CHEMISTRY OF 1.3-BIFUNCTIONAL COMPOUNDS, XXVII* PREPARATION OF 4-N-SUBSTITUTED PIPERAZINYL-1-PROPYL ESTERS

By

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As a continuation of the synthesis and pharmacological examination of different aminoalkyl esters [1—6], esters containing the piperazine skeleton have been prepared by various methods. Some of them display coronary dilating and cardiac arrhythmia-inhibitory effects.

We earlier reported the synthesis and pharmacological properties of various aminoalkyl esters. In a number of cases, appreciable local anaesthetic [1], bronchial spasmolytic [3], coronary dilating [4, 5] and arrhythmia-inhibitory [6] effects were found. Numerous of the various piperazinyl-1-alkyl esters exhibit considerable phar-

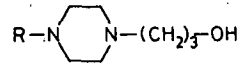
Table I

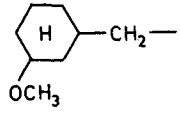
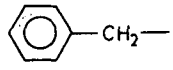
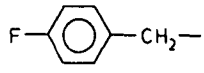
Pharmacologycal data of some esters

Compound	Elevation of the fibrillation threshold (%)		
	2 mg/kg	1 mg/kg	0.5 mg/kg
58	—	21.5	13.2
54	—	22.4	—
91	—	30.3	14.2
38	—	27.6	18.9
35	31.1	—	—
118	—	36.4	—
Chinidin	34.5	20.6	—

* Part XXVI: *M. Bartók, Á. Molnár, G. Bozóki—Bartók:* Acta Chim. Hung. in press.

Table II



No	R	B.p. (°C)	mm Hg	n_D^{20}	M.p. (°C)	R_F	Yield %	Method	Ref.
1	$i-C_3H_7-$	93—95	10	—	—	—	57	B	[12]
2	$n-C_4H_9-$	127—129	1	1.4793	—	—	72	A	—
3	$CH_2=CH-CH_2-$	98—100	3	1.4935	—	0.72	69	B	[13]
4	$CH_3-C(Cl)=CH-CH_2-$	148—150	6	—	2 HCl 209—211	—	49	B	—
5		—	—	—	—	0.88	—	C	—
6		160—163	1	—	55—56	0.85	77	A	—
7		165—167	4	1.5210	2 HCl 230—232	0.82	58	B	—

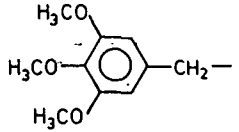
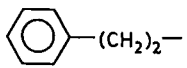
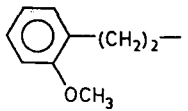
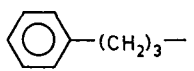
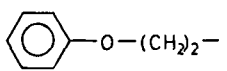
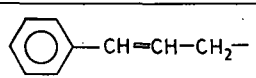
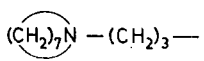
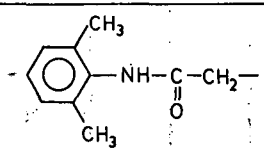
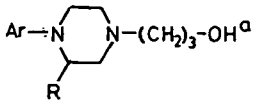
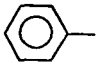
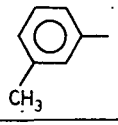
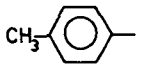
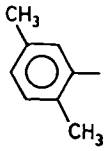
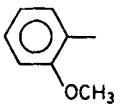
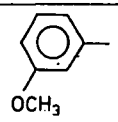
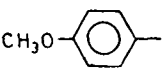
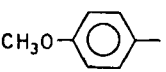
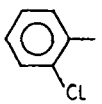
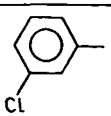
8		—	—	—	—	0.78	—	C	[14]
9		170—172	3	—	—	—	59	C	—
10		—	—	—	62—63	0.89	65	C	—
11		188—190	1	1.5323	—	—	75	C	—
12		185—188	0.5	—	36—37	—	63	C	—
13		165—170	1	1.5540	—	0.65	57	C	—
14		—	—	—	—	0.37	—	C	—
15	C_2H_5OOC-	148—150	2	1.4840	—	0.88	65	A	[15]
16		—	—	—	137—139	0.42	73	A	—

