A New Synthesis of (±)-Pseudoyohimbane. The Mercuric Acetate Oxidation of Decahydro-2-(2-indol-3-ylethyl)-*trans*-isoquinoline

GLENN C. MORRISON, WIACZESLAW CETENKO, AND JOHN SHAVEL, JR.

Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey

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Recently, Wenkert[1] has described the oxidative cyclization of 3-ethyl-1-(2-indol-3-ylethyl)piperidine to give four isomeric octahydroindoloquinolizines. This work suggests the possibility of a new synthesis of the yohimbane system from the oxidation of decahydro-2-(2-indol-3-ylethyl)-*trans*-isoquinoline (**1**). However, unless additional factors not operating in Wenkert's work are involved, the product would be a complex mixture of six compounds. Oxidation of the isoquinoline **1** at the 3 position would result in a dehydro intermediate (**2**) which could cyclize to either (±)-yohimbane[2] (**5**) or (±)-pseudoyohimbane[3] (**6**). Oxidation at the 1 position would give the dehydro compound **3** which could lead to *trans-anti* (**7**) or *trans-syn* (**8**) inside yohimbane.[4] Epimerization[5] of the dehydro compound *via* its enamine form leads to *cis-anti* (**9**) and *cis-syn* (**10**) inside yohimbane[4] *via* **4**.

During the oxidation step Wenkert found that the 3-substituted piperidine ring was attacked indiscriminately on both sides of the nitrogen. In our case this would lead to a *trans*-Δ^1- or -Δ^2-octahydroisoquinoline. It has been shown in the analogous carbocyclic case that *trans*-Δ^2-octalin is slightly more thermodynamically stable than *trans*-Δ^1-octalin.[6,7] Therefore we had assumed that the yohimbane series might be more favored.

If this consideration holds, then the possible products of the cyclization step would be (±)-pseudoyohimbane and (±)-yohimbane, of which (±)-yohimbane is more thermodynamically stable.[8] However, it has been shown in the carbocyclic case that electrophilic addition to a double bond normally gives the less thermodynamically stable *trans*-diaxial isomer.[7] In our system this mechanism would produce (±)-pseudoyohimbane *via* a chair transition state;[7] however, a less favorable boat transition state would be required for (±)-yohimbane. Therefore (±)-pseudoyohimbane might well be the predominant product of the reaction.

Although the preparation of the starting material

(1) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **84**, 4914 (1962).

(2) G. C. Morrison, W. A. Cetenko, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 2695 (1966), and references therein.

(3) For a description of the total synthesis of pseudoyohimbane from the zinc–acetic acid reduction of 3-dehydroyohimbane, see E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958).

(4) G. C. Morrison, W. A. Cetenko, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2768 (1967).

(5) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(6) G. Braddeley, *Ann. Rept. Progr. Chem.* (Chem. Soc. London), **51**, 173 (1954).

(7) L. Velluz, J. Valls, and G. Nimine, *Angew. Chem. Intern. Ed. Engl.*, **4**, 183 (1965), and references therein.

(8) That (±)-yohimbane is more thermodynamically stable was shown by the isomerization of pseudoyohimbane to yohimbane: E. Wenkert and L. H. Liu, *Experientia*, **11**, 302 (1955).

is described in the literature,[9] we chose another route since we had available supplies of tryptamine and diethyl *trans*-2-carboxycyclohexaneacetate.[10] Condensation of the amine and diester gave hexahydro-2-(2-indol-3-ylethyl)-*trans*-1,3(2H,4H)-isoquinolinedione which was converted to **1** by lithium aluminum hydride reduction.

Treatment of **1** with mercuric acetate in aqueous acetic acid solution led to a good recovery of crude bases from which (±)-pseudoyohimbane was isolated in 31% yield by recrystallization. Attempts to obtain any other products by fractional recrystallization or chromatography were fruitless. However, thin layer chromatography of the total reaction product indicated the presence of minor amount of (±) yohimbane (**5**) and the four inside yohimbanes (**7**–**10**) in addition to (±)-pseudoyohimbane.

Experimental Section

The melting points were determined using a Thomas-Hoover apparatus which had been calibrated against known standards. Thin layer chromatography was carried out on silica gel G (Stahl) using a 0.2:1:0.5 or 1:1:0.5 mixture of acetone, benzene, and *n*-heptane as the eluent in an ammonia atmosphere, the chromatograms being developed by spraying with a solution of potassium iodoplatinate.

Hexahydro-2-(2-indol-3-ylethyl)-*trans*-1,3(2H,4H)-isoquinolinedione.—A mixture of 62 g of tryptamine and 91 g of dimethyl *trans*-2-carboxycyclohexaneacetate was heated at 175° for 20 hr. The reaction mixture was digested with 700 ml of methanol on the steam bath for 20 min. After cooling to room temperature filtration gave 83 g (70%) of a crystalline solid, mp 251–252°. Recrystallization from methanol gave an analytical sample, mp 252–253°.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.15; N, 9.03. Found: C, 73.35; H, 7.31; N, 9.07.

