Synthesis of Some Halogenated and Disubstituted Amino Benzylacyclouridine Derivatives

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1'-Halogenomethyl, 1'-azidomethyl and 1'-disubstituted aminomethyl derivatives of BAU (5-benzylacyclouridine) and BBAU (5-benzyloxybenzylacyclouridine) were synthesized in the course of our studies of benzylacyclouridines. Two new and more convenient preparations of the previously known aminomethyl-and hydroxymethyl- parent compounds of these two series, AM-BAU, AM-BBAU and HM-BBAU are also reported. These compounds were synthesized during a search for potential antiviral agents and pyrimidine phosphorylase inhibitors.

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The effectiveness of 5-benzyl and 5-(3'-benzyloxy)benzylacyclouridines (BAU and BBAU) some of their analogs as potentiators of the fluoropyrimidine antineoplastic agents FUra (5-FU) and FdUrd [1,2] may be due at least in part to the fact that they are potent inhibitors of the enzyme uridine phosphorylase, an important enzyme in the salvage pathway of pyrimidine catabolism [3-5]. As inhibitors of uridine phosphorylase, these compounds would be expected to inhibit the conversion of FdUrd to the less effective and more toxic FUra. A number of derivatives and variants of benzylacyclouridines [6-10] have been synthesized in an effort to improve water solubility, maximize potentiation of fluoropyrimidines against tumor cells without increasing toxicity to the host, and to infer insofar as possible relationships between structural features and inhibitory and potentiating action. BAU and BBAU are nontoxic to normal cells which tend to depend less heavily than tumor cells on uridine phosphorylase for pyrimidine salvage [1].

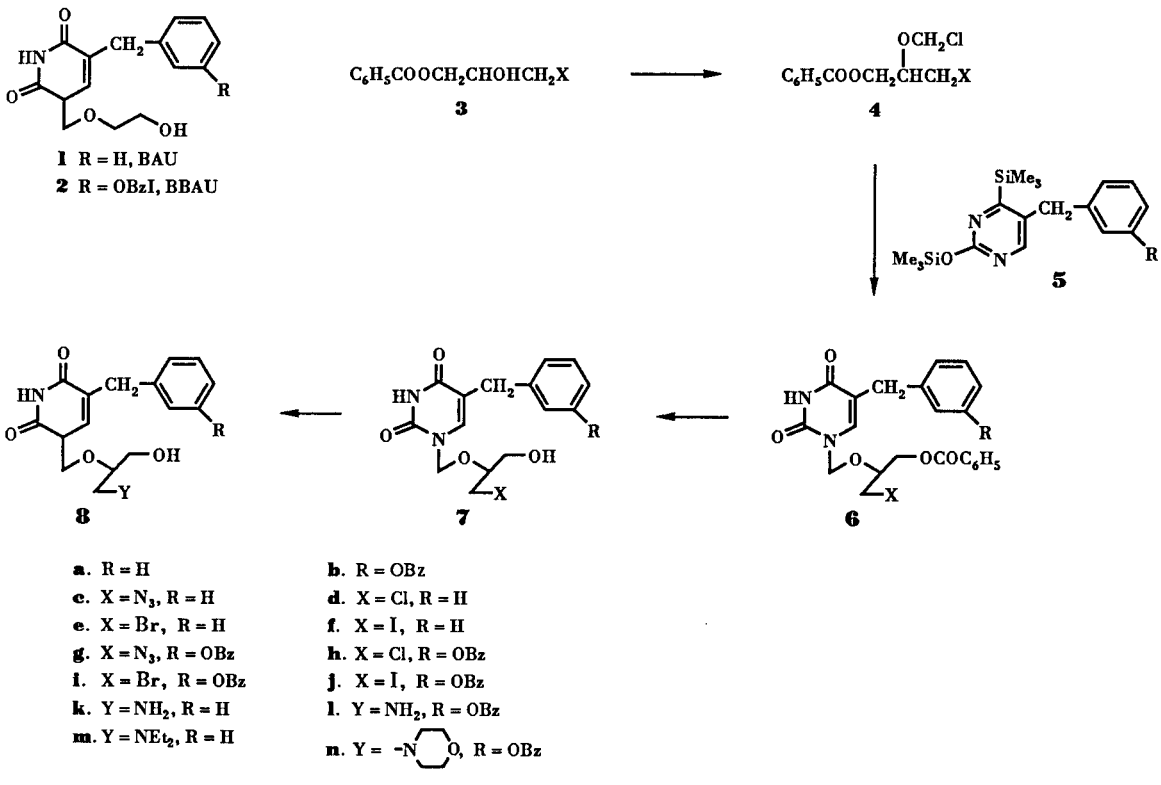
Benzylacyclouridines combine a 5-benzyl or 5-benzyloxybenzyl substituent on a uracil base [11] with a 1-(2'-hydroxyethoxymethyl) group similar to that of Acyclovir [12] as the saccharide moiety, equivalent to C(1)-O-C(4)-C(5) of the ribo/deoxyribofuranoside portion of natural nucleosides. Alternatively, the functionality of the side chain can be doubled to increase the solubility of the analog, as was done with Acyclovir [13-16]. This acyclo side chain is analogous to the C(1)-O-C(4)[C(3)OH]-C(5)OH portion of a ribo/deoxyribofurnnose ring, but numbered as a derivative of the ethoxy moiety [12,14,15] (HM-series). A derivative in which one of the two hydroxyls was substituted by an amino or alkyl-substituted amino group would yield an AM-series, or a halogen substituent an XM-BAU or XM-BBAU series. The addition of a 1'-aminomethyl substituent to the acyclo group was investigated by Siegel and Lin (17) and Lin and Liu (18), who synthesized AHPBU (AM-BAU) and found that this compound was a better inhibitor of uridine phosphorylase prepared from Sarcoma 180 cells than the corresponding dihydroxy analog by a factor of 5. Our subsequent preparation of AM-BBAU yielded a still more potent inhibitor, the most potent found to date, but this compound was toxic to normal cells [8] and not suitable for further development.

