Synthesis and Pharmacology of Centrally Acting Dopamine Derivatives and Analogs in Relation to Parkinson's Disease†

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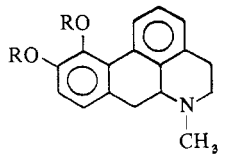
Labile, lipophilic derivatives and analogs of dopamine have been prepared by selective O-acetylation and N-alkylation procedures. Selective O-acetylation methods for the synthesis of *O,O'*-diacetyldopamine and 3,4-diacetoxy-β-phenethylmethylamine were developed. Several of the compounds reduced body temperature in the mouse, a response which has been shown to be dopaminergic, and one caused reversal of reserpine-induced CNS depression. The results suggest therefore that certain of these compounds cross the blood-brain barrier and activate dopamine receptors in the CNS.

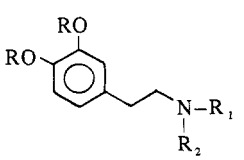
The dopamine derivatives and analogs reported in this study were designed to cross the blood-brain barrier and activate "dopaminergic" receptors in the central nervous system (CNS). Since dopamine (**3**) and related catecholamines evidently do not cross the blood-brain barrier,[1] it is necessary to devise a mechanism for their transport into the CNS.

One approach to provide transport is to structurally modify the molecule to make it a labile, lipophilic derivative, the expectation being to provide transport across the blood-brain barrier, entry into the CNS, and, by hydrolysis, generation of the parent molecule *in situ*. Creveling and coworkers[2] reported a successful application of this approach when they prepared 3,4,β-triacetylnorepinephrine and showed that it readily entered the CNS. In addition, it also has been shown that O-acetylation of apomorphine (**1**), a dopamine receptor agonist, does not prevent the emetic response[3,4] or the anti-Parkinson effect[5] of this compound. It is assumed that *in vivo* ester hydrolysis occurs prior to receptor activation for both 3,4,β-triacetylnorepinephrine and *O,O'*-diacetylapomorphine (**2**).

Alkylation of the nitrogen atom of dopamine would also be expected to increase the lipophilicity of this molecule. In concert with this idea are reports in the literature which indicate that the primary amine function of dopamine is not an essential requirement for dopaminergic activity. Epinine (**4**), a secondary amine, has been reported to activate putative dopamine receptors in the periphery[6,7] and apomorphine (**1**),



1, R = H
2, R = Ac



3, R = R_1 = R_2 = H
4, R = R_1 = H; R_2 = CH_3
5, R = H; R_1 = R_2 = CH_3
6, R = Ac; R_1 = R_2 = H
7, R = Ac; R_1 = H; R_2 = CH_3
8, R = Ac; R_1 = R_2 = CH_3

a tertiary amine, has been shown to activate dopamine receptors both in the periphery[6] and in the CNS.[8-13]

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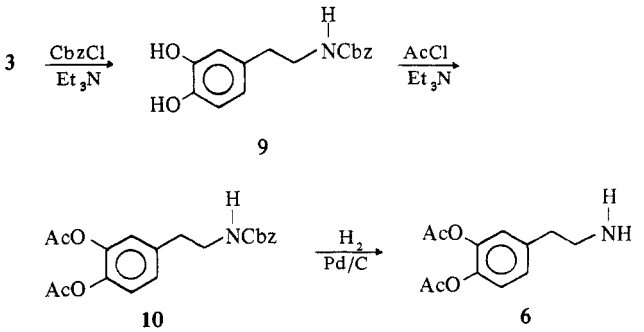
In light of these observations, *O,O'*-diacetyldopamine (**6**), 3,4-diacetoxy-β-phenethylmethylamine (**7**), 3,4-diacetoxy-*N,N*-dimethyl-β-phenethylamine (**8**), and the corresponding catechol derivatives **4** and **5** were synthesized and evaluated pharmacologically for central dopamine-receptor activation and anti-Parkinson activity.

Chemistry. Acetylation of phenolic groups in the presence of a primary or secondary amine function is often difficult. Generally, acetylation of nitrogen occurs more readily than oxygen. This report offers two methods (one novel for the catecholamines) for selective acetylation of phenolic groups on catecholamines.

