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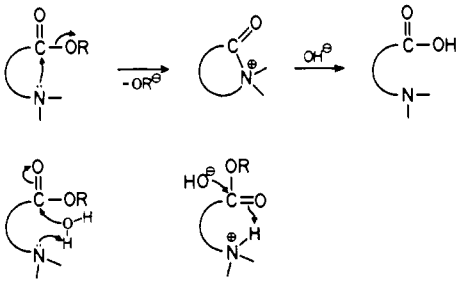
Communications to the Editor

A Novel Solution-Stable, Water-Soluble Prodrug Type for Drugs Containing a Hydroxyl or an NH-Acidic Group

Sir:

Formation of water-soluble ester prodrugs has long been recognized as an effective means of increasing the aqueous solubility of drugs containing a hydroxyl group, with the aim of developing improved preparations for parenteral or ophthalmic administration. The most commonly used esters for increasing the aqueous solubility of hydroxyl-containing agents are esters containing an ionic or ionizable group, i.e. dicarboxylic acid hemiesters (notably hemisuccinates), phosphate esters, sulfate esters, and α-amino acid esters.[1] However, their use is not without problems, considering the ideal properties of such prodrugs: they should possess a high water solubility at the pH of optimum stability and sufficient stability in aqueous solution to allow long-term storage (>2 years) of ready-to-use solutions and yet they should be converted quantitatively and rapidly in vivo to the active parent drug. For example, succinate esters have limited solution stability,[1-4] and in addition, they show a slow and incomplete conversion in vivo to the parent drug as has been reported for such esters of various corticosteroids,[5-7] chloramphenicol,[8-11] and metronidazole.[12-14] Phosphate esters as sodium salts are freely water soluble, generally readily hydrolyzed in vivo,[1] and more stable, allowing in some cases but not all the formulation of solutions with practical shelf-lives.[15] Sulfate esters are also rather stable in solution, but their deficiency is a high resistance to enzymatic hydrolysis in vivo.[16,17] Conversely, α-amino acid esters or related short-chained aliphatic amino acid esters are in general readily hydrolyzed by plasma enzymes[12,18,19] but exhibit a poor stability in aqueous solution as exemplified with esters of metronidazole,[18,20] corticosteroids,[21,22] paracetamol,[23,24] and acyclovir.[25]

Scheme I



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(12) Bundgaard, H.; Larsen, C.; Thorbek, P. *Int. J. Pharm.* **1984**, *18*, 67–77.
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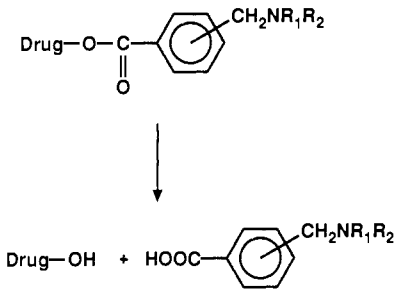
Scheme II



For drugs containing an NH-acidic group (e.g. hydantoins, imides, and imidazoles), N-acyloxymethylation has recently become a commonly used approach to obtain prodrug derivatives.[1] The regeneration of the parent drug from these derivatives occurs via a two-step reaction: enzymatic cleavage of the ester grouping followed by a spontaneous and fast decomposition of the *N*-hydroxymethyl intermediate. By incorporating an ionizable acyl group such as those described above in the ester part, derivatives with increased water solubility have been obtained as exemplified with allopurinol,[26] phenytoin,[27] and fetindomide.[28] The amino acid esters described in these references show, as expected, the same solution instability problem as for similar esters of hydroxyl-containing drugs.

The major reason for the high instability of α-amino acid and short-chained aliphatic amino acid esters in aqueous solution at pH values affording their favorable water solubility (i.e. pH 3–5) is partly due to the strongly electron withdrawing effect of the protonated amino group which activates the ester linkage toward hydroxide ion attack and partly (and predominantly) to intramolecular catalysis or assistance by the neighboring amino group (protonated or nonprotonated) of ester hydrolysis.[20,27,29,30] The mechanisms involved include intramolecular nucleophilic catalysis, intramolecular general-base catalysis, or general-acid–specific-base catalysis[30] as depicted in Scheme I. As recently described by Anderson et al.[31] in a study of prodrug esters of methylprednisolone, both of these effects can be depressed somewhat by placing the solubilizing amino group more distant from the ester linkage as in 6-aminocaproic acid esters or in esters with the acyl moiety having the structure $CO(CH_2)_6CON(CH_3)CH_2CH_2N(CH_3)_2$.

