ELSEVIER

Il Farmaco 53 (1998) 197–208

IL FARMACO

Synthesis of certain unsubstituted, 9-*exo*-(dialkylaminomethyl)-, and 9-*endo*-(aralkyl)-tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoxime esters and ethers with local anesthetic and analgesic activities

M.Nabil Aboul-Enein [a,*], Aida El-Azzouny [a], Nevine A. Abdallah [a], Yousreya A. Maklad [b], Ola A. Saleh [a], M.Y. Ebeid [c]

[a] *Pharmaceutical Chemistry Group, Department of Pharmaceutical Sciences, National Research Centre, Tahrir Street, Dokki, Cairo, Egypt*
[b] *Pharmacology Group, Department of Pharmaceutical Sciences, National Research Centre, Tahrir Street, Dokki, Cairo, Egypt*
[c] *Faculty of Pharmacy, Cairo University, Cairo, Egypt*

Received 20 November 1997; accepted 23 December 1997

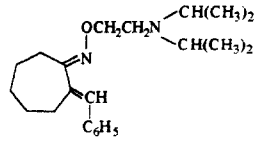
Abstract

The synthesis of series of unsubstituted, 9-*exo*-(dialkylaminomethyl)-, and 9-*endo*-(aralkyl)tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoximes esters and ethers **3a–j**, **4a–d**, **7a–j** and **13a–d** from the oxime synthons **2**, **6a–e**, **12a** and **12b**, respectively, is described. All the obtained compounds displayed noticeable local anesthetic potential. Among them, the oximino ether **4d** (ED_{50} = 0.15 mg/kg) and the oximino ester **3a** (ED_{50} = 0.23 mg/kg) are the most active of the series and possess higher potential than the reference standards. Some of the target compounds evoked analgesic effect, specially the oximino ether **7i** which is the most potent of the series and is stronger than acetylsalicylic acid but weaker than morphine hydrochloride.

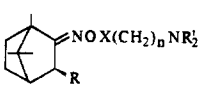
Keywords: Tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoxime esters and ethers; Stereochemistry; Local anesthetic activity; Analgesic activity; Structure–activity relationship

1. Introduction

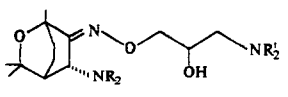
It has previously been reported that many oxime surrogates of various cycloalkyl **I** [1] and bicyclic structures **II** [2,3], **III** [4] and **IV** [5] elicit noticeable local anesthetic and analgesic properties.



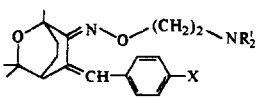
I, Stirocainide



II

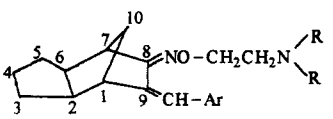


III

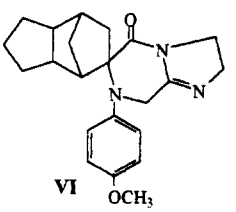


IV

In earlier communications we have documented the potent local anesthetic **V** [6] and analgesic **VI** [7] profiles among many tricyclo[5.2.1.$0^{2,6}$]decane derivatives. This tricyclic system possesses considerable lipophilicity, which is one of the factors required for the enhancement of the local anesthetic and analgesic effects [8,9].



V



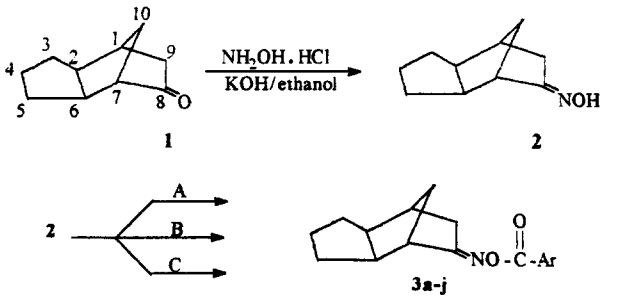
VI

Accordingly, it is envisioned to design and synthesize certain tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoxime esters **3a–j** and ethers **4a–d**, **7a–j** and **13a–d** to be pharmacologically evaluated for both their local anesthetic and analgesic potential.

The strategies for the synthesis of these derivatives **3a–j**, **4a–d**, **7a–j** and **13a–d** are outlined in Schemes 1–3.

* Corresponding author.

0014-827X/98/$19.00
PII S0014-827X(98)00008-1

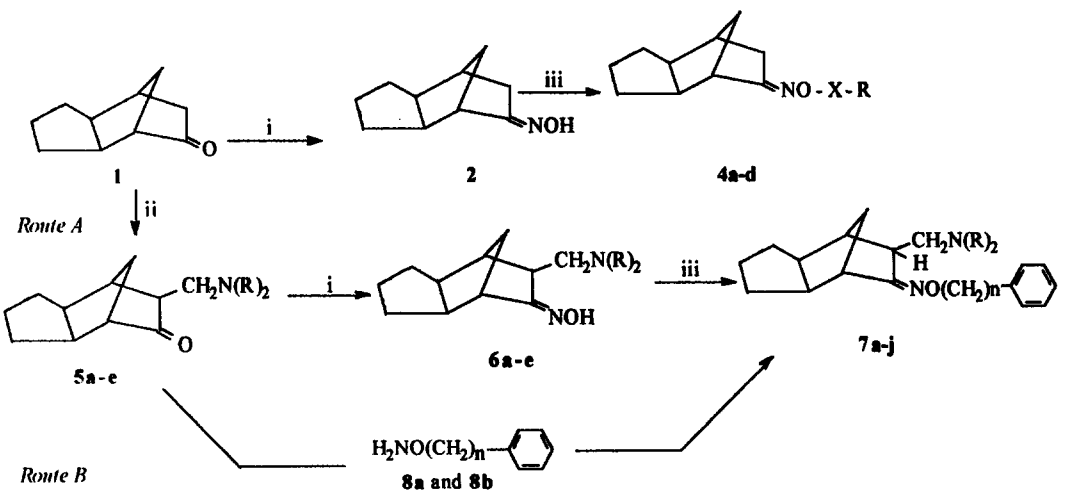


Scheme 1. Esters of tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoximes (**3a–j**, Table 1). Method A: C_6H_5COCl/TEA/dry benzene. Method B: ArCOOOH/DCCDI/DMAP/THF. Method C: ArCOOH/$ClCOOC_2H_5$/TEA/dry CH_2Cl_2.

