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Synthesis of Pyrrolopyrimidines and Thienopyrimidines[1]

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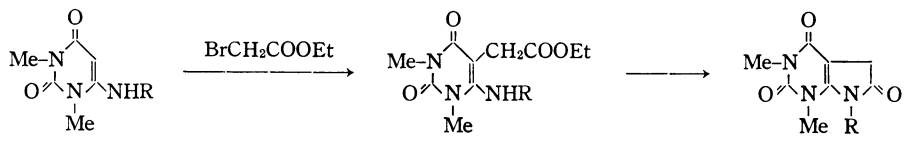
7-Substituted 1,3-dimethyl-7*H*-2,4,6-(5*H*,6*H*)pyrrolo[2,3-*d*]pyrimidinetriones (IIIa, b,c) were prepared from 6-amino-1,3-dimethyluracil (I) and ethyl α-bromoacetate. Reaction of I and α-bromo-ketones afforded 6,7-disubstituted 1,3-dimethyl-7*H*-2,4-pyrrolo-[2,3-*d*]pyrimidinediones (IV, V, VI). On the other hand, reaction of 6-mercapto-1,3-dimethyluracil (VIII) and α-bromocarbonyl compound afforded thieno[2,3-*d*]pyrimidines (X, XI).

A number of antibiotics of pyrrolopyrimidine series have been discovered and synthesis of these compounds have been reported.[3,4,5] We now wish to report the synthesis of pyrrolo[2,3-*d*]pyrimidines and thieno[2,3-*d*]pyrimidines in connection with the synthesis of modified pyrrolopyrimidine antibiotics.

Noell and Robins[6] have recently reported the reaction of 6-amino-1,3-dimethyluracil (Ia) with chloroacetaldehyde to give 1,3-dimethyl-7*H*-2,4-pyrrolo[2,3-*d*]pyrimidinedione (IV; R=R'=H). Synthetic approach to this ring system was done by Taylor, *et al.*[3] with the condensation of 6-anilino-1,3-dimethyluracil (Ib) and phenacylpyridinium bromide to yield 1,3-dimethyl-6,7-diphenyl-7*H*-2,4-pyrrolo[2,3-*d*]pyrimidinedione (Vc).

The present report describes the reaction of 6-amino-1,3-dimethyluracil[7] (Ia) or its derivatives[8,9] (Ib,c) and 6-mercapto-1,3-dimethyluracil (XI) with α-halogenocarbonyl compounds.



Ia, b, c — IIa — IIIa, b, c

a: R=H, b: R=CH_3, c: R=C_6H_5

Chart 1

When I was reacted with ethyl α-bromoacetate at room temperature for 2 weeks, ethyl 5-(6-amino-1,3-dimethyluracilyl)acetate (IIa) was obtained in 25% yield. IIa showed strong bands at 3380 and 3450 cm^{-1} in its infrared (IR) spectrum, due to an amino group, and did not show C-5 proton in its nuclear magnetic resonance (NMR) spectrum in trifluoroacetic acid. Further cyclization occurred on heating IIa in polyphosphoric acid at 140—150° to 1,3-dimethyl-7*H*-2,4,6-(5*H*, 6*H*) pyrrolo[2,3-*d*]pyrimidinetrione (IIIa). Treatment of Ib (R=CH_3)

1) This constitutes Part IX of a series entitled "Studies on Heterocyclic Compounds." Part VIII: H. Ogura, T. Itoh, and S. Sugimoto, *Chem. Pharm. Bull.* (Tokyo), **18**, 2204 (1970).
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5) R.L. Tolman, R.K. Robins, and L.B. Townsend, *J. Heterocycl. Chem.*, **4**, 230 (1967).
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or Ic (R=C_6H_5) with ethyl α-bromoacetate by the similar procedure afforded the cyclized compounds (IIIb, c) directly.

