Substituted Pyrimidines. I. N^4-Substituted 1,3-Dialkylcytosines

Hubert Maehr, Michael Leach and Voldemar Toome

Chemical Research Department, Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Received August 10, 1972

Our interest in the chemical aspects of the antibiotic albomycin led us to investigate various 1,3-N^4-trisubstituted cytosines. Representatives of 1,3-N^4-trialkylcytosines are known and can be prepared from 1-N^4-dialkylcytosines with subsequent alkylation at N^3. 1,3-N^4-Trimethylcytosine (**11e**) was synthesized from 1-N^4-dimethylcytosine with methyl iodide (1,2) and 2,3-dihydro-6-methyl-5-oxoimidazo[1,2-c]pyrimidine was obtained by cyclization of N^4-(β-chloroethyl)-1-methylcytosine (3). N^4-Acetyl- and N^4-benzoyl-1,3-disubstituted cytosines have been prepared directly by acetylation and benzoylation, respectively, of 1,3-disubstituted cytosines (4,5) or by alkylation of 1-substituted N^4-acetyl- and N^4-benzoylcytosines at N^3 (1,6). Treatment of *N*-(1-methyl-2-oxo-4-pyrimidinyl)alanine with acetic acid and acetic anhydride gave 3-acetoxy-2,6-dimethyl-5-oxoimidazo[1,2-c]pyrimidine (7). Reaction of hydroxylamine with 1,3-dimethylcytosine or with 1,3-dimethyl-4-thiouracil afforded N^4-hydroxy-1,3-dimethylcytosine (**11f**) and N^4-amino-1,3-dimethylcytosine was prepared similarly (8). Methylation with diazomethane converted 1-methyl-N^4-methoxycytosine to 1,3-dimethyl-N^4-methoxycytosine (8). Further, a series of new 6-substituted 1,3-dimethylcytosines as well as 1,3-dimethylcytosine (**11a**) were synthesized from 6-chloro-1,3-dimethylcytosines (9).

Although not characterized, 3-N^4-dimethylcytidine had been prepared from cytidine (10) and 3-methylcytidine (2) with dimethyl sulfate in dimethylformamide under alkaline conditions. Upon treatment of cytidine with dimethyl sulfate and barium hydroxide-barium oxide in dimethylformamide (11), we obtained 3-N^4-dimethyl-1-(2′,3′,5′-tri-*O*-methyl-β-D-ribofuranosyl)cytosine (**13**). The siderochrome albomycin ε which contains a 1-substituted 3-methylcytosine moiety was methylated at the N^4-position by treatment with diazomethane in alcohol-ether (2). 3-Methylcytidine yielded 3-methylcytosine (**6a**) (12) and both 3-N^4-dimethylcytidine (10) and N^4-methylalbomycin ε (2) yielded 3-N^4-dimethylcytosine (**6b**) upon vigorous acid treatment, thus providing evidence of the pathway of methylation. Compounds **6a** and **6b** are accessible in five steps from 2-thiouracil (**1**) as indicated in Scheme 1.

Thiopyrimidone (**3**) is a very weak base and is degradable to 3-methyluracil upon acid treatment (13). Under controlled conditions, however, acid hydrolysis of **3** can be stopped at the 4-thiouracil stage to give **4** in good

