STUDIES IN THE CYCLOBUTANEDICARBOXYLIC ACID FIELD

IV. SYNTHESIS OF BIS-QUATERNARY SALTS OF ALKYLAMINO ESTERS OF α-TRUXILLIC ACID

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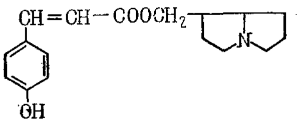
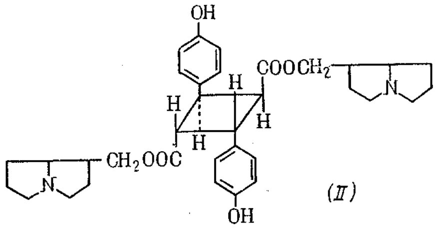
Some dialkylaminoalkyl esters of α-truxillic acid and their bis-quaternary salts have been synthesized, and their properties and pharmacological activity have been studied.

In the preceding works of this series [1-3] we presented results of studies connected with determination of the structure of new thesimine and thesine alkaloids which were isolated from the plant Thesium Minkwitzianum of the sandalwood family [4]. It was established that thesimine is the α-isoretronecanol ester of p-hydroxycinnamic acid (I), while thesine is di-α-isoretronecanyl p,p'-dihydroxy-α-truxillate (II).



(I)



(II)

The new type of pyrrolizidine alkaloid we have found is interesting because of the fact that thesine displays curare-like action which is markedly enhanced by converting it to the bis-methiodide [5]. And up till now the preparation of many medicinal preparations has been based on directed changes in structure of natural biologically active substances. In this connection, investigation of the pharmacological properties of a number of derivatives of cyclobutanecarboxylic acids has merited attention, especially the search for new active miorelaxants among compounds structurally close to thesine. In the molecule of thesine bis-methiodide there are two cationic centers (quaternary nitrogen atoms) which are distinguished by their behavior toward alkali, contain ester groups, and are a part of the cyclobutane and pyrrolizidine systems. It is known that the spacing between the quaternary nitrogen atoms and the structure of the part of the organic molecule which contains them determine the presence of curare-like properties in tubocurarine chloride and other synthetic curare-like compounds. It was of interest to synthesize a number of bis-quaternary salts of dialkylaminoalkyl esters of the stereoisomeric cyclobutanedicarboxylic acids and to investigate them for curare-like activity as a function of changes in structure of the amino alcohol and acid fragments of the molecule.

In the present communication we describe the preparation and properties of bis-dialkylaminoalkyl esters of α-truxillic acid (III) and their bis-quaternary salts, and also the results of pharmacological testing of the latter (see Table 1).

The starting α-truxillic acid was synthesized by photodimerization of transcinnamic acid under the action of direct sunlight; we also used artificial light sources successfully for photodimerization—the best results were attained in the case where an RV-350 lamp was used. The esters (III) were prepared by the reaction of α-truxilloyl chloride with 4 moles of the α, ω-dialkylaminoalkanol in benzene medium:

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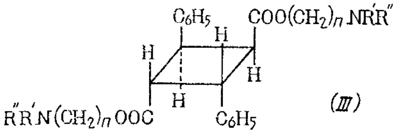
Dialkylaminoalkyl Esters of α-Truxillic Acid and Their Bis-quaternary Salts (III · 2RX)



(III)

