= 4-$CF_3C_6H_4$), 74467-05-3; **2** (Ar = 3-$O_2NC_6H_4$), 33512-94-6; **2** (Ar = 3-NCC_6H_4), 20680-35-7; 2,4-dimethoxybenzaldehyde oxime, 31874-34-7; 5-chloro-2,4-dimethoxybenzaldehyde oxime, 74467-06-4; 2,4-dimethoxybenzohydroximinoyl chloride, 74467-07-5; *N*-chlorosuccinimide, 128-09-6; DMF, 68-12-2.

Preparation of (-)-[8,9-^{3}H]Apomorphine[1] at High Specific Activity

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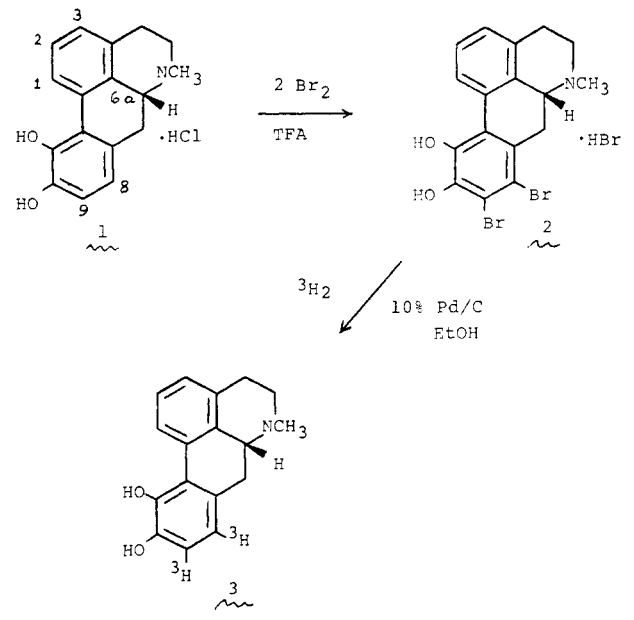
Received April 24, 1980

Dopaminergic agonists radiolabeled at high specific activity are exceedingly useful probes for elucidating the underlying causes of a wide range of neurological disorders at the receptor level.[2] (-)-Apomorphine (**1**) is a potent dopaminergic agonist,[3] but prior attempts to prepare a tritiated version of **1** have achieved only extremely low specific activities and have not rigorously demonstrated the position of radiolabeling.[4] We now disclose a very simple preparation of (-)-[8,9-^{3}H]apomorphine (**3**) at high specific activity and proof of labeling specificity via triton magnetic resonance spectroscopy.

Treatment of (-)-apomorphine hydrochloride (**1**) with bromine in trifluoroacetic acid (TFA)[5] yielded pure (-)-8,9-dibromoapomorphine hydrobromide (**2**)[6] as a crystalline precipitate in 60% yield (Scheme I). All spectral and chromatographic data for **2** were consonant with its proposed structure, but especially telling was the conspicuous absence of the 8 and 9 position protons (δ 6.70) in the ^{1}H NMR spectrum (CD_3OD) of **2**. In contrast to **1**, which slowly oxidizes to an emerald green orthoquinone,[3a] dibromide **2** showed little tendency to discolor upon standing in air. Too hasty an addition of bromine to **1** caused a monobromide[7] to coprecipitate with **2**. The ^{1}H NMR spectrum (CD_3OD) of this monobromo side product was characterized by an added singlet (δ 7.03) in the aromatic region.

