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Potential Psychotomimetics. 2-Amino-1,2,3,4-tetrahydronaphthalene Analogs†

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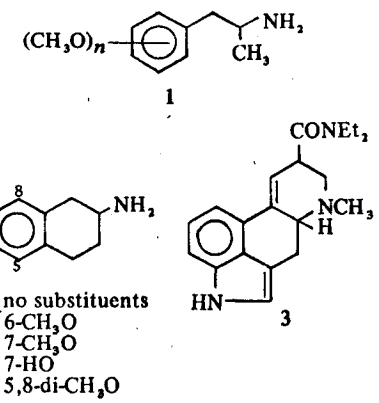
The synthesis of 2-amino-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (5,8-ADT) and evaluation of ADT and 2-amino-1,2,3,4-tetrahydronaphthalene (2-AT) as partial congeners of LSD and restricted conformers of psychotomimetic phenylisopropylamines were undertaken. Theoretical aspects of psychotomimetics are discussed. Both compounds depressed spontaneous motor activity in mice and had a pressor effect in the anesthetized dog. In the Sidman avoidance test in rats, 2-AT was probably hallucinogenic, while 5,8-ADT had only an amphetamine-like, stimulatory effect. In the isolated rat fundus strip, 2-AT caused contraction and was antagonized at low doses by BOL. Agonistic effects were not seen for 5,8-ADT.

In the study of psychotomimetic indolealkylamines, phenylisopropylamines, and lysergic acid analogs, many theories have been advanced to explain the mechanism of psychotomimetic action. In the early literature,[2-5] lysergic acid derivatives were considered phenylethylamines primarily for purposes of exploring the structural features required for oxytocic activity. Later, in studying the structure-activity relationships of psychotomimetic activity, the analogy to the 3-indoleethylamines received widespread attention.[6,7]

The methoxylated phenylisopropylamines 1 are potent psychotomimetics. Since the isopropylamine side chain is flexible, a large number of conformations are possible. Many of these are unfavorable for receptor interaction. Restricting the number of conformations may result in enhanced potency for the drug if one of the remaining conformations is favorable for interaction with the receptor. Using molecular models, it can be shown that 1 and 2-amino-1,2,3,4-tetrahydronaphthalenes (2) are nearly superimposable on the structures of LSD (3), where the aromatic ring of 1 and 2 corresponds to the A ring of 3 and the amino functions correspond to the N-6. Analogs of 2 with the proper activation would be expected to exhibit enhanced potency over the corresponding 1 analog.

Violland, *et al.*,[8] have also considered this approach and prepared 2 analogs. They surveyed the derivatives of 2 which have been synthesized and evaluated for a number of other pharmacological activities.

The importance of the 2-aminotetralin moiety to the



activities of lysergic acid derivatives was suggested by Marini-Bettolo and coworkers,[9] as a result of the study of 2 analogs as oxytocic drugs, and by Kang and Green,[10] as based on stereochemical and electronic considerations of psychotomimetic effects. Recently, Green and coworkers‡ have predicted psychotomimetic activity in 2b–d using quantum mechanics. In their experimental studies 2d showed cross tolerance with mescaline, as does LSD. 2b and 2c, which were predicted to be mescaline-like, resembled amphetamine in their central effects. The central effects of 2a have been examined by a number of groups who characterized the effects as amphetamine-like.

In selecting molecules for synthesis and evaluation, we have considered points of electron density as suggested by

†For a preliminary report, see ref 1.

‡J. P. Green, K. Dressler, and N. Khazan, unpublished results.

the correlations of Chothia and Pauling.[11] Specifically, points of density corresponding to the position of the indole nitrogen and the 9,10 double bond in LSD were deemed important. 2-Amino-5,8-dimethoxytetralin (2e, 5,8-ADT) satisfies these requirements and, in addition, its open chain analog, 2,5-dimethoxyphenylisopropylamine, is a potent psychotomimetic in man. This A,C-ring LSD congener approach is in contrast to some current theories[6,7] of psychotomimetic activity which suggest that 1 analogs somehow mimic the indole nucleus of 3 by hydrogen bonding of the amino group to the π electrons of the aromatic ring. This suggestion has been previously opposed on theoretical grounds. The work of Green and coworkers[‡] also argues against the indole-like theories.

