SYNTHETIC RESEARCHES IN THE FIELD OF CURARE ALKALOIDS

XVII. Synthesis of 1-(3'-Bromo-4'-Methoxybenzyl)-6-Methoxy-7-Hydroxy-N-Methyl-1,2,3,4-Tetrahydroisoquinoline*

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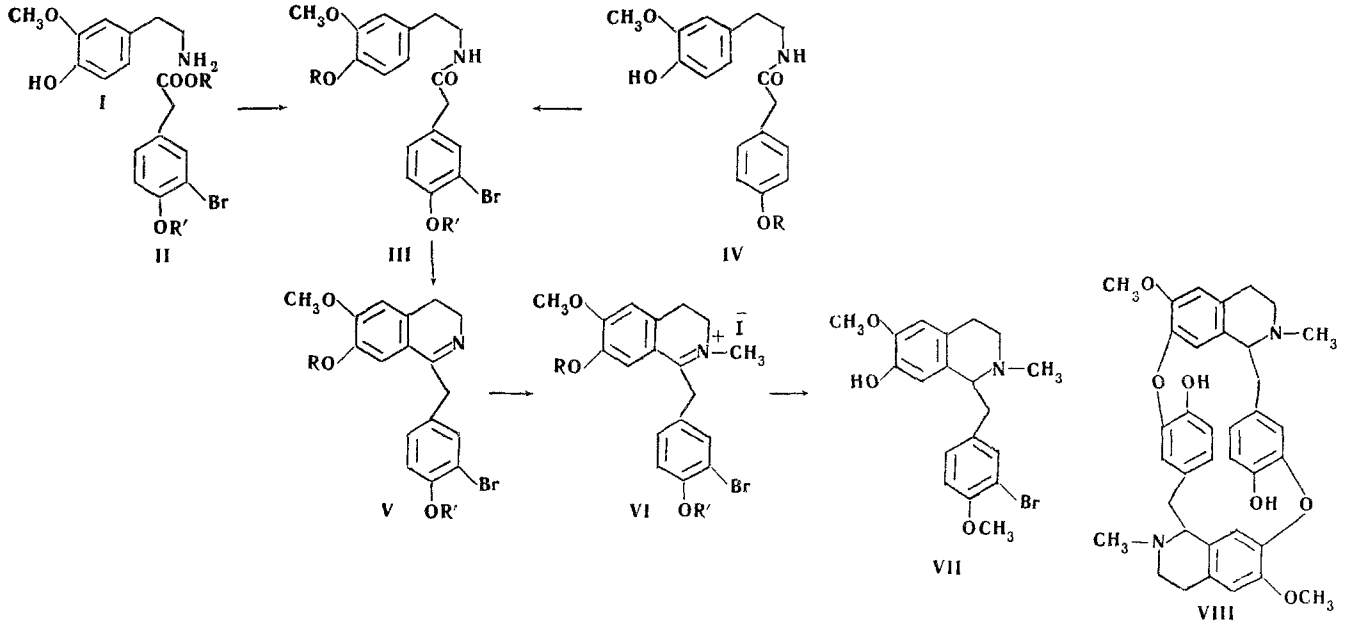
1-(3'-Bromo-4'-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline is synthesized. It is an intermediate in preparing bisbenzylisoquinoline alkaloids of the gaiatin and dauritsin type.

Bisbenzylisoquinoline alkaloids of symmetrical structure, along with alkaloids of the isochondodendrine group, also represented by gaiatin VIII, including an optically inactive compound were isolated from Kashmir Cisspelos pareira [2]. Its methiodide is a powerful nerve blocking agent like tubocurarine [3]. Because of this property its clinical use has been suggested [4].

We have developed synthesis of 1-(3'-bromo-4'-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (VII), which is a basic intermediate in preparing gaiatin and alkaloids of the dauritsin group. The synthesis of this compound is also interesting from the point of view of studying the effect of substituents on properties and reactivity of compounds of the group being investigated. Compound VII was synthesized by the following route:



