

SYNTHETIC INVESTIGATIONS IN THE FIELD OF THE CURARE ALKALOIDS

XIII. Synthesis of Isomeric Tubocurarin Iodides*

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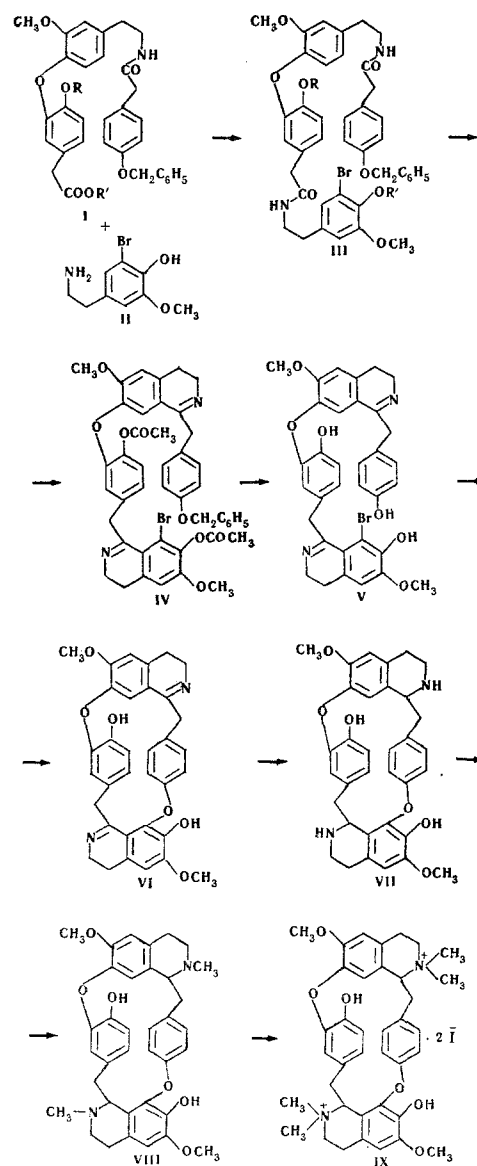
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It has been shown that the compounds obtained previously corresponding in comparison to the β -[4'-(5"-carboxymethyl-2"-hydroxyphenoxy)-3'-methoxyphenyl]ethylamide of 4-benzyloxyphenylacetic acid have practically the same spectra and on further condensation with 3-bromo-4-hydroxy-5-methoxyphenylethylamine give an equilibrium mixture of diamide compounds. The difference in the physicochemical properties of the diphenyl esters and the diamides can be explained by steric differences. On cyclization, the diamides are converted into bis-dihydroisoquinoline compounds of the same elementary composition. The hydrochloride of 7-[2'-acetoxy-5'-(7"-acetoxy-8"-bromo-6"-methoxy-3",4"-dihydroisoquinol-1"-ylmethyl)phenoxy]-1-(4"-benzyloxybenzyl)-6-methoxy-3,4-dihydroisoquinoline, with mp 180-181° C, after saponification, intramolecular Ullman condensation, reduction, and stepwise methylation, was converted into isomeric tubocurarin iodides with mp 189-190.5° C, 164-166.5° C, 257-260.5° C, and 210-212° C, which were separated on the basis of their different solubilities in organic solvents and water.

In the course of the performance of the synthesis of the dimethyl ether of racemic tubocurarin [2, 3], the applicability of this scheme for producing the alkaloid tubocurarin itself was investigated. Production of isomeric compounds of this type is of great interest. It has been reported previously [4] that the macrocyclic system of the alkaloid, which contains two centers of asymmetry, permits the possibility of the existence of a series of isomeric compounds. In view of this, we chose a scheme in which the asymmetric centers are formed in the last stages of the synthesis, after the formation of the macrocyclic system.

