# A Unified Approach to Systematic Isosteric Substitution for Acidic Groups and Application to NMDA Antagonists Related to 2-Amino-7-phosphonoheptanoate

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A systematic approach to the replacement of acidic groups with potential bioisosteres is described. The strategy involves simple nucleophilic displacement of a common alkyl halide precursor with a variety of mercaptoazoles and related molecules. The mercaptoazoles and their oxidized derivatives (sulfinyl- and sulfonylazoles) represent a series of possible surrogates for acidic groups which span a $pK_a$ range from about 4.5–11.5. This simple strategy was extended to include 2-hydroxy- or 2-aminothiophenyl groups which function as relatively nonacidic isosteres for a phosphonic acid. By replacing the phosphonic acid of 2-amino-7-phosphonoheptanoate (AP-7) with these groups, we have synthesized novel *N*-methyl-*d*-aspartate (NMDA) antagonists.

The medicinal chemist is frequently confronted with the problem of developing surrogates for functional groups in biologically active molecules to eliminate undesirable properties intrinsic in the group. Numerous isosteric relationships for both polar and nonpolar substituents[1] have been designed to mimic the parent functional group, and physicochemical parameters such as $pK_a$ and partition coefficient may be varied to optimize activity.[2]

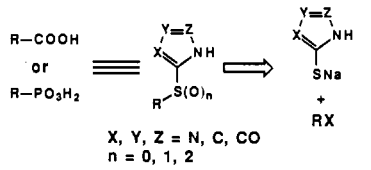
Acidic group isosteres such as tetrazole,[3] hydroxamic acid,[4] and various heterocycles[5] have been used primarily as carboxylic acid or phenol replacements in attempts to prepare more efficacious drugs. In contrast, replacements for a phosphonic acid group have not been described.

Few of the known acidic isosteres can be derived from a common precursor. These are each made by a different synthetic sequence and therefore a separate synthesis for each derivative must be designed. This limitation may restrict choices to only a few possible surrogates. Moreover, the structure of the substrate may not lend itself to the synthetic route required for preparation of a particular bioisostere.

Thus there is a need for a "family" of potential acidic bioisosteres with the flexibility to potentially replace carboxylic acid, phenol, or phosphonate which can easily be prepared from some common and readily accessible synthetic precursor (Scheme I). A family of bioisosteres spanning the pH range 9.5–4.5 (phenol to carboxylic acid) would be ideal since replacement of these types of groups is a common need. The ability to incorporate structural features of phosphonate/phosphate would further expand the general utility of the method.

One approach to this problem is by the use of a series of mercaptoazoles and closely related moieties as acidic isosteres which can span a $pK_a$ range of nearly 6 log units. The complete series is derived from a single intermediate alkyl halide and effectively takes advantage of the high nucleophilicity of the thio anion of the heterocyclic precursors. This simple concept was used in the synthesis of selective glutamate receptor antagonists by replacement of the highly acidic phosphonate moiety of 2-amino-7-phosphonoheptanoic acid (AP7). These glutamate antagonists are the first functional phosphonate bioisosteres to be described.

**Scheme I.** Strategy for Acidic Group Replacement




## Results and Discussion

**1. Model Studies.** Two key elements were incorporated into the design of potential acid/weak acid bioisosteres. The first was the recognition that the literature shows that azoles such as imidazole, 1,2,4-triazole, and 1,2,3-triazole can span the acid $pK_a$ range 14.5–4.8, depending on the nature of the substituent.[6]

Second, because alkyl sulfide, sulfoxide, and sulfone moieties span a wide range of electron-withdrawing ability ($\sigma_m$ 0.15–0.60),[7] these linkages can function both to adjust the acidity of the azole ring and to anchor an azole to the parent backbone. Azole sulfides, sulfoxides, and sulfones would be anticipated to have $pK_a$'s between 12 and 4.5. Moreover, a sulfide linkage incorporates both increased structural flexibility and the long bond lengths of a C–P or O–P bond, and the sulfoxide or sulfone linkages combine long bond lengths with tetrahedrally disposed oxygens as in phosphonate or phosphate groups.

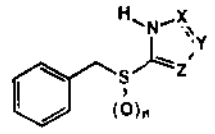
The chemistry used to prepare a series of mercaptoazoles is exceedingly simple. The sulfoxides and sulfones are prepared from the precursor sulfides. The sulfides in turn are all accessible from reaction of an alkyl halide with the commercially available mercaptoazoles[8] or easily prepared carbethoxythiosemicarbazide.[9]

In order to measure the $pK_a$'s of mercapto-substituted azoles, a series of 12 benzyl-substituted prototypes (**1a–c–4a–c**, Table I) was prepared and the $pK_a$'s were measured in water by measuring the ultraviolet absorbance versus pH according to a published method.[10] The benzyl

(1) Lipinski, C. A. *Annu. Rep. Med. Chem.* **1986**, *21*, 283. Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563. Hansch, C. *Intra-Sci. Chem. Rep.* **1974**, *8*, 17.
(2) Burger, A., Ed. *Medicinal Chemistry, 4th ed.*; Wiley-Interscience: New York, 1980; Chapters 8 and 10.
(3) Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds., Elsevier/North Holland Biochemical Press: Amsterdam, 1980; Vol. 17, Chapter 4.
(4) Demay, F.; De Sy, *J. Curr. Ther. Res.* **1982**, *31*, 113. Almquist, R. G.; Chao, W. R.; Jennings-White, C. *J. Med. Chem.* **1985**, *28*, 1067.
(5) See ref 1 for more details on heterocyclic bioisosteres for a carboxylic acid.
(6) *Adv. Heterocycl. Chem.* **1970**, *12*, 142 (Perrin, D. J., Ed., *Dissociation Constants of Organic Bases in Solution Suppl.*). Barlin, G. B. *J. Chem. Soc.* **1967**, *13*, 641. Bagal, L. I.; Pevzner, M. S. *Khim. Geterotsikl Soedin.* **1970**, *70*, 558. Katritzky, A. R., Ed. *Physical Methods in Heterocyclic Chemistry*; Academic Press: New York, **1963**; Vol. 1. Maiorana, S.; Pocar, D.; Dalla Croce, P. *Tetrahedron Lett.* **1966**, 6043.
(7) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley-Interscience: New York, 1975; p 66.
(8) 2-Mercaptoimidazole and 3-mercapto-1*H*-1,2,4-triazole were from Aldrich. 5-Mercapto-1,2,3-triazole sodium salt was from TCI (Japan).
(9) Fromm, E.; Nehring, E. *Chem. Ber.* **1923**, *56*, 1370.

0022-2623/90/1833-1077$02.50/0 

**Table 1.** Benzyl-Substituted Mercaptoazoles



| compd | *n* | X | Y | Z | formula | mp, °C | p$K_a$° | % yield |
|---|---|---|---|---|---|---|---|---|
| **1a** | 0 | CH | CH | N | $C_{10}H_{10}N_2S$ | 147–149 | 11.6[b] | 44 |
| **1b** | 1 | CH | CH | N | $C_{10}H_{10}N_2OS$ | 159–160 | 9.80 ± 0.11 (4) | 97 |
| **1c** | 2 | CH | CH | N | $C_{10}H_{10}N_2O_2S$ | 213–215[c] | 8.67[d] ± 0.03 (4) | 55 |
| **2a** | 0 | N | CH | N | $C_9H_9N_3S$ | 77–79[e] | 9.50 ± 0.07 (4) | 64 |
| **2b** | 1 | N | CH | N | $C_9H_9N_3OS$ | 135–137[f] | 7.38 ± 0.04 (4) | 77 |
| **2c** | 2 | N | CH | N | $C_9H_9N_3O_2S$ | 154–156[g] | 6.23 ± 0.10 (4) | 56 |
| **3a** | 0 | N | N | CH | $C_9H_9N_3S$ | 64–66 | 8.20 ± 0.10 (4) | 90 |
| **3b** | 1 | N | N | CH | $C_9H_9N_3OS$ | 120–122 | 6.09[h] ± 0.14 (3) | 77 |
| **3c** | 2 | N | N | CH | $C_9H_9N_3O_2S$ | 169–171 | 5.15[i] (2) | 85 |
| **4a** | 0 | CO | NH | N | $C_9H_9N_3OS$ | 190–192[j] | 7.85[k] ± 0.10 (3) | 49 |
| **4b** | 1 | CO | NH | N | $C_9H_9N_3O_2S$ | 237–239 | 5.2[l] | 52 |
| **4c** | 2 | CO | NH | N | $C_9H_9N_3O_3S$ | 260–263 | 4.79[m] ± 0.18 (4) | 63 |

