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Pivaloyl Esters of N,N-Dialkylated Dopamine Congeners. Central Dopamine-Receptor Stimulating Activity

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In order to test for dopamine-receptor stimulating activity a new, sensitive biochemical screening method was designed. For behavioral studies and for determination of the duration of action on the compounds, motor activity measurements were used. *O,O'*-Dipivaloyl-*N,N*-dipropyldopamine (**4**) was the only derivative of a series of dipivaloyl-*N,N*-dialkyldopamines studied that showed any significant activity. However, the monopivaloyl ester 2-(3-pivaloyloxyphenyl)-*N,N*-dipropylethylamine (**8**) seemed to be more potent. The same relationship was found for the corresponding phenols, *N,N*-dipropyldopamine (**3**) and 2-(3-hydroxyphenyl)-*N,N*-dipropylethylamine (**7**), although both were more active than their pivaloyl esters.

Substances which stimulate dopamine receptors in the central nervous system have attracted increasing clinical interest.[1] Such compounds are known to induce hyperactivity and stereotyped behavior in animals. Numerous papers describing syntheses and pharmacology of such dopamine receptor agonists have appeared in the literature over the last decade.[2-13]

Dopamine itself does not pass the blood–brain barrier. Several simple dopamine derivatives, however, have shown central dopaminergic activity after peripheral administration.[4,13] Thus some *N,N*-dialkyldopamine derivatives, e.g., *N*-methyl-*N*-propyl-, *N*-butyl-*N*-methyl-, and *N*-butyl-*N*-propyldopamine, have been shown to induce turning in nigral-lesioned rats when given intraperitoneally.[4]

Apomorphine is a direct stimulant of dopamine receptors in the brain.[14] Its clinical use, however, is limited because of short duration and low bioavailability when administered orally. Borgman et al.[15-17] have studied diester derivatives of apomorphine, e.g., *O,O'*-dipivaloylapomorphine, and reported a prolonged duration of action. This compound was independently synthesized and

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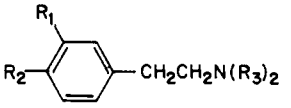
Table I. Physical and Biochemical Data for the Compounds Tested



compd	R_1	R_2	R_3	formula	mp, °C	dose, μmol/kg, giving 50% decrease of Dopa accumulation[b,c] limbic	striatum
1	PiO[a]	PiO	CH_3	$C_{20}H_{31}NO_4 \cdot HBr$	203–204	>45[d]	>45[d]
2	PiO	PiO	C_2H_5	$C_{22}H_{35}NO_4 \cdot HCl$	172–173	>27[d]	>27[d]
3	HO	HO	*n*-C_3H_7	$C_{14}H_{23}NO_2 \cdot HCl$	140–142	25	20
4	PiO	PiO	*n*-C_3H_7	$C_{24}H_{39}NO_4 \cdot HI$	135–136	28	33
5	PiO	PiO	*n*-C_4H_9	$C_{26}H_{43}NO_4 \cdot HCl$	142–143	>180[d]	>180[d]
6	CH_3O	H	*n*-C_3H_7	$C_{15}H_{25}NO \cdot HCl$	104–106	>45[d]	>45[d]
7[e]	HO	H	*n*-C_3H_7	$C_{14}H_{23}NO \cdot HBr$	149–151	5.7	1.8
8	PiO	H	*n*-C_3H_7	$C_{19}H_{31}NO_2 \cdot HBr$	154–155	2.7	1.8
apomorphine						0.23	0.23

[a] Pivaloyloxy. [b] Dopa values in the hemisphere and 5-HTP values were unaffected. [c] Linear double-reciprocal (1/percentage difference from control vs. 1/dose) diagrams were constructed and regression lines for each compound and brain area were determined by the method of least squares. The dose giving 50% decrease of Dopa accumulation was then derived from these lines. [d] Inactive. [e] When this manuscript was in preparation, this compound was described by Geissler.[28]

studied, with similar results, by our group.[18] This led us to study a series of *O,O'*-dipivaloyl-*N,N*-dialkyldopamine derivatives possessing identical *N*-alkyl groups.

Dopamine receptor agonists with only one hydroxyl group in the aromatic nucleus have also been reported.[19-22] Most of these compounds are tetracyclic apomorphine analogues. In addition, a very potent monohydroxytetralin derivative (5-hydroxy-2-dipropylaminotetralin) has been reported.[22] We have therefore synthesized a corresponding monohydroxyphenethylamine, 2-(3-hydroxyphenyl)-*N*,-*N*-dipropylethylamine (7), and its pivaloyl ester 8.

