# Cyclizing Compounds. 3. Local Anesthetic Action of *N*-(ω-Haloalkyl)-*N*-methylaminoaceto-2,6-xylidides[1]

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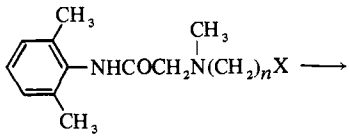
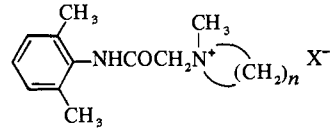
A series of *N*-(ω-chloroalkyl)-*N*-methylaminoaceto-2,6-xylidides which are able to cyclize to quaternary ammonium derivatives was synthesized and examined for local anesthetic action. As reference compounds the corresponding series of *N*-alkylamine derivatives were synthesized and tested. In both series of compounds the duration of anesthesia was prolonged by increasing the size of the side chain. In the *N*-alkylamine series an optimal effect was obtained for the *N*-hexylamine derivative. The duration of anesthesia produced by the cyclizing compounds in the sciatic nerve test *in vivo* was somewhat shorter than that for the noncyclizing compounds. The observation that the *N*-4-chlorobutyl derivative produced a longer block than the 5-chloropentylamine in this test indicates that the quaternary compounds formed may contribute to the duration of anesthesia.

In a previous study the observation was made that some *N*-(haloalkyl)-*N*-ethyl-2,6-dimethylphenoxyethylamine derivatives had a long-lasting local anesthetic action.[1] Since these haloalkylamines are able to cyclize to the corresponding quaternary ammonium derivatives, even under physiological conditions,[1-3] and the long-lasting effect could possibly be due to the quaternary compound formed in the nerves, we have synthesized and tested a homologous series of *N*-ω-chloroalkylamine derivatives structurally related to lidocaine. In order to evalute the effect on duration of local anesthesia caused by prolonging the side chain, we also synthesized and examined the local anesthetic effect of the corresponding *N*-alkylamine derivatives II. The haloalkylamines I cyclize to quaternary compounds III according to following reaction.



I, X = Cl, Br
II, X = $CH_3$



III, X = Cl, Br

## Results

**Chemistry.** The haloalkyl derivatives were prepared from the corresponding alcohols by means of $SOCl_2$ in $CHCl_3$ or HBr gas in AcOH. The alcohols were obtained from chloroaceto-2,6-xylidide by reaction with appropriate ω-methylaminoalkanol except for the hydroxypropyl compound which was prepared from methylaminoaceto-2,6-xylidide and chloropropanol (Tables I and II). 6-Methylamino-1-hexanol (**1**) has not been described previously. The preparation of this compound is given in the Experimental Section. The alkyl derivatives were prepared from methylaminoaceto-2,6-xylidide and the appropriate alkyl iodide (Table III).

**Physicochemical Properties.** Since local anesthetic agents pass nerve sheaths and membranes in un-ionized basic form but the anesthetic action is at least partly due to the ionized form,[4] the physicochemical properties of these agents are very important. In fact, most useful local anesthetics have dissociation constants, water solubilities, and partition coefficients within rather narrow ranges.[5]

The physicochemical properties are given in Table IV. Since the haloalkylamines are more or less cyclizing during the determination no such data were obtained for this class of compounds. However, the chloropropyl derivative **8** cyclized very slowly and the water solubility of the basic form could be determined. Lidocaine was included as reference substance.

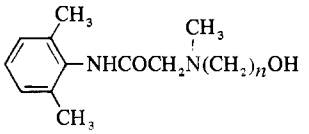
The dissociation constant was almost independent on the size of the substituent (Table IV). However, the water solubility of the basic form and the partition coefficient were greatly affected by the size of the alkyl group; the former decreased and the latter increased with increasing lipophility of the compounds. The water solubility of the chloropropyl derivative **8** was about the same as that of the *N*-pentyl derivative **16** indicating that a chlorine atom in this respect is equivalent to two methylene groups.