Acyclonucleosides and their antiviral effects were reviewed by C. K. Chu and S. J. Cutler in 1986 [19]. 5-Benzylacyclopyrimidines are not generally inhibitory against viruses, although BAU has some protective action against the bone marrow toxicity of AZT used to treat AIDS [20]. Some 5,6-disubstituted acyclopyrimidines however have been reported by Tanaka *et al* to be active against the HIV virus [21]. Another biological effect of further interest is that of the benzylacyclouridine variant BBBAU (5-[3'-(4-''-benzyloxy)benzyloxy]benzylacyclouridine), which while not an inhibitor of uridine phosphorylase, is an inhibitor of thymine synthase and a potentiator of the action of fluoropyrimidines against otherwise refractory colon tumor cell lines [22].

The aminomethyl analogs [8,9] of the AM series are the most potent inhibitors of UrdPase known to date, and the best potentiators of FdUrd, but tend to be more toxic than other derivatives. The substituted amino analogs described in this report were synthesized to determine whether substitution on the amino group of AM-benzylacyclouridines by alkyl groups would reduce host toxicity without loss of water solubility or the potentiating effect.

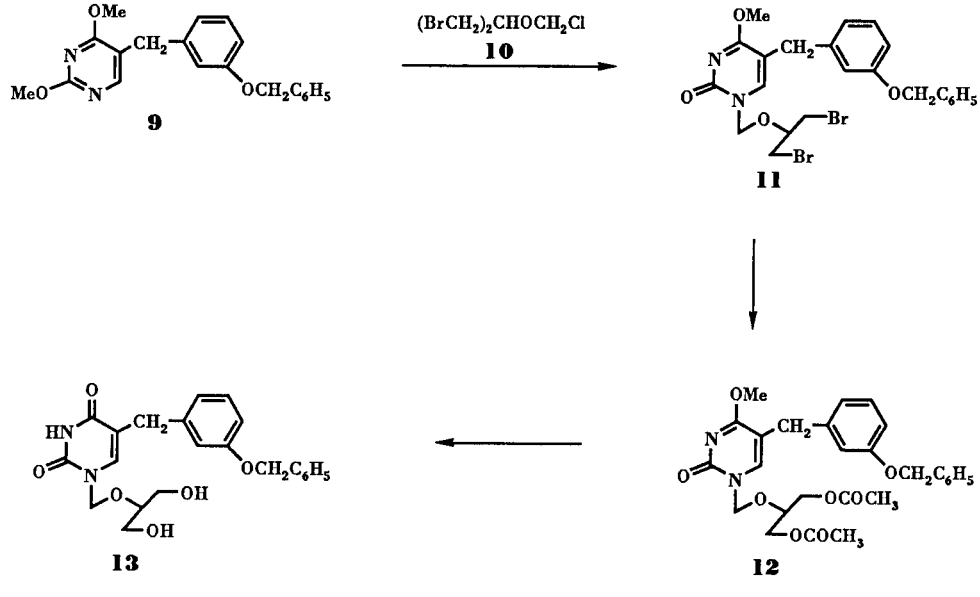
Azidomethyl compounds in addition to being useful intermediates were also candidates for testing for biological activity. Synthesis of azido analogs was achieved by reacting 1-benzoyloxypropylene oxide with sodium azide and magnesium perchlorate in aqueous solution, to give 1-benzoyloxy-3-azido-2-propanol (**3c**), which was treated with paraformaldehyde and dry hydrogen chloride in methylene chloride, to afford the chloromethyl ether **4c**. The latter was then condensed with the 2,4-bis-silylated derivatives of 5-benzyl or 5-benzyloxybenzyluracil, (**5a** or **5b**) in the presence of anhydrous potassium carbonate in methylene chloride to yield 5-benzyl or 5-benzyloxybenzyl-1-[(1'-azidomethyl-2'-benzoyloxyethoxy)methyl]uracil, **6c**

Scheme 1



a. R = H
b. R = OBz
c. X = N_3, R = H
d. X = Cl, R = H
e. X = Br, R = H
f. X = I, R = H
g. X = N_3, R = OBz
h. X = Cl, R = OBz
i. X = Br, R = OBz
j. X = I, R = OBz
k. Y = NH_2, R = H
l. Y = NH_2, R = OBz
m. Y = NEt_2, R = H
n. Y = , R = OBz

Scheme 2



or **6g**.

Hydrolysis of **6c** or **6g** with potassium carbonate in methanol gave 5-benzyl or 5-benzyloxybenzyl-1-[(1′-azidomethyl-2′-hydroxyethoxy)methyl]uracil, **7c** or **7g** respectively.

5-Benzyl-1-[(1′-azidomethyl-2′-hydroxyethoxy)methyl]-uracil in methanol was subjected to catalytic hydrogenation in the presence of 5% Pd on carbon. Treatment with hydrogen chloride afforded the hydrochloride salt of 1′-aminomethyl-5-benzylacyclouridine, AM-BAU·HCl (**8k**). On the other hand, aminomethyl-5-benzyloxybenzylacyclouridine (**8l**) was obtained by reduction of the corresponding azido compound with triphenylphosphine.

A general preparation of halogenated analogs was as follows: 1-halogeno-3-benzoyloxypropanol-2 were converted into the corresponding chloromethylated ethers, **4d** and **4e** or **4f**, by reaction with paraformaldehyde and dry hydrogen chloride in methylene chloride. Condensation of the chloromethylated ethers with 5-benzyl-2,4-di(trimethylsilyloxy)pyrimidines was accomplished by stirring with anhydrous potassium carbonate in methylene chloride to give 5-benzyl-1-[(1′-halogenomethyl-2′-benzoyloxyethoxy)-methyl]uracils **6d**, **6e**, and **6f**. 5-Benzyloxybenzyl-1-[(1′-halogenomethyl-2′-benzoyloxyethoxy)methyl]uracils **6h**, **6i**, and **6j** were also prepared in this manner.

Hydrolysis of the benzoates with methanolic potassium carbonate gave 5-benzyl-1-[(1′-halogenomethyl-2′-hydroxyethoxy)methyl]uracils **7d**, **7e**, and **7f**; and 5-benzyloxybenzyl-1-[(1′-halogenomethyl-2′-hydroxyethoxy)methyl]uracils **7h**, **7i**, and **7j**.