Scheme I



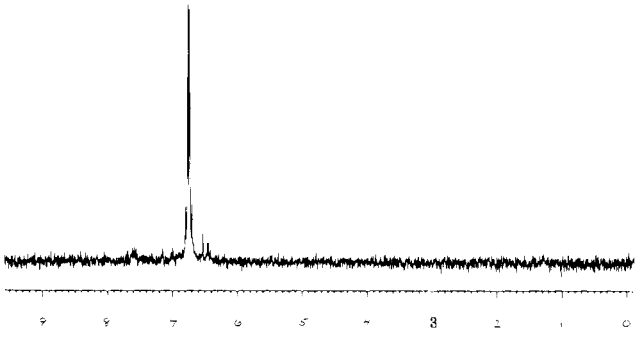


Figure 1. ^{3}H NMR of (-)-[8,9-^{3}H]apomorphine (**3**) in CD_3OD. Chemical shift values are in parts per million downfield from internal $(CH_3)_4Si$.

Reduction of **2** in ethanol with tritium over 10% Pd/C occurred smoothly, to yield (-)-[8,9-^{3}H]apomorphine (**3**). Purification of crude **3** by high-performance LC easily afforded millicurie amounts of **3** at 98% radiochemical purity (TLC, high-performance LC) with a specific activity consistently in the range of 30–40 Ci/mmol, as ascertained by UV spectroscopy.[8] A triton magnetic resonance spectrum of the free base of **3** in CD_3OD (Figure 1) clearly indicates essentially exclusive tritium incorporation in the 8 and 9 ring positions (δ 6.70). We infer that **3** is optically active in view of the fact that reduction of **2** with hydrogen yielded **1** with retention of optical activity.[9]

Experimental Section

General Methods. Evaporations were carried out on a Büchi rotary evaporator in vacuo at bath temperatures below 40 °C. TLC was performed on Analtech 5 × 15 cm, 250 μm (analytical), and 20 × 20 cm, 1000 μm (preparative), silica gel GF coated glass plates. Common solvent combinations were S_1 (EtOH–HOAc–H_2O, 6:3:1) and S_2 (CH_3OH–PhH–H_2O–HOAc, 15:2:5:2). Autoradiography was performed at 0 °C after spraying TLC plates with PPO (New England Nuclear) and exposure to Eastman Kodak SB-5 film. TLC plates were also scanned for activity by

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(5) Our use of TFA as a solvent for the bromination of **1** was prompted by the recollection of its marked utility in another instance of apomorphine chemistry (Borgman, R. J.; Smith, R. V.; Keiser, J. E. *Synthesis* **1975**, 249).

(6) Dibromide **2** has been cited in the pharmacology literature (Lal, S.; Sourkes, T. L.; Missala, K.; Belendiuk, G. *Eur. J. Pharmacol.* **1972**, 20, 71), but its preparation and characterization have not been reported.

(7) Because bromination of phenol occurs predominantly at the para position and only the 8 position of **1** can be considered as para to a phenol, the monobromide side product is most likely 8-bromoapomorphine. This is also consistent with the observation that treatment of 10,11-dimethoxyaporphine with 1 equiv of bromine yielded mainly 8-bromo-10,11-dimethoxyaporphine whose ^{1}H NMR spectrum ($CDCl_3$) contained a singlet at δ 7.11 for the remaining 9-position proton (Smith, R. V.; Stocklinski, A. W. *Tetrahedron Lett.* **1973**, 1819). The monobromide side product we observed was easily separated from **2** on TLC (silica gel, S_1) as a faster moving spot (R_f 0.6).

(8) By way of comparison, the specific activities of the generally labeled apomorphines of ref 4a and 4b were 0.02 Ci/mmol and 0.01 Ci/mmol, respectively. For a successful receptor-binding assay experiment, a minimum specific activity of 20 Ci/mmol is required for a radioligand.

(9) For further evidence that the apomorphine ring system retains its optical activity at the 6a position after exposure to 10% Pd/C, see ref 2 and references cited therein.

