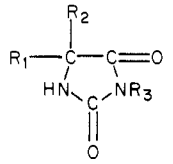
Table IV. Physical Properties of Substituted Hydantoins[a]



no.	R_1	R_2	R_3	procedure	yield, %	mp, °C	solvent[b]	formula
11	3-BrC_6H_4CH=		H	c	37	252-254.5	B	$C_{10}H_7BrN_2O_2$
10	3-$ClC_6H_4CH_2$	H	H	e	58	193-194	B	$C_{10}H_9ClN_2O_2$
13	3-$CF_3C_6H_4CH$=		H	c	63	226.5-228	C	$C_{11}H_7F_3N_2O_2$
14	3-$CF_3C_6H_4CH_2$	H	H	d	85	170.5-172	B	$C_{11}H_9F_3N_2O_2$
16	3-$BrC_6H_4CH_2$	H	CH_3	f	70	147-148	D	$C_{11}H_{11}BrN_2O_2$
17	3-$CF_3C_6H_4CH_2$	H	CH_3	f	87	153-154	D	$C_{12}H_{11}F_3N_2O_2$
20	3-$CF_3C_6H_4CH_2$	CH_3	H	h	20	218-220	A	$C_{12}H_{11}F_3N_2O_2$
5	2,5-$(OCH_3)_2C_6H_3CH_2$	H	H	d	64	171-173	E	$C_{12}H_{14}N_2O_4$
21	3-$CF_3C_6H_4CH_2$	H	CH_2CH_2Br	f	10	114-117	G	$C_{13}H_{12}BrF_3N_2O_2$
18	3-$CF_3C_6H_4CH_2$	H	CH_2CH_2OH	f	22	115-117.5	H	$C_{13}H_{13}F_3N_2O_3$
22	3-$CF_3C_6H_4CH_2$	H	CH_2CH_2CN	g	24	151-152	J	$C_{14}H_{12}F_3N_3O_2$
8	β-naphthyl-CH_2	CH_3	H	h	61	254-255	I	$C_{15}H_{14}N_2O_2$
19	3-$CF_3C_6H_4CH_2$	H	CH_2CO_2Et	f	62	148.5-150	D	$C_{15}H_{15}F_3N_2O_4$
15	3-$CF_3C_6H_4$	C_6H_5	H	h	70	213-214.5	C	$C_{16}H_{11}F_3N_2O_2$

[a] This table is arranged in increasing number of carbon atoms. However, the compound numbers are the same as those in the earlier tables. [b] Solvents: A = methylcellusolve; B = ethanol; C = acetone; D = benzene/hexane; E = methanol/ethyl acetate; F = methylcellusolve/water; G = carbon tetrachloride; H = aqueous ethanol; I = boiling water; J = benzene. [c] Reference 15. [d] See Experimental Section. [e] Reference 16. [f] Reference 17. [g] Reference 18. [h] Reference 19.

mice in each group were tested for protection against maximal electroshock seizures 30 min after dosing. All mice were sacrificed and examined after testing.

Analysis and Spectral Data. Melting points for all compounds were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected. (The melting points for compounds in Table I were not presented in Chemical Abstracts and the corresponding journals were difficult to obtain.) NMR spectra were obtained in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as an internal standard on either a Varian A-60 or Perkin-Elmer 24A spectrometer. Infrared spectra were run as Nujol mulls on a Perkin-Elmer Model 21 spectrophotometer. Mass spectra, where necessary, were recorded on a Varian MAT CH5-DF instrument. Microanalyses were within ±0.3% of the theroretical values.

5-[3-(Trifluoromethyl)benzyl]hydantoin (14). Compound 13 (11.3 g, 0.04 mol) in ethanol (200 mL) was reduced in a Parr hydrogenator using 5% palladium on carbon as a catalyst. The mixture was filtered and concentrated, and the resulting white solid (14) recrystallized from hot ethanol: yield 9.8 g (86%); mp 171-174 °C.

3-(2,5-Dimethoxyphenyl)-2-ureidopropionic Acid (24). It was prepared by the procedure described.[12] Recrystallization from methanol gave a white solid, mp 190.5-191 °C. Anal. ($C_{12}H_{16}N_2O_5$) C, H, N.

Compound **25**, 3-[3-(trifluoromethyl)phenyl]-2-ureidopropionic acid, was prepared in a similar manner and crystallized from boiling ethanol: 50% yield; mp 195-197 °C. Anal. ($C_{11}H_{11}F_3N_2O_3$) C, H, N.