Experimental Section

A. Chemistry. 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 Midwest Microlab Ltd., Indianapolis, Ind., and by the Division of Medicinal Chemistry, University of Iowa. Where analyses are indicated by symbols of the elements, the analytical results obtained were within ±0.4% of the theoretical values. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian \ssociates T-60 spectrometer using tetramethylsilane as an internal standard.

3-(2′,5′-Dimethoxybenzoyl)propanoic Acid Methyl Ester (I). To a cold solution of 9.2 g (0.067 mol) of *p*-dimethoxybenzene and 10.0 g (0.067 mol) of 3-carbomethoxypropionyl chloride[12] in 200 ml of methylene chloride was added 38.2 g (0.146 mol) of $SnCl_4$. The mixture was stirred for 5 hr while warming to 25° at which time it was poured onto ice–water and extracted with ether. The organic extracts were washed with 10% HCl, 5% $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated. The residue was recrystallized from hexane–ether: yield, 12.0 g (71%); mp 51–53° (lit.[13] mp 52–53°).

4-(2′,5′-Dimethoxyphenyl)butanoic Acid Methyl Ester (II). To a slurry of 0.5 g of 5% Pd/C in 25 ml of H_2O was added 5.0 g (0.02 mol) of I, 75 ml of MeOH, and 0.9 ml of 72% $HClO_4$. Reduction occurred in less than 2 hr at 60 psig of H_2. The solution was neutralized with KOAc, filtered, reduced in volume to one-third, taken up in water, and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated. The product was distilled: yield, 3.7 g (75%); bp 120–123° (0.25 mm) [lit.[14] bp 180° (13 mm)].

4-(2′,5′-Dimethoxyphenyl)butanoic Acid (III). A solution of 5 g (0.021 mol) of II and 3.4 g (0.084 mol) of NaOH in 15 ml of H_2O was refluxed for 30 min. The solution was made acidic with concentrated HCl and cooled. The crystalline product was filtered off and air-dried: yield, 4.7 g (quantitative); mp 65–67° (lit.[15] mp 64–65°).

5,8-Dimethoxy-1-tetralone (IV). Following the method of Moore and Rahm,[15] a mixture of 10 g (0.045 mol) of III and 200 g of PPA was heated on steam for 45 min. After pouring over ice, the mixture was extracted with ether which was then washed with water, dried (Na_2SO_4), and evaporated. The residue was crystallized from ether–hexane: yield, 7.15 g (78%); mp 58–62° (lit.[15] mp 58–62°).

5,8-Dimethoxy-2-bromo-1-tetralone (V). Using a modification of Wilds[16] procedure, 8.8 g (0.055 mol) of Br_2 was added to a cold solution of 10.3 g (0.05 mol) of IV in a 1:1 mixture of Et_2O and $CHCl_3$. The mixture was stirred for 3 hr, then washed with water, dilute $NaHSO_3$, dilute $NaHCO_3$, and water again, dried ($CaSO_4$), and evaporated. The product was recrystallized from Et_2O: yield, 11.7 g (82%); mp 99–101°. *Anal.* ($C_{12}H_{13}O_3Br$) C, H.

5,8-Dimethoxy-2-nitro-1-tetralone (VI). After the method of Kornblum,[17] 4 g (0.014 mol) of V was added to a solution of 1.9 g (0.028 mol) of $NaNO_2$ and 2.4 g (0.015 mol) of phloroglucinol in 12 ml of DMSO and stirred for 2 hr. The mixture was taken up in 100 ml of H_2O and extracted with CH_2Cl_2. The extracts were washed with water, dried ($MgSO_4$), and evaporated. The product was recrystallized from absolute EtOH: yield, 2.9 g (82%); mp 162–164°. *Anal.* ($C_{12}H_{13}NO_5$) C, H, N.

