Synthesis of Variants of 5-Benzylacyclouridine and 5-Benzyloxybenzylacyclouridine

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A number of variations and derivatives of BAU (5-benzylacyclouridine) and BBAU (5-benzyloxybenzylacyclouridine), potent inhibitors of uridine phosphorylase were synthesized for evaluation as potential cancer chemotherapeutic agents. ("Acyclo" = 2'-hydroxymethoxymethyl-). These included a modification of the methylene group at N-1, esters of the terminal hydroxyl of the acyclo group, and extension of the benzyl chain at position 5 of the uracil base. BBBAU was a very good potentiator of FUdR in cell culture.

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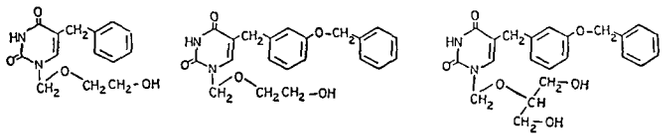
5-Benzylacyclouridine (BAU) and 5-benzyloxybenzylacyclouridine (BBAU), (Scheme 1) two nucleoside analogs synthesized in our laboratory are potent inhibitors of uridine phosphorylase [1-3]. This enzyme is important in the pyrimidine salvage pathway of nucleic acid synthesis, and therefore drugs that inhibit it are candidates for assay as potential cancer chemotherapeutic agents. A uridine phosphorylase inhibitor, for instance, even if not cytotoxic itself, could serve to diminish the intracellular degradation of the drug FUdR to the more toxic 5-FU and thus increase the clinical effectiveness of FUdR against solid tumors.

We have synthesized several analogs and modifications of BAU and BBAU, in search of the structures that will be most effective as inhibitors of uridine phosphorylase [1-3]; as inhibitors of growth of tumor cells in culture [4]; and as potentiators of the action of FUdR against solid tumors [4]. The acyclo moiety (2'-hydroxyethoxymethyl-) is analogous to the C_1-O-C_4-C_5 portion of the deoxyribose of natural nucleosides and identical to the side chain of the anti-viral agent acyclovir [5]. HM-BBAU (Scheme 1), a promising modification of the acyclo side chain to (1-hydroxymethyl-2-hydroxy-ethoxy)methyl-, has already been reported [6].

We now report examples of a) modification at the methylene group of the acyclo side chain, b) esterification of the terminal hydroxyl of the side chain, and c) modification of the benzyl side chain on the pyrimidine ring.

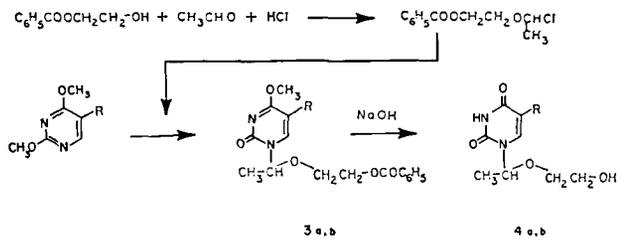
Scheme 1



1. BAU 2. BBAU HM-BBAU

As phosphorolysis by the enzyme takes place by attack at C_1 of the ribose, it was proposed to investigate the effect of a substituent on the carbon attached to N-1 of the pyrimidine which might deter the enzyme reaction and leave the nucleoside analog blocking the active site. Accordingly, *C*-methyl derivatives of BAU and BBAU were synthesized by modifying the acyclo reagent used to alkylate the uracil bases at N_1, as shown in Scheme 2.

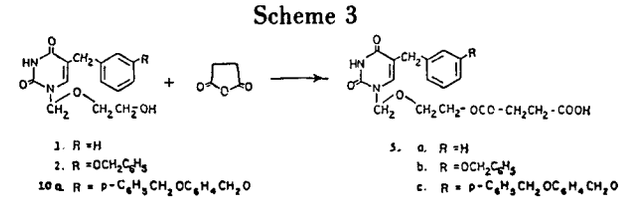
Scheme 2



3a,b 4a,b

A second type of modification was exemplified by esterifying the acyclo hydroxyl with a bifunctional acid. The choice of ester was suggested by the work of Colla *et al* (7), who have reported four esters of acyclovir to improve its solubility by a factor of 30 without decreasing its anti-viral effectiveness. Succinyl monoesters (Scheme 3) were chosen for ease of synthesis from succinic anhydride and tested as either free acid or sodium salt. The success of esters as inhibitors could depend upon the presence of an esterase in the target cell to regenerate the parent inhibitor *in situ*. The succinate esters were a little less active than BAU and BBAU but this small disadvantage might easily be offset in experimental or clinical circumstances by the improved solubility characteristics.

