STUDIA UNIVERSITATIS BABEŞ-BOLYAI, CHEMIA, L, 1, 2005

SYNTHESIS AND STRUCTURE ASSIGNMENT OF SOME NEW ALKYL-(10H-PHENOTHIAZIN-3-YL)-CARBONATES

RADU GROPEANU,[a] TEODORA PANEA,[b] IOAN PANEA[a]

a: Organic Chemistry Department, Faculty of Chemistry and Chemical Engineering, Babes-Bolyai University,11th Arany Janos st., 400028 Cluj-Napoca, Romania
b: Research and Production Centre "BIOS", Academy of Agricultural and Forest Sciences, OP1 CP2, Cluj-Napoca, Romania

ABSTRACT. By acylation with alkyl chloroformate **1** of six N(10)-unsubstituted- (**2a-c,e,g,h**) and two N(10)-methyl substituted- (**5a,b**) 3-hydroxy-10H-phenothiazine derivatives eight new alkyl-(10H-Phenothiazin-3-yl)-carbonates (**4a-c,e,g,h,7a,b**) were synthesized. Two carbonates **7e,f** were obtained by 5,5-dioxidation with peroxybenzoic acid. The structural assignments were made on the basis of chemical and spectral methods, and by a study of the derivatization effects (acylation, methylation and 5,5-dioxidation effect) on the chemical shifts of the phenothiazine protons.

Keywords: 3-hydroxy-10H-phenothiazines, Selective O-alkoxycarbonylation; Derivatization effect on ^{1}H-NMR chemical shifts.

INTRODUCTION

Some carbamates, derivatives of phenothiazine, are drugs[1] or exhibit other biological actions, respectively are intermediates for such compounds.[2-7] It is claimed[3,5b] that several of these have been synthesized by N-acylation with alkyl chloroformates of the corresponding 10-unsubstituted 10H-phenothiazines, including derivatives of 3-hydroxy-10H-phenothiazine. At the same time it was shown [5b] that some 3-hydroxy-10H phenothiazines and theirs 5,5-dioxides, as well as different acylation products of these, exhibit therapeutic actions. All these have prompted us to investigate the monoacylation with alkyl chloroformates **1** of some 3-hydroxy-10H-phenothiazines (**2a-h**). As it is known[8] the alkyl chloroformates are acylation agents that act as acyl chlorides, introducing thus the alkoxycarbonyl group (COOR) into a substrate.

The 3-hydroxy-10H-phenothiazines **2a-h** have two acylable groups, namely a phenolic type –OH group (in position 3) and a secondary aromatic amine (the bridging NH, position 10). Consequently, the monoacylation of **2a-h** with **1** may take place, like to the few other previously [1b,5b,9] acylated 3-hydroxy-10H-phenothiazines, either at N(10)H or at 3-OH, leading to carbamates **3** or/and to alkyl (10H-phenothiazin-3-yl) carbonates **4**.

Therefore we have attempted a selective monoacylation of **2a-h** by two procedures ("a" or "b", see Experimental) that would should lead one ("a") to N-acyl derivatives **3a-h** and the other ("b") to O-acyl derivatives**4a-h**. Indeed, previously it was claimed that the "a" procedure leads to N-acylation.[5] Otherwise, owing to the *p*-amino-phenol nature[10] of the 3-hydroxy-10H-phenothiazines **2a-h** it was expected that theirs monoacylation to occur at aromatic type N(10)H group, since in amino phenols the amino group reacts with acyl chlorides prior to the phenolic group.[8,11] The

"b" procedure correspond to the Schotten-Baumann conditions when the acylation should take place at the phenolate anion (3-O^-) that is more reactive as nucleophile[8] comparative to the secondary aromatic amine type NH[12,13] from phenothiazine heterocycle. Otherwise, for such acylations of the 3-hydroxy-phenothiazines carried out previously[9] it is claimed the obtainment of O-acylderivatives. Consequently, the goal of this work is the selective obtainment of monoacylation products from some 3-hydroxy-10H-phenothiazine derivatives **2a-h** and alkylchloroformates **1**, as well as the determination of N- (**3**) or O- (**4**) acyl derivatives nature of these. With the aim to make this determination reliable it was attempted also the monoacylation of some 3-hydroxy-10H-phenothiazines protected by N- (**5a,b**) or O- (**6c,d**) methylation. The possible structure corresponding to the studied transformations are presented in Scheme 1.