I(a,b,c) were reacted with bromoacetone, phenacyl bromide, and *p*-bromophenacyl bromide, 6,7-disubstituted pyrrolo[2,3-*d*]pyrimidines were obtained as shown in Chart 2 and the data of these compounds are summarized in Table I.

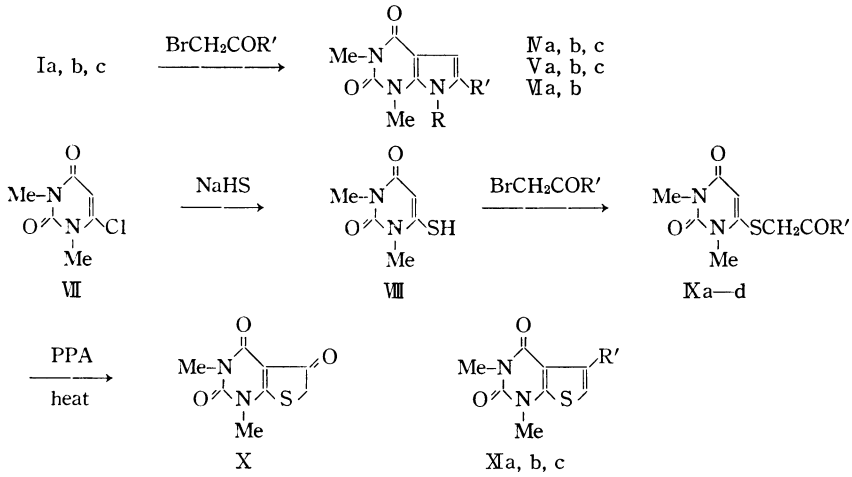

Chart 2

In contrast, 1,3-dimethyl-6-mercaptouracil (VIII), which was prepared from 6-chloro-1,3-dimethyluracil (VII) and sodium hydrogen sulfide, was reacted with α-halogenocarbonyl compounds to yield 2,4-(6-substituted acylthio)pyrimidinediones (IXa,b,c,d) as the intermediate (Table II). In this case, substitution reaction occurred at C-6 mercapto-hydrogen, and this result is the same as the reaction of 2,4-diamino-6-mercaptopyrimidine and α-halogenoketones,[10] and the reaction of 2-mercaptobenzimidazole[11] or -benzothiazole[12] with α-halogenocarbonyl compounds. The intermediate pyrimidyl sulfide (IXa; R'=OEt) was treated with polyphosphoric acid and cyclized to X. Similar treatment of these intermidiates (IXb,c,d) caused the cyclization to 1,3-dimethyl-2,4-thieno[2,3-*d*]pyrimidinediones (XIa,b,c). Their data summarized in Table III.

Experimental

Melting points were determined with a Yamato melting point apparatus Type MP. 1, and are uncorrected. NMR spectra were measured in $CDCl_3$ with a Varian T-60 spectrometer unless otherwise stated, and tetramethylsilane was used as an internal standard. UV spectra were determined with a Hitachi EPS-3 spectrophotometer and IR spectra with a Shimadzu IR-27G spectrometer. Mass spectra were taken with a Japan Electron Optics JMS-01S mass spectrometer.

Ethyl 5-(6-amino-1,3-dimethyluracilyl)acetate (IIa)——A mixture of 6-amino-1,3-dimethyluracil (0.31 g) and ethyl α-bromoacetate (0.335 g) in dimethylformamide (5 ml) was allowed to stand at room temperature for 2 weeks. The separated white crystals were collected and recrystallized from EtOH to yield 0.13 g (25%) of ethyl 5-(6-amino-1,3-dimethyluracilyl)acetate (IIa) as white needles, mp 181—182°. NMR δ ppm (CF_3COOH): 4.35 (2H, quartet, -CH_2CH_3), 3.70 (2H, singlet, -CH_2CO), 3.65 (3H, singlet, NMe), 3.55 (3H, singlet, NMe), 1.35 (3H, triplet, -CH_3). Mass Spectrum *m/e*: 213 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3450, 3380, 3258 (NH_2), 1700 (COOEt). *Anal.* Calcd. for $C_{10}H_{15}O_4N_3$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.56; H, 6.23; N, 17.39.