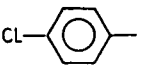
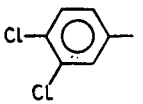
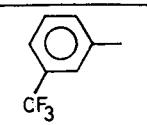
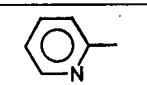
Table III



No	Ar	R	M.p. (°C)	R_F	Yield %	Ref.
17		H	73—74	0.9	77	[16]
18		CH_3	144—148[b]	—	68	—
19		CH_3	158—160[b]	—	65	—
20		H	58—59	—	52	—
21		H	92—93	0.67	77	[17]
22		H	94—95	—	68	—
23		H	87—89	—	75	[8]
24		CH_3	69—71	—	48	—
25		H	99—100	—	52	[18]
26		H	84—85	0.87	82	

[a] Method A
[b] Boiling point at 1 mm Hg.

Table III

No	Ar	R	M.p. (°C)	R_F	Yield %	Ref.
27		H	109—110	0.85	75	[8]
28		H	86—88	0.76	82	—
29		H	158—160[b]	0.85	68	—
30		H	80—81	0.86	75	—

macological effects, *e.g.* central nervous system [7], sedative and hypotensive [8] and tranquillant [9] effects.

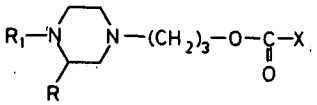
Some of the new compounds we have prepared display good anti-arrhythmic action in anaesthetized cats [10] in comparison with that of quinidine used as reference substance (Table I).

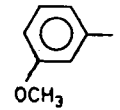
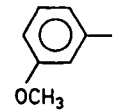
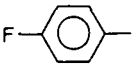
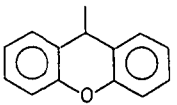
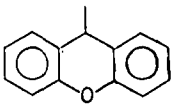
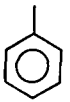
Experimental

The esters were prepared from the corresponding piperazinylpropanols and acid chlorides in acetone or benzene; by the addition of HCl dissolved in ethanol, the dihydrochloride salts were then precipitated and subsequently purified by recrystallization from aqueous ethanol (Table IV). Besides the data resulting from microanalytical elemental analysis (C, H and Cl^-), thin-layer chromatography was used to check the purity.

Of the starting materials, *N*-carbethoxypiperazine, *N*-benzylpiperazine, *N*-butylpiperazine and the *N*-arylpiperazines were products of Aldrich. 3-Chloropropanol, p-fluorobenzyl chloride, 3-phenylpropyl bromide, 3-chlorocrotyl chloride, 2-phenylethyl bromide and 3-phenylallyl bromide were products of Fluka. 1-Methoxy-3--chloromethylcyclohexane (b.p.: 95—100 °C/2 mm Hg; n_D^{20}: 1.4682), 3, 4, 5-trimethoxybenzyl chloride, 2-(2-methoxyphenyl)-ethyl chloride (b.p.: 74—76 °C/7 mm Hg; n_D^{20}: 1.5345) and 2-phenoxyethyl chloride (b.p.: 68—70 °C/6 mm Hg; n_D^{20}: 1.5342) were prepared with $SOCl_2$ from the alcohols, synthetized by $LiAlH_4$ reduction of the esters of the corresponding carboxylic acids (Fluka products), and were purified by distillation. 3-Heptamethyleniminopropyl chloride was prepared as in [2]. Some of the carboxylic acid chlorides were Fluka products; the others were prepared from the corresponding carboxylic acids with $SOCl_2$ or oxalyl chloride and were purified by distillation.

Table IV



No	R_1	R_2	X	Formula	Derivative M.p. (°C)
31	$i-C_3H_7-$	H		$C_{18}H_{30}Cl_2N_2O_3$	2 HCl 228—229
32	$n-C_4H_9-$	H		$C_{19}H_{32}Cl_2N_2O_3$	2 HCl 215—217
33	$n-C_4H_9-$	H		$C_{18}H_{29}Cl_2FN_2O_2$	2 HCl 224—226
34	$n-C_4H_9-$	H		$C_{25}H_{34}Cl_2N_2O_3$	2 HCl 188—190
35	$n-C_4H_9-$	H		$C_{27}H_{38}J_2N_2O_3$	2 CH_3I 193—195
36	$CH_2=CH-CH_2-$	H		$C_{17}H_{26}Cl_2N_2O_2$	2 HCl 189—191

