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Figure 1: Structural formulas I, IV, and V

Abstract

Full Text

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Synthesis of Methyl Esters of Isomeric Chondropholines, Chondodendrines, and Tubocurarines

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Considering the molecule of *d*-tubocurarine (I) ([1]), one can see that it has two centers of asymmetry, which, according to the classical theory of structure, presupposes the existence of two racemic forms and four optically active isomers.

Taking into account the basic propositions of conformational analysis, for the tertiary base chondodendrine (II a, , , ; $R = H$, $R' = CH_3$) and its quaternary salt, tubocurarine (III a, , , ; $R = H$), only as a result of isomerism at C_1 and C'' can four racemic formulas be accepted.

The formulas given for the basic alkaloids of tube curare do not yet reflect isomerism caused by the cis and trans positions of the substituents at the nitrogen of the tertiary bases, as well as by the conformation of the tetrahydroisoquinoline nuclei.

There are no definite data in the literature concerning the configuration of tetrahydroisoquinolines. However, in accordance with recent work on tetralin and its derivatives, it may be assumed that tetrahydroisoquinoline nuclei in some cases may exist in various forms: chair (IV a, , ,) and boat (V a, , ,), distorted owing to the presence of an aromatic ring in the condensed system of the tetrahydroisoquinoline nucleus. These types of isomerism, apparently, must also occur for curare alkaloids, which correspondingly increases the number of possible isomers.

Moreover, in view of the nonplanar structure of the macrocyclic diether system, which can be arranged ambiguously in space, the number of possible isomers increases still further.

We developed a scheme for the synthesis of chondropholine, chondodendrine, tubocurarine, and their esters, which is distinguished by the fact that the centers of asymmetry appear at the final stages of the synthesis, which are carried out under mild conditions not leading to various kinds of isomerizations, inversions, etc.

Fig. 1. Ultraviolet spectra of dimethyl ethers of tubocurarin iodide. 1—4—numbers of salts (corresponding to the numbers in the text), 5—natural ether

Figure 2: Fig. 1. Ultraviolet spectra of dimethyl ethers of tubocurarin iodide. 1—4—numbers of salts (corresponding to the numbers in the text), 5—natural ether

By selecting appropriate conditions, we were able to carry out reactions with the formation of different isomers and thus to accomplish the synthesis of two isomeric *O*-methylchondropholines (II, a—b, v—g; R = CH_3; R′ = H), two isomeric O,O′-dimethylchondodendrines (II, a—b, v—g; R = R′ = CH_3), and four isomeric O,O′-dimethyltubocurarin iodides (III, a, b, v, g; R = CH_3; X = J).

Fig. 1. Ultraviolet spectra of dimethyl ethers of tubocurarin iodide. 1—4—numbers of the salts (correspond to the numbers in the text), 5—natural ether.

The synthesis was carried out as follows:

The previously obtained 1-(4′-oxybenzyl)-6-methoxy-7-[2'‘-methoxy-5'‘-(6"‘,7"‘-dimethoxy-8'' ‘-bromo-3'' ‘,4'' ‘-dihydroisoquinolyl-1'' ‘-methyl)-phenoxy]-3,4-dihydroisoquinoline (ˆ{1}) (VI) was subjected to Ullmann condensation in the presence of copper, potash, and pyridine, and the product, without isolation, was reduced with zinc in dilute acetic acid; in this way the hydrochlorides of two isomeric forms of *O*-methylchondropholine (II, R = CH_{3}, R' = H) were isolated: A—m.p. 120-125° and B—m.p. 181-185°.

It should be noted that this reaction proceeds in higher yield when substances with unprotected phenolic hydroxyls are used, i.e., in the synthesis of chondropholine and tubocurarin.

The bases II (R = CH_{3}, R' = H), A and B, under the action of methyl iodide, were converted into the hydriodides of the corresponding isomeric O,O-dimethylchondodendrines (II, R = R' = CH_{3}): A—m.p. 159-163° (from ethyl alcohol) and B—m.p. 173-176.5° (from ethyl alcohol).

From the latter, the iodides of four quaternary ammonium bases III (R = CH_{3}, a, b, v, g) were then obtained.

From base II (R = CH_{3}, R' = H), A, the following salts were obtained (see Fig. 1).

1. M.p. 198-201° (from water). λ_{max} (alcohol) 230, 280 mμ ($\lg \varepsilon$ 4.5752; 3.9403); λ_{min} 265 mμ ($\lg \varepsilon$ 3.7795).

$$C_{40}H_{48}O_6N_2J_2 \cdot 3H_2O.$$

Found, %: C 49.6; 49.97; H 5.11; 4.95; N 2.71; 2.72
Calculated, %: C 50.0; H 5.59; N 2.92.

structural scheme

Figure 3: structural scheme

2. M.p. 137-139° (from an ethyl alcohol–ether mixture). λ_{max} (alcohol) 225, 280 mμ ($\lg \varepsilon$ 4.5996; 4.2748); λ_{min} 265 mμ ($\lg \varepsilon$ 4.1763).

$$C_{40}H_{48}O_6N_2J_2 \cdot 3H_2O.$$

Found, %: C 50.22; 50.10; H 5.33; 5.38; N 2.81
Calculated, %: C 50.0; H 5.59; N 2.92.

From base II (R = CH_3, R′ = H), B, the following salts were obtained:

3. M.p. 257.5-259° (from ethyl alcohol). λ_{max} (alcohol) 225, 280 mμ ($\lg \varepsilon$ 4.5090; 4.0426); λ_{min} 260 mμ ($\lg \varepsilon$ 3.8353).

$$C_{40}H_{48}O_6N_2J_2 \cdot 3H_2O.$$

Found, %: C 49.5; 49.85; H 5.41; 5.1; N 3.07; 2.90
Calculated, %: C 50.0; H 5.59; N 2.92.

4. M.p. 195-197° (from an acetone–ether mixture). λ_{max} (alcohol) 225, 280 mμ ($\lg \varepsilon$ 4.4920; 4.1323); λ_{min} 260 mμ ($\lg \varepsilon$ 3.9780).

$$C_{40}H_{48}O_6N_2J_2.$$

Found, %: C 53.16; H 5.2; N 3.00
Calculated, %: C 52.9; H 5.29; N 3.09.

The third sample proved to correspond most closely to the natural dimethyl ether of tubocurarin iodide.

M.p. 262-264° (from ethyl alcohol). λ_{max} (alcohol) 225, 280 mμ ($\lg \varepsilon$ 4.7585; 4.0735); λ_{min} 260 mμ ($\lg \varepsilon$ 3.7308).

Found, %: C 49.9; H 4.58

$$C_{40}H_{48}O_8N_2J_2 \cdot 3H_2O.$$

Calculated, %: C 50.0; H 5.59.

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REFERENCES

1. L. V. Volkova, O. N. Tolkachev, N. A. Preobrazhenskii, *DAN*, **102**, No. 3, 521 (1955).

Note: Figure translations are in progress. See original paper for figures.