SYNTHETIC STUDIES IN THE FIELD OF THE CURARE ALKALOIDS

XIV. Synthesis of 1-(4'-Benzyloxybenzyl)-6-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 5, pp. 831–837, 1969

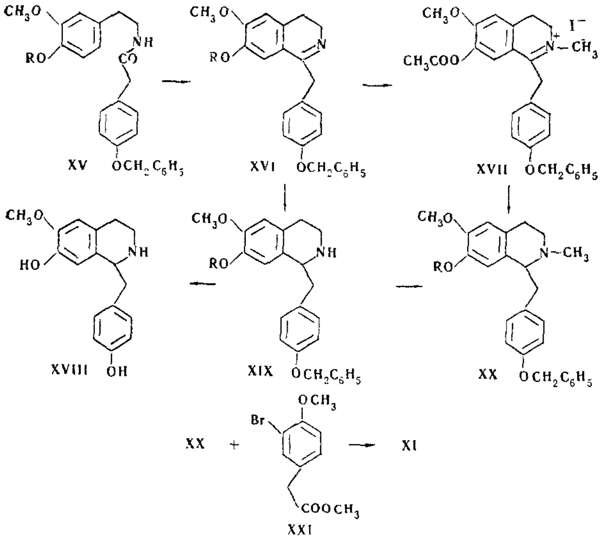
UDC 547.833.3.9.07: 542.943

By oxidation and the identification of the oxidation products, it has been shown that the β-[4-(2"-alkoxy-5"-alkoxycarbonylmethylphenoxy)-3-methoxyphenyl]ethylamides of 4'-benzyloxyphenylacetic acid obtained previously and differing in their physicochemical properties are based on the same skeleton and differ only in their spatial configuration, since on Bischler-Napieralski cyclization they give isomeric dihydroisoquinoline compounds. The structure of the latter was established by oxidation to the isomeric acids 2, 2'-dimethoxy-3, 4, 5'-tricarboxy(diphenyl ether) and 2, 2'-dimethoxy-4, 5, 5'-tricarboxy-(diphenyl ether); the latter is identical with the compound obtained by the degradation of the methyl ester of natural tubocurarine. 1-(4'-Benzyloxybenzyl)-6-methoxy-7-(2'-methoxy-5"-methoxycarbonylmethylphenoxy)-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline and a compound isomeric with it have also been synthesized, and the former has been shown to be identical with a substance obtained by independent synthesis from the 4'-benzyl ether of N-methylcoclaurine. During the synthesis of the latter it was shown that cyclization takes place unambiguously without the formation of isomeric compounds.

As reported previously [1], the diphenyl ethers I (R = H, CH_3; R' = H, CH_3, C_2H_5) were isolated in two forms identical in composition but differing in physicochemical properties. Separation was carried out by chromatography on alumina or silica or on the basis of the different rates of saponification of their esters. It was shown that the alkylation of the phenolic hydroxyl in the initial bromoether shifts the equilibrium in the direction of the formation of the low-melting form of the diphenyl ether. In order to study their structure, the diphenyl ethers I (R = CH_3; R' = H; mp 66–68° C and 107–108° C) were oxidized with potassium permanganate, and they both gave a compound which was identified as 4, 5'-dicarboxy-2, 2'-dimethoxy(diphenyl ether) (II), obtained by independent synthesis from methyl vanillate (III) and methyl 3-bromoanisate (IV). Since the two diphenyl ethers I (R = R' = H) have practically the same IR spectra and under the conditions of amide condensation give an equilibrium mixture of identical compounds, their difference is explained by steric factors [2].

On reaction with phosphorus oxychloride, compound I (R = R' = CH_3) gave, correspondingly, two cyclization products (mp 59–66° C and 121–126° C) which were also oxidized in order to confirm their structure. The sample with mp 59–66° C gave the previously-described [3] 4,5,5'-tricarboxy-2,2'-dimethoxy(diphenyl ether) (VI). The sample with mp 121–126° C gave a tricarboxylic acid with the same elementary composition but showing a depression of the melting point with the first acid; this was 3, 4, 5'-tricarboxy-2, 2'-dimethoxy(diphenyl ether) VIII. Thus, the substance with mp 59–66° C is 1-(4'-benzyloxybenzyl)-6-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-3, 4-dihydroisoquinoline (V), and the substance with mp 121–126° C is 1-(4'-benzyloxybenzyl)-8-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-3, 4-dihydroisoquinoline (VII). Their methiodides IX and X were reduced with zinc in acetic acid to, respectively, 1-(4'-benzyloxybenzyl)-6-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (XI) and compound XII isomeric with it. The latter were also obtained from the dihydroisoquinoline compounds V and VII by reduction with zinc in an acid medium and subsequent methylation of the tetrahydroisoquinoline derivatives XIII and XIV with methyl iodide.

