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Potential hypotensive agents: synthesis and hypotensive activity of oxime ethers derived from 1-naphthoxepines and related compounds

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Abstract—The synthesis and pharmacological evaluation of substituted oximino-ethers **1** and **2** of naphth[1,2-*b*]- and naphth[2,1-*b*]-oxepin-5-ones (**4** and **8**) were carried out. The hypotensive activity of oximino-ethers **1** and **2** was evaluated on anaesthetized cats. The results indicated that **1c** caused a fall of 80 mm/Hg for >100′ at a dose of 5 mg/kg iv in anaesthetized cats.

Hypertension, the most common cardiovascular disease, is a major risk factor in cardiovascular mortality. Enormous efforts have been made during last three decades in the development of new antihypertensive agents.[1,2] The β-adrenergic receptor antagonists as antihypertensive drugs led to the development of selective β_1- and β_2-adrenoceptor blocking agents. The structure activity relationship of two well-identified classes: (i) 1-phenyl-2-aminoethanols **I** and (ii) 1-aryloxy-3-aminopropanols **II** as β-blocking agents have been studied. Most of the β-blocking drugs presently belong to type **II** and are in clinical use. In an effort to understand the role of $ArOCH_2$ in β-blockers belonging to class **II** led to the emergence of oxime ethers as selective β_2-blockers (Fig. 1).[3] The β_2-selective adrenergic blocking activity of **III** (IPS-339)[4] has met with extensive exploration of oxime ethers.[5,6] Martani et al.[7] and Ferrarini et al.[8] have also reported β-adrenergic activity of some aromatic oxime ethers.

A number of recent publications have described the discovery and characterization of the biological,[9–11] microbiological[12,13] and pharmacological[14,15] properties of novel oxime ethers.

To potentially further increase the usefulness of oxime ethers, the possibility of preparing oxime ethers **1** and **2** were investigated. Since ketones are easily converted to oximes and the oxime ethers can be prepared by nucleophilic substitution with various nucleophiles, a number of oxime ethers **1** and **2** of naphth[1,2-*b*]-oxepin-5-ones **4** and naphth[2,1-*b*]-oxepin-5-ones **8** were prepared maintaining the oxime ether chain present in IPS-339 (**III**, Fig. 1).

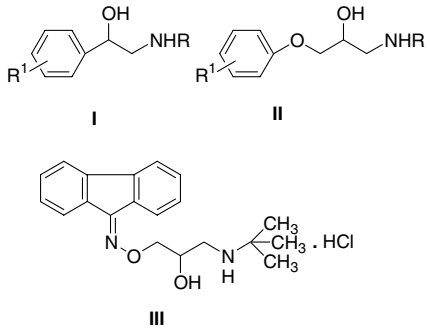

Figure 1. (**I**) 1-Phenyl-2-aminoethanols; (**II**) 1-aryloxy-3-amino-2-prapanolols; (**III**) IPS-339.

The hypotensive activity of oxime ethers **1** and **2** has been compared with the hypotensive drug propranolol[16] (**IV**, Fig. 2). These results are summarized in Table 1. Substitution of R with *n*-propyl, *iso*-propyl and *tert*-butyl in **1a–c** caused significant fall of blood pressure in cats at dose of 5 mg/kg iv. Replacement of R by *n*-propyl group (**1a**) caused a fall of blood pressure (BP) of 60 mm of Hg for 11 min whereas replacement of R by *iso*-propyl resulted in considerable fall of BP that is 110 mm of Hg for 35 min. Replacement of R by *tert*-butyl resulted

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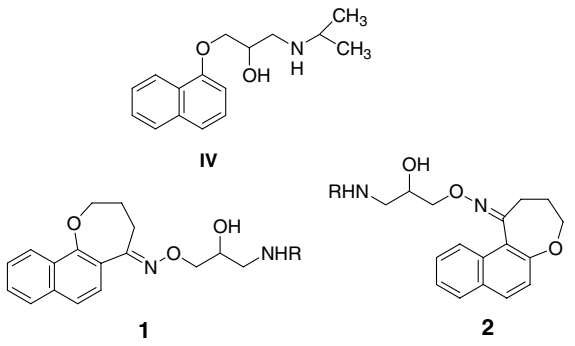