We have now found that a most effective and simple approach to totally block the hydrolysis-facilitating effect of the amino group and yet retain a rapid rate of enzymatic ester hydrolysis is to incorporate a phenyl group between the ester moiety and the amino group. By doing so the intramolecular catalytic reactions of the amino group as outlined in Scheme I are no longer possible for sterical reasons. Because of the requirement of a pK_a value greater than 5–6 for the amino group (for solubility reasons), the group is not directly attached to the phenyl nucleus but separated from this by an alkylene group, in the most simple case a methylene group. In this paper we report that such 3- or 4-(aminomethyl)benzoate esters (Scheme II) may be a promising and generally useful prodrug type for hydroxyl-containing drugs to improve the water solubility due to their combination of a high stability in aqueous solution with a high susceptibility to undergo enzymatic hydrolysis in plasma. We also show that the same approach can be used for drugs containing an NH-acidic group by firstly converting these compounds into an *N*-hydroxymethyl derivative which is then aminomethylbenzoylated (Scheme III).

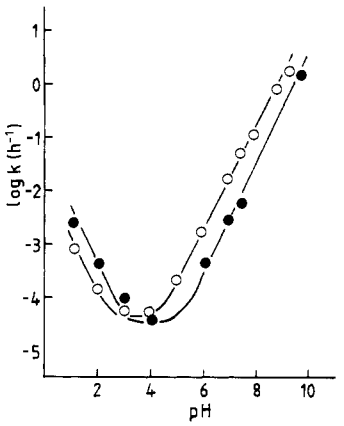
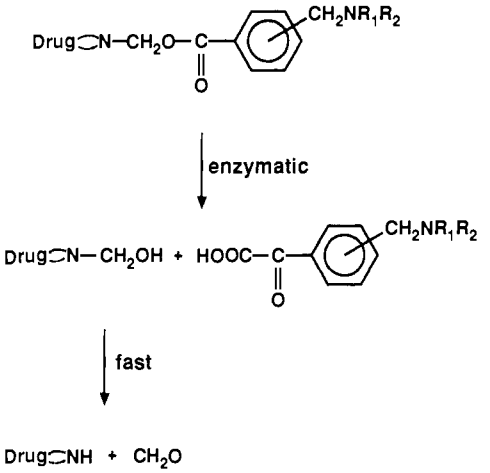


Figure 1. The pH–rate profiles for the hydrolysis of the N-substituted (aminomethyl)benzoate esters **8** (○) and **20** (●) in aqueous solution (μ = 0.5) at 60 °C.

Scheme III



A series of N-substituted 3- or 4-aminobenzoate esters of various hydroxyl group containing drugs (**1**–**27**) (Table I) were synthesized by esterifying the drugs with (3- or 4-chloromethyl)benzoyl chloride under normal esterification conditions and then reacting the (chloromethyl)-benzoate esters obtained with the appropriate amine in acetone, dichloromethane, or dimethylformamide solutions, in most cases in the presence of catalytic amounts of sodium iodide. In some cases, the esters were obtained by reacting the drug with the appropriate (3- or 4-aminomethyl)benzoic acid[32] in the presence of dicyclohexylcarbodiimide. The compounds, isolated as free bases, were converted to HCl or fumarate salts by standard techniques.[33] Similarly, a series of [[3- or 4-[(alkylamino)-

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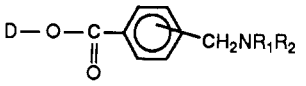
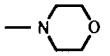
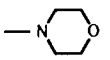
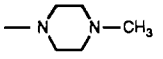
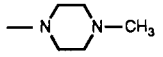
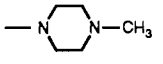
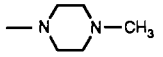
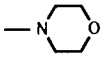
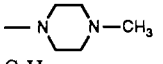
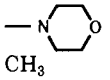
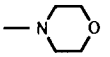
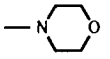
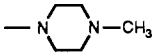
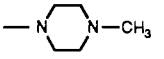
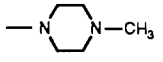
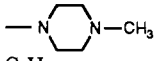
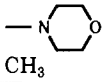
(31) Anderson, B. D.; Conradi, R. A.; Knuth, K. E. *J. Pharm. Sci.* **1985**, *74*, 365–374.
(32) Prepared by reacting (3- or 4-chloromethyl)benzoic acid with the appropriate amine in ethanol; cf. Lombardino, J. G. U.S. Pat. 4,623,486, 1986.
(33) Spectral and elemental analysis of all the compounds were consistent with their structures.

