Psychopharmacology 51, 169–173 (1977)

Psycho–
pharmacology

Behavioral Comparisons of R-2-Amino-1-(2,5-Dimethoxy-4-Methylphenyl) Butane (BL-3912A) with R-DOM and S-Amphetamine

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Abstract. The behavioral effects of R-2-amino-1-(2,5-dimethoxy-4-methylphenyl) butane or BL-3912A were compared with those of S-Amphetamine and R-DOM. BL-3912A facilitated acquisition of shuttle box responding by rats without increasing noncontingent intertrial (ITI) activity, while S-Amphetamine increased both avoidance and ITI responding. R-DOM had a biphasic effect on avoidance responding, increasing it at low doses and disrupting at higher doses. At doses that facilitated shuttle box responding, BL-3912A had no effect on unacclimated motor activity of rats nor on the rate of continuous avoidance responding by rats. S-Amphetamine increased the frequency of both motor activity and operant avoidance responding, while R-DOM decreased motor activity and increased operant avoidance responding. By facilitating avoidance behavior without increasing other measures of psychomotor activity, BL-3912A represents a unique psychopharmacological agent clearly different from R-DOM and S-Amphetamine.

Key words: BL-3912A – S-Amphetamine – R-DOM – Facilitation of behavior – Locomotor activity.

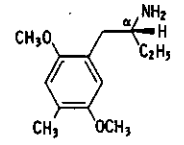
In humans, lower doses of 2-amino-1-(2,5-dimethoxy-4-methylphenyl)propane (DOM) reportedly produce subjective effects of well being without the hallucinogenic activity generally associated with higher doses (Snyder et al., 1968, 1970). Likewise, in animals lower doses of DOM increase the frequency of some types of conditioned behavior, while higher doses result in disruption of these behaviors (Beaton et al., 1969; Tilson et al., 1975). The finding that low doses of DOM facilitate behavior has prompted us to search for agents having a wider dose range, which produce positive effects on behavior without the undesirable side effects normally associated with stimulants or hallucinogens. In the present communication, we report the unique psychopharmacological profile of R-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane (BL-3912A). The cardiovascular effects of BL-3912A, DOM, and amphetamine have been reported elsewhere (Buyniski et al., 1974). Chemical synthesis of BL-3912A, as well as preliminary pharmacological data, have been reported by Standridge et al. (1976).

METHODS

Subjects. Adult, male rats of the Long-Evans strain (Blue Spruce Farms, Altamont, N.Y.) were housed in groups of 3–4 per cage in a room with a 12-h day-night cycle (light 6:00 a.m. to 6:00 p.m.). All subjects were given free food and water in their home cages.

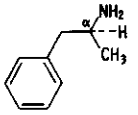
Drugs Tested. R-(-)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane hydrochloride (BL-3912A; Fig. 1) and R-(-)-2-amino-1-(2,5-

I. BL-3912-A



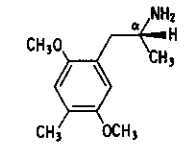
R-(−)-2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane

III. S-Amphetamine



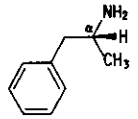
S-(+)-2-Amino-1-phenylpropane (*d*-Amphetamine)

II. R-DOM



R-(−)-2-Amino-1-(2,5-dimethoxy-4-methylphenyl)propane

IV. R-Amphetamine



R-(−)-2-Amino-1-phenylpropane (*l*-Amphetamine)

Fig. 1. Structures of I. BL-3912A, II. R-DOM, III. S-Amphetamine, IV. R-Amphetamine. R- or S- and (-) and (+) refer to the absolute structural configuration and optical rotation, respectively

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dimethoxy-4-methylphenyl) propane hydrochloride (R-DOM) were synthesized and tested for optical purity at Bristol Laboratories, Syracuse, N.Y. S-(+)-2-amino-1-phenylpropane sulfate (S-amphetamine) was obtained from Aldrich Chemical Co. (Cedar Knolls, New Jersey) and tested for optical purity at Bristol Laboratories. Magnesium pemoline was obtained from Abbott Laboratories, Chicago, Ill. Drugs were dissolved in 0.9% isotonic saline (NaCl) and administered i.p. in a volume of 1 ml/kg of body weight. Dosages are expressed in terms of the salt.

