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Studies on the Synthesis of Some Novel Oxime Ether Derivatives

Yeni Bazı Oksim Eter Türevleri Üzerinde Sentez Çalışmaları

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Abstract

Synthesis and some physico-chemical properties of six propafenone oxime ether derivatives are described. Their chemical structures have been elucidated by IR, ^{1}H NMR, mass spectra and elementary analysis.

Key words: Propafenone, Oxime ethers

Introduction

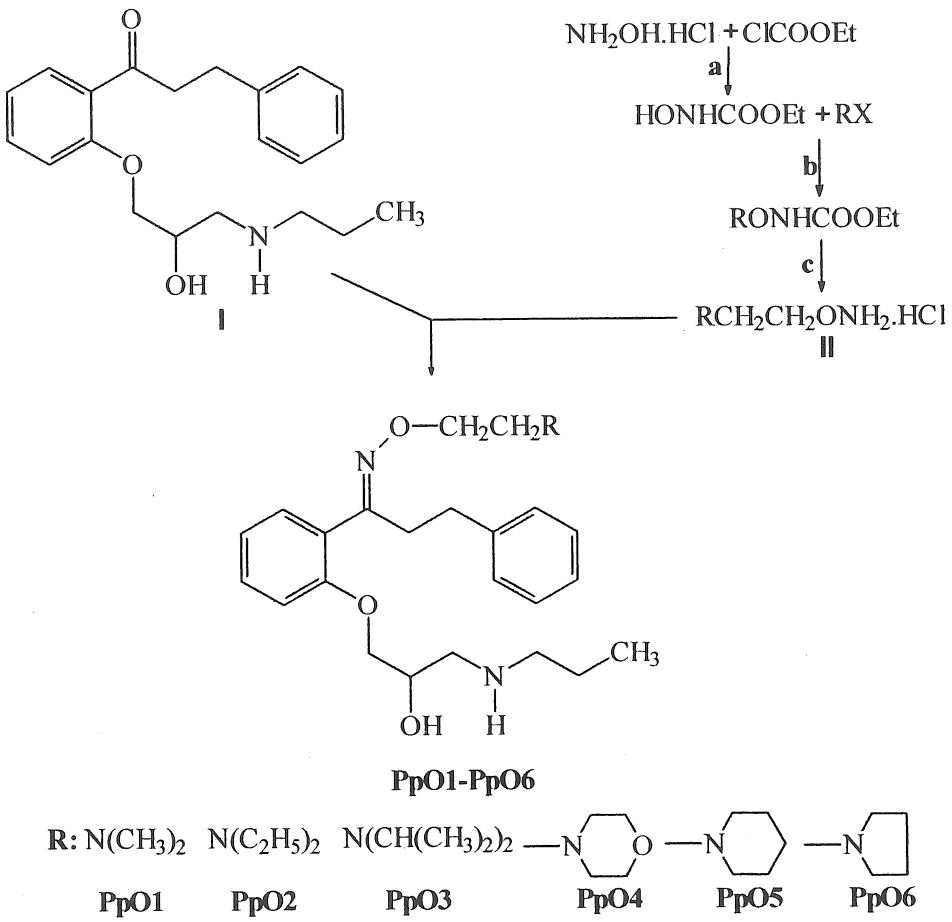
Oxygen substituted oxime ether derivatives present great interest as potential biologically active substances, since these compounds can react with the active groups of biological compounds. Studies of the biological properties of these compounds have shown that some of them possess antidepressant (Dijk and Davies, 1976), anticonvulsant (Philips, 1967), antifungal (Mixich and Thiele, 1979), antibacterial (Brain *et al.*, 1989; Balsamo *et al.*, 1990), antiviral (Wikel *et al.* 1980), antiinflammatory (Lapucci *et al.*, 1994), antihistaminic (Gootjes *et al.* 1972), antiandrogenic (Villani *et al.* 1969) and smooth muscle relaxant activities (Schenone and Minardi, 1968).
The present paper reports the synthesis of some new propafenone oxime ether derivatives, with the objective of investigating new biologically active compounds.

