Aporphines. 28.[1] Preparation of (–)-*N*-*n*-[^{3}H- and -^{2}H]Propylnorapomorphine

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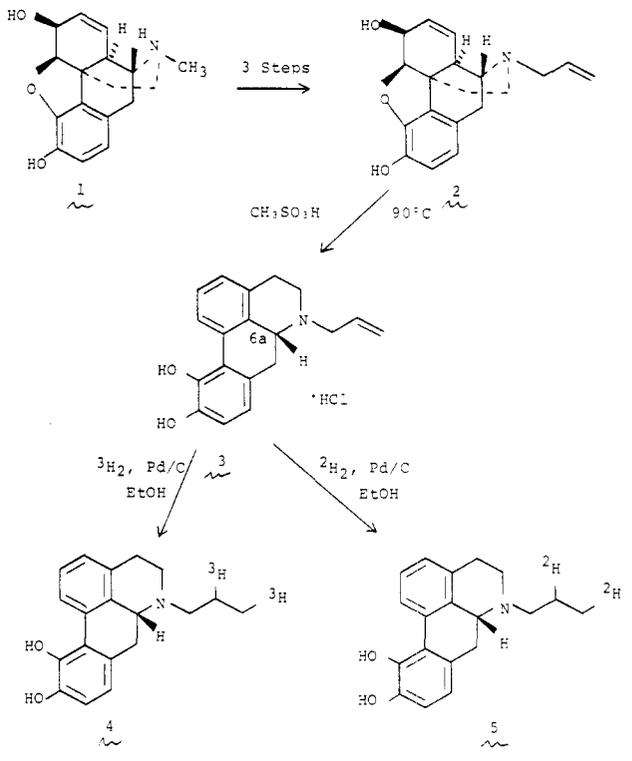
The synthesis of (–)-*N*-*n*-propylnorapomorphine ([^{3}H]-propyl, **4**, and [^{2}H]propyl **5**) was investigated for use in receptor binding studies. The title compounds were prepared through an improved methanesulfonic acid rearrangement of (–)-nalorphine (**2**) to (–)-*N*-allylnorapomorphine (**3**), followed by catalytic tritiation or deuteration. The tritium and deuterium incorporation to the terminal ethyl group was confirmed by triton magnetic resonance and mass spectroscopy, respectively.

The role of abnormal dopaminergic transmission in a wide variety of neurological disorders including Parkinson's disease,[3] schizophrenia,[4] Huntington's disease,[5] Gilles de la Tourette's syndrome,[6] neuroleptic induced tardive dyskinesia,[7] and Lesch-Nyhan syndrome[6] continues to be an active area of research. Study of the dopaminergic receptor has been facilitated in the past several years by direct radioligand binding using high-specific-activity, tritiated, dopaminergic agonists and antagonists.[8] The former have proved especially useful in understanding the role of dopaminergic mechanisms in the central nervous systems and in human diseases.[9]

Prior attempts to prepare aryl-radiolabeled aporphines, in particular the two dopaminergic agonists (–)-amomorphine[10,11] and (–)-*N*-*n*-propylnorapomorphine,[11] have only met with modest success. Those radiolabeled aporphines obtained by exchange processes with tritiated water under acidic conditions have been of exceedingly low specific activity, and the position of labeling has not been rigorously demonstrated. Recently the synthesis of aporphine [4,5,6a,7-$^2H_4$] was reported by deuteration of an unsaturated precursor, 4,5,6a,7-tetradehydroaporphine.[12] In principle, this method could also be applied to the preparation of apomorphine and its analogues by the reduction of suitable precursors with tritium. We have chosen to specifically label the dopaminergic agonist (–)-*N*-*n*-propylnorapomorphine with tritium at high specific activity for receptor binding studies since it has been shown that (–)-*N*-*n*-propylnorapomorphine elicited stereotyped behavior in the rat,[13] stimulated striatal adenylate cyclase activity in the rat brain,[14] and strongly inhibited binding of tritiated neuroleptics,[15] [^{3}H]apomorphine[8] and [^{3}H]-dopamine.[15b] Herein, we describe the preparation of the high-specific-activity, *n*-[^{3}H]propyl isomer of this dopaminergic agonist and its deuterated counterpart. The labeling specificity of the former is confirmed by triton magnetic resonance while deuterium incorporation in the *n*-propyl side chain of the latter is demonstrated by mass spectroscopy.

Scheme I



(1) Part 27: F. E. Granchelli, C. N. Filer, S. J. Law, A. H. Soloway and J. L. Neumeyer, *J. Org. Chem.*, in press.

(2) (a) New England Nuclear. (b) Northeastern University.