EXPERIMENTAL

The starting materials (**2a-h**), were prepared as previously described.[14-17] The melting points were determined on a Kleinfold Apotek apparatus and are uncorrected. Elemental analyses for the acylation products isolated by us were carried out at the Chemistry and Pharmaceutical Research Institute Cluj-Napoca, and the obtained data correspond satisfactorily to the assigned monoacylation products structures.

The IR spectra were recorded with a JASCO 615 FT-IR spectrometer in KBr pellets, as dispersion in Nujol or as film. Mass spectra were performed using a Matt 3.11 spectrometer using electron impact technique. The NMR spectra were recorded using a Varian Gemini 300 (300 MHz) spectrometer and hexadeuterated dimethylsulfoxide (DMSO–d_6) or deuterochloroform ($CDCl_3$) as solvent, at room temperature. The chemical shifts are related to tetramethylsilane and the signal of the solvent was the internal standard. The NMR data were obtained directly from the spectra. A combination of the chemical shifts, multiplicities and integration data obtained in the case of each spectrum has allowed us the assignment of the present signals to the individual types of protons characteristic to the corresponding 10H-phenothiazine derivative (Table 1, 2). This assignment has been facilitated by a) the existence of very good analyses on the ^{1}H-NMR spectra of the 10H-phenothiazine itself and of some derivatives of this;[1c, 17-22] b) the fact that the two benzene rings of the phenothiazine system can be considered[1c,20] independent of each other, being possible the analysis of the spectra as sum of the quasi-first order subspectra of the two marginal benzene rings; c) the simplification of the spectra brought by the substitution in the phenothiazine system; d) the known effects of the substituents (OH, OCH_3, Cl, Br)[23] and the derivatization (O-acylation, N- or O- methylation)[1c,23] on the chemical shift of the protons from the system in which has been introduced the substituent, respectively is present the derivatized group.

General procedures for the preparation of alkyl (10-H-phenothiazin-3-yl) carbonates 4a-h:

Procedure "a"

The 3-hydroxy–10–H–phenothiazine derivative (**2a**-**h**) was refluxed with alkylchloroformate (**3**) in THF for 20 hours, in the conditions described in some patents.[5] By column chromatography (silica gel, petroleum ether : ethyl acetate = 5:1), we could isolate each time only the alkoxycarbonylation product at the 3-hydroxy-

group (**4a**-**h**), but only in very low yields. The most of the starting 3-hydroxy–10–H–phenothiazine derivative has been recovered unchanged.

Procedure "b"

To 10^{-3} Mol 3-hydroxy-10H-phenothiazine derivative (**2a**-**h**) dissolved in 50 mL isopropanol were added 70 mg ($1.2 \cdot 10^{-3}$ Mol) KOH and the mixture was refluxed for 5 minutes; after cooling down to room temperature, 1 mL ($9 \cdot 10^{-3}$ Mol) ethyl- or methyl-chloroformate (**3**) was added. The precipitate which appeared in 5-10 minutes was filtered of, washed with isopropanol and crystallized from benzene or toluene.

Some characteristics of the carbonates **4a-h** are presented in Tables 1 and 2. The reported yields (Table 1) are referring to the *Procedure "b"*.

General procedure for the methylation of 3-hydroxy-10H-phenothiazines (2a-d)

A mixture of 0.01 Mol 3-hydroxy-10H-phenothiazine derivative, 1 g potassium carbonate, 2 mL methyl iodide and 50 mL DMF was stirred at room temperature. After 2 hours potassium carbonate (1 gram) and methyl iodide (2 mL) were added, followed by two other such additions at two hours intervals. The stirring of the mixture is continued over the night. Next day the reaction mixture was poured into 100 mL water and was extracted with 3×25 mL ethyl acetate. The organic layer was washed twice with water, dried over anhydrous sodium sulfate and the solvent removed in vacuum. The residue was purified by column chromatography (silica gel, petroleum ether:ethyl acetate=5:1). This procedure is similar to that indicated[5] for the O- methylation of the 3-hydroxy-10H-phenothiazine derivatives.

