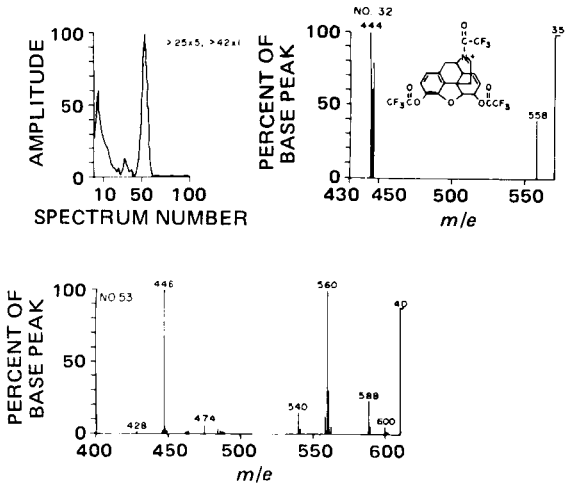

Figure 3—*Integrated total ion current chromatogram of an extract of the free base drug fraction as the trifluoroacetyl derivative. Mass spectrum No. 32 showed characteristics of dehydronormorphine, and No. 53 showed characteristics of normorphine.*

sponding to dehydronormorphine as the trifluoroacetyl derivative, was observed in the eluate of the 140–155-mm zone (R_f 0.9) of the thin-layer chromatogram of the free base drug fraction (Fig. 3). Although there is no direct evidence for the presence of *N*-hydroxynormorphine, dehydronormorphine may have resulted from dehydration of *N*-hydroxynormorphine during purification, derivatization, and GLC analysis. Meperidine *N*-oxide has been shown to undergo dehydration during GLC analysis (15, 16).

Morphine, norcodeine, and codeine were not detected in the free or the conjugated form. This result confirms the reports that the methylation of normorphine does not play a significant role in the metabolism of normorphine (17–20).

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Local Anesthetic Activity and Acute Toxicity of *N*-Substituted 1,2,3,4-Tetrahydro-1- and 2-naphthylamines

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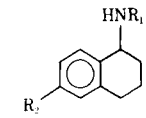
Received August 16, 1976, from the *Department of Pharmacology and Medicinal Chemistry and the Department of Organic Research, Abbott Laboratories, North Chicago, IL 60064.* Accepted for publication September 29, 1977.

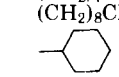
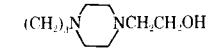
Abstract □ Seven *N*-substituted 1,2,3,4-tetrahydro-1- and three 2-naphthylamines were prepared and tested for local anesthetic activity in the rabbit corneal reflex test and the mouse sciatic nerve block test. At 0.1 and 1%, three 1-alkylamino compounds had durations of action comparable to that of tetracaine in the rabbit corneal reflex test and were considerably more potent than lidocaine. The other four 1-alkylamino derivatives were inactive or at best minimally active. The durations of action of 1% concentrations of the three 2-alkylamino compounds were equivalent to that of 1% lidocaine in the corneal reflex test. In the mouse sciatic nerve block test, the three active 1-alkylamino compounds were considerably longer acting than either tetracaine or lidocaine. Three 1-alkylamino and the three 2-alkylamino compounds showed toxicity equal to or greater than lidocaine, while two 1-alkylamino and two 2-alkylamino compounds showed toxicity equal to or greater than tetracaine by the intraperitoneal route in mice. *N*-Heptyl-1,2,3,4-tetrahydro-6-methoxy-1-naphthylamine methanesulfonate was the most promising local anesthetic in these series.

