Table I. Rearrangement of *dl*-3,4-Diphenylhexa-1,5-diene in *n*-Heptane (5×10^{-5} M)[a]

temp, °C	10^4k, s^{-1} [b]	E, kcal/mol[c]	log A[c]
90.0	0.540 ± 0.003	24.7 ± 0.2	10.6 ± 0.1
100.0	1.37 ± 0.003		
109.9	3.32 ± 0.01		

[a] Uncertainties are standard deviations. [b] First-order rate constants (weighted means). [c] Arrhenius parameters.

Table II. First-Order Rate Constants for Rearrangement of 4[a]

temp, °C	10^4k, s^{-1}
90.03	0.535 ± 0.007
90.03	0.541 ± 0.004
89.90	0.545 ± 0.003
100.01	1.33 ± 0.02
100.02	1.38[b] ± 0.004
100.02	1.36 ± 0.01
100.02	1.38[c] ± 0.02
100.02	1.38 ± 0.03
109.90	3.33 ± 0.01
109.90	3.17 ± 0.03
109.89	3.14[d] ± 0.05

[a] Uncertainties are standard deviations. [b] Samples contained 5×10^{-8} M *N*-phenyl-β-naphthylamine free-radical inhibitor. [c] Samples contained 5×10^{-7} M *N*-phenyl-β-naphthylamine. [d] Surface-to-volume ratio increased 8-fold.

2,5-diphenylhexa-1,5-diene rearrangement in *o*-dichlorobenzene (E = 21.9 kcal/mol, log A = 8.86). The most direct comparison is between the rate constant at 100.0 °C reported above for **4** and the observed $k = 2.85 \times 10^{-4}$ s^{-1} at 100.95 °C for the 2,5 derivative. The effect of solvent differences is such that the 3,4 derivative would probably have the larger rate constant if measurements were made in the same solvent.[6]

Activation by unsaturated substituents in the 3 and/or 4 as well as the 2 and/or 5 positions in Cope substrates can be accounted for by a spectrum of transition states influenced by the substitution pattern.[7] One component of the spectrum is approximated by the bonding in cyclohexane-1,4-diyl, another by a pair of interacting allyl radicals.

Experimental Section

Replicate kinetic measurements were carried out on ca. 5×10^{-5} M *n*-heptane solutions of **4** in sealed evacuated Pyrex ampules in a thermostatted oil bath. Thermometers were calibrated against NBS standards. Ampules were withdrawn periodically and the contents were analyzed directly with a Cary 14 recording ultraviolet spectrophotometer. Relative concentrations of starting and rearranged diene were calculated from absorbance measurements at 256 nm.

Since product decomposition became perceptible after about 85% reaction, rate constants were obtained from data points obtained up to three half-lives (generally ten ampules). Excellent first-order plots were observed, with rate constants calculated by standard least-squares methods. The reaction was found to be homogeneous, in that eightfold increase in the surface-to-volume ratio had a negligible effect on the reaction rate at 110 °C. VPC analysis[5] of the product of rearrangement of **4** at 110 °C for 12 h (20 half-lives) in dilute *n*-heptane in a sealed, evacuated ampule indicated >99.9% **5**.

Activation parameters were calculated from the observed rate constants as given in Table II. Weighted means[8] are given in Table I.

Registry No. **4**, 74467-15-5; **5**, 58463-02-8.

(6) The Cope rearrangement of 3-phenylhexa-1,5-diene at 190 °C is about four times faster in *o*-dichlorobenzene than in the gas phase (ref 3a).

(7) (a) J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, **101**, 6693 (1979); (b) R. Wehrli, D. Bellus, H.-J. Hansen, and H. Schmid, *Chimia*, **30**, 416 (1976).

(8) C. L. Perrin, "Mathematics for Chemists", Wiley-Interscience, New York, 1970, p 159.