[a] Apparent p$K_a$ at 23 °C in water ± standard deviation by UV at *n* wavelengths. See the Experimental Section. [b] From Perrin in ref 6. [c] Literature mp 211.5–213 °C (U.S. Patent 3,499,001. *Chem. Abst.* 1970, *73*, 25465a). [d] Value in **1**:1 acetonitrile–water is 9.49 ± 0.05 (4). [e] Literature mp 84–85 °C (Beyer, H.; Kroger, C.-F. *Ann. Chem.* 1960, *637*, 135). [f] Literature[11] mp 134–136 °C. [g] Literature[11] mp 147–149 °C. [h] Potentiometric p$K_a$ (water) = 6.03, p$K_a$ (**1**:1 acetonitrile/water) = 6.54. [i] Potentiometric p$K_a$ (1:1 acetonitrile/water) = 5.81. [j] Literature[9] mp 182 °C. [k] Value in 1:1 acetonitrile/water is 8.19 ± 0.30 (4). [l] Extrapolated from value of 5.84 ± 0.06 (4) in 1:1 acetonitrile/water. [m] Value in **1**:1 acetonitrile/water is 4.96 ± 0.09 (4).

substituent was chosen as a small group likely to lead to good aqueous solubility—a choice which proved correct since the p$K_a$'s of 10 of the 12 derivatives could be measured in water. p$K_a$ values for **1c**, 3b, and **4a–c** were measured in **1**:1 acetonitrile/water. The p$K_a$'s for compounds **1c**, **3b**, 4a, and **4c** were also measured in water, allowing an estimate to be made for the aqueous p$K_a$ of the less soluble **4a** and 4b. The p$K_a$ value for **1a** is too high to measure from the UV technique and was estimated from the literature aqueous value for the 2-mercapto-substituted imidazole.

The p$K_a$'s of derivatives **1a–c–4a–c** uniformly span the p$K_a$ range **11**.6–4.7. Derivatives **1a**, **1b**, and **2a** (Table I) are phenol-like in acidity while **1c**, 2b, **3a**, and **4a** have a p$K_a$ range ±**1**.3 units from pH 7.4 (physiological pH). Compounds **2c** and 3b with p$K_a$'s of 6 are similar to imidic heterocycles such as oxazolidine or thiazolidinedione while **3c**, 4b, and **4c** have p$K_a$'s very similar to those of carboxylic acids.

The UV assay used to measure p$K_a$'s for **1a–c–4a–c** contains internal checks designed to detect compound hydrolytic instability. No sign of hydrolysis of any of these derivatives was observed as would be anticipated on the basis of the known stability of sulfinyl- and sulfonyl-**1**,2,4-triazoles.[11]

Thus we now had a simple, efficient method available to prepare acidic isosteres which sequentially spanned a broad p$K_a$ range. Moreover, in contrast to the uniform planarity of carboxylic isosteres, sulfinyl and sulfonyl members of these series contain a tetrahedral oxygenated sulfur which is noncoplanar to the appended delocalized acidic azole ring. To investigate whether this concept of a unified systematic approach to acidic bioisostere identification could be used to discover new biologically active agents, we chose to examine the $\omega$-phosphonic $\alpha$-amino acid (AP) class of glutamate antagonists.

**2. Application to NMDA Antagonists.** Glutamate is an excitatory neurotransmitter in the mammalian central nervous system (CNS). In addition to its transmitter properties, extracellular glutamate has demonstrated excitotoxic effects[12] particularly in cultured neurons.[13] There

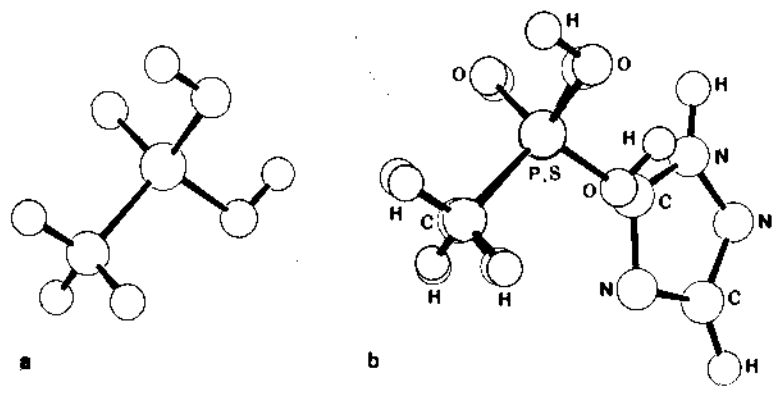
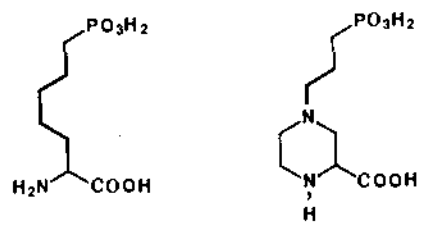



**Figure 1.** Computer images of MM2-minimized structures of (a) methylphosphonic acid and (b) overlapping structures of methylphosphonic acid (shaded) and 5-(methylsulfonyl)-**1**,2,4-triazole.

are at least three classes of glutamate receptors: *N*-methyl-*d*-aspartate (NMDA), kainate (K), and quisqualate (Q).[14]

Of particular interest to us were competitive antagonists of the NMDA receptor. These agents exemplified by AP7 and CPP have been suggested to be useful in a number of diseases.[15] The competitive NMDA antagonists described to date are all highly polar molecules. As such, they would not be expected to cross the blood–brain barrier. A lipophilic replacement for the phosphonic acid could be expected to greatly enhance the CNS penetration of these molecules. We have attempted to develop surrogates for the phosphonic acid group based on the strategy outlined above.

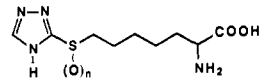



Presently there are no known bioisosteres for phosphonate. To aid in our search, we considered the prop-

(10) Lipinski, C. A.; Craig, R. H.; Wright, R. B. *J. Heterocycl. Chem.* **1985**, *22*, 1723.
(11) Blackman, A. J.; Polya, J. B. *J. Chem. Soc. C* **1970**, 2403.
(12) Olney, J. W.; Ho, O. C.; Rhee, V. *Exp. Brain Res.* **1971**, *14*, 61.
(13) Choi, D. W.; Maulucci-Gedde, M.; Kriegstein, A. R. J. *Neuroscience* 1987, *7*, 357.
(14) For a good discussion of the glutamate receptors, see: Johnson, R. L.; Koerner, J. F. *J. Med. Chem.* **1988**, *31*, 2057.
(15) Meldrum, B. *Clin. Sci.* **1985**, *68*, 113.

erties of methyl phosphonic acid, the simplest member of this class of acids. The $pK_a$'s of 2.3 and 7.9 for this acid[16] predicted that at physiological pH the molecule will be 24% monoanion and 76% dianion.[17] Thus a single acidic site in a potential isostere is not totally unreasonable (especially one which contains an additional electronegative site in close proximity to the acidic group). Figure 1a shows a computer-generated picture of methyl phosphonic acid. Figure 1b shows the superimposed image of sulfonyl-1,2,4-triazole **2c** on methyl phosphonic acid. From this overlay we observed that when S and P were superimposed, the two sulfonyl oxygen atoms matched well with two of the phosphonate oxygens as would be expected based on similar S–O and P–O bond lengths and angles. Furthermore, the acidic, potentially tautomeric azole proton (whose acidity could be fine-tuned) was within 1 Å of the phosphonate proton. Thus the azole sulfones in particular seemed ideally suited to test the hypothesis that this type of structural array might function as a phosphonate isostere.

