Synthesis of 5,6,8,9,14,14a-Hexahydroisoquino[1,2-*b*][3]benzazepines

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Syntheses of 5,6,8,9,14,14a-hexahydroisoquino[1,2-*b*][3]benzazepine-2,3,11,12-tetrol and related compounds are described. Key steps involve an initial construction of the isoquinoline ring under the Bischler-Napieralski conditions, which is followed by the building of the azepine ring *via* an intramolecular lactam formation on to the isoquinoline nucleus.

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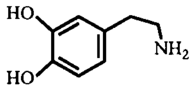
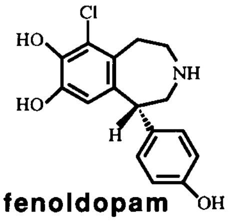
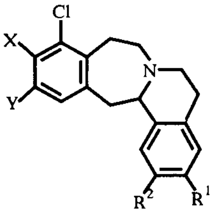
The discovery of the renal vasodilating and naturetic activities of dopamine [1] led to the speculation that dopamine may be involved in the etiology of hypertension. Subsequently, it was found that the stimulation of D-1 receptors causes smooth muscle relaxation in the kidney with resultant renal vasodilation and an increase of blood flow in the kidney [2,3]. This finding eventually led to the development of a clinically useful D-1 receptor agonist, fenoldopam, which improves cardiac output and lowers high blood pressure in human [4,5,6].



dopamine



fenoldopam



I

a : R^1-R^2-X-Y-OH

b : R^1-X-Y-OH, R^2-H

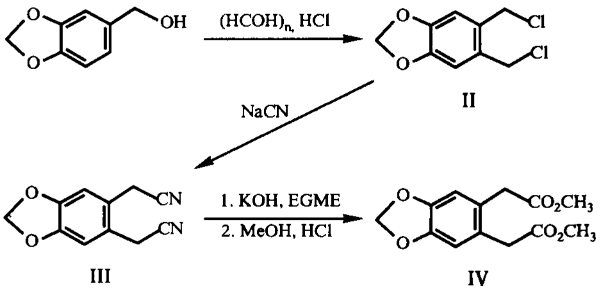
c : R^1-R^2-OH, X-Y-H

Isoquino[1,2-*b*][3]benzoazepines exemplified by I_a were interest to us as potential dopaminergic agents. Like fenoldopam, these compounds contain dopamine moieties as a partial structure in their molecules, and thus may be recognized by dopamine receptors in the body with subsequent binding with them, causing dopamine related biological activities.

Although the isoquino-[1,2-*b*][3]benzazepine ring system has been known since 1983 as the basic structural skeleton for alkaloids, puntarenine [7] and saulatine [8] isolated from Brazilian plants, no report on the synthesis of this type of compounds has appeared in the literature. This report describes the synthetic details for the preparation of I and related compounds.

Our initial synthetic plan for the target compounds was to construct the azepine ring on to the readily available 1-benzyltetrahydroisoquinolines having the required hydroxyl groups in a protected form under the Friedel-Crafts alkylation or acylation conditions, but in practice it met with failures. An alternative approach which involves the building of the 7-membered ring *via* lactam formation was proven to be successful. For this approach 1,3-benzodioxole-5,6-diacetic acid was used as the key starting material.

