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Synthesis of Prodrugs and a Mutual Prodrug of Chlorzoxazone and Acetaminophen Based on a Masked Benzoxazolone

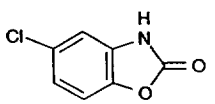
Alain Vigroux and Michel Bergon *

Laboratoire de Synthèse et Physicochimie Organique associé au CNRS - Université Paul Sabatier
118 route de Narbonne - 31062 Toulouse Cedex (France)

Abstract: A series of alkyl and aryl N-(5-chloro-2-hydroxyphenyl)carbamates, prodrugs of chlorzoxazone, have been synthesized. The synthesis in a five-step process of one of them, 4-acetamidophenyl ester, a mutual prodrug of chlorzoxazone and acetaminophen, is described.

The prodrug approach has been developed to improve drug delivery by optimization of the biopharmaceutical and pharmacokinetics properties of a drug substance.[1] The fact that esterases are widespread in the human organism and are very efficient in hydrolyzing various esters has lead to a large scale use of prodrug esters for drugs containing carboxyl or hydroxyl functions.[2,3]

Recently, carbamates obtained by carbamylation of nucleophile groups NH_2 and OH have been used in order to increase the lipophilicity of β-blockers [4] or to diminish the first-pass effects against (-)-3-(3-hydroxyphenyl)-N-propylpiperidine.[5] Chlorzoxazone (5-chloro-2(3H)-benzoxazolone) **1** is a centrally active skeletal muscle relaxant[6] whilst acetaminophen (N-acetyl-p-aminophenol) **2** exhibits analgesic properties. Owing to their synergistic effects, these two drugs can be prescribed together.[6]



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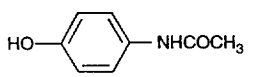

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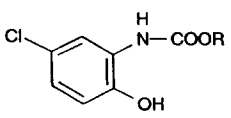
We report here the synthesis of a series of alkyl and aryl N-(5-chloro-2-hydroxyphenyl)carbamates **3** as prodrugs of chlorzoxazone. One of them, 4-acetamidophenyl ester **4**, can be considered as the first example of a mutual prodrug of chlorzoxazone and acetaminophen.



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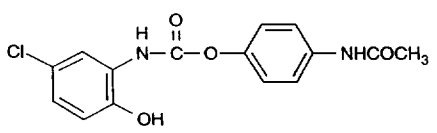
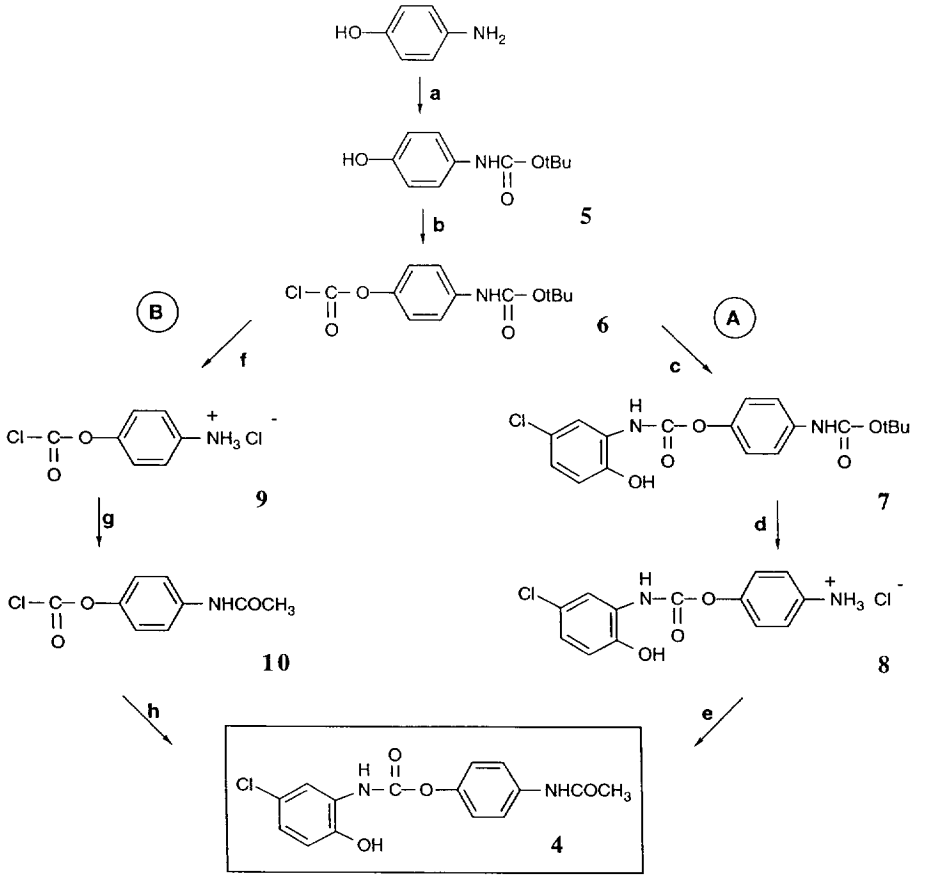