Material and Methods

Chemistry: All the instrumental analysis were performed at the Institut für Pharmazeutische Chemie, Münster University (Münster, Germany) with a Jasco FT/IR 420 spectrometer (IR spectra were recorded as KBr discs), a Bruker GmbH DPX-400, 400 MHz NMR spectrometer (the ^{1}H NMR spectra were measured in $CDCl_3$, all chemical shifts were reported as δ (ppm) values) and VG Platform II Micromass Spectrometer. Elementary analysis were performed on a Leco CHNS 932 analyzer at Instrumental Analysis Lab. of Scientific and Technical Research Council of Turkey (TUBITAK, Ankara) and satisfactory results ±0.4% of calculated values (C, H, N, S) were obtained. For the chromatographic analysis Merck Silica Gel 60 (230-400 mesh ASTM) was used. The chemical reagents used in synthesis were purchased from E. Merck (Darmstadt, FRG) and Aldrich (Milwaukee, MI, USA). Propafenone was kindly supplied by Servier Pharmaceuticals (Istanbul, Turkey). O-

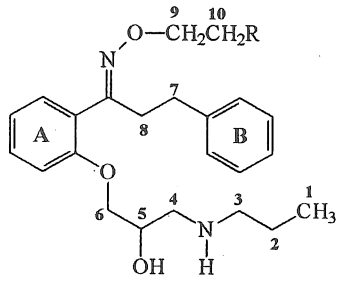
substituted hydroxyl amine derivatives were synthesized according to the literature(Winternitz and Lachazette, 1958).

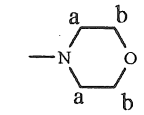
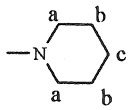
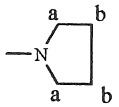
General procedure for the synthesis of compounds PpO1-PpO6 : 0.01mol of propafenone (I) and 0.01 mol O-substituted hydroxyl amine derivatives (II) were heated in 1 ml pyridine/10 ml abs. EtOH for 10 h (Scheme 1). The mixture was evaporated to dryness in vacuo and the residue was dissolved in water and made alkaline with NaOH 50% solution. The aqueous solution was extracted with $CHCl_3$ and the organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography through silica gel 60 (230-400 mesh ASTM) using $CHCl_3$:i-propanol (9:1) as the eluent. Some physical properties of the compounds are given in Table 1.



Scheme 1. General synthesis of **PpO1-PpO6**.
a:Na_2CO_3/ether-water,**b**: KOH/Abs.EtOH, **c**: HCl 30%

Table 1. Some physicochemical properties of compounds **PpO1-PpO6**

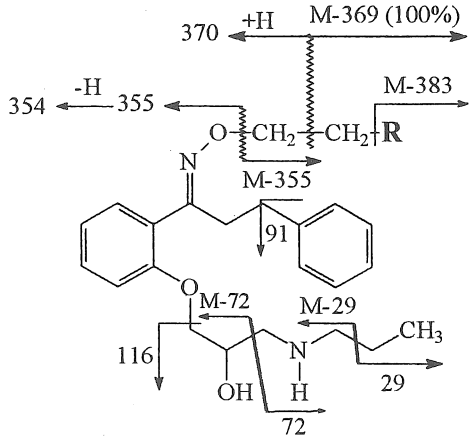


Comp*	R	Yield (%)	Formula	Analysis
PpO1	$N(CH_3)_2$	71.9	$C_{25}H_{37}N_3O_3$ Propafenone-O-(2-dimethylaminoethyl) oxime	C, H, N
PpO2	$N(C_2H_5)_2$	47.7	$C_{27}H_{41}N_3O_3$ Propafenone-O-(2-diethylaminoethyl) oxime	C, H, N
PpO3	$N(CH(CH_3)_2)_2$	57.9	$C_{29}H_{45}N_3O_3$ Propafenone-O-(2-di-isopropylaminoethyl) oxime	C, H, N
PpO4		77.6	$C_{27}H_{39}N_3O_4$ Propafenone-O-[2-(4-morpholino)ethyl] oxime	C, H, N
PpO5		63.6	$C_{28}H_{41}N_3O_3$ Propafenone-O-[2-(1-piperidino)ethyl] oxime	C, H, N
PpO6		61.7	$C_{27}H_{39}N_3O_3$ Propafenone-O-[2-(1-pyrolidino)ethyl] oxime	C, H, N

*All compounds were viscous-liquid.

Results and Discussion

Derivatives **PpO1- PpO6** were synthesized starting from propafenone (I) and treating with the appropriate O-substituted hydroxyl amine derivatives (II) in the presence of pyridine/abs EtOH (Scheme 1, Table 1) and only one isomer was obtained for synthesized compounds. The oxime ethers are theoretically able to exist as E and Z isomers. According to the literature of NMR spectra, E and Z isomers exhibited two signals for the C=N-O-CH_2- protons at 4.35-4.45 ppm (E isomer) and 4.20-4.30 ppm (Z isomer), O-CH_2 resonance for E isomer occurs at higher δ ppm than for Z isomer (Karabatsos and Hsi, 1967; Haney *et al.*, 1977; Boschmann and Winter, 1980). During our study C=N-O-CH_2- protons were observed at 4.14-4.31 ppm. Aromatic **A** and **B** ring protons were seen at 6.89-7.03 and 7.12-7.35 ppm, respectively. IR spectra of the compounds showed C=N stretching bonds at 1599-1601 cm^{-1}. In mass spectra, all the compounds had molecular (M^+) and M+1 ion peaks. M-369 ion peak was a base peak for all the compounds. Other fragments appeared at the expected m/z values (Scheme 2). Necessary spectral data are given in Table2.



