# BISQUATERNARY SALTS OF PYRROLIZIDINE ALKALOIDS AND THEIR DERIVATIVES

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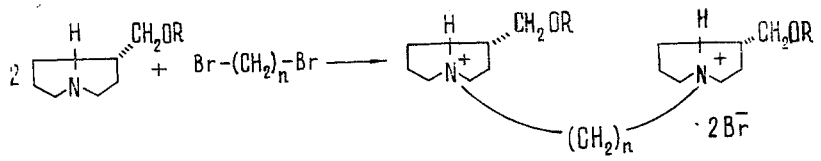
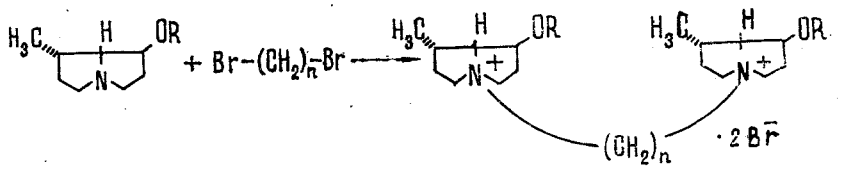
A bisquaternary salt of the pyrrolizidine series — a salt of 1,3-di(β-platynecinioethoxy)benzene — possesses curaremimetic properties and has been introduced into medical practice under the name of "diplacine" [1]. In order to synthesize potential pharmacologically active compounds among bisquaternary ammonium salts of the pyrrolidizine series, we have studied the reaction of α,ω-dibromoalkanes with lindelofidine (Ia) and hydroxyheliotridane (IIIa) and their derivatives (Ib-e, IIIb-m). As the α,ω-dibromoalkanes we used 1,10-dibromodecane, 1,9-dibromononane, and 1,8-dibromooctane.

The bisquaternary compounds were obtained with high yields (80-90%) by the reaction of the α,ω-dibromoalkanes with compounds mentioned above or their derivatives by heating their mixtures in ethanolic solution (boiling for 1-5 h).



Ia-e IIa-e

a) R=—H, b) R=—$COCH_3$, c) R=—$COCH_2CH(CH_3)_2$, d) R=—$COC_7H_{15}$, e) R=—$COC_6H_5$; $n$=8—10.



IIIa-m IVa-m

a) R=H, b) R=$COCH_3$, c) R=$COCH_2CH(CH_3)_2$, d) R=$COC(CH_3)$=$=CH_2$, e) R=CH=CH—$CH_3$, f) R=COCH=$CHC_6H_5$, g) R=$COC_6H_5$, h) R=$COC_6H_4CH_3$ -p, i) R=$COC_6H_4OCH_3$ -p, j) R=$COC_6H_4Br$ -p, k) R=$COC_6H_5NO_2$ -p, l) R=$COCH_2C_6H_5$, m) R=$COCH_2C_6H_4OCH_3$ -p, $n$=8—10.

The initial lindelofidine and hydroxyheliotridane esters of aliphatic, unsaturated, and aromatic acids (Ib-e) and (IIIb-m) were obtained from lindelofidine (Ia) or hydroxyheliotridane (IIIa) and the chlorides or anhydrides of the corresponding acids with good yields (Table 1).

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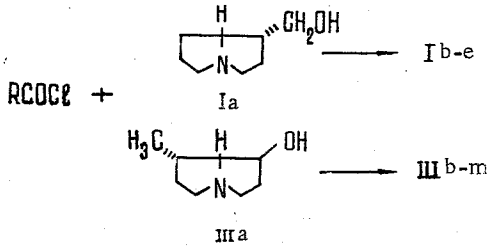


The structures of the compounds obtained were shown by the results of elementary analysis and by IR spectroscopy. The IR spectra of (Ib-e) (IIIb-m) contained absorption bands in the 1720-1750 $cm^{-1}$ region that are characteristic for the carbonyls of ester groups, and the absorption bands of hydroxy groups for the initial (Ia) and (IIIa) had disappeared.

The bisquaternary compounds (IIa-e) and (IVa-m) synthesized were crystalline substances or, in some cases, viscous oils readily soluble in water and ethanol and sparingly soluble in ether. The yields and some physical properties of the bisquaternary salt of the pyrrolizidine series obtained are given in Table 2.

