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QUATERNARY AMMONIUM SALT DERIVATIVES OF ALLYLPHENOLS WITH PERIPHERAL ANALGESIC EFFECT

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Ammonium salt derivatives of natural allylphenols were synthesized with the purpose of obtaining potential peripheral analgesics. These drugs, by virtue of their physicochemical properties, would not be able to cross the blood brain barrier. Their inability to enter into the central nervous system (CNS) should prevent several adverse effects observed with classical opiate analgesics (Ferreira et al., 1984). Eugenol (1) O-methyleugenol (5) and safrole (9) were submitted to nitration, reduction and permethylation, leading to the ammonium salts 4, 8 and 12. Another strategy applied to eugenol (1), consisting in its conversion to a glycidic ether (13), opening the epoxide ring with secondary amines and methylation, led to the ammonium salts 16 and 17. All these ammonium salts showed significant peripheral analgesic action, in modified version of the Randall-Sellito test (Ferreira et al., 1978), at non-lethal doses. The ammonium salt 8 showed an activity comparable to that of methylnalorphinium, the prototype of an ideal peripheral analgesic (Ferreira et al., 1984).

Key words: allylphenol – analgesic – eugenol – peripheric analgesic – safrole

Allylphenols occur in the essential oil of various plants, some of which are used in folk medicine. A great variety of pharmacological and toxicological data on the isolated constituents of the volatile oil fractions are described (Dallmeier & Carlini, 1981). Eugenol is reported to show antiseptic and analgesic properties, local anesthetic activity, spasmolytic activity, parasympathetic effects and direct peripheral vasodilatation (Dallmeier & Carlini, 1981). Safrole showed litle anesthetic activity and is known for its hepatocarcinogenic properties (Dallmeier & Carlini, 1981). Methyleugenol revealed pronounced central-nervous-system-depressant effects, being an effective anesthetic for rats, mice and rabits (Dallmeier & Carlini, 1981). Ammonium salt derivatives of allylphenols were synthesized with the purpose of obtaining potential peripheral analgesics. These drugs, by virtue of their physicochemical properties, would not be able to cross the blood-brain barrier and therefore reach the CNS. The inability of these drugs to enter into the CNS prevents several adverse effects observed when using classical opiates, such as respiratory depression and addiction liability (Ferreira et al., 1984).

MATERIALS AND METHODS

Chemistry – Eugenol (1) (Leving & Lowy, 1933), O-methyleugenol (5) (Clemo & Turnbull, 1949) and safrole (9) (Costa et al., 1980) were submitted to nitration with nitric acid, reduction with stanous chloride (Argus & Shafer, 1958) and permethylation with methyl iodide leading to the ammonium salts 4, 8, and 12 (Fig. 1). In an another strategy, eugenol (1) was converted to the glycidic ether 13 by reaction with sodium hydride and epychloridrine (Cox et al., 1978). Opening the epoxide ring with dimethyl and diethylamine (Cox et al., 1978) followed by methylation with methyl iodide, led to the ammonium salts 16 and 17 (Fig. 2). All the compounds were fully characterized by infra red espectrometry, ^{1}H and ^{13}C nuclear magnetic ressonance and mass spectroscopy. The compounds 4, 8, 12, 16 and 17 had their formulas confirmed by elemental analysis (Silva, 1989).

Pharmacology – Hyperalgesia was induced in the rat hind paws by intraplantar administration of 100 ng of prostaglandin E2 and