The mercaptoazole series **5a–c** based on AP7 was prepared in straightforward fashion (see the Chemistry section) with the anticipation that if sulfonyl azoles were phosphonate surrogates, **5c** might be active. To test our



**5a**, n = 0
**5b**, n = 1
**5c**, n = 2

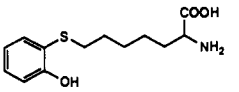
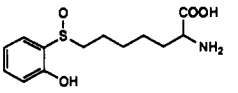
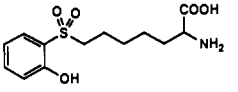
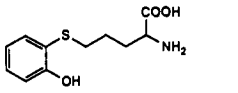
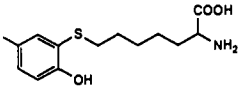
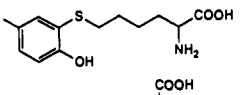
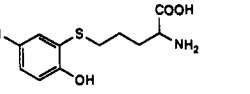
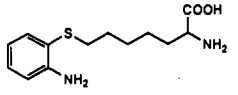
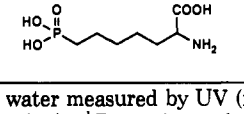
compounds we used a standard in vitro assay which measures the ability of a potential antagonist to block increases in cyclic GMP in rat cerebellar slices in response to NMDA application.[18] All members of the series were inactive. In addition, other mercaptoazole series (imidazole, 1,2,3-triazole, benzimidazole) were also inactive.

There are several possible explanations for the total lack of activity. Since the acidic proton of the azole moiety in **5a–c** is farther away from the amino acid end of the molecule, a chain-shortened version might have been more appropriate. This possibility was disproved as the hexanoate and pentanoate analogues were also inactive. Other explanations could be that the azole ring is too large to fit in the active site or possibly the additional nitrogen atoms in the azoles adversely affect binding. Although the acidic proton is tautomeric, the nitrogen atom adjacent to the sulfonyl group may not be sufficiently negatively polarized in the anionic state.

To address some of these questions the 2-hydroxythiophenol series (**6a–c**) was prepared. This series had a $pK_a$ range of 9.4–7.2 and would effectively localize the acidic proton ortho to the thio group while still retaining the tetrahedral sulfoxide and sulfone moieties. From the phenol series **6a** possessed a modest activity in the cyclic GMP assay while **6b** and **6c** were completely inactive (Table II). This is a surprising result since **6a** is the least acidic molecule and lacks the tetrahedrally disposed oxygen atoms in contrast to our simple modeling which clearly favors sulfone structures. In subsequent study we confirmed that NMDA blockade was only observed with sulfides. We next sought to determine whether the alternating structure–activity relationship (SAR) pattern of the AP series in which AP5 and AP7 are active while AP6 and AP8 are inactive could be duplicated in ortho-substituted aryl sulfide derivatives. This pattern found in the phosphonates was not seen since **7a**, the di-nor-homologue of the active **6a**, was inactive. However chlorinated derivatives **8a–10a** did match the interesting alternating SAR of the amino phosphonates. In this series the shorter chain, chlorinated **10a** was somewhat weaker than the extended **8a**.

Other modifications of **6a** were examined while trying to define the scope of the activity. Thus sulfur was replaced (O, N), the hydroxyl group was replaced (H, OMe, F, $NH_2$), and the hydroxyl group and its replacements were moved to the meta and para positions. Superimposed on this, the sulfur oxidation state was varied when present in the products. Apart from the aromatic halogen substitution, only one change, the replacement of hydroxyl with amino, yielded the most active compound (**11a**) with an $IC_{50}$ of $1 \times 10^{-4}$ M. This was totally unexpected since this substituent is weakly basic. Moreover, based on a $pK_a$ of 3.45 for 2-methylthioaniline,[19] it is unlikely that this group is exerting its effect as a rather acidic anilinium

**Table II.** $pK_a$ and Potency in Inhibition of NMDA-Induced Cyclic GMP Increases

| | compound | phenol $pK_a$[a] | $IC_{50}$ ($\times 10^{-4}$), M (*n*) |
|---|---|---|---|
| **6a** |  | 9.35 ± 0.05 (4) | 3.1 ± 0.5 (5) |
| **6b** |  | | >100 |
| **6c** |  | 7.38 (2) | >100 |
| **7a** |  | | >100 |
| **8a** |  | 8.55 ± 0.01 (3) | 2.2 ± 0.4 (3) |
| **9a** |  | | >100 |
| **10a** |  | | 2.6 ± 0.4 (2) |
| **11a** |  | | 1.4 ± 0.3 (4) |
| **AP-7** |  | 2.64 ± 0.03 (3)[b]<br>7.72 ± 0.11 (3)[b]<br>9.84 ± 0.07 (3)[b] | 0.35 ± 0.06 (3) |

[a] $pK_a$ in water measured by UV (ref a in Table I; see the Experimental Section). [b] Potentiometric titration in 25 mL of water, 5 mL of 1 M NaCl (to maintain constant ionic strength) at 23 °C. See text for discussion. (Clarke, F. H.; Cahoon, N. M. *J. Pharm. Sci.* **1987**, *76*, 611.)

(16) *Phosphorous and Its Compounds Vol. 1: Chemistry*; Van Wazer, J. R., Interscience: New York, 1958, p 360.
(17) Scherrer, R. A.; Howard, S. M. *J. Med. Chem.* **1977**, *20*, 53.
(18) Wood, P. L.; Richard, J. W.; Pipapil, C.; Nair, N. P. V. *Neuropharmacology* **1982**, *21*, 1215. See also Tsai, C.; Steel, D. J.; McPherson, S.; Taylor, C. A.; Wood, P. L.; Lehmann, J. In *Excitatory Amino Acid Transmission*; Hicks, T. P.; Lodge, D.; McLennan, H., Eds., Alan R. Liss, Inc.: New York, 1987; pp 79–82.
(19) *Dissociation Constants of Organic Bases in Aqueous Solution: Supplement* **1972**; Perrin, D. D., Ed.; Butterworths: London, 1972.

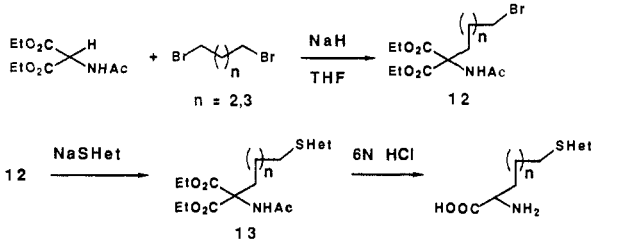
species since the proportion of this species at pH 7.4 would be expected to be negligible. However, the neutral thioaniline moiety might substitute either as a hydrogen-bond donor or acceptor for the ionized form of a moderately strong acid (for example a monodeprotonated phosphonic acid). For comparison, we measured the $pK_a$ values for AP7 by potentiometric titration (Table II) and found that only three deprotonations could be observed ($pK_a$'s at 2.64, 7.72, and 9.84). These values represent the carboxylic acid, the second phosphonate, and the ammonium ionizations, respectively. Under our experimental conditions, the first ionization of the phosphonic acid is too low to measure ($\ll 2$). Thus proton dissociation from the thioanilinium ion, while still at least 1.5 log units higher than the first phosphonate ionization, possesses intrinsic acidity closest to that of a phosphonic acid. It should be noted that the alternating SAR described above did not follow for **11a** as the one- and two-carbon-shortened analogues were both inactive.

Selectivity for NMDA versus K receptors was examined in a final test of our new family of glutamate antagonists. Kainic acid also causes cyclic GMP increases, so the same assay described above was used. Only **11a** showed a 20% inhibition at the K receptor at 200 $\mu$M. Therefore it appears that these nonphosphonate antagonists are selective for the NMDA receptor. We have not assessed their affinity for the Q receptor.

