH to afford IIIi—k (Table II).

5,7-Diethyl-3-methylaminoisothiazolo[3,4-*d*]pyrimidin-4(5H)-one-6(7H)-thione (IIIs)——To a suspension of IIs (2.4 g) in AcOEt (50 ml) was added bromine (1.3 ml) and the mixture stirred at room temperature for 1 hr. The mixture was evaporated to dryness *in vacuo* and bromine was removed from the residue by repeated addition of toluene followed by evaporation *in vacuo*. The residue was washed with EtOH and recrystallized from $CHCl_3$–hexane (1: 1, v/v) to afford pale-yellow needles (1.8 g, 75%), mp 218—221°; UV λ_{max}^{EtOH} nm: 270, 304 (Fig. 2). *Anal.* Calcd. for $C_{10}H_{14}ON_4S_2$: C, 44.42; H, 5.22; N, 20.72; S, 23.70. Found: C, 43.64; H, 4.97; N, 20.54; S, 24.27. NMR (d_6-DMSO) δ: 0.95—1.55 [6H, m, $(CH_3)_2$], 3.0 (3H, s, NCH_3), 4.2—5.0 [4H, m, $(CH_2)_2$].

6-Amino-1-benzyl-5-methyluracil (IV)——To a solution of IIIa (910 mg, 3 mmoles) in BuOH (50 ml) was added Raney Ni (5 ml, previously washed well with BuOH[1]) and the mixture refluxed for 4 hr under vigorous stirring. The Ni was filtered off from the mixture and the filtrate evaporated to dryness *in vacuo* to afford colorless syrup (550 mg), which was crystallized from EtOH to afford colorless prisms (340 mg, 49%), mp 235—237°; UV λ_{max}^{EtOH} nm: 277. *Anal.* Calcd. for $C_{12}H_{13}O_2N_3$: C, 62.38; H, 5.67; N, 18.18. Found: C, 61.18; H, 5.49; N, 18.00. NMR (d_6-DMSO) δ: 1.60 (3H, s, CH_3), 5.08 (2H, s, CH_2), 6.30 (2H, NH_2), 7.22 (5H, s, C_6H_5).

3-(N,N-Disubstituted)aminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H, 7H)-diones (V)——Mixtures of IIIa—n (2 mmoles), K_2CO_3 (0.5 g) and MeI (or EtI) (0.5 ml) in DMF (10—20 ml) were stirred at room temperature for 20 hr (in the cases of IIIk, n, stirred for 1 week). The mixtures were evaporated to dryness *in vacuo* and the residues shaken with $CHCl_3$ and H_2O (100 ml each). The $CHCl_3$ layers were washed with H_2O, evaporated to dryness *in vacuo* and the residues crystallized to afford Va—i (Table IV).

Selective Alkylation of N^5H of 3-(Monosubstituted)aminoisothiazolo[3,4-*d*]pyrimidin-4,6(5H, 7H)-diones (III, R_2=H)——Mixtures of IIIa, e, h (2 mmoles), K_2CO_3 (0.5 g) and MeI (or EtI) (0.5 ml) in DMF (20 ml) were stirred at room temperature for 2 hr (in the case of IIIh, stirred for 50 hr). In the cases of IIIa, e, the

10) It is known that 5-carbamoylbarbituric acid forms a cupric salt.[11]
11) H. Scarborough and W.A. Gould, *J. Org. Chem.*, **26**, 3720 (1961).
12) Melting points were taken on a Yanaco micro melting point apparatus and are uncorrected. Unless otherwise stated, NMR spectra were recorded on a Hitachi R-24 spectrometer at 60 MHz using tetramethylsilane as an external reference. Thin-layer chromatography (TLC) was carried out on Merck aluminum sheets Silica gel F_{254}.

reaction mixtures were worked up as described above to afford IIIl, m. In the case of IIIh, the resultant IIIn was insoluble in the solvent so that it was collected by filtration and recrystallized (Table III).

5,7-Diethyl-3-dimethylaminoisothiazolo[3,4-*d*]pyrimidin-4(5H)-one-6(7H)-thione (Vs)——A mixture of IIIs (1.3 g), K_2CO_3 (1.3 g) and MeI (1.3 ml) in DMF (50 ml) was stirred at room temperature for 16 hr. The mixture was worked up as described above and recrystallized from EtOH to afford pale-yellow needles (1.1 g, 85%), mp 164—176°; UV λ_{max}^{EtOH} nm: 274, 308 (Fig. 2) (authentic sample,[1] mp 163—168°; UV λ_{max}^{EtOH} nm: 274, 308).

