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New derivatives of *trans* 2-phenoxycyclohexanol with potential local anesthetic activity

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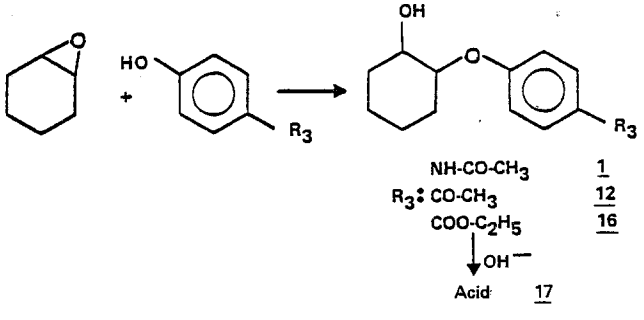
trans 2-phenoxycyclohexanol / local anesthetic activity

Introduction

According to the scheme of Löfgreen [1] for anesthetic compounds, and in the continuation of our earlier works [2, 3] on derivatives of phenoxy cyclohexanic structure, we synthesized some additional new para-substituted aromatic compounds (Table I: classes I—IV) and investigated their potential local anesthetic activity based upon a structural analogy with procaine and xylocaine. In addition we have tested derivatives substituted in the cyclohexane ring, the piperidino ether I_A and the diethylamino ethylester **33**. Syntheses, NMR study of the stereochemistry and anti-inflammatory activities of these last two compounds have recently been published [3, 4].

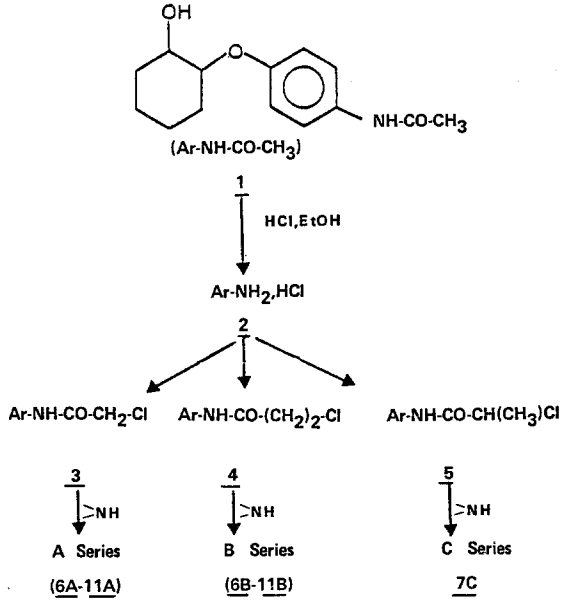
Chemistry

The starting materials **1, 12, 16, 17** were synthesized according to Scheme 1 by the reaction of epoxycyclohexane with the corresponding phenols and refluxed in ethanol with Na.



Scheme 1. Preparation of the starting compounds.

Class I alkylaminoacylanilines have been synthesized (Scheme 2) by the condensation of the appropriate chloride with the *trans*-4-(2-hydroxycyclohexyloxy)aniline **2** followed by treatment in ethanol and refluxed with various primary or secondary amines (in the presence of NaI in the case of **7c**). The synthesis of the chloroacyl derivatives **3**, **4** and **5** was performed with the following three variants: Löfgreen method [5] using an acetic acid—Na acetate buffer (method A; 55% yield); use of solid K_2CO_3 in acetone [6] (method B; 51% yield) or a two-phase system (aqueous base / organic solvent) [7]. This latter (method C) gave the best yields (70%).

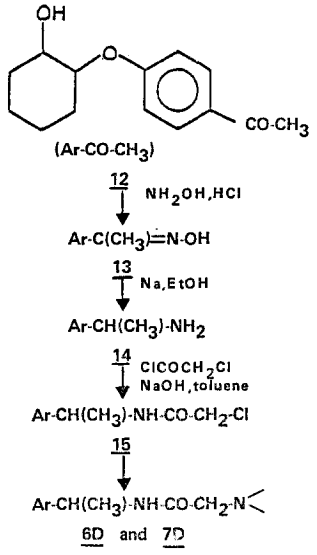


Scheme 2. Synthesis of the compounds of class I.

