solid was collected, washed with EtOAc, and dried to give title compound **25**: yield 0.49 g (34%); mp 110–115 °C. Anal. ($C_{22}H_{28}Cl_2N_2O_6 \cdot C_4H_4O_4$) C, H, N.

4-(2,3-Dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-2-(propoxymethyl)-1,4-dihydropyridine (26). A solution of **13** (2.0 g, 4.46 mmol) in MeOH (60 mL) containing $Pd/BaSO_4$ catalyst (200 mg) and quinoline (5 drops) was stirred under an atmosphere of hydrogen at room temperature for 1 h, filtered, and evaporated. The residue was chromatographed on silica with CH_2Cl_2 as eluant. Appropriate fractions were combined and evaporated, and the residue was crystallized from MeOH to give title compound **26**: yield 1.67 g (83%); mp 118–119 °C. Anal. ($C_{21}H_{25}Cl_2NO_5$) C, H, N.

Acknowledgment. We thank S. M. Denton and S. F. Tickner for their able technical assistance, G. N. Thomas for the synthesis of **3**, and K. E. Bill for the synthesis of **11** and **26**. We also thank A. J. Carter for performing the in vivo hemodynamic measurements on **2** and **27** and M. J. Humphrey and D. A. Stopher for performing pharmacokinetics on **2**, **27**, and felodipine. We are also grateful to P. F. Wadsworth and his staff for analytical and spectra data.

R and *S* Enantiomers of 11-Hydroxy- and 10,11-Dihydroxy-*N*-allylnoraporphine: Synthesis and Affinity for Dopamine Receptors in Rat Brain Tissue

John L. Neumeyer,*,† Yigong Gao,†,§ Nora S. Kula,‡ and Ross J. Baldessarini‡

Section of Medicinal Chemistry, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115, and Departments of Psychiatry and Neuroscience Program, Harvard Medical School and Mailman Research Center, McLean Division of Massachusetts General Hospital, Belmont, Massachusetts 02178. *Received March 8, 1990*

The *R*-(−)- and *S*-(+)-enantiomers of 11-hydroxy-*N*-allyl (**4**), and 10,11-dihydroxy-*N*-allyl (**3**) congeners of 11-hydroxy-*N*-*n*-propylnoraporphine (11-OH-NPa, **2**) or *N*-*n*-propylnorapomorphine (NPA, **1**) were synthesized. Binding affinity of these compounds at dopamine (DA) receptor sites was evaluated with a membrane preparation of corpus striatum from rat brain. The *R*/*S* enantiomeric receptor affinity ratio was enhanced by allylic substitution of **3** and **4** and their *R* isomers had high DA receptor affinity similar to that of the *N*-*n*-propyl congeners. These *N*-allylaporphines are proposed as useful precursors to the preparation of their tritiated *N*-*n*-propyl enantiomers.

Introduction

Recently, the *R*-(−)- and *S*-(+)-isomers of certain mono and dihydroxy-*N*-alkylnoraporphines, including 11-hydroxy-*N*-*n*-propylnoraporphine (11-OH-NPa) and *N*-*n*-propylnorapomorphine (NPA), were used to characterize dopamine receptors.[1,2] The monohydroxy aporphines appear to be highly stereoselective D_2-selective agents that can interact at dopaminergic autoreceptor to inhibit tyrosine hydroxylase[3,4] without a direct inhibitory effect on this rate-limiting step in DA synthesis that may occur with catechol aporphines.[5,6] DA autoreceptors have been located on presynaptic dopaminergic neurons possessing a D_2 receptor character with regard to stereospecificity and potency series relationships.[7,8] However, postsynaptic D_2 receptors in the mammalian corpus striatum, and in the anterior pituitary mammotrophs, which regulate the secretion of prolactin, have lower affinity for typical DA agonists than at striatal autoreceptors.[9-11] Accordingly, DA partial agonists with low intrinsic activity can elicit autoreceptor activity selectively.[12-16] Though still unsolved, the mechanism and molecular consequences of activating DA autoreceptors are now receiving intense interest.[17,18] Selective autoreceptor ligands may provide functional modulation of the DA system of the brain without the excessive interference with neuronal activity believed to induce the adverse effects of typical DA antagonists used in the treatment of various neuropsychiatric disorders.[19,20]

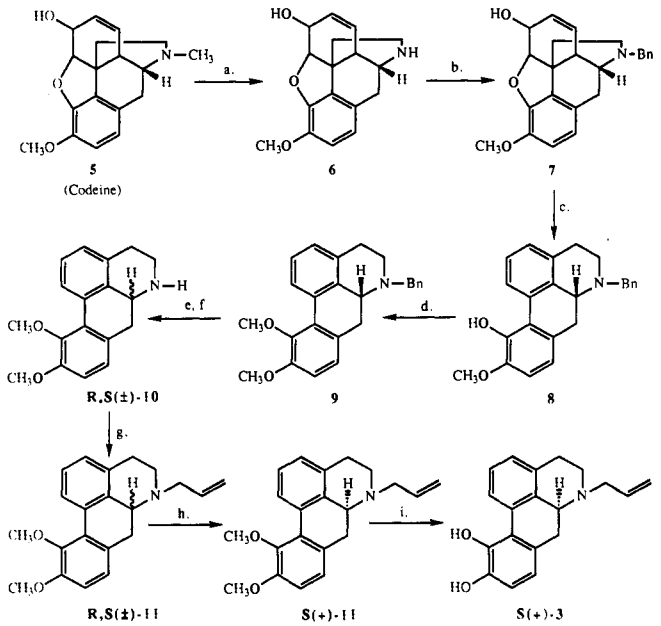
It is known that the *R*-(−)-enantiomers of hydroxyaporphines are highly selective agonists at DA receptors, while *S*-(+)-isomers of aporphine analogues, notably NPA and especially its monohydroxy congener 11-OH-NPa, show a moderate affinity for postsynaptic DA receptor sites.[21,22] Behavioral evidence indicates that these *S*-(+)-isomers exert functional antagonism of DA receptor

† Northeastern University.
‡ Harvard Medical School.
§ Present address: Research Triangle Institute, North Carolina.