Other compounds were prepared by known procedures as shown in Table IV.

Acknowledgment. The authors are indebted to R. E. Bache and B. T. Kenney for their excellent technical assistance. In addition, the authors thank Dr. B. Stuart Hurlbert for microanalysis and Spectral Data and its interpretations. Thanks are also due to Dr. Allen A. Lai for perusing the manuscript and making useful suggestions.

Synthesis and Antitumor Activity of Simple Vinyl and α-Methylene-γ-butyrolactone Sulfonate Esters and Silyl Enol Ethers[1]

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A number of simple silyl enol ethers and vinyl trifluoromethanesulfonates, a relatively new class of organic compounds capable of undergoing alkylation by a nucleophilic addition–elimination process, were evaluated in the P388 lymphocytic leukemia system. No activity (ILS = 8–22%) was observed in the simple vinyl derivatives. Some activity (ILS = 20–42%) was observed for a series of siloxy and sulfonate (CH_3SO_2 and CF_3SO_3) functionalized α-methylene lactone systems. The enhanced activity of the functionalized systems over the parent methylene lactone is ascribed to a possible *irreversible* alkylation by cellular nucleophiles via a nucleophilic addition–elimination process.

Alkylating agents were one of the first cancer chemoteraputic agents employed and are amongst the most widely and successfully used antitumor agents in clinical use to date.[2] The most recent member of this class of chemoterapeutic agents is the α-methylenebutyrolactone containing sesquiterpenes derived from plant extracts.[3] It

(1) Abstracted in part from the Ph.D. Dissertation of W. L. Treptow, The University of Utah, 1980.

(2) Livingston, R. B.; Carter, S. K. "Single Agents in Cancer Chemotherapy"; Plenum: New York, 1970. Becker, F. F., Ed. "Cancer a Comprehensive Treatise"; Plenum Press: New York, 1977; Vol. 5. Pratt, W. B.; Ruddon, R. W. "The Anticancer Drugs"; Oxford University Press: Oxford, 1979.

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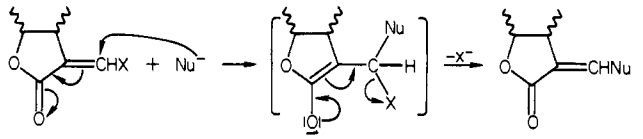
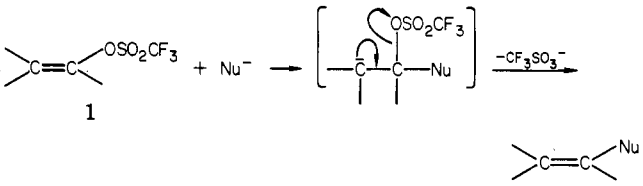
Scheme I



Scheme II



is well established that the alkylating nature and, hence, potential tumor inhibition of these sesquiterpene lactones derives from Michael-type interaction of the α,β-unsaturated carbonyl with biological nucleophiles.[3,5] It is also widely recognized that the usefulness of most natural sesquiterpene lactones has been limited by their relatively high toxicity.[4] This combination of potential antitumor activity coupled with high toxicity has resulted in widespread exploration of synthetic modification of α-methylene lactones and preparation and testing of synthetic analogues.[6-10]

An obvious modification that has been little explored is functionalization of the exocyclic methylene with a good leaving group.[11] Such a modification would allow for *irreversible* alkylation by replacement of the leaving group with a biological nucleophile as shown in Scheme I. Such irreversible alkylation might result in enhanced selectivity and/or activity of these methylene lactone moieties.

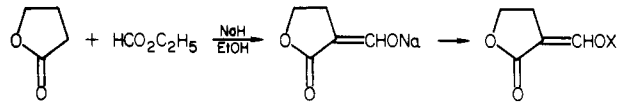
Because of our extensive experience[12] with vinyl sulfonate esters and silyl enol ethers, we chose to initially investigate methanesulfonyl (CH_3SO_3), trifluoromethanesulfonyl (CF_3SO_3), and siloxy (Me_3SiO) substituted α-methylene-γ-butyrolactones and related compounds. Similarly, simple vinyl trifluoromethanesulfonates, 1, a relatively new class of organic compounds,[12] might serve as alkylating agents via a well-known[13] nucleophilic addition–elimination process as shown in Scheme II. Furthermore, there is evidence[14] that the increased acidity and lipophilicity that are imparted by the inclusion of the trifluoromethanesulfonyl moiety often transforms compounds of moderate biological activity into highly active species. Furthermore, sulfonate esters and methanesulfonates (mesylates) in particular, such as busulfan (2)

