Mammalian Alkaloids. 8.[1] Synthesis and Biological Effects of Tetrahydropapaveroline Related 1-Benzyltetrahydroisoquinolines

Arnold Brossi,* Kenner C. Rice, Ching-Pong Mak, Jürgen Reden, Arthur E. Jacobson,

Medicinal Chemistry Section, Laboratory of Chemistry

Yuthasak Nimitkitpaisan, Phil Skolnick, and John Daly

Laboratory of Bioorganic Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20205. *Received December 14, 1979*

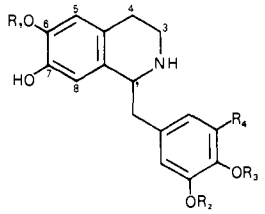
(±)-Tetrahydropapaveroline (THP, 1), its optical isomers (**1a** and **1b**), and related compounds were studied for their binding to β-adrenergic, dopaminergic, and α-adrenergic receptors from rat cerebral cortex. The related compounds were (±)-trimetoquinol (**2**); (±)-, (*S*)-(−)-, and (*R*)-(+)-*N*-norreticuline (**3**, **3a**, and **3b**); papaveroline (**4**); 6,7-dihydroxy-1-(4-hydroxy-3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**5**) and 6,7-dihydroxy-1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**6**), the latter two compounds prepared by a reaction between the precursor keto acids (**23** and **24**) and dopamine hydrobromide; 6,7-dihydroxy-1-(4-hydroxy-3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**7**) from acid hydrolysis of the tris(benzyloxy)tetrahydroisoquinoline **10**; 1-(3,4-dihydroxybenzyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**11**) from reduction of its protected quaternary catechol salt and subsequent hydrolysis; 6,7-dihydroxy-1-(6-bromo-3,4-dihydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline ("6′-Br-THP", **14**); norlaudanosine (**15**); 2,3,9,10-tetraacetoxydibenzo[*bg*]-pyrrocoline ("benzopyrrocoline tetraacetate", **16**); 2,3,8,9-tetrahydroxyisopavinan (**20**) and 2,3,8,9-tetrahydroxypavinan (**21**), the last two compounds from O-demethylation of *N*-northalidine and *N*-norbisnorargemonine, respectively. THP has been considered a "mammalian alkaloid"; its endogenous formation in mammals prompted us to examine its interactions with mammalian receptors and to examine compounds related to THP. (±)-Trimetoquinol (**2**) was among the most potent of these compounds in inhibiting binding to β-adrenergic receptors, and 6′-Br-THP (**14**) was more potent than dopamine in the α-adrenergic assay and equipotent to it in the dopaminergic receptor assay. Stereospecificity was observed in the interaction with these receptors, and those compounds which were reasonably potent were conformationally mobile, flexible secondary amines. The (±)-, (−)-, and (+)-norreticulines were also examined in the hot-plate antinociceptive assay, since reticulines are intermediates in the plant synthesis of morphine alkaloids.

Tetrahydropapaveroline (THP; **1**), a urinary excretion product of parkinsonian patients treated with L-Dopa,[2,3] is a "mammalian alkaloid".[4] The mechanism and origin of THP formation in patients with parkinson's disease are still unknown, as is whether the THP is excreted in the form of its racemate **1** or its optical isomer **1a,b**. The possible involvement of **1**, or the enantiomers **1a** and **1b** in alcoholism,[5,6] and its ability to inhibit the binding of radioligands to catecholamine receptors in the CNS[7] make THP, its optical isomers, and related compounds molecules of potential biological importance. The use of trimetoquinol (**2a**; an optically active isomer of a close relative of THP[8]) as a bronchodilator[9] suggests that catecholic 1-benzyltetrahydroisoquinolines which interact with catecholamine receptors may have potential as therapeutic agents. Optical resolution of THP[10] supported earlier findings[8] that the *S* isomer **1a** was markedly more active in several bioassays than the racemate or its *R* enantiomer.[11] It was also demonstrated that N-methylated THP[10,12] and reticuline (*N*-Me in **3**) have markedly decreased activities,[7] whereas *N*-norreticuline (**3**), an *O,O*-dimethyl ether of THP, maintained substantial inhibitory activity against catecholamine receptor agonists.[7] A major in vitro metabolic route for (±)-THP (**1**) or (*S*)-(−)-THP (**1a**) was found to be via O-methylation in the isoquinoline ring to yield 6-MeO-THP (**11**).[13] 7-MeO-THP was the major metabolic product from (*R*)-(+)-THP (**1b**) and a minor metabolite from (±)- and (*S*)-(−)-THP.[13]

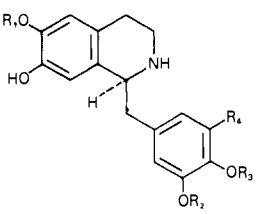
To further explore the structural features necessary for binding to the α- and β-adrenergic and dopaminergic receptors in vitro, we have synthesized and studied the neurochemical action of compounds related to THP.[14] These include 1-benzyltetrahydroisoquinolines biochemically related to THP, as well as polycyclic isoquinolines chemically derived from THP. Since reticulines are recognized intermediates in the plant biosynthesis of morphine alkaloids,[3] several of these compounds were also evaluated in an antinociceptive assay in vivo.

