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Short communication

Synthesis and central relaxant activity of thiophene analogs of mephenesin and methocarbamol

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Summary — The thiophene analogs of mephenesin, mephenesin carbamate and methocarbamol have been synthesized and subjected to pharmacological evaluation. Two of these compounds showed interesting muscle relaxant activity and seem worthy of further study.

Résumé — **Synthèse et activité relaxante centrale d'analogues thiophéniques de la méphénésine et du méthocarbamol.** *Les analogues thiophéniques de la méfénésine, du carbamate de méfénésine et du métocarbamol ont été synthétisés et soumis à des essais pharmacologiques. Deux de ces composés montrent une intéressante activité relaxante musculaire et semblent mériter une étude plus approfondie.*

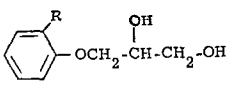
thiophene derivatives / mephenesin, mephenesin carbamate, methocarbamol (thiophene analogs) / skeletal muscle relaxants

Introduction

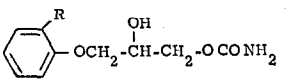
Many drugs act on the central nervous system to produce skeletal muscle relaxation as a primary or secondary pharmacological effect. Within the first category, there are relatively few drugs of different potency and, without doubt, the classic prototype is mephenesin.

The relative lack of clinical effectiveness of mephenesin has promoted intensive research in order to increase activity and/or prolong the duration of action, leading to the introduction of mephenesin carbamate and methocarbamol.

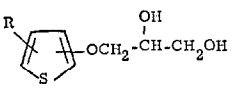
As a consequence of our interest in the thiophene analogs of useful drugs, we now describe the synthesis and a preliminary pharmacological study of the muscle relaxation properties of eight new thiophene derivatives. The glycerol ether side chain, a characteristic feature of mephenesin-like drugs, is incorporated in the suitably substituted heterocyclic ring. These compounds include the three possible thiophene analogs of mephenesin **1** (**a**—**c**), their respective carbamates **2** (**a**—**c**) and two thiophene analogs of guayaphenesin **1d** and of methocarbamol **2d**.



Mephenesin: R=CH_3
Guayaphenesin: R=OCH_3

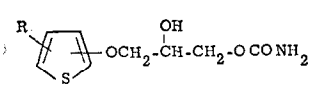


Mephenesin carbamate: R=CH_3
Methocarbamol: R=OCH_3



1

Compd	R	Chain position
1a	2-CH_3	3
1b	3-CH_3	2
1c	4-CH_3	3
1d	4-OCH_3	3

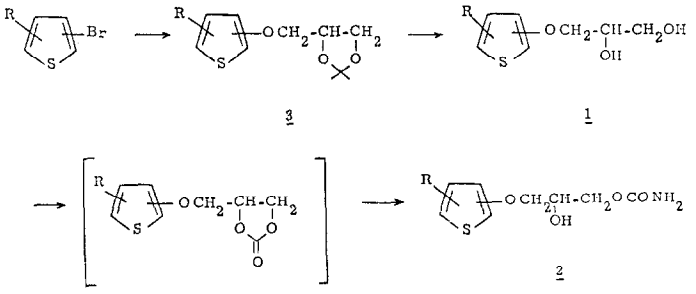


2

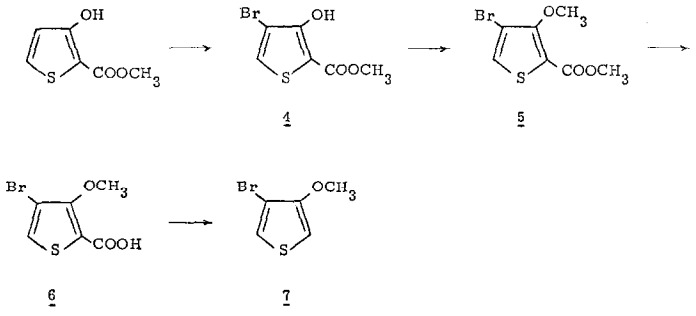
Compd	R	Chain position
2a	2-CH_3	3
2b	3-CH_3	2
2c	4-CH_3	3
2d	4-OCH_3	3

