Intramolecular Cyclization of 1-(3-Bromopropyl)uracils

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The intramolecular *O*-alkylation of 1-(3-bromopropyl)uracils proceeds smoothly in basic conditions and yields cyclic ethers as the major products. This reaction competes with the intermolecular *N*-alkylation of uracil and its derivatives. The mechanism of this reaction is also discussed in terms of reactivity indices calculated using the HMO method.

The alkylation of uracils and their derivatives is a well known process.[1] It is widely accepted that the most reactive sites of the molecule in this reaction are the N-1 and N-3 positions. In contrast, the *O*-alkylation of pyrimidine-2,4-diones is a difficult reaction and only very few *O*-alkylated derivatives have been obtained, even when very reactive alkylating agents such as CH_2N_2 are used.[2] For example, the methylation of pyrimidin-2-one with diazomethane gives, as a major product, the N^1-methylated compound in 52% yield, whereas the *O*-methylated compound is formed in only 17% yield.[2] The situation is somewhat different with 2-thiopyrimidines where *S*-alkylated products are readily formed owing to the enhanced nucleophilicity of sulphur.

Leonard[1] suggested that in the reaction of 1-(3-bromoalkyl)-uracils with other uracil derivatives (under basic conditions) intramolecular cyclization might occur as a competing process with the intermolecular reaction; however, no further experimental data were reported.

In this paper we discuss and report on some properties of cyclic ethers derived from the intramolecular *O*-alkylation of 1-(3-bromopropyl)uracil; these contrast former findings.

Results and Discussion

1-(3-Bromopropyl)-5-bromouracil (**1a**) was obtained according to the known procedure.[3,4] This compound is considered to be a synthon in the preparation of 1,1′-trimethylenebis-5-bromouracils which are model compounds for dinucleotides.[1,4] Surprisingly enough, none of the expected products in the intermolecular alkylation of uracil derivatives were obtained, and 1,1′-trimethylenebisuracils containing the 5-bromouracil moiety were synthesized using an alternative synthetic route.[4]

Compound (**1a**) itself when treated with an equimolar amount of 0.1 mol dm^{-3} NaOH in water solution gives the cyclic ether (**2a**) in high yield (85%) as the sole product as the result of an internal *O*-alkylation of 5-bromouracil. Similar results were obtained when the reaction was carried out using Me_2SO–K_2CO_3, $N(C_2H_5)_3$ or potassium salts of 5-bromouracil in place of NaOH (Scheme 1).

The reaction proceeds smoothly for a few hours at room temperature and compound (**2a**) is obtained as a fine crystalline material. The structure of (**2a**) was determined from its spectroscopic data. The i.r. spectrum displays a very strong signal at 1 525 cm^{-1} due to the imine C(2)=N(3) fragment, not observed in the starting material, and both ^1H and ^{13}C n.m.r. spectra are consistent with the proposed structure. The mass spectrum (electron impact), however, displays a molecular ion at *m/z* 460, which corresponds to dimeric (**2a**). This phenomenon can be explained by a thermal oligomerization (dimerization) of (**2a**) which easily takes place on thermal activation, even in the mass spectrometer. In a separate experiment, (**2a**) was heated to *ca.* 200–260 °C, to yield a crystalline material, which had a mass spectrum similar to that obtained for (**2a**) (the relative intensities have of the peaks were slightly different). The substance obtained was insoluble in most solvents, and only sparingly soluble in trifluoroacetic acid. A thin-layer chromatogram did, however, show a differentiation between (**2a**) and its thermally obtained oligomer, but the low solubility made it impossible to obtain an n.m.r. spectrum. Unambiguous proof of the structure of (**2a**) has been obtained from *X*-ray analysis.[5]

Table 1. The π-electron charge (Δρ), bond orders ($P_{C(2)=O}$) and indices of reactivity: the free valence (F_e), the frontier electron density (f_e) and the superdelocalizability (S_e) for an electrophilic attack at 2=O position of the substrates examined.