## Chemistry

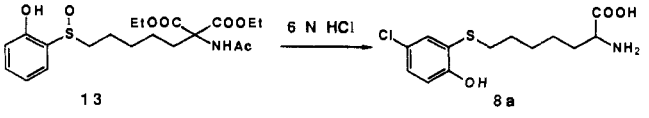
For the prototype study, compounds **1a–4a** were prepared by simple alkylation of the appropriate heterocyclic thiol with benzyl bromide. The sulfoxides (**1b–4b**) and sulfones (**1c–4c**) were obtained by standard oxidation procedures (see the Experimental Section).

The NMDA antagonists were prepared in racemic form as outlined below. Diethyl acetamidomalonate was alkylated with the appropriate length alkyl dibromide to give **12**. Nucleophilic substitution with the appropriate thiol




and acidic hydrolysis gave the very hygroscopic amino acids which were purified by ion exchange and lyophilization. In the case where $n = 1$, the alkylation could not be used to prepare **12** as an inseparable mixture of the product and starting materials were formed in an exceedingly slow reaction. Fortunately the alternative procedure of Moe and Warner provided easy access to this intermediate.[20]

The sulfones were easily prepared by MCPBA oxidation prior to final hydrolysis; however, this process proved to be problematic for the sulfoxide derivatives. For the *o*-hydroxyphenyl compounds, final hydrolysis in 6 N HCl caused an aromatic variant of the Pummerer rearrangement to take place. Thus for example, hydrolysis of **13**




($n = 2$, Het = *o*-hydroxyphenyl) gave **8a** and not **6b**. This reaction has been observed previously and the assignment of regiochemistry for the chloro substitution is based on the literature assignment.[21] We have not made an extensive survey of this chemistry, but it appears to be general for *o*-hydroxyphenyl and sometimes occurs with the unsubstituted phenyl group. Interestingly, the *o*-aminophenyl group is inert to these conditions since it is protonated and thus deactivated in the strong acid.

The required sulfoxides were obtained in unequivocal fashion by esterification of the acids **6a–10a**, MCPBA oxidation, and basic hydrolysis.

## Summary

We have developed a systematic approach to SAR development by designing a series of simple acidic replacement groups. The strategy allows for sequential introduction of a large number of acidic azoles and related heterocycles adjacent to tetrahedral oxygenated sulfur which can be tuned to almost any pH through the range 4.8–11.6. From our studies in the specific application of this concept to NMDA antagonists, it is clear that the range of potentially useful thiols should be expanded to include *o*-hydroxy and *o*-aminothiophenols. Including all the sulfur oxidation states we propose a list of "first pass" acidic substitutions composed of 18 compounds, all easily available from a single synthetic precursor. In addition to the wide acidic $pK_a$ range spanned by our basic probe groups, we include weakly basic aniline derivatives as probes for noncharge-reinforced hydrogen bonding.

This unified approach to isosteric substitution allowed us to discover new NMDA antagonists, thus demonstrating the utility of the approach. While these antagonists are relatively weak agents, it is important to keep the work in perspective. First, these are the only nonphosphonate-based NMDA antagonists presently known. Second, the activity in the cyclic GMP assay was only 3–10 times weaker than that of AP7, the compound they were designed to mimic. Finally, these results suggest that better nonacidic isosteres for phosphonate likely exist which will greatly improve the CNS-penetrating ability of the competitive NMDA antagonists and improve their chances to be developed for the treatment of excitatory amino acid based disease.

## Experimental Section

**General Procedures.** Melting points were taken with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 283B or 1420 spectrophotometers in chloroform solution unless otherwise stated and are reported in reciprocal centimeters. Only strong bands are reported unless otherwise stated. Proton NMR were obtained at 300 MHz with Bruker AM 300 or Varian XL-300 instruments. NMR data are reported in parts per million ($\delta$) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform, unless otherwise stated). Analyses were determined by our own analytical group. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use. All nonaqueous reactions were carried out under a nitrogen atmosphere in flame-dried apparatus and were stirred magnetically unless otherwise specified. Analytical data for **1a–c–4a–c** agreed with the calculated values as follows: C $\pm$ 0.39; H $\pm$ 0.15; N $\pm$ 0.4. Compounds **6a–c**, and **7a–11a** (Table II) were exceedingly hygroscopic in the free base and hydrochloride salt forms and analysis rests on spectral and high-resolution or FAB mass spectroscopic data. Because of the moisture sensitivity of these compounds, purity was assessed by HPLC in two different solvent systems (Zorbax C8 column, 30% acetonitrile/water and 50–70%

(20) Moe, O. A.; Warner, D. T. *J. Am. Chem. Soc.* **1948**, *70*, 2763.

(21) King, R. R. *J. Org. Chem.* **1978**, *43*, 3784.

methanol/water). All were greater than 95% pure by this analytical procedure.

**Biological Testing.** The cyclic GMP assay used to test the compounds prepared in this manuscript was essentially that described by Garthwaite.[22]

(Benzylthio)azoles **1a**, **2a**, and **3a** were prepared by alkylation of benzyl chloride on sulfur with the commercially available 2-mercaptoimidazole, 4-mercapto-1,2,3-triazole, and 3-mercapto-1*H*-1,2,4-triazole in ethanol with triethylamine as base. 5-(Benzylthio)-2*H*-1,2,4-triazol-3(4*H*)-one (**4a**) was prepared by reaction of carbethoxythiosemicarbazide[9] with benzyl bromide.

**2-(Benzylthio)imidazole (1a).** A mixture of benzyl chloride (5.0 g, 39.5 mmol), 2-mercaptoimidazole (3.95 g, 39.5 mmol), and triethylamine (5.5 mL, 39.5 mmol) in absolute ethanol (100 mL) was warmed to 60 °C for 1 h and then left for 48 h at ambient temperature. The reaction was concentrated in vacuo, diluted with water, extracted with ethyl acetate, dried over magnesium sulfate, and concentrated in vacuo to a white solid. Trituration with ethyl ether, filtration, and drying at 25 °C (0.01 mm) gave 3.3 g (44%) of **1a**: mp 147–149 °C; NMR (DMSO-$d_6$) 7.22 (br s, 5 H), 7.02 (br s, 2 H), 4.21 (s, 2 H). Anal. ($C_{10}H_{10}N_2S$) C, H, N.

Sulfoxides 1b–**4b** were prepared by oxidation of precursor sulfides **1a**–**4a** with MCPBA in methylene chloride. Very little over oxidation was observed.

**5-(Benzylsulfinyl)-2*H*-1,2,4-triazol-3(4*H*)-one (4b).** To **4a**[9] (2.5 g, 12.1 mmol) in methylene chloride (50 mL) was added MCPBA (2.3 g, 13.3 mmol). After stirring at 25 °C for 20 h the reaction was filtered and the filtrate was recrystallized from absolute ethanol to yield 1.41 g (52%) of **4b**: mp 237–239 °C; NMR (DMSO-$d_6$) 7.50–7.24 (m, 5 H), 4.61 (AB q, $\Delta\nu_{1-3}$ = 18 Hz, $J$ = 12 Hz, 2 H). Anal. ($C_9H_9N_3O_2S$) C, H, N.

Sulfones **1c**–**4c** were prepared by oxidation of the precursor sulfoxides **1b**–**4b** with aqueous hydrogen peroxide in acetic acid.

**4-(Benzylsulfonyl)-3*H*-1,2,3-triazole (3c).** To a solution of hydrogen peroxide (15 mL, 30%) and acetic acid (10 mL) was added **3b** (1.0 g, 4.83 mmol). The reaction was stirred at 50 °C for 20 h, cooled to ambient temperature, and filtered. The filtrate was washed with water and petroleum ether and dried at 25 °C (0.01 mm) to give 0.91 g (84%) of **3c**: mp 169–171 °C; NMR (DMSO-$d_6$) 8.45 (s, 1 H), 7.30 (m, 3 H), 7.17 (m, 2 H), 4.73 (s, 2 H). The analytical sample was prepared by slow evaporation of a methanol solution of **3c**. Anal. ($C_9H_9N_3O_2S$) C, H, N.

