Synthesis and Pharmacological Study of a Thiophene Analogue of Moprolol and Related Compounds

M.B.El-Ashmawy and J. Lissavetzky*

Instituto de Quimica Médica (C.S.I.C.), Juan de la Cierva 3, 28006 -Madrid, Spain

V. Darias and D. Martín-Herrera

Departamento de Farmacagnosia-Farmacodinamia, Facultad de Farmacia, Universidad de la Laguna, Tenerife, Spain

Received August 4, 1989

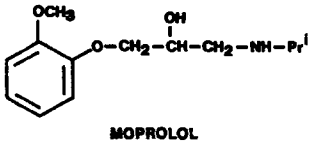
The syntheses of the thiophenic analogue of Moprolol (**1d**) and of its related compound **1a** are described. From a preliminary pharmacological evaluation compound **1d** seems worthy of further studies due to its notable β-blocking activity and its remarkable anti-platelet aggregation action.

Synthese und pharmakologische Untersuchung eines Thiophen-Analogen von Moprolol und verwandter Verbindungen

Die Synthese des Thiophenisosters **1d** des Moprolols und der verwandten Verbindung **1a** wird beschrieben. Aus einer vorläufigen pharmakologischen Untersuchung geht hervor, daß **1d** wegen seiner β-Rezeptoren blockierenden Wirkung und seiner beachtenswerten antiaggregatorischen Eigenschaften weiter untersucht werden sollte.

Moprolol[1] is an interesting β-blocker commercialized in Italy as Omeral, being of clinical importance[2,3].

We describe in this paper the synthesis and a preliminary pharmacological evaluation of the β-adrenergic blocking activity of the thiophene isoster of Moprolol **1d**. The pharmacological profile of this compound is completed with the study of its *in vitro* antiplatelet aggregation activity.

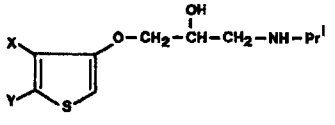


MOPROLOL

Besides, we wish to report the synthesis and pharmacological evaluation of compound **1a**, in which the presence of a lipophilic chloro substituent at the thiophenic ring can be interesting for the antiplatelet aggregation activity. Unfortunately compounds **1b** and **1c** could not be synthesized so that structure-activity relationship studies could not be performed.

Compound **1d** has been prepared as depicted in Scheme 1. 3-Bromo-4-methoxythiophene (**2**), recently synthesized by a new method in our laboratory[4], has been used as a convenient starting material to obtain the oxirane derivative **5** in an acceptable global yield. Treatment of **5** with a great excess of isopropylamine afforded **1d**.

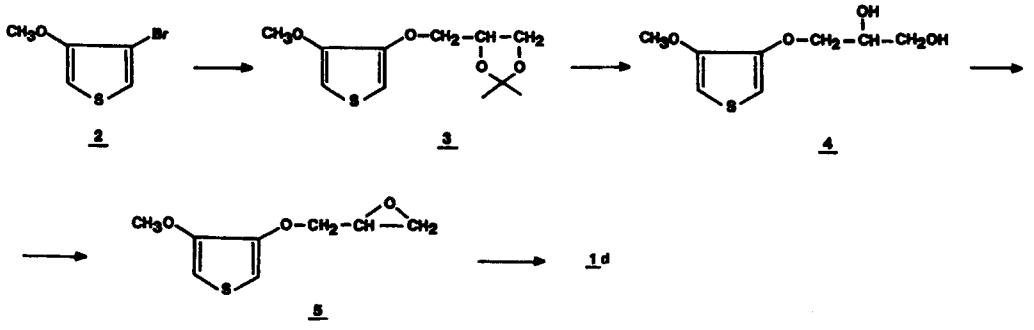
The planned synthesis of the other thienyloxy propanolamine derivatives **1a-c** has been approached by an alternative route starting from the hydroxythiophene compounds **6a-c** as depicted in Scheme 2.