(1) Baldessarini, E. R.; Marsh, E. R.; Kula, N. S.; Zong, R.; Gao, Y.; Neumeyer, J. L. *Biochem. Pharmacol.*, in press.
(2) Campbell, A.; Baldessarini, R. J.; Gao, Y.; Zong, R.; Neumeyer, J. L. *Neuropharmacol.* **1990**, *29*, 527–536.
(3) Wolf, M. E.; Roth, R. H. In *Dopamine Receptors*; Creese, I., Fraser, C. M., Eds.; Alan R. Liss, Inc.: New York, 1987; pp 45–96.
(4) Baldessarini, R. J.; Neumeyer, J. L.; Teicher, M.; Kula, N. S.; Campbell, A.; Marsh, E. *Neurosc. Abstr.* **1987**, *13*, 192 (Abs. No. 58.12).
(5) Musacchio, J. M. In *Handbook of Psychopharmacology*; Iversen, L. L., Iversen, S. D., Snyder, S. H., Eds.; Plenum Press: New York, 1975, Vol. 3, pp 1–35.
(6) Booth, R.; Kula, N. S.; Neumeyer, J. L.; Baldessarini, R. J. *Neurosc. Abstr.* **1989**, *15*, 427 (Abs. No. 170.25).
(7) Wazer, D. E.; Rotrosen, J.; Stanley, M. *Adv. Biochem. Psychopharmacol.* **1982**, *35*, 83–95.
(8) Bagetta, G.; De Sarro, G. B.; Priolo, E.; Nistico, G. *Br. J. Pharmacol.* **1988**, *95*, 860–866.
(9) Argiolas, A.; Merea, G.; Serra, G.; Merlis, M. R.; Fadda, F.; and Gessa, G. L. *Brain Res.* **1982**, *231*, 109–116.
(10) Claustre, Y.; Fage, D.; Zivkovic, B.; Scatton, B. *J. Pharmacol. Exp. Ther.* **1986**, *232*, 519–525.
(11) Bymaster, F. P.; Reid, L. R.; Nichols, C. L.; Kornfield, E. C.; Wong, D. T. *Life Sci.* **1986**, *38*, 317–322.
(12) Mikuni, M.; Gudelsky, G. A.; Simonovic, M.; Meltzer, H. Y. *Life Sci.* **1984**, *34*, 239–246.
(13) Eriksson, E.; Svensson, K.; Clark, D. *Life Sci.* **1985**, *36*, 1819–1827.
(14) Clemens, J. A.; Fuller, R. W.; Phebus, L. A.; Smalstig, E. B.; Dynes, M. D. *Life Sci.* **1984**, *34*, 1015–1022.
(15) Wachtel, H.; Dorow, R. *Life Sci.* **1983**, *32*, 421–432.
(16) Anden, N.-E.; Golembiowska-Nikitin, K.; Thornstrom, U. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1982**, *321*, 100–105.
(17) Clark, D.; Carlsson, A.; Hjorth, S.; Svensson, K.; Liljequist, S.; Engel, J.; Engberg, G.; Svensson, T. H.; Wikstrom, H. *Acta Pharma Suec.* **1983** (Suppl. 1), 145–153.
(18) Booth, R. G.; Baldessarini, R. J.; Kula, N. S.; Gao, Y.; Zong, R.; Neumeyer, J. L. *Mol. Pharmacol.* **1990**, *38*, 92–101.
(19) Antelman. S.; Chiodo, L. *Biol. Psychiatry* **1981**, *16*, 717–727.

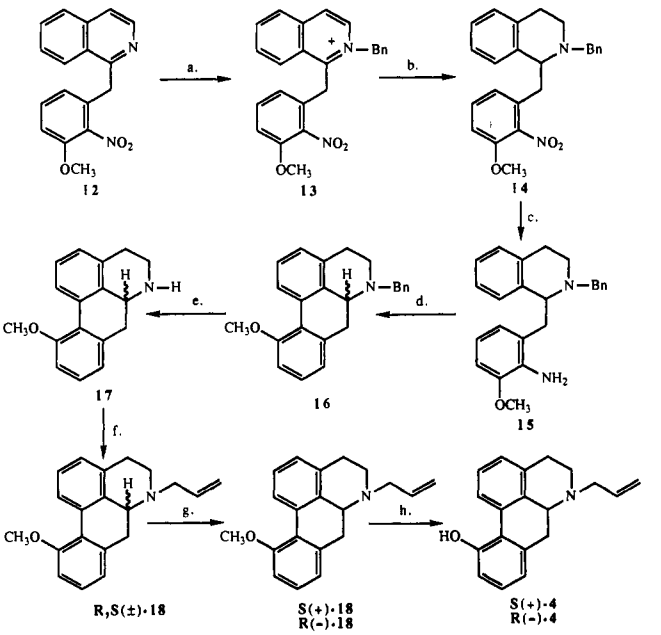
0022-2623/91/1834-0024$02.50/0

Scheme I[a]



[a] Reagents: (a) methyl chloroformate; NH_2NH_2; (b) BnCl, K_2CO_3; (c) CH_3SO_3H, Δ; (d) CH_2N_2; (e) 10% Pd-C, CH_3CN; (f) $NaCNBH_3$, pH = 3; (g) allyl bromide, K_2CO_3; (h) (−)-dibenzoyl-L-tartaric acid; (i) BBr_3, CH_2Cl_2.