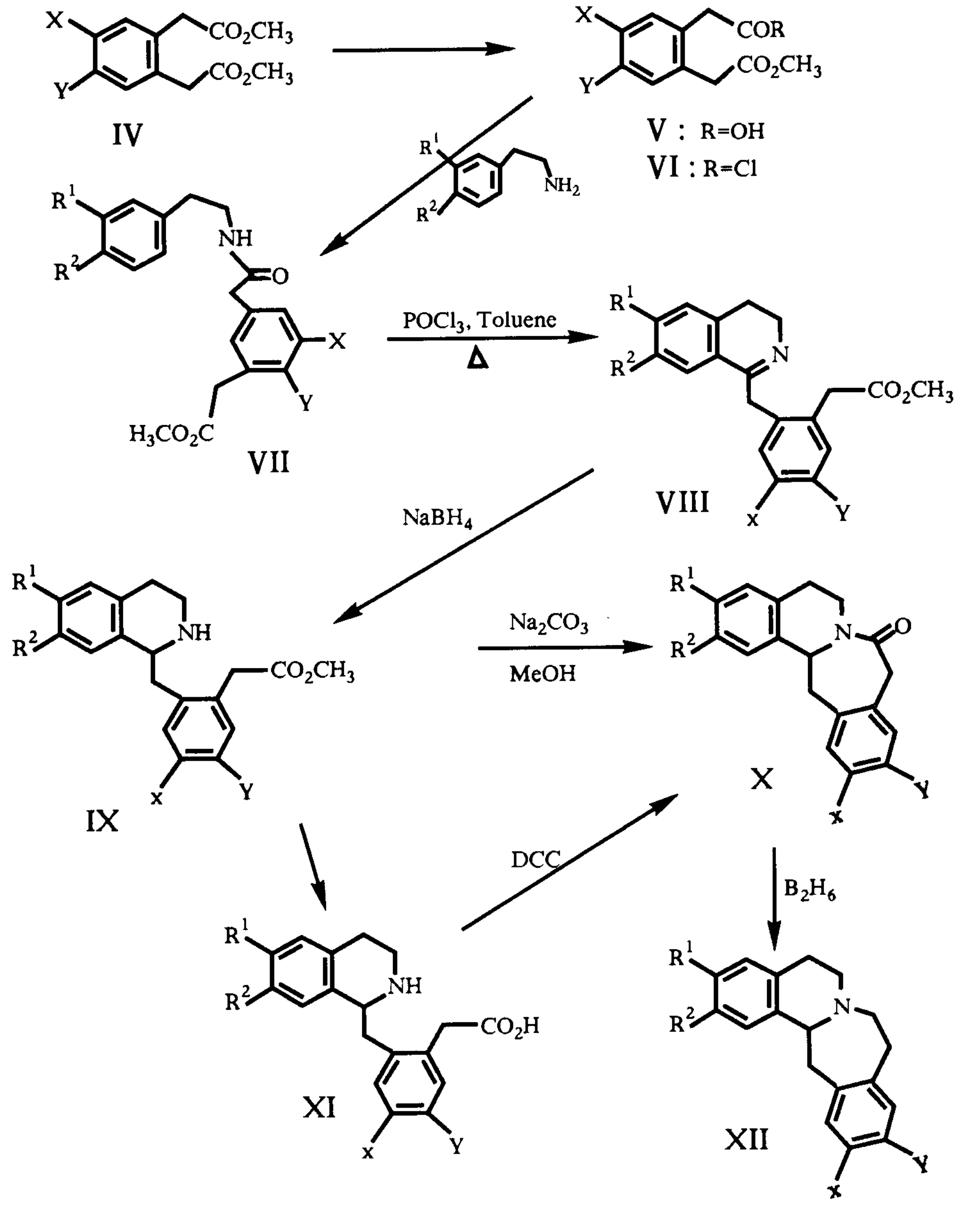
Scheme I



5,6-Dichloromethyl-1,3-benzodioxazole (**II**) that was prepared from piperonyl alcohol by the method of Dallecker *et al* [9] was converted to the corresponding dicyano compound **III** by the procedure described by Pecherer *et al* [10]. The latter **III** was then hydrolyzed to the corresponding diacid by the treatment with potassium hydroxide in ethylene glycol monomethyl ether under reflux for 7 hours, and then esterified with methanol under acidic conditions to give dimethyl ester **IV** (Scheme 1).

Treatment of the dimethyl ester **IV** with an equimolar aqueous solution of sodium hydroxide in methanol gave acid ester **V** in a 76% yield. The latter was then converted to the corresponding acid chloride **VI**. The subsequent treatment of **VI** with 3,4-dimethoxyphenethylamine in methylene chloride in the presence of triethylamine gave the amide **VII** in a 93% yield.