1

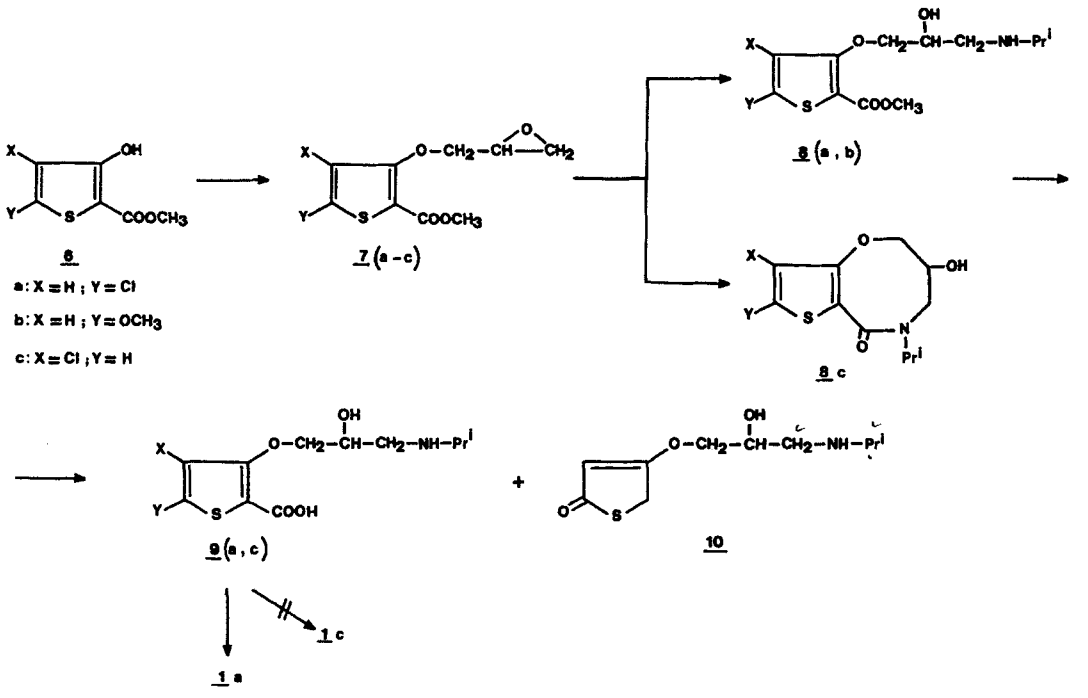
a: X = H ; Y = Cl
(b: X = H ; Y = OCH_3)
c: X = Cl ; Y = H
d: X = OCH_3 ; Y = H

The reaction of the potassium salts of **6a-c**, prepared from K-*tert*-butoxide with epichlorohydrin in DMSO led to the epoxides **7a-c**, which were reacted with a great excess of isopropylamine at room temp. The expected open chain pro-



Scheme 1

  0365-6233/91/0101-0045 $ 3.50 + .25/0



Scheme 2

ducts **8a** and **8b** were successfully isolated, but in the case of **8c** a lactamic neutral compound was obtained in 61% yield which was identified by its spectral and analytical data (Table 1).

Hydrolysis of compounds **8a-c** by heating at refluxing temp. with 1N NaOH gave only two of the desired carboxylic acids **9a** and **9c**, corresponding to the monochlorosubstituted derivatives in good yield. On the other hand, the acid derivative **9b** could not be obtained, neither by the described isolation method nor by any modification performed. The reaction product has been assigned as **10** based on its analytical and spectral data. This compound was probably formed via hydrolysis and subsequent demethylation and decarboxylation of the corresponding not isolated derivative **9b**.

Thermal decarboxylation of the thiophene-2-carboxylic acid **9a** gave the desired final product **1a** in 56% yield, isolated as its HCl salt. Unfortunately, the decarboxylation product from **9c** could not be isolated. Decomposition in the reaction medium was observed, probably due to the thermal instability of the product.

The results of a preliminary pharmacological testing of the thienyloxypropanolamine **1a** and **1d** are presented in tables 2 and 3.

Compound **1d**, a thiophenic isoster of Moprolol, displays a level of activity in inhibiting positive chronotropic and hypotensive responses similar to Alprenolol and about 80% of that of Propranolol. This compound presents a greater capacity for blocking the vascular than the myocardic receptors. This lack of cardioselectivity must, however, be confirmed in further experiments on animals capable of yielding more meaningful results.

Direct cardiovascular effects of these compounds are weaker than those of the reference drugs (Table 2).

In contrast with the lack of partial agonist activity of Moprolol[2], the thiophenic isoster **1d** shows a moderate intrinsic sympathomimetic action in reserpinized rats higher than that observed for Alprenolol (Table 2).

These compounds decrease the responses to a nociceptive stimulus, this effect being smaller and shorter lasting than that shown by Propranolol and Alprenolol.

On the other hand compounds **1a** and **1d** show a remarkable *"in vitro"* antiplatelet aggregation activity, specially that referred to the inhibition of the aggregation induced by collagen, having IC_{50} values lower than Aspirin (Table 3).

In the assays of approximate acute toxicity carried out on mice, these new compounds, which were administered in two different ways, proved to be much less toxic than Alprenolol and Propranolol.