Scheme II[a]



[a] Reagents: (a) benzyl bromide; (b) KBH_4; (c) PtO_2, H_2; (d) Pshorr cyclization; (e) $Pd(OH)_2$, EtOH; (f) allyl bromide, K_2CO_3; (g) (+)- or (−)-dibenzoyltartaric acid; (h) BBr_3, CH_2Cl_2.

stimulation in rat brain[2,22] and this action appears to be selective for the *limbic* system while sparing the extrapyramidal system.[1,23] Differences in affinity states or differences between receptor subtypes may play a role in such regional selectivity. The ability of *S*-(+)-enantiomers of such aporphines to antagonize locomotor arousal in the rat induced by direct DA agonists (notably, systemic apomorphine or intralimbic injection of DA) suggests a direct competitive effect as postsynaptic sites (very weak agonism). In addition, however, *S*(+)NPA (but not *S*(+)-11-OH-NPa) can act paradoxically as an autoreceptor agonist.[1,18] Radioactive forms of these ligands should help to clarify their sites of interaction with brain target sites and so contribute to defining the peculiar actions of (*S*)-(+)-hydroxyaporphines.

To pursue development of such ligands, we prepared and partially characterized the DA receptor affinities of (*S*)-(+)-11-hydroxy-*N*-allylnoraporphine (*S*(+)-11-OH-NPa) and (*S*)-(+)-*N*-allylnorapomorphine (*S*(+)-*N*-allylnorAPO), precursors suitable for the tritiation to the *N*-propyl congeners. Also obtained in these syntheses was (*R*)-(−)-11-hydroxy-*N*-allylnoraporphine, the potential precursor of tritiated (*R*)-(−)-11-hydroxy-*N*-*n*-propylnoraporphine. These *N*-allylaporphines also were compared with their *N*-*n*-propyl congeners for DA agonist sites and D_1 and D_2 receptor sites in mammalian forebrain tissue.

Chemistry

(*S*)-(+)-*N*-Allylnorapomorphine [(*S*)-**3**], a potential precursor of [^{3}H]*S*(+)-NPA, was prepared from codeine (**5**) as outlined in Scheme I. N-Demethylation of codeine using a previously reported procedure[24] gave norcodeine (**6**), which was benzylated with benzyl chloride and K_2CO_3 to afford **7**. Rearrangement of **7** with methanesulfonic acid[25] provided aporphine **8**, which was then O-methylated with diazomethane in ether to give (*R*)-(−)-10,11-dimethoxy-*N*-benzylnoraporphine (**9**). Racemization of **9** was carried out with 10% Pd on carbon in acetonitrile, presumably via the 6a,7-dehydro intermediate, which was then reduced with $NaCNBH_3$ to afford a racemic derivative. By this method, (*RS*)-10,11-dimethoxy-*N*-benzylnoraporphine was the expected product, but after purification by column, the major product isolated was found to be the racemic compound (*RS*)-**10**. Apparently, debenzylation also occurred during the dehydrogenation step. Treatment of compound **10** with 1.3 equiv of allyl bromide in the presence of an excess of K_2CO_3 in EtOH gave the *N*-allyl racemic compound (*RS*)-**11**, which was resolved with (−)-dibenzoyl-L-tartaric acid to give (*S*)-**11**. The desired product, compound (*S*)-**3**, was obtained by O-demethylation of (*S*)-**11** with BBr_3. The specific rotation of (*S*)-(+)-*N*-allylnorapomorphine (**3**) was identical with that of its *R* antipode, (R)-(−)-*N*-allylnorapomorphine, which was derived from (*R*)-(−)-morphine by a previously reported scheme.[26]

The synthesis of (*RS*)-11-methoxynoraporphine (**17**) was achieved by a procedure, reported previously for the synthesis of corresponding racemic desmethyl derivative of (*RS*)-11-hydroxyaporphine,[27] and is partially depicted in Scheme II. Racemic compound **17** was then alkylated with allyl bromide to afford compound (*RS*)-**18**. The racemate **18** was converted to a (−)-dibenzoyl-L-tartaric acid salt. Several crystallizations of this salt with MeOH provided a (*S*)-(+)-11-methoxy-*N*-allylnoraporphine (−)-dibenzoyl-L-tartrate with a constant melting point. In an

(20) Nilsson, J. L. G.; Carlsson, A. *Trends Pharmacol. Sci.* **1982**, *3*, 322.
(21) Froimowitz, M.; Neumeyer, J. L.; Baldessarini, R. J. *J. Med. Chem.* **1986**, *29*, 1570–1573.
(22) Gao, Y.; Zong, R.; Campbell, A.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **1988**, *31*, 1392–1396.
(23) Campbell, A.; Baldessarini, R. J.; Teicher, M. H.; Neumeyer, J. L. *Neuropharmacology* **1985**, *243*, 391–399.
(24) Rice, K. C. *J. Org. Chem.* **1975**, *40*, 1850.
(25) Granchelli, F. E.; Filer, C. N.; Soloway, A. H.; Neumeyer, J. L. *J. Org. Chem.* **1980**, *45*, 2275–2278.
(26) Filer, C. N.; Ahern, D.; Granchelli, F. E.; Neumeyer, J. L.; Law, S.-J. *J. Org. Chem.* **1980**, *45*, 3465–3467.
(27) Neumeyer, J. L.; Granchelli, F. E.; Fuxe, K.; Ungderstedt, U.; Corrodi, H. *J. Med. Chem.* **1974**, *17*, 1090–1095.

