Synthesis of Pyrimidine Acyclonucleosides

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Nucleoside analogues of uridine, 5-bromo-, 5-iodo-, and 5-fluorouridines, thymidine and cytidine were prepared by condensing appropriately substituted 2,4-dimethoxypyrimidines with an acyclic side chain in the form of a benzoylated halo-ether, and subsequent removal of the protecting benzoyl group in base. The 2′-*O*-*p*-tosylates of these nucleoside analogues could then be modified to 2′-halo-, azido-, and amino derivatives. Many of these compounds are competitive inhibitors of uridine phosphorylase *in vitro*, the most active being 5-methyl-1-(2′-hydroxyethoxymethyl)uracil.

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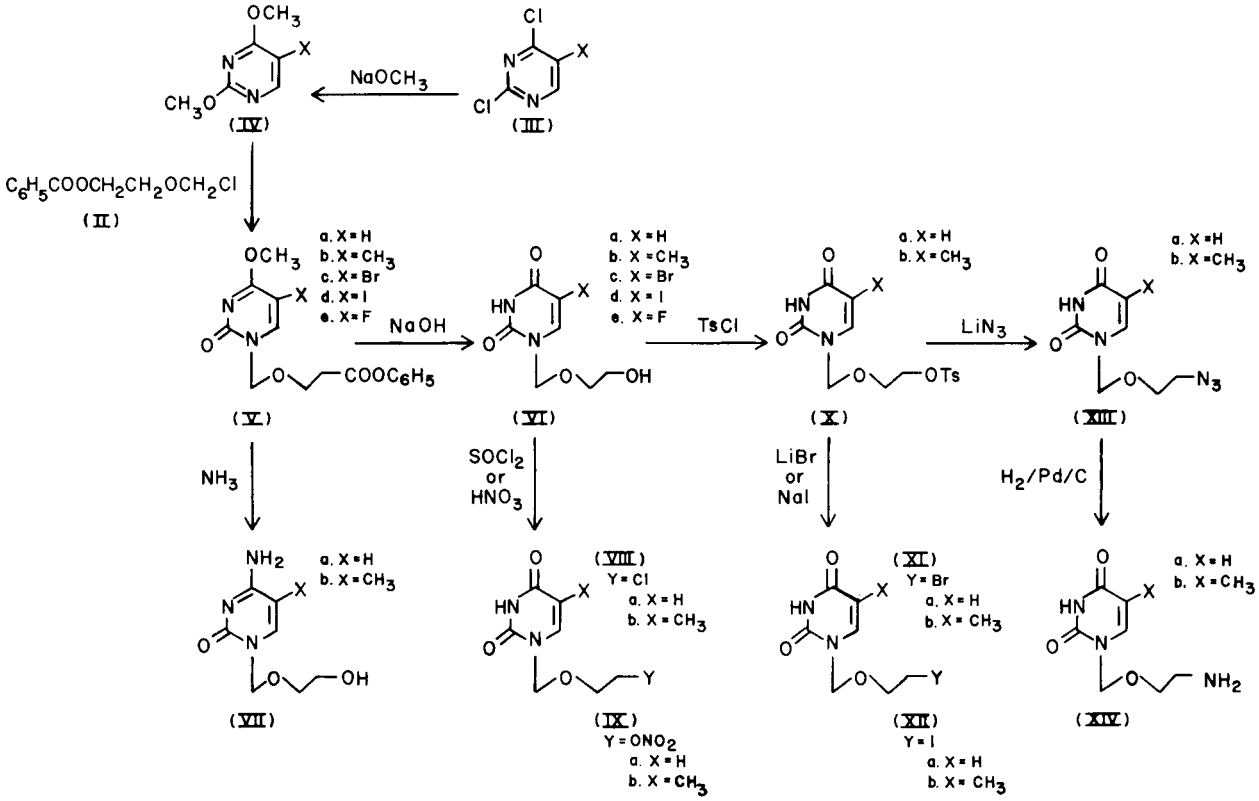
The search for more effective antiviral agents has so far developed only a few that have reached prominence on the clinical level, such as 1-methylisatin 3-thiosemicarbazone (1), 1-aminoadamantane hydrochloride (2), 5-iodo-2′-deoxyuridine (3), 9-β-D-arabinofuranosyladenine (4) and trifluorothymidine (5). Recently, 9-(2′-hydroxyethoxymethyl)-guanine was shown to have pronounced activity against Type I herpes virus, with low host toxicity (6). This compound, known as acycloguanosine, possesses an acylic side chain attached to the base by a glycosidic bond. We now report the synthesis of a series of new pyrimidine nucleosides in which the carbohydrate moiety has been replaced by an acyclic side chain. The synthesis of some 5-substituted acyclouridines, thymidines and cytidines is shown in the scheme, including compounds modified at the terminal group of the side chain (2′-position).