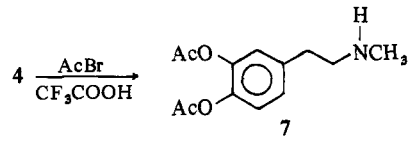
O,O'-Diacetyldopamine (**6**) was synthesized indirectly from dopamine by protecting the nitrogen atom through preparation of the *N*-carbobenzyloxy derivative **9**. The carbobenzyloxy derivative **9** is then O-acetylated with acetyl chloride, followed by removal of the protecting group by hydrogenolysis. The right conditions must be found in the hydrogenolysis step to avoid O → N acyl migration (Scheme I). This method is generally unsatisfactory due to the number of steps involved and the low yield obtained from the hydrogenolysis reaction.

Scheme I



A more direct and rewarding method for O-acetylation of catecholamines (Scheme II) was developed for the preparation of 3,4-diacetoxy-β-phenethylmethylamine (**7**). This procedure involves an adaptation of the method of Previero, *et al.*,[14] for O-acetylation of hydroxyamino acids. The amine hydrobromide is simply dissolved in anhydrous trifluoroacetic acid and treated with acetyl bromide. This synthetic method offers the dual advantages of simplicity and greater yields.

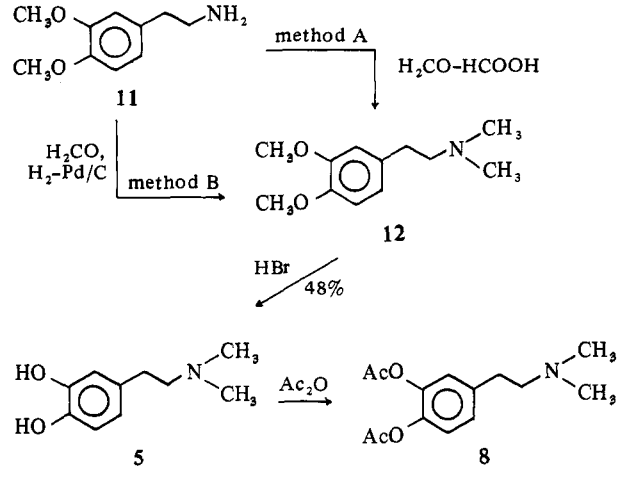
Scheme II



An excellent method for the preparation of epinine (**4**) from 3,4-dimethoxy-β-phenethylamine (**11**) was adapted from the method of Kiefer.[15] This procedure involves the formation of a Schiff base of **11** (benzaldehyde) followed by treatment with dimethyl sulfate and then subsequent hydrolysis. The resulting diether **13** is then cleaved to **4** with hydrobromic acid.

3,4-Diacetoxy-*N,N*-dimethyl-β-phenethylamine (**8**) was prepared from **12** as shown in Scheme III. The intermediate

Scheme III



12 was prepared from **11** by two methods. The Eschweiler-Clarke modification (method A) as reported by Baltzly[16] results in low yields due to the competitive formation of the corresponding 2-methyltetrahydroisoquinoline. The reductive methylation procedure (method B) is far superior, giving almost quantitative yields.

Pharmacology. Preparations. Hydrochloride or hydrobromide salts of all compounds were dissolved in appropriate volumes of physiological saline. The solutions were prepared immediately before use.

Standards. Apomorphine hydrochloride, U.S.P. (S. B. Penick and Co.) and/or dopamine hydrobromide (Aldrich Chemical Co.) were included in the series of compounds examined and served as reference standards. Activities of the test compounds were compared with those evoked by the standard.

Biological Activities Investigated. Studies evaluating the potential anti-Parkinson effects of the dopamine analogs are reported in Tables I-III. Each compound was tested in three separate animal model situations, two of which simulate Parkinson's disease. The models were chosen either because they mimicked some aspect of the clinical symptomatology of the disease or because they allowed an estimate of the agent's ability to stimulate central dopamine receptors. These included (a) protection against oxotremorine-induced tremor in mice, (b) antagonism of reserpine-induced depression in mice, and (c) the hypothermic effect in mice.

