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Syntheses of 2-amino-7-(2-hydroxyethoxymethyl)imidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-one (**2**) and 6-amino-3-(2-hydroxyethoxymethyl)-1,2,4-triazolo[3,4-*f*]-1,2,4-triazin-8(7*H*)-one (**3**), novel isosteres of the antiviral agent acyclovir, are reported.

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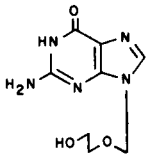
9-(2-Hydroxyethoxymethyl)guanine (acyclovir) (**1**), an acyclic purine nucleoside analogue, is a potent and selective inhibitor of herpes simplex virus replication *in vitro* and in animals, and is showing considerable promise in the treatment of herpes virus infections in man [2]. The therapeutic potential of acyclovir clearly advocates the synthesis of structurally related systems.

The synthesis of *C*-nucleoside isosteres of natural purine nucleosides has recently been shown to be an effective means of providing nucleoside analogues with potent biological activity [3]. Thus, as part of our studies on *C*-nucleosides [4] we have undertaken the preparation of novel *C*-nucleoside isosteres of acyclovir. We herein describe a short synthesis of the bridgehead-nitrogen systems 2-amino-7-(2-hydroxyethoxymethyl)imidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-one (**2**) and 6-amino-3-(2-hydroxyethoxymethyl)-1,2,4-triazolo[3,4-*f*]-1,2,4-triazin-8(7*H*)-one (**3**), isosteres which retain the Watson-Crick hydrogen bonding sites of the guanine nucleus.



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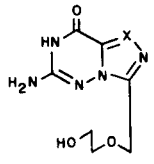
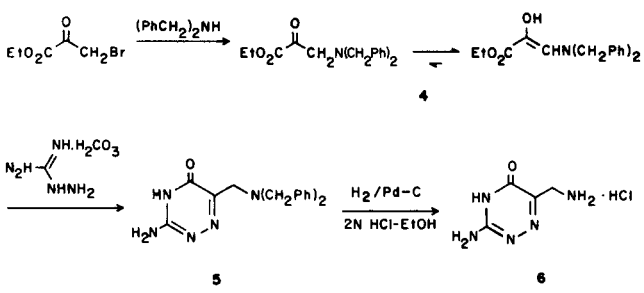


2 X = CH
3 X = N

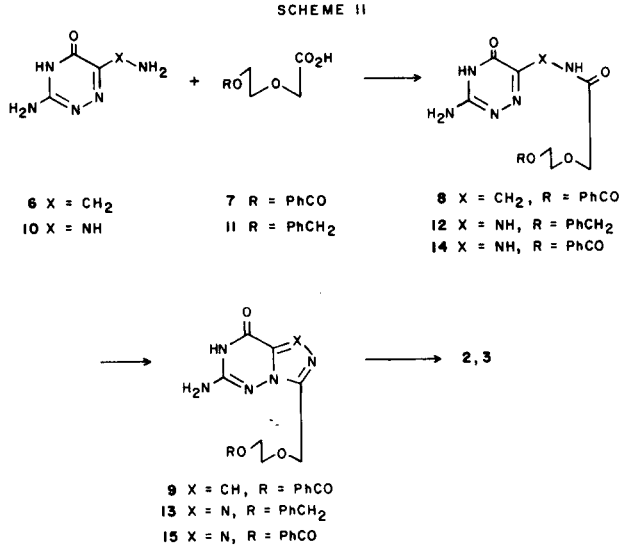
Our synthesis of (**2**) required the novel 3-amino-6-aminomethyl-1,2,4-triazin-5(4*H*)-one (**6**). This intermediate was prepared *via* the route outlined in Scheme I. Treatment of

SCHEME I



ethyl bromopyruvate with dibenzylamine (2 equivalents) afforded the unstable aminopyruvate derivative (**4**), which exists almost entirely as its enol tautomer (^{1}H nmr spectrum). Condensation of **4** with aminoguanidine bicarbonate in ethanol at reflux gave 3-amino-6-dibenzylaminomethyl-1,2,4-triazin-5(4*H*)-one (**5**) in 20% overall yield from ethyl bromopyruvate. Hydrogenolytic removal of the benzyl groups provided the requisite triazinone **6**, isolated as its hydrochloride salt.