Using a modification of the Hilbert-Johnson procedure (7), we have selectively coupled an acyclic side chain with a number of 5-substituted pyrimidine bases at the 1-position of the ring by reacting the appropriate 2,4-dialkoxypyrimidine derivative (IV) with the halo-ether moiety (II). The heterocyclic base (I) was first chlorinated at the C-2 and C-4 positions to form the dichloropyrimidine (III) and then treated with sodium methoxide to give the 2,4-dimethoxy derivative (IV).

The side chain was synthesized in two steps, the first being the reaction of sodium benzoate with 2-chloroethanol to give ethylene glycol monobenzoate. The reaction of this



SCHEME I

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alcoholic ester with paraformaldehyde and dry hydrogen chloride gas in dichloroethane yielded the benzoyl-protected side chain, 1-benzoyloxy-2-chloromethoxy ethylene (II), (6,8). The reaction could be followed by the disappearance of the OH peak and appearance of R-C-Cl absorption at 650 cm^{-1} in the infrared spectrum.

The 5-substituted uridine derivatives (IV) were condensed with II in dichloromethane in the presence of anhydrous sodium carbonate to give 2-oxo-4-methoxy-1-(2′-benzoyloxyethoxymethyl)pyrimidines (V). Hydrolysis of the condensation product in base gave the acyclouridine derivative (VI), while treatment with methanolic ammonia yielded the cytidine analog (VII). Further modification of the acyclouridine derivatives could be made at the terminal hydroxyl group of the acyclic side chain. Treatment of VI with thionyl chloride in hexamethylphosphoramide, or with fuming nitric acid converted VI directly to the 2′-chloro and 2′-*O*-nitro derivatives (VIII) and (IX), respectively. Tosylation of VI was easily performed in dry pyridine with *p*-toluenesulfonyl chloride, and the products identified by a characteristic peak at 1190 cm^{-1} in the infrared. The intermediate tosylates (X) could then be converted to 2′-bromo (XI) or 2′-iodo derivatives (XII) with lithium bromide or sodium iodide respectively.

The azido derivatives (XIII), prepared from the tosylates (X) and lithium azide (9) were reduced with palladium on charcoal to the corresponding amino analogs (XIV). Azido derivatives showed a characteristic peak at 2100 cm^{-1} in the infrared spectrum, while the disappearance of this peak and appearance of a broad peak between 3400-3800 cm^{-1} was used to monitor reduction to the amine. A positive ninhydrin test provided further evidence for the presence of the amino group.

The potency of these acyclopyrimidines as inhibitors of uridine phosphorylase from various murine and human tissues has been assayed by Niedzwicki and Cha, and is being reported elsewhere (10,11). The most potent of the series is VIb, acyclothymidine (5-methyl-1-(2′-hydroxyethoxymethyl)uracil) with a Ki of 3μM.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ultraviolet spectra were determined on a Perkin-Elmer Model 402 spectrophotometer, and infrared spectra on a Perkin-Elmer Model 457 spectrophotometer. Nmr spectra were measured on a Varian A-60A spectrometer in DMSO-d_6 with tetramethylsilane as the internal standard. Elemental analyses were performed by Baron Consulting Co., Orange, CT., and by Galbraith Laboratories, Inc., Knoxville, TN.

1,2-Dihydro-4-methoxy-2-oxo-1-(2′-benzoyloxyethoxymethyl)pyrimidine (V).

The uracil derivatives were first converted to the corresponding 2,4-dichloro compounds (III) by the method of Bhat and Munson (12), modified by the addition of freshly distilled diethylaniline, and then to 2,4-dimethoxypyrimidines (IV) with sodium methoxide (12). IVa,b (12), IVc (13), IVd (14) and IVe (15,16) were then condensed with II according to the method of Noell and Cheng (7).

A mixture of IVa (7.0 g, 0.05 mole), II (11.0 g, 0.05 mole) and anhydrous sodium carbonate (6.0 g, 0.055 mole) in dry dichloromethane (100 ml) was stirred for 24 hours at room temperature. The mixture was filtered and the solvent removed under diminished pressure. The oily residue was washed with petroleum ether (3 × 30 ml) and ether (3 × 30 ml) and the residual white solid collected by filtration and dried *in vacuo* over phosphorous pentoxide to give 11 g (75%) of Va. The product was recrystallized from ethanol, mp 103°; uv (ethanol): λ max 222 nm (13,300), 273 (5,700); nmr (DMSO-d_6): δ 3.80 (s, 3H, -OCH_3 at C_4), 3.80-4.05 (m, 2H, OCH_2CH_2-benzoyl), 4.28-4.55 (m, 2H, OCH_2CH_2-benzoyl), 5.30 (s, 2H, -CH_2- at N_1), 6.00 (d, C_5-H, $J_{5,6}$ = 7.0 Hz), 7.50-8.08 (m, 5H, ArH), 8.03 (d, C_6-H, $J_{5,6}$ = 7.0 Hz).