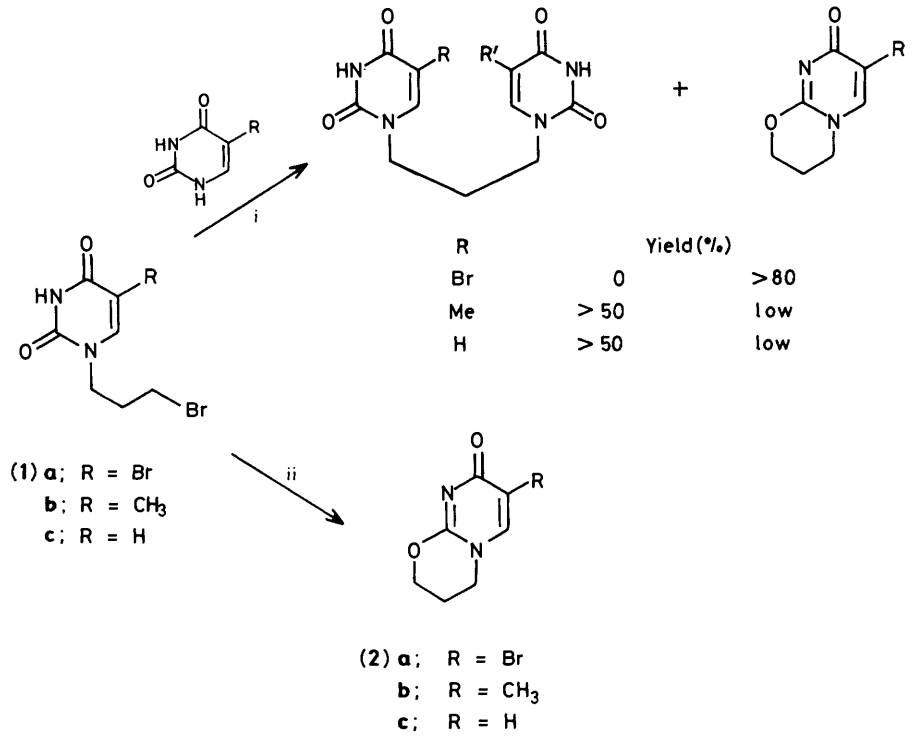
Compound	Δρ	F_e	f_e	S_e	$P_{C(2)=O}$
(**1a**)	−0.471	0.908	0.123	0.917	0.802
(**1b**)	−0.470	0.906	0.116	0.934	0.803
(**1c**)	−0.467	0.904	0.129	0.892	0.806

The u.v. spectrum of (**2a**) displays a significant hypsochromic shift (λ_{max} 268 nm in water) by comparison with (**1a**) (λ_{max} 282 nm in water). Compound (**2a**), when stored in aqueous solution, slowly undergoes ring-opening to yield the ω-hydroxy derivative of 1-alkyluracil (**3a**). This transformation can be monitored by u.v. spectroscopy. The structure of (**3a**) was determined from its spectroscopic data.

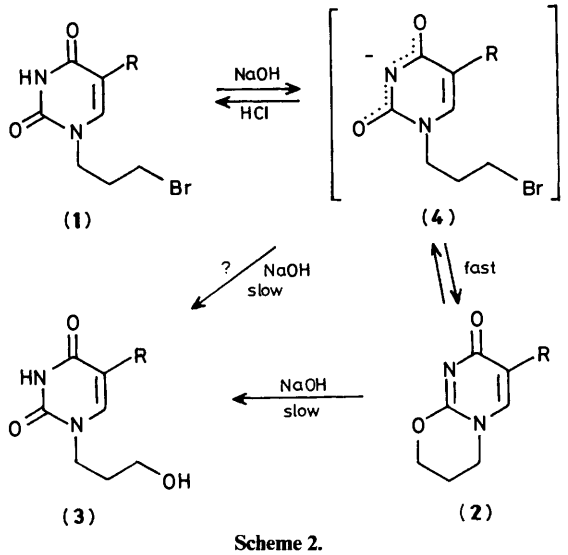
The lability of (**2a**) was thought to be an interesting subject for further studies. It was shown that (**2a**), when dissolved in acidic or basic media, easily undergoes ring-opening to give 1-(3-substituted-propyl)-5-bromouracils. All of these transformations enabled us to propose the pathway given in Scheme 2.

According to the values determined for the p*K* of similar compounds[7] under basic conditions, the anion (**4**) will be a reactive intermediate and its subsequent cyclization leading to the ether (**2**) can be observed. As a competing reaction, the intermolecular nucleophilic substitution of (**4**) can be considered. However, the latter process seems to be the minor one when bromine is the 5-substituted uracil. Our finding suggests that the formation of (**2a**) is the result of kinetic control of the reaction. Fast equilibration of (**1a**) and (**2a**) under basic conditions seems to be responsible for the fact that the 5-bromo-1-(3-hydroxypropyl)uracil (**3a**) is not observed at the beginning of the reaction, although it becomes the only product when an excess of the base (0.1 mol dm^{-3} NaOH) is used. The acid-induced internal ring-opening of (**2a**) seems to proceed faster than that under basic conditions.