SCHEME II



6 X = CH_2
10 X = NH

7 R = PhCO
11 R = $PhCH_2$

8 X = CH_2, R = PhCO
12 X = NH, R = $PhCH_2$
14 X = NH, R = PhCO

9 X = CH, R = PhCO
13 X = N, R = $PhCH_2$
15 X = N, R = PhCO

Completion of the synthesis of **2** was then achieved in three stages (Scheme II). Dehydrative coupling of **6** with [2-(benzoyloxy)ethoxy]acetic acid (**7**), using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), gave the amide **8**. Cyclization of **8**, using phosphorus oxychloride in 1,2-dichloroethane at reflux, proceeded smoothly to afford the imidazotriazinone **9**. Treatment of **9** with methanolic ammonia gave the acyclovir isostere **2**, the structure of which was supported by its ^{1}H nmr spectrum and comparison of uv spectral data with that of a related system [5].

The synthesis of **3** followed a similar strategy. Thus, coupling of 3-amino-6-hydrazino-1,2,4-triazin-5(4*H*)-one (**10**) [6] with [2-(benzyloxy)ethoxy]acetic acid (**11**), in the

presence of EEDQ, afforded the hydrazide **12**. Treatment of **12** with hydrogen bromide in 2-methoxyethanol, at reflux, caused ring closure to **13**. Subsequent hydrogenolysis of the benzyl protecting group provided the acyclovir isostere **3** which showed the expected [6] spectral properties (^{1}H nmr, uv and ir). Alternatively, thermal cyclization of **14** gave **15** which was debenzoylated using methanolic ammonia to provide **3**.

Compounds **2** and **3** showed no activity against Herpes simplex virus types I and II in cell culture.

EXPERIMENTAL

The ^{1}H nmr spectra were measured (TMS or sodium 3-(trimethylsilyl)-propane-1-sulphonate internal standards) on a Varian EM 390 (90 MHz) or a Bruker WM 250 (250 MHz) spectrometer (by Dr. J. Hunt and his staff). The ir spectra were recorded on Perkin-Elmer 357 or 377 spectrophotometers and the uv spectra were measured on a Perkin-Elmer 402 spectrophotometer (by Dr. J. Hunt and his staff). Microanalyses were performed by Dr. T. Cholerton and his staff. All mps are uncorrected.

3-Amino-6-dibenzylaminomethyl-1,2,4-triazin-5(4*H*)-one (**5**).

A mixture of ethyl bromopyruvate (90%, 10.8 g, 7 ml, equivalent to 50 mmoles) and dibenzylamine (19.2 g, 18.7 ml, 97 mmoles) in butanone (250 ml) was heated at reflux, under nitrogen, for 45 minutes. The mixture was cooled, the precipitated dibenzylamine hydrobromide filtered off, and the solvent removed to yield the crude enamine as a dark brown oil. The latter is best used directly in the condensation with aminoguanidine, but for analytical purposes the product can be purified by flash chromatography on silica gel eluting with toluene-hexane (85:15). This affords pure **4** as a yellow oil, which solidifies on standing and can be recrystallized from ethanol as oily yellow needles, mp not defined; ir (bromoform): ν max 3480, 1640 cm^{-1}; uv (ethanol): λ max, nm (ϵ) 306 (21900); ^{1}H-nmr (deuteriochloroform): δ 1.30 (t, 3H, $CO_2CH_3CH_3$), 3.9-5.2 (br, 1H, OH), 4.25 (q, 2H, $CO_2CH_2CH_3$), 4.45 (s, 4H, CH_2Ph), 6.70 (s, 1H, =C*H*), 7.14-7.46 (m, 10H, aromatic).