10) B. Roth, *J. Med. Chem.*, **12**, 227 (1969).
11) H. Ogura, T. Itoh, and Y. Shimada, *Chem. Pharm. Bull.* (Tokyo), **16**, 2167 (1968).
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1,3-Dimethyl-7*H*-2,4,6-(5*H*,6*H*)pyrrolo[2,3-*d*]pyrimidinetrione (IIIa)——a) A mixture of IIa (0.13 g) in polyphosphoric acid (5.0 g) was heated at 140—150° for 4 hr. The cooled reaction mixture was poured into ice-water (20 ml) and then extracted with $CHCl_3$. After evaporation of the dried $CHCl_3$ solution, the residual solid was recrystallized from EtOH to 0.05 g (49%) of IIIa as pale red needles, mp 265°. NMR δ ppm: 3.29 (2H, singlet, $-CH_2-$), 3.28 (3H, singlet, NMe), 3.11 (3H, singlet, NMe). Mass Spectrum *m/e*: 195 (M^+). UV λ_{max}^{EtOH} nm (log ε): 234 (3.59), 290 (3.93). IR ν_{max}^{KBr} cm^{-1}: 1760 (lactam carbonyl), 1705, 1660 (CO). *Anal.* Calcd. for $C_8H_9O_3N_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.43; H, 4.85; N, 21.35.

b) A mixture of Ia (1.55 g) and ethyl bromoacetate (1.67 g) in dimethylformamide (20 ml) was refluxed for 6 hr, and the separated reddish brown crystals were collected and recrystallized from EtOH to yield 0.4 g (21%) of IIIa, mp and mixed mp 265°.

1,3,7-Trimethyl-2,4,6-pyrrolo[2,3-*d*]pyrimidinetrione (IIIb)——A mixture of 1,3-dimethyl-6-methylaminouracil (Ib) (1.69 g, 0.01 mole) in dimethylformamide (20 ml) was refluxed for 6 hr. When cooled the separated pale red crystals were collected and recrystallized from EtOH to 0.54 g (26%) of IIIb as pale

TABLE I. 1,3,6-Trimethyl-2,4-pyrrolo[2,3-*d*]pyrimidinediones

Compd.	R	R′	mp (°C)	Yield (%)	Mass *m/e* (M^+)	IR $\nu_{C=O}^{KBr}$ cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)
IVa	H	CH_3	260 (yellow needles)	16	193	1715, 1660	233 (4.23), 289 (3.36),[a] 339 (3.88)
IVb	H	C_6H_5	256 (white powder)	10	255	1675, 1630	303 (4.48)
IVc	H	C_6H_4Br (*p*)	300 (white needles)	12	333, 335	1690, 1630	287 (4.13), 315 (4.33), 332 (4.13)
Va	CH_3	CH_3	187 (white needles)	13	207	1690, 1650	220 (4.19), 252 (3.74), 286 (3.65)
Vb	CH_3	C_6H_5	168 (white needles)	10	269	1690, 1645	220 (4.17), 287 (4.00)
Vc	CH_3	C_6H_4Br (*p*)	244 (white needles)	10	347, 349	1690, 1650	224 (4.50), 299 (4.37)
VIa	C_6H_5	C_6H_5	218 (white needles)	14	331	1695, 1658	221 (4.45), 285 (4.26)
VIb	C_6H_5	C_6H_4Br (*p*)	188 (white needles)	13	409, 411	1695, 1660	222 (4.43), 294 (4.22)