We have already reported the preparation of the diphenyl ethers I ($R = R' = H$) [5] which have the same elementary compositions but differ in physicochemical properties. They are usually formed together. Their separation was performed by their chromatography in the form of esters on alumina. Subsequently, the synthesis was carried out with each compound I ($R = R' = H$, mp 83.5-85° C and mp 136-138° C) separately. On condensation with β -(3-bromo-4-hydroxy-3-methoxyphenyl)ethylamine (II) [6], both substances formed a mixture of compounds corresponding in composition to the β -{4'-(5"-[β -(3"-bromo-4"-hydroxy-3"-methoxyphenyl)ethylcarbamidomethyl]-2"-hydroxyphenoxy)-3'-methoxyphenyl]ethylamide of 4-benzyloxyphenylacetic acid (III, $R = R' = H$, mp 119.5-120.5° C and mp 184-188° C), which were also separated by chromatography. This shows the mutual conversion of the two diphenyl esters I ($R = R' = H$) under the conditions of the condensation. Since they have practically

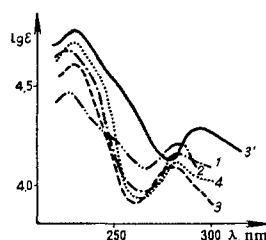
the same IR spectra, their difference may be due to steric factors. For the subsequent operations, the hydroxyl groups were protected.



The corresponding dimethyl derivatives III ($R = R' = CH_3$) were obtained by methylation with diazomethane or methyl iodide, and the diacetyl derivatives III ($R = R' = COCH_3$) by acetylation with acetic anhydride in pyridine. The latter were subjected to cyclization in the presence of phosphorus oxychloride in chloroform, two compounds again being isolated which corre-

*For part XII, see [1].

sponded in composition to the dehydrochloride of 7-[2"-acetoxy-5"-(7"-acetoxy-8"-bromo-6"-methoxy-3", 4"-dihydroisoquinol-1"-ylmethyl)phenoxy]-1-(4'-benzyloxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (IV, mp 180–181° C and a compound which did



UV spectra of the quaternary ammonium salts IX: 1) mp 189–190.5° C; 2) mp 164–166.5° C; 3) mp 257–260.5° C; 3') mp 257–260.5° C in 0.05 N KOH; 210–212° C.

not melt below 360° C). The saponification of a sample of IV (mp 180–181° C) gave 7[2"-hydroxy-5"-(8"-bromo-7"-hydroxy-6"-methoxy-3", 4"-dihydroisoquinol-1"-ylmethyl)phenoxy]-1-(4'-hydroxybenzyl)-3,4-dihydroisoquinoline (V). The latter was subjected to cyclization by being heated with copper, potassium carbonate, and pyridine, to give N,N"-bisdemethyl-1,2,1", 2"-tetrahydrochondodendrin (VI), formed together with a certain amount of a copper complex difficult to separate which, however, was decomposed on reduction with zinc in acetic acid. The reduction by this method of the dehydrogenated macrocyclic system VI gave two fractions of N,N"-bisdemethylchondodendrin (VII). By further methylation with methyl iodide they were converted into the corresponding N-methyl derivatives VIII. On repeated treatment with methyl iodide and subsequent fractional crystallization, four racemic methiodides IX with compositions identical with that of tubocurarin iodide were obtained. One of these salts had a melting point close to that of natural d-tubocurarin and gave no depression of the melting point in admixture with it. The UV spectrum of this compound coincided with that of d-tubocurarin and showed the same displacement of the curve in an alkaline medium.

EXPERIMENTAL

The purity of the intermediate basic compounds was checked by paper chromatography in the butanol–water–acetic acid (87:27:10) system).

The β-[4'-(5"-carboxymethyl-2"-hydroxyphenoxy)-3'-methoxyphenyl]ethylamide of 4-benzyloxyphenylacetic acid (I, R = R' = H). A) This was obtained by a method described previously [5]. For separation, 4.5 g of the crude diphenyl ether I (R = H, R' = C₂H₅) was passed through a column (22 × 170 mm) of alumina containing 10% of water. Chloroform (120 ml) and acetone (150 ml) fractions were collected and from these, after the elimination of the solvent and saponification of the residue, the corresponding acids I (R = R' = H) were obtained: 1) mp 83.5–85° C, 2.26 g; 2) mp 136–138° C, 1.01 g.

