CHEMISTRY OF 1,3-BIFUNCTIONAL COMPOUNDS, XXIII.* AMINOALKYL ESTERS OF XANTHENE-9-CARBOXYLIC ACID, II.** CHOLINOLYTIC AND BRONCHODILATOR ACTIVITY OF QUATERNARY SALTS OF NEW DIAMINOALKYL-XANTHENE-9-CARBOXYLATES

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Quaternary salts of diaminoalkyl esters of xanthene-9-carboxylic acid were synthetized, and their cholinolytic and bronchodilator activities were examined as referred to atropine. The compounds were prepared by quaternization of the esters obtained from the appropriate diaminoalcohol and xanthene-9-carboxylic acid chloride. The connection was studied between the activity and the number of carbon atoms in the substituents. An outstandingly good effect was observed for two compounds.

The quaternary salts of aminoalkyl esters of xanthene-9-carboxylic acid are known to possess ganglion-blocking activity [1]. Some of them (Banthin, Probanthin) also display a strong cholinolytic effect [2]. It has further been reported [3] that the quaternary salts of certain esters of diaminoalcohols exhibit ganglion-blocking and hypotensive activity. Accordingly, we considered that the quaternary salts of diaminoalkyl-xanthene-9-carboxylates too migh well possess cholinolytic activity.

The innervation of the respiratory tract is known to be in part parasympathetic, and in part sympathetic. The parasympathetic innervation is ensured by the vagal nerve. The innervation of the vagus ensures the tonicity of the respiratory tract [4], and transection of the nerve or chemical blocking of the postganglionic efferent pathways results the dilation of the airways. Since the state of the airways is a decisive factor as regards the extent of pulmonary resistance [5], the possibility of influencing the tonicity of the respiratory tract with pharmacons is of primary impor-

* Part XXII: *M. Bartók, K. Felföldi, G. Bozóki—Bartók:* Helv. Chim. Acta: **63**, 2172 (1980)
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tance in respiratory diseases. In asthma, histamine brings about constriction of respiratory tracts directly, but nevertheless the main direction of the effect is a reflex one, and this arises *via* the mediation of the vagal nerve. This is proved by the fact that the asthmatic attacks of dogs can be reduced by cooling of the vagus or by administration of atropine [6]. From the animal-experimental and clinical results it appears that acetylcholine or an enhanced parasympathetic activity plays a decisive role in the pathomechanism of chronic respiratory obstruction. In this case, cholinolytics are more effective than sympathomimetics, they have a longer duration of action, and they are free of side-effects [7]. In asthma, the sympathomimetics are the more effective, but combined administration of the two types of drug, with their different mechanisms of action, results in a greater and more lasting reaction than any one of them alone [8]. For this reason, after determining the cholinolytic activities of our new compounds, we also examined them with regard to bronchodilator activity.

A close correlation was found between the cholinolytic and bronchodilator activities of the new compounds: the two activities vary in parallel. Both effects depend to a large extent on the numbers of carbon atoms in the hydrocarbon chain and in the substituents on the nitrogen atoms (Table III), similarly as was observed for the quaternary salts of aminoalkyl-xanthene-9-carboxalates with simpler structures [9].

In both respects, the highest activity is displayed by **21**. The activity changes are correlated most strongly with the variation in m, the maximum occurring for $m=3$ (see **20**, **21**, **23**, **26**, **27** and **28**). The increase of n from two to three likewise raises the activities (see the pairs **18** and **20**, and **19** and **21**). With the increase of the number of carbon atoms in the substituents R_1 and R_2 ($n=m=3$), the activities vary according to a maximum curve (see **16**, **17**, **21** and **24**). If R_1 and R_2 form a ring with the nitrogen, the activities decrease strongly (see **21** and **25**).

Increase of the number of carbon atoms in the substituent R_3 or the quaternizing alkyl group reduces the activity values (see **21** and **22**, and **21** and **23**).

High activities are similarly to be observed for **29**, which has a slightly different structure.

The esters were prepared by the reaction of the appropriate diaminoalcohol and xanthene-9-carboxylic acid chloride in anhydrous acetone or benzene. After boiling for a short time, the base was obtained in the customary way from the precipitating hydrochloride salt, and was quaternized in a mixture of acetone and methanol. Two methods were used to prepare the diaminoalcohols: reaction of the appropriate diamine with haloalcohol (Method A), or reaction of dialkylamino-alkyl chloride with alkylamino-alcohol (Method B). Different methods were employed to prepare two of the diaminoalcohols **9** and **14** (see Experimental section). The dialkylamino-alkyl chlorides were prepared by known methods [10, 11]. A new methods was used to prepare 3-methyl- and ethylamino-propanol-1.

