Syntheses of Some Derivatives of 7-Hydroxydecahydroisoquinoline

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The syntheses described in this paper were undertaken to prepare some compounds related to reserpine, an important alkaloid found in *Rauwolfia* species. Sastry and Lasslo[1] and Miller and Weinberg[2] have reported syntheses and significant reserpine-like activities of the 3-(*N*, *N*-diethylaminopropyl) and 4-(*N*, *N*-diethylaminobutyl) esters of 3, 4, 5-trimethoxybenzoic acid, and a considerable number of compounds in which the alcohol moiety of the carboxylic ester and the acyl moiety of the trimethoxybenzoic acid ester functions vary have been reported in the patent literature. However, little information is available regarding the related derivatives of decahydroisoquinoline. Of special interest were decahydroisoquinoline derivatives, which contain a peripheral *N*-alkyl group simulating the cut-away indole portion of reserpine. Such a derivative corresponds to that part of reserpine shown by solid line in Formula 1. The present paper is concerned with the synthesis of methyl quaternary bromides of 7-methoxybenzoyloxy-2-methyldecahydroisoquinolines and of 7-methoxybenzoyloxy-2-ethyldecahydroisoquinolines[3].

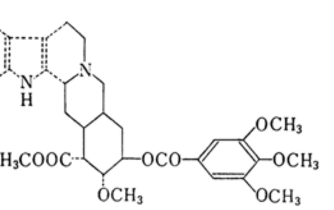

Chart 1

7-Hydroxy-2-methyl- and 7-hydroxy-2-ethyl decahydroisoquinoline and their derivatives were prepared by the general scheme outlined in Chart 2:

Methiodide (I) of 7-hydroxyisoquinoline was reduced with sodium borohydride to yield 7-hydroxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline (II) in a 76.5% yield. The catalytic hydrogenation of II with Raney nickel proceeded smoothly, affording an 84.2% yield of 7-hydroxy-2-methyldecahydroisoquinoline (III), an oily product with a b. p. of 110∼115°C (2 mmHg). The structure of III was confirmed by elemental analysis and by the formation of a methiodide derivative. Ochiai and Nakagome[4] reported a b. p. of 105∼115°C (3 mmHg, bath temperature) for the material obtained on the catalytic hydrogenation of 2-methyl-7-oxo-Δ^8-octahydroisoquinoline with platinum oxide; moreover, they reported a m. p. of 257∼258°C for its methiodide. It was found that the melting point of our sample varied with the nature of the solvent used for recrystallization. Repeated recrystallization from alcohol gave a m. p. of 277.5∼278.5°C, and recrystallization from alcohol-petroleum ether gave a m. p. of 253∼257°C, substantially the same melting point as that described by Ochiai and Nakagome. Although stereoisomeric separation was not attempted, III can be assumed to be a mixture of stereoisomers.

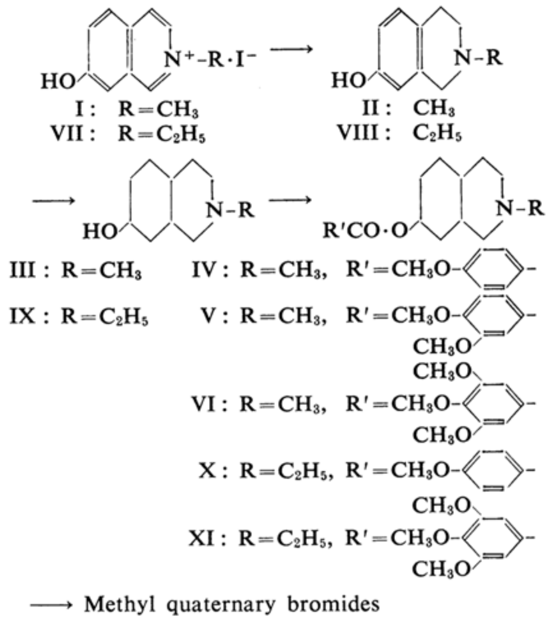

Chart 2

Compounds of Formulas IV, V and VI were prepared by the treatment of 7-hydroxy-2-methyldecahydroisoquinoline (III) with anisoyl

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[1] B. V. R. Sastry and A. Lasslo, *J. Org. Chem.*, **23**, 1577 (1958).

