CYCLOBUTANEDICARBOXYLIC ACIDS. IX. SALTS OF BIS(DIALKYLAMINOALKYLAMIDES) OF α-TRUXILLIC ACID WITH CURARIFORM ACTIVITY*

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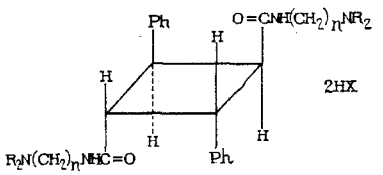
It has been previously demonstrated that biquaternary salts of ω-dialkylaminoalkyl esters [3] or ω-dialkylaminoalkyl amides [1, 2] of 1,3-diphenylcyclobutane-2,4-dicarboxylic acids exhibit pronounced curariform actitity.

We have found that in a number of cases the conversion of ω-dialkylaminoalkyl amides of α-truxillic acid into acid addition salts (I) also leads to the formation of quite active and selectively functioning myorelaxants that are devoid of the undesirable side effects characteristic of the corresponding biquaternary salts. This was an unexpected result since most of the curariform drugs currently used in medicine belong to the derivatives of mono- or biquaternary ammonium salts whereas the known salts of the mono- and bitertiary amines are significantly less active [4].

The addition salts I were obtained by reacting a dichloroanhydride of α-truxillic acid with primary-tertiary diamines $H_2N(CH_2)_nNR_2$ (II). For the purposes of our study we synthesized the compounds at n and NR_2 values which led to the formation of the most active myorelaxants in the series of biquaternary salts of aminoalkanol esters and aminoalkylamides of α-truxillic acid [2, 3].



I

The reaction was conducted in an inert organic solvent (benzene, $CHCl_3$, or dichloroethane) at room temperature. At equimolar proportions of reagents, the released hydrogen chloride bonded with the bis(aminoamide) being formed which was subsequently converted to dichlorohydrate. The resultant substances were separated and purified by extracting them from the organic layer with an acidic solution followed by the fractional alkalization of the acid solution which released the bis(aminoamide) from the diamine II mixture. Then the aminoamide bases were recrystallized (see [2] for analysis results and base constants), and by reacting solutions of physiologically acceptable inorganic or organic salts with the base solution in a suitable solvent, we obtained the acid addition salts I which were purified by recrystallization when necessary (see Table 1). Some of the salts were strongly hygroscopic. When salts of compound I were obtained with dibasic acids, we found it more preferable to separate the better crystallizing acid salts that contained two molecules of acid per one mole of bis(aminoamide) base.

The examined salts of bis(aminoamides) and α-truxillic acid exhibited pronounced curariform properties. They significantly exceed the action of known bisecondary and bitertiary myorelaxant amines [4]. Curariform activity is reduced when the n value is lowered to two or increased to four (see Table 1). The highest level of curariform is exhibited when the molecule's salt-forming centers are comprised of diethylamino-, N-pyrrolidyl or N-piperidyl groups.

*Previous communication [2].

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TABLE 1. Salts of α-Truxillic Acid Bis(dialkylaminoalkylamides) I and Their Curariform Activity