Experimental

Pharmacology. The pupilla diameter in mice (CFLP) was determined by the method of PULEWKA et al [12]. Various doses of the substances were administered subcutaneously to groups of 10 animals. The peak pupilla dilations were averaged and plotted against log dose. The relative potencies were calculated from dose-response curves.

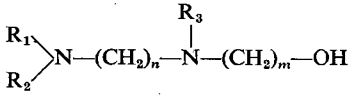
The antispasmodic effects were examined on isolated guinea-pig ileum by the method of MAGNUS [13]. Acetylcholine (ACh) was employed as agonist. The examination materials were tested on 10 preparations per dose, and the relative potencies were calculated from the ED_{50} values [14].

Isolated, intact guines-pig trachea was prepared according to the method of FARMER and COLEMAN [15]. The trachea was stimulated by square-wave pulse of supramaximal voltage and 1 msec duration, repeated for 5 sec with a frequency of 20 Hz in each minute. Cumulative dose-response curves were plotted from the inhibition of the rise in intraluminal pressure. For each substance 10 preparations were used. The relative potencies were calculated from the pA_2 values [16].

The bronchial resistance of guinea-pigs was measured on the basis of the method of KONZETT and RÖSSLER [17, 18]. The inhibition of the bronchostriction induced with intravenous ACh injections was plotted against log dose. The relative potencies

Table I

Physical constants of

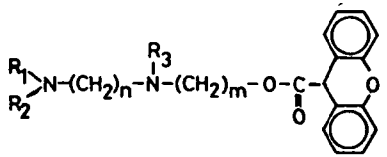


Compd.	R_1	R_2	R_3	n	m	Formula	B. p. °C (Hgmm)	n_D^{20}	Yield	Method
1[a]	CH_3	CH_3	CH_3	2	2	$C_7H_{18}N_2O$	85—88 (30)	1.4555	44	A
2	CH_3	CH_3	CH_3	3	3	$C_9H_{22}N_2O$	88—97 (7)	1.4612	43	A
3	C_2H_5	CH_3	CH_3	3	3	$C_{10}H_{24}N_2O$	118—120 (25)	1.4585	38	A
4[b]	C_2H_5	C_2H_5	CH_3	2	2	$C_9H_{22}N_2O$	136—138 (30)	1.4585	84	A
5	C_2H_5	C_2H_5	CH_3	2	3	$C_{10}H_{24}N_2O$	142—144 (30)	—	72	A
6	C_2H_5	C_2H_5	CH_3	3	2	$C_{10}H_{24}N_2O$	124—126 (8)	—	77	B
7	C_2H_5	C_2H_5	CH_3	3	3	$C_{11}H_{26}N_2O$	145—146 (15)	1.4608	74	B
8	C_2H_5	C_2H_5	C_2H_5	3	3	$C_{12}H_{28}N_2O$	118—120 (6)	1.4636	48	A
9	C_2H_5	C_2H_5	CH_3	3	4	$C_{12}H_{28}N_2O$	123—125 (4)	1.4614	42	—
10	C_2H_5	C_2H_5	CH_3	3	5	$C_{13}H_{30}N_2O$	125—127 (3)	1.4645	68	B
11	C_3H_7	C_3H_7	CH_3	3	3	$C_{13}H_{30}N_2O$	111—112 (3)	1.4696	75	A
12	$-(CH_2)_4-$		CH_3	3	2	$C_{10}H_{22}N_2O$	147—150 (30)	—	62	A
13	$-(CH_2)_4-$		CH_3	3	3	$C_{11}H_{24}N_2O$	157—160 (30)	—	42	A
14	X[c]	CH_3	CH_3	3	3	$C_{11}H_{26}N_2O_2$	150—154 (2)	1.4793	51	—

[a] Lit. [20] b.p. 52 °C (1 Hgmm), n_D^{20}: 1.4550
[b] Lit. [20] b.p. 96 °C (7 Hgmm), n_D^{20}: 1.4580
[c] X: 3-hydroxypropyl-1