Chemistry. 1-Benzyltetrahydroisoquinolines. Papaveroline (**4**), the known nonchiral aromatic relative of THP, was prepared by the reported procedure.[15] The

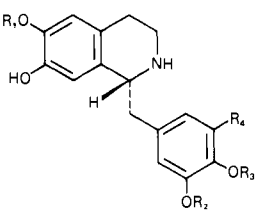
(1) Paper 7: J. Reden, W. C. Ripka, K. C. Rice, and A. Brossi, "International Symposium on Biological Research in Alcoholism", Plenum Press, New York, 1979, in press.
(2) T. L. Sourkes, *Nature (London)*, **229**, 413 (1971).
(3) M. Sandler, S. B. Carter, K. R. Hunter, and G. M. Stern, *Nature (London)*, **241**, 439 (1973).
(4) A. Brossi, *Heterocycles*, **3**, 343 (1975); M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research: 1972-1977", Plenum Press, New York, 1978, pp 20-22.
(5) C. L. Melchior and R. D. Myers, *Pharmacol. Biochem. Behav.*, **7**, 19 (1977).
(6) G. Bringmann, *Naturwissenschaften*, **66**, 22 (1979).
(7) Y. Nimitkitpaisan and P. Skolnick, *Life Sci.*, **23**, 375 (1978).
(8) E. Yamato, M. Hirakura, and S. Sugasawa, *Tetrahedron, Suppl.*, **8**, 129 (1966).
(9) "Merck Index", 9th ed., Merck & Co., Inc., Rahway, N.J., 1976, no. 9389.
(10) S. Teitel, J. O'Brien, and A. Brossi, *J. Med. Chem.*, **15**, 845 (1972).
(11) G. Cohen, R. E. Heikklia, D. Dembiec, D. Sang, S. Teitel, and A. Brossi, *Eur. J. Pharmacol.*, **29**, 292 (1974); G. Cohen, in "Membrane Mechanisms of Drugs of Abuse", C. Sharp and L. G. Abood, Eds., Allen Liss, New York, 1979, pp 73-90.
(12) H. Sheppard, C. R. Burghardt, and S. Teitel, *Mol. Pharmacol.*, **12**, 854 (1976); *Res. Commun. Chem. Pathol. Pharmacol.*, **17**, 53 (1977).
(13) L. R. Myerson, J. L. Cashaw, K. B. McMurtrey, and V. E. Davis, *Biochem. Pharmacol.*, **28**, 1745 (1979).
(14) H. Bruderer, J. Metzger, A. Brossi, and J. J. Daly, *Helv. Chim. Acta*, **59**, 2793 (1976).
(15) A. Brossi and S. Teitel, *J. Org. Chem.*, **35**, 1684 (1970).



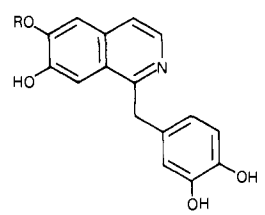
1, $R_1 = R_2 = R_3 = R_4 = H$
2, $R_1 = H, R_2 = R_3 = CH_3, R_4 = OCH_3$
3, $R_1 = R_3 = CH_3, R_2 = R_4 = H$
7, $R_1 = R_3 = R_4 = H, R_2 = CH_3$



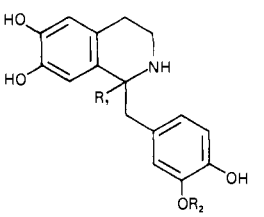
1a, $R_1 = R_2 = R_3 = R_4 = H$
2a, $R_1 = H, R_2 = R_3 = CH_3, R_4 = OCH_3$
3a, $R_1 = R_3 = CH_3, R_2 = R_4 = H$



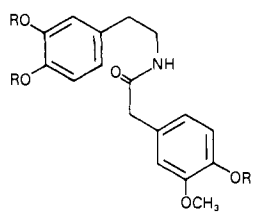
1b, $R_1 = R_2 = R_3 = R_4 = H$
3b, $R_1 = R_3 = CH_3, R_2 = R_4 = H$



4, R = H
12, R = CH_3



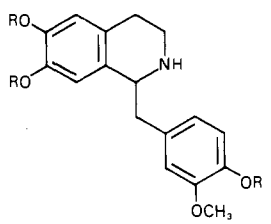
5, $R_1 = COOH, R_2 = CH_3$
6, $R_1 = COOH, R_2 = H$



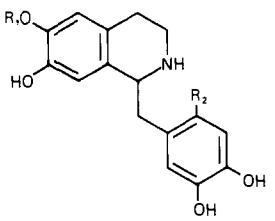
8, R = H
9, R = $CH_2C_6H_5$

tetrahydroisoquinoline-1-carboxylic acid **5**, a major metabolite of L-Dopa-treated patients,[16] and **6**, a biosynthetic precursor of THP in plants,[17] were prepared by a modified Pictet–Spengler condensation. The possibility that **5** might be converted in vivo into the previously undetected 3′-monomethyl ether **7** by oxidative decarboxylation[18] and reduction was intriguing and prompted the synthesis of **7** by a classical sequence.

