not weighed directly. The weight of the thyroid glands was calculated in the usual manner by multiplying the animal weight by (7.5 mg/100 g).

**Imaging Studies.** Imaging studies were obtained with sodium pentabarbital anesthetized rats following administration of the $^{123}$I-labeled agents. Images were obtained with a 20% window with a Technicare 414 camera with a 5-mm pinhole collimator. Images were accumulated as 128 × 128 matrices.

**General Procedure 1. Synthesis of (*E*)-1-Borono-1-penten-5-yl-Trisubstituted Onium Iodides.** A solution of (*E*)-1-borono-5-iodo-1-pentene (**2**, 5 mmol) and trisubstituted substrate (5 mmol) in 2-butanone (5 mL) was refluxed for 16 h. The (*E*)-1-borono-1-penten-5-yl-trisubstituted onium iodide separated from the reaction solution as a crystalline precipitate and was collected by filtration and washed with cold acetone to yield 57 ± 5% of the pure product. An analytical sample was obtained by recrystallization from chloroform–acetone: NMR ($Me_2SO$-$d_6$) δ 5.3 and 6.3 (d and d, 1 H and 1 H, vinyl), 1.68, 2.3, and 3.5 [m, m and m, 2 H, 2 H, and 2H, $(CH_2)_3$].

**General Procedure 2. Synthesis of (*E*)-1-Iodo-1-penten-5-yl-Trisubstituted Onium Iodides. Method A.** A solution of diiodopentene **3** (322 mg, 1 mmol) and trisubstituted substrate (1 mmol) in 2-butanone (4 mL) was refluxed for 18 h. Separated (*E*)-1-iodo-1-penten-5-yl-trisubstituted onium iodide was collected by filtration and washed with acetone to yield the pure iodo compound. After crystallization (chloroform–acetone), the compound obtained by method A was identical (melting point, TLC, NMR) with an authentic sample prepared by method B.

**Method B.** A solution of chloramine-T (450 mg, 1.6 mmol) in 50% aqueous tetrahydrofuran (THF, 15 mL) was added to a stirred solution of borono analogue (general procedure, 1, 1 mmol) and NaI (150 mg, 1 mmol) in 50% aqueous THF (15 mL) protected from light. The solution was stirred at room temperature for 30 min in the dark. The reaction mixture was diluted with $CHCl_3$ and washed with water.[8] The $CHCl_3$ layer was separated and washed thoroughly with 10% aqueous $Na_2S_2O_5$ followed by water. The $CHCl_3$ portion was dried ($Na_2SO_4$) and the solvent was evaporated under vacuum. The syrupy residue was treated with acetone (10 mL) containing NaI (150 mg, 1 mmol) to give a crystalline product, which was collected by filtration, washed with acetone, and recrystallized from $CHCl_3$–petroleum ether: yield 288 mg (49, ±5% of the iodo compound); NMR ($CDCl_3$) δ 6.13–6.51 (m, 2 H, vinyl), 1.29–2.24 (m, 2 H $CH_2CH_2CH_2$).

**General Chromatographic Purification (CP).** The compounds obtained as a syrup (general procedures 1–3) were passed through a column packed with silica gel (Davison, Sigma Sil B was used for RR′R″M = $NEt_3$) slurry in $CHCl_3$. Elution with $CHCl_3$ (10 fractions, 25 mL each) removed unreacted substrates and/or less polar impurities. The more polar, desired quaternary product was isolated by elution with 10–15% (v/v) $CH_3OH$ in $CHCl_3$ or 30% (v/v) acetone in $CHCl_3$ and identified by TLC, NMR, and elemental analyses.

**General Procedure 3. Radiolabeling Synthesis of (*E*)-1-[$^{125}$I]Iodo-1-penten-5-yl-Trisubstituted Onium Iodides. Method A.** The radioactive (*E*)-1,5-[1-$^{129}$I]diiodo-1-pentene was prepared as described previously[7,9] and condensed with RR′R″M in 2-butanone [toluene was used for RR′R″M = $(C_6H_{11})_3P$] according to the general procedure 2, method A. The solvent was evaporated and the desired radioiodinated quaternary product was isolated by general chromatographic purification method (Table II).

**Method B.** The direct radioiodination of borono analogues was accomplished as follows. A solution of (*E*)-1-borono-1-penten-5-yl-trisubstituted onium iodide (25 μmol, prepared by general procedure 1) and Na$^{125}$I (10–15 mCi, 3.8 mg, 25 μmol) in 50% aqueous THF (3 mL) was stirred with chloramine-T (7 mg, 25 μmol) for 30 min in the dark. Excess NaI (30 mg, 0.2 mmol) was added, and the reaction solution was stirred for an additional 10 min. The solution was partitioned between $CHCl_3$ (15 mL) and $H_2O$ (15 mL).[9] The $CHCl_3$ layer was washed with 10% aqueous $Na_2S_2O_5$ followed by $H_2O$, dried ($Na_2SO_4$), and evaporated under argon to provide a residue. The quaternary radioiodinated product was isolated from the residue by using the general chromatographic purification procedure. The corresponding iodine-123-labeled compounds were prepared similarly (Table II). Each radiolabeled agent showed a single radioactive spot which cochromatographed with the unlabeled standard on thin-layer radiochromatographic analysis.

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# Synthesis and Biological Activities of 2-Pyrimidinone Nucleosides. 2. 5-Halo-2-pyrimidinone 2′-Deoxyribonucleosides†

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1-(2-Deoxy-β-D-ribofuranosyl)-5-bromo-2-pyrimidinone (BrPdR) and 1-(2-deoxy-β-D-ribofuranosyl)-5-iodo-2-pyrimidinone (IPdR) have been synthesized by condensation of the appropriate silylated bases **2a** and **2b**, respectively, with 3,5-bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl chloride (**8**) in 1,2-dichloroethane, in the presence of $SnCl_4$, followed by separation of the anomeric blocked nucleosides via column chromatography and subsequent deprotection with methanolic ammonia. Both BrPdR and IPdR exhibited significant antiherpes activities against various strains of HSV-1 and HSV-2, the latter compound (IPdR) showing the higher activity as well as the stronger binding to the virus-specific thymidine kinase.

