SYNTHESIS OF SOME THEOPHYLLINE DERIVATIVES

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ABSTRACT *Eight new theophyllines derived from the methyl esters of chlorosulphonyl-aryloxyalkylcarboxylic acids, with a possible action on the vascular system have been prepared. Their structures have been elucidated by IR, ¹H- NMR and elementary analysis.*

RESUMO *Foram sintetizados oito novos derivados da teofilina a partir de ácidos clorosulfonil ariloxialquil-carboxílicos. Eles tem uma possível ação sobre o sistema vascular. As suas estruturas foram elucidadas por infravermelho, ¹H-RMN e análise elementar.*

KEYWORDS 8-substituted theophyllines, theophyllinyl-sulphonyl-phenoxyacetats, phenoxyacetic esters, esters of sulphonamidated aryloxyalkylcarboxylic acids.

INTRODUCTION

In recent years theophyllines have become particularly important among the agents for vascular diseases.

Numerous studies are to be found in the literature on theophylline derivatives that are aimed to obtain products with hypotensive or antihypertensive, vasodilatory, coronarodilatory or antiarrhythmic properties and with low toxicity¹⁻⁶.

R = various substituents

Since more selective compounds in this area are still a challenge, new theophylline derivatives continue to be synthesized and screened for their cardiovascular activities.

In the present paper we report the results of new studies obtained for some theophyllines derived from methyl chlorosulphonylphenoxyacetates, with possible hypotensive and vasodilatory actions, of low toxicity and a prolonged time of action.

RESULTS AND DISCUSSION

The method of synthesis used for obtaining the above mentioned theophylline derivatives is based on the condensation reaction of the esters of chlorosulphonyl aryloxy-carboxylic acids in acetone, in the presence of triethylamine⁷.

The reactions carried out are shown below. The aryloxyalkylcarboxylic acids were submitted successively to esterification, chlorosulphonation and condensation with theophylline⁸⁻¹³.

where: $\text{R}_1 = \text{H}, \text{CH}_3, \text{Cl}, \text{OCH}_3$;

$\text{R}_2 = \text{H}, \text{CH}_3$.

The final products have been purified by washing with acetone and hot water and recrystallization from acetic acid-water.

The theophylline derivatives obtained are solid, amorphous substances, with characteristic melting points. The compounds obtained were characterized by means of elementary analysis and IR and ¹H-NMR spectral measurements. (Table 1.)

Infrared spectra were recorded as KBr pellets using a UNICAM SP.100 apparatus (infrared spectrophotometer).

The ¹H-NMR spectra were determined with JEOL- 60 MHz spectrometer using dimethylsulfoxide as solvent.

Table 1. Theophyllines derived from methyl esters of chlorosulphonyl-phenoxyacetic acids

No	Compound	Formula	%N		M.p. °C
			calc.	found	
1.	methyl 4-teophyllinylsulphonyl phenoxyacetate	$C_{16}H_{16}N_4O_7S$	13.7	13.7	200
2.	methyl 2-cloro-4-teophyllinylsulphonyl phenoxyacetate	$C_{16}H_{15}N_4O_7ClS$	12.6	12.4	212-214
3.	methyl 4-chloro-2-teophyllinylsulphonyl phenoxyacetate	$C_{16}H_{15}N_4O_7ClS$	12.6	12.5	247-249
4.	methyl 2-methyl-4-teophyllinylsulphonyl phenoxyacetate	$C_{17}H_{18}N_4O_7S$	13.2	13.1	215-216
5.	methyl 3-methyl-4-teophyllinylsulphonyl phenoxyacetate	$C_{17}H_{18}N_4O_7S$	13.2	13.0	209-211
6.	methyl 2-methoxy-4-teophyllinylsulphonyl phenoxyacetate	$C_{17}H_{18}N_4O_8S$	12.7	12.5	170
7.	methyl 2,3-dimethyl-4-teophyllinylsulphonyl phenoxyacetate	$C_{18}H_{20}N_4O_7S$	12.8	12.47	188-190
8.	methyl 4,6-dimethyl-2-teophyllinylsulphonyl phenoxyacetate	$C_{18}H_{20}N_4O_7S$	12.8	12.6	177-178

The IR spectral analysis allowed us to reach conclusions on both the substituent positions in the aromatic ring as well as on the new bonds formed by synthesis. (Table 2.)