The question arises as to why 5-bromouracil derivatives are exceptionally reactive towards internal cyclization, *i.e.*, intramolecular nucleophilic substitution. Our calculations (HMO method) demonstrate the enhanced π-electron charge at 2=O and the lowered C(2)=O bond order in 5-bromouracil, thymine, and uracil derivatives.



Scheme 1. *Reagents:* i, base; ii, NaOH (0.1 mol dm^{-3}).



Scheme 2.

Other reactivity indices, namely free valence, frontier electron density, and superdelocalizability, for an electrophilic attack at 2=O appear to favour 5-bromouracil, although their values, as well as the π-electron charge at 2=O for all of the compounds examined (Table 1), are similar enough to predict similar behaviour for all three in this particular reaction. The calculation of reactivity indices carried out for the anionic structure (**4**) did not contradict the proposed reaction path. This assumption led us to the idea of obtaining cyclic ethers derived from thymine and uracil. Using identical reaction conditions (0.1 mol dm^{-3} NaOH, room temperature, prolonged reaction time) we were able to isolate (**2b**); this compound readily undergoes ring-opening when heated or treated with acid or base. An analogous way of obtaining (**2c**) derived from uracil required an even more prolonged reaction time. Isolated from this reaction was the analogous cyclic ether (**2c**) which underwent facile ring-opening at slightly elevated temperatures. This may explain the fact that during the work-up of the reaction, (**2c**) was not actually observed.

We employed the same semiempirical method of calculation to rationalize the ring-opening of cyclic ether (**2**) under basic and acidic conditions. The results show that: (*a*) the uracil derivative is less stable and more susceptible to protonation at N^3, 4=O, or 2=O than are the other compounds under consideration; and (*b*) all of the compounds are able to react with ^-OH at C-2 and CH_2 atoms, although the difference in their reactivities is fairly small (Table 2).

The intramolecular substitution should be disfavoured by entropy: the transition state seems to be highly organized and a significant loss of entropy is required to reach this state. Conversely, there should be no additional strain introduced into the molecule caused by the formation of a new six-membered ring.

The fact that the 1-(3-bromopropyl)thymine and 1-(3-bromopropyl)uracil react easily with uracil derivatives to yield intermolecular products, while 5-bromo-1-(3-bromopropyl)-uracil does not, still requires further investigation. Moreover, Wenska[6] reports having obtained a cyclic *O*-alkylated product analogous to (**2**) as a by-product of the reaction of adenine sodium salt with 1-(3-bromopropyl)-5-propyluracil. We would like to suggest that in the initial stage the formation of the cyclic ether (**2**) proceeds in all cases. This may be treated as an equilibrium of (**1**) $\rightleftharpoons$ (**2**) in the reaction media shifted toward products or substrates. The next step, however, *i.e.* the ring opening of (**2**), occurs much faster in the case of thymine and uracil derivatives than in the case of 5-bromouracil.

These results led us to the conclusion that the reaction is kinetically controlled [assuming comparable thermodynamic stability of (**2**) in all of the cases discussed]. Also, competing intermolecular *vs.* intramolecular alkylation seems to be consistent with our suggestion. Further studies to prove our observation (such as intermolecular *O*-alkylation) of 5-bromouracil and related compounds are in progress.

Table 2. Reactivity indices (the free valence, the frontier electron density and the superdelocalizability) and the π-electron charge distribution in the cyclic ether (**2**) molecules at the positions influencing the ring-opening process.

