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REDUCTIVE DEBROMINATION OF 5-BROMOURACILS BY 1-BENZYL-1,4-DIHYDRONICOTINAMIDE

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Abstract—N(1)-Unsubstituted 5-bromouracils with or without a substituent in position 6 undergo reductive debromination with ease most likely *via* a one-electron transfer process upon treatment with 1-benzyl-1,4-dihydronicotinamide under thermal conditions.

After extensive studies on the mechanism for reduction with 1,4-dihydropyridine derivatives, it has been proposed that the reduction is composed of an initial electron transfer.[1] Thus, the reaction of α-bromonitroalkanes,[2] α-nitronitriles,[3] α-nitrocarbonyl compounds,[3] or α-nitrosulfones[4] with 1-benzyl-1,4-dihydronicotinamide (BNAH)[5] gives debrominated, denitrated or desulfonylated products, as a result of the electron transfer from BNAH to the substrate in the initial stage of the reaction.

On the other hand, our recent work[6] has demonstrated that thermolysis of various 5-bromouracils in N,N-dialkylamides causes cleavage of the C(5)-bromine bond by way of an initial electron transfer process to give debrominated and coupling products.

We now report here a first example of reductive debromination of N(1)-unsubstituted 5-bromouracils (**1**) by BNAH, a simple model of NAD(P)H, under thermal conditions, which most likely involves an initial one-electron transfer process and depends largely upon the nature of the substituents at the C(6)-position of the uracil ring. The present result is also intriguing from the biological point of view. Previous papers have documented that 5-halogenouracils are metabolized by *dihydrouracil dehydrogenase* to give uracil and halide ions *in vivo*. Although the enzyme requires absolutely reduced nicotinamide adenine dinucleotide phosphate (NADPH), the dehalogenated process has not yet been clarified. For a pertinent review, see E. G. Sander in ref. 10, Vol. II, p. 273.

RESULTS AND DISCUSSION

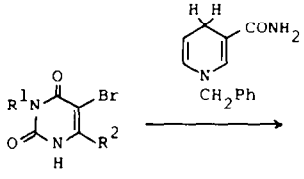
5-Bromo-3-methyluracil (**1a**)[7] was heated with an equimolar amount of BNAH without solvent at 180° for 3 h under an argon atmosphere. Silica gel column chromatography of the reaction mixture gave 3-methyluracil (**2a**, 54%), 5-benzyl-3-methyluracil (**3a**, 19%), and 1-benzyl-3-methyluracil (**4a**, 10%). Nicotinamide was detected by TLC analysis of the reaction mixture. Analogous results were also obtained even under mild conditions (130° for 8 h).

In a similar manner, 5-bromouracil (**1b**)[8] gave uracil (**2b**), 5-benzyluracil (**3b**), and 1-benzyluracil (**4b**) in 53, 11 and 6% yields, respectively, together with a small amount of nicotinamide.

The debrominated uracils (**2a,b**) and the benzylated uracils (**3a,b** and **4a,b**) obtained above were identical in every respect with the authentic samples.

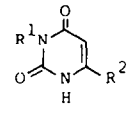
In a sharp contrast to N(1)-unsubstituted 5-bromouracils (**1a,b**) described above, N(1)-substituted 5-bromouracils, e.g. 5-bromo-1,3-dimethyluracil,[9] were inert upon treatment with BNAH under the analogous conditions. Thus, non-substitution at the N(1)-position of the uracil ring is the requisite for this type of debromination.

The significant substituent effect on the reductive debromination can be rationalized by considering involvement of a tautomeric form (**5**) in the reaction. The C(5)-bromine of the tautomeric form (**5**) is activated by adjacent carbonyl and acylimino groups. Reductive



(1)

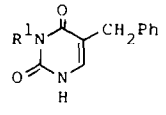
a : R^1= Me, R^2= H.
b : R^1= H, R^2= H.
c : R^1= Me, R^2= NMePh(p-Br).
d : R^1= Me, R^2= OPh.
e : R^1= Me, R^2= SPh.



(2)

a : R^1= Me, R^2= H.
b : R^1= H, R^2= H.
c : R^1= Me, R^2= NMePh(p-Br).
d : R^1= Me, R^2= OPh.
e : R^1= Me, R^2= SPh.

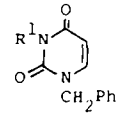
+



(3)

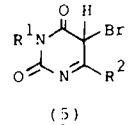
a : R^1= Me.
b : R^1= H.

+



(4)

a : R^1= Me.
b : R^1= H.



(5)

Scheme I.

dehalogenation of activated halides, e.g. α-haloketones, by BNAH has been already observed.[10]

The tautomeric form (**5**) could be stabilized efficiently by the introduction of a substituent such as anilino, phenoxy, or phenylthio at the C(6)-position of the uracil ring. The C(5)-hydrogen-deuterium exchange reaction of N(1)-unsubstituted uracils (**2**) is accelerated in the presence of C(6)-substituents such as anilino, phenoxy, and phenylthio groups. This fact is also reasonably accounted for by the contribution of the analogous tautomeric form. In agreement with this aspect, N(1)-unsubstituted 5-bromouracils (**1c–e**) possessing these substituents at the C(6)-position were debrominated with ease by BNAH under much more mild conditions comparing with the case of **1a,b**.

