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Synthesis and Pharmacological Properties of Three Lidocaine Cyclovinylogues

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Three isomeric lidocaine cyclovinylogues in which a benzene ring is interposed between the carbamidic and diethylaminomethyl groups of the glycinamide chain, are described. The meta derivative possesses greater local anesthetic and antiarrhythmic activities than the parent compound.

Synthese und pharmakologische Eigenschaften von drei Lidocain-Zyklovinylogen

Es werden drei Lidocain-Zyklovinyloge beschrieben, in denen ein Benzolring zwischen die Carbamid- und die Diethylaminomethylgruppen der Seitenkette eingefügt ist. Das m-Isomer weist im Vergleich mit Lidocain größere lokalanaesthetische und antiarrhythmische Aktivitäten auf.

The papers on the structure-activity relationships of lidocaine-type local anesthetic drugs recently appeared in pharmaceutical literature[1,2,3,4], prompted us to publish this preliminary report which is part of a larger research program with similar scope. A more immediate purpose, however, is that of submitting the new drugs for practical use, as we believe that the therapeutic armamentarium should be constantly renewed. In fact, the utility of local anesthetic drug often does not depend only upon its local anesthetic properties *per se*, but upon other factors such as local tolerability, vasoconstrictive and central stimulating actions as well as on its stability and nature of its degradation products[5]. In particular, we were interested in potentiating the antiarrhythmic component of lidocaine so as to permit its oral use[6], and in this connection tocainide[6] and mexiletine[7] are worthy of mention.

Lidocaine **(1)** was modified by introducing a benzene ring between the carbamidic and diethylaminomethyl groups of the glycinamide chain, in other words by preparing the corresponding cyclovinylogues in the three possible ortho, meta and para isomers.

These new structural models could be useful as such and also through subsequent nuclear substitutions in further evaluating the contribution of stereochemical and electronic factors to the control of local anesthetic activity. While the work in this direction is in progress, we submit here a preliminary pharmacological profile of the new derivatives showing the validity of this modification.

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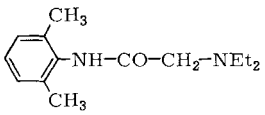

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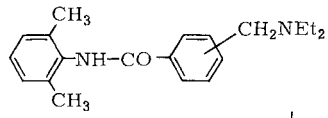

2

a	*o*
b	*m*
c	*p*

Compounds **2a–c** were prepared by condensation of 2,6-dimethylaniline with *o*-, *m*- and *p*-chloromethylbenzoyl chloride and subsequent amination of the intermediate chloromethylbenzamides with diethylamine.

Pharmacology

1. Methods

Local anesthesia. Intracutaneous local anesthetic potency was determined by the method of *Bulbring* and *Wajda*[8] using guinea-pigs of both sexes weighing between 600–700 g. For each experiment, test and standard drugs, each in two different concentrations, were injected intracutaneously into four injection sites. The flinch responses to six needle pricks on each site at 5 min intervals up to 30 min were recorded. Surface anesthetic potency was determined in rabbits according to the method of *Bulbring* and *Wajda*[8]. The test drugs were dissolved in saline and the solution (0.1 ml) instilled into the open eye. The corneal reflex was tested by touching the eye surface with a horse-hair six times, at 5 min intervals for 20 min.

Antiarrhythmic action. Delay in onset of aconitine-induced ventricular arrhythmias was examined in Wistar rat of both sexes (300–400 g body wt.) anesthetized with ethylurethane (1 g/kg i. p.). Animals were prepared with test and standard drugs intravenously, 3 min before infusion of aconitine (10 μg/kg/min) by intravenous route according to the method of *Vargaftig* and *Coignet*[9].

Standard drugs. Lidocaine hydrochloride, aconitine, quinidine sulphate.

2. Results

The data of Table 1 show that only compound **2a** and **2b** retain local anesthetic activity, while **2c** is almost inactive; also, **2b** in surface as well as in infiltration anesthesia is more active than the reference compound.