Scheme 1

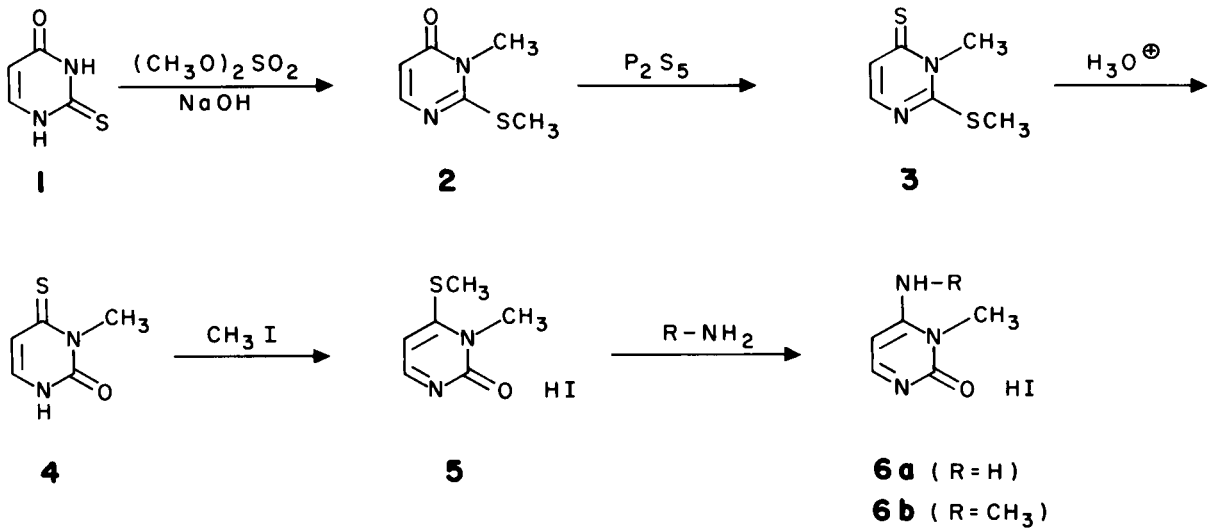


TABLE I

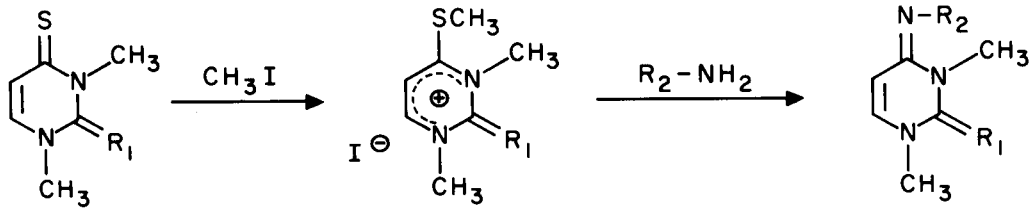
Compound	Composition	M.p.	pK_a	Solvent	^1H NMR Chem. Shifts (δ) N-Me (N^4-Me)	S-Me	H-5	H-6	(J, Hz)	UV Absorption Data, λ max in nm (ε x 10^{-3}) 0.1 N HCl	Buffer pH 7.0	0.1 N KOH
2	$C_6H_8N_2OS$	125-126	1.05 ± 0.05	a	3.37	2.52	6.15d	7.81d	(6)	221 (8.54), 240 i (6.32), 284 (8.43)	220 i (6.50), 236 (5.60), 291 (10.28)	220 i (6.50), 236 (5.59), 291 (10.29)
3	$C_6H_8N_2S_2$	136-138	−0.3 ± 0.1	a	3.89	2.56	7.13d	7.69d	(6)	239 (14.12), 282 (8.04), 342 (13.22)	239 (14.12), 282 (8.04), 341 (13.40)	239 (14.46), 282 (7.61), 339 (13.80)
4	$C_5H_6N_2OS$	186	8.20 ± 0.05	a	3.56		6.41d	7.28d	(7)	245 (3.51), 259 (3.49), 322 (18.75)	245 (3.50), 259 (3.49), 322 (18.73)	233 (6.15), 253 i (4.50), 333 (22.50)
5	$C_6H_8N_2OS\cdot HI$	189-191	4.07 ± 0.05	a	3.56	2.86	6.88d	8.43d	(7)	223 (16.59), 269 (4.75), 321 (17.32)	226 (21.30), 320 (15.30)	225 (21.40), 320 (15.20)
				c	3.57	2.62	6.57d	8.21d	(6)			
6a	$C_5H_7N_3O\cdot HI$	274-277	7.38, 13-14 (3)	a	3.32		6.06d	7.76d	(7.5)	222 (19.16), 273 (9.78)	233 (19.50), 276 (8.37)	226 (20.75), 293 (11.78)
				c	3.47		6.20d	7.68d	(7.5)			
6b	$C_6H_9N_3O\cdot\frac{1}{2}HI$	273-274	7.35 ± 0.05	a	3.28 (2.94)		5.96d	7.73d	(7)	222 (12.11), 280 (11.60)	223 (12.72), 283 (10.19)	223 (15.25), 299 (14.80)
			14.3 ± 0.1	c	3.42 (3.03)		6.15d	7.85d	(7)			
				b	3.86 (3.47)		6.59d	8.29d	(7)			