A suspension of 5 - bromo - 3 - methyl - 6 - (N - methyl - p - bromoanilino)uracil (**1c**)[6] and an equimolar amount of BNAH in acetonitrile was refluxed for 10 min under an argon atmosphere. After removal of the deposited 1-benzylnicotinamidium bromide (BNA.Br) by filtration, the filtrate was evaporated to dryness under reduced pressure and purified by silica gel column chromatography to give 3 - methyl - 6 - (N - methyl - *p* - bromoanilino)uracil (**2c**) in 91% yield. No other products were detected by TLC and NMR spectra of the reaction mixture.

Under analogous conditions, thermal reactions of 5 - bromo - 3 - methyl - 6 - phenoxy- and -6-phenylthiouracil (**1d** and **1e**)[6] with BNAH gave the corresponding debrominated uracils (**2d** and **2e**) in 81 and 15% yields, respectively, along with BNA·Br and the unchanged starting materials (**1d** and **1e**). Treatment of the 5 - bromo - 3 - methyluracil (**1a**) with BNAH in refluxing acetonitrile, however, the starting materials were recovered unchanged even after a prolonged reaction time (11 h).

As mentioned above, thermolysis of N(1)-unsubstituted 5-bromouracils (**1a,b**) in the presence of BNAH afforded the benzylated uracils (**3** and **4**) as by-products besides the debrominated uracils (**2a,b**). The thermal reaction of the 5-bromo-3-methyluracil (**1a**) with BNA·Br recovered the starting materials unchanged under drastic conditions (at 180° for 3 h). The 3-methyluracil (**2a**) also did not give any benzylated products in the reaction with BNAH or BNA·Br even under more drastic conditions. These facts accommodate that the formation of (**3** and **4**) in the thermal reactions of 5-bromouracils (**1a,b**) with BNAH originate from a transient species such as a cation radical (**B**) (*vide infra*) rather than BNAH and BNA·Br. Analogous benzylation of the substrate has been observed in the reduction of diaryl disulfides by BNAH.[11]

The reduction of (**1a**) by usual electron transfer reagents such as sodium hydrosulfite[12] gave the debrominated product (**2a**) in an excellent yield, whereas employment of sodium borohydride, a hydride transfer reducing reagent, did not cause the reductive debromination of (**1a**). Analogous results were also realized in the case of (**1d**).

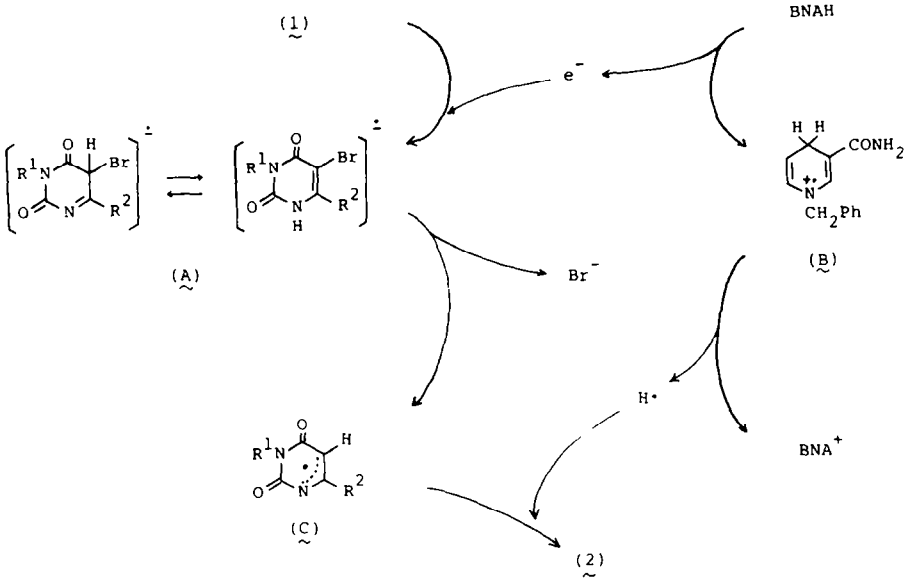
These observations provide a piece of evidence supporting that the electron transfer process is involved in the debromination of (**1**) by BNAH.

On the basis of the above results and the widely accepted reactivities of BNAH as an electron donor, we present a conceivable reaction sequence for the debromination of (**1**) by BNAH as depicted in Scheme II.

The initiation step of the reaction could involve a one-electron transfer from BNAH to 5-bromouracils (**1**) to give a uracilyl anion radical (**A**) and a cation radical (**B**). As a result of loss of a bromide ion, the anion radical (**A**) is converted into a σ radical (**C**).[13] Hydrogen abstraction of the σ radical (**C**) from the cation radical (**B**) results in the formation of the debrominated uracils (**2**) and BNA·Br as final products.

