A New Type of Nucleophilic Substitution with a Concomitant Migration to an Allylic Position. From 5-Bromo-6-methyluracils to 6-(Substituted methyl)uracils

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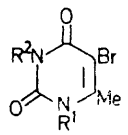
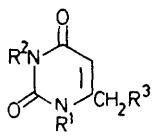
Summary 1-Substituted or 1,3-disubstituted 5-bromo-6-methyluracil derivatives react with nucleophiles such as aromatic amines and sodium acylates to yield 6-arylaminomethyl- and 6-acyloxymethyl-uracils.

IT has been reported[1] that the treatment of *N*-unsubstituted 5-bromo-6-methyluracil with aniline in ethylene glycol under reflux gave 5-anilino-6-methyluracil. We recently reported[2] that 1,3-disubstituted 5-bromo-6-methyluracil derivatives were treated with aliphatic amines in dimethylformamide (DMF) at 100° to give the 5-alkylamino-6-methyluracils.





	R^1	R^2		R^1	R^2	R^3
(I)	Me	Me	(VII)	Me	Me	PhNH
(II)	Me	Ph	(VIII)	Me	Me	PhNMe
(III)	Bu	H	(IX)	Me	Me	*p*-MeC_6H_4NH
(IV)	Ph	H	(X)	Me	Me	*p*-MeO·C_6H_4NH
(V)	H	H	(XI)	Me	Me	β-naphthylamino
(VI)	H	Me	(XII)	Me	Ph	PhNH
			(XIII)	Bu	H	PhNH
			(XIV)	Ph	H	PhNH
			(XV)	Me	Me	AcO
			(XVI)	Me	Me	BzO
			(XVII)	Me	Ph	OHC·NH

In this connection, we have found that the reaction of 1-substituted or 1,3-disubstituted 5-bromo-6-methyluracils with aromatic amines caused a new type of nucleophilic substitution with a concomitant migration to an allylic position to afford 6-arylaminomethyluracil derivatives.† Thus, the reaction of 5-bromo-1,3,6-trimethyluracil (I) with aniline in DMF (reflux, 5 h) gave 6-anilinomethyl-1,3-dimethyluracil (VII), which was identical with an authentic sample prepared by methylation of 6-anilinomethyluracil (m.p. 228°), obtained by condensation of 6-chloromethyluracil[3] with aniline.

Similarly, the treatment of 1-substituted or 1,3-disubstituted 5-bromo-6-methyluracils (I)—(IV) with a variety of aromatic amines gave the corresponding 6-arylaminomethyluracil derivatives (VIII)—(XIV), whose structure was assigned on the basis of the ^1H n.m.r. spectra. However, no reaction occurred between the uracils (V) and (VI) and aniline.

Furthermore, (I) reacted with sodium acetate and sodium benzoate, instead of aromatic amines, under the same conditions to form the 6-acetoxymethyl- and 6-benzoyloxymethyl-derivatives (XV), (XVI), respectively. Heating (II) in formamide at 170° in the absence of a nucleophile gave 6-formylamino-1-methyl-3-phenyluracil (XVII).

To our knowledge, nucleophilic substitution of this type has not been reported previously.

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† All new compounds gave satisfactory elemental analyses and n.m.r. spectra.

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[2] S. Senda, K. Hirota, and K. Banno, *J. Medicin. Chem.*, 1972, **15**, 471.
[3] K. J. Boosen, Ger. Offen., 2,025,247 (*Chem. Abs.*, 1971, **74**, 31770).