To synthesize the substituted amino derivatives, 5-benzyl-1-[(1′-bromomethyyl-2′-hydroxyethoxy)methyl]uracil (**7e**) was reacted with diethylamine in boiling ethanol, to yield 5-benzyl-1-[(1′-diethylamino-2′-hydroxyethoxy)methyl]uracil (**8m**). 5-Benzyloxybenzyl-1-[(1′-morpholinomethyl-2′-hydroxyethoxy)methyl]uracil (**8n**) was prepared similarly, from 5-benzyloxybenzyl-1-[(1′-bromomethyl-2′-hydroxyethoxy)methyl]uracil and morpholine (Scheme 1).

1,3-Dibromopropanol-2 was converted to its chloromethyl ether, **10**, and reacted with 5-benzyloxybenzyl-2,4-dimethoxypyrimidine, **9**, in the presence of anhydrous potassium carbonate in methylene chloride, to give 5-benzyloxybenzyl-1-[di(bromomethyl)methoxymethyl]-2-oxo-4-methoxypyrimidine, **11**. Replacement of bromo by acetoxy groups was accomplished by treatment with anhydrous potassium acetate in dry dimethylformamide. The resulting 5-benzyloxybenzyl-1-[di(acetoxymethyl)methoxymethyl]-2-oxo-4-methoxypyrimidine, **12** was hydrolyzed with methanolic potassium carbonate to give hydroxymethyl-5-benzyloxybenzylacyclouridine, **13** (Scheme 2).

None of the azido-, substituted amino- nor halogenomethyl analogs were active against the CEM-IW virus of the Drug Development Branch of the NIH. Studies of pyrimidine phosphorylase activity are in progress.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The uv spectra were obtained on a Perkin-Elmer Model 402 recording spectrophotometer. The ^{1}H nmr spectra were measured on a Bruker Model WM-400 instrument, using tetramethylsilane as an internal standard. All samples were run in deuteriochloroform. Analyses were performed by the Baron Consulting Laboratory of Orange, Conn. or the Galbraith Laboratories of Knoxville, Tenn.

1-Benzyloxy-3-azido-propanol-2 (**3c**).

Magnesium perchlorate (9 g, 50.6 mmoles) was dissolved at 0° in 35 ml of water containing 11.5 g (64 mmoles) of 1-benzoyloxypropylene oxide. Sodium azide (5.9 g, 90.8 mmoles) was added at 0° and the mixture stirred for 2 hours at 0° and then for 2 days at room temperature. The solution was extracted with ether and the ethereal solution dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residual oil chromatographed on silica gel. Elution with a solution of methylene chloride:ether (1:1, v/v) gave 8.7 g (77%) of azido compound **3c**; ^{1}H nmr (deuteriochloroform): δ 2.82 (br s, 1H, OH), 3.44-3.54 (m, 2H, CH_2N_3), 4.13-4.19 (m, 1H, CHOH), 4.36-4.45 (m, 2H, CH_2OBz), 7.43-7.48 (m, 2H, ArH), 7.56-7.62 (m, 1H, ArH), 8.03-8.07 (m, 2H, ArH).

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.50; H, 5.30; N, 19.12.

5-Benzyl-1-[(1′-azidomethyl-2′-benzoyloxyethoxy)methyl]uracil (**6c**).

Dry 5-benzyluracil (2.02 g, 10 mmoles) and 50 mg of ammonium sulfate were suspended in 10 ml of hexamethyldisilazane and heated under reflux for approximately 3 hours with the exclusion of moisture, until all of the 5-benzyluracil was dissolved. Excess hexamethyldisilazane was evaporated under reduced pressure, leaving as a residue 5-benzyl-2,4-bis(trimethylsilyloxy)-pyrimidine. A suspension of 2.88 g (13 mmoles) of **3c** and 780 mg of paraformaldehyde in 45 ml of methylene chloride was cooled to 0° and dry hydrogen chloride bubbled through the suspension until it was saturated. The reaction mixture was allowed to stand at 0° overnight, then washed with 5 ml of water and dried over anhydrous magnesium sulfate.

The filtered solution of the chloromethylated product in methylene chloride was added to a suspension of the bis-trimethylsilylated 5-benzyluracil and finely powdered anhydrous potassium carbonate in 15 ml of methylene chloride and stirred at room temperature for 24 hours. The reaction mixture was then cooled to 0° and treated with 10 ml of water, added dropwise. The methylene chloride layer was separated, washed with water, freed from solvent and chromatographed on silica gel. Elution with a 10:1 mixture of methylene chloride and ether yielded 3.15 g (72%) of an oily product; uv (ethanol): λ max 266 (ϵ 9093); ^{1}H nmr (deuteriochloroform): δ 3.43 (d, 2H, CH_2N_3, J = 5.8 Hz), 3.53 (d, 1H, CH_2 at C_5, J = 16.2 Hz), 3.60 (d, 1H, CH_2 at C_5, J = 16.2 Hz), 4.15-4.20 (m, 1H, *tert* H), 4.32 (dd, 1H, CH_2O, J = 12.0, 5.8 Hz), 4.44 (dd, 1H, CH_2O, J = 12.0, 9.2 Hz), 5.17 (d, 1H, OCH_2N, J = 10.8 Hz), 5.29 (d, 1H, OCH_2N, J = 10.8 Hz), 6.88 (t, 1H, C_6-H, J = 1.1 Hz), 7.16-7.32 (m, 5H, ArH of Bzl), 7.42-7.47 (m, 2H, ArH of Bz), 7.56-7.61 (m, 1H, ArH of Bz), 7.97-8.05 (m, 2H, ArH of Bz).

Anal. Calcd. for $C_{22}H_{21}N_5O_5$: C, 60.68; H, 4.86; N, 16.09. Found: C, 60.90; H, 4.98; N, 16.35.

5-Benzyloxybenzyl-1-[(1′-azidomethyl-2′-benzoyloxyethoxy)methyl]uracil (**6g**).

