Synthesis of (*R*)-1,2,11-Trihydroxy-, (*R*)-2,11-, and (*R*)-2,10-Dihydroxyaporphines — Non Naturally Occurring Aporphine Alkaloids from Pukateine and Thebaine

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The synthesis of (*R*)-2,10-dihydroxyaporphine (**3a**), (*R*)-2,10-dihydroxy-*N*-*n*-propylnoraporphine (**3b**) from thebaine and (*R*)-2,11-dihydroxyaporphine (**7**), and 1,2,11-trihydroxyaporphine (**9**), from pukateine is reported. The rearrangement of thebaine and northebaine with methanesulfonic acid to **1a** and **1b** with subsequent *N*-propylation gave **1b**. Tetrazolyation of **1a**, **1b** and hydrogenolysis of **2a** and **2b** on Pd/C in acetic acid with subsequent *O*-demethylation with hydrobromic acid (48%) led to **3a** and **3b**. *R*(-)-2,11-Dihydroxyaporphine (**7**) was prepared by lithium/ammonia reduction of pukateine. (*R*)-1,2,11-Trihydroxyaporphine (**9**) was synthesized by reaction of pukateine with boron tribromide in dichloromethane.

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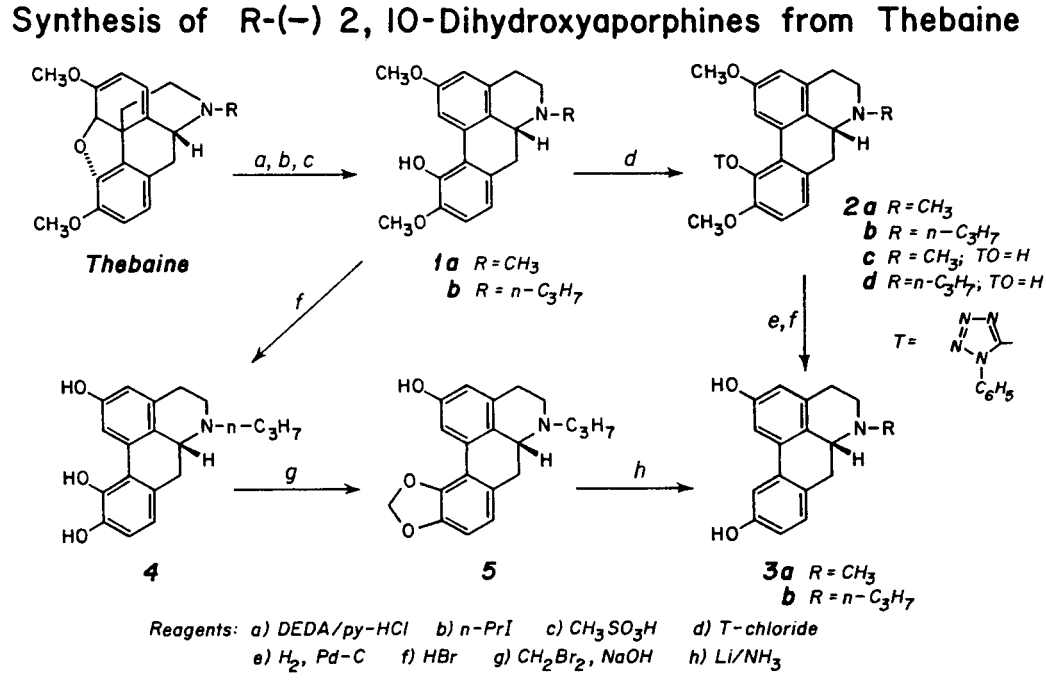
In our continuing studies of the biological activity of hydroxylated aporphines, we have found that the tetracyclic aporphine ring system has been shown to be a useful template to probe dopamine receptors. The presence of the A ring of aporphines and the addition of substituents to it and to other portions of the aporphine ring system can result in compounds useful in extending explorations of the dimensions and other characteristics (*i.e.*, binding sites) of the dopamine (**DA**) receptor. While it is generally accepted that the catechol moiety is required to produce optimum interactions with dopamine receptors, the presence of a catechol in itself is not sufficient to confer agonist activity on aporphines [1,2].

