CHEMISTRY OF 1,3-BIFUNCTIONAL COMPOUNDS, XXIV* PREPARATION AND PHARMACOLOGY OF CYCLOALKYLAMINOPROPYL TRIMETHOXYBENZOATES

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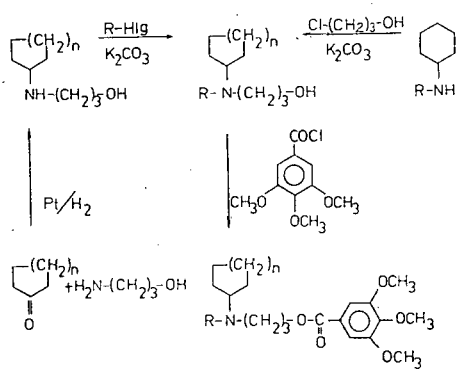
3,4,5-Trimethoxybenzoate esters of 3-(*N*—R—*N*-cycloalkyl)-aminopropanols were synthetized. The quaternary salts of the esters display considerable pharmacological activity, and in particular a coronary vasodilator effect.

The aminoalcohols and their esters are widely used in therapy. Such compounds are prepared in large numbers from plant extracts and also synthetically. Depending on their structures, they can have many effects, the most important being those on the nervous system, the musculature and the vascular system.



Scheme of the preparation of the esters

* Part XXIII: see reference [3].

We reported earlier [1—3] on the synthesis of piperidino-, morpholino-, heptamethylenimino- and diaminoalkylpropyl esters. The new compounds possess valuable local anaesthetic, coronary vasodilator, cholinolytic and bronchodilator properties. In the present paper an account is given of the synthesis (see the reaction scheme) and pharmacological activities of some 3-(*N*—R—*N*-cycloalkyl)-aminopropyl trimethoxybenzoates. It is known [5] that diphenylpropylaminoalkyl esters with similar structures have coronary vasodilator, spasmolytic and hypotensive effects. The new compounds were subjected to pharmacological examination in the Pharmacological Laboratory of the Chemical Works of Gedeon Richter Ltd. The coronary vasodilator effects were investigated on isolated rat heart [4], and the pharmacological characteristics were compared with those of Persantin (Dipyridamole), previously employed effectively in therapy. The compound exhibiting the most striking properties was 3-[*N*-(3-phenylallyl)-*N*-cyclohexyl]-aminopropyl trimethoxybenzoate HCl (**13a**) (Table I). The flow enhancement indicates the extent of the vasodilation.

Table I
Pharmacological data of the compounds **13a**

Compound	Doses g	Flow enhancement %
Persantin	5	11.8
	50	32.4
13a	5	35.9
	50	64.9

Experimental

The temperatures given in Table II are uncorrected. The purities of substances were checked by thin-layer chromatography too (Kieselgel (Merck) plate, developing solvent: 4% diethylamine—petroleum ether; detecting agent: Draggendorf reagent). Most of the chemicals used were commercial products of Fluka, but some were prepared by known methods. Apart from a few exceptions (see below), the tertiary aminoalcohols were obtained by the reaction of the appropriate 3-cyclo-alkylaminopropanol-1 and alkyl halide. The esters were produced with a yield of 40—70% by the reaction of the aminoalcohol and 3,4,5-trimethoxybenzoyl chloride; the hydrochloride was purified by repeated recrystallization from ethanol. Quaternary salts were prepared by a known method.

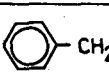
3-Cycloheptylaminopropanol-1

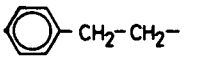
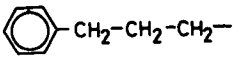
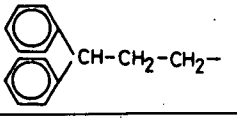
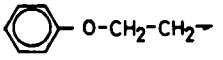
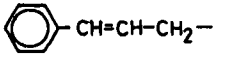
0.15 g PtO_2 was prehydrogenated for 1 h at room temperature in 30 ml ethanol, at a hydrogen pressure of 1.5 atm. Next, 30 ml of an ethanolic solution of 33.6 g (0.3 mole) cycloheptanone and 22.5 g (0.3 mole) 3-aminopropanol-1 was added to the catalyst, and hydrogenation was continued for a further 5 h. The catalyst was filtered off, the reaction mixture was evaporated, and the residue was distilled. The product weighed 37.5 g (73% yield), with b.p. 140—142 °C (6 Hgmm), and n_D^{25}: 1.4906.