This compound was prepared similarly in 72% yield by the condensation of 2,4-bis(trimethylsilyl) derivative of 5-benzyloxybenzyluracil with the chloromethylated product of 1-benzyloxy-3-azido-propanol-2 (**3c**); uv (ethanol): λ max 266 (ϵ 9214); ^{1}H nmr (deuteriochloroform): δ 3.43 (d, 2H, CH_2N_3, J = 5.6 Hz), 3.49 (d, 1H, CH_2 at C_5, J = 15.2 Hz), 3.57 (d, 1H, CH_2 at C_5, J = 15.2 Hz), 4.15-4.20 (m, 1H, *tert* H), 4.32 (dd, 1H, CH_2O, J = 12.0, 5.9 Hz), 4.44 (dd, 1H, CH_2O, J = 12.0, 4.1 Hz), 5.03 (s, 2H, OCH_2Ph), 5.16 (d, 1H, OCH_2N, J = 10.8 Hz), 5.27 (d, 1H, OCH_2N, J = 10.8 Hz), 6.76-6.85 (m, 3H, *o*-H and *p*-H of inner Bzl), 6.89 (s, 1H, C_6-H),

7.21 (t, 1H, *m*-H of inner Bzl, J = 7.8 Hz), 7.30-7.46 (m, 8H, ArH), 7.55-7.60 (m, 1H, ArH of Bz), 7.97-8.04 (m, 2H, ArH of Bz).

Anal. Calcd. for $C_{29}H_{27}N_5O_6$: C, 64.32; H, 5.03; N, 12.93. Found: C, 64.17; H, 5.06; N, 12.70.

5-Benzyl-1-[(1′-azidomethyl-2′-hydroxyethoxy)methyl]uracil (**7c**).

A mixture of 1.4 g (3.2 mmoles) of 5-benzyl-1-[(1′-azidomethyl-2′-benzoyloxyethoxy)methyl]uracil and 1 g (7.2 mmoles) of powdered potassium carbonate in 30 ml of methanol was stirred at room temperature for 3 hours and then neutralized with 3 *N* hydrochloric acid. Methanol and water were evaporated under reduced pressure. The residue was extracted with methylene chloride. After evaporation of methylene chloride the residual oil was chromatographed on silica gel and eluted with methylene chloride:ether (1:1, v,v) to give 0.9 g of **7c**, (85%); uv (ethanol): λ max 266 nm (ε 9121), ^{1}H nmr (deuteriochloroform): δ 3.32 (d, 2H, CH_2N_3, J = 5.5 Hz), 3.60-3.64 (m, 2H, CH_2O), 3.65 (s, 2H, CH_2 at C_5), 3.79-3.85 (m, 1H, *tert* H), 5.16 (d, 1H, OCH_2N, J = 10.5 Hz), 5.23 (d, 1H, OCH_2N, J = 10.5 Hz), 6.96 (t, 1H, C_6-H, J = 1.1 Hz), 7.21-7.33 (m, 5H, ArH).

Anal. Calcd. for $C_{15}H_{17}N_5O_4$: C, 54.37; H, 5.17; N, 21.14. Found: C, 54.60; H, 5.38; N, 21.08.

5-Benzyloxybenzyl-1-[(1′-azidomethyl-2′-hydroxyethoxy)methyl]-uracil (**7g**).

This compound was obtained in 78% yield by the hydrolysis of the corresponding 2′-benzoyloxyethoxy derivative with methanolic potassium carbonate; uv (ethanol): λ max 266 nm (ε 9087); ^{1}H nmr (deuteriochloroform): δ 3.29-3.38 (m, 2H, CH_2N_3), 3.58-3.70 (m, 2H, CH_2O), 3.64 (s, 2H, CH_2 at C_5), 3.79-3.85 (m, 1H, *tert* H), 5.03 (s, 2H, CH_2 of term Bzl), 5.20 (s, 2H, OCH_2N), 6.82 (m, 3H, *o*- and *p*-H of inner Bzl), 6.93 (t, 1H, C_6-H, J = 1.1 Hz), 7.23 (dd, 1H, *m*-H of inner Bzl, J = 7.2, 1.6 Hz), 7.30-7.45 (m, 5H, ArH of Bzl).

Anal. Calcd. for $C_{22}H_{23}N_5O_5$: C, 60.40; H, 5.30; N, 16.01. Found: C, 60.63; H, 5.37; N, 16.29.

5-Benzyl-1-[(1′-aminomethyl-2′-hydroxyethoxy)methyl]uracil (**8k**).

5-Benzyl-1-[(1′-azidomethyl-2′-hydroxyethoxy)methyl]uracil, **7c**, (200 mg, 0.46 mmoles) was dissolved in 20 ml of methanol containing 0.4 ml of 6 *N* hydrochloric acid. 5% Palladium on carbon (0.2 g) was added to the solution and subjected to catalytic hydrogenation. The catalyst was filtered off and the solvent evaporated under reduced pressure and the product recovered from the residue. The ^{1}H nmr, uv spectra and tlc were identical to that of an authentic sample [7].

5-Benzyloxybenzyl-1-[(1′-aminomethyl-2′-hydroxyethoxy)methyl]-uracil (**8l**).

5-Benzyloxybenzyl-1-[(1′-azidomethyl-2′-hydroxyethoxy)methyl]uracil, **7g**, (437.5 mg, 1 mmole), and 524 mg (2 mmoles) of triphenylphosphine in 5 ml of dioxane was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure. The residue was chromatographed on silica gel and eluted with methylene chloride:ethanol (4:1, v/v) to give **8l**. The ^{1}H nmr, uv spectra, and tlc were identical with those of AM-BBAU [8].

5-Benzyloxybenzyl-1-[di(bromomethyl)methoxymethyl]-2-oxo-4-methoxypyrimidine (**11**).

1,3-Dibromopropanol (714 mg, 3 mmoles) was chloromethylated by standard procedure to its chloromethylated product, and dissolved in 5 ml of methylene chloride. To this solution there was added a suspension of 0.67 g (2 mmoles) of 5-benzyloxybenzyl-2,4-dimethoxypyrimidine (**9**), and 4.14 mg of powdered anhydrous potassium carbonate in 5 ml of dry methylene chloride, and the mixture was stirred at room temperature for 2 days. It was filtered and washed with methylene chloride. The filtrate and washings were combined and evaporated to dryness. The residue was chromatographed on silica gel and eluted with methylene chloride:ether (20:1, v/v) to give 812 mg of white crystals (74%), mp 95-96°; uv (ethanol): λ max 266 nm (ε 9217); ^{1}H nmr (deuteriochloroform): δ 3.48-3.57 (m, 4H, CH_2Br x 2), 3.61 (s, 2H, CH_2 at C_5), 3.98 (s, 3H, OCH_3), 4.12 (t, 1H, *tert* H, J = 5.09 Hz), 5.04 (s, 2H, CH_2 of term Bzl), 5.30 (s, 2H, OCH_2N), 6.76-6.90 (m, 3H, *o*-H and *p*-H of inner Bzl) 7.13 (s, 1H, C_6-H), 7.21-7.25 (m, 1H, *m*-H of inner Bzl), 7.30-7.45 (m, 5H, ArH).

