at room temperature for 6.0 h. (Use of less reagent or shorter time resulted in the recovery of starting material with less than 2% of product.) A workup similar to that used for compounds IV–VI gave benzyl *O*-carbamoyl-3,5-dibromosalicylate (VII) as white crystals: yield (0.12 g, 12.7%); mp 170–172 °C (ethyl acetate–petroleum ether); TLC R_f 0.8 in solvent A; product was UV positive but gave negative $FeCl_3$ test, whereas starting compound with R_f 0.94 was UV and $FeCl_3$ positive); ^1H NMR ($CDCl_3$–Me_2SO-d_6, 5:1) δ 7.85, 7.98 (2 H, dd, substituted aryl), 7.4 (5 H, s, phenyl of benzyl), 6.9 (2 H, br, s, $OCONH_2$), 5.3 (2 H, s, $OCH_2C_6H_5$). Elemental analysis is given in Table I.

The mother liquor from the above crystallization gave 65% of starting material, benzyl 3,5-dibromosalicylate, as confirmed by NMR and melting point and mixture melting point.

Benzyl *O*-(Dimethylcarbamoyl)salicylate (VIII). To a stirred solution of benzyl salicylate (1.82 g, 8.0 mmol) in 8.0 mL of dry dimethylformamide was added *N*-methylmorpholine (1.12 mL, 10.0 mmol) followed by 4-(dimethylamino)pyridine (0.25 g, 2.0 mmol) and dimethylcarbamoyl chloride (0.92 mL, 10.0 mmol). The reaction mixture was stirred at 60 °C for 22 h and dimethylformamide was removed under reduced pressure. The residue was distributed between cold dilute (0.5 N) HCl and ethyl acetate. The ethyl acetate extract was washed with water and saturated sodium chloride and then dried. The concentrated extract was diluted with petroleum ether and cooled, and the precipitated product was recrystallized from petroleum ether to which a few drops of ethyl acetate had been added. After several hours at −10 °C, the crystalline product was filtered off and dried to give 1.19 g (50%); mp 45–47 °C; TLC R_f 0.4 in solvent B; UV positive, $FeCl_3$ negative, whereas starting benzyl salicylate, R_f 0.8, was UV and $FeCl_3$ positive; ^1H NMR ($CDCl_3$) δ 7.0–8.0 (9 H, m, aryl + s, phenyl of benzyl with the latter centered at 7.33), 5.25 (2 H, s, $OCH_2C_6H_5$), 2.83 (6 H, s, $N(CH_3)_2$). Elemental analysis is listed in Table I.

***O*-(Dimethylcarbamoyl)salicylic Acid (IX).** The benzyl ester precursor VIII (1.0 g, 3.34 mmol) was catalytically hydrogenated, by the procedure described for the synthesis of I and VI, to give the deblocked product IX as an oil, which failed to crystallize from absolute ethanol–ether. Recrystallization from anhydrous ether–petroleum ether gave a low-melting solid, an oil at room temperature: yield 87%; TLC R_f 0.5 in solvent A, 0.1 in solvent B; ^1H NMR ($CDCl_3$) δ 9.75 (1 H, br, COOH), 7.1–8.15 (4 H, m, aromatics), 3.05 (6 H, d with 7-Hz separation, $N(CH_3)_2$). The NMR spectrum also showed the presence of ethanol with a (3.5 q and 1.2 t) which was not removable despite several hours of drying in vacuo. Elemental analysis is listed in Table I.

Benzyl *O*-(Dimethylcarbamoyl)-3,5-dibromosalicylate (X). Benzyl 3,5-dibromosalicylate was mixed with 50% molar excess of the reagent dimethylcarbamoyl chloride in refluxing pyridine or in benzene with 150% molar excess of the reagent and *N*-methylmorpholine. Refluxing was continued for 18 h. After a similar workup to the reaction mixture as that for compound VIII, *O*-dimethylcarbamoyl derivative X was obtained as white crystals: yield 41%; mp 89–90 °C (ethyl acetate–petroleum ether); TLC R_f 0.6 in solvent B (starting material R_f 0.8); ^1H NMR ($CDCl_3$) δ 8.16, 7.96 (2 H, dd, substituted aryl), 7.45 (5 H, s, phenyl of benzyl), 5.33 (2 H, s, $OCH_2C_6H_5$), 2.9 (6 H, d with 6-Hz separation, $N(CH_3)_2$). Elemental analysis is listed in Table I.