Table II

Physical constants of dimethoiodide quaternary salt of



Compd.	R_1	R_2	R_3	*n*	*m*	Formula	Melting point, °C
15	CH_3	CH_3	CH_3	2	2	$C_{23}H_{32}I_2N_2O_3$	217—218
16	CH_3	CH_3	CH_3	3	3	$C_{25}H_{36}I_2N_2O_3$	193—195
17	CH_3	C_2H_5	CH_3	3	3	$C_{26}H_{38}I_2N_2O_3$	176—178
18	C_2H_5	C_2H_5	CH_3	2	2	$C_{25}H_{36}I_2N_2O_3$	199—200
19	C_2H_5	C_2H_5	CH_3	2	3	$C_{26}H_{38}I_2N_2O_3$	186—188
20	C_2H_5	C_2H_5	CH_3	3	2	$C_{26}H_{38}I_2N_2O_3$	189—190
21	C_2H_5	C_2H_5	CH_3	3	3	$C_{27}H_{40}I_2N_2O_3$	156—157
22	C_2H_5	C_2H_5	C_2H_5	3	3	$C_{28}H_{42}I_2N_2O_3$	154—156
23[a]	C_2H_5	C_2H_5	CH_3	3	3	$C_{29}H_{44}I_2N_2O_3$	142—143
24	C_3H_7	C_3H_7	CH_3	3	3	$C_{29}H_{44}I_2N_2O_3$	175—176
25	$-(CH_2)_4-$		CH_3	3	3	$C_{27}H_{38}I_2N_2O_3$	180—181
26	$-(CH_2)_4-$		CH_3	3	2	$C_{26}H_{36}I_2N_2O_3$	218—219
27	C_2H_5	C_2H_5	CH_3	3	4	$C_{28}H_{42}I_2N_2O_3$	149—151
28	C_2H_5	C_2H_5	CH_3	3	5	$C_{29}H_{44}I_2N_2O_3$	143—145
29	X[b]	CH_3	CH_3	3	3	$C_{41}H_{48}I_2N_2O_6$	194—195

[a] Diethoiodide [b] X: 3-(xanthene-9-carbonyloxy)-propyl-1

werecalculated from dose-response curves. For each substance and each dose, 6—9 experiments were performed. The substances were administered intravenously.

Guinea-pigs were placed individually in plexi-glass boxes exposed to an aerosol of a 1% aqueous ACh solution. The time elapsed between the beginning of the aerosol exposure and severe dyspnea in individual animals was recorded as the prostration time, a prolongation of which was considered indicative of bronchodilator activity. The substances were administered subcutaneously, and the maximum enhancement of the prostration time was evaluated as percentage inhibition compared to the control group. The relative potency was calculated from the dose-response curves. A total of 12 animals were used per dose.

Table III

Pharmacological properties of quaternary salts

Compd.	Cholinolytic activity[a]		Bronchodilator activity[a]		
	Pupil size	ACh-induced contraction of ileum	Isolated trachea	Bronchial resistance	ACh-induced prostration
15	0.52	0.04	0.05	0.02	0.09
16	42	3.1	11	35	42
17	95	7.2	17	57	61
18	0.31	0.05	0.01	0.03	0.08
19	2.9	0.31	0.12	0.21	6.2
20	3.7	0.29	0.21	0.17	7.1
21	311	25	60	270	214
22	45	2.9	9.6	17	44
23	101	6.2	12.3	65	63
24	15	1.5	5.7	19	11
25	89	5.6	15	34	57
26	4.2	0.36	0.17	0.09	7.3
27	27	1.8	0.97	22	15
28	0.62	0.07	0.05	0.05	0.08
29	305	107	50	157	131

[a] Atropine = 100

Chemistry. Constants relating to the diaminoalcohols and quaternary salts prepared are listed in Tables I and II. The melting and boiling point values are not corrected. The tlc examinations were made on Kieselgel HF (Merck) plates, with ethanol-diethylamine (96:4, v/v) as solvent mixture, and the Draggendorf reagent as developer. The quaternary salts were recrystallized from aqueous ethanol, the yield being in general 40—60%. The C, H and N analyses were within 0.4% of the theoretical for all compounds.

3-Methylamino-propanol-1

A solution of 3-chloro-propanol-1 (71 g, 0.75 mole) and methylamine (62 g, 2 mole) in EtOH (400 ml) was shaken for 15 hr at 130 °C in an autoclave. After cooling, the EtOH was distilled off and the residue was dissolved in concentrated aqueous KOH solution. The organic phase was separated, dried and distilled. Yield

37 g (55%), b.p. 95—100 °C (30 Hgmm), n_D^{20}: 1.4450; lit. [19] b.p. 175—177 °C (750 Hgmm), n_D^{20}: 1.4479.
3-Ethylamino-propanol-1 was prepared in an analogous manner. Yield 48%, b.p. 96—98 °C (30 Hgmm), n_D^{20}: 1.4452; lit. [19] b.p. 184—187 °C (750 Hgmm), n_D^{22}: 1.4475.