A number of uracil and cytosine nucleosides have shown significant activity against herpes viruses.[1,2] Among the uracil nucleosides, 2′-deoxyuridine derivatives carrying the following substituents at C-5 of the pyrimidine moiety were found to have antiviral activity: iodo,[2] ethynyl,[3] propyl,[4] nitro,[5] trifluoromethyl,[6] and propynyl.[7] For many of the

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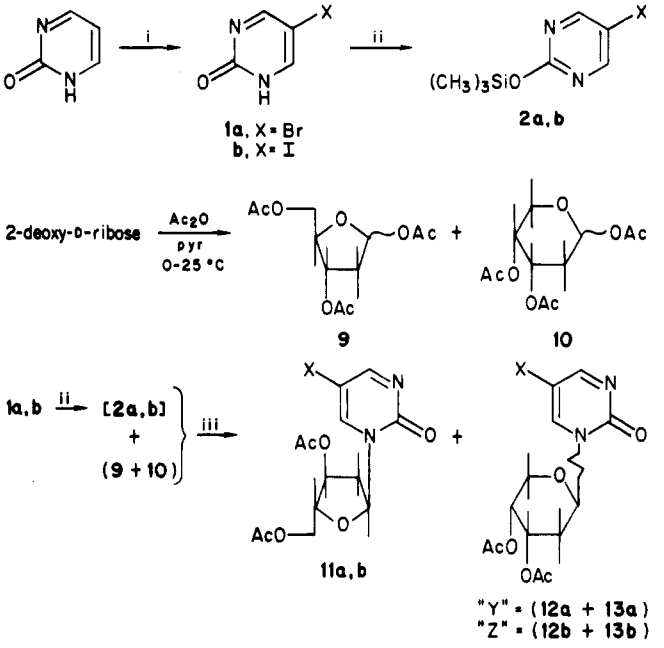
antiviral 5-substituted uracil nucleosides, the corresponding cytosine nucleosides have been found to exhibit a similar activity profile. Furthermore, the cytosine nucleosides are generally more selective with respect to antiviral activity than the corresponding uracil compounds.[5] Although this observation would point to the apparent desirability of cytosine nucleosides as antiviral agents, the latter compounds are generally deaminated in vivo, resulting in decrease of selectivity or (as in the case of the arabinosides) loss of activity. The situation is further exacerbated by the susceptibility of these products of deamination, which are analogues of thymidine, to degradation by thymidine phosphorylase. The availability of more metabolically stable and selective nucleosides is therefore of interest.

Previous work in our laboratory included the synthesis of 1-(2-deoxy-β-D-ribofuranosyl)-5-(methylthio)-2-pyrimidinone; this compound showed significant activity against herpes simplex type 1 and 2 viruses.[8] It was far superior from the point of view of stability as well as antiviral activity to the corresponding 4-oxo and 4-amino analogues, i.e., 5-(methylthio)-2′-deoxyuridine and 5-(methylthio)-2′-deoxycytidine, which we had previously synthesized and reported to have antiherpes activities.[9,10] This discovery turned our attention to the 2-pyrimidinone nucleosides as potential antiherpes agents.

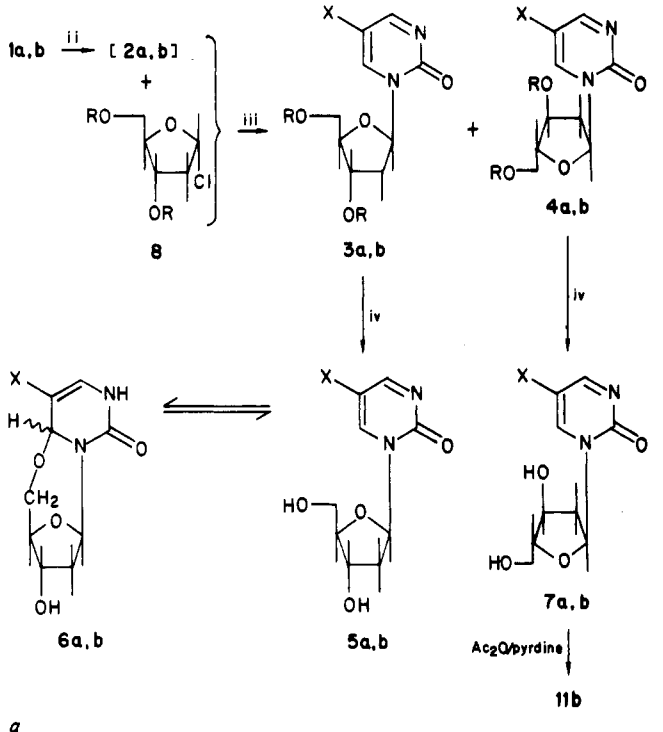
The intermediacy of 2(1*H*)-pyrimidinone in the exhaustive reduction of either cytosine or uracil was demonstrated several years ago.[11,14] Several 2-pyrimidinone nucleosides have been previously synthesized.[12-14] The ribonucleosides reportedly inhibit the growth of *Escherichia coli*.[12] Furthermore, the 5-halo-2-pyrimidinone ribonucleosides have been reported to inhibit cytidine deaminase and to exhibit modest cytotoxicity.[15] The inhibition of cytidine deaminase may be related to the property of covalent adduct formation exhibited by the 2-pyrimidinone nucleosides. Their hydrated species[16] would be structurally similar to the tetrahedral carbon intermediates postulated to occur in the enzymatic deamination of cytosine nucleosides.[17] The deoxyribosides of 5-methyl- and 5-fluoro-2(1*H*)-pyrimidinone were reported to inhibit thymidylate synthase, a key enzyme in the de novo synthesis of thymidylate.[18] These compounds as well as the 5-(methylthio)-2-pyrimidinone 2′-deoxyribonucleoside[8] show resistance to degradation by thymidine phosphorylase.[8,12] In addition, the metaphase-arresting properties of 5-halo-2(1*H*)-pyrimidinones have been documented.[19,20] The available information would therefore

Scheme I[a]




[a] i = NBS or NIS, in DMF; ii = hexamethyldisilazane (+ trimethylchlorosilane), reflux; iii = $SnCl_4/C_2H_4Cl_2$.

Scheme II[a]




[a] R = *p*-chlorobenzoyl. Series a, X = Br; b, X = I. ii = hexamethydisilazane + trimethylchlorosilane, reflux; iii = $SnCl_4/C_2H_4Cl_2$; iv = $NH_3$/MeOH.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point to the desirability of further investigation into this area.

Research conducted in this laboratory has been directed toward the synthesis of 2-pyrimidinone 2′-deoxyribonucleosides carrying C-5 substituents such as have been shown to confer biological activity in the case of the analogous uracil or cytosine nucleosides. The present paper describes the syntheses and properties of the 5-bromo- and 5-iodo-2-pyrimidinone 2′-deoxyribonucleosides.

**Chemistry.** 5-Bromo-2(1*H*)-pyrimidinone[21] (**1a**) and 5-iodo-2(1*H*)-pyrimidinone[22] (**1b**) were obtained in good yield by the reaction of the appropriate *N*-halosuccinimide with 2(1*H*)-pyrimidinone in dry DMF. The 5-halopyrimidines were silylated in the usual manner, by refluxing with excess hexamethyldisilazane, with or without the addition of a catalytic amount of trimethylsilyl chloride, to give the corresponding 2-[(trimethylsilyl)oxy]-5-halopyrimidines **2a** and **2b**, respectively, which were used, without purification, for coupling with the sugar reactants (Scheme I).