In conclusion the thiophenic isoter of Moprolol **1d** seems to be worthwile of further study. This compound has a notable β-blocking activity and unlike the benzenic Moprolol, shows a weak partial agonist activity. Furthermore, this compound has a remarkable antiplatelet aggregation activity, that improves considerably its pharmacological profile.

Experimental Part

Melting points: Büchi 510 m.p. apparatus. Melting and boiling points are uncorrected. - IR spectra: Perkin-Elmer 257 spectrophotometer. - ^{1}H-NMR-spectra: Varian EM 390 (90 MHz) spectrometer in the solvent indicated, using TMS as int. stand.; chemical shifts in δ-ppm. - Analysis of C.H.N. are within ±0.3% of the theoretical values and were done at the Microanalysis Department at C.N.Q.O. (Madrid).

2,3-Epoxy-1-(4-methoxy-3-thienyloxy)propane[5] (**5**),
5-chloro-3-hydroxy-2-methoxycarbonylthiophene[6] (**6a**),
3-hydroxy-5-methoxy-2-methoxycarbonylthiophene[7] (**6b**),
4-chloro-3-hydroxy-2-methoxycarbonylthiophene[8] (**6c**)

These compounds were prepared according to the lit. cited.

Table 1: Physical and spectroscopic data of the thiophenic compounds **1** and **7 - 10**.
[a] D_2O; [b] $CDCl_3$.

Comp.	M.p. °C	Yield %	Mol. Formula (M. Wt.)	Analysis Calc./Found %C	%H	%S	IR (Nujol) cm^{-1}	^{1}H-NM	M.S. (Rel. Int.)
1a	121-2	56	$C_{10}H_{16}Cl_2NO_2S$ (285.2)	42.1 42.4	5.65 5.57	11.2 11.0	3180(OH) 2520(NH)	1.40 (d, 6H,$(CH_3)_2C$); 3.30 (m, 2H, CH_2-N); 3.55 (m, 1H, N-CH); 4.05-4.45 (m, 3H, -OCH_2-CH); 6.40 (d, 1H, $J_{3,4}$=2Hz, H-4 thiophenic); 6.85 (d, 1H, $J_{2,4}$=2Hz, H2 thiophenic)[a].	
1d	65-6	57	$C_{11}H_{19}NO_3S$ (245.3)	53.9 53.7	7.81 7.92	13.1 13.3	3280(OH) 3120(NH)	1.10 (d, 6H, $(CH_3)_2C$); 1.85-2.05 (m, 2H, NH, OH); 2.75-2.95 (m, 3H, CH_2-NH-CH-); 3.95 (s, 3H, OCH_3); 4.00-4.41 (m, 3H, -OCH_2-CH-); 6.25 (d, 1H, $J_{2,5}$=3.9Hz, H-2 thiophenic); 6.35 (d, 1H, $J_{2,5}$=3.9Hz, H-5 thiophenic)[b].	245(3) 72(100)
7a	83-4	63	$C_9H_9ClO_4S$ (248.7)	43.5 43.2	3.65 3.39	12.9 13.1	1680(C=O)	2.85 (m, 2H, -CH_2-epoxy); 3.30 (m, 1H -CH, -epoxy); 3.80 (s, 3H, $COOCH_3$); 4.30 (m, 2H, -OCH_2-); 6.75 (s, 1H, H-4 thiophenic).	
7b	68-9	77	$C_{10}H_{12}O_5$ (244.3)	49.2 49.0	4.95 4.66	13.1 12.8	1670(C=O)	2.80 (m, 2H, -CH_2-epoxy); 3.30 (m, 1H -CH-epoxy); 3.80 (s, 3H, -OCH_3); 3.90 (s, 3H, $COOCH_3$); 4.25 (m, 2H, -OCH_2); 6.10 (s, 1H, H-4 thiophenic)[b].	
7c	50-1	52	$C_9H_9ClO_4S$ (248.7)	43.5 43.2	3.65 3.73	12.9 12.7	1710(C=O)	2.80 (m, 2H, -CH_2-epoxy); 3.40 (m, 1H, -CH-epoxy); 3.90 (s, 3H, $COOCH_3$); 4.35 (m, 2H, -OCH_2); 7.45 (s, 1H, H-5 thiophenic)[b].	
8a	128-9	63	$C_{12}H_{19}Cl_2NO_4S$ (344.3)	41.9 41.8	5.56 5.82	9.3 9.6	3400(OH) 2450(NH) 1680(C=O)	1.45 (d, 6H, $(CH_3)_2$-C); 3.30-3.60 (m, 3H, CH_2-NH-CH); 3.85 (s, 3H, $COOCH_3$); 4.25-4.35 (m, 3H, -OCH_2CH-); 7.05 (s, 1H, H-4 thiophenic)[a].	308(3) 72(100)
8b	103-4	72	$C_{13}H_{22}ClNO_5S$ (339.8)	45.9 45.7	6.52 6.37	9.4 9.3	3480(OH) 2470(NH) 1670(C-O)	1.55 (d, 6H, $(CH_3)_2C$), 3.20-3.60 (m, 3H, CH_2-NH-CH); 3.80 (s, 3H, -OCH_3); 4.00 (s, 3H, -$COOCH_3$); 4.20-4.50 (m, (m, 3H, OCH_2-CH-); 6.25 (s, 1H, H-4 thiophenic)[a].	304(2) 72(100)
8c	142-3	61	$C_{11}H_{14}ClNO_3S$ (275.7)	47.9 47.7	5.12 5.33	11.6 11.4	3440(OH) 1590(C=O)	1.20 (d, 6H, $(CH_3)_2C$); 2.45 (bs, 1H, HO-C); 3,50 (d,2H, CH_2N); 3.95 (m, 1H, N-CH); 4.40 (d, 2H, -OCH_2); 4.65 (m, 1H, -CH-O); 7.25 (s, 1H, H-5 thiophenic)[a].	275(56) 160(100)
9a	196-7	82	$C_{11}H_{17}Cl_2NO_4S$ (330.2)	40.0 39.9	5.19 5.07	9.7 9.6	3390(OH) 2470(NH) 1660(C=O)	1.35 (d, 6H,$(CH_3)_2C$); 3.30 (m, 2H, CH_2-H); 3.50 (m, 1H, N-CH); 4.15-4.45 (m, 3H, OCH_2-CH): 6.95 (s, 1H, H-4 thiophenic)[a].	295(1) 72(100)
9c	170-1	81	$C_{11}H_{17}Cl_2NO_4S$ (330.2)	40.0 40.2	5.19 5.12	9.7 9.6	3290(OH) 2440(NH) 1690(C=O)	1.25 (d, 6H, $(CH_3)_2C$); 3.15-3.55 (m, 3H, CH_2-N-CH); 4.10-4.30 (m, 3H, -OCH_2CH); 7.30 (s, 1H, H-5 thiophenic)[a].	295(2) 72(100)
10	188-9	55	$C_{10}H_{18}ClNO_3S$ (267.8)	44.9 44.9	6.77 6.65	12.0 12.3	3270(OH) 2400(NH) 1670(C=O) 1610(C=C)	1.35 (d, 6H, $(CH_3)_2C$); 3.20 (m, 2H, -CH_2-N); 3.50 (m, 1H, N-CH); 4.20-4.40 (m, 4H, OCH_2-CH, H-5 thiophenic); (s, 1H, H-3 thiophenic).	

