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LETTERS

## SYNTHESIS OF WATER-SOLUBLE PHENYTOIN PRODRUGS

Joan Bosch,<sup>a\*</sup> Tomàs Roca,<sup>a</sup> Josep Domènech,<sup>b</sup> and Montserrat Suriol<sup>b</sup>

<sup>a</sup>Laboratory of Organic Chemistry, <sup>b</sup>Laboratory of Biopharmacy and Pharmacokinetics,  
Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

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**Abstract:** The synthesis of novel water-soluble phenytoin derivatives, bearing an ionizable group, and a preliminary study for *in vitro* blood hydrolysis are reported. The results show that hydrolysis of amino esters **8** is very fast, much more than that of fosphenytoin. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Phenytoin (**1**) is one of the most widely used drugs in the therapy of epilepsy. However, its low solubility in water, both as free acid and sodium salt, makes its administration to patients difficult and seldom satisfactory. Phenytoin is given orally as sodium salt in a strong alkaline solution, since it requires a pH between 10 and 12 to be maintained in solution. The alkalinity of this dosage form often causes gastric irritation, which is a serious drawback for its use. Phenytoin can also be given by the intramuscular route, but the product commonly precipitates at the injection site, leading to unreliable blood levels of the drug. Moreover, absorption of intramuscular phenytoin is very slow, so it is not appropriate for treating epileptic seizures, in which a loading dose of the product is required. Intravenous administration is the most useful route in such cases. For parenteral use, sodium phenytoin is formulated in aqueous alkaline solution (pH 12) containing 40% of propylene glycol and 10% of ethanol. The risks associated with the use of this formulation are obvious, taking into account its high pH as well as the precipitation of the free acid **1**.

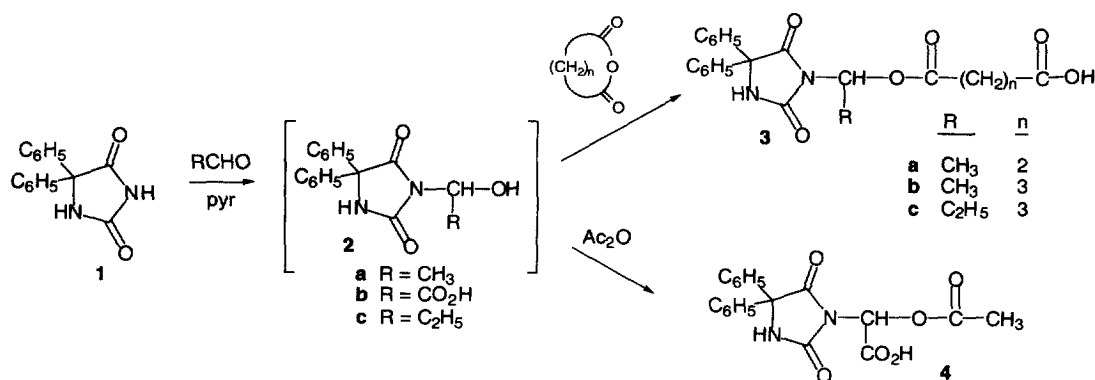
A solution to these problems has consisted in the development of prodrugs of phenytoin with more desirable physico-chemical properties, although only a limited number of parenteral prodrugs of phenytoin have been described in the literature.<sup>1</sup> The acylation of the 3-position of the hydantoin nucleus provides phenytoin prodrugs, which are quite unstable chemically or do not improve phenytoin solubility.<sup>2</sup> In contrast, *N*-aminomethyl derivatives (Mannich bases) of phenytoin possess good aqueous solubility (as hydrochlorides) and release the drug rapidly.<sup>3</sup> More recently, there has been a growing interest in *N*-hydroxymethyl derivatives of hydantoins bearing bioreversible water solubilizing functional groups.<sup>4</sup> In this context, Varia *et al.*<sup>5</sup> have described a series of esters derived from 3-(hydroxymethyl)phenytoin (**2d**), including fosphenytoin,<sup>6</sup> launched as Cerebyx<sup>®5a</sup> in the US in 1996. Other 3-hydroxymethyl derivatives of phenytoin containing a dihydropyridine subunit as a redox brain delivery system for phenytoin,<sup>7</sup> and highly water-soluble potential phenytoin prodrugs containing polyethylene glycols as the promoieties<sup>8</sup> have recently been reported.

