tert-Butoxycarbonyl as a Convenient Protecting Group in Synthesis of Potential Centrally Active Dopamine Derivatives

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Abstract □ Several pivaloyl and pivaloyloxy esters and amides of dopamine were synthesized for possible antiparkinson activity. The compounds were synthesized by select *O*- and *N*-acylation and *N*-methylation procedures. The *tert*-butoxycarbonyl function is an effective and easily removed nitrogen-protecting group for dopamine. Preliminary biological testing results showed that all compounds tested elicited a hypothermic response in mice, while only *O,O*-dipivaloyl-*N,N*-dimethyldopamine reversed reserpine-induced motor depression in mice. However, it is difficult to conclude from the preliminary data that the observed biological effects were due to central dopaminergic receptor stimulation.

Keyphrases □ Dopamine derivatives, various—synthesized with *tert*-butoxycarbonyl as protecting group, CNS activity evaluated in mice □ CNS activity—various dopamine derivatives synthesized with *tert*-butoxycarbonyl as protecting group, evaluated in mice □ Structure–activity relationships—various dopamine derivatives synthesized with *tert*-butoxycarbonyl as protecting group, CNS activity evaluated in mice

Various 3,4-diesters of dopamine have been proposed as agents capable of crossing the blood–brain barrier and activating central dopamine receptors by hydrolytic release of dopamine in the brain (1–4). *N,N*-Dimethyl-*O,O*-diacetyldopamine effectively induced hypothermia (5, 6) and partially reversed oxotremorine-induced tremor in mice (2). Casagrande and Ferrari (3) synthesized 4-pivaloyl- and 3,4-dipivaloyldopamine plus several other dopamine esters containing more bulky acyloxy groups and suggested, without providing pharmacological data, that these compounds would provide sufficient lipophilicity and resistance to hydrolysis for entry into the central nervous system (CNS) before releasing the parent phenethylamine.

BACKGROUND

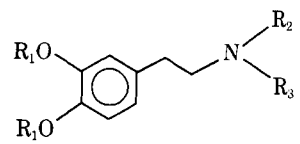
Various peptides of levodopa (L-3,4-dihydroxyphenylalanine) (7) and dopamine (8, 9) have both peripheral and central dopaminergic activity. In mice, various carbamates of amphetamine readily entered the CNS and released free amphetamine in the brain (10). Several other carbamate-latentiated drugs, such as normeperidine (11) and chlorphentermine (12), also were reported to have similar activity to the parent drug.

These reports suggest that certain amides as well as esters of dopamine should be capable of crossing the blood–brain barrier, and subsequent hydrolysis would release dopamine at the desired site of action. Such compounds may be potentially useful as antiparkinson agents, eliminating the high doses and subsequent peripheral side effects associated with levodopa.

Esters (II–IV) and amides (V and VI) of dopamine (I) containing either the pivaloyl or pivaloyloxy function were, therefore, synthesized and examined in mice for hypothermic activity and the ability to reverse reserpine-induced motor depression.

RESULTS AND DISCUSSION

Chemistry—The search for labile, lipophilic, centrally active dopamine analogs has been somewhat hindered by lack of a good protective group for the amino function. The benzyloxycarbonyl function has been used most often (1, 3). However, upon *O*-acylation, *N*-benzyloxycarbonyldopamine often gives oily products that resist crystallization. Difficulties in removal of the benzyloxycarbonyl moiety and N→O acyl migration also have been reported (13). In light of these reports, a protecting group was sought that is easily introduced, readily gives crystalline derivatives upon *O*-acylation, and is easily removed to yield *O*-acyldopamines in good yield. The *tert*-butoxycarbonyl function was found to meet these requirements (14).



I: $R_1 = R_2 = R_3 = H$, hydrochloride
II: $R_1 = (CH_3)_3CCO$, $R_2 = R_3 = H$, hydrochloride
III: $R_1 = (CH_3)_3CCO$, $R_2 = R_3 = CH_3$, hydrochloride
IV: $R_1 = R_2 = (CH_3)_3CCO$, $R_3 = H$
V: $R_1 = (CH_3)_3CCO$, $R_2 = (CH_3)_3COCO$, $R_3 = H$
VI: $R_1 = R_3 = H$, $R_2 = (CH_3)_3COCO$

N-tert-Butoxycarbonyldopamine (VI) was synthesized from dopamine and *tert*-butoxyazidoformate in excellent yield. Best results were obtained by using a slight excess of reagent in the presence of triethylamine, with aqueous dioxane as the solvent. When a large excess of reagent was used, partial *O*-acylation occurred. The nitrogen-protecting group could be removed readily by treatment of VI with hydrogen chloride in ether.