Decahydro-2-(2-indol-3-ylethyl)-*trans*-isoquinoline (1).—To a solution of 12 g of lithium aluminum hydride in 500 ml of tetrahydrofuran was added over a 1-hr interval a hot solution of 10.5 g of hexahydro-2-(2-indol-3-ylethyl)-*trans*-1,3(2H,4H)-isoquinolinedione in 900 ml of tetrahydrofuran. After the addition had been completed, refluxing was continued for an additional 6 hr. The reaction mixture was decomposed by the addition of water. The tetrahydrofuran solution was decanted from the precipitate and the solvent was removed. Recrystallization of the residue from acetonitrile gave 7.6 g (80%) of a crystalline solid, mp 151–152° (lit.[9] 150–151°).

Anal. Calcd for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.64; H, 9.39; N, 9.70.

(±)-Pseudoyohimbane (6). Oxidation Method.—A solution of 14.1 g of decahydro-2-(2-indol-3-ylethyl(-*trans*-isoquinoline and 190 g of mercuric acetate in 1250 ml of 5% acetic acid was heated at 70–75° for 12 hr. The reaction mixture was saturated with hydrogen sulfide and was filtered while hot. The precipitate was washed with an additional 1500 ml of 5% acetic acid. The filtrates were combined, concentrated to 200 ml *in vacuo*, and 500 ml of methanol was added. The pH of the solution was adjusted to 5 with 10% sodium hydroxide solution and 25 g of sodium borohydride added at 10–20°. After standing at 25° for 20 hr the methanol was removed *in vacuo* and the solution was extracted with three 100-ml portions of chloroform. The chloroform layers were combined, washed with water, and dried over sodium sulfate, and the solvent was removed. The residue (12.9 g) after recrystallization from acetonitrile gave 4.4 g (31%) of a crystalline solid, mp 217–220°. Recrystallization from ethanol gave an analytical sample, mp 220–221°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.83; H, 8.63; N, 9.99. Found: C, 81.08; H, 8.67; N, 9.75.

From (±)-3-Dehydroyohimbane Chloride.—To a solution of 20 g of (±)-3-dehydroyohimbane chloride, 50 ml of perchloric acid, 250 ml of water, and 400 ml of tetrahydrofuran in 1.2 l. of methanol was added 50 g of zinc dust portionwise over a 30-min interval. After the addition had been completed the mixture was refluxed for an additional 3 hr. The reaction mixture was filtered and the solvent was removed. The residue was treated with 270 ml of 20% sodium hydroxide solution and 1.7 l. of chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and the solvent was removed. Recrystallization of the residue from 400 ml of acetonitrile gave 8.9 g (50%) of a solid, mp 221–222°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.08; H, 8.53; N, 10.24.

The mother liquor was concentrated to 100 ml. On standing there was deposited 4.3 g (24%) of (±)-yohimbane, mp 179–181°.

Registry No.—**1**, 14325-28-1; **6**, 14210-12-9; hexahydro-2-(2-indol-3-ylethyl)-*trans*-1,3(2H,4H)-isoquinolinedione, 14210-22-1; mercuric acetate, 1600-27-7.

(9) E. E. van Tamelen, M. Shamma, and P Aldrich, *J. Am. Chem. Soc.*, **78**, 4628 (1956).

(10) J. Rubinfeld, Ph.D. Thesis, Columbia University, 1961.

Quinazolines. V. Synthesis and Proof of Structure of 1,3-Diamino-5,6-dihydrobenzo[*f*]quinazoline[1]

ELIZABETH P. BURROWS, ANDRE ROSOWSKY, AND EDWARD J. MODEST

The Children's Cancer Research Foundation and the Departments of Biological Chemistry and Pathology, Harvard Medical School at The Children's Hospital Medical Center, Boston, Massachusetts

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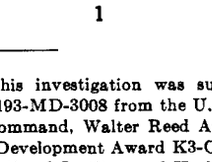
The direct synthesis of various monocyclic and condensed pyrimidines by condensation of acyclic and alicyclic ketones with dicyandiamide under fusion conditions has been reported previously from these laboratories.[2] Among the ketones investigated was 2-tetralone, which could be expected to yield either 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (**1**) or 2,4-diamino-5,10-dihydrobenzo[*g*]quinazoline (**2**), depending upon the direction of cyclization. Earlier experiments in these laboratories suggested that cyclization had occurred at the 3 position, giving **2**.[3] In the present



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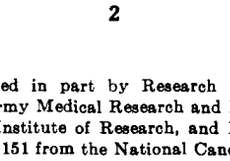

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(2) E. J. Modest, S. Chatterjee, and H. Kangur, *J. Org. Chem.*, **27**, 2708 (1962).

(3) S. K. Sengupta, S. Chatterjee, H. Kangur, and E. J. Modest, Abstracts of Papers, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 3, 1963, p 37-L. The tentative structural assignment was based on the isolation of 2,4-diaminobenzo[*g*]quinazoline as the major product (13% yield) of dehydrogenation of the dicyandiamide–2-tetralone fusion product with palladium–charcoal in tetralin and 2-[(2′-ethoxy)-ethoxy]ethanol. Apparently the benzo[*g*]quinazoline resulted from a skeletal rearrangement under disproportionation conditions (to be submitted for publication).