6-Amino-1-ethyl- or -1-phenylpyrimidin-4(1H)-one (VIIa, b)——6-Amino-1-ethyl-2-thiouracil (17.1 g, 0.1 mole) was dissolved in 40% EtOH (240 ml) containing NaOH (4.4 g, 0.11 mole), MeI (15 ml) was added to the solution and the mixture stirred at room temperature for 2 hr. The mixture was evaporated to dryness *in vacuo* and the residue washed with H_2O to afford colorless powder (SMe derivative). To a suspension of this powder in EtOH–H_2O (1: 3, v/v, 400 ml) was added Raney nickel (80 ml) and the mixture refluxed for 16 hr under vigorous stirring.[13] The Ni was filtered off from the hot solution and the filtrate concentrated *in vacuo* to *ca.* 50 ml to afford VIIa as colorless prisms (5.2 g, 37%), mp 215—217°; UV λ_{max}^{EtOH} nm: 223, 259 (Fig. 1). *Anal.* Calcd. for $C_6H_9ON_3$: C, 51.75; H, 6.52; N, 30.18. Found: C, 51.72; H, 6.34; N, 29.89. NMR (d_6-DMSO) δ: 0.97 (3H, t, CH_3), 2.7—3.2 (2H, m, CH_2), 4.86 (1H, s, 5–H), 6.8 (1H, OH), 7.75 (1H, s, 2–H), 11.3 (1H, NH).

6-Amino-1-phenyl-2-thiouracil[14] (6.6 g, 30 mmoles) was treated in the same manner as above to afford VIIb as colorless prisms (2.1 g, 37%), mp 259—261° (EtOH); UV λ_{max}^{EtOH} nm: 249, 289. *Anal.* Calcd. for $C_{10}H_9ON_3$: C, 64.20; H, 4.85; N, 22.44. Found: C, 64.14; H, 4.80; N, 22.40. NMR (d_6-DMSO) δ: 5.39 (1H, s, 5–H), 6.8—7.5 (5H, C_6H_5), 7.94 (1H, s, 2–H), 9.0 (1H, OH), 11.7 (1H, NH).

6-Amino-5-*p*-chlorophenylthiocarbamoyl-1-ethyl or-1-phenylpyrimidin-4(1H)-one (VIIIa, b)——A mixture of VIIa (1.39 g, 10 mmoles) and *p*-Cl-C_6H_4NCS (3.38 g, 20 mmoles) in pyridine (50 ml) was stirred under reflux for 24 hr. The mixture was evaporated to dryness *in vacuo* and the residue recrystallized twice from EtOH to afford VIIIa as yellow needles (2.3 g, 75%), mp 235—242°; UV λ_{max}^{EtOH} nm: 235, 339 (Fig. 1). *Anal.* Calcd. for $C_{13}H_{13}ON_4SCl$: C, 50.55; H, 4.24; N, 18.12; S, 10.38; Cl, 11.47. Found: C, 50.47; H, 4.17; N, 18.14; S, 10.72; Cl, 12.36. NMR (d_6-DMSO) δ: 1.38 (3H, t, CH_3), 3.68 (2H, q, CH_2), 7.65 (4H, s, C_6H_4), 8.24 (1H, s, 2–H), 12.6 (2H, NH), 14.76 (1H, NH). Compounds VIIb (1.73 g, 9.3 mmoles) was treated in the same manner as above to afford VIIIb as yellow powder (2.1 g, 60%). This was slightly soluble in hot EtOH and recrystallized from dioxane. mp 282—286°. UV λ_{max}^{EtOH} nm: 242, 262, 353. *Anal.* Calcd. for $C_{17}H_{13}ON_4SCl$: C, 57.23; H, 3.67; N, 15.68; S, 8.99; Cl, 9.94. Found: C, 57.04; H, 3.65; N, 15.55; S, 8.92; Cl, 10.59.