Scheme II



a: $R^1=R^2=OCH_3$, X+Y=OCH_2O

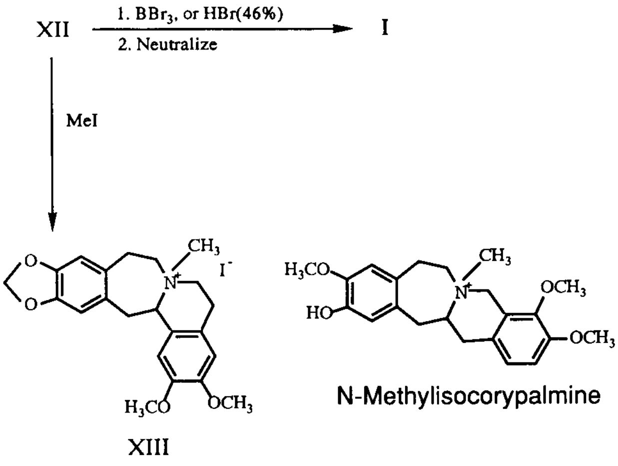
B: $R^1=OCH_3$, R^2=H, X+Y=OCH_2O

c: $R^1=R^2=OCH_3$, X=Y=H

Cyclization of **VII** to form the dihydroisoquinoline **VIII** was effected under the Bischler-Napieralski conditions. Thus, treatment of **VII** with phosphorus oxychloride in toluene under reflux for 30 minutes afforded the key intermediate **VIII** in a 62% yield. The ring closure reaction was confirmed by the disappearance of the infrared amide carbonyl absorption band present in $\mathbf{VII_a}$ at 1640 cm^{-1}. Sodium borohydride reduction of $\mathbf{VIII_a}$ in aqueous methanol yielded the tetrahydroisoquinoline $\mathbf{IX_a}$ which on treatment with sodium carbonate in methanol cyclized, giving the isoquino[1,2-*b*][3]benzazepinone $\mathbf{X_a}$. Alternatively, but less efficiently, the transformation of **IX** to **X** could also be effected *via* **XI** using dicyclohexylcarbodiimide. The lactam carbonyl group of $\mathbf{X_a}$ was reduced smoothly with diborane (Scheme II). The demethylation of **XII** was effected using boron tribromide or hydrobromic acid to give the target compound $\mathbf{I_a}$ (Scheme III). The structure of $\mathbf{I_a}$ [11] was supported by the nmr and elemental analysis. By following the synthetic route parallel to the one used for the preparation of $\mathbf{I_a}$, (Schemes II and III) $\mathbf{I_b}$ was prepared starting with **VI** and 3-methoxyphenethylamine, and $\mathbf{I_c}$ from 1,2-benzenediacetic acid 1-methyl ester and 3-(3,4-dimethoxyphenyl)-ethylamine, respectively.

Cavé *et al* [12] reported that *N*-methylisocorypalmine which was isolated from *Cymbopetalum brasiliense* Benth showed an inotropic activity. It was thus thought to be interesting to prepare quartenary salt **XIII** and **XII**, which has structural resemblance to the alkaloid. The compound **XIII** was readily prepared by allowing **XII** to react with methyl iodide in dimethylformamide.

Scheme III



5,6,8,9,14,14a-Hexahydroisoquino[1,2-*b*][3]benzazepine-3,11,12-triol ($\mathbf{I_b}$) showed a marked antihypertensive activity when tested on the spontaneously hypertensive rat, lowering blood pressure by 82 mm Hg and 65 mm Hz at 1.5 hours and 4.0 hours, respectively, after oral dosing of 25 mg/Kg, and 5,6,8,9,-15,15a-hexahydro-2,3-dimethoxy-7-methyl[1,3]dioxolo[4,5-*h*]isoquino[1,2-*b*][3]benzazepinium iodide (**XIII**) exhibited a moderate antihypertensive activity, lowering 41 mm Hg at 1.5 hours after oral dosing of 25 mg/Kg on the rat. The causes of these antihypertensive effects remain to be determined.

EXPERIMENTAL

Melting points were taken in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. The ir spectra were obtained in potassium bromide pellets using a Perkin-Elmer 21 spectrophotometer. The nmr spectra were determined on a Varian XL-300 or a Varian FT-80A spectrometer using tetramethylsilane as the internal reference. The mass spectral data were obtained with Kratos 20 mass spectrometer. Combustion elemental analyses were performed by the Analytical Section of these Laboratories.

1,3-Benzodioxole-5,6-diacetic Acid (III).

Potassium hydroxide pellets (87%) (64.57 g, 1 mole) were dissolved in ethylene glycol monomethyl ether (300 ml). To this solution was added 1,3-benzodioxole-5,6-diacetonitrile [10] (40.04 g, 0.2 mole), and the resulting mixture was heated under reflux for 7 hours. The reaction was cooled to room temperature, and ether (320 ml) was added. The resulting mixture was chilled in ice, and a precipitate was collected on a filter and washed with ethanol repeatedly until a colorless washing was obtained. The filter residue was dissolved in hot water (150 ml), and the solution was filtered. Acidification of the filtrate with dilute hydrochloric acid followed by chilling in ice caused separation of a precipitate which was collected on a filter and washed with water several times to give the product (10.16 g, 21%), mp 206-208° dec.