Figure 2. (**IV**) Propranolol; (**1**) **1a**–**c**; (**2**) **2a**–**c**.

in 80 mm of Hg fall of BP for >100 min at a dose of 5 mg/kg iv. This compound **1c** also caused 60 mm of Hg fall of BP for 75 min at a dose of 1 mg/kg iv. Based on the hypotensive activity observed for series of oxime ethers **1a**–**c**, the lead compound **1c** was found to be more potent than propranolol (**IV**, Fig. 2).

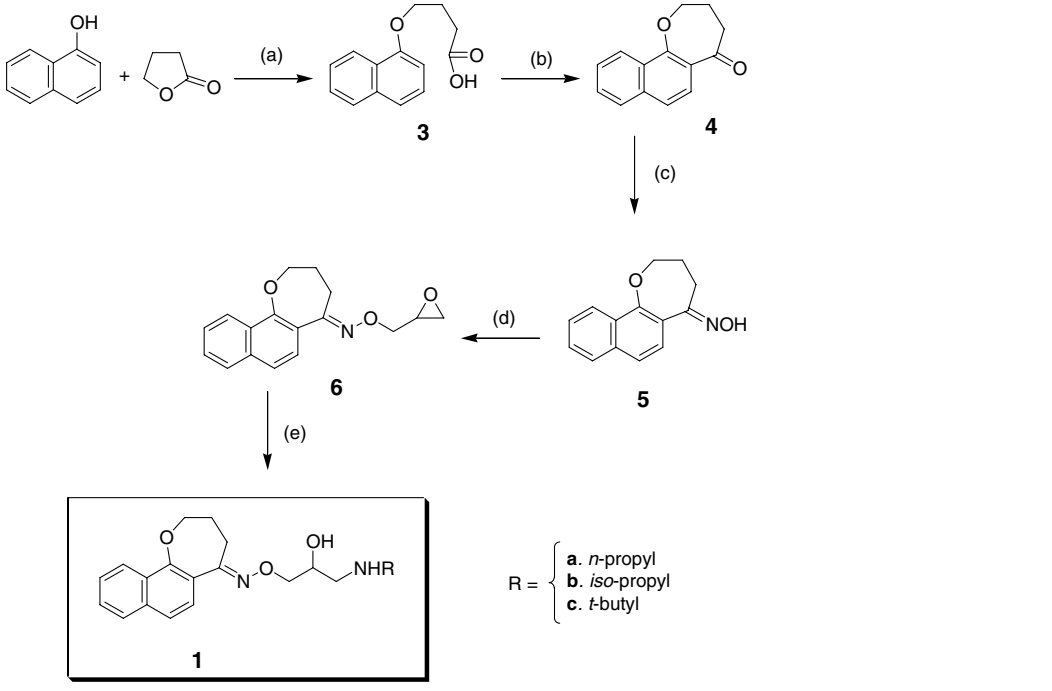
The substitution of R with *n*-propyl, *iso*-propyl and *tert*-butyl in oxime ether **2** resulted in substantial fall of BP as reported in Table 1. It is interesting to note that maximum effect of fall of BP and its duration was observed in *tert*-butyl analogue.

The comparison of oxime ethers **1** and **2** for their hypotensive activity leads to conclusion that oxime ethers **1** were more active hypotensive compounds. Although **1c**, the lead compound has shown the profile of a potent hypotensive agent, **1b** has also comparable hypotensive activity. In parallel experiment propranolol exhibited 50 mm of Hg fall for >60 min at an intravenous dose of 5 mg/kg in anaesthetized cats.