2. Chemistry

The oxime esters **3a–j** (Scheme 1 and Table 1) were obtained by the oximation of the tricyclic ketone **1** to give the oxime **2** [10]. The latter underwent esterification either by (i) benzoyl chloride in the presence of triethylamine in dry benzene [11]; (ii) dicyclohexylcarbodiimide (DCCDI) coupling [12] with the appropriate acid in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) in tetrahydrofuran (THF); or (iii) the mixed anhydride route [13] using the appropriate acid, ethylchloroformate and triethylamine in dry methylene chloride (Scheme 1). In Scheme 2, the basic tricyclic ketones **5a–e** [14] were assembled through Mannich reaction, in which the ketone **1** was refluxed with paraformaldehyde and the appropriate secondary amine hydrochloride [15]. Under these reaction conditions the dialkylaminomethyl Mannich groupings acquire the 9-*exo* position, following the *exo* rule of Mannich reaction in the bicyclic system ketones [16]. The oximes **2** and **6a–e** were obtained from their corresponding ketones **1** and **5a–e** by the conventional oximation reaction. Elaboration of compounds **2** and **6a–e** to the targeted oximino ethers **4a–d** (Table 2) and **7a–j** (Table 4) was accomplished through etherification with the appropriate alkyl halide in the presence of sodium hydride in *N,N*-dimethylformamide (DMF). Due to the scarce yields of **7c,f–h** on following route A, an alternative synthetic pathway was adopted to give higher yields (route B). Thus, **5a–e** were refluxed with benzyl- and/or phenethyloxyamines **8a,b** [17] (Scheme 2) to obtain the desired ethers **7c,f–h**. The arylidenes **9a,b**, described in Scheme 3, were prepared by the reaction of the tricyclic ketone **1** with benzaldehyde and/or 3,4,5-trimethoxybenzaldehyde and potassium hydroxide in ethanol [6]. Subsequent catalytic hydrogenation with 10% Pd/C in THF under normal pressure and at room temperature resulted in a mixture of both the required ketones **10a,b** and the alcohols **11a,b**, as shown by the infrared bands at 3477 and 1739 cm^{-1} for the OH and C=O groups, respectively. This mixture was subsequently subjected to Jones' oxidation reaction conditions [18] with an aqueous solution of chromic acid and ether to lead cleanly and exclusively to the desired ketones **10a,b**. Sequential oximation of **10a** and **10b** with hydroxylamine hydrochloride and potassium hydroxide in ethanol yielded the oximes **12a** and **12b**, respectively.

Confirmation of the stereochemistry of the aralkyl group of the oximes **12a,b** was achieved by the $LiAlH_4$ reduction of **12a,b** to afford exclusively — according to the *exo* attack of complex hydride ions on unsaturated groups of the 1 and 7 unsubstituted norbornanone system [10] — the *endo*-amine **14**.



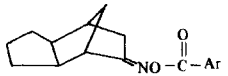
i : NH_2OH·HCl and ethanolic KOH or pyridine for **6c**, reflux for **18h**.

ii : $(R)_2$ NH·HCl/$(CH_2O)_n$/AcOH (at 100°C for **18h**).

iii : NaH/DMF/the appropriate alkylhalide at 80°C for **4 h**

Scheme 2. Aralkyl- and dialkylaminoethyl ethers of tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoximes (**4a–d**, Table 2) and aralkyl ethers of 9-*exo*-(dialkylaminomethyl)tricyclo[5.2.1.$0^{2,6}$] decane-8-ketoximes (**7a–j**, Table 4).

Table 1
Esters of tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoximes, **3a–j**



3a–j

No. [a]	Aromatic	Method	Yield (%)	M.p. [b] (°C)	Formula (mol. wt.)	Anal. (%): calc. (found)			EI/MS, *m/z* (%)	^{1}H NMR ($CDCl_3$): δ (ppm)
						C	H	N		
3a	C_6H_5	A	43	122–124	$C_{17}H_{19}NO_2$ (269.345)	75.81 (75.55)	7.11 (6.85)	5.20 (5.05)	269, M^+ (12); 105 (100)	0.95–2.55 (cm, 14H [d]), 7.35–8.10 (m, 5H [e])
3b	4-Cl–C_6H_4	B, C	30, 31	166–170	$C_{17}H_{18}ClNO_2$ (303.789)	67.21 (66.85)	5.97 (6.00)	4.61 (4.50)	303, M^+ (6); 139 (100)	
3c	2-Br–C_6H_4	C	54	oil [c]	$C_{17}H_{18}BrNO_2$ (348.241)	58.63 (58.40)	5.21 (4.90)	4.02 (3.90)	348, M^+ (1); 268 (100); 184 (100)	
3d	4-Br–C_6H_4	B, C	32, 34	114–117	$C_{17}H_{18}BrNO_2$ (348.241)	58.63 (58.70)	5.21 (5.15)	4.02 (4.20)	348, M^+ (4); 184 (100)	
3e	4-(CH_3O)–C_6H_4	C	50	88–92	$C_{18}H_{21}NO_3$ (299.371)	72.22 (71.85)	7.07 (6.90)	4.68 (4.40)	299, M^+ (20); 135 (100); 107 (43)	0.85–2.45 (cm, 14H [d]), 3.7 (s, 3H, CH_3O), 6.75–6.85 and 7.8–7.9 (m, 4H [e])
3f	4-NO_2–C_6H_4	C	73	128–130	$C_{17}H_{18}N_2O_4$ (314.342)	64.96 (64.75)	5.77 (5.80)	8.91 (8.65)	314, M^+ (4); 150 (100)	0.95–2.55 (cm, 14H [d]), 8.15–8.35 (m, 4H [e])
3g	2,4-$(Cl)_2$–C_6H_3	C	61	72–74	$C_{17}H_{17}Cl_2NO_2$ (338.235)	60.37 (60.15)	5.07 (4.85)	4.14 (4.20)	302.5, $M^+ - 35.5$ (20); 173 (100) [f]	0.8–2.4 (cm, 14H [d]), 7.1–7.7 (m, 3H [e])
3h	3,4,5-$(CH_3O)_3C_6H_2$	C	36	96–98	$C_{20}H_{25}NO_5$ (359.424)	66.84 (66.70)	7.01 (6.85)	3.89 (3.75)	359, M^+ (19); 195 (100)	
3i		C	34	132–134	$C_{16}H_{18}N_2O_2$ (270.332)	71.09 (70.95)	6.71 (6.50)	10.36 (10.10)	270, M^+ (4); 106 (100)	0.95–2.55 (cm, 14H [d]), 7.4–8.8 (m, 4H [e])
3j		C	32	94–98	$C_{16}H_{18}N_2O_2$ (270.332)	71.09 (70.80)	6.71 (6.50)	10.36 (10.20)	269, $M^+ - 1$ (35); 106 (100)	0.95–2.55 (cm, 14H [d]), 7.35–9.25 (m, 4H [e])

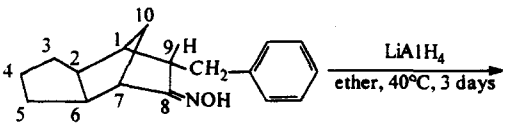
[a] IR (KBr) of **3a–j** showed bands at 1730–1759 (C=O ester) and 1662–1666 (C=N) cm^{-1}.
[b] Crystallization solvent: isopropanol.
[c] Purified by column chromatography using solvent A.
[d] Protons of tricyclo[5.2.1.$0^{2,6}$]decane system.
[e] Aromatic protons.
[f] CI/MS: 338.