The main informations on the substituent position in the aromatic ring are given by the out-of-plane deformation vibration of the C-H bond. The vibration frequency is dependent on the substituent number and position and practically independent of their nature. Thus, the $\gamma_{\text{C-H}}$ absorption band within the 805 - 825 cm^{-1} range indicates the presence of two adjacent hydrogen atoms in the ring, while the deformation band of the single hydrogen is to be found within the 870-885 cm^{-1} range and is less intensive. Consequently, these two absorption bands in the IR spectrum are indicative of the 1,4-; 1,2,4-; 1,3,4-; 1,2,3,4- or 1,2,4,6- substitutions which confirm the presence of the sulphonamidated group in the position para to the ether oxygen or in the ortho position when the para is not free.

The aryloxyalkylcarboxylic derivatives have an extended conjugation between the ether oxygen, aromatic ring and sulphonamide group. As a consequence, the IR spectra show absorption bands that can be attributed to the C — S, S — N and S — O bonds.

The band of the C — S bond is to be found between 1080-1100 cm^{-1} being characteristic to all aromatic compounds containing a S atom directly bound to the ring.

The absorption bands characteristic to the S — O and S — N bonds appear within the 1020-1040 cm^{-1} and 1040-1080 cm^{-1} ranges, respectively.

The SO₂ group shows two intense bands corresponding to the symmetric and nonsymmetric vibration within the 1120-1180 cm^{-1} and 1300-1360 cm^{-1} regions, respectively.

Table 2. IR and ¹H- NMR data of the new substances.

Compound	IR (cm ⁻¹)	¹ H-NMR (ppm)
1.	1130, 1340 (SO ₂); 1735 (C=O), 1180 (C-O); 1090 (C-S) ; 1260 (C-O-C _{aryl}); 1670(CON _{amidic}); 1620(C=N); 2910(NCH ₃); 1430(CH ₂); 825(1,4-disubstituted benzene)	3.22(3H,s,CH ₃ teophylline); 3.41(3H,s,CH ₃ ester); 3.68(3H,s,CH ₃ teophylline); 4.8(2H,s,CH ₂); 6.8(2H,d,aryl); 7.6(2H,d,aryl); 8.04(1H,s,teophylline)
2.	1120,1330 (SO ₂); 1750 (C=O); 1180(C-O); 1080(C-S); 1260 (C-O-C _{aryl}); 1670(CON _{amidic}); 1610(C=N); 2900(N-CH ₃), 1440(CH ₂); 850,880(1,2,4-trisubstituted benzene)	3.24(3H,s,CH ₃ teophylline); 3.48(3H,s,CH ₃ ester); 3.78(3H,s,CH ₃ teophylline); 5.08(2H,s,CH ₂); 7.4(1H,d,aryl); 8.2(1H,d,aryl); 8.68(1H,s,teophylline)
3.	1120,1320(SO ₂); 1720(C=O); 1180(C-O); 1080(C-S); 1260(C-O-C _{aryl}); 1680(CON _{amidic}); 1610(C=N); 2900(N-CH ₃); 1430(CH ₂); 850,880(1,2,4-trisubstituted benzene)	3.2(3H,s,CH ₃ teophylline); 3.47(3H,s,CH ₃ ester); 3.76(3H,s,CH ₃ teophylline); 5.04(2H,s,CH ₂); 7.36(1H,d,aryl); 8.15(1H,d,aryl); 8.64(1H,s,teophylline)
4.	1120,1330(SO ₂); 1735(C=O); 1180(C-O); 1090(C-S); 1260(C-O-C _{aryl}); 1670(CON _{amidic}); 1610(C=N); 2900(N-CH ₃), 1450(CH ₂); 845,880(1,2,4-trisubstituted benzebe)	2.25(3H,s,CH ₃ aryl); 3.22(3H,s,CH ₃ teophylline); 3.48(3H,s,CH ₃ ester); 3.75(3H,s,CH ₃ teophylline); 4.98(2H,s,CH ₂); 7.1(1H,d,aryl); 8.02(1H,d,aryl); 8.62(1H,s,teophylline)
5.	1120,1330(SO ₂); 1730(C=O); 1180(C-O); 1090(C-S); 1260(C-O-C _{aryl}); 1670(CON _{amidic}); 1610(C=N); 2900(N-CH ₃), 1450(CH ₂)	2.3(3H,s,CH ₃ aryl); 3.25(3H,s,CH ₃ teophylline); 3.5(3H,s,CH ₃ ester); 3.8(3H,s,CH ₃ teophylline); 5.0(2H,s,CH ₂); 7.1(1H,d,aryl); 8.1(1H,d,aryl); 8.65(1H,s,teophylline)
6.	1120,1330(SO ₂); 1720(C=O); 1170(C-O); 1090(C-S); 1280(C-O-C _{aryl}); 1670(CON _{amidic}); 1610(C=N); 2900(N-CH ₃), 1445(CH ₂); 1010,2850(CH ₃ O-C _{aryl})	3.25(3H,s,CH ₃ teophylline); 3.45(3H,s,CH ₃ ester); 3.7(3H,s,CH ₃ teophylline); 3.82(3H,s,OCH ₃); 4.82(2H,s,CH ₂); 7.3(1H,d,aryl); 7.9(1H,d,aryl); 8.7(1H,s,teophylline)
7.	1130,1340(SO ₂); 1720(C=O); 1180(C-O); 1090(C-S); 1270(C-O-C _{aryl}); 1670(CON _{amidic}); 1610(C=N); 2900(N-CH ₃), 1450(CH ₂)	2.15(3H,s,CH ₃ aryl); 2.5(3H,s,CH ₃ aryl); 3.25(3H,s,CH ₃ teophylline); 3.45(3H,s,CH ₃ ester); 3.7(3H,s,CH ₃ teophylline); 4.75(2H,s,CH ₂); 6.7(1H,d,aryl); 7.65(1H,d,aryl); 8.8(1H,s,teophylline)
8.	1120,1390(SO ₂); 1730(C=O); 1190(C-O); 1080(C-S); 1260(C-O-C _{aryl}); 1680(CON _{amidic}); 1610(C=N); 2900(N-CH ₃), 1450(CH ₂)	2.18(3H,s,CH ₃ aryl); 2.5(3H,s,CH ₃ aryl); 3.22(3H,s,CH ₃ teophylline); 3.43(3H,s,CH ₃ ester); 3.7(3H,s,CH ₃ teophylline); 4.7(2H,s,CH ₂); 6.85(1H,s,aryl); 7.2(1H,s,aryl); 8.7(1H,s,teophylline)