Compound XI was also identical with a sample obtained by independent synthesis. For this purpose, the β-(4-hydroxy-3-methoxyphenyl)ethylamide of 4'-benzyloxyphenylacetic acid (XV, R = H) [1, 4] was acetylated with acetic anhydride in the presence of pyridine to give the β-(4-acetoxy-3-methoxyphenyl)ethylamide of 4'-benzyloxyphenylacetic acid (XV, R = $COCH_3$). The latter was cyclized in the presence of phosphorus oxychloride to form 7-acetoxy-1-(4'-benzyloxybenzyl)-6-methoxy-3, 4-dihydroisoquinoline (XVI, R = $COCH_3$). After its reduction with zinc in acetic acid and subsequent alkaline saponification of the 7-acetoxy-1-(4'-benzyloxybenzyl)-6-methoxy-1, 2, 3, 4-tetrahydroquinoline (XIX, R = $COCH_3$), the 4'-benzyl ether of coclaurine (XIX, R = H) was isolated. A compound identical with this was also obtained from XVI (R = $COCH_3$)



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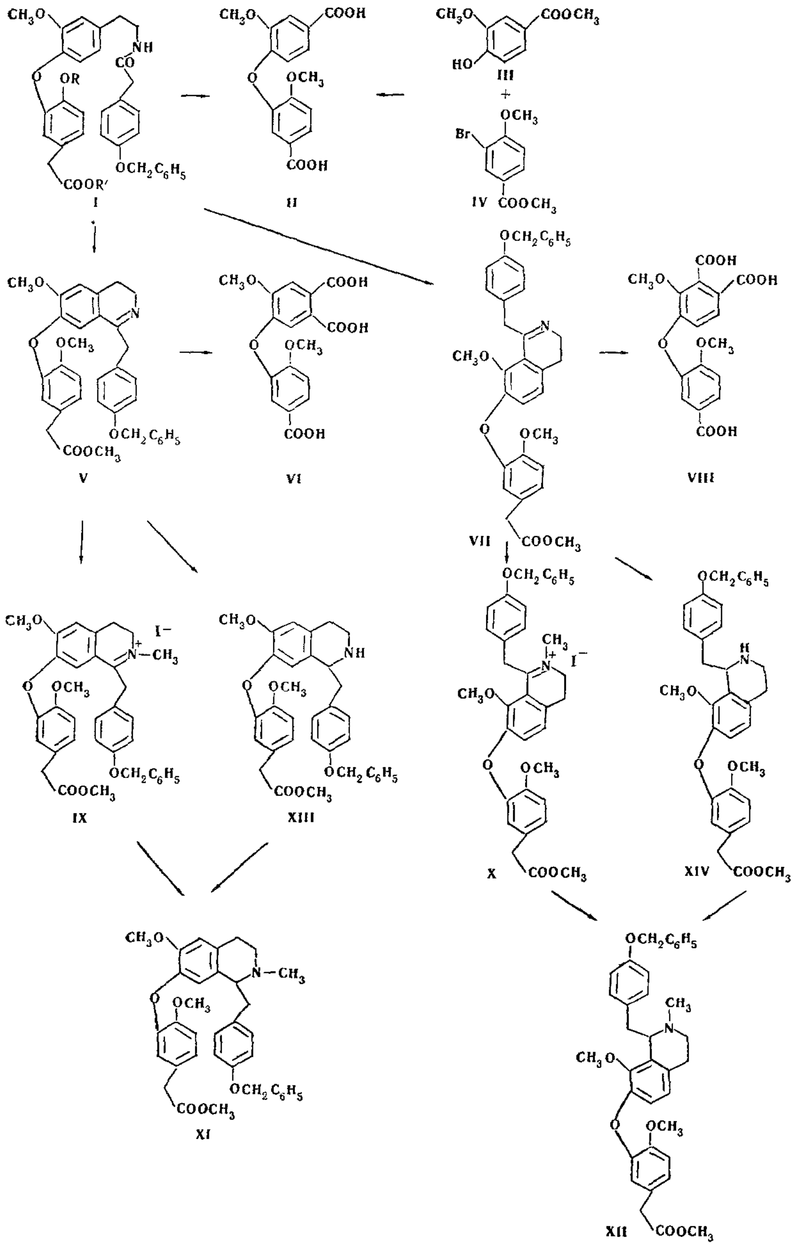
*For part XIII, see [2].