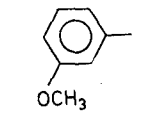
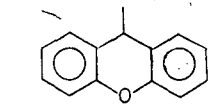
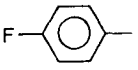
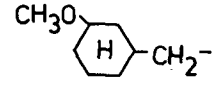
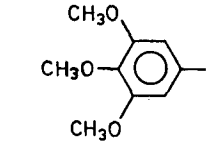
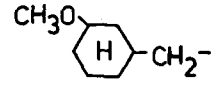
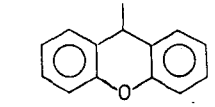
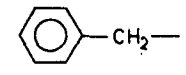
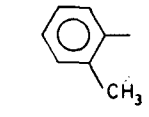
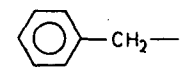
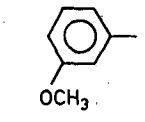
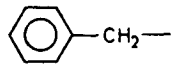
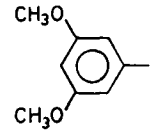
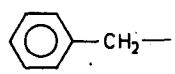
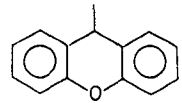
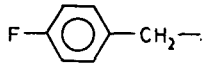
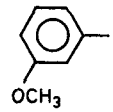
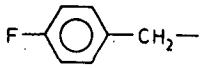
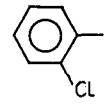
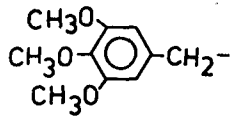
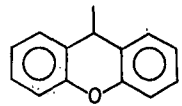
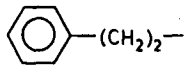
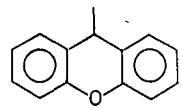
37	$CH_2=CH-CH_2-$	H		$C_{18}H_{28}Cl_2N_2O_3$	2 HCl 189—190
38	$CH_2=CH-CH_2-$	H		$C_{24}H_{30}Cl_2N_2O_3$	2 HCl 209—210
39	$CH_3-\underset{Cl}{C}=CH-CH_2-$	H		$C_{18}H_{26}Cl_3FN_2O_2$	2 HCl 185—187
40		H		$C_{25}H_{42}Cl_2N_2O_6$	2 HCl 189—191
41		H		$C_{29}H_{40}Cl_2N_2O_4$	2 HCl 186—188
42		H		$C_{22}H_{30}Cl_2N_2O_2$	2 HCl 196—199
43		H		$C_{22}H_{30}Cl_2N_2O_3$	2 HCl 158—159

Table IV

No	R_1	R_2	X	Formula	Derivative M.p. (°C)
44		H		$C_{23}H_{32}Cl_2N_2O_4$	2 HCl 219—221
45		H		$C_{28}H_{32}Cl_2N_2O_3$	2 HCl 204—206
46		H		$C_{22}H_{29}Cl_2FN_2O_3$	2 HCl 220—221
47		H		$C_{21}H_{26}Cl_3FN_2O_2$	2 HCl 229—231
48		H		$C_{31}H_{38}Cl_2N_2O_6$	2 HCl 196—198
49		H		$C_{29}H_{34}Cl_2N_2O_3$	2 HCl 193—194

