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Abstract

Full Text

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SYNTHESIS OF RACEMIC TUBOCURARINE

(Presented by Academician A. N. Nesmeyanov, 30 IV 1958)

The active principle of tube curare consists of alkaloids of the bisbenzyltetrahydroisoquinoline group of asymmetric structure, which differ from one another in the degree of methylation of the nitrogens and phenolic hydroxyls. The secondary and tertiary bases include: *l*-chondrofoline, *d*- and *l*-curines, and several others. The principal representative of the quaternary ammonium salts is *d*-tubocurarine chloride (tubocurarine, curarine) (X), which possesses high physiological activity, causing relaxation of striated musculature.

The chemical structure of tubocurarine has until recently remained unconfirmed synthetically, although intensive work is being carried out in this direction.

The scheme of synthesis of phenolic alkaloids of the chondodendrine series carried out by us is based on the successive construction of a system containing the elements of the natural alkaloid (see the scheme on p. 78).

Condensation of β-(3-methoxy-4-hydroxyphenyl)ethylamine, m.p. 156–157°, with 4-benzyloxyphenylsuccinic acid, m.p. 120–121°, leads to the formation of β-(3-methoxy-4-hydroxyphenyl)ethylamide of 4′-benzyloxyphenylsuccinic acid (I), m.p. 121–122°. Compound (I), by the action of ethyl 3-bromo-4-hydroxyphenylacetate, m.p. 36–36.5°, is converted into β-[3-methoxy-4-(2″-hydroxy-5″-carbethoxymethylenoxy)-phenyl]-ethylamide of 4′-benzyloxyphenylsuccinic acid ((II) $R = C_2H_5$), m.p. 65–67°, which on saponification gives the corresponding acid ((II) $R = H$), m.p. 83.5–85°. The latter, on interaction with β-(3-methoxy-4-hydroxy-5-bromophenyl)ethylamine, m.p. 169–170°, forms β-{3-methoxy-4-[2″-hydroxy-5″-(β′″-(3′″-methoxy-4′″-hydroxy-5′″-bromophenyl)-ethylcarbamidomethyl)-phenoxy]-phenyl}-ethylamide of 4′-benzyloxyphenylsuccinic acid (III), m.p. 119.5–120.5°. The phenolic hydroxyls in diamide (III) are protected by acetylation, and the diacetyl derivative (IV), m.p. 64–68°, is subjected to the Bischler–Napieralski reaction with phosphorus oxychloride in chloroform. The resulting dihydrochloride of 1-(4′-benzyloxybenzyl)-6-methoxy-7-[2″-acetoxy-5″-(6′″-methoxy-7′″-acetoxy-8′″-bromo-3′″,4′″-dihydroisoquinolyl-1′″-methyl)-phenoxy]-3,4-dihydroisoquinoline (V) is saponified with 20% hydrochloric acid to 1-(4′-hydroxybenzyl)-6-methoxy-7-[2″-hydroxy-5″-(6′″-methoxy-7′″-hydroxy-8′″-bromo-3′″,4′″-dihydroisoquinolyl-1′″-methyl)-phenoxy]-3,4-

dihydroisoquinoline (VI), m.p. 174–180°. The final stage is the formation of the macrocyclic system by closure of the second ether bond in the compound of structure (VII), hydrochloride, m.p. 176–180°. On subsequent reduction, three isomeric norchondrofolines (VIII) were isolated:

1. Hydrochloride, m.p. 174–176° (from an alcohol–ether mixture, 1 : 1). Base, m.p. 132–134°.

Found %:	*C* 72.04; *H* 5.9; *N* 4.98; 4.92
$C_{34}H_{34}O_6N_2$. Calculated %:	*C* 72.00; *H* 6.01; *N* 4.94

2. Hydrochloride, m.p. 194–196.5° (from an alcohol–ether mixture, 1 : 1).

$$C_{34}H_{34}O_6H_2 \cdot 2HCl \cdot H_2O.$$

Found, %: C 62.3; H 6.54; N 4.44
Calculated, %: C 62.2; H 5.82; N 4.28

3. Hydrochloride, m.p. 185–187.5° (from an acetone–ether mixture, 1 : 1).

$$C_{34}H_{34}O_6N_2 \cdot 2HCl \cdot \tfrac{1}{2}H_2O.$$

Found, %: C 63.25; H 6.59; N 4.54
Calculated, %: C 63.1; H 5.72; N 4.33

The first two of these were converted by methylation into quaternary bases corresponding in composition to chondodendrine (IX):

1. M.p. 207.5–110.5°.

$$C_{36}H_{38}O_6N_2 \cdot \tfrac{1}{2}H_2O.$$

Found, %: C 71.2; 71.2; H 6.61; 6.70; N 4.69; 4.38
Calculated, %: C 71.6; H 6.5; N 4.65

2. M.p. 128–130.5°.

Each of these bases was converted, by the action of methyl iodide followed by crystallization, into four methiodides, identical with one another in chemical composition (X):

1. M.p. 164–166.5° (from an acetone–ether mixture, 1 : 2)

$C_{38}H_{44}O_6N_2J_2$.	Found %:	N 3.43
	Calculated %:	N 3.19

2. M.p. 189–190.5° (from alcohol).

$C_{38}H_{44}O_6N_2J_2$.	Found %:	C 52.2; 52.15; H 5.05; 5.14; N 3.20; 3.18
	Calculated %:	C 52.00; H 5.05; N 3.19

3. M.p. 210-212° (from alcohol).

$C_{38}H_{44}O_6N_2J_2$.	Found %:	C 52.5; H 5.23; N 3.08; 3.17
	Calculated %:	C 52.00; H 5.05; N 3.19

4. M.p. 257-260.5° (from water).
   λ_{max} (alcohol) 225, 280 mμ ($\lg\varepsilon$ 4.5488; 4.0832); λ_{min} 260 mμ ($\lg\varepsilon$ 4.0425).
   λ_{max} (0.05 N KOH) 225, 295 mμ ($\lg\varepsilon$ 4.763; 4.225); λ_{min} 280 mμ ($\lg\varepsilon$ 4.1715).

$C_{38}H_{44}O_6N_2J_2$.	Found %:	C 52.33; 52.29; H 4.94; 5.20; N 2.97; 3.12
	Calculated %:	C 52.00; H 5.05; N 3.19

The fourth of these salts has a melting point close to that of natural *d*-tubocurarinioiodide (m.p. 263-265°) and gives no depression of the melting point of a sample mixed with it. The ultraviolet spectrum of this compound coincides with the spectrum of *d*-tubocurarinioiodide and shows the same shift of the curve as a function of the pH of the solution.

Thus, the synthetic compound may be regarded as the racemate of the natural alkaloid.

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