n	—NR_2	HX	mp, °C (with decomposition)	Found		Empirical formula	Calculated		Dose blocking neuromuscular transmission (tests on narcotized cats), μg/kg intravenously[e]
				element	%		element	%	
2	—NEt_2	HCl	Strongly hygroscopic	N	9,03	$C_{30}H_{44}N_4O_2 \cdot 2HCl$	N	9,89	5500—6500
2	—N $(CH_2)_5$	HCl	254—7	Cl	12,04	$C_{32}H_{44}N_4O_2 \cdot HCl$	Cl	11,90	3500—4500
3	—NEt_2	HCl	150—2	Cl	11,66	$C_{32}H_{48}N_4O_2 \cdot 2HCl$	Cl	11,94	400—450
3	—N $(CH_2)_4$	HCl	148—53	Cl[a]	11,20	$C_{32}H_{44}N_4O_2 \cdot 2HCl \cdot 2H_2O$	Cl	11,33	120—130
3	—N $(CH_2)_4$	HBr	153—6	Br[b]	23,65	$C_{32}H_{44}N_4O_2 \cdot HBr$	Br	23,55	170—180
3	—N $(CH_2)_4$	H_2SO_4	135—8	N	7,66	$C_{32}H_{44}N_4O_2 \cdot 2H_2SO_4$	N	7,86	150—160
3	—N $(CH_2)_4$	Maleic acid	183—7	N	7,36	$C_{32}H_{44}N_4O_2 \cdot 2C_4H_4O_4$	N	7,48	150—160
3	—N $(CH_2)_4$	Fumaric acid	207—10	N	7,66	$C_{32}H_{44}N_4O_2 \cdot 2C_4H_4O_4$	N	7,48	160—170
3	—N $(CH_2)_5$	HCl	260—4	Cl[c]	11,37	$C_{34}H_{48}N_4O_2 \cdot 2HCl$	Cl	11,47	150—180
3	—N $(CH_2)_5$	HBr	150—4	Br[d]	22,88	$C_{34}H_{48}N_4O_2 \cdot 2HBr$	Br	22,62	180—200
3	—N $(CH_2)_5$	Fumaric acid	190—3	N	7,09	$C_{34}H_{48}N_4O_2 \cdot 2C_4H_4O_4$	N	7,21	180—200
4	—NEt_2	HCl	Strongly hygroscopic	N	8,56	$C_{34}H_{52}N_4O_2 \cdot 2HCl$	N	9,01	750—800
4	—N $(CH_2)_5$	HCl	162—5	N	8,79	$C_{36}H_{52}N_4O_2 \cdot 2HCl$	N	8,68	450—500

[a]Found, %: C 61.22, H 7.97, N 8.10. Calculated, %: C 61.42, H 8.05, N 8.95.
[b]Found, %: N 7.95. Calculated, %: N 8.26.
[c]Found, %: N 8.92. Calculated, %: N 9.07.
[d]Found, %: N 7.95. Calculated, %: N 7.93.
[e]For turbarine (calibrated) 18 ± 230 μg/kg.

As can be seen from Table 1, the compounds under study are no less effective than tubarine, and some of them exceed its myoparalytic activity. The substances under examination are characterized by a rapid onset of a short-acting block, and rapid restoration of neuromuscular transmission. Their myoparalytic action is of a considerably broad nature that is similar to the action of competitive myorelaxants. Neostigmine is their antagonist.

Arterial pressure and cardiac function are not affected by these compounds at myoparalytic doses. Their effect on acetylcholine's negaive chronotropic action is insignificant at myoparalytic doses with practically no induction of tachycardia. In addition, it has been shown that the compounds under study have no effect on hemodynamics, and are without ganglion-blocking properties or the ability to release histamine which are advantages over tubarine. No other side effects were detected.

Thus, in comparison to the biquaternary salts of α-truxillic acid complex esters (anatruxonium and cyclobutonium), the corresponding bitertiary aminoamide salts are shorter-acting, assure rapid recovery from myorelaxation, and do not induce tachycardia and other side effects [5].

EXPERIMENTAL

α-Truxillic Acid Bis[1,2-(N-piperidyl)ethylamide]dichlorohydrate (model example). A solution of 29 g of 1,2-(N-piperidyl)ethylamine was added, while stirring and cooling to a solution of 3.7 g of α-truxillic acid dichloroanhydride in 30 ml of dichloroethane. The reaction mixture was kept at room temperature for 18 h after which 20 ml of water was added to the mixture. The organic layer was then separated and successively extracted 2 times (10 ml each time) with 5% H_2SO_4 and 1 time with 10 ml of water. The aqueous extracts were then combined and treated with activated charcoal. The filtrate was made alkaline by an ammonia solution up to pH 9.0. The separated residue was filtered off, washed with water, and dried. Yield 4.3 g. After crystallization, 4 g of base were obtained from the acetone mixture with alcohol, mp 192-194°C (with decomposition). Literature data [2]: mp 190-191°C.

A hydrogen chloride ester solution was added to a solution of 2 g of the base in 50 ml of absolute ethanol up to the acid point. The solvents were distilled off, and the remaining residue was washed with ether and recrystallized from the alcohol mixture with acetone. Yield 2 g (see Table 1).

The other salts of α-truxillic acid bis(aminoamides) were obtained in a similar fashion.

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