

# Synthesis of 4-Alkyl-4*H*-benzo[*e*]- and 4*H*-Pyrido[2,3-*e*]-1,2,4-triazin-3-one 1-Oxides for Potential Anticancer Activity

William O. Foye\*, Joel M. Kauffman and Young Ho Kim

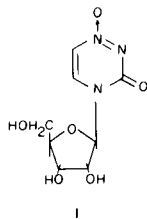
Department of Chemistry, Massachusetts College of Pharmacy and Allied Health Sciences, Boston, Massachusetts 02115  
Received September 23, 1981

Alkylation of the sodium salt of 4*H*-benzo[*e*]-1,2,4-triazin-3-one 1-oxide and its 7-methyl homolog with benzyl bromide and chloromethoxyethyl acetate gave the 4-substituted products. Alkylation with acetobromoglucose formed the 3-ether. Alkylation of 4*H*-pyrido[2,3-*e*]-1,2,4-triazin-3-one 1-oxide gave the 4-substituted products with both benzyl bromide and acetobromoglucose. Deacetylation of both the tetra-*O*-acetylglucosyl and acetoxyethoxymethyl derivatives was accomplished. Antileukemia tests for several of the 4-alkyl derivatives showed no activity.

*J. Heterocyclic Chem.*, **19**, 497 (1982).

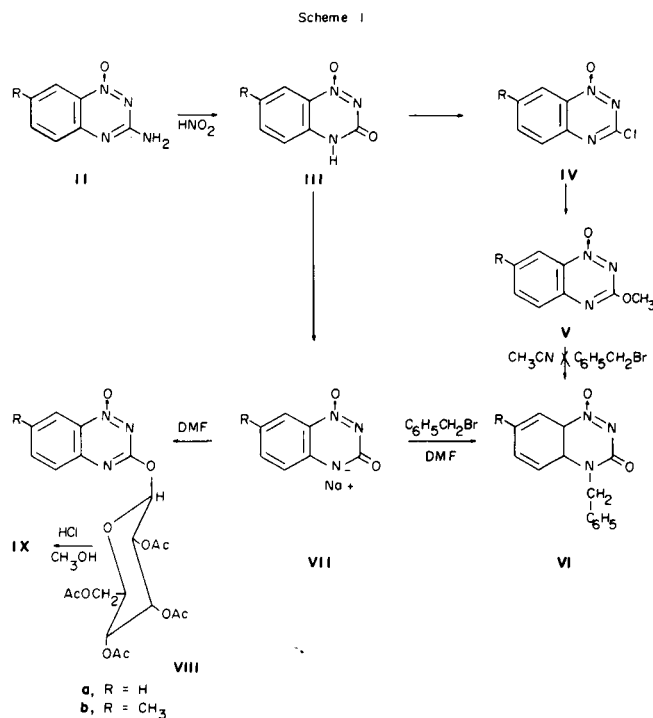
Uricytin, or 4- $\beta$ -D-ribofuranosyl-1,2,4-triazin-3-one 1-oxide (I), a potent antileukemic agent, has been claimed to achieve its antineoplastic effect by binding preferentially to tumor cell membranes, causing the host to produce antibodies (1). The mode of binding was thought to be through reaction with membrane thiols (2). Preparation of the fused ring benzo[*e*]- and pyrido[2,3-*e*]- derivatives could provide compounds of improved binding ability by a thiol binding mechanism, if the binding takes place at C<sub>3</sub>, in view of Carbon's findings of the action of hydroxyl ion on benzotriazole (3). If thiol binding takes place by addition to the 5,6 position, then these fused ring analogs should show less binding, and presumably less anticancer activity. If thiol binding is not a valid mechanism, the fused ring analogs might be expected to bind more strongly to the membrane.

Antileukemic activity of a series of quinolinium-2-dithioacetic acid zwitterions showed that a 7-methyl substituent improved the activity somewhat (4). Accordingly, the 7-methyl analog of the benzo[*e*]-1,2,4-triazin-3-one 1-oxide was also prepared. Attempts to prepare a 4-glycoside analog were made with tetraacetylglucose, and with the open chain hydroxyethoxymethyl analog shown to be of antiviral value by Schaeffer (5) in substituting for a ribosyl group.