[2] F. M. Miller and M. S. Weinberg, *Chem. Eng. News*, **34**, 4760 (1956); *Chem. Abstr.*, **53**, 18079 (1959).

[3] Recently, syntheses of 5-hydroxy-2-methyldecahydroisoquinoline and 6-hydroxy-2-methyldecahydroisoquinoline have been reported by S. Kimoto and M. Okamoto, *Chem. & Pharm. Bull.*, **9**, 480 (1961); **10**, 368 (1962).

[4] E. Ochiai and T. Nakagome, *J. Pharm. Soc. Japan*, **78**, 1438 (1958).

chloride, veratroyl chloride and tri-*O*-methylgalloyl chloride respectively in benzene at 45°C for 6 hr. After removal of the solvent, each of the reaction mixtures was treated with water, each giving an insoluble part which was confirmed to be anisic anhydride, veratric anhydride or tri-*O*-methylgallic anhydride respectively. The water-layers were evaporated under reduced pressure, and the viscous products were treated with silver carbonate in acetone-methanol. Each of the resulting free bases was chromatographed on alumina and eluted with ether to give two fractions, namely, the first and second fractions. The second fractions were 7-hydroxy-2-methyldecahydroisoquinoline, unchanged and converted to its crystalline methiodide, which was identified by comparison with the methiodide of III. After removal of ether from the first fractions, each of the resulting syrups was treated with an excess of methyl bromide to yield a crystalline mixture of stereoisomers of methyl 7-aroyloxy-2-methyldecahydroisoquinolinium bromide. Extraction of each of the stereoisomeric mixtures with a large quantity of acetone left a relatively insoluble isomer (A), while evaporation of the acetone-extract gave a soluble isomer (B). Thus, each of the methiodides of 7-anisoyloxy-2-methyldecahydroisoquinoline, 7-veratroyloxy-2-methyldecahydroisoquinoline and 7-tri-*O*-methylgalloyloxydecahydroisoquinoline was separated into two corresponding isomers, A and B.

The synthesis of 7-hydroxy-2-ethyldecahydroisoquinoline (IX) was carried out by procedures analogous to those used for the preparation of the 2-methyl derivative III. The condensation products of 7-hydroxy-2-ethyldecahydroisoquinoline (IX) with anisoyl chloride and tri-*O*-methylgalloyl chloride were treated with water, giving again anisic anhydride and tri-*O*-methylgallic anhydride respectively. The viscous products obtained from the water-layers by evaporation were treated with silver carbonate in acetone, and the resulting free bases were subjected to alumina chromatography to yield again two fractions, the second fraction being unchanged IX. Evaporation of each of the first fractions gave an oily mixture of stereoisomers of 7-aroyloxy-2-ethyldecahydroisoquinoline. The oily product of 7-anisoyloxy-2-ethyldecahydroisoquinoline was treated with an excess of methyl bromide to yield a crystalline product of methyl 7-anisoyloxy-2-ethyldecahydroisoquinolinium bromide (XV). The treatment of this product with acetone again gave two fractions, one soluble and one relatively insoluble; however, only one isomer could be obtained from the soluble fraction.

The oily product of 7-(tri-*O*-methylgalloyloxy)-2-ethyldecahydroisoquinoline was also treated with an excess of methyl bromide, producing a crystalline product of methyl 7-(tri-*O*-methylgalloyloxy)-2-ethyldecahydroisoquinolinium bromide (XVI). Treatment of the product with acetone also gave two fractions, one soluble and one relatively insoluble, from which one isomer could be obtained.

Although stereochemical assignments for the above-mentioned isomers have not yet been made, material differences have been discerned between the biological properties of the stereoisomeric derivatives of methyl quaternary bromide, and some of them look promising for clinical use. Details of the studies of the hypotensive activity and toxicity of the above-mentioned stereoisomeric derivatives will be published elsewhere in the near future.