Also with regard to antiarrhythmic properties only **2b** is higly effective in delaying the onset of the first burst of ventricular arrhythmias induced by a slow intravenous infusion of aconitine into the anesthetized animals. Fig. 1 illustrates the increase in aconitine amount tolerated after pretreatment with **2a–c.** Comparison was effected with lidocaine and quinidine.

Table 1: *Anesthetic activity* of **2a–c**

Compound	Surface anesthesia			Infiltration anesthesia		
	Mean number of pricks failing to elicit					
	the rabbit corneal reflex* C %			the flinch response (guinea-pig)** C %		
	0.1	0.3	0.5	0.1	0.3	0.5
2a	9 ± 1.08	14.5 ± 1.04	19.25 ± 0.85	11.5 ± 0.8	15 ± 0.8	25 ± 1.4
2b	11.25 ± 1.71	21.5 ± 2.17	24 ± 0	14.5 ± 1.2	19.75 ± 0.8	26.5 ± 1.8
2c	–	–	1.5 ± 0.2	–	2.25 ± 0.4	4 ± 1.08
Lidocaine	–	4.5 ± 1.04	9 ± 1	6.5 ± 0.6	10.5 ± 2.4	21 ± 0.7

Each value represents the mean ± SE of 4 animals per treatment group.
* The rabbit cornea was stimulated by an horse-hair 6 times at 5 min intervals for 20 min.
** The guinea-pig skin was stimulated by steel needle 6 times for 30 min.

This preliminary data would confirm the validity of the modification, which makes it possible to apply on this new structure selected nuclear and nitrogen substituents, already proved successful on lidocaine itself.

Experimental

2-Chloromethyl-2',6'-dimethylbenzanilide **(3)**

To a solution of 18.9 g (0.1 mole) 2-chloromethylbenzoyl chloride in 200 ml Acetone, 12.1 g (0.1 mole) of 2,6-dimethylaniline and 30 g K_2CO_3 were added and the mixture refluxed for 2 h. After cooling and filtering, the solvent was removed and the residue on crystallizing from EtOH gave 16.3 g (60 % yield) of white product, m. p. 170–172°C. $C_{16}H_{16}ClNO$ (273.6) Ber.: C 70.2 H 5.89 Cl 13.0 N 5.1; Gef.: C 70.0 H 5.82 Cl 13.0 N 5.1.

3-Chloromethyl-2',6'-dimethylbenzanilide **(4)**

In a similar manner starting from 18.9 g (0.1 mole) 3-chloromethylbenzoyl chloride and 12.1 g (0.1 mole) 2,6-dimethylaniline, 19 g (70 % yield) of **4** were obtained, m. p. 130–132°C (ligroin). $C_{16}H_{16}ClNO$ (273.6) Ber.: C 70.2 H 5.89 Cl 13.0 N 5.1; Gef.: C 70.1 H 5.95 Cl 12.9 N 5.1.

4-Chloromethyl-2',6'-dimethylbenzanilide **(5)**

With the above procedure 18.9 g (0.1 mole) of 4-chloromethylbenzoyl chloride and 12.1 g (0.1 mole) 2,6-dimethylaniline, gave 19 g (70 % yield) of **5**, m. p. 160–163°C (EtOH). $C_{16}H_{16}ClNO$ (273.6) Ber.: C 70.2 H 5.89 Cl 13.0 N 5.1; Gef.: C 69.9 H 5.71 Cl 12.8 N 5.2.