In this context we present herein the synthesis of several series of phenytoin derivatives as potential phenytoin prodrugs<sup>9</sup>. Most of them are esters (**3**, **4**, **6**, **8**) bearing an additional ionizable group, and the corresponding salts, either a carboxylate or a protonated amine, were expected to be soluble in water and to be

\* E-mail: jbosch@farmacia.far.ub.es; FAX: 34.93.402.18.96

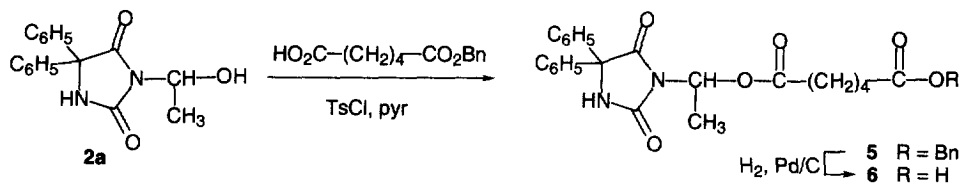
cleaved by esterases to phenytoin alcohols **2**, which break down further into phenytoin. A similar easy hydrolysis to phenytoin was expected from phosphate **11**, the  $\alpha$ -methyl analog of fosphenytoin. On the other hand, the *N*-acyl derivatives **12**, bearing a protected carboxy function, were also envisaged as precursors of phenytoin soluble prodrugs, although their conversion to the latter could only be accomplished from **12c** due to the lability of the *N*-acyl bond. The target molecules were synthesized as outlined in Schemes 1–5.

The sodium salts derived from acids **3** and **4** (Scheme 1) were obtained by reaction of phenytoin (**1**) with an appropriate aldehyde (acetaldehyde, propionaldehyde or glyoxylic acid) and anhydride (succinic, glutaric or acetic anhydride), without isolation of intermediate alcohols **2**, followed by treatment of the resulting carboxylic acids **3a–c** and **4** with sodium methoxide. The use of pyridine both as a solvent and as a base was found to be crucial for the formation of alcohols **2a–c**, as the reaction failed in the presence of the aqueous bases usually used in the synthesis of (3-hydroxymethyl)phenytoin (**2d**).<sup>5b</sup>



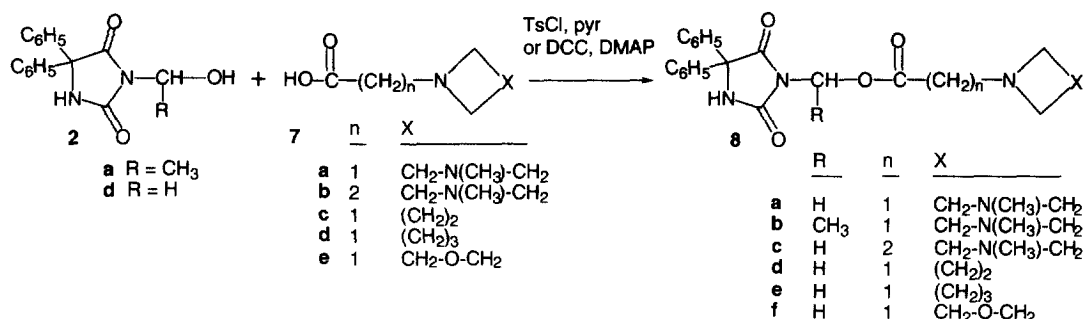
Scheme 1

Alternatively, the sodium salt of the adipic derivative **6** was more conveniently prepared (Scheme 2) by esterification of phenytoin alcohol **2a** with benzyl hydrogen adipate,<sup>10</sup> using tosyl chloride as the carboxy group activator, followed by hydrogenolysis of the benzyl moiety in the resulting diester **5** and, finally, treatment with sodium methoxide.



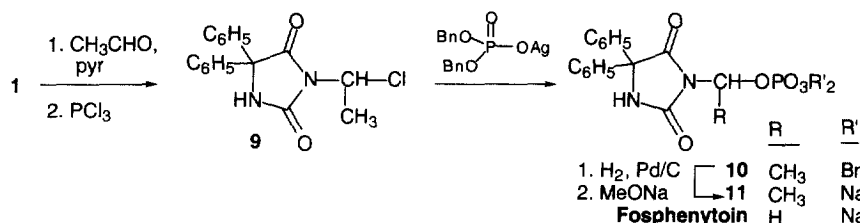
Scheme 2

Prodrugs with piperazine, pyrrolidine, piperidine or morpholine moieties **8a–f** were synthesized (Scheme 3) by esterification of the appropriate heterocyclic amino acids **7a–e**<sup>11,12</sup> with phenytoin alcohols **2a** or **2d**,<sup>5b</sup> using either tosyl chloride as the carboxy group activator or dicyclohexylcarbodiimide as the dehydrating agent. Treatment of amino esters **8** with hydrogen chloride or succinic acid yielded the corresponding water-soluble prodrugs.