A Particularly Convenient Preparation of Benzohydroximinoyl Chlorides (Nitrile Oxide Precursors)

Kou-Chang Liu,*† Becky R. Shelton, and Robert K. Howe*

Research Department, Monsanto Agricultural Products Company, St. Louis, Missouri 63166

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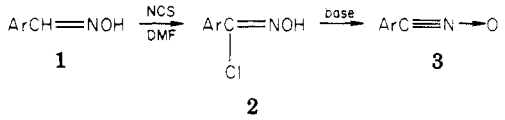
Nitrile oxides have found extensive utility in preparation of heterocycles via 1,3-dipolar cycloadditions.[1,2] Benzohydroximinoyl chlorides (**2**) are especially useful, stable, storable precursors of the relatively unstable benzonitrile oxides (**3**), which tend to dimerize within a few minutes to several days.[2] The most widely employed method of preparation of **2** is chlorination of oximes with chlorine gas; however, chlorine gas is hazardous and ring chlorination occurs with benzaldehyde oximes that contain electron-donating substitutents.[3,4]

We have found that *N-chlorosuccinimide (NCS) in DMF*[5,6] *provides a particularly selective and by far the most convenient method of preparation of 2.* Yields are



1 2 3

excellent (see Table I). The crude products are almost invariably sufficiently pure to be employed without purification for nitrile oxide reactions. The experimental procedure is quite simple and suitable for large-scale preparations. NCS is a solid and thus is easy to handle and to measure accurately. Ring chlorination occurs only with very strongly activated aromatic rings.

Mesitaldehyde oxime could not be chlorinated by any of the previously known procedures without ring chlorination.[7] Treatment of mesitaldehyde oxime with exactly 1 equiv of NCS in DMF gave fairly pure mesitohydroximinoyl chloride in 92% yield, without any purification. The product contained no detectable ring-chlorinated material (NMR analysis of hydroximinoyl chloride and GC analysis of derived nitrile oxide) and gave pure mesitonitrile oxide, mp 110–112 °C (lit.[7] mp 110–112 °C), in 95% yield upon treatment with triethylamine in ether.

Previous attempts[4,8] to prepare 2-methoxybenzohydroximinoyl chloride by chlorination of 2-methoxybenzaldehyde oxime with chlorine in various solvents were unsuccessful; ring-chlorinated products were obtained in each case. Use of NCS in DMF gave 2-methoxybenzohydroximinoyl chloride in 92% yield, with no detectable ring chlorination (NMR analysis).

The very strongly activated 2,4-dimethoxybenzaldehyde oxime reacted with NCS in DMF to give a mixture of products, in 92% yield, of which two-thirds was 5-chloro-2,4-dimethoxybenzaldehyde oxime from ring chlo-

† Research Center, GAF Co., Wayne, NJ 07470.

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Table I. Preparation of Benzohydroximinoyl Chlorides 2 with NCS/DMF

	crude product		purified product	
2, Ar =	% yield	mp, °C	% yield	mp, °C
2,4,6-$(CH_3)_3C_6H_2$	92	61-69[a-c]		
2-$CH_3OC_6H_4$	92	105-108[a,d]	57	112-112.5[e]
3-$C_6H_5OC_6H_4$	92	84-85[e]		
2-$CH_3C_6H_4$	84	oil[f]		
4-$C_6H_5C_6H_4$	89	148-164 dec	62	150-156 dec[e,g]
3-ClC_6H_4	96	58-61	70	65-67[h]
4-ClC_6H_4	75	87.5-89[i]		
2-$CF_3C_6H_4$	99	70-81	68	78-82[e]
4-$CF_3C_6H_4$	85[j]	89.5-91.5[e]		
3-$O_2NC_6H_4$	96	94-96.5[k]		
3-NCC_6H_4	80	133.5-135[l]		

[a] Possibly a syn-anti mixture.[3] [b] NMR ($CDCl_3$) δ 8.55 (br s, 1, NOH), 6.88 (s, 1.93 H), 2.40 (s, 0.77 H), 2.27 (s, 8.23 H); no trace of CH_2Cl was detected. [c] Lit.[7] mp 72 °C. [d] NMR ($CDCl_3$) δ 9.95 (br s, 1, NOH), 7.7-6.83 (multiplets, 4.08 H), 3.91 (s, 2.55 H), 3.88 (s, 0.45 H). [e] C, H analyses within 0.3% of theoretical values. [f] NMR ($CDCl_3$) δ 9.5 (br s, NOH), 7.43-6.93 (m, 4.04 H), 2.31 (s, 3.00 H). [g] Lit.[3] mp 129-130 °C. [h] Lit. mp 72-73 °C: A. Battaglia, A. Dondoni, and O. Exner, *J. Chem. Soc., Perkin Trans. 2*, 1911 (1972). [i] Lit.[4] mp 88-90 °C. [j] After trituration with cold pentane. [k] Lit. mp 101-102 °C,[4] 96 °C.[8] [l] Lit. mp 137-137.5 °C: D. A. Klein and R. A. Fouty, *Macromolecules*, 1, 318 (1968).

rination and one-third was 2,4-dimethoxybenzohydroximinoyl chloride.[9] Pure 5-chloro-2,4-dimethoxybenzaldehyde oxime,[10] mp 162–163.5 °C, was isolated by base extraction of an ether solution of the product mixture and subsequent acidification of the base extracts.

