BISQUATERNARY SALTS OF ALKALOIDS OF THE HELIOTRIDANE SERIES AND SOME PRODUCTS OF THEIR TRANSFORMATION

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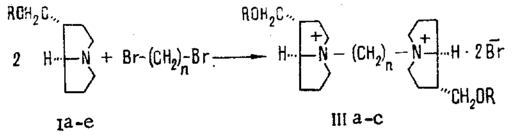
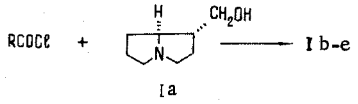
We have previously effected the synthesis of bisquaternary salts of pyrrolizidine bases [1, 2]. Continuing these investigations, we have studied the reactions of 1,10-dibromodecane and 1,5-dibromopentane with trachelanthamidine and its derivatives (Ia-b) and of di(4-chlorobutyl) ether with the alkaloids viridiflorine (IIa) and lindelofine (IIb). The bisquaternary compounds (IIIa-c) were obtained by the reaction of α,ω-dibromoalkanes (Ia-e) by heating a mixture of them in boiling ethanol.



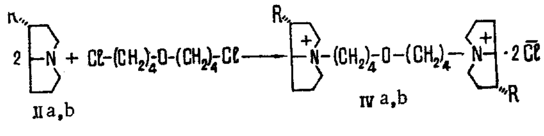
a. $R = H$; b. $R = COCH_3$; c. $R = COCH_2 - CH(CH_3)_2$;
d. $R = COCH = C(CH_3)_2$; e. $R = COC_6H_5$; $n = 5,10$.

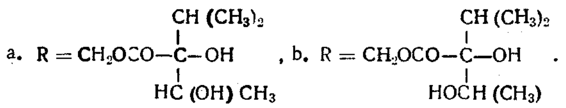
The initial trachelanthamidine esters of aliphatic, unsaturated, and aromatic acids (Ib-e) were obtained from trachelanthamidine (Ia) and the chlorides or anhydrides of the corresponding acids in good yields:

Initial compound	R	Yield, %	bp, °C (mm)	n_D^{20}	Empirical formula
Ia. Trachelanthamidine	H	87	114—115 (3)	—	$C_8H_{15}ON$
Ib. Acetate of (Ia)	$COCH_3$	51	96(2)	1,4700	$C_{10}H_{17}O_2N$
Ic. Isovalerate of (Ia)	$COCH_2CH(CH_3)_2$	59	136—137 (5)	1,4592	$C_{13}H_{23}O_2N$
Id. β,β-Dimethylacrylate of (Ia)	$COCH{=}C(CH_3)_2$	56	139—140 (4)	1,4930	$C_{13}H_{21}O_2N$
Ie. Benzoate of (Ia)	COC_6H_5	64	182—183 (6)	1,5315	$C_{15}H_{19}O_2N$



The reaction of di(4-chlorobutyl) ether with (IIa-b) under the conditions described above for the α,ω-dibromoalkanes, and also at 140-150°C in the absence of solvents gave low yields of the reaction products (less than 10%). The reaction takes place smoothly when one equivalent of di(4-chlorobutyl) ether is boiled with two equivalents of viridiflorine or lindelofine in amyl alcohol; under these conditions the yields of (IVa,b) were high (90-95%).





a. $R = CH_2OCO-\underset{HC(OH)CH_3}{\overset{CH(CH_3)_2}{C}}-OH$, b. $R = CH_2OCO-\underset{HOCH(CH_3)}{\overset{CH(CH_3)_2}{C}}-OH$.

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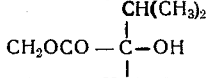
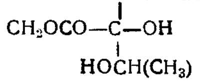
The necessity for using a higher temperature for the reaction of di(4-chlorobutyl) ether is due to the fact that it requires more energy to cleave a C−Cl bond than for a C−Br bond in the α,ω-dibromoalkanes [3].

The yields and some physicochemical properties of the bisquaternary salts of the pyrrolizidine series obtained are given below (compounds IIIa-e) and (IVa, b) were purified by reprecipitating ethanolic solutions with ether):

Compound	*R*	*n*	Yield, %.	mp, °C	Empirical formula
IIIa	H	5	65	228—229	$C_{21}H_{40}O_2N_2Br_2$
III^{a}	H	10	97	Oil	$C_{26}H_{50}O_2N_2Br_2$
IIIb	$COCH_3$	10	93	Oil	$C_{30}H_{54}O_4N_2Br_2$
III^{c}	$COCH_2—CH(CH_3)_2$	10	86	58—60	$C_{36}H_{66}O_4N_2Br_2$
IIId	$COCH{=}C(CH_3)_2$	10	92	77—78	$C_{36}H_{62}O_4N_2Br_2$
IIIe	COC_6H_5	10	87	71—72	$C_{40}H_{58}O_4N_2Br_2$
IVa	 $CH_2OCO-\overset{CH(CH_3)_2}{\underset{HC(OH)CH_3}{C}}-OH$	—	95	162—163	$C_{38}H_{70}O_9N_2Cl_2$
IVb	 $CH_2OCO-\overset{CH(CH_3)_2}{\underset{HOCH(CH_3)}{C}}-OH$	—	90	219—220	$C_{38}H_{70}O_9N_2Cl_2$

The structures of the compounds obtained were confirmed by the results of elementary analysis and IR spectroscopy. The IR spectra of (Ib-e) show absorption bands in the 1720-1750 cm^{-1} region that are characteristic for the carbonyl of an ester group, and the absorption bands of a hydroxy group have disappeared.