## Synthesis.

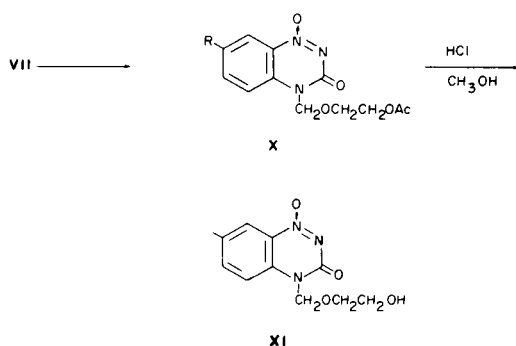
Reaction Scheme I illustrates the preparative route for the benzo[*e*]-1,2,4-triazin-3-one 1-oxide derivatives. The known 3-amino-1,2,4-benzotriazine 1-oxides IIa and IIb (6)



were converted to the "3-hydroxy" compounds (7) with nitrous acid, with 95% ethyl alcohol used to control extreme foaming. The nmr spectra showed the structures to be 3-ones rather than 3-ols. The N-H proton appeared at 9.50 ppm as a broad peak which disappeared on addition of deuterium oxide.

Conversion of III to the 3-chloro compounds IV was done with phosphorus oxychloride, and conversion of IV to the 3-methoxy derivatives V was done with sodium cyanide in methanol (7). New compounds were obtained with the 7-methyl homolog. It was intended to follow Szekeres' (8) method for 4-*N*-alkylation, but reaction of Va with benzyl bromide gave no product after a week at reflux temperature.

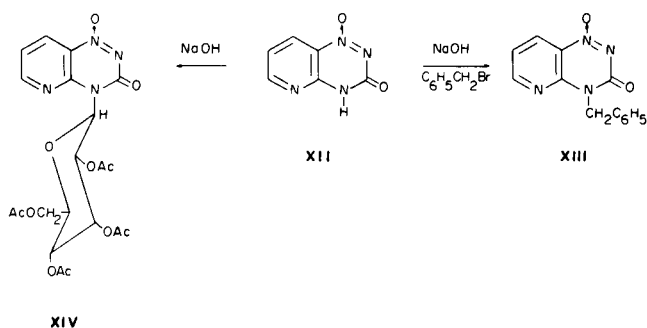
Scheme II



*N*-Alkylation of the sodium salt of the amide, VIIa, with benzyl bromide gave a good yield of the 4-benzyl derivative VIa, as shown by consistent nmr and ir spectra, with strong amide absorption at 1715 and 1690  $\text{cm}^{-1}$ . Attempts to prepare the two tetraacetylglucose derivatives were made in the same manner from the sodium salts VIIa and b. The product from VIIa was obtained in low yield (19%). The ir spectra, however, indicated *O*-alkylation, as the only bond in the carbonyl area was the very strong acetyl absorption at 1762  $\text{cm}^{-1}$ , completely unlike the spectrum of the benzyl derivative.

The tetraacetylglucosyl derivative of the 7-methyl homolog was obtained in similar yield (23%), with much recovered amide, and the ir spectrum again showed strong acetyl absorption at 1758  $\text{cm}^{-1}$  but no absorption due to amide. The nmr spectrum showed the three nearly equivalent protons on the 2,3,4 carbons of the pyranose ring at 4.90-5.75 ppm, with 8 Hz couplings clearly visible, showing the beta form of the glycoside, and the anomeric proton appeared as a doublet ( $J = 8$  Hz) at 6.45 ppm confirming the beta anomer (9). The aromatic protons at C5 and C6 appeared nearly as a singlet at 7.81 ppm, but the expected ortho couplings were not visible. This failure of a 1,2,4-trisubstituted benzene to show the ortho coupling has also been reported (10) for 2,5-dichloronitrobenzene, where the nitro group corresponds to the *N*-oxide function of VIIIb.

Scheme III



The customary method of deacetylation of glycosides, using ammonia in methanol (11), failed to give the de-

acetylated glycoside IX, but use of diethylamine in methanol gave a small yield of material which showed neither acetyl nor amide absorption in the ir and the nmr spectrum was consistent with the expected structure. An equal amount of the ether, Vb, was obtained with the 7-methyl derivative.

Because the desired 4-glycosylated products were not obtained using the sodium salts of the amides, the use of mercury salts was investigated. Following Fox's procedure for *N*-acetylcytosine mercury (12), a 2:1 adduct was obtained, the bis(4-*N*-benzo[*e*]-1,2,4-triazin-3-one 1-oxide) mercury, which failed to produce a glycoside on treatment with acetobromoglucose.