Pharmacological investigations showed that all the compounds synthesized possess curaremimetic activity.

## EXPERIMENTAL

Lindelofidine Acetate (Ib). A mixture of 2.82 g (0.02 mole) of lindelofidine and 15 ml (0.15 mole) of acetic anhydride was heated at 60-80°C for 2 h. The excess of acetic anhydride was driven off in vacuum and the residue was distilled. This gave 3.0 g (99%) of lindelofidine acetate with mp 80-82°C (4 mm); $n_D^{20}$ 1.4685.

TABLE 1

| Initial compound | R | Yield, % | bp, °C (mm) or mp, °C | $n_D^{20}$ | Empirical formula |
|---|---|---|---|---|---|
| Ia.* Lindelofidine | H | 43 | 107—108(3) (40—41) | — | $C_8H_{15}ON$ |
| Ib. Acetate of Ia | $COCH_3$ | 99 | 80—82(4) | 1,4685 | $C_{10}H_{17}O_2N$ |
| Ic. Isovalerate of Ia | $COCH_2CH(CH_3)_2$ | 55 | 120(3) | 1,4676 | $C_{13}H_{23}O_2N$ |
| Id. Caprylate of Ia | $COC_7H_{15}$ | 70 | 166—167(5) | 1,4672 | $C_{16}H_{29}O_2N$ |
| Ie.† Benzoate of Ia | $COC_6H_5$ | 75 | 159—160(4) | 1,5520 | $C_{15}H_{19}O_2N$ |
| IIIa.‡ Hydroxyheliotridane | H | 85 | 103—104(3) | — | $C_8H_{15}ON$ |
| IIIb. Acetate of IIIa | $COCH_3$ | 56 | 67—68(2) | 1,4713 | $C_{10}H_{17}O_2N$ |
| IIIc. Isovalerate of IIIa | $COCH_2CH(CH_3)_2$ | 55 | 111—112(3) | 1,4611 | $C_{13}H_{23}O_2N$ |
| IIId. Methacrylate of IIIa | $COC(CH_3)=CH_2$ | 55 | 93—94(2) | 1,4762 | $C_{12}H_{19}O_2N$ |
| IIIe. Crotonate of IIIa | $COCH=CHCH_3$ | 53 | 102—103(2) | 1,4823 | $C_{12}H_{19}O_2N$ |
| IIIf. β-Phenylacrylate of IIIa | $COCH=CHC_6H_5$ | 52 | 162—164(2) | 1,5646 | $C_{17}H_{21}O_2N$ |
| IIIg. Benzoate of IIIa | $COC_6H_5$ | 64 | 155—156(2) | 1,5295 | $C_{15}H_{19}O_2N$ |
| IIIh. 4-Methylbenzoate of IIIa | $COC_6H_4CH_3$—4 | 55 | 72—74 | — | $C_{16}H_{21}O_2N$ |
| IIIi. 4-Methoxybenzoate of IIIa | $COC_6H_4OCH_3$—4 | 52 | 113—114 | — | $C_{16}H_{21}O_3N$ |
| IIIj. 4-Bromobenzoate of IIIa | $COC_6H_4Br$—4 | 56 | 71—72 | — | $C_{15}H_{18}O_2BrN$ |
| IIIk. 4-Nitrobenzoate of IIIa | $COC_6H_4NO_2$—4 | 52 | 51—52 | — | $C_{15}H_{18}O_4N_2$ |
| IIIl.** Phenylacetate of IIIa | $COCH_2C_6H_5$ | 54 | Oil | 1,5010 | $C_{16}H_{21}O_2N$ |
| IIIm.** 4-Methoxyphenylacetate of IIIa | $COCH_2C_6H_4OCH_3$ | 55 | Oil | 1,5018 | $C_{17}H_{23}O_3N$ |

*Obtained by the hydrolysis of lindelofine, according to the method described in [2].
†Melting point of the hydrochloride 180-181°C, which agrees with the figure given in the literature [2].
‡Synthesized by the Adams reduction of rinderine.
**The products were purified by passage through a column of alumina.