Anal. Calcd. for $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 9.21. Found: C, 58.75; H, 5.34; N, 9.24.

Compounds Vb-e were prepared from IVb-e, respectively, in the same way as for Va. Physical constants and spectral data for each are given below.

1,2-Dihydro-5-methyl-4-methoxy-2-oxo-1-(2′-benzoyloxyethoxymethyl)-pyrimidine (Vb).

The reaction of IVb (2.2 g, 0.0143 mole) with II (3.43, 0.016 mole) gave 1.56 g (34%) of Vb. The product was recrystallized from ethanol, mp 107°; uv (ethanol): λ max 223 nm (14,920), 281 (5,561); nmr (DMSO-d_6): δ 1.80 (s, 3H, CH_3 at C_5), 3.86 (s, 3H, OCH_3 at C_4), 3.72-3.98 (m, 2H, OCH_2CH_2O-benzoyl), 4.24-4.50 (m, 2H, OCH_2CH_2O-benzoyl), 5.25 (s, 2H, CH_2 at N_1), 7.47-8.02 (m, 6H, C_6-H and ArH).

Anal. Calcd. for $C_{16}H_{18}N_2O_5 \cdot 0.25\ H_2O$: C, 59.53; H, 5.78; N, 8.69. Found: C, 59.16; H, 5.72; N, 8.39.

1,2-Dihydro-5-bromo-4-methoxy-2-oxo-1-(2′-benzoyloxyethoxymethyl)-pyrimidine (Vc).

The reaction of IVc (3.8 g, 0.02 mole) with II (4.3 g, 0.02 mole) gave 3.5 g (46%) of Vc. The product was recrystallized from ethanol, mp 131°; uv (ethanol): λ max 224 nm (22,296), 295 (4,529); nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3 at C_4), 3.80-4.10 (m, 2H, OCH_2CH_2O-benzoyl), 4.25-4.52 (m, 2H, OCH_2CH_2O-benzoyl), 5.27 (s, 2H, CH_2 at N_1), 7.40-8.10 (m, 5H, ArH), 8.48 (s, C_6-H).

Anal. Calcd. for $C_{15}H_{15}BrN_2O_5$: C, 47.01; H, 3.95; N, 7.31. Found: C, 47.21; H, 4.02; N, 7.21.

1,2-Dihydro-5-iodo-4-methoxy-2-oxo-1-(2′-benzoyloxyethoxymethyl)-pyrimidine (Vd).

The reaction of IVd (14 g, 0.052 mole) with II (12 g, 0.056 mole) gave 17 g (96%) of Vd. The product was recrystallized from ethanol, mp 205°; uv (ethanol): λ max 228 nm (23,900), 300 (4,100); nmr (DMSO-d_6): δ 3.85 (s, 3H, OCH_3 at C_4), 3.82-4.10 (m, 2H, OCH_2CH_2O-benzoyl), 4.28-4.53 (m, 2H, OCH_2CH_2O-benzoyl), 5.26 (s, 2H, CH_2 at N_1), 7.5-8.0 (m, 5H, ArH), 8.43 (s, C_6-H).

Anal. Calcd. for $C_{15}H_{15}IN_2O_5$: C, 41.88; H, 3.51; N, 6.52. Found: C, 41.86; H, 3.62; N, 6.60.

1,2-Dihydro-5-fluoro-4-methoxy-2-oxo-1-(2′-benzoyloxyethoxymethyl)-pyrimidine (Ve).

The reaction of IVe (7.8 g, 0.05 mole) with II (10.8, 0.05 mole) gave 4.7 g (25%) of Ve. The product was recrystallized from ethanol, mp 125°; uv (ethanol): λ max 223 nm (15,000), 281 (5,400); nmr (DMSO-d_6): δ 3.90 (s, 3H, OCH_3 at C_4), 3.77-4.00 (m, 2H, -OCH_2CH_2-benzoyl), 4.20-4.50 (m, 2H, OCH_2CH_2O-benzoyl), 5.25 (s, 2H, CH_2 at N_1), 7.45-8.05 (m, 5H, ArH), 8.20 (d, C_6-H, $J_{5,6}$ = 6.0 Hz).

Anal. Calcd. for $C_{15}H_{15}FN_2O_5 \cdot 0.25\ H_2O$: C, 55.12; H, 4.78; N, 8.57. Found: C, 54.87; H, 4.76; N, 8.40.