Acquisition of Active Avoidance. The effects of BL-3912A, R-DOM, and S-amphetamine on active avoidance acquisition were investigated using young rats (at 2 months or younger or retired breeder rats at 12 months or older). Experiments were conducted in two automated shuttle cages (BRS/LVE, Model No. 146-04) contained within a light and sound-attenuated chamber equipped with a ventilation fan. Control of the shuttle box and recording of responses were accomplished by means of standard electromechanical modules. Injection of drugs i.p. and placement of the subjects into the shuttle cage were followed by a 1-min pre-session acclimation period. The first avoidance trial was then initiated by activating a white light on the side of the shuttle cage occupied by the subject. If the animal did not cross to the other side of the chamber within 5 s (avoid), the grid floor under the animal was electrified with 0.8 mA of scrambled shock (BRS/LVE, Model No. 1531 shocker). The animal was allowed 5 s to make an escape response before the trial was terminated. Avoidance responses terminated the light, while escape responses terminated both the electric shock and light. Either response initiated the intertrial interval (ITI), which was 20–30 s depending on the response. Shuttles during the ITI were recorded as a measure of non contingent motor activity. Each subject received 120 avoidance trials during a 1 h session.

Motor Activity. Young, male Long-Evans rats weighing 200–250 g were used to evaluate drug effects on unacclimated motor activity. At least 1 week after arrival, the subjects were given various dosages of BL-3912A, S-amphetamine, R-DOM or NaCl vehicle i.p. and placed individually into motor activity chambers (Tilson et al., 1975). Horizontally-directed spontaneous motor activity was measured for a 1-h period.

Unsignalled Continuous Avoidance. The effects of 10 or 20 mg/kg of BL-3912A, 0.5, 1, or 2 mg/kg of S-amphetamine, 1 or 2.5 mg/kg of R-DOM, and isotonic saline vehicle on unsignalled avoidance responding were evaluated in 4 Long-Evans rats weighing 486 ± 59 g at the beginning of the study. The subjects were trained over a period of 2 months to press a lever to avoid a 2 mA footshock applied to the grids of an operant chamber (Tilson et al., 1975). Each lever press postponed shock for 30 s and, if no response was made within this time, the subject received shocks (0.5 s) every 5 s until a lever press was made. Drugs or vehicles were injected i.p. 15 min prior to 180 min behavioral sessions. The order of drugs studied was S-amphetamine, BL-3912A, and R-DOM, with lower doses tested first. At least 72 h separated drug sessions.

RESULTS

Active Avoidance. The main finding of this experiment was the observation that BL-3912A and to some extent S-amphetamine, differentially affected the acquisition of an active avoidance by young adult rats (2 months or younger and retired breeders, 12 months or older). As seen in Figure 2, 20 mg/kg of BL-3912A significantly increased and decreased the number of avoidance and escape responses, respectively, in