Scheme 3

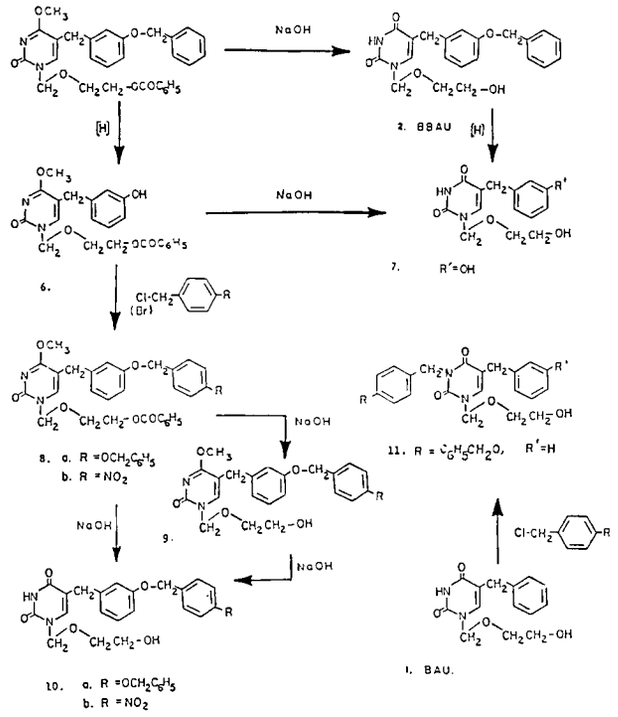


1. R = H
2. R = $OCH_2C_6H_5$
10a R = p-$C_6H_5CH_2OC_6H_4CH_2O$

5. a. R = H
b. R = $OCH_2C_6H_5$
c. R = p-$C_6H_5CH_2OC_6H_4CH_2O$

A third structural variation was made by extending the benzyl side chain on position 5 of uracil. BBAU is a more effective inhibitor of uridine phosphorylase than BAU by a factor of 3-5, and several orders of magnitude better than all previously known inhibitors. Niedzwicki *et al* [8] have postulated that this is due to a second, hydrophobic, binding site, adjacent to the active site of the enzyme. In order to examine the extent of this region, we substituted the terminal benzyloxy group of BBAU with another benzyloxy group (hydrophobic), as in compound **10a** (BBBAU), or with a nitro group to make **10b** (hydrophyllic), as shown in Scheme 4.

Scheme 4



Compounds BBBAU and *p*-nitro-BBAU were synthesized by removing the terminal benzyloxy group from BBAU by hydrogenolysis and reacting the resulting 5'-hydroxy-BAU with a commercially available substituted benzyl halide in the presence of base. Early attempts by this route, starting with unprotected BBAU, disclosed that alkylation of the hydroxy-BAU also took place readily at N-3. Repeating the alkylation procedure with unblocked BAU (no m-OH) confirmed the ease with which N-3 alkylation took place under the conditions that were used. The nmr spectra of N-3 substituted analogs lacked a proton signal for N_3-H at 11.35 and retained the single proton preak at 9.3 (unreacted aryl-OH). A third product was found, presumably disubstituted, that displayed five 2-proton peaks in the 4.9-5.4 region (CH_2-O and CH_2-N) but was not further investigated.

Alkylation exclusively at the 3'-OH position was successfully accomplished by starting with the protected 4-methoxy benzoate precursor of BBAU and postponing deblocking to the last step.

Lastly, we combined two variations by converting BBBAU to its succinyl monoester.

To date, studies of BBBAU as a potentiator of FUdR are promising, as may be seen from Table 1, and indicate that it may be an even better potentiator than BAU or BBAU [4]. Unlike BAU or BBAU, this compound has cytoxic activity of its own in the absence of FUdR.

Table 1

Effects of BBBAU on the Inhibitory Activity of FUdR Against HCT-8 *in vitro*

FUdR (uM)	% Inhibition None	Potentiator BBBAU 50 uM	BBBAU 10 uM
0	0	79	20
0.3	0	>100	37.2
1.0	3.1	>100	47.5
3.0	82.5	>100	>100

Growth inhibition was calculated as the reduction in the number of cell doublings after 72-hour incubation as determined by the trypan blue exclusion method. Cells were pretreated with BBBAU for 5 minutes before the addition of FUdR. In each experiment, the non-treated control cells reached at least 3 doublings.

Further study of BBBAU is continuing in order to confirm and extend these results. Studies of *p*-nitro-BBAU and the succinyl monoesters of BBBAU and *p*-nitro-BBAU are currently in process. Evaluation of the inhibitory activities of the synthesized compounds against the enzyme uridine phosphorylase are to be reported elsewhere.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The uv absorption maxima and extinction coefficients were obtained using a Perkin-Elmer Model 402 recording spectrophotometer, and ^{1}H nmr spectra were run on a Bruker WM-250 instrument in DMSO-d_6 or deuteriochloroform using trimethylsilane as an internal standard. Analyses were performed by the Baron Consulting Co. of Orange, Ct, and the Galbraith Laboratories of Knoxville, Tenn.

1-(2-Benzoyloxyethoxy)ethyl Chloride.