**Ethyl 2-Acetamido-2-carbethoxy-7-[(2-hydroxyphenyl)thio]heptanoate.** Sodium hydride (0.682 g, 17.0 mmol, 60% in oil) was suspended in tetrahydrofuran (THF, 30 mL) and treated dropwise with a solution of 2-hydroxythiophenol (2.14 g, 17.0 mmol in 30 mL of THF). A vigorous evolution of hydrogen gas occurred. The reaction was stirred for 15 min and then ethyl 2-acetamido-7-bromo-2-carbethoxyheptanoate (6.22 g, 17 mmol in 20 mL of THF) was added dropwise. The mixture was stirred at ambient temperature for 16 h; then it was carefully quenched with water. The reaction was extracted with ethyl acetate (3×). The combined organic phase was washed with brine and dried over calcium sulfate. Concentration afforded a yellow oil, which was flash chromatographed on silica gel. Elution with 10% ethyl acetate/hexane gave 6.97 g (100%) of product as a clear yellow oil: NMR 7.40 (dd, $J$ = 1, 7.5 Hz, 1 H), 7.22 (t, $J$ = 7.5 Hz, 1 H), 6.93 (dd, $J$ = 1, 8 Hz, 1 H), 6.82 (dt, $J$ = 1, 7.5 Hz, 1 H), 6.70 (s, 1 H), 4.20 (q, $J$ = 7 Hz, 4 H), 2.62 (t, $J$ = 7.5 Hz, 2 H), 2.30–2.24 (m, 2 H), 2.00 (s, 3 H), 1.50 (quintet, $J$ = 7.5 Hz, 2 H), 1.36 (quintet, $J$ = 7.5 Hz, 2 H), 1.20 (t, $J$ = 7 Hz, 6 H), 1.14–1.0 (m, 2 H); IR 3409, 2927, 1734, 1678, 1488, 1469, 1444, 1370, 1272–1154 (br), 1011; HRMS $m/e$ calcd for $C_{20}H_{29}NO_6S$ 411.1715, observed $m/e$ 411.1692.

**Ethyl 2-acetamido-2-carbethoxy-5-[(2-hydroxyphenyl)thio]pentanoate** was prepared by following the above procedure with ethyl 2-acetamido-5-bromo-2-carbethoxypentanoate. The product was obtained as a white solid in 72% yield; mp 76–78 °C (hexane trituration); NMR 7.39 (dd, $J$ = 1, 7.5 Hz, 1 H), 7.24–7.19 (m, 1 H), 6.93 (dd, $J$ = 1, 8 Hz, 1 H), 6.82 (dt, $J$ = 1.5, 7.5 Hz, 1 H), 6.70 (s, 1 H), 6.63 (s, 1 H), 4.20 (q, $J$ = 7 Hz, 4 H), 2.65 (t, $J$ = 7.5 Hz, 2 H), 2.43–2.37 (m, 2 H), 1.99 (s, 3 H), 1.37–1.26 (m, 2 H), 1.20 (t, $J$ = 7 Hz, 6 H); HRMS $m/e$ calcd for $C_{18}H_{25}NO_6S$ 383.1401, observed $m/e$ 383.1409.

**Ethyl 2-acetamido-2-carbethoxy-6-[(2-hydroxyphenyl)thio]hexanoate** was prepared by following the above procedure as a clear oil in 91% yield: NMR 7.39 (dd, $J$ = 1.5, 7.5 Hz, 1 H), 7.23 (dt, $J$ = 1.5, 8 Hz, 1 H), 6.95 (dd, $J$ = 1, 8 Hz, 1 H), 6.84 (dt, $J$ = 1.5, 7.5 Hz, 1 H), 6.73 (s, 1 H), 4.26–4.21 (m, 4 H), 2.65 (t, $J$ = 7 Hz, 2 H), 2.35–2.22 (m, 2 H), 2.01 (s, 3 H), 1.53 (quintet, $J$ = 7.5 Hz, 2 H), 1.26–1.14 (m, 8 H); IR 3409, 2973, 2930, 1734, 1679, 1493, 1469, 1371, 1298, 1286–1191 (br); high-resolution FAB MS MH$^+$ calcd for $C_{19}H_{28}NO_6S$ 398.1638, observed $m/e$ 398.1633.

**Ethyl 2-acetamido-2-carbethoxy-7-[(2-aminophenyl)thio]heptanoate** was prepared by following the above procedure as a clear oil in 95% yield: NMR 7.28 (dd, $J$ = 1.5, 7.5 Hz, 1 H), 7.03 (t, $J$ = 8 Hz, 1 H), 6.71 (s, 1 H), 6.67–6.58 (m, 2 H), 4.30 (br s, 2 H), 4.18 (q, $J$ = 7 Hz, 4 H), 2.66 (t, $J$ = 7 Hz, 2 H), 2.28–2.23 (m, 2 H), 1.99 (s, 3 H), 1.49 (m, 2 H), 1.34 (quintet, $J$ = 7.5 Hz, 2 H), 1.21 (t, $J$ = 7 Hz, 6 H), 1.10–1.00 (m, 2 H); IR 3411 (w), 1735, 1678, 1606, 1490, 1477, 1300, 1270; HRMS $m/e$ calcd for $C_{20}H_{30}N_2O_5S$ 410.1871, observed $m/e$ 410.1824.

**Ethyl 2-Acetamido-2-carbethoxy-7-[(2-hydroxyphenyl)sulfonyl]heptanoate.** Ethyl 2-acetamido-2-carbethoxy-7-[(2-hydroxyphenyl)thio]heptanoate (0.5 g, 1.2 mmol) was dissolved in methylene chloride (30 mL) and *m*-chloroperoxybenzoic acid (MCPBA, 0.486 g, 2.4 mmol, 85%) was added all at once at ambient temperature. The mixture was stirred for 16 h; then it was concentrated directly onto silica gel and flash chromatographed. Elution with 10% ethyl acetate/hexane removed the unreacted MCPBA. Continued elution with ethyl acetate afforded 0.411 g (77%) of a clear, oily product: NMR 7.60 (dd, $J$ = 1.5, 8 Hz, 1 H), 7.51 (dt, $J$ = 1, 7.5 Hz, 1 H), 7.03–6.98 (m, 2 H), 6.73 (s, 1 H), 4.21 (q, $J$ = 7 Hz, 4 H), 3.12–3.07 (m, 2 H), 2.28–2.22 (m, 2 H), 2.0 (s, 3 H), 1.72–1.61 (m, 2 H), 1.35 (quintet, $J$ = 7.5 Hz, 2 H), 1.22 (t, $J$ = 7 Hz, 6 H), 1.11–1.05 (m, 2 H); IR 3403 (w), 1732, 1677, 1605, 1491, 1469, 1372, 1317, 1273, 1234, 1206, 1114, 1317–1206 (br); high-resolution FAB MS MH$^+$ calcd for $C_{20}H_{30}NO_8S$ 444.1693, observed $m/e$ 444.1774.

**Ethyl 2-Acetamido-2-carbethoxy-7-[(2-hydroxyphenyl)sulfinyl]heptanoate.** Ethyl 2-acetamido-2-carbethoxy-7-[(2-hydroxyphenyl)thio]heptanoate (0.5 g, 1.2 mmol) was dissolved in methylene chloride (30 mL) and MCPBA (0.244 g, 1.2 mmol) was added. The mixture was stirred at ambient temperature for 16 h; then it was concentrated directly onto silica gel and flash chromatographed. Elution with 10% ethyl acetate/hexane removed the unreacted MCPBA. Continued elution with ethyl acetate gave 0.246 g (48%) of product as a clear oil: NMR 7.31 (t, $J$ = 8 Hz, 1 H), 7.0 (dd, $J$ = 1.5, 8 Hz, 1 H), 6.91–6.85 (m, 2 H), 6.77 (s, 1 H), 4.20 (q, $J$ = 7 Hz, 4 H), 3.16–3.06 (m, 1 H), 2.98–2.87 (m, 1 H), 2.32–2.26 (m, 2 H), 2.0 (s, 3 H), 1.78–1.64 (m, 2 H), 1.48–1.34 (m, 2 H), 1.20 (t, $J$ = 7 Hz, 6 H), 1.20–1.06 (m, 2 H); IR 3404 (w), 1735, 1677, 1491, 1469, 1301, 1253–1213 (br), 986; HRMS $m/e$ calcd for $C_{20}H_{29}NO_7S$ 427.1664, observed $m/e$ 427.1656.