The above crude enamine and aminoguanidine bicarbonate (6.8 g, 50 mmoles) in ethanol (250 ml) were heated at reflux under nitrogen for 18 hours. The reaction mixture was cooled and the precipitated product filtered off and washed with ethanol. Recrystallization from methanol afforded the triazinone **5** (3.1 g, 20% yield from ethyl bromopyruvate) as a fawn crystalline powder, mp 226-229°; ir (Nujol): ν max 3360, 3140, 1660 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.55 (s, 2H, CH_2N), 3.70 (s, 4H, CH_2Ph), 6.80 (br s, 2H, NH_2), 7.3-7.6 (m, 10H, aromatic), 12.2 (br s, 1H, N*H*CO).

Anal. Calcd. for $C_{18}H_{19}N_5O$: C, 67.25; H, 5.95; N, 21.79. Found: C, 66.85; H, 5.96; N, 21.58.

3-Amino-6-aminomethyl-1,2,4-triazin-5(4*H*)-one Hydrochloride (**6**).

Triazinone **5** (2.62 g, 8.16 mmoles) was dissolved in 2*N* hydrochloric acid (100 ml)-ethanol (30 ml) and the solution added to a pre-reduced suspension of palladium oxide on charcoal (10%, 1.5 g) in ethanol (100 ml). The mixture was vigorously stirred under hydrogen (1 atmosphere) until uptake ceased. The mixture was filtered through Hyflo and the filtrate evaporated to dryness. Recrystallization of the residue from aqueous ethanol gave 3-amino-6-aminomethyl-1,2,4-triazin-5(4*H*)-one hydrochloride (**6**) (0.96 g, 66%) as white needles, mp >300° dec; uv (water): λ max nm (ϵ) (*p*H 1) 255 (6000); (*p*H 7) 236 (5900), 250 sh (2000); (*p*H 13), 227 (9000), 288 (7300); ^{1}H-nmr (deuterium oxide): δ 4.2 (s, 2H, CH_2N).

Anal. Calcd. for $C_4H_7N_5O$·HCl: C, 27.05; H, 4.54; Cl, 19.96; N, 39.44. Found: C, 26.94; H, 4.58; Cl, 20.17; N, 39.57.

[2-(Benzoyloxy)ethoxy]acetic Acid (**7**).

Jones reagent (3.9*M*, 610 ml, 2.38 moles) was added dropwise to a solution of 2-[2-(benzoyloxy)ethoxy]ethanol [7] (80.0 g, 0.70 mole) in acetone (2 *l*) at 0°. The reaction mixture was stirred at room temperature for 18 hours and then quenched with 2-propanol. The resultant mixture was concentrated to a small volume and extracted with ethyl acetate (3 × 500 ml). The combined organic extracts were washed with water and extracted with saturated aqueous sodium bicarbonate solution. The combined alkaline extracts were acidified with 2*N* hydrochloric acid and extracted with ethyl acetate to afford [2-(benzoyloxy)ethoxy]acetic acid (**7**) (66.9 g, 78%), which was recrystallized from petroleum ether (bp 60-80°) as white crystals mp 48-50°; ir (bromoform): ν max 3480, 3420, 1770, 1715 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.90 (m, 2H, -OCH_2CH_2O$_2$CPh), 4.20 (s, 2H, CH_2CO$_2$H), 4.50 (m, 2H, -OCH$_2$CH_2O$_2$CPh), 7.25-7.70 (m, 3H, aromatic), 8.07 (dd, J = 8 Hz and 2 Hz, 2H, aromatic).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 59.01; H, 5.31.

2-[[[(3-Amino-4,5-dihydro-5-oxo-1,2,4-triazin-6-yl)methyl]amino]carbonyl]-methoxy]ethanol Benzoate (**8**).