1-(2′-Hydroxyethoxymethyl)uracil (VIa).

Following the method of Noell and Cheng (7), with slight modification, a mixture of Va (3.0 g, 0.010 mole) in 2*M* sodium hydroxide (25 ml) was

stirred at room temperature for 26 hours. The solution was either: a) neutralized by stirring with excess Dowex 50 (H^+), evaporated to dryness and the residue washed with ether; or b) acidified with glacial acetic acid, evaporated to dryness and the bulky salts washed with ether and then extracted into hot ethyl acetate. Method a) doubled the yields given below for VIa and VIb. The resulting solid (0.8 g, 44%) was recrystallized from ethanol, mp 140°; uv (*p*H 1): λ max 206 nm (12,400), 258 (8,800); (*p*H 11): λ max 201 nm (14,100), 258 (6,900); nmr (DMSO-d_6): δ 3.50 (s, 4H, $(CH_2)_2OH$), 5.10 (s, 2H, CH_2 at N_1), 5.65 (d, C_5-H, $J_{5,6}$ = 8 Hz), 7.70 (d, C_6-H, $J_{5,6}$ = 8 Hz).

Anal. Calcd. for $C_7H_{10}N_2O_4$: C, 45.18; H, 5.41; N, 15.05. Found: C, 44.94; H, 5.49; N, 14.98.

Compounds VIb-e were prepared from Vb-e, respectively, in the same way as for VIa. Spectral data and physical constants for these compounds are given below.

5-Methyl-1-(2'-hydroxyethoxymethyl)uracil (VIb).

The reaction of Vb (0.95 g, 0.003 mole) with 25 ml of 2*N* sodium hydroxide after evaporation of the ethyl acetate extract, gave 0.1 g (17%) of VIb. The product was recrystallized from ethanol, mp 139°; uv (*p*H 1): λ max 211 nm (8,712), 265 (8,295); (*p*H 11): λ max 213 nm (12,276), 265 (6,705); nmr (DMSO-d_6): δ 1.8 (s, 3H, CH_3 at C_5), 3.50 (s, 4H, $(CH_2)_2OH$), 5.00 (s, 2H, CH_2 at N_1), 7.50 (s, C_6-H).

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 48.00; H, 6.04; N, 14.00. Found: C, 48.10; H, 6.21; N, 13.76.

5-Bromo-1-(2'-hydroxyethoxymethyl)uracil (VIc).

The reaction of Vc (1.5 g, 0.004 mole) with 25 ml of 2*N* sodium hydroxide gave 0.37 g (35%) of VIc which was recrystallized from ethanol, mp 153°; uv (*p*H 1): λ max 211 nm (9,940), 277 (7,731); (*p*H 11): λ max 215 nm (15,559), 275 (6,915); nmr (DMSO-d_6): δ 3.50 (s, 4H, $(CH_2)_2OH$), 5.10 (s, 2H, CH_2 at N_1), 8.20 (s, C_6-H).

Anal. Calcd. for $C_7H_9BrN_2O_4$: C, 31.72; H, 3.42; Br, 30.14; N, 10.57. Found: C, 31.89; H, 3.56; Br, 29.85; N, 10.48.

5-Iodo-1-(2'-hydroxyethoxymethyl)uracil (VId).

The reaction of Vd (6.0 g, 0.014 mole) with 70 ml of 2*N* sodium hydroxide gave 3.1 g (71%) of VId which was recrystallized from ethanol, mp 175-176°; uv (*p*H 1): λ max 210 nm (15,300), 285 (6,400); (*p*H 11): λ max 210 nm (19,800), 279 (4.400); nmr (DMSO-d_6): δ 3.50 (s, 4H, $(CH_2)_2OH$), 5.10 (s, 2H, CH_2 at N_1), 8.20 (s, C_6-H).

Anal. Calcd. for $C_7H_9IN_2O_4$: C, 26.94; H, 2.91; I, 40.67; N, 8.98. Found: C, 26.79; H, 3.00; I, 40.61; N, 8.75.

5-Fluoro-1-(2'-hydroxyethoxymethyl)uracil (VIe).

The reaction of Ve (0.7 g, 0.02 mole) with 7 ml of 2*N* sodium hydroxide gave 0.2 g (65%) of VIe, which was recrystallized from ethanol, mp 155°; uv (*p*H 1): λ max 209 nm (7800), 266 (7300); (*p*H 11): λ max 211 nm (11,500), 266 (5,400); nmr (DMSO-d_6): δ 3.50 (s, 4H, $(CH_2)_2OH$), 5.10 (s, 2H, CH_2 at N_1), 8.05 (d, C_6-H, $J_{5,6}$ = 6.5 Hz).