The *C*-methylacyclo reagent, 1-(2-benzoyloxyethoxy)ethyl chloride was prepared in essentially the same manner as the usual sidechain reagent for BAU and BBAU [9]. A solution of 40 g (0.24 moles) of ethylene glycol monobenzoate and 50 g (1.14 moles) of acetaldehyde in 300 ml of methylene chloride was cooled to 0° and saturated with dry, gaseous hydrogen chloride passed rapidly into the solution for 3 hours. The reaction mixture was stoppered and allowed to stand overnight in the refrigerator. It was then cooled to -50°, filtered quickly to remove ice, and dried over anhydrous calcium chloride. After filtering from the drying agent the solvent was evaporated under reduced pressure several times with methylene chloride to remove excess hydrogen chloride and acetaldehyde (aspirator). The oily residue was used directly for condensation with the desired base by either the carbonate method [10], or the

trimethylsilyl method [11]. Although the trimethylsilyl method was used initially and is reported below, it was found later that the carbonate method gave considerably better yields in the case of the *C*-methyl compounds.

5-Benzyl-1-[1-(2-benzoyloxyethoxy)ethyl]uracil (**3a**).

5-Benzyluracil (1.8 g, 8.9 mmoles) in 40 ml of hexamethyldisilazane containing 400 mg of ammonium sulfate was heated under reflux with protection from moisture for 3 hours, when the solution had cleared. The solution was evaporated to dryness and the residue taken up in 120 ml of dry benzene. To this there was added 2 g of mercuric cyanide and the mixture further heated for 30 minutes. A solution of 3 g of the *C*-methyl reagent in 50 ml of dry benzene was then added and heating continued for an additional 2 hours. The reaction mixture was cooled and diluted with 150 ml of chloroform. The organic phase was separated, washed with 30 ml of aqueous sodium bicarbonate, followed by 50 ml of 1 *M* potassium iodide solution and dried over anhydrous sodium sulfate. After filtering and evaporating the solvent, 1.2 g of an oily residue was obtained, which after purification by means of preparative tlc yielded 0.88 g (24%) of the benzoate **3a** as a crystalline solid melting at 156°; uv (ethanol): λ max 267 nm (10,600); nmr (DMSO-d_6: δ 1.41 (d, 3H, C-CH_3, J = 6 Hz), 3.42-3.60 (m, 2H, CH_2 at C_5), 3.63-3.88 (m, 2H, C$H_2$$CH_2$OBzt), 4.26-4.50 (m, 2H, $CH_2C$$H_2$OBzt), 5.88 (m, 1H, CH at N_1), 7.20 (br s, 5H, ArH of Bzl), 7.47-7.74 (m, 4H, C_6-H and 3 ArH of Bzt), 7.97 (d, 2H, ArH of Bzt, $J_{o,m}$ = 6 Hz), 11.35 (s, 1H, N_3-H).

Anal. Calcd. for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.84; H, 5.60; N, 7.02.

5-Benzyl-1-[1-(2-hydroxyethoxy)ethyl]uracil (**4a**).

The benzoate ester **3a** of *C*-methyl BAU (1 g, 2.5 mmoles) was hydrolyzed in a mixture of 50 ml of methanol and 10 ml of 2*N* sodium hydroxide by stirring at room temperature overnight. The solution was acidified cautiously to *p*H 5 by 6*N* hydrochloric acid with efficient stirring, and evaporated to dryness. The residue was extracted with ethanol, filtered from precipitated sodium chloride, and the filtrate evaporated to yield 0.38 g (52%) of **4a** as a waxy solid liquefying at about 50°; uv (*p*H 1): λ max 269 nm (5700); (*p*H 11): λ max 267 nm (4100); nmr (DMSO-d_6): δ 1.39 (d, 3H, C-CH_3, J = 8 Hz), 3.33-3.63 (m, 6H, CH_2CH_2OH and CH_2 at C_5 overlap), 4.70 (br s, 1H, OH), 5.77 (m, 1H, CH at N_1), 7.12-7.36 (m, 5H, ArH), 7.58 (s, 1H, C_6-H), 11.31 (br s, 1H, N_3-H).

Anal. Calcd. for $C_{15}H_{18}N_2O_4 \cdot 0.25\ H_2O$: C, 61.11; H, 6.32; N, 9.50. Found: C, 60.95; H, 6.33; N, 9.16.

5-Benzyloxybenzyl-1-[1-(2-benzoyloxyethoxy)ethyl]uracil (**3b**).