Alkylation to give the 4-*N*-hydroxyethoxymethyl derivatives was attempted, in view of the ability of this group to substitute for ribose or deoxyribose in pyrimidine derivatives active against DNA or RNA viruses (5). Both the benzyl ether and acetate ester have been used as blocking functions for this group, but the lability of the *N*-oxide precluded the use of the benzyl group. The required halide was prepared from dioxolane and acetyl chloride (13), and reaction of this compound with VIIa (Scheme II) gave a 20% yield of compound whose nmr spectrum fit the expected product Xa. The ir absorption showed both acetate carbonyl at 1738  $\text{cm}^{-1}$  and amide carbonyl at 1690  $\text{cm}^{-1}$  confirming that 4-*N*-alkylation had taken place. It appeared that the original condensation took place in higher yield, but decomposition occurred during purification to give amide IIIa. Similar alkylation of VIIb gave the 4-*N*-alkylated product Xb in 19% yield.

In an attempt to explain the different positions of alkylation from use of the sodium salts VIIa and b, the sodium salts were isolated and the ir absorption spectra observed. The strongest absorption appeared at 1685  $\text{cm}^{-1}$ , unfortunately coinciding with some weak to medium C=C and C=N stretching. The strength of the bond, however, suggests a C=O function with considerable single bond character, so the resonance form shown in VII is most probable.

An attempt to remove the acetyl from the acetoxyethoxymethyl group was unsuccessful using diethylamine in tetrahydrofuran. It was removed by 3*N* hydrochloric acid in methanol to give good yields of the hydroxyethoxymethyl derivative XIIb.

The synthetic method for the pyrido[2,3-*e*]triazin-3-one 1-oxides is shown in Scheme III. Commercially available 2-chloro-3-nitropyridine was converted to the amide XII without difficulty using literature procedures (14). The potentially competitive alkylation of the pyridine nitrogen was investigated by treatment with methyl iodide in acetonitrile. No reaction had occurred after 20 hours at reflux temperature. *N*-Benzoylation of the sodium salt of the amide XII, however, went similarly to that of the benzo analog to give XIII.

Treatment of the amide XII (sodium salt) with acetobromoglucose gave a low yield of the 4-*N*-alkylated product, XIV, as shown by its absorption at 1709  $\text{cm}^{-1}$  for amide C=O along with acetyl C=O absorption at 1755  $\text{cm}^{-1}$ . Starting amide was isolated (36% recovery) but no other products were detected on chromatography of the reaction mixture. The nmr spectrum again indicated the  $\beta$  anomer with the anomeric proton appearing at 7.0 ppm ( $J = 9$  Hz) as a doublet.

A possible explanation for the formation of the 3-ethers on alkylation of the benzo-*as*-triazin-3-one 1-oxides with acetobromoglucose, rather than the 4-alkylations observed in the other cases, was the generally much longer reaction times used to obtain appreciable yields in the cases where 3-ethers resulted. However, the benzylation reactions were carried out overnight, and the acetoxyethoxymethylation of the 7-methylbenzo-*as*-triazin derivatives was continued for 3 days, with no indication of 3-ether forming. Also, chromatography of the reaction mixtures did not indicate any shifts from an initial 4-alkylation to a 3 ether formation.

#### Anticancer Testing.

Compounds VIIIb, Xa, and XIa were tested by the National Cancer Institute against P338 lymphocytic leukemia in  $\text{CD}_2\text{F}_1$  mice, according to NCI protocol (15). Compounds were administered intraperitoneally, at dosage levels of 50, 100, and 200 mg/kg. No activity was indicated.

d1, d2, d3, d4

#### EXPERIMENTAL

Melting points were determined in capillaries using a Mel-Temp Apparatus and required no correction. IR spectra were measured with a Perkin-Elmer model 457 grating spectrophotometer. Nmr spectra were obtained with a Varian T-60 spectrometer generally using dimethyl sulfoxide- $d_6$  as solvent and tetramethylsilane as internal standard. Elemental analyses were done by F. B. Strauss, Oxford, England or by Instranal Laboratory, Rensselaer, N. Y. The tlc was carried out using silica gel plates, and the products were detected by exposure to iodine vapor or ultraviolet light.