As we shown (see results and discussion) the methylation by this procedure of the 3-hydroxy-10H-phenothiazines (**2a**-**d**) has furnished the O-methylated derivatives (**6c**,**d**) only for **2c**,**d** while in the case of **2a**,**b** the corresponding N(10)-methyl derivatives (**5a**,**b**) were isolated. Some ^{1}H-NMR data for **6c**,**d** and **5a**,**b** are presented in Table 2.

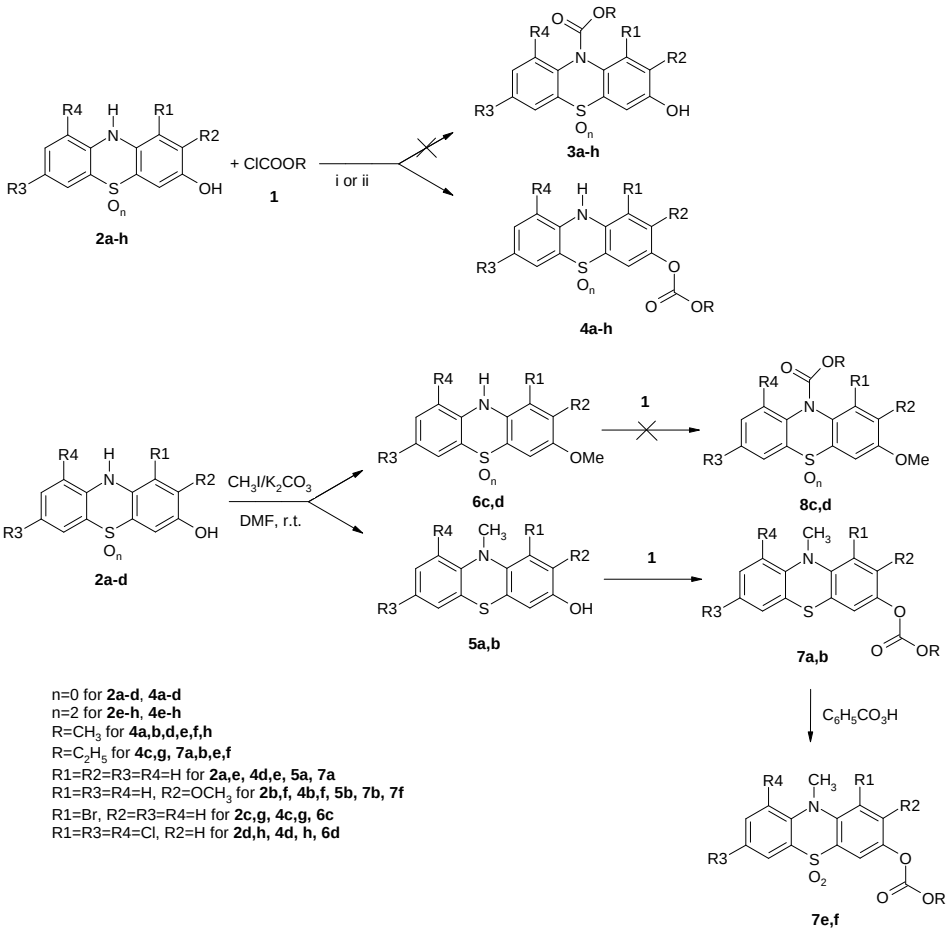
Procedure for the preparation of ethyl [N(10- methyl-10H-phenothiazin-3-yl] carbonates 7a,b[9c]

To a solution of 10^{-3} Mol N(10)-methyl-3-hydroxy-10H-phenothiazine derivative (**5a**,**b**) in 20 mL pyridine was added dropwise and under vigorous stirring 1 mL ($9 \cdot 10^{-3}$ Mol) ethylchloroformate and the solution was stirred at 20-50°C for 1 hour. After cooling down, the solution was poured over 100 mL water and ice and was extracted with 3×25 mL ethyl acetate; the organic layer was dried over anhydrous sodium sulfate, the solvent was removed in vacuum and the residue was purified by column chromatography on silica gel and eluting with petroleum ether: ethyl acetate (5:1). Some characteristics of **7a**,**b** are presented in Tables 1,2.