CH3O
NH
CO
OR
OCH2C6H5
COOR′
I
COOH
OCH3
II
COOCH3
HO
III
+
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IV
V
VI
VII
VIII
I−
N−CH3
IX
XIII
X
XIV
XI
XII

by gentle saponification to the corresponding 7-hydroxy derivative XVI (R = H) and subsequent reduction of the double bond. The saponification of the secondary base XIX (R = H) to form coclaurine (XVIII) shows the expected direction of cyclization. The tertiary base XX (R = $COCH_3$) was obtained by the methylation of 7-acetoxy-1-(4'-benzyloxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (XIX, R = $COCH_3$) and also by the reduction of the methiodide of 7-acetoxy-1-(4'-benzyloxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (XVII). 1-(4'-Benzyloxybenzyl)-7-hydroxy-6-methoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (XX, R = H) was obtained from its acetyl derivative XX (R = $COCH_3$) by saponification in an alkaline medium. Then compound XX (R = H) was converted by condensation with methyl 3-bromo-4-methoxyphenylacetate (XXI) into 1-(4'-benzyloxybenzyl)-6-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-N-methyl-1,2,3,4-tetrahydroisoquinoline (XI).

EXPERIMENTAL

The β-[3-methoxy-4-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)phenyl]ethylamide of 4'-benzyloxyphenylacetic acid (I, R = = CH_3, R' = H). This was obtained by a method described previously [1]. From 5.0 g (0.0125 mole) of the β-(4-hydroxy-3-methoxyphenyl)-ethylamide of 4'-benzyloxyphenylacetic acid (XV, R = H) was isolated 4.7 g of a mixture of the ethyl esters I (R = CH_3, R' = C_2H_5), which was chromatographed on alumina of activity grade IV–V in a column 22 × 220 mm. Benzene (420 ml) and acetone (100 ml) fractions were collected and from these saponification yielded, respectively, two substances with mp 66–68° C and 107–108° C.

4,5'-Dicarboxy-2,2'-dimethoxy(diphenyl ether) (II). A) To a solution of 1.5 g (0.0025 mole) of the diphenyl ether I (R = CH_3, R' = = H, mp 66–68° C) in 100 ml of pyridine was added 8.5 g (0.0538 mole) of finely-ground potassium permanganate. The mixture was stirred at 18–20° C for 15 hr and at 98–100° C for 1 hr. The solvent was distilled off in vacuum, and the residue was treated with 100 ml of saturated aqueous sodium bisulfite solution and was separated from the manganese dioxide that had deposited. The filtrate was acidified with 25 ml of HCl (d 1.19). The precipitate that deposited was separated off and dried. Colorless crystalline substance. Yield 0.13 g (15.2%). Mp 267–268° C (from 50% ethanol). Found, %: C 60.22; H 4.60. Calculated for $C_{16}H_{14}O_7$, %: C 60.38; H 4.43.

B) The analogous oxidation of 1.2 g (0.0022 mole) of the diphenyl ether I (R = CH_3, R' = H, mp 107–108° C) gave a dicarboxylic acid. Yield 0.17 g (24.7%). Mp 266–267° C (from 50% ethanol). A mixture with the sample from the preceding experiment had mp 266–267° C. Found, %: C 60.32; H 4.13. Calculated for $C_{16}H_{14}O_7$, %: C 60.38; H 4.43.

C) To a solution of 0.70 g (0.108 g-at) of potassium in 20 ml of anhydrous methanol was added 5.0 g (0.027 mole) of methyl vanillate. When dissolution was complete, the alcohol was distilled off in vacuum and the residue was treated with 5.0 g of copper powder and 4.5 g (0.018 mole) of methyl 3-bromo-4-methoxybenzoate. The mixture was heated in an atmosphere of nitrogen at 195–200° C for 1 hr with stirring. The cooled reaction mixture was extracted with ether (200 ml), and the extract was washed with 3% caustic soda solution (50 ml) and dried with sodium sulfate, and the solvent was evaporated in vacuum. The resulting oily substance (3.6 g, 51%) was mixed with 2 ml of 30% caustic soda solution and 2 ml of methanol and was boiled for 1.5 hr. The solvent was driven off in vacuum, and the residue was diluted with 20 ml of water and extracted with ether (50 ml). Acidification with dil HCl (1 : 1) to pH 2 (6 ml) yielded a precipitate which was separated off, washed with water (20 ml) and dried. After two crystallizations from 50% ethanol, yield 0.9 g (78.4%). Mp 266–268° C. A mixture with a sample from the preceding experiment had mp 266–267° C. Found, %: C 60.54, 60.23; H 4.44, 4.53. Calculated for $C_{16}H_{14}O_7$, %: C 60.38; H 4.43.