Concerning NMR spectra, for all class I compounds, the two protons C*H*OH and C*H*OAr gave two overlapping multiplets at about 3.5 ppm. Study of the *O*-acetylated compounds (for example, **2** *O*-Ac and **7A** *O*-Ac) obtained [8] by *O*-acetylation (by acetyl chloride in trifluoroacetic

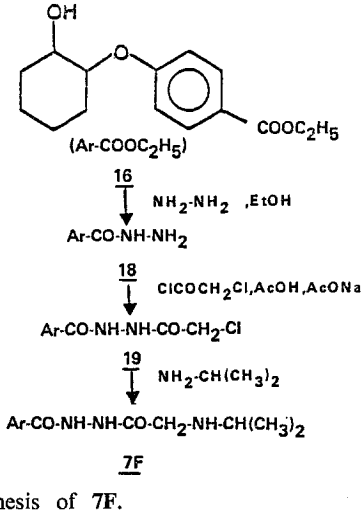
acid) of the corresponding alcohols permitted an easier analysis of the *trans* stereochemistry by determination of the width (about 22 Hz) of the two distinct multiplets of the C*H*OAr (4 ppm) and C*H*OAc (5 ppm) protons.

Class II amides were obtained according to Scheme 3 and the preparation of the basic esters **6E**, **9E** and **10E** was accomplished [9] by reaction of acid **17** with the corresponding β-chloroamine hydrochlorides in isopropanol at reflux in the presence of triethylamine.



Scheme 3. Synthesis of amides of class II.

Dihydrazide **7F** was obtained (Scheme 4) from the ester **16** *via* **18** and **19**.



Scheme 4. Synthesis of **7F**.

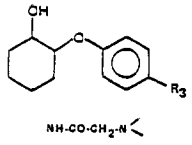
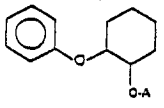
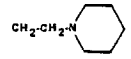
Pharmacological activity

Compounds were compared to xylocaïne on female Swiss OFl mice in the thermal pain stimulus test of D'Amour and Smith [10] modified by Mack and Nelson [11] in the study of the local conduction of anesthetic activity.

The results obtained 5 min after subcutaneous injection into the tail of mice are summarized in Table I. In each series, diethylamino (**6A**, **6E**, **33**) and piperidino compounds (**9A**, **9E**, I_A). were the most effective, particularly the piperidinoether I_A. In the amides series, the lengthening or ramification of the alkanoyl chain did not improve the activity.

For the most active compound I_A, we have determined the protection effect 15 min after administration (87.29%), DE_{50} (25 mg/kg; subcutaneously), DL_{50} (260 mg/kg; intraperitoneally) and due to lack of specificity of the test used (analgesic activity or local anesthetic activity), we have studied the analgesic activity of I_A using the

Table I. General structure and biological activity of the studied compounds.

				Protection in %
		$N(C_2H_5)_2$	6A	52.51
		$NH-CH(CH_3)_2$	7A	25.82
		$NH(CH_2)_2-CH_3$	8A	27.21
			9A	50.95
			10A	25.64
			11A	10.75
Class I	$NH-CO-CH_2-CH_2-N<$	$N(C_2H_5)_2$	6B	37.18
		$NH-CH(CH_3)_2$	7B	26.25
		$NH(CH_2)_2-CH_3$	8B	21.04
			9B	24.37
			10B	17.81
			11B	24.27
	$NH-CO-CH(CH_3)-NH-CH(CH_3)_2$		7C	25.64
Class II	$CH(CH_3)-NH-CO-CH_2-N<$	$N(C_2H_5)_2$	6D	36.77
		$NH-CH(CH_3)_2$	7D	36.66
Class III	$COO-CH_2-CH_2-N<$	$N(C_2H_5)_2$	6E	56.66
			9E	58.75
			10E	33.85
Class IV	$CO-NH-NH-CO-CH_2-NH-CH(CH_3)_2$		7F	20.52
				
			I_A	86.77
	$CH_2-COOCH_2-CH_2-N(C_2H_5)_2$		33	56.25
	Xylocaïne with adrenaline			75.56

Koster acetic acid test [12]. In this test, I_A showed an analgesic activity of only 25% which was not significant in the Student's *t*-test.

Experimental protocols

Chemistry

Melting points were determined in open capillary tubes using a Büchi apparatus and are uncorrected.

Elemental analyses, which were performed by the CNRS and which are, for most of the compounds, in agreement with the theoretical values within ±0.4% are not reported here.

Infrared spectra were obtained on an Acculab 4 Beckman instrument in KBr. NMR spectra were recorded on a Bruker WP 80 (80 MHz) or on a Cameca 350 (350 MHz) spectrometer with tetramethylsilane as the internal standard. The observed chemical shifts are consistent with the assigned structures.

The 2-(*trans* 2-phenoxycyclohexyloxy) piperidinoethane I_A and the diethylaminoethyl 2-phenoxycyclohexyloxyacetate **33**, were obtained as previously described [3, 4].

The characteristics of the synthesized compounds are summarized in Table II.