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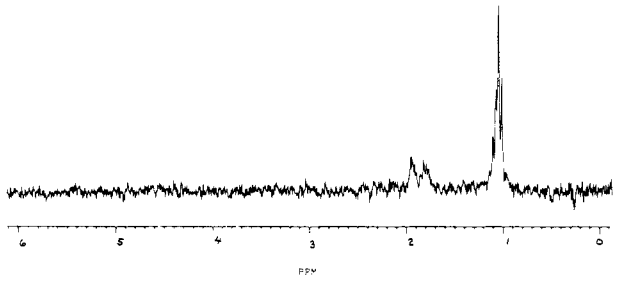


Figure 1. ^3H NMR of (−)-*N*-*n*-[^{3}H]propylnorapomorphine (**4**) in CD_3OD. Chemical shift values in parts per million downfield from internal $(CH_3)_4Si$.

Results and Discussion

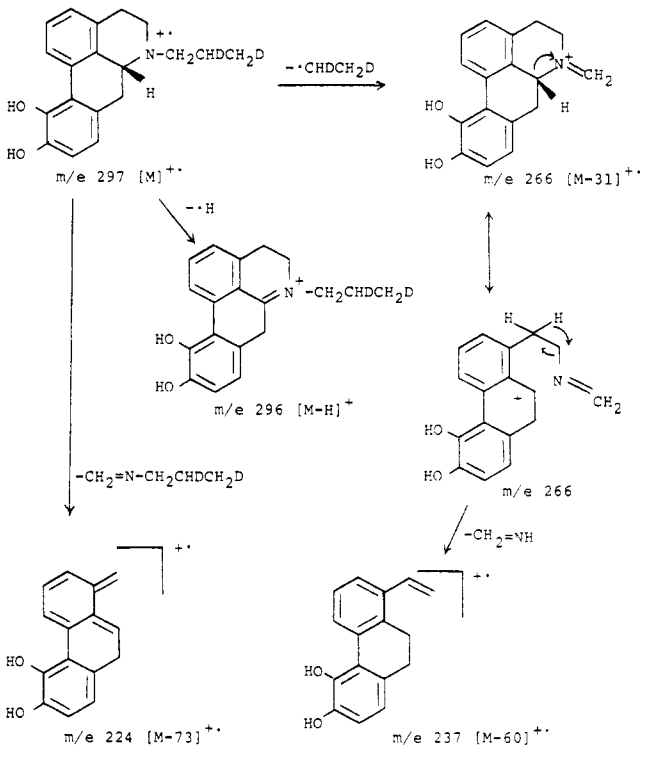
For the incorporation of tritium at high specific activity in (−)-*N*-*n*-propylnorapomorphine, double bond reduction also appeared to be an inviting strategy, and (−)-*N*-allylnorapomorphine (**3**) seemed to be an appropriate and accessible precursor. The preparation of (−)-*N*-*n*-[^{3}H]-propylnorapomorphine (**4**) is outlined in Scheme I. (−)-Morphine (**1**) was converted to (−)-*N*-allylnormorphine[16] (**2**, (−)-nalorphine) and rearranged to (−)-*N*-allylnorapomorphine (**3**) by employing methanesulfonic acid at elevated temperature, an improved modification[17] of existing literature procedures for the preparation of **3**[18a] and other aporphines.[18b] The rearrangement of morphine to apomorphine is known to be a stereospecific one and does not racemize the optically active 6a carbon of 3.[19] Tritiation of **3** proceeded smoothly with tritium gas and 10% Pd/C in ethanol for 2 h at room temperature. Purification of the crude reaction mixture by thin-layer chromatography (TLC) followed by high-pressure liquid chromatography afforded (−)-*N*-*n*-[^{3}H]propylnorapomorphine (**4**) in 98% radiochemical purity as ascertained by TLC and high-pressure LC. The specific activity of **4** as determined by UV spectroscopy was consistently in the range of 60–80 Ci/mmol, the highest of any dopaminergic agonist prepared to date.[20]

A triton magnetic resonance spectrum (Figure 1) was performed on the free base of **4**. Two signals whose chemical shifts were consistent with the terminal methyl (δ 1.05) and aliphatic methylene (δ 1.90) groups of (−)-*N*-*n*-propylnorapomorphine were obtained. Each signal was composed of several lines which were caused by the coupling of tritons on adjacent carbon atoms as well as the presence of polytritiated species. This implies that there are several species in the sample such as C^3H_3, $C^1H^3H_2$, and $C^1H_2{}^3H$ representing the terminal methyl group. Similar polytritiated species may exist also for the methylene group, thus accounting for the multiplet nature of the signals associated with these positions. Integration of the spectrum indicates that most of the tritons are attached to the terminal methyl group with a lesser amount attached to the methylene position. This uneven distribution of tritium upon double bond reduction has also been documented by triton magnetic resonance spectra in the case of [^{3}H]dihydroalprenolol.[21] No aromatic resonances were observed in the triton magnetic resonance spectrum of **4**.