Table I. Affinity of Hydroxy-*N*-allylnoraporphines at Striatal Dopamine Receptors[a]

no.	compound	K_i, nM agonist	K_i, nM D_1	K_i, nM D_2	D_2/D_1 potency ratio
(*R*)-1	(*R*)-(−)-*N*-*n*-propylnorapomorphine	1.5	340	0.80	425
(*S*)-1	(*S*)-(+)-*N*-*n*-propylnorapomorphine	370	1,345	38.0	35.4
(*R*)-2	(*R*)-(−)-11-hydroxy-*N*-*n*-propylnoraporphine	5.3	434	0.90	482
(*S*)-2	(*S*)-(+)-11-hydroxy-*N*-*n*-propylnoraporphine	305	1,414	35.0	40.4
(*R*)-3	(*R*)-(−)-*N*-allylnorapomorphine	4.2	617	0.24	2,571
(*S*)-3	(*S*)-(+)-*N*-allylnorapomorphine	112	1,973	12.6	157
(*R*)-4	(*R*)-(−)-11-hydroxy-*N*-allylnoraporphine	0.034	452	2.0	226
(*S*)-4	(*S*)-(+)-11-hydroxy-*N*-allylnoraporphine	1,595	>10,000	155	>65

[a] Radioreceptor assays were carried out with the following ligands: D_1 antagonist, [^{3}H]SCH-23390; D_2 antagonist, [^{3}H]spiperone; and dopamine agonist, (±)-[^{3}H]ADTN. Values of experimentally determined IC_{50} (SEM of which average ≤10% of the mean) were converted to K_i values. D_2/D_1 potency ratio = $K_i(D_1)/K_i(D_2)$.

identical manner, (*R*)-18 was prepared via recrystallization from MeOH of (*R*)-(−)-11-methoxy-*N*-allylnoraporphine (+)-dibenzoyl-D-tartrate. The optical purity of (*S*)- and (*R*)-18 was determined by reducing the double bond to afford the known corresponding compounds (*R*)-(−)- and (*S*)-(+)-11-methoxy-*N*-*n*-propylnoraporphine. Subsequent O-demethylation of (*R*)-18 or (*S*)-18 with BBr_3, as described for (*S*)-11 in Scheme I, afforded the desired products (*S*)-(+)- and (*R*)-(−)-11-hydroxy-*N*-allylnoraporphine [(*S*)-4 and (*R*)-4].

Pharmacology

Radioreceptor assays were carried out with the following selective ligands for D_1 and D_2 receptor sites in rat striatal homogenates: [^{3}H]SCH-23390 (0.3 nM) for D_1 and [^{3}H]-spiperone (0.15 nM) for D_2 sites, by using methods described in detail previously.[28-31] In addition, comparisons were made with an agonist ligand [^{3}H]-(±)-2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (aminodihydroxytetralin, ADTN), using a preparation of membranes from caudate nucleus tissue obtained from calf brain and optimized for this purpose, as described previously;[32] this ligand appears to bind selectively to a high-affinity state of dopaminergic receptors, reflecting interactions with agonists, and was previously found to represent particularly high affinities for aporphines with dopamine agonist activity.[33] In presenting data on the affinity of experimental compounds with these dopaminergic receptor sites in mammalian brain tissue, IC_{50} values were obtained experimentally from at least two independent replications involving at least six concentrations of test agent in duplicate or triplicate, and then fit by computer to a function which provides a value for IC_{50} ± SEM;[34] reported values are converted to K_i from the relationship proposed by Cheng and Prusof,[35] on the basis of the following values for ligand affinity (K_d): 0.34 nM ([^{3}H]SCH-23390), 0.15 nM ([^{3}H]spiperone), and 1.5 nM ([^{3}H]ADTN). For reasons of clarity, individual variances are not reported in Table I (SEM/mean was ≤10%).

Results and Discussion

The dual aim of this work was to prepare the precursors of tritiated aporphines and to compare their pharmacological profiles with those of previously reported mono- and dihydroxy-*N*-*n*-propylnoraporphine enantiomers. These allylic compounds show interesting results in terms of structure–affinity relationships. Not only is the allyl moiety used widely to introduce tritium as radiolabeling marker, but it also has a role in many pharmacologically active compounds. The novel allylic N-substituted aporphines obtained from this study were evaluated for their binding affinity to D_1 and D_2 receptors as well as agonist (ADTN) sites and the results are presented in Table I. Results with the enantiomers of mono- and dihydroxy-*N*-*n*-propylnoraporphines (11-OH-NPa and NPA; compounds 1 and 2) were included for comparison.