Anal. Calcd. for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23. Found: C, 55.53; H, 4.22.

1,3-Benzodioxole-5,6-diacetic Acid Dimethyl Ester (IV).

A mixture of 1,3-benzodioxole-5,6-acetic acid (16.66 g, 0.07 mole) and methanol (167 ml) was saturated with hydrogen chloride gas at 0°, and the resulting solution was stirred at 45° overnight, then concentrated on a steam bath to about 60 ml. Chilling of the concentrated solution in ice caused separation of a precipitate which was collected on a filter and washed with methanol to give 16.9 g (91%) of the product, mp 79-82°. An analytical sample obtained by recrystallization from methanol melted at 81-83°.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.55; H, 5.30.

1,3-Benzodioxole-5,6-diacetic Acid 5-Methyl Ester (V).

Sodium hydroxide solution (1.0 *N*, 526 ml, 52.6 mmoles) was added over the period of 1 hour with vigorous stirring to a solution of **IV** (15.5 g, 52.6 mmoles) and methanol (700 ml). Anhydrous ether (250 ml) was added. The resulting mixture was stirred at room temperature for 20 hours, then chilled in ice. The precipitate that separated was filtered and the filter residue was washed with methanol. The combined filtrate and washings were evaporated on a rotary evaporator to give a gummy residue which was dissolved in a mixture of water (70 ml) and ether (70 ml). The aqueous layer was collected, and washed with ether two times, then acidified with dilute hydrochloric acid. Chilling of the acidic solution in ice caused separation of a precipitate which was collected on a filter and washed with water to give 10.9 g (76%) of the title product, mp 105-107°; ir: 1700 (CO_2H) and 1730 cm^{-1} (CO_2CH_3).

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 56.83; H, 4.72.

6-[2[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-oxoethyl]-1,3-benzodioxole-5-acetic Acid Methyl Ester ($\mathbf{VII_a}$).

To a mixture of **IV** (17.65 g, 0.07 mole), anhydrous ether (700 ml) and thionyl chloride (9.16 g, 0.077 mole) was added 3 drops of triethylamine. The resulting mixture was stirred at room temperature overnight, then heated under reflux for 2 hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated on a rotary evaporator to give an oily residue. The residue was coevaporated with anhydrous ether several times, then placed *in vacuo* to give the corresponding acid chloride. The latter acid chloride was dissolved in methylene chloride (50 ml), and was added to a stirred ice-chilled mixture of 3,4-dimethoxyphenethylamine (12.69 g, 0.07 mole), triethylamine (7.07 g, 0.07 mole), and methylene chloride (300 ml). The resulting mixture was stirred at room temperature for 2 hours, washed with water, dried (sodium sulfate), and evaporated on a rotary evaporator to give a solid residue. Recrystallization of the crude product from methanol afforded 27 g (93%) of the product, mp 122-125°. The analytical sample that was recrystallized from methanol melted at 124-126°; ir: 1640 (CON) and 1750 cm^{-1} (CO_2Me).

Anal. Calcd. for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.21; H, 5.86; N, 3.43.

6-[2[[2-(3-Methoxyphenyl)ethyl]amino]-2-oxoethyl]-1,3-benzodioxole-5-acetic Acid Methyl Ester (**VII**$_b$).

This compound was prepared analogously. Thus, 1,3-Benzodioxole-5,6-diacetic acid 5-methyl ester (17.655 g, 0.07 mole) was converted into the corresponding acid chloride by the treatment with thionyl chloride (9.163 g, 0.077 mole). The acid chloride that was obtained was then allowed to react with 3-methoxyphenthylamine (10.58 g, 0.07 mole) in the presence of triethylamine (7.07 g, 0.07 mole) in methylene chloride. The product that was obtained initially as an oil solidified on standing. Recrystallization from methanol afforded 18.9 g (70%) of the titled compound, mp 81-83°.

Anal. Calcd. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.01; N, 3.63. Found: C, 65.63; H, 6.03; N, 3.58.

2-[2-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-2-oxoethyl]benzeneacetic Acid Methyl Ester (**VII**$_c$).