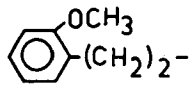
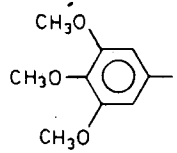
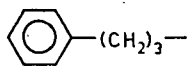
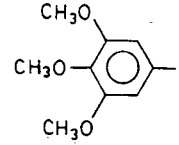
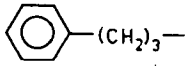
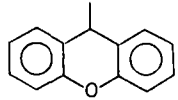
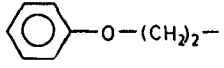
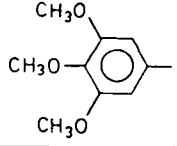
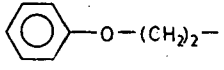
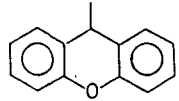
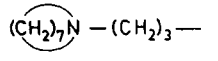
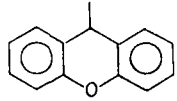
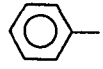
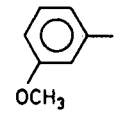
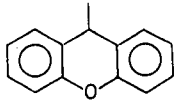
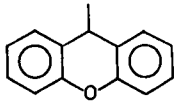
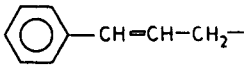
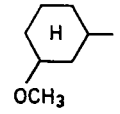
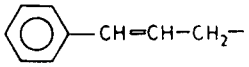
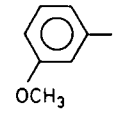
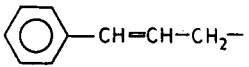
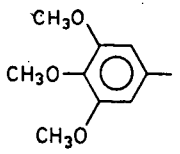
50		H		$C_{26}H_{38}Cl_2N_2O_6$	2 HCl 182—183
51		H		$C_{26}H_{38}Cl_2N_2O_5$	2 HCl 192—193
52		H		$C_{30}H_{36}Cl_2N_2O_3$	2 HCl 176—178
53		H		$C_{25}H_{36}Cl_2N_2O_6$	2 HCl 187—189
54		H		$C_{29}H_{34}Cl_2N_2O_4$	2 HCl 181—182
55		H		$C_{31}H_{45}Cl_2N_3O_3$	2 HCl . H_2O 205—206
56	C_2H_5OOC-	H		$C_{17}H_{25}ClN_2O_4$	HCl 145—148

Table IV

No	R_1	R_2	X	Formula	Derivative M.p. (°C)
57	C_2H_5OOC-	H		$C_{18}H_{27}ClN_2O_5$	HCl 162—164
58	C_2H_5OOC-	H		$C_{24}H_{29}ClN_2O_5$	HCl 144—145
59	C_2H_5OOC-	H		$C_{25}H_{31}JN_2O_5$	CH_3I decomp.
60		H		$C_{24}H_{38}Cl_2N_2O_3$	2 HCl 179—181
61		H		$C_{24}H_{32}Cl_2N_2O_3$	2 HCl 200—201
62		H		$C_{20}H_{30}Cl_2N_2O_5$	2 HCl 215—217

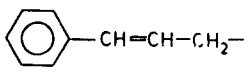
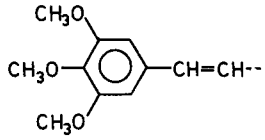
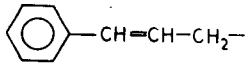
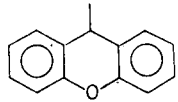
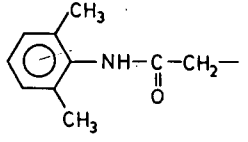
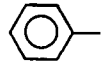
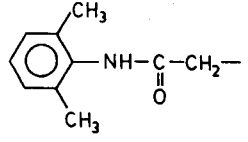
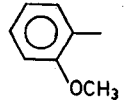
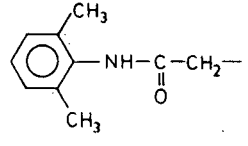
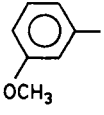
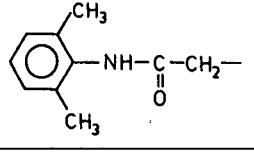
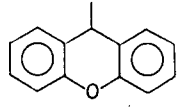
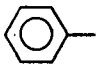
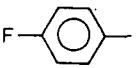
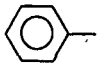
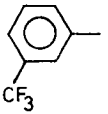
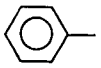
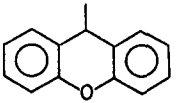
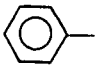
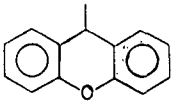
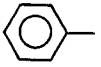
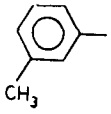
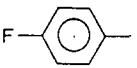
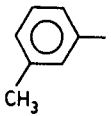
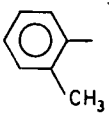
63		H		$C_{28}H_{38}Cl_2N_2O_5$	2 HCl 197—199
64		H		$C_{30}H_{34}Cl_2N_2O_3$	2 HCl 190—192
65		H		$C_{24}H_{33}Cl_2N_3O_3$	2 HCl 208—209
66		H		$C_{25}H_{35}Cl_2N_3O_4$	2 HCl 205—208
67		H		$C_{25}H_{35}Cl_2N_3O_4$	2 HCl 176—178
68		H		$C_{31}H_{37}Cl_2N_2O_4$	2 HCl 187—189

