Studies on Heteroaromaticity. XXII.⁽¹⁾ Bromination of 6-Substituted Uracils with NBS

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N-bromosuccimide (NBS) is known to effect the side-chain bromination of aromatic hydrocarbons[2] and of 3-methylthiophene[3] and the allylic bromination.[4] Nishiwaki and Goto[5] have reported that 6-methyl- (Ia), 2-mercapto-6-methyl- and 2-amino-6-methyluracil are brominated with NBS in the presence of benzoyl peroxide (BPO) to afford the corresponding brominated products at the 5-position of a pyrimidine ring and from this fact, they have disclosed that the reactions proceed *via* an ionic mechanism by the electrophilic attacks of NBS at the 5-position, since the yields did not change even in the absence of BPO. However, the yield of the produced 5-bromo-6-methyluracil (IIa), for instance, is as low as 45%. We presumed that this

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[1] Part XXI of this series: T. Sasaki and M. Ando, This Bulletin, in press.

[2] N. B. Chapman and J. F. A. Williams, *J. Chem. Soc.*, **1952**, 5044.

[3] F. L. Greenwood, M. D. Kellert and J. Sedlak, "Org. Synth.," Coll. Vol. IV, p. 108 (1963).

[4] E. Campaigne and B. F. Tuller, *ibid.*, IV, 921 (1963).

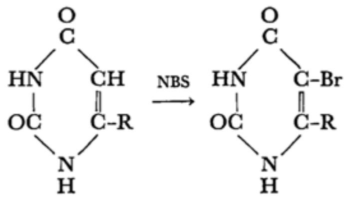
[5] T. Nishiwaki and T. Goto, This Bulletin, **33**, 26 (1960).

TABLE 1. BROMINATION OF 6-SUBSTITUTED URACILS

Uracil	Reaction temp., °C	Reaction time, hr	Product (Mp, °C)	Yield %	Microanalysis Found (Calcd) C	H	N
Ia	55	12	IIa	85	29.20	2.42	13.66
	r*	2	(270—275♯)	88	(29.29	2.46	13.67)
Ib	70	10	IIb	88			
	r*	2	(295♯♯)	88			
	r*	2		88			
Ic	r*	2	IIc	88	34.92	3.21	10.30
			(228—230**)		(34.69	3.27	10.11)
Id	r*	2	IId	65	36.78	4.41	9.29
	r*	8	(193—195)	85	(36.88	4.47	9.56)
Ie	r*	2	IIe	57	32.12	2.53	10.43
	r*	8	(264—265)	70	(31.96	2.68	10.65)

r*: reflux
**: decomposition
♯: mp 230°C, R. Behrend, *Ann.*, **229**, 17 (1885).
mp 247°C (decomp), T. Matsukawa *et al.*, *Yakugaku Zasshi*, **70**, 134 (1950).
mp 241°C (decomp), B. Kurtev *et al.*, *Chem. Abstr.*, **47**, 1607 (1953).
mp 251°C (decomp).[9]
♯♯: mp 293°C, G. H. Hitchings, G. B. Elion and E. A. Falco, *J. Biol. Chem.*, **185**, 643 (1950).

result is due to the poor solubility of Ia in carbon tetrachloride used as the solvent, though this solvent is commonly used in this type of reactions.[6] We changed the solvent from this non-polar carbon tetrachloride to polar ethanol, in which the solubility of uracil derivatives is larger than that in carbon tetrachloride. This increased solubility might favor the ionic reactions and as a result, the yield of IIa could be improved up to 85%. This note deals with the results of the similar procedure applied to other 6-substituted uracils. The structural elucidation of the products was done by the NMR spectra, since Nishiwaki and Goto[5] have demonstrated the site of the bromine atom to be at the 5-position by its characteristic reactivity[7] and by the chemical conversion to the known compounds. The NMR spectrum of IIa in DMSO-d_6, as an example, showed the presence of methyl protons and the absence of a C-5 proton, indicating IIa to be 5-bromo-6-methyluracil. The bromination is expected to proceed more readily as the electron-density at the 5-position of a pyrimidine ring increases by the stronger electron-donating nature of a 6-substituent R. Uracil[8] (Ib, R=H), 6-uracil acetate[9] (Ic, R=CH_2COOEt), orotaldehyde[10] (Id, R=CHO), and orotate[11] (Ie, R=COOEt) were treated with NBS and the considerable yields of the corresponding 5-bromo compounds were obtained, except the case when the bromination of Id afforded IId. The structure of IId was found to be the diethylacetal instead of the expected 5-bromoorotaldehyde from the elemental analysis and the spectral data; the NMR spectrum in DMSO-d_6 exhibited the chemical shifts at −1.53 τ (s, –NH, disappeared on deuteration), −0.78 (s, –NH, disappeared on deuteration), 4.50 (s), 6.36 (q, J=6.8 cps) and 8.22 (t, J=6.8 cps) in the proton ratio of 1 : 1 : 1 : 4 : 6, among which a signal at 4.50 τ is assignable either to an acetal proton[12] or to a C-5 proton[13] and therefore, the ultraviolet spectrum was inspected. As shown in Table 2, an absorption maximum is