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using a Packard 7201 scanner. UV spectra were measured on a Beckman Model 25 spectrophotometer and optical rotations were obtained on a Perkin-Elmer 141 polarimeter. The IR spectrum was measured on a Perkin-Elmer Model 700 spectrophotometer. The proton and triton magnetic resonance spectra were obtained on a Bruker WP 200-MHz NMR. Chemical shift values are expressed in parts per million downfield from internal $(CH_3)_4Si$. The high-resolution mass spectrum was performed by Shrader Analytical Laboratories, Detroit, MI, and the elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Preparative and analytical high-performance LC were run on a Waters instrument, using μ-Bondapak CN and μ-Bondapak C_{18} columns (Waters) eluted with S_3 (5% EtOH in 0.01 N KH_2PO_4 (pH 3) buffer). Peak detection was performed at 280 nm with a Waters 440 UV detector.

(−)-8,9-Dibromoapomorphine Hydrobromide (2). To a solution of 100 mg (0.33 mmol) of apomorphine hydrochloride **1** (Merck) in 30 mL of TFA was added dropwise at room temperature over 20 min 35 μL (0.678 mmol) of bromine in 7 mL of TFA with rapid stirring in the dark. A crystalline precipitate was observed to form several minutes after completion of the addition of bromine. After the mixture was stirred for a total of 1.5 h, the precipitate was filtered, washed with a few mL of cold TFA, and dried under vacuum to yield 100 mg (60%) of **2** as an off-white solid, mp 281–283 °C dec. TLC of **2** on silica gel eluted with S_1 yielded a single spot (R_f 0.39) which turned only light green when visualized with iodine vapors. Apomorphine **1** in the same TLC system (R_f 0.49) turned emerald green with iodine visualization. High-performance LC of **2** on a μ-Bondapak CN column eluted with S_3 at 2 mL/min yielded a single peak (retention time = 27 min; whereas the retention time of **1** in this system is 7 min) by UV detection. Spectral and analytical data for **2** now follow: ^1H NMR (CD_3OD) δ 8.40 (d, 1, J = 8.07 Hz, H-1), 7.40 (t, 1, J = 8.07 Hz, H-2), 7.25 (d, 1, J = 7.80 Hz, H-3) (the two proton singlet (δ 6.70) for H-8 and H-9 was absent); IR (KBr) 3700–2900 (br), 2700, 1590, 1470, 1410, 1375, 1150 cm^{-1}; UV (EtOH) λ max 220 (log ε 4.48), 272 (4.22), 320 (3.55); $[\alpha]^{25}_D$ −131.4° (c 0.59, CH_3OH); exact mass calcd for $C_{17}H_{14}NBr_2O_2$ (M^+ − 423.9368, found 423.9377.

Anal. Calcd for $C_{17}H_{15}NBr_2O_2$·HBr: C, 40.35; H, 3.19; N, 2.71. Found C, 40.28; H, 3.23; N, 2.63.

(−)-[8,9-^{3}H]Apomorphine (3). Dibromide **2** (13 mg, 0.026 mmol) was reduced with tritium (100 Ci) in 10 mL of EtOH, using 26 mg of 10% Pd/C at room temperature in the dark for 2 h with stirring. After catalyst removal, excess solvent was evaporated and the crude residue was taken up in 20 mL of CH_3OH (total radioactivity = 804 mCi; a 94% crude yield of **3** based on dibromide **2**). TLC (silica gel eluted with S_1 or S_2) of crude **3** underspotted with **1** showed the reduction to consist of **3** at 95% radiochemical purity. Final purification of **3** was performed by high-performance LC using a μ-Bondapak CN column eluted with S_3 (1 mL/min). Typically, 804 mCi of crude **3** yielded 100 mCi (a 12% overall yield of pure **3** based on dibromide **2**) of **3** (retention time = 12 min) at 98% radiochemical purity (silica gel TLC eluted with S_1 or S_2; μ-Bondapak CN and C_{18} high-performance LC eluted with S_3).[10] Compound **3** cochromatographed (TLC, high-performance LC) with **1** and afforded a UV spectrum superimposable on that of **1**. The specific activity of **3** was determined to be 33 Ci/mmol by UV spectroscopy (272 nm (ε 17 000) for **1**). A sample of **3** (free base) for the triton magnetic resonance spectrum was obtained by silica gel TLC (S_1).