Acylation of VI with pivaloyl chloride gave *N-tert*-butoxycarbonyl-*O,O*-dipivaloyldopamine (V); upon removal of the protecting group, V provided *O,O*-dipivaloyldopamine hydrochloride (II) in good yield. *N,N*-Dimethyl-*O,O*-dipivaloyldopamine (III) was synthesized from II by an adaption of the method of Schellenberg (13). The amine hydrochloride was dissolved in methanol and treated with formaldehyde and excess sodium borohydride. Treatment with hydrogen chloride in ether gave the hydrochloride. *O,O,N*-Tripivaloyldopamine (IV) was readily prepared from dopamine and excess pivaloyl chloride in high yield.

Biological Activity—Preliminary tests of five analogs of pivaloyl and pivaloyloxy esters and amides of dopamine were examined for potential antiparkinson activity. The two models used to estimate the agent's ability to stimulate dopaminergic receptors were the production of hypothermia (5, 6) and the antagonism of reserpine-induced motor depression in mice (15).

Barnett *et al.* (5) demonstrated that stimulation of dopaminergic receptors in the CNS produces hypothermia in mice. Horst *et al.* (15) demonstrated that reserpine-induced catatonia was reversed by levodopa and that this effect was directly correlated with brain dopamine levels. They suggested that the reversal of reserpine-induced catatonia is a good model to use in a search for antiparkinson drugs.

All compounds tested elicited hypothermic responses in mice 90 min after intraperitoneal injection. However, it is not possible to conclude from these preliminary results that the hypothermia elicited in mice following the administration of the test compounds was due to central dopaminergic stimulation, except perhaps for III, which also elicited a positive reserpine-induced motor depression reversal response.

EXPERIMENTAL

Chemistry—Melting points were determined in open glass capillaries and are uncorrected[1]. All compounds appeared as a single spot by TLC

[1] Thomas-Hoover Unimelt.

in two different solvent systems [petroleum ether–ether–chloroform (2:1:1) or butyl alcohol–chloroform (9:1)]. All compounds were characterized by elemental analyses[2], NMR spectroscopy[3], and IR spectroscopy[4].

N-tert-*Butoxycarbonyldopamine* (*VI*)—Dopamine hydrochloride (18 g, 0.1 mole) was dissolved in 70 ml of 70% aqueous triethylamine. The mixture was stirred in an ice bath under nitrogen, and a solution of 15 ml (0.015 mole) of *tert*-butoxycarbonyl azide in 50 ml of dioxane was added through a dropping funnel. The ice bath was removed, and the mixture was stirred 5 hr at room temperature under nitrogen. Water, 100 ml, was added, and the mixture was adjusted to pH 2 with 1 *N* HCl and then extracted with 2 × 75 ml of ether, which, in turn, was extracted with 100 ml of saturated aqueous sodium bicarbonate.

The ether layer was dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo*, leaving a clear oil. This oil crystallized upon addition of petroleum ether, yielding 23.8 g (94%) of product. Recrystallization from benzene gave white crystals, mp 137–138°; IR: 1720 (ester, C=O), 1690 (amide, C=O), and 1520 (CN) cm^{-1}.

Anal.—Calc. for $C_{13}H_{19}NO_4$: C, 61.67; H, 7.51; N, 5.53. Found: C, 61.92; H, 7.53; N, 5.43.

N-tert-*Butoxycarbonyl*-O,O-*dipivaloyldopamine* (*V*)—Compound VI (2.41 g, 0.009 mole) was dissolved in 10 ml of triethylamine stirring in an ice bath under nitrogen. A solution of 3.6 ml (0.03 mole) of pivaloyl chloride in 10 ml of dioxane was added dropwise, and the mixture was stirred 2 hr at room temperature. Then water (50 ml) was added, and the pH was lowered to 4 with 1 *N* HCl. The mixture was extracted with 2 × 30 ml of ether, which, in turn, was extracted with 2 × 20 ml of saturated aqueous sodium bicarbonate.