Table 2
Aralkyl- and dialkylaminoethyl ethers of tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoximes, **4a–d**

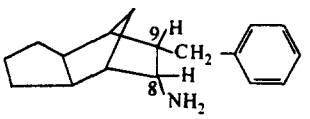
4a–d

No. [a,b]	R	X	Yield (%)	Formula (mol. wt.)	Anal. (%): calc. (found)			EI/MS, m/z (%)	^{1}H NMR ($CDCl_3$): δ (ppm)
					C	H	N		
4a	C_6H_5	CH_2	60	$C_{17}H_{21}NO$ (255.361)	79.96 (79.75)	8.29 (7.95)	5.49 (5.30)	255, M^+ (16); 91 (100)	0.9–2.65 (cm, 14H [c]), 5.05 (s, 2H, OCH_2), 7.25–7.40 (m, 5H, arom. protons)
4b	C_6H_5	CH_2CH_2	70	$C_{18}H_{23}NO$ (269.388)	80.26 (80.10)	8.61 (8.40)	5.20 (4.95)	270, $M^+ + 1$ (74); 165 (100); 105 (49); 91 (54)	
4c	$N(C_2H_5)_2$	CH_2CH_2	65	$C_{16}H_{28}NO$ (264.410)	72.68 (72.55)	10.67 (10.35)	10.59 (10.20)	264, M^+ (6); 86 (100)	0.85–2.7 (cm, 26H of which 14H [c] and 12H of $-CH_2N(C_2H_5)_2$), 3.95–4.05 (m, 2H, OCH_2)
4d	$N[CH(CH_3)_2]_2$	CH_2CH_2	56	$C_{18}H_{32}N_2O$ (292.464)	73.92 (73.65)	11.03 (10.80)	9.58 (9.20)	292, M^+ (35); 114 (100)	0.85–2.6 (cm, 28H of which 14H [c], 2H of CH_2N and 12H of $N(CH(CH_3)_2)_2$), 2.8–2.95 (m, 2H, $N(CH(CH_3)_2)_2$), 3.8–3.9 (m, 2H, OCH_2)

[a] IR (liquid film) of **4a–d** showed bands at 1650–1670 (C=N) cm^{-1}.
[b] All compounds (**4a–d**) were obtained as viscous oils and purified by column chromatography using alumina neutral I and solvent A.
[c] Protons of tricyclo[5.2.1.$0^{2,6}$]decane.



12a



14

The ^{1}H NMR of **14**·HCl showed a doublet of doublets at 3.7—3.8 ppm, for H-8 proton geminal to $\overset{\oplus}{N}H_3$, with $J_{8,9}$ = 15 Hz which entails a proof that emphasizes the *endo* configuration of the 9-benzyl group [19,20]. Etherification of the oximes **12a,b** with either diethyl- or diisopropylaminoethyl chloride using NaH in DMF led to the targeted oximino ethers **13a–d** (Table 5).

3. Pharmacology

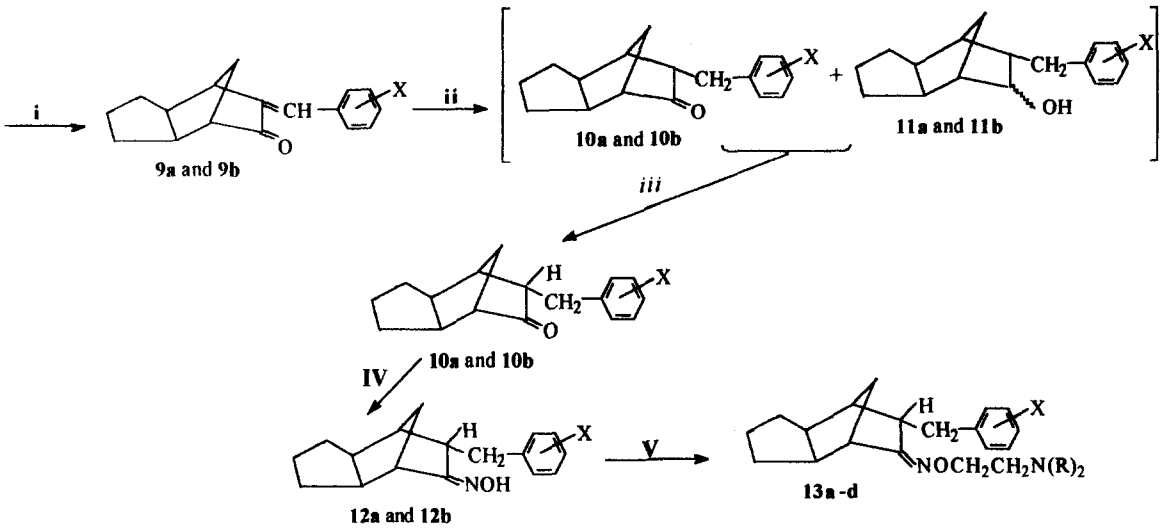
The prepared compounds **3a–j**, **4a–d**, **7a–j** and **13a–d** were evaluated for their local anesthetic and analgesic activities using the twitch-response test [21] and the hot-plate technique [22], respectively.

4. Experimental

4.1. Chemistry

All melting points were determined with electrothermal capillary melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded as thin film on NaCl discs (for oils) or as KBr pellets (for solids) with Philips PU 9712-JR and Shimadzu IR 435 spectrometers and values are presented in cm^{-1}. ^{1}H NMR spectra were carried out on a Jeol Ex-270 MHz spectrometer using tetramethylsilane (TMS) as the internal standard and chemical shift values are recorded in ppm on δ scales (cm = complicated multiplet, d = doublet, dd = doublet of doublets, and s = singlet). The mass spectra were run on Hewlett-Packard 3988 and Finnigan Mat SSQ-7000 spectrometers. Elemental analyses were carried out at the Microanalytical Centre, Cairo University, Egypt. The analytical results deviated by a maximum of ±0.4% from the theoretical values of C, H and N.

Column chromatography was performed with alumina neutral I for gravity columns. The solvents used in column elution were petroleum ether 40–60°C (solvent A) and/or n-pentane (solvent B). The purity of the compounds was checked by thin layer chromatography (TLC) on aluminium 60 G F_{254} neutral plates and spots were visualized by UV-light source (254 nm).



i $HC(=O)-C_6H_4-X$/KOH/ethanol (stirring for 24 h) **12a** and **12b**

ii H_2/Pd/C (10%)/THF (stirring for 24 h)

iii Chromic acid solution (Jone's reagent)/ether

iv $NH_2OH{\cdot}HCl$/KOH/ethanol (reflux for 18 h)

v NaH/DMF/$ClCH_2CH_2N(C_2H_5)_2$ or $ClCH_2CH_2N(i\text{-}C_3H_7)_2$

Scheme 3. Dialkylaminoethyl ethers of 9-*endo*-(aralkyl)tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoximes (**13a–d**, Table 5).

Tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoxime **2** was prepared according to the reported procedure cited in Ref. [10], m.p. 81–84°C, 95% yield (isopropanol).

*4.1.1. Benzoyl ester **3a** (method A)*

1.39 ml (0.012 mol) of benzoyl chloride were added dropwise at room temperature to a stirred mixture of 1.65 g (0.010 mol) of **2** and 1.1 ml of triethylamine in dry benzene (30 ml). The reaction mixture was stirred for 18 h, refluxed for 4 h, cooled, filtered off and the filtrate was washed with 10% Na_2CO_3 and then with water. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to afford **3a** (Table 1).

*4.1.2. 4-Chloro- and/or 4-bromobenzoyl esters **3b** and **3d** (method B)*

2.47 g (0.012 mol) of dicyclohexylcarbodiimide and 0.15 g (0.0012 mol) of 4-dimethylaminopyridine were added to a stirred solution of 0.012 mol of 4-chloro- and/or 4-bromobenzoic acid in dry THF (30 ml), followed by 1.98 g (0.012 mol) of **2**. The reaction mixture was stirred at ambient temperature for 24 h; a precipitate of dicyclohexylurea was formed and filtered off. The filtrate was evaporated, extracted with ethyl acetate and washed with 10% Na_2CO_3. The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to afford **3b** and/or **3d** (Table 1).

*4.1.3. Esters **1b–j** (method C)*

6.64 ml (0.088 mol) of ethyl chloroformate were added dropwise to an ice-cold mixture of 0.080 mol of the appropriate acid and 14.50 ml of triethylamine in dry methylene chloride (200 ml). Stirring was continued for a further 30 min at ambient temperature. Thereafter, 13.20 g (0.080 mol) of the oxime **2** was added portionwise and the reaction mixture was further stirred at room temperature for 18 h. The organic phase was washed with 10% $NaHCO_3$ and then with water, dried ($MgSO_4$), filtered and evaporated in vacuo to afford the oximino esters **3b–j** (Table 1).