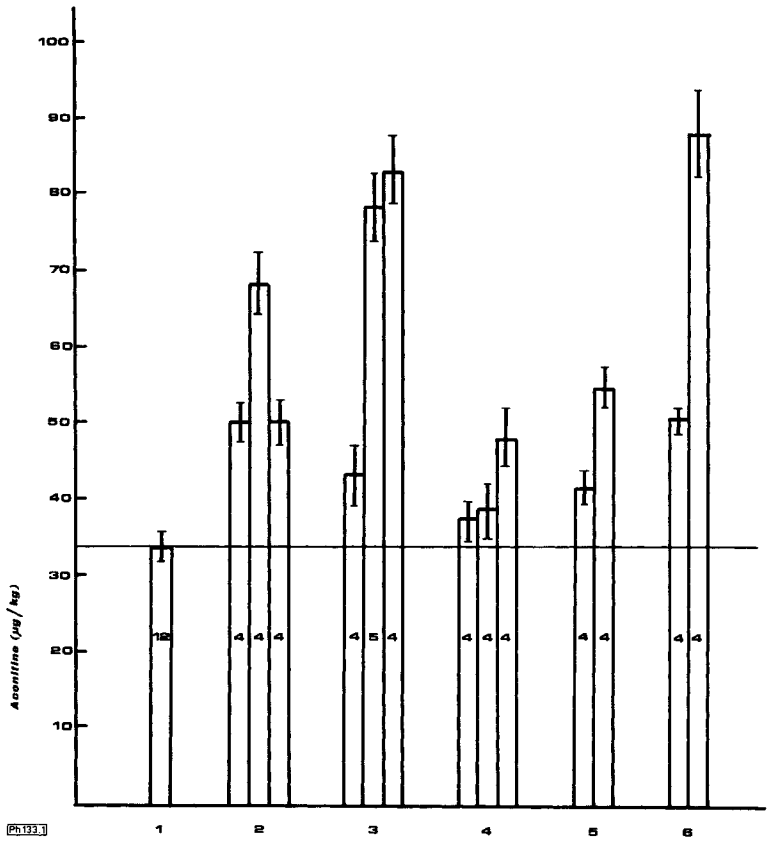

Fig. 1: Amount of aconitine (µg/kg) necessary to induce ventricular arrhythmias in the rat. Figures inside columns indicate number of animals; bars indicate confidence limit 95 %. Horizontal line: results from untreated animals.

1. Control animals.
2. **2a:** 0.6, 1 and 3 mg/kg.
3. **2b:** 1, 3 and 6 mg/kg.
4. **2c:** 1, 3 and 8 mg/kg.
5. Lidocaine: 12.5 and 25 mg/kg.
6. Quinidine sulphate: 10 and 40 mg/kg.

2-Diethylaminomethyl-2',6'-dimethylbenzanilide **(2a)**

To a solution of 2.72 g (0.01 mole) of **3** in 200 ml benzene, a slight excess of Et_2NH was added and the mixture was refluxed for 5 h. After cooling and filtering, the solvent was removed and the residue on crystallizing from ligroin gave 2.7 g (90 % yield) of white solid m. p. 99–101°C. $C_{20}H_{26}N_2O$ (310.2) Ber.: C 77.4 H 8.45 N 9.0; Gef.: C 77.4 H 8.52 N 9.0

2a-Hydrochloride: White product, m. p. 215–217°C ($MeOH/Et_2O$). $C_{20}H_{27}ClN_2O$ (346.7) Ber.: Cl 10.2 N 8.1; Gef.: Cl 10.3 N 8.1.

3-Diethylaminomethyl-2',6'-dimethylbenzanilide **(2b)**

As described for **2a,** starting from 2.72 g (0.01 mole) of **4** and Et_2NH, 2.45 g (80 % yield) of **2b** were obtained, m. p. 100–102°C (ligroin). $C_{20}H_{26}N_2O$ (310.2) Ber.: C 77.4 H 8.45 N 9.0; Gef.: C 77.3 H 8.40 N 9.1.

2b-Hydrochloride: White product, m. p. 162–165°C ($MeOH/Et_2O$). $C_{20}H_{27}ClN_2O$ (346.7) Ber.: Cl 10.2 N 8.1; Gef.: Cl 10.1 N 8.1.

4-Diethylaminomethyl-2',6'-dimethylbenzanilide **(2c)**

With the same procedure, starting from 2.72 g (0.01 mole) of [5] and Et_2NH, 2.43 g (80 % yield) of **2c** were obtained, m. p. 141–142 °C (ligroin). $C_{20}H_{26}N_2O$ (310.2) Ber.: C 77.4 H 8.45 N 9.0; Gef.: C 77.5 H 8.35 N 9.1.

2c-Hydrochloride: White product, m. p. 247–250°C ($MeOH/Et_2O$) $C_{20}H_{27}ClN_2O$ (346.7) Ber.: Cl 10.2 N 8.1; Gef.: Cl 10.4 N 7.7.

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