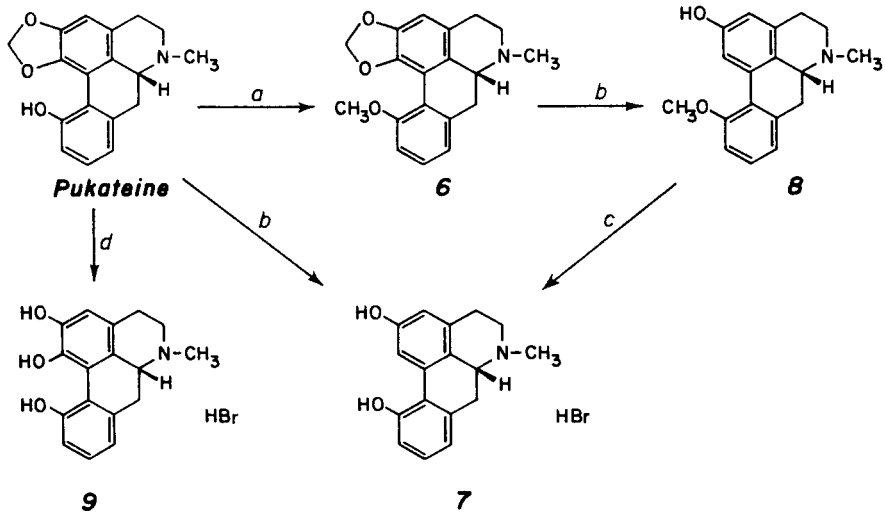
In order to examine dopamine receptor interactions of non-catechol aporphines we have prepared (*R*)-2,11-, (*R*)-2,10-dihydroxyaporphine and (*R*)-1,2,11-trihydroxyaporphine for further biological investigation [2]. The dopamine agonist binding of these aporphines at central dopamine receptors have been previously reported [1,2]. This report describes the synthesis of the 6a*R* isomers of **3a**, **3b**, **7** and **9** since it has been shown that the DA agonist activity resides principally in the *R*-(*levo*) isomer of such

Scheme 1



Scheme 2

Synthesis of R-(−) 2, 11-Dihydroxyaporphine and 1, 2, 11-Trihydroxyaporphine from Pukateine



aporphines [2-4]. In order to preserve the desired stereochemistry at the 6a chiral carbon atom of these aporphines, the synthesis of the target compounds utilized natural products with the appropriate stereochemistry. Thus, the key starting point for the synthesis of the 2,10-dihydroxyaporphines was 2-*O*-methylmorphothebaine (**1a**) and 2-*O*-methyl-*N*-*n*-propylnormorphothebaine (**1b**), prepared by the rearrangement of thebaine or northebaine in methanesulfonic acid [5]. The selective removal of the 11-hydroxy group in **1a** and **1b** was accomplished by the preparation of the phenyl tetrazolyl ethers **2a** and **2b** with subsequent hydrogenolysis over 5% palladium on carbon in acetic acid at room temperature [6], to give **2c** and **2d**. Removal of phenolic hydroxy groups by the hydrogenolysis of the phenyltetrazolyl ether has been shown not to cause racemization in such aporphines [7]. *O*-Demethylation of **2c** or **2d** with hydrogen bromide (48%) at 130° under an atmosphere of nitrogen for 4-5 hours resulted in the isolation of **3a** or **3b** in 71-72% yield. An alternative route to the preparation of the diol **3b** was also investigated starting from the 2,10,11-triol **4** [8]. In this instance the preparation of the 10,11-methylenedioxy derivative **5** [11] with methylene bromide in alkaline medium [6] followed by the lithium metal reduction [10] of the methylenedioxy ring led to **3b**, identical to the product obtained from **2b** (Scheme 1).

The synthesis of 2,11-dihydroxyaporphine (**7**) was accomplished by starting with the naturally occuring alkaloid pukateine [9] which contains a 1,2-methylenedioxy group and the appropriate 6a*R* configuration. Methylation of the 11-hydroxy group in pukateine with diazomethane followed by reduction of the 11-*O*-methyl ether **6** with lithium in ammonia led to a mixture of 2,11-dihydroxyaporphine (**7**) and the 11-*O*-methylated compound **8**. The mixture of **7** and **8** was converted with hydrogen bromide into the diol **7**, isolated as the hydrobromide salt. A more direct route to the formation of **7** involved the lithium in ammonia reduction of pukateine to give a 78% yield of **7** isolated as the hydrochloride salt (Scheme 2).

1,2,11-Trihydroxyaporphine (**9**) was prepared by opening the methylenedioxy ring in pukateine with boron tribromide under nitrogen in methylene chloride.

EXPERIMENTAL

General Methods.

