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STUDY OF *BIS*CARBAMATES DERIVED FROM 2-AMINOBENZYLAMINES AS MODELS FOR ALCOHOL PRODRUGS

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Abstract: Unsubstituted N-arylcarbamate of title compound does not cyclize to the corresponding cyclic urea, with ROH liberation, under mild conditions (40°C). Substitution of the benzylic position by two methyl groups promotes slow cyclisation while N-methylation of the N-aryl carbamate has a more important effect. Relative cyclisation rates are in agreement with barrier heights obtained from *ab initio* calculations. The calculations also suggest that the highest cyclisation rate of the latter is a consequence of the steric hindrance caused by the N-methyl substituent. © 1999 Elsevier Science Ltd. All rights reserved.

The efficiency of cancer chemotherapy is mainly limited by the lack of selectivity of cytotoxic agents for cancer cells. In order to avoid this drawback the use of non-toxic prodrugs, converted to the corresponding drug by an enzyme which is either targeted (ADEPT protocol)¹ or present in higher concentration in necrotic areas (*i.e.* β -glucuronidase), is an area of great current interest.^{2,3} The required plasma stability of the prodrug rules out esters or carbonates as connecting groups between the active moiety and the enzyme substrate. Thus carbamates have been mainly studied, but few known anticancer agents have an amino group for this purpose (doxorubicin, mitomycin C,...) and thus it seems worthwhile to explore new approaches to prepare prodrugs linked to an hydroxyl, a more ubiquitous group among these drugs.

We now propose a *bis*carbamate structure such as A (Scheme 1). Cleavage of the first carbamate may be carried out as for amine prodrugs (eventually after a first spacer decomposition) and decarboxylation of the resulting carbamic acid should give aminocarbamate **B** which may then cyclize to cyclic urea **C** with elimination of Drug-OH.



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0040-4020/99/\$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved. PII: S0040-4020(99)00139-8 The spacer group X should be designed to induce fast decomposition of **B** under physiological conditions. Recently, a related approach has been published by Monneret⁴ using the cyclisation of a phenol with an *ortho*-substituted carbamate (a process studied earlier by Hutchins⁵ and Vigroux and Bergon⁶), thereby liberating a phenolic nitrogen mustard. Scheeren⁷ and Haisma³ have proposed a strategy based on the hydrolysis of a carbamate to generate an amine followed by an attempted internal nucleophilic displacement of another amine from an amide moiety. However no cyclisation was observed after carbamate hydrolysis with an aliphatic or an *ortho*-substituted benzyl spacer.³

These observations led us to study the preparation and behavior of model *bis*carbamates derived from substituted 2-aminobenzylamines. Key features of such structures are the presence of two structurally different amines and possible nitrogen, ring and benzyl substitutions for steric or electronic control.^{8,9} These model studies were carried out with diamines 1-3 (Scheme 2).



Reagents and conditions: *i*: BnOCOOpNO₂Ph, Et₃N; *ii*: R₁OCOCl. pyridine; *iii*: H₂, 10% Pd/C. EtOH; *iv*: CH₂Cl₂, 20-40°C. Scheme 2

The novel amine 2 was prepared from 2-aminobenzonitrile and MeMgI (6 eq.) by extension of the procedure of Laurent (in 59% yield as its hydrochloride salt)¹⁰ and, amine 3¹¹ was prepared by reduction (H₂, Pd/C, AcOH) of N-methyl-2-aminobenzonitrile. Condensation of benzyl *para*-nitrophenyl carbonate¹² with 1-3,

respectively, afforded the *mono*carbamates 4-6 (60%, except for 5: 25%) which upon treatment with either (-)menthyl chloroformate or ethyl chloroformate¹³ gave *bis*carbamates 7-9 (80-85%). Hydrogenolysis (10% Pd/C, EtOH, 20°C, 20-60 min) of the benzyl group afforded amines 10-11a,b from *bis*carbamates 7-8a,b in over 95% yield.