Anal. Calcd. for $C_{23}H_{24}N_2O_4Br_2$: C, 50.02; H, 4.38; N, 5.07; Br, 28.94. Found: C, 50.13; H, 4.38; N, 3.20; Br, 28.71.

5-Benzyloxybenzyl-1-[di(acetoxymethyl)methoxymethyl]-2-oxo-4-methoxypyrimidine (**12**).

5-Benzyloxybenzyl-1-[di(bromomethyl)methoxymethyl]-2-oxo-4-methoxypyrimidine (1.1 g, 2 mmoles) was dissolved in 10 ml of dry DMF, and treated with 782 mg (20 mmoles) of anhydrous potassium acetate. The mixture was stirred and heated at 80° for 15 hours. The solvent was removed under reduced pressure and the residue subjected to chromatography on silica gel. Elution with methyl chloride:ether (4:1, v/v) gave 631 mg of **12** (64%); uv (ethanol): λ max 266 nm (ε 9314); ^{1}H nmr (deuteriochloroform): δ 2.01 (m, 6H, CH_3 x 2), 3.65 (s, 2H, CH_2 at C_5), 3.98 (s, 3H, OCH_3), 4.02-4.07 (m, 1H, *tert* H), 4.16-4.24 (m, 4H, CH_2O x 2), 5.04 (s, 2H, CH_2 of term Bzl), 5.30 (s, 2H, OCH_2N), 6.76-6.89 (m, 3H, *o*- and *p*-H of inner Bzl), 7.13 (s, 1H, C_6-H), 7.24 (t, 1H, *m*-H of inner Bzl, J = 7.90 Hz), 7.30-7.45 (m, 5H, ArH).

Anal. Cacld. for $C_{27}H_{30}N_2O_8 \cdot H_2O$: C, 61.35; H, 6.10; N, 5.30. Found: C, 61.58; H, 5.99; N, 5.26.

5-Benzyloxybenzyl-1-[(1′-hydroxymethyl-2′-hydroxyethoxy)methyl]uracil (HM-BBAU).

A mixture of 5-benzyloxybenzyl-1-[di(acetoxymethyl)methoxymethyl]-2-oxo-4-methoxypyrimidine, **12**, (992 mg, 2 mmoles), and 552.8 mg (4 mmoles) of potassium carbonate dissolved in 10 ml of methanol was stirred at room temperature overnight. The solution was neutralized with hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with methylene chloride and combined extracts washed with water. After removal of solvent the residue was chromatographed on silica gel and eluted with 2% methanol in methylene chloride to give HM-BBAU. The nmr, uv spectra and tlc were identical with those of authentic samples of HM-BBAU [4].

5-Benzyl-1-[(1′-chloromethyl-2′-benzoyloxyethoxy)methyl]uracil (**6d**).

A suspension of 1-chloro-3-benzoyloxy-2-chloromethoxypropane (prepared from 2.15 g (10 mmoles) of 1-chloro-3-benzoyloxypropanol-2 [23]), 5-benzyl-2,4-di(trimethylsilyloxy)pyrimidine (prepared from 1.62 g, 8 mmoles of 5-benzyluracil), and 2.07 g (15 mmoles) of anhydrous powdered potassium carbonate in 25 ml of dry methylene chloride was stirred at room temperature for 24 hours and then cooled to 0°. Ten ml of water was added and the methylene chloride layer separated and washed with water. The solvent was removed under reduced pressure and the residue chromatographed on silica gel. It was eluted with methylene chloride:ether (10:1, v/v) to yield **6d**; uv (ethanol): λ max 266 nm (ε

9342); ^{1}H nmr (deuteriochloroform): δ 3.45-3.95 (m, 4H, CH_2Cl and CH_2 at C_5), 4.24 (m, 1H, *tert* H), 4.38 (dd, 1H, CH_2O, J = 11.90, 5.88 Hz), 4.48 (dd, 1H, CH_2O, J = 11.90, 4.16 Hz), 5.22 (dd, 1H, OCH_2N, J = 14.04, 10.96 Hz), 6.87 (s, 1H, C_6-H), 7.15-7.32 (m, 5H, ArH of Bzl), 7.40-7.50 (m, 2H, ArH of Bz), 7.56-7.61 (m, 3H, ArH of Bz), 7.97-8.06 (m, 2H, ArH of Bz).

Anal. Calcd. for $C_{22}H_{21}N_2O_5Cl$: C, 61.61; H, 4.94; N, 6.53. Found: C, 61.28; H, 5.11; N, 6.86.

5-Benzyloxybenzyl-1-[(1′-chloromethyl-2′-benzoyloxyethoxy)methyl]uracil (**6h**).

This compound was prepared from 5-benzyloxybenzyluracil by the same method as in the preceding preparation; uv (ethanol): λ max 266 nm (ε 9802); ^{1}H nmr (deuteriochloroform): δ 3.45-3.95 (m, 4H, CH_2Cl and CH_2 at C_5), 4.24 (m, 1H, *tert* H), 4.38 (dd, 1H, CH_2O, J = 11.93, 5.94 Hz), 4.48 (dd, 1H, CH_2O, J = 11.93, 4.19 Hz), 5.03 (s, 2H, CH_2 of term Bzl), 5.21 (dd, 2H, OCH_2N, J = 18.08, 13.15 Hz), 6.75-6.87 (m, 3H, *o*-H and *p*H or inner Bzl), 6.88 (t, 1H, C_6-H, J = 1.12 Hz), 7.21 (t, *m*-H of inner Bzl, J = 8.39 Hz), 7.30-7.47 (m, 7H, ArH), 7.55-7.61 (m, 1H, ArH of Bz), 7.96-8.04 (m, 2H, ArH of Bz).