Evaporations were carried out in a Buchi rotary evaporator *in vacuo* at bath temperatures below 50°. Melting points were determined on a Thomas Hoover apparatus (capillary method) and are uncorrected. Analysis were performed by Galbraith Laboratories, Knoxville, TN. Samples for analysis were dried at 10^{-1} mm over silica gel at 55°. Preparative tlc was carried out on silica gel (Analteck, 20 x 20 cm, 2000 microns). Column chromatography was performed on silica gel (Baker, 5-3405, 60-200 mesh). Detection was carried out with uv light (minerallight) or with iodine vapors. The nmr spectra were obtained with a Varian T-60 spectrometer in dimethyl sulfoxide-d_6; tetramethylsilane methanol

was used as an internal standard. The uv spectra were determined in methanol with a Beckman DB-G grating spectrophotometer. Mass spectra were determined on a 12-90-G Nuclide mass spectrometer. Optical rotations were obtained on a Perkin-Elmer polarimeter model 142.

R(-)-2,10-Dimethoxy-11-hydroxyaporphine (**1a**) was prepared [5] by the rearrangement of thebaine from methane sulfonic acid in 65% yield, crystallized from acetonitrile, mp 159-160°.

R(-)-2,10,11-Trihydroxy-*N*-propylnoraporphine hydrobromide (**4**) was prepared *via* the rearrangement of northebaine from concentrated hydrochloric acid with subsequent *N*-propylation and *O*-demethylation in 70% overall yield as described previously [8], mp 203-206°.

R(-)-2,10-Dimethoxy-11-hydroxy-*N*-*n*-propylnoraporphine Hydrochloride (**1b**).

A mixture of 2,10-dimethoxy-11-hydroxynoraporphine (3.2 g, 8.5 mmoles), *n*-propyl iodide (2.0 g, 12 mmoles), and sodium bicarbonate (1.0 g) in acetonitrile was allowed to reflux for 24 hours, cooled and filtered. The filtrate was evaporated to dryness and the crude material was applied to silica column using ether as eluant. The free base was converted into its hydrochloride salt by adding ethereal hydrochloric acid, to yield 2.7 g, mp 145-147°.

Anal. Calcd. for $C_{21}H_{25}NO_3 \cdot HCl \cdot 1/2H_2O$: C, 65.54; H, 7.20; N, 3.64. Found: C, 65.82; H, 7.21; N, 3.47.

R(-)-2,10-Dimethoxy-11-*O*-(1-phenyltetrazol-5-yl)aporphine Hydrochloride (**2a**).

A suspension of **1a**-HCL (1.0 g, 2.9 mmoles) in acetonitrile was allowed to reflux with 5-chloro-1-phenyl-1-tetrazole (0.55 g, 3.0 mmoles) and potassium carbonate (0.9 g) for 20 hours, cooled and filtered. The filtrate was evaporated to dryness. The residue was dissolved in ether chloroform mixture, filtered and ethereal hydrochloric acid was added. A white precipitate of **2a**, 1.42 g (100%) mp 175-180° was isolated; tlc showed a single spot.

Anal. Calcd. for $C_{26}H_{25}N_5O_3 \cdot HCl \cdot 1/2H_2O$: C, 62.34; H, 5.39; N, 13.99. Found: C, 62.47; H, 5.48; N, 14.35.

R(-)-2,10-Dimethoxy-11-*O*-(1-phenyltetrazol-5-yl)-*N*-*n*-propylnoraporphine Hydrochloride (**2b**).

This compound was similarly prepared from **1b** (1.5 g, 3.99 mmoles), and 5-chloro-1-phenyl-1*H*-tetrazole (0.72 g, 3.99 mmoles) in acetonitrile using potassium carbonate as base. The free base was converted into the hydrochloride salt by adding ethereal hydrochloric acid, yield 1.75 g (84%), mp 203-205°; $[\alpha]_{578}^{25}$ + 31.28; ^{1}H nmr (DMSO-d_6): 1.0 (t, 3H), 1.8 (b, 2H), 2.8-3.8 (m, 6H), 3.5 (s, 3H), 3.77 (s, 3H), 6.8 (d, 1H), 7.1 (d, 1H), 7.31 (d, 1H), 7.47-7.9 (m, 8H).

Anal. Calcd. for $C_{28}H_{29}N_5O_3 \cdot HCl \cdot 1/2H_2O$: C, 63.57; H, 5.91; N, 13.24. Found: C, 63.26; H, 5.94; N, 12.99.

R(-)-2,10-Dimethoxyaporphine Hydrochloride (**2c**).

