A Facile Synthesis of 5-Substituted 1-Methyluracils and Cytosine (1)

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A facile, general synthesis for a number of 5-substituted-1-methyluracils and cytosine which is suitable for the preparation of micro-quantities is reported. In contrast to other methods, the 5-substituent plays no role in determining the position of alkylation. 1-Methyl-5-hydroxymethyluracil and 1-methyl-5-formyluracil have also been synthesized by an alternate route.

In the course of our investigations we encountered a need for small quantities of a number of 1-methyluracils bearing substituents at the 5-position (III). Because of the unavailability of large amounts of the parent pyrimidines (I), it was essential that the synthetic method used be applicable to small quantities of I and proceed in high yield. Although the reported procedures (3) for the synthesis of 1-alkyluracils are quite suitable for large scale preparations, they possess certain disadvantages (3b) that precluded their use in our laboratory; moreover, these procedures are not applicable to all 5-substituted uracils (3d).

Two of the most convenient methods for the synthesis of pyrimidine nucleosides are the related Hilbert-Johnson (4) and Wittenburg (5) procedures. Whereas 2,4-dialkoxypyrimidines are required precursors for the former procedure, Wittenburg's method (5) simply involves treatment of readily prepared trimethylsilylated pyrimidines with a suitably blocked chlorosugar; recently, this procedure has been utilized (6) for the direct synthesis of nucleoside 5′-phosphates. We wish to report a further extension of this method for a general synthesis of 5-substituted 1-methyluracils (7) and cytosine.

The procedure involves the formation of the bis(trimethylsilyl)uracil (II) followed by *in situ* reaction with an excess of methyl iodide (the trimethylsilyl groups are lost during isolation). The entire sequence is performed in a single reaction vessel without isolation of intermediates and gives essentially quantitative yields of III. Since hexamethyldisilazane (HMDS) and methyl iodide are always present in large excess, the amount of I used can be greatly varied without altering the general procedure. Thus, the method is ideally suited for the preparation of small amounts of III for spectral and radiological studies. We have obtained a quantitative yield of 1-methyluracil-2-^{14}C from as little as 0.45 mg. (4 μmole) of uracil-2-^{14}C.

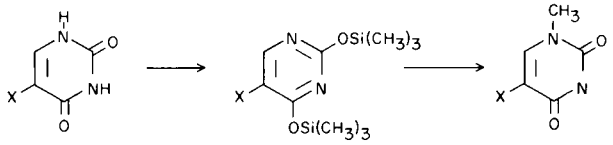
In contrast to previous methods (3), the nature of the 5-substituent of the pyrimidine appears to have no role in determining the position of alkylation. Whereas alkylation of 5-fluorouracil (If) (3d) with 1-bromopentane or 5-chloropentyl-*p*-nitrobenzoate in dimethyl sulfoxide-potassium carbonate yields the 3-monoalkylated pyrimidine along with significant amounts of the 1,3-dialkylated pyrimidine, methylation of IIf gave exclusively 1-methyl-5-fluorouracil (IIIf). In the case of 5-trifluoromethyluracil (Id), direct alkylation is precluded by its instability (8) in basic media; however, utilizing the procedure described herein, 1-methyl-5-trifluoromethyluracil (IIId) was obtained in 77% yield. The procedure is also applicable to pyrimidines other than uracils as illustrated by the conversion of cytosine to 1-methylcytosine (IV) in 70% yield.

Inherent in this procedure is the obvious advantage that functional groups that are silylated by HMDS need not be masked prior to reaction. Thus, 5-hydroxymethyluracil (Ic) and 5-formyluracil (Ie) can be converted to the corresponding 1-methylpyrimidines (IIIc and IIIe) in a single step. This facet should be quite useful in the preparation of 1-alkylpyrimidines which possess polyfunctional substituents at the 5-position, such as 5-β-ribosyluracil (9) and glucosylated 5-hydroxymethylcytosine (10) which are available only in limited quantities.

1-methyl-5-hydroxymethyluracil (IIIc) and 1-methyl-5-formyluracil (IIIe) were also prepared by an alternate route. Chloromethylation of Ia, followed by hydrolysis at neutral *p*H provided IIIc; however, difficulties were often encountered in the crystallization of IIIc from the reaction mixture. Treatment of IIIc with activated manganese dioxide afforded 1-methyl-5-formyluracil (IIIe) which was identical to the sample prepared by methylation of Ie.

TABLE I

Synthesis of 1-Methyluracils (a)



I II III

	X	Rxn time (hr.) HMDS	Rxn time (hr.) MeI	% yield isolated (b)	M.P.	R_f (c)
a	H	1.5	18	63	231-232 (d)	0.63
	H	2	24	100 (e)		0.63
b	CH_3	1.5	12	75	295-297 (f)	0.76
c	CH_2OH	2	24	68	239-242 (g)	0.48
d	CF_3	1	56	77 (h)	244-248	0.99
e	CHO	3	4	71 (i)	227-229	0.47
f	F	1.5	8	73 (j)	236 (subl.)	0.72

(a) Known compounds had identical spectral (Table II) and chromatographic properties as authentic samples prepared by literature procedures or obtained from commercial sources. (b) All yields were shown to be quantitative by tlc (11a). Crystallization solvent was water unless noted otherwise. (c) Reference 11b. (d) Reported (3c) m.p. 230-231°. (e) From 0.45 mg. of uracil-2-^{14}C (7.1 μCi); isolated by paper chromatography (11b). (f) Reported (12) m.p. 291°. (g) Identical to a sample prepared by acid-catalyzed hydroxymethylation of IIIa. (h) Recrystallized from ethyl acetate-petroleum ether; *Anal.* Calcd. for $C_6H_5F_3N_2O_2$: C, 37.13; H, 2.60; N, 14.43. Found: C, 37.16; H, 2.57; N, 14.21. (i) Identical to a sample prepared by oxidation of IIIc. (j) Recrystallized from 95% ethanol; *Anal.* Calcd. for $C_5H_5FN_2O_2$: C, 41.67; H, 3.50; N, 19.44. Found: C, 41.78; H, 3.55; N, 19.25.