We reported previously[21,22] that the R-(−)-enantiomers of compounds 1 and 2 have higher affinity for DA receptors than their *S*-(+)-antipodes (Table I). The introduction of an *N*-allyl group resulted in a 2.2-fold lower affinity for D_2 receptor sites compared to that of 11-OH-NPa [(*R*)-2], and *R*/*S* enantioselectivity was enhanced from 39 to almost 78 (11-OH-NPa vs 11-hydroxy-*N*-allylnoraporphine). The S-(+)-allylic monohydroxy analogue (*S*)-4 had the lowest affinities for all DA sites of compounds in the present series. By contrast, dihydroxy analogue (*R*)-3 had slightly higher affinity than reference *N*-*n*-propyl congener (*R*)-1 at D_2. In the case of (*R*)-(−)-*N*-allylnorapomorphine [(*R*)-3], D_2/D_1 selectivity was enhanced 6 times above that of the *N*-*n*-propyl compound *R*-(−)-1, but there was an 11.4-fold decrease in selectivity shown in the 11-monohydroxy allylic derivative (*R*)-4, vs. (*R*)-3, corresponding to an 8.3-fold loss in D_2 affinity. Despite a decrease of *R*/*S* enantioselectivity and D_2/D_1 selectivity of 11-hydroxy-*N*-allylnoraporphine (*R*)-4, one striking result is that (*R*)-4 showed the highest affinity for the agonist ADTN binding site in this study: respectively, 124-, 156-, and 44.1 times higher than (*R*)-3, (*R*)-2, and (*R*)-1 to provide an agonist potency series of (*R*)-11-hydroxy-*N*-allylnoraporphine > (*R*)-NPA > (*R*)-*N*-allylnorapomorphine > *R*-11-OH-NPa. Agonist binding at DA receptors probably involves two receptor affinity states[36,37] (high-affinity and low-affinity states). ADTN is a D_1-D_2 nonselective DA agonist which occupies both receptor subtypes, especially in their high-affinity states.[38] The correlation of affinity between the agonist site and D_1 or D_2 antagonist sites has not been

(28) Faedda, G.; Kula, N. S.; Baldessarini, R. J. *Biochem. Pharmacol.* **1989**, *27*, 473–480.
(29) Cohen, B. M.; Herschel, M.; Miller, E.; Mayberg, H.; Baldessarini, R. J. *Neuropharmacology* **1980**, *19*, 663–668.
(30) Kula, N. S.; Baldessarini, R. J.; Bromley, S.; Neumeyer, J. L. *Life Sci.* **1985**, *37*, 1051–1057.
(31) Svendsen, C. N.; Froimowitz, M.; Hrbek, C.; Campbell, A.; Kula, N.; Baldessarini, R. J.; Cohen, B. M.; Babb, S.; Teicher, M. H.; Bird, E. D. *Neuropharmacology* **1988**, *27*, 1117–1124.
(32) Arana, G. W.; Baldessarini, R. J.; Lamont, J. S.; Amlicke, D.; Neumeyer, J. L. *Biochem. Pharmacol.* **1983**, *32*, 2873–2880.
(33) Neumeyer, J. L.; Arana, G. W.; Ram, V. J.; Baldessarini, R. J. *Acta Pharm. Suec.* **1983** (Suppl. 2), *271*, 11–24.
(34) Teicher, M. H. MED-65: Allfit, Grafit (Applesoft); Biomedical Computing Technology Information Center: Vanderbilt University, Nashville, TN, 1983.
(35) Cheng, Y.-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.
(36) Wreggett, K. A.; Seeman, P. *Mol. Pharmacol.* **1984**, *25*, 10–17.
(37) Hess, E. J.; Battaglia, G.; Norman, A. B.; Torio, L. C.; Creese, I. *Eur. J. Pharmacol.* **1986**, *121*, 31–38.
(38) Seiler, M. P.; Markstein, R. *Mol. Pharmacol.* **1982**, *22*, 281.

consistent,[39] but high affinity at the ADTN site usually corresponds to high potency with respect to in vivo functional activities.[40] Further in vivo investigations are required to clarify a prediction that (R)-(−)-11-hydroxy-N-allylnoraporphine may have particularly potent activity expected of a DA agonist.

In summary, we have described the synthesis and resolution of novel N-allyl-substituted mono- and dihydroxynoraporphines and their preliminary in vitro DA receptor affinities. The (R)-(−)-11-monohydroxy- and 10,11-dihydroxy-N-allylnoraporphines should be potent DA agonists. In addition, these allylic aporphine analogues should be useful as precursors to the preparation of their tritiated N-n-propyl congeners as ligands of value for the further characterization of DA receptors.

Experimental Section

All chemicals were used as received from the manufacturer. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectrum were obtained with a Varian T-60 and XL-300 spectrometer using tetramethylsilane (TMS) as the internal reference. Mass spectra of novel compounds were determined with a high-resolution Finnigan 4021 mass spectrometer. Optical rotations were obtained on a Perkin-Elmer polarimeter Model 241. Elemental analyses were performed by Atlantic Microlab Inc, Atlanta, GA, and such analyses reported by symbols of the elements indicate observed values that were within ±0.4% of the calculated values.

N-Benzylnorcodeine Methanesulfonate (7·CH_3SO_3H). Norcodeine[24] (6, 5 g, 17.5 mmol) was dissolved in 50 mL of absolute EtOH, containing 2.9 g (22.9 mmol) of benzyl chloride and 4 g (28.9 mmol) of anhydrous K_2CO_3. The mixture was stirred at 80 °C overnight. After filtration the solution was concentrated. Purification by flash chromatography using 5:1 (v/v) hexane/acetone as eluent afforded an oily product which was extracted into ether. The ethereal extract was filtered and methanesulfonic acid in ether was dropped into the filtrate. The methanesulfonate salt of 7 was collected by filtration to afford 7.8 g (94% yield) of a white solid: mp 153–156 °C; mass spectrum m/z 375 (M^+); ^{1}H NMR ($CDCl_3$) δ 7.5–7.70 (m, 5 H, ArH) 6.72 (d, 1 H, ArH), 6.65 (d, 1 H, ArH), 5.8 (d, 1 H, CH=), 5.1 (d, 1 H CH=), 5.0 (d, 1 H), 4.7 (dd, 1 H), 4.5 (s, 3 H, CH_2ArH), 4.1–4.22 (m, 2 H), 3.8 (s, 3 H, OCH_3), 3.7 (dd, 1 H), 3.2 (m, 2 H), 2.85 (s, 3 H, CH_3), 2.6–2.8 (m, 2 H), 2.1 (dd, 1 H).