Anal. Calcd. for $C_{29}H_{27}N_2O_6Cl$: C, 65.10; H, 5.09; N, 5.24. Found: C, 64.89; H, 5.29; N, 5.12.

5-Benzyl-1-[(1′-bromomethyl-2′-benzoyloxyethoxy)methyl]uracil (**6a**).

A solution of 1.78 g (10 mmoles) of 1-benzoyloxypropylene oxide in 18 ml of methylene chloride was cooled to −5° and treated with 1.22 g (15 mmoles) of hydrogen bromide in 12 ml of methylene chloride, added dropwise over a period of 4 hours. After addition was complete, the reaction mixture was further stirred at 0° for 20 hours. The solvent and excess hydrogen bromide were removed under reduced pressure and the residue dissolved in 30 ml of methylene chloride. To this solution there was added 600 mg (20 mmoles) of paraformaldehyde and the whole cooled to 0°. Dry hydrogen chloride was bubbled through the suspension until saturated. It was allowed to stand at 0° overnight, washed with cold water and then dried over magnesium sulfate. After evaporation of solvent, the residue was mixed with 5-benzyl-2,4-di(trimethylsilyloxy)pyrimidine (prepared from 1.62 g (8 mmoles) of 5-benzyluracil) and 2.07 g (15 mmoles) of powdered anhydrous potassium carbonate in 25 ml of methylene chloride. The mixture was stirred at room temperature for 1 day. After treatment with water, the methylene chloride solution was separated and evaporated under reduced pressure. The residue was chromatographed on silica gel and eluted with methylene chloride:ether (10:1, v/v) to give **6a**; uv (ethanol): λ max 266 nm (ε 9354); ^{1}H nmr (deuteriochloroform): δ 3.45 (dd, 1H, CH_2Br, J = 11.15, 6.37 Hz), 3.53 (dd, 1H, CH_2Br, J = 11.15, 4.56 Hz), 3.51 (d, 1H, CH_2 at C_5, J = 14.81 Hz), 3.62 (d, 1H, CH_2 at C_5, J = 14.81 Hz), 4.24 (m, 1H, *tert* H), 4.39 (dd, 1H, CH_2O, J = 11.90, 5.84 Hz), 4.49 (dd, 1H, CH_2O, J = 11.90, 4.16 Hz), 5.22 (dd, 2H, OCH_2N, J = 17.28, 10.96 Hz), 6.88 (t, 1H, C_6-H, J = 1.20 Hz), 7.15-7.32 (m, 5H, ArH of Bzl), 7.40-7.50 (m, 2H, ArH of Bz), 7.56-7.41 (m, 1H, ArH of Bz), 7.98-8.05 (m, 2H, ArH of Bz).

Anal. Calcd. for $C_{22}H_{21}N_2O_5Br$: C, 55.82; H, 4.47; N, 5.92. Found: C, 56.07; H, 4.53; N, 5.82.

5-Benzyloxybenzyl-1-[(1′-bromomethyl-2′-benzoyloxyethoxy)methyl]uracil (**6i**).

This compound was prepared from 5-benzyloxybenzyluracil by the same method as indicated above; uv (ethanol): λ max 266 nm (ε 9525); ^{1}H nmr (deuteriochloroform): δ 3.42-3.63 (m, 4H, CH_2 at C_5, CH_2Br), 4.20-4.28 (m, 1H, *tert* H), 4.39 (dd, 1H, CH_2O, J = 11.9, 5.9 Hz), 4.48 (dd, 1H, CH_2O, J = 11.9, 4.2 Hz), 5.01 (s, 2H, CH_2 of term Bzl), 5.21 (dd, 2H, OCH_2N, J = 19.0, 10.9 Hz), 6.76-6.89 (m, 3H, O-H and *p*-H of inner Bzl), 6.90 (t, 1H, C_6-H, J = 1.1), 7.21 (t, 1H, *m*-H of inner Bzl, J = 7.9 Hz), 7.30-7.47 (m, 7H, Ar-H), 7.56-7.61 (m, 1H, ArH of Bz), 7.96-8.04 (m, 2H, ArH of Bz).

Anal. Calcd. for $C_{29}H_{27}N_2O_6Br$: C, 60.11; H, 4.70; N, 4.84. Found: C, 60.30; H, 4.75; N, 4.79.

5-Benzyl-1-[(1′-iodomethyl-2′-benzoyloxyethoxy)methyl]uracil (**6f**).

This compound was prepared from 1-iodo-3-benzoyloxypropanol-2 and 5-benzyluracil by the method used for the preparation of the corresponding chloro derivative above, colorless oil; uv (ethanol): λ max 266 nm (ε 9472); ^{1}H nmr (deuteriochloroform): δ 3.25 (dd, 1H, CH_2I, J = 10.96, 6.54 Hz), 3.34 (dd, 1H, CH_2I, J = 10.96, 4.67 Hz), 3.51 (d, 1H, CH_2 at C_5, J = 15.43 Hz), 3.61 (d, 1H, CH_2 at C_5, J = 15.43 Hz), 4.02-4.08 (m, 1H, *tert* H), 4.37 (dd, 1H, CH_2O, J = 11.86, 5.85 Hz), 4.46 (dd, 1H, CH_2O, J = 11.86, 4.20 Hz), 5.21 (dd, 2H, OCH_2N, J = 26.50, 11.92 Hz), 6.90 (t, 1H, C_6-H, J = 1.20 Hz), 7.16-7.31 (m, 5H, ArH of Bzl), 7.42-7.41 (m, 2H, ArH of Bz), 7.56-7.61 (m, 1H, ArH of Bz), 7.97-8.03 (m, 2H, ArH of Bz).

Anal. Calcd. for $C_{22}H_{21}N_2O_5I$: C, 50.78; H, 4.07; N, 5.29. Found: C, 50.39; H, 4.09; N, 5.25.

5-Benzyloxybenzyl-1-[(1′-iodomethyl-2′-benzoyloxy)ethoxy]methyl Uracil (**6j**).