Procedure for the S,S-dioxidation[18] of ethyl [N(10)-methyl–10–H–phenothiazin-3-yl] carbonates 7a,b

To a solution of 10^{-3} Mol **7a**,**b** in 20 mL 1,4-dioxane was added dropwise 2 mL 7% chloroform solution of peroxybenzoic acid and stirred over night; next day the solution was poured onto 100 mL 2% aqueous $NaHCO_3$ solution and extracted

with 3×25 mL ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent removed in vacuum. The residue was crystallized from petroleum ether: methylene chloride (5:1). Some characteristics of the obtained dioxides **7e**,**f** are presented in Tables 1 and 2.



Scheme 1. Conditions: i: THF, reflux; ii: KOH, 2-propanol.

RESULTS AND DISCUSSION

The isolated acylation products, their yields and some characteristic properties of these are presented in Table 1. As is shown in Experimental part, the expectations for the obtainment of two different monoacylation products from each 3-hydroxy-10H-phenothiazine derivatives **2a-h** namely of the N- (**3**, by "a" procedure) and of the O- (**4**, by "b" procedure) monoacyl derivative, respectively, have not been confirmed. The acylation product isolated by us from the resulted mixture in the reaction of each 3-hydroxy-10H-phenothiazine **2a-h** with a certain chloroformate,

in both experienced procedures ("a" or "b") has been the same. Anyway, the acylation in the examined conditions has been selective. In addition the mass and NMR spectra (Tables 1,2) have proved that each acylation product isolated by us is a monoacyl derivative. Thus, e.g., in ^{1}H-NMR spectrum in DMSO-d_6 of the acylation product **4a** (prepared from **2a** and methyl chloroformate) appears (Table 1) one singlet due to three protons that was absent in the spectrum of the starting **2a**. The chemical shift of this singlet (3.79 ppm) is characteristic[19,24,25] for the methoxycarbonyl group. On the other hand, in the same ^{1}H-NMR spectrum of the **4a** appears only one singlet due to a sole exchangeable hydrogen atom (NH or OH) at 8.68 ppm, whilst in spectrum of **2a** were two such singlets (8.27 and 9.05 ppm). These data are compatible only with a a monoacyl derivative nature of **4a**. This is also confirmed by the ^{13}C-NMR spectrum of **4a** that presents 14 signals corresponding to 14 unequivalent carbon atoms, exactly the number of the carbon atoms in **4a**. Among these signals, only one corresponds to a sp^3 hybridized carbon (55.37 ppm) with a chemical shift characteristic to the methoxy group C-atom from methoxycarbonyl group.[24]

Table 1.

Some physical-chemical data of the synthesized alkyl-(10H-phenothiazin-3-yl)-carbonates

Compd.	m.p. (℃)	yield (%)	^{1}H-NMR data* for substituents				$\nu_{C=O}$ (cm^{-1})	MS
			3-OCOO-*alkyl*	N^{10}-CH_3	2-OCH_3	Solvent		
4a	188-9	73	CH_3: 3.79; s; 3H	-	-	DMSO-d_6	1769	273; 60
4b	128-30	64	CH_3: 3.78; s; 3H	-	3.72	DMSO-d_6	1768	303; 100
4c	80-2	81	CH_3-CH_2: 1.38; t; 3H; J=7.08; 4.31; q; 2H	-	-	$CDCl_3$	1759	-
4e	216-8	71	CH_3: 3.85; s; 3H	-	-	DMSO-d_6	1759	305; 5
4g	143-5	68	CH_3-CH_2: 1.42; t; 3H; J=7.14; 4.36; q; 2H	-	-	$CDCl_3$	1761	-
4h	181-2	74	CH_3: 3.87; s; 3H	-	-	DMSO-d_6	1769	407; 03
7a	72-3	73	CH_3-CH_2: 1.29; t; 3H; J=7.08; 4.26; q; 2H	3.28; s; 3H	-	DMSO-d_6	1761	-
7b	134-5	64	CH_3-CH_2: 1.26; t; 3H; J=7.0; 4.20; q; 2H	3.35; s; 3H	3.82	DMSO-d_6	1760	-
7e	149-50	67	CH_3-CH_2: 1.29; t; 3H; J=7.08; 4.26; q; 2H	3.73; s; 3H	-	DMSO-d_6	1760	-
7f	181-2	61	CH_3-CH_2: 1.29; t; 3H; J=7.08; 4.25; q; 2H	3.77; s; 3H	4.00	DMSO-d_6	1757	-