No cyclization was observed in CH_2Cl_2 or EtOH from 10 after 48 h at rt or after 24 h at 40°C (10 was recovered unchanged). Slow cyclization of 11a,b to 13^{14} was observed at 40°C in CH_2Cl_2 (11/13 ratio: 3/2 after 20 h). Hydrogenolysis of 9 as above (1 h) gave a mixture of the expected amine 12 and the cyclized urea 14^{14} (2/1 to 2/3 ratio depending on experiments).¹⁵ Cyclization of 12 to 14 (93% overall yield from 9) was completed in 6.5 h at 40°C in CH_2Cl_2 . Indeed, as expected, cyclization was found to proceed more rapidly under protic conditions : 12 was converted to 14 in EtOH/ 0.02M phosphate buffer (pH 4.5 and pH 7, 37°C) in 0.5 h.¹⁶

These results show that cyclization is induced by substitution at the benzylic position and more rapidly by N-methylation of the aromatic amine. The latter effect has been observed in the cyclization of a phenol with an *ortho*-substituted carbamate by Hutchins (although at high pH) and a conformational effect was tentatively proposed. To obtain a deepened understanding of the factors controlling the rates of cyclization (step iv in Scheme 2), we have performed *ab initio* calculations¹⁷ on model reactions. From our experiments, these rates appear R- and R'- sensitive but R₁- nonsensitive. Thus, we have studied these cyclizations using 15, 16 and 17 as model reactants respectively for 10, 11 and 12 (figure 1).



Figure 1

Table 1. 15-, 16- and 17-Cyclisation transition structures. Energetics and key geometrical parameters.

Transition	RHF/3-21G ^(a)	B3LYP/6-31G*	N-C ^(c)	N-H ^(c)	O–H ^(c)	C-O(c)
Structure		//RHF /3-21G ^{(a) (b)}				
15-TS	-602.985953(60.7)	-610.062711(55.2)	1.602	1.231	1.329	1.357
16-TS	-680.631071(58.1)	-688.689088(52.8)	1.587	1.230	1.333	1.359
17-TS	-641.798277(52.6)	-649.365355(48.5)	1.592	1.232	1.334	1.358

(a) Energies in hartrees (Barrier heights in kcal/mol are indicated in parentheses).

(b) Density-functional energy calculations on RHF/3-21G geometries.

(c) Distances in Å. N, C, H and O atoms are those involved in the four center transition structures.

The transition structures (TS) were located at the RHF/3-21G level. The energetics and some geometrical parameters are reported in Table 1.

The examination of these TS reveals that the cyclization and the hydrogen migration are concerted (Figure 2). Such four-center transition states in carbonyl additions have already been obtained from *ab initio* calculations.¹⁸ The barrier heights are slightly reduced upon including electron correlation at the density-functional B3LYP/6-31G* level of calculation,¹⁹ but they remain in the same order. The calculated barrier heights are in good agreement with the experimental observations under aprotic conditions : the cyclization of 12 was complete in 6.5 h whereas 10 did not cyclize in 24 h.



Figure 2 : 15 TS (Atoms : N : light grey ; O : grey ; C,H : white)

The predicted 8 kcal/mol difference in barrier heights is consistent with experimental observation regarding reactivity. The barrier to cyclization of 16 is intermediate in comparison with 15 and 17. Thus, it would be expected that the rate of cyclization of 11 would also be intermediate. The 40% cyclization of 11 after 20 h supports this analysis. The satisfying agreement between the relative *ab initio* barrier heights and the experimentally observed rates is probably related to the fact that these experiments were conducted in an aprotic solvent (CH₂Cl₂). The examination of some key geometrical parameters (Table 1) show that the three TS are very similar. Therefore, the differences in the calculated barrier heights should originate in the reactant structures. The Φ_1 , Φ_2 and Φ_3 torsion angles as defined in Figure 1 are expected to be key geometrical parameters for the reactants. Their values for the lowest energy conformer for each reactant are reported in Table 2.

Reactant	RHF/3-21G ^(a)	B3LYP/6-31G*	${f \Phi_1}^{(c)}$	$\Phi_2^{(c)}$	$\Phi_3^{(c)}$
		//RHF /3-21G ^{(a) (b)}			
15	-603.082603	-610.150713	53.6	168.4	-1.8
16	680.723576	-688.773284	46.5	170.2	-1.9
17	-641.882168	649.442610	90.9	-80.1	4.7

Table 2. 15, 16 and 17 model reactants. Energetics and geometrical parameters.

(a) Energies in hartrees.