Chemistry

In a recent paper [1], we described the synthesis of compounds **1** (**a**—**c**) as intermediates in the reaction sequence of the preparation of thienyloxypropanolamine β-adrenergic blockers. The same procedure (Scheme 1) has now been extended to the synthesis of the *ortho*-methoxy derivative **1d**, through reaction of the sodium salt of glycerol acetonide with the newly prepared 3-bromo-4-methoxythiophene **7**. Compound **7** was obtained according to a simple new route starting from methyl 3-hydroxythiophene-2-carboxylate [2], as illustrated in Scheme 2.



Scheme 1



Scheme 2

Bromination of the starting material yielded methyl 4-bromo-3-hydroxy-thiophene-2-carboxylate (**4**) [3]. Methylation of **4** with one equivalent of dimethyl sulfate in boiling 2-butanone, in the presence of anhydrous K_2CO_3 led exclusively to compound **5**. Alkaline hydrolysis of the ester group gave **6** in nearly quantitative yield, which could be thermally decarboxylated to **7** by heating it 20°C above its melting point.

Treatment of the substituted propanediols **1** (**a**—**d**) (Scheme 1) with phosgene in benzene, in the presence of pyridine, followed by ammonolysis of the cyclic carbonate intermediates, gave the desired carbamate derivatives **2** (**a**—**d**).

Pharmacology

An indirect method of evaluation of the muscle relaxant activity of the compounds **1** and **2** was chosen, based on the observation that mephenesin and compounds of similar action are able, in small doses, to prevent death from otherwise lethal doses of strychnine in mice [4].

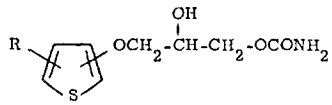
The results obtained (Table II) showed that compounds **1c** and **2c** were clearly the most active of the series in protecting mice against strychnine-induced death.

The activity of compounds **1c** and **2c** on postural, corneal and pinna reflexes was then studied, in order to confirm their relaxation effects and to clarify their site of action [5]. A summary of data obtained is presented in Table III. Both compounds (at a dose of 400 mg/kg) produced a total loss of the righting reflex, with deep CNS depression, followed by complete recovery within 1 h. The effect was produced in less than 5 min after i.p. administration which indicates the rapid absorption of both products and the easy crossing of the blood—brain barrier.

Moreover, the finding that the pinna reflex, rather than the corneal one, was selectively depressed, confirmed the spinal cord depressing action of these compounds [6].

On the other hand, compounds **1d** and **2d**, at a dose of 400 mg/kg, did not affect the righting reflex; however, a decrease of muscle tone (70 and 33%, respectively) was noted.

Table I. Physical and spectral data of 3-(thienyloxy)-1,2-propanediol 1-carbamates.



Compound	M. p. (° C)	Yield (%)	IR (KBr)	^{1}H NMR ($CDCl_3$)			
				Thiophene	NH_2	Th-OCH_2-CH(OH)-CH_2-O-CO	R
2a	104	52	3440 (OH) 3200 (NH_2) 1700 (C=O)	6.75 (d, 1H, H-4) 6.95 (d, 1H, H-5) J = 4.9 Hz	4.75 (bs)	2.80 (s, 1H, OH) 3.95 (m, 2H, CH_2-OTh) 4.20-4.35 (m, 3H, CH(OH)-CH_2OCO)	2.25 (s, CH_3)
2b	103	39	3340 (OH) 3200 (NH_2) 1710 (C=O)	6.60 (s, 2H)	4.65 (bs)	2.75 (s, 1H, OH) 3.85 (m, 2H, CH_2OTh) 3.95-4.15 (m, 3H, CH(OH)-CH_2OCO)	2.00 (s, CH_3)
2c	72	65	3370 (OH) 3200 (NH_2) 1690 (C=O)	6.20 (d, 1H, H-2) 6.85 (d, 1H, H-5) J = 2.9 Hz	4.75 (bs)	2.80 (s, 1H, OH) 4.00 (m, 2H, CH_2-OTh) 4.25-4.35 (m, 3H, CH(OH)-CH_2OCO)	2.10 (s, CH_3)
2d	106	61	3480 (OH) 3200 (NH_2) 1685 (C=O)	6.25 (d, 1H, H-2) 6.35 (d, 1H, H-5) J = 3.9 Hz	4.70 (bs)	2.95 (bs, 1H, OH) 4.05 (m, 2H, CH_2-OTh) 4.25-4.35 (m, 3H, CH(OH)-CH_2-OCO)	3.85 (s,OCH_3)