TABLE 2

| Compound | R | n | Yield, % | mp, °C | Empirical formula |
|---|---|---|---|---|---|
| IIa | H | 8 | 89 | 159–161 | $C_{24}H_{46}O_2N_2Br_2$ |
| IIa | H | 9 | 88 | 164–165 | $C_{25}H_{48}O_2N_2Br_2$ |
| IIa | H | 10 | 90 | 175–177 | $C_{26}H_{50}O_2N_2Br_2$ |
| IIb | $COCH_3$ | 10 | 97 | Oil | $C_{30}H_{54}O_4N_2Br_2$ |
| IIc | $COCH_2CH(CH_3)_2$ | 10 | 90 | 95–97 | $C_{36}H_{66}O_4N_2Br_2$ |
| IId | $COC_7H_{15}$ | 10 | 88 | Oil | $C_{42}H_{78}O_4N_2Br_2$ |
| IIe | $COC_6H_5$ | 10 | 89 | Oil | $C_{40}H_{58}O_4N_2Br_2$ |
| IVa | H | 10 | 88 | 197–198 | $C_{26}H_{50}O_2N_2Br_2$ |
| IVb | $COCH_3$ | 10 | 82 | 81–83 | $C_{30}H_{54}O_4N_2Br_2$ |
| IVc | $COCH_2CH(CH_3)_2$ | 10 | 89 | 56–58 | $C_{36}H_{66}O_4N_2Br_2$ |
| IVe | $COCH{=}CHCH_3$ | 10 | 94 | 64–66 | $C_{34}H_{58}O_4N_2Br_2$ |
| IVf | $COCH{=}CHC_6H_5$ | 10 | 94 | 96–98 | $C_{44}H_{62}O_4N_2Br_2$ |
| IVg | $COC_6H_5$ | 10 | 94 | 106–108 | $C_{40}H_{58}O_4N_2Br_2$ |
| IVh | $COC_6H_4-CH_3-4$ | 10 | 90 | 97–98 | $C_{42}H_{66}O_4N_2Br_2$ |
| IVi | $COC_6H_4-OCH_3-4$ | 10 | 90 | 77–78 | $C_{42}H_{66}O_6N_2Br_2$ |
| IVj | $COC_6H_4-Br-4$ | 10 | 85 | 161–162 | $C_{40}H_{56}O_4N_2Br_2$ |
| IVk | $COC_6H_4-NO_2-4$ | 10 | 88 | 75–76 | $C_{40}H_{56}O_8N_4Br_2$ |
| IVm | $COCH_2C_6H_4OCH_3-4$ | 10 | 85 | 93–94 | $C_{44}H_{66}O_6N_2Br_2$ |

Hydroxyheliotridane Isovalerate (IIIc). To a solution of 1.41 g (0.01 mole) of hydroxyheliotridane in 5 ml of dry chloroform was added 1.21 g (0.011 mole) of isovaleryl chloride. The reaction mixture was heated on the water bath for 2 h, left overnight, and poured into water. The aqueous layer was separated off, made alkaline with a solution of ammonia, and extracted with chloroform, and the extract was dried over magnesium sulfate. The residue after the evaporation of the solvent was distilled. This gave 1.24 g (55%) of hydroxyheliotridane isovalerate with bp 111-112°C (3 mm); $n_D^{20}$ 1.4611.

Hydroxyheliotridane Benzoate (IIIg). A mixture of 1.41 g (0.01 mole) of hydroxyheliotridane and 1.46 g (0.01 mole) of benzoyl chloride in 5 ml of chloroform was boiled for 3 h and poured into water, the aqueous layer was separated off, made alkaline with ammonia solution, and extracted with chloroform, and the extract was dried over sodium sulfate and the solvent was evaporated off. Distillation of the residue yielded 1.5 g (64%) of hydroxyheliotridane benzoate. bp 155-156°C (2 mm); $n_D^{20}$ 1.5275. Compound Ic-e and IIIb, d-f, h-m were obtained similarly.

Octamethylene Bis(lindelofidinium bromide) (IIa, n = 8). A solution of 0.48 g (0.0175 mole) of 1,8-dibromooctane and 0.53 g (0.035 mole) of lindelofidine in 5 ml of absolute ethanol was boiled for 4 h and cooled, and the reaction product was extracted with absolute ether. This gave 0.9 g (89%) of octamethylene bis(lindelofidinium bromide) with mp 159-161°C.