Acknowledgment. We gratefully acknowledge the technical assistance of K. Bradley (NEN) in the tritiation of **2** to **3** and the help of Professor L. J. Altman (Stony Brook) in obtaining the triton magnetic resonance spectrum of **3**. A stimulating discussion with Dr. C. Kelley (Massachusetts College of Pharmacy) is also acknowledged.

Registry No. **1**, 314-19-2; **2**, 40609-52-7; **3**, 74467-14-4.

(10) The loss of product **3** attending this stage of the purification is undoubtedly due to product decomposition during rotary evaporator concentration of crude **3** in CH_3OH to a volume suitable for high-performance LC injection, as well as peak shaving during the high-performance LC of **3**.

Pyrimido[4,5-*c*]pyridazines. 2. Preferential Formation of Pyrimido[6,1-*c*][1,2,4]triazines by Cyclizations with Simple and Complex α-Halo Ketones

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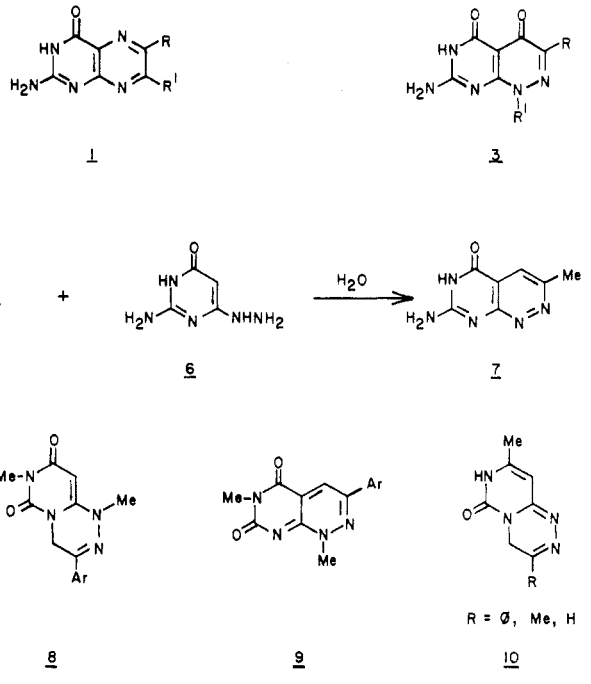
Received March 31, 1980

Our search for analogues of the naturally occurring pterins (**1**) led us initially to successful cyclizations of 6-(1-alkylhydrazino)isocytosines (**2**, Table I) with α-keto esters to give pyrimido[4,5-*c*]pyridazine-4,5-diones (**3**).[1] We now report that **2** cyclizes with one simple and two complex α-halo ketones (**4**) under acidic conditions to give pyrimido[6,1-*c*][1,2,4]triazines (**5**) and that we did not isolate any pyrimidopyridazines from these reactions. In contrast, the reaction between bromoacetone (**4a**) and 6-hydrazinoisocytosine[2] (**6**) under similar conditions afforded pyrimidopyridazine **7** in low yield with no evidence of pyrimidotriazine formation.



The pyrimido[6,1-*c*][1,2,4]triazine ring system has been reported only twice in the literature. Yoneda[3] isolated both pyrimidotriazines **8** and pyrimidopyridazines **9** from reactions of phenacyl bromides with 3-methyl-6-(1-methylhydrazino)uracil, and La Noce reported[4] the exclusive formation of pyrimidotriazines **10** by reaction of simple α-halo ketones with 4-hydrazino-2-hydroxy-6-methylpyrimidine. In contrast with La Noce's results, Senga[5] obtained only pyrimido[4,5-*c*]pyridazines from the reaction of another unsubstituted hydrazinopyrimidine (6-hydrazino-3-methyluracil) with phenacyl bromides.

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