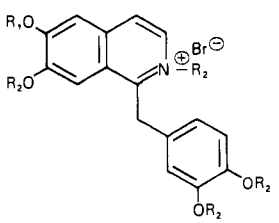
The synthesis of the methyl ether **7** was started with the intermediate amide **8** obtained from dopamine and 3-methoxy-4-hydroxyphenylacetic acid. Protection by O-benzylation afforded the amide **9**, which was cyclized and reduced to the tetrahydroisoquinoline. Catalytic O-debenzylation of **10** was unusually difficult and afforded the



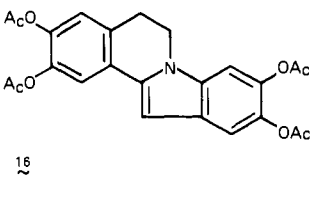
10, R = $CH_2C_6H_5$
15, R = CH_3



11, $R_1 = CH_3, R_2 = H$
14, $R_1 = H, R_2 = Br$



13, $R_1 = CH_3, R_2 = CH_2C_6H_5$



16

methyl ether **7** in low yield, isolated as its hydrochloride salt. However, **7** could be prepared efficiently by the hydrolysis of **10** with aqueous HCl in methanol. A similar difficulty was noted in the hydrogenolysis of the *O*-benzyl ether of **11**, suggesting that the catechols formed during these reductions bind, and possibly further react, on the surface of the Pd/C catalyst.

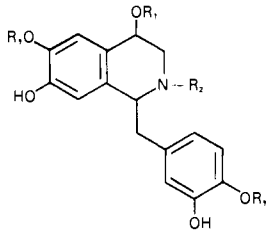
The preparation of the isomeric 6-monomethyl ether **11**, formally derived from the human metabolite L-Dopa 3-*O*-methyl ether,[19] could not be accomplished by direct catalytic reduction of the known papaveroline 6-*O*-methyl ether (**12**).[15] Instead, it was prepared by reduction of the quaternary salt of the protected catechol **13**, followed by removal of the protecting groups by catalytic hydrogenolysis.

The 6′-Br-THP (**14**) was prepared[20] and tested in the adrenergic receptor assay systems in order to ascertain the effect of a bromine atom in the 6′ position, which can protect the molecule against oxidation and further reaction.[21]

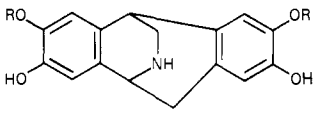
The well-known, fully methylated THP derivative, norlaudanosine (**15**), was prepared by diazomethane treatment of norreticuline.

Reaction Products of THP. THP (**1**) is readily oxidized to dibenzopyrrocolines by a variety of chemical oxidizing agents.[22] Therefore, we undertook the biological evaluation of the known tetraacetate **16**,[23] which is more stable than the free catechol. An aqueous solution of the crystalline tetraphenol (OH in **16**, instead of OAc) quickly becomes colored. A freshly prepared solution of **16** appeared to have remarkable activity in the β-receptor assay and will be examined in greater detail. The *N*-formyl-4-methoxynorreticuline (**17**) has recently been utilized for the synthesis of isopavinans and pavinans,[24] as well as nor

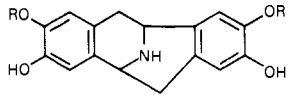
(16) C. J. Coscia, W. Burke, G. Jamroz, J. M. Lasala, J. McFarlane, J. Mitchell, M. O'Toole, and M. L. Wilson, *Nature (London)*, **269**, 617 (1977).
(17) M. L. Wilson and C. J. Coscia, *J. Am. Chem. Soc.*, **97**, 431 (1975).
(18) J. M. Bobbitt, Ch. L. Kulkarni, and P. Wiriyachitra, *Heterocycles*, **4**, 1645 (1976).
(19) G. C. Cotzias, M. H. Van Woert, and L. M. Schiffer, *New Engl. J. Med.*, **276**, 374 (1967); G. C. Cotzias, P. S. Papavasiliou, and R. Gellene, *ibid.*, **280**, 337 (1969).
(20) K. C. Rice and A. Brossi, *J. Org. Chem.*, **45**, 592 (1980).
(21) P. A. Wehrli, F. Pigott, U. Fischer, and A. Kaiser, *Helv. Chim. Acta*, **55**, 3057 (1972).
(22) M. Shamma in "The Isoquinolines Alkaloids", Academic Press, New York, 1972, pp 172–174.
(23) J. Harley-Mason, *J. Chem. Soc.*, 1465 (1953); C.-P. Mak and A. Brossi, *Heterocycles*, **12**, 1413 (1979).
(24) K. C. Rice, W. C. Ripka, J. Reden, and A. Brossi, *J. Org. Chem.*, **45**, 601 (1980).



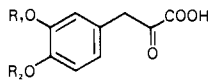
17, $R_1 = CH_3$, $R_2 = CHO$
22, $R_1 = R_2 = H$



18, $R = CH_3$
20, $R = H$



19, $R = CH_3$
21, $R = H$



23, $R_1 = CH_3$, $R_2 = H$
24, $R_1 = R_2 = H$

compounds in both series of alkaloids. O-Demethylation of the nor representatives **18** and **19** with aqueous hydrobromic acid provided the isopavinan tetrol **20** and the pavinan tetrol **21**, both isolated as hydrobromides. These two catechols can be considered hypothetical condensation products of 4-OH-THP (**22**), a postulated intermediate in the plant isoquinoline alkaloids biosynthesis[25] and, formally, a condensation product of norepinephrine with Dopa aldehyde.[1] The mild conditions applied in the acid-catalyzed cyclization of **17**,[24] and its derived 1,2-dihydroisoquinoline, to the tetracyclic species[24] suggests that **20** and **21** might be formed during workup of the 4-OH-THP species.