Experimental

7-Hydroxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline (II).—A solution of 1.19 g. of 7-hydroxyisoquinoline methiodide (I) in 25 ml. of 10% aqueous methanol was added to 0.66 g. of sodium borohydride and refluxed for 5 min. After the addition of 10 ml. of acetone, the reaction mixture was allowed to cool to room temperature. After removal of the solvent, the residue was mixed with 15 ml. of a 3.5% sodium carbonate solution to give colorless crystals of the title compound; m. p., 169~170°C, 0.52 g. (76.5%). Repeated recrystallizations from acetone raised the m. p. to 171~172°C (reported[5]: 171~172°C).

7-Hydroxy-2-methyldecahydroisoquinoline (III).—A solution of 2.99 g. of 7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (II) in 330 ml. of absolute ethanol was hydrogenated with 3.5 g. of Raney nickel at 155~160°C for 16 hr. at a pressure of 200~202 kg./cm^2. After removal of the catalyst by filtration, the reaction mixture was evaporated to give an oily residue, which was then distilled under reduced pressure to give 2.61 g. (84.2%) of 7-hydroxy-2-methyldecahydroisoquinoline; b. p., 110~115°C (2 mmHg). The b. p. reported by Ochiai and Nakagome[4] is 105~115°C (3 mmHg, bath temperature).

Methiodide of III. — A mixture of 7-hydroxy-2-methyldecahydroisoquinoline and of an excess of methyl iodide in ethyl acetate, when warmed for a while and then allowed to cool to room temperature, gave colorless crystals of methyl iodide; m. p., 229~253°C. Repeated recrystallizations from ethanol raised the m. p. to 277.5~278.5°C.

Found: C, 42.28; H, 7.23; N, 4.76. Calcd. for $C_{11}H_{22}ONI$: C, 42.44; H, 7.07; N, 4.50%.

Recrystallizations of the crude methiodide from ethanol-petroleum ether gave a m. p. of 253~257°C (reported[4] 257~258°C).

Found: C, 42.17; H, 7.15%.

7-Anisoyloxy-2-methyldecahydroisoquinoline (IV).—A solution of 1.29 g. of anisoyl chloride in 15 ml.

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[5] F. L. Pyman and F. G. P. Remfry, *J. Chem. Soc.*, **101**, 1595 (1912).

of dried benzene was stirred drop by drop into a solution of 1.28 g. of 7-hydroxy-2-methyldecahydroisoquinoline (III) in dried benzene. This solution was warmed at 45°C for 6 hr. and then distilled under reduced pressure to give 2.80 g. of a viscous residue. This residue was triturated with 50 ml. of water, and the aqueous layer was separated from the insoluble part by filtration. Recrystallization of the insoluble part (0.66 g.) from ethanol-water gave colorless crystals of anisic anhydride; m. p., 98~99°C (reported m. p., 99°C)[6].

Found: C, 67.12; H, 4.69. Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93%.

The above-mentioned aqueous layer was treated with a small quantity of active charcoal and evaporated under reduced pressure. The viscous residue was then dissolved in a mixture of 50 ml. of acetone and 20 ml. of methanol and mixed thoroughly with 3.0 g. of silver carbonate. After removal of the precipitate by filtration, the solution was evaporated under reduced pressure, and the residue was taken up in a small quantity of ether. The ether solution was evaporated to give an oily product (1.56 g.). This product was chromatographed on alumina and then developed and eluted with ether to give two fractions. The second fraction was treated with methyl iodide to yield a methiodide with a m. p. of 266~269°C, which was identical with the methiodide of 7-hydroxy-2-methyldecahydroisoquinoline.

The first fraction was evaporated to give an oily product of 7-anisoyloxy-2-methyldecahydroisoquinoline (IV) (0.75 g.) (32.8%).

