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Short Communication

O-[2-Hydroxy-3-(dialkylamino)propyl]ethers of (+)-1,7,7-trimethyl bicyclo[2.2.1]heptan-2-one oxime (camphor oxime) with analgesic and antiarrhythmic activities

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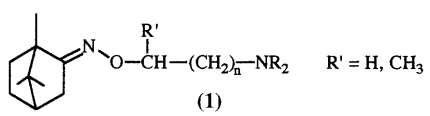
Abstract

A novel series of *O*-[2-hydroxy-3-(dialkylamino)propyl]ethers of (+)-camphor oxime was prepared and tested for its cardiovascular, analgesic and anti-inflammatory properties. No significant anti-inflammatory and hypotensive activities were displayed by any of the compounds, whereas several of them are reasonably active as antiarrhythmic and analgesic agents.

Keywords: ω-Dialkylaminohydroxy ethers of (+)-camphor oxime; Analgesic agents; Antiarrhythmic agents

1. Introduction

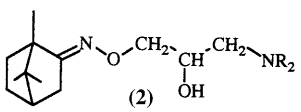
In earlier communications a variety of aminoethers of cyclanone-oximes have been reported to possess interesting pharmacological properties [1–3]. Even recently a number of tricyclic ketoxime esters and ethers have been described as showing local anaesthetic and analgesic activities [4]. Among them in particular a series of ω-dialkylamino alkylethers of (+)-camphor oxime **1** was recognized to be endowed, inter alia, with hypotensive, antiarrhythmic and analgesic properties.



(1)

It seems worthwhile to us to further investigate derivatives in the bornane series by introducing the characteristic β-blocking chain on the oxime function in order to evaluate their potential as cardiovascular agents.

Accordingly we planned the synthesis of compounds **2** to be tested in a preliminary screening.



(2)

2. Chemistry

The synthetic procedure is outlined in Scheme 1. Camphor oxime [4] sodium salt was treated with epichlorohydrin and the resulting epoxy-ether **3** was reacted with the proper alkyl/dialkylamine to give the target compounds **2a**–**2h** in good yields.

3. Pharmacology

Compounds **2a**–**2h** were submitted to a preliminary screening for anti-inflammatory, analgesic, antiarrhythmic and hypotensive activities.

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4. Experimental

4.1. Chemistry

Melting points were determined with a Buchi 530 apparatus. IR spectra were measured in KBr with a Perkin–Elmer 398 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ solution on a Hitachi Perkin–Elmer R-600 (60 MHz) and on a Varian Gemini 200 instrument; chemical shifts were reported as δ (ppm) relative to TMS as internal standard; J is reported in Hz. Analyses for C, H, N were within $\pm 0.3\%$ of the theoretical values.

4.1.1. General procedure for O-glycidyl camphor oxime 3

A 60% sodium hydride dispersion in mineral oil (0.44 g, 11 mmol) was added to a solution of (+)-camphor oxime (1.38 g, 10 mmol) in anhydrous DMF (10 ml). The resulting mixture was heated with stirring at 60°C for 1 h and cooled. A solution of epichlorohydrin (1.02 g, 11 mmol) in anhydrous DMF (10 ml) was added, the mixture was stirred for 1 h at room temperature, and poured into water (100 ml). The solution was extracted thoroughly with chloroform, the extracts were washed twice with water, dried (an. $MgSO_4$) and evaporated under reduced pressure to afford a liquid which was distilled in vacuo.

3: Yield 72%; viscous colourless liquid, bp 110–115°C (0.2 mmHg). IR ($CHCl_3$): 1660 (C=N) cm^{-1}. ^{1}H NMR (200 MHz): δ 0.75, 0.89 and 0.96 (3s, 9H, $3CH_3$), 1.10–2.10 (multiplets, 6H, $3CH_2$), 2.40–2.55 (2m, 1H, CH), 2.55–2.62 (2d, 1H of CH_2O epox) and 2.75–2.80 (near t, 1H of CH_2O epox), 3.15–3.25 (m, 1H, CHO), 3.87–4.00 (2dd, 1H of CH_2ON) and 4.13–4.25 (2d, 1H of CH_2ON). *Anal.* $C_{13}H_{21}NO_2$ (C, H, N).

4.1.2. General procedure for O-[2-hydroxy-3-(dialkylamino)propyl]ethers of camphor oxime 2a–2h

A solution of the camphor oxime glycidyl ether **3** (2.23 g, 10 mmol) in 95% ethanol (10 ml) was added to a solution of the appropriate primary or secondary amine (11 mmol) in the same solvent (10 ml). The resulting solution was heated at reflux for 12 h and evaporated under reduced pressure.