Experimental Section

Melting points were determined in open capillaries with a Mel-Temp apparatus and are corrected.

General Procedure for Oxime Preparations.[11] To a mixture of 0.5 mol of aldehyde in 125 mL of water, 125 mL of ethanol, and 215 mL of ice was added 0.55 mol of hydroxylamine hydrochloride. Then, 1.25 mol of 50% NaOH was added with stirring. Enough ice to keep the temperature at 25–30 °C was added. The mixture was stirred for 1 h, extracted with 500 mL of ether to remove neutral impurities, acidified with concentrated hydrochloric acid to pH 6 (ice was added to keep the temperature at 20–30 °C), and extracted with two 500-mL portions of ether (or dichloromethane). These latter two extracts were combined, dried ($CaSO_4$), and concentrated under vacuum to solid oxime. Oximes prepared in this manner did not require further purification for conversion to the hydroximinoyl chlorides. In a few cases, small samples of crude oximes were recrystallized for comparison of melting points with literature values.

Oximes: **mesitaldehyde oxime**, 38% yield, mp 125–127 °C (lit.[7] mp 124 °C for syn isomer); **2-methoxybenzaldehyde oxime**, 99% yield, mp 91.5–93 °C (lit.[8] mp 100–101 °C); **3-phenoxybenzaldehyde oxime**, 98% yield, oil (lit.[12] mp 45–46 °C); **2-methylbenzaldehyde oxime**, 50% yield, mp 47–49 °C (lit.[13] mp 48 °C for syn isomer); **4-phenylbenzaldehyde oxime**, 98% yield, mp 115–121 °C [a sample was recrystallized from toluene, mp 148–150.5 °C (lit.[8] mp 147–149 °C)]; **3-chlorobenzaldehyde oxime**, 70% yield, mp 62–64 °C [a sample was recrystallized from toluene–hexane, mp 68–69.5 °C (lit.[13] mp 75 °C for syn isomer)]; **4-chlorobenzaldehyde oxime**, 94% yield, mp 105.5–108 °C (lit.[8] mp 107–109 °C); **2-(trifluoromethyl)benzaldehyde oxime**, 84% yield, mp 51–56 °C [a sample was recrystallized from toluene–hexane, mp 52–54 °C (lit.[14] mp 54–55 °C)]; **4-trifluoromethyl)benzaldehyde oxime**, 72% yield, mp 100–101.5 °C (lit.[14] mp 100–101 °C); **3-nitrobenzaldehyde oxime**, 93% yield, mp 119–120 °C (lit.[13] mp 123 °C for syn isomer); **3-cyanobenzaldehyde oxime**, 94%, mp 130–132 °C (lit.[13] mp 136 °C for syn isomer).

General Procedure for Benzohydroximinoyl Chloride Preparations. Reaction of *N*-chlorosuccinimide with benzaldoximes in DMF exhibits an induction period and can become farily exothermic for most substrates if the reaction initiates after a considerable portion of the NCS has been added. We found it desirable to initiate the reaction prior to addition of more than one-fifth of the NCS. This is accomplished by addition of small amounts of HCl gas[15] and for deactivated benzaldoximes by application of heat.