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Imidazole Anticonvulsants: Structure–Activity Relationships of [(Biphenylyloxy)alkyl]imidazoles

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The [(biphenylyloxy)alkyl]imidazoles were found to be potent anticonvulsants. The most potent compound of the series, 1-[2-([1,1′-biphenyl]-2-yloxy)ethyl]-1*H*-imidazole (**4**), had an ED_{50} of 15.5 mg/kg against maximal-electroshock-induced seizures in mice after oral administration; the horizontal screen ED_{50} was 320 mg/kg, revealing that the compound has a protective index of 21. Homologues bearing three- and four-carbon tethers between the imidazole and biphenylyloxy moieties were also active, but their potency was attenuated relative to **4**. Congeners with the imidazolylalkoxy moiety at the meta or para positions of biphenyl were also less active. All these compounds were potent potentiators of hexobarbital-induced sleeping time in mice, presumably via the well-known imidazole-mediated inhibition of cytochrome P-450. The structural features governing the anticonvulsant and sleeping-time activities appear to be distinct, but a complete dissociation of these two effects has not been achieved. Thus, the potential of these compounds as clinically useful antiepileptic drugs would appear to be limited.

We recently reported the potent and highly selective anticonvulsant activity of α-9*H*-fluoren-2-yl-α-methyl-1*H*-imidazole-1-ethanol (**1**, LY177165) and its congeners.[1] This agent, along with denzimol (**2**) and nafimidone (**3**) (Chart I), is a member of a structurally novel class of anticonvulsants, the (arylalkyl)imidazoles.[2,3] Our previous structure–activity relationship (SAR) studies suggested that the pharmacophore of this class of anticonvulsants is the alkylimidazole portion of the molecule, with the lipophilic aryl portion enabling penetration of the blood–brain barrier.[1]

An impressive feature of the pharmacology of these drugs is their high degree of selectivity; they antagonize maximal electroshock (MES) induced seizures at doses far below those required to produce sedation or neurological impairment but do not antagonize clonic seizures induced by administration of threshold doses of pentylenetetrazole, bicuculline, or picrotoxin.[1,4,5] Although this class of

Chart I

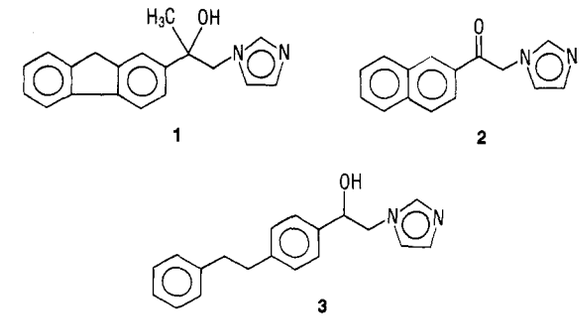

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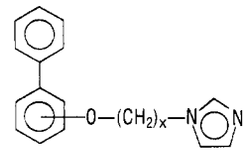
Table I. Structures and Physical Properties of [(Biphenylyloxy)alkyl]imidazoles



no.	x	biphenylyl	recryst solvent	mp, °C	formula	anal.
4	2	2	$EtOH/Et_2O$	172–173	$C_{17}H_{16}N_2O$·HCl	C, H, N
5	3	2	$EtOH/Et_2O$	122–123	$C_{18}H_{18}N_2O$·HCl	C, H, N
6	4	2	$EtOH/Et_2O$	79–80	$C_{19}H_{20}N_2O$·HCl	C, H,N
7	2	3	$EtOH/Et_2O$	140–144	$C_{17}H_{16}N_2O$·HCl	C, H, N
8	2	4	Me_2CO	224–226	$C_{17}H_{16}N_2O$·HCl	C, H, N, Cl