1,3-Diethyl-5-dimethylcarbamoyl-5-hydroxybarbituric Acid (Xa)——To an ice-cooled solution of Vb (3.2 g, 12 mmoles) in AcOH (32 ml) was added dropwise 30% H_2O_2 (10 ml) and the mixture stirred at room temperature for 16 hr. H_2O and $CHCl_3$ (100 ml each) were added to the solution and the mixture shaken well. The $CHCl_3$ layer was washed successively with 10% $NaHCO_3$ and H_2O (100 ml each) and evaporated to dryness *in vacuo*. The residue was dissolved in ether (15 ml) and dropwise addition of hexane afforded colorless needles (1.9 g, 59%), mp 110—112°; UV λ_{max}^{EtOH} nm (ε): 230 (6.8×10^3). *Anal.* Calcd. for $C_{11}H_{17}O_5N_3$: C, 48.75; H, 6.33; N, 15.48. Found: C, 48.46; H, 6.23; N, 15.50. NMR (d_6-DMSO) δ: 1.05 [6H, t, $(CH_3)_2$], 2.85, 3.10 (3H each, s, NCH_3), 3.75 [4H, q, $(CH_2)_2$], 7.32 (1H, OH). Mass Spectrum *m/e*: 271 (M^+), 254 (M—OH), 200, 171, 72 [$CON(CH_3)_2$].

1,3-Diethyl-5-dimethylcarbamoylbarbituric Acid (XII)——i) A mixture of Xa (0.9 g, 3.3 mmoles) and Raney Ni (3 ml) in EtOH (30 ml) was refluxed for 3 hr under vigorous stirring. The Ni was filtered off from the mixture and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in EtOH and addition of acetone–ether precipitated pale-blue powder (0.7 g, 74%). *Anal.* Calcd. for $C_{22}H_{32}O_8N_6Ni$: C, 46.62; H, 5.68; N, 14.82. Found: C, 45.16; H, 5.28; N, 14.42. Mass Spectrum *m/e*: 313, 255.

ii) Compound (Xa) (3.3 g, 12.2 mmoles) was treated in the same manner as above and the product passed through a column of Amberlite CG-50 (NH_4^+) (20 ml) and the column washed with H_2O. The passed solution was evaporated to dryness *in vacuo* and the residue dissolved in EtOH. Addition of acetone–ether to the solution afforded colorless needles (2.3 g, 67%), mp 113—130°; UV $\lambda_{max}^{H_2O}$ nm (ε): 261 (16.9×10^3). *Anal.* Calcd. for $C_{11}H_{20}O_4N_4$: C, 48.45; H, 7.36; N, 20.55. Found: C, 48.46; H, 7.46; N, 20.35. NMR (d_6-DMSO) δ: 1.14 [6H, t, $(CH_3)_2$], 2.97 [6H, s, $N(CH_3)_2$], 3.82 [4H, q, $(CH_2)_2$], 6.5—8 (4H, NH_4).

1,3-Diethyl-5-methylcarbamoyl-5-hydroxybarbituric Acid (Xb)——i) To an ice-cooled solution of IIIb (4 g, 15.7 mmoles) in AcOH (15 ml) was added dropwise 30% H_2O_2 (15 ml) and the mixture stirred at room temperature for 16 hr. The mixture was worked up as described for the synthesis of Xa and recrystallized from $CHCl_3$–ether to afford colorless prisms (1.1 g, 28%), mp 157—180°; UV λ_{max}^{EtOH} nm: 230. *Anal.* Calcd. for $C_{10}H_{15}O_5N_3$: C, 46.70; H, 5.88; N, 16.34. Found: C, 46.40; H, 5.93; N, 16.71. NMR (d_6-DMSO) δ: 1.10 [6H, t, $(CH_3)_2$], 2.6 (3H, d, $J=5$ Hz, NCH_3), 3.8 [4H, q, $(CH_2)_2$], 7.10 (1H, s, OH). Mass Spectrum *m/e*: 256 (M—1), 200, 186, 172, 58 ($CONHCH_3$).

13) W. Pfleiderer and E. Liedek, *Ann. Chem.*, **612**, 163 (1958).
14) T. Kishikawa and H. Yuki, *Chem. Pharm. Bull.* (Tokyo), **14**, 1365 (1966).

ii) To an ice-cooled solution of IIb (0.1 g, 0.4 mmole) in AcOH (2 ml) was added 30% H_2O_2 (0.3 ml) and the mixture stirred at room temperature for 16 hr. TLC of the reaction solution revealed that a main UV spot was identical with that of Xb with respect to its *Rf* value and UV spectrum.

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