Anal. Calcd. for $C_7H_9FN_2O_4$: C, 41.18; H, 4.44; F, 9.31; N, 13.73. Found: C, 41.38; H, 4.61; F, 9.33; N, 13.75.

1-(2'-Hydroxyethoxymethyl)cytosine (VIIa), (17).

Following the method of Noell and Cheng (7), with slight modification, a mixture of Va (3.0 g, 0.01 mole) and methanolic ammonia (20 ml) was heated in a bomb at 100° for 24 hours. The mixture was evaporated to dryness under diminished pressure and the residue extracted with hot benzene (10 ml), and with ether (10 ml). The remaining solid was then extracted with hot ethyl acetate (150 ml), the ethyl acetate removed under diminished pressure and the resulting solid (1.0 g, 53%) recrystallized from ethanol, mp 157°; uv (*p*H 1): λ max 212 nm (11,800), 287 (12,200); (*p*H 11): λ max 209 nm (13,400), 268 (7,100); nmr (DMSO-d_6): δ 3.50 (s, 4H, $(CH_2)_2OH$), 4.65 (broad s, 2H, NH_2 at C_4), 5.10 (s, 2H, CH_2 at N_1), 5.75 (d, C_5-H, $J_{5,6}$ = 7.0 Hz), 7.60 (d, C_6-H, $J_{5,6}$ = 7.0 Hz).

Anal. Calcd. for $C_7H_{11}N_3O_3 \cdot 0.25\ H_2O$: C, 44.32; H, 6.11; N, 22.15. Found: C, 44.68; H, 5.90; N, 21.80.

5-Methyl-1-(2'-hydroxyethoxymethyl)cytosine (VIIb).

Compound VIIb was prepared in the same way as VIIa, from Vb (1.6 g, 0.005 mole) to afford 0.095 g (95%) of VIIb. The product was recrystallized from ethanol, mp 171-172°; uv (*p*H 1): λ max 216 nm (12,046), 285 (11,060); (*p*H 11): λ max 216 nm (13,258), 276 (7,759); nmr (DMSO-d_6): δ 1.85 (s, 3H, CH_3 at C_5), 3.5 (s, 4H, $(CH_2)_2OH$), 4.65 (broad s, 2H, NH_2 at C_4), 5.10 (s, 2H, CH_2 at N_1), 7.48 (s, C_6-H).

Anal. Calcd. for $C_8H_{13}N_3O_3$: C, 48.23; H, 6.58; N, 21.09. Found: C, 48.09; H, 6.75; N, 20.98.

1-(2'-Chloroethoxymethyl)uracil (VIIIa).

Following the method of Hrebabecky and Beranek (18) with slight modification, VIa (0.5 g, 0.003 mole) was added to a stirred mixture of hexamethylphoshoramide (5 ml) and thionyl chloride (0.5 ml) under nitrogen. The mixture was stirred at ambient temperature overnight, poured into a saturated sodium bicarbonate solution (100 ml) cooled with ice, and extracted with ethyl acetate (2 × 20 ml). The organic layer was washed with water (2 × 15 ml) and saturated sodium chloride solution (10 ml), dried over magnesium sulfate and evaporated under reduced pressure to give 0.1 g (16%) of VIIIa. The product was recrystallized from ethanol, mp 97-98°; uv (ethanol): λ max 214 nm (6,832), 259 (9,605); ir (potassium bromide): 670 cm^{-1} (C-Cl); nmr (DMSO-d_6): δ 3.77 (s, 4H, $O(CH_2)_2Cl$), 5.16 (s, 2H, CH_2 at N_1), 5.63 (d, C_5-H, $J_{5,6}$ = 8 Hz), 7.73 (d, C_6-H, $J_{5,6}$ = 8 Hz).

Anal. Calcd. for $C_7H_9ClN_2O_3$: C, 41.09; H, 4.43; Cl, 17.33; N, 13.69. Found: C, 40.82; H, 4.80; Cl, 17.47; N, 13.51.

5-Methyl-1-(2'-chloroethoxymethyl)uracil (VIIIb).

Compound VIIIb was prepared in the same way as VIIIa, from VIb (0.5 g, 0.003 mole) to give 0.4 g (61%) of VIIIb. The product was recrystallized from ethanol mp 126-127°; uv (ethanol): λ max 215 nm (7,137), 264 (7,931); ir (potassium bromide): 670 cm^{-1} (C-Cl); nmr (DMSO-d_6): δ 1.80 (s, 3H, CH_3 at C_5), 3.77 (s, 4H, $O(CH_2)_2Cl$), 5.10 (s, 2H, CH_2 at N_1), 7.60 (s, C_6-H).

Anal. Calcd. for $C_8H_{11}N_2O_3Cl$: C, 43.95; H, 5.07; Cl, 16.22; N, 12.81. Found: C, 43.71; H, 5.40; Cl, 16.32; N, 12.70.

