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Papaverine and Related Compounds. XVII. Synthesis of 1-Phenyl-2-methyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (1,2)

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The synthesis of 1-phenyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (II) was reported previously (4). This paper describes the synthesis of 1-phenyl-2-methyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (I), which was expected to have physiological activity.

Isovanillin was treated with benzyl chloride in the presence of potassium carbonate to produce *O*-benzylisovanillin (III). When III was allowed to react with nitromethane, (Knoevenagel reaction) 3-benzyloxy-4-methoxy-β-nitrostyrene (IV) was produced. Reduction of IV with lithium aluminum hydride using Tomita's method (7) afforded 3-benzyloxy-4-methoxyphenylethylamine (V), which was identified as the oxalate.

The reaction of V with benzoyl chloride produced the amide (VI). Compound VI was treated with phosphoryl chloride (Bischler-Napieralski reaction) to produce the dihydroisoquinoline derivative (VII), which in turn was methylated with methyl iodide to give the methiodide (VIII). The methiodide VIII was reduced with sodium borohydride in methanol to produce the tetrahydroisoquinoline derivative (IX), which was hydrolyzed with methanol-concentrated sulfuric acid to afford 1-phenyl-2-methyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline I. Compound I was also obtained by reduction of VIII with zinc powder and hydrochloric acid. Furthermore, reduction of VII with zinc and acid produced (X) which was subjected to the Eschweiler-Clarke reaction to produce I. The infrared spectrum of I was identical with that obtained from an authentic sample.

Methylation of I with diazomethane gave compound (XI) which had the same melting point and infrared spectrum as an authentic sample of XI (4).

EXPERIMENTAL

Infrared spectra were determined with a Type EPI-2 Hitachi infrared spectrophotometer. Melting points were determined on a Kofler block and are uncorrected.

N-(3-Benzyloxy-4-methoxyphenylethyl)benzamide (VI).

Four grams of 3-benzyloxy-4-methoxyphenylethylamine (V) oxalate was made basic with 10% sodium hydroxide solution and extracted with ether. To the cooled mixture of the above extract of V and 50 ml. of 5% sodium hydroxide, was added in small portions with shaking a solution of 2 g. of benzoyl chloride in dry ether. After the addition, the mixture was stirred at room temperature for one hour and then extracted with chloroform. The solvent was washed with water, 10% hydrochloric acid and again with water, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure to give 3.8 g. (92%) of the amide (VI) as a colorless powder, m.p. 140-144°. Recrystallization from methanol gave a colorless powder, m.p. 143-144°. IR cm^{-1}: ν (NH) 3350, ν (C=O) 1648 (KBr).

Anal. Calcd. for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 75.87; H, 6.48; N, 4.15.

1-Phenyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline (VII).

A mixture of 800 mg. of the above amide (VI), 20 ml. of dry benzene and 600 mg. of phosphoryl chloride was heated under reflux for 2 hours. After the reaction mixture was distilled, the resultant viscous syrup was extracted with hot water and the water solution was extracted with benzene. The aqueous acidic solution was cooled and allowed to stand for a short time, 770 mg. (92%) of the hydrochloride of VII separated as a yellow powder, m.p. 161-165°. Recrystallization from ethanol gave pale yellowish-green needles. IR cm^{-1} ν (NH^+) 2801 - 2203, ν (C=N) 1647 (KBr).

To the above hydrochloride was added an excess of 10% ammonium hydroxide and the resultant alkaline solution was extracted with benzene. The benzene extract was washed with water, dried over anhydrous potassium carbonate and the solvent evaporated to give 750 mg. (90%) of VII as a yellow powder, m.p. 142-143°. Recrystallization from methanol gave colorless needles, m.p. 143-145°. IR cm^{-1}: ν (C=N) 1610 (KBr).

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.42; H, 6.16; N, 4.07. Found: C, 80.00; H, 6.15; N, 4.28.

Anal. Calcd. for $C_{23}H_{21}NO_2 \cdot HCl$: C, 72.72; H, 5.83; N, 3.68. Found: C, 72.35; H, 5.96; N, 3.51.

1-Phenyl-6-benzyloxy-7-methoxy-3,4-dihydroisoquinolinium methiodide (VIII).