Both 2-deoxy-D-ribose triacetate[23-26] and 3,5-bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl chloride[27,31] (**8**) were used in the coupling reactions. 2-Deoxy-D-ribose was acetylated at room temperature to give a mixture of the triacetates **9** and **10** (Scheme I). When a solution of this mixture and the silylated pyrimidine **2b** was treated with $SnCl_4$ and stirred at room temperature for several hours, the α-anomer **11b** and an unidentified component, "Z", giving the same elemental analysis, were isolated; none of the β-anomer **14b** was detected. The assignment of anomeric configuration was based on the $^1H$ NMR data; the structure of **11b** was also confirmed by comparison with the product obtained by acetylating the free α-nucleoside **7b**, derived from **4b** according to Scheme II. Component "Z", although it appeared homogeneous by TLC, was subsequently identified via conversion to the 5-(1-propynyl) derivatives (which could be separated) as a mixture of the anomeric 1-(3,4-di-*O*-acetyl-2-deoxy-D-ribopyranosyl)-5-iodo-2-pyrimidinones (**12b** + **13b**).[28] Analogous products (**11a** and "Y" = **12a** + **13a**) were obtained (in much smaller yields) when the silylated derivative of 5-bromo-2(1*H*)-pyrimidinone, **2a**, was subjected to essentially similar conditions.

The products of acetylation of 2-deoxy-D-ribose are known to vary with the conditions employed: the furanosyl acetate **9** predominates at high temperature while the pyranosyl isomer predominates at, or below, room temperature.[23-26] Studies conducted by Vorbrüggen have demonstrated that suitably blocked pyranose derivatives are able to react in Lewis acid catalyzed Hilbert–Johnson reactions, although they do so under more stringent conditions and at a slower rate than their corresponding furanose isomers.[29,30] The strength of the Lewis acid ($SnCl_4$) as well as its quantity (1.1 equiv) and the long reaction time employed in our studies would certainly be conducive to the formation of the pyranosides **12** and **13** from the corresponding pyranosyl acetate. These conditions would also appear to have favored the almost exclusive formation of the α anomers of the furanoside forms (**11a** and **11b**).

In order to circumvent the problem of pyranoside formation, further work in this area was carried out with the *p*-chlorobenzoyl-protected halogenose **8**. The $SnCl_4$-catalyzed condensation of **2a** with **8** (in either acetonitrile or 1,2-dichloroethane) at room temperature yielded almost exclusively the α-anomer **4a** (Scheme II). In our previous work, the fusion of a silylated uracil with the halogenose **8** has been shown to yield favorable β/α ratios when carried out at reduced pressure.[31] However, when this procedure was applied to the silylated 2-pyrimidinone **2a**, again almost exclusively the α-anomer **4a** was formed. In light of the fact that in these $SnCl_4$-catalyzed condensations the product distribution is presumed to be independent of the anomeric configuration of the protected sugar reactant,[32,33] the interplay of other facts is strongly indicated. Previous studies of these reactions have generally addressed thermodynamic and kinetic factors and their roles as determinants of product distribution. Solvent polarity and basicity of the pyrimidine have been shown to affect reactivity and product distribution significantly.[32,34] Furthermore, the interconversions of isomers, promoted by Friedel–Crafts catalysts, have been demonstrated both by the conversion of pyrimidine $N^3$-nucleosides to pyrimidine $N^1$-nucleosides and by the conversion of a pyrimidine α-deoxyribonucleoside to an equilibrium mixture of the α and β anomers.[29] Thus, it would appear from our results that, under the "equilibrating" conditions employed, the formation of the α anomers (**11a** and **11b** and **4a**, respectively) was thermodynamically favored.

For this reason, the reaction conditions were modified. With use of a low reaction temperature (0 °C), the $SnCl_4$-catalyzed condensation of 5-bromo-2-[(trimethylsilyl)oxy]pyrimidine (**2a**) with the halogenose **8** in 1,2-dichloroethane yielded both anomers of the protected nucleoside, the desired β-anomer **3a** (9.1%) together with the α-anomer **4a** (7.7%). A similar, low-temperature, $SnCl_4$-catalyzed condensation of **2b** and **8** yielded the blocked nucleoside **3b** (19.5%) and **4b** (20.4%). In the case of the iodo derivative, the β-anomer **3b** is light sensitive and decomposes in chloroform after a few days of exposure to light; the decomposition is greatly accelerated by incandescent light. Although the lability of other pyrimidine C-5–iodine bonds has been reported,[35] the sugar moiety of **3b** appears to be implicated in the decomposition of this compound. This is indicated by the greater tolerance of the α anomer to light; the latter remains unchanged after several months of exposure.

The blocked nucleosides **3a** and **3b** were subsequently deprotected with anhydrous methanolic ammonia to yield the target compounds, 1-(2-deoxy-β-D-ribofuranosyl)-5-bromo-2-pyrimidinone (BrPdR, **5a**) and 1-(2-deoxy-β-D-ribofuranosyl)-5-bromo-2-pyrimidinone (IPdR, **5b**), respectively.

The NMR spectrum of the 5-iodo compound **5b** shows a pair of doublets at δ 8.62 and 8.75 for the H-6 and H-4, respectively, and a triplet at δ 6.0 for the anomeric proton,

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**Table I.** Antiherpes Activities of (2-Deoxy-β-D-ribofuranosyl)-5-bromo- and -5-iodo-2-pyrimidinone

| | plaque-forming units as % of control | | | |
|---|---|---|---|---|
| virus[a] | BrPdR (5a) (100 μM) | IPdR (5b) (100 μM) | BVdU (30 μM) | ACG (5 μM) |
| HSV-1 (KOS) | 0.6 | 0.27 | 0.1 | 6.5 |
| HSV-1 (CL101) | | 1.6 | 0.4 | 4 |
| HSV-2 (333) | 4.5 | 2.8 | 1.7 | |
| HSV-2 (CEU-G) | 7.1 | 9.3 | | |
| ACG$^r$ (S1) | | 22 | 3.7 | 100 |
| ACG$^r$ (Tr7) | | 2.6 | 0.8 | 85 |
| BVdU$^r$ | | 14 | 52 | 0.7 |
| PFA$^r$ | | 0.1 | | 100 |

[a] For origin of virus strains, see Experimental Section.