5,8-Dimethoxy-2-amino-1-tetralol Hydrochloride (VII). A warm solution of 2.5 g (0.01 mol) of VI in 150 ml of benzene was added dropwise to 26 g of a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (Red-Al). After refluxing for 6 hr, the reaction was decomposed with 70 ml of H_2O and filtered. The alumina was washed with Et_2O. The combined washings and filtrate were evaporated. The residue was dissolved in benzene and the hydrochloride salt was precipitated with HCl gas. The product was recrystallized from *i*-PrOH: yield, 1 g (39%); mp 199–202° (erythro and threo mixture). *Anal.* ($C_{12}H_{18}NO_3Cl$) C, H, N.

5,8-Dimethoxy-2-aminotetralin Hydrochloride (VIII). A mixture of 1.0 g (0.004 mol) of VII, 0.5 g of 10% Pd/C catalyst, 20 ml of glacial HOAc, and 0.5 ml of 72% $HClO_4$ was heated to 60° and shaken in a 500-ml Parr bottle at 60 psig. Heating was stopped after 3 hr and the reaction was complete in 4 hr. The mixture was filtered and 1.6 g of KOAc was added. After filtering again, the solvent was evaporated; the residue was taken up in water, made basic with 10% NaOH, and extracted with ether. The ether was evaporated and the hydrochloride salt was precipitated from dry ether with HCl gas. The product was recrystallized from ethanol–ether: yield, 0.55 g (59%); mp 265.5–267.5° dec. *Anal.* ($C_{12}H_{18}NO_2Cl$) C, H, N.

B. Spontaneous Activity Studies. Male, Swiss-Webster mice, 20–28-g weight, were used in this evaluation procedure. Mice were housed in cages of ten mice each and allowed free access to food and water. A 24-hr stabilization period was observed for each new group entering the laboratory. All drugs were prepared in saline at a concentration which allowed administration of no more than 0.01 ml of fluid per gram of body weight. Through each experiment room temperature was maintained between 26 and 28°.

Spontaneous activity patterns were obtained by using the Model S selective activity meter (Columbus Instruments).[18] Mice were randomly divided into groups of three per cage. The mice remained in this original cage throughout the entire experiment. Test compound or saline (control) (20 μmol/kg) was randomly assigned and administered intraperitoneally to each group. Activity was measured during a 1-min counting period at 5, 10, 20, 30, 40, 50, 60, 90, and 120 min following injection and recorded as counts per minute. The data for each time were analyzed by analysis of variance, completely random design. The mean for each dose at a particular time was then compared to control at that time at a least significant difference (LSD) test. These statistical methods are described by Steel and Torrie.[19]

C. Blood Pressure Studies. Mongrel dogs weighing 8–13 kg were anesthetized with barbital sodium (200 mg/kg). The right carotid blood pressure was monitored using a Statham pressure transducer and recorded using an Offner RS dynograph. All injections were made into the cannulated right femoral vein. Each dog received three different doses of each compound. The injections were made only when the blood pressure had returned to control levels. Five dogs were used for each compound.