Table IV

No	R_1	R_2	X	Formula	Derivative M.p. (°C)
69		H		$C_{20}H_{25}Cl_2FN_2O_2$	2 HCl 196—198
70		H		$C_{21}H_{25}Cl_2F_3N_2O_2$	2 HCl 178—180
71		H		$C_{27}H_{30}Cl_2N_2O_3$	2 HCl 152—153
72		H		$C_{28}H_{31}JN_2O_3$	CH_3I 169—170
73		H		$C_{18}H_{24}Cl_2N_2O_3$	2 HCl 166—167
74		CH_3		$C_{22}H_{29}Cl_2FN_2O_2$	2 HCl 188—190
75		CH_3		$C_{23}H_{32}Cl_2N_2O_2$	2 HCl 166—168

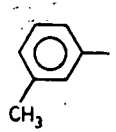
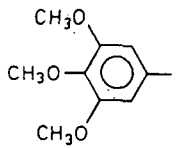
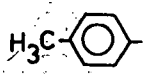
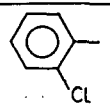
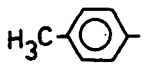
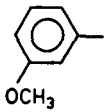
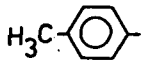
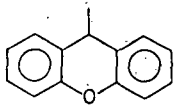
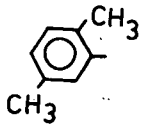
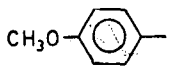
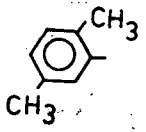
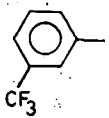
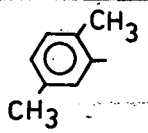
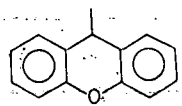
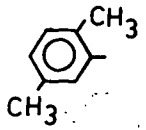
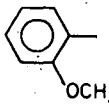
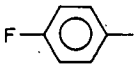
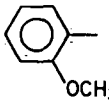
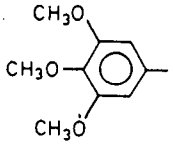
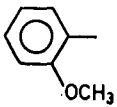
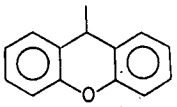
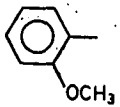
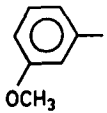
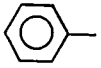
76		CH_3		$C_{25}H_{36}Cl_2N_2O_5$	2 HCl 139—140
77		CH_3		$C_{22}H_{29}Cl_3N_2O_2$	2 HCl 167—168
78		CH_3		$C_{23}H_{32}Cl_2N_2O_3$	2 HCl 148—149
79		CH_3		$C_{29}H_{34}Cl_2N_2O_3$	2 HCl 168—170
80		H		$C_{23}H_{32}Cl_2N_2O_3$	2 HCl 211—212
81		H		$C_{23}H_{29}Cl_2F_3N_2O_2$	2 HCl 205
82		H		$C_{29}H_{34}Cl_2N_2O_3$	2 HCl 209—210

Table IV

No	R_2	R_1	X	Formula	Derivative M.p. (°C)
83		H		$C_{20}H_{27}ClN_2O_3$	HCl 210—211
84		H		$C_{21}H_{27}Cl_2FN_2O_3$	2 HCl 181
85		H		$C_{24}H_{34}Cl_2N_2O_6$	2 HCl 167
86		H		$C_{28}H_{32}ClN_2O_4$	HCl 193—195
87		H		$C_{19}H_{26}Cl_2N_2O_4$	2 HCl 165—166
88		H		$C_{21}H_{28}Cl_2N_2O_3$	2 HCl 167—168