Method A. 3-[N-Methyl-N-(3-dipropylamino-propyl)]-amino-propanol-1 (**11**)

3-Methylamino-propanol-1 (17 g, 0.19 mole), 3-dipropylamino-propyl-chloride (34.4 g, 0.2 mole) and anhydrous K_2CO_3 (35 g) were stirred in EtOH (150 ml) during boiling for 15 hr. After filtration of the cooled reaction mixture, the filtrate was evaporated and the residue was distilled. Yield 35 g (75%).

Method B. 3-[N-Methyl-N-(3-diethylamino-propyl)]-amino-propanol-1 (**7**)

N,N-Diethyl-*N'*-methyl-propane-1,3-diamine (Fluka) (16.6 g, 0.115 mole), 3-chloropropanol-1 (11 g, 0.116 mole) and anhydrous K_2CO_3 (15 g) were stirred in EtOH (75 ml) during boiling for 15 hr. The mixture was worked up as in Method A. Yield 17.2 g (74%).

N,N'-Dimethyl-N,N'-bis(3-hydroxypropyl)-propane-1,3-diamine (**14**)

A solution of 3-methylaminopropanol-1 (8.9 g, 0.1 mole) in EtOH (40 ml) was added dropwise with stirring to a mixture of 1,3-dibromopropane (10.1 g, 0.05 mole) and anhydrous K_2CO_3 (15 g) in EtOH (75 ml), and the reaction mixture was then boiled for 15 hr. After filtration, the filtrate was evaporated and the residue was distilled. Yield 5.5 g (51%), m.p. of dihydrochloride 144—146 °C.

4-[N-Methyl-N-(3-diethylamino-propyl)]-aminobutanol-1 (**9**)

A mixture of *N,N*-diethyl-*N'*-methylpropane-*1,3*-diamine (20.2 g, 0.14 mole) and butyrolactone (12 g) was heated at 100° for 24 hr. The reaction product was dissolved in abs. Et_2O (100 ml), the solution was added with stirring and cooling to a solution of $Li[AlH_4]$ (4.7 g, 0.12 mole) in Et_2O (100 ml), and the reaction mixture was then boiled for 6 hr. With cooling and stirring, 9 ml water and then 9 ml 65% NaOH solution were added dropwise to the reaction mixture. The Et_2O solution was evaporated and the residue was distilled. Yield 12.6 g (42%).

3-[N-Methyl-N-(3-diethylamino-propyl)]-amino-propyl-xanthene-9-carboxylate dihydrochloride and dimethoiodide (**21**)

A solution of diaminoalcohol **7** (5.2 g, 0.025 mole) in Me_2CO (20 ml) was added dropwise with stirring and cooling to a solution of xanthene-9-carboxylic acid chloride (6.4 g, 0.026 mole) in Me_2CO (40 ml), and the reaction mixture was

then boiled for 20 min. An EtOH—HCl solution was added to the still hot mixture, and after cooling the precipitated dihydrochloride salt was filtered off and recrystallized from EtOH. Yield 9.6 g (80%), m.p. of dihydrochloride salt 195—196 °C.

The dihydrochloride salt (4.8 g, 0.01 mole) was dissolved in cold NaOH solution. After Et_2O extraction, the Et_2O solution was dried and evaporated. The residue was dissolved in Me_2CO (40 ml), MeI (3 g) was added, and the mixture was boiled for 20 min and then cooled. The dimethoiodide (**21**) which separated out was filtered off and recrystallized from EtOH. Yield 5 g (72%).

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ХИМИЯ 1,3-БИФУНКЦИОНАЛЬНЫХ СОЕДИНЕНИЙ, XXIII. АМИНОАЛКИЛЬНЫЕ ЭФИРЫ КСАНТЕНО-9-КАРБОКСИЛЬНЫХ КИСЛОТ, II. ХОЛИНОЛИТИЧЕСКАЯ И БРОНХОДИЛАТОРНАЯ АКТИВНОСЬ ЧЕТВЕРТИЧНЫХ СОЛЕЙ НОВЫХ ДИАМИНОАЛКИЛ-КСАНТЕНО-9-КАРБОКСИЛАТОВ

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

Синтезированы четвертичные соли диаминоалкильных эфиров ксантено-9-карбоксильных кислот и изучены их холинолитическая и бронходилаторная активность в сравнении с атропином. Соединения были синтезированы при кватернизации эфиров, полученных из соответствующих диаминоспиртов и хлорангидридов ксантено-9-карбоксильных кислот. Изучена связь между активностью действия и числом углеродных атомов в заместителях. Исключительно хороший эффект найден для двух соединений.