A mixture of 3 g (9.7 mmoles) of 5-benzyloxybenzyluracil, 1 g of ammonium sulfate and 80 ml of hexamethyldisilazane was stirred and heated to reflux with exclusion of moisture until the solution became clear (3 hours). The volatile materials were then evaporated *in vacuo* with protection against moisture. The residue was taken up in 150 ml of dry benzene and 6.5 g of mercuric cyanide was added. The mixture was stirred under nitrogen and heated to reflux temperature for 30 minutes. 1-(2-benzoyloxyethoxy)ethyl chloride, (5 g) in 100 ml of dry benzene was then added and heating continued for 2 hours. After cooling, the mixture was diluted with 200 ml of methylene chloride and the organic phase washed with 50 ml of saturated aqueous sodium bicarbonate, followed by 30 ml of 1 *M* potassium iodide solution. The organic layer was dried over anhydrous sodium sulfate and evaporated, to yield 3.7 g (crude yield, 76%) of the benzoate **3b** as a yellowish oil; uv (ethanol): λ max 271 nm (10,700); nmr (DMSO-d_6); δ 1.41 (d, 3H, C-CH_3, J = 5 Hz), 3.42-3.60 (m, 2H, CH_2 at C_5), 3.65-3.87 (m, 2H, C$H_2$$CH_2$OBzt), 4.25-4.51 (m, 2H, $CH_2C$$H_2$OBzt), 5.06 (s, 2H, CH_2 of OBzl), 5.87 (m, 1H, CH at N_1), 6.67-6.93 (m, 3H, ArH of C_5-Bzl), 7.08-7.20 (m, 1H, ArH of C_5-Bzl), 7.20-7.75 (m, 9H, ArH of OBzl(5), Bzt(3) and C_6-H overlap), 7.97 (d, 2H, remaining ArH of Bzt, $J_{o,m}$ = 5 Hz), 11.35 (s, 1H, N_3-H).

Anal. Calcd. for $C_{29}H_{28}N_2O_6$: C, 69.58; H, 5.64; N, 5.60. Found: C, 69.89; H, 5.81; N, 5.49.

5-Benzyloxybenzyl-1-[1-(2-hydroxymethyl)ethyl]uracil (**4b**).

The benzoate ester **3b** of *C*-methyl BBAU was hydrolyzed by dissolving 3.0 g (6 mmoles) in a mixture of 100 ml of methanol and 10 ml of 2 *N* sodium hydroxide, and stirring overnight at room temperature. The solution was acidified to *p*H 5, evaporated to dryness under reduced pressure, taken up in ethanol and filtered from insoluble sodium chloride. On evaporation of the ethanol, *C*-methyl BBAU (**4b**) was obtained as a crystalline solid. Recrystallization from ethanol yielded 1.6 g (67%), melting at 118°; uv (*p*H 1): λ max 269 nm (14,000); (*p*H 11): λ max 269 nm (5,600); nmr (DMSO-d_6): δ 1.39 (d, 3H, C-CH_3, J = 5 Hz), 3.33-3.58 (m, 6H, CH_2CH_2OH and CH_2 at C_5 overlap), 4.70 (m, 1H, OH), 5.08 (s, 2H, CH_2 of OBzl), 5.77 (m, 1H, CH at N_1), 6.80-6.95 (m, 3H, ArH of C_5-Bzl), 7.13-7.27 (m, 1H, ArH of C_5-Bzl), 7.27-7.51 (m, 5H, ArH of OBzl), 7.61 (s, 1H, C_6-H), 11.31 (s, 1H, N_3-H).

Anal. Calcd. for $C_{22}H_{24}N_2O_5 \cdot 0.25\ H_2O$: C, 65.90; H, 6.16; N, 6.99. Found: C, 66.02; H, 6.22; N, 6.65.

5-Benzyl-1-[(2-(3-carboxypropionyloxy)ethoxy)methyl]uracil (**5a**).

A solution of 1.4 g (5 mmoles) of BAU, 1.0 g (10 mmoles) of succinic anhydride, and 0.8 g (8 mmoles) of triethylamine (dried over calcium hydride and distilled) in 25 ml DMF was heated to 60° (oil bath) for two hours. After cooling, the volatile constituents were removed under vacuum and the residue taken up in water and adjusted to *p*H 2 with hydrochloric acid. The resulting oil was washed with water and passed through a silica gel column using methylene chloride/methanol (20:1) as the solvent, to yield 1.1 g (58%) of **5a** as a colorless oil; uv (*p*H 1): λ max 266 nm (12,400); (*p*H 11); λ max 263 nm (6000); nmr (DMSO-d_6): δ 2.47 (s, 4H, CH_2 of succinate), 3.56 (s, 2H, CH_2 at C_5), 3.70 (t, 2H, C$H_2$$CH_2$OSucc, J = 3 Hz), 4.13 (t, 2H, $CH_2C$$H_2$OSucc, J = 3 Hz), 5.11 (s, 2H, CH_2 at N_1), 7.12-7.38 (m, 5H, ArH), 7.64 (s, 1H, C_6-H), 11.39 (br s, 1H, N_3-H).

Anal. Calcd. for $C_{18}H_{20}N_2O_7 \cdot 0.25\ H_2O$: C, 56.76; H, 5.42; N, 7.35. Found: C, 56.67; H, 5.40; N, 7.16.

5-Benzyloxybenzyl-1-[(2-(3-carboxypropionyloxy)ethoxy)methyl]uracil (**5b**).

The BBAU-succinate was prepared in the same manner as the BAU analog, starting with 1.9 g (5 mmoles) of BBAU, 1.3 g (13 mmoles) of succinic anhydride and 1.3 ml (10 mmoles) of triethyl amine in 25 ml of DMF. The reaction mixture was stirred at 60° for 16 hours. DMF was evaporated and the residue twice taken up in 150 ml of water, adjusted to *p*H 2 and the liquid decanted to remove excess succinic acid, and then put through a short silica column. Fractions containing the product (tlc) on evaporation of the solvent yielded 1.8 g of pure monosuccinate **5b** (75%) as a colorless oil.