(R)-N-Benzylnorapocodeine Hydrochloride (8·HCl). The methanesulfonate of 7 (6.0 g, 12.7 mmol) from the preceding step was dissolved in 20 mL of methanesulfonic acid and was heated at 90–95 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with H_2O and adjusted to pH 8.0 with concentrated aqueous NH_3. The mixture was extracted with $CHCl_3$, and the combined extracts were washed and dried over anhydrous $MgSO_4$. The filtered $CHCl_3$ extract was then evaporated to dryness. The residue was purified by flash chromatography eluted with CH_2Cl_2 and MeOH (20:1, v/v). The desired fraction was collected and then converted to the HCl salt with HCl/ether to give 2.55 g (56% yield) of 8·HCl: mp 214–219 °C; mass spectrum m/z 357 (M^+); ^{1}H NMR (CD_3OD) δ 8.4 (d, 1 H, 1-H), 7.5–7.7 (m, 5 H, ArH), 7.3 (t, 1 H, 2-H), 7.15 (d, 1 H, 3-H), 6.9 (q, 2 H, 8-, 9-H), 5.0 (d, 2 H), 4.2 (d, 2 H), 3.9 (s, 3 H, OCH_3), 3.0–3.8 (m, 5 H). Anal. ($C_{24}H_{23}NO_2$·HCl·0.5H_2O) C, H, N.

(R)-10,11-Dimethoxy-N-benzylnoraporphine [(R)-9]. Compound (R)-8·HCl (6 g, 15.2 mmol) was dissolved in 15 mL of MeOH and allowed to react with an excess of CH_2N_2 in ether (prepared from 42 g of Diazald) for 3 days. The solvent was evaporated and the crude products were purified by flash chromatography using 5:1 (v/v) hexane/acetone as eluent. The resulting oil was crystallized from EtOH to give 3.5 g (62% yield) of 9: mp 158–160 °C; mass spectrum m/z 371 (M^+); ^{1}H NMR ($CDCl_3$) δ 8.25 (d, 1 H, 1-H), 7.25–7.5 (m, 6 H, ArH), 7.1 (d, 1 H, 3-H), 7.1 (d, 1 H, 8- or 9-H), 6.85 (d, 1 H, 8- or 9-H), 4.35 (d, 1 H, NCHAr), 3.9 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.5 (dd, 1 H), 3.4 (d, 1 H, NCHAr), 3.25 (dd, 1 H), 3.1 (m, 2 H), 2.72 (dd, 1 H), 2.65 (t, 1 H), 2.4.5 (m, 1 H). Anal. ($C_{25}H_{25}NO_2$) C, H, N.

(RS)-(±)-10,11-Dimethoxynoraporphine Hydrochloride [(RS)-10·HCl]. Compound (R)-9 (4.5 g, 12.1 mmol) in 150 mL of CH_3CN was allowed to reflux with 4 g of 10% Pd on charcoal under nitrogen. After 5 h, TLC indicated complete conversion. The catalyst was filtered off, and the filtrate was evaporated to afford a yellow-greenish oil. The oily product was dissolved in 50 mL of absolute EtOH, and 2.3 g (36.6 mmol) of $NaCNBH_3$ was added; EtOH/HCl was added until the pH was 3.0, and this pH was maintained over 4 h by several additions of the HCl/EtOH. After evaporation of the reaction mixture, the pH was adjusted to 8.0 with saturated aqueous K_2CO_3 solution, and the free base was extracted from $CHCl_3$ as an oil. Purification by flash chromatography using 1:1 (v/v) $CHCl_3$/MeOH as eluent afforded an oily product which extracted into ether and was converted to the HCl salt with HCl/ether. After crystallization from MeOH/ether, 0.7 g (two step yield: 18%) of (RS)-10·HCl was obtained: mp 257–258 °C; $[\alpha]^{25}_D$ = 0° (c 0.34, MeOH); mass spectrum m/z 281 (M^+); ^{1}H NMR (CD_3OD) δ 8.25 (d, 1 H, 1-H), 7.33 (t, 1 H, 2-H), 7.19 (d, 1 H, 3-H), 7.02 (d, 1 H, 8 or 9-H), 6.93 (d, 1 H, 8- or 9-H), 4.35 (dd, 1 H), 3.82 (s, 3 H, OCH_3), 3.7 (m, 1 H), 3.6 (s, 3 H, OCH_3), 3.26–3.40 (m, 3 H), 3.0–3.12 (m, 1 H), 2.80 (t, 1 H). Anal. ($C_{18}H_{19}NO_2$·HCl) C, H, N.

(RS)-10,11-Dimethoxy-N-allylnoraporphine [(RS)-11]. (RS)-10,11-Dimethoxynorapoprhine hydrochloride (compound 10; 650 mg, 2.01 mmol) was dissolved in 30 mL of absolute EtOH, containing 450 mg (3.72 mmol) of allyl bromide and 340 mg (2.46 mmol) of anhydrous K_2CO_3. The mixture was stirred at 70 °C for 4 h. After removal of all solvent in vacuum, water was added, and the mixture was extracted repeatedly with ether. The combined organic extracts were washed with H_2O, dried ($MgSO_4$), and filtered. Evaporation of the organic solution left 430 mg (65% yield) of (RS)-11 as a clear oil with only single spot on TLC at R_f 0.71 (silica gel 60 F254, 10% MeOH/$CHCl_3$): ^{1}H NMR ($CDCl_3$) δ 8.25 (d, 1 H, 1-H), 7.3 (t, 1 H, 2-H), 7.15 (d, 1 H, 3-H), 7.05 (d, 1 H, 8- or 9-H), 6.89 (d, 1 H, 8- or 9-H), 6.0 (m, 1 H, CH=), 5.3 (m, 2 H, CH_2=), 3.9 (s, 3 H, OCH_3), 3.7 (s, 3 H, OCH_3), 3.45 (dd, 1 H), 3.1–3.3 (m, 5 H), 2.5–2.8 (m, 3 H).

