SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF BISQUATERNARY SALTS OF THE PYRROLIZIDINE SERIES

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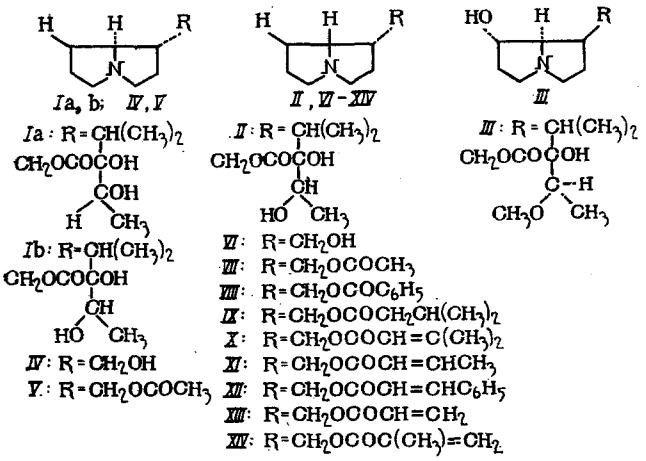
It is well known that certain bisquaternary ammonium salts of alkaloids have curare-like properties [1-3]. Among them, a bisquaternary salt of the pyrrolizidine series — 1,3-di[β-(1-hydroxy-7-hydroxymethylpyrrolizin-4-yl)ethoxy]benzene — has come into medical practice as a curare-like preparation under the name "Diplacin."

With the objective of preparing potential curare-like substances, we have synthesized α,ω-bisquaternary salts of pyrrolizidine alkaloids of the pseudohelioetridane series [viridiflorin (Ia), trachelanthamin (Ib)], and heliotridane series [lindelophin (II), heliotrin (III)], and certain of their cleavage products [trachelanthamidin (IV), trachelanthamidin acetate (V), lindelophidin (VI), lindelophidin acetate (VII), lindelophidin benzoate (VIII), lindelophidin isovalerate (IX), lindelophidin β,β-dimethylacrylate (X), lindelophidin crotonate (XI), lindelophidin β-phenylacrylate (XII), lindelophidin acrylate (XIII), and lindelophidin methacrylate (XIV)].



The starting compounds IV and VI were prepared by alkaline hydrolysis of I and II [4, 5]. Compounds V and VII-XIV were synthesized from IV and VI and the appropriate acid chlorides. Yields and certain physicochemical properties of compounds V and VII-XIV are given in Table 1.

The bisquaternary salts were prepared in high yield by the reaction of α,ω-dibromoalkanes with the alkaloids indicated above or their cleavage products upon heating in alcoholic solution:

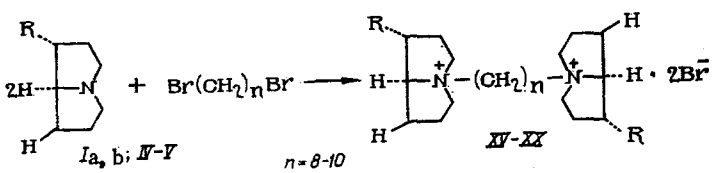


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TABLE 1. Esters of Pyrrolizidine Alcohols V and VII-XIV

Compound	Boiling point, °C/mm	n_D^{20}	Yield, %	N found, %	Empirical formula	N calculated, %
V	96/2	1,4700	51	7,5	$C_{10}H_{17}O_2N$	7,6
VII	80—2/4	1,4685	99	7,5	$C_{10}H_{17}O_2N$	7,6
VIII	159—60/4	1,5520	75	5,6	$C_{15}H_{19}O_2N$	5,7
IX	120/3	1,4676	55	6,1	$C_{13}H_{23}O_2N$	6,2
X	118—9/2	1,4926	60	6,2	$C_{13}H_{21}O_2N$	6,3
XI	100—1/1	1,4866	55	6,6	$C_{12}H_{19}O_2N$	6,7
XII	199—200/3	1,5640	55	5,1	$C_{17}H_{21}O_2N$	5,2
XIII	117—8/6	1,4838	40	7,0	$C_{11}H_{17}O_2N$	7,1
XIV	102—3/2	1,4836	38	6,6	$C_{12}H_{19}O_2N$	6,7