B) A solution of 1.0 g of the β-(4'-hydroxy-3'-methoxyphenyl)ethylamide of 4-benzyloxyphenylacetic acid in a solution of potassium methoxide (from 0.1 g of potassium and 8.3 ml of methanol) was evaporated and then 1.0 g of copper powder and 0.7 g of methyl 4-acetoxy-3-

bromo-phenylacetate [bp 149–152° C (1.5 mm); found, %: C 46.2; H 3.95. Calculated for C₁₁H₁₁BrO₄, %: C 46.01; H 3.86; obtained by the acetylation of methyl 3-bromo-4-hydroxyphenylacetate with a yield of 61.4%] were added and the mixture was heated in an atmosphere of nitrogen with stirring at 190–200° C for 1 hr. The cooled reaction mixture was dissolved in chloroform (30 ml), and the copper and potassium bromide were eliminated. After passage through a column of alumina, compound I (R = COCH₃, R' = CH₃) was obtained in the form of an amorphous substance. Yield 0.9 g (59.1%). Mp 110° C (deformation at 90–92° C). Found, %: N 3.49. Calculated for C₃₅H₃₅NO₈, %: N 2.34.

The acid I (R = R' = H) was obtained by saponification with 1.5% of caustic soda. Mp 82–85.5° C. Found, %: C 71.01; H 5.62; N 2.55. Calculated for C₃₂H₃₁NO₇, %: C 70.96; H 5.57; N 2.59.

A mixture with a sample from the first experiment (mp 83.3–85° C) had mp 83–85° C.

The β-[4'-(5"-β-(3"-bromo-4"-hydroxy-3"-methoxyphenyl)ethylcarbamidomethyl)-2"-phenoxy]-3'-methoxyphenyl]ethylamide of 4-benzyloxyphenylacetic acid (III, R = R' = H). A) A mixture of 1.63 g of the amide I (R = R' = H, mp 83.5–85° C) and 0.70 g of β-(3-bromo-4-hydroxy-3-methoxyphenyl)ethylamine (II) was heated at 185–190° C in an atmosphere of nitrogen. The cooled reaction mixture was dissolved in 100 ml of 2.5% caustic soda and precipitated with 12 ml of dil (1:1) HCl; the gel that had deposited was coagulated by heating to 60° C, filtered off, washed with water (300 ml), and dried. For purification, the substance obtained (1.85 g) was chromatographed on alumina of activity grade V (45 g). An acetone eluate yielded 0.59 g (27.4%) of the amorphous diamide. Mp 119.5–120.5° C (deformation at 110° C). Found, %: C 62.81, 62.82; H 5.44, 5.58; Br 9.98, 9.71; N 3.53, 3.76. Calculated for C₄₁H₄₁BrN₂O₈·H₂O, %: C 62.51; H 5.59; Br 10.16; N 3.56.

A high-melting form was isolated from the fraction eluted by a solution of acetic acid in methanol (1:3, 300 ml). For purification, the substance was dissolved in anhydrous acetone, the solution was filtered, the solvent was driven off, and the residue was recrystallized from isopropanol. Yield 0.58 g (27.0%). Mp 184–188° C (deformation at 160° C). Found, %: C 64.21; H 5.53; N 3.41. Calculated for C₄₁H₄₁BrN₂O₈, %: C 63.98; H 5.37; N 3.64.

B) Similarly, the high-melting diphenyl ether I (R = R' = H, mp 136–138° C) gave two diamide fractions: 1) mp 120–121° C (deformation at 110° C), 5.53%; and 2) mp 183–188° C (deformation at 160° C from isopropanol), 53.0%. Found, %: C 63.81; H 5.13; Br 10.52; N 3.28. Calculated for C₄₁H₄₁BrN₂O₈, %: C 63.98; H 5.37; Br 10.36; N 3.64.

β-[4'-(2"-acetoxy-5"-(β-(4"-acetoxy-5"-bromo-3"-methoxyphenyl)ethylcarbamidomethyl)phenoxy)-3'-methoxyphenyl]ethylamide of 4-benzyloxyphenylacetic acid (III, R = R' = COCH₃). A) A solution of 0.26 g of the ethylamide III (R = R' = H, mp 119.5–120.5° C) in 2.9 ml of pyridine and 0.17 ml of acetic anhydride was heated at the boil for 2 hr. The solvent was driven off in vacuum and the residue was triturated with dry ether (5 × 10 ml) and dried. Amorphous substance. Yield 0.14 g (50.2%). Mp 120° C (deformation at 90° C). Found, %: C 63.39; H 5.25; N 2.83, 3.21. Calculated for C₄₅H₄₅BrN₂O₁₀, %: C 63.30; H 5.31; N 3.28.