yield and in high purity. The significant uv spectral differences between the neutral species of **4** and the free base of **5** confirms the tautomeric structure of **4** as that of 3-methyl-4-thio-2-pyrimidinone (3). The conversion of **4** to hydroiodide **5** with methyl iodide and the subsequent reaction with ammonia or methylamine yielded the hydroiodide **6a** or, more surprisingly, the hemihydroiodide **6b**, respectively. The uv spectral properties and pK_a values of **6a** and **6b** are very similar, permitting an extension of the tautomeric assignments from **6a** (3) to **6b**. Physical constants of compounds **2-6** are summarized in Table I.

We have now found that 1,3-dimethyl-4-thiouracil (**7**) (14,15) is readily alkylated by methyl iodide to yield the relatively stable 1,3-dimethyl-4-methylthio-2-oxo-pyrimidinium iodide (**9**) which reacts smoothly with many amines to afford N^4-substituted 1,3-dimethylcytosines (**11**). The reaction can be carried out with excess amine as solvent or in dimethylformamide solution with either one equivalent of amine and at least one equivalent of triethylamine or with the amine salt and at least two equivalents of triethylamine. Reaction of **9** with liquid ammonia is instantaneous and results in a quantitative yield of 1,3-dimethylcytosine (**11a**), a substance not readily accessible by previous methods (16,1,9,6). In similar fashion 1,3-dimethyl-4-methylthio-2- thiopyrimidinium iodide (**10**) is prepared from 1,3-dimethyl-2,4-dithiouracil (**8**) (15) and affords compounds of structure **12** upon treatment with amines (Scheme 2). Examples of these reaction products (**11a-12d**) are listed in Table II and representative examples of preparation are given for compounds **11ℓ** and **12a**.

The chemical shifts of the nuclear *N*-methyl groups of the bases of type **11** in dimethylsulfoxide fall into a narrow range between δ 3.05-3.27 with distances between the two signals ranging from 0 to 0.08 ppm. These signals, together with those for H-5 (δ 5.65-6.16) and H-6 (δ 6.93-7.48) are subject to paramagnetic shifts either upon replacement of the 2-oxo by a 2-thio function (13) or introduction of a positive charge. The changes in chemical shifts resulting from replacement of the 2-oxo by the 2-thio function appear to be slightly more pronounced for nuclear *N*-methyl groups (0.32-0.49 ppm) than for olefinic hydrogen atoms (H-5: 0.28-0.35 ppm; H-6: 0.22-0.33 ppm). Introduction of a positive charge into compounds of type **11** or **12**, on the other hand, exhibits moderate effects on the chemical shifts of *N*-methyl groups (0.20-0.37 ppm) but extensive shifts of the signals of the olefinic hydrogens (H-5: 0.46-0.84 ppm; H-6: 1.02-1.09 ppm). The chemical shifts of the N^4-methyl groups of the hydroiodides **6b** and **11e** are

Scheme 2



7 (R_1 = O) **9** (R_1 = O) **11** (R_1 = O)

8 (R_1 = S) **10** (R_1 = S) **12** (R_1 = S)

observed at fields some 0.30-0.40 ppm higher than those of the nuclear *N*-methyl groups.

As expected, the 2-oxo compounds of type **11** are relatively strong bases, exceeding the base strength of the corresponding thio analogs by 0.5 to 0.9 p*K* units (17). Alkylation at N^4 increases basicity inductively (18); as a result, N^4-adamantyl-1,3-dimethylcytosine (**11k**) is approximately 15 times as strong a base as 1,3-dimethylcytosine (**11a**). The electron withdrawing ability of the phenyl group is apparent in **11j** rendering the compound some 2200 times less basic than the unsubstituted imine **11a**.