Compound		N-1	C-2	N-3	O(2)	O(4)
		π-Electron charge (Δρ)				
(**2a**)		+0.435	+0.205	−0.442	+0.111	−0.463
(**2b**)		+0.430	+0.198	−0.445	+0.110	−0.463
(**2c**)		+0.414	+0.218	−0.438	+0.113	−0.460
		Free valence F_e(e) and F_n(n)				
(**2a**)	e	0.441	0.168	0.663	1.327	0.892
	n	0.626	0.394	0.884	1.414	0.956
(**2b**)	e	0.444	0.171	0.657	1.325	0.893
	n	0.632	0.418	0.899	1.422	0.958
(**2c**)	e	0.484	0.160	0.676	1.328	0.889
	n	0.671	0.376	0.874	1.404	0.953
		Frontier electron density f_e(e) and f_n(n)				
(**2a**)	e	0.606	0.019	0.285	0.013	0.272
	n	0.004	0.438	0.319	0.045	0.024
(**2b**)	e	0.573	0.030	0.238	0.018	0.257
	n	0.001	0.467	0.329	0.047	0.026
(**2c**)	e	0.600	0.006	0.350	0.005	0.304
	n	0.007	0.414	0.311	0.043	0.026
		Superdelocalizability S_e(e) and S_n(n)				
(**2a**)	e	−1.759	−0.532	−1.701	−1.170	−4.072
	n	−0.346	−1.015	−0.428	−0.096	−0.337
(**2b**)	e	−1.873	−0.560	−1.736	−1.180	−1.122
	n	−0.341	−1.003	−0.419	−0.094	−0.339
(**2c**)	e	−1.587	−0.496	−1.646	−1.156	−1.010
	n	−0.334	−1.036	−0.432	−0.099	−0.342

Experimental

All melting points were determined using a hot-plate Boetius microscope and are uncorrected. U.v. spectra were recorded on a Specord UV–Vis spectrometer. ^{1}H N.m.r. spectra were determined at 90 MHz on a JEOL FX-90 spectrometer in $(CD_3)_2SO$ solution using Me_4Si as an internal reference. Mass spectra were determined on a JEOL JMS-D-100 mass spectrometer operating at 25 eV and i.r. spectra on a Bruker JFS-113v in KBr pellets. Elemental analyses were carried out on an Elemental Analyser Perkin-Elmer 240.

HMO calculations were performed using parameters given by Pullmann.[8] Reactivity indices were calculated and interpreted according to generally accepted definitions.[8–14]

T.l.c. was performed on glass plates coated to a thickness of 0.25 mm with silica gel $60F_{254}$ (Merck) using, as the eluants: $CHCl_3$–CH_3OH (9:1 v/v) and CCl_4–acetone (1:1 v/v). For column chromatography, Machery Nagel Silica Gel 100–200 mesh ASTM was used.

5-Bromo-1-(3-bromopropyl)uracil (**1a**) was synthesized by a method developed earlier.[3,4] Dimethylformamide was dried by distillation with phosphorus pentaoxide and stored over molecular sieves, Union Carbide type 4A.

Cyclization of 5-Bromo-1-(3-bromopropyl)uracil (**1a**).—5-Bromo-1-(3-bromopropyl)uracil (**1a**) (400 mg; 1.3 mmol) was dissolved in aqueous NaOH (0.1 mol dm^{-3}; 12.8 cm^3). The resulting solution was stirred at ambient temperature for 20 h and the solvent was removed under reduced pressure to yield the crude product (a colourless solid) which was chromatographed on a silica-gel column with $CHCl_3$–CH_3OH (9:1 v/v) to yield (**2a**) as colourless prisms (251 mg, 85%), m.p. 259 °C (decomp.). Further crystallization from acetone–CH_3OH (5:1 v/v) yielded analytically pure material (240 mg). λ_{max} 267 nm (ε 9 860 dm^3 mol^{-1} cm^{-1}), *cf.* λ_{max}(**1a**) 285 nm (ε 8 560 dm^3 mol^{-1} cm^{-1}); ν_{max} 1 525s cm^{-1} [C(2)=N(3)]; *m/z* (relative intensity) 459.9 (55%, M^+), 461.9 (100), and 463.9 (51); δ[$(CD_3)_2SO$] 8.08 (s, 1 H, 6-H), 4.41 (t, 2 H, *J* 5.4 Hz, OCH_2), 3.95 (t, 2 H, *J* 6 Hz, NCH_2), and 2.13 (m, 2 H, CCH_2C) (Found: C, 36.45; H, 2.95; N, 12.1. Calc. for $C_7H_7N_2O_2Br$: C, 36.53; H, 3.07; N, 12.18%).

The cyclization of (**1b**) and (**1c**) were carried out using an analogous procedure. However, prolonged reaction times were required for completion [in the case of (**1c**), 10 days]. The structure of the products (**2b**) and (**2c**) were determined on the basis of their spectroscopic data.

(**2b**): Yield 60%; m.p. 191–192 °C; ν_{max} 1 527 cm^{-1} (N=C); δ[$(CD_3)_2SO$] 7.36 (s, 1 H, 6-*H*), 4.36 (t, 2 H, OCH_2, ^3J 5.5 Hz), 3.88 (t, 2 H, NCH_2, ^3J 6 Hz), 2.25–2.0 (m, 2 H, CCH_2C), and 1.77 (s, 3 H, 5-CH_3); *m/z* 166 (M_2^+, 100%).