Stereoisomers (XII-A, XII-B) of Methyl 7-Anisoyloxy-2-methyldecahydroisoquinolinium Bromide.—A mixture of 0.75 g. of the crude product of 7-anisoyloxy-2-methyldecahydroisoquinoline (IV) and an excess of methyl bromide in 20 ml. of ether was sealed in a test tube and allowed to stand at room temperature for 2 days. Removal of the solvent from the reaction mixture gave 0.97 g. of crude crystals of quaternary ammonium salt. This crude product was thoroughly triturated with 110 ml. of acetone, and the acetone-layer was separated from the insoluble part by filtration. The insoluble part weighed 0.32 g. (33.0%) and melted at 262.5~265.5°C. Repeated recrystallizations from ethanol-petroleum ether gave colorless needles with a m. p. of 281~282°C. Elemental analysis indicated the product to be a stereoisomer (XII-A) of methyl 7-anisoyloxy-2-methyldecahydroisoquinolinium bromide.

Found: C, 57.60; H, 7.32; N, 3.67. Calcd. for $C_{19}H_{28}O_3NBr$: C, 57.29; H, 7.08; N, 3.52%.

The above-mentioned acetone-layer was evaporated, and the residue was again dissolved in 60 ml. of acetone, leaving a small insoluble part. The acetone solution was concentrated to 20 ml., and the separated crystals were collected; 0.25 g. (25.8%); m. p., 216~221°C. Recrystallizations from acetone-ethyl acetate gave colorless needles with a m. p. of 220~223°C. Elemental analysis indicated the product to be another isomer (XII-B) of methyl 7-anisoyloxy-2-methyldecahydroisoquinolinium bromide.

Found: C, 57.63; H, 7.28; N, 3.79. Calcd. for $C_{19}H_{28}O_3NBr$: C, 57.29; H, 7.08; N, 3.52%.

The mixed melting point of the two above-mentioned isomers showed considerable depression and a wide range.

Evaporation of the mother-liquor from the isomer (XII-B) left 0.33 g. of a viscous residue.

7-Veratroyloxy-2-methyldecahydroisoquinoline (V).—In a manner similar to that used for the preparation of IV, 1.47 g. of 7-hydroxy-2-methyldecahydroisoquinoline (III) was treated with 1.78 g. of veratroyl chloride in benzene to give 3.49 g. of a viscous product. Trituration of the product with 250 ml. of water left an insoluble part (0.60 g.), which was recrystallized from ethanol to give colorless needles of veratric anhydride; m. p., 118~120°C (reported m. p., 124~125°C)[7]. The aqueous layer was treated with active charcoal and evaporated. The viscous residue was dissolved in a mixture of 50 ml. of acetone and 20 ml. of methanol and mixed thoroughly with 3.8 g. of silver carbonate. After removal of the precipitate, the solution was evaporated and the residue was taken up in a small quantity of ether. The oily product obtained by the evaporation of the ether solution was chromatographed on alumina and then developed and eluted with ether to give two fractions. The first fraction was evaporated to give 1.05 g. (36.2%) of an oily product of 7-veratroyloxy-2-methyldecahydroisoquinoline (V).

The Stereoisomers (XIII-A, XIII-B) of Methyl 7-Veratroyloxy-2-methyldecahydroisoquinolinium Bromide.—In a manner similar to that used for the preparation of XII-A and XII-B, 1.05 g. of the crude product of 7-veratroyl-2-methyldecahydroisoquinoline was treated with an excess of methyl bromide to give 1.31 g. of crude crystals of quaternary ammonium salt. The crude product was thoroughly triturated with 350 ml. of acetone, and the acetone-layer was separated from the insoluble part. The insoluble part weighed 0.30 g. (22.0%) and melted at 252~255°C. Repeated recrystallizations from ethanol-petroleum ether gave colorless needles; m. p., 263~264°C. Elemental analysis indicated the product to be a stereoisomer (XIII-A) of methyl 7-veratroyloxy-2-methyldecahydroisoquinolinium bromide.

Found: C, 56.08; H, 7.03; N, 3.32. Calcd. for $C_{20}H_{30}O_4NBr$: C, 56.08; H, 7.06; N, 3.27%.

The acetone-layer was evaporated, and the residue was again dissolved in 130 ml. of acetone, leaving a small insoluble part. Concentration of the acetone solution to 17 ml. separated 0.58 g. (43.0%) of crystals; m. p., 157~162°C. Recrystallizations from acetone gave colorless hygroscopic needles with a m. p. of 169~170°C. Elemental analysis indicated the product to be another stereoisomer (XIII-B) of methyl 7-veratroyloxy-2-methyldecahydroisoquinolinium bromide.