1-(2'-*O*-Nitroethoxymethyl)uracil (IXa).

Following the method of Duschinsky (19), VIa (0.3 g, 0.002 mole) was added to ice-cold fuming nitric acid (1.0 ml) with stirring. The solution was kept at 0° for 1 hour, after which ester formation was complete (tlc: silica gel, 1:1 ethyl acetate:ethanol). The solution was added to ice (5 g) with stirring and the white precipitate filtered, washed with water until the washings were neutral, and dried. The product was recrystallized from ethanol, mp 95-96°; uv (ethanol): λ max 214 nm (8,607), 259 (10,083); ir (potassium bromide): 1285, 1637 cm^{-1} ($O-NO_2$); nmr (DMSO-d_6): δ 3.83 (m, 2H, $CH_2CH_2O-NO_2$), 4.68 (m, 2H, $CH_2CH_2O-NO_2$), 5.12 (s, 2H, CH_2 at N_1), 5.63 (d, C_5-H, $J_{5,6}$ = 8 Hz), 7.73 (d, C_6-H, $J_{5,6}$ = 8 Hz).

Anal. Calcd. for $C_7H_9N_3O_6$: C, 36.37; H, 3.92; N, 18.17. Found: C, 36.41; H, 4.01; N, 18.21.

5-Methyl-1-(2'-*O*-nitroethoxymethyl)uracil (IXb).

Compound IXb was prepared in the same way as IXa, from fuming nitric acid (1.2 ml) and VIb (0.5 g, 0.003 mole) to afford 0.3 g (41%) of IXb. The product was recrystallized from ethanol, mp 108-110°; uv (ethanol): λ max 215 nm (10,106), 264 (9,112); ir (potassium bromide): 1285, 1615 cm^{-1} ($O-NO_2$); nmr (DMSO-d_6): δ 1.81 (s, 3H, CH_3 at C_5), 3.82 (m, 2H, $CH_2CH_2O-NO_2$), 4.70 (m, 2H, $CH_2CH_2O-NO_2$), 5.11 (s, 2H, CH_2 at N_1), 7.60 (s, C_6-H).

Anal. Calcd. for $C_8H_{11}N_3O_6$: C, 39.18; H, 4.52; N, 17.14. Found: C, 39.25; H, 4.61; N, 17.09.

1-(2'-*O*-*p*-Tolylsulfonylethoxymethyl)uracil (Xa).

Following the method of Lin, *et al.* (9), *p*-tolunesulfonyl chloride (1.25 g, 0.007 mole) was added to an ice-cooled solution of VIa (1.5 g, 0.008 mole) in dry pyridine (15 ml) and left to stand overnight at 4°. The pyridine was removed under reduced pressure (25°/0.01 torr) and the resulting gum was extracted with ether (3 × 20 ml) and triturated with ice water. The product solidified as a white precipitate and was collected

by filtration, washed with water, a small amount of cold ethanol, and ether and dried to afford 1.35 g (50%) of Xa. The product was recrystallized from ethanol mp 128-129°; uv (ethanol): λ max 222 nm (22,488), 260 (12,358); ir (potassium bromide): 1199 cm^{-1} (O-SO_2); nmr (DMSO-d_6): δ 2.43 (s, 3H, $ArCH_3$), 3.70 (m, 2H, OCH_2CH_2-OTs), 4.12 (m, 2H, CH_2-OTs), 5.05 (s, 2H, CH_2 at N_1), 5.60 (m, C_5-H), 7.33-7.88 (m, 5H, C_6-H and ArH overlap).

Anal. Calcd. for $C_{14}H_{16}N_2O_6S \cdot 0.25\ H_2O$: C, 48.76; H, 4.82; N, 8.12. Found: C, 48.77; H, 5.13; N, 7.94.

5-Methyl-1-(2′-*O*-*p*-tolylsulfonylethoxymethyl)uracil (Xb).

Compound Xb was prepared in the same way as Xa, from VIb (1.0 g, 0.005 mole), to give 0.9 g (51%) of Xb. The product was recrystallized from ethanol, mp 125-126.5°; uv (ethanol): λ max 223 nm (29,533), 264 (19,189); ir (potassium bromide): 1190 cm^{-1} (O-SO_2); nmr (DMSO-d_6): δ 1.80 (s, 3H, CH_3 at C_5), 2.45 (s, 3H, Ar-CH_3), 3.70 (m, 2H, OCH_2CH_2-OTs), 4.13 (m, 2H, -CH_2OTs), 5.02 (s, 2H, CH_2 at N_1), 7.33-7.88 (m, 5H, C_6-H and ArH overlap).