confirming that this molecule exists in the free nucleoside form as indicated in structure **5b**. On repeated coevaporation with acetone, formation of the cyclonucleoside **6b** (estimated at 25% of the mixture) occurred, which was indicated by the appearance of singlets at δ 6.58 and 5.49 (in $Me_2SO$-$d_6$/$D_2O$). On the other hand, the NMR spectrum of the 5-bromo analogue **5a** (in $Me_2SO$-$d_6$) shows a doublet at δ 6.60 and a singlet at δ 5.43 for H-4 and H-6, respectively. The anomeric proton appears as a doublet of doublets at δ 5.82. The foregoing indicates that this molecule exists almost exclusively as the 5′,$O^6$-cyclonucleoside **6a**. Molecular models indicate an unfavorable dihedral angle between H-6 and H-4; this would account for the absence of coupling between these two protons. Covalent adduct formation of 2-pyrimidinones and 2-pyrimidinone nucleosides has been reported by several workers[16,36,37] and the NMR data given above are in agreement with data published by Liu et al.[37] for the 5′,$O^6$-cyclonucleoside obtained from the 2′,3′-isopropylidene-substituted 2-pyrimidinone β-D-ribonucleoside. Although the facile cyclic adduct formation may earlier have been attributed to the strain introduced by the presence of the isopropylidene functionality,[37] there is little doubt that the propensity for covalent adduct formation, such as we have seen above, and the stability of such adducts reflect the level of electron deficiency at C-4 and C-6 of the pyrimidine ring. The electron density at these positions is, in turn, dependent on the nature of the substituent at C-5. In our experiments the distributions of **5a** and **6a** remained unchanged in 50% $D_2O$–$Me_2SO$-$d_6$. However, in the largely aqueous biological media the existence of an equilibrium state between the cyclic and open forms may be expected, and therefore the binding of the open form to an enzyme or receptor may shift such equilibrium toward the open nucleoside form, in which case the biological activity of the nucleoside analogue may not be significantly affected by cycloadduct formation.

## Biological Results

The β-2′-deoxyribofuranosides of both 5-bromo- and 5-iodo-2-pyrimidinone, BrPdR (**5a**) and IPdR (**5b**), respectively, were tested for antiherpes activity according to previously described procedures.[4] Both compounds showed significant activity against various strains of herpes simplex type 1 and 2, as indicated by the data in Table I.

IPdR was, in addition, tested and found to exhibit somewhat reduced but still significant activity against acycloguanosine (ACG) and (bromovinyl)deoxyuridine (BVDU) resistant strains of HSV-1 in which the resistance was due to modification of the thymidine kinase. The more highly ACG-resistant strain (S1) showed more cross resistance toward IPdR than the one with a lower level of ACG resistance (Tr7). Against PFA-resistant strains (modification in the DNA polymerase), IPdR retained full activity.

Since they lack a 4-amino group, it is obvious that both IPdR and BrPdR are stable to degradation by deoxycytidine deaminase. This property is particularly important in the light of the reported overproduction of virus-specific deoxycytidine deaminase in HSV-1 infected cells.[38]

BrPdR and IPdR were tested both as inhibitors and substrates of the thymidine kinases from various sources. The enzymes were purified as previously described[39-41] and the kinetic constants were determined according to the procedure of Cheng and Prusoff,[42] with 0.02, 0.02, 0.02, or 0.01 unit of the enzyme derived from HSV-1 (KOS), HSV-1 (333), the cytosol of human KB/6B cells, and the mitochondria of leukemic blast cells, respectively. The results, expressed as $K_i$ (μM) and relative phosphorylation rate (rV), respectively are given in Table II.

Thus, when used as inhibitors in the presence of thymidine, IPdR is more strongly bound than BrPdR to the two virus-specific thymidine kinases (particularly, to the one induced by HSV-2). At the same time, IPdR is more slowly phosphorylated by these enzymes than is BrPdR. It is important to note that IPdR is a much more powerful inhibitor of the viral thymidine kinases than of the corresponding human cellular enzymes, having over 1–2 orders of magnitude smaller $K_i$ values for the former. This result is consistent with the notion that IPdR might be found capable of exhibiting considerable selectivity against HSV-1 and HSV-2 infections in man.

## Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer 197 spectrophotometer. NMR spectra were taken on a Varian T-60 with tetramethylsilane as the internal reference. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA, and Galbraith Laboratories, Knoxville, TN. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter at 589 nm (Na lamp). Thin-layer chromatography was performed on Analtech GHLF TLC plates and visualization was done in a UV and/or iodine chamber. Preparative thin-layer chromatography was carried out on 20 × 20 silica gel plates prepared from Macherey-Nagel MN-Kieselgel P/$UV_{254}$. Flash chromatography was performed with Baker silica gel for flash chromatography. UV spectra were taken on a Beckman Model 25 spectrophotometer. Column chromatography with gradient elution was performed with the Glenco medium-pressure linear gradient system (with VWR silica gel of particle size 60–200 μm). The column was connected to two solvent chambers (in series) positioned high above the column and the flow rate was maintained at 12–15 mL/min.

**5-Iodo-2(1*H*)-pyrimidinone (1b).**[22] 2-Pyrimidinone (6 g, 62.4 mmol) and *N*-iodosuccinimide (14.7 g, 65.3 mmol) in dry DMF (30 ml) were stirred for 48 h at room temperature with the exclusion of both light and moisture. The mixture was added to ether (50 mL) with stirring and the supernatant was decanted. The precipitate was collected by filtration and repeatedly washed with acetone and finally with methanol until the filtrate became light yellow. After drying in vacuo the yellow granular product

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Table II. Inhibition Constants ($K_i$) and Relative Phosphorylation Rates (rV) of (2-Deoxy-β-D-ribofuranosyl)-5-bromo- and -5-iodo-2-pyrimidinones with Thymidine Kinases from Various Sources[a]

| | HSV-1 (KOS) | | HSV-2 (333) | | human ($K_i$ only) | |
|---|---|---|---|---|---|---|
| compd | $K_i$, μM | rV[b] | $K_i$, μM | rV[b] | CYTO | MITO |
| BrPdR | 5.06 ± 2.47 | 44 ± 4 | 25 | 23 ± 7 | | |
| IPdR | 1.84 ± 0.55 | 3 ± 2 | 3.98 ± 0.91 | 12 ± 6 | 100 | 51.67 ± 26.4 |

[a] For enzyme preparation and assay methods, see Experimental Section. [b] rV = relative phosphorylation rate, at 400 μM of the analogues, based on thymidine = 100.

appeared to be pure by TLC and spectra, but the elemental analysis indicated that it was contaminated with a trace amount of DMF: yield 11.35 g (77.5%); IR (KBr) 3700–2400 (OH and aromatic), 1710, 1680, 1660 (C=O), 1600 (pyrimidine), 1360, 900 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 8.48 (s, $C_4$-H, $C_6$-H).

The known 5-bromo-2(1*H*)-pyrimidinone[21] (**1a**) was prepared in an analogous manner.

**Anomeric 2-Deoxy-3,5-di-*O*-acetyl-D-*erythro*-pentofuranosyl Acetate (9) and 2-Deoxy-3,4-di-*O*-acetyl-D-*erythro*-pentopyranosyl Acetate (10).** Acetic anhydride (24.6 mL, 0.26 mol) was added dropwise to a cooled solution of 10.0 g (74.6 mmol) of 2-deoxy-D-ribose in 30 mL of anhydrous pyridine. The ice bath was removed after completion of addition and the reaction mixture was stirred, with exclusion of moisture, at room temperature for 25 h. The reaction mixture was then concentrated to a syrup, which was coevaporated with ethanol (2 × 30 mL). The resulting syrup was diluted with methylene chloride (200 mL) and this solution was washed successively with saturated bicarbonate (50 mL) and water (50 mL). The solution was dried over magnesium sulfate and concentrated to an oil. The latter was coevaporated with ethanol (2 × 50 mL) and dried in vacuo to give a syrup containing a mixture of the triacetates **9** and **10** (total yield 18.50 g, 95.4%). This material became partially crystalline upon standing at room temperature for about 2 days: $[\alpha]^{25}_D$ −55.9° ($CHCl_3$, *c* 0.097 M) (lit.[23] $[\alpha]^{17}_D$ −52.5°); NMR ($CDCl_3$) δ 2.10 (m, acetyl), 2–2.72 (m, H′-2), 3.78 (d), 3.95 (m, H-5), 4.25 (m, H-5), 5.22 (m, H-3, H-4), 5.83 (t, H-1), 6.33 (m, H-1).