Pharmacology

Local anesthetic activity

Preliminary screening was done by subcutaneous injection of the tested compounds into the tail of female Swiss OF1 mice according to the thermal pain test of D'Amour and Smith modified by Mack and Nelson to study local anesthetics. Hydrochloride (2%, w/v) solutions were prepared by adding the exact amount of titrated 0.1 N HCl and dilution with distilled water and adding 31 μl of 0.10% adrenaline hydrochloride/2.5 ml of solution. Groups of 10 mice with an average weight of 20 g were injected subcutaneously with 0.1 ml (100 mg/kg) of test solution in the tail at about 1 cm from the base. 5 min later, the thermal pain stimulus reflex was evaluated as the time required for the tail's first movement. The time of response was compared to that of an isotonic saline solution alone, to give the percentage of protection, and to that of 2% xylocaine containing adrenaline. In the absence of a response, the thermal stimulus was limited to 12 s (conventionally 100% protection). The experimental results were analyzed using the Student's *t* test.

Potential analgesic activity of the ether I_A *(Koster acetic acid method)*

Acetic acid (300 mg/kg) was injected intraperitoneally into 6 mice. After 5 min, writhings were counted for 10 min. I_A oxalate (100 mg/kg) was administrated orally 1 h before acetic acid and exhibited an insignificant percentage of analgesia: 25.32%.

Table II. Characteristics of the synthesized compounds.

Product	mp °C	Yield	Formula
1	139—140 (ethylacetate)	68	$C_{14}H_{19}NO_3$
2 HCl	220 (methanol—ether)	87	$C_{12}H_{18}NO_2Cl$
3	156 (ethylacetate—petroleum ether)	74*	$C_{14}H_{18}NO_3Cl$
4	139—140 (benzene)	70**	$C_{15}H_{20}NO_3Cl$
5	146—147 (benzene)	70***	$C_{15}H_{20}NO_3Cl$
6A	67— 68 (ether—petroleum ether)	67	$C_{18}H_{28}N_2O_3$
6B oxalate	79— 80 (ethanol—water)	55	$C_{19}H_{30}N_2O_3$; $0.5(COOH)_2$; $2H_2O$
6D	108 (ethylacetate—petroleum ether)	30	$C_{20}H_{32}N_2O_3$
6E oxalate	124—126 (acetone—ether)	50	$C_{21}H_{31}NO_8$
7A	134—136 (ethylacetate)	69	$C_{17}H_{26}N_2O_3$
7A *O*-Ac oxalate	215—216 (ethanol)	55	$C_{21}H_{30}N_2O_8$
7B	97 (ethylacetate—petroleum ether)	50	$C_{18}H_{28}N_2O_3$
7C HCl	216—217 (ethanol—ether)	42	$C_{18}H_{29}N_2O_3Cl$
7D oxalate	187—188 (acetonitrile)	62	$C_{21}H_{32}N_2O_7$
7F oxalate	149 (isopropanol—ether)	45	$C_{18}H_{27}N_3O_4$; $(COOH)_2$; H_2O
8A	136—137 (ethylacetate)	65	$C_{17}H_{26}N_2O_3$
8B	106—107 (ethylacetate)	66	$C_{18}H_{28}N_2O_3$
9A	127—129 (acetonitrile)	65	$C_{19}H_{28}N_2O_3$
9B	105—106 (benzene—petroleum ether)	69	$C_{20}H_{30}N_2O_3$
9E oxalate	89— 90 (acetonitrile)	41	$C_{20}H_{29}N_2O_4$
10A	141—143 (ethanol—water)	63	$C_{18}H_{26}N_2O_3$
10B	130—131 (benzene—petroleum ether)	37	$C_{19}H_{28}N_2O_3$
10E	87— 88 (acetonitrile)	35	$C_{19}H_{27}NO_4$
11A	147—148 (ethanol—water)	84	$C_{18}H_{26}N_2O_4$
11B	127—128 (benzene—petroleum ether)	69	$C_{19}H_{28}N_2O_4$
12	124—125 (carbontetrachloride)	60	$C_{14}H_{18}O_3$
13	148—150 (acetonitrile)	84	$C_{14}H_{19}NO_3$
14 oxalate	224—225 (ethanol)****	60	$C_{14}H_{21}NO_2$; $0.5(COOH)_2$; $0.5H_2O$
15	114 (benzene—petroleum ether)	68	$C_{16}H_{22}NO_3Cl$
16	69— 70 (carbontetrachloride)	51	$C_{15}H_{20}O_4$
17	158—160 (acetonitrile)	74	$C_{13}H_{16}O_4$
18	185—186 (ethanol)	71	$C_{13}H_{18}N_2O_3$
19	172—174 (ethylacetate)	84	$C_{15}H_{19}N_2O_4Cl$

* Method C; 50% (method A) and 51% (method B).
** Method C and 57% (method A).
*** Method C and 58% (method A).
**** bp (**14** base): 146—150°C (0.2 mm).

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