$$CH_3O_2SOCH_2CH_2CH_2CH_2OSO_2CH_3$$
2

$$Cl^-H_2N^+(CH_2CH_2CH_2OSO_2CH_3)_2$$
3

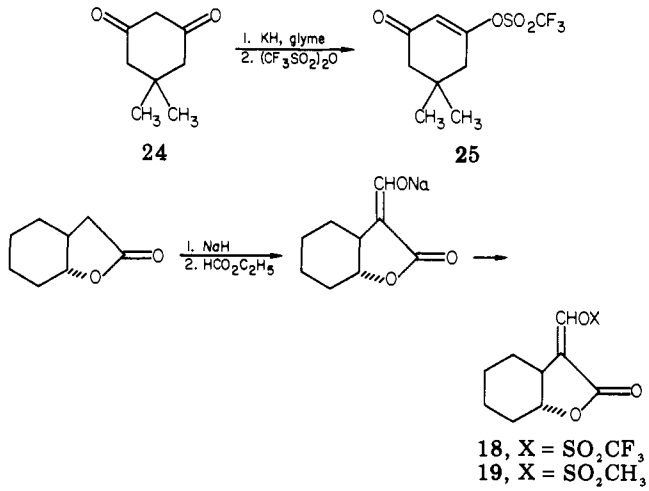
and the nitrogen mustard analogue[15] 3, have shown considerable antitumor activity. Moreover, a comprehensive study of the activity of busulfan-related compounds clearly showed that the better the leaving group the more active the compound.[16] Hence, in this paper we report the

Scheme III



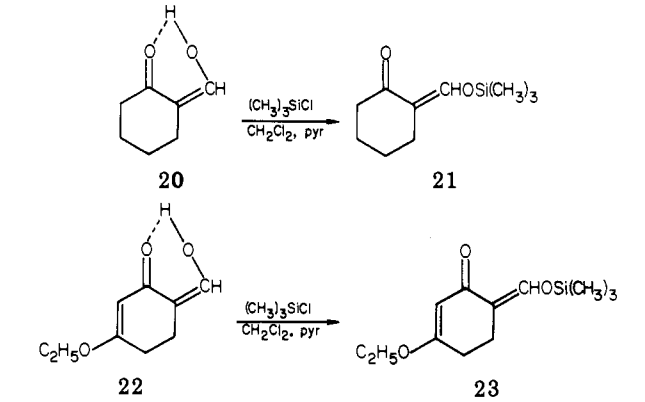
15, X = $SiMe_3$
16, X = SO_2Me
17, X = SO_2CF_3

Scheme IV



18, X = SO_2CF_3
19, X = SO_2CH_3

Scheme V



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(10) Cassady, J. M.; Byrn, S. R.; Stamos, I. K.; Evans, S. M.; McKenzie, A. *J. Med. Chem.* **1978**, *21*, 815.
(11) Howie, G. A.; Stamos, I. K.; Cassady, J. M. (*J. Med. Chem.* **1976**, *19*, 309) reported the preparation of the tosylate of the α-methylene-γ-lactone, i.e., 16 (X = p-$CH_3C_6H_4SO_2$) and the bicyclic isomer 19 (X = p-$CH_3C_6H_4SO_2$); neither showed an in vivo activity in the L1210 lymphoid leukemia system.
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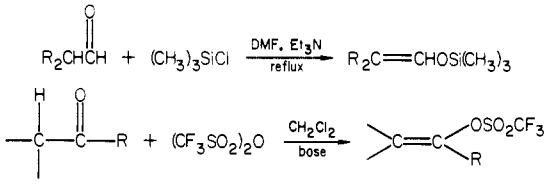
Table I. Summary of P388 Test Results for Simple Silyl Enol Ethers and Vinyl Triflates

no.	compd	dose, mg/kg of body wt[a]	toxicity day survivors[a]	% ILS[a]
4	$C_6H_5(CH_3)C{=}CHOSiMe_3$	100	5/6	8
5	$(CH_3)_2C{=}CHOSiMe_3$	200	6/6	14
6	$c\text{-}C_6H_{10}{=}CHOSiMe_3$	100	6/6	22
7	$(CH_3)_2C{=}CHOSO_2CF_3$	50	6/6	−1
8	$(CH_3)_2C{=}C(CH_3)OSO_2CF_3$	100	6/6	14
9	$(C_6H_5)_2C{=}C(C_6H_5)OSO_2CF_3$	100	6/6	16
10	$c\text{-}C_6H_{10}{=}CHOSO_2CF_3$	200	5/6	12
11	$c\text{-}C_5H_9\text{-}OSO_2CF_3$	50	6/6	14
12	$c\text{-}C_7H_{11}\text{-}OSO_2CF_3$	400	5/5	15
13	$c\text{-}C_8H_{13}\text{-}OSO_2CF_3$	200	5/6	14
14	$c\text{-}C_8H_{13}\text{-}OSO_2CF_3$	100	6/6	13