#### 7-Methyl-4*H*-benzo[e]-1,2,4-triazin-3-one 1-Oxide (IIIb).

A solution of 140 ml of water and 52 ml of 98% sulfuric acid in a 600 ml tall beaker was heated to 60°, and 3-amino-7-methylbenzo[e]-1,2,4-triazin 1-oxide (16) (13.15 g, 0.08 mole) was added in one portion. The mixture was cooled to 10°, and 25.2 g of sodium nitrite in 40 ml of water was added dropwise at 10-20° during 2 hours. Addition of 95% ethyl alcohol was required periodically to inhibit foaming. Following storage at 25° for 3 days, the mixture was diluted with 1 l of water, filtered, and the yellow solid was slurried with 8.8 g of sodium carbonate in 400 ml of water and treated with 0.8 g of Aqua Nuchar A and stirred 15 minutes. The filtered solution was acidified cautiously with 16 ml of acetic acid, and the product was filtered and dried to give 11.5 g (88% yield), mp 227-229° dec; nmr:  $\delta$  2.40 (s, 3H), 7.22 (d, 1H,  $C_5\text{H}$ ,  $J = 8$  Hz), 7.60 (dd, 1H,  $C_7\text{H}$ ,  $J = 8, 2$  Hz), 7.85 (d, 1H,  $C_8\text{H}$ ,  $J = 2$  Hz), 9.50 (br, 1H, N-H, disappears with deuterium oxide) ppm.

Anal. Calcd. for  $\text{C}_8\text{H}_7\text{N}_3\text{O}_2$ : C, 53.92; H, 3.88; N, 24.31. Found: C, 53.93; H, 3.96; N, 23.89.

#### 3-Chloro-6-methylbenzo[e]-1,2,4-triazine 1-Oxide (IVb).

Phosphorus oxychloride (75 ml) and IIIb (8.73 g, 0.05 mole) were refluxed with stirring for 1 hour, and cooled to 25° overnight. The dark liquid was cooled in an ice bath and diluted with 50 ml of hexane. After being stirred for 30 minutes, the product was filtered on a glass pad, slurried with 50 ml of water and ice for 90 minutes, filtered, washed with 100 ml of water, and dried at 25°/0.5 torr for 16 hours over sodium hydroxide to yield a white solid, and recrystallized from toluene to give 7.5 g (73%), mp 177-179°; nmr (deuteriochloroform):  $\delta$  2.60 (t, 3H,  $J = 1$  Hz), 7.81 (q, 2H,  $J = 1$  Hz), 8.13 (s, 1H) ppm.

Anal. Calcd. for  $\text{C}_8\text{H}_6\text{ClN}_3\text{O}$ : Cl, 18.13. Found: Cl, 17.77.

#### 3-Methoxy-7-methylbenzo[e]-1,2,4-triazine 1-Oxide (Vb).

Sodium cyanide (1.96 g, 0.04 mole) and IV b (1.90 g, 0.01 mole) were refluxed in 50 ml of methanol for 3 hours. The dark solution was distilled to remove 40 ml of methanol, 20 ml of water was added to precipitate crude product, and the mixture was chilled in an ice bath for 30 minutes. The solid was filtered, washed with 20 ml of water, and dried at 25°/0.8 torr for 18 hours to give dark crystals, which were continuously extracted from 15 g of alumina with 50 ml of cyclohexane for 7 hours. The extract was stored at 3°, and the yellow needles were filtered and washed with hexane to give 1.88 g (49%), mp 148-149°; nmr (deuteriochloroform):  $\delta$  2.50 (s, 3H), 4.12 (s, 3H), 7.65 (s, 2H), 8.05 (s, 1H) ppm.

Anal. Calcd. for  $\text{C}_9\text{H}_8\text{N}_3\text{O}_2$ : C, 56.24; H, 4.72; N, 21.87. Found: C, 56.29; H, 4.61; N, 22.24.

#### 4*H*-Benzo[e]-1,2,4-triazin-3-one 1-Oxide Sodium Salt (VIIa).

To a solution of sodium hydroxide (0.40 g, 0.01 mole) in 20 ml of water was added IIIa (1.64 g, 0.01 mole) with stirring. The yellow solution was evaporated (0.5 torr) over sulfuric acid, and the yellow residue was extracted in a Soxhlet with 50 ml of 95% ethyl alcohol. The extract was cooled, and the yellow spars were filtered and dried (80°/30 torr) for 6 hours to give 1.48 g (80%), mp 304-307° dec; nmr  $\delta$  6.95 (tt, 1H,  $J = 6, 2$  Hz), 7.20 (dd, 1H,  $J = 8, 2$  Hz), 7.48 (tt, 1H,  $J = 8, 2$  Hz), 7.95 (d, 1H,  $J = 8$  Hz) ppm.

Anal. Calcd. for  $\text{C}_8\text{H}_6\text{N}_3\text{NaO}_2 \cdot \text{H}_2\text{O}$ : C, 41.38; H, 2.98; N, 20.69. Found: C, 41.20; H, 3.14; N, 20.50.