The residue was treated with 1 M HCl (20 ml) and the solution was extracted twice with diethyl ether. The acid solution was basified with 4 M NaOH and extracted with diethyl ether. The organic extracts were dried (an. $MgSO_4$) and evaporated under reduced pressure to give viscous oils which were distilled in vacuo (only the solid compound **2h** was crystallized from absolute ethanol) (Table 1). To obtain correct values of elemental analysis, the free bases were transformed into the corresponding hydrochlorides with a saturated hydrogen chloride ether solution and purified by crystallization from absolute ethanol:an. diethyl ether (1:1).

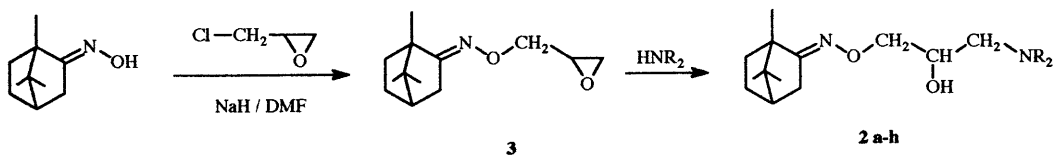
4.2. Pharmacology

Anti-inflammatory activity was evaluated by carrageenan-induced paw edema in rats [5]; analgesic activity was evaluated by the acetic acid writhing test in mice [6]; antiarrhythmic activity was evaluated as protection index against ecgraphic effects from aconitine in rats [7] and hypotensive activity, evaluated by oral administration in conscious rats [8].

5. Results and discussion

The tested compounds **2a**–**2h** showed no significant anti-inflammatory activity and a very weak hypotensive activity (data not reported). This last result is in contrast with earlier findings for congeners **1** and with the structural features of β-blocking agents.

However, a certain degree of cardiovascular action is retained because a good level of antiarrhythmic activity is present in several derivatives and in particular in **2h** having an ED_{50} of 44.31 (6.61–296.98) mg/kg i.v. (Table 2).



Comp	NR_2		NR_2
2a	$N(C_2H_5)_2$	**2e**	Morpholino
2b	$NHCH(CH_3)_2$	**2f**	1-Hexahydroazepino
2c	Pyrrolidino	**2g**	3,5-(Dimethyl)piperidino
2d	Piperidino	**2h**	2,6-(Dimethyl)morpholino

Scheme 1.

Table 1
Yields, physical and spectroscopic data [a] of compounds **2a**–**2h**

Comp.	B.p. (°C (mmHg))	Yield (%)	^{1}H NMR δ (ppm)	Formula (C, H, N)
2a	155–160 (0.2)	87	0.81, 0.92 and 1.02 (3s, 9H, $3CH_3$), 1.03 (t, $J = 6.6$, 6H, $2CH_3$ Et), 1.35–2.02 (m, 6H, $3CH_2$), 2.14 (near s, 1H, CH), 2.30–2.85 (m, 6H, $3CH_2N$), 3.45–3.70 (m, 1H, OH, disappears with D_2O), 3.90–4.21 (m, 3H, CHO + CH_2O)	$C_{17}H_{32}N_2O_2$
2b	160–165 (0.2)	75	0.79, 0.92 and 1.00 (3s, 9H, $3CH_3$), 1.06 (d, $J = 7.2$, 6H, $2CH_3$ isopr.) 1.35–2.01 (m, 6H, $3CH_2$), 2.11 (near s, 1H, CH), 2.28–3.11 (m, 3H, CHN + CH_2N), 3.80–4.20 (m, 3H, CHO + CH_2O), NH and OH not detectable	$C_{16}H_{30}N_2O_2$
2c	145–150 (0.2)	75	0.80, 0.91 and 1.00 (3s, 9H, $3CH_3$), 1.15–2.02 (m, 10H, $5CH_2$), 2.15 (near s, 1H, CH), 2.25–2.80 (m, 6H, $3CH_2N$), 3.40–3.60 (m, 1H, OH, disappears with D_2O), 3.90–4.20 (m, 3H, CHO + CH_2O)	$C_{17}H_{30}N_2O_2$
2d	170–175 (0.3)	76	0.80, 0.92 and 1.00 (3s, 9H, $3CH_3$), 1.15–2.05 (m, 12H, $6CH_2$), 2.15 (near s, 1H, CH), 2.25–2.80 (m, 6H, $3CH_2N$), 3.90–4.20 (m, 3H, CHO + CH_2O), 4.68 (near s, 1H, OH, disappears with D_2O)	$C_{18}H_{32}N_2O_2$
2e	160–165 (0.3)	80	0.80, 0.92 and 1.00 (3s, 9H, $3CH_3$), 1.10–2.00 (m, 6H, $3CH_2$), 2.11 (near s, 1H, CH), 2.20–2.80 (m, 6H, $3CH_2N$), 3.20–3.50 (m, 1H, OH, disappears with D_2O), 3.60–3.80 (m, 4H, $2CH_2O$ morph.), 3.90–4.20 (m, 3H, CHO + CH_2O)	$C_{17}H_{30}N_2O_3$
2f	155–160 (0.3)	68	0.80, 0.92 and 1.00 (3s, 9H, $3CH_3$), 1.12–2.00 (m, 14H, $7CH_2$), 2.12 (near s, 1H, CH), 2.30–2.90 (m, 6H, $3CH_2N$), 3.65–3.85 (m, 1H, OH, disappears with D_2O), 3.95–4.20 (m, 3H, CHO + CH_2O)	$C_{19}H_{34}N_2O_2$
2g	m.p. 97–98	45	0.80, 0.91 and 1.00 (3s, 9H, $3CH_3$), 1.08 (d, $J = 6$, 6H, $2CH_3$ pip), 1.29–2.00 (m, 10H, $4CH_2$ + 2CH pip), 2.01 (near s, 1H, CH), 2.27–3.03 (m, 6H, $3CH_2N$), 3.70–4.14 (m, 4H, CHO + CH_2O + OH, 1H disappears with D_2O)	$C_{20}H_{36}N_2O_2$
2h	175–180 (0.3)	65	0.80, 0.92 and 1.01 (3s, 9H, $3CH_3$), 1.15 (d, $J = 6.6$, 6H, $2CH_3$ morph), 1.40–2.02 (m, 6H, $3CH_2$), 2.13 (near s, 1H, CH), 2.20–3.00 (m, 6H, $3CH_2N$), 3.40–4.30 (m, 6H, 3CHO + CH_2O + OH, 1H disappears with D_2O)	$C_{19}H_{34}N_2O_3$