Biological Results. The ability of a number of THP derivatives to inhibit the binding of [^{3}H]dihydroalprenolol (DHA) to β-adrenergic receptors, [^{3}H]spiroperidol to dopaminergic receptors, and [^{3}H]WB-4101 (2-[[[2-(2,6-dimethoxyphenoxy)ethyl]amino]methyl]-1,4-benzodioxane) to α-adrenergic receptors, in rat cerebral cortex or striatum, is seen in Table I.

(±)-Trimetoquinol (**2**), a known β-adrenergic agonist,[26] was among the most potent of the various compounds examined in inhibiting [^{3}H]dihydroalprenolol binding to β-adrenergic receptors in rat cerebral cortex. The K_i value of this compound was found to be 0.1 μM. THP (**1**), its monomethylated compounds **7** and **11**, and norlaudanosine (**15**) were found to be about equipotent. (±)-Norreticuline (**3**) had an intermediate potency, while the carboxylic acids **5** and **6** were among the least potent compounds tested in these series, with K_i values greater than 100 μM. Finally, papaveroline (**4**) and the polycyclic isoquinolines **16**, **20**, and **21** were found to be inactive in the β-adrenergic receptor binding assay. The K_i value generated for the standard compound, (±)-norepinephrine, under comparable conditions was estimated to be 1.0 μM.[7] The levo enantiomer of THP (**1a**, series 2 in Table I) possesses almost all of the activity of THP, since the dextro enantiomer **1b** was about 100 times less effective in displacing [^{3}H]DHA from the β-adrenergic receptor. There was not quite as large a difference between the enantiomeric norreticulines, where the levo enantiomer **3a** was about 25 times as effective as the dextrorotatory compound **3b**. Thus, the interaction of THP and analogues with β-adrenergic receptors appears to be stereospecific.

Table I. Inhibition of ^{3}H Radioligand Binding to Catecholamine Receptors

	K_i, μM[a]		
no.	β receptor[b]	dopamine receptor[c]	α receptor[d]
	series 1[e]		
1	0.3	10.0	40.0
2	0.1	5.0	10.0
4	inactive	inactive	inactive
5	>100	>100	>100
6	>100	>100	>100
7	0.5	5.0	4.5
11	0.2	4.5	7.5
15	1.0		10.0
16	inactive	inactive	inactive
20	inactive	inactive	inactive
21	inactive	inactive	inactive
	series 2[f]		
1	0.5	3.0	15.0
1a	0.3	2.0	5.0
1b	30.0	35.0	25.0
3	4.0	3.8	7.5
3a	1.3	1.5	5.0
3b	30.0	30.0	10.0
14	40.0	1.5	0.5

[a] K_i (μM) = $IC_{50}/1 + (C/K_d)$, where C = ligand concentration (μM); IC_{50} (μM) values were calculated from log-probit analysis of inhibition curves using concentrations from 10^{-4} to 10^{-9} M. Values for K_d were calculated from Scatchard analysis of binding curves determined by ^{3}H radioligand binding to each receptor. All of the inhibition experiments were run using K_d concentrations of the radioligand. [b] [^{3}H]Dihydroalprenolol (specific activity 51.4 Ci/mmol) displacement from β-adrenergic receptors. The K_i for (±)-norepinephrine was 1.0 μM. [c] [^{3}H]Spiroperidol (specific activity 26.4 Ci/mmol) displacement from dopamine receptors. The K_i value for dopamine was 1.25 μM. [d] [^{3}H]WB-4101 (specific activity 30.0 Ci/mmol) displacement from α-adrenergic receptors. The K_i value for (±)-norepinephrine was 1.0 μM. [e] Mean values from three or four experiments. Estimated standard error was ±20% for β and dopamine receptor assays and ±30% for the α-receptor assay. Any value which is twice that of a reference or standard may be considered significantly different. [f] Mean values from two experiments. The estimated standard error was the same as in experiment 1.

All of the tested compounds were less active in the dopaminergic receptor assay than in the β-adrenergic receptor assay, except (*R*)-(+)-THP (**1b**) and (±)-, (−)-, and (+)-*N*-norreticuline (**3**, **3a**, and **3b**), which were about equipotent. A more striking exception was 6′-Br-THP **14**, which was found to be more than an order of magnitude more potent in the dopaminergic receptor assay. The 6′-Br-THP **14**, (−)-THP (**1a**), and (−)-norreticuline (**3a**) were almost as potent as dopamine in this assay system. The K_i value for dopamine in the dopamine receptor binding assay was estimated to be 1.0 μM. The carboxylic acids **5** and **6** were found to be among the least potent compounds in inhibiting [^{3}H]spiroperidol binding, and compounds **4**, **16**, **20**, and **21** were inactive.