EXPERIMENTAL

Melting points were observed on a Reichert Thermopan hot stage and are uncorrected (e = m.p. after metamorphic change). Nmr spectra were recorded on a Varian HA-100 spectrometer (s = singlet, d = doublet) using deuteriodimethylsulfoxide with tetramethylsilane as internal reference (a), deuterium oxide with tetramethylsilane as external reference (b) and deuterium oxide with internal Uvasol [2,2,3,3-tetradeutero-3(trimethylsilyl)propionic acid sodium salt], EM Reagents Division, Brinkmann Instruments Inc., Westbury, N.Y., as internal reference (c). Uv spectra were obtained on a Cary 14 spectrophotometer in aqueous solution (i = inflection). The apparent dissociation constants were computed from uv spectral data at different *p*H values at ionic strength of buffers of 0.01 (19) (f = not stable in alkali). Elemental analytical data are reported in Table III.

3-Methyl-2-methylthio-4(3*H*)pyrimidinethione (**3**)(16).

A mixture of 5 g. (0.032 mole) of 3-methyl-2-methylthio-4(3*H*)-pyrimidinone (**2**), previously prepared from 2-thiouracil (**1**) (20), and 8 g. of phosphorus pentasulfide in 40 ml. of pyridine was refluxed in an oil bath (bath temperature 125-135°) for 5.5 hours. To the hot solution, 40 ml. of toluene were added and the supernatant decanted. Two additional hot toluene extracts with 40 ml. of solvent each, were combined with the first and concentrated to dryness. The resulting residue was again extracted with 40 ml. of hot toluene and the residue obtained upon concentration of the toluene was recrystallized from aqueous ethanol to yield 4.5 g. (0.025 mole) of **3** as pale yellow plates (82%).

3-Methyl-4-thiouracil (**4**) (2,16).

To 250 ml. of 6 *N* hydrochloric acid, maintained at 95° on a steam bath, were added in one portion and under stirring 32.3 g. (0.187 mole) of **3**. The flask was removed from the steam bath after 38 minutes and immediately immersed in an ice bath. The crystalline deposit was collected after 2 hours, washed with ice-cold water and dried (sodium hydroxide) at reduced pressure to yield 20 g. (0.142 moles) of **4** as yellow needles (76%).

3-Methyl-4-methylthio-2(3*H*)pyrimidinone Hydroiodide (**5**) (13).

A solution of 20 g. of **4** in 120 ml. of methanol and 300 ml. of methyl iodide was kept in the dark at room temperature for 40 hours. Addition of 250 ml. of ether and 200 ml. of petroleum ether (b.p. 30-60°) precipitated 36 g. (0.127 mole) of the hydroiodide of **5** as yellow crystals which were collected by filtration, washed with petroleum ether and dried under reduced pressure (89%).

3-Methylcytosine (**6a**) and 3-N^4-Dimethylcytosine (**6b**).

A sealed tube containing 6 g. (0.021 mole) of **5** and approximately 10 ml. of liquid ammonia was kept at room temperature for 90 hours. After removal of most of the ammonia, the tube content was dried at 50° under reduced pressure for 30 minutes, the resulting solids were redissolved in methanol and crystallized after addition of 2-propanol and removal of most of the methanol, to afford 4.49 g. (0.018 mole) of the hydroiodide of **6a** (needles, 85%). Compound **6b** was prepared analogously with methylamine and analyzed consistently for the hemihydroiodide (45%).

Anal. Calcd. for $C_6H_9N_3O \cdot \frac{1}{2}HI$: I, 31.24. Found: I, 31.27.

1,3-Dimethyl-2,4-dithiouracil (**8**).

A mixture of 15.1 g. (0.108 mole) of 1,3-dimethyluracil, 55 g. of phosphorus pentasulfide, 200 ml. of pyridine and 200 ml. of toluene was heated at 180-200° and 70-100 atmospheres for 6 hours. A dark brown supernatant was decanted from the hot reaction mixture, the residual brown syrup was extracted twice more with 140 ml. each of a mixture of equal volumes of pyridine and toluene. The combined supernatants were concentrated and the resulting crystalline mass extracted twice with 125 ml. of hot toluene. The toluene extracts were concentrated to a volume of 50 ml. and upon addition of hexane crude **8**