B) Similarly, the high-melting sample of the diamide III (R = R' = H, mp 184–188° C) gave a diacetyl derivative with mp 140–155° C (deformation at 130° C). Yield 78.7%. Found, %: C 63.20; H 4.97; Br 9.29, 9.14; N 3.10, 3.48. Calculated for C₄₅H₄₅BrN₂O₁₀, %: C 63.30; H 5.31; Br 9.36; N 3.28.

β-[4'-(5"-β-(5"-bromo-3", 4"-dimethoxyphenyl)ethylcarbamidomethyl)-2"-methoxyphenoxy]-3'-methoxyphenyl]ethylamide of 4-benzyloxyphenylacetic acid (III, R = R' = CH₃). A) A mixture of 0.12 g of the diamide III (R = R' = H, mp 119.5–120.5° C), 10 ml of methanol, 0.05 g of caustic soda, and 0.15 ml of methyl iodide was boiled for 3 hr. The reaction mixture was concentrated in vacuum, the residue was dissolved in chloroform (30 ml), and the extract was washed with water (5 ml), dried with sodium sulfate, and passed through a column of alumina of activity grade IV. The residue after the elimination of the solvent in vacuum was triturated with ether (10 ml) and dried. Amorphous substance. Yield 0.03 g (24.1%). Mp 99–103° C (deformation at 85° C). Found, %: N 3.21. Calculated for C₄₃H₄₃BrN₂O₈, %: N 3.51.

B) A solution of 0.13 g of the diamide **III** ($R = R' = H$, mp 184–188° C) in 10 ml of methanol was treated with 4 ml of ether containing diazomethane (from 0.35 g of nitrosomethylurea) and the mixture was left overnight at 20° C. The solvent was distilled off in vacuum and the residue was triturated with ether (3 × 2 ml). Yield 0.11 g (81.6%). Amorphous substance. Mp 130–150° C (sintering). Found, %: C 64.49, 64.52; H 5.22, 5.22. Calculated for $C_{43}H_{45}BrN_2O_8$, %: C 64.74; H 5.69.

7-[2''-Acetoxy-5''-(7'''-acetoxy-8'''-bromo-6'''-methoxy-3''', 4'''-dihydroisoquinol-1'''-ylmethyl)phenoxy]-1-(4'-benzyloxybenzyl)-6-methoxy-3, 4-dihydroisoquinoline (IV). A) A solution of 60.0 g of the diacetyl derivative **III** ($R = R' = COCH_3$, mp 120° C) in 200 ml of chloroform and 200 ml of phosphorus oxychloride was boiled in an atmosphere of nitrogen for 3 hr. The reaction mixture was poured into 800 ml of dry ether and the precipitate that deposited was washed with dry ether (5 × 200 ml) and dried in vacuum. Crystallization from anhydrous ethanol gave the diphosphate. Yield 4.5 g (15.9%). Mp 178–182° C. Found, %: C 53.49, 53.48; H 5.07, 4.95; Br 7.10; N 2.72, 2.62. Calculated for $C_{45}H_{41}BrN_2O_8 \cdot 2H_3PO_4$, %: C 53.37; H 4.67; Br 7.89; N 2.77. The ethanolic mother liquor was concentrated in vacuum to dryness and the residue was recrystallized from 200 ml of water. The dihydrochloride formed a colorless crystalline substance. Yield 7.16 g (11.4%). Mp 180–181° C. Found, %: N 2.84, 3.09. Calculated for $C_{45}H_{41}BrN_2O_8 \cdot 2HCl$, %: N 3.14. $C_{45}H_{41}BrN_2O_8 \cdot 2H_3PO_4$, %: N 3.14.

B) By a similar reaction, the high-boiling sample of **III** ($R = R' = COCH_3$, mp 140–155° C) gave a crystalline dihydrochloride which did not melt below 360° C (in vacuum, from a mixture of ethanol and chloroform, 3:1). Yield 95.8%. Found, %: C 60.70; H 4.81; N 2.80. Calculated for $C_{45}H_{41}BrN_2O_8 \cdot 2HCl$, %: C 60.70; H 4.86; N 3.15.