[a] Reference 25.

preparation and test results of a series of simple vinyl trifluoromethanesulfonates, vinyl silyl enol ethers, as well as sulfonate and siloxy functionalized α-methylene lactones.

Chemistry. Both the preparation and the biological activity of these compounds are best described in two parts, namely, simple vinyl compounds and functionalized α-methylene lactones and related compounds. Silyl enol ethers **4–6** were prepared by standard literature procedures[17] by interaction of the appropriate aldehyde with trimethylchlorosilane. Simple vinyl triflates **7–14** were prepared by methods developed in our laboratories[18-20] via interaction of the appropriate carbonyl precursor with trifluoromethanesulfonic acid anhdyride, $(CF_3SO_2)_2O$:



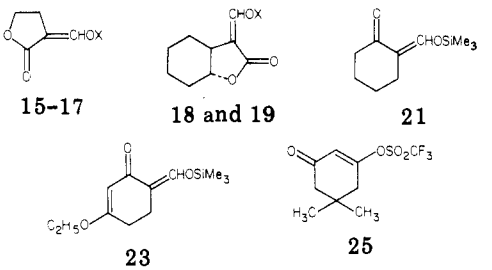
The functionalized α-methylene-γ-butyrolactones **15–17** were prepared by trapping of the enolate salt prepared[11,21] from γ-butyrolactone and ethyl formate as shown in Scheme III.

The functionalized bicyclic lactones **18** and **19** were obtained from the bicyclic lactone prepared from cyclohexene oxide and diethyl malonate by standard procedures[11,22] as shown in Scheme IV.

Silyl enol ethers **21** and **23** were made from their respective enols **20**[23] and **22**[24] by interaction with $(CH_3)_3SiCl$ (Scheme V); the corresponding methanesulfonates and trifluoromethanesulfonates were also obtained but proved to be much too unstable to evaluate.

Finally, functionalized enone **25** was prepared by reaction of dimedone **24** with $(CF_3SO_2)_2O$.

Table II. Summary of Test Results for Functionalized Lactones and Related Compounds



15–17 18 and 19 21

23 25

no.	X	test syst[a]	dose, mg/kg of body wt[a]	toxicity day surv[a]	% ILS[a]
15	$SiMe_3$	CD8F	250	10/10	42
		P388	200	6/6	25
		L1210	400	6/6	12
		B16	200	10/10	6
		LL	12.5	10/10	16
16	SO_2CH_3	L1210	25	5/6	6
		P388	50	6/6	32
17	SO_2CF_3	L1210	25	5/6	6
		P388	37.5	6/6	26
18	SO_2CF_3	L1210	200	6/6	17
19	SO_2CH_3	L1210	22.5	6/6	11
		P388	120	6/6	25
21		P388	50	6/6	26
		L1210	200	10/10	5
		C-8	25	10/10	21
23		P388	50	6/6	3
25		L1210	50	6/6	3
		P388	25	6/6	12

[a] Reference 25.

Biological Results and Discussion

All compounds were evaluated by the NIH, via the P388 and some cases L1210 leukemia and other test systems in white mice, by standard NCI protocols.[25] The results for the simple silyl enol ethers and vinyl triflates are summarized in Table I and those for the functionalized lactones and related systems in Table II. Tests were done in duplicate, and the activities reported in the tables are confirmed.

Perusal of the data in the tables reveals a number of facts and trends. The simple silyl enol ethers **4–6** and vinyl triflates **7–14** of Table I show no activity despite their ability to undergo alkylation reactions.[26] These results do, however, establish that such siloxy and trifluoromethanesulfonyl functionalized compounds are nontoxic. Some antitumor activity is displayed by five (**15–17**, **19** and **21**) of the methylene lactone type compounds of Table II.