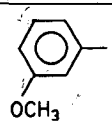
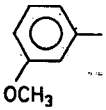
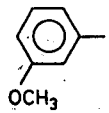
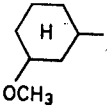
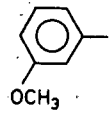
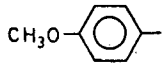
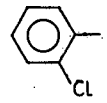
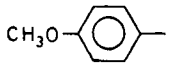
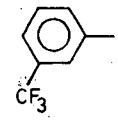
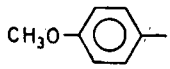
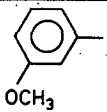
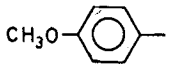
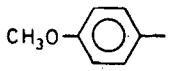
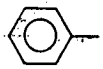
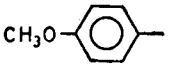
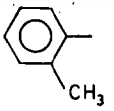
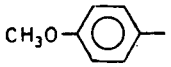
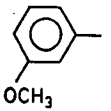
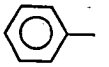
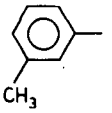
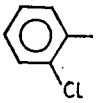
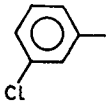
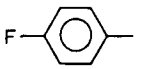
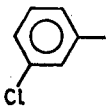
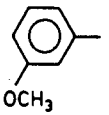
89		H		$C_{22}H_{30}Cl_2N_2O_4$	2 HCl 176—177
90		H		$C_{22}H_{35}ClN_2O_4$	HCl 178—179
91		H		$C_{19}H_{26}Cl_2N_2O_4$	2 HCl 180—181
92		H		$C_{21}H_{27}Cl_3N_2O_3$	2 HCl 161—163
93		H		$C_{22}H_{27}Cl_2F_3N_2O_3$	2 HCl 171—173
94		H		$C_{22}H_{30}Cl_2N_2O_4$	2 HCl 171—173
95		H		$C_{19}H_{26}Cl_2N_2O_4$	2 HCl 162—163
96		CH_3		$C_{22}H_{30}Cl_2N_2O_3$	2 HCl 172—174

Table IV

No	R_1	R_2	X	Formula	Derivative M.p. (°C)
97		CH_3		$C_{23}H_{32}Cl_2N_2O_3$	2 HCl 168—169
98		CH_3		$C_{23}H_{32}Cl_2N_2O_4$	2 HCl 151—152
99		H		$C_{20}H_{24}Cl_2N_2O_2$	HCl 179—180
100		H		$C_{21}H_{26}Cl_2N_2O_2$	HCl 193—194
101		H		$C_{20}H_{23}Cl_3N_2O_2$	HCl 193—194
102		H		$C_{20}H_{24}Cl_3FN_2O_2$	2 HCl 187—188
103		H		$C_{21}H_{26}Cl_2N_2O_3$	HCL.H_2O 172—173

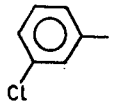
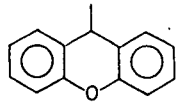
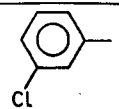
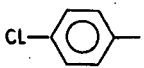
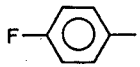
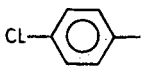
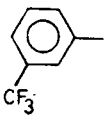
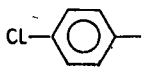
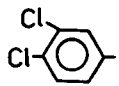
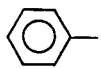
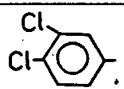
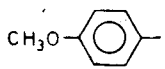
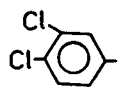
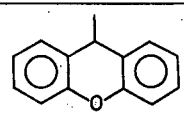
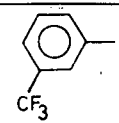
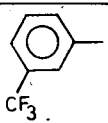
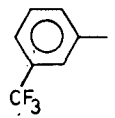
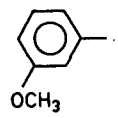
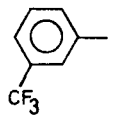
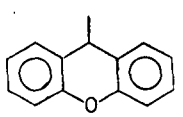
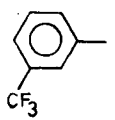
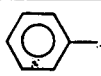
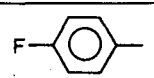
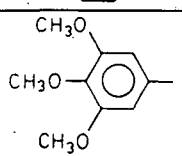
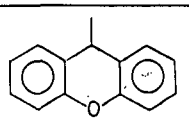
104		H		$C_{27}H_{28}Cl_2N_2O_3$	$HCl.H_2O$ 161
105		H		$C_{18}H_{23}Cl_3N_2O_3$	2 HCl 170—171
106		H		$C_{20}H_{24}Cl_3FN_2O_3$	2 HCl 173
107		H		$C_{21}H_{23}Cl_2F_3N_2O_2$	$HCl.H_2O$ 154—155
108		H		$C_{18}H_{22}Cl_2N_2O_3$	$HCl.H_2O$ 149—150
109		H		$C_{20}H_{24}Cl_3N_2O_2$	$HCl.H_2O$ 205—207
110		H		$C_{21}H_{25}Cl_3N_2O_3$	HCl 170—171
111		H		$C_{27}H_{27}Cl_3N_2O_3$	$HCl.H_2O$ 179
112		H		$C_{22}H_{24}Cl_2F_6N_2O_2$	2 HCl 169—171