The compounds were tested both for potency and duration of action. A new, sensitive biochemical screening method based on the work of Carlsson et al.[23] has been used to estimate the dopamine–receptor stimulating potency of the compounds. The compounds synthesized and the biological data obtained are presented in Table I and Figure 1.

Chemistry. Compounds 1–8 were prepared essentially according to literature procedures (see the Experimental Section). The pivaloyl esters were obtained from the phenols by acylation with pivaloyl chloride in trifluoroacetic acid.[24]

Pharmacology. The compounds were tested biochemically for central dopamine–receptor stimulating activity and functionally for duration of action, in both cases using reserpinized rats. The concept of the biochemical screening method is that a dopamine–receptor agonist (e.g., apomorphine) will stimulate the receptor, which through feedback systems will cause a decline in tyrosine hydroxylase activity, thus reducing the synthesis of Dopa in the presynaptic neuron. Similar feedback systems probably exist also for 5-HT neurons.[25] The amount of accumulated Dopa and 5-HTP in the striatum, the limbic forebrain, and the remaining hemispheral portions of the rat cerebrum was determined after in vivo inhibition of the aromatic L-amino acid decarboxylase. Several doses were tested in order to obtain a dose–response curve for each compound. The dose of the drug reducing the Dopa level to 50% of that found in the corresponding brain portions of control animals was estimated for each compound, and these values are presented in Table I.

For behavior and duration studies the reserpinized rats were given the drug either subcutaneously or orally and the duration of action was measured in a motility meter as described in the Experimental Section. The dose of test compounds for sc administration was 20 μmol/kg and for apomorphine and its pivaloyl ester 2 μmol/kg. (For oral administration ten times the sc dose was given.) The results of the duration studies (sc administration) are presented in Figure 1.

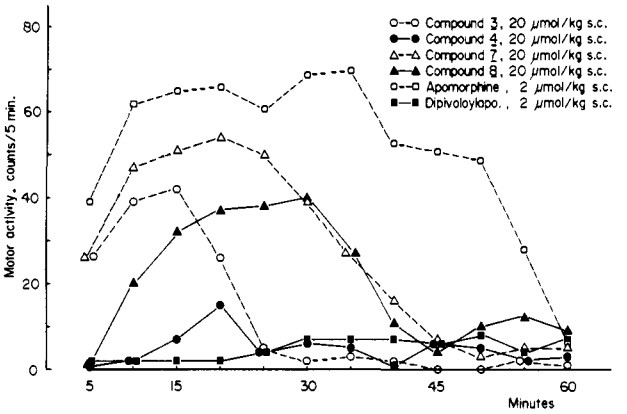


Figure 1. Rat motor activity measurements. Open symbols represent compounds with free hydroxyl groups, i.e., 3, 7, and apomorphine (Apo), and filled symbols their corresponding pivaloyl esters 4, 8, and dipivaloylapomorphine (dpApo), respectively. Shown are the means (n = 4–5). Significant ($p < 0.025$ or less) differences were obtained for 3 vs. 4 at 5, 10, and 15 min; 7 vs. 8 at 5 and 10 min; Apo vs. dpApo at 5–50 min; 3 vs. 7 at 20–40 min; and 4 vs. 8 at 10–35 min.

Results and Discussion

As seen in Table I the compounds were less potent than apomorphine. The *N,N*-dipropyl derivatives 3 and 4 were the only dopamine analogues of the series 1–5 that showed any significant activity. This is in good agreement with the results of McDermed et al.[5] who, in a series of 2-(*N,N*-dialkylamino)-5,6-dihydroxytetralins, found maximal activity for the dipropyl derivative. In contrast, Ginos and Cotzias[13] have reported that among a number of N,N-disubstituted dopamines the N,N-dialkylated analogues possessing identical alkyl groups had no effect, while, e.g., *N*-butyl-*N*-propyldopamine, showed strong dopaminergic activity.

The notably small difference in stereotype-inducing activity between 5,6-dihydroxy-2-dipropylaminotetralin and its dimethyl ether[5] led us to test the methyl ether 6. However, no activity was observed for this compound in our biochemical test.