(b) Density-functional energy calculations on RHF/3-21G geometries.

(c) Torsions angles in degrees.

A significant difference appears between 17 ($\Phi_2 = -80.1^\circ$) and 15 and 16 ($\Phi_2 \approx 170^\circ$). The reason is probably the steric hindrance caused by the N-methyl group in 17. Then, the conjugation between the benzenic

ring and the carbamate group in 15 and 16 no longer holds in 17 (Figure 3).²⁰ This effect induces a relative destabilisation of 17.²¹ Since the geometries of the TS's are very similar (Table 1), this explains the corresponding lower barrier height. This barrier height is indeed lower than the corresponding 15 and 16 barrier heights by 8 and 5.4 kcal/mol respectively.



Figure 3

In conclusion, the liberation of an alcohol species from a *bis*carbamate after initial cleavage of the benzylic carbamate group is possible under mild conditions using compounds such as 12. Introduction of an N-alkyl group on the aromatic amine appears essential for mild cyclization. Thus, for example, it is anticipated that formation of the benzylic amino group following glucuronide hydrolysis (the glycoside may be directly connected via a carbamate group³ or via a suitable self-immolative spacer^{22,23}) should result in ROH liberation. Further studies are underway.

Experimental section

Melting points are uncorrected. ¹H NMR and ¹³C NMR were recorded on a 300 MHz (Bruker Advance DPX300) spectrometer with TMS as internal standard. High resolution MS were performed by the "Service Central de Microanalyse" (CNRS, Lyon). Organic extract mixtures were dried over anhydrous MgSO₄, filtered and the solvent was then removed under reduced pressure. All separations were done under flash chromatography conditions on silica gel (Matrex, 25-40 mµ) and thin layer chromatography (TLC) were performed on silica gel plates (Merck, 60GF₂₅₄).

2-(1-Amino-1-methylethyl)aniline (2). A solution of CH_3MgBr (50 mL, 3 M in Et_2O) was introduced in 80 mL of toluene at reflux. 2-Aminobenzonitrile (22.3 mmol) was then added and the reaction mixture was stirred at reflux for 3 h. Toluene was removed (rotavapor) and the residue was diluted with a saturated aqueous solution of sodium carbonate. The mixture was extracted with CH_2Cl_2 . The residue was acidified with a solution of EtOH/HCl (5/0.8; v/v) to obtain the hydrochloride salt. After evaporation of the solvents under reduced pressure, dilution with MeOH and filtration of insoluble material, CH_2Cl_2 was added until the

hydrochloride salt precipitated as an oil. Yield : 59%; gum;¹H NMR (CD₃SOCD₃) δ (ppm) : 1.69 (s, 6 H), 6.72 (dd, 1H, J 7.5 Hz), 6.90 (d, 1 H, J 7.5 Hz), 7.08 (dd, 1 H, J 7.5 Hz), 7.16 (d, 1 H, J 7.5 Hz); ¹³C NMR (CD₃SOCD₃) δ (ppm) : 25.8, 56.0, 118.4, 120.0, 125.7, 127.2, 128.8, 144.7; HRMS: C₉H₁₄N₂ calculated: 150.1157, found: 150.1174.

General method for the synthesis of monocarbamates 4-6.

To a solution of substituted 2-aminobenzylamine (1-3) in DMF (3 mL/mmol) was added benzyl paranitrophenyl carbonate (0.5 eq) and triethylamine (1.5 eq). The reaction mixture was stirred at room temperature for 12 h under nitrogen atmosphere. The solvent was removed and the residue dissolved in CH_2Cl_2 . A saturated aqueous solution of sodium carbonate was added and the organic layer was dried over MgSO₄ and concentrated *in vacuo* to afford the crude *mono*carbamate. Purification was done by flashchromatography using ethyl acetate/petroleum ether.

Benzyl N-(2-aminobenzyl)carbamate (4). Yield : 60%; mp 74 °C; ¹H NMR (CDCl₃) δ (ppm) : 4.17 (broad s, 2 H), 4.30 (d, 2 H, *J* 6.0 Hz), 5.05 (broad s, 1 H), 5.12 (s, 2 H), 6.66 to 6.70 (m, 2 H), 7.02 to 7.13 (m, 2 H), 7.35 (s, 5 H); ¹³C NMR (CDCl₃) δ (ppm) : 42.7, 67.0, 116.0, 118.2, 122.0, 128.1, 128.2, 128.5, 129.0, 130.0, 137.2, 145.2, 157.0; FABHR: C₁₅H₁₆N₂O₂ MH⁺calculated: 257.1290, MH⁺found: 257.1283.