The rates of cyclization of the haloalkyl derivatives are given as half-life times ($t_{1/2}$) at pH 7.4 in Table V. The reaction was of first order. The relative rates of cyclization followed the same pattern as previously observed for two other series of *tert*-haloalkylamines.[1,2] The length of the haloalkyl chain was very important for the cyclization rate, with a maximum for the chlorobutyl compound. The reaction was more rapid for the 2-chloroethyl (**7**) than for the 3-chloropropyl derivative **8**. While the 5-chloropentyl derivative **10** was cyclized comparatively rapidly to the piperidinium compound, the cyclization of the 6-chlorohexyl derivative **12** was very slow. The order of reactivity is in accordance with an intramolecular cyclization as discussed in previous papers.[1,2] Evidence for the formation of the piperidinium derivative from *N*-(5′-chloropentyl)-*N*-methylaminoaceto-2,6-xylidide (**10**) is given elsewhere.[6,7]

**Pharmacology. Toxicity.** The intravenous toxicity in mice was determined (Figure 1). The very rapidly cyclizing 4-chlorobutyl derivative **9** was the most toxic compound, indicating that the quaternary derivatives formed are more toxic than the tertiary amines. Accordingly, the 5-bromopentyl derivative **11** was more toxic than the corresponding chloro compound, both compounds forming the same piperidinium derivative but the bromo compound about 40 times more rapidly. The 2-chloroethyl and 3-chloropropyl derivatives **7** and **8** were the least toxic of all compounds examined. The toxicity of the *N*-alkyl derivatives varied much less than that of the chloroalkyl derivatives.

**Irritancy.** Tissue irritancy produced by intradermal injection in the ear of the rabbit was determined (Figure 1). In the *N*-alkyl series the ethyl (**13**), propyl (**14**), and butyl (**15**) derivatives caused somewhat greater irritation than lidocaine whereas the higher homologs were considerably

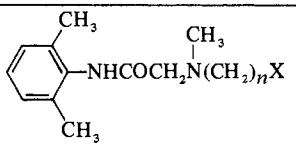
Table I. *N*-(ω-Hydroxyalkyl)-*N*-methylaminoaceto-2,6-xylidides



| Compd no. | n | Solvent | HCl scavenger | Yield, % | Bp (nm) and/or mp, °C | Mp, °C[a] | Formula[b] |
|---|---|---|---|---|---|---|---|
| 2 | 2 | Dioxane | | 64 | 89-95[c] | 140-142[d] | $C_{13}H_{20}N_2O_2 \cdot HCl$ |
| 3 | 3 | [g] | | 67 | 165-168 (0.01)[e] | | $C_{14}H_{22}N_2O_2$ |
| 4 | 4 | $C_6H_6$ | Triethylamine | 52 | | 162.3-164.5[d] | $C_{15}H_{24}N_2O_2 \cdot HCl$ |
| 5 | 5 | Dioxane | Ethyldiisopropylamine | 62 | 204-210 (0.05)<br>73.5-75.5[f] | | $C_{16}H_{26}N_2O_2$ |
| 6 | 6 | $C_6H_6$ | Triethylamine | 47 | 160-170 (0.02) | | $C_{17}H_{28}N_2O_2$ |

[a]Hydrochloride. [b]The compounds were analyzed for N and the equivalent weights were obtained by titration. Analytical results were within ±0.4% of the theoretical values. [c]N. Löfgren and G. Widmark [*Sv. Kem. Tidskr.*, 323 (1946)] give mp 92-94°. [d]From AcOEt-MeOH. [e]$n^{25}$D 1.5336. [f]From (*i*-Pr)$_2$O-MeOH. [g]See Experimental Section.

Table II. *N*-(ω-Haloalkyl)-*N*-methylaminoaceto-2,6-xylidides



| Compd no. | n | X | Yield, % | Mp, ° C | Formula[a] |
|---|---|---|---|---|---|
| 7 | 2 | Cl | 44 | 65-66[b] | $C_{13}H_{19}N_2OCl$ |
| 8 | 3 | Cl | 63 | 115.5-117.5[c] | $C_{14}H_{21}N_2OCl$ |
| 9 | 4 | Cl | 72 | 151-155[d] | $C_{15}H_{23}N_2OCl \cdot HCl$ |
| **10** | 5 | Cl | 93 | 142-144.5[e] | $C_{16}H_{25}N_2OCl \cdot HCl$ |
| 11 | 5 | Br | 83 | 158.5-160[f] | $C_{16}H_{25}N_2OBr \cdot HBr$ |
| 12 | 6 | Cl | 92 | 140-143[e] | $C_{17}H_{27}N_2OCl \cdot HCl$ |

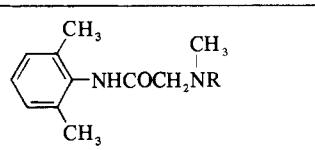
[a]The compounds were analyzed for N and the equivalent weights were obtained by titration. Analytical results were within ±0.4% of the theoretical values. [b]From petroleum ether. [c]From ligroin (96-100°). [d]From 2-pentanone-EtOH. [e]From 2-pentanone. [f]From 2-pentanone-MeOH.

more irritating, the degree increasing with the size of the alkyl group. A similar pattern was found for the *N*-chloroalkyl derivatives but the higher homologs were less irritating than the corresponding alkyl compounds. The bromopentyl derivative **11** produced about the same degree of irritation as the chloro analog.