As expected from the respective leaving abilities, sulfonate functionalized lactones **16** and **17** are more active than the siloxy functionalized system **15** in the P388 system. However, the activity peaks with the methanesulfonate despite the much better leaving ability of the CF_3SO_3 group.[12] This is most likely a result of the fact that **17** does not survive the aqueous nucleophilic conditions of living cells due precisely to the very high reactivity[12] of the CF_3SO_3 group.

Significant is the fact that all three functionalized α-methylene-γ-butyrolactones **15-17** show enhanced activity compared to the parent α-methylene-γ-butyrolactone particularly in the P388 system. In fact, even the 5-uracil

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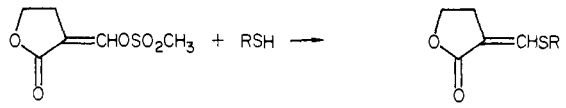
substituted methylenebutyrolactone shows a ILS of only 15% in the P388 test.[9]

The possible importance of irreversible alkylation in these systems is indicated by the fact that compound **16**



16

26a, R = C_6H_5
b, R = *t*-Bu
c, R = $CH_2CH(NH_2)COOH$

undergoes rapid adduct formation with thiophenol, *tert*-butyl mercaptan, as well as L-cysteine, resulting in thiomethylene lactones **26**.

It is evident from the foregoing that the concept of *irreversible* alkylation may have considerable merit. Sulfonate functionalized enones should undergo a Michael-type nucleophilic addition–elimination much more readily than simple enones[13] and result in possible enhanced antitumor activity. The present results suggest this to be the case, and further application of this concept is under active investigation.

Experimental Section

All melting and boiling points are uncorrected. Melting points were taken either on a Thomas-Hoover or a Mel-temp melting point apparatus. Infrared spectra were recorded on either a Beckman IR 5A or a Beckman Acculab 3 spectrometer and are reported in wavenumbers (cm^{-1}) calibrated to the 1603-cm^{-1} line of polystyrene. NMR spectra were recorded on either a Varian EM-360 or EM-390 spectrometer and are reported in parts per million (δ) downfield from internal Me_4Si. Mass spectra were obtained with a Varian MAT 112 spectrometer. All solvents employed were purified and dried by standard procedures[27] immediately prior to use. Satisfactory C and H elemental analyses were obtained for all new stable compounds reported.

Preparation of Silyl Enol Ethers 4–6 and Vinyl Triflates 7–14. These compounds were prepared in multigram quantities by procedures developed in our laboratories as previously reported.[18-20,26]

Dihydro-3-[[(trimethylsilyl)oxy]methylene]-2(3*H*)-furanone (15). To a 500-mL three-necked flask under N_2 was added 11.3 g (83 mmol) of sodium α-formyl-γ-butyrolactone[21] in 200 mL of ether. After the solution was cooled and equilibrated at −78 °C, 9.5 g (88 mmol) of Me_3SiCl was added dropwise over 0.5 h. The reaction was stirred an additional 3 h while warming to room temperature. The reaction mixture was extracted twice with 100 mL of 5% $NaHCO_3$ and dried over $MgSO_4$, and, after filtration, the solvent was removed by vacuum distillation. The residue was distilled to yield 12.1 g (79%) of colorless **15**: bp 74–75 °C (0.5 mm); IR (neat) 1755 (C=O), 1675 (C=C), 1200, 860, 770 cm^{-1}; NMR ($CDCl_3$) δ 0.2 (s, 9 H), 2.8 (dt, 2, J = 2.6 and 7.2 Hz), 4.3 (t, 2, J = 7.2 Hz), 7.34 (t, 1, J = 2.6 Hz); mass spectrum, m/e 186 (M^+, 7), 171 (94), 147 (36), 96 (67), 73 (100).

Dihydro-3-[[(methylsulfonyl)oxy]methylene]-2(3*H*)-furanone (16). In a manner similar to the preparation of **15** above, 9 g (66 mmol) of sodium enolate[21] reacted with 8 g (70 mmol) of mesyl chloride in 200 mL of glyme. The residue after solvent evaporation was twice recrystallized from 50:50 1,2-dichloroethane/hexane to give 7.8 g (62%) of product **16**: mp 76–77 °C; IR (Nujol) 1750 (C=O), 1677 (C=C), 1215 and 1185 cm^{-1}; NMR ($CDCl_3$) δ 3.05 (dt, 2, J = 2.2 and 6.9 Hz), 3.24 (s, 3), 4.4 (t, 2, J = 6.9 Hz), 7.03 (t, 1, J = 2.2 Hz), 7.75 (t, 1, J = 3 Hz), the olefinic protons at δ 7.03 and 7.75 indicate a mixture of E/Z isomers in a ratio of 1:5. The compound was tested as the mixture of isomers; mass spectrum, m/e 192 (M^+, 4), 96 (52), 83 (41), 68 (100).