Oxotremorine-Induced Tremor in Mice. Leslie and Maxwell[17] have suggested that oxotremorine appears to be a particularly useful agent in screening compounds for anti-Parkinson activity. One of the most striking effects produced by oxotremorine administration to mice (600 μg/kg ip) is the disruption of locomotor activity. This is characterized by sustained generalized tremor, muscular rigidity, and decreased spontaneous movement. Although oxotremorine is generally used for screening compounds that have anticholinergic activity, Everett, *et al.*,[18] have reported that L-DOPA and apomorphine (a dopamine-mimetic drug) are both effective in antagonizing many of the symptoms of oxotremorine in mice. Analogously, Ambani and Van Woert[19] have shown that L-DOPA can reduce the tremor induced by physostigmine in rats pretreated with reserpine. For comparison purposes the oxotremorine model was included in this study. Test drugs (100 mg/kg ip) were given 10 min prior to administration of oxotremorine and then were evaluated for their ability to antagonize both the tremor and the diminished locomotor activity produced by oxotremorine. The latter test involved placing the animal in a 1-ft square box divided into sixteen 3-in. squares and counting the number of times the animal crossed from one square to another. None of the test compounds were able to

Table I. Antagonism of Oxotremorine (OT)[a]-Induced Tremor and Decreased Motor Activity in Mice

Compd no.	Motor activity[b]	Tremor severity[c]
Saline	170 ± 15	0
OT	76 ± 12	+++
Apomorphine + OT	154 ± 32	++
4 + OT	49 ± 32	++
5 + OT	50 ± 18	+++
6 + OT	33 ± 9	++
7 + OT	64 ± 16	+++
8 + OT	28 ± 11	+

[a] Motor activity and tremor rating were determined beginning 3 min after the OT administration. Apomorphine was given in a dose of 50 mg/kg ip. [b] Squares crossed per 6 min. [c] 0 (none), + (mild), ++ (moderate), +++ (severe).

Table II. Antagonism of Reserpine (R)[a]-Induced Motor Depression in Mice

Compd no.	Dose, mg/kg[b]	Motor activity[c]
None		128 ± 13
R	5	2 ± 1
R + apomorphine	25	25 ± 15
R + **4**	50	1 ± 1
R + **5**	6	8 ± 4
R + **6**	50	5 ± 4
R + **7**	50	8 ± 3
R + **8**	25	108 ± 24

[a] Animals were given reserpine (5 mg/kg ip) 24 hr prior to drug testing. [b] The compounds were given at approximately their maximally tolerated dose in reserpine-treated animals. [c] Squares crossed per 6 min.

Table III. Hypothermia in Mice

Compd no.	Dose, mg/kg[a]	Change in body temp, °C[b]
Saline		0
Dopamine	50	−2.4 ± 0.6
Apomorphine	1	−3.3 ± 0.6
4	1	−0.7 ± 0.2
5	1	−0.1 ± 0.7
6	50	−0.0 ± 0.5
7	50	−0.9 ± 0.4
8	5	−4.5 ± 0.6

[a] Compounds were given at approximately their maximally tolerated intravenous dose. [b] Rectal temperatures were obtained 30 min postintravenous administration of the test compound.

increase spontaneous motor activity (Table I). However, compound **8** was able to partially antagonize the severity of the tremor, reducing it from severe to mild. Apomorphine completely restored motor activity to normal but had only a slight effect on tremor.

Reserpine-Induced Depression. Since the test compounds are dopamine analogs, it was decided to test their anti-Parkinson effects in a model which more closely mimics the biochemical picture found in Parkinson's disease, namely an organism lacking brain dopamine. Everett, *et al.*,[18] have suggested using reserpine-treated mice to simulate certain aspects of Parkinson's disease. Reserpine depletes brain stores of dopamine and markedly decreases spontaneous motor activity. Compounds **4–8** plus apomorphine were tested for their ability to restore motor activity in reserpinized mice (5 mg/kg ip) in a manner similar to that described above in the oxotremorine model. Of the compounds tested (Table II) apomorphine and compound **8** were highly effective while compounds **5** and **7** had some slight ability to reverse reserpine depression. Compounds **4** and **6** were essentially inactive.