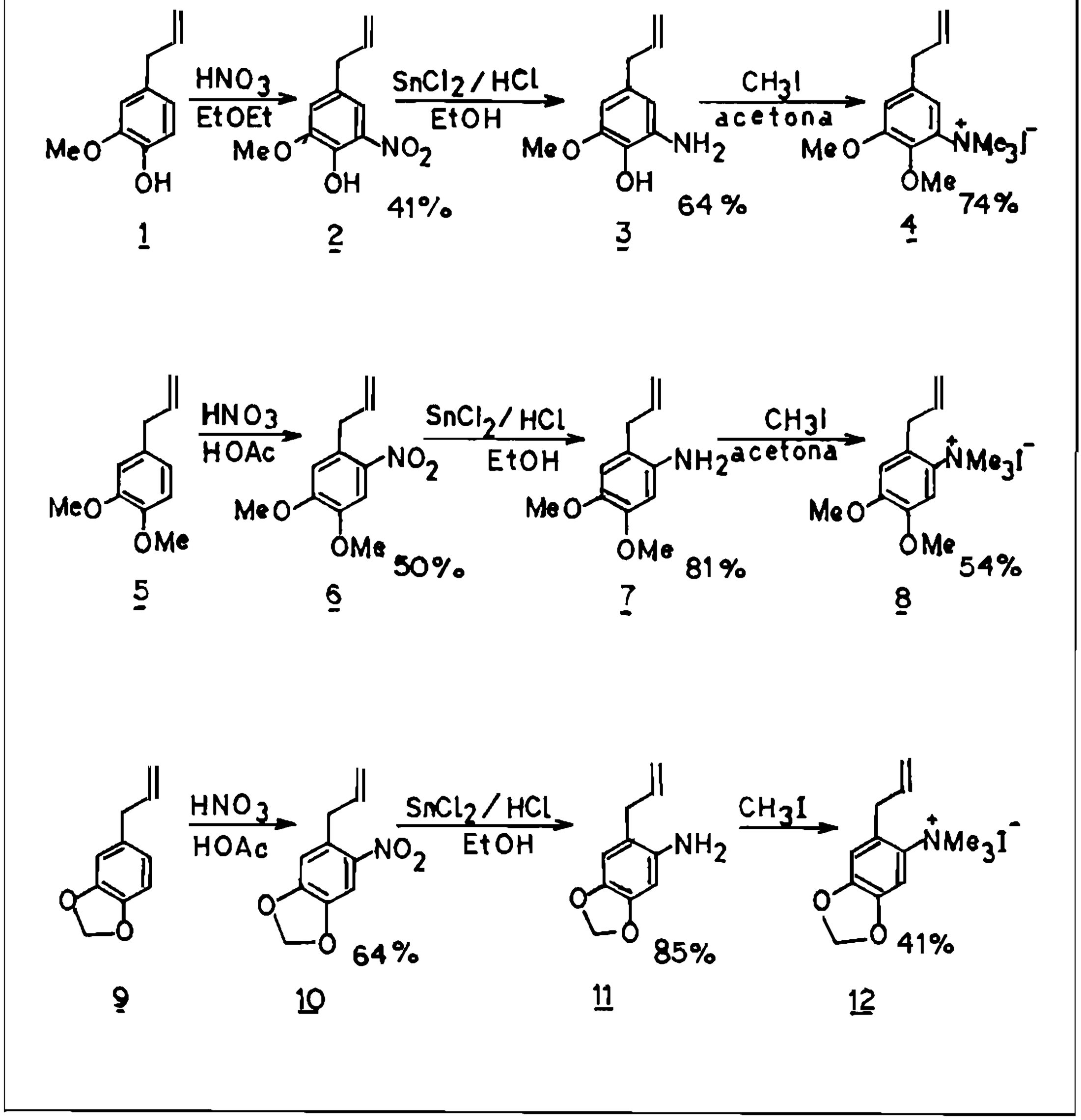

Fig. 1: synthesis of aromatic ammonium salt derivatives of eugenol, methyleugenol and safrole.

measured by a modified version of the Randall-Sellito test. In this test, a constant pressure of 20 mm Hg is applied to the rat paw and discontinued (reaction time) when the animals presented a reaction characterized by a reduction of escape movements (the animal usually makes several atempts to escape from the position imposed by the experimental situation), a variation of the respiratory frequency and the appearence of a typical shivering reaction (sucessive waves of muscular tremor). The intensity of hyperalgesia was quantified as the reaction time (Δ reaction time) obtained by substrating the value measured 3 h after administration of the hyperalgesic substance from the control reaction time (zero time). All the