**Local Anesthetic Action.** In accordance with earlier observation[8] the higher homologs in the *N*-alkyl series examined produced long-lasting anesthesia, which was particularly pronounced in the sciatic nerve tests *in vitro* and *in vivo* but also shown in the cornea and wheal tests (Figures 2 and 3). In the sciatic nerve test *in vivo* the pentyl (**16**) and hexyl (**17**) derivatives acted "irreversibly" as judged from the lack of recovery from the anesthesia within 7 days. The increase in the duration of anesthesia with prolongation of the side chain in this series is obviously due to increasing lipophility of the compounds. The "irreversibility" may thus be due to a very low rate of loss of these compounds from the nerves. However, the pronounced irritancy of these compounds may cause damage to the nerves causing failure of nerve impulse propagation. The comparatively short duration of the heptyl derivative **18** is probably due to the very low water solubility of the basic form, which may become a limiting factor for the local anesthetic effect with increasing lipophility of the compounds.

With the exception of the wheal test, the duration of local anesthesia produced by the compounds in the chloroalkyl series was shorter than that produced by the corresponding alkyl compounds (Figures 2 and 3). The higher homologs were not so extremely long-acting in the sciatic nerve test *in vivo;* the chlorohexyl derivative **12** at the higher does examined was the only compound in this series acting "irreversibly." Another difference between the two classes of compounds was observed in this test. At both doses employed the chloropentyl derivative **10** produced a shorter duration of anesthesia than both its next higher and lower homologs. The bromopentyl derivative **11** caused also a longer block than the corresponding chloro compound **10**. These observations indicate that the formation of the quaternary derivatives contributes to the duration of anesthesia produced by the chlorobutyl (**9**), bromopentyl (**11**), and chloropentyl (**10**) derivatives. Among the haloalkylamines examined only these compounds cyclize rapidly enough forming sufficient amounts of the quaternary derivatives to

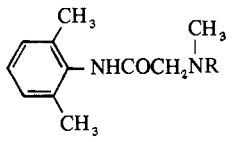
Table III. *N*-Alkyl-*N*-methylaminoaceto-2,6-xylidides



| Compd no. | R | Yield, % | Bp (mm), °C | $n^{25}$D, deg | Mp, °C[a] | Formula[b] |
|---|---|---|---|---|---|---|
| 13 | $C_2H_5$[c] | 51 | 122-125 (0.01) | 1.5228 | 170-172[g] | $C_{13}H_{20}N_2O \cdot HCl$ |
| 14 | $C_3H_7$[d] | 74 | 131-137 (0.01) | [f] | 126.5-129.5[h] | $C_{14}H_{22}N_2O \cdot HCl$ |
| 15 | $C_4H_9$[e] | 42 | 130-135 (0.002) | [f] | 128.5-131.5[h] | $C_{15}H_{24}N_2O \cdot HCl$ |
| 16 | $C_5H_{11}$[e] | 35 | 132-136 (0.001) | 1.5098 | 152-154[h] | $C_{16}H_{26}N_2O \cdot HCl$ |
| 17 | $C_6H_{13}$[e] | 79 | 148-155 (0.005) | 1.5080 | 142-144.5[i] | $C_{17}H_{28}N_2O \cdot HCl$ |
| 18 | $C_7H_{15}$[e] | 41 | 150-160 (0.002) | 1.5050 | 148-151[h] | $C_{18}H_{30}N_2O \cdot HCl$ |

[a]Hydrochloride. [b]The compounds were analyzed for N and Cl. Analytical results were within ±0.4% of the theoretical values. [c]Solvent $C_6H_6$. [d]Solvent toluene. [e]Solvent xylene. [f]Crystalline. [g]From butanone-MeOH. [h]From EtOAc-MeOH. [i]From 2-pentanone.