Only one compound, 6′-Br-THP (**14**), was found to be substantially more potent in the α-adrenergic receptor assay than in the dopaminergic assay. It was about two orders of magnitude more potent in the α-adrenergic assay than in the β-adrenergic assay and was more potent than (±)-norepinephrine in the α-adrenergic receptor binding assay system; the K_i of (±)-norepinephrine in this assay was estimated to be 1.25 μM. Again, the carboxylic acids **5** and **6** were among the least potent compounds, and **4**, **16**, **20**, and **21** were inactive. The remainder of the compounds displayed some ability to displace [^{3}H]WB-4101.

(25) S. F. Dyke, *Heterocycles*, **6**, 1451 (1977).
(26) Y. Iwasawa and A. Kiyomoto, *Jpn. J. Pharmacol.*, 17, 143 (1967).

The antinociceptive activity (ED_{50} in μmol/kg, in mice, subcutaneous injection, hot plate assay)[27] of norreticuline hydrochloride (3·HCl) was found to be 27.3 (19.3–38.4), the parenthesized numbers representing the 95% confidence interval on probit analysis. All of the activity resided in the (S)-(−) enantiomer (3a·HCl), which had an ED_{50} = 9.9 (7.7–13.4). The corresponding (R)-(+)-norreticuline (3b) was essentially inactive. Thus, the (S)-(−) enantiomer had about one-third the potency of morphine sulfate (ED_{50} = 3.0 [2.1–4.2]) in this assay.

Structure–Activity Relationships. All of the active compounds which bind as well as or better than (±)-norepinephrine in the β-adrenergic receptor assay system are conformationally mobile, or flexible, compounds. Their benzyl groups can twist around the C-1 position of the tetrahydroisoquinoline moiety. This conformational flexibility, and the presence of a secondary amine, appears to enable these molecules (compounds 1–3, 7, 11, and 15) to interact with the β-adrenergic receptors. Tertiary amines have been noted to be inactive in a β-adrenergic binding system;[12] compound 4, an aromatic isoquinoline, was inactive, as were other compounds (16, 20, and 21) which are multiring, conformationally inflexible molecules. Since it is very unlikely that the O-methyl ethers can be converted to catechols or that the catechols can be O-methylated under the in vitro assay conditions, it is apparent that the catechol moiety is not essential for this interaction. Obviously, however, the most potent of the studied compounds in binding to the β-adrenergic system is (±)-trimetoquinol (2), which has a catechol group. Thus, catechol groups may aid in the interaction. The carboxylic acid derivatives (5 and 6) were very much less active than the other tetrahydroisoquinolines. It is possible that these compounds are much less conformationally mobile than the active tetrahydroisoquinolines. Similar carboxylic acids have been noted to be geometrically fixed, with the benzylic portion of the molecule twisted away from the tetrahydroisoquinoline moiety.[28] The carboxylic acid moiety apparently lies close to the tetrahydroisoquinoline C-8 proton, which has been observed, in the NMR, to be deshielded, presumably due to the influence of the CO_2H group.[29] Thus, it is possible that the conformation of the active compounds responsible for binding in this assay system is one in which the aromatic part of the benzylic group is in close proximity to the aromatic ring of the tetrahydroisoquinoline moiety.[12] Only the secondary amines 1–3, 7, 11, and 15, and their active enantiomers, can attain that conformation.

The structure–activity relationship for binding in the α-adrenergic and dopaminergic assay systems appears similar to that in the β-adrenergic assay system. However, virtually all of the compounds in the β-adrenergic assay system are at least an order of magnitude less potent in the dopaminergic and α-adrenergic assay systems. The only exceptions were (−)-N-norreticuline (3a), which was equipotent in the β-adrenergic and dopaminergic receptor assays, and the 6′-Br-THP (14), which was very much more potent in the α-adrenergic assay than in the β-adrenergic assay and somewhat more potent in the α-adrenergic assay than in the dopaminergic assay. Stereoselectivity for the optical isomers of THP (1a and 1b) and the N-norreticulines (3a and 3b) appears less for the α-adrenergic receptors than for either the β-adrenergic or dopaminergic receptors.

A more detailed study of the 6′-Br-THP (14) and its optical isomers, and their evaluation as antihypertensives, will be reported elsewhere.

Experimental Section

Chemical Methods. Melting points were determined on a Fisher-Johns melting point apparatus. Elemental analysis were performed by the Section on Microanalytical Services and Instrumentation of this Laboratory. IR were obtained on a Beckman 4230 and mass spectra on a Hitachi RMU-6E (70eV) and Finnigan 1015D (CI). ^1H NMR were obtained (using tetramethylsilane at 0.0 ppm as internal reference) on a Varian HR-220 spectrometer.