Scheme 2. Mass fragmentation of the synthesized compounds

Table 2. Spectral data of **PpO1- PpO6**

No	^{1}H NMR (ppm)	MS (70 eV) m/z	IR(cm^{-1}) (C=N)
PpO1	0.92 (t, 3H, **1**), 1.53-1.64 (m, 2H, **2**), 2.37 (s, 6H, $N(CH_3)_2$), 2.62-3.10 (m, 11H, **3+4+7+8+10**+NH), 3.39 (s, 1H, OH), 4.03 (d, 2H, **6**), 4.11-4.19 (m, 1H, **5**), 4.28 (t, 2H, **9**), 6.89-7.00 (m, 4H, **A**), 7.12-7.36 (m, 5H, **B**)	427 (M+), 428 (M+1), 398, 357, 339, 116, 91, 87, 72, 58 (100%)	1600
PpO2	1.06 (t, 3H, **1**), 1.24 (t, 6H, $N(CH_2\underline{CH_3})_2$, 1.40-1.58 (m, 2H, **2**), 1.74 (s, 1H, OH), 2.53-3.09 (m, 13H, **3+4+8+10**+NH+$N(CH_2)_2$), 3.72 (dd, 2H, **7**), 4.01-4.05 (m, 3H, **5+6**), 4.25 (t, 2H, **9**), 6.90-6.99 (m, 4H, **A**), 7.13-7.36 (m, 5H, **B**)	455 (M+), 456 (M+1), 426, 383, 357, 116, 99, 91, 86 (100%), 72	1599
PpO3	1.02 (d, 12H, $N(CH(\underline{CH_3})_2)_2$), 1.25 (t, 3H, **1**), 1.37-1.55 (m, 2H, **2**), 1.72 (s, 1H, OH), 2.53-3.11 (m, 11H, **3+4+8+10**+NH+$N(\underline{CH}(CH_3)_2)_2$), 3.71 (dd, 2H, **7**), 3.78-4.03 (m, 3H, **5+6**), 4.14 (t, 2H, **9**), 6.90-6.99 (m, 4H, **A**), 7.16-7.35 (m, 5H, **B**)	483 (M+), 484 (M+1), 480 (M-3), 454, 411, 356,128, 116, 114 (100%), 91	1599
PpO4	1.25 (t, 3H, **1**), 1.42-1.61 (m, 2H, **2**), 2.31 (s, 1H, OH), 2.57-3.08 (m, 13H, **3+4+8+10**+NH+a), 3.66-3.77 (m, 6H, 7+b), 4.04-4.15 (m, 3H, **5, 6**), 4.30 (t, 2H, **9**), 6.91-7.00 (m, 4H, **A**), 7.13-7.37 (m, 5H, **B**)	469 (M+), 470 (M+1), 440, 397, 357, 130, 116, 114, 100 (100%), 91, 72	1600
PpO5	0.90 (t, 3H, **1**), 1.21-1.28 (m, 6H, b+c), 1.38-1.60 (m, 2H, **2**), 2.09 (s, 1H, OH), 2.34-2.76 (m, 12H, **3+4+8+10**+a), 2.80 (s, 1H, NH), 3.72 (dd, 2H, **7**), 4.02-4.05 (m, 3H, **5+6**), 4.18 (t, 2H, **9**), 6.91-7.03 (m, 4H, **A**), 7.16-7.30 (m, 5H, **B**)	467 (M+), 468 (M+1), 438, 356, 128, 116, 111, 98 (100%), 91, 70	1601
PpO6	0.91 (t, 3H, **1**), 1.44-1.55 (m, 6H, b+**2**), 1.80 (s, 1H, OH), 2.53-3.09 (m, 13H, **3+4+8+10**+NH+a), 4.04 (dd, 2H, **7**), 4.12-4.20 (m, 3H, **5+6**), 4.31 (t, 2H, **9**), 6.91-6.99 (m, 4H, **A**), 7.13-7.31 (m, 5H, **B**)	453 (M+), 454 (M+1), 452 (M-1), 424, 381, 357, 116, 114, 91, 84 (100%), 72	1601

Özet

Altı propafenon oksim eter türevi bileşiğin sentezi yapılmış ve bazı fizikokimyasal özellikleri incelenmiştir. Bileşiklerin kimyasal yapıları IR, ^{1}H NMR, Mass spektrumu ve elemanter analiz bulguları ile aydınlatılmıştır.

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