To a solution of 3-amino-6-aminomethyl-1,2,4-triazin-5(4*H*)-one hydrochloride (**6**) (355 mg, 2.0 mmoles) in water (10 ml) was added 2*N* sodium hydroxide (1 ml), followed by [2-(benzoyloxy)ethoxy]acetic acid (**7**) (450 mg, 2.0 mmoles) in ethanol (20 ml). The reaction mixture was warmed to 60°, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (543 mg, 2.2 mmoles) was added, and heating continued at 70° for 3 hours. The reaction mixture was cooled and evaporated *in vacuo* to give a white solid. This solid was recrystallized from methanol to provide the title compound **8** (325 mg, 43%), mp 196-199°; ir (Nujol): ν max 3420, 3300, 3140, 1720, 1670 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.90 (m, 2H, -OCH_2CH_2O$_2$CPh), 4.06 (s, 2H, NHCOCH_2), 4.18 (d, 2H, CH_2NH), 4.50 (m, 2H, -OCH$_2$CH_2O$_2$CPh), 6.97 (br s, 2H, NH_2), 7.50-7.75 (m, 3H, aromatic), 7.91 (t, 1H, CH$_2$N*H*), 8.02 (dd, 2H, aromatic).

Anal. Calcd. for $C_{15}H_{17}N_5O_5$: C, 51.87; H, 4.93; N, 20.16. Found: C, 51.63; H, 4.85; N, 20.12.

2-[(2-Amino-3,4-dihydro-4-oxoimidazo[5,1-*f*]-1,2,4-triazin-7-yl)methoxy]-ethanol Benzoate (**9**).

Amide **8** (1.10 g, 3.16 mmoles) in dry 1,2-dichloroethane (50 ml) was heated to reflux and phosphorus oxychloride (2 ml) was added. The reaction mixture was heated at reflux for a further 1 hour. After cooling, the solvent and excess phosphorus oxychloride were removed and the residue partitioned between ethyl acetate (50 ml) and saturated aqueous sodium bicarbonate solution (50 ml). The organic phase was separated and the aqueous phase was further extracted with ethyl acetate (2 × 50 ml). The combined ethyl acetate extracts were dried (magnesium sulfate) and evaporated to leave a yellow solid. Recrystallization of this material from ethanol gave the title compound **9** (402 mg, 39%) as a cream solid, mp 207-208°; ir (Nujol): ν max 3480, 3320, 3260, 3180, 2730, 1720, 1655 cm^{-1}; λ max nm (ϵ) 226 (40500), 264 (6000), 280 sh (4700); ^{1}H-nmr (DMSO-d_6): δ 3.88 (m, 2H, -OCH_2CH_2O$_2$CPh), 4.42 (m, 2H, -OCH$_2$CH_2O$_2$CPh), 4.73 (s, 2H, Het-CH_2), 6.25 (br s, 2H, NH_2), 7.67 (s, 1H, 5-H), 7.45-7.80 (m, 3H, aromatic), 7.85-8.10 (m, 2H, aromatic), 10.90 (br s, 1H, N*H*CO).

Anal. Calcd. for $C_{15}H_{15}N_5O_4$: C, 54.71; H, 4.59; N, 21.27. Found: C, 54.52; H, 4.28; N, 21.03.

2-Amino-7-(2-hydroxyethoxymethyl)imidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-one (**2**).

Imidazotriazinone **9** (369 mg, 1.12 mmoles) was dissolved in saturated methanolic ammonia (75 ml) and allowed to stand at room temperature for 5 days. The solution was evaporated to dryness and the residue recrystallized from ethanol to give 2-amino-7-(2-hydroxyethoxymethyl)-imidazo[5,1-*f*]-1,2,4-triazin-4(3*H*)-one (**2**) (179 mg, 71%) as a white crystalline solid, mp 216-217°; ir (Nujol): ν max 3420, 3320, 3180, 1710, 1670 cm^{-1}; uv (ethanol): λ max, nm (ϵ) 226 (32700), 263 (6000); ^{1}H-nmr (DMSO-d_6): δ 3.50 (s, 4H, -OCH$_2$CH$_2$O-), 4.63 (s, 2H, Het-CH_2), 6.22 (br s, 2H, NH_2), 7.65 (s, 1H, 5-H), 11.00 (br s, 1H, NHCO).

Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.67; H, 4.92; N, 31.10. Found: C, 42.56; H, 4.79; N, 30.85.

[2-(Benzyloxy)ethoxy]acetic Acid (**11**).