TABLE II

Compound No.	R_1	R_2	Composition	M.p.	pK_a	Solvent	^{1}H NMR Chem. Shifts (δ) Nuclear N-CH_3	H-5	H-6	(J, Hz)	R_2	UV Absorption Data λ max in nm ($\epsilon \times 10^{-3}$) 0.1 N HCl	Buffer *p*H 7.0	0.1 N KOH
9			$C_7H_{11}IN_2OS$	218.5		a	3.60, 3.62	7.03d	8.72d	(7.5)	2.88	225 (16.09), 270 (4.40), 331 (20.40)	225 (16.09), 270 (4.40), 331 (20.40)	f
10			$C_7H_{11}IN_2S_2$	145-146		a	3.92, 4.08	7.41d	8.93d	(7.5)	2.92	225 (15.82), 287 (28.80), 361 (4.81)	226 (16.00), 288 (28.40), 362 (4.62)	f
11a	O	H	$C_6H_9N_3O$	147	9.40 ±0.05	a	3.13, 3.15	5.65d	6.96d	(8)	~7.2	210 (9.53), 280 (11.10)	210 (9.45), 281 (11.19)	224 (9.59), 272 (8.50)
			$C_6H_9N_3O$·HI	259-260		a	3.36, 3.40	6.11d	7.98d	(8)	9.32			
12a	S	H	$C_6H_9N_3S$	162	8.62 ±0.05	a	3.51, 3.64	6.00d	7.20d	(8)	7.70	227 (28.90), 274 (17.45) 305i (6.85)	227 (28.90), 274 (17.25) 305i (6.84)	230 (24.85), 245i (21.00), 294 (7.35)
			$C_6H_9N_3S$·HI	206		a	3.76, 3.84	6.50d	8.26d	(7.5)	9.60			
11b	O	CH_2CN	$C_8H_{10}N_4O$	183-184	5.96 ±0.05	a	3.17, 3.22	5.82d	7.36d	(8)	4.24	210 (9.14), 291 (14.25)	222 (11.11), 284 (10.92)	222 (10.32), 283 (10.80)
12b	S	CH_2CN	$C_8H_{10}N_4S$	169	5.12 ±0.05	a	3.58, 3.66	6.17d	7.69d	(8)	4.29	228 (15.58), 273 (22.95), 320 (5.94)	252 (26.45), 304 (8.40)	252 (27.15), 303 (8.50)
11c	O	$NHCONH_2$	$C_7H_{11}N_5O_2$	268e	4.03 ±0.05 14.1 ±0.1	a	3.15, 3.21	6.10d	7.07d	(8)	6.00 (NH_2), 8.76 (NH)	210 (9.11), 291 (14.82)	232 (12.82), 245i (7.35), 295 (8.67)	232 (12.75), 245i (7.82), 294 (8.58)
12c	S	$NHCONH_2$	$C_7H_{11}N_5OS$	263e	3.30 ±0.05 13.7 ±0.1	a	3.51, 3.65	6.42d	7.29d	(8)	6.12 (NH_2), 8.85 (NH)	229 (12.36), 275 (21.58), 321 (5.85)	271 (29.12), 340i (3.10)	273 (28.00), 320i (6.35)
11d	O	$COCH_3$	$C_8H_{11}N_3O_2$	156	3.71 ±0.05	a	3.23, 3.27	6.16d	7.48d	(8)	2.06	213 (10.55), 241 (7.56), 314 (13.05)	222 (5.60), 253i (4.21), 305 (13.14)	f
						b	3.81, 3.86	6.74d	7.94d	(8)	2.68			