Anal. Calcd. for $C_{25}H_{26}N_2O_8 \cdot 0.5\ H_2O$: C, 61.09; H, 5.54; N, 5.70. Found: C, 61.15; H, 5.50; N, 5.60.

It could also be isolated as the sodium salt; uv (*p*H 1): λ max 267 nm (8400); (*p*H 11): λ max 268 nm (7300); nmr (DMSO-d_6): δ 2.44 (s, 4H, CH_2 of succinate), 3.51 (s, 2H, CH_2 at C_5), 3.70 (m, 2H, C$H_2$$CH_2$OSucc), 4.12 (m, 2H, $CH_2C$$H_2$OSucc), 5.06 (s, 2H, CH_2 of Bzl), 5.11 (s, 2H, CH_2 at N_1), 6.80-6.95 (m, 3H, ArH of 5-Bzl), 7.14-7.27 (m, 1H, ArH of 5-Bzl), 7.27-7.30 (m, 5H, ArH of OBzl), 7.64 (s, 1H, C_6-H), 11.39 (br s, 1H, N_3-H).

Anal. Calcd. for $C_{25}H_{25}N_2O_8Na \cdot H_2O$: C, 57.47; H, 5.21; N, 5.36. Found: C, 57.13; H, 4.83; N, 4.91.

5-(3-Hydroxybenzyl)-1-[(2-benzoyloxyethoxy)methyl]-2-keto-4-methoxypyrimidine (**6**).

The 4-methoxy benzoate intermediate from the synthesis of BBAU (6 g, 12 mmoles) was added to 200 ml of methanol and 1 ml of 6 *N* hydrochloric acid, and reduced under 3 atmospheres of hydrogen, using 5 g of 5% Pd on charcoal as the catalyst. Tlc showed that the reaction was complete in one hour. After uptake of hydrogen had ceased the solution was immediately brought to *p*H 7.3 with sodium hydroxide solution, filtered from the catalyst, and evaporated to dryness under reduced pressure. The residue was washed well with water to remove sodium chloride. Recrystallization from ethanol yielded 3.2 g (65%) of analytically pure **6**, mp 158°; uv (ethanol): λ max 281 nm (6600); nmr (DMSO-d_6): δ 3.51 (s, 2H, CH_2 at C_5), 3.81 (s, 3H, OCH_3), 3.90 (m, 2H, C$H_2$$CH_2$OBzt), 4.39 (m, 2H, $CH_2C$$H_2$OH), 5.28 (s, 2H, CH_2 at N_1), 6.56-6.63 (m, 3H, ArH

of HO-Bzl), 7.00-7.09 (m, 1H, ArH of HO-Bzl), 7.48-7.58 (m, 2H, ArH of Bzt), 7.64-7.71 (m, 1H, C_6-H), 7.86-7.97 (m, 3H, ArH of Bzt), 9.30 (br s, 1H, ArOH), no peak at 11.4 (N_3-H).

Anal. Calcd. for $C_{22}H_{22}N_2O_6 \cdot 0.25\ H_2O$: C, 63.68; H, 5.47; N, 6.75. Found: C, 63.94; H, 5.63; N, 6.75.

5-(3-Hydroxybenzyl)-1-[(2-hydroxyethoxy)methyl]uracil (**7**).

The 5-(3'-hydroxy)-BAU **7** could be prepared by removal of the protecting groups from compound **6** in aqueous sodium hydroxide. Alternatively, this compound could be prepared by reductive cleavage of the terminal benzyloxy group from BBAU, using a Pd catalyst and 3 atmospheres of hydrogen. However the latter product is not protected at the 3-position by conversion of the 4-keto group to methoxyl. When this compound is used as the intermediate in a subsequent alkylation step, alkylation takes place at N_3 as well or more readily than at the 3'-hydroxyl.

This intermediate was most easily prepared in one step by catalytic hydrogenation of the 4-methoxy-2'-benzyllic ether of BBAU, rather than the benzoate ester. A sample recrystallized from methanol for analysis melted at 168-169°; uv (*p*H 1): λ max 267 nm (11,600); (*p*H 11): λ max 265 nm (6900); nmr (DMSO-d_6): δ 3.46 (s, 2H, CH_2 at C_5), 3.50 (s, 4H, CH_2CH_2OH), 4.69 (br s, 1H, OH-aliph), 5.09 (s, 2H, CH_2 at N_1), 6.55-6.70 (m, 3H, ArH), 7.01-7.11 (m, 1H, ArH), 7.61 (s, 1H, C_6-H), 9.27 (br s, 1H, Ar-OH), 11.37 (br s, 1H, N_3-H).

Anal. Calcd. for $C_{14}H_{16}N_2O_5 \cdot 0.25\ H_20$: C, 56.65; H, 5.60; N, 9.44. Found: C, 56.33; H, 5.19; N, 9.45.