4

Condensation of 5-chloro-2-hydroxyaniline on alkyl and aryl chlorocarbonates, commercial or synthesized by action of phosgene[7] (or its substitution derivatives, diphosgene and triphosgene)[8] on the corresponding alcohols or phenols, affords a series of carbamates 5-Cl-2-$OHC_6H_3NHCOOR$ **3** (R = C_2H_5, CH_3, CH_2CH_2Cl, $CH_2C{\equiv}CCH_3$, $CH_2C{\equiv}CH$, CH_2CHCl_2, CH_2CCl_3, CH_2CF_3 and XC_6H_5 with X = H, 3-AcNH, 3-Cl, 3-CF_3).[9] To obtain **4**, this route needs the preparation of 4-acetamidophenyl chlorocarbonate not described in the literature. Direct synthesis of this chlorocarbonate was unsuccessful because the amide function is more reactive against phosgene than the phenol group. Indeed, by addition of an excess of phosgene to 4-hydroxyacetanilide dissolved in THF, a yellow iminium salt precipitated and disappeared when N,N-dimethylaniline was added. Then, according to a von Braun reaction, this intermediate adduct thermally decomposed to p-chlorophenol and acetonitrile which has been identified from the νC≡N vibration at 2300 cm^{-1} by IR spectroscopy.[10]

Therefore, synthesis of **4** was achieved in a five-step process as depicted in scheme 1.



Scheme 1 : (**a**) $(Boc)_2O$, THF, r.t., 24 h, 93%; (**b**) $COCl_2$, DMA, AcOEt, 0-5°C, 2 h, 93%; (**c**) 5-chloro-2-hydroxyaniline 2 eq, reflux in ether, 4 h, 85%; (**d**) HCOOH, HCl 1M in THF, r.t., 24 h, 84%; (**e**) Ac_2O 2 eq., pyridine 5 eq., THF, r.t., 15 min, 76%; (**f**) HCl gas, THF, r.t., 4 h, 95%; (**g**) CH_3COCl large excess, THF, r.t., 4 h, 86%; (**h**) same conditions as (**c**), 80%.

First, protection of the amine group of 4-aminophenol by the t-butoxycarbonyl group (Boc) using di-t-butyl dicarbonate in THF gave t-butyl N-(4-hydroxyphenyl)carbamate **5**. Phosgenation of **5** afforded 4-(t-butoxycarbonylaminophenyl) chlorocarbonate **6**. Deprotection of the amine group can be carried out in acidic media at different stages of the synthesis of **4** according to pathways A and B.

Pathway, A involving condensation between 5-chloro-2-hydroxyaniline and chlorocarbonate **6**, gave the bis-carbamate **7** followed by removal of the Boc group with formic and hydrochloric acids to produce 4-aminophenyl N-(5-chloro-2-hydroxyphenyl)carbamate **8**. Finally, the mutual prodrug **4** was obtained by acetylation of **8** using acetic anhydride with pyridine as catalyst. The reaction sequence was reversed in pathway B, i.e. deprotection preceded condensation. So, 4-aminophenyl chlorocarbonate **9** was first obtained as stable HCl salt then acetylated with acetyl chloride in THF to give 4-acetamidophenyl chlorocarbonate **10**. Further condensation of **10** in ether with the appropriately substituted aniline afforded **4**. It should be noted that every step of scheme 1 was characterized by good yields and **4** was obtained in a overall yield of 47% and 57% for pathways A and B, respectively.[11]

Over the pH range 5-12 and under physiological conditions of pH and temperature (phosphate buffer 7.4 and 37°C) as well as in plasma, prodrugs **3**, from an intramolecular nucleophilic attack of the ionized hydroxyl group on the carbamate function followed by elimination of the leaving group RO^-, release chlorzoxazone whilst **4** regenerates simultaneously and quantitatively chlorzoxazone and acetaminophen. Liberation of the two drugs was confirmed, under the same experimental conditions, by comparison of the UV spectrum of the products of **4** with that of a synthetic mixture of **1** and **2** and by the capacity factor k' values of the substances released in plasma from **4** with those obtained for **1** and **2** (**1**: k' = 1.86 and **2**: k' = 0.12, HPLC reverse phase Waters μ Bondapak C_{18} and eluant methanol/pH 4 buffer with elution gradient).