A mixture of 1.5 g. of the preceding dihydroisoquinoline (VII), 30 ml. of methanol and 7 ml. of methyl iodide was refluxed at 50-60° on a water-bath. Removal of the solvent gave 1.9 g. (86%) of the methiodide (VIII) as yellow crystals, m.p. 183-186°. Recrystallization from methanol afforded pale yellow needles, m.p. 186-187°.

Anal. Calcd. for $C_{24}H_{24}INO_2$: C, 59.39; H, 4.97; N, 2.87. Found: C, 58.87; H, 5.05; N, 3.28.

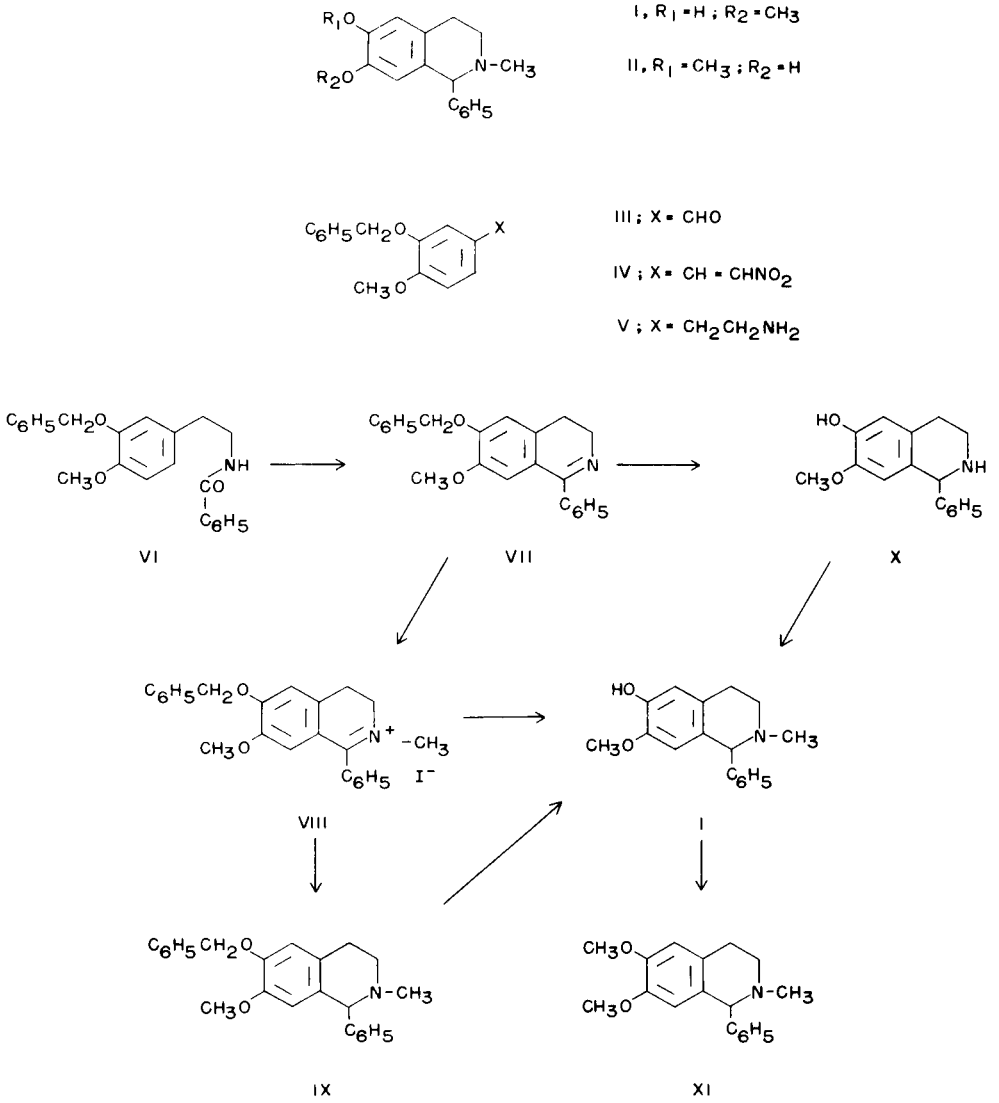
1-Phenyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (X).

