Rohglykosidgehalt konnte, nach Einengen und Einstellen auf eine Glykosidkonzentration von ca. 0,8 mg/ml, in das System injiziert werden. Nähere Angaben auch zur quantitativen Analyse s.[12,13].

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[Ph 527]

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Cyclovinylogues of Procainamide

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Three isomeric cyclovinylogues of procainamide, in which a benzene ring is interposed between the methylene groups of the basic chain, are described. Appreciable dissociation has been achieved between local anesthetic and antiarrhythmic activities.

Procainamid-Zyklovinyloge

Es werden drei Procainamid-Zyklovinyloge beschrieben, in denen ein Benzolring zwischen den Methylengruppen der basischen Seitenkette eingefügt ist. Zwischen der lokalanästhetischen und der antiarrhythmischen Wirkung wurde eine nennenswerte Trennung erzielt.

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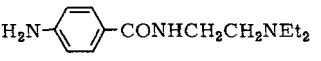
The amazing results obtained by converting some glycinanilide|type local anesthetics (lidocaine, tolicaine, butanilicaine) into their cyclovinylogues as recently described[1,2,3], prompted us to verify the validity of this modification in the ,,quasi" isomeric class of procainamide type derivatives. This attempt is part of a general research program on cyclovinylogues of different drug classes and precedes an interesting result in the field of cholinergics[4].

As above stated, we have modified the procainamide structure **1** by introducing a benzene ring between the two methylene groups of the basic chain so obtaining the corresponding cyclovinylogues in the three possible ortho, meta and para isomers.



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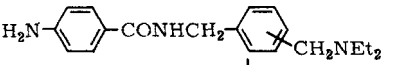

2

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

Compounds **2a–c** were prepared by condensing o-, m- and p-diethylaminomethylbenzylamine with p-nitrobenzoyl chloride and subsequent reduction of the nitroamide intermediates with Fe in hydrochloric ethanol.

Pharmacology

Methods

Experiments were performed on Swiss-Webster albino mice body weigth of 20 g, Pirbrigth guinea pigs body weigth of 350 g and New Zealand rabbits body weigth of 2.5 kg. All substances were dissolved in water. An approximate intraperitoneally LD_{50} was determined in mice and mortality was recorded over 7 days. Following activities were furthermore tested:

- antiarrhythmic activity against chloroform induced ventricular fibrillations in mice, according to the method of *Lawson*[5], 10 min after intraperitoneal administration of substances to be tested.

The ED_{50} were determined according to the method of *Litchfield* and *Wilcoxon*[6].

- antiarrhythmic activity on isolated guinea pig atria in spontaneous contractions or electrically driven, according to the method of *Alles* and *Ellis*[7], using 3 atria for each drug concentration.

In both experiments the rate and amplitude of contractions were recorded; for the electrically driven atria the highest rate followed was also recorded.

- local anesthetic activity on the rabbit's eye, according to the method of *Bülbring* and *Wajda*[8], using 3 animals for each concentration.

Results

The values of approximate LD_{50} ranged from about 60 to 400 mg/kg.

2a seems to be the most interesting drug, showing an antiarrhythmic activity both in mice and on isolated atria. At a concentration of 10 mcg/ml it showed about the same effect as propranolol-HCl at a concentration of 8 mcg/ml on the rate of spontaneously contracting atria.

On electrically driven atria at a concentration of 3 mcg/ml it lowered about 23 % the highest rate followed, showing about the same activity as propranolol-HCl at a

concentration of 4 mcg/ml. In both preparations **2a**, unlike propranolol-HCl, did not depress the amplitude of contractions (tables 1 and 2).

Table 1: *Activity on guinea pig spontaneously contracting atria. Per cent variations after 30 min of contact with the test substances.*

Compound	Concentration mcg/ml	Amplitude of contractions	Rate of contractions
2a	3	+ 23	− 26
	10	+ 5	− 47
2b	3	+ 11	− 7
	10	+ 2	− 17
2c	3	+ 2	− 9
	10	− 7	− 12
Propranolol-HCl	4	− 32	− 39
	8	− 54	− 50

Table 2: *Antiarrhythmic activity on electrically driven guinea pig atria. Per cent variations after 30 min of contact with the test substances.*

Compound	Concentration mcg/ml	Amplitude of contractions	Rate of contractions	Highest rate followed
2a	3	+ 29	− 31	− 23
2b	10	+ 6	− 14	0
2c	10	+ 9	− 12	0
Propranolol-HCl	4	− 40	− 23	− 22
	8	− 72	− 44	− 36

Table 3: *Pharmacological profile of the isomeric procainamide cyclovinylogues*

Compound	Approximate LD_{50} mouse i.p.	Antiarrhythmic activity ED_{50} mouse i.p.	Local anesthetic activity ED_{50} mg/ml
2a	60	37.6 (34.2–41.4)	5.60
2b	300	100	0.43
2c	400	200	0.58
Procainamide	360 (330–392)	200	20.32
Propranolol-HCl	125 (116–133)	6.3 (3.9–10.2)	–

The antiarrhythmic activity of **2a** on mice was about 6 times lower than that of propranolol-HCl (table 3), furthermore its ED_{50} was very close to the toxic doses.