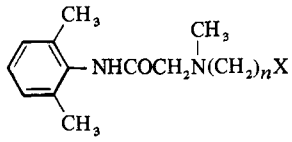
Table IV. Physicochemical Properties of the *N*-Alkylamines



| Compd no. | R | Dissociation constant, $pK_a$ | Solubility of the base in water, mmol/l. | Partition coefficient, cod liver oil/water |
|---|---|---|---|---|
| 13 | $C_2H_5$ | 7.65 | 80 | 8.5 |
| 14 | $C_3H_7$ | 7.72 | 25 | 39 |
| 15 | $C_4H_9$ | 7.66 | 8 | 159 |
| 16 | $C_5H_{11}$ | 7.44 | 3 | 527 |
| 17 | $C_6H_{13}$ | 7.42 | *a* | *a* |
| 8 | $(CH_2)_3Cl$ | *b* | 2.6 | *b* |
| | Lidocaine | 7.85 | 30 | 36 |

[a]Unmeasurable. [b]Not measured.

Table V. Rate of Cyclization of the Haloalkylamines Examined



| Compd no. | *n* | X | Half-life time,[a] $t_{1/2}$, min |
|---|---|---|---|
| 7 | 2 | Cl | 108 |
| 8 | 3 | Cl | 1320 |
| 9 | 4 | Cl | 0.32 |
| 10 | 5 | Cl | 50 |
| 11 | 5 | Br | 1 |
| 12 | 6 | Cl | 3000 |

[a]Determined by potentiometric titration of the halide ion formed on warming a 5 m*M* solution in 50% ethanol, pH 7.4 at 37°.

be involved in the anesthesia. Since the cyclization of the chlorobutyl (**9**) compound is over 100 times more rapid than that of the chloropentyl (**10**) homolog, the amount of the pyrrolidinium compound formed in the nerves may be higher than that of the piperidinium compound formed from the 5-chloropentyl derivative. If the quaternary compounds have local anesthetic activity, the anesthesia can be expected to be long-lasting because the nerve sheaths and membranes are strong hindrances for the outward passage of the completely dissociated quaternary ions. This is in accordance with the observations made. However, in order to establish the hypothesis that the quaternary derivatives formed from the 4- and 5-haloalkyl derivatives contribute to the duration of local anesthesia, it is necessary to demonstrate that the quaternary derivatives are formed within the nerves, that the duration of anesthesia correlates with the loss of the quaternary derivatives from the nerves, and that the quaternary compounds have local anesthetic activity *per se*. Observations reported elsewhere[6,7] indicate that these conditions are fulfilled and thus the hypothesis is supported.

Stubbins, *et al.*,[9] have examined a different approach for producing long-acting local anesthesia, *viz.* the alkylating property of *N*-(2-chloroethyl)-*N*-ethylaminoaceto-2,6-xylidide. In contrast to the observations with this compound the corresponding *N*-methyl derivative **7** did not produce long-lasting effect in our experiments. This discrepancy may in part be due to the different methods used but also

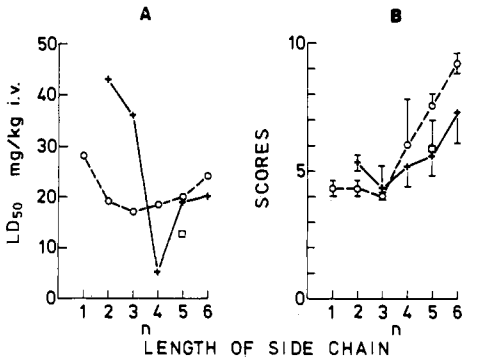



Figure 1. Toxicity and local irritancy: *N*-alkyl-*N*-methylaminoaceto-2,6-xylidide derivatives, (○) and broken lines; *N*-(ω-chloralkyl)-*N*-methylaminoaceto-2,6-xylidide derivatives, (×) and solid line; *N*-(5-bromopentyl)-*N*-methylaminoaceto-2,6-xylidide, (□). *n* = number of methylene groups. (A) Intravenous toxicity in mice expressed as $LD_{50}$ (mg/kg). (B) Tissue irritancy, rabbit ear. Each value is the mean of three determinations. The vertical bars are S.E.M.