β-(3-Methoxy-4-hydroxyphenyl)ethylamides of 3'-bromo-4'-alkoxyphenylacetic acids (III) are obtained by condensing β-(3-methoxy-4-hydroxyphenyl)ethylamine (I) with esters of 3-bromo-4-alkoxyphenylacetic acid (II). The dihydroxy derivative III (R = R' = H) is obtained from the β-(3-methoxy-4-hydroxyphenyl)ethylamide of 4'-hydroxyphenylacetic acid (IV, R = H) by brominating with dioxane bromide. It is of interest to note that under similar conditions, the 4'-benzyl ester (IV, $R = CH_2C_6H_5$) gives only an inclusion compound with bromine. The free hydroxyl group at position 4 was acetylated, and then the acetyl derivative III ($R = COCH_3$, $R' = CH_3$, $CH_2C_6H_5$) was cyclized by phosphorus oxychloride in chloroform solution. The resultant 1-(3'-bromo-4'-alkoxybenzyl)-6-methoxy-7-acetoxy-3,4-dihydroisoquinolines (V, $R = COCH_3$, $R' = CH_3$, $CH_2C_6H_5$), were converted into methiodides VI ($R = COCH_3$, $R' = CH_3$, $CH_2C_6H_5$), the first of which was reduced and saponified to 1-(3'-bromo-4'-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (VII). The literature synthesis of this compound, via the corresponding 7-benzyl derivative, differs in that yields are low, and the final product was characterized only as a picrate [5].

*For Part XVI see [1].

EXPERIMENTAL

β-(3-Methoxy-4-hydroxyphenyl)ethylamide of 3' bromo-4'-methoxyphenyl-acetic acid (III, R=H, R'= =CH_3). A mixture of 5.9 g β-(3-methoxy-4-hydroxyphenyl) ethylamine and 4.2 g ethyl 3-bromo-4-methoxyphenylacetate was heated and stirred under N at 180° for 40 min in the presence of 4 drops of pyridine catalyst. After cooling the reaction products were triturated with dry ether (40 ml), the crystalline precipitate separated off and recrystallized from iso-PrOH + benzene (1:2). Yield 6.2 g (57.8%), mp 124.1–125.3°, Found: C 54.53; H 4.8; Br 20.05; 19.91; N 3.22%. Calculated for $C_{18}H_{20}BrNO_4$: C 54.82; H 5.0; Br 20.3; N 3.55%.

β-(3-Methoxy-4-acetoxyphenyl)ethylamide of 3'-bromo-4'-methoxyphenylacetic acid (III, R=CH_3). A mixture of 6.2 g β-(3-methoxy-4-hydroxyphenyl)-ethylamide of 3'-bromo-4'-methoxyphenylacetic acid, 19.2 ml pyridine, and 4.5 ml Ac_2O was heated for 2 hr at 98–100°. The pyridine and excess Ac_2O were vacuum-distilled off, the residue treated with anhydrous ether (20 ml), the substance which crystallized out was separated off, and dried, yield 3.8 g (55.9%), mp 108.2–109.5° (ex iso-PrOH). Found: Br 18.61; N 3.16%. Calculated for $C_{20}H_{22}BrNO_5$: Br 18.35; N 3.30%.

β-(3-Methoxy-4-hydroxyphenyl)ethylamide of 3'-bromo-4'-benzyloxyphenylacetic acid (III, R=H, R' =$CH_2C_6H_5$). This was prepared from β-(3-methoxy-4-hydroxyphenyl)ethylamine and ethyl 3-bromo-4-benzyloxyphenylacetate under conditions similar to those described for the 4'-methoxy derivative III(R=H, R' =CH_3). Yield 55.6%, mp 123–124° (ex iso-PrOH). Found: C 61.12; H 5.10; N 3.17%. Calculated for $C_{24}H_{24}BrNO_4$: C 61.28; H 5.15; N 2.98%.

β-(3-Methoxy-4-acetoxyphenyl)ethylamide of 3'-bromo-4'-benzyloxyphenylacetic acid (III, R=$COCH_3$, R'=$CH_2C_6H_5$). Prepared from β-(3-methoxy-4-hydroxyphenyl)ethylamide of 3'-bromo-4'-benzyloxyphenylacetic acid by acetylation, similarly to the 4'-methoxy analog. Yield 78.6%, mp 125.0–125.1° (ex iso-PrOH). Found: C 61.17; H 5.09; Br 15.98; N 2.76%. Calculated for $C_{26}H_{26}BrNO_5$: C 60.94; H 5.12; Br 15.59; N 2.73%.

β-(3-Methoxy-4-hydrophenyl)ethylamide of 3'-bromo-4'-hydroxyphenylacetic acid (III, R=R'=H). 2.0 g β-(3-Methoxy-4-hydroxyphenyl)ethylamide of 4'-hydroxyphenylacetic acid (mp 108–110°, ex benzene + iso-PrOH 1:4) and 1.65 g dioxane bromide were mixed, when the mixture liquefied (3 min). Heated at 85°, it solidified. It was treated with 35 ml ether, and recrystallized from 12 ml EtOH, yield 0.88 g (53.3%), mp 176–178°. Found: C 53.90; H 4.64; Br 22.08; N 3.79%. Calculated for $C_{17}H_{18}BrNO_4$: C 53.72, H 4.76; Br 22.06; N 3.68%.