Compd.	NMR δ ppm ($CDCl_3$)	Formula		Analysis (%) C	H	O
IVa	8.30 (1H, singlet, CH), 3.25 (3H, singlet, NMe), 3.15 (3H, singlet, NMe), 3.10 (3H, singlet, CH_3)	$C_9H_{10}O_2N_3 \cdot H_2O$	Calcd.	51.42	5.75	19.99
			Found	51.23	5.49	20.11
IVb	7.55 (5H, multiplet, C_6H_5), 6.82 (1H, singlet, =CH–), 3.52 (3H, singlet, NMe), 2.37 (3H, singlet, NMe)	$C_{14}H_{13}O_2N_3$	Calcd.	65.87	5.13	16.46
			Found	65.70	5.26	16.73
IVc	7.50 (4H, multiplet, C_6H_4), 6.87 (1H, singlet, =CH–), 3.76 (3H, singlet, NMe), 3.56 (3H, singlet, NMe)	$C_{11}H_{12}O_2N_3Br$	Calcd.	50.31	3.61	12.57
			Found	50.11	3.63	12.54
Va	6.30 (1H, singlet, =CH–), 3.81 (3H, singlet, NMe), 3.78 (3H, singlet, NMe), 3.41 (3H, singlet, NMe), 2.28 (3H, singlet, Me)	$C_{10}H_{13}O_2N_3$	Calcd.	57.96	6.32	20.28
			Found	57.79	6.22	19.96
Vb	7.45 (5H, singlet, phenyl), 6.64 (1H, singlet, CH), 3.82 (3H, singlet, NMe), 3.78 (3H, singlet, NMe), 3.45 (3H, singlet, NMe)	$C_{15}H_{15}O_2N_3$	Calcd.	66.90	5.61	15.60
			Found	66.72	5.68	15.48
Vc	7.50 (4H, multiplet, C_6H_4), 6.63 (1H, singlet, =CH–), 3.83 (3H, singlet, NMe), 3.77 (3H, singlet, NMe), 3.43 (3H, singlet, NMe)	$C_{15}H_{14}O_2N_3Br$	Calcd.	51.74	4.05	12.06
			Found	51.41	4.07	11.89
VIa	7.29 (10H, multiplet, C_6H_5), 6.77 (1H, singlet, =CH–), 3.48 (3H, singlet, NMe), 3.02 (3H, singlet, NMe)	$C_{20}H_{17}O_2N_3$	Calcd.	72.49	5.17	12.68
			Found	72.65	5.19	12.33
VIb	7.44 (9H, phenyl), 6.80 (1H, singlet, =CH–), 3.50 (3H, singlet, NMe), 3.06 (3H, singlet, NMe)	$C_{20}H_{16}O_2N_3Br$	Calcd.	56.09	4.24	9.81
			Found	56.29	4.03	9.65

a) in DMSO-d_6 *b*) reported mp 223—224°

TABLE II. 6-Substituted-thio-1,3-dimethyluracil (IX)

Compd.	R′	mp (°C)	Yield (%)	Mass *m/e* (M^+)	IR $\nu_{C=O}^{KBr}$ cm^{-1} side chain	IR ring	UV λ_{max}^{EtOH} nm (log ε)
IXa	OEt	149 (white needles)	97	258	1705	1698 1650	223 (4.02), 281 (4.10)
IXb	CH_3	161 (white needles)	93	228	1733	1702 1660	221 (4.26), 280 (4.20)
IXc	C_6H_5	206 (white needles)	94	290	1700	1698 1648	244 (4.11), 282 (3.96)
IXd	C_6H_4Br (*p*)	203 (white needles)	92	368, 370	1700	1698 1645	214 (4.36), 263 (4.43)