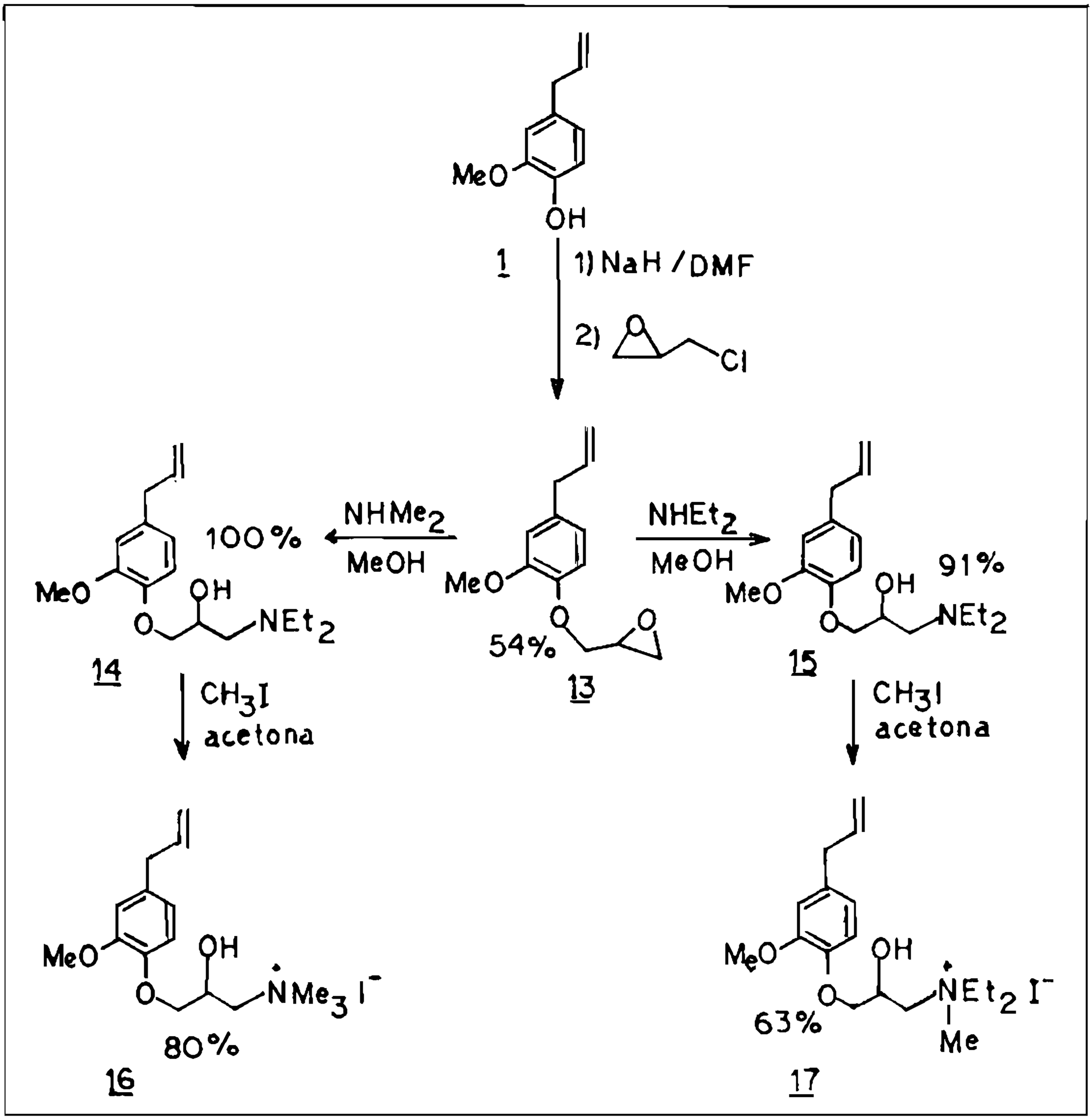

Fig. 2: synthesis of the oxipropanolammonium salt derivatives of eugenol.

ammonium salts were given by intraplantar route 1 h before measurement of hyperalgesia. Male wistar rats were employed. Results are presented as mean ± S. E. M.