Table I. Half-Lives ($t_{1/2}$) of Hydrolysis of Various N-Substituted (Aminomethyl)benzoate Esters of Drugs Containing a Hydroxyl Group (D–OH) in 80% Human Plasma (pH 7.4) at 37 °C



compd	drug (D–OH)	position of $CH_2NR_1R_2$	R_1	R_2	$t_{1/2}$, min
1	hydrocortisone[a]	3	H	CH_3	25
2		3	H	C_3H_7	38
3		3	C_2H_5	C_2H_5	34
4		4	C_2H_5	C_2H_5	107
5		3	C_2H_5	$CH_2CH_2N(C_2H_5)_2$	8.0
6		3			62
7		4			92
8		3			15
9		4			147
10	prednisolone[a]	3			18
11	methylprednisolone[a]	3			29
12		3	CH_3	$CH_2CH_2N(CH_3)_2$	18
13	acyclovir	4			3.7
14	chloramphenicol[b]	3			5.0
15		3	C_2H_5	$CH_2CH_2N(C_2H_5)_2$	0.9
16		3	C_2H_5	C_2H_5	8.0
17		3			55
18	metronidazole	4	CH_3	CH_3	4.7
19		3			5.0
20		4			0.4
21		3			0.6
22		4			2.4
23	paracetamol (acetaminophen)	3			27
24		4			487
25		3	C_2H_5	$CH_2CH_2N(C_2H_5)_2$	15
26		3			56
27		4	CH_3	CH_3	87

[a] Ester formed at the C-21 position. [b] Ester formed at the C-3 position.

methyl]benzoyl]oxy]methyl derivatives of various NH-acidic compounds (**28–41**) (Table II) were prepared by reacting the corresponding *N*-hydroxymethyl derivative, obtained by treating the drug with formaldehyde as described previously,[34-37] in an analogous manner.

The kinetics of hydrolysis of the esters was determined in aqueous buffer solutions of various pH values as well as in freshly prepared human plasma solutions. The rates of hydrolysis were followed by reversed-phase HPLC methods[38] capable of separating the esters and their products of hydrolysis. At constant pH and temperature the hydrolysis followed strict first-order kinetics. The pH–rate profiles for the esters were U-shaped as illustrated in Figure 1 for two esters, indicating the occurrence of specific acid and base catalysis as well as a water-catalyzed reaction. Maximal stability generally occurs in the pH range 3–5. By performing stability studies at these pH

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(35) Sloan, K. B.; Bodor, N. *Int. J. Pharm.* **1982**, *12*, 299–313.
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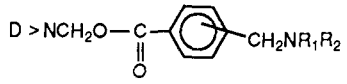
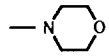
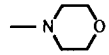
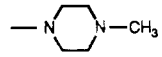
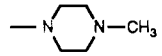
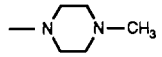
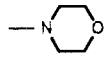
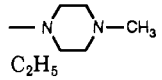
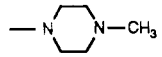
(37) Varma, R. S.; Nobles, L. *J. Pharm. Sci.* **1968**, *57*, 39–44.

(38) A supelcosil LC-8DB column (33 × 4.6 mm) was eluted with mixtures of 0.1% H_3PO_4, methanol, and acetonitrile. Occasionally, triethylamine was added to the eluent in a concentration of 10^{-4} M in order to improve peak shape. The column effluent was monitored spectrophotometrically at an appropriate wavelength.

Table II. Half-Lives ($t_{1/2}$) of Hydrolysis of Various N-Substituted *N*-[[[(Aminomethyl)benzoyl]oxy]methyl] Derivatives of Drugs Containing an NH-Acidic Group in 80% Human Plasma (pH 7.4) at 37 °C



compd	drug[a] (D>NH)	position of $CH_2NR_1R_2$	R_1	R_2	$t_{1/2}$, min
28	allopurinol (1)	4	CH_3	CH_3	9.4
29		4			1.9
30		3			8.5
31		4			11
32		3			0.5
33		3			3.6
34	theophylline (7)	3	C_2H_5	C_2H_5	0.4
35		3			0.4
36		3			2.8
37		3			0.9
38	phenytoin (3)	3	C_2H_5	C_2H_5	20
39		3			7
40	chlorzoxazone (3)	3	C_2H_5	C_2H_5	28
41		3			1.9

