CHEMISTRY OF 1,3-BIFUNCTIONAL COMPOUNDS, XXV* SYNTHESIS OF SOME ESTERS CONTAINING SUBSTITUTED PIPERIDINE AND TETRAHYDROPYRIDINE SKELETONS

By

K. FELFÖLDI, Á. MOLNÁR, M. BARTÓK and R. A. KARAKHANOV

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

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The synthesis and pharmacologic characteristics of 3-piperidinyl esters were reported earlier [1]. The present paper describes the synthesis of 43 esters containing substituted piperidine and tetrahydropyridine skeletons. Most of the new esters display a coronary vasodilator effect.

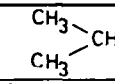
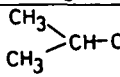
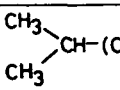
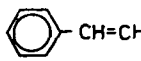
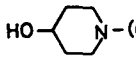
In this work esters of *N*-substituted-4-piperidinol and various 4-substituted-piperidinyl and tetrahydropyridinylpropyl esters were synthetized. Some *N*-alkyl-4-piperidinyl esters are known to exhibit valuable pharmacological properties, *e.g.* local anaesthetic, reserpine-like, parasympatholytic, hypotensive, ganglion blocker, and central nervous system tranquillizing effects [2—8]. It is similarly known [9] that the 1-(3-aroylpropyl)-4-aryl-1,2,3,6-tetrahydropyridines display analgetic, spasmolytic and central nervous system tranquillizing effects. The new compounds we have prepared were subjected to pharmacological investigation in the Pharmacological Laboratory of the Gedeon Richter Pharmaceutical Works. Mainly the coronary vasodilator effect was found to be significant, particularly in the case of **18**, *N*-(3-methylbutyl)-4-piperidinylxanthene-9-carboxylate.

Experimental

The temperature values given in the Tables have not been corrected. The courses of the reactions and the purities of the end-products were examined by, among others, thin-layer chromatography. Of the compounds used, 4-piperidinol, 4-(pyrrolidinyl-1)-piperidine, 4-(piperidinyl-1)-piperidine and 1,4-dioxa-8-azaspiro [4,5]-decane were Fluka products, while 4-phenyltetrahydropyridine, 4-*p*-chlorophenyltetrahydropyridine and 4-hydroxy-4-*p*-chlorophenylpiperidine were made available by the Gedeon Richter Pharmaceutical Works. The aminoalcohols were prepared by reacting the appropriate secondary amine with alkyl halide or with 3-chloropropyl alcohol [1, 10, 11], and purified by distillation or recrystallization. The *N*-cyanoethyl-4-pipe-

* Part XXIV: see reference [11].

Table I
N-substituted-4-piperidinols

No.	R	B.p. (°C) Hgmm	n_D^{20}	Yield %
1[a]		110—114 20	1.4750	58
2		84—86 5	1.4674	62
3		124—126 2	1.4710	75
4	$CH_2=CH-CH_2-$	98—100 8	1.4907	79
5		111—113[b]	—	35
6		202—204[b]	—	40

[a] Lit. [12]: b.p. 113—114 °C (23 Hgmm)
[b] Melting point

ridinol necessary for the preparation of esters **25** and **26** was obtained by the reaction of acrylonitrile and 4-piperidinol [11]; the reaction product was acylated without further purification. The esters were obtained from the reaction of the appropriate aminoalcohol and acid halide, and purified by recrystallization from ethanol.