Kinetic studies were carried out to examine the effect of the basicity of the leaving groups RO^- upon the release rate of chlorzoxazone from prodrugs **3** including **4**. Cyclization half-lives $t_{1/2}$ of prodrugs **3** are collected in Table 1.

Table 1: Kinetic Data of Release of Chlorzoxazone from Prodrugs **3** and **4**

	$t_{1/2}$, s (37° C)		
R	7.4 Phosphate buffer	plasma pH 7.4	
		Human	Rat
CH_2CH_2Cl	78 320		
$CH_2C{\equiv}C\text{-}CH_3$	33 990		
$CH_2\text{-}C{\equiv}CH$	6 509		
CH_2CHCl_2	2 546	6 305	3 225
CH_2CCl_3	192	605	450
CH_2CF_3	155		
C_6H_5	12		
$3\text{-}AcNHC_6H_4$	7.5		
$4\text{-}AcNHC_6H_4$ (**4**)	7.1; 36[a]	66[a]	50[a]
$3\text{-}ClC_6H_4$	3.8		
$3\text{-}CF_3C_6H_4$	3.1		

a) $t_{1/2}$ values measured at 25 °C

Brönsted-type relationship log $t_{1/2}$ *vs* pKa of ROH, the conjugated acid of the leaving group, for prodrugs shows a break and allows to divide them among two groups. Indeed, aryl and trifluoroethyl N-(5-chloro-2-hydroxyphenyl)carbamates cyclize to **1** according to eq 1: log $t_{1/2}$ = 0.46 pKa - 3.60 (r = 0.996, s = 0.01, n = 6) whilst alkyl derivatives possess a higher sensitivity leading to eq 2: log $t_{1/2}$ = 1.46 pKa - 16.03 (r = 0.988, s = 0.12, n = 5). Hydrolysis half-live $t_{1/2}$ for trichloroethyl carbamate lies on the intersecting point of the two Brönsted lines. Half-lives values for ethyl and methyl derivatives extrapolated from eq 2 are equal respectively to 290 and 73 days. These results put forward that the rate of cyclization of prodrugs **3** to chlorzoxazone is strongly dependent on the pKa of ROH.

In human and rat plasma, the rate of liberation of chlorzoxazone is decreased by a factor ~ 2.5. These results show that the formation of chlorzoxazone is slightly dependent on the presence of enzymes. This is consistent with a preeminent chemical regeneration of the drug as was observed with similar drug delivery systems involving cyclization mechanisms.[12,13,14]

Exploration of a more direct route to **4** and derivatization of the hydroxyl group of prodrugs **3** and **4** to modulate their physicochemical properties according to the pro-prodrug approach[15] are now in progress.

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9. Compounds **3** were characterized by IR, ^1H, ^{13}C NMR spectrometry and elemental analysis (± 0.4% of the theoretical values).
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11. (a) The structures of compounds **5-10** were determined by IR, ^1H, ^{13}C NMR spectrometry and elemental analysis (± 0.4% of the theoretical values). (b) Analytical data for **4**: $C_{15}H_{13}ClN_2O_4$, Elemental analysis: Calculated %: C, 56.17; H, 4.09; N, 8.73; Found %: C, 55.92; H, 4.09; N, 8.51. m.p. = 194 °C; R_f 0.36 (AcOEt); UV (EtOH) λ_{max} 289 nm (log ε 3.81), 247 (4.43); IR (KBr): 3400 et 3327 (νN-H carbamate and amide), 3400-3200 (νOH), 1724 (νC=O carbamate), 1647 (νC=O amide), 1605 (νC=C aromatics), 1529 et 1502 cm^{-1} (νNH-CO); ^1H NMR (DMSO d6, 250 MHz) δ: 2.04 (d, 3H, CH_3), 6.87 (d, 1H, ArH, J = 8.63 Hz), 7.00 (dd, 1H, ArH, J = 8.63 et 2.6 Hz), 7.13 (d, 2H, ArH, J = 8.95 Hz), 7.60 (d, 2H, ArH, J = 8.95 Hz), 7.64 (d, 1H, ArH, J = 2.6 Hz), 9.08 (s, 1H, OH), 9.99 (s, 1H, NH), 10.15 (s, 1H, NH); ^{13}C NMR (DMSO d_6, 62.90 Hz) δ: 23.84 (CH_3), 116.38; 119.69; 121.90; 122.07; 124.05; 126.75; 136.59; 145.69; 147.38 (ArC); 152.21 (C=O carbamate); 166.12 (C=O amide).
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