Anal. Calcd. for $C_{15}H_{18}H_2O_6S \cdot 0.5\ H_2O$: C, 49.51; H, 5.26; N, 7.70. Found: C, 49.63; H, 5.67; N, 7.79.

1-(2′-Bromoethoxymethyl)uracil (XIa).

A solution of Xa (0.3 g, 0.0009 mole) and lithium bromide (0.63 g, 0.007 mole) in dry *N,N*-dimethylformamide (20 ml) was heated at 85° for 2.5 hours. The solvent was removed under reduced pressure (60°/0.01 torr) and the residue washed thoroughly with ether and triturated with ice water. The product precipitated as a white solid and was filtered and dried to afford 0.06 g (27%) of XIa. Recrystallization from ethanol gave an analytically pure sample, mp 92.5-94°; uv (ethanol): λ max 213 nm (6,972), 259 (9,118); ir (potassium bromide): 495, 600 cm^{-1} (C-Br); nmr (DMSO-d_6): δ 3.50-3.90 (m, 4H, $O(CH_2)_2Br$), 5.15 (s, 2H, CH_2 at N_1), 5.65 (dd, C_5-H, $J_{5,6}$ = 8 Hz), 7.77 (d, C_6-H, $J_{5,6}$ = 8 Hz).

Anal. Calcd. for $C_7H_9BrN_2O_3$: C, 33.76; H, 3.64; Br, 32.08; N, 11.25. Found: C, 33.54; H, 3.67; Br, 31.94; N, 11.23.

5-Methyl-1-(2′-bromoethoxymethyl)uracil (XIb).

Compound XIb was prepared in the same way as XIa, from Xb (0.3 g, 0.00085 mole) to give 0.15 g (67%) of XIb. The product was recrystallized from ethanol, mp 119.5-120.5°; uv (ethanol): λ max 214 nm (9,349), 264 (9,553); ir (potassium bromide): 480, 585 cm^{-1} (C-Br); nmr (DMSO-d_6): δ 1.80 (s, 3H, CH_3 at C_5), 3.50-3.85 (m, 4H, OCH_2CH_2Br), 5.12 (s, 2H, CH_2 at N_1), 7.60 (s, C_6-H).

Anal. Calcd. for $C_8H_{11}BrN_2O_3 \cdot 0.25\ H_2O$: C, 35.91; H, 4.33, Br, 29.86; N, 10.47. Found: C, 35.90; H, 4.49, Br, 30.16; N, 10.49.

1-(2′-Iodoethoxymethyl)uracil (XIIa).

Sodium iodide (1.08 g, 0.007 mole) was added to a solution of Xa (0.3 g, 0.0009 mole) in dry acetone (20 ml) and the mixture refluxed for 8 hours under anhydrous conditions. Sodium tosylate was removed by filtration, sodium sulfite (0.5 ml of a 10% aqueous solution) added to the acetone solution, and the solvent removed under reduced pressure. The residue was shaken with a mixture of water (10 ml) and with ethyl acetate (25 ml) and the organic layer dried over sodium sulfate. The solvent was removed and the remaining oil washed with ether and dried to afford 0.1 g (37%) of XIIa. The product was recrystallized from ethanol, mp 99.5-101°; uv (ethanol): λ max 213 (7,556), 259 (9,838); ir (potassium bromide): 590 cm^{-1} (C-I); nmr (DMSO-d_6): δ 3.30-3.90 (m, 4H, $O(CH_2)_2I$), 5.15 (s, 2H, CH_2 at N_1), 5.65 (dd, C_5-H, $J_{5,6}$ = 8 Hz), 7.74 (d, C_6-H, $J_{5,6}$ = 8 Hz).

Anal. Calcd. for $C_7H_9IN_2O_3 \cdot 0.25\ H_2O$: C, 27.97; H, 3.19; I, 42.22; N, 9.32. Found: C, 28.06; H, 2.97; I, 41.90; N, 9.28.

5-Methyl-1-(2′-iodoethoxymethyl)uracil (XIIb).

Compound XIIb was prepared in the same way as XIIa, from Xb (0.3 g, 0.00085 mole) to give 0.23 g (88%) of XIIb. The product was recrystallized from ethanol, mp 124.5-125.5°; uv (ethanol): λ max 214 nm (8,860), 264 (9,698); ir (potassium bromide): 595 cm^{-1} (C-I); nmr (DMSO-d_6): δ 1.80 (s, 3H, CH_3 at C_5), 3.25-3.90 (m, 4H, $O(CH_2)_2I$), 5.12 (s, 2H, CH_2 at N_1), 7.60 (s, C_6-H).

Anal. Calcd. for $C_8H_{11}IN_2O_3 \cdot 0.5\ H_2O$: C, 30.11; H, 3.79; I, 39.77; N, 8.78. Found: C, 30.15; H, 4.19; I, 39.52; N, 9.01.