This compound was prepared from 1-iodo-2-benzoyloxypropanol-2 and 5-benzyloxybenzyluracil by the method indicated above; uv (ethanol): λ max 266 nm (ε 9301); ^{1}H nmr (deuteriochloroform): δ 3.22-3.28 (m, 1H, CH_2I), 3.31-3.36 (m, 1H, CH_2I), 3.47 (d, 1H, CH_2 at C_5, J = 15.8 Hz), 3.60 (d, 1H, CH_2 at C_5, J = 14.8 Hz), 4.02-4.11 (m, 1H, *tert* H), 4.37 (dd, 1N, CH_2, J = 11.9, 5.9 Hz), 4.46 (dd, 1H, CH_2, J = 11.9, 4.2 Hz), 5.03 (s, 2H, CH_2 of term Bzl), 5.17 (d, 1H, OCH_2N, J = 10.9 Hz), 6.76-6.87 (m, 3H, *o*-H and *p*-H of inner Bzl), 6.90 (t, 1H, C_6-H, J = 1.1 Hz), 7.21 (t, 1H, *m*-H of inner Bzl, J = 7.8 Hz), 7.30-7.47 (m, 7H, ArH), 7.55-7.61 (m, 1H, ArH of Bz), 7.96-8.03 (m, 2H, ArH of Bz).

Anal. Calcd. for $C_{29}H_{27}N_2O_6I$: C, 55.60; H, 4.35; N, 4.47. Found: C, 55.29; H, 4.55; N, 4.54.

5-Benzyl-1-[(1′-chloromethyl-2′-hydroxyethoxy)methyl]uracil (**7d**).

A mixture of 858 mg, (2 mmoles) of 5-benzyl-1-[(1′-chloromethyl-2′-benzoyloxyethoxy)methyl]uracil (**6d**), 414 mg (3 mmoles) of potassium carbonate and 15 ml of methanol was stirred at room temperature for 5 hours. When the hydrolysis was complete, it was neutralized with 6*N* hydrochloric acid and then evaporated to dryness. The residue was extracted with methylene chloride and purified by chromatography. Elution with 3% methanol in methylene chloride gave 521 mg (80%) of **7d**, mp 117-118°; uv (ethanol): λ max 266 nm (ε 9302); ^{1}H nmr (deuteriochloroform): δ 2.54 (br s, 1H, OH), 3.47-3.59 (m, 2H, CH_2Cl), 3.66 (s, 2H, CH_2 at C_5), 3.65-3.68 (m, 2H, CH_2O), 3.92-3.99 (m, 1H, *tert* H), 5.12 (s, 2H, OCH_2N), 6.85 (t, 1H, C_6-H, J = 1.3 Hz), 7.22-7.36 (m, 5H, ArH).

Anal. Calcd. for $C_{15}H_{17}N_2O_4Cl$: C, 55.47; H, 5.30; N, 8.63. Found: C, 55.54; H, 5.34; N, 8.53.

5-Benzyloxybenzy-1-[(1′-chloromethyl-2′-hydroxyethoxy)methyl]-uracil (**7h**).

5-Benzyloxybenzyl-1-[(1′-chloromethyl-3′-benzoyloxyethoxy)-methyl]uracil (**6h**) was hydrolyzed by the method indicated above

in 81% yield, mp 110-112°; uv (ethanol): λ max 266 nm (ε 9475); ^{1}H nmr (deuteriochloroform): δ 2.33 (t, 1H, OH, J = 5.9 Hz), 3.51 (dd, 1H, CH_2Cl, J = 11.43, 6.68 Hz), 3.60 (dd, 1H, CH_2Cl, J = 11.78, 4.53 Hz), 3.63 (s, 2H, CH_2 at C_5), 3.64-3.76 (m, 2H, CH_2O), 3.84-3.91 (m, 1H, *tert* H), 5.03 (s, 2H, CH_2 of term Bzl), 5.20 (dd, 2H, OCH_2N, J = 13.42, 10.52 Hz), 6.81-6.90 (m, 3H, *o*- and *p*-H of inner Bzl), 6.94 (s, 1H, C_6-H), 7.21-7.45 (m, 1H, *m*-H of inner Bzl), 7.30-7.45 (m, 5H, ArH).

Anal. Calcd. for $C_{22}H_{23}N_2O_5Cl$: C, 61.32; H, 5.35; N, 6.50. Found: C, 61.44; H, 5.32; N, 6.51.

5-Benzyl-1-[(1′-bromomethyl-2′-hydroxyethoxy)methyl]uracil (**7e**).

5-Benzyl-1-[(1′-bromomethyl-2′-benzoyloxyethoxy)methyl]-uracil, **6e**, was hydrolyzed by the method indicated above in 83% yield, mp 120-122°; uv (ethanol): λ max 266 nm (ε 9381); ^{1}H nmr (deuteriochloroform): δ 2.38 (br s, 1H, OH), 3.36 (dd, 1H, CH_2Br, J = 11.0, 6.8 Hz), 3.46 (dd, 1H, CH_2Br, J = 11.0, 4.3 Hz), 3.67 (s, 2H, CH_2 at C_5), 3.64-3.76 (m, 2H, CH_2O), 3.86-3.92 (m, 1H, *tert* H), 5.21 (s, 2H, OCH_2N), 6.93 (t, 1H, C_6-H, J = 1.2 Hz), 7.22-7.36 (m, 5H, ArH).

Anal. Calcd. for $C_{15}H_{17}N_2O_4Br$: C, 48.79; H, 4.64; N, 7.59. Found: C, 49.01; H, 4.76; N, 7.60.

5-Benzyloxybenzyl-1-[(1′-bromomethyl-2′-hydroxyethoxy)methyl]uracil (**7i**).