Keyphrases □ 1,2,3,4-Tetrahydro-1- and 2-naphthylamines, *N*-substituted—synthesized, local anesthetic activity and toxicity evaluated □ Local anesthetic activity—various *N*-substituted 1,2,3,4-tetrahydro-1- and 2-naphthylamines evaluated □ Toxicity—various *N*-substituted 1,2,3,4-tetrahydro-1- and 2-naphthylamines evaluated □ Structure-activity relationships—various *N*-substituted 1,2,3,4-tetrahydro-1- and 2-naphthylamines evaluated for local anesthetic activity and toxicity

A series of methoxy-1- and 2-aminoindans and naphthylamines previously was synthesized as potential antiparkinsonian agents (1). When these compounds were tested for dopaminergic activity, some were inhibitors of monoamine oxidase. Subsequently, additional compounds were prepared in which the substituent on the amine was

Table I—Physical and Chemical Data for *N*-Substituted 1,2,3,4-Tetrahydro-1-naphthylamines



Compound	R_1	R_2	Formula	Salt	Melting Point
I	$(CH_2)_6CH_3$	6-OCH_3	$C_{18}H_{29}NO$	Methanesulfonate	88–90.5°
II	$(CH_2)_6CH_3$	5-OCH_3	$C_{18}H_{29}NO$	Hydrochloride	126–128.5°
III	$(CH_2)_7CH_3$	6-OCH_3	$C_{19}H_{31}NO$	Hydrochloride	118–120°
IV	$(CH_2)_8CH_3$	6-OCH_3	$C_{20}H_{33}NO$	Hydrochloride	125–127°
V		6-OCH_3	$C_{17}H_{25}NO$	Hydrochloride	216°
VI		6-OCH_3	$C_{20}H_{33}N_3O_2$	3-Hydrochloride	225°
VII	$CH_2CH_2CONH_2$	6-OCH_3	$C_{14}H_{20}N_2O_2$	Hydrochloride	205–206°

varied to examine the relationship between physical properties and the potency of monoamine oxidase inhibition (2). In a broad pharmacological screening program, it was observed that one of the naphthylamines had local anesthetic activity. This paper describes the synthesis of *N*-substituted 1,2,3,4-tetrahydro-1- and 2-naphthylamines (Tables I and II) and testing for local anesthetic activity.

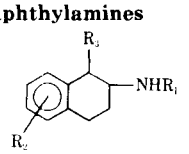
EXPERIMENTAL

Chemistry—N-*Substituted 1,2,3,4-Tetrahydro-1-naphthylamines (I–VII)*—To prepare I–VII, 5- or 6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone was reacted with the appropriate alkyl- or cycloalkylamines to produce substituted ketamines, which, in turn, were hydrogenated to give the final amine products. A benzene solution of the appropriate naphthalenone and amine was refluxed for approximately 72 hr until 1 molar equivalent of water was collected in a water separator. *p*-Toluenesulfonic acid was employed as a catalyst. The ketamines were isolated by removal of the solvent and then reduced with Raney nickel catalyst in ethanol until no additional uptake of hydrogen was noted. The reaction mixture was filtered, the solvent was removed, and the product was purified by distillation. The free bases could be converted to the salt form by reaction with a pharmaceutically acceptable acid, *e.g.*, hydrochloric, methanesulfonic, or acetic.

N-*Substituted 1,2,3,4-Tetrahydro-2-naphthylamines (VIII–X)*—To prepare VIII and IX, 5-methoxy-1-methyl-3,4-dihydro-2(1*H*)-naphthalenone and 6-methoxy-2(1*H*)-naphthalenone were reacted with cyclopropylamine and cyclopropylcarbinylamine, respectively, as already described. The ketamines were reduced with sodium borohydride in methanol solution. The crude product was made basic and extracted in ether, and the ethereal solution was then washed with hydrochloric acid; this process was repeated as necessary. The product was purified by distillation, treated with ethereal hydrochloric acid, and crystallized.

A second method was used in the preparation of X. *N*-Hydroxypropyl-1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine and thionyl chloride were allowed to react overnight in chloroform solution at room temperature. The crude hydrochloride was precipitated, filtered, washed with ether, and recrystallized from methanol–ether solution.

Table II—Physical and Chemical Data for *N*-Substituted 1,2,3,4-Tetrahydro-2-naphthylamines



Compound[a]	R_1	R_2	R_3	Formula	Melting Point
VIII		6-OCH_3	H	$C_{15}H_{21}NO$	231–232°
IX		5-OCH_3	CH_3	$C_{15}H_{19}NO$	187–189°
X	$(CH_2)_3Cl$	6-OCH_3	H	$C_{14}H_{20}ClNO$	207–208.5°

[a] All were hydrochlorides.