A portion of this material was triturated with isopropyl ether to give a white crystalline product (chromatographically homogeneous), presumably a relatively pure anomer of **10** (as indicated by the specific rotation): mp 95–97 °C (lit.[24] mp 98 °C, lit.[25] mp 90–91 °C); $[\alpha]^{27}_D$ −296.3° ($CHCl_3$, *c* 5.47 × $10^{-4}$ M) (lit.[24] $[\alpha]^{23}_D$ −166.6° in $CHCl_3$); NMR ($CDCl_3$) δ 2.03 (s, 3, acetyl), 2.10 (s, 3, acetyl), 2.13 (s, 3, acetyl), 1.7–2.7 (m, 2, H-2), 3.97 (m, 2, H-5), 5.25 (d, 1, H-3), 5.40 (m, 1, H-4), 6.28 (t, 1, H-1); IR ($CHCl_3$) 3010, 2950, 1740 (br), 1440, 1370, 1240 $cm^{-1}$.

**Reaction of the 2-Deoxy-D-ribose Triacetates 9 and 10 with the Silylated 5-Iodo-2(1*H*)-pyrimidinone 2b.** A mixture of 5-iodo-2(1*H*)-pyrimidinone (**1b**; 5.0 g, 22.5 mmol) and hexamethyldisilazane (40 mL) was refluxed for 1 h. The reaction mixture was cooled and concentrated to a residue. A solution of this residue and a mixture of 2-deoxy-D-ribose triacetates **9** and **10** (7.50 g, 28.8 mmol) in 100 mL of dry 1,2-dichloroethane was added dropwise to a solution of $SnCl_4$ (4.0 mL, 34.7 mmol) in 50 mL of dry 1,2-dichloroethane; the reaction mixture, subsequent to this addition, was allowed to stir at room temperature for 12 h. The reaction mixture was then added to 300 mL of 1,2-dichloroethane and 400 mL of saturated sodium bicarbonate solution, and the resulting mixture was filtered over a bed of Celite. The Celite bed was subsequently washed with 1,2-dichloroethane and the combined organic extract was dried over anhydrous sodium sulfate. This solution was then concentrated in vacuo to provide a brown syrup, which was chromatographed on 150 g of silica gel (initially eluted with ethyl acetate and subsequently with 2% acetone in ethyl acetate) to give two major eluate fractions; the second of these on evaporation yielded 1.0 g (10.5%) of a pure compound, identified as 1-(3,5-di-*O*-acetyl-2-deoxy-α-D-ribofuranosyl)-5-iodo-2-pyrimidinone (**11b**): mp 50–53 °C; $[\alpha]$ −11° ($CHCl_3$, *c* 1.2 M); UV $\delta_{max}$ 338 nm; IR (KBr) $\nu_{max}$ 1740, 1660, 1500, 1380, 1240, $cm^{-1}$; NMR ($CDCl_3$) δ 2.0–3.20 (m, 8, acetyl and 2′-H), 4.24 (d, 2, 5′-H), 4.74 (t, 1, 4′-H), 5.25 (d, 1, 3′-H), 6.30 (dd, 1, 1′-H, $J_{1',2'}$ = 5.8 Hz), 8.10 (d, 1, 6-H, $J_{4,6}$ = 2.50 Hz), 8.64 (d, 1, 4-H). Anal. ($C_{13}H_{15}IN_2O_6$) C, H, I, N.

The first major fraction eluted from the column was rechromatographed on 50 g of silica gel (eluted with ethyl acetate) to yield 1.46 g (15.4%) of the unknown component "Z": mp 70–73 °C; UV ($CHCl_3$) $\lambda_{max}$ 338 nm; $[\alpha]_D$ 10.7° ($CHCl_3$, *c* 1.20 M); IR (KBr) $\nu_{max}$ 1740, 1600, 1500, 1380, 1230 $cm^{-1}$; NMR ($CDCl_3$) δ 1.80–3.0 (m, 8), 3.60–4.50 (m, 2), 4.9–5.40 (m, 2), 5.40–6.00 (m, 1), 8.10 (t, 1), 8.55 (t, 1). Anal. ($C_{13}H_{15}IN_2O_6$) C, H, N; I: calcd, 30.06; found, 30.64.

For further structural proof of **11b**, this compound was also prepared by acetylation of the free α-nucleoside **7b** (obtained by deprotection of the corresponding 3′,5′-bis-*O*-(*p*-chlorobenzoyl) derivative **4b**, see below), in the following manner: 0.59 g (0.95 mmol) of **7b** was added to a cold, anhydrous, saturated solution of methanolic ammonia (30 mL); the flask was sealed and the mixture was stirred at 4 °C overnight. The resulting solution was concentrated in vacuo to a syrup, which was then diluted with 6 mL of dry pyridine. This solution was cooled in an ice bath and to it was added dropwise 0.9 mL (9.5 mmol) of acetic anhydride. This mixture was allowed to warm up to room temperature after completion of addition, and stirring was continued overnight. The reaction mixture was concentrated to a syrup, and the residual solvent was removed by coevaporation with ethanol (5 mL). The resulting oil was chromatographed on 20 × 20 silica gel plates (5% $MeOH/CH_2Cl_2$). The desired band was extracted with 20% $MeOH/CH_2Cl_2$ and concentrated to an oil. After drying, this material, which was chromatographically homogeneous, weighed 0.36 g (90.6%); $[\alpha]^{34}_D$ −10.89° ($CHCl_3$, *c* 0.104 M); $^1H$ NMR ($CDCl_3$), identical with that of the blocked α-nucleoside **11b** obtained above in the coupling reaction of the 2-deoxyribose triacetate **9** and **10** with the silylated pyrimidine base.

