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OXYGEN-ALKYL ESTER CLEAVAGE OF 5-ACETOXYMETHYL URACILS

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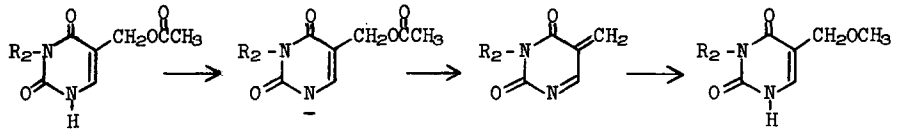
A number of 5-hydroxymethylpyrimidines are of interest because of their biological activity or occurrence (1). We have been particularly interested in the chemistry of derivatives of 5-hydroxymethyluracil (Ia) because of possible analogies to certain enzymic reactions (2) and to the naturally occurring 5-ribosyluracil (1). The 5-hydroxymethyl group of Ia has been stated to possess "benzylic" (3) or "vinylogous-carbinolamine" (4) character because of the extreme ease with which it is converted to ethers (5) and amines (4) under slightly acidic conditions; the reactivity of Ia toward nucleophilic displacements is further amplified by the interesting observation (6) that it C-alkylates phenols in the ortho and para positions.

We have recently observed (4) an unprecedented alkylation of an aromatic amine with Ia in aqueous NaOH. In order to establish the mechanistic pathway of this unusual reaction, we have initiated studies on nucleophilic substitution reactions of 5-acetoxymethyluracil (Ib) and its 1- and 3-methylated derivatives.

Treatment of 5-acetoxymethyluracil (Ib) with a two-fold excess of NaOMe-MeOH at ambient temperature (23-25°) rapidly (7) afforded a 73% yield of 5-methoxymethyluracil (Ic) (Table I, run 1). Other products were tentatively identified as polymeric on the basis of their chromatographic and spectral properties. Similar treatment (run 2) of 3-methyl-5-acetoxymethyluracil (IIb) gave a quantitative yield of 3-methyl-5-methoxymethyluracil (IIc). Methanolic solutions of Ib and IIb were stable for at least 24 hr in the absence of NaOMe; IIb could, in fact, be recrystallized from hot MeOH without noticeable transformation. In contrast to the facile formation of ethers from Ib and IIb, NaOMe catalyzed methanolysis (run 3) of 1-methyl-5-acetoxymethyluracil (IIIb) yielded only 1-methyl-5-hydroxymethyluracil (IIIa). Moreover, methanolysis of IIIb was observed to be considerably slower ($t_{\frac{1}{2}} \simeq 23$ min) than the 1-NH pyrimidines Ib and IIb (7). That the corresponding 5-hydroxymethylpyrimidines (Ia, IIa) were

not intermediates in the formation of the methyl ethers Ic and IIc was demonstrated by their stability in NaOMe-MeOH for as long as three days.

These data provide conclusive evidence that the base catalyzed methanolysis of 5-hydroxymethyluracil acetate (Ib) and its 3-methyl derivative (IIb) proceed exclusively by oxygen-alkyl scission of the pyrimidine 1-anion (IV); with IIIb, where ionization is precluded by the presence of the 1-methyl substituent, the normal $B_{AC}2$ mechanism appears to be operative. Precedent for the intermediate V can be found in the base catalyzed hydrolysis of 4(5)-hydroxymethyl-



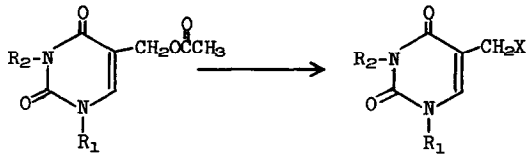
Ib, IIb IV V Ic, IIc

imidazole acetate (8) and nucleophilic substitutions of indoles (9) of the gramine type.

The numerous resonance hybrids that can be conjured for V indicate that the exocyclic methylene group possesses substantial carbonium ion character. Recently, Bell and Brown (10) have described the use of $NaBH_4$ as a convenient carbonium ion trapping agent. When Ib was treated under the suggested (10) conditions (2M $NaBH_4$ in 80% aqueous diglyme) a quantitative yield of thymine (Id) was obtained. When methanol was substituted as solvent (run 4) with 0.02 M $NaBH_4$, competition for V between hydride and methanol was observed to give Id (67%) and Ic (33%); when the concentration of $NaBH_4$ was raised to 0.1N (run 5), Id was the sole detectable product. Similar results were obtained with 3-methyl-5-acetoxymethyluracil (IIb) (run 6). However, treatment of the 1-methyl pyrimidine (IIIb) with a methanolic solution of $NaBH_4$ (run 7) resulted in a relatively slow ($t_{\frac{1}{2}}$ > 24 hr) transesterification to give 1-methyl-5-hydroxymethyluracil (IIIa) and methyl acetate in quantitative yield. Under the conditions used the corresponding hydroxymethyl-(I, II or IIIa) and methoxymethylpyrimidines (I, II or IIIc) were completely inert toward $NaBH_4$. Complete studies on nucleophilic substitution reactions of derivatives of Ia will be published elsewhere.