Table II. Biological Activities of [(Biphenylyloxy)alkyl]imidazoles after Oral Administration to Mice

no.	TPE,[a] h	MES[b] ED_{50}, mg/kg	HS[c] ED_{50}, mg/kg	hexobarb ST,[d] min
4	1.0	15.5 (12.0–20.2)[e]	320 (244–420)	252.1 ± 13.2*[f]
5	1.0	21.3 (18.05–25.13)	>280 [92][g]	126.7 ± 12.5*
6	0.5	29.8 (25.3–35.2)	>200 [92]	124.3 ± 7.1*
7	4.0	20.5 (18.1–23.2)	>200 [75]	334.0 ± 29.5*
8	2.0	44.0 (31.7–61.2)	>400 [100]	697.5 ± 30.9*
9[h]	4.0	130.0 (110–153)	>280 [75]	434.2 ± 19.5*
phenytoin	1.0	9.4 (8.5–10.4)	210 (160–275)	

[a] TPE = time to peak anticonvulsant effect. [b] MES = maximal electroshock assay. [c] HS = horizontal screen test. [d] Hexobarb ST = hexobarbital-induced sleeping time assay. A hypnotic dose of hexobarbital (100 mg/kg, ip) was administered at the time of peak effect of the test compound. Test compounds were administered orally at their respective anticonvulsant ED_{50}'s, and reported values are the mean ± SEM for 10 animals. In this experiment, control animals slept 69.2 ± 4.0 min. [e] Values in parentheses represent 95% confidence limits. [f] (*) $p < 0.001$. [g] Values in brackets represent percent of animals returning to the top of the screen at the highest dose tested. [h] 1-(2-Phenoxyethyl)-1*H*-imidazole.

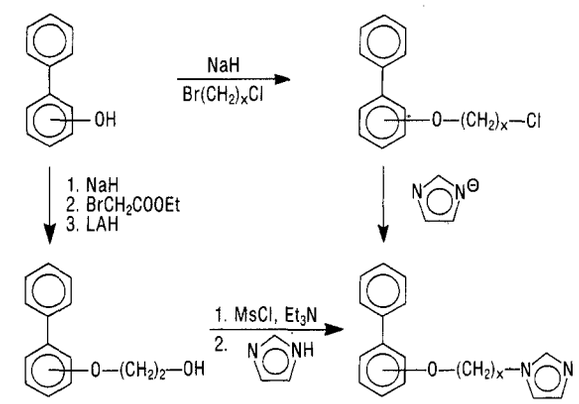
agents, like phenytoin, exert their anticonvulsant activities by limiting seizure spread, the molecular mechanism of action of these agents is not well-defined. However, they do increase the number of [^{3}H]flunitrazepam binding sites in the cortex and hippocampus of rats[1,6] and potentiate the depressant and antipentylenetetrazole activities of diazepam in a dose- and time-dependent fashion.[7] A few reports on the clinical pharmacology of denzimol and nafimidone have appeared, and they appear to have potential efficacy in the treatment of medically intractable elementary and complex partial seizures.[8]

We have continued to explore the SAR of imidazole anticonvulsants. Herein we report the SAR of the [(biphenylyloxy)alkyl]imidazoles, a potent series of compounds that antagonize MES-induced convulsions.

Results and Discussion

Chemistry. These compounds were readily prepared by generation of the appropriate hydroxybiphenyl anions with sodium hydride, followed by alkylation with various 1,ω-dihaloalkanes. Reaction with the sodium salt of imidazole completed the syntheses (Scheme I). Because of the attenuated reactivity of 1,2-dihaloethanes, compounds bearing a two-carbon tether between the ether oxygen and the imidazole nitrogen could be most expeditiously prepared by reaction of the hydroxybiphenyl anion with ethyl bromoacetate to form the desired (biphenylyloxy)acetate. Reduction with lithium aluminum hydride, activation with methanesulfonyl chloride, and reaction with imidazole furnished the target compounds (Scheme I). The structures and physical properties of the [(biphenylyloxy)alkyl]imidazoles employed in this study are displayed in Table I.