TABLE II

NMR and Ultraviolet Spectral Characteristics of 1-Methylpyrimidines

	NMR parameters (a)			Ultraviolet absorption spectra, λ max, mμ (log ε) (b)	
	1-CH	6-H	5-substituent	*p*H 1	*p*H 13
IIIa	3.23	7.15 (d, J = 6.9)	5.54 (d, J = 6.9)	266 (3.94)	265 (3.87)
IIIb	3.20	6.97 (d, J = 1.0)	1.78 (d, J = 1.0)	273 (3.96)	270 (3.77)
IIIc	3.22	7.20 (d, J = 0.8)	4.18 (d, J = 0.8)	269 (3.98)	267 (3.80)
IIId	3.28	7.72 (d, J = 1.1)		265 (4.00)	263 (3.79)
IIIe	3.35	7.97	9.24	283 (4.09)	287 (3.95)
IIIf	3.19	7.30 (d, J = 5.6)		272 (3.91)	271 (3.80)
IV	3.23	7.32 (d, J = 6.9)	5.76 (d, J = 6.9)	282 (4.08)	274 (3.89)

(a) Chemical shifts were determined with a Varian A-60 Spectrometer in 0.5 *N* sodium deuterioxide-deuterium oxide and δ recorded in p.p.m. downfield from 3-(trimethylsilyl)propanesulfonic acid sodium salt as internal standard. Unless otherwise specified, protons exhibited single peaks; coupling constants (J) for doublets (d) are reported in c.p.s. (b) Determined using a Cary Model 15 recording spectrophotometer.

EXPERIMENTAL

Melting points are corrected and were determined in capillary tubes on a Mel-Temp block (Laboratory Devices, Cambridge, Massachusetts). Chromatography was performed as described in reference 11. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

General Procedure for Preparation of 5-Substituted 1-Methyluracils (III).

Up to 1 mmole of the pyrimidine (I), 2.5 ml. of hexamethyldisilazane (HMDS), and 0.05 ml. of trimethylchlorosilane (TMCS) were refluxed until complete dissolution. After cooling to ambient temperature, 5 ml. of methyl iodide was added and refluxing continued until I could no longer be detected by tlc (11a). The reaction mixture was evaporated *in vacuo* and triturated with 5 ml. of 6*N* acetic acid to hydrolyze trimethylsilyl groups. The mixture was concentrated to a residue which could be purified from colored side products by recrystallization or, for micro-scale preparations, by paper chromatography (11b).

1-Methylcytosine (IV).

As described above, 55.6 mg. (0.5 mmole) of cytosine was refluxed in 2.5 ml. of HMDS and 0.05 ml. of TMCS for 1 hour followed by treatment with 5 ml. of methyl iodide for 2 hours at reflux, yield 43 mg. (69%), m.p. 285° dec. Spectral (Table II) and chromatographic properties (11) were identical to those of an authentic sample (Cyclo Chemical Corp.).

1-Methyl-5-hydroxymethyluracil (IIIc).

Hydrogen chloride was bubbled through a solution of 7.0 g. (0.055 mole) of 1-methyluracil and 5.5 ml. of 37% formalin in 25 ml. of concentrated hydrochloric acid for 1.5 hours at 70°. The reaction mixture was evaporated *in vacuo* and the residual white solid was slurried in 100 ml. of 1*N* potassium bicarbonate for 24 hours. After the addition of 150 ml. of water, the suspension was gently refluxed for 5 minutes and filtered. After standing at ambient temperature for two days, 1.2 g. of unreacted 1-methyluracil which crystallized was removed by filtration. The mother liquor was concentrated *in vacuo* to 30 ml. and chilled to give 4.8 g. (55.9%) of white crystals, m.p. 222-226° dec. A portion was recrystallized from 1,4-dioxane to give the analytical sample, m.p. 239-242°.

Anal. Calcd. for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.12; H, 5.36; N, 17.78.

1-Methyl-5-formyluracil (IIIe).

A vigorously stirred mixture of 0.780 g. (0.005 mole) of IIIc and 4.5 g. of activated manganese dioxide (Beacon Chemical Industries, Inc.) in 25 ml. of 1,4-dioxane was heated at 75° for 4 hours. The manganese dioxide was filtered from the hot solution and washed with two 10 ml. portions of hot dioxane. The combined mother liquor and washings were evaporated *in vacuo* to give 0.365 g. (47.5%) of a white solid, which contained only traces of IIIc. Recrystallization from aqueous ethanol gave 0.270 g. (35%) of the analytical sample, m.p. 225-226°.

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 47.04; H, 4.02; N, 18.05.

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(11) Aliquots were removed from the reaction mixture and treated with 6*N* acetic acid prior to chromatography. (a) Thin layer chromatography (tlc) was performed with silica gel GF using the solvent system chloroform-ethanol (3:1); (b) Ascending paper chromatography was performed with Whatman No. 1 paper using the solvent system ethyl acetate-formic acid-water (7:2:1). Spots were detected under ultraviolet light or, for ^{14}C-labeled compounds, with a Packard model 7201 strip scanner.

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