5-[3-(4-Benzyloxybenzyloxy)benzyl]-1-[(2-benzoyloxyethoxy)methyl]-2-keto-4-methoxypyrimidine (**8a**).

Compound **6** (1.4 g, 3.4 mmoles) was dissolved in a suspension of 3 g of finely ground solid anhydrous potassium carbonate in 10 ml of DMF and alkylated by stirring overnight at 40° with 0.9 g (3.9 mmoles) of *p*-benzyloxybenzyl chloride. After stirring for 48 hours at room temperature the solvent was evaporated, and the residue applied to a preparative tlc plate (Analtech) and developed using a mixture of methylene chloride and ethyl acetate. Separation of the appropriate band of the chromatogram and elution with methanol yielded 1.45 g (70%) of **8a**, the 4-methoxy benzoate of compound **10** (BBBAU). A sample for analysis was recrystallized from ethanol-2-propanol, mp 95-97°; uv (ethanol): λ max 274 nm (8500); nmr (DMSO-d_6): δ 3.54 (s, 2H, CH_2 at C_5), 3.79 (s, 3H, OCH_3), 3.90 (t, 2H, CH_2CH_2OBzt, $J_{1',2'} = 3$ Hz), 4.39 (t, 2H, CH_2CH_2OBzt, $J_{1',2'} = 3$ Hz), 4.97, 5.13, 5.28 (3s, 3 x 2H, CH_2 of term Bzl, CH_2 at N_1 and CH_2 of mid Bzl), 6.72-6.86 (m, 3H, ArH, *o*-H and *p*-H of C_5-Bzl), 6.97-7.05 (m, 2H, ArH, *m*-H of mid Bzl), 7.10-7.24 (m, 1H, ArH, *m*-H of C_5-Bzl), 7.29-7.57 (m, 9H, ArH of term Bzl, (5), *m*-H of mid Bzl, (2) and *m*-H of Bzt, (2)), 7.68 (t, 1H, C_6-H), 7.88-7.97 (m, 3H, ArH, *o*-H and *p*-H of Bzt), no peaks at 9.4 (Ar-OH) or 11.3 (N_3-H).

Anal. Calcd. for $C_{36}H_{34}N_2O_7 \cdot H_2O$: C, 70.22; H, 5.73; N, 4.55. Found: C, 70.44; H, 5.66; N, 4.92.

5-[3-(4-Benzyloxybenzyloxy)benzyl-1-[(2-hydroxyethoxy)-2-keto-4-methoxypyrimidine (**9**).

A solution of 0.85 g (1.4 mmoles) of compound **8a** in 200 ml of methanol was warmed to dissolve the solid. Aqueous sodium hydroxide (0.5 g in 8 ml of water) was added and the mixture stirred at room temperature for 4 hours, after which tlc showed a single spot with no starting material remaining. On concentrating the solution to 20 ml under vacuum a solid precipitated. The solution was diluted with 50 ml of distilled water and filtered, to yield 0.6 g (85%) of compound **9**. Recrystallization from ethanol gave a white crystalline product, mp 148-149°, with a double peak in the uv spectrum (ethanol) with maxima at 275 nm (7800) and 281 nm (7900). Its nmr spectrum showed that it still contained a 4-methoxyl group; nmr (deuteriochloroform): δ 3.65 (s, 2H, CH_2 at C_5), 3.71 (s, 4H, CH_2CH_2OH), 4.00 (s, 3H, OCH_3), 4.99, 5.10, 5.27 (3s, 3 x 2H, CH_2 of Bzl, CH_2 at N_1, and CH_2 of Bzl), 6.76-6.93 (m, 4H, ArH), 6.95-7.05 (m, 3H, ArH), 7.10 (s, 1H, ArH), 7.19-7.50 (m, 6H, ArH and C_6-H), no Ar-OH or N_3 peaks.

Anal. Calcd. for $C_{29}H_{30}N_2O_6$: C, 69.32; H, 5.98; N, 5.58. Found: C, 69.10; H, 6.18; N, 5.33.

5-[3-(4-Benzyloxybenzyloxy)benzyl]-1-[(2-hydroxyethoxy)methyl]uracil (**10a**).

Product **9** (0.4 g, 0.8 mmole), in 100 ml of methanol to which had been added 0.5 g of sodium hydroxide (12.5 mmoles) in 8 ml of water, was stirred in a water bath at 60° for 48 hours. Hydrolysis was complete, as indicated by tlc and the uv peak which had shifted to 269 nm. The solution was neutralized to *p*H 4 with small amounts of concentrated hydrochloric acid and concentrated to 20 ml, when a solid precipitated out. The precipitate was filtered, washed with a total of 20 ml of distilled water to remove sodium chloride and a few drops of ethanol, and then recrystallized from ethanol to yield 0.3 g (77%) of compound **10a**, "BBBAU", melting at 131°; uv (*p*H 1): λ max 267 nm (10,700); (*p*H 11): λ max 267 nm (10,700); nmr (DMSO-d_6): δ 3.51 (s, 6H, CH_2CH_2OH and CH_2 at C_5 overlap), 4.69 (br s, 1H, OH-aliph), 4.98, 5.10, 5.12 (3s, 3 x 2H, CH_2 at term Bzl, CH_2 at N_1 and CH_2 at mid Bzl), 6.78-6.91 (m, 3H, *o*-H and *p*-H of inner Bzl), 6.97-7.06 (m, 2H, *m*-H of mid Bzl), 7.15-7.22 (m, 1H, *m*-H of inner Bzl), 7.29-7.50 (m, 7H, ArH of term Bzl, 5, and *o*-H of mid Bzl, 2), 7.64 (s, 1H, C_6-H), 11.37 (br s, 1H, N_3-H).