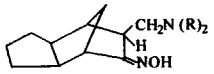
9-*exo*-(Dialkylaminomethyl)tricyclo[5.2.1.$0^{2,6}$]decan-8-ones **5a–e** were synthesized according to Ref. [14]. Unreported pyrrolidino derivative **5c**, m.p. (HCl, isopropanol) 198–200°C, was obtained in 70% yield. EI/MS, *m/z* (%): 233, M^+, $C_{15}H_{23}NO$ (3); 84 (100). *Anal.* Calc. C, 66.77; H, 8.97; N, 5.19; Found. C, 66.60, H, 8.75; N, 5.00%.

The oximes of **6a,b** and **6d,e** were synthesized by adopting the procedure cited in Refs. [10,18] (Table 3). The unreported oxime **6c** was prepared by refluxing a mixture of 35 g (0.150 mol) of **1**, 42 g (0.600 mol) of hydroxylamine hydrochloride in dry pyridine (200 ml) for 18 h. Thereafter, the pyridine was evaporated in vacuo and the residual oxime hydrochloride was dissolved in water (100 ml). The aqueous solution was washed with CH_2Cl_2, then basified with 10% NaOH to give a white precipitate of the oxime **6c** (Table 3).

*4.1.4. Aralkyl- and dialkylaminoethyl ethers **4a–d** (Table 2) and aralkylethers **7a–j** (Table 4)*

6 mmol of the appropriate aralkyl halide or 2-dialkylaminoethyl chloride (Scheme 2) in DMF (5 ml) was added dropwise to a stirred mixture of 5 mmol of either oxime **2** or **6a–e** and 0.19 g (8 mmol) of sodium hydride in DMF (15 ml). The reaction mixture was stirred at room temperature for 30 min, heated at 80°C for 4 h, cooled (10°C), diluted

Table 3
9-*exo*-(Dialkylaminomethyl)tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoximes, **6a–e**

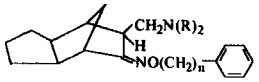


6a–e

No. [a,b]	N(R)$_2$	Yield (%)	M.p. [b]	Formula (mol. wt.)	Analysis (%): calc. (found)			EI/MS, m/z (%)	^{1}H NMR ($CDCl_3$): δ (ppm)
					C	H	N		
6a	$N(CH_3)_2$	46	168–170 (IP)	$C_{13}H_{22}N_2O$ (222.330)	70.23 (69.95)	9.97 (9.75)	12.59 (12.20)	222, M^+ (8); 58 (100)	1.4–2.85 (cm, 21H of which 13H [f] and 8H of $CH_2N(CH_3)_2$), 9.35 (br s, 1H)
6b	$N(C_2H_5)_2$	60	180–184 (EA/PE)	$C_{15}H_{26}N_2O$ (250.383)	71.95 (71.60)	10.46 (10.10)	11.19 (10.85)	251, $M^+ + 1$ (4); 86 (100)	1.00–3.60 (cm, 25H of which 13H [f] and 12H of $CH_2N(C_2H_5)_2$), 11.7 (br s, 1H)
6c	C_4H_8N [c]	83	176–178 (IP)	$C_{15}H_{24}N_2O$ (248.374)	72.54 (72.40)	9.74 (9.80)	11.28 (10.95)	248, M^+ (40); 231 (90); 84 (100)	0.95–2.75 (cm, 23H of which 13H [f] and 10H of pyrrolidinomethyl protons), 9.40 (br s, 1H [g])
6d	$C_5H_{10}N$ [d]	52	136–140 (IP)	$C_{16}H_{26}N_2O$ (262.394)	73.24 (73.60)	9.98 (10.05)	10.67 (10.95)	263, $M^+ + 1$ (5); 98 (100)	0.90–2.80 (cm, 25H of which 13H [f] and 12H of piperidinomethyl protons), 12.8 (br s, H [g])
6e	C_4H_8NO [e]	3	130–134 (EA/PE)	$C_{15}H_{24}N_2O_2$ (264.367)	68.15 (68.05)	9.15 (9.00)	10.60 (10.25)	264, M^+ (6); 100 (100)	0.90–2.85 (cm, 19H of which 13H [f] and 6H of $CH_2N(CH_2)_2$ of morpholino), 3.65–3.80 (m, 4H, $(CH_2)_2O$ of morpholino), 12.8 (br s, H [g])

[a] IR (KBr) of **6a–e** showed bands at 2971–3530 (OH) and 1653–1675 (C=N) cm^{-1}.
[b] Crystallization solvents: IP = isopropanol and EA/PE = ethyl acetate/petroleum ether at 60–80°C.
[c] Pyrrolidino.
[d] Piperidino.
[e] Morpholino.
[f] Protons of tricyclo[5.2.1.$0^{2,6}$]decane system.
[g] Protons of =NO*H*, D_2O exchangeable.

Table 4
Aralkyl ethers of 9-*exo*-(dialkylaminomethyl)tricyclo[5.2.1.$0^{2,6}$]decane-8-ketoximes, **7a–j**