The ether layer was dried over anhydrous sodium sulfate and removed *in vacuo*, yielding 4.7 g of clear oil. This oil crystallized upon standing overnight in a refrigerator; the yield was 3.3 g (87%). Petroleum ether crystallization gave 2.8 g of white crystals, mp 94–95°; IR: 1720 (ester, C=O) and 1690 (amide, C=O) cm^{-1}.

Anal.—Calc. for $C_{23}H_{35}NO_5$: C, 68.15; H, 9.64; N, 3.46. Found: C, 67.92; H, 8.68; N, 3.57.

O,O-*Dipivaloyldopamine Hydrochloride* (*II*)—Compound V (4.24 g, 0.01 mole) was dissolved in 25 ml of dry ether through which was passed a stream of hydrogen chloride gas for 10 min. The flask was stoppered and refrigerated for 1 hr. Then the ether was removed *in vacuo*, leaving a glassy solid. This solid solidified on standing in petroleum ether; the yield was 2.8 g (80%). Recrystallization from benzene–petroleum ether gave the pure product, mp 175–176°; IR: 1720 (ester, C=O) cm^{-1}.

Anal.—Calc. for $C_{18}H_{28}ClNO_4$: C, 60.42; H, 7.83; Cl, 9.93; N, 3.92. Found: C, 60.15; H, 7.81; Cl, 9.83; N, 3.94.

N,N-*Dimethyl*-O,O-*dipivaloyldopamine Hydrochloride* (*III*)—Compound II (1.8 g, 0.005 mole) was dissolved in 15 ml of absolute methyl alcohol, and 1.0 ml of 37% formaldehyde was added. Sodium borohydride, 1.0 g (0.025 mole), was added over 15 min. The mixture was then cooled to room temperature. Another 1.0 ml of formaldehyde was added, and the mixture was stirred 30 min. Then 20 ml of water was added, and the mixture was extracted with 3 × 20 ml of ether.

The ether layers were dried over anhydrous sodium sulfate and removed *in vacuo*, leaving a clear oil. This oil was dissolved in benzene saturated with hydrogen chloride gas. Removal of solvents gave 0.6 g (31%) of white crystals, mp 196–198°. Recrystallization from benzene–petroleum ether gave the pure product; IR: 1720 (ester, C=O) cm^{-1}.

Anal.—Calc. for $C_{20}H_{32}ClNO_4$: C, 62.23; H, 8.30; Cl, 9.21; N, 3.63. Found: C, 61.21; H, 8.20; Cl, 9.29; N, 3.78.

O,O,N-*Tripivaloyldopamine* (*IV*)—Dopamine hydrochloride (1.89 g, 0.01 mole) was placed in 20 ml of triethylamine–dioxane (1:1). Pivaloyl chloride (4.8 ml, 0.04 mole) was added dropwise under nitrogen, and the mixture was stirred for 2 hr at room temperature. Water (50 ml) was added, and the mixture was extracted with 3 × 25 ml of ether, which, in turn, was extracted with 2 × 25 ml of 0.1 *N* HCl.

The ether layer was dried over anhydrous sodium sulfate, filtered over charcoal, and removed *in vacuo*, leaving a golden oil. This oil crystallized upon addition of petroleum ether; the yield was 3.5 g (86%) of white crystals. Recrystallization from petroleum ether–benzene gave the pure product, mp 100–101°; IR: 1720 (ester, C=O) and 1680 (amide, C=O) cm^{-1}.

Anal.—Calc. for $C_{23}H_{35}NO_5$: C, 68.15; H, 8.64; N, 3.46. Found: C, 68.07; H, 8.68; N, 3.64.

Biology—Male albino mice[5], 20–30 g, were used in groups of three for each test compound in all experiments. Arbitrary doses of 250 mg/kg ip were used for the hypothermia testing; 125 mg/kg ip was used for the reserpine-induced motor depression reversal test. Rectal temperatures were measured by an electronic thermometer[6]. Motor activities were recorded on an activity counter[7].

Compounds I–III were dissolved in normal saline. Compounds IV–VI were dissolved in an ethanol–propylene glycol (1:3) solution. Reserpine[8] (5 mg/kg ip) was administered 24 hr prior to testing. All solutions were prepared immediately prior to use.

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[3] Varian Associates model EM-360 with tetramethylsilane as the internal standard.

[4] Perkin-Elmer model 727.

[5] Carworth Farms No. 1.

[6] TRI Instruments.

[7] Lehigh Valley Electronics.

[8] Ciba Pharmaceutical Co.