**Reaction of the 2-Deoxy-D-ribose Triacetates 9 and 10 with the Silylated 5-Bromo-2(1*H*)-pyrimidinone 2a.** A mixture of 5-bromo-2(1*H*)-pyrimidinone (**1a**; 5.0 g, 28.57 mmol) and hexamethyldisilazane (25 mL) was refluxed for 24 h, cooled, and decanted to remove the insoluble material. The solution was then coevaporated three times with dry toluene to give 6.8 g of a residue, which was added to a solution of the 2-deoxy-D-ribose triacetates **9** and **10** (6.90 g, 26.50 mmol) in 250 mL of dry 1,2-dichloroethane. To this mixture was added dropwise a solution of 4 mL (34.7 mmol) of $SnCl_4$ in 100 mL of dry 1,2-dichloroethane. Subsequent to this addition, the reaction mixture was allowed to stir at room temperature for 5 h. The mixture was then treated with 200 mL of 1,2-dichloroethane and 500 mL of a saturated bicarbonate solution. The resulting mixture was filtered over a bed of Celite and the cake was thoroughly washed with dichloroethane and discarded. The organic extract was dried over anhydrous sodium sulfate and evaporated to give a residue, which was chromatographed on a loose column of 100 g of silica gel (eluted with 11% acetone in ethyl acetate). The crude material was rechromatographed on 20 cm × 20 cm silica gel plates to give 200 mg (2.0%) of 1-(3,5-di-*O*-acetyl-2-deoxy-α-D-ribofuranosyl)-5-bromo-2-pyrimidinone (**11a**): mp 44–46 °C; UV ($CHCl_3$) $\lambda_{max}$ 336 nm; $[\alpha]^{18}_D$ −32.2° ($CHCl_3$, *1*.68 M); IR (neat) $\nu_{max}$ 3400, 1740, 1660, 1500, 1380, 1230 $cm^{-1}$; NMR ($CDCl_3$) δ 1.80–3.20 (m, 8, acetyl and 2′-H), 4.18 (d, 2, 5′-H), 4.75 (t, 1, 4′-H), 5.26 (d, 1, 3′-H), 6.20 (dd, 1, 1′-H, $J_{1',2'}$ = 5.8 Hz), 8.00 (d, 1, 6-H), $J_{4,6}$ = 2.8 Hz), 8.56 (d, 1, 4-H). Anal. ($C_{13}H_{15}BrN_2O_6$) C, H, N, Br.

The other component isolated, "Y", weighed 163 mg (1.5%): mp 44–48 °C; UV ($CHCl_3$) $\lambda_{max}$ 336 nm; $[\alpha]^{18}_D$ +10° ($CHCl_3$, *c* 1.20 M); IR (neat) $\nu_{max}$ 3400, 3150–2800, 1740, 1660, 1500, 1380, 1250 $cm^{-1}$; NMR ($CDCl_3$) 1.65–2.87 (m, 8, acetyl and 2′-H), 3.60–4.50 (m, 2), 4.80–5.40 (m, 2), 5.46–6.27 (m, 1), 8.05 (d, 1, *J* = 2.9 Hz), 8.35–8.75 (m, 1). Anal. ($C_{13}H_{15}BrN_2O_6$·EtOAc) C, H, N, Br.

**1-[3,5-Bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl]-5-bromo-2-pyrimidinone (4a) and 1-[3,5-Bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-β-D-ribofuranosyl]-5-bromo-2-pyrimidinone (3a).** A suspension of 4.14 g (23.64 mmol) of 5-bromo-2(1*H*)-pyrimidinone (**1a**) in 25 mL of hexamethyl-

disilazane and 1 mL of chlorotrimethylsilane was refluxed for 1 h (with exclusion of moisture), cooled, and concentrated to an oil. Residual solvent was then removed by coevaporation with 1,2-dichloroethane (15 mL). The syrup was dissolved in 125 mL of 1,2-dichloroethane and the solution was cooled in an ice bath. To this was added 11.05 g (25.7 mmol) of 3,5-bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl chloride[31] (**8**) in 125 mL of dry 1,2-dichloroethane. A solution of 0.4 mL (3.42 mmol) of $SnCl_4$ in 25 mL of dry 1,2-dichloroethane was then added dropwise over a period of 15 min. The mixture was stirred at 0 °C and the reaction was monitored by TLC. After $1^1/_2$ h, the reaction mixture was diluted with 100 mL of 1,2-dichloroethane and 100 mL of cold saturated sodium bicarbonate. The aqueous layer, subsequent to separation, was extracted with dichloroethane (2 × 60 mL). The organic extract was washed with water (100 mL), dried over anhydrous magnesium sulfate, and concentrated to a residue, which was subjected to flash chromatography on 180 g of silica gel. The fractions containing the less mobile component **4a** (the α anomer) were pooled and concentrated to a solid, which was recrystallized from toluene and dried to yield 1.04 g (7.7%) of a white product: mp 182–185 °C; $[\alpha]^{25}_D$ −8.4° ($CH_2Cl_2$, *c* 1.76 × $10^{-3}$ M); $^1$H NMR ($CDCl_3$) δ 2.25–3.38 (m, 2, 2′-H), 4.58 (d, 2, 5′-H), 5.03 (t, 1, 4′-H), 5.68 (d, 1, 3′-H), 6.30 (d, 1, 1′-H), $J_{1'2'}$ = 6 Hz), 7.28–8.00 (m, 8, phenyl), 8.13 (d, 1, 6-H), 8.60 (d, 1, 4-H); IR ($CHCl_3$) $\nu_{max}$ 3075, 2962, 2927, 1721, 1664, 1594, 1501, 1297 $cm^{-1}$; UV ($CHCl_3$) $\lambda_{max}$ 335 nm (ε 6200). Anal. ($C_{23}H_{17}BrCl_2N_2O_6$) C, H, N, Br, Cl.

The more mobile β anomer **3a** was recrystallized from toluene and dried to give 1.22 g (9.1%) of the white product: mp 171–173 °C; $[\alpha]^{25}_D$ +3.4° ($CH_2Cl_2$, *c* 1.76 × $10^{-3}$ M); $^1$H NMR ($CDCl_3$) δ 1.97–2.5 (m, 2, 2′-H), 4.75 (m, 3, 4′-H, 5′-H), 5.62 (d, 1, 3′-H), 6.27 (t, 1, 1′-H, $J_{1'2'}$ = 6 Hz), 7.17–8.10 (m, 8, phenyl), 8.17 (d, 1, 6-H), 8.55 (d, 1, 4-H); IR ($CHCl_3$) $\nu_{max}$ 3091, 2971, 1732, 1710, 1661, 1591, 1499, 1400, 1379 $cm^{-1}$; UV ($CHCl_3$) $\lambda_{max}$ 335 nm (ε 6400). Anal. ($C_{23}H_{17}BrCl_2N_2O_6$) C, H, Br, Cl, N.