7a–j

No. [a]	*n*	N(R)$_2$	Route	Yield (%)	M.p. [b] (°C)	Formula (mol. wt.)	Analysis (%): calc. (found)			EI/MS, *m/z* (%)	^{1}H NMR ($CDCl_3$): δ (ppm)
							C	H	N		
7a	1	$N(CH_3)_2$	A	66	192–194 (IP)	$C_{20}H_{28}N_2O \cdot HCl$ (348.918)	68.85 (68.60)	8.38 (8.05)	8.03 (8.30)	312, M^+ (33); 91 (70); 58 (100)	1.05–2-75 (cm, 21H of which 13H [g] and 8H of $CH_2N(CH_3)_2$), 4.95–5-05 (m, 2H, O–CH_2), 7.25–7.40 (m, 5H [h])
7b	1	$N(C_2H_5)_2$	A	55	98–100 (IP)	$C_{22}H_{32}N_2O \cdot HCl$ (376.972)	70.10 (70.05)	8.82 (8.65)	7.43 (7.50)	340, M^+ (33); 86 (100)	0.85–2-95 (cm, 25H of which 13H [g] and 12H of $CH_2N(C_2H_5)_2$), 4.95–5.0 (m, 2H, OCH_2), 7.2–7.35 (m, 5H [h])
7c	1	C_4H_8N [d]	A, B	36, 69	152–154 (IP)	$C_{22}H_{30}N_2O \cdot HCl$ (374.956)	70.47 (70.30)	8.33 (8.15)	7.47 (7.20)	339, $M^+ + 1$ (54); 231 (88); 84 (100)	0.9–2.65 (cm, 23H of which 13H [g] and 10H of pyrrolidinomethyl protons), 4.45–5.05 (m, 2H, OCH_2), 7.2–7.4 (m, 5H [h])
7d	1	$C_5H_{10}N$ [e]	A	60	148–156 (IP)	$C_{23}H_{32}N_2O \cdot HCl$ (388.983)	71.02 (70.70)	8.55 (8.25)	7.20 (7.05)	352, M^+ (3); 98 (100)	0.9–2.75 (cm, 25H of which 13H [g] and 12H of piperidinomethyl protons), 4.8–4.95 (m, 2H, OCH_2), 7.1–7.35 (m, 5H [h])
7e	1	C_4H_8NO [f]	A	56	200–204 (IP)	$C_{22}H_{30}N_2O_2 \cdot HCl$ (390.955)	67.59 (67.25)	7.99 (7.75)	7.17 (7.20)	354, M^+ (8); 100 (100)	0.9–2.8 (cm, 19H of which 13H [g] and 6H of $CH_2N(CH_2)_2$), 3.6–3.75 (m, 4H, $(CH_2)_2O$), 4.95–5.05 (m, 2H, OCH_2), 7.25–7.4 (m, 5H [h])
7f	2	$N(CH_3)_2$	A, B	41, 52	170–174 (IP)	$C_{21}H_{30}N_2O \cdot HCl$ (362.945)	69.50 (69.35)	8.61 (8.40)	7.72 (7.55)	326, M^+ (10); 105 (18); 58 (100)	0.8–3.0 (cm, 23H of which 13H [g], 8H of CH_2N $(CH_3)_2$ and 2H of CH_2–C_6H_5), 4.15–4.25 (m, 2H, OCH2), 7.15–7.35 (m, 5H [h])
7g	2	$N(C_2H_5)_2$	A, B	29, 56	oil [c]	$C_{23}H_{34}N_2O$ (354.538)	77.92 (77.70)	9.67 (9.50)	7.90 (7.70)	355, $M^+ + 1$ (10); 105 (18); 58 (100)	
7h	2	C_4H_8N [d]	A, B	30, 68	oil	$C_{23}H_{32}N_2O$ (352.522)	78.37 (78.15)	9.15 (8.80)	7.95 (7.70)	353, $M^+ + 1$ (4); 231 (36); 84 (100)	0.8–3.2 (cm, 25H of which 13H [g], 10H of pyrrolidinomethyl protons and 2H of CH_2–C_6H_5), 4.15–4.3 (m, 2H, OCH_2), 7.15–7.40 (m, 5H [h])
7i	2	C_5H_6N [e]	A	52	220–224 (IP)	$C_{24}H_{34}N_2O \cdot HCl$ (403.010)	71.53 (70.35)	8.75 (8.50)	6.95 (7.05)	367, $M^+ + 1$ (36); 245 (58); 98 (100)	1.0–2.5 (cm, 25H of which 13H [g] and 12H of piperidinomethyl protons), 2.9–3.0 (m, 2H, CH_2–C_6H_5), 4.15–4.25 (m, 2H, OCH_2), 7.15–7.30 (m, 5H [h])
7j	2	C_4H_8NO [f]	A	50	oil [c]	$C_{23}H_{32}N_2O_2$ (368.521)	74.96 (75.00)	8.75 (8.50)	7.60 (7.50)	368, M^+ (20); 247 (84); 100 (100)	

[a] IR (liquid film) of **7a–d** bands at 1653–1660 (C=N) cm^{-1}.
[b] Crystallization solvent: IP = isopropanol.
[c] Purified by column chromatography using alumina neutral I and solvent A.
[d] Pyrrolidino.
[e] Piperidino.
[f] Morpholino.
[g] Protons of tricyclo[5.2.1.$0^{2,6}$]decane system.
[h] Aromatic protons.

with water (100 ml) and extracted with ether. For compounds **4a,b**: the ethereal extracts were dried ($MgSO_4$), filtered and evaporated in vacuo to give **4a,b** as viscous oils which were purified by column chromatography using solvent A. For compounds **4c,d** (Table 2) and **7a–j** (Table 4) the ethereal layers were extracted with 2N HCl, basified with 2N NaOH, extracted with ether, dried ($MgSO_4$), filtered and evaporated in vacuo to afford oily products which were purified by column chromatography using solvent B (Tables 2 and 4). Compounds **7a–f,i** were converted to their hydrochloride salts (Table 4).

O-(Benzyl- and phenethyl)oxyamine **13a,b** were synthesized using the procedure of Nicholaus et al. [16] from hydroxyurethane.

9-(Arylidene)tricyclo[5.21.$0^{2,6}$]decan-8-ones **9a,b** were prepared according to Ref. [6] in 57% and 54% yields, respectively.

To prepare 9-*endo*-(aralkyl)tricyclo[5.21.$0^{2,6}$]decan-8-ones **10a,b**, a solution of 2.19 g (0.009 mol) of **9a** and/or 3.00 g (0.009 mol) of **9b** in THF (60 ml) was hydrogenated using 0.90 g of Pd/C (10%) at room temperature and under normal pressure for 24 h. The catalyst was removed by filtration over celite and the filtrate was evaporated in vacuo to give a mixture of ketone **10** and their respective alcohol **11**. The appropriate mixture was subjected to Jones' oxidation procedure [18] using 9 ml of chromic acid to afford exclusively the ketones **10a,b** in 85% and 83% yields, respectively, which were used as such in the next step.

9-*endo*-(Aralkyl)tricyclo[5.21.$0^{2,6}$]decan-8-one oximes **12a,b** were prepared as cited in Ref. [10]. **12a**: m.p. 118°C (isopropanol, 60%); **12b**: viscous oil purified by column chromatography using solvent A (65%). IR: 3264–3384 cm^{-1} (OH) and 1680–1685 cm^{-1} (C=N).

Dialkylaminoethyl ethers **13a–d** of 9-*endo*-(aralkyl)tricyclo[5.2.1.$0^{2,6}$]decan-8-one oximes were achieved following the same procedure adopted for **6a–e**, **4a–d** and **7a–j** and were obtained as oils, purified by acid–base treatment, then by column chromatography using solvent A (Table 5).

(*E*)-2-Benzylidenecycloheptanone(*E*)-*O*-(2-diisopropylaminoethyl) oxime, 'stirocainide **I**' [1], was synthesized as cited in Refs. [1,6] starting from cycloheptanone.

2-Benzylcycloheptanone(*E*)-*O*-(2-diisopropylaminoethyl) oxime, 'reduced stirocainide **15**', was prepared by following the same method used for the synthesis of **13a–d** (Scheme 3) using cycloheptanone as a starting material.

5. Results and discussion

5.1. Local anesthetic activity

The oximino esters **3a–j** (Table 6, Fig. 1) showed significant local anesthetic potential with rapid onset (5 min) of anesthesia. Compound **3a** (ED_{50} = 0.23 mg/kg) is the most active one of this series, as well as of the reference standards, procaine (ED_{50} = 18 mg/kg), xylocaine (2.13 mg/kg) and stirocainide (0.39 mg/kg).

The ethers **4a–d** (Table 6, Fig. 2) exhibited high local anesthetic potency. The *N*-diisopropylaminoethyl oximino ether **4d** showed the highest activity (ED_{50} = 0.15 mg/kg), higher also than the reference standards, whereas the Mannich compounds **7a–j** (Table 6, Fig. 3) displayed a higher local anesthetic effect than xylocaine and procaine, but slightly lower activity than stirocainide, **4d** and **3a**.