12d	S	$COCH_3$	$C_8H_{11}N_3OS$	157-158	3.2 ±0.1	a	3.64, 3.70	6.44d	7.73d	(8)	2.10	221 (6.30), 277 (26.10), 353 (3.60)	213 (6.10), 270 (26.20), 315i (9.00)	f
11e	O	CH_3	$C_7H_{11}N_3O$·HI	179-180	9.78 ±0.05	a	3.39, 3.43	6.39d	8.18d	(8)	3.03 (CH_3), 9.13 (NH)	224 (19.20), 288 (13.28)	224 (19.22), 288 (13.27)	224 (24.55) 283 (8.20)
						b	3.92, 3.93	6.76d	8.35d	(8)	3.55			
						c	3.49, 3.50	6.32d	7.92d	(8)	3.12			
11f	O	OH	$C_6H_9N_3O_2$	170	2.7 (8)	a	3.05, 3.13	5.99d	6.93d	(8)	9.53	216 (7.39), 290 (13.00)	227 (12.04), 292 (5.95)	230 (11.90), 250i (8.41), 313 (4.10)
11g	O	CH_2CONH_2	$C_8H_{12}N_4O_2$	256	7.55 ±0.05	a	3.21, 3.21	5.76d	7.24d	(8)	3.64 (CH_2), 7.16 (NH_2)	212 (8.33), 289 (14.62)	213 (8.62), 288 (13.65)	222 (11.35), 283 (9.90)
11h	O	$CH_2CONHOH$	$C_8H_{12}N_4O_3$	147-149	7.42 ±0.05 9.3 ±0.1	a	3.19, 3.19	5.77d	7.21d	(8)	3.72 (CH_2) 8.68, 10.11 (NHOH)	209 (10.00), 290 (14.79)	212 (10.50), 288 (13.55)	222 (16.79), 283 (10.10)
11i	O	$CH_2CH(OCH_3)_2$	$C_{10}H_{17}N_3O_3$·HI	135-136	8.45 ±0.05	a	3.41, 3.42	6.52d	8.16d	(8)	3.33, 3.33 (OCH_3) 3.58 (CH_2), 4.51 (CH), 9.12 (NH)	213 (20.50), 288 (15.21)	214 (20.65), 288 (14.88)	224 (25.80), 283 (9.55)
11j	O	C_6H_5	$C_{12}H_{13}N_3O$·HI	220-222	6.00 ±0.05	a	3.44, 3.56	5.86d	8.05d	(7.5)	7.25-7.70	225 (20.15) 295 (15.90)	223 (22.90), 273i (10.55) 294 (11.49)	221 (23.68), 275i (10.60), 290 (11.15)
11k	O	1-adamantyl	$C_{16}H_{23}N_3O$	162-163	10.60 ±0.05	a	3.10, 3.15	5.86d	6.99d	(8)	1.66, 1.82 2(CH_2)$_3$; 2.03 (CH)$_3$, 1.70 (CH_2)$_3$, 2.10 (CH, CH_2)$_3$, 7.55 (NH)	214 (6.78), 291 (15.88)	214 (6.98), 291 (15.88)	228 (9.52), 284 (9.07)
			$C_{16}H_{23}N_3O$·HCl	217-220e		a	3.43, 3.52	6.70d	8.08d	(8)				
11l	O	3,4-dihydroxy-phenethyl	$C_{14}H_{17}N_3O_3$·HCl	285-295 (dec)	~8.5f	a	3.42, 3.46	6.40d	8.10d	(8)	2.75 (CH_2), 3.60 (NCH_2), 6.44-6.68 (3H), 8.69, 8.75 (2OH)	217i (13.90), 287 (15.20)	217i (13.90), 287 (15.20)	f