Table II. Central muscle relaxant activity.

Compound	Dose mg/kg i.p.	Nº of animals survivors/treated	Death Time $\bar{x}$ (sec.)	% Protection respect control	% Relaxation Activity		Correlation coefficient	ED_{50} mg/kg i.p.
					respect mephenesin (150 mg/kg)	expected value		
1a	100	0/10	34.3	30.4	2.9			
1b	100	0/10	21.9	-16.7	-1.6			
1c	50	0/10	43.7	66.1	6.4	9.6		
	100	2/10	148.6	465.0	44.7	38.2	0.98	132.6
	200	3/10	201.0	664.3	63.8	67.0		
1d	100	1/10	69.4	163.9	15.8			
2a	100	0/10	37.0	40.7	3.9			
2b	100	0/10	23.3	-11.4	-1.1			
2c	50	1/10	77.2	193.5	18.6	9.5		
	100	1/10	112.0	225.9	31.5	49.4	0.93	101.0
	200	9/10	296.0	1025.5	98.5	89.5		
2d	100	0/10	29.0	10.3	1.0			
Mephenesin	50	0/10	16.9	-35.7	-3.4	-11.1		
	100	2/10	120.0	356.3	34.2	55.5	0.96	94.4
	150	10/10	300.0	1040.7	100.0	93.2		
Methocarbamol	100	0/10	120.0	356.3	34.2			
	150	10/10	300.0	1040.7	100.0			
	200	10/10	300.0	1040.7	100.0			
Control	-	0/40	26.3	-				

Table III. Activity of Compounds **1c** and **2c** on reflexes.

Compound	Doses mg/kg i.p.	Nº of animals Dead / Treated	Postural Reflex		Corneal Reflex		Pinna Reflex	
			Loss	% Response	Loss	% Response	Loss	% Response
1c	125	0/10	0/10	0	0/10	0	0/10	0
	185	0/4	0/4	0	0/4	0	0/4	0
	220	0/2	0/2	0	0/2	0	0/2	0
	235	0/4	0/4	0	0/4	0	0/4	0
	250	0/13	9/13	70	1/13	8	8/13	61
	400	0/5	5/5	100	0/5	0	5/5	100
	500	0/10	10/10	100	1/7	14	7/7	100
2c	250	0/3	0/3	0	0/3	0	0/3	0
	275	0/3	0/3	0	0/3	0	0/3	0
	300	0/6	6/10	60	0/10	0	4/10	40
	400	0/4	4/4	100	0/4	0	2/4	50
Mephenesin	125	0/5	0/5	0	0/5	0	0/5	0
	200	0/9	8/9	89	3/9	33	7/9	78
	250	0/5	5/5	100	3/5	60	5/5	100
	300	0/5	5/5	100	4/5	80	5/5	100
	450	4/5	1/1	100	1/1	100	1/1	100
	500	5/5	-	-	-	-	-	-

Despite the fact that the compounds **1c** and **2c** appear to be somewhat less active than mephenesin as muscle relaxants, they were found to be less toxic. They could be administered intraperitoneally in mice at a dose of 750 mg/kg without causing death or any signs of intoxication.