The identity of the products described in this report was established by comparison to authentic samples. In addition to the methods described, all new compounds were prepared by alternative routes. Treatment of 3-methyluracil with a 10% excess of formaldehyde in 0.5 N NaOH (5) afforded IIa (80%, mp 170-171°). Chloromethylation (12) of 1-methyluracil followed by hydrolysis at pH 7 gave IIIa (40%, mp 239-242°); alternatively, IIIa was prepared by treatment of tris(trimethylsilyl)-5-hydroxymethyluracil with methyl iodide (13). Fischer esterification

TABLE I. Nucleophilic Substitution Reactions of 5-Acetoxymethyluracils in MeOH[a]



I, $R_1 = R_2 = H$

II, $R_1 = H$, $R_2 = CH_3$

III, $R_1 = CH_3$, $R_2 = H$

a, X = -OH

b, X = $-O_2CCH_3$

c, X = $-OCH_3$

d, X = -H

Run No.	R_1	R_2	nucleophile (M. conc.)	Product -X (% yield)[b]
1	-H	-H	NaOMe (0.02)	$-OCH_3$ (73)
2	-H	$-CH_3$	NaOMe (0.02)	$-OCH_3$ (98)
3	$-CH_3$	-H	NaOMe (0.02)	-OH (100)[c]
4	-H	-H	$NaBH_4$ (0.02)[d]	-H (67), $-OCH_3$ (33)
5	-H	-H	$NaBH_4$ (0.10)[d]	-H (100)
6	-H	$-CH_3$	$NaBH_4$ (0.02)[d]	-H (57), $-OCH_3$ (43)
7	$-CH_3$	-H	$NaBH_4$ (0.02)[d]	-OH (100)

[a]All reactions (7) were performed at ambient temperature and were 0.01 M in substrate. [b]Products were identified (11) and quantitatively isolated by chromatography; yields were determined by uv spectrophotometry. [c]After 2 hr starting material could not be detected by tlc. [d]3% DMF added to aid solubility.

of IIa and IIIa yielded the esters IIb (90%, mp 144-145°) and IIIb (89%, mp 155-157°). The methyl ethers IIc (mp 144-146°) and IIIc (mp 142-143°) were obtained in quantitative yield after treatment of IIa and IIIa with 1% methanolic-HCl (5). Catalytic hydrogenation (5% Pt/C) of IIa in 10% AcOH-EtOH afforded 3-methylthymine (IId) (98%, mp 216-218°).

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REFERENCES

1. T. L. V. Ulbricht in Progress in Nucleic Acid Research, Vol. 4, J.N. Davidson and W.E.

Cohn, Eds., Academic Press, New York, N.Y., pp. 189-216.

2. D.V. Santi and C.F. Brewer, J. Amer. Chem. Soc., 90, 000 (1968).
3. D.M. Brown, M.G. Burdon and R.P. Slatcher, J. Chem. Soc. (C), 1051 (1968); M. Green, H.D. Barner, and S.S. Cohen, J. Biol. Chem., 228, 621 (1957).
4. D.V. Santi, J. Heterocycl. Chem., 4, 475 (1967).
5. R.E. Cline, R.M. Fink and K. Fink, J. Amer. Chem. Soc., 81, 2521 (1959).
6. R. Brossmer, Angew. Chem. (Internat. Edit.), 6, 702 (1967).
7. Although reactions of Ib and IIb were routinely allowed to proceed for 15 min before quenching with HOAc, tlc demonstrated all reactions to be complete before aliquots could be withdrawn and quenched ($t_{\frac{1}{2}}$ is < 30 sec).
8. T.C. Bruice and T.H. Fife, J. Amer. Chem. Soc., 83, 1124 (1961).
9. (a) J.D. Albright and H.R. Snyder, ibid., 81, 2239 (1959); (b) E. Baciocchi and A. Schiroli, J. Chem. Soc.(B), 1968, 401.
10. H.M. Bell and H.C. Brown, J. Amer. Chem. Soc., 88, 1473 (1966).
11. Spectra and elemental analyses were consistent with assigned structures.
12. J.H. Burckhalter, F.J. Seiwald and H.C. Scarborough, J. Amer. Chem. Soc., 82, 991 (1960).
13. T.T. Sakai, A.L. Pogolotti, Jr. and D.V. Santi, J. Heterocycl. Chem., submitted.