(R)- and (S)-10,11-Dimethoxy-N-allylnoraporphine Hydrochloride [(R)- and (S)-11·HCl]. Racemic (RS)-11 (430 mg, 1.34 mmol) and (+)-dibenzoyl-D-tartaric acid (300 mg, 0.8 mmol) was dissolved under reflux in EtOAc (20 mL) for 30 min. After the mixture cooled down to room temperature, white solids present were collected by filtration and washed with EtOAc. The colorless diastereomeric salt obtained was recrystallized repeatedly with EtOH/MeOH (1:10, v/v) to obtain a constant mp 179–180 °C. Anal. ($C_{39}H_{37}NO_{10}$) C, H, N.

Of this dibenzoyltartrate salt, 350 mg was converted to the HCl salt to afford 120 mg of (R)-11·HCl: mp 220–221 °C; $[\alpha]^{25}_D$ = −101.8° (c 0.284, MeOH); mass spectrum m/z 321 (M^+). ^{1}H NMR spectrum was identical with that of (RS)-11.

The combined mother liquors containing (S)-11 were treated with saturated aqueous K_2CO_3 to liberate the free base, extracted with methylene chloride, and evaporated to dryness. The remaining 230 mg (0.716 mmol) of oil was dissolved in 5 mL of ethyl acetate and treated with 270 mg (0.717 mmol) of (−)-dibenzoyl-L-tartaric acid to yield 460 mg of a solid. Two recrystallizations gave material with a constant mp 179–180 °C (Anal. ($C_{39}H_{37}NO_{10}$) C, H, N), which was converted to the hydrochloride salt to give 130 mg of (S)-11·HCl: mp 220–221 °C; $[\alpha]^{25}_D$ = +101.2° (c 0.173, MeOH); mass spectrum m/z 321 (M^+); ^{1}H NMR spectrum was identical with that of (RS)-11 and (R)-11.

(S)-N-allylnorapomorphine Hydrobromide [(S)-3·HBr]. Compound (S)-11·HCl (50 mg, 0.14 mmol) was dissolved in 2 mL of CH_2Cl_2 under a N_2 atmosphere and 2 mL of 1 M BBr_3 in hexane was added at 0 °C, followed by stirring at room temperature for 1.5 h. The reaction then was quenched with MeOH and evaporated to dryness. The residue was dissolved in MeOH, refluxed for 15 min, and evaporated again. The resulting material was dissolved in small amount of MeOH and added to ether. After filtration, white solids were collected to give 41 mg (79% yield) of (S)-3·HBr: mp 251–252 °C dec; mass spectrum m/z 293 (M^+); ^{1}H NMR (CD_3OD) δ 8.39 (d, 1 H, 1-H), 7.3 (t, 1 H, 2-H), 7.1 (d,

(39) Creese, I.; Sibley, D. R.; Hamblin, M. W.; Leff, S. E. A. Rev. Neurosci. 1983, 6, 43–71.
(40) Gao, Y.; Ram, V. J.; Campbell, A.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. J. Med. Chem. 1989, 33, 39–44.

1 H, 3-H), 6.7 (m, 2 H, 8, 9-H), 6.0 (m, 1 H, CH=), 5.65 (m, 2 H, CH_2=), 4.3 (m, 2 H), 3.8–3.95 (m, 3 H), 3.1 (m, 1 H), 2.75 (t, 1 H); $[\alpha]^{25}_D$ = +56.9° (c 0.29, MeOH). Anal. ($C_{19}H_{19}NO_2$·HBr·0.5H_2O) C, H, N.

In order to determine the enantiomeric purity of the resolved N-allyl derivative, a small amount (25 mg) of (S)-3·HBr was treated with saturated aqueous K_2CO_3 to liberate the free base, extracted with CH_2Cl_2, and evaporated to dryness. The residue was converted to the HCl salt by HCl/ether to give 16 mg of off-white solids of (S)-3·HCl: $[\alpha]^{25}_D$ = +63.7° (c 0.12, H_2O) [optical rotation of (R)-3·HCl: lit.[26] $[\alpha]^{25}_D$ = −66.1° (c 0.378, H_2O); lit.[41] $[\alpha]^{30}_D$ = −64.0° (c 0.328, H_2O)].

(*RS*)-11-Methoxy-*N*-allylnoraporphine [(*RS*)-18]. Compound (RS)-17[27] (1.33 g, 4.6 mmol) was allylated with allyl bromide (0.6 g, 5.0 mmol) and K_2CO_3 (0.95 g 6.9 mmol) as described for (RS)-11 to give 1 g (74.2% yield) of an oil: ^{1}H NMR (CD_3OD) δ 8.2 (d, 1 H, 1-H), 7.29 (t, 1 H, 2-H), 7.2 (t, 1 H), 7.1 (d, 1 H), 7.0 (d, 1 H), 6.9 (d, 1 H), 6.0 (m, 1 H, CH=), 5.6 (m, 2 H, CH_2=), 4.3 (m, 2 H), 3.9 (m, 2 H), 3.8 (s, 3 H, OCH_3), 3.3–3.4 (m, 3 H), 3.1 (m, 1 H), 2.8 (t, 1 H).