Similar means were used to prepare 3-cyclopentylaminopropanol-1 (80%), b.p. 192—196 °C (5 Hgmm), n_D^{27}: 1.4883; 3-cyclohexylaminopropanol-1 (65%), m.p. 66—69 °C; and 3-cyclooctylaminopropanol-1 (78%), b.p. 146—148 °C (4 Hgmm), n_D^{22}: 1.4965.

Table II

3-(N-R-substituted-N-cycloalkyl)-aminopropyl-alcohols and their 3,4,5-trimethoxybenzoate esters

No.	c-alkyl	R	B.p. (°C) Hgmm	n_D^{20}	Yield (%)	Salts of trimethoxybenzoat esters			
						Formula	M.p. (°C)	Analysis Calc. C	Analysis Found H
1	c-hexyl	CH_3>CH– CH_3	104—106 4	—	32	$C_{22}H_{36}ClNO_5$	HCl 162—163	61.45 61.41	8.25 4.17
2	c-hexyl	CH_2=CH-CH_2–	114—117 4	—	30	$C_{22}H_{34}ClNO_5$	HCl 118—119	61.74 61.35	8.01 8.03
3a	c-hexyl	CH_3-CH =CH-CH_2–	121—125 5	—	40	$C_{23}H_{36}ClNO_5$	HCl 105—106	62.50 62.18	8.20 7.82
3b	c-hexyl	—"—	121—125 5	—	—	$C_{24}H_{38}INO_5$	CH_3I 129—130	52.65 52.57	6.99 6.63
4	c-hexyl	CH_3-C(Cl)=CH-CH_2–	145—146 5	—	56	$C_{24}H_{37}ClJNO_5$	CH_3I 125—126	49.53 49.42	6.41 6.30
5	c-hexyl	CH≡C-CH_2–	118—120 6	1.4962	40	$C_{22}H_{32}ClNO_5$	HCl 138—139	61.90 61.67	7.57 7.37
6	c-hexyl	CH_3O-CH_2-CH_2–	123—125 6	1.4763	25	$C_{22}H_{36}ClNO_6$	HCl 121—122	59.20 58.90	8.10 7.90
7	c-hexyl	NC-CH_2-CH_2–	168—172 8	1.4887	37	$C_{22}H_{33}ClN_2O_5$	HCl 163—164	59.80 59.78	7.55 7.30
8	c-hexyl	 CH_2–	188—192 6	1.5272	67	$C_{26}H_{36}ClNO_5$	HCl 147—148	65.45 65.25	7.40 7.20

9	*c*-hexyl		182—185 6	1.5242	50	$C_{28}H_{40}INO_5$	CH_3I 112—114	56.25 55.95	6.75 6.71
10	*c*-hexyl		158—160 4	1.5217	52	$C_{29}H_{42}INO_5$	CH_3I 100—101	57.10 56.95	6.92 7.10
11	*c*-hexyl		80—81[a]	—	40	$C_{34}H_{44}ClNO_5$	HCl 128—130	70.15 69.95	7.62 8.62
12	*c*-hexyl		205—210 5	1.5228	41	$C_{27}H_{38}ClNO_6$	HCl 115—116	63.80 64.07	7.54 7.22
13a	*c*-hexyl		195—196 3	—	70	$C_{28}H_{38}ClNO_5$	HCl 158—159	66.72 66.47	7.60 7.33
13b	*c*-hexyl	—"—	—	—	—	$C_{29}H_{40}INO_5$	CH_3I 148—150	57.14 56.95	6.61 6.81
14	*c*-pentyl	—"—	188—190 5	1.5325	70	$C_{27}H_{36}ClNO_5$	HCl 130—131	66.04 65.85	7.24 7.42
15	*c*-heptyl	—"—	192—196 4	1.5388	65	$C_{29}H_{40}ClNO_5$	HCl 165—166	67.23 66.90	7.78 7.97
16	*c*-octyl	—"—	204—208 3	—	42	$C_{30}H_{42}ClNO_5$	HCl 145—146	67.71 67.44	7.95 8.03
17[b]	*c*-hexyl-methyl	—"—	—	—	—	$C_{30}H_{42}INO_5$	CH_3I 135—136	55.78 55.50	6.79 6.89

[a] Melting point
[b] Aminoalcohol was not isolated

Tertiary aminoalcohol preparation (Standard method)

A mixture of 0.2 mole secondary aminoalcohol, 0.22 mole alkyl halide and 25 g anhydrous potassium carbonate was boiled under stirring for 15 h. After cooling of the reaction mixture, the inorganic salt was filtered off, the filtrate was evaporated, and the residue was distilled.