* There are presented the chemical shift (δ, ppm), the multiplicity (s=singlet, d=doublet, t=triplet, q=quartet) and the coupling constant (J, Hz)

The O-acyl derivative nature of our acylation products **4a-h** was established especially on the basis of the comparative analysis of the ^{1}H-NMR data for each pair starting 3-hydroxy-10H-phenothiazine derivative and its acylated product. Thus the effects caused by the introduction of the alkoxycarbonyl group on the chemical shifts of the protons from phenothiazine core in each 3-hydroxy-10H-phenothiazine derivative **2a-h** have been assigned. The use of these effects for the determination

of N- or O- derivative nature of the acylation products takes into account the known fact that the N-acylation (at position 10) causes [2d,21] a significant and relative constant (~ 0.5 ppm) deshielding of each proton (H^1-H^9) from both benzene rings of each 10-acylated 10H-phenothiazine, as compared with the correspondent proton in the starting compound. For the same goal it was taken into account also the fact that the O-acylation at the 3-OH group of some 3-hydroxy-10H-phenothiazines determines[18] a significant deshielding (0.17-0.37 ppm) only of the protons (H^1, H^2, H^4) from the benzene ring that contains the 3-O-acylated group. The deshielding for the protons (H^6-H^9) of the other benzene ring is much lower (0.06-0.1 ppm). Consequently the manifestation manner (alike or differently) and the size (significant or unsignificant) of the deshielding of the protons from two benzene ring of each previously N(10)-[2d,21] or O-[18] acylated phenothiazine derivative is a function of the N- or O- acyl derivative nature of this. The mentioned deshielding of the protons express the difference ($\Delta\delta_i$) between chemical shifts of two protons located in the same position (i), one in the acylated derivative ($\delta_{i\text{-}a}$) and the other in the starting 3-hydroxy-10H-phenothiazine ($\delta_{i\text{-}u}$). Such a deshielding effect ($\Delta\delta_i$) is called often "acylation shift".[23,26] Just the evaluation of the acylation shift of the aromatic protons in the acylated products isolated by us proves the O-acyl derivative nature of the products **4a-h**. Indeed, the evaluated acylation shifts ($\Delta\delta_i$, Table 2) have a significant size (0.11-0.77 ppm) only for the protons (H^1, H^2, H^4) of the OH-substituted benzene ring. The acylation shifts of the protons H^6-H^9 from the other benzene is much lower (0.00-0.10 ppm). These results are compatible only with a 3-O-acyl derivative nature of the acylation products.

Table 2.

The ^{1}H-NMR chemical shifts (δ_i)[a] in the different type of 10H-phenotiazine derivatives and the effect of the derivatization on the ^{1}H chemical shifts ($\Delta\delta_i$)[b]