Table IV

No	R_1	R_2	X	Formula	Derivative M.p. (°C)
113		H		$C_{22}H_{27}Cl_2F_3N_2O_3$	2 HCl 159—161
114		H		$C_{28}H_{29}Cl_2F_3N_2O_3$	2 HCl 124—126
115		H		$C_{19}H_{23}Cl_2F_3N_2O_3$	2 HCl 167—168
116		H		$C_{19}H_{25}Cl_2N_3O_2$	2 HCl 197—199
117		H		$C_{19}H_{24}Cl_2FN_3O_2$	2 HCl 188—190
118		H		$C_{22}H_{31}Cl_2N_3O_5$	2 HCl 199—201
119		H		$C_{26}H_{29}Cl_2N_3O_3$	2 HCl 168—171

The piperazinylpropyl alcohols (Tables II—III) were prepared in one or other of the following three methods (Methods A, B and C). In three cases (**5**, **8** and **14**) the resulting aminoalcohol was not purified, because of the small amount of material; instead, the crude reaction product was reacted with the acid chloride.

The thin-layer chromatographic examinations were performed on a Kieselgel (Merck) layer 0.5 mm in thickness; the running mixture was 5% NH_4OH — ethanol, and the developer was the Draggendorf reagent.

Method A

A mixture of 0.15 mole *N*-substituted-piperazine, 15.5 g (0.16 mole) 3-chloropropanol and 20 g anhydrous, well-powdered K_2CO_3 was boiled for 20—25 hr with stirring in 120 ml ethanol. 100 ml ether was added to the cooled reaction mixture, the precipitated inorganic salt was filtered off, the filtrate was evaporated to dryness, and the residue was distilled or recrystallized from a benzene — petroleum ether mixture.

Method B

A mixture of 32 g (0.2 mole) *N*-carbethoxypiperazine, 0.22 mole halogen compound and 25 g anhydrous K_2CO_3 was boiled for 30 hr with stirring in 150 ml ethanol. The inorganic salt was filtered off the cooled reaction mixture, the filtrate was evaporated to dryness, and the residue was boiled with 60 ml conc. HCl for 24 hr [19]; after renewed evaporation to dryness, the residue was triturated in ethanol, and the mixture was filtered. The crystalline *N*-substituted-piperazine dihydrochloride was dissolved in water, and concentrated NaOH solution was added to liberate the free base, which was extracted with ether. The solution in ether was dried and evaporated to dryness, and the resulting crude substituted piperazine was reacted with 3-chloropropanol as in Method A.

Method C

N-(3-Hydroxypropyl)-piperazine was prepared as in [11]. From this the aminoalcohols were obtained by Method A with the use of the corresponding halogen compound; the aminoalcohols were purified by distillation or by recrystallization.

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ХИМИЯ 1,3-БИФУНКЦИОНАЛЬНЫХ СОЕДИНЕНИЙ, XXVII
СИНТЕЗ СЛОЖНЫХ ЭФИРОВ 4-N-ЗАМЕЩЕННЫХ ПИПЕРАЗИНИЛ-1-ПРОПАНОЛОВ

К. Фелфельди, А. Молнар, Й. Апйок, Й. Цомбош, Ф. Нотейс и Э. Карпати

В продолжение исследований в области синтеза и изучения фармакологического действия сложных эфиров разных аминоспиртов [1—6], синтезированы разными методами сложные эфиры, имеющие пиперазиновое кольцо. Некоторые соединения обладают венечным вазодилятаторным и антиаритмическим действием.