#### 7-Methyl-4*H*-benzo[e]-1,2,4-triazin-3-one 1-Oxide Sodium Salt (VIIb).

This compound was prepared in the same manner as described for VIIa. The yield was 44%, mp 291-294° dec.

Anal. Calcd. for  $\text{C}_9\text{H}_8\text{N}_3\text{NaO}_2 \cdot \text{H}_2\text{O}$ : C, 44.24; H, 3.72; N, 19.35. Found: C, 44.23; H, 3.85; N, 19.15.

#### 4-Benzyl-4*H*-benzo[e]-1,2,4-triazin-3-one 1-Oxide (VIa).

Compound VIIa (0.56 g, 0.003 mole), dimethylformamide (6 ml), and benzyl bromide (0.51 g, 0.003 mole) were stirred at 30° overnight in a flask protected from moisture. Addition of 15 ml of water gave a precipitate which was filtered, washed with water, and recrystallized from 20 ml of 1-propanol and 5 ml of water. The yellow plates were dried at 20°/0.5 torr for 20 hours over sulfuric acid, yielding 0.39 g (51%), mp 197-197.5°; nmr:  $\delta$  5.41 (s, 2H), 7.30 (s, 5H), 7.15-7.90 (m, 4H), 8.18 (dd, 1H,  $J = 8, 2$  Hz) ppm; ir (chloroform):  $\nu$  1715 (C=O), 1690 (C=O)  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2$ : C, 66.39; H, 4.38; N, 16.59. Found: C, 66.48; H, 4.37; N, 16.45.

#### 3-[ $\beta$ -D-(2,3,4,6-Tetra-*O*-acetylglucopyranosyloxy)]benzo[e]-1,2,4-triazin 1-Oxide (VIIIa).

To a solution of  $\alpha$ -D-2,3,4,6-tetra-*O*-acetylglucopyranosyl bromide (0.44 g, 0.001 mole) in 2 ml of dimethylformamide was added VIIa (0.20 g, 0.001 mole) with stirring. A solid appeared which was nearly all dissolved in 30 minutes. Stirring was continued for 5 days, the mixture was filtered, and the crude product was precipitated from the filtrate by dilution with 10 ml of water. The product was collected, washed with water, and dried at 20°/0.4 torr for 16 hours. It was stirred in aqueous sodium carbonate (1%) for 10 minutes, filtered, washed with water, and dried as

before to give 0.1 g (19%), mp 158-159°; nmr:  $\delta$  1.97 (s, 6H), 2.00 (s, 3H), 2.05 (s, 3H), 4.0-4.5 (m, 3H), 4.90-5.75 (m, 3H), 6.46 (d, 1H,  $J = 8$  Hz), 7.50-8.07 (m, 3H), 8.30 (d, 1H,  $J = 8$  Hz) ppm; ir (chloroform):  $\nu$  1762 (C=O)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_{11}$ : C, 51.11; H, 4.70; N, 8.52. Found: C, 51.01; H, 4.39; N, 8.36.

7-Methyl-3-[ $\beta$ -D-(2,3,4,6-tetra-*O*-acetylglucopyranosyloxy)]benzo[e]-1,2,4-triazin-1-Oxide (VIIIb).

A mixture of IIIb (0.76 g, 0.004 mole), water (10 ml), and 50% sodium hydroxide (0.34 g, 0.004 mole) was stirred for 1 hour, and the solution was lyophilized. The yellow sodium salt was treated with  $\alpha$ -D-2,3,4,6-tetra-*O*-acetylglucopyranosyl bromide (1.93 g, 0.004 mole) in 10 ml of dimethyl formamide and stirred (rt) for 2 weeks. The mixture was filtered, the filtrate was added dropwise to 50 ml of water with stirring, and the yellow precipitate was filtered. It was slurried with aqueous sodium carbonate (1%) for 10 minutes, filtered, and dried at 25°/0.5 torr for 16 hours to give 0.49 g (23%), mp 175-177°; nmr:  $\delta$  2.00 (s, 6H), 2.01 (s, 3H), 2.04 (s, 3H), 2.60 (s, 3H), 4.00-4.50 (m, 3H), 4.90-5.75 (m, 3H), 6.45 (d, 1H,  $J = 8$  Hz), 7.81 (s, 2H), 8.05 (s, 1H) ppm; ir (chloroform):  $\nu$  1758 (C=O)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_{11}$ : C, 52.07; H, 4.97; N, 8.28. Found: C, 52.05; H, 4.68; N, 8.22.