Compounds / The significa-tion of the $\Delta\delta i$	The ^{1}H-chemical shifts (δ_i) and the $\Delta\delta_i$ values, for the 10-H-phenothiazine hydrogens in the following positions:								Other hydrogens/ Type of derivatization
	1	2	4	6	7	8	9	10	
2a	6.54	6.43	6.89	6.92	6.70	6.96	8.65	8.27	3-OH : 9.05
4a	6.68	6.85	6.87	6.92	6.77	7.00	6.68	8.68	3-$OCOOCH_3$: 3.79
$\Delta\delta i=\delta i_{4a}-\delta i_{2a}$	0.14	0.42	0.49	0.03	0.07	0.04	0.03	0.41	3-O-acylation
2b	6.39	-	6.39	6.90	6.70	6.96	6.64	8.26	2-OCH_3 : 3.69 3-OH : 8.60
4b	6.50	-	6.85	6.93	6.78	7.01	6.69	8.70	2-OCH_3 : 3.72 3-$OCOOCH_3$: 3.78
$\Delta\delta i=\delta i_{4b}-\delta i_{2b}$	0.11	-	0.46	0.03	0.08	0.05	0.05	0.44	3-O-acylation
2c	-	6.79	6.53	7.00	6.86	7.04	6.66	6.31	3-OH: 4.52
6c	-	6.83	6.59	7.01	6.86	7.04	6.66	6.32	3-OCH_3: 3.73
$\Delta\delta i=\delta i_{6c}-\delta i_{2c}$	-	0.04	0.06	0.01	0.00	0.00	0.00	0.01	3-O-methylation
2h	-	7.37	7.37	8.20	-	8.07	-	8.59	3-OH: 10.34
4h	-	8.14	8.05	8.30	-	8.14	-	8.93	3-$OCOOCH_3$: 3.87
$\Delta\delta i=\delta i_{4h}-\delta i_{2h}$	-	0.77	0.68	0.10	-	0.07	-	0.34	3-O-acylation
5a	6.78	6.63	6.60	7.12	6.91	7.19	6.90	-	N(10)-CH_3: 3.23 3-OH: 9.26
$\Delta\delta i=\delta i_{5a}-\delta i_{2a}$	0.24	0.20	0.22	0.23	0.21	0.23	0.25	-	N(10)-methylation

Compounds / The significa-tion of the Δδi	The ^{1}H-chemical shifts (δ_i) and the $\Delta\delta_i$ values, for the 10-H-phenothiazine hydrogens in the following positions:								Other hydrogens/ Type of derivatization
	1	2	4	6	7	8	9	10	
7a[C]	6.94	7.06	7.09	7.15	6.96	7.22	6.93	-	N(10)-CH_3: 3.28
$\Delta\delta i=\delta i_{7a}-\delta i_{5a}$	0.16	0.43	0.49	0.03	0.05	0.03	0.03	-	O-acylation
7e[C]	7.61	7.66	7.89	7.99	7.37	7.77	7.64	-	N(10)-CH_3: 3.73
$\Delta\delta i=\delta i_{7e}-\delta i_{7a}$	0.67	0.60	0.80	0.84	0.41	0.55	0.71	-	5,5-dioxidation
7b[C]	6.69	-	7.05	7.16	6.97	7.23	6.98	-	N(10)-CH_3: 3.73 2-OCH_3: 3.83
7f[C]	7.13	-	7.82	7.96	7.37	7.76	7.62	-	N(10)-CH_3: 3.77 2-OCH_3: 4.00
$\Delta\delta i=\delta i_{7f}-\delta i_{7b}$	0.44	-	0.77	0.80	0.40	0.53	0.64	-	5,5-dioxidation

a) The ^{1}NMR spectra of the compounds **2a**, **2b**, **2h**, **4a**, **4b**, **4e**, **4h**, **5a**, **7a**, **7e**, **7f** were recorded in DMSO-d_6 and those of **2c** and **6c** in $CDCl_3$.

b) (Δδi) represent the derivatization effect through functionalization on the chemical shift of the protons of the phenothiazine heterocycle. It express the difference between the chemical shifts (δi) of the corresponding protons (i) in the derivatized (δi_d) and the starting (δi_s) 3-hydroxy-10H-phenothiazine derivative.

c) See Table 1 for the ^{1}H-NMR data of the ethoxycarbonyloxy group in the corresponding compound.