1-(2′-Azidoethoxymethyl)uracil (XIIIa).

Following the method of Lin, *et al.* (9) with slight modification, a mixture of Xa, (0.6 g, 0.0018 mole) and lithium azide (0.22 g, 0.005 mole) in dry *N,N*-dimethylformamide (5 ml) was heated for 2 hours at 80°. The solvent was removed under reduced pressure and the remaining syrup triturated with ice water. A white precipitate was collected by filtration, washed with ice water and ether and dried to afford 0.214 g (56%) of XIIIa. The product was recrystallized from ethanol, mp 87.0-88.5°; uv (ethanol): λ max 213 nm (6,796), 259 (9,322); ir (potassium bromide): 2110 cm^{-1} (-N_3); nmr (DMSO-d_6): δ 3.28-3.85 (m, 4H, $O(CH_2)_2$-N_3), 5.15 (s, 2H, CH_2 at N_1), 5.61 (d, C_5-H, $J_{5,6}$ = 8 Hz), 7.73 (d, C_6-H, $J_{5,6}$ = 8 Hz).

Anal. Calcd. for $C_7H_9N_5O_3$: C, 39.81; H, 4.30; N, 33.16. Found: C, 39.99; H, 4.37; N, 33.10.

5-Methyl-1-(2′-azidoethoxymethyl)uracil (XIIIb).

Compound XIIIb was prepared in the same way as XIIIa, from Xb. The product was recrystallized from ethanol, mp 141-142.5°; uv (ethanol): λ max 214 nm (9,173), 264 (9,489); ir (potassium bromide): 2100 cm^{-1} (-N_3); nmr (DMSO-d_6): δ 1.80 (s, 3H, CH_3 at C_5), 3.35-3.80 (m, 4H, $O(CH_2)_2$-N_3), 5.15 (s, 2H, CH_2 at N_1), 7.63 (s, C_6-H).

Anal. Calcd. for $C_8H_{11}N_5O_3 \cdot 0.25\ H_2O$: C, 41.83; H, 5.05; N, 30.49. Found: C, 41.69; H, 5.36; N, 30.13.

1-(2′-Aminoethoxymethyl)uracil (XIVa).

Following the method of Lin and Prusoff (20), a solution of XIIIa (0.25 g, 0.0012 mole) in ethanol (20 ml) was hydrogenated at room temperature and 50 psi of hydrogen pressure in the presence of 10% palladium on charcoal (0.05 g) for 5 hours. The mixture was filtered through a celite pad and the filtrate evaporated to dryness. The remaining syrup was extracted with ether and the resulting solid dried to give 0.12 g (55%) of XIVa. Recrystallization from ethanol gave an analytically pure sample, mp 139-141.5°; uv (*p*H 1): λ max 212 nm (9,645), 259 (9,279); (*p*H 11): λ max 214 nm (11,131), 260 (6,453); ir (potassium bromide): 3400-3500 cm^{-1}, (-NH_2); nmr (DMSO-d_6): δ 2.65 (m, 2H, CH_2CH_2-NH_2), 3.45 (t, 2H, CH_2CH_2-NH_2), 4.45 (broad s, 2H, NH_2), 5.12 (s, 2H, CH_2 at N_1), 5.65 (d, C_5-H, $J_{5,6}$ = 8 Hz), 7.76 (d, C_6-H, $J_{5,6}$ = 8 Hz).

Anal. Calcd. for $C_7H_{11}N_3O_3 \cdot 0.5\ H_2O$: C, 43.29; H, 6.23; N, 21.64. Found: C, 43.42; H, 6.30; N, 21.71.

5-Methyl-(2′-aminoethoxymethyl)uracil (XIVb).

Compound XIVb was prepared in the same way as XIVa, from XIIIb (0.5 g, 0.0022 mole) to give 0.26 g (50%) of XIVb. The product was recrystallized from ethyl acetate, mp 125-126°, uv (*p*H 1): λ max 213 nm (9,500), 264 (9,131); (*p*H 11): λ max 214 nm (12,285), 266 (7,194); ir (potassium bromide): 3400-3500 cm^{-1}, (-NH_2); nmr (DMSO-d_6): δ 1.80 (s, 3H, CH_3 at C_5), 2.68 (m, 2H, -CH_2CH_2-NH_2), 3.47 (t, 2H, CH_2CH_2-NH_2), 4.40 (broad s, 2H, -NH_2), 5.10 (s, 2H, CH_2 at N_1), 7.61 (s, C_6-H).

Anal. Calcd. for $C_8H_{13}N_3O_3$: C, 48.23; H, 6.58; N, 21.09. Found: C, 48.22; H, 6.56; N, 21.11.

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