A solution of chromic trioxide (15.6 g, 0.16 mole) in water (156 ml)-con-

centrated sulphuric acid (24 ml) was added to a cooled (0°) solution of 2-[2-(benzyloxy)ethoxy]ethanol [8] (18.0 g, 0.092 mole) in acetone (540 ml). The reaction mixture was stirred at 10° for 7 hours and then quenched with 2-propanol. The resultant mixture was concentrated to a small volume and extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were washed with water (3 × 100 ml) and extracted with saturated aqueous sodium bicarbonate solution (3 × 100 ml). The combined alkaline extracts were acidified with 5*N* hydrochloric acid and extracted with ethyl acetate to afford [2-(benzyloxy)ethoxy]acetic acid (**11**) (13.8 g, 71%) as a colourless oil. Attempted distillation of **11** resulted in its decomposition and it was therefore characterized as its methyl ester, bp 150° (1.5 mm Hg, Kugelrohr); ir (bromoform): ν max 1750 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.70 (m, 7H, -OCH_2CH_2O-, CO_2CH_3), 4.13 (s, 2H, -$OCH_2CO_2CH_3$), 4.52 (s, 2H, CH_2Ph), 7.30 (m, 5H, aromatic).

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.96; H, 6.96.

[2-(Benzyloxy)ethoxy]acetic Acid, 2-(3-Amino-4,5-dihydro-5-oxo-1,2,4-triazin-6-yl)hydrazide (**12**).

A solution of [2-(benzyloxy)ethoxy]acetic acid (**11**) (3.15 g, 15.0 mmoles) and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (3.71 g, 15.0 mmoles) in ethanol (250 ml) was added to a suspension of 3-amino-6-hydrazino-1,2,4-triazin-5(4*H*)-one (**10**) (2.14 g, 15.0 mmoles) in water-ethanol (1:9) (600 ml) and the mixture heated at 60-70° for 18 hours. Unreacted **10** was removed by filtration and the filtrate was evaporated to dryness. The resulting residue was triturated with diethyl ether and the crude hydrazide collected by filtration. Recrystallization from ethanol yielded **12** (1.81 g, 35%), mp 201-203°; ir (Nujol): ν max 3430, 3360-2500, 1680 cm^{-1}; uv (ethanol): λ max nm (ϵ) 240 sh, 272 sh (4000); ^{1}H-nmr (DMSO-d_6): δ 3.70 (s, 4H, -OCH_2CH_2O-), 4.05 (s, 2H, $COCH_2$), 4.55 (s, 2H, CH_2Ph), 6.54 (br s, 2H, NH_2), 7.36 (s, 5H, aromatic), 8.00 (br, 1H, NH), 9.55 (br, 1H, NH), 11.40 (br, 1H, NH).

Anal. Calcd. for $C_{14}H_{18}N_6O_4 \cdot \frac{1}{2}H_2O$: C, 48.98; H, 5.58; N, 24.48. Found: C, 48.93; H, 5.28; N, 24.38.

[2-(Benzoyloxy)ethoxy]acetic Acid, 2-(3-Amino-4,5-dihydro-5-oxo-1,2,4-triazin-6-yl)hydrazide (**14**).

Following the above procedure, from [2-(benzoyloxy)ethoxy]acetic acid (**7**) and 3-amino-6-hydrazino-1,2,4-triazin-5(4*H*)-one (**10**), compound **14** was obtained as a fawn solid, 31% yield, mp 195-197°; ^{1}H-nmr (DMSO-d_6): δ 3.90 (m, 2H, -$OCH_2CH_2O_2CPh$), 4.10 (s, 2H, $NHCOCH_2$), 4.50 (m, 2H, -$OCH_2CH_2O_2CPh$), 6.60 (br s, 2H, NH_2), 7.50-7.80 (m, 3H, aromatic), 7.96-8.15 (m, 3H, aromatic, NH).

Anal. Calcd. for $C_{14}H_{16}N_6O_5 \cdot \frac{1}{2}H_2O$: C, 47.06; H, 4.80; N, 23.52. Found: C, 47.27; H, 4.42; N, 23.92.