Such a determination of the N- or O-acyl derivative nature should be more precise in the case of the acylation products obtained from 3-hydroxy-10H-phenothiazines protected by N- (**5a,b**) or O- (**6c,d**) methylation. Therefore, we have methylated some 3-hydroxy-10H-phenothiazine derivatives in conditions that are claimed [5] to lead to O-methylation. The ^{1}H-NMR spectra of the isolated methylation products have shown that only the products obtained from **2c,d** are 3-O-methyl derivatives (**6c,d**), while those from **2a,b** are N(10)-methyl derivatives. The N(10)-methyl derivative nature of **5a,b** is proved by the chemical shifts of the methyl group protons that have practically the same values (3.25 ppm in DMSO-d_6, respectively 3.36 ppm in $CDCl_3$) with those of the methyl group in other 10-methyl-10H-phenothiazines[1c,e,19,27] and correspond to the chemical shifts range of the N-CH_3 protons (3-3.5 ppm).[28] The 10-methyl derivative structure of **5a,b** is confirmed by a significant and relative constant deshielding of all of the aromatic protons (~0.25 ppm, Table 2) comparative to the correspondent protons in the starting **2a,b**, since it is known[1f] that N-methylation of 10H-phenothiazines determines such a deshielding. Similarly, the 3-methoxy-10H-phenothiazine derivative nature of **6c,d** is proved by the chemical shift values of their methyl group protons (3.73 ppm, in $CDCl_3$, Table 2). This value corresponds to the chemical shift range of the OCH_3 group protons (3.5-4 ppm)[23a,24,28] and was found[1c,f,22] in other 3-methoxy-10H-phenothiazines. The unsignificant values of the deshielding effect for the aromatic protons in this case confirm the 3-methoxy derivative structure of **6c,d** since it is known[23a] that the derivatization of the phenolic 3-OH to 3-OCH_3 has a very low effect on the chemical shift of the protons in the afferent benzene ring.

The acylation of **5a,b** with ethyl chloroformate may lead only to the O-acylated products **7a,b**. In accordance with this, the ^{1}H-NMR spectra of **7a,b** show the presence of the N-CH_3 group by a singlet at 3.30 ppm and the corresponding acylation shifts ($\Delta\delta_i$) are significant (up to 0.5 ppm) only for the protons of 3-OH substituted benzene ring (Table 1,2). So is undoubtfully confirmed that the acylation at the group situated unsymmetrical with respect to the two benzene rings of a 10H-phenothiazine derivative (3-OH, in our case) determines significant acylation shifts only for the protons of the benzene ring in which is located the acylated group.

The carbonate structures of the products **7a,b** is confirmed by their ^{13}C-NMR spectra. Thus, in both spectra of these compounds appears a signal (35.3 ppm) corresponding to a N-CH_3 group[28b,29] inclusively in 10-methyl phenothiazine.[1g] In addition, in each ^{13}C-NMR spectrum of **7a,b** appear another two signals (65 and 14 ppm) corresponding to the ethoxycarbonyl group introduced by acylation of **5a,b**.

These carbonates (**7a,b**) were converted by oxidation with peroxybenzoic acid into the corresponding 5,5-dioxides **7e,f**. The sulfone structure of the oxidation products was confirmed by the NMR spectra, in which all the aromatic protons are strong deshielded relative to the protons of the starting compounds **7a,b** (Table 2). Such strong deshielding effects were found previously[1c,h,17,18] even by derivatization through 5,5-dioxidation.

The O-acylderivative structure of all acylation products described in this paper has been confirmed also by their IR spectra, in which appear an absorption band in the range 1757-1769 cm^{-1} (Table 1) characteristic[30] for the C=O of organic carbonates.

The carbamates **3a,h** and **8c,d** could not have been isolated in the acylation conditions examined by us, even using as starting compounds the 3-methoxy derivatives **6c,d**.

CONCLUSIONS

By selective alkoxycarbonylation of some 3-hydroxy-10H-phenothiazine derivatives **2a-c,e,g,h, 5a,b** were synthesized eight new mixed alkyl (10H-phenothiazin-3-yl) carbonates **4a-c,e,g,h, 7a,b**. Two of these were transformed into the corresponding sulfones (**7a,b**) by oxidation. The structure of the synthesized compounds was established chemically and by spectral analysis. The presented data proved the utility for structure elucidation of the derivatization effects on the proton chemical shift by the N- (or O-) methylation, O-acylation or 5,5-dioxidation of 3-hydroxy-10H-phenothiazine derivatives.

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