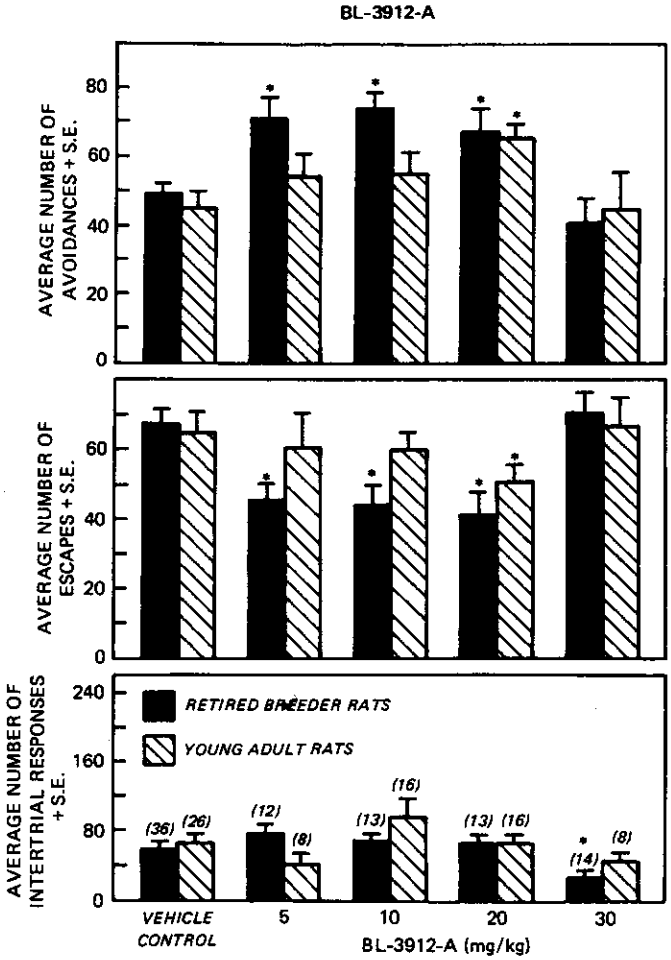

Fig. 2. The effects of various doses of BL-3912A injected i.p. on shuttle box responding of retired breeder and young adult Long-Evans rats. Data are mean + S.E. of avoidances, escapes and intertrial interval (ITI) responses made during 120 massed acquisition trials. Numbers in parenthesis indicate number of subjects per group. Asterisks denote statistical difference from vehicle control of the same age group (*t*-test, $P < 0.05$)

younger rats. Similar increases in avoidance responding and decreases in escape responses were noted in retired breeder rats after 5, 10 and 20 mg/kg of BL-3912A. The highest dose of BL-3912A (30 mg/kg) had no significant effect on the avoidance or escape responding or either group of rats. This dose of BL-3912A, however, significantly decreased the number of shuttle responses made during the ITI by retired breeder rats. BL-3912A did not increase ITI responding at any other dose in either group of rats. A two-way analysis of variance (Hayes, 1965) of avoidance responding indicated a significant Dose effect ($F = 5.91$, $P < 0.01$, $df = 3/92$) and Age effect ($F = 4.01$, $P < 0.05$, $df = 1/92$), while the Dose × Age interaction was not statistically reliable ($F = 1.33$, $P > 0.05$, $df = 3/92$). An analysis of escape responding revealed a significant Dose effect ($F = 3.74$, $P < 0.05$, $df = 3/92$) and Age effect ($F = 7.00$,

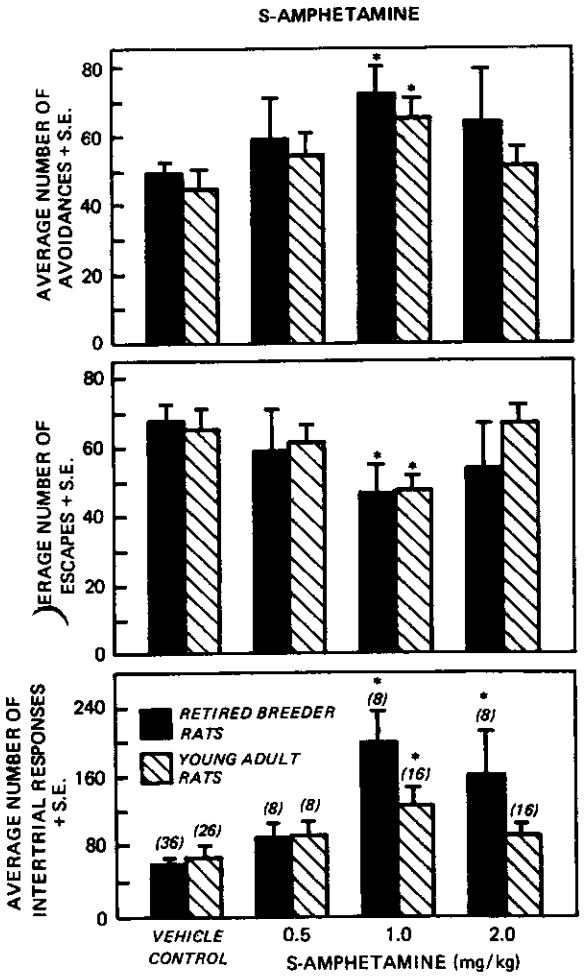

Fig. 3. The effects of various doses of S-amphetamine injected i.p. on shuttle box responding of retired breeder and young adult Long-Evans rats. Data are mean + S.E. avoidances, escapes and intertrial interval (ITI) responses made during 120 massed acquisition trials. Numbers in parenthesis indicate number of subjects per group. Asterisks denote statistical difference from vehicle control of the same age group (t-test, $P < 0.05$)

$P < 0.01$, $df = 1/92$). The Dose × Age interaction for escapes was not statistically significant ($F = 1.88$, $P > 0.05$, $df = 3/92$). An analysis of variance of ITI responding revealed a significant Dose effect ($F = 5.17$, $P < 0.01$, $df = 3/92$), while the Age effect ($F = 0.09$, $P > 0.05$, $df = 1/92$) and Dose × Age interaction ($F = 0.93$, $P > 0.05$, $df = 3/92$) were not significant. Thus, these data indicate that BL-3912A produced dose related facilitation of shuttle box responding, and that the effect was related to the age of the subject tested.