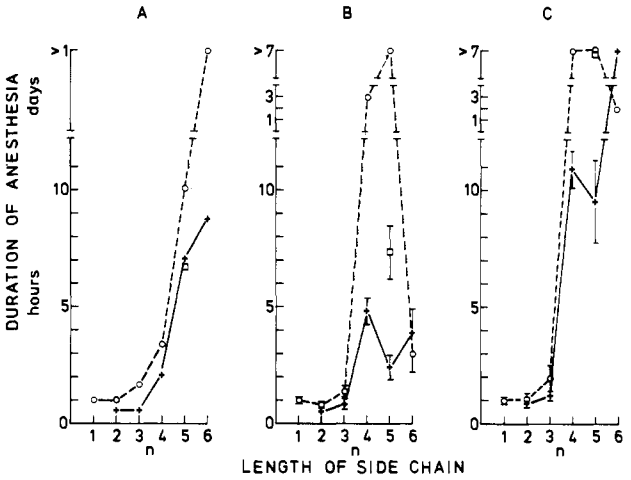



Figure 2. Duration of local anesthetic effect: *N*-alkyl-*N*-methylaminoaceto-2,6-xylidide derivatives, (○) and broken line; *N*-(ω-chloroalkyl)-*N*-methylaminoaceto-2,6-xylidide derivatives, (×) and solid line; *N*-(5-bromopentyl)-*N*-methylaminoaceto-2,6-xylidide, (□). *n* = number of methylene groups. (A) Block of the action potential of the sciatic nerve of the frog *in vitro*. Each value is the mean of four determinations. (B) Sciatic nerve block in the guinea pig *in vivo* by 1% solution of the compounds examined. Each value is the mean of six determinations. (C) Sciatic nerve block in the guinea pig *in vivo* by 2% solution of the compounds examined.

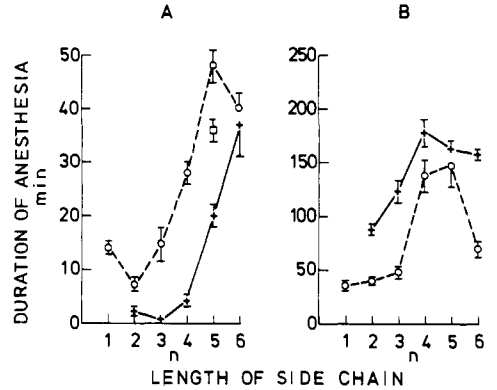



Figure 3. Duration of local anesthetic effect: *N*-alkyl-*N*-methylaminoaceto-2,6-xylidide derivatives, (○) and broken line; *N*-(ω-chloroalkyl)-*N*-methylaminoaceto-2,6-xylidide derivatives, (×) and solid line; *N*-(5-bromopentyl)-*N*-methylaminoaceto-2,6-xylidide, (□). *n* = number of methylene groups. (A) Rabbit cornea. Mean of six determinations. (B) Wheal test in the guinea pig. Each value is the mean of 3–6 determinations.

to the rather low rate of formation of the reactive aziridinium derivative (Table V).

## Experimental Section

Melting points were taken by a Büchi melting point apparatus and are uncorrected. Where analyses are indicated in Tables I, II, and III and the following text by the symbols of elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

**Chemistry. 6-Methylamino-1-hexanol (1).** To a solution of 57 g (1.83 mol) of $MeNH_2$ in 80 ml of MeOH was added 34 g (0.25 mol) of 6-chloro-1-hexanol. The mixture was heated in a 250-ml steel autoclave at 100° for 44 hr. After removal of the solvent under reduced pressure, the residue was distilled *in vacuo* affording 21.4 g (66%) of amino alcohol [bp 117–118.5° (8 mm), $n^{25}$D 1.4554] which by glc (20% Dowfax + 2.5% NaOH on Chromosorb N at 180°) was found to be about 99% pure. *Anal.* ($C_7H_{17}NO$) N.

***N*-(ω-Hydroxyalkyl)-*N*-methylaminoaceto-2,6-xylidides. A.** A mixture of chloroaceto-2,6-xylidide, the ω-methylaminoalkanol, and triethylamine or *N*-ethyldiisopropylamine, 0.1 mol of each, in 200 ml of dioxane or 250 ml of $C_6H_6$, was refluxed for 5 hr. The reaction mixture was filtered to remove precipitated salt and the filtrate, if a dioxane solution, evaporated and the residue dissolved in dilute hydrochloric acid or, if a $C_6H_6$ solution, extracted directly with the mineral acid. The aqueous acid solution was washed with $Et_2O$ and then made alkaline with 30% NaOH solution. The liberated base was extracted with $Et_2O$ or $CHCl_3$ and the extracts were dried over $MgSO_4$. The product was then either distilled or converted directly to hydrochloride.

**B.** A mixture of 11.6 g (0.06 mol) of methylaminoacetoxylidide, 5.7 g (0.06 mol) of 3-chloro-1-propanol, and 7.6 g (0.072 mol) of $Na_2CO_3$ in 200 ml of dry xylene was stirred under reflux for 89 hr. After cooling, the salts were removed by filtration and the filtrate was extracted with dilute HCl. The work-up procedure was then the same as for method A.