[a] The number in parentheses refers to the position of NH derivatization.

values at different temperatures (50–80 °C) and using the Arrhenius equation, shelf-lives (i.e. the time for 10% degradation) at normal storage temperatures were predicted. For example, the hydrocortisone ester **8** was predicted to possess a shelf-life in aqueous solution of pH 4.0 of 6 years at 25 °C whereas the metronidazole esters **20** and **21** showed predicted shelf-lives of 14 and 12 years, respectively, at the same conditions. As was shown in a comparative stability study of these metronidazole esters and metronidazole benzoate, the (aminomethyl)benzoate esters possess almost the same stability characteristics as the plain unsubstituted benzoic acid ester. Whereas no intramolecular catalytic effect of the amino group occurs in the (3- and 4-aminomethyl)benzoate esters, such an effect may certainly occur in (2-aminomethyl)benzoate esters[39] and such esters are therefore not considered as useful prodrugs.

An interesting feature of the (aminomethyl)benzoate esters with regard to providing highly stable aqueous solutions is the solubilizing capacity of the compounds for their parent drugs. Thus, whereas the solubility of hydrocortisone in water is 0.40 mg mL^{-1} at 21 °C, the solubility was found to be increased to 3.5 mg mL^{-1} in a 10% w/v solution of the ester **8** (dihydrochloride salt). This behavior, which has been observed before with other

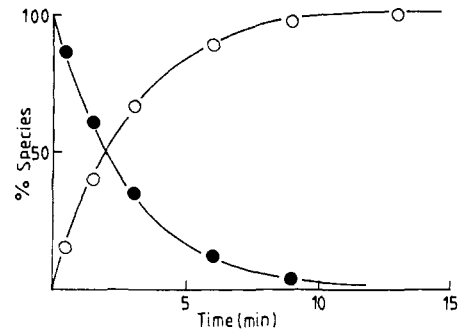


Figure 2. Time courses for 1-[[[4-(morpholinomethyl)-benzoyl]oxy]methyl]allopurinol (**29**) (●) and allopurinol (○) during hydrolysis of the prodrug derivative in 80% human plasma at 37 °C. The initial prodrug concentration was 10^{-4} M.

water-soluble prodrugs,[20,27,40] greatly prolongs the shelf-life of aqueous prodrug solutions in cases where the shelf-life is limited by precipitation of parent drug formed upon hydrolysis rather than loss in prodrug.

The various ester derivatives investigated were found to be cleaved quantitatively to the parent drugs in human plasma solutions at 37 °C. An example is shown in Figure 2. The observed half-lives of hydrolysis in 80% plasma solutions at 37 °C are given in Tables I and II. As can be seen from the data, the derivatives are readily converted to the parent drugs at conditions similar to those prevailing in vivo. In the absence of plasma, i.e. in a pH 7.4 phosphate buffer at 37 °C, half-lives exceeding 200–400 h were generally obtained, thus demonstrating the high catalytic effect by plasma enzymes. This was further supported by the finding that when the plasma was preheated to 80 °C for 2 h, less than 5% degradation of the esters took place following incubation for 24 h. As expected the structure of the alcohol moiety of the esters (i.e. the parent drug) has an influence on the enzymatic hydrolysis. The data also show that the structure of the amino group as well as the position of the aminomethyl group relative to the ester moiety have an influence on the rate of the plasma-catalyzed hydrolysis. These influences appear to be unpredictable from drug to drug, cf. for example the much greater reactivity of the ester **23** relative to the parasubstituted ester **24** and, conversely, the greater reactivity of the para-substituted (morpholinomethyl)benzoate ester **20** relative to the meta-substituted ester **19**. In all cases studied, however, it is readily feasible to select an ester prodrug with a rapid rate of hydrolysis in plasma, which is a desirable feature for prodrugs designed to overcome solubility problems in formulating intravenous injection solutions.[41]

The water solubility of the compounds shown in Tables I and II was determined by rotating mixtures of excess amounts of the compounds (as hydrochloride or fumarate salts) in water for 24–28 h and analyzing an aliquot of the

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(40) Anderson, B. D.; Conradi, R. A.; Knuth, K. E.; Nail, S. L. *J. Pharm. Sci.* **1985**, *74*, 375–381.