The bromination of the β-(3-methoxy-4-hydroxyphenyl)ethylamide of 4'-benzyloxyphenylacetic acid (IV) was effected similarly. A molecular compound with bromine was isolated. Colorless crystalline compound. Mp 125.5–126.2° (ex EtOH, AcOH, nitromethane, and MeEt ketone). Found: C 55.39; 55.31; H 4.30; 4.28; N 2.72; 2.91%. Calculated for $C_{24}H_{25}O_4N \cdot 0.7Br_2$: C 55.24; H 4.95; N 2.78%. On heating with water, the compound was decomposed into the starting components.

1-(3'-Bromo-4'-methoxybenzyl)-6-methoxy-7-acetoxy-3,4-didhydroisoquinoline (V, R=$COCH_3$, R'= =CH_3). A solution of 3.0 g β-(3-methoxy-4-acetoxyphenyl)ethylamide of 3'-bromo-4'-methoxyphenylacetic acid in 50 ml dry $CHCl_3$ was heated for 2 hr 30 min (refluxing) with 5.4 ml $POCl_3$ under N. The $CHCl_3$ and excess $POCl_3$ were vacuum-distilled off, and the viscous residue triturated with dry ether (50 ml), then with water (5 × 20 ml), until a powdery mass resulted. Recrystallization from EtOH (8 ml) in the presence of a few drops of HCl have a colorless crystalline compound, the hydrochloride. Yield 2.6 g (67.5%), mp 198.2–199.1°. Found: C 52.58; H 4.81; N 3.20%. Calculated for $C_{20}H_{20}BrNO_4$; C 52.47; H 4.62; N 3.06%.

Base mp 98.7–99.2° (ex EtOH + water, 2:5).

1-(3'-Bromo-4'-benzyloxybenzyl)-6-methoxy-7-acetoxy-3,4-dihydroquinoline (V, R = $COCH_3$, R' = = $CH_2C_6H_5$). Prepared similarly. Hydrochloride, yield 82.1%, mp 179.1–179.6° (ex E+OH or dilute AcOH, 1:1). Found: C 57.12; H 4.57%. Calculated for $C_{26}H_{24}BrNO_4 \cdot HCl \cdot H_2O$: C 56.90; H 4.92%.

Methiodide of 1-(3'-bromo-4'-methoxybenzyl)-6-methoxy-7-acetoxy-3,4'-dihydroisoquinoline (VI, R= =$COCH_3$, R'=CH_3). A solution of 0.8 g base, 1-(3'-bromo-4'-methoxybenzyl)-6-methoxy-7-acetoxy-3, 4-dihydroisoquinoline in 20 ml MeOH was refluxed with 2 ml MeI for 3 hr. MeOH and excess MeI were vacuum-distilled off. The residue was triturated with anhydrous ether (25 ml), and dried in a vacuum-desiccator. Amorphous substance, yield 1.1 g (94.3%), mp 140–152° (def at 92.5°). Found: C 44.70; H 4.28; N 2.31%. Calculated for $C_{27}H_{27}BrINO_4$; C 45.02; H 4.14; N 2.50%.

Methiodide of 1-(3'-bromo-4'-benzyloxybenzyl)-6-methoxy-7-acetoxy-3,4-dihydroisoquinoline (VI, R=$COCH_3$, R'=$CH_2C_6H_5$). This was prepared similarly to the 4'-methoxy derivative VI (R=$COCH_3$, R'=CH_3), yield 45.7%, mp 202.2–203.1° (ex MeOH, AcOH, or acetone). Found: N 2.34%. Calculated for $C_{27}H_{27}BrINO_4$; N 2.20%.

1-(3'-Bromo-4'-methoxybenzyl)-6-methoxy-7-hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (VII). A solution of 1.1 g methiodide of 1-(3'-bromo-4'-methoxybenzyl)-6-methoxy-7-acetoxy-3,4-dihydroisoquinoline in 25 ml dilute (1:1) AcOH was refluxed for 1 hr with 5 ml Zn dust, and stirred. The unreacted Zn was filtered off, the filtrate cooled, and treated with 20 ml saturated aqueous ammonia solution. The precipitated base was extracted with ether (75 ml), the extract dried over Na_2SO_4, and the solvent distilled off, giving a viscous oily mass (1.45 g). The base was stirred for 12 hr with 15 ml 1 N NaOH at 18–20°, until completely dissolved. Then the reaction mixture was neutralized with dilute HCl (8 ml, 1:1), the precipitate filtered off, washed with water, and dried. Yield 0.35 g (47.7%), mp 84.3–85.5° (decomp). Found: Br 20.50; N 3.80%. Calculated for $C_{19}H_{22}BrNO_3$: Br 20.37; N 3.57%.

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