7-[5''-(8'''-Bromo-7'''-hydroxy-6'''-methoxy-3''', 4'''-dihydroisoquinol-1'''-ylmethyl)phenoxy]-1-(4'-hydroxybenzyl)-6-methoxy-3, 4-dihydroisoquinoline (V). A mixture of 6.7 g of the hydrochloride of the base **IV** (mp 180–181° C) and 100 ml of 20% hydrochloric acid was boiled for 2 hr. The benzyl chloride formed was extracted with ether (2 × 50 ml). The acid solution was diluted with water (100 ml) and neutralized with saturated ammonia solution. The liberated base was separated off, washed with water (70 ml), and dried. In the moist state and in solutions the substance rapidly oxidized in the air, which was confirmed by the appearance of additional spots on chromatograms. Yield 4.41 g (91.3%). Mp 174–180° C. Rf 0.72. Found, %: C 63.89; H 5.43; N 4.21, 4.26. Calculated for $C_{34}H_{31}BrN_2O_6$, %: C 63.45; H 4.85; N 4.36. **Dimethiodide.** Mp 229–230° C (decomp., from acetone). Rf 0.73. Found, %: C 46.57, 46.63; H 4.25, 4.26; N 2.88, 2.78. Calculated for $C_{36}H_{37}BrI_2N_2O_6$, %: C 46.60; H 4.02; N 3.02.

N,N''-Bisdemethyl-1, 2, 1''2-tetradehydrochondodendrin (VI). A mixture of 1.0 g of compound **V**, 0.95 g of copper powder, 0.95 g of potassium carbonate, and 3 ml of dry pyridine was heated at 160–165° C for 30 min and at 180–185° C for another 30 min in an atmosphere of nitrogen. After the elimination of the pyridine in vacuum, the residue was extracted with water (30 ml) and the insoluble part was treated with 10 ml of acetic acid and filtered from the copper. The acetic acid was distilled off in vacuum and the residue was suspended in water (10 ml) and treated with saturated aqueous ammonia (10 ml). The yellow solid liberated was separated off, washed with water and dried in a vacuum desiccator (weight 0.5 g, carbonizing at 215–220° C). The substance was treated with 40 ml of anhydrous acetone, the insoluble copper complex was separated off, and the hydrochloride was precipitated by the addition of an ethereal solution of hydrogen chloride. Mp 176–180° C. Rf 0.87. Found, %: C 63.89; H 5.43; N 4.15. Calculated for $C_{34}H_{30}N_2O_6 \cdot 2HCl$, %: C 64.16; H 5.23; N 4.41.

N,N''-Bisdemethylchondodendrin, bisnorchondodendrin (VII). A mixture of 1.5 g of compound **V**, 0.8 g of potassium carbonate, 1.5 g of copper catalyst, and 5 ml of pyridine was heated in an atmosphere of nitrogen at 155–160° C for 30 min and at 180–185° C for 30 min. The pyridine was distilled off in vacuum and the residue was treated with water (3 × 15 ml) and filtered. The insoluble part was treated with 10 ml of glacial acetic acid, the copper was separated off, and the filtrate was diluted with 10 ml of water and boiled with 3 g of zinc dust for 3 hr. The zinc was filtered off, 30 ml of water was added, the

precipitate that deposited was separated off, the acid mother liquor was neutralized with saturated aqueous ammonia and the base was extracted successively with ether (4 × 150 ml) and chloroform (4 × 100 ml). After being washed with a small amount of water (5–10 ml), the extracts were concentrated in vacuum and the residues were dried.

The ethereal residue was again dissolved in dry ether (10 ml) and the hydrochloride of **A** was precipitated by the addition of hydrogen chloride in ether. Yield 0.25 g (16.8%). Mp 194–196.5° C (from a mixture of ethanol and ether, 1:1). Rf 0.80. Found, %: C 62.30; H 6.54; N 4.44. Calculated for $C_{34}H_{34}N_2O_6 \cdot 2HCl \cdot H_2O$, %: C 62.20; H 5.80; N 4.28.