Compd.	NMR δ ppm ($CDCl_3$)	Formula		Analysis (%) C	H	O
IXa	5.59 (1H, singlet, =CH–), 4.31 (2H, quartet, $-CH_2CH_3$), 3.76 (2H, singlet, $-CH_2-$), 3.56 (3H, singlet, NMe), 3.37 (3H, singlet, NMe), 1.35 (3H, triplet, $-CH_2CH_3$)	$C_{10}H_{14}O_4N_2S$	Calcd. Found	46.50 46.52	5.46 5.45	10.85 10.75
IXb	5.45 (1H, singlet, =CH–), 3.94 (2H, singlet, CH_2), 3.56 (3H, singlet, NMe), 3.37 (3H, singlet, NMe), 2.40 (3H, singlet, $COCH_3$)	$C_9H_{12}O_3N_2S$	Calcd. Found	47.36 47.40	5.30 5.29	12.27 12.49
IXc	7.80 (5H, multiplet, C_6H_5), 5.57 (1H, singlet, =CH–), 4.50 (2H, singlet, $-CH_2-$), 3.56 (3H, singlet, NMe), 3.30 (3H, singlet, NMe)	$C_{14}H_{14}O_3N_2S$	Calcd. Found	57.92 57.91	4.86 4.92	9.65 9.87
IXd	7.81 (4H, multiplet, C_6H_4), 5.58 (1H, singlet, =CH–), 4.49 (2H, singlet, $-CH_2-$), 3.57 (3H, singlet, NMe), 3.35 (3H, singlet, NMe)	$C_{14}H_{13}O_3N_2BrS$	Calcd. Found	45.54 45.29	3.55 3.53	7.59 7.85

TABLE III. 1,3-Dimethyl-2,4-thieno[2,3-*d*]pyrimidinediones (XI)

Compd.	R′	mp (°C)	Yield (%)	Mass *m/e* (M^+)	IR $\nu_{C=O}^{KBr}$ cm^{-1}	UV λ_{max}^{EtOH} nm (log ε)
XIa	CH_3	146 (pale yellow needles)	57	210	1700, 1660	229 (4.26), 254 (3.61), 295 (3.47)
XIb	C_6H_5	174 (white needles)	55	272	1696, 1655	236 (4.62), 289 (3.91)
XIc	C_6H_4Br (*p*)	220 (white needles)	40	350, 352	1705, 1660	240 (4.37), 283 (3.75)

Compd.	NMR δ ppm ($CDCl_3$)	Formula		Analysis (%) C	H	O
XIa	6.48 (1H, doublet, =CH–), 3.56 (3H, singlet, NMe), 3.42 (3H, singlet, NMe), 2.50 (3H, doublet, CH_3)	$C_9H_{10}O_2N_2S$	Calcd. Found	51.41 51.19	4.79 4.88	13.32 13.03
XIb	7.42 (5H, multiplet, C_6H_5), 6.71 (1H, singlet, =CH–), 3.59 (3H, singlet, NMe), 3.38 (3H, singlet, NMe)	$C_{14}H_{12}O_2N_2S$	Calcd. Found	61.75 61.49	4.44 4.45	10.29 10.08
XIc	7.49 (4H, multiplet, C_6H_4), 6.79 (1H, singlet, =CH–), 3.65 (3H, singlet, NMe), 3.45 (3H, singlet, NMe)	$C_{14}H_{11}O_2N_2SBr$	Calcd. Found	47.88 47.82	3.16 3.18	7.98 7.81

red needles, mp 224°. NMR δ ppm: 3.71 (3H, singlet, NMe), 3.44 (3H, singlet, NMe), 3.40 (2H, singlet, $-CH_2-$), 3.35 (3H, singlet, NMe). Mass Spectrum *m/e*: 209 (M^+). UV λ_{max}^{EtOH} nm (log ε): 241 (3.63), 297 (4.07). IR ν_{max}^{KBr} cm^{-1}: 1760 (lactam carbonyl), 1705, 1655 (CO). *Anal.* Calcd. for $C_9H_{11}O_3N_3$: C, 51.67; H, 5.30; N, 20.08. Found: C, 51.55; H, 5.36; N, 19.94.