Dihydro-3-[[[(trifluoromethyl)sulfonyl]oxy]-methylene]-2(3*H*)-furanone (17). This compound was prepared from 0.1 mol of the sodium enolate[20] and 0.1 mol of $(CF_3SO_2)_2O$[18] in 200 mL of glyme. The residue, after solvent removal, was chromatographed on silica gel with ether as the eluent, yielding first the E isomer, followed by the Z isomer. The solvent was removed by vacuum distillation at 0 °C for a combined yield of 12.8 g (53%) in an E/Z ratio of 5:1, (*E*)-**17**: mp 41–42 °C; IR (melt), 1768 (C=O), 1694 (C=C), 1250, 855, 797 cm^{-1}; NMR ($CDCl_3$) δ 3.1 (dt, 2, J = 3.0 and 7.2 Hz), 4.5 (t, 2, J = 7.2 Hz), 7.68 (t, 1, J = 3.0 Hz); mass spectrum m/e 246 (M^+, 16), 181 (6), 152 (23), 124 (69), 96 (25), 83 (44), 69 (100). (*Z*)-**17** (oil) IR ($CHCl_3$), 1770 (C=O), 1684 (C=C), 1250 cm^{-1}; NMR ($CDCl_3$) δ 2.03 (dt, 2, J = 2.4 and 7.2 Hz), 4.3 (t, 2, J = 7.2 Hz), 6.94 (t, 1, J = 2.4 Hz); mass spectrum, m/e 246 (M^+, 14), 181 (13), 152 (21), 124 (53), 96 (30), 83 (48), 69 (100).

Hexahydro-3-[[[(trifluoromethyl)sulfonyl]oxy]-methylene]-2(3*H*)-benzofuranone (18). In a similar manner to the preparation of **15** above, 15.6 g (82 mmol) of bicyclic lactone enolate salt[21] was reacted with 23.1 g (82 mmol) of $(CF_3SO_2)_2O$ in glyme. The usual workup was followed by column chromatography on silica gel with ether as eluent, yielding 10.1 g (43%) of **18** as an equal mixture of E/Z isomers: IR (neat) 1780 (C=O), 1694 (C=C), 1260, 1220 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.9 (m, 9), 3.85 (dt, 1, J = 3.9 and 10.8 Hz), 6.85 (d, 1, J = 3.2 Hz), 7.75 (d, 1 , J = 3.3 Hz); mass spectrum, m/e 300 (M^+, 11), 256 (25), 149 (100), 121 (80), 69 (77).

Hexahydro-3-[[(methylsulfonyl)oxy]methylene]-2(3*H*)-benzofuranone (19). The bicyclic lactone enolate salt,[21] 13.7 g (72 mmol), was reacted with 8.4 g (73 mmol) of mesyl chloride in glyme at −78 °C. The crude product was chromatographed on silica gel with 1:1 pentane/CH_2Cl_2 as eluent to give 8.9 g (50%) of white solid **19** as a 1:1 mixture of E/Z isomers: mp 61–75 °C; IR (KBr), 1755 (C=O), 1682 (C=C), 1187, 1090, 835 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.7 (m, 9), 3.2 (s, 3), 3.75 (m, 1), 6.8 (d, 1, J = 2.4 Hz, Z isomer), 7.6 (d, 1, J = 3.3 Hz, E isomer); mass spectrum, m/e 246 (M^+, 9), 167 (25), 150 (60), 122 (100), 79 (28).

6-[(Trimethylsiloxy)methylene]cyclohexen-2-one (21). To a 250-mL round-bottom flask were added 3.9 g (31 mmol) of enol **20**[23] in 30 mL of CH_2Cl_2, 2.7 g (34 mmol) of pyridine, and 3.7 g (34 mmol) of Me_3SiCl. After the mixture was stirred for 2 h at room temperature, the precipitated pyridinium hydrochloride salt was removed by filtration, the solvent was evaporated, and the residue was vacuum distilled to yield 5.7 g (94%) of **21**: bp 62–65 °C (0.22 mm); IR (neat) 1680 (C=O), 1595 (C=C) 855, 765 cm^{-1}; NMR ($CDCl_3$) δ 0.25 (s, 9), 1.5–2.5 (m, 8), 7.38 (t, 1 J = 2 Hz); mass spectrum, m/e 198 (M^+, 5), 183 (30), 125 (11), 73 (100).