3-Isopropylamino-1-(4-methoxy-3-thienyloxy)-2-propanol (**1d**)

Isopropylamine (10 ml) was added to 2,3-epoxy-1-(4-methoxy-3-thienyloxy)propane **5** (2.04 g; 0.01 mole). The mixture was left at room temp. for 4 days and then evaporated to dryness. The residue was crystallized from n-hexane to give **1d** as a colourless solid in 57% yield.

1-(2-Methoxycarbonyl-3-thienyloxy)-2,3-epoxypropane **7a-c**

Epichlorohydrin (14 g; 0.15 mole) was added dropwise to a stirred mixture of the respective 3-hydroxy-2-methoxycarbonyl-thiophene **6a-c** (0.1 mole) and K-tert.butoxide (12.3 g; 0.11 mole) in 170 ml of DMSO. The mixture was heated at 90°C for 3 h, left to cool and then evaporated *in vacuo* (0.1 mm Hg) to dryness. The residue was thoroughly extracted with boiling n-hexane. The extract was concentrated and the solid so formed was filtered and recrystallized from isopropanol (Table 1).

Reactions of the epoxy compounds **7a-c** *with isopropylamine*

This reaction was carried out similarly to that for **1d**. After distilling off the excess amine, the different products **8** were obtained as follows:

a) *1-(5-Chloro-2-methoxycarbonyl-3-thienyloxy)-3-isopropylamino-2-propanol-HCl* (**8a**)

8a-HCl was precipitated upon treating the ethereal solution of the base with HCl-gas in ether and recrystallized from ethanol/ether.