β-(4-Acetoxy-3-methoxyphenyl)ethylamide of 4'-benzyloxyphenylacetic acid (XV, R = $COCH_3$). A mixture of 20.0 g (0.052 mole) of the β-(4-hydroxy-3-methoxyphenyl)ethylamide of 4'-benzyloxyphenylacetic acid (mp 123–124° C [1]), 25.0 ml of pyridine, and 12.0 ml (0.127 mole) of acetic anhydride was heated at 98–100° C for 2 hr. The pyridine and the excess of acetic anhydride were distilled off in vacuum. The residue was treated with ether (4 × 40 ml), and the substance that separated out was filtered off and recrystallized from 60 ml of isopropanol. Yield 16.08 g (75.8%). Mp 76.8–97.2° C (from ethanol or carbon tetrachloride). Found, %: C 72.31; H 5.89; N 3.55, 3.49. Calculated for $C_{26}H_{27}NO_5$, %: C 72.05; H 6.25; N 3.25.

7-Acetoxy-1-(4'-benzyloxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (XVI, R = $COCH_3$). A solution of 7.82 g (0.018 mole) of XV (R = $COCH_3$) in 30 ml of dry chloroform was heated to the boil with 18 ml (0.209 mole) of phosphorus oxychloride for 2 hr. The solvent and the excess of phosphorus oxychloride were distilled off in vacuum and the residue was triturated successively with ether (3 × 25 ml) and water (30 ml), which converted it into the pulverulent state, and it was then recrystallized from 85 ml of a mixture of ethanol and water (2 : 5). Colorless crystalline substance. Yield 7.68 g (94.2%). Mp 167.8–168.0° C (decomp.). Found, %: C 69.10; H 5.75; N 3.10. Calculated for $C_{26}H_{25}NO_4 \cdot HCl$, %: C 69.09; H 5.75; N 3.37. **Picrate.** Mp 175.6–176.1° C (from acetic acid or from a mixture of ethanol, methanol, and acetone, 1 : 1 : 1). Found, %: C 59.84; H 4.35; N 8.83. Calculated for $C_{26}H_{25}NO_4 \cdot C_6H_3N_3O_7$, %: C 59.62; H 4.38; N 8.69. **Base.** Mp 125.2–126.0° C (from ethanol). Found, %: N 3.15. Calculated for $C_{26}H_{25}NO_4$, %: N 3.37. **Oxalate.** Mp 179.0–179.4° C (decomp., from ethanol). Found, %: C 66.60; H 5.47; N 2.90. Calculated for $C_{26}H_{25}NO_4 \cdot C_2H_2O_4$, %: C 66.52; H 5.38; N 2.77.

1-(4'-Benzyloxybenzyl)-7-hydroxy-6-methoxy-3,4-dihydroisoquinoline (XVI, R = H). This was obtained by the saponification of compound XVI (R = $COCH_3$) with an aqueous ethanolic solution of hydrochloric acid (24 hr at 18–20° C). **Hydrochloride.** Mp 106–107° C (decomp., from ethanol). Found, %: C 70.22; H 5.86; N 3.42; Cl 8.60, 8.71. Calculated for $C_{24}H_{23}NO_3 \cdot HCl$, %: C 70.32; H 5.90; N 3.42; Cl 8.65.

Methiodide of 7-acetoxy-1-(4'-benzyloxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (XVII). A suspension of 12.66 g (0.031 mole) of the base XVI (R = $COCH_3$) in 50 ml of methanol and 5 ml (0.080 mole) of methyl iodide was heated at the boil for 2 hr. The reaction mixture was cooled to 20° C and the methiodide that had precipitated was separated off. Yellow crystalline substance. Yield 13.60 g (78.8%). Mp 185.2–186.0° C (from acetic acid). Found, %: C 58.27; H 5.23; N 2.41. Calculated for $C_{27}H_{28}INO_4$, %: C 58.17; H 5.06; N 2.51. On crystallization from ethanol or acetone, the methiodide was converted into a sparingly soluble form. Mp 196–197° C. Found, %: C 57.92; H 5.27; N 2.42. Calculated for $C_{27}H_{28}INO_4$, %: C 58.17; H 5.06; N 2.51.