Table I. Partial Mass Spectrum of *N*-*n*-[^{2}H]Propylnorapomorphine (5)

ions	rel intens	ions	rel intens
299 $(M\text{-}d_2)^{+\cdot}$	38	266 $(M-31)^+$	100
298 $(M\text{-}d_1)^{+\cdot}$	65	237 $(M-60)^{+\cdot}$	60
297 $M^{+\cdot}$	61	224 $(M-73)^{+\cdot}$	36
296 $(M-H)^+$	47		

Scheme II



By a procedure analogous to the preparation of **4**, (−)-*N*-*n*-[^{2}H]propylnorapomorphine (**5**) was also synthesized as shown in Scheme I from **3** and deuterium. The partial mass spectrum of **5** is summarized in Table I. The mechanism leading to the formation of these major ions is outlined in Scheme II. The deuterium incorporation in this compound was confirmed by the ion at *m/e* 297, $[M]^{+\cdot}$. The ions at *m/e* 298 and 299 of relatively high intensities should likewise suggest the presence of polydeuterated species. However, the absence of the ion peaks that are shifted 1–2 amu higher from the most abundant ion at *m/e* 266, $(M-31)^{+\cdot}$, implies that the deuteration occurred exclusively at the terminal ethyl group. Additionally, the splitting patterns giving rise to the major ions of $(M-H)^+$, $(M-31)^+$, $(M-60)^+$, and $(M-73)^+$ have been characteristic of *N*-propylnorapomorphine derivatives.[22]

We have assumed that the optical integrity of the 6a carbons in **4** and **5** have been maintained during the process of reducing **3** with isotopes of hydrogen over 10% Pd/C in ethanol. Adding credence to our assumption, we have observed that the exposure of (−)-apomorphine hydrochloride [$[\alpha]^{25}_D$ −48° (*c* 1.2)] to hydrogen over Pd/C in ethanol for 2 h at room temperature does *not* racemize

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(20) By way of comparison, the specific activity of generally labeled *N*-*n*-[^{3}H]propylnorapomorphine in ref 11 was only 0.017 Ci/mmol.

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its optically active 6a carbon. This retention of optical activity of apomorphine under such conditions parallels the observations of Kametani with the aporphine-like protoberberines[23] and 1-benzyltetrahydroisoquinolines.[24] It should be noted, however, that exposure of apomorphine[25] and related ring systems[23,24] to PtO_2 and hydrogen has been found to cause almost complete racemization of the 6a chiral center.

The successful use of **4** as a novel high-specific-activity, tritiated dopaminergic agonist has recently been documented.[26]

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 ($CHCl_3$–CH_3OH, 9:1), S_2 ($CHCl_3$–HOAc–CH_3OH, 10:2:2), S_3 (EtOH–HOAc–H_2O, 6:3:1), and S_4 (CH_3OH–PhH–H_2O–HOAc, 15:2:5:2). Autoradiography was performed at 0 °C after spraying the TLC plates with PPO (New England Nuclear) and exposing them to Eastman Kodak SB-5 film. TLC plates were also scanned for activity by using a Packard 7201 scanner. UV spectra were measured on a Beckman Model 25 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. The proton and triton magnetic resonance spectra were obtained on a Bruker WP 200-MHz NMR spectrometer. High-resolution mass spectra were performed by Shrader Analytical Laboratories. Preparative and analytical high-pressure LC was performed on a Waters high-pressure LC instrument using μ-Bondapak CN and μ-Bondapak C_{18} columns (Waters) eluted with S_5 [5% EtOH in 0.01 N KH_2PO_4 (pH 3) buffer] at 1.0 mL/min. Peak detection was performed at 280 nm by using a Waters 440 UV detector.