Thionyl chloride (4.0 g, 0.0336 mole) was added dropwise to a solution obtained by dissolving 1,2-benzenediacetic acid 1-methyl ester (6.25 g, 0.03 mole) in anhydrous ether (250 ml). The resulting mixture was stirred at room temperature overnight, then evaporated on a rotary evaporator to give an oily residue. The residue was dissolved in anhydrous ether, and the solution was evaporated on a rotary evaporator. This dissolution in ether and evaporation on a rotary evaporator was repeated two additional times. The residue was dissolved in methylene chloride (20 ml). The solution was added dropwise to a well stirred and ice-chilled methylene chloride solution of 3-(3,4-dimethoxyphenyl)-ethylamine (5.43 g, 0.03 mole) and triethylamine (3.03 g, 0.03 mole) in methylene chloride (100 ml). The chilling source was removed, and the stirring was continued for 2 hours. The reaction mixture was washed with water twice, then with brine and dried over anhydrous sodium sulfate. Evaporation of methylene chloride on a rotary evaporator gave a thick oil which solidified upon chilling with scratching. The crude product was recrystallized from ether to give the titled product (3.3 g, 30%), mp 88-91°; an analytical sample recrystallized from ether melted at 92-94°.

Anal. Calcd. for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.82; H, 6.66; N, 3.66.

6-[(3,4-Dihydro-6,7-dimethoxy-1-isoquinolinyl)methyl]-1,3-benzodioxole-5-acetic Acid Methyl Ester (**VIII**$_a$).

Four g (0.01 mole) of **VII**$_a$ was dissolved in warm toluene which had been dried using a Dean-Stark trap. Phosphorus oxychloride (3.383 g, 0.025 mole) was added to the toluene solution, and the reaction mixture was heated under reflux for 30 minutes, then chilled in ice with addition of anhydrous ether (120 ml). A precipitate was collected on a filter, washed with acetone, and recrystallized from a mixture of methanol and acetone to give the titled product (2.76 g, 62%), mp 191-193° dec. The analytical sample that was obtained by recrystallization once more from methanol and acetone melted at 194-196° dec; ir: 1750 cm^{-1} (CO_2CH_3).

Anal. Calcd. for $C_{22}H_{23}NO_6\cdot HCl\cdot 0.5H_2O$: C, 59.66; H, 5.69; N, 3.16. Found: C, 59.57; H, 5.71; N, 3.17.

6-[(3,4-Dihydro-6-methoxy-1-isoquinolinyl)methyl]-1,3-benzdioxole-5-acetic Acid Methyl Ester (**VIII**$_b$).

This compound was prepared analogously from **VII**$_b$ (7.71 g, 0.02 mole) and phosphorus oxychloride (7.66 g, 0.05 mole). The crystalline product that was obtained was recrystallized from acetonitrile. The product was amounted to 1.4 g (15%), and melted at 182-184° dec.

Anal. Calcd. for $C_{21}H_{21}NO_5\cdot H_3PO_4\cdot 1/2H_2O$: C, 53.16; H, 5.31; N, 2.95. Found: C, 53.17; H, 5.08; N, 3.09.

2-[(3,4-Dihydro-6,7-dimethoxy-1-isoquinolyl)methyl]benzeneacetic Acid Methyl Ester (**VIII**$_c$).

This compound was prepared analogously from **VII**$_c$ (3.0 g, 8 mmoles) and phosphorus oxychloride (1.53 g, 10 mmoles) in boiling toluene. A crude product was purified by recrystallization from ethanol to give the titled product (1.8 g, 50%) as the phosphoric acid salt, mp 108-110°; ms: (CI) m/z 354 (M+H); (EI) m/z 353, 280.

Anal. Calcd. for $C_{21}H_{23}NO_4\cdot H_3PO_4$: C, 55.87; H, 5.80; N, 3.10. Found: C, 55.75; H, 5.78; N, 3.11.

6-[(1,2,3,4-Tetrahydro-6,7-dimethoxy-1-isoquinolinyl)methyl]-1,3-benzodioxole-5-acetic Acid Methyl Ester (**IX**$_a$).

Six and one-half g (14 mmoles) of **VIII**$_a$ hydrochloride was dissolved in methanol (40 ml) and water (120 ml), and the solution was chilled in ice. Aqueous sodium borohydride obtained by dissolving 1.0 g of sodium borohydride in 20 ml of water was added dropwise with vigorous stirring. The resulting mixture was allowed to sit at room temperature with occasional hand swirling for 45 minutes. About 100 ml of ether was added, and the mixture was stirred vigorously, and the ether layer was collected. The aqueous layer was made alkaline by the addition of dilute sodium hydroxide solution and extracted with ether twice. The combined ether extracts were washed with brine, dried (sodium sulfate), then evaporated on a rotary evaporator to give an oily residue which solidified on standing to give the titled product (4.0 g, 68%). Recrystallization from ether afforded an analytical sample, mp 99-101°.