S-Amphetamine also facilitated shuttle box responding of naive retired breeder and young adult rats (Fig. 3). Significant increases in avoidance responding and decreases in escape responses were noted in both groups of rats following 1 mg/kg of S-amphetamine. Although 0.5 and 2 mg/kg of S-amphetamine tended to facilitate active avoidance, the changes were not statistically reliable. Unlike BL-3912A, S-amphetamine increased ITI responding at the dose where facilitation of avoidance was observed (1 mg/kg). A significant increase in ITI activity was also noted in the retired breeder rats following 2 mg/kg. S-Amphetamine also differed from BL-3912A in that it did not affect the retired breeder rats more than the young adults in terms of facilitating avoidance responding. An analysis of variance for avoidances indicated no significant Dose effect ($F = 1.31$, $P > 0.05$, $df = 2/58$), Age effect ($F = 0.40$, $P > 0.05$, $df = 1/58$), or Dose × Age interaction ($F = 0.19$, $P > 0.05$, $df = 2/58$). Likewise, for escapes, there was no significant Dose effect ($F = 1.88$, $P > 0.05$, $df = 2/58$), Age effect ($F = 1.75$, $P > 0.05$, $df = 1/58$), or Dose × Age interaction ($F = 0.44$, $P > 0.05$, $df = 2/58$). There was, however, a significant Dose ($F = 3.16$, $P < 0.05$, $df = 2/58$) and Age effect ($F = 6.62$, $P < 0.05$, $df = 1/58$) for ITI activity following S-amphetamine. The Dose × Age interaction ($F = 2.22$, $P > 0.05$, $df = 2/58$) was not statistically reliable. These data indicate that S-amphetamine altered only ITI activity as a function of dose, and that this effect was related to the age of the rats.

Table 1. Effects of R-DOM on the acquisition of shuttle box responding by retired breeder rats. Average number of responses ± S.E. in 120 trials

Treatment (mg/kg, i.p.)	N	Avoidances	Escapes	Intertrial interval responses
Vehicle (1 mg/kg)	24	46.0 ± 6.5	69.3 ± 6.4	47.3 ± 9.3
R-DOM				
0.5	8	70.9 ± 4.8*	45.9 ± 4.3*	62.4 ± 12.1
1	8	36.1 ± 4.5	74.8 ± 2.9	46.9 ± 9.6
5	8	13.8 ± 7.3*	55.3 ± 9.5	38.6 ± 8.8

* Statistically different from vehicle control (t-test, $P < 0.05$)

Since the retired breeder rats appeared to be more responsive to drug effects than the younger rats in this test, it was decided to test R-DOM in the older rats. The i.p. injection of 0.5 mg/kg of R-DOM significantly increased the number of avoidance responses and decreased the number of escapes, while responses during the ITI were not affected (Table 1). At 1 mg/kg, R-DOM disrupted avoidance responding and increased escapes, but the changes were not statistically significant. The highest dose of R-DOM tested (5 mg/kg) decreased avoidances significantly. Although escape responses and responses during the ITI were decreased, the effect was not statistically reliable. A significant decrease in avoidances associated with little or no change in escape responses indicates

an increase in the number of trials in which the subjects were shocked, but did not escape.