Scheme I



Anticonvulsant Structure–Activity Relationships. The first compound of the series, 4, proved to be a potent anticonvulsant, with an oral ED_{50} of 15.5 mg/kg (Table II) against MES-induced convulsions. This agent is 3.6-fold more potent than nafimidone and almost as potent as 1 (ED_{50}'s = 56 and 10 mg/kg, respectively).[9] Thus, the alkoxy bridge between the imidazole and aryl moieties

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(9) Nafimidone and denzimol data are from ref 1.

proved to be as effective as the previously described hydroxy- or keto-substituted-alkyl bridges, which are present in compounds **1–3**. Compound **4** was a selective anticonvulsant, with a horizontal screen ED_{50} of 320 mg/kg, yielding a protective index of approximately 21. Employing a three- or four-carbon alkoxy tether (**5** and **6**, respectively) resulted in attenuated potency (ED_{50}'s = 21.3 and 29.8 mg/kg, respectively), but both these homologues were more potent than the prototypical imidazole anticonvulsant, nafimidone.

The impact on anticonvulsant activity of transferring the imidazolylalkoxy moiety to the 3- and 4-positions of biphenyl was examined. The meta isomer **7** (ED_{50} = 20.5 mg/kg) was almost as potent as **4**, whereas the para isomer **8** (ED_{50} = 44.0 mg/kg) was significantly less potent.

Finally, the importance of the biphenyl moiety was probed by investigating the anticonvulsant activity of 1-(2-phenoxyethyl)-1*H*-imidazole (**9**). This agent proved to be impotent in the MES assay, with an ED_{50} of 130 mg/kg. This result underscores the necessity of sufficient lipophilicity in order to achieve useful degrees of anticonvulsant activity in this series.[1]

Potentiation of Hexobarbital-Induced Sleeping Time. The most widely used antiepileptic drugs, including phenytoin, carbamazepine, and phenobarbital, are extensively metabolized by cytochrome P-450. For example, in humans phenytoin is at least 90% metabolized via phenyl ring oxygenation to produce 5-(4-hydroxyphenyl)-5-phenyl-2,4-imidazolidinedione, 5-(3,4-dihydroxy-1,5-cyclohexadien-1-yl)-5-phenyl-2,4-imidazolidinedione, and additional hydroxylated metabolites.[10,11] Since multiple drugs are often administered simultaneously in the management of epilepsy, it is imperative that new therapeutic entities not inhibit cytochrome P-450 and thereby impair the metabolism of the classical antiepileptic drugs since this would lead to severe intoxication with the latter compounds because of their relatively narrow therapeutic indices.[12,13] It is well-known that 1-alkyl- and 1-aryl-substituted imidazoles are often inhibitors of cytochrome P-450. Microsomal studies conducted by other investigators have shown that nafimidone and denzimol are potent inhibitors of the metabolism of phenytoin, carbamazepine, and other cytochrome P-450 substrates.[14–16] We have previously demonstrated that nafimidone, denzimol, and the (fluorenylalkyl)imidazoles (e.g., **1**) are potent potentiators of hexobarbital-induced sleeping time,[1] probably by imidazole-mediated inhibition of hexobarbital metabolism, a cytochrome P-450 dependent event. Thus, it was of interest to examine the effects of [(biphenylyloxy)alkyl]imidazoles on hexobarbital-induced sleeping time.