TABLE III

Compound	Composition	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
2	$C_6H_8N_2OS$	46.14	5.16	17.93	46.28	5.31	18.03
3	$C_6H_8N_2S_2$	41.84	4.68	16.26	41.87	4.69	16.47
4	$C_5H_6N_2OS$	42.23	4.25	19.70	42.30	4.18	19.88
5	$C_6H_8N_2OS \cdot HI$	25.37	3.19	9.86	25.21	2.96	9.88
6a	$C_5H_7N_3O \cdot HI$	23.73	3.19	16.60	23.79	3.02	16.65
6b	$C_6H_9N_3O \cdot \frac{1}{2}HI$	35.48	4.71	20.69	35.11	4.75	20.63
9	$C_7H_{11}IN_2OS$	28.20	3.72	9.39	28.04	3.63	9.30
10	$C_7H_{11}IN_2S_2$	26.76	3.53	8.91	26.62	3.51	8.72
11a	$C_6H_9N_3O$	51.78	6.52	30.20	51.62	6.53	30.22
	$C_6H_9N_3O \cdot HI$	26.99	3.77	15.73	26.85	3.76	15.70
12a	$C_6H_9N_3S$	46.43	5.84	27.07	46.32	5.78	27.27
	$C_6H_9N_3S \cdot HI$	25.45	3.56	14.84	25.35	3.69	14.77
11b	$C_8H_{10}N_4O$	53.92	5.66	31.45	53.63	5.73	31.52
12b	$C_8H_{10}N_4S$	49.46	5.18	28.84	49.72	5.19	29.04
11c	$C_7H_{11}N_5O_2$	42.63	5.62	35.51	42.50	5.76	35.65
12c	$C_7H_{11}N_5OS$	39.42	5.19	32.84	39.55	5.09	32.44
11d	$C_8H_{11}N_3O_2$	53.03	6.12	23.19	52.72	6.08	23.09
12d	$C_8H_{11}N_3OS$	48.71	5.62	21.30	48.89	5.71	21.11
11e	$C_7H_{11}N_3O \cdot HI$	29.91	4.30	14.95	29.85	4.31	15.14
11f	$C_6H_9N_3O_2$	46.44	5.85	27.08	46.57	5.91	27.14
11g	$C_8H_{12}N_4O_2$	48.97	6.16	28.55	48.74	6.25	28.78
11h	$C_8H_{12}N_4O_3$	45.28	5.70	26.40	45.24	5.84	26.69
11i	$C_{10}H_{17}N_3O_3 \cdot HI$	33.82	5.11	11.83	33.65	5.03	11.75
11j	$C_{12}H_{13}N_3O \cdot HI$	42.00	4.11	12.25	41.99	4.31	12.07
11k	$C_{16}H_{23}N_3O$	70.29	8.48	15.37	70.20	8.48	15.39
	$C_{16}H_{23}N_3O \cdot HCl$	62.02	7.80	13.56	62.21	7.97	13.30
11ℓ	$C_{14}H_{17}N_3O_3 \cdot HCl$	53.94	5.81	13.48	54.03	5.76	13.26
13	$C_{14}H_{23}N_3O_5$	53.66	7.40	13.41	53.50	7.38	13.53

crystallized. After two further crystallizations from aqueous ethanol, 11.7 g. (0.068 mole, 63%) of **8**, m.p. 121-123°, was obtained.

1,3-Dimethyl-4-methylthio-2-oxo-pyrimidinium Iodide (**9**) and 1,3-Dimethyl-4-methylthio-2-thiopyrimidinium Iodide (**10**).

A suspension of 10 g. (0.064 mole) of **7** in 60 ml. of methyl iodide was stirred at room temperature for 24 hours. The crystalline product was precipitated by the addition of 50 ml. of petroleum ether, the liquid phase decanted, and the yellow crystals washed with petroleum ether and dried to afford 18.09 g. (0.061 mole) of **9** (95%) which was used without further purification for the preparation of compounds of the type **11**. Compound **9** was characterized after one crystallization from methanol.

Compound **10** was obtained in an analogous manner from **8** as ochre crystals in 98% yield and recrystallized twice from methanol prior to analysis.

1,3-Dimethyl-2-thiocytosine (**12a**).

Approximately 40 ml. of ammonia were condensed into a flask containing 5.40 g. (0.0172 mole) of pyrimidinium iodide (**10**) at dry-ice acetone temperature. The suspension was stirred at that temperature for approximately 2 hours, then allowed to attain room temperature. The resulting residue was recrystallized from methanol-ether to yield 4.22 g. (0.149 mole) of the hydroiodide **12a** (87%). A solution of this product in methanol-water (9:1) was passed through a column containing 35 ml. of Dowex 1-X2 (OH⁻) previously washed with 90% methanol. The column was eluted with the same solvent and the effluent concentrated to dryness. The crystalline residue was recrystallized from ethyl acetate-hexane to furnish 2.14 g. (0.38 mole) of **12a** base (93%).

N^4-acetyl-1,3-dimethyl-2-thiocytosine (**12d**).

A suspension of 102 mg. (0.66 mmole) of **12a** base in 0.7 ml. of acetic anhydride was agitated at 90°; a solution resulted within a few minutes and long needles of **12d** deposited upon cooling. After washing with ether and cyclohexane 100 mg. of **12d** were obtained, an additional 15 mg. were recovered from the mother liquor totalling 0.58 mmole (88%).

3,4-Dihydroxyphenethyl-1,3-dimethylcytosine (**11ℓ**).