(41) Evidently, to the full evaluation of the esters as prodrug candidates belongs an assessment of the safety of the promoieties. The unsubstituted 4-(aminomethyl)benzoic acid has long been used as an antifibrinolytic agent.[42] However, N-substituted 4-(aminomethyl)benzoic acids such as 4-(*N,N*-dimethylaminomethyl)benzoic acid are devoid of any antifibrinolytic effect or trypsin-inhibiting effect.[43]

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filtered saturated solutions. The solubilities were generally found to exceed 10% w/v.

In addition to be useful for parenteral or ophthalmic administration the novel prodrugs may be applied to improve the peroral or rectal bioavailability of slightly water-soluble drugs. Thus, whereas allopurinol and acyclovir are both highly nonlipophilic compounds with log P values[44] of −0.55 and −1.47, respectively, and also poorly soluble in water (0.5 mg mL^{-1} for allopurinol and 1.2 mg mL^{-1} for acyclovir) prodrug derivatives of the present type with both increased lipophilicity and solubility can readily be designed as exemplified with the derivatives **29** (log P = 1.13), **31** (log P = 0.53), **32** (log P = 0.97), and **13** (log P = −0.05). It is apparent that the lipophilicity of the prodrug derivatives can be readily modified or controlled by the appropriate selection of the amino group both in terms of amine basicity,[45] and hence degree of ionization at physiological pH, and in terms of hydrophobicity of the substituents on the nitrogen atom. Indeed, preliminary experiments in rabbits have shown that the allopurinol prodrugs **29** and **32** are much better absorbed than allopurinol itself upon rectal administration.

In conclusion, N-substituted (3- or 4-aminomethyl)benzoate esters are shown to be a potentially useful biolabile and solution-stable prodrug type for drugs containing hydroxyl groups or NH-acidic groups, in the latter case with the corresponding N-hydroxymethyl or, in general, N-(α-hydroxylalkyl) derivatives as a synthetic "handle". The esters are highly water soluble at pH 1–6 and combine a high stability in weakly acidic aqueous solution with a rapid rate of hydrolysis in plasma.

(44) P is the partition coefficient between octanol and 0.05 M phosphate buffer of pH 7.4.

(45) For example, (morpholinomethyl)benzoate esters possess pK_a values of 6.0–6.1 at 25 °C whereas (*N,N*-dimethylaminomethyl)benzoate esters have pK_a values around 7.8 as determined by titration.

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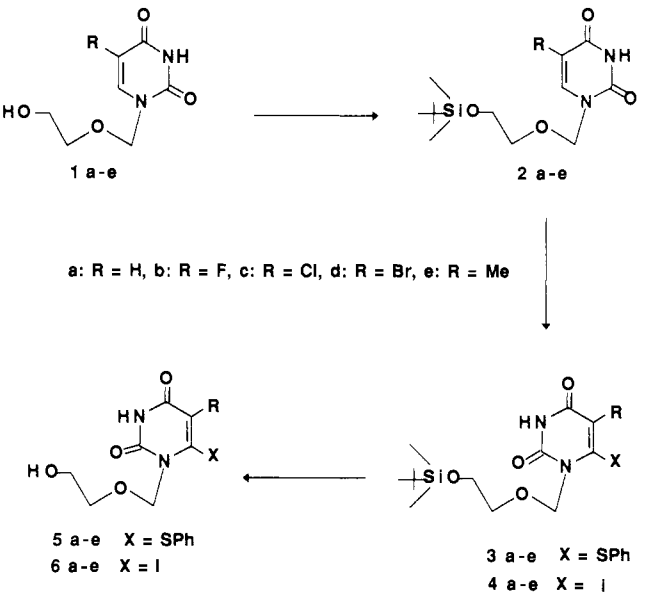
A Novel Lead for Specific Anti-HIV-1 Agents: 1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine

Sir:

As a result of the clinical efficacy of 3′-azido-3′-deoxythymidine (AZT, retrovir) in the treatment of AIDS (acquired immunodeficiency syndrome),[1-3] a large number of nucleoside analogues,[4-17] including acyclonucleosides,[18-20]

Scheme I



have been synthesized and evaluated as potential drug candidates against this disease.

Base-modified pyrimidine nucleoside analogues, so far synthesized in the above context,[13-17] have always been substituted at the C-5 position, presumably because of the ease of substitution at this position. Consequently, to the best of our knowledge, no information seems to be available concerning the anti-HIV (human immunodeficiency virus) activity of C-6 substituted derivatives.

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