Pharmacology and Toxicology—*Rabbit Corneal Reflex Test*—Topical anesthetic activity was evaluated in the rabbit corneal reflex test originally described by Sollmann (3). A volume of 0.1 ml of the local anesthetic solution (0.1 or 1%) was instilled into the conjunctival sac of each eye; the cornea was not rinsed following drug application. The presence or absence of the corneal reflex (blinking) was determined by touching the cornea with a stiff hair at 5-min intervals. Tetracaine hydrochloride (0.1%) and lidocaine hydrochloride (1%) were used as reference standards. Each concentration was tested in three to six rabbit eyes.

Mouse Sciatic Nerve Block Test—Conduction anesthesia was evaluated using the mouse sciatic nerve block test, a modification of the method in rats originally described by Camougis and Takman (4). A volume of 0.05 ml of a 1% solution was injected into the midthigh region of female ICR mice so that the drug was localized around the sciatic nerve. Following injection, the mice were observed to determine the frequency and duration of the motor nerve blocks as well as any systemic effects. Tetracaine hydrochloride (1%) and lidocaine hydrochloride (1%) were used as reference standards. Each compound was tested in 10 mice. The results are expressed as the mean duration of anesthesia ± *SEM*.

Acute Toxicity—The compounds were administered intraperitoneally to groups of three female ICR mice in doses ranging from 30 to 1000 mg/kg. The LD_{50} values were estimated graphically.

RESULTS

The results of testing derivatives I–VII in the rabbit corneal reflex test are presented in Table III. Compounds I–III were active at a concentration of 0.1% and were comparable in potency to tetracaine. Neither changing the position of the methoxy group (I and II) nor increasing the length of the alkyl chain on the nitrogen by one carbon (I and III) appreciably affected activity. Compound I also was tested as the acetate salt. The durations of action of both the methanesulfonate and acetate salts of I were similar, but the acetate appeared to be less irritating to tissue.

Table III—Activity of *N*-Substituted 1,2,3,4-Tetrahydro-1-naphthylamines

Compound	Rabbit Corneal Reflex Test: Concentration, %	Rabbit Corneal Reflex Test: Mean Duration (Range) of Anesthesia, min	Mouse Sciatic Nerve Block Test[a], Duration of Action, min, Mean ± *SE*
I	1.0	140.0 (120–150)	96.8 ± 17.4
	0.1	43.3 (35–52)	
II	1.0	130.0 (120–135)	40.0 ± 5.1
	0.1	30.0 (20–40)	
III	1.0	140.0 (135–150)	96.3 ± 23.3
	0.1	38.0 (25–55)	
IV	1.0	3.3 (0–10)	—
V	1.0	17.5 (0–45)	—
VI	1.0	No effect	—
VII	1.0	No effect	—
Tetracaine hydrochloride	1.0	55.0 (45–60)	13.6 ± 5.8
	0.1	32.5 (22–42)	
Lidocaine hydrochloride	—	—	5.7 ± 1.9

[a] All compounds were tested at 1%.

Table IV—Activity of *N*-Substituted 1,2,3,4-Tetrahydro-2-naphthylamines in Rabbit Corneal Reflex Test[a]

Compound	Mean Duration (Range) of Anesthesia, min
VIII	21.8 (15–27)
IX	9.4 (5–15)
X	20.5 (15–27)
Lidocaine hydrochloride	13.3 (10–15)

[a] All compounds were tested at 1%.

In contrast to these highly active derivatives, IV, which has a nine-carbon chain on the nitrogen, was active in only one of three eyes but was relatively insoluble. The compound with a cyclohexyl ring (V) rather than the straight alkyl chain was active at 1% but had a relatively short duration of action; it also was only partially soluble at 1%. The introduction of hetero chains on the alkylamino group resulted in two compounds, VI and VII, which were inactive in the rabbit corneal reflex test.