The frequency of the C — O ether bond in the aromatic compounds is to be found between 1200-1260 cm^{-1} and the ester group shows two bands within 1735-1750 cm^{-1} and 1050-1300 cm^{-1} ranges, respectively.

The IR spectrum of the theophylline derivatives under study also show bands characteristic of the CO-N (1650-1680 cm^{-1} , 2890-2910 cm^{-1}) and C — N (1600-1620 cm^{-1}) vibration.

The ^1H -NMR spectra of the compounds show singlets at about 2.15-3.8 ppm that may be attributed to methyl protons. The CH_2 protons are seen at 4.7- 5.08 ppm as a singlet. Phenyl protons are seen at expected values. In addition the theophylline proton is seen at 8.04-8.8 ppm as a singlet. The elementary analysis of the compounds gave further support for the reported structure ^{14,15}.

EXPERIMENTAL

Methyl 4-theophyllinyl-sulphonyl phenoxyacetate

A sample of 2.645 g (0,01 mole) of the methyl ester of 4-chlorosulphonyl phenoxyacetic acid was dissolved in 30 ml acetone. Subsequently, 1.8 g (0,01 mole) theophylline and 1,5 ml triethylamine were then added. The reaction mixture was refluxed 2 hours. After filtering the product it was washed with 10 ml of acetone and 15 ml of hot water and than recrystallized from 30 ml acetic acid, washed with 15 ml methyl alcohol and dried. The pure product was finally obtained in a 75 % yield. (M.p. = 200° C).

CONCLUSIONS

Eight new theophyllines with possible hypotensive and vasodilating actions have been prepared by the reaction of some esters of chlorosulphonylaryloxyalkylcarboxylic acids with theophylline in the presence of triethylamine. The structures of the compounds obtained have been elucidated by means of elementary analysis and IR and $^1\text{H-NMR}$ spectral measurements.

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