These imidazole anticonvulsants were quite active in this assay (Figure 1, Table II). The most potent anticonvulsant of this series, **4**, potentiated hexobarbital-induced sleeping time in a dose-dependent manner (Figure 1). For example,

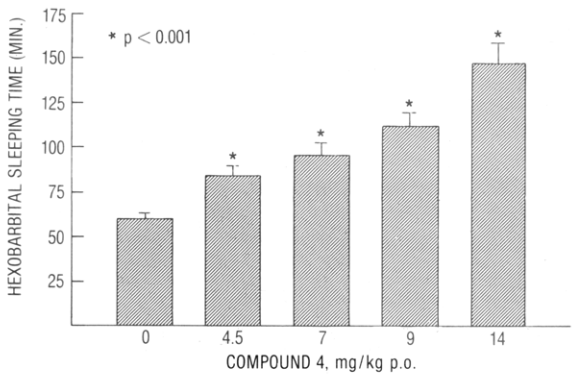

Figure 1. Dose-dependent effects of **4** on hexobarbital-induced sleeping time in mice. A hypnotic dose of hexobarbital (100 mg/kg, ip) was administered 1 h following oral administration of the indicated doses of **4**. The duration of loss of righting reflex was monitored. Values are the mean ± SEM for 10 animals. In this experiment, control animals slept 59.6 ± 1.4 min.

a 14 mg/kg dose of **4** resulted in a 149% increase in sleeping time. The 4.5 mg/kg dose, which is considerably less than the anticonvulsant ED_{50}, also resulted in a statistically significant increase (42%; $p < 0.001$) relative to control values. In our studies with the (fluorenylalkyl)-imidazoles, we found a highly significant correlation between the potency of the compounds as anticonvulsants and their potency as potentiators of hexobarbital-induced sleeping time.[1] To determine if a similar correlation existed in the [(biphenylyloxy)alkyl]imidazoles, all compounds in Table II were studied in the hexobarbital sleeping time assay. The compounds were administered to mice at their respective anticonvulsant ED_{50}'s, and if the sleeping time and anticonvulsant effects were highly correlated, similar sleeping times would be anticipated for each group of animals (assuming that the administered doses of compounds do not differ significantly in their degree of saturation of hepatic cytochrome P-450). However, considerable differences in sleeping times were observed (Table II). Compounds **5** and **6**, possessing three- and four-carbon tethers, respectively, were both less effective potentiators of hexobarbital-induced sleeping time than **4**. Transfer of the imidazolylethoxy moiety to the 3- or 4-position of biphenyl resulted in progressively greater potentiation of hexobarbital-induced sleeping times. Compound **8**, the least potent biphenyl anticonvulsant, when administered at its ED_{50} (44.0 mg/kg), produced the greatest potentiation of hexobarbital-induced sleeping time (10-fold). Moreover, **9**, which is approximately one-eighth as potent as **4** as an anticonvulsant (ED_{50}'s = 130 and 15.5 mg/kg, respectively), produced a 2-fold greater potentiation of hexobarbital-induced sleeping time (527% and 264% increases, respectively). Whereas the ortho analogue **4** possesses the optimal orientation between the imidazolylethoxy moiety and the phenyl ring for anticonvulsant activity, the para orientation appeared to be optimal for potentiating hexobarbital-induced sleeping time. In the ortho-substituted compounds (e.g., **4–6**), the monosubstituted phenyl ring may interact with portions of cytochrome P-450 so as to preclude optimal coordination of the imidazole N-3 nitrogen electrons to the fifth or sixth ligand position of the heme iron.

Conclusions. We have demonstrated that the [(biphenylyloxy)alkyl]imidazoles represent a potent series of anticonvulsants. In the ortho-substituted-biphenyl analogues, the ethoxy tether proved to be a suitable surrogate for the hydroxy- or keto-substituted-alkyl bridges present in **1**, denzimol, and nafimidone. Homologation to propoxy and butoxy tethers reduced anticonvulsant potency in a

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progressive fashion. These data suggest that the exact chemical nature of the tether is not as important as the spatial relationship it creates between the imidazole and aryl moieties. The monosubstituted phenyl ring's lipophilicity as well as its ortho orientation relative to the imidazolylethoxy moiety appeared to maximize anticonvulsant potency. Importantly, while this ortho orientation was optimal for anticonvulsant activity, the para orientation was optimal for potentiation of hexobarbital-induced sleeping time. Thus, in these [(biphenylyloxy)alkyl]-imidazole anticonvulsants, the structural features governing the anticonvulsant and sleeping-time activities appear to be distinct, but a complete dissociation of these two effects has not been achieved.