[a] All of **2a**–**2h** have an O–H absorption at 3420 and a C=N absorption at 1660 cm^{-1} in the IR spectra.

Table 2
Activity against ventricular fibrillation caused by aconitine in albino rats [a]

Comp.	Dose (mg/kg p.o.)	Appearance time (s ± SE) of extrasystoles	Death time (s ± SE)
Control (aconitine HCl)	[b]	178 ± 18.2	669 ± 20.6
Quinidine	25	421 ± 21.5 [d]	981 ± 23.5 [d]
2a	50	294 ± 26.2 [d]	789 ± 21.3 [d]
2b	50	212 ± 27.4	731 ± 28.7 [c]
2c	50	316 ± 23.2 [d]	814 ± 22.5 [d]
2d	50	233 ± 28.1 [c]	811 ± 27.1 [d]
2e	50	194 ± 29.6	701 ± 24.2
2f	50	208 ± 23.5	707 ± 26.9
2g	50	239 ± 22.6 [c]	802 ± 25.3 [c]
2h	12.5	189 ± 18.7	715 ± 22.7
	25	206 ± 19.3	806 ± 20.8
	50	287 ± 27.1 [d]	902 ± 29.1 [d]

[a] Ten animals (200–250 g) per group.
[b] 15 μg/kg i.v. until death.
[c] Statistically significant value calculated in comparison with the test performed with aconitine only ($P < 0.05$).
[d] Statistically significant value calculated in comparison with the test performed with aconitine only ($P < 0.01$).

Once again the antinociceptive activity is present in almost all compounds **2a**–**2h**, likewise their analogues **1**; a maximum of activity is elicited by the piperidine derivative **2d** with an ED_{50} of 57.12 (38.18–85.46) mg/kg o.s. in the acetic acid writhing test (Table 3).

In conclusion this series of terpenoid hydroxyaminoethers **2a**–**2h** seems to maintain only the antiharrhytmic and analgesic features of the earlier analogues **1** without substantial strengthening of potency.

In any case the antinociceptive action of these camphor oxime derivatives is superior to that shown by the other carbocyclic oxime derivatives recently reported [4].

Table 3
Analgesic activity by acetic acid writhing test [a]

Comp.	Dose (mg/kg p.o.)	Mean number of writhes in 25 min period after treatment ± SE [b]	Decrease relative to control (%)
Control (acetic acid)	0.5%	46.1 ± 5.7	
Indomethacin	5	23.6 ± 3.9	−53
2a	50	34.5 ± 3.7	−26
2b	50	27.2 ± 2.9	−41
2c	50	25.1 ± 2.4	−45
2d	12.5	33.4 ± 4.2	−28
	25	28.9 ± 5.1	−37
	50	24.7 ± 3.3	−48
2e	50	26.5 ± 4.2	−42
2f	50	28.3 ± 3.6	−38
2g	50	25.9 ± 2.8	−44
2h	50	26.8 ± 5.2	−42

[a] Each compound was tested on a group of ten mice (20–25 g).
[b] Mean value of five determinations.

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