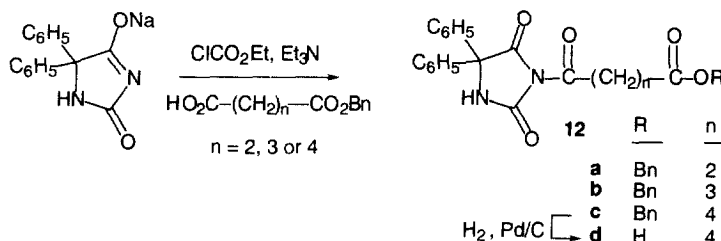
Scheme 3

On the other hand, disodium phosphate **11** (Scheme 4) was prepared by a route similar to that reported<sup>5b</sup> for the synthesis of fosphenytoin, by treatment of phenytoin with acetaldehyde, conversion of the resulting alcohol **2a** to halide **9**, alkylative esterification with silver dibenzyl phosphate, hydrogenolysis of the resulting dibenzyl phosphate **10** and, finally, treatment with sodium methoxide.



Scheme 4

Finally, *N*-acyl derivatives **12a-c** (Scheme 5) were prepared by reaction of sodium phenytoin with the appropriate half benzyl esters of succinic,<sup>13</sup> glutaric,<sup>10</sup> and adipic<sup>10</sup> acids, respectively, previously activated with ethyl chloroformate. Unfortunately, the conversion of **12a-c** into water-soluble phenytoin prodrugs could not be accomplished, since deprotection of the benzyl group in **12a** and **12b** yielded phenytoin (**1**) and succinic or glutaric anhydride due to an intramolecular cyclization of the initially formed carboxylic acids. In the case of **12c**, the formation of adipic anhydride is not favoured, and the acid **12d** was obtained in good yield. However, this acid could not be converted into its corresponding sodium salt owing to the fast hydrolysis of *N*-acyl bond under alkaline conditions.



Scheme 5

A study for *in vitro* blood hydrolysis<sup>14</sup> of the above prodrugs was carried out. Some representative data are shown in Table 1. The hydrolysis of some of the compounds (for instance amino esters **8**) was very fast, much more than that of fosphenytoin. Lower hydrolysis rates were observed from the carboxylate salts **3**. Since phenytoin is used for treating seizures requiring a high blood level of the drug to be reached quickly,

these new products are potentially useful and advantageous as anticonvulsivant and antiarrhythmic agents. Complete pharmacokinetic data of *in vitro* and *in vivo* hydrolysis will be reported in due time.

**Table 1.** % Hydrolysis (Mean  $\pm$  SD) of Phenytoin Prodrugs in Whole Blood.<sup>14</sup>

Prodrug	Time (min)					
	0.5	2.0	7.0	15.0	60.0	180.0
<b>3a.Na salt</b>	25.68 $\pm$ 2.64	42.42 $\pm$ 4.69	52.76 $\pm$ 4.68	55.87 $\pm$ 1.71	59.59 $\pm$ 4.23	69.17 $\pm$ 4.01
<b>3b.Na salt</b>	14.98 $\pm$ 2.67	26.74 $\pm$ 2.10	36.88 $\pm$ 1.97	37.21 $\pm$ 1.09	39.63 $\pm$ 2.17	45.15 $\pm$ 3.37
<b>8e.HCl</b>	49.25 $\pm$ 7.20	96.52 $\pm$ 7.15	97.53 $\pm$ 4.91 <sup>a</sup>	-	-	-
<b>8f.HCl</b>	28.70 $\pm$ 4.23	80.13 $\pm$ 7.75	90.98 $\pm$ 7.82 <sup>a</sup>	93.64 $\pm$ 6.43	99.30 $\pm$ 1.20	-
<b>fosphenytoin</b>	7.95 $\pm$ 1.52	11.63 $\pm$ 1.80	24.97 $\pm$ 4.42	45.42 $\pm$ 6.98	87.49 $\pm$ 11.89	95.30 $\pm$ 9.75

<sup>a</sup>5 min instead of 7 min

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- Franz-type permeation cells were used. The receiving compartment was equipped with a magnetic stirrer and a water recirculator to keep the system at 37 °C. Male Wistar albino rats weighing 200–275 g were used. The animals were fasted for 20 h before the experiments, but were allowed water ad libitum. In order to avoid coprophagy, the animals were placed in cages with a broad wire netting bottom. After anesthetizing the rat, blood was drawn by cardiac puncture, and 4.5 mL were introduced in the receiving compartment. Then, the aqueous prodrug solution (0.5 mL, 400 µg/mL) was added. Blood samples (0.5 mL) were taken at predetermined times and added to tubes containing acetonitrile (1.5 mL), internal standard [50 µL, 5-(*p*-methylphenyl)-5-phenylhydantoin, 100 µg/mL], and deionized water (50 µL). After stirring for 5 min, the samples were centrifuged (1310 g) at 4 °C for 10 min. The supernatant (0.5 mL) was diluted with water (0.5 mL), and phenytoin and the prodrug in the resulting solution were determined by HPLC. The hydrolysis percentages shown in Table 1 were the mean of five replicates.