**Ethyl 2-Acetamido-2-carbethoxy-5-[(2-hydroxyphenyl)sulfinyl]pentanoate.** The product was prepared as in the previous example in 75% yield as a white solid: mp 144–145 °C; NMR 10.22 (s, 1 H), 7.33 (dt, $J$ = 1.5, 8 Hz, 1 H), 7.04 (dd, $J$ = 1.5, 8 Hz, 1 H), 6.90–6.88 (m, 2 H), 6.79 (s, 1 H), 4.26–4.16 (m, 4 H), 3.17–3.08 (m, 1 H), 2.99–2.90 (m, 1 H), 2.48–2.43 (m, 2 H), 2.02 (s, 3 H), 1.65–1.55 (m, 2 H), 1.22 (t, $J$ = 7 Hz, 6 H); IR 3408, 2975, 1740, 1682, 1591, 1487, 1471, 1372, 1301, 1244, 1220, 1193, 992; high-resolution FAB MS MH$^+$ calcd for $C_{18}H_{26}NO_7S$ 400.1430, observed $m/e$ 400.1441. Anal. ($C_{18}H_{25}NO_7S$): C, H, N.

**Ethyl 2-acetamido-2-carbethoxy-6-[(2-hydroxyphenyl)sulfinyl]hexanoate** was prepared as in the above example as a white solid in 55% yield: mp 45–46 °C; NMR 10.35 (br s, 1 H), 7.33 (dt, $J$ = 1.5, 7.5 Hz, 1 H), 7.05 (dd, $J$ = 1.5, 8 Hz, 1 H), 6.92–6.87 (m, 2 H), 6.78 (s, 1 H), 4.21 (dq, $J$ = 2, 7 Hz, 2 H), 3.17–3.04 (m, 1 H), 3.01–2.90 (m, 1 H), 2.38–2.29 (m, 1 H), 2.01 (s, 3 H), 1.82–1.64 (m, 2 H), 1.30–1.18 (m, 8 H); IR 3409, 2977, 2934, 1741, 1733, 1681, 1589, 1489, 1469, 1371, 1301–1194 (br), 1016, 988; high-resolution FAB MS MH$^+$ calcd for $C_{19}H_{28}NO_7S$ 414.1509, observed $m/e$ 414.1616.

**2-Amino-7-[(2-hydroxyphenyl)thio]heptanoic Acid (6a).** Ethyl 2-acetamido-2-carbethoxy-7-[(2-hydroxyphenyl)thio]heptanoate (1.56 g, 3.8 mmol) was dissolved in warm 6 N HCl (10

(22) Garthwaite, J. *Neuroscience* **1982**, 7, 2491.

mL) and refluxed 4 h. The reaction was concentrated and the residue was dissolved in water (1 mL) and purified by ion-exchange chromatography on Dowex 1x-8. Elution with water and concentration of the ninhydrin-positive fractions gave 0.88 g (86%) of a white solid: NMR ($D_2O$) 7.38 (d, $J$ = 7.5 Hz, 1 H), 7.24 (t, $J$ = 7.5 Hz, 1 H), 6.99–6.94 (m, 2 H), 4.07 (t, $J$ = 6 Hz, 1 H), 2.85 (t, $J$ = 6.5 Hz, 2 H), 2.05–1.87 (m, 2 H), 1.65–1.37 (m, 6 H); HRMS $m/e$ calcd for $C_{13}H_{19}NO_3S$ 269.1085, observed $m/e$ 269.1068. A sample lyophilized from water had mp 212–215 °C dec.

**2-Amino-7-[(2-hydroxyphenyl)sulfonyl]heptanoic Acid (6c).** Ethyl 2-acetamido-2-carbethoxy-7-[(2-hydroxyphenyl)-sulfonyl]heptanoate was hydrolyzed as above to give the product in 52% yield as a hygroscopic, white solid after ion-exchange chromatography and lyophilization: mp 247–249 °C; NMR ($D_2O$) 7.84 (d, $J$ = 8 Hz, 1 H), 7.69 (t, $J$ = 7.5 Hz, 1 H), 7.18 (t, $J$ = 8 Hz, 2 H), 3.75 (t, $J$ = 6 Hz, 1 H), 3.60 (t, $J$ = 7.5 Hz, 2 H), 1.89–1.79 (m, 2 H), 1.75–1.66 (m, 2 H), 1.50–1.33 (m, 4 H); high-resolution FAB MS $MH^+$ calcd for $C_{13}H_{20}NO_5S$ 302.1063, observed $m/e$ 302.1073.

**2-Amino-5-[(2-hydroxyphenyl)thio]pentanoic acid (7a)** was prepared as above as a hygroscopic white solid in 70% yield: mp 186–194 °C slow dec; NMR ($D_2O$) 7.45 (dd, $J$ = 1, 8 Hz, 1 H), 7.26 (dt, $J$ = 1, 7.5 Hz, 1 H), 7.01–6.96 (m, 2 H), 3.89 (t, $J$ = 6 Hz, 1 H), 2.94 (t, $J$ = 7 Hz, 2 H), 2.11–2.01 (m, 2 H), 1.80–1.64 (m, 2 H); high-resolution FAB MS $MH^+$ calcd for $C_{11}H_{16}NO_3S$ 242.0846, observed $m/e$ 242.0879.

**2-Amino-7-[(2-hydroxy-4-chlorophenyl)thio]heptanoic Acid (8a).** Ethyl 2-acetamido-2-carbethoxy-7-[(2-hydroxyphenyl)sulfinyl]heptanoate was hydrolyzed as above to give the product as an amorphous, tan solid in 75% yield: mp 83–90 °C dec; NMR (DMSO-$d_6$) 7.18–6.70 (m, 3 H), 3.60–3.18 (br s, 1 H), 3.16 (t, 1 H), 2.84 (t, 2 H), 1.74–1.43 (m, 4 H), 1.34 (br s, 4 H); IR (KBr) 3260–2665 (br), 1740, 1580, 1485, 1465, 1275, 1225–1200 (br); high-resolution FAB MS $MH^+$ calcd for $C_{13}H_{19}ClNO_3S$ 304.0776, observed $m/e$ 304.0790.

**2-Amino-6-[(5-chloro-2-hydroxyphenyl)thio]hexanoic Acid (9a).** Ethyl 2-acetamido-2-carbethoxy-6-[(2-hydroxyphenyl)-sulfinyl]hexanoate (0.569 g, 1.38 mmol) was dissolved in warm 6 M hydrochloric acid (25 mL) and refluxed for 16 h. The mixture was cooled and concentrated at reduced pressure. The residue was taken up in water (2 mL) and passed through a Dowex 1x-8 ion-exchange resin. Elution with water and concentration of the ninhydrin-positive fractions gave 0.28 g (79%) of a white, amorphous, solid product: mp 99–106 °C dec; NMR ($D_2O$) 7.32 (d, $J$ = 2.5 Hz, 1 H), 7.23 (dd, $J$ = 2.5, 8.5 Hz, 1 H), 6.86 (d, $J$ = 8.5 Hz, 1 H), 4.00 (t, $J$ = 6 Hz, 1 H), 2.88 (t, $J$ = 7 Hz, 2 H), 2.05–1.87 (m, 2 H), 1.69–1.49 (m, 4 H), a minor impurity was noted in the NMR spectrum; IR (KBr) 3255–2675 (br), 1740, 1580, 1495, 1470, 1275, 1221–1200 (br); high-resolution FAB MS $MH^+$ calcd for $C_{12}H_{17}NO_3ClS$ 290.0619, observed $m/e$ 290.0631.