Motor Activity. BL-3912A could be readily differentiated from S-amphetamine and R-DOM in terms of affecting horizontally-directed unacclimated motor activity (Fig. 4). BL-3912A had no consistent effects on activity at 2–20 mg/kg, which overlaps those doses found to be effective in facilitating shuttle box responding (Fig. 2). Significant decreases in activity were noted following 30 and 40 mg/kg of BL-3912A. The effect of BL-3912A on activity was clearly different from the stimulatory effects of S-amphetamine. In addition, S-amphetamine demonstrated an inverted U dose-response curve. That is, although 10 mg/kg of S-amphetamine increased activity, the effect was less than that following 5 mg/kg of S-amphetamine. R-DOM produced dose-related decreases in motor activity at 1–10 mg/kg (Fig. 4). Thus, at doses affecting the acquisition of shuttle box responding, BL-3912A had no significant effect on unacclimated motor activity, while S-amphetamine increased and R-DOM decreased this behavior.

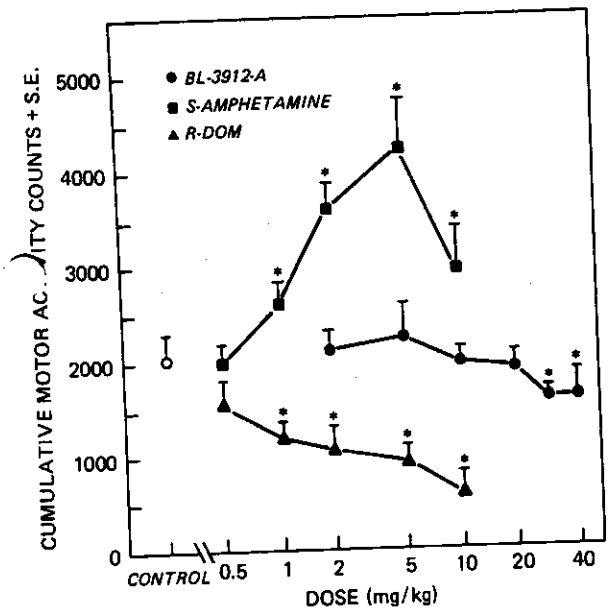

Fig. 4. The effects of BL-3912A, S-amphetamine and R-DOM injected i.p. on unacclimated motor activity of rats. Data are mean + S.E. number of activity counts made in 2 h. There were 6–12 subjects per group. Asterisks denote statistical difference from vehicle control mean (*t*-test, $P < 0.05$)

Unsignalled Continuous Avoidance. The i.p. administration of 10 or 20 mg/kg of BL-3912A did not significantly affect the rate of continuous avoidance responding at any time during the 3-h behavioral session (Fig. 5). S-Amphetamine at 1 and 2 mg/kg significantly increased lever pressing throughout the 3-h session, while 0.5 mg/kg produced significant effects at 30–90 min only. R-DOM significantly increased response rates in 4–5 of the 6 time periods following both 1 and 2.5 mg/kg. Thus, BL-3912A was clearly different from S-amphetamine and R-DOM in affecting continuous avoidance responding of rats.

DISCUSSION

These investigations indicate that substantial changes in CNS activity follow the substitution of an ethyl for