Recently published clinical studies with nafimidone and denzimol indicate that inhibition of cytochrome P-450 by the imidazole anticonvulsants is apparent in humans.[8,17,18] For example, in nine patients on carbamazepine therapy, addition of nafimidone resulted in a mean 100% increase in serum carbamazepine concentrations, requiring a reduction of the carbamazepine dosage.[8,19] Since the [(biphenylyloxy)alkyl]imidazole anticonvulsants are considerably more potent than nafimidone as potentiators of hexobarbital-induced sleeping time,[20] presumably due to more potent inhibition of cytochrome P-450, their potential as clinically useful antiepileptic drugs would appear to be limited.

Experimental Section

Methods. Melting points are determined on a Thomas-Hoover capillary melting point apparatus and are not corrected. Proton magnetic resonance (^{1}H NMR) spectra were taken on a Bruker WM-270 spectrometer. Chemical shifts are reported in ppm downfield from a tetramethylsilane internal standard (δ scale). The ^{1}H NMR data are presented in the following form: (solvent in which spectra were taken), δ value of signal (peak multiplicity, integrated number of protons, and assignment). Mass spectra were recorded from a Varian MAT CH-5 spectrometer, at the ionization voltage expressed in parentheses. Only the peaks of high relative intensity or of diagnostic importance are presented in the following form: m/e (intensity relative to base peak). Preparative HPLC was performed on a Waters Prep 500A instrument with an Isco Model UA-5 absorbance monitor set at 280 nm, using Waters Preppak-500 silica cartridges. Microanalytical data were provided by the Physical Chemistry Department of the Lilly Research Laboratories; only symbols of elements analyzed are given, and they were within 0.4% of theoretical values unless indicated otherwise.

Except where noted, a standard procedure was used for product isolation. This involved quenching by addition to water, filtration or exhaustive extraction with a solvent (washing of extract with aqueous solutions, on occasion), drying over an anhydrous salt, and evaporation of solvent under reduced pressure. Particular solvents, aqueous washes (if needed), and drying agents are mentioned in parentheses after the phrase "product isolation". Compound **9** was prepared as previously described.[21]

Syntheses of [(Biphenylyloxy)alkyl]imidazoles. The following procedures illustrate the synthetic methods used in this study.

1-[3-([1,1′-Biphenyl]-2-yloxy)propyl]-1*H*-imidazole Monohydrochloride (5). 2-Phenylphenol (10 g, 58.8 mmol) was added in portions to a suspension of sodium hydride (2.58 g, 64.7 mmol) in 200 mL of DMF. After hydrogen evolution ceased (ca. 45 min), 1-chloro-3-iodopropane (6.6 mL, 61.8 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 2 h. Product isolation (water, ethyl acetate, 1 N sodium hydroxide, water, brine, Na_2SO_4) afforded 12.2 g of an oil. Preparative HPLC (0–2.5% ethyl acetate in hexane gradient) produced 9.0 g (62%) of homogeneous 2-(3-chloropropoxy)-1,1′-biphenyl (**10**) as an oil.

A solution of imidazole (830 mg, 12.2 mmol) in 20 mL of DMF was added in a dropwise fashion to a suspension of sodium hydride (512 mg, 12.8 mmol) in 50 mL of DMF at room temperature. After 30 min, a solution of **10** (3.0 g, 12.2 mmol) in 20 mL of DMF was added and the reaction was stirred at room temperature overnight. Product isolation (water, ethyl acetate, water, brine, Na_2SO_4), formation of the hydrochloride salt, and recrystallization from ethanol/ether afforded 2.5 g (74%) of **5** as white crystals with mp 122–123 °C. Anal. ($C_{18}H_{18}N_2O$·HCl) C, H, N.