6-[(Trimethylsiloxy)methylene]-3-ethoxycyclohex-2-enone (23). This compound was prepared similar to **21** from 16.9 g (0.1 mol) of enol **22**,[24] 11.9 g (0.11 mol) of Me_3SiCl, and 8.7 g (0.11 mol) of pyridine in 100 mL of CH_2Cl_2. Distillation gave 14.5 g (86%) of colorless **23**: bp 98–104 °C (0.2–0.3 mm); IR (neat) 1655 (C=O), 1600 (C=C), 1375, 855, 750 cm^{-1}; NMR ($CDCl_3$) δ 0.1 (s, 9), 1.18 (t, 3, J = 6.9 Hz), 2.1–2.6 (m, 4), 3.71 (q, 2, J = 6.9 Hz), 5.17 (s, 1), 7.2 (t, 1, J = 1.6 Hz).

5,5-Dimethyl-3-[[(trifluoromethyl)sulfonyl]oxy]cyclohex-2-enone (25). To a 100-mL three-necked round-bottom flask, equipped with a magnetic stir bar, constant-pressure addition funnel, and N_2 inlet, was added 7.5 g (45 mmol) of 24% KH dispersion. Under a stream of N_2 the KH dispersion was twice washed with 30 mL of pentane with solvent decantation by syringe. To the residue was added 125 mL of glyme all at once. Via the addition funnel 6.0 g (42.8 mmol) of dimedone in 25 mL of glyme was added over 15 min at 25 °C. After visible hydrogen evolution ceased, the mixture was stirred for an additional 20 min at room temperature and then cooled to −78 °C. Over a period of 5–10 min, 12.4 g (44 mol) of $(CF_3SO_2)_2O$ was added via a syringe. After addition, the light yellow solution was allowed to warm to room temperature and the glyme was removed on a rotary evaporator. To the residue was added 200 mL of pentane and precipitated $KOSO_2CF_3$ filtered off. The pentane was evaporated on a rotary evaporator and the residue distilled to yield 4.3 g (80%) of colorless **25**: bp 47–49 °C (0.07 mm); IR (neat) 1688 (C=O), 1649 (C=C), 1251, 1220, 1064, 840 cm^{-1}; NMR ($CDCl_3$) δ 1.2 (s, 6), 2.3 (s, 2), 2.6 (d, 2, J = 1.2 Hz), 6.1 (t, 1, J = 1.2 Hz); mass spectrum, m/e 272 (M^+, 12), 216 (100), 123 (28), 69 (68).

Reaction of Lactone 16 with Thiophenoxide. Formation of 26a. To a 50-mL Erlenmeyer flask was added 0.40 g (2.1 mmol)

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of lactone **16** in 30 mL of DMF, along with 0.93 g (6.3 mmol) of potassium thiophenoxide. The mixture was stirred for 12 h, during which time it turned dark brown. The solution was partitioned between 150 mL of ether and 50 mL of 1 N NaOH. The ether layer was dried over K_2CO_3, and the solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel with CH_2Cl_2 as the eluent to give **26a** as an oil in 61% yield: IR (neat) 1750 (C=O), 1625 (C=C), 1190, 855 cm^{-1}; NMR ($CDCl_3$) δ 2.7 (dt, 2, J = 2.8 and 7.2 Hz), 4.3 (t, 2, J = 7.2 Hz), 7.2–7.3 (m, 5), 7.51 (t, J = 2.8 Hz); mass spectrum, m/e 206 (M^+, 100), 161 (25), 147 (71), 129 (27), 109 (10), 77 (12).

Reaction of Lactone 16 with *tert*-Butyl Mercaptan. Formation of 26b. To a 125-mL Erlenmeyer flask was added 0.5 g (2.6 mmol) of lactone **16** in 50 mL of ether, followed by 0.5 g (5 mmol) of *tert*-butyl mercaptan. The mixture was stirred for 12 h at room temperature and then extracted twice with 30 mL of 1 N NaOH. The ether layer was dried over K_2CO_3 and the solvent removed by rotary evaporator. The residue was purified by column chromatography on silica gel with CH_2Cl_2 as eluent. Evaporation of the solvent gave 0.30 g (63%) of light yellow crystalline solid **26c**: mp 120–123 °C; IR (KBr) 1710 (C=O), 1590 (C=C), 1190, 1020, 855 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (s, 9), 3.15 (dt, 2, J = 2.1 and 7.2 Hz), 4.5 (t, 2, J = 7.2 Hz), 7.3 (t, 1, J = 2.1 Hz).

