

PREPARATION AND PHARMACOLOGY OF ESTERS OF HYDROXYMETHYLPYRIDINES

By

F. NOTHEISZ, K. FELFÖLDI, M. BARTÓK

Department of Organic Chemistry,
Attila József University, 6720 Szeged, Hungary
and

E. KÁRPÁTI

Pharmacological Laboratory,
Chemical Works of Gedeon Richter Ltd.,
1475 Budapest P.O.B. 27, Hungary

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Various esters of hydroxymethylpyridine were synthesized and their pharmacological properties were investigated. Some of the compounds (1, 8 and 9) displayed better anti-arrhythmic effects than that of the quinidine used as reference substance.

We earlier described the synthesis and pharmacological properties of numerous (mainly 1,3-) aminoalkyl esters [1—5]. In some cases considerable local anaesthetic [1], coronary vasodilator [4, 5] and bronchial spasmolytic [3] effects were found. In the present work the synthesis of various esters of hydroxymethylpyridines is reported, together with pharmacological data. A number of benzoate esters of hydroxymethylpyridine are known in the literature [6—9]; a few of these possess important pharmacological (particularly cholinergic and hypotensive) effects [10—13]. The new derivatives we prepared have been examined with regard to their action in inhibiting cardiac arrhythmia in anaesthetized cats [14]. This inhibitory effect is expressed in an elevation of the electric fibrillation threshold of the heart. The extent of the effect was calculated as the percentage increase in the fibrillation threshold compared to the level in the untreated control animals, and in Table I the results are compared with those for quinidine,

Table I
Pharmacological data of some esters

Compound	Elevation of the fibrillation threshold (%)	
	2 mg/kg	1 mg/kg
1	—	27.6
2	—	13.5
7	14.1	—
8	—	32.1
9	—	34.8
15	14.2	—
Quinidine	34.5	20.6

Table II
Physical constants of pyridinemethanols

Compound	B.p. (°C) H _g mm	M.p. (°C) of hydrochlorid	Analysis				B.p. Lit. [11]
			Calc./Found			Cl ⁻	
			C	H			
2-pyridinemethanol	95—100 5	105—106	49.50 49.30	5.54 5.77	24.35 24.52	124—127 23	
3-pyridinemethanol	136—138 10	116—118	49.50 49.34	5.54 5.82	24.35 24.70	142—144 14	
4-pyridinemethanol	115—120 5	178—180	49.50 49.25	5.54 5.62	24.35 24.60	147—148 15	

employed successfully as an anti-arrhythmic in therapy. In some cases (1, 8 and 9) an improved effect is observed. The esters were prepared from the corresponding hydroxymethylpyridine on the basis of previous descriptions [11]. 2-Hydroxymethylpyridine was prepared from 2-picoline [11, 15], and 3- and 4-hydroxymethylpyridines from the ethyl esters of nicotinic and isonicotinic acids by a further modification of a known method [16].

Experimental

The temperature values given in Tables II—V have not been corrected. The purities of the compounds were checked by, among others, thin-layer chromatography. Of the compounds used, nicotinic acid, isonicotinic acid and 2-picoline were Fluka products. The customary method was followed to prepare the ethyl esters.

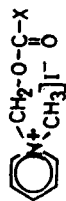
4-Hydroxymethylpyridine

A solution of 60 g (0.4 mole) of the ethyl ester of isonicotinic acid in 400 ml abs. ether was added dropwise during 1.5 h to a solution of 10 g (0.38 mole) $\text{Li}[\text{AlH}_4]$ in 600 ml abs. ether; 64 ml water was next added. The reaction mixture was filtered, and the white precipitate was extracted with 2×200 ml ethanol. The organic phases were combined, and after a 12-h standing period the solution was again filtered. The filtrate was evaporated to dryness, and the residue was distilled. Yield 25.6 g (59%).

3-Hydroxymethylpyridine

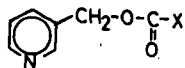
This was prepared in a similar way as the 4-substituted compound, from the ethyl ester of nicotinic acid. Yield 63%.

Table III



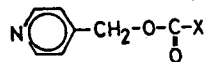
No.	X	M.p. (°C)	Formula	Analysis		
				Calc./Found		
				C	H	N
1		154—155	C ₁₄ H ₁₃ ClINO ₂	43.16	3.36	3.60
				43.14	3.43	3.50
2		178—180	C ₁₄ H ₁₃ FINO ₂	45.05	3.52	3.75
				44.93	3.62	3.85
3		152—153	C ₁₆ H ₁₆ INO ₃	46.77	4.19	3.64
				46.94	4.22	3.55
4		162—163	C ₁₅ H ₁₆ INO ₃	46.77	4.19	3.64
				46.80	4.21	3.60
5		180—181	C ₁₅ H ₁₆ INO ₃	46.77	4.19	3.64
				46.93	4.10	3.58
6		157—159	C ₂₁ H ₁₈ INO ₃	55.04	3.74	3.06
				54.88	4.10	3.00

Table IV



No.	X	M.p. (°C)	Formula	Analysis		
				Calc./Found		
				C	H	N
7		HCl 141—143	$C_{13}H_{11}ClFNO_2$	58.33 57.96	4.12 4.48	5.23 5.10
8		Methiodide 132—133	$C_{14}H_{13}FINO_2$	45.05 44.75	3.52 3.67	3.75 3.55
9		Methiodide 138—139	$C_{16}H_{13}F_3INO_2$	42.58 42.15	3.10 2.92	3.31 3.45
10		HCl 151—152	$C_{14}H_{14}ClNO_3$	60.20 60.14	5.04 5.09	5.00 5.15
11		HCl 136—137,5	$C_{14}H_{14}ClNO_3$	60.20 60.39	5.04 5.19	5.00 4.92
12		Methiodide 172—173	$C_{16}H_{16}INO_3$	46.77 46.87	4.19 4.20	3.64 3.75
13		Methiodide 150—151	$C_{21}H_{18}INO_3$	55.04 54.85	3.74 4.08	3.06 3.00
14		Ethiodide 141—142	$C_{22}H_{20}INO_3$	55.95 55.63	4.24 4.46	2.98 3.05