Found: C, 55.14; H, 6.93; N, 2.93. Calcd. for $C_{20}H_{30}O_4NBr \cdot 1/2H_2O$: C, 54.93; H, 7.14; N, 3.20%.

The mixed melting point of the two above-mentioned isomers showed considerable depression and

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[6] F. Pisani, *Ann.*, **102**, 284 (1857).

[7] J. Shinoda and S. Sato, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), No. 540, 24 (1927).

wide range.

7-(Tri-*O*-methylgalloyloxy)-2-methyldecahydroisoquinoline (VI).—In a manner similar to that used for the preparation of IV, 1.50 g. of 7-hydroxy-2-methyldecahydroisoquinoline (III) was treated with 2.06 g. of tri-*O*-methylgalloyl chloride in benzene to give 3.56 g. of a viscous product. Trituration of the product with 320 ml. of water left an insoluble part (0.93 g.), which was then recrystallized from acetone to give colorless needles of tri-*O*-methylgallic anhydride with a m. p. of 159∼160°C (reported m. p., 159∼160°C)8).

Found: C, 59.32; H, 5.53. Calcd. for $C_{20}H_{22}O_9$: C, 59.11; H, 5.46%.

After the aqueous layer had been processed, an oily product (1.86 g.) was chromatographed on alumina by a similar procedure to give two fractions. The oily product from the second fraction gave methiodide (m. p., 261∼266°C) which was identical with the methiodide of the starting substance III. The first fraction gave 1.04 g. (32.2%) of an oily product of 7-(tri-*O*-methylgalloyloxy)-2-methyldecahydroisoquinoline.

The Stereoisomers (XIV-A, XIV-B) of Methyl 7-(Tri-*O*-methylgalloyloxy)-2-methyldecahydroisoquinolinium Bromide.—In a manner similar to that used for the preparation of XII-A and XII-B, 1.04 g. of 7-(tri-*O*-methylgalloyloxy)-2-methyldecahydroisoquinoline was reacted with an excess of methyl bromide to give 1.29 g. of crude crystals of quaternary ammonium salt. Fractionation of the product with acetone gave two fractions. The more insoluble fraction weighed 0.29 g. (21.9%) and melted at 260∼263°C. Recrystallizations from ethanol-petroleum ether gave colorless needles with a m. p. of 262.5∼264.0°C. Elemental analysis indicated the product to be a stereoisomer (XIV-A) of methyl 7-(tri-*O*-methylgalloyloxy)-2-methyldecahydroisoquinolinium bromide.

Found: C, 54.58; H, 7.37; N, 3.36. Calcd. for $C_{21}H_{32}O_5NBr$: C, 55.02; H, 7.04; N, 3.06%.

The soluble fraction weighed 0.47 g. (36.3%) and melted at 192∼198°C. Recrystallizations from acetone gave colorless hygroscopic plates with a m. p. of 201.5∼203.5°C. Elemental analysis indicated the product to be another isomer (XIV-B) of methyl 7-(tri-*O*-methylgalloyloxy)-2-methyldecahydroisoquinolinium bromide.

Found: C, 55.01; H, 7.04; N, 3.27. Calcd. for $C_{21}H_{32}O_5NBr$: C, 55.02; H, 7.04; N, 3.06%.

7-Hydroxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline (VIII).—The reduction of 7.08 g. of 7-hydroxyisoquinoline methiodide with 3.57 g. of sodium borohydride in 10% aqueous methanol gave 4.08 g. (97.8%) of crude crystals. Recrystallization from acetone-petroleum ether gave colorless needles with a m. p. of 144∼147°C.

Found: C, 74.13; H, 8.48. Calcd. for $C_{11}H_{15}ON$: C, 74.53; H, 8.53%.