***N*-[3,4-Bis(benzyloxy)phenethyl]-2-[4-(benzyloxy)-3-methoxyphenyl]acetamide (9).** Dopamine hydrobromide (5.85 g, 25 mmol) was dissolved in 5 mL of H_2O and applied on a column of acidic cation exchange resin, previously washed with H_2O until neutral (Dowex 50W-4, ~50 mequiv). This column was then again washed with H_2O until neutral. The free base was collected by eluting the column with 250 mL of 7% aqueous NH_4OH. After the solvent was removed, the light brown residue was washed with H_2O and again evaporated to dryness. This was taken up in H_2O (10 mL) and a suspension of 4-hydroxy-3-methoxyphenylacetic acid (4.45 g, 25 mmol) in H_2O (10 mL) was added. The mixture was stirred for 5 min and then evaporated in vacuo. The crude salt obtained was heated under an atmosphere of argon at 200 °C for 2 h. After cooling, the glassy residue was taken up in acetone (300 mL) and heated at reflux under argon for 16 h, in the presence of benzyl bromide (20 mL) and potassium carbonate (23.1 g). Acetone was then removed in vacuo, and the residue was taken up in $CHCl_3$, washed with H_2O, saturated $NaHCO_3$, and saturated NaCl, and dried ($MgSO_4$). Removal of solvent gave a yellow solid, which was recrystallized from hot EtOAc/Et_2O to give a total of 9.6 g (65%) of amide 9 as white crystals: mp 119–120 °C; IR ($CHCl_3$) 3430 (NH), 1660 (NCO) cm^{-1}; MS (70 eV) *m/e* (relative intensity) 587 (M^+, 95), 91 (100); NMR ($CDCl_3$) δ 2.61 (t, 2, *J* = 7 Hz, $ArCH_2$–), 3.39 (t, 2, *J* = 7 Hz, NCH_2–), 3.43 (s, 2, $ArCH_2CO$), 3.82 (s, 3, OCH_3), 5.14 (s, 6, $ArOCH_2$–), 5.36 (br, 2, NH), 6.47–6.86 (m, 6, ArH), 7.27–7.55 (m, 15, ArH). Anal. ($C_{38}H_{37}NO_5$) C, H, N.

1-[4-(Benzyloxy)-3-methoxybenzyl]-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10·HCl). Dropwise, $POCl_3$ (2 mL) was added to a refluxing solution of amide 9 (5.88 g, 10 mmol) in CH_3CN (40 mL). The reaction mixture was heated for 1.5 h and cooled, and the solvent was removed to give a yellow foam. This was dissolved in a solvent mixture of THF–2-propanol–H_2O (30:25:10) and the pH was adjusted with NH_4OH to about 8. To this stirred and cooled (ice bath) mixture was added, in small portions, $NaBH_4$ (2 g), and the reaction mixture was stirred at 25 °C for 20 min, diluted with saturated NaCl solution, and extracted thoroughly with $CHCl_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated to give about 6 g of white foam. This was dissolved in MeOH and treated with ethanolic HCl. Solvent was evaporated in vacuo, and the residue was treated again with ethanolic HCl and, after removal of solvent, afforded an off-white crystalline solid. Recrystallization from $CHCl_3$–ether gave 5.34 g (88%) of off-white crystals. Further recrystallization from $CHCl_3$–Et_2O gave 10·HCl as white crystals: mp 178–179 °C; IR ($CHCl_3$) 3400 cm^{-1} (NH); MS (CI, NH_3) 571 (M^+, free base); NMR ($CDCl_3$) δ 2.66–3.52 (m, 6, $-CH_2$), 3.73 (s, 3, OCH_3), 4.66 (br, 1, CH), 4.71 (d, 1, J_{AB} = 14 Hz, $ArCH_AH_B$), 4.80 (d, 1, J_{AB} = 14 Hz, $ArCH_AH_B$) (the δ 4.71 and 4.80 signals coalesced on heating), 5.02 (s, 2, $ArCH_2$), 5.07 (s, 2, $ArCH_2$), 6.20 (s, 1, ArH), 6.53 (d, 1, *J* = 7 Hz, ArH), 6.59 (s, 1, ArH), 6.72 (s, 1, ArH), 6.75 (d, 1, *J* = 7 Hz, ArH), 7.18–7.45 (m, 15, ArH), 9.82 (br, 1, NH_2^+), 10.16 (br, 1, NH_2^+). Anal. ($C_{38}H_{37}NO_4$·HCl) C, H, N.

6,7-Dihydroxy-1-(4-hydroxy-3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (7·HCl). A suspension of the tris(benzyloxy)tetrahydroisoquinoline 10 (0.61 g, 1 mmol) in MeOH (30 mL) and 10% aqueous HCl (30 mL) was heated at reflux under argon for 65 h, during which time the mixture

(27) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, **107**, 385 (1953); A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965); L. Atwell and A. E. Jacobson, *Lab Anim.*, **7**, 42 (1978).

(28) J. M. Bobbitt and T. Y. Chen, *J. Org. Chem.*, **41**, 443 (1976).

(29) Compound 11 was mentioned by D. S. Bhakuni, A. N. Singh, S. Tewari, and R. S. Kapil, *J. Chem. Soc., Perkin Trans. 1*, 1662 (1977), without physical data.

became homogenous. The cooled mixture was concentrated to give a white solid, which on recrystallization afforded the analytically pure hydrochloride of **7** (220 mg, 65%): mp 252–254 °C dec; IR (KBr) 3400, 3160, 1320 cm^{-1} (NH, OH); MS (CI, NH_3) 301 (M^+, free base); NMR (CD_3OD–D_2O) δ 2.80–3.16 (m, 6, $-CH_2-$), 3.80 (s, 3, OCH_3), 4.64 (t, 1, J = 7 Hz, –CH), 6.66 (s, 1, ArH), 6.70 (s, 1, ArH), 6.77 (d, 1, J = 8 Hz, ArH), 6.80 (s, 1, ArH), 6.86 (d, 1, J = 8 Hz, ArH). Anal. ($C_{17}H_{19}NO_4 \cdot HCl \cdot 0.5CH_3OH$) C, H, N.