***N*-(ω-Chloroalkyl)-*N*-methylaminoaceto-2,6-xylidides.** A mixture of 0.015 mol of the hydrochloride of the amino alcohol and 0.030 mol of $SOCl_2$ in 100 ml of $CHCl_3$ was refluxed for 20 hr whereupon the solvent was evaporated. The chloroethyl and the chloropropyl derivatives could not be obtained crystalline, but the free bases were crystallized and were stable enough to be recrystallized (from petroleum ether and ligroin, respectively). In the other cases the compounds were directly recrystallized as hydrochlorides.

***N*-(ω-Bromopentyl)-*N*-methylaminoaceto-2,6-xylidide Hydrobromide (11).** HBr gas was passed through three wash bottles containing in order, concentrated $H_2SO_4$, tetralin, and paraffin chips and then into 250 ml of cooled glacial AcOH until 100 g had been absorbed; 25.6 g (0.092 mol) of *N*-methyl-*N*-(ω-hydroxypentyl)aminoaceto-2,6-xylidide was then added and the mixture was heated on an oil bath at 90° for 23 hr. The solvent was then evaporated and the crystalline residue dried in a vacuum desiccator over KOH pellets. Recrystallization from 2-pentanone and a small amount of MeOH yielded 31.9 g (83%) of product with mp 158–161°.

***N*-Alkyl-*N*-methylaminoaceto-2,6-xylidides.** A solution of 0.1 mol of methylaminoaceto-2,6-xylidide and 0.1 mol of alkyl iodide in 150 ml of $C_6H_6$, toluene, or xylene was stirred under reflux in the presence of 0.1 mol of $K_2CO_3$ for 24 hr. The salts were removed by filtration, the solvent was evaporated, and the residue was distilled. The bases were converted to hydrochlorides by means of ethereal HCl gas and recrystallized.

**Physicochemical Properties.** The dissociation constants, the water solubility of the basic form, and the partition coefficients for the system cod liver oil and water were determined according to Brändström.[19] The rate of cyclization was determined by means of potentiometric titration of the halide ions released from a 5 m*M* solution in 50% EtOH containing 50 m*M* Na phosphate buffer, pH 7.4 at 37°.

**Pharmacology.** To avoid cyclization of the compounds, the solutions were prepared immediately before use and the pH was kept about 4.

**Toxicity.** The intravenous toxicity was determined in male albino mice (NMRI) weighing 18–22 g. The injected volume did not exceed 0.5 ml. The $LD_{50}$ values were calculated from dose–response curves based on at least five doses with ten animals to each dose.

**Irritancy.** The local irritation produced by the compounds was determined on rabbit ears. A volume of 0.1 ml of a 0.5% solution containing adrenaline (1:200,000) was injected between the dermal layers of the ear. The site of the injection was observed at regular intervals up to 1 week after administration. The tissue irritation produced by the compound was scored from 0 to 3 with respect to size, redness, oedema, and necrosis. The sum of the scores at the time for maximum tissue irritancy was determined.

**Local Anesthetic Effect. Isolated Sciatic Nerve of Frog *in Vitro*.** Excitation block *in vitro* was tested on sciatic nerves of the frog (Rana pipiens).[11,12] A segment of about 1.5 cm of the nerve lying between the stimulation sites and the recording electrodes was incubated in a 5 m*M* solution of the test compound in Tasaki–Ringer buffer, pH 7.2 for 20 min. The decrease in the action potential was followed. After washing out the test solution the recovery of the action potential was determined. The time for complete recovery was measured.

**Sciatic Nerve Block *in Vivo*.** The block of the sciatic nerve of the guinea pig was tested according to Shackell.[13] A volume of 0.2 ml of 1 or 2% solution of the test compound was injected in the hip to groups of six animals. Lidocaine was used as reference drug and was injected in the opposite leg. The time of onset, duration, and frequency of block were measured by observation of the motor paralysis of the legs.

**Topical Anesthesia.** The topical anesthetic effect was tested on rabbit cornea according to Wiedling.[14] Latency period and duration of block were measured after application of 0.25 ml of a 2% solution of the test compound.

**Infiltration Anesthesia.** The infiltration anesthetic effect was determined by the wheal test according to Bülbring and Wajda.[15] A volume of 0.25 ml of 1% solution was injected intracutaneously on the shaven backs of guinea pigs. The sensitivy to six pin pricks within each wheal was tested at intervals.

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