Benzyl N-(1-(2-aminophenyl)-1-methylethyl)carbamate (5). Yield 25%; oil; ¹H NMR (CDCl₃) δ (ppm) : 1.71 (s, 1 H), 1.50 (broad s, 2 H), 5.01 (s, 2 H), 5.23 (broad s, 1 H), 6.59 (d, 1 H, J 7.8 Hz), 6.73 (dd, 1 H, J 7.8 Hz), 7.05 (dd, 1 H, J 7.8 Hz), 7.21 (d, 1 H, J 7.8 Hz), 7.28 (s, 5 H); ¹³C NMR (CDCl₃) δ (ppm) : 27.0, 55.9, 66.7, 115.6, 117.8, 118.6, 126.4 to 128.9, 136.1, 144.1, 162.6; HRMS: C₁₇H₂₀N₂O₂ calculated: 284.1525, found: 284.1515.

Benzyl N-(2-(methylamino)benzyl)carbamate (6). Yield 60%; oil; ¹H NMR (CDCl₃) δ (ppm) : 2.81 (s, 3 H), 4.28 (d, 2 H, *J* 6.1 Hz), 4.68 (broad s, 1 H), 4.99 (broad s, 1 H), 5.12 (s, 2 H), 6.60 to 6.66 (m, 2 H), 7.02 (d, 1 H, *J* 7.3 Hz), 7.20 (dd, 1 H, *J* 7.5 Hz), 7.35 (s, 5 H); ¹³C NMR (CDCl₃) δ (ppm) : 30.4, 42.7, 67.0, 109.8, 116.1, 122.4, 128.0, 128.1, 128.6, 129.5, 130.1, 136.4, 147.6, 157.1; HRMS: C₁₆H₁₈N₂O₂ calculated: 270.1368, found: 270.1350.

General method of preparation of biscarbamates 7-9.

To a solution of *mono*carbamate (4-6) in DMF (5 mL/mmol) was added ethyl chloroformate or menthyl chloroformate (1.3 eq) and pyridine (10 eq). After stirring for 2 h, at room temperature, under nitrogen atmosphere, the solvent was removed and the residue dissolved in CH_2Cl_2 . After successive washings with a

solution of HCl (0.1 N) and water, the organic layer was dried over MgSO₄ and concentrated *in vacuo* to afford the crude *biscarbamate* which was purified by flash column using ethyl acetate/petroleum ether.

Menthyl N-(2-(benzyloxycarbonylamino)benzyl)carbamate (7). Yield : 80%; mp 98 °C; ¹H NMR (CDCl₃) δ (ppm) : 0.83 (d, 3 H, J 7.1 Hz), 0.91 (d, 6 H, J 7.1 Hz), 1.00 to 2.20 (m, 9 H), 4.30 (d, 2 H, J 6.1 Hz), 4.67 (td, 1 H, J 10.8 and 4.3 Hz), 5.12 (s, 2 H), 5.29 (broad s, 1 H), 7.04 (dd, 1 H, J 8.0 Hz), 7.18 (d, 1 H, J 8.0 Hz), 7.29 (dd, 1 H, J 8.0 Hz), 7.33 (s, 5 H), 7.88 (d, 1 H, J 8.0 Hz), 8.08 (broad s, 1 H); ¹³C NMR (CDCl₃) δ (ppm) : 16.8, 20.8, 22.1, 24.0, 26.7, 31.6, 34.5, 41.5, 42.1, 47.4, 67.3, 75.4, 122.8, 124.2, 128.2, 128.3, 128.6, 128.9, 130.1, 136.4, 136.8, 154.5, 157.1; FABHR: C₂₆H₃₄N₂O₄ MH⁺calculated: 439.2599, MH⁺found: 439.2610.