Hypothermia in Mice. This model assesses the ability of the test compounds to stimulate a central dopamine receptor. Barnett, *et al.*,[20] and Fuxe and Sjögvist[21] have demonstrated that direct stimulation of dopamine receptors in the brain leads to a pronounced lowering of body temperature and that this effect is relatively specific. In this procedure, the body temperature of the mice was determined and then dopamine, apomorphine, and compounds **4–8** were administered intravenously and the rectal temperature was again measured 30 min later (Table III). By this parameter dopamine (in high doses), apomorphine, and compound **8** were quite potent in lowering body temperature. Compound **7** was also slightly effective.

Discussion

These data are consistent with the speculation presented above, namely that labile, lipophilic analogs of dopamine should cross the blood-brain barrier and stimulate dopamine receptors in the CNS. The high activity of **8**, the slight activity of **7**, and the inactivity of **4–6** suggest that both O-acetylation and N-alkylation of the dopamine molecule are required to provide entry into the CNS while retaining intrinsic dopaminergic activity.

Experimental Section‡

***N*-Carbobenzyloxydopamine (9).** Dopamine hydrobromide (2 g, 0.0085 mol) was dissolved in 5 ml of DMF, and the system was flushed with N_2. Et_3N (0.86 g, 0.0085 mol) was then added dropwise and the resulting mixture stirred for 0.25 hr. Then carbobenzyloxy chloride (0.72 g, 0.004 mol) was added, followed by 0.43 g (0.0043 mol) of Et_3N. After stirring an additional 0.25 hr, carbobenzyloxy chloride (0.72 g, 0.004 mol) was again added, followed by 0.43 g (0.004 mol) of Et_3N. The resulting mixture was stirred for 1 hr and then added to 100 ml of Et_2O. The Et_2O solution was washed with two 25-ml portions of H_2O, then dried (Na_2SO_4), and evaporated under reduced pressure. The residue was recrystallized from PhH to yield 1.7 g (70%) of product, mp 128–129°. *Anal.* ($C_{16}H_{17}NO_4$) C, H, N.

‡All boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical value. Ir absorption spectra were recorded on a Beckmann Model 18A spectrophotometer. The nmr spectra were recorded on a Varian T-60 spectrometer using TMS or DSS as internal standards.

***N*-Carbobenzyloxy-*O,O'*-diacetyldopamine (10).** To 4.8 g (0.16 mol) of **9** in 300 ml of $CHCl_3$ was added 5.2 g (0.067 mol) of AcCl, followed by dropwise addition of 15 ml of Et_3N over 0.5 hr. After stirring for an additional 0.5 hr, the solution was washed successively with two 50-ml portions of H_2O, 5% aqueous HCl (50 ml), and H_2O (50 ml). The $CHCl_3$ layer was then dried (Na_2SO_4) and evaporated under reduced pressure to give a solid which was recrystallized from Et_2O to yield 4 g (64%) of product, mp 86–87°. *Anal.* ($C_{20}H_{21}NO_6$) C, H, N.

***O,O'*-Diacetyldopamine Hydrochloride (6).** Compound **10** (2.8 g, 0.0075 mol) was dissolved in 200 ml of Et_2O which was previously dried (Na^0) and distilled from $LiAlH_4$. The solution was hydrogenated over 3.16 g of 10% Pd/C at room temperature (0.25 hr) in a Parr apparatus with an initial H_2 pressure of 4.2 kg/cm². The catalyst was removed by filtration and the filtrate treated immediately with Et_2O·HCl to yield a solid which was recrystallized from *i*-PrOH–Et_2O to afford 0.6 g (29%) of product: mp 118–119°; ir (KBr) 1780 (ester C=O); nmr (D_2O) δ 2.39 (s, 6, CH_3COOAr), 3.19 (m, 4, CH_2CH_2), 7.30 (m, 3, Ar H). *Anal.* ($C_{12}H_{16}ClNO_4$) C, H, N.