2-Benzyl-7-(benzyloxy)-1-[3,4-bis(benzyloxy)benzyl]-6-methoxyisoquinolinium Bromide (13). A solution of 6-*O*-methylpapaveroline hydrobromide[15] (**12**; 380 mg, 1 mmol) in 5 mL of dry DMF was added dropwise to a stirred suspension of NaH (190 mg, prewashed with hexane) in 5 mL of dry DMF at 0 °C. The evolution of H_2 ceased after 15 min. To this stirred solution was added benzyl bromide (0.78 mL, 6 mmol) in 1 mL of dry DMF. The mixture was warmed to 25 °C and stirred for 24 h, after which time it was diluted with water and extracted thoroughly with EtOAc. Combined organics were washed with H_2O (3×), dried ($MgSO_4$), concentrated to a brown foam in vacuo, and triturated in hot EtOAc to afford 340 mg (46%) of cream-colored crystals. Further recrystallization from hot EtOAC gave **13** as white crystals: mp 205–206 °C; IR ($CHCl_3$) 2940, 1615, 1495 cm^{-1}; MS (CI, NH_3) 658 (M^+ – Br), 568 ([M^+ + 1] – BzBr); NMR ($CDCl_3$) δ 4.18 (s, 3, OCH_3), 4.77 (s, 2, ArOH, Ar), 5.00 (s, 2, OCH_2Ar), 5.16 (s, 4, OCH_2Ar), 5.98 (s, 2, NCH_2Ar), 6.30 (d, 1, J = 8 Hz, ArH), 6.36 (s, 1, ArH), 6.74 (d, 1, J = 8 Hz), 6.95 (s, 1, ArH), 7.05–7.57 (m, 20), 7.80 (s, 1, ArH), 8.41 (d, 1, J = 7 Hz, ArH), 8.80 (d, 1, J = 7 Hz, ArH). Anal. ($C_{45}H_{40}NO_4Br$) C, H, N.

1-(3,4-Dihydroxybenzyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11·HCl).[29] Excess $NaBH_4$ (0.5 g) was slowly added to a stirred solution of the quaternary salt **13** (0.74 g, 1 mmol) in MeOH (15 mL). The mixture was heated at reflux for 30 min, cooled, and concentrated in vacuo. The residue was taken up in dilute HCl, made alkaline with 10% NaOH, and extracted with $CHCl_3$. The combined organic solution was dried (Na_2SO_4) and concentrated. The resultant oil was passed quickly through a short column of basic alumina, eluting with 10% EtOAc in petroleum ether. A yellow foam (0.43 g) was obtained from the combined initial fractions. This was dissolved in ethanolic HCl (100 mL) containing a trace amount of EtOAc, and hydrogenated at 36 psi over 10% Pd/C (150 mg). After filtration and removal of solvent in vacuo, a brown oil was obtained which crystallized when triturated with MeOH–Et_2O. The hydrochloride of **11** was obtained as beige crystals (97 mg, 26% overall from **13**) and recrystallized from MeOH–Et_2O: mp 240–242 °C dec; IR (KBr) 3340, 3100 (NH, OH) cm^{-1}; MS (CI, NH_3) 302 (M^+ + 1); NMR (CD_3OD) δ 2.80–3.20 (m, 6, $-CH_2-$), 3.88 (s, 3, OCH_3), 4.60 (m, 1, –CH), 6.60–6.92 (m, 5, ArH). Anal. ($C_{17}H_{19}NO_4 \cdot HCl \cdot 0.5CH_3OH$) C, H, N.

6,7-Dihydroxy-1-(4-hydroxy-3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (5). A mixture of the keto acid **23**[30] (4.5 g, 21.4 mmol) in H_2O (28 mL) and NH_4OH (28%, 5 mL) and dopamine hydrobromide (4.57 g, 19.5 mmol) in 6 mL of H_2O was allowed to stand at 25 °C for 2 days to give a cream-colored solid. The solid was filtered, washed with 1% aqueous HBr, and dried in vacuo, to afford 5.1 g (75%) of the grayish-white carboxylic acid **5**: mp 225–228 °C dec; IR (KBr) 1630 cm^{-1} (C=O); MS (CI, NH_3) 346 (M^+ + 1); NMR (Me_2SO-d_6) δ 3.57 (s, 3, OCH_3), 6.41 (s, 1, ArH), 6.59 (s, 1, ArH), 6.59 (s, 2, ArH), 6.70 (s, 1, ArH), 7.55 (s, 1, ArH), 8.75 (br, 3, OH). Anal. ($C_{18}H_{19}NO_6 \cdot H_2O$) C, H, N.

6,7-Dihydroxy-1-(3,4-dihydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (6). A mixture of the keto acid **24**[31] (430 mg, 2.2 mmol) in H_2O (8 mL) containing 5 drops of NH_4OH (28%) and dopamine hydrobromide (470 mg, 2 mmol) in H_2O (3 mL) was allowed to stand at 25 °C for 24 h. The crystals which formed were filtered, washed (1% aqueous HBr), and dried to give 370 mg (56%) of the carboxylic acid **6**, as beige crystals: mp 218–221 °C. Anal. ($C_{17}H_{17}NO_6 \cdot 2.5H_2O$) C, H, N.