I a	($R=CH_3$)	II a	($R=CH_3$)
b	(R=H)	b	(R=H)
c	($R=CH_2COOEt$)	c	($R=CH_2COOEt$)
d	(R=CHO)	d	($R=CH(OEt)_2$)
e	(R=COOEt)	e	(R=COOEt)

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[6] C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

[7] J. Chesterfield, *J. Chem. Soc.*, **1955**, 3478.

[8] D. Davidson and O. Bandisch, *J. Am. Chem. Soc.*, **48**, 2379 (1926).

[9] G. E. Hilbert, *ibid.*, **54**, 2076 (1932).

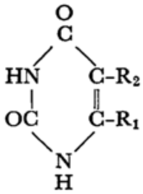
[10] K. Y. Zee-Cheng and C. C. Cheng, *J. Heterocyclic Chem.*, **4**, 163 (1967).

[11] M. Ridi and G. Aldo, *Gazz. Chim. Ital.*, **82**, 13 (1952).

[12] 5.28 τ for $MeC\underline{H}(OEt)_2$: N. S. Bhacca, L. F. Johnson and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif. U.S.A. (1962). Spectrum No. 143.

[13] NMR of Ia (DMSO-d_6) τ: −0.85 (broad s, -NH, disappeared on deuteration), 4.65 (s, C-5-H), 7.95 (s, $-CH_3$).
It should be noted here that a broad signal due to NH protons was split into two sharp signals after bromination.

TABLE 2. UV ABSORPTION OF 6-SUBSTITUTED URACILS AND THEIR 5-BROMO DERIVATIVES



R_1	$R_2=H$		$R_2=Br$	
	λ^{MeOH}_{max} mμ	log ε	λ^{MeOH}_{max} mμ	log ε
H	258	3.80	270	3.90
CH_3	259	4.02	273	3.96
COOEt	286	3.87	290	3.82
CH_2COOEt	260	4.02	278	3.94
$CH(OEt)_2$*	260	3.90	278	3.93

* T. Sasaki, unpublished data.

located at 278 mμ, which is shifted 18 mμ bathochromically from that of 5-unsubstituted orotaldehyde diethylacetal and this is in good accordance with the general trend of other products as manifested in this table. From these facts, IId was concluded to be 5-bromoorotaldehyde diethylacetal. It should be mentioned as a conclusion that the yields decreased in the following sequence as the electron-donating nature decreased:

$$R = CH_3 \geq H \gtrsim CH_2COOEt > CH(OEt)_2 > COOEt$$

Experimental[14]

5-Bromo-6-methyluracil (IIa). 0.6 g of 6-methyluracil (Ia)[13] and 1 g of NBS were suspended in 50 m*l* of ethanol and the reaction mixture was stirred at 55°C for 12 hr after addition of a catalytic amount of BPO. After the suspension dissolved, precipitation occurred again. Precipitated crystals were collected and recrystallized from ethanol. NMR (DMSO-d_6) τ: -1.40 (s, NH[13]), -1.28 (s, NH[13]), 7.80 (s, CH_3).

The above reaction without BPO afforded the same product in almost the same yield.

The yields, melting points and elemental analyses are summarized in Table 1 and the data on the ultraviolet analyses are summarized in Table 2, with those of other products.

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[14] The melting points were measured on a micro hot stage and were not corrected. The microanalyses were carried out with a Yanagimoto C. H. N. Corder, Model MT-1. The ultraviolet spectra were measured on a Nippon-Bunko optical rotary dispersion recorder, Model ORD/UV-5. The NMR spectra were taken on a Varian A-60 spectrometer, using tetramethylsilane as an internal standard and the chemical shifts are presented in terms of τ-values; where singlet is designated as s, doublet as d, triplet as t, quartet as q and multiplet as m.