To a stirred solution of 0.300 mol of benzaldoxime in 250 mL of DMF at 25–30 °C is added about one-tenth to one-fifth of 0.300 mol of solid NCS. The initial NCS addition results in a slight temperature decrease (negative heat of solution). If the reaction does not self-initiate within 10 min, as indicated by a slight temperature rise (at first), 20 mL of gas from the head space of a concentrated hydrochloric acid reagent bottle is collected in a syringe and then is bubbled into the DMF solution. Reaction normally initiates within another 10–15 min, except for strongly deactivated (e.g., nitro substituted) benzaldoximes which require heating to 45–60 °C to initiate. Once the reaction begins, the temperature is kept below 35 °C for benzaldoximes with electron-donating substituents (below 50 °C for benzaldoximes with strong electron-withdrawing substituents) by the rate of addition of the rest of the NCS and by intermittent cooling (dry ice–acetone bath). Completion of the reaction is indicated by cessation of the exotherm and by formation of no (or a very weak) dark colored ring[16] upon application of a small drop of reaction mixture to starch–iodide paper previously moistened with distilled water. The solution is poured into four volumes of ice water. The mixture is extracted twice with ether. The combined ether extracts are washed three times with water, dried ($CaSO_4$), and concentrated under vacuum to give the hydroximinoyl chloride product.

Registry No. 1 (Ar = 2,4,6-$(CH_3)_3C_6H_2$), 40188-34-9; 1 (Ar = 2-$CH_3OC_6H_4$), 29577-53-5; 1 (Ar = 3-$C_6H_5OC_6H_4$), 74482-46-5; 1 (Ar = 2-$CH_3C_6H_4$), 14683-79-5; 1 (Ar = 4-$C_6H_5C_6H_4$), 40143-27-9; 1 (Ar = 3-ClC_6H_4), 34158-71-9; 1 (Ar = 4-ClC_6H_4), 3848-36-0; 1 (Ar = 2-$CF_3C_6H_4$), 74467-00-8; 1 (Ar = 4-$CF_3C_6H_4$), 66046-34-2; 1 (Ar = 3-$O_2NC_6H_4$), 3431-62-7; 1 (Ar = 3NCC_6H_4), 64847-76-3; 2 (Ar = 2,4,6-$(CH_3)_3C_6H_2$), 2904-63-4; 2 (Ar = 2-$CH_3OC_6H_4$), 74467-01-9; 2 (Ar = 3-$C_6H_5OC_6H_4$), 74467-02-0; 2 (Ar = 2-$CH_3C_6H_4$), 74467-03-1; 2 (Ar = 4-$C_6H_5C_6H_4$), 42202-94-8; 2 (Ar = 3-ClC_6H_4), 29203-59-6; 2 (Ar = 4-ClC_6H_4), 28123-63-9; 2 (Ar = 2-$CF_3C_6H_4$), 74467-04-2; 2 (Ar

(1) C. Grundmann, *Fortschr. Chem. Forsch.*, 7, 62 (1966).
(2) C. Grundmann and P. Grünanger, "The Nitrile Oxides", Springer-Verlag, New York, 1971.
(3) Reference 2, pp 48–51.
(4) Y. H. Chiang, *J. Org. Chem.*, 36, 2146 (1971).
(5) NCS in DMF has been employed previously to prepare aliphatic hydroximinoyl chlorides; see R. V. Stevens, *Tetrahedron*, 32, 1599 (1976). Although no solvent was specified in this article, we learned subsequent to the completion of our work that DMF was used (private communication from R. V. Stevens).
(6) The reagent system NBS–base–DMF has been employed to prepare 2,6-disubstituted benzonitrile oxides, which dimerize slowly due to steric hindrance: C. Grundmann and R. Richter, *J. Org. Chem.*, 33, 476 (1968).
(7) C. Grundmann and J. M. Dean, *J. Org. Chem.*, 30, 2809 (1965).
(8) R. H. Wiley and B. J. Wakefield, *J. Org. Chem.* 25, 546 (1960).
(9) For very strongly activated benzaldehyde oximes, the more hazardous, more expensive, and much less convenient reagent system nitrosyl chloride in ether may be employed to prepare the hydroximinoyl chlorides: H. Rheinboldt, *Justus Liebigs Ann. Chem.*, 451, 161 (1927).
(10) NMR ($CDCl_3$) δ 8.43 (s, 1, CH=N), 8.07 (s, 1, NOH), 7.77 (s, 1, H_6), 6.50 (s, 1, H_3), 3.95 (s, 3, OCH_3), 3.90 (s, 3, OCH_3). This new compound gave C, H, Cl analyses within 0.1% of theoretical values.
(11) Minor modifications of a procedure reported in *Beilstein*, *4th ed.*, 7, 218.
(12) G. Lock and F. H. Kempter, *Monatsch. Chem.*, 67, 24 (1935); *Chem. Abstr.*, 30, 2938 (1936).
(13) J. Schnekenburger, *Z. Anal. Chem.*, 263, 23 (1973).
(14) C. F. Barfknecht and T. R. Westby, *J. Med. Chem.*, 10, 1192 (1967).
(15) Presumably, the hydrogen chloride reacts with NCS to generate chlorine which initiates the reaction; see P. S. Skell and J. C. Day, *Acc. Chem. Res.*, 11, 381 (1978).
(16) Use of a slight excess of NCS will negate this test.