3,4-Dimethoxy-β-phenethylmethylamine (13). 3,4-Dimethoxy-β-phenethylamine (18.1 g, 0.1 mol, Aldrich Chemical Co.) and 13.25 g (0.125 mol) of PhCHO were refluxed in PhH (100 ml) until no more H_2O was present in the condensate (*ca.* 2 hr). Then, without cooling, an attached Dean-Stark trap was replaced by a reflux condenser and a solution of 15.75 g (0.125 mol) of Me_2SO_4 in PhH (50 ml) was added over 0.25 hr through the condenser. The resulting mixture was heated with vigorous stirring for 2 hr on a steam bath, cooled slightly, treated with 200 ml of H_2O, and stirred vigorously under gentle reflux for 0.5 hr. After cooling in ice, the aqueous layer was washed twice with Et_2O to remove unreacted PhCHO and then made strongly basic with 50% aqueous NaOH. Two Et_2O extracts of the basic aqueous phase were added to the amine layer which separated. The volatiles were removed under reduced pressure and the oil was distilled through a short-path apparatus, bp 101–102° (0.3 mm) [lit.[22] bp 99–112° (0.075–0.12 mm)].

3,4-Dihydroxy-β-phenethylmethylamine Hydrobromide (4). Compound **13** (3 g, 0.015 mol) was slowly added to cold 48% HBr (15 ml). The system was flushed with N_2 for 0.5 hr and then heated to 125° for 2 hr. The excess acid was removed under reduced pressure to afford a solid which was recrystallized from EtOH to give 2.5 g (68%) of the product, mp 165–166°.

3,4-Diacetoxy-β-phenethylmethylamine Hydrobromide (7). Compound **4** (2.48 g, 0.01 mol) was dissolved in 20 ml of anhydrous CF_3COOH and treated with 3.69 g (0.03 mol) of purified AcBr. After stirring for 0.5 hr at room temperature, 2 drops of H_2O was added and the volatiles were removed under reduced pressure. *i*-PrOH (5 ml) was added to the residue followed by anhydrous Et_2O to produce turbidity. The solid which separated was recrystallized form *i*-PrOH–Et_2O to afford 1.8 g (54%) of the product: mp 119–120° (lit.[23] reports a HCl salt, mp 143°); ir (KBr) 1775 (ester C=O); nmr (D_2O) δ 2.41 (s, 6, CH_3COOAr), 2.77 (s, 3, NCH_3), 3.20 (m, 4, CH_2CH_2), 7.34 (m, 3, Ar H). *Anal.* ($C_{13}H_{18}BrNO_4$) C, H, N.

***N,N*-Dimethyl-3,4-dimethoxy-β-phenethylamine Hydrochloride (12). Method A.** The compound was prepared from 3,4-dimethoxy-β-phenethylamine *via* an Eschweiler–Clarke modification by the method of Baltzly.[16]

Method B. 3,4-Dimethoxy-β-phenethylamine (10 g, 0.055 mol) in 200 ml of anhydrous CH_3OH was added to 3 g of Pd/C (10%) in a pressure bottle. Then 50 ml of H_2CO (37%) was added and the resulting mixture was hydrogenated at room temperature in a Parr apparatus (72 hr) with a H_2 pressure of 4 kg/cm². The catalyst was removed by filtration and washed with CH_3OH. The filtrate and washings were combined and the volatiles removed under reduced pressure. Then H_2O (100 ml) and concentrated HCl (20 ml) were added and the volatiles again removed under reduced pressure. An additional 100 ml of H_2O was added and the procedure repeated. The residue was made basic with 50% aqueous NaOH and the amine was extracted (Et_2O), dried (Na_2SO_4), and distilled through a short-path apparatus: bp 93–96° (0.05 mm); yield, 9 g (78%). The product was made into a hydrochloride salt and recrystallized from EtOH–EtOAc to afford the product, mp 192–193° (lit.[24] 197°).