1-[2-([1,1′-Biphenyl]-2-yloxy)ethyl]-1*H*-imidazole Monohydrochloride (4). A solution of 2-phenylphenol (25 g, 147 mmol) in 150 mL of DMF was added in a dropwise fashion to a suspension of sodium hydride (6.2 g of a 60% suspension in oil, 154 mmol) in 100 mL of DMF at 0 °C. After evolution of hydrogen ceased, ethyl bromoacetate (16.3 mL, 147 mmol) was added in a dropwise fashion, and the reaction mixture was warmed to room temperature and stirred overnight. Product isolation (water, ethyl acetate, brine, Na_2SO_4) and preparative HPLC (0–7.5% ethyl acetate in hexane gradient) provided 22 g (59%) of ethyl ([1,1′-biphenyl]-2-yloxy)acetate (**11**) as a light-pink oil: ^{1}H NMR (Me_2SO-d_6) δ 1.18 (t, 3, CH_3), 4.15 (q, 2, CH_2CH_3), 4.78 (s, 2, $CH_2C(O)$), 6.96–7.65 (m, 9, Ar H); mass spectrum (70 eV), m/e (relative intensity) 256 (100, M^+).

A solution of **11** (22.0 g, 85.9 mmol) in 100 mL of THF was added in a dropwise fashion to a suspension of lithium aluminum hydride (3.1 g, 85.9 mmol) in 20 mL of THF at 0 °C. After 1 h, 25 mL of water was slowly added, the aluminum salts were filtered, and solvent was removed under reduced pressure to provide 17.4 g (95%) of homogeneous 2-([1,1′-biphenyl]-2-yloxy)ethanol (**12**) as an oil: ^{1}H NMR (Me_2SO-d_6) δ 3.65 and 4.02 (t, each 2, OCH_2CH_2OH), 6.98–7.62 (m, 9, Ar H); mass spectrum (70 eV), m/e (relative intensity) 214 (55, M^+).

Methanesulfonyl chloride (6.1 mL, 78.5 mmol) was added in a dropwise fashion to a solution of triethylamine (10.9 mL, 78.5 mmol) and **12** (16 g, 74.7 mmol) in 400 mL of THF at 0 °C. The reaction mixture was allowed to warm to room temperature, and after 1 h, product isolation (water, ethyl acetate, water, brine, Na_2SO_4) yielded 22.0 g of 2-([1,1′-biphenyl]-2-yloxy)ethanol methanesulfonate (**13**) as a light-pink oil, which was used in the following reaction without purification: ^{1}H NMR (Me_2SO-d_6) δ 3.04 (s, 3, CH_3), 4.30 and 4.50 (m, each 2, OCH_2CH_2O), 7.04–7.62 (m, 9, Ar H); mass spectrum (70 eV), m/e (relative intensity) 292 (53, M^+).

A solution of **13** (21.8 g, 74.7 mmol) in 50 mL of DMF was added in one portion to a solution of imidazole (15.2 g, 224 mmol) in 50 mL of DMF, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then heated to 100 °C for 4 h and cooled. Product isolation (water, chloroform, water, brine, Na_2SO_4) yielded 17.9 g of an oil. Preparative HPLC (0–5% ethyl acetate in hexane gradient) provided 6.7 g (34%) of homogeneous product as a solid. Formation of the hydrochloride salt and recrystallization from ethanol/ether provided 5.9 g of product as white crystals with mp 172–173 °C. Anal. ($C_{17}H_{16}N_2O$·HCl) C, H, N.

Pharmacological Methods. Effects on Horizontal Screen (HS).[22] Three groups of four fasted male mice (Crl: CF1^{R}BR; Charles River; 20–25 g) were administered a range of oral doses of each compound as a suspension in 5% acacia/water. Treated

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animals were placed individually on top of a square (13 cm × 13 cm) wire screen (no. 4 mesh), which was mounted on a metal rod. The rod was rotated 180°, and the number of mice that returned to the top of the screen within 1 min was determined. This measurement was performed 0.5, 1, 2, 3, and 4 h posttreatment to determine the approximate time of peak effect. Each compound was then retested at the estimated time of peak effect by using at least four doses with 12 mice at each dose. The HS ED_{50} was calculated according to the method of Litchfield and Wilcoxon.[23]