Decamethylene Bis(O-acetyllindelofidinium bromide) (IIb). To a solution of 0.3 g (0.001 mole) of 1,10-dibromodecane in 5 ml of absolute ethanol was added 0.37 g (0.0021 mole) of lindelofidine acetate, and the mixture was boiled for 4 h. After cooling, absolute ether was added. The oil that precipitated was separated off and was purified by reprecipitation with ether from ethanolic solution. This gave 0.65 g (97%) of decamethylene bis(O-acetyllindelofidinium bromide).

Decamethylene Bis(O-benzoylhydroxyheliotridanium bromide) (IVg). A mixture of 0.3 g (0.001 mole) of 1,10-dibromodecane and 0.49 g (0.0021 mole) of hydroxyheliotridane benzoate in 5 ml of absolute ethanol was boiled for 4 h. After the cooling of the reaction mixture, the reaction product was precipitated with ether. This gave 0.74 g (94%) of decamethylene bis(O-benzoyl-hydroxyheliotridanium dibromide) with mp 106-108°C.

The bisquaternary salts (IIa) (n = n = 9, 10), (IIc-d), and IVa-f, h-m) were synthesized similarly.

## SUMMARY

α,ω-Bisquaternary salts of the pyrrolizidine series have been synthesized by the reaction of α,ω-dibromoalkanes with some products of the cleavage of pyrrolizidine alkaloids (lindelofidine, hydroxyheliotridene, and their esters).

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# *Berberis* ALKALOIDS.

## THE NEW ALKALOID OBLONGAMINE

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Continuing a study of the alkaloid composition of some species of *Berberis*, we have investigated young shoots of *B. integerrima*, collected in July, 1974, in Kirghizia in the fruit-bearing phase and of *B. oblonga*, collected in May, 1975, in the Tashkent oblast in the flowering phase.

The total amount of tertiary bases from *B. integerrima* was 0.17%. When they were separated on a column of silica gel, berbamunine (I), identified by comparison with physical constants and spectra with those given in the literature [1], was obtained. In the study of about 50 species of barberry, only one species, *B. amurensis* [2] yielded berbamunine. A second alkaloid isolated from the tertiary bases of *B. integerrima* was hydroxyacanthine (II).

From the combined quaternary bases we isolated, in the form of iodides, 0.35% of magnoflorine and 0.11% of berberine.

The amount of tertiary bases in *B. oblonga* was 0.33%. From them we isolated substances (I) and (II). The combined quaternary bases yielded 0.6% (on the weight of the raw material) of berberine, magnoflorine, and palmatine iodides. The bases were identified by comparison with authentic samples.

A comparison of the alkaloid compositions of the roots [3], leaves [4], and the stems of *B. integerrima* and *B. oblonga* showed that in spite of the absence of substance (I), from the roots, the combined alkaloids of the roots and stems were qualitatively similar while the mixture of bases in the leaves differed greatly.

Continuing the separation of the combined tertiary bases from the roots of *B. oblonga* [3], we isolated a new alkaloid in the form of an iodide with mp 198-200°C, which we have called oblongamine (III). UV spectrum: $\lambda_{max}^{ethanol}$ 284 nm (log ε 3.97). The mass spectrum of (III) had peaks with m/e 622, 607, 577, 564, 550, 501, 411, 396, 395, 381, 220, 206, 198, 175, 174, 58 (100%). The NMR spectrum of oblongamine taken in deuteropyridine showed the signals of $N{-}CH_3$, $\overset{+}{N}{-}(CH_3)_2$, and three $OCH_3$ groups at 3.1, 3.15, 3.31, and 3.61 ppm, respectively; and of 10 aromatic protons in the 6.39-7.0 ppm region. These facts show that (III) belongs to the group of monoquaternary dimeric bisbenzylisoquinoline alkaloids [5]. Judging from the mass spectrum, (III) must be assigned to the hydroxyacanthine type. Since the methiodide of (III) (IV) differed from the dimethiodide of hydroxyacanthine (V) not only by its melting point but also by its $R_f$ value, we performed a Hofmann degradation of (IV) and isolated two des bases: A and B. Correspondingly, (V) yielded A' and B'. Products A and A' proved to be identical (TLC, IR). Thus, the methiodides (IV) and (V) must be diastereomers and the nature of the heterocyclic skeleton and the positions of the hydroxy and methoxy groups and of the oxygen bridges in oblongamine have been shown.

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