The compounds synthesized consist of crystalline substances or in some cases viscous oils readily soluble in water and ethanol and sparingly soluble in ether.

The results of pharmacological trials have shown that all the compounds synthesized possess curare-mimetic activity.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument. The alkaloids viridiflorine (IIa), lindelofine (IIb), and trachelanthamine were isolated from plants [4]. Trachelanthamidine (Ia) was obtained by the alkaline hydrolysis of the alkaloid trachelanthamine [5]. The di(4-chlorobutyl) ether and the α,ω-dibromoalkanes were obtained by standard methods [6].

Trachelanthamidine Isovalerate (Ic). To a solution of 1.41 g (0.01 mole) of trachelanthamidine in 5 ml of dry chloroform was added 1.21 g (0.011 mole) of isovaleryl chloride, and the mixture was heated in an air bath for 2 h and was poured into water. The aqueous layer was separated off, made alkaline with ammonia solution, and extracted with chloroform, and the extract was dried with sodium sulfate. The residue after the evaporation of the solvent was distilled. This gave 1.34 g (59%) of trachelanthamidine isovalerate with mp 136-137°C (5 mm Hg); $n_D^{20}=1.4592$.

Trachelanthamidine Benzoate (Ie). A mixture of 1.41 g (0.01 mole) of trachelanthamidine, 1.46 g (0.011 mole) of benzoyl chloride, and 5 ml of dry chloroform was boiled for 3 h and extracted with water; the solution was made alkaline with ammonia and extracted with chloroform. The extract was dried (magnesium sulfate) and evaporated, and the residue was distilled. This gave 1.54 g (64%) of trachelanthamidine benzoate with bp 182-183°C (6 mm Hg); $n_D^{20}=1.5315$. Compounds (Ib and d) were obtained similarly.

Pentamethylene-1,5-bistrachelanthamidine Dibromide (IIIa). To a solution of 3.45 g (0.15 mole) of 1,5-dibromopentane in 30 ml of absolute methanol was added 4.4 g (0.31 mole) of trachelanthamidine (Ia), and the mixture was boiled for 4 h. After the reaction mixture had cooled, the solvent was distilled off to small volume, and absolute ether was added. The crystals that deposited were filtered off and washed with ether, giving 5 g (65%) of pentamethylene-1,5-bistrachelanthamidine dibromide with mp 228-229°C.

Decamethylenebis(O-β,β-dimethylacryloyltrachelanthamidine) Dibromide (IIId). A mixture of 0.3 g (0.001 mole) of 1,10-dibromodecane and 0.446 g (0.0021 mole) of trachelanthamidine β,β-dimethylacrylate in 5 ml of absolute ethanol was boiled for 4 h. The decamethylenebis(O-β,β-dimethylacryloyltrachelanthamidine) dibromide was precipitated with ether. Yield 0.7 g (92%), mp 77-78°C. The bisquaternary salts (IIIb, c and d) were obtained similarly.

Oxybisbutylviridiflorine Dichloride (IVa). To a solution of 0.1 g (0.005 mole) of bis(4-chlorobutyl) ether in 3 ml of amyl alcohol was added 0.3 g (0.011 mole) of viridiflorine and the mixture was boiled for 5 h. The crystals that deposited on the addition of ether were filtered off, washed with ether, and dried. This gave 0.38 g (95%) of oxybis(butylviridiflorine) dichloride with mp 162-163°C. Compound (IVb) was obtained similarly.

SUMMARY

The reaction of α,ω-dibromoalkanes with trachelanthimidine and its derivatives and of bis(4-chlorobutyl) ether with the alkaloids lindelofine and viridiflorine have yielded bisquaternary salts of the pyrrolizidine series.

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SYNTHESIS OF SOME BISQUATERNARY SALTS OF THE ALKALOIDS LOLINE AND LOLININE

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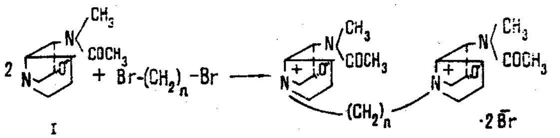
Continuing investigations of the synthesis of bisquaternary salts of the pyrrolizidine bases [1], in order to obtain potential curaremimetic compounds we have studied the reaction of 1,10-dibromoedecane, 1,9-dibromononane, and 1,8-dibromooctane with the alkaloid lolinine (I). Bisquaternary compounds of the latter (IIa-c) were obtained by the reaction of the α,ω-dibromoalkanes with lolinine at room temperature in a ratio of one equivalent of dihalogenoalkane to two equivalents of alkaloid in ethanolic solution with high yields (78-96%).

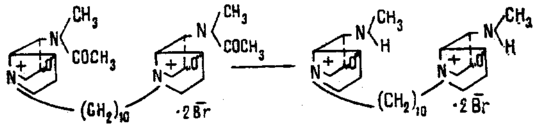
A bisquaternary salt of the alkaloid loline (IIIa) was obtained by hydrolyzing (IIc) with concentrated hydrochloric acid at room temperature.



I

IIa-c

a. n = 8
b. n = 9
c. n = 10



IIc

IIIa

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