7-Hydroxy-2-ethyldecahydroisoquinoline (IX).—A sample of 3.22 g. of 7-hydroxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline was hydrogenated with 4.0 g. of Raney nickel in absolute ethanol at about 165°C for 16 hr. at a pressure of 191 kg./cm^2. After processing, the colorless oil of 7-hydroxy-2-ethyldecahydroisoquinoline with a b. p. of 122.5∼126.5°C (3 mmHg) was obtained; 2.59 g. (77.8%). The product gave methiodide with a m. p. of 214∼219°C.

Found: C, 44.61; H, 7.31; N, 4.64. Calcd. for $C_{12}H_{24}ONI$: C, 44.31; H, 7.44; N, 4.31%.

7-Anisoyloxy-2-ethyldecahydroisoquinoline (X).—The reaction of 1.20 g. of 7-hydroxy-2-ethyldecahydroisoquinoline (IX) with 1.12 g. of anisoyl chloride in dried benzene gave 2.04 g. of a viscous product. The trituration of the product with 100 ml. of water left an insoluble part (0.48 g.) which, after recrystallization from ethanol-water, melted at 98∼99°C and which was identical with anisic anhydride. The aqueous layer was processed in a manner similar to that described for the preparation of IV, and the viscous product was chromatographed on alumina to give two fractions. The second fraction gave methiodide (m. p., 216∼218°C) which was identical with the methiodide of 7-hydroxy-2-ethyldecahydroisoquinoline. The first fraction gave an oily product (0.68 g., 32.9%) of 7-anisoyloxy-2-ethyldecahydroisoquinoline.

Methyl 7-Anisoyloxy-2-ethyldecahydroisoquinolinium Bromide (XV).—In a manner similar to that used for preparation of XII-A and XII-B, 0.68 g. of 7-anisoyloxy-2-ethyldecahydroisoquinoline was reacted with an excess of methyl bromide to give 0.87 g. of crude crystals of quaternary ammonium salt. Fractionation of the product with 150 ml. of acetone gave two fractions. The more insoluble fraction weighed 0.054 g. (6.1%) and melted at 243.5∼245°C. The soluble fraction was concentrated to 12 ml. to give 0.26 g. (29.1%) of colorless crystals with a m. p. of 224.5∼228°C. Recrystallization from acetone raised the m. p. to 234∼237.5°C.

Found: C, 58.33; H, 7.42; N, 3.25. Calcd. for $C_{20}H_{30}O_3NBr$: C, 58.25; H, 7.33; N, 3.40%.

7-(Tri-*O*-methylgalloyloxy)-2-ethyldecahydroisoquinoline (XI).—The treatment of 1.21 g. of 7-hydroxy-2-ethyldecahydroisoquinoline with 1.52 g. of tri-*O*-methylgalloyl chloride in dried benzene gave 2.94 g. of a viscous product. The trituration of the product with 250 ml. of water left an insoluble part (1.21 g.) which, after recrystallization from ethanol, melted at 159∼160°C and was identical with tri-*O*-methylgallic anhydride. The aqueous extract was processed to give a viscous product, which was then chromatographed on alumina to give two fractions. The first fraction gave 0.50 g. (20.0%) of an oily product of 7-(tri-*O*-methylgalloyloxy)-2-ethyldecahydroisoquinoline.

Methyl 7-(Tri-*O*-methylgalloyloxy)-2-ethyldecahydroisoquinolinium Bromide (XVI).—The treatment of 0.50 g. of 7-(tri-*O*-methylgalloyloxy)-2-ethyldecahydroisoquinoline with an excess of methyl bromide gave 0.61 g. of crude crystals of quaternary ammonium salt. Trituration with 16 ml. of acetone left 0.087 g. (14.0%) of an insoluble solid with a m. p. of 241∼243.5°C. Recrystallization from ethanol-petroleum ether gave colorless needles with a m. p. of 244.5∼245.0°C.

Found: C, 55.89; H, 7.37. Calcd. for $C_{22}H_{34}O_5NBr$: C, 55.93; H, 7.25%.

Evaporation of the acetone solution gave 0.52 g.

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8) T. Heap and R. Robinson, *J. Chem. Soc.*, **1929**, 69.

of a viscous product which could not be caused to crystallize.

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