In addition, the data revealed that the pyrrolidino **7h** (ED_{50} = 0.40 mg/kg), the diethylamino **7b** (ED_{50} = 0.42 mg/kg) and the morpholino **7j** (ED_{50} = 0.43 mg/kg) derivatives were nearly equipotent and were the most active members among the group **7a–j** with a rapid onset of action. These compounds showed 3.8–5 times and 32–45 times the

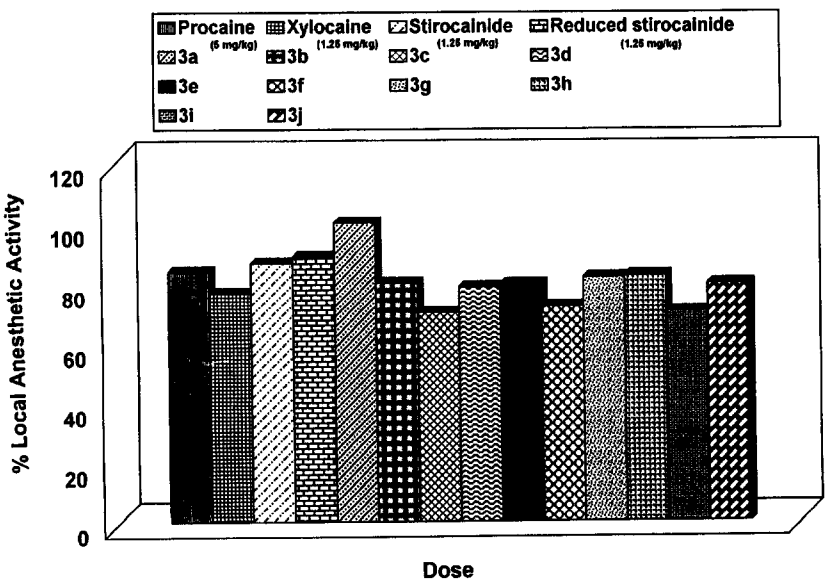
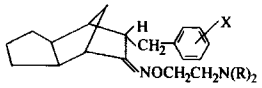


Fig. 1. Local anesthetic activity of compounds **3a–j** (1.25 mg/kg).

Table 5
Dialkylaminoethyl ethers of 9-*endo*-benzyltricyclo[5.2.1.$0^{2,6}$]decane-8-ketoximes, **13a–d**



13a–d

No. [a,b]	X	$N(R)_2$	Yield (%)	Formula (mol. wt.)	Analysis (%): calc. (found)			EI/MS, m/z (%)	^{1}H NMR ($CDCl_3$): δ (ppm)
					C	H	N		
13a	H	$N(C_2H_5)_2$	87	$C_{23}H_{34}N_2O$ (354.538)	77.92 (77.70)	9.67 (9.35)	7.90 (8.00)	355, $M^+ + 1$ (52); 91 (18); 86 (100)	0.85–2.80 (cm, 26H of which 12H [c], 12H of $CH_2N(C_2H_5)_2$ and 2H of CH_2–C_6H_5), 2.95–3.15 (dd, 1H), 4.0–4.2 (m, 2H, 0–CH_2), 7.1–7.35 (m, 5H [d])
13b	H	$N(i\text{-}C_3H_7)_2$	53	$C_{25}H_{38}N_2O$ (382.592)	78.48 (78.30)	10.01 (9.90)	7.32 (7.50)	382, M^+ (100); 339 (19); 127 (96); 91 (90)	0.85–3.20 (cm, 31H of which 13H [c], 16H of CH_2N–$(CH(CH_3)_2)_2$ and 2H of CH_2–C_6H_5)), 3.9–4.05 (m, 2H, OCH_2), 7.1–7.35 (m, 5H [d])
13c	3,4,5-$(CH_3O)_3$	$N(C_2H_5)_2$	63	$C_{26}H_{40}N_2O_4$ (444.617)	70.24 (70.40)	9.07 (9.20)	6.30 (6.40)	445, $M^+ + 1$ (1); 181 (16); 86 (100)	
13d	3,4,5-$(CH_3O)_3$	$N(i\text{-}C_3H_7)_2$	66	$C_{28}H_{44}N_2O_4$ (472.671)	71.15 (70.90)	9.38 (9.15)	5.93 (5.80)	472, M^+ (86); 181 (100); 114 (67)	0.85–2.7 (cm, 28H of which 12H [c], 14H of CH_2–$N(CH(CH_3)_2)_2$ and 2H of CH_2–arom.), 2.9–3.1 (m, 3H of which 2H of N–(CH–) and 1H), 3.7–3.85 (m, 9H, $(CH_3O)_3$), 3.85–4.10 (m, 2H, OCH_2), 6.4–6.5 (d, 2H [d])

[a] IR (liquid film) of **13a–d** showed bands at 1656–1658 (C=N) cm^{-1}.
[b] All compounds (**13a–d**) were obtained as oils, and purified by column chromatography using alumina neutral I and solvent A.
[c] Protons of the tricyclo[5.2.1.$0^{2,6}$]decane system.
[d] Aromatic protons.

Table 6
Local anesthetic activity of compounds **3a–j**, **4a–d**, **7a–j** and **13a–d** using the twitch-reponse test

Compound [a]	5 min [c]	30 min [c]	ED_{50} (mg/kg) (confidence limits)	Compound [a]	5 min [c]	30 min [c]	ED_{50} (mg/kg) (confidence limits)
Xylocaine [a]	100.00	76.27	2.13 (1.72–3.84)	**4c**	100.00	77.08	0.37 (0.24–0.57)
Procaine [b]	95.83	75.00	18 (14.99–21.01)	**4d**	100.00	100.00	0.15 (0.12–0.19)
Stirocainide **I** [a]	91.67	83.33	0.39 (0.26–0.58)	**7a**	95.92	54.17	0.44 (0.28–0.70)
Reduced stirocainide **15** [a]	100.00	70.83	0.32 (0.19–0.75)	**7b**	100.00	89.53	0.42 (0.27–0.64)
3a	100.00	100.00	0.23 (0.15–0.35)	**7c**	91.67	72.92	0.51 (0.29–0.88)
3b	89.58	75.00	0.48 (0.29–0.78)	**7d**	100.00	63.89	0.55 (0.31–0.98)
3c	100.00	64.58	0.62 (0.37–0.11)	**7e**	100.00	74.17	0.50 (0.32–0.78)
3d	95.83	83.33	0.50 (0.29–0.88)	**7f**	93.75	58.33	0.50 (0.32–0.79)
3e	100.00	66.67	0.50 (0.40–0.63)	**7g**	98.31	66.67	0.51 (0.29–0.90)
3f	97.36	73.14	0.59 (0.36–0.97)	**7h**	100.00	75.00	0.40 (0.38–0.43)
3g	97.92	82.63	0.45 (0.28–0.72)	**7i**	100.00	70.83	0.49 (0.36–0.79)
3h	91.67	62.50	0.44 (0.28–0.69)	**7j**	100.00	89.58	0.43 (0.28–0.67)
3i	87.50	64.58	0.63 (0.37–1.09)	**13a**	100.00	75.00	0.47 (0.29–0.77)
3j	100.00	70.83	0.50 (0.32–0.79)	**13b**	100.00	83.33	0.45 (0.37–0.74)
4a	97.62	73.81	0.60 (0.35–1.03)	**13c**	95.83	64.58	0.64 (0.37–1.12)
4b	97.92	80.95	0.49 (0.27–0.88)	**13d**	93.75	66.67	0.57 (0.34–0.95)

[a] 1.25 mg/kg.
[b] 5 mg/kg.
[c] Percent of animals showing anesthesia, 5 and 30 min from compound administration.