**1-(2-Deoxy-β-D-ribofuranosyl)-5-bromo-2-pyrimidinone (5a).** A 0.70-g (1.23 mmol) sample of **3a** was added to a flask containing 25 mL of cold anhydrous saturated methanolic ammonia and the flask was sealed. The mixture was then stirred at 4 °C and the reaction was monitored by TLC (10% methanol in methylene chloride; silica gel); the reaction was complete in 5 h. The resulting solution was concentrated in vacuo to a syrup; the latter was then treated with a minimum amount of ethanol and chilled to give a crystalline material. The product was collected by filtration, washed with a small amount of cold ethanol, and dried to provide 0.22 g (60%) of the analytically pure **5a**: mp 120–124 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 2.08–2.68 (m, 2, 2′-H), 3.73 (d, 2, 5′-H), 3.97–4.40 (m, 2, 3′-H, 4′-H), 5.08 (d, 1, exchangeable), 5.43 (s, 1, 6-H), 5.82 (dd, 1, 1′-H, $J_{1'2'}$ = 6 Hz), 6.60 (d, 1, 4-H), 10.0 (br s, 1, exchangeable); IR (KBr) $\nu_{max}$ 3500, 3281, 3225, 1665, 1473, 1390, 1370, 1329 $cm^{-1}$. Anal. ($C_9H_{11}BrN_2O_4$) C, H, Br, N.

**1-[3,5-Bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-α-D-ribofuranosyl]-5-iodo-2-pyrimidinone (4b) and 1-[3,5-Bis-*O*-(*p*-chlorobenzoyl)-2-deoxy-β-D-ribofuranosyl]-5-iodo-2-pyrimidinone (3b).** A suspension of 0.86 g (3.87 mmol) of **1b** in 15 mL of hexamethyldisilazane and 0.3 mL of chlorotrimethylsilane was refluxed for 2 h (with the exclusion of moisture), cooled, and concentrated in vacuo to yield a yellow oil. Residual solvent was removed by coevaporation with 1,2-dichloroethane (2 × 10 mL), and 1.65 g (3.84 mmol) of the halogenose **8** was added; the resulting mixture was dissolved in 50 mL of anhydrous 1,2-dichloroethane and cooled in an ice bath. To the cooled solution was added dropwise a solution of 0.2 mL (1.7 mmol) of $SnCl_4$ in 25 mL of anhydrous dichloroethane. The reaction mixture was stirred at 0 °C for $2^1/_2$ h at which time TLC (17% ethyl acetate in dichloroethane) showed disappearance of the starting material, indicating that the reaction was essentially complete. The mixture was diluted with 60 mL of dichloroethane and 50 mL of saturated $NaHCO_3$, and the resulting emulsion was filtered through Celite, the precipitate being washed several times with 1,2-dichloroethane. The organic layer was washed with 50 mL of water, dried over anhydrous magnesium sulfate, and concentrated to a residue, which on TLC showed two major spots of equal intensity ($R_f$ values 0.19 for **4b** and 0.3 for **3b**; 17% ethyl acetate in dichloroethane; Macherey-Nagel silica gel G). This residue was chromatographed on 90 g of silica gel and eluted with a gradient of 0–15% ethyl acetate in dichloroethane. The fractions, containing the slower moving α anomer **4b**, were pooled and concentrated to a residue, which weighed after drying 0.48 g (20.4%). The white crystalline compound was obtained by recrystallization from ethanol–acetone: mp 175–176 °C; $[\alpha]^{26}_D$ +20.03° ($CHCl_3$, *c* 0.108 mM); NMR ($CDCl_3$) δ 2.88 (m, 2, 2′-H), 4.6 (d, 2, 5′-H), 5.0 (t, 1, 4′-H), 5.65 (d, 1, 3′-H), 6.27 (d, 1, 1′-H, $J_{1'2'}$ = 7 Hz), 7.25–8.12 (m, 8, phenyl), 8.18 (d, 1, 6-H, $J_{6,4}$ = 3 Hz), 8.68 (d, 1, 4-H, $J_{4,6}$ = 3 Hz); IR ($CHCl_3$) $\nu_{max}$ 3000, 1725, 1665, 1595, 1490, 1380, 1260, 1090, 1010 $cm^{-1}$; UV ($CHCl_3$) $\nu_{max}$ 340 nm (ε 3600). Anal. ($C_{23}H_{17}Cl_2IN_2O_6$) C, H, Cl, I, N.

The faster moving β anomer was obtained in the same manner described for the α anomer: yield 0.46 g (19.5%) of **3b**; mp 136–138 °C; $[\alpha]^{26}_D$ −13.66° ($CHCl_3$, *c* 0.10 M); $^1$H NMR ($CDCl_3$) δ 2.32 (m, 1, 2′-H), 3.2 (m, 1, 2′-H), 4.75 (m, 3, 4′-H, 5′-H), 5.62 (d, 1, 3′-H), 6.27 (t, 1, 1′-H, $J_{1'2'}$ = 7 Hz), 7.30–8.17 (m, 8, aromatic), 8.27 (d, 1, 6-H, $J_{6,4}$ = 3 Hz), 8.57 (d, 1, 4-H, $J_{4,6}$ = 3 Hz); IR ($CHCl_3$) $\nu_{max}$ 3000, 1725, 1675, 1595, 1500, 1380, 1260, 1090, 1010 $cm^{-1}$; UV ($CHCl_3$) $\lambda_{max}$ 341 nm (ε 3500). Anal. ($C_{23}H_{17}Cl_2IN_2O_6$) C, H, Cl, I, N.

**1-(2-Deoxy-β-D-ribofuranosyl)-5-iodo-2-pyrimidinone (5b).** A 0.41-g (0.67 mmol) sample of **3b** was added to a cold anhydrous methanolic ammonia solution (25 mL); the flask was sealed and the mixture was stirred at 4 °C for 5 h. The reaction was complete as indicated by TLC (10% MeOH/$CH_2Cl_2$). The solution was concentrated to a syrup, which was subsequently treated with acetone and chilled (−20 °C) to give, after several days, the crystalline material. The product was collected by filtration, washed with acetone, and dried to provide 100 mg (45.1%) of the pale yellow **5b**: mp 160–170 °C dec; $^1$H NMR ($Me_2SO$-$d_6$) δ 2.35 (m, 2, 2′-H), 3.65 (m, 2, 5′-H), 3.90 (m, 1, 4′-H), 4.22 (m, 1, 3′-H), 5.22 (t, 2, OH), 6.0 (t, 1, 1′-H, $J_{1'2'}$ = 6 Hz), 8.62 (d, 1, 6-H, $J_{6,4}$ = 3 Hz), 8.75 (d, 1, 4-H); IR (KBr) $\nu_{max}$ 3390, 3140 (br), 2925, 1640, 1600 (sh), 1500, 1390, 1290, 1250, 1100, 1070 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 335 nm (ε 2830). Anal. ($C_9H_{11}IN_2O_4$) C, H, I, N.

**1-(2-Deoxy-α-D-ribofuranosyl)-5-iodo-2-pyrimidinone (7b).** A 1-g (1.62 mmol) sample of **4b** was added to a cold anhydrous methanolic ammonia solution and the mixture was stirred, after sealing the reaction flask, at 4 °C for 11 h. The resulting solution was concentrated at 25 °C to a residue, which was treated with acetone and chilled to give crystalline material. This was collected by filtration, washed with cold acetone, and dried to give 0.28 g (51%) of the off-white material: mp 127–131 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 1.77–2.9 (m, 2, 2′-H), 3.45 (d, 2, 5′-H), 4.33 (m, 2, 3′-H, 4′-H), 5.98 (d, 1, 1′-H, $J_{1'2'}$ = 6 Hz), 8.33 (d, 1, 6-H, $J_{6,4}$ = 3.5 Hz), 8.65 (d, 1, 4-H, $J_{4,6}$ = 3.5 Hz); IR (KBr) $\nu_{max}$ 3600–2500 (br), 2980 (sh), 1630, 1590, 1500, 1480, 1250, 1070, 980 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 334 nm (ε 3560). Anal. ($C_9H_{11}IN_2O_4$) H, N; C: calcd, 31.97; found, 32.50.