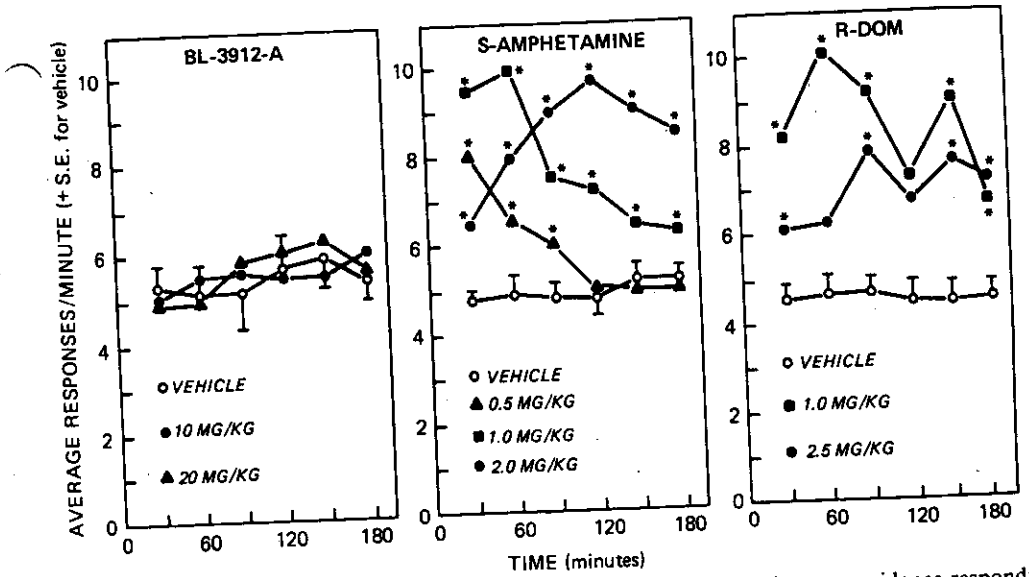

Fig. 5. The effects of BL-3912A, S-amphetamine and R-DOM on continuous avoidance responding of rats. Data are means (+ S.E. for vehicle controls) of response rates for 4 rats responding during 6 successive 30 min time periods. Drugs or vehicle were injected i.p. 15 min prior to 3-h sessions. Asterisks denote statistical difference between drug mean and respective mean of matched vehicle control (matched pair *t*-test, $P < 0.05$)

a methyl group at the α-carbon of the alkyl side chain of the R-DOM molecule (see Fig. 1). The resulting compound R-(-)-2-amino-1-(2,5-dimethoxy-4-methylphenyl)butane or BL-3912A has a psychopharmacological profile that is clearly different from R-DOM. For example, most doses of R-DOM disrupted the acquisition and performance of a shuttle box response and produced dose-related decreases in spontaneous motor activity, while most doses of BL-3912A facilitated avoidance behavior and decreased motor activity at higher doses only. BL-3912A, at doses which facilitate avoidance responding in the shuttle box, had no effect on the rate of responding during the 3-h unsignalled continuous avoidance test. R-DOM, on the other hand, increased the rate of responding throughout most of the session. Rate-increasing effects by R-DOM on unsignalled and signalled continuous avoidance responding have been noted previously (Marquis et al., 1973; Tilson et al., 1975). BL-3912A has also been shown to differ from R-DOM in terms of affecting steady-state levels of brain serotonin (5-HT) and 5-hydroxyindole acetic acid, as well as on the rate of 5-HT turnover (Cavanagh et al., manuscript in preparation). Thus, BL-3912A can be differentiated behaviorally and neurochemically from R-DOM in animals. This corresponds well to initial clinical observations that BL-3912A does not produce hallucinations (clinical files, Bristol Laboratories), which is in contrast to the well known hallucinogenic activity of DOM (Snyder et al., 1968).

Like S-amphetamine, BL-3912A facilitated the acquisition and performance of active avoidance responding. However, other behavioral effects of BL-3912A could be differentiated from those of S-amphetamine. For example, in the shuttle box avoidance task, BL-3912A facilitated avoidance responding without increasing noncontingent activity during the ITI. S-amphetamine increased avoidance responding which was associated with increased activity during the ITI. In addition, BL-3912A decreased spontaneous motor activity at higher doses and had no effect on the rate of continuous avoidance responding, whereas S-amphetamine produced dose-related increases in the frequency of both of these behavioral parameters.

It was noteworthy that BL-3912A facilitated the avoidance responding of retired breeder rats to a greater extent than young adult rats. This observation concerning responsivity of the two groups most likely reflects differences in body weight. As reported by Honecker and Coper (1975) for amphetamine in 200–240 g (young) and 460–600 g (older) rats, experiments in our laboratory have revealed that, although the brain half-life of BL-3912A in young and old rats is approximately the same (about 60 min), the peak concentration of BL-3912A in the brain of old rats is almost twice that found in young rats following the same mg/kg dosage (Cavanagh, unpublished observation). Differences in metabolism or binding of the drug to plasma may also be a factor since we have observed a trend toward a longer plasma half life for BL-3912A in older rats than in younger rats. A similar trend toward longer plasma half-lives in older rats has also been noted for amphetamine (Honecker and Coper, 1975).

BL-3912A presents a psychopharmacological profile that differentiates it from both R-DOM and S-amphetamine. BL-3912A appears to facilitate behavior under selected test conditions without increasing noncontingent motor activity. Such an agent may be useful in the treatment of patients exhibiting cognitive and psychomotor deficits, particularly those who do not tolerate the frank stimulation produced by psychostimulants such as amphetamine.

Acknowledgement. The authors wish to thank Mr. T. G. Baker for assistance in the collection and Mr. L. L. Gaede in the analysis of some of these data.

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Received April 13, 1976; Final Version August 19, 1976