Anal. Calcd. for $C_{22}H_{26}NO_6$: C, 65.98; H, 6.55; N, 3.50. Found: C, 66.17; H, 6.28; N, 3.53.

6-[(1,2,3,4-Tetrahydro-6-methoxy-1-isoquinolinyl)methyl]-1,3-benzodioxole-5-acetic Acid Methyl Ester (**IX**$_b$).

This compound was prepared analogously by reducing **VIII**$_b$ with sodium borohydride. The resinous product that was obtained was used in the subsequent reaction without purification.

2-[(1,2,3,4-Tetrahydro-6,7-dimethoxy-1-isoquinolyl)methyl]benzeneacetic Acid Methyl Ester (**IX**$_c$).

This compound was prepared analogously from **VIII**$_c$, and the oily product was used in the subsequent reaction without purification.

5,9,15,15a-Tetrahydro-2,3-dimethoxy[1,3]dioxolo[4,5-*h*]isoquino[1,2-*b*][3]benzazepin-8(6*H*)-one (**X**$_a$).

A mixture of **IX**$_a$ (8.0 g, 0.02 mole), sodium carbonate (1.6 g, 0.015 mole) and methanol (210 ml) was heated under reflux for 3.5 hours. Addition of water (100 ml) and chilling in ice caused separation of a precipitate which was collected on a filter and washed with water to give the titled product (7.03 g, 96%), mp 207-209°. Recrystallization from ethanol gave an analytical sample, mp 208-210°; ir: 1635 cm^{-1} (CON); ms: (CI) m/z 383 (M + H).

Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.62; H, 5.77; N, 3.84.

5,9,15,15a-Tetrahydro-3-methoxy[1,3]dioxolo[4,5-*h*]isoquino[1,2-*b*][3]benzazepin-8(6*H*)-one (**X**$_b$).

This compound was prepared analogously by treating **IX**$_b$ with sodium carbonate in methanol. The crude product (mp 154-156°) obtained in 82% yield was recrystallized from ethanol, mp 154-156°; ms: (CI) m/z 338 (M + H).

Anal. Calcd. for $C_{20}H_{19}NO_4 \cdot 1/2EtOH$: C, 69.98; H, 6.15; N, 3.89. Found: C, 69.61; H, 5.80; N, 3.91.

5,9,14,14a-Tetrahydro-2,3-dimethoxyisoquino[1,2-*b*][3]benzazepin-8(6*H*)-one (**X**$_c$).

A mixture of **IX**$_c$ (6.8 g, 0.019 mole), sodium carbonate (2.01 g, 0.019 mole) was heated under reflux for 2 hours, then chilled in ice. A precipitate was collected on a filter and washed with water, then with methanol to give the titled product (4.8 g, 78%), mp 195-197°.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.22; H, 6.55; N, 4.33. Found: C, 74.17; H, 6.82; N, 4.37.

To an ice-chilled solution of **XI**$_c$ (0.4 g, 1.17 mmoles) and 4-dimethylamonopyridine (0.15 g, 1.23 mmoles) in dry acetonitrile (45 ml) was added with stirring dicyclohexylcarbodiimide (0.24 g, 1.17 mmoles). The resulting mixture was stirred at room temperature for 6 hours, then heated to boiling briefly. When the mixture was cooled to room temperature, there was separated a precipitate which was removed by filtration. The filtrate was concentrated to about 10 ml, and chilled in ice to cause a separation of a precipitate. The precipitate was collected on a filter and recrystallized from ethanol, giving the titled product (0.26 g, 69%).

2-[(1,2,3,4-Tetrahydro-6,7-dimethoxy-1-isoquinolinyl)methyl]benzeneacetic Acid (**XI**$_c$).

A mixture of **IX**$_c$ (1.0 g, 2.8 mmoles), 1.0 *N* sodium hydroxide solution and methanol (10 ml) was heated under reflux for 1.5 hours and filtered after being cooled to room temperature. The filtrate was acidified with dilute hydrochloric acid, and chilled in ice with scratching. A white cotton-like precipitate was collected on a filter and washed with cold water to give the titled product (0.45 g, 41%), mp 129-145° dec.

Anal. Calcd. for $C_{20}H_{23}NO_4 \cdot HCl \cdot 1/2H_2O$: C, 62.09; H, 6.51; N, 3.62. Found: C, 61.90; H, 6.65; N, 3.71.