Menthyl N-(2-(1-benzyloxycarbonylamino-1-methylethyl)phenyl)carbamate (8a). Yield 85%; oil; ¹H NMR (CDCl₃) δ (ppm) : 0.80 (d, 3 H, J 7.1 Hz), 0.91 (d, 6 H, J 7.1 Hz), 1.70 (s, 6 H), 1.00 to 2.20 (m, 9 H), 4.67 (td, 1 H, J 10.8 and 4.3 Hz), 5.00 (s, 2 H), 5.12 (s, 1 H), 7.06 (dd, 1 H, J 7.6 Hz), 7.19 to 7.35 (m, 7 H), 7.71 (broad s, 1 H), 7.86 (d, 1 H, J 7.6 Hz); ¹³C NMR (CDCl₃) δ (ppm) : 16.6, 20.7, 22.1, 23.7, 26.5, 27.9, 31.4, 34.3, 41.3, 47.1, 55.6, 66.8, 75.1, 123.9, 125.9, 126.1, 127.7 to 128.7, 135.7, 136.0, 153.7, 155.3; HRMS: C₂₈H₃₈N₂O₄ calculated: 466.2832, found: 466.2826.

Ethyl N-(2-(1-benzyloxycarbonylamino-1-methylethyl)phenyl)carbamate (8b). Yield 85%; oil; ¹H NMR (CDCl₃) δ (ppm) : 1.28 (t, 3 H, J 7.1 Hz), 1.70 (s, 6 H), 4.19 (q, 2 H, J 7.1 Hz), 5.01 (s, 2 H), 5.13 (s, 1 H), 7.06 (dd, 1 H, J 7.9 Hz), 7.20 to 7.36 (m, 7 H), 7.80 (broad s, 1 H), 7.86 (d, 1 H, J 7.9 Hz); ¹³C NMR (CDCl₃) δ (ppm) : 14.7, 28.0, 55.6, 61.2, 66.8, 123.9, 125.9, 126.1, 127.7 to 128.7, 135.6, 136.0, 153.9, 155.3; HRMS: C₂₀H₂₄N₂O₄ calculated: 356.1737, found: 356.1736.

Ethyl N-(2-(benzyloxycarbonylamino)benzyl)-N-methylcarbamate (9). Yield 81%; oil; ¹H NMR (CDCl₃) δ (ppm) : 1.11 and 1.30 (2 broad s, 3 H), 3.21 (s, 3 H), 4.00 to 4.70 (m, 4 H), 5.12 (s, 2 H), 7.10 to 7.45 (m, 9 H); ¹³C NMR (CDCl₃) δ (ppm) : 14.8, 37.8, 41.1, 61.9, 66.6, 126.0 to 130.0, 135.7, 137.0, 155.6, 156.5; HRMS: C₁₉H₂₂N₂O₄ calculated: 342.1580, found: 342.1582.

General procedure of hydrogenolysis.

Biscarbamates 7-9 were diluted in EtOH (40 mL/mmol) with a catalytic amount of 10% Pd/C. The reaction mixture was stirred at room temperature under a hydrogen atmosphere until total hydrogenolysis of the benzyl group (20-60 min) was completed. After filtration of the catalyst, EtOH was removed and the residue dissolved in CH_2Cl_2 . The cyclisation rate was followed by TLC and ¹H NMR.

Menthyl N-(2-(aminomethyl)phenyl)carbamate (10). Yield 100%; oil; ¹H NMR (CDCl₃) δ (ppm) : 0.83 (d, 3 H, J 7.1 Hz), 0.91 (d, 6 H, J 7.1 Hz), 1.00 to 2.20 (m, 9 H), 3.97 (s, 2 H), 4.67 (td, 1 H, J 10.8-4.3 Hz), 6.94 (dd, 1 H, J 8.0 Hz), 7.08 (d, 1 H, J 8.0 Hz), 7.27 (dd, 1 H, J 8.0 Hz), 8.03 (d, 1 H, J 8.0 Hz), 9.76 (broad s, 1 H); ¹³C NMR (CDCl₃) δ (ppm) : 16.8, 20.8, 22.1, 24.0, 26.7, 31.6, 34.5, 41.5, 45.7, 47.4, 74.8, 120.3, 122.5, 125.2, 128.3, 128.9, 139.1, 154.0; HRMS: C₁₈H₂₈N₂O₂ calculated: 304.2151, found: 304.2143.