5-Benzyloxybenzyl-1-[(1′-bromomethyl-2′-benzoyloxyethoxy)-methyl]uracil, **6i**, was hydrolyzed by the method indicated above in 83% yield, mp 88-90°; uv (ethanol): λ max 266 nm (ε 9414); ^{1}H nmr (deuteriochloroform): δ 2.28 (t, 1H, OH), 3.36 (dd, 1H, CH_2Br, J = 11.0, 6.7 Hz), 3.45 (dd, 1H, CH_2Br, J = 11.0, 4.5 Hz), 3.64 (s, 2H, CH_2 at C_5), 3.64-3.76 (m, 2H, CH_2O), 3.85-3.92 (m, 1H, *tert* H), 5.03 (s, 2H, CH_2 of term Bzl), 5.20 (dd, 2H, OCH_2N, J = 12.6, 10.5 Hz), 6.82-6.89 (m, 3H, *o*-H and *p*-H of inner Bzl), 6.93 (t, 1H, C_6-H, J = 1.9 Hz), 7.23 (m, 1H, *m*-H of inner Bzl), 7.30-7.45 (m, 5H, ArH).

Anal. Calcd. for $C_{22}H_{23}N_2O_5Br$: C, 55.59; H, 4.88; N, 5.89. Found: C, 56.00; H, 4.57; N, 5.51.

5-Benzyl-1-[(1′-iodomethyl-2′-hydroxyethoxy)methyl]uracil (**7f**).

5-Benzyl-1-[(1′-iodomethyl-2′-benzoyloxyethoxyl)methyl]uracil, **6f**, was hydrolyzed by the method indicated above in 81% yield, mp 123-125°; uv (ethanol): λ max 266 nm (ε 9372); ^{1}H nmr (deuteriochloroform): δ 2.28 (br s, 1H, OH), 3.16 (dd, 1H, CH_2I, J = 10.8, 6.6 Hz), 3.26 (dd, 1H, CH_2I, J = 10.8, 4.5 Hz), 3.67 (s, 2H, CH_2 at C_5), 3.64-3.76 (m, 3H, CH_2O and *tert* H), 5.20 (dd, 2H, OCH_2N, J = 12.9, 10.4 Hz), 6.95 (t, 1H, C_6-H, J = 1.2 Hz), 7.23-7.35 (m, 5H, ArH).

Anal. Calcd. for $C_{15}H_{17}N_2O_4I$: C, 43.28; H, 4.12; N, 6.73. Found: C, 43.65; H, 4.09; N, 6.61.

5-Benzyloxybenzyl-1-[(1′-iodomethyl-2′-hydroxyethoxy)methyl]uracil (**7j**).

5-Benzyloxybenzyl-1-[(1′-iodomethyl-2′-benzoyloxyethoxy)-methyl]uracil, (**6j**), was hydrolyzed by the method indicated above in 78% yield, mp 91-93°, uv (ethanol): λ max 266 nm (ε 9714); ^{1}H nmr (deuteriochloroform): δ 2.38 (t, 1H, OH), 3.16 (dd, 1H, CH_2I, J = 10.8, 6.7 Hz), 3.26 (dd, 1H, CH_2I, J = 1.08, 4.6 Hz), 3.64 (s, 2H, CH_2 at C_5), 3.64-3.75 (m, 3H, CH_2O, *tert* H), 5.05 (s, 2H, CH_2 of term Bzl), 5.20 (s, 2H, OCH_2N), 6.82-6.88 (m, 3H, *o*-H and *p*-H of inner Bzl), 6.95 (t, 1H, C_6-H, J = 1.1 Hz), 7.21-7.25 (m, 1H, *m*-H of inner Bzl), 7.30-7.45 (m, 5H, ArH).

Anal. Calcd. for $C_{22}H_{23}N_2O_5I$: C, 50.59; H, 4.44; N, 5.36. Found: C, 50.62; H, 4.25; N, 5.31.

5-Benzyl-1-[(1′-diethylaminomethyl-2′-hydroxyethoxy)methyl]-uracil (**8m**).

A mixture of 369 mg (1 mmole) of 5-benzyl-1-[(1′-bromomethyl-2′-hydroxyethoxy)methyl]uracil (**7a**), 730 mg (10 mmoles) of diethylamine, and 10 ml of ethanol was stirred under reflux for 20 hours. Ethanol and excess diethylamine were removed under reduced pressure, and the residue extracted with methylene chloride. The methylene chloride layer was washed with water and evaporated to dryness. The residue was purified by chromatography on silica gel and eluted with 3% methanol in methylene chloride to give 202 mg (56%) of the diethylamino product, **8m**; uv (ethanol): λ max 266 nm (ε 9087); ^{1}H nmr (deuteriochloroform): δ 1.02 (t, 6H, CH_3, J = 7.1 Hz), 2.46-2.68 (m, 6H, NCH_2), 3.66 (s, 2H, CH_2 at C_5), 3.68-3.73 (m, 3H, CH_2O and *tert* H), 5.13 (dd, 2H, OCH_2N, J = 20.3, 10.3 Hz), 6.90 (t, 1H, C_6-H, J = 1.2 Hz), 7.21-7.35 (m, 5H, ArH).

Anal. Calcd. for $C_{19}H_{27}N_3O_4$: C, 63.14; H, 7.53; N, 11.63. Found: C, 62.84; H, 7.50; N, 11.32.

5-Benzyloxybenzyl-1-[(1′-morpholinomethyl-2′-hydroxyethoxy)-methyl]uracil (**8n**).

This compound was prepared in 51% yield by the reaction of 5-benzyloxybenzyl-1-[(1′-bromomethyl-2′-hydroxyethoxy)methyl]-uracil (**7i**) by the preceding procedure; uv (ethanol): λ max 266 nm (ε 9079); ^{1}H nmr (deuteriochloroform): δ 2.44-2.62 (m, 6H, NCH_2 x 3), 3.62-3.72 (m, 8H, OCH_2 x 3, CH_2 at C_5), 3.74-3.80 (m, 1H, *tert* H), 5.05 (s, 2H, CH_2 of term Bzl), 5.11 (d, 1H, OCH_2N, J = 10.2 Hz), 5.21 (d, 1H, OCH_2N, J = 10.2 Hz), 6.81-6.89 (m, 3H, *o*-H and *p*-H of inner Bz), 6.91 (t, 1H, C_6-H, J = 1.1 Hz), 7.21-7.25 (m, 1H, *m*-H of inner Bzl), 7.30-7.45 (m, 5H, remaining ArH).

Anal. Calcd. for $C_{26}H_{31}N_3O_6$: C, 64.85; H, 6.49; N, 8.73. Found: C, 64.59; H, 6.72; N, 9.04.

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