In conclusion, the pharmacological profiles of the 3,4-substituted isomer of the thiophene analogs of mephenesin (**1c**) and of its corresponding carbamate **2c** were found to be similar to those reported for mephenesin. The possible site of action is also considered to be in the spinal interneurons. Further studies are in progress.

Experimental protocols

Chemistry

Melting points were determined on a Büchi 510 melting point apparatus. Boiling and melting points are uncorrected. IR spectra were obtained with a Perkin—Elmer 257 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM 390 (90 MHz) spectrometer in the solvent indicated, using TMS as the internal standard. Chemical shifts are given in ppm (δ scale) and signals are described as: s = singlet; b.s. = broad singlet; d = doublet and m = multiplet. Analyses indicated by elemental symbols were made at the Microanalysis Unit at C.N.Q.O. (Madrid); they are within ± 0.4% of the theoretical values.

Methyl 4-bromo-3-methoxythiophene-2-carboxylate **5**

Dimethyl sulfate (12.1 g; 0.11 mol) was added to a stirred mixture of **4** (23.7 g; 0.1 mol) and anhydrous potassium carbonate (13.8 g; 0.1 mol) in 150 ml of dry 2-butanone. The reaction mixture was heated at reflux temperature for 6 h, then evaporated to dryness. The residue was treated with water and the product extracted with ether. Evaporation of the organic solvent *in vacuo* led to a solid product recrystallized from isopropanol. Mp 78—79°C. Yield: 75%. Analysis $C_7H_7BrO_3S$ (C, H, Br, S). IR (nujol): 1720 (C=O). ^{1}H NMR ($CDCl_3$): 3.85 (s, 3H, OCH_3); 4.00 (s, 3H, $COOCH_3$); 7.40 (s, 1H, H-5 thiophenic).

4-Bromo-3-methoxythiophene-2-carboxylic acid **6**

A suspension of **5** (25.1 g; 0.1 mol) in 150 ml of 1 N sodium hydroxide solution was heated to reflux for 30 min. After cooling, the reaction mixture was acidified with 1 N hydrochloric acid, and the solid product, so formed, was filtered off and recrystallized from benzene. Mp 191—192°C (d); yield: 95%. Analysis $C_6H_5BrO_3S$ (C, H, Br, S). IR (nujol): 3200—2500 (OH); 1660 (C=O). ^{1}H NMR ($CDCl_3$): 3.90 (s, 3H, OCH_3); 7.95 (s, 1H, H-5 thiophenic); 12.10 (bs, 1H, disappeared with D_2O, OH).

3-Bromo-4-methoxythiophene **7**

Compound **6** (23.7 g; 0.1 mol) was heated at 210°C at reduced pressure (11 mm Hg). After the evolution of CO_2 had ceased, the resulting oil was distilled to give 13.9 g (72%) of pure 3-bromo-4-methoxythiophene **7** as a colorless liquid. Bp 108—109°C (11 mm Hg). Analysis C_5H_5BrOS (C, H, Br, S). ^{1}H NMR (CCl_4): 3.95 (s, 3H, OCH_3); 6.35 (d, 1H, $J_{2.5}$ = 3.9 Hz, H-5 thiophenic); 7.30 (d, 1H, $J_{2.5}$ = 3.9 Hz, H-2 thiophenic).