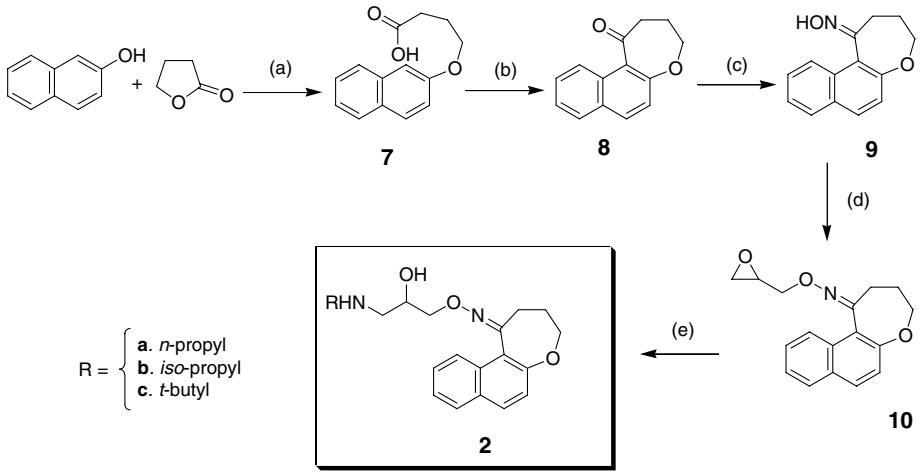
The syntheses of oxime ethers **1a**–**c** and **2a**–**c** are shown in Schemes 1 and 2, respectively. In Schemes 1 and 2, a two-step regioselective synthesis of naphth[1,2-*b*]-oxepin-5-one **4** and naphth[2,1-*b*]-oxepin-5-one **8** is depicted. The synthesis of **4** and **8** was achieved from 1- and 2-naphthols, respectively, by first conversion of

Table 1. Summary of hypotensive activity of compounds **1** and **2**

Compound	Cat			
	1 mg/kg iv		5 mg/kg iv	
	Fall of BP mmHg	% of maximum effect m ± SE	Fall of BP mmHg	% of maximum effect m ± SE
1a	20 (2′)	21 ± 2	60 (11′)	50 ± 5
1b	20 (2′)	14 ± 2	110 (35′)	88 ± 8
1c	60 (75′)	40 ± 4	80 (>100′)	55 ± 5
2a	18 (2′)	17 ± 2	16 (2′)	17 ± 2
2b	10 (2′)	7 ± 1	80 (16′)	70 ± 7
2c	18 (2′)	21 ± 2	50 (>35′)	41 ± 4
Propranolol	46 (40′)	35 ± 3	50 (>60′)	41 ± 4



Scheme 1. Synthesis of **1a**–**c**. Reagents and conditions: (a) NaOEt, 150 °C, dil HCl; (b) PPA, 100 °C; (c) $NH_2OH{\cdot}HCl$; (d) epichlorohydrin, DMF; (e) RNH_2, benzene.



Scheme 2. Synthesis of **2a–c**. Reagents and conditions: (a) NaOEt, 150 °C, dil HCl; (b) PCl_5, $AlCl_3$, benzene; (c) $NH_2OH{\cdot}HCl$; (d) epichlorohydrin, DMF; (e) RNH_2, benzene.

Table 2. Substituted 5-[(3-alkyl amino-2-hydroxypropyl)oximino]-2,3,4,5-tetrahydronaphth[1,2-*b*]-oxepines **1** and 5-[(3-alkyl amino-2-hydroxypropyl)oximino]-2,3,4,5-tetrahydronaphth[2,1-*b*]-oxepines **2**

Compound	R	Free base/hydrochloride	Yield (%)	Mp (°C)
1a	*n*-Propyl	Hydrochloride[a]	82	188
1b	*iso*-Propyl	Free base[b]	84	68
1c	*tert*-Butyl	Hydrochloride[a]	90	175
2a	*n*-Propyl	Hydrochloride[a]	82	163
2b	*iso*-Propyl	Hydrochloride[a]	78	174
2c	*tert*-Butyl	Hydrochloride[a]	88	183