The monohydroxy compound 7 and its pivaloyl ester 8 appear to be more potent than the corresponding catechol 3 and its dipivaloyl ester 4, respectively. Thus the catechol moiety is not a requirement for dopaminergic activity, which has also been demonstrated for aminotetralins[22] and apomorphines.[19]

The compounds which gave no decrease in Dopa accumulation were also inactive in the behavioral stimulation test, indicating a correlation between biochemical and behavioral effect. Amphetamine, known to act via transmitter release, did not influence the Dopa levels when tested (1 mg/kg sc) in our biochemical model. This strongly indicates that our active compounds have a direct stimulating activity of the dopamine receptors of the limbic forebrain and the striatum. The unaffected 5-HTP and hemispheral Dopa values indicate respectively the absence of serotoin and noradrenaline receptor activity.

The duration of action was studied only for the active *N,N*-dipropyl derivatives 3, 4, 7, and 8 as well as for apomorphine and its dipivaloyl ester (Figure 1). The motor activity consisted of stereotyped movements (licking, gnawing, and sniffing) and occasional jerks as well as locomotion. No attempt was made to differentiate between the different types of movements.

The duration of action of the monohydroxy compound 7 is significantly longer than that of the catechol 3. Pivaloylation of the phenols affording 8 and 4 does not alter this relationship. This might reflect a higher metabolic stability of monohydroxy compounds as compared to the corresponding catechols. As shown in Figure 1, both the monophenol 7 and its pivaloyl ester 8 induce motor activity in the animals as could be expected from the biochemical data. The latter compound has a latency period of 10 min, suggesting that conversion to free phenol is necessary for activity. In the biochemical test (Table I) the pivaloyl ester 4 is equipotent to the catechol 3. However, in the duration studies the ester 4 is almost devoid of effect. This relationship between 3 and 4 is similar to that obtained for apomorphine and its dipivaloyl ester (Figure 1).

The findings presented here are in agreement with the low stereotypic and turning activity for several apomorphine esters at low doses as observed by Baldessarini et al.[17] The prolonged duration of action obtained after large doses of the apomorphine esters might possibly reflect a saturation of hydrolytic enzymes. The compounds tested for duration (3, 4, 7, and 8) were almost devoid of activity when given orally (results not shown). This is also in parallel to what has been reported for apomorphine esters.[17] The low activity after oral administration and the high doses required for prolonged duration limit the clinical interest in these esters.

Experimental Section

General. Uncorrected melting points were determined in open glass capillaries on a Thomas-Hoover apparatus. ^1H NMR spectra, recorded for identification purposes on a Varian EM-360 spectrometer, were in all cases in agreement with expected data. The analyses of C, H, and N for the new substances (Elementaranalystjänst, Chemical Center, Lund, Sweden) were within 0.4% of the theoretical values. No attempts were made to increase the yields obtained. For purity tests, TLC was performed using fluorescent silica gel plates developed in CH_2Cl_2–MeOH (9:1). The amine bases as well as their salts (which move as ion pairs) can be chromatographed in this system. The spots were visualized using UV light and I_2 vapor. The analytical samples gave only one spot in this test.

***N,N*-Dimethyl-2-(3,4-dipivaloyloxyphenyl)ethylamine (1).** 2-(3,4-Dihydroxyphenyl)-*N,N*-dimethylethylamine hydrobromide (11 g, 0.043 mol) (prepared in 30% yield from 3,4-dimethoxyphenethylamine by alkylation with formaldehyde–formic acid in DMF[26] followed by ether cleavage using refluxing 48% HBr, 2 h, under N_2) was dissolved in trifluoroacetic acid (20 mL) and treated with pivaloyl chloride (20 mL, 0.162 mol) at room temperature overnight.[24] After evaporation of the solvent, the residue was partitioned between H_2O and CH_2Cl_2. The organic phase, thus containing the hydrobromide of 1 (as an ion pair),[27] was concentrated and applied to a SiO_2 column and the product was eluted with CH_2Cl_2–MeOH (9:1). Evaporation of the solvent followed by recrystallization (EtOAc) yielded 3.2 g (17%) of 1·HBr, mp 203–204 °C. Anal. ($C_{20}H_{31}NO_4$·HBr) C, H, N.