6-Amino-3-[[2-(benzyloxy)ethoxy]methyl]-1,2,4-triazolo[3,4-*f*]-1,2,4-triazin-8(7*H*)-one (**13**).

A solution of the hydrazide **12** (3.92 g, 12.0 mmoles) in 2-methoxyethanol (300 ml) containing a trace of hydrogen bromide catalyst was heated at reflux for 4 hours. The solvent was removed *in vacuo* and the residue treated with aqueous sodium bicarbonate solution, filtered and washed well with water. Recrystallization from ethanol-water afforded **13** (1.85 g, 49%), mp 231-234°; ir (Nujol): ν max 3340, 3200, 2700, 1730 cm^{-1}; uv (ethanol): λ max nm (ϵ) 242 sh, 278 (2800); ^{1}H-nmr (DMSO-d_6): δ 3.58 (m, 4H, -OCH_2CH_2O-), 4.42 (s, 2H, CH_2Ph), 4.70 (s, 2H, Het-CH_2), 6.44 (s, 2H, NH_2), 7.28 (s, 5H, aromatic).

Anal. Calcd. for $C_{14}H_{16}N_6O_3$: C, 53.16; H, 5.10; N, 26.57. Found: C, 52.82; H, 4.81; N, 26.66.

2-[(6-Amino-7,8-dihydro-8-oxo-1,2,4-triazolo[3,4-*f*]-1,2,4-triazin-3-yl)methoxy]ethanol Benzoate (**15**).

The hydrazide **14** (180 mg) was suspended in ethylene glycol (10 ml) and then heated at 200° for 1 hour. After cooling to room temperature the solution was poured into water (70 ml) and the resultant precipitate **15** (85 mg, 48%) collected by filtration. Recrystallization from ethanol-water gave mp 270-272°; ir (Nujol): ν max 3340, 3190, 2800-2200, 1720, 1660 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.88 (m, 2H, -$OCH_2CH_2O_2CPh$), 4.40 (m, 2H, -OCH_2CH_2CPh), 4.82 (s, 2H, Het-CH_2), 6.54 (br s, 2H, NH_2), 7.54 (t, 2H, aromatic), 7.69 (t, 1H, aromatic), 7.93 (d, 2H, aromatic).

Anal. Calcd. for $C_{14}H_{14}N_6O_4$: C, 50.91; H, 4.27; N, 25.45. Found: C, 50.84; H, 3.88; N, 25.15.

6-Amino-3-[(2-hydroxyethoxy)methyl]-1,2,4-triazolo[3,4-*f*]-1,2,4-triazin-8(7*H*)-one (**3**). Method A.

Triazolotriazinone **13** (172 mg, 0.54 mmoles) was suspended in methanol (100 ml) and added to a suspension of 10% palladium oxide on charcoal (25 mg) in methanol (25 ml). The mixture was hydrogenated at 1 atmosphere for 22 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness to give a white solid. Recrystallization from ethanol-water afforded 6-amino-3-[(2-hydroxyethoxy)methyl]-1,2,4-triazolo[3,4-*f*]-1,2,4-triazin-8(7*H*)-one (**3**) (104 mg, 75%), mp 251-253°; ir (Nujol): ν max 3460, 3420, 3330, 3210, 2700, 1730 cm^{-1}; λ max nm (ϵ) 275 (2500); ^{1}H-nmr (DMSO-d_6): δ 3.54 (s, 4H, -OCH_2CH_2O-), 4.74 (s, 2H, Het-CH_2), 6.50 (br s, 2H, NH_2).

Anal. Calcd. for $C_7H_{10}N_6O_3$: C, 37.15; H, 4.46; N, 37.15. Found: C, 36.75; H, 4.29; N, 36.75.

Method B.

The benzoate **15** was treated with methanolic ammonia, as described for the preparation of **2**, to give **3** in 59% yield.

Acknowledgements.

We thank Dr. Brian Judkins for the initial preparation of [2-(benzoyloxy)ethoxy]acetic acid and Jane Squires for excellent technical assistance.

REFERENCES AND NOTES

[1] Although not true nucleosides this term is used here to emphasize the structural analogy with normal *C*-nucleoside systems.

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