[a]Recrystallized from anhydrous ethanol–ether.
[b]Hydrochloride could not be isolated due to hygroscopic nature.

naphthols into naphthoxy butyrates and subsequent hydrolysis to the corresponding acids **3** and **7**, respectively.[17] The compound **3** on cyclization with PPA gave ketone **4** whereas regioselective cyclization of **7** was accomplished with PCl_5 and $AlCl_3$ leading to formation of ketone **8** analogous to the procedure reported by Tandon and co-workers.[17,18]

Oxime ethers **1** and **2** were prepared from 5-oximino-naphth[1,2-*b*]-oxepine **5** and 5-oximino-naphth[2,1-*b*]-oxepine **9**, respectively.[19] Oximes **5** and **9** were prepared from ketones **4** and **8**, respectively, by reaction with 1 equiv of $NH_2OH{\cdot}HCl$ in ethanolic NaOH. The sodium salts of oximes **5** and **9** were reacted with epichlorohydrin in anhydrous DMF to form epoxides **6** and **10**, respectively. The epoxides **6** and **10** on heating with aliphatic primary amines in benzene afforded oxime ethers **1** and **2**, respectively (Table 2). The hydrochloride salts of **1** and **2** were prepared for pharmacological evaluation.

In conclusion we have described the synthesis and hypotensive activity of new series of oxime ether **1** and **2**. Compounds **1b** and **1c** have shown promising hypotensive activity. Compound **1c** is being further evaluated for future drug development.

Acknowledgements

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16. The hypotensive activity of oxime ether **1** and **2** was carried out in the pharmacology division of Central Drug Research Institute, Lucknow, India. Cats (2.5–4.0 kg) were anaesthetized with pentobarbitone sodium (35.0 mg/kg ip) and their blood pressure (BP) was recorded from a carotid artery.
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19. General procedure for preparation of **1a**–**c** and **2a**–**c**. Compound **6** or **10** (1.42 g, 5 mmol) was dissolved in benzene (10 mL) and amine (**a**–**c**) (5 mmol) was added to the solution. The mixture was heated for 12 h in a steel bomb at 150 °C. The solution was cooled and the solvent was removed in vacuo. The oil thus obtained was dissolved in anhydrous ether and ethereal hydrochloric acid solution added. The precipitated hydrochloride was filtered and crystallized from anhydrous EtOH and Et_2O to give **1a**–**c** or **2a**–**c**. For example; 5-[(3-*tert*-butylamino-2-hydroxypropyl)oximino]-2,3,4,5-tetrahydronaphth-[1,2-*b*]-oxepine·HCl (**1c**). Yield 90%; mp 175 °C; IR (KBr): *v* 3200–3500 cm^{-1} (OH and NH); MS *m*/*z* (free base): 356 (M^+). ^1H NMR (400 MHz, CCl_4, δ): 1.42 (s, 9H, $(CH_3)_3C$), 1.93 (m, 2H, C_3-H), 2.02 (bh, 2H, CHOH and NH), 2.72 (m, 3H, C_4-H and NCH_2), 3.54–3.68 (m, 3H, OCH_2 and CHOH), 3.94 (t, 2H, $J = 7.05$ Hz, C_2-H), 6.88–7.87 (m, 5H, naphth-H), 8.17 (m, 1H, naphth H). ^{13}C NMR (CCl_4, δ): 25.92, 31.30, 37.84, 48.30, 72.70, 73.20, 76.52, 106.30, 120.20, 121.90, 125.00, 125.60, 126.22, 127.32, 136.70, 155.82, 164.60. Anal. Calcd for $C_{21}H_{28}N_2O_3$ (356): C, 70.78; H, 7.86; N, 7.86. Found: C, 70.92; H, 7.66; N, 7.92.