7-Acetoxy-1-(4'-benzyloxybenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (XIX, R = $COCH_3$). A) A solution of 10.0 g (0.022 mole) of the hydrochloride of the base XVI (R = $COCH_3$) in 30 ml of acetic acid and 30 ml of water was heated with 4.9 g (0.075 g-at) of zinc dust at 92–95° C with stirring for 2 hr. The zinc was separated off, the filtrate was cooled to 20° C, and the base was precipitated by the action of 43 ml of saturated aqueous ammonia. It was filtered off, washed with water (30 ml), and dried. Amorphous substance. Yield 7.20 g (78.0%). **Oxalate.** Colorless crystalline substance, mp 194.2–194.5° C (decomp., from methanol). Found, %: C 66.20; H 5.56; N 2.72. Calculated for $C_{26}H_{27}NO_4 \cdot C_2H_2O_4$, %: C 66.26; H 5.76; N 2.76.

B) The identical substance XIX (R = $COCH_3$) was formed by the catalytic reduction of the base XVI (R = $COCH_3$) in methanol in the presence of platinum oxide (18–20° C, 5 hr 30 min). Yield 80.1%. Amorphous substance. Found, %: C 75.13; H 6.33. Calculated for $C_{26}H_{27}NO_4$, %: C 4.80; H 6.51.

1-(4'-Benzyloxybenzyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (XIX, R = H). A) The hydrochloride of the base XVI (R = H) was reduced by the method described for the 7-acetoxy derivative **XIX** (R = $COCH_3$), experiment (A). Yield 91.8%. Mp 154–156° C (from ethanol). Found, %: C 77.00; H 6.50; N 3.65. Calculated for $C_{24}H_{25}NO_3$, %: C 76.77; H 6.71; N 3.65. **Hydrochloride**, colorless rhombic plates. Mp 182.5–183.5° C (from acetone). Found, %: C 70.30; H 6.44; N 3.46. Calculated for $C_{24}H_{25}NO_3 \cdot HCl$, %: C 69.97; H 6.36; N 3.40. **Picrate**, yellow crystalline substance. Mp 193–193.8° C (from ethanol). Found, %: C 59.61; H 4.40. Calculated for $C_{24}H_{25}NO_3 \cdot C_6H_3N_3O_7$, %: C 59.59; H 4.67.

B) A mixture of 0.55 g (0.0013 mole) of the base **XIX** (R = $COCH_3$), 1 g (0.018 mole) of caustic potash, and 10 ml of water was boiled for 5 min. The resulting solution was cooled and acidified with hydrochloric acid to pH 5, and the excess of acid was neutralized with ammonia. The substance that deposited was separated off, washed with water (5 ml), dried, and recrystallized from 10 ml of ethanol. Colorless lenses. Yield 0.48 g (97.1%). Mp 155–157° C. A mixture with a sample from the preceding experiment had mp 154–156° C.

7-Acetoxy-1-(4'-benzyloxybenzyl)-6-methoxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (XX, R = $COCH_3$). A) A solution of 0.7 g (0.00122 mole) of the methiodide **XVII** in 40 ml of methanol was treated with 1 g (0.007 mole) of silver chloride and the mixture was shaken for 2 hr. After the separation of the silver halide, the filtrate was concentrated in vacuum. The methochloride obtained (0.45 g, 0.00093 mole) was dissolved in 15 ml of methanol and reduced in the presence of 0.5 g of platinum oxide (5 hr at 18–20° C). The catalyst was separated off, the solvent was distilled off, and the substance was extracted with ether (3 × 30 ml). The extract was concentrated to 1/3 volume and the hydrochloride was precipitated by the addition of an ethereal solution of hydrogen chloride. Mp 112–112.5° C (deformation at 101° C). Found, %: C 66.89; H 6.75. Calculated for $C_{27}H_{29}NO_4 \cdot HCl \cdot H_2O$, %: C 66.73; H 6.59.