Resolution of (*RS*)-11-Methoxy-*N*-allylnoraporphine [(*RS*)-18]. Racemic (RS)-18 (1 g, 3.43 mmol) and (+)-dibenzoyl-D-tartaric acid (650 mg, 1.73 mmol) were dissolved in EtOAc (20 mL) and refluxed for 30 min. After cooling to room temperature, the white solids were collected by filtration and washed with EtOAc. The colorless diastereomeric salt was recrystallized with MeOH repeatedly to provide a constant mp 178–179 °C. The resulting 410 mg of salt [$[\alpha]^{25}_{436}$ = +51.45° (c 0.23, MeOH)] then was converted to the HCl salt to afford 190 mg of (R)-18·HCl: mp 197–198 °C; $[\alpha]^{25}_D$ = −89.8° (c 0.3, MeOH); mass spectrum m/z 291 (M^+). ^{1}H NMR spectrum was identical with that of (RS)-18. Anal. ($C_{20}H_{21}NO$·HCl) C, H, N.

The combined mother liquors containing (S)-18 were treated with saturated aqueous K_2CO_3 to liberate the free base, extracted with methylene chloride, and evaporated to dryness. The remaining 550 mg (1.89 mmol) of oil was dissolved in 15 mL of ethyl acetate and treated with 710 mg (1.89 mmol) of (−)-dibenzoyl-L-tartaric acid to yield 740 mg of a solid. Three recrystallizations gave 420 mg of crystals [$[\alpha]^{25}_{436}$ = −50.0° (c, 0.19, MeOH)] with a constant melting point of 177–178 °C, which was converted to the hydrochloride salt to give 200 mg of (S)-18·HCl: mp 197–198 °C; $[\alpha]^{25}_D$ = +90.0° (c 0.21, MeOH); mass spectrum m/z 291 (M^+). ^{1}H NMR spectrum was identical with that of (RS)- and (R)-18. Anal. ($C_{20}H_{21}NO$·HCl·0.25H_2O) C, H, N.

The enantiomeric purity of (R)-18·HCl and (S)-18·HCl was determined by reducing the allylic double bond to afford the known N-propyl compounds (R)-(−)- and (S)-(+)-11-methoxy-N-n-propylnoraporphines.[22] Compound (R)-18·HCl (15 mg, 0.046 mmol) dissolved in 5 mL of EtOH was stirred with 7 mg of 10% Pd/C under an atmosphere of hydrogen in the dark for 4 h at ambient temperature. Millipore filtration of the catalyst yielded a solution which was treated with excess ethereal HCl, concentrated to approximately 0.5 mL, and then diluted with 15 mL of ether to yield 8 mg of product: $[\alpha]^{25}_{578}$ = −76.9° (c, 0.18, MeOH). The ^{1}H NMR spectrum was identical with that of (R)-(−)-11-methoxy-N-n-propylnoraporphine[22] [lit.[22] $[\alpha]^{25}_{578}$ = −79.3° (c 0.26, MeOH)].

Compound (S)-18·HCl was treated by the same procedure to obtain (S)-(+)-11-methoxy-N-n-propylnoraporphine hydrochloride: $[\alpha]^{25}_{578}$ = +77.7° (c 0.15, MeOH) [lit.[22] $[\alpha]^{25}_{578}$ = +79.6° (c 0.2, MeOH)].

(*R*)-11-Hydroxy-*N*-allylnoraporphine Hydrobromide [(*R*)-4·HBr]. Compound (R)-18·HCl (25 mg, 0.076 mmol) was O-demethylated with excess BBr_3 as described above for (S)-3 to give 25 mg (92% yield) of white solids of (R)-4 as the HBr salt: mp 174–176 °C; mass spectrum m/z 277 (M^+); ^{1}H NMR spectrum (CD_3OD) δ 8.4 (d, 1 H, 1-H), 7.3 (t, 1 H), 7.1 (d, 1 H), 7.0 (t, 1 H), 6.8 (m, 2 H, 8; 9-H), 6.0 (m, 1 H, CH=), 5.56 (m, 2 H, CH_2=), 4.3 (m, 2 H), 3.8–3.95 (m, 2 H), 3.45 (dd, 1 H), 3.3 (m, 2 H), 3.1 (m, 1 H), 2.8 (t, 1 H); $[\alpha]^{25}_D$ = −52.5° (c 0.16, MeOH). Anal. ($C_{19}H_{19}NO$·HBr·1.5H_2O) C, H, N.

(*S*)-11-Hydroxy-*N*-allylnoraporphine Hydrobromide [(*S*)-4·HBr]. Compound (S)-18·HCl (24 mg, 0.073 mmol) was O-demethylated with excess of BBr_3 as previously described for (S)-3 to give 24 mg (92% yield) of white solids as the HBr salt: mp 174–176 °C; mass spectrum m/z 277 (M^+); the ^{1}H NMR spectrum was identical with that of (R)-4·HBr; $[\alpha]^{25}_D$ = +52.8° (c 0.11, MeOH). Anal. ($C_{19}H_{19}NO$·HBr·H_2O) C, H, N.

Acknowledgment. This work was supported by USPHS Grants MH-47370 and MH-34006 and an award from the Bruce J. Anderson Foundation (R.J.B.). We thank Mallinckrodt, Inc. for the generous gift of codeine, Research Biochemicals, Inc. for (R)-(−)- and (S)-(+)-N-n-propylnorapomorphine, and Dr. Rushi Zong for preparation of 1-(2′-nitro-3′-methoxybenzyl)isoquinoline.

(41) Hensiak, J. F.; Cannon, J. G.; Burkman, A. M. *J. Med. Chem.* **1965**, *8*, 557.