Serial No.[1]	n	R^I	R^{II}	Base III					Bis-quaternary salt (III·2RX)				
				empirical formula	melting point (°C)	found (in %)[2]	calculated (in %)		RX	m.p. (in °C). Recrystallization solvent in parentheses	I^- found[2], % calcd. in parentheses	sol. in water (in %) at 20°	Curare-like activity of salt III · 2RX[3]
						C	H	N					
1	2	CH_3	CH_3	$C_{26}H_{34}N_2O_4$	52—53	71,79 (71,23)	8,07 (7,76)	6,26 (6,39)	CH_3I	280-281 dec., methanol	35,32 (35,18)	0,3	545 (519—588)
2	2	C_2H_5	C_2H_5	$C_{30}H_{42}N_2O_4$	4	71,84 (72,05)	8,63 (8,58)	5,99 (5,71)	CH_3I	205-206 ace., methanol	32,58 (32,60)	2,0	170 (147,8—195,5)
3	2	—$(CH_2)_5$—		$C_{32}H_{42}N_2O_4$	Liquid	74,31 (74,32)	8,15 (8,11)	5,10 (5,37)	CH_3I	245-246 acetone	31,22 (31, 67)	0,3	73 (62,0—84,7)
4	3	CH_3	CH_3	$C_{28}H_{38}N_2O_4$	78—79[5]	71,87 (72,10)	8,10 (8,15)	6,10 (6,00)	CH_3I	230-232 acetone	24,33 (34,86)	1,4	255,0 (232,8—279.2)
5									C_2H_5I	225-226 acetone	32,36 (32,60)		78,0 (55,7—109,2)
6	3	C_2H_5	C_2H_5	$C_{32}H_{46}N_2O_4$	Liquid	73,71 (73,62)	8,80 (8,81)	5,10 (5,36)	CH_3I	211-212 methanol	31,56 (31,67)	1,0	37,5 (32,4—43,3)
7									C_2H_5I	224-225 water	30,17 (30,41)	0,3	34,0 (31,6—36,5)

(Table cont.)

8	3	—$(CH_2)_4$—		$C_{32}H_{42}N_2O_4$	Liquid				CH_3I	248-249 water	31,40 (31,67)	0,5	31,5 (28,8—34,4)
9									C_2H_5I	230-231 aque. alcohol	30,38 (30,64)	0,2	24,2 (21,8—26,9)
10	3	—$(CH_2)_5$—		$C_{34}H_{46}N_2O_4$	64—65	74,81 (75,00)	8,38 (8,45)	5,12 (5,14)	CH_3I	258-259 aque. methanol	30,38 (30,64)	0,15	22,5 (15,6—32,4)
11									C_2H_5I	220-221 aque. alcohol	29,90 (29,60)	0,5	21,7 (17,3–27,12)
12	3	—$(CH_2)_2O(CH_2)_2$—		$C_{32}H_{42}N_2O_6$	108—109	69,81 (69,72)	7,74 (7,68)	(5,08)	CH_3I	240-241 methanol	30,49 (30,41)	0,7	
13	4	C_2H_5	C_2H_5	$C_{34}H_{50}N_2O_4$	Liquid	73,55 (74,18)	9,57 (9,16)	6,07 (5,90)	CH_3I	141-142 acetone	30,20 (30,40)	3,0	48,0 (41,3–55,7)
14									C_2H_5I	180-182 acetone	30,04 (29,46)	1,0	41,0 (34,7—50,8)
15	4	—$(CH_2)_4$—		$C_{34}H_{40}N_2O_4$	Liquid				CH_3I	178-179 water	30,52 (30,64)	1,0	46,0 (41,0—51,5)
16									C_2H_5I	174-175 ace. -methanol	29,60 (29,20)	2,0	37,5 (33,6—41,7)
17	4	—$(CH_2)_5$—		$C_{36}H_{50}N_2O_4$	56—57	75,55 (75,48)	8,85 (8,79)	5,01 (4,80)	CH_3I	228-229 methanol	29,70 (29,60)	0,1	46,0 (48,3—48,7)
18									C_2H_5I	167-168 abs. alcohol	28,78 (28,69)	0,5	41,0 (39,0—43,0)
19									C_3H_7I	187-188 alcohol	27,21 (27,79)	0,25	
20									$C_9H_{12}O_3S$	?		3,0	52,0 (44,8—60,3)

(Table cont.)