Table 2: Pharmacological data

Compound	% Inhibition of isoproterenol effects in rats		Direct effects in rats[a]		Partial agonist activity[b]	Local anesthesia % inhibition of response[c]		Acute toxicity Aprox. LD_{50}	
	Tachycardia	Hypotension	Heart rate	Blood pressure		10 min.	45 min.	iv	ip
1 a	0	64.5	25	20.05	4	20	0	>200	>200
1 d	79.5	88	21	20	17	60	30	>200	>200
Alprenolol	82.5	73	38	31.5	13	85	40	32	100
Propranolol	100	100	35	35	0	90	70	22	75
Procaine	—	—	—	—	—	50	0	—	—

a Single i.v. doses of 4 mg/Kg. all standard errors of the mean fell within the range of 6-13% of the mean

b Maximun per cent increase in the heart rate reached in the 0.01-4 mg/Kg iv dose range. Standard error of the mean fell within the range of 5-10% of the mean.

c % inhibition of response to 0.5% solution of test compound

b) 3-Isopropylamino-1-(5-methoxy-2-methoxycarbonyl-3-thienyloxy)-2-propanol·HCl (**8b**)

8b-HCl was obtained as **8a**-HCl.

c) *9-Chloro-3-hydroxy-5-isopropyl-3,4,5,6-tetrahydro-2H-thieno[3,2-b] 1,5-oxazocin-6-one* (**8c**)

This product was isolated as shiny crystals upon triturating the reaction residue with diethyl ether.

Hydrolysis of **8**

0.01 Mole of the appropriate compound **8a-c** was refluxed with 30 ml of N NaOH for 1 h. The mixture was left to cool, treated with N HCl until slightly acidic pH and then evaporated *in vacuo* to dryness. The residue was triturated with absol. ethanol; inorganic salts were filtered off and the filtrate was diluted with ether. The desired acid *1-(2-carboxy-5-chloro-3-thienyloxy)-3-isopropylamino-2-propanol · HCl* (**9a**) was obtained as colourless crystals, while compound **10** (*1-(2,5-dihydro-2-oxo-4-thienyloxy)-isopropylamino-2-propanol · HCl*) was obtained from **8b**.

Table 3: Inhibition of platelet aggregation

COMPOUND	IC_{50} (g/ml)		
	ADP	Adrenaline	Collagen
1 a	50	<15	<15
1 d	>250	100	<15
Propranolol	80	<15	24
Aspirin	≫250	60	15
Ticlopidine	110	85	≫250

1-(2-Chloro-4-thienyloxy)-3-isopropylamino 2-propanol·HCl (**1a**)

Compound **9a** (1g) was heated, under reduced pressure (0.1 mm Hg), at 270°C for 30 min untill CO_2 evolution had ceased. The residue was purified by crystallization from an ethanol/ether to give 0.5 g (56%) of **1a** as a colourless solid of m.p. 121°C

Pharmacology

Direct effects of β-adrenergic blocking activity[9], partial agonist activity[10], local anaesthesia[9], inhibition of *in vitro* platelet aggregation[5] and acute toxicity[9] were determined as described.

References

1 D.J. Crowther, D.J. Gilman, B.J. McLoughlin, L.H. Smith, R.W. Turner, and T.M. Wood, J. Med. Chem. *12*, 638 (1969).

2 R. Ferrini, G. Miragoli, and G. Groce, Arzneim.-Forsch. *20*, 1974 (1970).

3 M. Radice, G. Folli, A. Tavecchia, G. Mariotti, and E. Cameroni, Arzneim.-Forsch. *28*, 2160 (1978).

4 C. Corral, M.B. El-Ashmawy, J. Lissavetzky, A. Basilio, and A. Giraldez, Eur. J. Med. Chem. - Chim. Ther. *22*, 251 (1987).

5 C. Corral, M.B. El.-Ashmawy, J. Lissavetzky, L. Bravo, V. Darias, and D. Martin, Il Farmaco-Ed. Sci. *42*, 268 (1987).

6 C. Corral and J. Lissavetzky, Synthesis *1984*, 847.

7 C. Corral and J. Lissavetzky, J. Chem. Soc. Perkin Trans. I, 2711 (1984).

8 J. Buendia, J. Nierat, and R. Deroy, Ger. Pat. 2719244 (1977), Roussel-UCLAF; C.A. *88*, 67047 (1978).

9 S. Conde, C. Corral and J. Lissavetzky, Arch. Pharm. (Weinheim) *316*, 537 (1983).

10 C. Corral, M.B. El-Ashmawy, J. Lissavetzky, R. Madronero, V. Darias, D. Martín, and E. Estevez, Eur. J. Med. Chem. - Chim. Ther. *20*, 133 (1985). [Ph726]