In the cases of aminoalcohols **1** and **2**, the appropriate secondary amine (Fluka), *i.e.* isopropyl cyclohexyl amine or allyl cyclohexyl amine, was reacted with 3-chloropropanol-1 by the above method.

3-[N-cyclohexyl-N-(2-methoxyethyl)]-aminopropanol-1 (**6**)

29.4 g (0.3 mole) cyclohexanone and 22.5 g (0.3 mole) 2-methoxyethylamine were reacted together under reductive conditions (Pt, H_2), and the 2-methoxyethyl cyclohexyl amine obtained as product was reacted without purification with 3-chloropropanol-1 in the presence of potassium carbonate as above.

3-[N-cyclohexyl-N-(2-cyanoethyl)]-aminopropanol-1 (**7**)

A mixture of 31.2 g (0.2 mole) 3-cyclohexylaminopropanol-1 and 11.7 g (0.22 mole) acrylonitrile was boiled for 2 h, and the resulting product was purified by distillation.

3-Hexahydrobenzylaminopropanol-1

20 ml anhydrous benzene solution of 20 g (0.2 mole) ethyl acrylate was added dropwise at 0 °C under stirring to 25 g (0.22 mole) aminomethylcyclohexane (Fluka), the reaction mixture was then stirred for 2 h at room temperature and subsequently filtered, the filtrate was evaporated, and the residue was distilled. The resulting ethyl β-hexahydrobenzylaminopropionate weighed 30 g (61% yield), with b.p. 164—168 °C (30 Hgmm) and n_D^{25}: 1.4780.

100 ml anhydrous ether solution of 30 g (0.14 mole) ethyl β-hexahydrobenzylaminopropionate was added dropwise under cooling and stirring to 50 ml anhydrous ether solution of 3.2 g (0.085 mole) $Li[AlH_4]$. The reaction mixture was then boiled for 2 h. Next, 6.5 ml water and 6.5 ml 70% sodium hydroxide solution were added under cooling. The ether phase was dried and evaporated, and the residue was distilled. The product weighed 13 g (54%), with b.p. 118—122 °C (2 Hgmm) and m.p. 39—41.5 °C.

The infrared spectra of some esters were recorded. Characteristic bands: $\nu C{=}O$: 1720 cm^{-1}; ester and ether bonding $\nu_{as}C{-}O{-}C$ and $\nu_s C{-}O{-}C$: 1260, 1230, 1130 and 1010 cm^{-1}; $\nu C{=}C$: **2**: 1650 cm^{-1}, **3a, b**: 1680 cm^{-1}, **4**: 1670 cm^{-1}, **13a, b, 15, 16**: 1660 cm^{-1}; $\nu{\equiv}N^+{-}H$: 2500 cm^{-1}; **7**: $\nu C{\equiv}N$: 2290 cm^{-1}; **5**: $\nu{\equiv}C{-}H$: 3300 cm^{-1}, $\nu C{\equiv}C$: 2145 cm^{-1}.

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ХИМИЯ 1,3-БИФУНКЦИОНАЛЬНЫХ СОЕДИНЕНИЙ, XXIV СИНТЕЗ И ФАРМАКОЛОГИЧЕСКОЕ ДЕЙСТВИЕ ЦИКЛОАМИНОПРОПИЛ-ТРИМЕТОКСИБЕНЗОАТОВ

К. Фелфелди, М. Лаславик, М. Барток и Э. Карпати

Синтезированы 3,4,5-триметоксибензоатные эфиры 3-(*N*—R—*N*-циклоалкил)-аминопропанолов. Четвертичные соли эфиров обладают значительной фармакологической активностью, в частности, венечным вазодилятаторным эффектом.