= 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

Crist N. Filer* and David G. Ahern

Ligands Group, New England Nuclear, Boston, Massachusetts 02118

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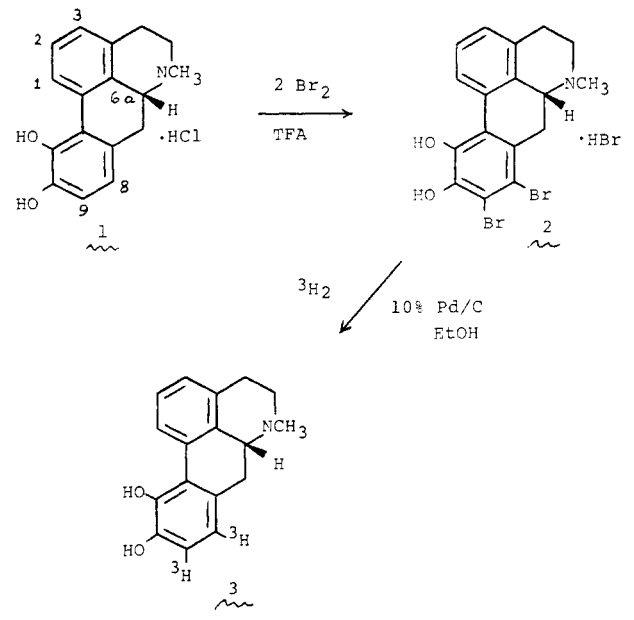
Dopaminergic agonists radiolabeled at high specific activity are exceedingly useful probes for elucidating the underlying causes of a wide range of neurological disorders at the receptor level.[2] (-)-Apomorphine (**1**) is a potent dopaminergic agonist,[3] but prior attempts to prepare a tritiated version 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



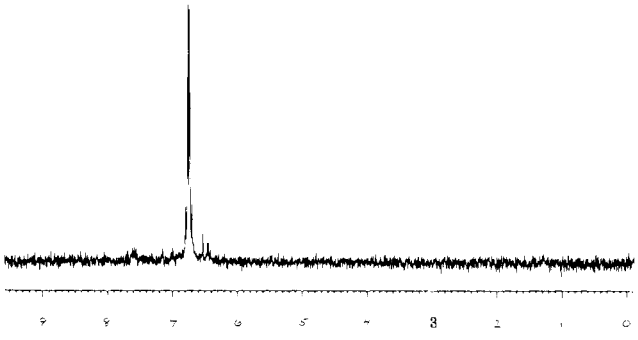


Figure 1. ^{3}H NMR of (-)-[8,9-^{3}H]apomorphine (**3**) in CD_3OD. Chemical shift values are in parts per million downfield from internal $(CH_3)_4Si$.

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

(1) Presented, in part, at the tenth Northeast Regional Meeting (NERM 10) of the American Chemical Society, Postsdam, NY, July 1980, ORGN 40.

(2) Filer, C. N.; Ahern, D. G.; Granchelli, F. E.; Neumeyer, J. L.; Law, S. J. *J. Org. Chem.* **1980**, *45*, 3465 and references cited therein.

(3) (a) Colpaert, F. C.; Van Bever, W. F. M.; Leysen, J. E. M. F. *Int. Rev. Neurobiol.* **1976**, *19*, 225. (b) Sourkes, T. L.; Lal, S. In "Advances in Neurochemistry"; Agranoff, B. W., Aperson, M. H., Eds.; Plenum: New York, 1975; Vol. 1, p 247.

(4) (a) Ginos, J. Z.; LoMonte, A.; Cotzias, G. C.; Bose, A. K.; Brambilla, R. J. *J. Am. Chem. Soc.* **1973**, *95*, 2991. (b) Soine, W. H.; Salgo, P.; Smith, R. V. *J. Labelled Compd.* **1979**, *16*, 597.

(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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