Serial No.[1]	n	R^I	R^{II}	Base III					Bis-quaternary salt (III · 2RX)				
				empirical formula	melting point (°C)	found (in %)	calculated (in %)		RX	m.p. (in °C). Recrystallization solvent in parentheses	I^- found[2], % calc. in parentheses	sol. in water (in %) at 20°	Curare-likeactivity of salt III · 2RX[3]
						C	H	N					
21	4	$-(CH_2)_2O(CH_2)_2-$		$C_{36}H_{46}N_2O_6$	69—70	70,92 (70,65)	8,20 (8,02)	4,70 (4,83)	CH_3I	218-219 methanol	29,70 (29,46)	0,3	181,0 (152,1–215,4)
22	5	C_2H_5	C_2H_5	$C_{36}H_{54}N_2O_4$	Liquid				CH_3I	155-156 alcohol	29,83 (29,50)	0,6	43,5 (37,3—49,6)
23	5	$-(CH_2)_5-$		$C_{38}H_{54}N_2O_4$	62—63	76,34 (75,75)	8,93 (8,90)	4,49 (4,64)	CH_3I	200-201 methanol	28,67 (28,69)	0,2	48,0 (42,8—53,7)
24									C_2H_5I	166-167 ace.-methanol	27,09 (27,79)	0,2	57,0 (52,0—62,4)
25	7	C_2H_5	C_2H_5	$C_{40}H_{62}N_2O_4$	Liquid	74,95 (75,71)	10,23 (9,85)	4,73 (4,41)	CH_3I	188-189 acetone	[8]	0,5	98,0 (87,5–109,7)
26	7	$-(CH_2)_5-$		$C_{42}H_{62}N_2O_4$	Liquid				CH_3I	202-203 methanol	[9]	0,01	140,0 (107,6–182,0)

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[1] The serial number refers to the bis-quaternary salt III · 2RX.

[2] Results given are the average of 2 duplicate analyses.

[3] According to head depression symptoms in rabbits. Data are average effective doses (ED_{50}) (in micrograms/kg) with confidence limits; the head depression symptom is caused in rabbits by α-tubocurarine chloride at a dose of 261 micrograms/kg.

[4] Dihydrochloride: hygroscopic crystals %: Cl 12.54. $C_{30}H_{42}N_2O_4 \cdot 2HCl$. Calculated %: Cl 12.52.

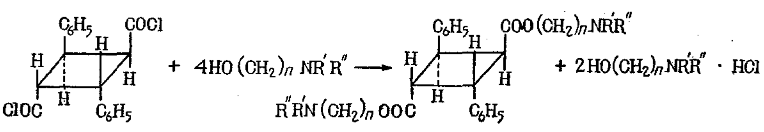
[5] Dihydrochloride: m.p. 186°. Found %: Cl 12.79. $C_{28}H_{38}N_2O_4 \cdot 2HCl$. Calculated %: 13.18.

[6] Dihydrochloride: m.p. 149-150°. Found %: Cl 11.25. $C_{34}H_{50}N_2O_4 \cdot 2HCl$. Calculated %: Cl 11.39.

[7] Methyl p-toleunesulfonate; the salt is hygroscopic. Found %: C 66.77; H 7.71; N 2.91. $C_{36}H_{50}N_2O_4 \cdot 2C_9H_{12}O_3S$. Calculated %: C 66.53; H 7.59; N 2.93.

[8] Found %: C 54.44; H 7.78. $C_{40}H_{62}N_2O_4 \cdot 2CH_3I$. Calculated %: C 54.90; H 7.72.

[9] Found %: C 56.00; H 7.41. $C_{42}H_{62}N_2O_4 \cdot 2CH_3I$. Calculated %: C 56.04; H 7.22.



(III)

After separation of the precipitated amino alcohol hydrochloride, the ester base III remained in the form of an oil which could not always be induced to crystallize; the bases were then converted to the bis-quaternary salts, and in some cases to the dihydrochlorides.

The esters (III) synthesized differed among themselves in length of hydrocarbon chain in the dialkylaminoalkyl radicals, which changed the spacing between cationic centers; and also in the nature of the substituents on the quaternary nitrogen atom, by which the character of the shielding around the positive charge in the cations was varied; and in the nature of the anions, which permitted increasing the solubility of the salts in some cases.

EXPERIMENTAL*

The amino alcohols $R_2N(CH_2)_nOH$ were prepared by known methods, starting from allyl alcohol for n = 3 [6], from γ-butyrolactone for n = 4 [7], and from the ω-chlorocarboxylic acids for n = 5 or 7 [8].