The substance insoluble in dry ether was treated with 3 ml of acetone and the hydrochloride was precipitated similarly. Yield 0.05 g (3.36%). Mp 185–187.5° C (from a mixture of acetone and ether (1:1). Found, %: C 63.25; H 6.59; N 4.54. Calculated for $C_{34}H_{34}N_2O_6 \cdot 2HCl \cdot 0.5H_2O$, %: C 63.10; H 5.72; N 4.33.

The chloroform residue yielded the hydrochloride of **B** with mp 174–176° C (from a mixture of ethanol and ether, 1:1). Rf 0.55.

The base was isolated by the neutralization of an aqueous solution of the hydrochloride with dilute (1:1) ammonia. Yield 0.4 g (30.2%). Mp 132–134° C. Found, %: C 72.04; H 5.90; N 4.98, 4.92. Calculated for $C_{34}H_{34}N_2O_6$, %: C 72.00; H 6.01; N 4.94.

Chondodendrin (VIII). A mixture of 0.12 g of the base **A**, 5 ml of anhydrous methanol, and 1.5 ml of methyl iodide was heated at the boil for 3 hr. The ethanol and the excess of methyl iodide were driven off in vacuum and the residue was triturated with dry ether (5 × 5 ml). The hydriodide of chondodendrin (Rf 0.79) was dissolved in 30 ml of water (60° C) and neutralized with aqueous ammonia and the tertiary base (**A**) was extracted with ether. Yield 0.09 g (71.3%). Mp 128–130.5° C.

The tertiary base **B** was obtained in a similar manner from the secondary base **B**. Yield 57.3%. Mp 107.5–110.5° C. Rf 0.73. Found, %: C 71.20, 71.20; H 6.61, 6.70; N 4.69, 4.38. Calculated for $C_{36}H_{38}N_2O_6 \cdot 0.5H_2O$, %: C 71.60; H 6.50; N 4.65. **Hydriodide:** mp 181–185° C; Rf 0.80.

Chondodendrin dimethiodide, racemic tubocurarin iodide (IX).

A) A mixture of 0.08 g of the tertiary base **A** (**VIII**), 3 ml of anhydrous methanol, and 0.75 ml of methyl iodide was boiled for 2 hr. The residue after the elimination of the methanol and the excess of methyl iodide was triturated with dry ether (6 × 10 ml). After recrystallization from ethanol, a yellow crystalline substance was obtained. Yield 0.045 g (38.1%). Mp 189–190.5° C. Found, %: C 52.20, 52.15; H 5.05, 5.14; N 3.20, 3.18. Calculated for $C_{38}H_{44}I_2N_2O_6$, %: C 52.00; H 5.05; N 3.19. The residue insoluble in ethanol was reprecipitated from 1 ml of dry acetone with 2 ml of ether. Yield 0.02 g (16.9%). Mp 164–166.5° C). Found, %: N 3.43. Calculated for $C_{38}H_{44}I_2N_2O_6$, %: N 3.19.

B) Similarly, the tertiary base **B** (**VIII**) yielded two salts: 1) yield 45.2%. Mp 257–260.5° C (from water). Spectrum in ethanol λ_{max} , nm (lg ϵ) 225, 280 (4.5488, 4.0832), λ_{min} , nm (lg ϵ) 260 (4.0425). Spectrum in 0.05 N KOH λ_{max} , nm (lg ϵ) 225, 295 (4.763, 4.225), λ_{min} , nm (lg ϵ) 280 (4.1715). Found, %: C 52.33, 52.29; H 4.94, 5.20; N 2.97, 3.12. Calculated for $C_{38}H_{44}I_2N_2O_6$, %: C 52.00; H 5.05; N 3.19. 2) A second salt was obtained from the aqueous mother liquors. Yield 16.4%. Mp 210–212° C (from ethanol). Found, %: C 52.50, 51.80; H 5.23, 4.93; N 3.08, 3.17. Calculated for $C_{38}H_{44}I_2N_2O_6$, %: C 52.00; H 5.05; N 3.19.

The salt with mp 257–260.5° C had a UV spectrum coinciding with that of the natural alkaloid (see figure) and showed the same displacement of the curve in 0.05 N caustic solution. A mixture with natural tubocurarin iodide (mp 263–265° C) had mp 257–262° C.

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