Derivatives VIII–X were tested at a concentration of 1% and were all active in this test (Table IV). The potency and duration of anesthesia with these compounds were less than those observed with I–III but were generally comparable to those of lidocaine.

Derivatives I–III, which were active in the rabbit corneal reflex test, also were tested in the mouse sciatic nerve block test (Table III). Changing the position of the methoxy group from six to five (I and II) appeared to decrease the duration of action; increasing the length of the alkylamino group by one carbon (I and III) had no effect on the local anesthetic activity in this test.

The estimated intraperitoneal LD_{50} values are presented in Table V. The LD_{50} values of I and III, which exhibited the best local anesthetic activity in the rabbit corneal reflex and mouse sciatic nerve block tests, were similar. These LD_{50} values were lower than the value of lidocaine but comparable to that of tetracaine.

These preliminary pharmacological evaluations suggested that the potency, duration of action, and relative safety of I and III were as great or greater than those of tetracaine. Compound I, *N*-heptyl-1,2,3,4-tetrahydro-6-methoxy-1-naphthylamine methanesulfonate, was identified as the most promising local anesthetic compound in these series and has been examined in more detail (5).

Table V—Estimated LD_{50} Values of *N*-Substituted 1,2,3,4-Tetrahydro-1- and 2-naphthylamines, Tetracaine, and Lidocaine in Mice

Compound	Estimated LD_{50}, mg/kg ip
I	50
II	100
III	50
IV	200
V	200
VI	500
VII	300
VIII	80
IX	175
X	40
Tetracaine hydrochloride	75
Lidocaine hydrochloride	175

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Local Anesthetic Activity and Acute Toxicity of *N*-Heptyl-1,2,3,4-tetrahydro-6-methoxy-1-naphthylamine Methanesulfonate

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Received August 16, 1976, from the *Department of Pharmacology and Medicinal Chemistry, Abbott Laboratories, North Chicago, IL 60064.* Accepted for publication September 29, 1977.

Abstract □ *N*-Heptyl -1,2,3,4- tetrahydro-6-methoxy-1-naphthylamine methanesulfonate (I) is a potent, long lasting local anesthetic. It was as potent as tetracaine and at least 10 times more potent than lidocaine in the rabbit corneal reflex, guinea pig wheal, and mouse sciatic nerve block tests. The threshold anesthetic concentration (TAC), defined as the concentration required to produce anesthesia lasting 5 min, was calculated from each linear regression line fitted to the log dose–duration data, and these values were used to compare the potencies of the local anesthetics. In the rabbit corneal reflex test, the TAC values were 0.04% for I, 0.04% for tetracaine, and 0.66% for lidocaine. In the guinea pig wheal test, I had a TAC of 0.02%, which was equipotent to tetracaine and 11 times more potent than lidocaine; epinephrine (1:100,000) prolonged the duration of action of all three local anesthetics but had the least effect with I. In the mouse sciatic nerve block test, the TAC values were 0.06% for I, 0.10% for tetracaine, and 0.86% for lidocaine. The acute LD_{50} values of I in mice were 138 mg/kg sc and 26 mg/kg iv. By either route, I was less toxic than tetracaine and more toxic than lidocaine. Comparison of the LD_{50} and TAC values in the mouse sciatic nerve block test indicated that I had a greater therapeutic index than either reference standard.

Keyphrases □ *N*-Heptyl -1,2,3,4- tetrahydro-6-methoxy-1-naphthylamine methanesulfonate—local anesthetic activity and acute toxicity evaluated □ Local anesthetic activity—*N*-heptyl-1,2,3,4-tetrahydro-6-methoxy-1-naphthylamine methanesulfonate evaluated □ Toxicity—*N*-heptyl-1,2,3,4-tetrahydro-6-methoxy-1-naphthylamine methanesulfonate evaluated

Several *N*-substituted 1,2,3,4-tetrahydro-1-naphthylamines, originally synthesized as antiparkinsonian agents (1) and monoamine oxidase inhibitors (2), showed potent local anesthetic activity in the rabbit corneal reflex test. Consequently, other 1- and 2-alkylamino derivatives were prepared and tested for local anesthetic activity (3). This