7-Methyl-3-[ $\beta$ -D-(glucopyranosyloxy)]benzo[e]-1,2,4-triazin-1-Oxide (IXb).

To a mixture of VIIIb (0.507 g, 0.001 mole) in 20 ml of methanol was added diethylamine (0.292 g, 0.004 mole) with stirring at 0° for 8 hours and at 20-30° for 17 days. The suspension was filtered, and the solid was washed with 5 ml of methanol and dried at 25°/0.5 torr for 16 hours over sodium hydroxide to give a pale solid, 0.05 g (12%), mp 228-231° dec; nmr:  $\delta$  4.46 (m, 3H), 4.90 (m, 2H), 5.13 (m, 1H), 6.65 (d, 1H,  $J = 6$  Hz), 7.75 (s, 2H), 8.05 (s, 1H) ppm.

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_7$ : C, 49.55; H, 5.05; N, 12.39. Found: C, 49.64; H, 5.24; N, 12.29.

Bis[7-Methyl-4*H*-benzo[e]-1,2,4-triazin-3-one 1-Oxide-4-yl]mercury(II).

To a solution of IIIb (0.178 g, 0.001 mole) in 11 ml of 0.1*N* sodium hydroxide was added a solution of mercuric chloride (0.136 g, 0.0005 mole) in 3 ml of water dropwise. The mixture was heated to 70°, cooled, and filtered. The solid was washed with water and acetone and dried at 60°/30 torr for 4 hours to give a bright powder, 0.26 g (94%), mp yellow to white over 200°, darkened 270°.

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{12}\text{HgN}_6\text{O}_4$ : C, 34.75; H, 2.19; N, 15.20. Found: C, 34.45; H, 2.07; N, 14.79.

Chloromethoxyethyl Acetate.

The literature (13) method was modified. Freshly redistilled acetyl chloride (78.5 g, 1.0 mole) was added dropwise to 1,3-dioxolane (111 g, 1.5 moles) with stirring. After one-third of the acetyl chloride was added, the temperature was raised to reflux (70°), and the remaining acetyl chloride was added during 45 minutes. The solution was fractionally distilled to give 108 g (71%) of colorless liquid at 74-76°/5.0 torr (lit (13) 68°/4 torr); nmr (carbon tetrachloride): 2.03 (s, 3H), 3.80 (dd, 2H,  $J = 6, 4$  Hz), 4.17 (dd, 2H,  $J = 6, 4$  Hz), 5.45 (s, 2H).

4-(2-Acetoxyethoxymethyl)-4*H*-benzo[e]-1,2,4-triazin-3-one 1-Oxide (Xa).

To a suspension of VIIa (6.56 g, 0.004 mole) in 75 ml of dimethylformamide, a 5% excess of sodium methoxide (2.27 g, 0.042 mole) was added with stirring. The solution was heated to 35°, and methanol was removed by the water aspirator for 10 minutes. The reaction was cooled to room temperature, and chloromethoxyethyl acetate (6.55 g, 0.043 mole) in 10 ml of dimethylformamide was added dropwise. The temperature was raised to 50°, and stirring was continued for 2 hours. Solvent was removed at 110° under reduced pressure, and saturated aqueous sodium carbonate (200 ml) in 100 g of ice was added to the syrupy residue. The solution was extracted with ethyl acetate (5  $\times$  60 ml), the

combined extracts were dried (magnesium sulfate), and solvent was removed under reduced pressure to give a yellow solid. The tlc (silica gel plate) with chloroform-methanol 95:5 indicated both starting material ( $R_f = 0.15$ ) and product ( $R_f = 0.88$ ). The solid was suspended in 250 ml of chloroform, the solution was filtered and then stirred with alumina (100 g, chromatographic grade). The alumina was removed and washed with chloroform. The chloroform was evaporated under reduced pressure, and the solid was recrystallized from 95% ethyl alcohol to give 2.31 g (20.7%), mp 110-112°; nmr (deuteriochloroform):  $\delta$  1.98 (s, 3H), 3.80-4.00 (m, 2H), 4.04-4.32 (m, 2H), 5.75 (s, 2H), 7.2-8.4 (m, 4H) ppm; ir (chloroform):  $\nu$  1738 (C=O), 1690 (C=O)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_5$ : C, 51.61; H, 4.69; N, 15.05. Found: C, 51.59; H, 4.91; N, 15.04.