Menthyl N-(2-(1-amino-1-methylethyl)phenyl)carbamate (11a). Yield 100%; oil; ¹H NMR (CDCl₃) δ (ppm) : 0.82 (d, 3 H, J 7.0 Hz), 0.91 (d, 6 H, J 7.2 Hz), 1.70 (d, 6 H, J 8.3 Hz), 1.00 to 2.20 (m, 9 H), 4.67 (td, 1H, J 10.9 and 4.3 Hz), 6.96 (dd, 1 H, J 8.3 Hz), 7.22 to 7.27 (m, 2 H), 8.06 (d, 1 H, J 8.3 Hz), 11.30 (broad s, 1 H); ¹³C NMR (CDCl₃) δ (ppm) : 16.8, 20.7, 22.1, 23.9, 26.6, 31.5, 32.2, 34.4, 41.5, 47.3, 53.6, 74.3, 121.2, 122.3, 125.8, 127.9, 134.0, 138.7, 153.9; HRMS: C₂₀H₃₂N₂O₂ calculated: 332.2464, found: 332.2450.

Ethyl N-(2-(1-amino-1-methylethyl)phenyl)carbamate (11b). Yield 100%; oil; ¹H NMR (CDCl₃) δ (ppm) : 1.32 (t, 3 H, J 7.1 Hz), 1.56 (s, 6 H), 4.22 (q, 2 H, J 7.1 Hz), 6.96 (m, 1 H), 7.22 to 7.27 (m, 2 H), 8.08 (d, 1H, J 8.2 Hz), 11.43 (broad s, 1H); ¹³C NMR (CDCl₃) δ (ppm) : 14.8, 31.8, 53.7, 60.6, 120.8, 122.2, 125.8, 127.9, 133.8, 138.6, 154.0; HRMS: C₁₂H₁₈N₂O₂ calculated: 222.1368, found: 222.1364.

4,4-Dimethyl-1,2,3,4-tetrahydro-2-quinazolinone (13). Yield : 27% from 11b (recovered starting material : 33%); mp 148 °C (mp_{Litt}^{14} 161°C); ¹H NMR (CDCl₃) δ (ppm) : 1.56 (s, 6 H); 5.41 (broad s, 1 H); 6.75 (d, 1 H, *J* 7.8 Hz); 6.98 (dd, 1 H, *J* 7.8 Hz); 7.14 to 7.19 (m, 2 H); 8.12 (broad s, 1H); ¹³C NMR (CDCl₃) δ (ppm) : 31.2, 54.7, 114.4, 122.5, 123.9, 126.9, 128.2, 135.3, 154.6; HRMS: C₁₀H₁₂N₂O calculated: 176.0950, found: 176.0951.

1-Methyl-1,2,3,4-tetrahydro-2-quinazolinone (14). Yield : 93% from 9 (one pot); mp 134 °C (mp_{Lint}¹¹ 143°C); ¹H NMR (CDCl₃) δ (ppm) : 3.30 (s, 3 H), 4.43 (s, 2 H), 5.92 (broad s, 1 H), 6.87 (d, 1 H, *J* 7.0 Hz), 6.98 (dd, 1 H, *J* 7.0 Hz), 7.04 (d, 1 H, *J* 7.0 Hz), 7.25 (dd, 1 H, *J* 7.0 Hz); ¹³C NMR (CDCl₃) δ (ppm) : 29.6, 43.0, 112.9, 120.4, 122.0, 125.6, 128.1, 139.5, 156.2; HRMS: C₉H₁₀N₂O calculated: 162.0793, found: 162.0793.

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- 12. These were chosen as representative secondary and primary alcohols.
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- 14. Reaction with the corresponding chloroformate was not selective.
- 15. Slower debenzylation was observed with ethyl acetate as solvent (2 h). Under these conditions only 14 was isolated from the reaction mixture.
- 16. Cyclisation was followed by HPLC : reverse phase column : Zorbax, 5 μ ODS, 25 x 4.6 mm); eluent : 1/1 acetonitrile/0.02 M phosphate buffer (pH 4.5 or 7), UV detection at 486 nm. Retention time: 12: 14.7 min; 14 : 5.2 min.

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