5,6,8,9,15,15a-Hexahydro-2,3-dimethoxy[1,3]dioxolo[4,5-*h*]isoquino[1,2-*b*][3]benzazepine (**XII**$_a$).

To a well stirred and ice-chilled 1.0 *M* tetrahydrofuran solution of borane-tetrahydrofuran complex was added **X**$_a$ (7.0 g, 0.019 mole) suspended in tetrahydrofuran (350 ml) in 20 minutes, then the reaction mixture was heated under reflux for 1 hour. After the reaction mixture was cooled to room temperature, dilute hydrochloric acid (6.0 *N*, 24 ml) was added slowly, and the mixture was distilled at atmospheric pressure until 340 ml of tetrahydrofuran was collected. The residue was made alkaline by dropwise addition of 50% sodium hydroxide, whereby a precipitate was separated. The mixture was chilled in ice, and the precipitate was collected on a filter and washed with ethanol to give the product (5.15 g, 77%), mp 166-168°. The analytical sample that was obtained by recrystallization from ethanol melted at 168-170°.

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.48; H, 6.79; N, 3.61.

5,6,8,9,15,15a-Hexahydro-3-methoxy[1,3]dioxolo[4,5-*h*]isoquino[1,2-*b*][3]benzazepine (**XII**$_b$).

This compound was prepared by the reduction of **X**$_b$ hemiethanolate (3.60 g, 10 mmoles) with diborane in tetrahydrofuran (25 ml of 1.0 *M* solution). The product was extracted with methylene chloride. The methylene chloride extract was dried (sodium sulfate) and evaporated on a rotary evaporator to give an oil which solidified on standing. Recrystallization from ethanol afforded the titled compound (2.57 g, 80%), mp 133-135°.

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.54; N, 4.33. Found: C, 73.87; H, 6.67; N, 4.25.

A portion of the product was converted into hydrochloric acid salt by treating the compound dissolved in ethanol with ethanolic hydrogen chloride, mp 239-241° dec.

Anal. Calcd. for $C_{20}H_{21}NO_3 \cdot HCl$: C, 66.75; H, 6.16; N, 3.89. Found: C, 66.91; H, 6.13; N, 3.72.

5,6,8,9,14,14a-Hexahydro-2,3-dimethoxyisoquino[1,2-*b*][3]benzazepine (**XII**$_c$).

This compound was prepared by the reduction of **X**$_c$ (3.88 g, 0.012 mole) with diborane-tetrahydrofuran complex (1.0 *M*, 24 ml) in a 73% yield, mp 141-143.5°; ms: (CI) m/z 310 (M + H). This product was converted into the hydrochloric acid salt by treating the ethanolic solution with ethanolic hydrogen chloride solution, mp 222-224° dec.

Anal. Calcd. for $C_{20}H_{21}NO_3 \cdot HCl$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.91; H, 7.23; N, 4.25.

5,6,8,9,14,14a-Hexahydroisoquino[1,2-*b*][3]benzazepine-2,3,11,12-tetrol (**I**$_a$).

Boron tribromide (1.0 *M* solution of methylene chloride, 45 ml) was added dropwise to an ice-chilled, well stirred methylene chloride solution of **XII**$_a$ (1.77 g, 5 mmoles), and the resulting mixture was stirred at room temperature overnight. Methanol (45 ml) was added dropwise to the reaction mixture, then evaporated on a rotary evaporator to give a resinous material which was dissolved in 50% aqueous methanol solution. The solution was added to a separate funnel containing 5% aqueous sodium bicarbonate solution (100 ml), and was extracted with ethyl acetate repeatedly. The combined extracts were dried (anhydrous sodium sulfate), and evaporated on a rotary evaporator to afford a powdery residue. The residue was dissolved in a small amount of ethanol, and the solution was treated with ethanolic hydrogen chloride solution. Acetonitrile was added to the acidic solution until the solution became cloudy, and allowed to sit in a refrigerator overnight. The crystalline precipitate that was separated was collected on a filter and washed with acetonitrile to give the titled product (0.94 g, 55%) which was dried *in vacuo* at 78° overnight, mp 272-276° dec; ^{1}H nmr (DMSO-d$_6$): δ 2.60-3.80 (m, 10H, 5CH$_2$), 4.70 (broad s, 1H, CH), 6.60-6.90 (m, 4H, aromatic Hs which become 2s at 6.62 and 6.86 upon deuterium oxide treatment), 8.83-9.28 (m, 4H, 4OH which disappear upon deuterium oxide treatment), and 11.20 ppm (broad s, 1H, $\equiv$N$^+$H disappears upon deuterium oxide treatment); ms: (EI) m/z 313 (M$^+$).