References

[1] *Felföldi, K., Á. Molnár, M. Bartók:* Acta Chim. (Budapest) **90**, 75 (1976).
[2] Brit. pat. 899 605 (1962); C. A. **59**, 7497f (1963).
[3] *Renz, J., J. P. Bourquin:* Swiss. pat. 383 777 (1960); C. A. **62**, 7734f (1965).
[4] *Ganellin, C. R., R. G. W. Spickett:* J. Med. Chem. **8**, 619 (1968).
[5] *Biel, J. H.:* U. S. pat. 2 856 407 (1958); C. A. **53**, 5292a (1959).
[6] *Coon, S. B., D. Papa:* J. Org. Chem. **20**, 774 (1955).
[7] *Moffet, R. B.:* J. Med. Chem. **7**, 319 (1964).
[8] *Cusic, J. W.:* U. S. pat. 2 650 230 (1953); C. A. **48**, 11500c (1954).
[9] *Janssen, P. A. J.:* J. Med. Pharm. Chem. **1**, 281 (1959). U. S. pat. 2 973 363 (1961); C. A. **35**, 15514e (1961).
[10] *Felföldi, K., Á. Molnár, M. Bartók:* Acta Chim. Budapest **91**, 333 (1976).
[11] *Felföldi, K., M. Laszlavik, M. Bartók, E. Kárpáti:* Acta Phys. et Chem. Szeged, preceding paper.
[12] *McElvain, S. M., K. Rorig:* J. Am. Chem. Soc. **70**, 1820 (1948).

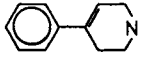
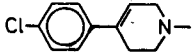
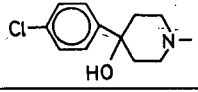
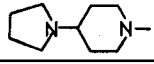
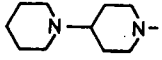
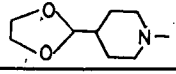
ХИМИЯ 1,3-БИФУНКЦИОНАЛЬНЫХ СОЕДИНЕНИЙ, XXV СИНТЕЗ НЕКОТОРЫХ ЭФИРОВ, ИМЕЮЩИХ ЗАМЕЩЕННЫЕ ПИПЕРИДИНОВЫЕ И ТЕТРАГИДРОПИРИДИНОВЫЕ СКЕЛЕТЫ

К. Фелфелди, А. Молнар, М. Барток и Р. А. Караханов

В работе описан синтез 43 эфиров, имеющих замещенные пиперидиновые и тетрагидропиридиновые скелеты. Болшинство синтезированных эфиров обладает венечным вазодилятаторным действием.

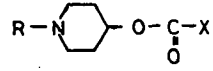
Table II

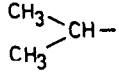
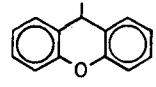
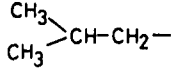
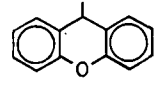
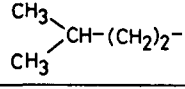
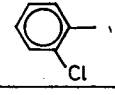
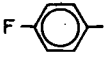
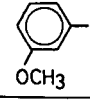
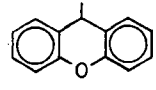
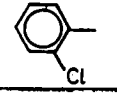
Z—CH_2—CH_2—CH_2—OH

No.	Z	B.p. (°C) Hgmm	M.p. (°C)	Yield %	Formula	Analysis Calc./Found		
						C	H	N
7		168—172/1	—	75	$C_{14}H_{16}NO$	78.50 78.25	7.52 7.72	6.53 6.82
8		178—184/1	189—190*	65	Methoiodide $C_{13}H_{21}ClINO$	45.76 45.40	5.37 5.39	3.65 3.65
9		—	106—107 236—238*	74	$C_{14}H_{20}ClNO_2$	62.33 62.12	7.47 7.45	5.19 5.27
10		158—160/1.5	57—58	70	$C_{12}H_{24}N_2O$	68.10 67.71	11.30 11.43	13.20 13.60
11		152—154/1	38—40	70	$C_{13}H_{26}N_2O$	69.00 68.87	11.60 11.53	12.37 12.52
12		—	84—85	45	$C_{10}H_{19}NO_3$	59.70 59.65	9.53 9.45	6.96 6.72