**Biological Methods. a. Cells.** The cells were grown at 37 °C in RPMI 1640 medium containing 100 μg of Kanamycin/mL and supplemented with 5% fetal bovine serum for Vero and HeLa Bu (TK-) cells and 5% horse serum for HeLa $S_3$ cells. All cultures were found to be mycoplasma free when tested by the 4,6-diamidino-2-phenylindole fluorescence technique.[43]

**b. Virus.** The laboratory strains of HSV CL101 parental and TK mutants $ACG^r$ (S1), $ACG^r$ (Tr7), and $BVdU^r$, isolated in the presence of acyclovir at 10 μg/mL and 1 mg/mL and (*E*)-5-(2-bromovinyl)-2′-deoxyuridine at 10 μg/mL, respectively, were gifts of G. Darby and H. Field (Cambridge, University, United Kingdom). The DNA polymerase mutants $PFA^r$ were cloned isolates of HSV-1 (KOS strain) grown in the presence of PFA.[44] The procedures for the maintenance of the laboratory strains for virus HSV-1 and HSV-2 and all mutants and the virus yield assay were described previously.[45]

**c. Enzyme Preparations and Assays.** The cellular cytosol thymidine kinase was isolated from human KB 6B cells and the

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mitochondrial enzyme from the peripheral blasts of patients with chronic lymphocytic leukemia. The viral dThd kinases were extracted from dThd kinase deficient HeLa (BU-25) cells infected with HSV-1 (strain KOS) or HSV-2 (strain 333). The enzymes were purified by affinity chromatography.[39-41] To estimate the inhibition constants of the compounds, several concentrations of dThd were employed; the methods were described previously.[42] To determine the ability of these compounds to act as alternative substrates for dThd kinases, the assay of Dobersen and Greer was employed.[46] The concentration of [$\gamma^{32}$P]ATP was 0.5 mM, and the concentration of substrate was 0.4 mM. The relative phosphorylation is based on dThd as 100%. The results are presented in Table II.

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**Registry No.** **1a**, 38353-06-9; **1b**, 79387-69-2; **2a**, 83768-01-8; **2b**, 88350-65-6; **3a**, 96245-83-9; **3b**, 96245-84-0; **4a**, 96245-85-1; **4b**, 96245-86-2; **5a**, 96245-87-3; **5b**, 93265-81-7; **6a**, 96245-88-4; **6b**, 96245-89-5; **7b**, 96245-90-8; **8**, 21740-23-8; α-**9**, 96291-74-6; β-**9**, 96291-75-7; α-**10**, 96291-76-8; β-**10**, 4258-01-9; **11a**, 96245-91-9; **11b**, 96245-92-0; α-Y, 96245-93-1; β-Y, 96245-94-2; α-Z, 96245-95-3; β-Z, 96245-96-4; 2-pyrimidinone, 557-01-7; 2-deoxy-D-ribose, 533-67-5.

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# *N*-[[(Mercaptoacetyl)amino]benzoyl]glycines as Mucolytic Agents

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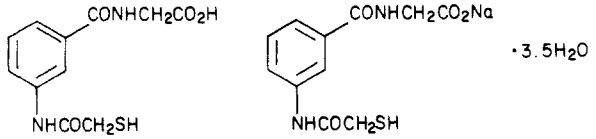
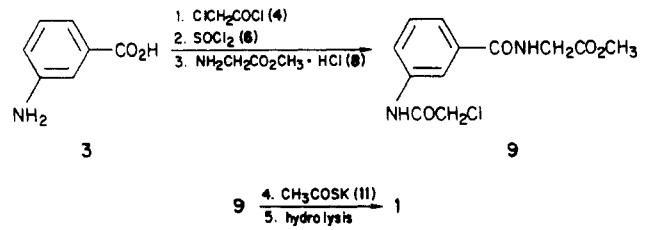
*m*- and *p*-aminobenzoic acids were converted to the title compounds by sequential use of $ClCH_2COCl$, $SOCl_2$, glycine methyl or ethyl ester, AcSK, and hydrolysis. The title compounds and a number of salts were compared for mucolytic activity, toxicity, stability, and hygroscopicity. When compared to *N*-acetyl-L-cysteine (NAC), the compounds exhibit several times the in vitro mycolytic activity of NAC on a molar basis. The most promising candidate appears to be the sodium salt $3.5H_2O$ **2** of the meta series.

Extensive investigations[1-4] followed the discovery of *N*-acetyl-L-cysteine (NAC)[5,6] as a mucolytic agent. The present paper deals with the preparation of the meta (**1**) and para (**21**) isomers of the title compounds (Table I) as well as six stable salts of **1** (Table II). The mucolytic activity of the representative sulfhydryl compounds is demonstrated (Tables III and IV). Compound **1** and some of its salts, especially the sodium salt $3.5H_2O$ **2**, were investigated in more detail.




**1** **2**

Scheme I (See Table I, 5, 7, 9, 12)




**3** **9** **9** → **1**

**Chemistry.** The synthesis[7] of compound **1** involved a five-step reaction (Scheme I). In step 1, anhydrous NaOAc in HOAc served as an excellent acid acceptor to give the *N*-chloroacetyl derivative **5**[8d] (Table I) in 92% yield. The preparation of the acid chloride **7** (Table I) was performed in a relatively small volume of $SOCl_2$–$CHCl_3$ by the batchwise addition of the benzoic acid derivative **5**. The glycine methyl ester derivative **9** was prepared in the reaction between **7** and glycine methyl ester hydrochloride (**8**)[9] in in the presence of $NaHCO_3$ and aqueous $CH_3OH$ as solvent. The thiol ester **12** (Table I) was prepared in the reaction between **9** and AcSK **11**[10] in methanolic solution. Both ester moieties (one thio) of the key intermediates **12** were hydrolyzed in aqueous methanolic NaOH solution to yield the meta isomer **1** in an acceptable

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(8) (a) This compound **31** was prepared similarly to preparative method H. (b) Friedman, M. "The Chemistry and Biochemistry of the Sulfhydryl Group in Amino Acids, Peptides and Proteins", 1st ed.; Pergamon Press: New York, 1973; Chapters 3, 8. (c) Reference 8b, pp 292–293. (d) *Beilstein 14(I)*, 562.

(9) The use of glycine ethyl ester gives **10** in 76% yield.

(10) The use of intermediate **10** and EtOH as reaction solvent gives **13** in 84% yield.

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