4-(2-Acetoxyethoxymethyl)-7-methyl-4*H*-benzo[e]-1,2,4-triazin-3-one 1-Oxide (Xb).

A solution of VIIIb (3.60 g, 0.018 mole) in 10 ml of dimethylformamide in a flask protected from moisture was cooled to 10°, and chloromethoxyethyl acetate (2.75 g, 0.018 mole) was added. The mixture was stirred for 1 hour at ice-bath temperature and then at 28° for 3 days. The yellow suspension was partitioned between 50 ml each of chloroform and water, filtered, and the chloroform layer was washed with aqueous sodium carbonate (2%). It was dried (calcium chloride) freed from solvent by rotary evaporation with nitrogen, and the resulting orange solid was leached with 50 ml of ethyl acetate, which was chromatographed on alumina, using the conditions of the previous experiment. The combined solids were dried at 25°/0.4 torr for 3 hours and recrystallized from ethanol to give 1.0 g (19%) of yellow spars, mp 129-130°; nmr (deuteriochloroform):  $\delta$  1.98 (s, 3H), 2.47 (s, 3H), 3.76-3.97 (m, 2H), 4.05-4.15 (m, 2H), 5.71 (s, 2H), 7.52 (s, 2H), 8.03 (s, 1H) ppm; ir (chloroform):  $\nu$  1739 (C=O), 1690 (C=O)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_5$ : C, 53.24; H, 5.16; N, 14.33. Found: C, 53.18; H, 5.32; N, 14.41.

4-(2-Hydroxyethoxymethyl)-4*H*-benzo[e]-1,2,4-triazin-3-one 1-Oxide (XIa).

To a suspension of Xa (0.85 g, 0.003 mole) in 150 ml of methanol was added 2.5 ml of 3*N* hydrochloric acid with stirring. The mixture became clear and was stirred at room temperature for 17 hours. Solvent was removed at 35° in a rotary evaporator, and the residual solid was recrystallized from 95% ethyl alcohol to give 0.67 g (94%), mp 118-120°; nmr:  $\delta$  3.60 (m, 4H), 5.50 (s, 2H), 7.70 (m, 4H) ppm; ir (potassium bromide):  $\nu$  1690 (C=O)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_4$ : C, 50.63; H, 4.67; N, 17.71. Found: C, 50.48; H, 4.71; N, 17.64.

4-(2-Hydroxyethoxymethyl)-7-methyl-4*H*-benzo[e]-1,2,4-triazin-3-one 1-Oxide (XIb).

To a mixture of Xb (0.138 g, 0.0005 mole) in 50 ml of methanol was added 0.5 ml of 3*N*-hydrochloric acid. The mixture was stirred at 30° for 3 days, and solvent was removed at 30° in a rotary evaporator and then co-evaporated with 5 ml of ethanol. The solid residue was recrystallized from ethanol to give 90 mg (75%), mp 144-145°; nmr:  $\delta$  2.48 (s, 3H), 3.60-4.00 (m, 4H), 6.30 (s, 2H), 7.70 (m, 2H), 8.03 (s, 1H) ppm; ir (potassium bromide):  $\nu$  1690 (C=O)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_4$ : C, 52.58; H, 5.21; N, 16.73. Found: C, 52.44; H, 5.48; N, 16.73.

4-Benzyl-4*H*-pyrido[2,3-*e*]-1,2,4-triazin-3-one 1-Oxide (XIII).

4*H*-Pyrido[2,3-*e*]-1,2,4-triazin-3-one 1-oxide (XII) (14) (0.4 g, 0.003 mole) was added to aqueous sodium hydroxide (0.12 g, 0.003 mole in 20 ml), and the solution was evaporated to dryness at 80° under reduced pressure. The residual sodium salt was further dried at 80°/30 torr, and dimethylformamide (6 ml) and benzyl bromide (0.51 g, 0.003 mole) were added. The mixture was stirred at 40° overnight and then at 140° for several hours to dissolve all solid. The solution was cooled to 25°, diluted with 15 ml of water, and the solid was filtered, washed with water, and dried at 80°/30 torr for 4 hours to give 0.55 g of brown solid, mp

208-211°. It was recrystallized from ethoxyethanol-water (10 ml each) and from 1-butanol and Nuchar C-115-N to give 0.15 g (36%) of tan solid, mp 217-220°; nmr:  $\delta$  5.50 (s, 2H), 7.10-7.60 (m, 6H), 8.55 (dd, 1H, J = 8, 2 Hz), 8.85 (dd, 1H, J = 5, 2 Hz) ppm; ir (chloroform):  $\nu$  1693 (C=O)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_2$ : C, 61.41; H, 3.96; N, 22.04. Found: C, 61.80; H, 3.81; N, 21.74.