***N,N*-Dimethyl-3,4-dihydroxy-β-phenethylamine Hydrobromide (5).** Compound **12** (4 g, 0.017 mol) was added to 20 ml of 48% HBr. The system was flushed with N_2 for 0.5 hr and then heated at 125° for 2 hr. The excess acid was removed under reduced pressure and the solid obtained was washed with Me_2CO and dried. The product was recrystallized from *i*-PrOH to yield 3 g (71%), mp 129–129.5° (lit.[24] reports a hydrochloride, mp 127°).

***N,N*-Dimethyl-3,4-diacetoxy-β-phenethylamine Hydrochloride (8).** Excess Ac_2O was added to 5 g (0.019 mol) of **5** and the mixture

was warmed on a steam bath for 2 hr. The volatiles were removed under reduced pressure and the residue was taken up in 5% aqueous HCl and washed with Et_2O. Excess K_2CO_3 was added and the product extracted (Et_2O), dried (Na_2SO_4), and treated with Et_2O·HCl. The salt was recrystallized twice from Me_2CO to afford 4.3 g (73%) of product: mp 160–161°; ir (KBr) 1770 (ester C=O); nmr (D_2O) δ 2.40 (s 6, CH_3COOAr), 2.95 (s, 6, $N(CH_3)_2$), 3.25 (m, 4, CH_2CH_2), 7.30 (m, 3, Ar H). *Anal.* ($C_{14}H_{20}NO_4Cl$) C, H, N.

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Amidines. 5.[1] Synthesis of Pyrrolo[2,3-*b*]isoquinoline, Imidazo[1,2-*b*]isoquinoline, Pyrrolo[2,1-*b*]quinazoline, and 1,3-Thiazino[2,3-*b*]quinazoline Derivatives and Related Heterocycles as Potential Antihypertensive Agents

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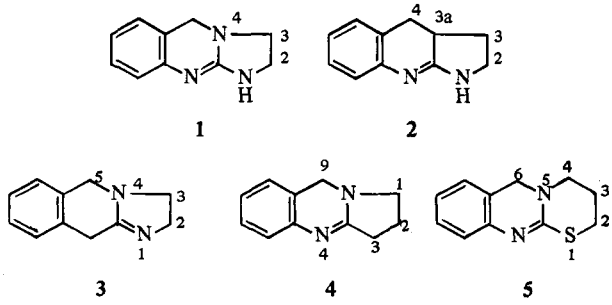
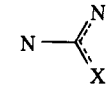
Further structural modifications of a new antihypertensive agent, 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**1**), were investigated. Syntheses of 2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,3-*b*]quinoline (**2**), 2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (**3**), 1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (**4**), 3,4-dihydro-2*H*,6*H*-[1,3]thiazino[2,3-*b*]quinazoline (**5**), 2,3,3a,4-tetrahydrofuro[2,3-*b*]quinoline (**9**), and related heterocycles are described. Compounds **4** and **5** showed antihypertensive activity.

Our recent discovery of the potent antihypertensive agent **1**[2] prompted us to investigate further the chemistry and biological activity of related heterotricyclic systems **2-5** (Chart I). All of these modifications retain the "amidine" moiety which may be an essential structural feature for producing antihypertensive activity (the term "amidine" is used here for those compounds containing the moiety A).

Chart I

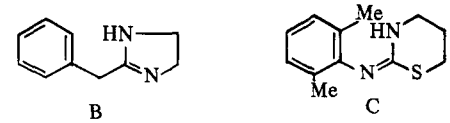


1 **2** **3** **4** **5**



A, X = C, N, O, or S

The imidazo[1,2-*b*]isoquinoline (**3**) and the 1,3-thiazino[2,3-*b*]quinazoline (**5**) may be considered "bridged" versions of tolazoline (B)[3] (an α-adrenergic blocking agent) and 2-(2,6-dimethylphenylimino)tetrahydro-2*H*-1,3-thiazine (C)[4] (an antihypertensive agent), respectively. Our previous application of this approach of structural modification on 2,6-dichlorophenylamino-2-imidazoline (clonidine) had led to the discovery of **1**.[2b]



B C

Despite the many publications dealing with the chemistry of the related pyrrolo[2,3-*b*]indole ring system which followed the discovery of physostigmine, only a few pyrrolo-