***N,N*-Diethyl-2-(3,4-dipivaloyloxyphenyl)ethylamine (2).** *N,N*-Diethyl-2-(3,4-dihydroxyphenyl)ethylamine hydrobromide (1.5 g, 0.0056 mol) (prepared in an overall yield of 12% from 3,4-dimethoxyphenylacetic acid analogously to the method used by Ginos et al.[4]) was esterified with pivaloyl chloride (3 mL, 0.024 mol) as described for compound 1. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and the solution extracted with 10% Na_2CO_3. The organic phase was acidified with ethereal HCl. Evaporation followed by recrystallization (EtOAc) gave 0.70 g (30%) of 2·HCl, mp 172–173 °C. Anal. ($C_{22}H_{35}NO_4$·HCl) C, H, N.

2-(3,4-Dihydroxyphenyl)-*N,N*-dipropylethylamine (3). A mixture of 3,4-dimethoxyphenethylamine (24 g, 0.14 mol), anhydrous K_2CO_3 (45 g, 0.33 mol), and 1-bromopropane (40 g, 0.33 mol) in CH_3CN (250 mL) was stirred at room temperature for 20 h. After filtration the filtrate was mixed with water (1500 mL) and extracted with ether. The ether extract was dried (Na_2SO_4) and the solvent evaporated, yielding 2-(3,4-dimethoxyphenyl)-*N,N*-dipropylethylamine (26 g) as an oil. This was further treated with 57% HI (65 mL, freshly distilled from red phosphorus) under reflux for 0.5 h (N_2 atmosphere). Evaporation yielded the hydroiodide of 3 (35 g) as an oily residue. The main part of this oil was used without further purification in the synthesis of compound 4.

A small portion of the crude oil (0.92 g, 0.0025 mol) dissolved in CH_2Cl_2 (25 mL) was extracted with an acidic (pH 3) aqueous solution of potassium 3,5-di-*tert*-butyl 2-hydroxyphenylsulfonate (0.96 g, 0.003 mol). The organic layer was separated and mixed with a CH_2Cl_2 solution of trioctylammonium chloride (1.2 g, 0.003 mol) and extracted with water.[27] The water was evaporated from the aqueous phase and the residue was recrystallized (EtOH–Et_2O) yielding 0.3 g (30% overall; based on the amount of 3·HI used) of 3·HCl, mp 140–142 °C. Anal. ($C_{14}H_{23}NO_2$·HCl) C, H, N.

2-(3,4-Dipivaloyloxyphenyl)-*N,N*-dipropylethylamine (4). The crude hydroiodide of 3 (32 g, 0.088 mol) was esterified with pivaloyl chloride as described from compound 1, yielding a crude hydroiodide of 4 (42 g). Part of this material (5.1 g) was chromatographed on a SiO_2 column with CH_2Cl_2–MeOH (19:1) as eluent. This gave 2.7 g (47%) of 4·HI, mp 135–136 °C (from EtOAc). Anal. ($C_{24}H_{39}NO_4$·HI) C, H, N.

***N,N*-Dibutyl-2-(3,4-dihydroxyphenyl)ethylamine.** This compound was prepared in 51% yield from 3,4-dimethoxyphenethylamine by alkylation with 1-bromobutane followed by ether cleavage using HI, both reactions performed as described for compound 3: mp (HCl) 155–160 °C (from EtOH–Et_2O). Anal. ($C_{16}H_{27}NO_2$·HCl) H, N; C: calcd, 63.7; found, 61.8. The main portion was used in the next step without further purification.

***N,N*-Dibutyl-2-(3,4-dipivaloyloxyphenyl)ethylamine (5).** 2-(3,4-Dihydroxyphenyl)-*N,N*-dibutylethylamine (11 g, 0.028 mol), as the crude oil (above), was esterified with pivaloyl chloride as described for compound 1. The crude product (8.3 g) was purified on a SiO_2 column eluted with CH_2Cl_2–MeOH (19:1) and then converted into the hydrochloride. This yielded 1.0 g (8%) of 5·HCl, mp 142–143 °C (from Et_2O). Anal. ($C_{26}H_{43}NO_4$·HCl) C, H, N.

2-(3-Methoxyphenyl)-*N,N*-dipropylethylamine (6). This compound was prepared from 3-methoxyphenylacetic acid (25 g, 0.15 mol) analogously to the preparation of *N,N*-diethyl-2-(3,4-dimethoxyphenyl)ethylamine (see above). Distillation gave 20 g (80%) of 6, bp 110–115 °C (0.5 mmHg). Part of this material (5.0 g, 0.021 mol) was treated with ethereal HCl yielding 6·HCl, mp 104–106 °C (from EtOAc). During the preparation of this manuscript this compound was described as the hydrobromide salt.[28] For identification purposes, an analytical amount of the hydrobromide of 6 was also prepared, mp 98–101 °C (from EtOAc) (lit.[28] 99 °C).