α-Truxillic Acid

A. Photodimerization of Cinnamic Acid under the Action of Sunlight. Cinnamic acid (1200 g) was placed in 10 cellophane bags (60 × 40 cm) and irradiated with sunlight for 40 days (from 8 a.m. to 1 p.m.; May-June), mixing the acid daily. The mixture of cinnamic and α-truxillic acid obtained was boiled for 1 h with 3 liters of dichloroethane. The undissolved precipitate was filtered off, washed with hot dichloroethane (2 × 250 ml), and again boiled with 1 liter of dichloroethane. The α-truxillic acid was filtered off, washed with hot dichloroethane (2 × 250 ml), and dried. There was obtained 500 g of α-truxillic acid, m.p. 280°;† lit. [9]: m.p. 280-283°. The yield was 41.6% based on cinnamic acid taken. By evaporation of the dichloroethane solutions, about 500 g of cinnamic acid of m.p. 128-130° was recovered. The yield of α-truxillic acid based on cinnamic acid consumed was 71%.

B. Irradiation of Cinnamic Acid with an RV-350 Mercury-Tungsten Lamp. Onto a rack of 20 × 15 cm dimensions was set 10 g of cinnamic acid, and it was irradiated for 150 h with a type RV-350 lamp suspended 15 cm away. Separation of the α-truxillic acid from the cinnamic acid was carried out just as described above. There was obtained 2 g of α-truxillic acid, m.p. 280-285° (50% yield, based on cinnamic acid consumed).

α-Truxilloyl Chloride.

A mixture of 29.6 g of α-truxillic acid, 60 ml of thionyl chloride and 200 ml of dichloroethane was heated on a water bath until the precipitate completely dissolved (about 1 h). The dichloroethane was stripped under vacuum, 200 ml of dichloroethane was added to the residue, and it was again stripped. The residue (32 g) had m.p. 114-120°; the pure acid chloride, m.p. 125°, was obtained by recrystallization from benzene; lit. [9]: m.p. 127.1-127.8°.

Bis-dialkylaminoalkyl Esters of α-Truxillic Acid (III).

(Typical experiment.) To a solution of 0.4 mole of the amino alcohol in 250 ml of dichloroethane was added, with stirring and cooling, a solution of the unrecrystallized di-acid chloride obtained above in 200 ml of dichlorethane, at such a rate that the temperature of the reaction mixture did not rise above 10°. The reaction mixture was stirred for 2 h and was then allowed to stand at 20-25° for 12 h; after this it was extracted several times with 300 ml of a 5% sulfuric acid solution. The acid extract was decolorized with charcoal, and then, with cooling, a 25% ammonia solution was added to pH 9.0. The precipitate which

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*T. V. Golovkina took part in the synthesis of the compounds in the experimental part of the work, and L. A. Kravchuk took part in their pharmacological investigation.

†Here, and in the table, we give uncorrected melting points.

separated was filtered off, washed with cold water, and dried. If the precipitated base could not be induced to crystallize, it was extracted with ether and the solvent was evaporated from the dried ether solution. Yields, analyses, and properties of the compounds obtained are given in the table.

Bis-quaternary Salts.

(Typical experiment.) A solution of 0.05 mole of the bis-alkylaminoalkyl ester and 0.2 mole of the alkyl halide in 100 ml of methanol was heated under reflux until the alkaline reaction disappeared. The methanol was stripped under vacuum, the residue was treated with acetone, recrystallized from a suitable solvent (alcohol, methanol, water, or acetone), and dried under vacuum over phosphorus pentoxide (see table).

LITERATURE CITED

1. A. P. Arendaruk and A. P. Skoldinov, Zh. Obshch. Khim., 30, 484 (1960).
2. A. P. Arendaruk and A. P. Skoldinov, ibid., 30, 489 (1960).
3. A. P. Arendaruk and A. P. Skoldinov, ibid., 30, 274 (1960).
4. A. P. Arendaruk, N. F. Proskurnina, and R. A. Konovalova, ibid., 30, 674 (1960).
5. M. D. Mashkovskii, Farmakol. i Toksikol., No. 1, 25 (1943); No. 6, 3 (1955).
6. A. Lespagnol and J. Deprey, Bull. soc. chim. France, 1117 (1962).
7. V. M. Solov'ev, A. P. Arendaruk, and A. P. Skoldinov, Zh. Obshch. Khim., 29, (1959).
8. V. M. Solov'ev, A. P. Arendaruk, and A. P. Skoldinov, ibid., 31, 2577 (1961).
9. E. H. White and H. C. Dunathan, J. Am. Chem. Soc., 78, 6055 (1956).