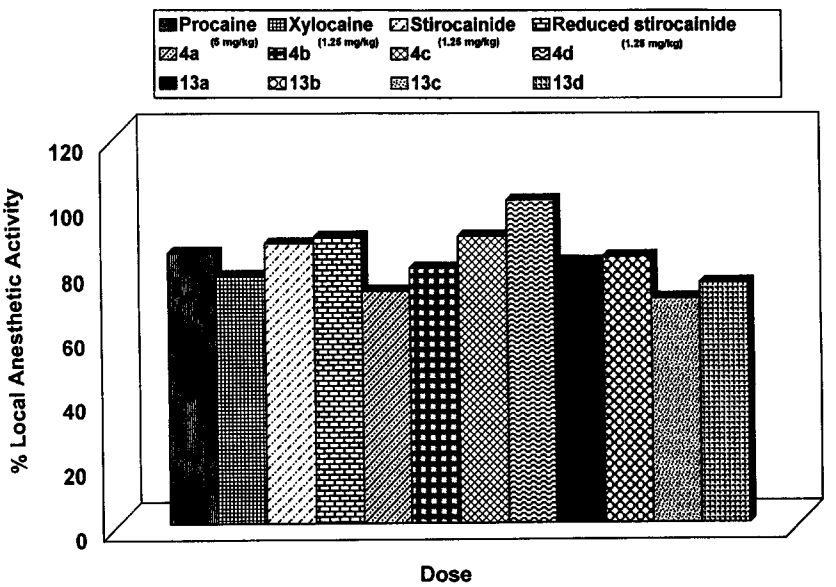


Fig. 2. Local anesthetic activity of compounds **4a–d** and **13a–d** (1.25 mg/kg).

local anesthetic potency of xylocaine (ED_{50} = 2.13 mg/kg) and procaine (ED_{50} = 18 mg/kg), respectively.

Moreover, among the 9-*endo*-benzyl ethers **13a–d** (Table 6, Fig. 2) the compounds **13a** (ED_{50} = 0.47 mg/kg) and **13b** (ED_{50} = 0.45 mg/kg) were nearly equipotent and exhibited higher local anesthetic potential than xylocaine (ED_{50} = 2.13 mg/kg) and procaine (ED_{50} = 18 mg/kg) with a rapid onset of action (5 min). Nevertheless, they were slightly less potent than stirocainide (ED_{50} = 0.39 mg/kg), **2d** and **1a**.

Regarding the reduced stirocainide **15** (ED_{50} = 0.32 mg/kg), it displayed a remarkable local anesthetic profile if compared with xylocaine and procaine but was nearly equipotent with the parent compound stirocainide **I**.

We can observe that the tested compounds **4d** (ED_{50} = 0.15 mg/kg) and **3a** (ED_{50} = 0.23 mg/kg) were more active than compound **15**. In addition, the benzyl derivatives **13a–d** as well as compound **15** were more active than their respective unsaturated benzylidene precursors, indicating that the saturation of the ylidene double bond augmented the local anesthetic potential. Figs. 1–3 show the percentage of the local anesthetic potency of the tested compounds and the standard references.

5.2. Analgesic activity

The data presented in Table 7 and Fig. 4 reveal that compound **3c** (ED_{50} = 108 mg/kg) was the most active among

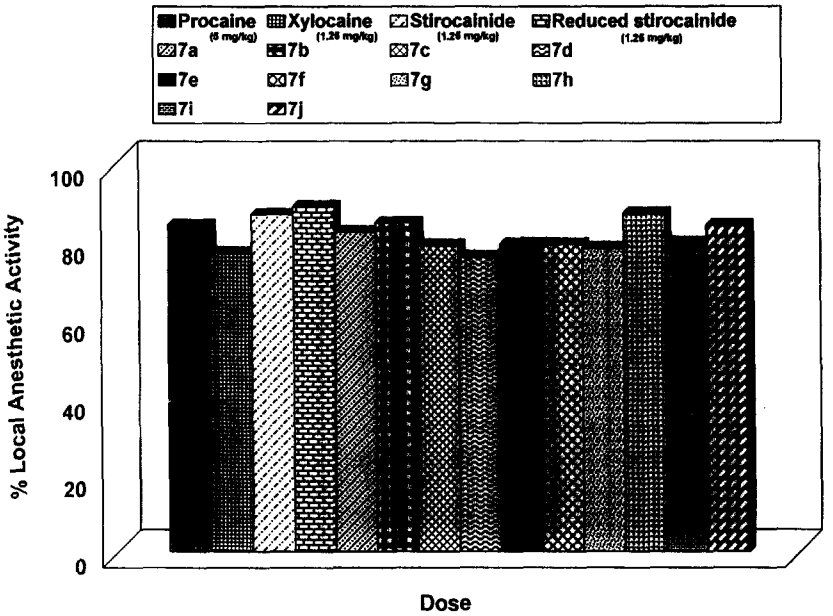


Fig. 3. Local anesthetic activity of compounds **7a–j** (1.25 mg/kg).

Table 7
Analgesic activity of compounds **3a–j**, **4a–d**, **7a–j** and **13a–d** by the hot-plate technique

Compound	ED_{50} (mg/kg) (confidence limits)	Compound	ED_{50} (mg/kg) (confidence limits)
Morphine	2.25 (1.60–3.16)	**4d**	inactive
Acetylsalicylic acid	115 (64.86–203.89)	**7a**	94 (59.84–147.67)
3a	130 (98.86–170.95)	**7b**	inactive
3b	120 (89.55–160.80)	**7c**	100 (73.00–136.42)
3c	108 (84.97–137.32)	**7d**	110 (84.75–142.77)
3d	154 (99.68–237.99)	**7e**	107 (84.41–135.60)
3e	122 (92.83–162.33)	**7f**	130 (110.71–152.64)
3f	inactive	**7g**	98 (80.07–119.95)
3g	137 (121.89–153.96)	**7h**	95 (68.05–132.62)
3h	118 (89.73–155.16)	**7i**	90 (51.57–157.05)
3i	inactive	**7j**	110 (88.07–137.39)
3j	115 (91.27–142.39)	**13a**	inactive
4a	140 (91.74–213.66)	**13b**	inactive
4b	inactive	**13c**	inactive
4c	inactive	**13d**	inactive

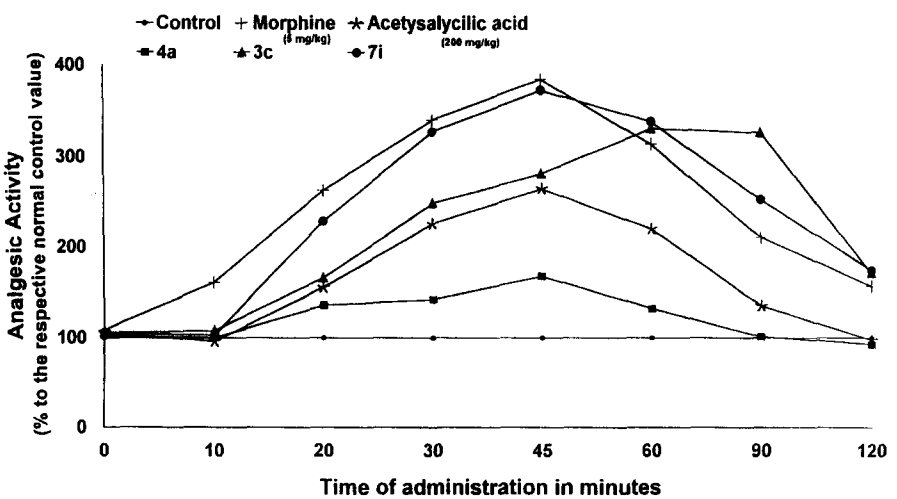


Fig. 4. Analgesic activity of compounds **3c**, **4a** and **7i** (150 mg/kg) in adult male mice after the respective time from compound administration.

the oximino esters **3a–j**. It exhibited a slightly higher analgesic potency than acetylsalicylic acid (ED_{50} = 115 mg/kg), as a peripheral-acting analgesic standard, but it was much less active than morphine (ED_{50} = 2.25 mg/kg), as a central-acting analgesic standard.