B) A solution of 1.75 g (0.0042 mole) of the base **XIX** (R = $COCH_3$) in 1.2 ml of 90% formic acid and 1.75 ml of formalin was heated at 95–97° C for 5 hr. The reaction mixture was treated with 20 ml of saturated aqueous sodium bicarbonate and the base was extracted with ether (4 × 20 ml). The substance was worked up further as in the preceding experiment. The yield of hydrochloride was 1.36 g (68.7%). Mp 112–113° C (deformation at 101° C). A mixture with a sample from experiment (A) had mp 112–113° C. Found, %: C 66.62, 66.82; H 6.40, 6.44. Calculated for $C_{27}H_{29}NO_4 \cdot HCl \cdot H_2O$, %: C 66.73; H 6.59. **Oxalate.** Mp 144.5–146° C (from ethanol). Found, %: C 66.59; H 5.83; N 2.74. Calculated for $C_{27}H_{29}NO_4 \cdot C_2H_2O_4$, %: C 66.78; H 5.99; N 2.69.

1-(4'-Benzyloxybenzyl)-7-hydroxy-6-methoxy-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (XX, R = H). This was obtained by the alkaline saponification of compound **XX** (R = $COCH_3$) by the method described for **XIX** (R = H), experiment (B). The time of saponification was 30 min. Yield 64.5%. Mp 132.5–134° C (from isopropanol). Found, %: C 77.38; H 6.87; N 3.53, 3.42. Calculated for $C_{25}H_{27}NO_3$, %: C 77.12; H 6.99; N 3.59.

Coclaurine (XVIII); A suspension of 0.20 g (0.00053 mole) of 4'-O-benzylcoclaurine (**XIX**, R = H) in 2.5 ml of ethanol and 5 ml of dil HCl (1 : 1) was heated to the boil until the solid matter had dissolved completely. The coclaurine hydrochloride that deposited on cooling was separated off and recrystallized from water. Yield 0.13 g (75.8%). Mp 255–258° C (from water and ethanol). According to the literature [5], mp 255–256° C. Found, %: C 63.27; H 5.34; N 4.47; Cl 11.11. Calculated for $C_{17}H_{19}NO_3 \cdot HCl$, %: C 63.45; H 6.26; N4.33; Cl 11.01.

1-(4'-Benzyloxybenzyl)-6-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-3, 4-dihydroisoquinoline (V). This was obtained from the diphenyl ether **I** (R = R' = CH_3) corresponding to the acid **I** (R = CH_3, R' = H, mp 66–68° C [1]) by the method described for compound XVI (R = $COCH_3$). For purification, the substance in the form of the hydrochloride was dissolved in chloroform and passed through a column of calcium carbonate or silica. Amorphous substance. Yield 83.6%. Mp 68–74° C. Found, %: N 2.44. Calculated for $C_{34}H_{33}NO_6 \cdot HCl$, %: N 2.38. **Base.** This was obtained by treating the hydrochloride with aqueous ammonia. Yield 77.5%. Mp 59–66° C. Found, %: C 72.83; H 6.20; N 2.51. Calculated for $C_{34}H_{33}NO_6 \cdot 0.5 H_2O$, %: C 72.88; H 6.07; N 2.50. **Methiodide (IX).** This was obtained in a similar manner to compound **XVII**. Mp 105–110° C (deformation at 100° C). Found, %: C 60.30; H 5.03; N 2.09. Calculated for $C_{35}H_{36}INO_6$, %: C 60.60; H 5.19; N 2.02.

1-(4'-Benzyloxybenzyl)-8-methoxy-7-(2'-methoxy-5'-methoxycarbonylmethylphenoxy)-3, 4-dihydroisoquinoline (VII). This was obtained by the analogous reaction from the high-melting diphenyl ether **I** (R = R' = CH_3) corresponding to the acid **I** (R = CH_3, R' = H) with mp 107–108° C. The hydrochloride was chromatographed on silica. Amorphous substance. Yield 86.6%. Mp 172–185° C (deformation at 160° C, from ethanol). Found, %: C 68.60; H 5.90; N 2.61, 2.60. Calculated for $C_{34}H_{33}NO_6 \cdot HCl \cdot 0.5 H_2O$, %: C 68.39; H 5.91; N 2.35. **Base.** Mp 121–126° C. Found, %: N 2.94. Calculated for $C_{34}H_{33}NO_6$, %: N 2.54. **Methiodide.** Mp 149–152° C (deformation at 125° C, from ethanol). Found, %: C 60.60; H 5.07; N 2.18. Calculated for $C_{35}H_{36}INO_6$, %: C 60.61; H 5.19; N 2.02.