In a separate run, after the reagents were mixed, the solution was adjusted to pH 5 with HOAc. After 24 h at 25 °C, the white crystalline carboxylic acid was collected, washed, and dried. A lower yield (38%) of **6** was obtained: IR (KBr) 1630 cm^{-1} (C=O); MS (CI, NH_3) 332 (M^+ + 1); NMR (Me_2SO-d_6) δ 6.36 (s, 1, ArH), 6.43 (d, 1, J = 7 Hz, ArH), 6.52 (d, 1, J = 7 Hz, ArH), 6.61 (s, 1, ArH), 7.41 (s, 1, ArH).

2,3,8,9-Tetrahydroxyisopavinan Hydrobromide (20·HBr). A mixture of 165 mg (0.5 mmol) of (±)-*N*-northalidine hydrate (**18**)[23] and 7 mL of 48% aqueous HBr was refluxed under argon for 2 h, cooled, and evaporated to a foam, which was dissolved in 5 mL of H_2O, boiled with norite, filtered through Celite, and evaporated. The residue was recrystallized from 1 mL of AcOH containing 1 drop of H_2O to afford 122 mg (67%) of **20**·HBr in two crops. An analytical sample was prepared by recrystallization of a portion of the first crop from 9:1 AcOH–H_2O: mp 285–287 °C dec; MS m/e 285 (M^+), 256 ($M^+ - CH_2{=}NH$). Anal. ($C_{16}H_{15}NO_4 \cdot HBr$) C, H, N.

2,3,8,9-Tetrahydroxypavinan Hydrobromide (21·HBr). A mixture of 161 mg (0.5 mmol) of (±)-*N*-norbisnorargemonine (**19**)[23] and 5 mL of 48% aqueous HBr was refluxed for 2.5 h under argon and evaporated to a crystalline solid, which was dissolved in 5 mL of H_2O and reevaporated. The residue was dissolved in 5 mL of H_2O, filtered through Celite, and evaporated. Recrystallization from 1.5 mL of 5% aqueous HBr afforded 135 mg (72%) of **21**·HBr·0.5H_2O: mp 297–301 °C dec; MS m/e 285 (M^+). Anal. ($C_{16}H_{15}NO_4 \cdot HBr \cdot 0.5H_2O$) C, H, N.

Biological Methods. Animals. Male, Sprague–Dawley rats (Taconic Farms, Germantown, N.Y.), 175–225 g, were used in all studies.

Determination of [^{3}H]Dihydroalprenolol Binding to Rat Cerebral Cortical Membranes. Binding of [^{3}H]dihydroalprenolol to β-adrenergic receptors and displacement by drugs was measured using a modification of the methods of Bylund and Snyder[32] and Alexander et al.,[33] as previously described.[7] Under these conditions, the binding of [^{3}H]dihydroalprenolol was linear with respect to protein concentration; the K_d value was estimated to be about 2 nM by Scatchard analysis. Total and nonspecific binding were determined in the absence and presence of 1 μM (±)-propranolol. Specific binding as previously defined[34] was 55–70% of total binding.

Determination of [^{3}H]WB-4101 Binding to Rat Cerebral Cortical Membranes. Measurement of [^{3}H]WB-4101 binding to α-adrenergic receptors and displacement by drugs was determined by the methods of U'Prichard et al.[35] The K_d for [^{3}H]WB-4101 under these conditions was found to be 1.4 nM. Total and nonspecific binding were determined in the absence and presence of 10 μM phentolamine. Specific binding as previously defined[36] was 50–70% of total binding.

Determination of [^{3}H]Spiroperidol Binding to Rat Striatum Membranes. The binding of [^{3}H]spiroperidol to rat striatum membranes and displacement by drugs was determined by the method described by Fields et al.,[37] with slight modifications (20-min incubation at 23 °C). The K_d for [^{3}H]spiroperidol under these conditions was found to be 0.2 nM. The total and nonspecific binding were determined in the absence and presence of either 0.1 μM (+)-butaclamol or 100 μM dopamine. Specific binding was about 50–60% of the total binding.

(30) G. Billek, *Monatsh. Chem.*, **92**, 335 (1961).
(31) M. L. Wilson and C. J. Coscia, *J. Org. Chem.*, 44, 301 (1979).
(32) D. B. Bylund and S. H. Snyder, *Mol. Pharmacol.*, **12**, 568 (1976).
(33) R. W. Alexander, J. N. Davis, and R. J. Leftkowitz, *Nature (London)*, **258**, 437 (1975).
(34) P. Skolnick, L. P. Stalvey, S. W. Daly, T. W. Stone, and D. Taylor, *Life Sci.*, 21, 1655 (1977).
(35) D. C. U'Prichard, D. A. Greenberg, and S. H. Synder, *Mol. Pharmacol.*, 13, 454 (1977).
(36) P. Skolnick, L. P. Stalvey, J. W. Daly, E. Hoyler, and J. Davis, *Eur. J. Pharmacol.*, 47, 201 (1978).
(37) J. Z. Fields, T. D. Reisine, and H. I. Yamamura, *Life Sci.*, **23**, 569 (1978).