(-)-*N*-Allylnorapomorphine (3). A solution of (-)-nalorphine (**2**;[16] 75 mg, 0.22 mmol) in 1 mL of argon-degassed methanesulfonic acid was heated at 90 °C under argon for 0.5 h and then cooled in an ice bath. After the mixture cooled, 20 mL of a 0.1% $Na_2S_2O_5$ aqueous solution was slowly added to the reaction. It was basified to pH 8 with NH_4OH and then extracted with three 30-mL portions of S_1. The combined extracts yielded a residue upon evaporation which was preparatively chromatographed on a 1000-μm silica gel plate eluted with S_2. A major band (short-wave UV, R_f 0.63) was scraped off and eluted with S_1. Concentration of the eluent yielded a residue that was taken up in a solution of 5 mL of $CHCl_3$ and 25 mL of Et_2O. Millipore filtration and acidification with excess ethereal HCl yielded 20 mg (27%) of **3**·HCl as a white solid: mp 263–266 °C (lit.[18a] 265–266 °C); ^1H NMR (CD_3OD) δ 8.42 (dd, 1, J = 7.57, 0.98 Hz, H-1), 7.35 (dd, 1, J = 7.57, 0.49 Hz, H-2), 7.18 (dd, 1, J = 7.57, 0.98 Hz, H-3), 6.75 (m, 2, H-8,9), 6.10 (m, 1, $NCH_2CH{=}CH_2$), 5.70 (m, 2, $NCH_2CH{=}CH_2$), 4.50–3.20 (m, 8, H-4,5,7, $NCH_2CH{=}CH_2$), 2.80 (t, 1, J = 14.16 Hz, H-6a); UV (EtOH) λ_{max} 273 nm (ε 14 156), 281 (16 783), 320 (3015); $[\alpha]^{25}_D$ -66.1° (c 0.378, water) [lit.[18a] $[\alpha]^{30}_D$ -64.0° (c 0.328, water)].

Anal. Calcd for $C_{19}H_{19}NO_2$ (molecular ion): m/e 293.1414. Found: m/e 293.1401.

(-)-*N*-*n*-[^{3}H]Propylnorapomorphine (4). A solution of 8 mg (0.023 mmol) of **3** in 1.5 mL of EtOH with 3 mg of 10% Pd/C was stirred under an atmosphere of 75 Ci of tritium for 2 h at ambient temperature in the dark. Catalyst filtration and volatile removal with EtOH was performed. The resulting residue was dissolved in 20 mL of EtOH (total activity 474 mCi). This solution was concentrated to a volume of 0.5 mL and preparatively chromatographed on two 1000-μm silica gel plates eluted with S_3. The major band (short-wave UV R_f 0.84) was scraped off and eluted with EtOH (total activity 204 mCi). Final purification was performed by high-pressure LC using a μ-Bondapak CN column eluted at 1.0 mL/min with S_5. Typically, 204 mCi of prepurified **4** yielded 20 mCi of **4** displaying 98% radiochemical purity by silica gel TLC (S_3 and S_4) and high-pressure LC on μ-Bondapak CN and C_{18} eluted with S_5.[27] In both TLC and high-pressure LC analyses of radiolabeled **4**, it coeluted with cold standard (-)-*N*-*n*-propylnorapomorphine. The specific activity of **4** [ε (273 nm) 17 000[13b]] as measured by UV spectroscopy was 72 Ci/mmol.

(-)-*N*-*n*-[^{2}H]Propylnorapomorphine (5). A solution of 10 mg of **3** in 1.5 mL of EtOH with 4 mg of 10% Pd/C was stirred under an atmosphere of deuterium for 2 h at ambient temperature in the dark. Millipore filtration of the catalyst yielded a solution which was treated with excess ethereal HCl and concentrated to approximately 0.3 mL. The solution was diluted with 15 mL of Et_2O to yield 3.9 mg (41%) of **5** as a white solid.

Acknowledgment. The authors gratefully acknowledge the technical assistance of K. Bradley in the tritiation of **3** to **4** and H. Maksoud for supplying mass spectral data for **5**, the help of Professor L. J. Altman (Stony Brook) in obtaining the triton magnetic resonance spectrum of **4** and the consultation of Professor P. Vouros (Northeastern University) regarding the mass spectrum of **5**. The research at Northeastern University was supported in part by Contract NOI-CM-53741 from the National Cancer Institute and by a grant from the National Institutes of Health (NS 15439-01).

Registry No. **2**, 62-67-9; **3**·HCl, 1477-58-3; **4**, 73728-30-0; **5**, 73728-31-1.

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(27) The loss of product **4** attending this stage of the purification is undoubtedly due to product decomposition during rotary evaporator concentration of crude **4** in EtOH to a volume suitable for high-pressure LC injection, as well as peak shaving during the high-pressure LC of **4**.

Ene Reaction of Triazolinediones with Alkenes. 1. Structure and Properties of Products

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The structures of the ene products from reaction of triazolinediones with alkenes and polyisoprene were studied by using ^1H NMR. The pK_a values of the ene products were measured. The reactivity and stability of the ene products were also studied.

The ene reaction of 4-substituted-1,2,4-triazoline-3,5-diones (4-R-TD) with alkenes (eq 1) was first studied by Pirkle and Stickler[1] and 4-methyl-1,2,4-triazoline-3,5-dione (MeTD) was found to be at least 30 000 times more reactive

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