1,3-Dimethyl-7-phenyl-2,4,6-pyrrolo[2,3-*d*]pyrimidinetrione (IIIc)——This compound was prepared in 10% yield by the same procedure as for IIIb. White needles, mp 253°. NMR δ ppm: 7.55 (5H, singlet, C_6H_5), 4.27 (1H, singlet, CH), 3.30 (3H, singlet, NMe), 2.90 (3H, singlet, NMe), 1.55 (1H, singlet, CH). Mass Spectrum *m/e*: 271 (M^+). UV λ_{max}^{EtOH} nm (log ε): 294 (3.37). IR ν_{max}^{KBr} cm^{-1}: 1755 (lactam carbonyl), 1698, 1675 (CO). *Anal.* Calcd. for $C_{14}H_{13}O_3N_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.74; H, 4.74; N, 15.30.

1,3,6-Trimethyl-2,4-pyrrolo[2,3-*d*]pyrimidinedione (IVa). General Procedure for IV, V, and VI (Table I)——A solution of I (1.55 g, 0.01 mole) and bromoacetone (1.64 g) in dimethylformamide (20 ml) was refluxed for 6 hr, cooled, and the separated yellow crystals were recrystallized from EtOH to yield 0.3 g (16%) of IVa as yellow needles, mp 260° (decomp.).

1,3-Dimethyl-6-mercaptouracil (VIII)——To a stirred solution of 6-chloro-1,3-dimethyluracil (4.0 g) in EtOH (50 ml), a solution of NaSH (1.5 g) in EtOH (50 ml) was added dropwise at 0° during 2 hr and the mixture was allowed to stand at room temperature over night. The separated precipitate was filtered off and the filtrate was evaporated under a reduced pressure at room temperature. The residual solid was dissolved in H_2O (20 ml), the solution was acidified with dil. HCl to pH 1.5, and then extracted with CH_2Cl_2. After evaporation of the dried CH_2Cl_2 solution, 2.5 g (64%) of pale yellow crystals (VIII), mp 126°, were obtained. NMR δ ppm: 5.90 (1H, singlet, NMe), 3.33 (3H, singlet, NMe). UV λ_{max}^{EtOH} nm (log ε): 239 (3.13), 314 (3.16). IR ν_{max}^{KBr} cm^{-1}: 1680 (CO). Mass Spectrum *m/e*: 172 (M^+). *Anal.* Calcd. for $C_6H_8O_2N_2S$: C, 41.85; H, 4.68; N, 16.27. Found: C, 41.64; H, 4.43; N, 16.01.

1,3-Dimethyluracilyl-6-thioacetone (IXb). General Procedure for IX (Table II)——To a solution of 1,3-dimethyl-6-mercaptouracil (VIII) (7 g, 0.01 mole) in EtOH (20 ml) a solution of bromoacetone (2.1 g, 0.015 mole) in EtOH (10 ml) was added, and the reaction mixture was allowed to stand at room temperature for 30 min. The separated white crystals were collected and recrystallized from EtOH to yield 2.12 g (93%) of IXb as white needles, mp 161°.

1,3-Dimethyl-2,4,5-thieno[2,3-*d*]pyrimidinetrione (X). General Procedure for XI (Table III)——A mixture of IXa (1.0 g) in polyphosphoric acid (15 g) was heated at 140—150° for 4 hr. The cooled solution was poured into ice–water and then extracted with $CHCl_3$. After evaporation of dried $CHCl_3$ solution, the residual solid was recrystallized from benzene to 0.48 g (57%) of X as white needles, mp 285°. UV λ_{max}^{EtOH} nm (log ε): 233 (3.66), 297 (3.23). IR ν_{max}^{KBr} cm^{-1}: 1700, 1660, 1640 (CO). Mass Spectrum *m/e*: 212 (M^+). *Anal.* Calcd. for $C_8H_8O_3N_2S$: C, 45.28; H, 3.80; N, 13.20. Found: C, 45.08; H, 3.65; N, 13.36.