However, the benzyloximino ether derivative **4a** (ED_{50} = 140 mg/kg) was the only compound among the group **4a–d** (Table 7) which showed analgesic activity. Its potency was lower than that of acetylsalicylic acid, and far less than that of morphine. Also, the data show that elongation of the side chain in this group abolished the analgesic activity. Meanwhile, the data presented in Table 7 demonstrate the analgesic activity of compounds **7a–j**. These results showed that compound **7i** (ED_{50} = 90 mg/kg) was the most active member among this series. Furthermore, compounds **3i** (ED_{50} = 90 mg/kg), **7a** (ED_{50} = 94 mg/kg), **7h** (ED_{50} = 95), **7g** (ED_{50} = 98 mg/kg), **7c** (ED_{50} = 100 mg/kg), **7e** (ED_{50} = 107 mg/kg), **7d,j** (each has ED_{50} = 110 mg/kg) exhibited higher potency than acetylsalicylic acid (ED_{50} = 115 mg/kg), but much less than morphine (ED_{50} = 2.25 mg/kg).

By contrast, the data in Table 7 show that the 9-*endo*-benzyl derivatives **13a–j** have no analgesic potential up to a dose of 200 mg/kg.

Fig. 4 indicates the duration of the analgesic potential of the most active candidates **3c, 4a** and **7i** compared with the standard references.

6. Conclusions

In these series of prepared compounds, the maximum local anesthetic activity was achieved with the oximino ether **4d** (ED_{50} = 0.15 mg/kg) and the oximino ester **3a** (ED_{50} = 0.23 mg/kg).

Compound **4d** displayed local anesthetic potential equivalent to 14 and 120 times that of the xylocaine and procaine, respectively, and 2.6 times that of the stirocainide. In addition, the anesthetic profile of the oximino ester **3a** was equal to 9 and 78 times that of the xylocaine and procaine, respectively, and 1.7 that of the stirocainide. Regarding the analgesic activity, the most active compound was the oximino ether **7i** (ED_{50} = 90 mg/kg) compared with acetylsalicylic acid (ED_{50} = 115 mg/kg). Furthermore, we can conclude that, the insertion of the dialkylaminomethyl Mannich radical in position 9 in addition to the 8-aralkyloximino ether moiety in the same tricyclic structure (**7a–j**) favours the analgesic activity.

References

[1] M. Nógrádi, Drugs of the Future 9 (1984) 34–35 and references cited therein.

[2] A. Ranise, F. Bondavalli, O. Bruno, P. Schenone, ω-Dialkylaminoalkyl ethers of 3-*exo*-dialkylamino-(Z)-camphoroximes with antiarrythmic and local anesthetic activities, Farmaco Ed. Sci. 45 (1990) 187–202.

[3] M. Dàmico, C. Vacca, M. Falciani, A. Filippelli, *O*-[ω-(Dialkylamino)alkyl] oximes of (+)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one with hypotensive, antiinflammatory, analgesic, local anesthetic and other activities, Farmaco Ed. Sci. 49 (1994) 545–550.

[4] S. Schenone, O. Bruno, A. Ranise, F. Bondavalli, N-substituted *O*-(3-amino-2-hydroxypropyl) oximes of 1,3,3-trimethyl-5-*endo*-(1-piperidinyl or 4-morpholinyl)-2-oxabicyclo[2.2.2]octan-6-ones with platelet antiaggregating and local anesthetic activities, Farmaco Ed. Sci. 47 (1992) 1249–1262.

[5] E. Mariani, A. Bargagna, M. Longobardi, P. Schenone, *O*-(2-Dialkylaminoethyl) oximes of 5-(aralkylmethylene)-1,3,3-trimethyl-2-oxabicyclo[2.2.2]octan-6-ones with hypotensive, antiarrythmic and other activities, Farmaco Ed. Sci. 49 (1994) 267–270.

[6] M.N. Aboul-Enein, A.A. Makhlouf, A.A. El-Azzouny, N.A. Abdallah, Synthesis of some basic ethers of 6-arylidenehexahydro-4,7-methanoindan-5-one oximes and their salts as local anesthetics, Sci. Pharm. 60 (1992) 57–64.

[7] M.N. Aboul-Enein, A.M. Maklouf, A.A. El-Azzouny, Synthesis of certain spirohexahydro-4,7-methanoindanpiperazine derivatives as analgesics, Sci. Pharm. 58 (1990) 263–271.

[8] J. Büchi, Grundlagen der Arzneimittel Forschung und der synthetischen Arzneimittel, Birkhäuser, Basel, 1963, pp. 369-379.

[9] W.H. Oldendorf, Blood–brain barrier permeability to drugs, Ann. Rev. Pharmacol. 14 (1974) 239–248.

[10] F. Bondavalli, S. Lanteri, M. Longobardi, P. Schenone, Synthesis and pharmacological activity of derivatives of *exo*-trimethylenenorbornane, Farmaco Ed. Sci. 34 (1979) 945–951.

[11] F.C. Uhle, Methylaminomethylsuccinic acid, J. Org. Chem. 27 (1962) 4081–4083.

[12] J.C. Sheehan, M. Goodman, G.P. Hess, Peptide derivatives containing hydroxyamino acids, J. Am. Chem. Soc. 78 (1995) 1367–1369.

[13] R.A. Boissonnas, Une nouvelle méthode de synthèse peptidique, Helv. Chim. Acta 34 (1951) 874–879.

[14] M. Nabil Aboul-Enein, A.A. El-Azzouny, N.A. Abdallah, S.M. Moharam, W. Werner, A. Eid, A.A. Makhluf, Synthesis of some 6-(alkylamino)methylhexahydro-5-aryl- and aralkyl-4,7-methanoindan-5-ols and certain of their propionate esters as analgesics, J. Islamic Acad. Sci. 6 (1993) 99–107.

[15] F.F. Blicke, in: R. Adams (ed.), Organic Reactions, vol. 1, Wiley, New York, 1947, pp. 303–341.

[16] J. Hine, W.S. Li, Synthesis of some *cis*- and *trans*-2-dimethylaminomethyl cyclic amines and related diamines, J. Org. Chem. 40 (1975) 289–292 and references cited therein.

[17] B.J. Nicholaus, G. Pagáni, E. Testa, Synthese und Eigenschaften der *O*-(Phenylalkyl)hydroxylamine, Helv. Chim. Acta 45 (1962) 1381–1395.

[18] Vogel's Textbook of Practical Organic Chemistry, 5th ed., Longman, Singapore, 1991, pp. 609–610.

[19] E. Pretsch, Th. Clerc, J. Seibl, W. Simon, Tabellen zur Strukturaufklärung Organischer Verbindungen mit Spektroskopischen Methoden, Springer, Berlin, 1976.

[20] G. Buchbauer, H. Spreitzer, C. Puringer, Zur Synthese von Fungizid wirksamen Norbornanderivaten, Arch. Pharm. (Weinheim) 323 (1990) 367–373.

[21] L.J. McLeod, Pharmacological Experiments on Intact Preparation, E. and S. Livingstone, Edinburgh, 1970, pp. 33–35.

[22] P.A. Janssen, A. Jageneau, Potent analgesics d-1-(2,2-diphenyl-3-methyl-4-morpholinobutyryl) pyrrolidine and related amides. (I) Structure and pharmacological activity, J Pharm. Pharmacol. 9 (1957) 381–386.