The formation of the benzylated uracils (**3**) and (**4**) could be explained in terms of coupling of the uracilyl radical (**C**) with the benzyl radical generated from (**B**) under the drastic conditions.

The enzymatic debromination of 5-bromo-2′-deoxyuridine (broxuridine) *in vivo* has been claimed to occur after de-deoxyribosidation.[14] The present experimental result on the reductive debromination of N(1)-unsubstituted 5-bromouracils by BNAH is of interest in connection with the enzymatic debromination of the 5 - bromo - 2′ - deoxyuridine.



Scheme II.

EXPERIMENTAL

All m.ps were determined on a Yanagimoto micro hot-stage apparatus and are uncorrected. Column chromatography was performed on silica gel (Wako gel C-300) using chloroform–acetone or chloroform–methanol as eluant. TLC analyses were carried out by using silica gel plates (Merck pre-coated plates silica gel 60 F-254) and mixed solvents (chloroform–acetone and chloroform–methanol).

Thermolysis of 5-bromo-3-methyluracil (**1a**) *in the presence of BNAH*

A mixture of (**1a**) (206 mg) and BNAH (215 mg) was heated without solvent at 180°C for 3 h under an argon atmosphere. The reaction mixture was subjected to silica gel column chromatography (eluant; chloroform–acetone = 20:1) to isolate 3-methyluracil (**2a**) (68 mg, 54.0%) 5-benzyl-3-methyluracil (**3a**) (42 mg, 19.4%); m.p. 156–7° (from EtOH) (lit,[15] 162–3°), and 1-benzyl-3-methyluracil (**4a**) (21 mg, 9.7%); m.p. 71–2° (from Et_2O) (lit[16] 75°). The presence of a small amount of nicotinamide was shown by TLC.

Thermolysis of 5-bromouracil (**1b**) *in the presence of BNAH*

Thermolysis of (**1b**) (191 mg) in the presence of BNAH (215 mg) was performed without solvent at 180° under an argon atmosphere for 3 h. Silica gel chromatography of the reaction mixture (eluant; chloroform–methanol = 20:1) gave uracil (**2b**) (59 mg, 52,6%), 5-benzyluracil (**3b**) (22 mg, 10.9%); m.p. 300-1° (from MeOH) (lit[17] 294–5°C), 1-benzyluracil (**4b**) (12 mg, 5.9%); m.p. 179–80° (from MeOH) (lit[16] 173°) and nicotinamide (trace).

Thermal reaction of 5-bromo-1,3-dimethyluracil with BNAH

Upon heating an equimolar mixture of 5-bromo-1,3-dimethyluracil (220 mg) and BNAH (215 mg) at 180°C for 3 h without solvent was afforded 1,3-dimethyluracil (29 mg, 20.7%) together with the unchanged starting material.

Thermal reaction of 5 - bromo - 3 - methyl - 6 - (N - methyl - p - bromoanilino)uracil (**1c**) *with BNAH*

A suspension of (**1c**) (389 mg) and BNAH (215 mg) in acetonitrile (10 ml) was refluxed for 10 min under an argon atmosphere. After separation of the deposited 1-benzylnicotinamidium bromide (167 mg, 57.0%) by filtration, the filtrate was evaporated to dryness under reduced pressure and purified by silica gel chromatography (eluant; chloroform–acetone = 20:1) to give 3 - methyl - 6 - (N - methyl - *p* - bromoanilino) uracil (**2c**) (281 mg, 90.6%).[18] No other products were confirmed by TLC and the NMR spectrum of the reaction mixture.

Thermal reaction of 5 - bromo - 3 - methyl - 6 - phenoxyuracil (**1d**) *with BNAH*

Treatment of (**1d**) (298 mg) with BNAH (215 mg) in refluxing acetonitrile (10 ml) for 1 h under an argon atmosphere gave 3-methyl-6-phenoxyuracil (**2d**) (178 mg, 81.3%)[19] together with the produced BNA·Br and the unchanged starting material (**1d**) (39 mg, 13.1%).

Thermal reaction of 5 - bromo - 3 - methyl - 6 - phenylthiouracil (**1e**) *with BNAH*

Refluxing a solution of (**1e**) (314 mg) and BNAH (215 mg) in acetonitrile (10 ml) under an argon atmosphere for 5 hr afforded 3-methyl-6-phenylthiouracil (**2e**) (36 mg, 15.3%)[20] along with a trace amount of BNA·Br and the starting material (**1e**) (252 mg, 80.3%).

Reduction of 5-bromouracils (**1a**) *and* (**1d**) *with* $Na_2S_2O_4$

To a suspension of (**1a**) (206 mg) in acetonitrile (5 ml), a solution of $Na_2S_2O_4$ (748 mg) and Na_2CO_3 (318 mg) in H_2O (5 ml) was added and stirred at room temperature for 1 h. The reaction mixture was purified by extraction with chloroform and silica gel column chromatography to isolate (**2a**) (108 mg, 85.6%).

In a similar manner, (**1d**) (298 mg) gave (**2d**) (210 mg, 96.0%) as sole product.

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