2,2-Dimethyl-4-[3-(4-methoxythienyl)oxymethyl]-1,3-dioxolane **3d**

Sodium (6.2 g; 0.27 mol) was dissolved in 139 ml of 1,2-*O*-isopropylideneglycerol. Compound **7** (19.3 g; 0.1 mol), potassium iodide (0.09 g, 0.54 mmol) and cupric oxide (4.0 g; 0.05 mol) were added and the reaction mixture was then heated at 90°C for 24 h. Excess isopropylideneglycerol was recovered by distillation (80—81°C/11 mm Hg) and the residue treated with water and extracted with ether. Evaporation of the dried extract yielded **3d**, which was purified by crystallization from *n*-hexane. Mp 30—31°C; yield: 74%. Analysis $C_{11}H_{16}O_4S$ (C, H, S). ^{1}H NMR (CCl_4): 1.35 (s, 3H, CH_3—C); 1.45 (s, 3H, CH_3—C); 3.85 (s, 3H, OCH_3); 3.90—4.50 (m, 5H, OCH_2—CH—CH_2); 6.25 (d, 1H, $J_{2.5}$ = 3.9 Hz, H-2 thiophenic); 6.35 (d, 1H, $J_{2.5}$ = 3.9 Hz, H-5 thiophenic).

1-O-(4-Methoxy-3-thienyl) glycerol **1d**

A solution of 24.4 g (0.1 mol) of **3d** in 125 ml of 80% acetic acid was heated at 60°C for 30 min. The solvent was removed *in vacuo* and the residue was purified by crystallization from toluene. Mp 80—82°C; yield: 92%. Analysis $C_8H_{12}O_4S$ (C, H, S); IR (KBr): 3500—3100 (OH); ^{1}H NMR ($CDCl_3$): 2.70 (bs, 2H, 2OH); 3.70 (m, 2H, CH_2—OH); 3.75—3.85 (m, 3H, OCH_2—CH(OH)); 4.05 (s, 3H, OCH_3); 6.15 (d, 1H, $J_{2.5}$ = 3.9 Hz, H-2 thiophenic); 6.25 (d, 1H, $J_{2.5}$ = 3.9 Hz, H-2 thiophenic).

3-(3-Thienyloxy)-1,2-propanediol 1-carbamates **2 (a—d)**

A solution of 9.9 g (0.1 mol) of phosgene in benzene (50 ml) was added dropwise to a stirred mixture of the appropriate propanediol (0.1 mol) in benzene (100 ml). To the resulting solution, pyridine (7.9 g; 0.1 mol) was added dropwise, maintaining the temperature at 25—30°C and stirring was continued for 30 min. Ice water was added, the benzene layer was separated and stirred with 15 ml of concentrated ammonium hydroxide for 6 h. The solvent and excess ammonia were removed by distillation and the residue crystallized from toluene.

Data relating to the compounds prepared in this manner are shown in Table I.

Pharmacology

Experiments were carried out on female Swiss mice, fed a standard diet. Test compounds were suspended in 1% carboxymethylcellulose and 0.1% Tween 80. Mephenesin and methocarbamol were used as standards.

Preliminary test for central muscle relaxant activity

Mice weighing 25—30 g were used. Compounds **1 (a—d)** and **2 (a—d)** were injected i.p. at a dose of 100 mg/kg, 15 min before the intravenous administration of strychnine (0.75 mg/kg). A control group which received only vehicle (0.01 ml/g i.p.) was included. The end point employed was the death time within a 5 min period; beyond this period, animals were considered survivors and the death time was estimated in 300 s.

Another two doses of compounds **1c** and **2c**, and of standards were injected. For statistical evaluation, a percentage of protection against death was calculated for each dose with respect to control by means of the Mann—Whitney *U* test; for variance analysis the Kruskal—Wallis *H* was calculated.

The percentage of muscle relaxation activity with respect to the standard (150 mg/kg i.p.) as well as the ED_{50}, the dose which prevents the lethal action of strychnine in 50% of the pretreated mice, were calculated.

Activity test of compounds **1c** *and* **2c** *on postural, corneal and pinna reflexes*

Adult mice weighing 40—47 g were used. Doses of different concentrations were injected intraperitoneally and the activity was then evaluated counting the number of animals in each group that lost any of these reflexes. The criteria observed consisted of the inability of the animal to turn over when placed on its back, the inability to close the eye and failure to fold the ear upon stimulation of the cornea and the auditory meatus, respectively, with a sthenometer. Time necessary for total recovery was also taken into account.

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