**2-Amino-5-[(5-chloro-2-hydroxyphenyl)thio]pentanoic acid (10a)** was prepared as above as a hygroscopic, amorphous solid (80%): mp 85–90 °C dec; NMR ($D_2O$) 7.43 (d, $J$ = 2.5 Hz, 1 H), 7.22 (dd, $J$ = 2.5, 8.5 Hz, 1 H), 6.92 (d, $J$ = 8.5 Hz, 1 H), 4.00 (t, $J$ = 6.5 Hz, 1 H), 2.98 (t, $J$ = 7 Hz, 2 H), 2.10–2.01 (m, 2 H), 1.80–1.63 (m, 2 H); IR (KBr) 3270–2660 (br), 1740, 1485, 1465, 1270, 1205; high-resolution FAB MS $MH^+$ calcd for $C_{11}H_{15}NO_3ClS$ 276.0456, observed $m/e$ 276.0562.

**Methyl 2-Amino-7-[(2-hydroxyphenyl)thio]heptanoate.** 2-Amino-7-[(2-hydroxyphenyl)thio]heptanoic acid (0.88 g, 3.27 mmol) was dissolved in methanol (25 mL) and HCl gas was passed through the solution for 20 min at ambient temperature. The mixture was stirred 1 h more; then the pH was adjusted to 7.0 with saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried over calcium sulfate, and concentrated to give 0.494 g (53%) of a white solid: mp 66–68.5 °C; NMR 7.44 (dd, $J$ = 1.5, 7.5 Hz, 1 H), 7.25 (dt, $J$ = 1.5, 7 Hz, 1 H), 6.97 (dd, $J$ = 1, 8 Hz, 1 H), 6.85 (dt, $J$ = 1, 7.5 Hz, 1 H), 3.70 (s, 3 H), 3.50–3.39 (m, 1 H), 2.67 (t, $J$ = 7 Hz, 2 H), 1.70–1.30 (m, 8 H); IR 2936, 2856, 1733, 1600, 1589, 1578, 1468, 1451, 1436, 1301, 1194, 987; high-resolution FAB MS $MH^+$ calcd for $C_{14}H_{22}NO_3S$ 284.1322, observed $m/e$ 284.1327.

**Methyl 2-Amino-7-[(2-hydroxyphenyl)sulfinyl]heptanoate.** Methyl 2-amino-7-[(2-hydroxyphenyl)thio]heptanoate (0.33 g, 1.17 mmol) was dissolved in methylene chloride (20 mL) and MCPBA (0.237 g, 1.17 mmol) was added all at once at ambient temperature. The mixture was stirred 16 h and then concentrated directly onto silica gel and flash chromatographed. Elution with 10% ethyl acetate/hexane removed unreacted MCPBA. Continued elution with 10% methanol/ethyl acetate gave 0.226 g (76%) of product as a clear oil: NMR 7.35 (dt, $J$ = 1.5, 7.5 Hz, 1 H), 7.03 (dd, $J$ = 1.5, 7.5 Hz, 1 H), 6.93–6.87 (m, 2 H), 3.70 (s, 3 H), 3.47–3.40 (m, 1 H), 3.23–3.12 (m, 1 H), 3.03–2.91 (m, 2 H), 1.83–1.70 (m, 2 H), 1.65–1.35 (m, 6 H); IR 2931, 2856, 1732, 1589, 1466, 1300, 1231, 987; high-resolution FAB MS $MH^+$ calcd for $C_{14}H_{22}NO_4S$ 300.1271, observed $m/e$ 300.1293.

**2-Amino-7-[(2-hydroxyphenyl)sulfinyl]heptanoic Acid (6b).** Methyl 2-amino-7-[(2-hydroxyphenyl)sulfinyl]heptanoate (0.279 g, 0.93 mmol) was dissolved in 1:1 methanol/water (36 mL) and potassium hydroxide (0.185 g, 3.3 mmol) was added. The mixture was stirred for 16 h at ambient temperature; then it was acidified to pH 6 with acetic acid and concentrated to about 2 mL. The residue was purified by ion-exchange chromatography (Dowex 1x-8) with water elution. The ninhydrin-positive fractions were lyophilized to give 0.213 g (80%) of a hygroscopic, amorphous, off-white solid: mp 70–78 °C dec; NMR ($D_2O$) 7.54 (dd, $J$ = 1.5, 8 Hz, 1 H), 7.45 (dt, $J$ = 1.5, 8 Hz, 1 H), 7.14 (t, $J$ = 7.5 Hz, 1 H), 6.98 (d, $J$ = 8 Hz, 1 H), 3.71 (t, $J$ = 7.5 Hz, 1 H), 3.19–3.08 (m, 1 H), 3.04–2.93 (m, 1 H), 1.87–1.32 (m, 8 H); IR (KBr) 3180–2460 (br), 1600–1545 (br), 1450, 1405, 1020, 760.

**2-Amino-7-[(2-aminophenyl)thio]heptanoic Acid (11a).** Ethyl 2-acetamido-2-carbethoxy-7-[(2-aminophenyl)thio]heptanoate was hydrolyzed under the acidic conditions described above in 32% yield after ion-exchange chromatography and lyophilization as a hygroscopic, fluffy, white solid: mp 94–96 °C; NMR ($D_2O$) 7.72 (d, 1 H), 7.55–7.42 (m, 3 H), 3.94 (t, 1 H), 3.02 (t, 2 H), 1.95–1.86 (m, 2 H), 1.68 (m, 2 H), 1.50–1.48 (m, 4 H); HRMS $m/e$ calcd for $C_{13}H_{20}N_2O_2S$ 268.1246, observed $m/e$ 268.1242.

**Apparent p$K_a$ Measurements.** The compound to be analyzed (2–2.5 mg) was dissolved in boiled, distilled water (100 mL) or a 1:1 (vol) mixture of acetonitrile/water. The solution was filtered as a precaution and was circulated through a UV flow cell. The solution pH at 23 °C was measured by a pH meter calibrated against pH 5, 7, and 9 buffers. UV absorbance curves were obtained at the starting pH and then at 3 and 10. The UV absorbance curves were then repeated at pH 3 and 10 to insure reproducibility and demonstrate that no decomposition had occurred. The solution pH was adjusted by addition of 6 N HCl or NaOH via a microsyringe so that seven to 15 absorbance readings were obtained in a pH range spanning the anticipated p$K_a$. After each addition of acid or base and after the pH had stabilized, the flow of solution through the cell was stopped and readings were taken at two to four wavelengths. With the seven to 15 readings at each wavelength, the p$K_a$ was calculated from the absorbance versus pH plot by a simplex curve fit to the equation $(Y_{acid} + Y_{base} \times K_a/[H^+])/(1 + K_a/[H^+])$ where $Y_{acid}$ and $Y_{base}$ are the absorbances for the compound in its fully protonated and deprotonated forms, respectively. The apparent p$K_a$'s are expressed as the mean ± standard deviation for values calculated at $n$ wavelengths.

At the completion of the experiment, UV absorbance curves were repeated at pH 3 and 10 and compared to the curves prior to the pH adjustment as a final check for decomposition and/or excessive volume changes due to the acid–base additions. Compounds were stable as assessed by the stability of isosbestic points and except for the case of **3b** only one UV-active species was detected in solution.

**p$K_a$ of 4-(Benzylsulfinyl)-3*H*-1,2,3-triazole (3b).** At wavelengths of 220, 230, and 255 nm an apparent p$K_a$ of 6.09 was measured while at 240 nm an apparent p$K_a$ of 4.24 was measured. Potentiometric determination of apparent p$K_a$ by titration with NaOH gave values of p$K_a$ = 6.03 (MW = 207.25, neutralization equivalent = 208.047) in water and p$K_a$ = 6.54 (neutralization equivalent = 207.852) in 1:1 acetonitrile/water.