1-(4'-Benzyloxybenzyl)-6-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-1, 2, 3, 4-tetrahydroisoquinoline (XIII). A solution of 2.0 g (0.0034 mole) of the hydrochloride of compound V in 50 ml of acetic acid and 20 ml of water was reduced with 2.76 g of zinc dust (2 hr at the boil). The hot reaction mixture was separated from the zinc, cooled to 20° C, and neutralized with 20 ml of aqueous ammonia, and the substance that separated out was extracted with chloroform (70 ml). The extract was washed with water (2 × 20 ml) and concentrated in vacuum. The residue (1.65 g, mp 100–105° C) was dissolved in 100 ml of anhydrous ethanol and the solution was kept for a day at 0° C, after which the precipitate that had deposited was separated off (mp 152–156° C), the filtrate was evaporated, and the residue was triturated with dry ether (2 × 10 ml). Yield 1.2 g (67.2%). Mp 105–110° C (deformation at 94° C). Found, %: N 2.58. Calculated for $C_{34}H_{35}NO_6$, %: N 2.53. **Hydrochloride.** Mp 72–74° C (deformation at 65–66° C). Found, %: C 69.45; 69.32; H 6.21, 6.23; N 2.68, 2.66. Calculated for $C_{34}H_{35}NO_6 \cdot HCl$, %: C 69.20; H 6.15; N 2.37.

1-(4'-Benzyloxybenzyl)-8-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-1, 2, 3, 4-tetrahydroisoquinoline (XIV). This was obtained similarly from the hydrochloride of compound **VII**. Yield 64.9%. Mp 146–150° C (deformation at 141° C, from anhydrous ethanol). Found, %: N 2.57. Calculated for $C_{34}H_{35}NO_6$, %: N 2.53. **Hydrochloride**, amorphous substance. Mp 148–159° C (deformation at 132°C, from ethanol). Found, %: C 69.27; H 6.18; N 2.44. Calculated for $C_{34}H_{35}NO_6 \cdot HCl$, %: C 69.20; H 6.15; N 2.37.

1-(4'-Benzyloxybenzyl)-6-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (XI). A) This was obtained by the reduction of the methiodide **IX** by the method described for compound **XIX** (R = $COCH_3$). For purification, the substance obtained was dissolved in acetone, the solution was filtered, the solvent was distilled off in vacuum, and the residue was triturated with water. Yield 17.5%. Mp 86–90° C (deformation at 77° C). Found, %: C 74.17; H 6.34. Calculated for $C_{35}H_{37}NO_6$, %: C 74.05; H 6.59. The **hydriodide** was obtained by the action of methyl iodide on compound **XIII**. Yield 76.0%. Deformation at 70–80° C (meniscus at 95° C, from anhydrous ethanol). R_f 0.96 [n-butanol–acetic acid–water (4 : 1 : 5), "V" paper of the Gosznak Leningrad paper mill]. Found, %: C 60.20; H 5.65; N 2.23. Calculated for $C_{35}H_{37}NO_6 \cdot HI$, %: C 60.43; H 5.51; N 2.01. **Hydrochloride.** Mp 110–115° C (deformation at 85° C). Found, %: C 66.74; H 5.80. Calculated for $C_{35}H_{37}NO_6 \cdot HCl \cdot 1.5 H_2O$, %: C 66.60; H 6.54.

B) 2.0 g (0.00514 mole) of **XX** (R = H) was dissolved in a solution of potassium methoxide [from 0.2 g (0.0051-g-at) of potassium and 16 ml of methanol] and the methanol was evaporated off in vacuum. To the dried and ground residue were added 1.5 g of copper powder and 3.25 g (0.0125 mole) of methyl 3-bromo-4-methoxyphenylacetate, and the mixture was heated at 185–192° C with stirring in an atmosphere of nitrogen for 50 min. The reaction mixture was treated with benzene (40 ml), filtered, and passed through a column of alumina of activity grade III (50 g). The first 70 ml of eluate gave the bromoester (2.02 g). The second 110 ml of the benzene eluate gave the diphenyl ether **XI** (0.34 g). An additional amount of the substance (0.41 g) was obtained by elution with ether (70 ml). Yield 0.75 g (25.74%). Amorphous substance. The **hydrochloride** was obtained by the addition of ether saturated with hydrogen chloride to an ethereal solution of the base. Mp

111–115° C (deformation at 75° C). Found, %: C 69.20; H 6.26; N 2.51. Calculated for $C_{35}H_{37}NO_6 \cdot HCl$, %: C 69.58; H 6.34; N 2.32. The **hydriodide** was obtained from the hydrochloride by the action of sodium iodide in acetone. Yellow powder. Deformation at 70–80° C (meniscus at 95° C, from isopropanol). R_f 0.96. A mixture with a sample from the preceding experiment deformed at 70–80° C (meniscus at 95° C).