Reaction of Lactone 16 with L-Cysteine. Formation of 26c. To a 125-mL Erlenmeyer flask was added 0.96 g (5 mmol) of lactone **16**, followed by 0.79 g (5 mmol) of L-cysteine hydrochloride in 60 mL of 50% aqueous methanol. The pH was adjusted to 7.0 with 1 N NaOH and the mixture stirred for 12 h at room temperature. The mixture was extracted with 50 mL of ether and the aqueous layer was cooled to -20 °C upon which 0.31 g (20%) of adduct **26c** precipitated: IR (KBr) 3400 (br, NH_2COOH) 1760 (C=O), 1715, 1200, 810 cm^{-1}; NMR (D_2O) δ 2.6 (s, 3, $CH_3SO_3^-$), 2.9–3.4 (m), 4.5 (br, exchangeable with D_2O), 7.21 (t, 1).

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Pyrimidine Acyclic Nucleosides. 5-Substituted 1-[(2-Aminoethoxy)methyl]uracils as Candidate Antivirals

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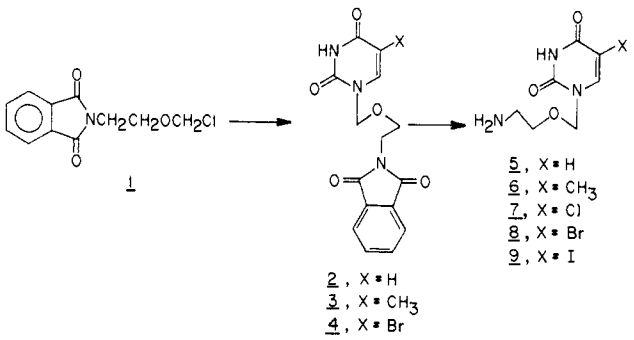
Several 5-substituted analogues of the acyclic aminonucleoside 1-[(2-aminoethoxy)methyl]uracil (**5**) were prepared for evaluation as antivirals. The uracil and thymine analogues were prepared in two steps from *N*-[2-(chloromethoxy)ethyl]phthalimide (**1**). The 5-chloro, 5-bromo, and 5-iodo analogues were prepared by halogenation of **5**. These acyclic aminonucleosides exhibited neither cell toxicity nor antiviral activity. This is compatible with their lack of substrate properties toward herpes simplex virus thymidine kinase.

A program initiated to synthesize nucleoside analogues in which the cyclic carbohydrate moiety is replaced by an acyclic side chain has led to the discovery of the potent antiherpetic drug acyclovir (9-[(2-hydroxyethoxy)methyl]guanine, ZOVIRAX).[1,2] Acyclovir possesses potent antiviral activity in cells infected with herpes simplex virus type 1 (HSV-1), but it is essentially nontoxic to uninfected host cells.[2,3] This selective toxicity is related to acyclovir being a unique substrate for HSV-1 encoded thymidine kinase.[4] Phosphorylation to acyclovir monophosphate occurs preferentially in HSV-1 infected cells, with subsequent selective inhibition of viral replication.[2,4]

Synthesis of 5′-amino analogues of certain pyrimidine nucleosides has resulted in 5′-amino-5-iodo-2′,5′-dideoxyuridine (AIU), an analogue of thymidine with selective activity against HSV-1.[5,6] AIU is also a unique substrate for HSV-1 encoded thymidine kinase, thereby exhibiting little or no uninfected cell toxicity.[7,8]

Scheme I



Other studies in these laboratories have found a series of pyrimidine acylic nucleosides analogous to acyclovir to have little or no in vitro antiviral activity.[9] In an attempt to find pyrimidine acyclic nucleosides with antiviral activity comparable to acyclovir, a series of 1-[(2-aminoethoxy)methyl]uracils has been synthesized. These compounds possess structural features in common with both AIU and acyclovir. The synthesis and antiviral effect of these compounds against HSV-1 are described in this report.

Chemistry. The 1-[(2-aminoethoxy)methyl]uracils **5–9** were prepared in two or three steps from *N*-[2-(chloromethoxy)ethyl]phthalimide (**1**)[10] (Scheme I). Alkylation

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