Anal. Calcd. for $C_{18}H_{19}NO_4 \cdot HCl \cdot 1/4H_2O$: C, 61.01; H, 5.83; N, 3.95. Found: C, 61.24; H, 5.81; N, 4.14.

5,6,8,9,14,14a-Hexahydroisoquino[1,2-*b*][3]benzazepine-3,11,12-triol (**I$_b$**).

This compound was prepared by the treatment of **XII$_b$** (0.9 g, 2.8 mmoles) with boron tribromide for 4 hours. Evaporation of ethyl acetate extracts on a rotary evaporator afforded a solid residue which was dissolved in hot ethanol (about 5 ml). A gummy material was separated upon the treatment of the ethanol solution with ethanolic hydrogen chloride solution. When the mixture was warmed on a steam bath with an additional amount of ethanol (15 ml), a crystalline product was separated. The mixture was chilled in a refrigerator, and the precipitate was collected on a filter and washed with ethanol to give the titled product (0.9 g, 97%). An analytical sample was obtained by dissolving the product in a mixture of ethanol and a small amount of water, and precipitation by an addition of a large amount of anhydrous ether. The product started to char at 282° and decomposed completely at 286°; ms: (CI) m/z 298 (M + 1) and 247.

Anal. Calcd. for $C_{18}H_{19}NO_3 \cdot HCl$: C, 64.76; H, 6.04; N, 4.20. Found: C, 64.70; H, 6.21; N, 4.07.

5,6,8,9,14,14a-Hexahydroisoquino[1,2-*b*][3]benzazepine-2,3-diol (**I$_c$**).

Hydrobromic acid (48%, 30 ml) was added to an glacial acetic acid (3 ml) solution of **XII$_c$** (0.928 g, 3 mmoles), and the resulting solution was heated under reflux for 2.5 hours, then evaporated on a rotary evaporator to give a resinous residue. The residue was dissolved in tetrahydrofuran (about 80 ml), and the solution was allowed to sit at room temperature over a weekend. The crystalline product that separated was collected on a filter, and washed with tetrahydrofuran. The product was recrystallized from ethanol (yield, 0.8 g), mp 270-272°.

Anal. Calcd. for $C_{18}H_{19}NO_2 \cdot HBr$: C, 59.84; H, 5.58; N, 3.88. Found: C, 59.59; H, 5.56; N, 4.11.

5,6,8,9,15,15a-Hexahydro-2,3-dimethoxy-7-methyl[1,3]dioxolo-[4,5-*h*]isoquino[1,2-*b*][3]benzazepinium Iodide (**XIII**).

A mixture of **XII$_a$** (0.71 g, 2 mmoles), sodium carbonate (0.15 g, 1.5 mmoles), methyl iodide (0.43 g, 3 mmoles) and dimethylformamide (10 ml) was stirred at room temperature under nitrogen atmosphere for 2 days and filtered. Addition of a large amount of anhydrous ether and chilling in ice caused separation of a precipitate which was collected on a filter. The filter residue was recrystallized from a mixture of ethanol and water to give 0.5 g (50%) of the titled product, mp 258-260°.

Anal. Calcd. for $C_{22}H_{26}NO_4I$: C, 53.34; H, 5.29; N, 2.83. Found: C, 53.41; H, 5.39; N, 2.90.

REFERENCES AND NOTES

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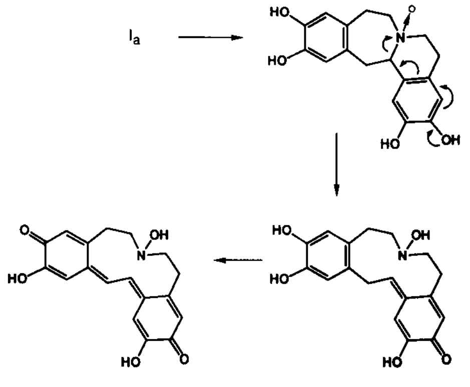
[11] Although the hydrochloride salt of **I$_a$** was stable in the air, the free base turned from white to yellow upon exposure to air. The coloring appears to be due to air oxidation of **I$_a$** with subsequent ring opening to give highly conjugated compound such as **XIV**:



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