A solution of **2a** (1.6 g) in acetic acid (125 ml) was hydrogenolyzed in the presence of paladium on carbon (5%) at room temperature and 46 Psi pressure for 13 days. The catalyst was removed and the filtrate was evaporated to dryness. The residue was dissolved in chloroform and made basic with aqueous potassium hydroxide. The chloroform layer was separated, washed with water, dried over anhydrous magnesium sulfate and evaporated to dryness. The crude material was applied to a silica column using ether as eluant. The desired fraction was collected and converted into the hydrochloride salt by adding ethereal hydrochloric acid, yield 0.8 g (69%), mp 215-219°; ms: M^+ 295; $[\alpha]_{578}^{25}$ -55.8 (c 0.2007, methanol).

Anal. Calcd. for $C_{19}N_{21}NO_2 \cdot HCl \cdot 1/2H_2O$: C, 66.95; H, 6.8. Found: C, 68.03; H, 6.73.

R(-)-2,10-Dimethoxy-*N*-*n*-propylnoraporphine Hydrochloride (**2d**).

This compound was prepared similarly by the hydrogenolysis of **2b** (1.3 g) in acetic acid for 12 days at room temperature. The crude product obtained was purified by passing the mixture through a silica column using ether:hexane (1:1) as eluant. The free base, on treatment with ethereal hydrochloric acid, gave **2d**·HCL, 0.7 g (57%), mp 209-213°; $[\alpha]_{278}^{25}$ -56.84 (c, 0.20, methanol).

Anal. Calcd. for $C_{21}H_{25}NO_2 \cdot HCl \cdot 1/2H_2O$: C, 68.37; H, 7.38. Found: C, 68.41; H, 7.23.

R(-)-2,10-Dihydroxyaporphine Hydrobromide (**3a**).

A suspension of **2a** (0.4 g) in hydrobromic acid (10 ml) was heated to 130-135° for 5 hours, cooled and the brown precipitate was filtered. The dried crude material was dissolved in methanol and added drop-wise with stirring to an excess of ether. The precipitate thus obtained was filtered, washed with ether and dried to give 0.3 g (71%) of **3a**, mp 255-256°; uv (methanol): max 272 nm (log 4.88), 302 (4.788), 320 (4.88); ms: M^+ 267, 266 (M^+-1), 224 (M^+-CH_2NCH_3); $[\alpha]_{578}^{23}$ -11.4 (c, 0.083, methanol).

Anal. Calcd. for $C_{17}H_{17}NO_2 \cdot HBr$: C, 58.64; H, 5.17; N, 4.02. Found: C, 58.44; H, 5.28; N, 3.90.

R(-)-2,10-Dihydroxy-*N*-*n*-propylnoraporphine Hydrobromide (**3b**).

Method A.

Method A involved the *O*-demethylation of **2d** with hydrobromic acid to give **3b** in 72% yield; $[\alpha]_{578}^{23}$ -57.1 (c, 0.613, methanol); ms: M^+ 295, 294 (M^+-1), 266 (M^+-Et), 237 (M^+-NCH_3H_7), 224 (M^+-CH_2=N-C_3H_7).

Anal. Calcd. for $C_{19}H_{21}NO_2 \cdot HBr$: C, 60.64; H, 5.89; N, 3.72. Found: C, 60.48; H, 6.04; N, 3.59.

The specific rotation, **3b**·HCl was also determined; $[\alpha]_{578}^{25}$ -53.78 (c, 0.0502, methanol).

Method B.

To a suspension of **5** (400 mg, 1.2 mmoles) in liquid ammonia, lithium metal (45 mg) was added portionwise until the blue color due to excess of lithium persisted for 2 hours. After evaporation of the ammonia, the reaction was quenched with a small quantity of methanol and then diluted with water. The aqueous solution was acidified with 37% hydrochloric acid to *p*H 8-9 and extracted with chloroform, dried over magnesium sulfate and filtered. The filtrate was evaporated to dryness and the crude material was purified on a preparative silica plate using chloroform:methanol (15:1) as eluant. The free base thus isolated was converted into **3**·HCl to give 0.1 g (24%), mp 190-196°. The tlc and mass spectra of the product were identical to the compound obtained by method A, $[\alpha]_{578}^{25}$ -54.17 (c, 0.07, methanol).

R(-)-2-Hydroxy-10-11-methylenedioxy-*N*-propylnoraporphine (**5**).