TABLE 2. Bisquaternary Salts XV-XXXII and Their Curare-Like Properties

Compound	Starting material	n	Yield, %	mp, °C	N found, %	Empirical formula	N, calculated, %	Dose causing complete blocking of neuromuscular transmission on irritation of peripheral end of cut sciatic nerve in narcotized dogs and cats, in mg/kg	*LD_{50}, mg/kg
XV	Ia	8	93	185—6	3,2	$C_{38}H_{70}Br_2N_2O_8$	3.3	0,8—0,9	4,15
XVI	Ia	9	91	75—6	3,2	$C_{39}H_{72}Br_2N_2O_8$	3,3	0,7—0,8	3,15
XVII	Ia	10	84	69—70	3,1	$C_{40}H_{74}Br_2N_2O_8$	3,3	0,6	1,35
XVIII	I	10	96	75—6	3,1	$C_{40}H_{74}Br_2N_2O_8$	3,2	0,8—1,0	1,82
XIX	IV	10	97	Oil	4,7	$C_{26}H_{50}Br_2N_2O_2$	4,8	2,0—2,5	0,83
XX	V	10	93	"	4,1	$C_{30}H_{54}Br_2N_2O_4$	4,2	5,0—6,0	6,75
XXI	II	8	89	140—2	3,2	$C_{38}H_{70}Br_2N_2O_8$	3,3	2,0—2,2	2,25
XXII	II	9	88	168—70	3,2	$C_{39}H_{72}Br_2N_2O_8$	3,3	1,0—1,2	1,85
XXIII	VI	8	89	159—61	4,9	$C_{24}H_{46}Br_2N_2O_2$	5,0	2,0—2,2	4,9
XXIV	VI	9	88	164—5	4,8	$C_{25}H_{48}Br_2N_2O_2$	4,9	1,8—2,0	4,1
XXV	VI	10	90	175,5—7,5	4,7	$C_{26}H_{50}Br_2N_2O_2$	4,8	1,5—1,7	4,1
XXVI	VII	10	97	Oil	4,1	$C_{30}H_{54}Br_2N_2O_4$	4,2	4,0—5,0	6.5
XXVII	VIII	10	89	"	3,4	$C_{40}H_{58}Br_2N_2O_4$	3,5	5,0—5,55	5,7
XXVIII	IX	10	90	95—7	3,6	$C_{36}H_{66}Br_2N_2O_4$	3,7	1,0—1,2	2.2
XXIX	X	8	93	74—6	3,8	$C_{34}H_{58}Br_2N_2O_4$	3,9	2,2—2,5	2,35
XXX	X	9	91	86—8	3,7	$C_{35}H_{60}Br_2N_2O_4$	3,8	2,0	3.1
XXXI	X	10	95	120—2	3,7	$C_{36}H_{62}Br_2N_2O_4$	3,8	1,0—1,2	1,8
XXXII	XI	10	89	68—9	3,8	$C_{34}H_{58}Br_2N_2O_4$	3,9	0,75—0,85	1,55
XXXIII	XII	10	90	78—80	3,2	$C_{44}H_{62}Br_2N_2O_4$	3,3	1,5—1,7	1,85
XXXIV	III	10	88	80—2	3,0	$C_{42}H_{74}Br_2N_2O_{10}$	3,0	1,4—1,6	4,45

*White mice, intravenous injection.

The corresponding bisquaternary salts XXI-XXXIII were prepared similarly from compounds of type II; and the bisquaternary salt XXXIV was similarly prepared from compound III. The structures, yields, certain physicochemical properties, and pharmacological activity of the bisquaternary compounds prepared are given in Table 2.