Table V



No.	X	M.p. (°C)	Formula	Analysis		
				Calc./Found		
				C	H	N
15		HCl 198—200	$\text{C}_{13}\text{H}_{11}\text{ClFNO}_2$	58.33 58.15	4.12 4.30	5.25 5.05
16		HCl 188—190	$\text{C}_{14}\text{H}_{14}\text{ClNO}_3$	60.20 60.35	5.04 5.08	5.00 4.87
17		HCl 182—183	$\text{C}_{14}\text{H}_{14}\text{ClNO}_3$	60.20 60.42	5.04 4.99	5.00 4.82
18		HCl 186—188	$\text{C}_{14}\text{H}_{14}\text{ClNO}_3$	60.20 60.08	5.04 4.85	5.05 5.15
19		HCl 170—172	$\text{C}_{20}\text{H}_{16}\text{ClNO}_3$	68.09 67.75	4.29 5.05	3.97 4.12
20		Methiodide 187.5—189	$\text{C}_{21}\text{H}_{18}\text{INO}_3$	55.04 55.12	3.74 3.44	3.06 3.20

2-Picoline-N-oxide

46.6 g (0.5 mole) 2-picoline was dissolved in 300 ml glacial acetic acid, 50 ml 30% H_2O_2 was added, and the solution was kept for 3 h at 70–80 °C. After the addition of a further 35 ml H_2O_2 , the reaction mixture was heated for an additional 9 h. The volume was then evaporated to 100 ml, 100 ml water was added, and the solution was evaporated to dryness. The residue was dissolved in 250 ml chloroform and the solution washed with sodium carbonate solution. After drying, the chloroform was evaporated off, and the residue was distilled. Yield 40 g (74%), with b.p. 130–135 °C at 20 mm Hg (lit. [15]: b.p. 123–125 °C at 15 mm Hg), and n_D^{20} : 1.5895.

Acetate ester of 2-hydroxymethylpyridine

40 g (0.37 mole) 2-picoline-N-oxide was added dropwise to 75 ml gently boiling acetic anhydride, and the reaction mixture was boiled for 20 min and then distilled. Yield 42.7 g (77%), with b.p. 128–130 °C at 30 mm Hg (lit. [15]: b.p. 115–118 °C at 22 mm Hg), and n_D^{20} : 1.4966.

2-Hydroxymethylpyridine

A mixture of 42.7 g (0.28 mole) of the acetate ester of 2-hydroxymethylpyridine and 100 ml 27% sodium hydroxide solution was stirred for 12 h at room temperature, and then extracted with chloroform (pH=7–8). The chloroform solution was dried and evaporated to dryness, and the residue was distilled. Yield 15.2 g (54%).

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References

- [1] Felföldi, K., Á. Molnár, M. Bartók: *Acta Chim. (Budapest)* **90**, 75 (1976).
- [2] Felföldi, K., Á. Molnár, M. Bartók: *Acta Chim. (Budapest)* **91**, 333 (1976).
- [3] Felföldi, K., M. Laszlavik, M. Bartók, E. Kárpáti: *Acta Phys. et Chem. Szeged* **26**, 163 (1980).
- [4] Felföldi, K., M. Laszlavik, M. Bartók, E. Kárpáti: *Acta Phys. et Chem. Szeged* **26**, 171 (1980).
- [5] Felföldi, K., Á. Molnár, M. Bartók, R. A. Karakhanov: *Acta Phys. et Chem. Szeged* **26**, 177 (1980).
- [6] Zymalkowski, F.: *Arch. Pharm.* **287**, 505 (1954).
- [7] Fromherz, K., H. Spielberg: *Helv. Physiol. et Pharmacol. Acta* **6**, 42 (1948).
- [8] Ponci, R., A. Baruffini, F. Gialdi: *Farmaco Ed. Sci.* **18**, 288 (1963).
- [9] Eistert, B., W. Kurze, G. W. Müller: *Annalen* **732**, 1 (1970).
- [10] Jezo, J., F. Selecký, P. Šefcovic: *Pharmazie* **13**, 195 (1958).
- [11] Vejdecký, Z. J., V. Trčka: *Chem. listy* **52**, 1622 (1958).
- [12] Cousse, H., G. Mouzin: *Chim. Ther.* **8**, 297 (1973).

- [13] *Rorig, K. J.*: U. S. pat. 3 100 775 (1963); C. A. **60**, 2903g (1964).
[14] *Szekeres, L., J. Papp*: British J. Pharmacol. **17**, 167 (1964).
[15] *Boekelheide, V., W. J. Linn*: J. Am. Chem. Soc. **76**, 1286 (1954).
[16] *Protiva, M.*: Chem. listy **45**, 20 (1951).

СИНТЕЗ И ФАРМАКОЛОГИЧЕСКОЕ ДЕЙСТВИЕ ЭФИРОВ ГИДРОКСИМЕТИЛПИРИДИНОВ

Ф. Нотейс, К. Фелфелди, М. Барток и Э. Карпати

Синтезирован ряд гидроксиметилпиридинов и изучено их фармакологическое действие. Некоторые из изученных соединений (**1**, **8**, **9**) обладают лучшим антиаритмическим действием, чем хинидин, применявшийся в качестве эталона.