(**2c**): Yield 54%, m.p. 178–170 °C, ν_{max} 1 520 cm^{-1} (N=C); δ[$(CD_3)_2SO$] 7.46 (d, 1 H, 6-*H*, ^3J 7 Hz), 5.82 (d, 1 H, 5-*H*, ^3J 7 Hz), 4.39 (t, 2 H, OCH_2, ^3J 5.5 Hz), 3.91 (t, 2 H, NCH_2, ^3J 6 Hz), and 2.25–2.0 (m, 2 H, CCH_2C); *m/z* 152.0 (M_2^+, 100%).

Ring Opening of Cyclic Ether (**2**) *with* HBr.—To a stirred solution of (**2a**) (0.01 g, 0.04 mmol) in water (1 cm^3) was added 40% HBr (0.5 cm^3). The reaction mixture was stirred at room temperature for 30 min and then heated to 100 °C to complete the reaction. After being cooled the mixture was extracted with chloroform (3 × 2 cm^3). Chloroform extracts were dried (sodium sulphate) and then concentrated under reduced pressure. To this solution was added hexane (20 cm^3) and the precipitated solid was filtered off. Recrystallization of this from isopropyl alcohol yielded analytically pure material (white needles, 0.011 g, 82%) identical with (**1a**) (i.r., n.m.r., mass spec.).[4]

Ring-opening reactions of (**2b**) and (**2c**) were carried out using identical procedures.

Ring Opening of the Cyclic Ether (**2**) *with* NaOH.—A solution of (**2a**) (20 mg, 0.09 mmol) in aqueous NaOH (1 mol dm^{-3}; 1.5 cm^3) was heated to *ca.* 80 °C for 20 min. The reaction mixture was cooled to room temperature, neutralized with 0.1 mol dm^{-3} HCl and extracted with chloroform (3 × 2 cm^3). The solvent was removed under reduced pressure and the crude product was purified by preparative t.l.c. (SiO_2) with $CHCl_3$–MeOH (9:1 v/v) as the eluant. Crystallization of the chromatographed product from isopropyl alcohol gave the analytically pure product (**3a**) (m.p. 193–195 °C) (17 mg, 78%). The structure of (**3a**) was determined on the basis of its spectroscopic data.

(**3a**): M.p. 193–195 °C; ν_{max} no absorption at *ca.* 1 520 cm^{-1}; δ[$(CD_3)_2SO$] 11.69 (s, 1 H, N^3-H), 8.15 (s, 1 H, 6-*H*), 4.54 (s, 1 H, OH), 3.73 (t, 2 H, OCH_2, ^3J 7 Hz), 3.43 (t, 2 H, NCH_2, ^3J 6 Hz), and 1.80–1.65 (m, 2 H, CCH_2C); *m/z* 247.9 (M^+, 81.2%) and 249.9 (71.7).

The ring opening of (**2b**) and (**2c**) with an excess of NaOH were carried out identically.

(**3b**): M.p. 127–128 °C; ν_{max} no absorption at *ca.* 1 520 cm^{-1}; δ[$(CD_3)_2SO$] 11.20 (br s, 1 H, N^3-H), 7.48 (s, 1 H, 6-H), 4.53 (br s, 1 H, OH), 3.68 (t, 2 H, OCH_2, ^3J 7 Hz), 3.41 (t, 2 H, NCH_3, ^3J 6 Hz), 1.75 (s, 3 H, 5-CH_3), and 2.0–1.5 (m, 2 H, CCH_2C); *m/z* 183.8 (M^+, 57%).

(**3c**): M.p. 121–122 °C; ν_{max} no absorption at *ca.* 1 520 cm^{-1}; δ[$(CD_3)_2SO$] 11.12 (s, 1 H, N^3-H), 7.59 (d, 1 H, 6-*H*, ^3J 8 Hz),

5.52 (d, 1 H, 5-*H*, ^3J 8 Hz), 4.58 (br s, 1 H, OH), 3.72 (t, 2 H, OCH_2, ^3J 7 Hz), 3.41 (t, 2 H, NCH_2, ^3J 7 Hz), and 1.9–1.5 (m or dd, 2 H, CCH_2C); *m/z* 170 (M^+, 47%).

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