Pharmacological studies showed that all the synthesized compounds possess curare-like activity (see Table 2). It is evident from Table 2 that among the substances synthesized the compounds with n = 10 (XVII, XXV, and XXXI) are more active curare-like media than the compounds with n equal to 8 or 9 (XV, XVI, XXIII, XXIV, XXIX, and XXX). Definite principles in activity are also observed as a function of the configuration of the pyrrolizidine ring. Thus, the bisquaternary salts of the pseudoheliotridane series (XIX, XX) have greater muscle-relaxing activity than the compounds of the heliotridane series (XXV, XXVI). The presence of a double bond in the pyrrolizidine ring leads to a decrease in curare-like activity. Among the compounds synthesized, decamethylene-1,10-bisviridiflorinium dibromide (XVII) and decamethylene-1,10-biscrotonyllindelophinium dibromide (XXXII) exert the greatest blocking effect on neuromuscular conductivity; in doses of 0.6-0.75 mg/kg these cause complete breakdown of neural excitation transfer in the neuromuscular synapses and they exceed the activity of Diplacin by a factor of 2-2.5.

EXPERIMENTAL

The alkaloids viridiflorin (Ia), trachelanthamin (Ib), lindelophin (II), and heliotrin (III) were isolated from plants [6]. The α,ω-dibromoalkanes were prepared by the procedures of [7, 8].

Decamethylene-1,10-bistrachelanthaminium Dibromide (XVIII). To a solution of 3 g (0.01 mole) of 1,10-dibromodecane in 10 ml of absolute methanol was added 5.8 g (0.021 mole) of Ib, and the mixture was boiled for 3 h. After the reaction mixture had been cooled, the solvent was distilled off to a low volume, and absolute ether was added. The crystals which separated were filtered off and washed with ether. Compound XVIII was obtained in a yield of 8.3 g (96%).

Octamethylene-1,8-bisviridiflorinium Dibromide (XV). 1,8-Dibromooctane (0.14 g, 0.005 mole) was dissolved in 3 ml of absolute ethyl alcohol, 0.3 g (0.011 mole) of Ia was added, and the mixture was boiled for 3 h. The crystals which fell upon addition of ether were filtered off, washed with ether, and dried. Compound XV was obtained in a yield of 0.41 g (93%); mp 185-186°.

Lindelophidin β,β-Dimethylacrylate (X). Lindelophidin (1.05 g, 0.007 mole) was dissolved in 5 ml of dry chloroform, and 1 g (0.009 mole) of β,β-dimethylacryloyl chloride was added. The mixture was heated on a water bath for 4 h, allowed to stand overnight, and poured into water. The water layer was separated, made alkaline with ammonia, extracted with chloroform, and the extract was dried with sodium sulfate. After evaporation of the solvent, the residue was distilled; 1.0 g of X (60%) was obtained.

Decamethylene-1,10-bis-β,β-dimethylacryloyllindelophinium Dibromide (XXI). A mixture of 0.30 g (0.001 mole) of 1,10-dibromodecane and 0.48 g (0.0021 mole) of lindelophidin β,β-dimethylacrylate in 3 ml of absolute alcohol was boiled for 4 h. After the reaction mixture had been cooled, the reaction product was precipitated with ether. Compound XXXI was obtained (0.74 g, 95%).

Nonamethylene-1,9-bislindelophinium Dibromide (XXII). A solution of 0.43 g (0.015 mole) of 1,9-dibromononane and 0.86 g (0.003 mole) of II in 10 ml of absolute ethanol was boiled for 4 h. The reaction product was precipitated with absolute ether; 1.14 g (88%) of XXII was obtained.

The bisquaternary salts XVI, XVII, XIX-XXI, XXIII-XXX, and XXXII-XXXIV were prepared similarly.

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