The corresponding acid was obtained by the saponification of the ester **XI** (1.13 g, 0.002 mole) with a solution of 1.0 g (0.019 mole) of caustic potash in 25 ml of water (2 hr at the boil), after which the solution was filtered and neutralized with HCl. The substance that deposited was separated off and crystallized from isopropanol (20 ml), and then picric acid was added to the filtrate from crystallization and the picrate was separated off. Mp 124–128° C (meniscus at 156° C, from isopropanol). Found, %: C 61.35; H 5.04; N 7.46. Calculated for $C_{34}H_{35}NO_6 \cdot C_6H_3N_3O_7$, %: C 61.35; H 4.89; N 7.54.

1-(4'-Benzyloxybenzyl)-8-methoxy-7-(2"-methoxy-5"-methoxycarbonylmethylphenoxy)-N-methyl-1, 2, 3, 4-tetrahydroisoquinoline (XII). This was obtained by the reduction of the methiodide **X** in a similar manner to compound **XI** [experiment (A)]. Mp 120–123° C, after which it solidified and melted again at 156–156.5° C (from ethanol). Found, %: N 2.44. Calculated for $C_{35}H_{37}NO_6$, %: N 2.47. **Hydriodide.** Mp 165–171° C (meniscus at 189° C, from methanol). Found, %: N 2.20, 2.33. Calculated for $C_{35}H_{37}NO_6 \cdot HI$, %: N 2.01.

4, 5, 5'-Tricarboxy-2, 2'-dimethoxy(diphenyl ether) (VI). With stirring, 38.7 g (0.245 mole) of finely ground potassium permanganate was added over 3 hr at 20–30° C to a solution of 6.82 g (0.0116 mole) of the hydrochloride of compound V in 300 ml of pyridine. After 40 hours' stirring, the pyridine was distilled off in vacuum, the last traces of pyridine being removed by distillation with 50 ml of water. The residue was treated with hot water (5 × 50 ml), and filtered, and the extract was acidified with hydrochloric acid to pH 3. The acid that deposited was coagulated by heating, and was then filtered off, washed with water (3 × 7 ml) and dried (0.95 g). To a solution of 1.1 g of oxidation product in 25 ml of methanol was added 60 ml of an ethereal solution of diazomethane (from 4.2 g of nitrosomethylurea) and the mixture was left to stand for 24 hr. The solvent was driven off in vacuum and the residue was covered with 9.5 ml of anhydrous acetone and left to stand for 24 hr. The impurities that had deposited were separated off, the solvent was distilled off, and the residue (1.2 g) was chromatographed on a column of alumina of activity grade III–IV (32 × 1 cm). It was eluted with benzene (40 ml). This gave 0.79 g of a substance which was saponified with a solution of 2 g of potash in 20 ml of water (30 min at the boil). The resulting solution was diluted with 20 ml of water, filtered, and neutralized with 40% sulfuric acid. The substance that separated out on long standing was separated off, washed with water (5 ml), and dried (0.43 g). After repeated recrystallization from water and then from acetic acid, the diphenyl ether VI was obtained. Mp 256–258° C [2]. Found, %: C 53.16; H 4.22. Calculated for $C_{17}H_{14}O_9 \cdot H_2O$, %: C 53.68; H 4.21. After drying in vacuum (15 mm, 100° C, 2 hr), the anhydrous form was obtained. Found, %: C 56.58; H 3.69. Calculated for $C_{17}H_{14}O_9$, %: C 56.36; H 3.89.

3, 4, 5'-Tricarboxy-2, 2'-dimethoxy(diphenyl ether) (VIII). This was obtained by the oxidation of the dihydroisoquinoline compound **VII** in a similar manner. After two recrystallizations from 50% acetic acid and trituration with chloroform, mp 277° C (decomp., deformation at 236–239° C). For analysis, a sample was dried at 100° C/20 mm for 2 hr. Found, %: C 56.25; H 4.11. Calculated for $C_{17}H_{14}O_9$, %: C 56.36; H 3.89. A mixture with a sample from the preceding experiment (**VI**, mp 256–258° C) had mp 235° C, deformation at 178° C.

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14 March 1967

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