A mixture of **4** HBr (1.0 g, 2.55 mmoles), sodium hydroxide (0.32 g, 8 mmoles) and methylene bromide (0.6 g, 3.5 mmoles) in 35 ml of DMSO was heated to 80-85° for 3.5 hours, the reaction was cooled and poured over crushed ice. A white precipitate im-

mediately separated, which was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and filtered. The filtrate was evaporated to dryness and the crude material was purified on a silica column eluting from ether:hexane (1:1) to yield **5**, 0.6 g (73%), mp 152-153°; ms: M^+ 323.

R(-)-11-*O*-Methylpukateine Hydrochloride (**6**).

A solution of pukateine [9] (1.2 g, 4.1 mmoles) in a mixture of ether and ethanol (4:1) was stirred overnight with an ethereal solution of diazomethane (3.0 g). Removal of solvent under reduced pressure gave a residue which was treated with charcoal, filtered and evaporated to dryness. The material was dissolved in a small quantity of chloroform and added dropwise to ethereal hydrogen chloride with stirring which gave a white precipitate of **6**, 1.4 g (100%), mp 195-202°; tlc showed a single spot.

Anal. Calcd. for $C_{19}H_{19}NO_3 \cdot HCl \cdot 1/2H_2O$: C, 64.31; H, 5.97; N, 3.95. Found: C, 64.91 [12]; H, 6.02; N, 4.1.

R(-)-2,11-Dihydroxyaporphine Hydrobromide (**7**).

Method A.

To 50 ml of liquid ammonia, 1.0 g (2.9 mmoles) of **6** was added and stirred under nitrogen at -78°. Lithium metal (0.11 g) was added portionwise within half an hour until the blue color persisted for 2 hours. The stirring was continued for 1½ hours and ammonia was evaporated by bringing the reaction to room temperature. The reaction was quenched with a small amount of water and then diluted further. The *p*H of the solution was adjusted to 9-9.5 and the mixture extracted with chloroform. The dried extract was evaporated to dryness, the crude material was applied to a silica column using ether as eluent. Three fractions were collected in which one fraction was starting material **6** (0.3 g) and the others were mainly **8** and **7** (0.2 g). The latter fractions were converted into the hydrochloride salt by adding ethereal hydrochloric acid. The mixture of **8** and **7** hydrochloride (0.2 g) was heated with hydrobromic acid (48-49%, 5 ml) at 120-130° for 6 hours, cooled, and the precipitate was filtered. The dried precipitate was dissolved in methanol, filtered and added to an excess of ether which gave a brown solid to yield 0.14 g of **7**, mp 256°. The tlc and mass spectra (M^+ 267) of this product were found identical to the product obtained by the procedure in Method B.

Method B.

To a suspension of pukateine (0.5 g, 1.7 mmoles) in liquid ammonia (75 ml), under nitrogen lithium metal (80 mg), was added with stirring in small pieces until the blue color persisted. The reaction was worked up as described above. The product was extracted with ether, dried over calcium chloride, filtered and treated with ethereal hydrochloric acid to give **7**·HCl, 0.4 g (78%), mp 257°; uv (methanol): max 264.5 nm (log 4.945), 272 (4.987), 302 (4.84), 325 (4.82); ms: M^+ 267, 266 (M^+-1), 224 (M^+-CH_2NCH_3); $[\alpha]_{578}^{23}$ -103.14 (c, 0.0446, methanol); ^{1}H nmr (DMSO-d_6): 7.8 (d, C_1H), 7.07-6.7 (m, $C_{8,9,10}$H), 6.57 (d, C_3H), 2.8-3.8 (m, 7H), 3.03 (s, 3H).

Anal. Calcd. for $C_{17}H_{17}NO_2 \cdot HCl$: C, 67.22; H, 5.93; N, 4.61. Found: C, 66.99; H, 6.08; N, 4.51.

R(-)1,2,11-Trihydroxyaporphine Hydrobromide (**9**).

To a solution of pukateine 0.2 g (0.68 mmoles) in methylene chloride (5 ml), bromine tribromide (1 ml, 1 *M* solution in dichloromethane) was added, dropwise, at room temperature under nitrogen. After stirring for 12 hours a few ml of methanol was added. The mixture was heated and filtered after charcoal treatment. Cooling of the filtrate gave a brown crystalline precipitate which was filtered and dried, yield 0.14 g (55%), mp 190-205°; $[\alpha]_{578}^{23}$ -185° (c, 0.2, methanol).

Anal. Calcd. for $C_{17}H_{17}NO_3 \cdot HBr$: C, 56.06; H, 4.98; N, 3.85. Found: C, 56.04; H, 4.94; N, 3.85.

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