2-(3-Hydroxyphenyl)-*N,N*-dipropylethylamine (7). 2-(3-Methoxyphenyl)-*N,N*-dipropylethylamine (6) (15 g, 0.064 mol) was refluxed with 48% HBr (75 mL) under an N_2 atmosphere for 2 h. Evaporation gave a crystalline material (16 g), which on recrystallization (from EtOAc) yielded 11 g (70%) of 7·HBr, mp 149–151 °C (lit.[28] 152 °C).

2-(3-Pivaloyloxyphenyl)-*N,N*-dipropylethylamine (8). Pivaloylation of the hydrobromide of 7 (6.3 g, 0.021 mol) was accomplished as described for compound 1. The crude product (6.4 g) was chromatographed on a SiO_2 column with CH_2Cl_2–MeOH (19:1) as eluent. This yielded 2.7 g (34%) of 8·HBr, mp 154–155 °C (from EtOAc). Anal. ($C_{19}H_{31}NO_4$·HBr) C, H, N.

***O,O'*-Dipivaloylapomorphine.** The hydrochloride of this compound was prepared as previously described:[16] mp 205–210 °C dec (from EtOAc–Et_2O) (lit.[16] 209–212 °C dec).

Pharmacology. Methods and Material. Animals used in the experiments were male rats of the Sprague–Dawley strain (Anticimex, Stockholm) weighing 200–350 g.

All substances to be tested were dissolved in saline (0.9%) immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Injection volumes were always 10 mL/kg, and injection solutions were at neutral pH.

Biochemistry. Eighteen hours prior to the biochemical testing the rats were pretreated with reserpine (Ciba) in a dose of 5 mg/kg ip. Substances to be tested were injected in various doses subcutaneously at the beginning of the experiments. Changes in motility, stereotypics, and other aspects of behavior were noted. Forty-five minutes later they received 3-hydroxybenzylhydrazine hydrochloride[29] (NSD 1015), an inhibitor of the L-aromatic amino acid decarboxylase, 100 mg/kg ip. After a further 30 min the rats were killed by decapitation and the brains were rapidly removed and dissected on an ice-cold glass plate.

The following brain parts were excised for analysis: (1) corpora striata, (2) the limbic forebrain containing, e.g., tuberculum olfactorium, nucleus accumbens (medial part), and nucleus amygdaleoideus centralis, and (3) the rest of the hemispheral portion.[30] Immediately after dissection the brain parts were frozen on dry ice. Brain parts from two brains were pooled, weighed, and then homogenized in 10 mL of 0.4 N perchloric acid containing 5 mg of $Na_2S_2O_5$ and 20 mg of EDTA. After centrifugation the supernatants were purified on a strong cation-exchange column (Dowex 50 X4).[31] Dopa and 5-HTP were determined by spectrofluorimetry.[32,33]

Motor Activity. The rat activity was measured by means of photocell recordings (M/P 40 Fc electronic motility meter, Motron Products, Stockholm). The instrument was equipped with photoconductive sensors, covered by a translucent floor, upon which was set a test cage (20 × 30 × 25 cm) where the animal was placed. The apparatus was housed in a soundproof box and connected to an external timer-controlled counter. A lamp was attached to the roof inside the soundproof box. One motor activity count was registered by the external counting device whenever as a result of animal movement a number of ten interruptions of the light beams on any sensor were accumulated. Four to eight motility meters were run in parallel.

Six hours prior to the motility testing the rats were intraperitoneally injected with reserpine, 10 mg/kg. The agents to be screened for central dopamine-receptor stimulating activity were then administered sc in the neck region, alternatively po via a stomach tube. Doses of tested substances were always 20 μmol/kg sc and 200 μmol/kg po. Because of their higher potency, apomorphine and its dipivaloyl ester were tested in ten times lower doses. Immediately following drug administration the animals were placed individually in the test cages (vide supra) and put into the motility meters. Motor activity was then followed and registered for each 5-min period during the consecutive 2 h. Each box was equipped with a semitransparent mirror that allowed gross behavior observations of the animals during the recordings.

Reserpinized rats, injected with vehicle only, gave control values ranging from 0 to 4 counts/5 min over the entire motor activity test period.

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