Anal. Calcd. for $C_{28}H_{28}N_2O_6$: C, 68.85, H, 5.78, N, 5.74. Found: C, 68.67; H, 5.83; N, 5.62.

5-Benzyl-3-*N*-(4-benzyloxybenzyl)-1-[(2-hydroxyethoxy)methyl]uracil (**11**).

BAU **1** (1.6 g, 5.8 mmoles) and 1.0 (4.3 mmoles) of *p*-benzyloxybenzyl chloride were stirred at room temperature for 48 hours in a suspension of 3.5 g of finely ground potasssium carbonate in methylene chloride. After filtering, the solution was evaporated to dryness. The residue was taken up in methylene chloride, washed with water and the layers separated. The organic layer was concentrated to 10 ml and applied to a preparative tlc plate. Isolation of the appropriate band, elution and evaportion of the solvent gave 1.42 g (52%) of the *N*-substituted BAU analog, isolated as an oil; uv (ethanol): λ max 266 nm (13,600); nmr (DMSO-d_6): δ 3.50 (br s, 4H, CH_2CH_2OH), 3.60 (s, 2H, CH_2 at C_5), 4.69 (br s, 1H, OH-aliph), 4.91, 5.06, 5.16 (3s, 3 x 2H, CH_2 at N_3, CH_2 of OBzl, and CH_2 at N_1), 6.89-6.98 (m, 2H, ArH), 7.15-7.48 (m, 12H, ArH), 7.72 (s, 1H, C_6-H), no peak at 11.3 (N_3-H).

Anal. Calcd. for $C_{28}H_{28}N_2O_5 \cdot 0.5\ H_2O$: C, 69.85; H, 6.07; N, 5.82. Found: C, 70.19; H, 6.11; N, 5.82.

5-[3-(4-Nitrobenzyloxy)benzyl]-1-[(2-benzoyloxyethoxy)methyl]-2-keto-4-methoxypyrimidine (**8b**).

To compound **6** (2 g, 5 mmoles) in 30 ml of DMF there was added 1.1 g (5 mmoles) of *p*-nitrobenzyl bromide and 3 g of finely ground potassium carbonate. The suspension was stirred for 48 hours at room temperature, filtered and evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride, applied to preparative tlc plates and developed with 2% methanol in methylene chloride. The appropriate band was identified (R_f 0.52), scraped off the plates and eluted with methanol, to yield 1.4 g (52%) of compound **8b** as a colorless oil which solidified on standing for several days, mp 90-92°. A sample recrystallized for analysis from ethanol melted at 94-95°; uv (ethanol): λ max 273 nm (16,500); nmr (DMSO-d_6): δ 3.57 (s, 2H, CH_2 at C_5), 3.81 (s, 3H, 4-OCH_3), 3.86-3.94 (m, 2H, CH_2CH_2-OBzt), 4.32-4.43 (m, 2H, CH_2CH_2-OBzt), 5.24, 5.28 (2s, 2 x 2H, CH_2 at N_1, CH_2 of term Bzl), 6.75-6.90 (m, 3H, *o*-H and *p*-H of inner Bzl), 7.15-7.24 (m, 1H, *m*-H of inner Bzl), 7.45-7.55 (m, 2H, *m*-H of Bzt), 7.61-7.73 (m, 3H, *m*-H of NO_2-Bzl and C_6-H overlap), 7.86-7.96 (m, 3H, *o*-H and *p*-H of Bzt), 8.20-8.28 (d, 2H, *o*-H of NO_2-Bzl, $J_{o,m} = 8$ Hz).

Anal. Calcd. for $C_{29}H_{27}N_3O_8$: C, 63.84; H, 5.00; N, 7.70. Found: C, 63.48; H, 5.03; N, 8.04.

5-[3-(4-nitrobenzyloxy)benzyl]-1-[(2-hydroxyethoxy)methyl]uracil (**10b**).