To a mixture of 500 mg. of the above base (VII), 40 ml. of ethanol and 20 ml. of concentrated hydrochloric acid was added 4 g. of zinc powder in small portions. After the mixture had been refluxed for 1 hour, the excess of zinc was filtered off and the solvent was removed by distillation. The acidic solution was washed with benzene in order to remove any unreacted substances. The resultant aqueous solution was treated with an excess of crystalline ammonium chloride and extracted with benzene. The benzene solution was washed with water, dried over anhydrous sodium sulfate and the solvent removed to give 200 mg. (54%) of X as a yellow powder, m.p. 173-175°. Recrystallization from ethanol gave colorless scales, m.p. 184.5-185.5°. IR cm^{-1}: ν (OH) 3500 ($CHCl_3$).

Anal. Calcd. for $C_{16}H_{17}NO_2 \cdot 1/4H_2O$: C, 73.96; H, 6.78; N, 5.40. Found: C, 74.09; H, 6.74; N, 5.63.

1-Phenyl-2-methyl-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (IX).

To a solution of 500 mg. of the above methiodide (VIII) in 40 ml. of methanol containing 2 drops of water was added in small portions 1 g. of sodium borohydride, and the mixture was refluxed for 30 minutes and then evaporated. The resultant residue was mixed with water and extracted with ether. The ethereal extract was washed, dried over anhydrous potassium carbonate and distilled to give 300



mg. (81%) of X as a colorless powder, m.p. 113-115°. Recrystallization from methanol gave colorless needles, m.p. 114-115°. IR cm^{-1}: ν ($-NCH_3$) 2700 (KBr).

Anal. Calcd. for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 79.94; H, 6.93; N, 4.17.

1-Phenyl-2-methyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (I).

(a) A mixture of 250 mg. of the above dihydroisoquinoline (IX), 15 ml. of methanol and 2 ml. of concentrated sulfuric acid was refluxed for 2 hours. The solvent was removed under reduced pressure, 20 ml. of water was added to the above residue, and the mixture was extracted with ether. The resultant acidic solution was made basic with 10% sodium hydroxide and extracted with ether. The solution was washed with water, dried over anhydrous potassium carbonate and distilled to give 150 mg. (80%) of I as a pale brown powder, m.p. 145-148°. Recrystallization from ethanol gave colorless prisms, m.p. 152°. IR cm^{-1}: ν (OH) 3500, ν ($-NCH_3$) 2700 ($CHCl_3$).

(b) To a mixture of 500 mg. of the methiodide (VIII), 40 ml. of ethanol and 20 ml. of concentrated hydrochloric acid was added 4 g. of zinc powder in small portions and the mixture refluxed for 1 hour. After removal of the excess of zinc powder, the mixture was evaporated and extracted with benzene. The resultant acidic solution was made basic with concentrated sodium hydroxide solution and extracted repeatedly with benzene. To the above alkaline solution was added an excess of crystalline ammonium chloride and the mixture was extracted with benzene. Evaporation of the washed and dried anhydrous sodium sulfate solution gave 180 mg. (64%) of I as a pale brown powder, which was recrystallized from ethanol to give colorless needles, m.p. 152°. This was identical with the above compound (method a) as shown by a mixed melting point and infrared spectra.

(c) A mixture of 150 mg. of X, 700 mg. of 37% formalin and 700 mg. of 98% formic acid was heated at 100° with occasional shaking for 4 hours. The reaction mixture was poured into 30 ml. of water, made basic with ammonium hydroxide and extracted with ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 150 mg. (94%) of I as a yellow residue. Recrystallization from ethanol afforded colorless needles, m.p. 152°, whose infrared spectrum was superimposable on that of the product obtained by the above procedures (a and b).

1-Phenyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XI).

To a solution of 300 mg. of I in 40 ml. of methanol was added an ethereal solution of diazomethane, which was obtained from 10 g. of N-nitroso-N-methyl-*p*-toluenesulfonamide. The mixture was allowed to stand in a refrigerator for 4 days. Evaporation of the solvent gave 250 mg. (81%) of XI as a pale brown powder, m.p. 76-79°. Recrystallization from hexane produced colorless needles, m.p. 81-82°, whose infrared spectrum was identical with that of an authentic sample. The melting point report (4) was 81-82°.

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