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# Novel Phosphinic and Phosphonic Acid Analogues of the Anticonvulsant Valproic Acid

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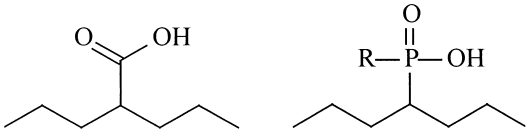
**Abstract**—1-Propylbutylphosphinic acid **2**, (1-propylbutyl)methylphosphinic acid **3** and 1-propylbutylphosphonic acid **4** have been synthesized as bioisosteres of the corresponding carboxylic acid valproate **1**, which is a potent anticonvulsant. The novel phosphinic and phosphonic acids were tested for their anticonvulsant activity and were found to be inactive. 

Valproic acid (VPA) **1** (Fig. 1) is currently one of the most widely used first-choice agents for the treatment of epilepsy, especially for the treatment of generalized seizures.[1] Recently, VPA has also been used as an effective antimanic agent,[2] as a mood stabilizer,[3] in migraine prophylaxis,[4] and with potential use in the treatment of Alzheimer patients.[5] Although VPA has been in use for more than 20 years, its mechanism of action is still unresolved. However, VPA has been shown to moderately elevate the levels of the major inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the brain, presumably by inhibiting GABA-transaminase and succinic semialdehyde dehydrogenase, and, hence the catabolism of GABA.[6]



**1**



**2**, R = H
**3**, R = Me
**4**, R = OH

**Figure 1.** Structures of valproic acid **1** and the phosphinic acid **2**, methylphosphinic acid **3** and phosphonic acid **4** analogues.

Furthermore, VPA inhibits cyclooxygenase[7] and influences the brain energy metabolism.[8] VPA is extensively metabolized by a variety of conjugation and oxidative processes and several of its metabolites are potent anticonvulsants.[1] Hundreds of analogues of VPA have been synthesized and evaluated as anticonvulsants, but the majority of the studies have concentrated on structure–activity studies in the carbon skeleton.[1] Only two analogues have been prepared in which the carboxylic acid moiety has been isosterically replaced with another acidic moiety, tetrazole[9] and 1,2,4-oxadiazolidine-3,5-dione,[10] respectively, and both compounds were equipotent with VPA in anticonvulsant studies. Phosphinic[11] and phosphonic acids[12] have attracted considerable attention in medicinal chemistry in recent years due to their ability to function as effective bioisosteres for the carboxylic acid group. As part of our ongoing research in the medicinal chemistry related to epilepsy,[13] we have recently reported the syntheses of phosphorus based analogues of GABA.[14] Here we wish to report the syntheses and anticonvulsant properties of novel phosphinic and phosphonic acid analogues **2**–**4** of VPA.

The phosphinic acid **2** and phosphonic acid **4** were synthesized from valproic acid (Scheme 1) by conversion to the *N*-hydroxy thiopyridone ester, a convenient precursor of the carbon radical, which can be trapped by yellow phosphorus and subsequently oxidized to the phosphinic acid **2** at 0 °C.[15] The phosphinic acid was separated from 25% contaminating phosphonic acid by fractional crystallization of their anilinium salts from

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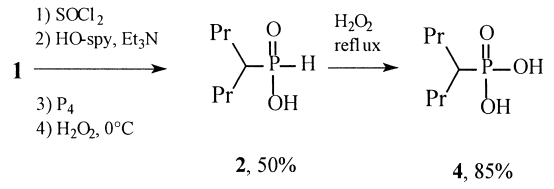
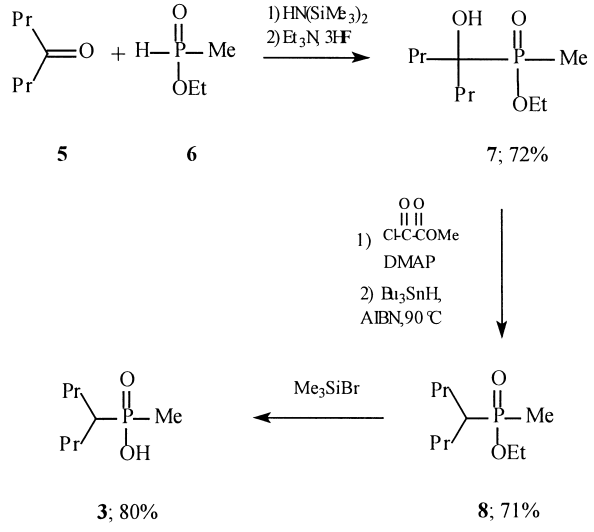



**Scheme 1.** Syntheses of the valproate analogues phosphinic acid **2**, and phosphonic acid **4**. HO-spy is *N*-hydroxythiopyridone.




**Scheme 2.** Syntheses of the valproate analogue methylphosphinic acid **3**.

acetonitrile. Further oxidation of **2** by refluxing 30% $H_2O_2$ for 12 h gave the phosphonic acid **4** in high yield.[15]

The methylphosphinic acid **3** was synthesized by a recently developed methodology[16] (Scheme 2). Silyl Abramov addition of ethyl methylphosphinate **6**[14b] to 4-heptanone catalyzed by hexamethydisilazane and subsequent removal of the trimethylsilyl group with triethylamine trihydrofluoride gave the α-hydroxyphosphinate **7** in good yield. Compound **7** was deoxygenated using a modified Barton deoxygenation procedure,[17] i.e., activation of the tertiary alcohol by methyl oxalyl chloride and dimethylaminopyridine (DMAP) followed by reduction under free radical conditions by tributyl tinhydride to give methylphosphinate **8** in good yield. Finally, the ethyl ester was cleaved by treatment with trimethylsilyl bromide (the McKenna reaction)[18] to give in good yield after standard aqueous extractive work up the methylphosphinic acid **3**.

The crystalline sodium salts of the VPA analogues **2**–**4** were tested for their anticonvulsant activity in amygdala kindled rats.[19] None of the novel compounds displayed any anticonvulsant activity. Apparently, **2**–**4** are not substrates for the enzymes or receptor(s) which mediate the anticonvulsant activity of VPA, or alternatively **2**–**4** are not substrates for the presumed carboxylic acid transporter responsible for transporting VPA over the blood–brain–barrier, thus preventing the access of **2**–**4** to the CNS.

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