* Melting point of methioiodide

Table III



No.	R	X	Formula	M.p. (°C)	Analysis Calcd./Found C	Analysis Calcd./Found H
13			$C_{22}H_{26}ClNO_3$	HCl 147—148	68.12 67.99	6.72 6.32
14			$C_{23}H_{28}ClNO_3$	HCl 194—195	68.73 68.36	7.02 7.04
15			$C_{17}H_{25}Cl_2NO_2$	HCl 176—178	58.96 58.68	7.28 7.48
16	—"—		$C_{17}H_{25}ClFNO_2$	HCl 208—210	61.90 61.78	7.64 7.64
17	—"—		$C_{18}H_{28}ClNO_3$	HCl 177—178	63.24 63.14	8.25 8.43
18	—"—		$C_{24}H_{30}ClNO_3$	HCl 206—208	69.30 69.05	7.27 7.41
19	$CH_2=CH-CH_2-$		$C_{15}H_{19}Cl_2NO_2$	HCl 160—163	56.97 56.76	6.06 6.06

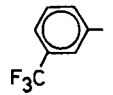
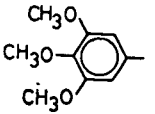
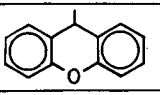
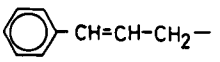
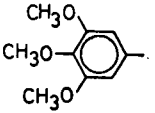
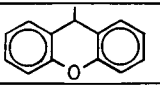
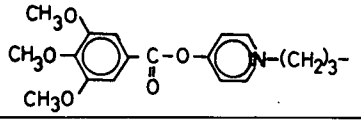
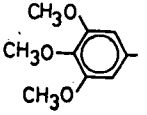
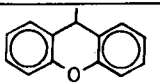
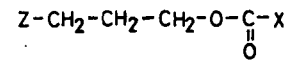
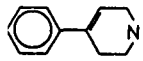
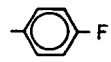
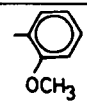
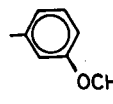
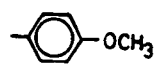
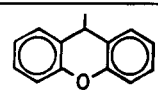
20	—"—		$C_{16}H_{19}ClF_3NO_2$	HCl 140—142	54.94 54.61	5.47 5.57
21	—"—		$C_{16}H_{22}ClNO_3$	HCl 173—175	61.33 61.12	7.11 7.09
22	—"—		$C_{18}H_{26}ClNO_5$	HCl 199—201	58.17 58.13	7.03 7.29
23	—"—		$C_{22}H_{24}ClNO_3$	HCl 132—134	68.47 68.13	6.27 6.48
24			$C_{22}H_{26}ClNO_3$	HCl 177—179	68.12 67.94	6.75 6.59
25	$NC-(CH_2)_2-$		$C_{18}H_{26}ClN_2O_5$	HCl 159—160	56.20 56.40	6.35 6.46
26	—"—		$C_{22}H_{23}ClN_2O_3$	HCl 154—155	66.24 65.93	5.61 5.85
27			$C_{35}H_{48}Cl_2N_2O_{10}$	2 HCl 208—209	56.33 56.70	6.88 7.17
28	—"—		$C_{41}H_{44}Cl_2N_2O_6$	2 HCl 148—149	67.30 67.18	6.06 6.36

Table IV



No.	Z	X	Formula	M.p. (°C)	Analysis Calc./Found		
					C	H	N
29		$-CH_3$	$C_{16}H_{22}ClNO_2$	HCl 159—161	66.48 65.84	7.32 7.42	4.85 5.00
30	—"—	$-C(CH_3)_3$	$C_{19}H_{28}ClNO_2$	HCl 173—174	67.54 67.81	8.53 8.47	4.15 4.25
31	—"—		$C_{21}H_{24}ClNO_2$	HCl 175—176	70.48 70.41	6.76 6.94	3.91 3.70
32	—"—		$C_{21}H_{23}ClFNO_2$	HCl 187—188	67.10 66.88	6.44 6.14	3.73 3.95
33	—"—		$C_{22}H_{26}ClNO_3$	HCl 163—164	68.12 68.18	6.76 6.90	3.61 3.70
34	—"—		$C_{22}H_{26}ClNO_3$	HCl 181—182	68.12 67.93	6.76 6.98	3.61 3.55
35	—"—		$C_{22}H_{26}ClNO_3$	HCl 174—175	68.12 67.85	6.76 6.68	3.61 3.47
36	—"—		$C_{28}H_{28}ClNO_3$	HCl 171—172	72.33 72.38	5.85 6.14	3.30 3.15