RESULTS

Intraplantar administration of quaternary ammonium salts reduces hyperalgesia. The data presented are the mean S. E. M. of 5 animals measured 3 h after PGE_2 injection (100 ng/paw) and 1 h after receiving saline (control) or the ammonium salts.

Dose – mg/kg (intraplantar)

Compound		5	20	30	50	100
4	IH	18,7 ± 0,4	13,0 ± 0,4		9,9	
	HR (%)	3	32	nt	48	nt
	D (%)	0	0		80	
8	IH	16,4 ± 0,3	8,6 ± 0,5	9,8 ± 0,9	6,6	
	HR (%)	15	55	49	66	nt
	D (%)	0	0	20	80	
12	IH	9,3 ± 0,6	4,5		4,4 ± 1,3	
	HR (%)	52	77	nt	77	nt
	D (%)	0	0		20	
16	IH	17,8 ± 0,8	11,5 ± 0,7		12,0	
	HR (%)	7	40	nt	38	
	D (%)	0	0		0	100
17	IH	13,2 ± 0,5	0,7 ± 0,4		9,8 ± 0,3	4,4
	HR (%)	6	55	nt	48	77
	D (%)	0	0		20	60

Control (saline) ± SEM = 19,2 ± 0,36; HR (%): percentage of hyperalgesia reduction; D (%): percentage of deaths; IH: intensity of hyperalgesia (± S.E.M.); Δ reaction time (sec); nt: not tested.

DISCUSSION

Two main classes of drugs are currently used in the management of pain: the aspirin like non-steroidal anti-inflamatory drugs and opiates. Both classes may produce serious adverse effects. Within the non-steroidal anti-inflamatory drugs which are cyclo-oxigenase inhibitors, antialgic and antioedematogenic effects are generally accompanied by gastric irritation and/or ulceration and inhibition of platelet aggregation (Ferreira & Vane, 1979). Opiate agonist, which do not share these aspirin like side effects are known to exhibit high addiction liability associated with tolerance, respiratory depression and constipation. Tiredness, drunkeness and dysphoria are common side effect of opiates, and of the mixed agonist-antagonist type (i.e. nalorphine, pentazocine) which has limited their clinical usefulness. With the exception of constipation, all the above mentioned opiate induced side effects are thought to be of central origin. The discovery of a peripheral analgesic effect of opiates raised the possibility of developing a new class of analgesics (Ferreira et al., 1979). The methylnalorphynium was considered the prototype of an ideal peripheral analgesic because it does not cross the blood-brain barrier, is orally active, does not cause tolerance or affect intestinal transitt (Ferreira et al., 1984). In contranst with nonsteroidal antiinflamatory drugs, the selectivity of methylnalorphinium in antagonizing hyperalgesia without affecting inflamatory oedema might be of pratical value, considering that the exudate contains several important mediators of host defense mechanisms (Ferreira et al., 1984). The ammonium salt derivatives of allyphenol (4, 8, 12, 16 and 17) showed significant peripheral analgesic action in the Randall-Sellito test at non-lettal doses. The ammonium salt 8 showed activity comparable to that of methilnalorphinium, that reduced hyperalgia by 45, 75 and 83% in doses of 10, 20 and 50 mg/kg (po) respectively (Ferreira et al., 1984). Futher studies must be done to determine the cause of the deaths. The compounds 3, 4, 7, 8, 11, 12, 13, 14, 15, 16 and 17 were not previously described.

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