2b and **2c** on the contrary seemed to be devoid of antiarrhythmic activity and showed instead a local anesthetic activity about 47 and 35 times, resp., than that of procainamide (table 3).

The results obtained confirm the validity of this structural modification which allowed to dissociate local anesthetic and antiarrhythmic activities.

Experimental

N,N-Diethyl 2-(p-nitrobenzamidomethyl)-benzylamine **(3)**

To a solution of 9.5 g (0,05 mole) of o-diethylaminomethylbenzylamine in 200 ml benzene, 9.7 g (0.05 mole) of p-nitrobenzoyl chloride and 20 g K_2CO_3 were added and the mixture refluxed for 3 h. After cooling and filtering, the solvent was removed and the residue on crystallizing from EtOH gave 10.2 g (60 % yield) of white product m.p. 170–172 °C. $C_{19}H_{23}N_3O_3$ (341.2) Calcd.: C 66.8 H 6.79 N 12.3; Found: C 66.7 H 6.56 N 12.1.

N,N-Diethyl 3-(p-nitrobenzamidomethyl)-benzylamine **(4)**

In similar manner from 9.5 g (0.05 mole) of m-diethylaminomethylbenzylamine and 9.7 g (0.05 mole) of p-nitrobenzoyl chloride, 9.3 g (55 % yield) of **4** were obtained, m.p. 84–86 °C (benzene-petrol ether). $C_{19}H_{23}N_3O_3$ (341.2) Calcd.: C 66.8 H 6.79 N 12.3; Found C 67,0 H 6.81 N 12.2.

N,N-Diethyl 4-(p-nitrobenzamidomethyl)benzylamine **(5)**

With the above procedure 9.5 g (0.05 mole) of p-diethylaminomethylbenzylamine and 9.7 g (0.05 mole) of p-nitrobenzoyl chloride, gave 10.2 g (60 % yield) of **5**, m.p. 93–95 °C (ligroin). $C_{19}H_{23}N_3O_3$ (341.2) Calcd.: C 66.8 H 6.79 N 12.3; Found: C 66.8 H 6.91 N 12.5.

N,N-Diethyl 2-(p-aminobenzamidomethyl)-benzylamine **(2a)**

To a solution of 3.4 g (0.01 mole) of **3** and 3 ml HCl in 150 ml ethanol, 4 g Fe powder under reflux were added by small amounts and the mixture refluxed for 3 h. After cooling, 10 g K_2CO_3 were added and the mixture filtered. The filtrate on removing of the solvent left a residue which on crystallizing from ligroin gave 2.5 g (80 % yield) of white solid, m.p. 105–107 °C. $C_{19}H_{25}N_3O$ (311.2) Calcd.: C 73.3 H 8.10 N 13.5; Found: C 73.0 H 7.82 N 13.9.

N,N-Diethyl 3-(p-aminobenzamidomethyl)-benzylamine **(2b)**

As described for **2a**, starting from 3.4 g (0.01 mole) of **4**, 2.2 g (70 % yield) of **2b** as hydrochloride were obtained, m.p. 197–200 °C (MeOH-Et_2O). $C_{19}H_{26}ClN_3O$ (347.7) Calcd.: C 65.6 H 7.54 N 12.1 Found: C 65.7 H 7.51 N 12.2.

N,N-Diethyl 4-(p-aminobenzamidomethyl)-benzylamine **(2c)**

With the same procedure, starting from 3.4 g (0.01 mole) of **5**, 2.5 g (80 % yield) of **2c** as hydrochloride were obtained, m.p. 167–170 °C (MeOH-Et_2O). $C_{19}H_{26}ClN_3O$ (347.7) Calcd.: C 65.6 H 7.54 N 12.1; Found: C 65.4 H 7.40 N 12.0.

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Studies on Potential Antiviral Compounds, XXII***)

Synthesis and in Vitro Antiviral Activity of 1-(Hydroxyalkyl)-1*H*-benzimidazoles**

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A series of 1-(hydroxyalkyl)-1*H*-benzimidazoles has been prepared and screened in vitro for activity against herpes simplex virus, type 2 (DNA) and poliovirus type 1 (RNA). 5,6-Dichloro-1-[2-(2-hydroxyethoxy)ethyl]-1*H*-benzimidazole (**9**, Table 1) was the most significant compound.

Potentiell antivirale Verbindungen, 22. Mitt.: Synthese und antivirale In-vitro-Aktivität von 1-(Hydroxyalkyl)-1*H*-benzimidazolen

Einige (1-Hydroxyalkyl)-1*H*-benzimidazole wurden hergestellt und in vitro gegen Herpes simplex Typ 2 (DNA) und Poliovirus Typ 1 (RNA) geprüft. Als wirksamste Verbindung zeigte sich 5,6-Dichlor-1-[2-(2-hydroxyethoxy)ethyl]-1*H*-benzimidazol (**9**, Tab. 1).

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