The potentiometric titration data and neutralization equivalent are consistent with a macro p$K_a$ value of about 6–6.1 in water. We were unable to detect any over oxidation to the sulfone in **3b** by proton NMR nor did we observe any detectable UV-positive impurities by thin-layer chromatography. The UV method can detect p$K_a$'s of tautomeric species, and the presence of two tautomers of **3b** at acid pH having differing UV absorptions could

explain the difference between the UV and titration values.

**p$K_a$ of 4-(Benzylsulfonyl)-3*H*-1,2,3-triazole (3c).** The mean apparent p$K_a$ in water at 220 and 225 nm was 5.15. Potentiometric determination of apparent p$K_a$ in 1:1 acetonitrile/water gave a value of 5.81 (MW = 223.250, neutralization equivalent = 225.464). Potentiometric titration in water was precluded by poor solubility.

**Acknowledgment.** We thank Matthew Teague for performing the p$K_a$ measurements and Dr. Dan Pentek (Yale University Instrumentation Center) for the high-resolution FAB mass spectrometric measurements.

**Note Added in Proof:** Since this manuscript was submitted, the use of a tetrazole as an isostere for phosphonate has been described: Ornstein, P. L. European Patent 330,353, published August 30, 1989.

**Registry No.** **1a**, 15139-30-7; **1b**, 124603-61-8; **1c**, 27099-02-1; **2a**, 21239-87-2; **2b**, 29982-78-3; **2c**, 29982-79-4; **3a**, 79100-69-9; **3b**, 124603-62-9; **3c**, 79100-71-3; **4a**, 65479-47-2; **4b**, 124603-63-0; **4c**, 124603-64-1; **6a**, 124603-73-2; **6b**, 124603-74-3; **6c**, 124603-75-4; **7a**, 124603-76-5; **8a**, 124603-77-6; **9a**, 124603-78-7; **10a**, 124603-79-8; **11a**, 124603-80-1; AP-7, 85797-13-3; 2-mercaptoimidazole, 872-35-5; 4-mercapto-1,2,3-triazole, 75232-02-9; 3-mercapto-1,2,4-triazole, 3179-31-5; carbethoxy thiosemicarbazide, 65479-56-3; 2-hydroxythiophenol, 1121-24-0; ethyl 2-acetamido-7-bromo-2-carbethoxyheptanoate, 5183-26-6; ethyl 2-acetamido-6-bromo-2-carbethoxyhexanoate, 5183-27-7; ethyl 2-acetamido-5-bromo-2-carbethoxypentanoate, 52892-17-8; ethyl 2-acetamido-2-carbethoxy-7-[(2-hydroxyphenyl)thio]heptanoate, 124603-65-2; ethyl 2-acetamido-2-carbethoxy-6-[(2-hydroxyphenyl)thio]hexanoate, 124603-66-3; ethyl 2-acetamido-2-carbethoxy-5-[(2-hydroxyphenyl)thio]pentanate, 124603-67-4; ethyl 2-acetamido-2-carbethoxy-7-[(2-aminephenyl)thio]heptanoate, 124603-68-5; 2-aminothiophenol, 137-07-5; ethyl 2-acetamido-2-carboethoxy-7-[(2-hydroxyphenyl)sulfonyl]heptanoate, 124603-69-6; ethyl 2-acetamido-2-carbethoxy-7-[(2-hydroxyphenyl)sulfinyl]heptanoate, 124603-70-9; ethyl 2-acetamido-2-carbethoxy-5-[(2-hydroxyphenyl)sulfinyl]pentamate, 124603-71-0; ethyl 2-acetamido-2-carbethoxy-6-[(2-hydroxyphenyl)sulfinyl]hexanoate, 124603-72-1; methyl 2-amino-7-[(2-hydroxyphenyl)thio]heptanoate, 124603-81-2; methyl 2-amino-7-[(2-hydroxyphenyl)-sulfinyl]heptanoate, 124603-82-3.

# *Book Reviews*

**Advances in Biotechnology of Membrane Ion Transport.** Edited by P. L. Jørgensen and R. Verna. Raven Press, New York. 1989. xv + 260 pp. 16.5 × 24 cm. ISBN 0-88167-423-0. $60.00.

This volume represents the proceedings of a Serono Symposia sponsored meeting of the same name that was held in L'Aquila, Italy on September 19–20, 1988. The purpose of the meeting was to bring together an international panel of experts on membrane transport processes to discuss timely biochemical, molecular biological, biophysical, and pharmacological aspects of this topic. Given the many significant advancements that have occurred in the field of ion transport over the last 5 years, this was a very ambitious undertaking. The proceedings of the meeting reflect the broadness of the organizers' approach. Unfortunately, this has resulted in a potpourri of minireview articles and minor scientific contributions that lack a high degree of cohesiveness.

The presentations in this book deal with ATPases ($Na^+$,$K^+$-ATPase, plasmalemmal $Ca^{2+}$-ATPase, sarcoplasmic reticulum $Ca^{2+}$-ATPase), ion channels (voltage sensitive $Na^+$, $Ca^+$, and $K^+$ channels, as well as the nicotinic acetylcholine receptor and neuronal $Cl^-$ channels), and several membraneous processes that are tangentially related to ion transport (nucleocytoplasmic transport, viral fusion, and the structure of membranes). Lacking in this symposium were topics related to ion transport in bacteria and bacterial vesicle systems which have seen significant mechanistic advances over the last 5 years. Although there are a couple of reports which present biophysical studies, most deal with biochemical and molecular biological data.

Perhaps the topic best represented at this meeting was the $Na^+$ pump. The chapter by Lingrell et al. on cardiac glycoside sensitivity of the $Na^+$,$K^+$-ATPase is interesting and compliments nicely a report from Karlish's laboratory dealing with canrenone and endogenous ouabain-like substances. There is also a chapter by Jørgensen, a coorganizer of the meeting, on the structure and mechanism of the $Na^+$,$K^+$-ATPase from mammalian kidney. Current understanding of the structure of the plasmalemmal $Ca^{2+}$-ATPase, as determined by proteolytic digestion, is outlined by work from Carafoli's laboratory. Of the studies on ion channels that were reported, Catterall reviews data regarding the molecular properties of $Na^+$ and $Ca^{2+}$ channels, while Lazdunski discusses the work from his laboratory on neuronal $K^+$ channels. Of interest to medicinal chemists is a chapter by Garay regarding the use of red blood cells to screen for selective inhibitors of transport systems. This listing is by no means complete, but cites some of the more notable contributions in this book.

As might be expected from a work which covers such a wide variety of areas, the review articles are timely, brief, and to the point, but cannot go into the depth that would interest a specialist in the field of ion transport. The original research reports are also of limited interest. Consequently, this book is directed to the nonspecialist, either someone with former knowledge of the field of ion transport who wants to be brought up to date or someone who wants to read a brief collection of reports to gain some appreciation of current trends in membrane transport.

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**Safe and Effective Control of Acid Secretion.** Edited by M. Mignon and J.-P. Galmiche. John Libby, London. 1988. xiii + 311 pp. 18 × 25 cm. ISBN 0-86196-176-5. $62.00.

This is a collection of presentations given at the International Symposium on Safe and Effective Control of Acid Secretion held in Fort-de-France/La Martinque, January 1988. The reader will find a broad range of topics from the physiology of gastric acid secretion to the socioeconomic aspects of ulcer disease management. The editors provided a balanced distribution of specific subjects within each topic. Readers who are unacquainted with this area of science will find this book an excellent and comprehensive learning tool, while those versed in the field will enjoy the in-depth and up-to-date nature of the chapters. The contributing authors include several internationally recognized investigators.

With the explosive interest in gastric acid secretion over the last 2 decades ignited by the introduction of the histamine $H_2$ receptor antagonist cimetidine, several questions needed to be addressed. Thus, the symposium was strategically designed to answer questions such as the following: what is our current understanding of the physiology and pharmacology of acid secretion, what are the safety issues with antisecretory therapy, what is thee pharmacological basis of treating reflux esophagitis with antisecretory drugs, and are there socioeconomic issues in the management of peptic ulcer disease.