4-[ $\beta$ -D-(2,3,4,6-Tetra-O-acetylglucopyranosyl)]-4H-pyrido[2,3-e]-1,2,4-triazin-3-one 1-Oxide (XIV).

The sodium salt of XII was prepared by suspending XII (5.78 g, 0.035 mole) in 80 ml of water and treating with 2.82 g (0.035 mole) of 50% aqueous sodium hydroxide. The lyophilized salt was treated with a solution of  $\alpha$ -D-2,3,4,6-tetra-O-acetylglucopyranosyl bromide (15.93 g, 0.039 mole) in 75 ml of dimethylformamide. After being stirred 70 minutes, the mixture was filtered, and the orange filtrate was added during 10 minutes to aqueous sodium carbonate (8.5 g in 150 ml) and ice. The mixture was stirred 5 minutes, washed with 100 ml of 30% ethyl alcohol, and the remaining solid was taken up in 50 ml of methanol and stored at 3° for 3 days to give 0.75 g (4%) of orange rosettes, mp 152-155°. The starting amide (56%) was recovered from the filtrates; nmr:  $\delta$  1.75 (d, 3H, J = 6 Hz), 2.00 (s, 6H), 2.03 (s, 3H), 4.05 (m, 2H), 4.45 (m, 1H), 5.04 (t, 1H, J = 10 Hz), 5.54 (t, 1H, J = 9 Hz), 6.52 (m, 1H), 7.00 (d, 1H, J = 9 Hz), 7.50 (dd, 1H, J = 8, 5 Hz), 8.52 (dd, 1H, J = 8, 2 Hz), 8.85 (m, 1H) ppm; ir (chloroform):  $\nu$  1755 (C=O), 1709 (C=O)  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_{11}$ : C, 48.58; H, 4.49; N, 11.33. Found: C, 48.88; H, 4.40; N, 11.36.

#### Acknowledgment.

The authors gratefully acknowledge the support of the John R. and Marie K. Sawyer Memorial Fund.

#### REFERENCES AND NOTES

- (1) T. A. Khwaja, T. T. Lee, J. C. Varven, A. M. Mian, and K. M. A. Sheikh, *Curr. Chemother., Proc. Int. Congr. Chemother.*, 10th, **2**, 1193 (1978).
- (2) T. A. Khwaja and T. T. Lee, *Proc. Am. Assoc. Cancer Res.*, **18**, 152 (1977).
- (3) J. A. Carbon, *J. Org. Chem.*, **27**, 185 (1962).
- (4) W. O. Foye and J. M. Kauffman, *J. Pharm. Sci.*, **68**, 336 (1979).
- (5) J. L. Kelley, J. E. Kelsey, W. R. Hall, M. P. Krochmal, and H. J. Schaeffer, *J. Med. Chem.*, **24**, 753 (1981).
- (6) F. J. Wolf, K. Pfister, R. M. Wilson, Jr., and C. A. Robinson, *J. Am. Chem. Soc.*, **76**, 3551 (1954).
- (7) J. Jiu and G. P. Mueller, *J. Org. Chem.*, **24**, 813 (1959).
- (8) G. L. Szekeres, R. K. Robins, P. Dea, M. P. Schweizer, and R. A. Long, *ibid.*, **38**, 3277 (1973).
- (9) R. W. Lenz and J. P. Heeschon, *J. Polym. Sci.*, **51**, 247 (1961).
- (10) M. Zanger, *Org. Mag. Reson.*, **4**, 1 (1972).
- (11) A. Thompson, M. L. Wolfrom, and E. Pacsu, "Methods in Carbohydrate Chemistry", Vol 2, R. L. Whistler and M. L. Wolfrom, eds, Academic Press, New York, 1963, pp 215-220.
- (12) J. J. Fox, N. Yung, I. Wempen, and L. Doerr, *J. Am. Chem. Soc.*, **79**, 5060 (1957).
- (13) F. Gresham, U. S. Patent 2,377,878 (1945); *Chem. Abstr.*, **39**, 4087 (1945).
- (14) J. A. Carbon and S. H. Tabata, *J. Org. Chem.*, **27**, 2504 (1962).
- (15) R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep.*, Part 3, **3**, 1 (1972).
- (16) J. C. Mason and G. Tennant, *J. Chem. Soc. B*, 911 (1970).