To a stirred solution of 380 mg. (2 mmoles) of 3-hydroxytryptamine hydrochloride in 3 ml. of dimethylformamide were added 597 mg. (2 mmoles) of **9** and 6 ml. of a triethylamine solution (6 mmoles) containing 1.39 ml. of triethylamine in dimethylformamide per 10 ml. volume. After 20 minutes, the crystalline suspension of the hydroiodide salt of the product was concentrated to a paste under reduced pressure, redissolved in water and concentrated again to remove most dimethylformamide. The residue was dissolved in a minimum amount of warm water and the hydrochloride salt crystallized immediately after addition of 1 ml. of concentrated hydrochloric acid. After refrigeration, filtration, washing with ice-cold water and drying (potassium hydroxide) 510 mg. (1.64 mmoles) of **11ℓ** (82%) were obtained.

3-N^4-Dimethyl-1-(2′,3′,5′-tri-*O*-methyl-β-D-ribofuranosyl)cytosine (**13**).

To a stirred mixture of 0.5 g. (2.15 mmoles) of cytidine, 18 ml. of dimethylformamide, 3 g. of barium oxide and 3 g. of barium hydroxide octahydrate were added 7 ml. of dimethylsulfate at 0° over a period of 45 minutes. Stirring was continued at room temperature for 24 hours, for 4 hours at 30°, and after addition of 4 ml. of concentrated ammonium hydroxide, for another 30 minutes at 30°. The mixture was then extracted five times with 35 ml. of chloroform each, the combined and water-washed chloroform extracts were dried (sodium sulfate) and concentrated to a thin syrup. Addition of 10 ml. of ether and some petroleum ether precipitated a brownish oil, the supernatant liquid was decanted, concentrated, the resulting colorless oil was treated with ether and petroleum ether and allowed to crystallize. Recrystallization from tetrahydrofuran and ether yielded 217 mg. (32%) of the product, m.p. 86°, λ max in 70% dioxane, nm. ($\epsilon \times 10^{-3}$), 218 (8.34), 289.5 (15.00), 0.1 *N* hydrochloric acid; 280.5 (13.18), *p*H 7; 280.5 (13.38), 0.1 *N* potassium hydroxide; Me groups at δ 3.71, 3.46, 3.49, 3.18 (2), H-6 at 8.04 (d, J = 8 Hz), H-5 at 5.82 (d, J = 8 Hz), H-1′ at 5.99 (s), H-2′-H-5′ at 3.54-4.30 (deuteriochloroform).

REFERENCES

(1) G. W. Kenner, C. B. Reese and A. R. Todd, *J. Chem. Soc.*, 855 (1955).

(2) G. I. Lavrenova, L. P. Revina and N. A. Poddubnaya, *J. Gen. Chem.* USSR, **36**, 2091 (1966).

(3) T. Ueda and J. J. Fox, *J. Am. Chem. Soc.*, **85**, 4024 (1963).

(4) D. M. Brown, A. R. Todd and S. Varadarajan, *J. Chem. Soc.*, 2384 (1956).

(5) H. U. Blank and W. Pfleiderer, *Ann. Chem.*, **742**, 16 (1970).

(6) R. S. Goody and R. T. Walker, *J. Org. Chem.*, **36**, 727 (1971).

(7) T. Ueda and J. J. Fox, *ibid.*, **29**, 1762 (1964).

(8) D. M. Brown, M. J. E. Hewlins and P. Schell, *J. Chem. Soc.* (C), 1925 (1968).

(9) K. Senga, F. Yoneda and S. Nishigaki, *J. Org. Chem.*, **36**, 1829 (1971).

(10) H. Bredereck, H. Haas and A. Martini, *Chem. Ber.*, **81**, 307 (1948).

(11) R. Kuhn and H. Trischmann, *ibid.*, **96**, 284 (1963).

(12) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 1348 (1962).

(13) D. J. Brown and B. T. England, *J. Chem. Soc.* (C), 2507 (1971).

(14) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **69**, 2138 (1947).

(15) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1298 (1961).

(16) G. E. Hilbert, *J. Am. Chem. Soc.*, **56**, 190 (1934).

(17) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1004 (1951).

(18) J. Clark and D. D. Parrin, *Quart. Rev.*, **18**, 295 (1964).

(19) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons Inc., New York 1962.

(20) D. J. Brown, E. Hoerger and F. S. Mason, *J. Chem. Soc.*, 211 (1955).