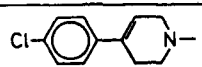
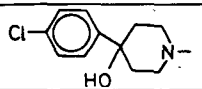
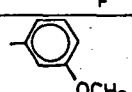
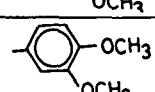
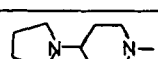
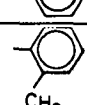
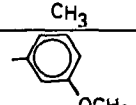
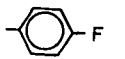
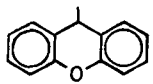
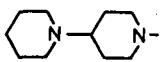
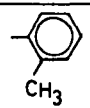
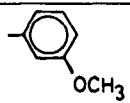
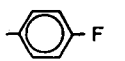
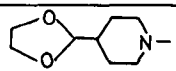
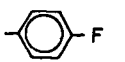
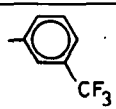
37		$-CH_3$	$C_{16}H_{21}Cl_2NO_2$	HCl 172—173	58.19 58.00	6.41 6.20	4.24 4.40
38	—"—		$C_{21}H_{23}Cl_2NO_2$	HCl 174—175	64.29 64.24	5.91 5.73	3.57 4.03
39	—"—		$C_{21}H_{22}Cl_2FNO_2$	HCl 179—182	61.47 61.23	5.40 5.26	3.41 3.65
40			$C_{21}H_{25}Cl_2NO_3$	HCl 161—162	61.47 61.05	6.14 5.85	3.41 4.03
41	—"—		$C_{21}H_{24}Cl_2FNO_3$	HCl 177—178	58.88 58.64	5.65 5.69	3.27 3.68
42	—"—		$C_{21}H_{24}Cl_2FNO_3$	HCl 179—180	58.88 58.69	5.65 5.62	3.27 4.06
43	—"—		$C_{22}H_{27}Cl_2NO_4$	HCl 160—161	60.00 59.92	6.18 6.41	3.18 3.42
44	—"—		$C_{23}H_{29}Cl_2NO_5$	HCl 181—182	58.72 58.66	6.21 6.43	2.98 3.05
45			$C_{19}H_{30}Cl_2N_2O_2$	2 HCl 263—265	58.61 58.60	7.77 7.80	7.19 7.18
46	—"—		$C_{20}H_{32}Cl_2N_2O_2$	2 HCl 258—260	59.55 59.25	8.00 8.23	6.95 6.80
47	—"—		$C_{20}H_{32}Cl_2N_2O_3$	2 HCl 250—254	57.28 57.08	7.69 7.81	6.68 6.88

Table IV (cnntinned)

No.	Z	X	Formula	M.p. (°C)	Analysis Calc./Found C	H	N
48	—"—		$C_{19}H_{20}Cl_2FN_2O_2$	2 HCl 262—265	56.05 55.85	7.09 7.25	6.88 7.12
49	—"—		$C_{26}H_{34}Cl_2N_2O_3$	2 HCl 242—245	63.28 62.95	6.95 7.27	5.67 5.31
50			$C_{20}H_{32}Cl_2N_2O_2$	2 HCl 260—262	59.65 59.45	8.05 8.14	6.94 6.81
51	—"—		$C_{21}H_{34}Cl_2N_2O_2$	2 HCl 258—262	60.43 60.18	8.21 8.31	6.70 6.74
52	—"—		$C_{21}H_{34}Cl_2N_2O_3$	2 HCl 261—264	58.40 58.20	7.15 7.35	6.47 6.45
53	—"—		$C_{20}H_{31}Cl_2FN_2O_2$	2 HCl 273—276	57.01 56.85	7.40 7.31	6.65 6.78
54			$C_{17}H_{23}ClFNO_4$	HCl 209—211	55.46 55.26	6.44 6.25	— —
55	—"—		$C_{18}H_{23}ClF_3NO_4$	HCl 177—178	52.76 52.95	5.66 5.86	— —