Compound **8b** (0.9 g, 1.7 mmoles) was dissolved in a mixture of 100 ml of methanol, 5 ml methylene chloride, and 10 ml of 10% sodium hydroxide and stirred at room temperature overnight. It was then neutralized

with small amounts of concentrated hydrochloric acid and evaporated to dryness under reduced pressure. The residue was taken up in methylene chloride, loaded onto a preparative tlc plate and developed 3 times with 4% methanol in methylene chloride. The band containing the product was scraped off and eluted with methanol to yield 0.19 g (27%) of 4-nitro-BBAU (**10b**), mp 120-122°; uv (*p*H 1): λ max 270 nm (13,900); (*p*H 11): λ max 272 nm (15,700); nmr (DMSO-d_6): δ 3.39-3.58 (m, 6H, CH_2 at C_5 and CH_2CH_2OH overlap), 4.69 (br s, 1H, OH-aliph), 5.10, 5.24 (2s, 2 x 2H, CH_2 of NO_2-Bzl and CH_2 at N_1), 6.81-6.94 (m, 3H, *o*-H and *p*-H of inner Bzl), 7.14-7.27 (t, 1H, *m*-H of inner Bzl, $J_{5',4';5',6'}$ = 8 Hz), 7.64 (s, 1H, C_6-H), 7.67-7.77 (m, 2H, *m*-H of NO_2-Bzl), 8.26 (d, 2H, *o*-H of NO_2-Bzl, $J_{o,m}$ = 8 Hz), 11.35 (br s, 1H, N_3-H).

Anal. Calcd. for $C_{21}H_{21}N_3O_7$: C, 59.01; H, 4.95; N, 9.83. Found: C, 58.93; H, 5.08; N, 9.53.

5-[3-(4-Benzyoxybenzyloxy)benzyl]-1-[(2-(3-carboxypropionyloxy)ethoxy)-methyl]uracil (**5c**).

A solution of 1 g (2 mmoles) of compound **10a** (3B), 0.7 g (7 mmoles) of succinic anhydride and 0.6 g of triethyl amine in 25 ml of DMF was heated for 2 hours at 60° in an oil bath. The volatile constituents were removed under vacuum and water added to the residue to decompose any remaining succinic anhydride. The solution was adjusted to *p*H 1-2 with hydrochloric acid and decanted from the semi-solid residue which was well washed with water. Recrystallization of the solid from methylene chloride yielded 1.1 g of white, crystalline succinic acid monoester, **5c** (91%), melting at 116-117°; uv (ethanol-*p*H 11, 19:1): λ max 267 nm (10,900); nmr (DMSO-d_6): δ 2.48 (s, 4H, CH_3 of succinate), 3.52 (s, 2H, CH_2 at C_5), 3.70 (t, 2H, CH_2CH_2OH, J = 5 Hz), 4.13 (t, 2H, CH_2CH_2OH, J = 5 Hz), 4.98, 5.11, 5.13 (3s, 6H, CH_2 of term Bzl, CH_2 at N_1, and CH_2 of mid Bzl), 6.78-6.92 (m, 3H, *o*-H and *p*-H of inner Bzl), 7.03 (d, 2H, *m*-H of mid Bzl, J = 9 Hz), 7.19 (t, 1H, *m*-H of inner Bzl, J = 8 Hz), 7.33-7.50 (m, 7H, *o*-H of mid Bzl and ArH of term Bzl), 7.64 (s, 1H, C_6-H), 11.40 (br s, 1H, N_3-H).

Anal. Calcd. for $C_{32}H_{32}N_2O_9 \cdot 0.25\ H_2O$: C, 64.79; H, 5.52; N, 4.72. Found: C, 64.96; H, 5.81; N, 4.47.

5-[3-(4-Benzyoxybenzyloxy)benzyl]-1-[(2-(3-carboxypropanoyloxy)ethoxy)-methyl]uracil (**5c**), sodium salt.

To 0.5 g (1 mmole) of the acidic form of 3B-succinate in 10 ml of water there was added 0.85 ml of 1*N* sodium hydroxide. After the acid had dissolved, the solution was filtered and evaporated to dryness, leaving a white powder, (0.4 g, 66%); uv (ethanol-water, 19:1): λ max 268 nm (11,100); nmr (DMSO-d_6): δ 2.09 (t, 2H, CH_2CH_2COO-, J = 7 Hz), 2.35 (t, 2H, CH_2CH_2COO-, J = 7 Hz), 3.51 (s, 2H, CH_2 at C_5), 3.68 (t, 2H, CH_2CH_2OSucc, J = 5 Hz), 4.27 (t, 2H, CH_2CH_2OSucc), 4.98, 5.10, 5.13 (3c, 6H, CH_2 of term Bzl, CH_2 at N_1, and CH_2 of mid Bzl), 6.77-6.93 (m, 3H, *o*-H and *p*-H of inner Bzl), 7.02 (d, 2H, *m*-H of mid Bzl, J = 9 Hz), 7.18 (t, 1H, *m*-H of inner Bzl, J = 9 Hz), 7.30-7.50 (m, 7H, *o*-H of mid Bzl and ArH of term Bzl), 7.67 (s, 1H, C_6-H), 11.35 (v broad, low s, N_3-H), no peak at 9.36 (Ar-OH).

Anal. Calcd. for $C_{32}H_{32}N_2O_9Na \cdot 0.25\ H_2O$: C, 62.03; H, 5.20; N, 4.52. Found: C, 62.23; H, 5.43; N, 4.47.

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