Inhibition of MES-Induced Seizures. Three groups of mice were administered a range of oral doses of each compound as a suspension in 5% acacia/water. The time to peak effect (TPE) was determined by challenging the mice with MES 0.5, 1, 2, 3, and 4 h posttreatment. Electroshock (40 mA, 0.1 s, ac) was administered through corneal electrodes, and the mice were observed for clonic, tonic-flexor, and tonic-extensor convulsions. Each compound was then retested at the estimated time of peak effect by using at least four doses with 12 mice at each dose. The MES ED_{50} for the prevention of tonic-extensor convulsions was calculated according to the method of Litchfield and Wilcoxon.[23]

Effects on Hexobarbital-Induced Sleeping Time. Groups of 10 fasted mice were treated orally with various doses of each compound in 5% acacia/water. At the previously determined time of peak effect, hexobarbital (100 mg/kg, ip) was administered to the mice. The hexobarbital was solubilized with stoichiometric quantities of sodium hydroxide, and the volumes of administration for all test compounds, acacia, and hexobarbital was 10 mL/kg. Sleeping time or the time of loss of righting reflex was determined to the nearest minute for each mouse.

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Synthesis and Biological Activity of Unsaturated Carboacyclic Purine Nucleoside Analogues†

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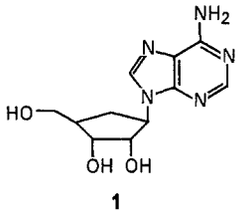
Two new carboacyclic nucleoside analogues, 9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]adenine (**6**) and 9-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]guanine (**5**), modeled on the unsaturated carbocyclic nucleoside analogue neplanocin A (**2**), have been synthesized and tested for antiviral activity against HSV-2 and, in the case of **6**, for activity against influenza and in vitro inhibition of *S*-adenosylhomocysteine hydrolase. The synthesis was accomplished through the coupling of either adenine or the guanine precursor 2-amino-6-chloropurine (**15**) to the key intermediate 1-(benzyloxy)-2-[(benzyloxy)methyl]-4-chloro-2-butene (**13**). Debenzylation of the N-9 adenine adduct gave **6** directly, while the product of the debenzylation of the N-9 adduct of **15** when treated with sodium hydroxide gave the guanine analogue **5**. The carboacyclic guanine analogue (**5**) exhibited significant antiviral activity against HSV-2 (VR = 1.5, MIC_{50} = 65.6 μg/mL), a level of activity that is superior to that of *ara*-A but inferior to that of acyclovir. The adenine analogue **6** was active against HSV-2 only at a very high dose; it was devoid of antiviral activity against influenza type A2, and it lacked inhibitory activity against *S*-adenosylhomocysteine hydrolase.

Many carbocyclic nucleoside analogues, in which the furanose oxygen atom has been replaced by a carbon, have been shown to have significant antiviral activity.[1] These carbocyclic analogues consist of two basic types, those with a cyclopentane ring, represented by aristeromycin (**1**), and those with a cyclopentene ring, represented by neplanocin A (**2**). Both types of carbocyclic adenosine analogues



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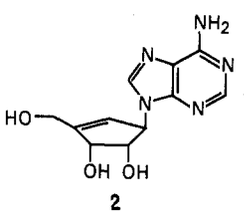

2

exhibit antiviral activity commensurate with their degree of inhibition of *S*-adenosylhomocysteine hydrolase (AdoHcy-ase) and the consequential inhibition of the maturation of viral RNA.[2] The synthesis of the guanosine analogue of **2** has been reported but with only limited accompanying biological activity data.[3]

Since the discovery of the potent and highly selective antiherpetic activity of acyclovir (**3**),[4] a guanine nucleoside analogue in which both the 2′- and the 3′-carbon atoms of the ribose sugar have been excised, many acyclic nucleoside analogues have been prepared and studied for antiviral activity.[5] It was found that 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, **4**), an analogue in which only the 2′-CHOH has been deleted from the natural nucleoside, had 10–100-fold higher potency against herpes viruses than does **3**.[6]

In an effort to develop more potent and selective antiviral agents, we attempted to combine in one molecule the

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