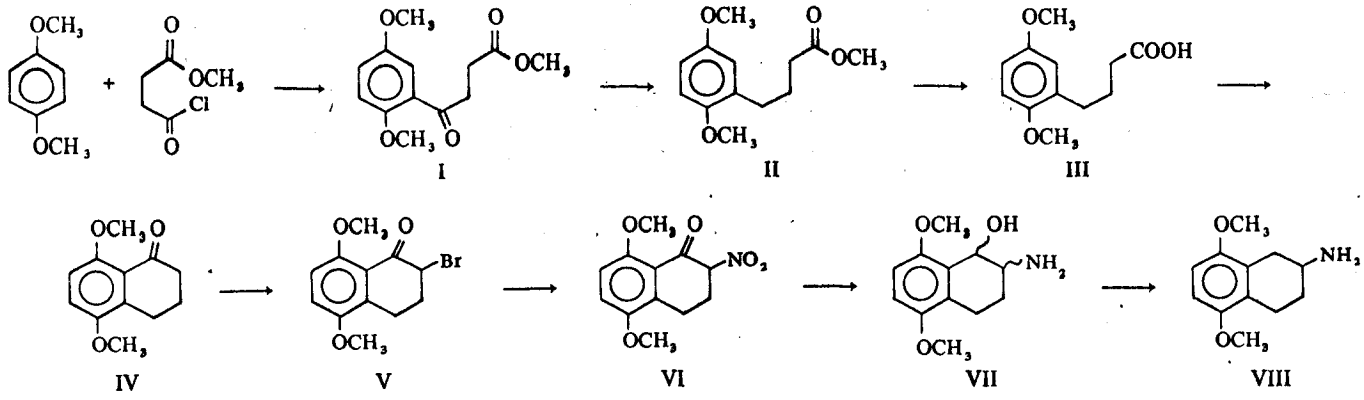
D. Conditioned Avoidance Studies. A discriminated Sidman avoidance schedule, Smythies, *et al.*,[20] with a response–shock interval of 30 sec and shock–shock interval of 10 sec was used in this study. A rat, enclosed in a standard Skinner box, receives a shock lasting 0.5 sec every 10 sec unless it makes a lever press which postpones the next shock for 30 sec. During the last 10 sec of this response–shock interval a discriminative stimulus light is turned on inside the Skinner box. The stimulus remains on until the rat makes a response which initiates a new cycle. All subjects were trained until at least 85% of their responses fell within the discriminative stimulus period.

Throughout the experiment subjects were tested for 130 min at the same time each day. The experimental session was subdivided into a 15-min "warm-up" period, a 15-min preinjection or control period, and a 100-min test period. Each subject served as his own control and was injected with the physiological saline vehicle on pre- and postdrug days. All injections were given intraperitoneally in a volune of 0.01 ml/10 g body weight after the preinjection control period. The subject was then placed in the experimental chamber for the 100-min test period. Each drug test was separated from the previous one by at least ten experimental sessions.

All interresponse times (IRT) were recorded sequentially thus indicating the exact timing of the response within the experimental cycle. Four types of response are possible: (1) a *burst* response, *i.e.*, one occurring 0–3 sec after the previous one; (2) a *premature* response, *i.e.*, one occurring after 3 sec but before the onset of the discriminative stimulus; (3) an *efficient* response, *i.e.*, one occurring during the discriminative or conditioned stimulus (CS) and before shock; or (4) a *late* response, *i.e.*, one occurring after the animal has taken shock. The distribution of responses in the ten consecutive 1-sec intervals of the CS was also calculated.

E. Studies at Serotonin Receptors. Responses to drugs were studied on isolated rat fundus strips prepared from albino rats (Sprague–Dawley) according to the method of Vane.[21] The fundus

Scheme I



strips were suspended in 5-ml isolated organ baths and bathed in Krebs–Henseleit solution containing one-fourth the usual calcium concentration. The temperature of the bath was maintained at 37° and the Krebs–Henseleit solution was oxygenated with 95% O_2–5% CO_2. Isotonic contractions under a 1-g load were magnified tenfold and recorded on a kymograph. All tissues were allowed to equilibrate in the isolated organ bath for 30–45 min before initiating the experiment. The maximum contraction of all tissues to serotonin was established by adding serotonin in cumulative amounts by micropipets. Responses to AT and ADT were also studied by adding them to the bath in cumulative amounts by micropipets. When 2-bromolysergic acid diethylamide (BOL) was used as an antagonist, it was incubated 10 min with the tissue prior to adding either serotonin, AT, or ADT to the bath.

Results

The synthesis of 5,8-ADT is presented in Scheme I. The advantage of this route over previous methods for making 2-aminotetralins is the convenient preparation of the crystalline 2-bromo-1-tetralone and the 2-nitro-1-tetralone. In addition, 1-tetralone oximes containing the 8-methoxyl group failed to form the oxime tosylate which is needed for the Neber rearrangement.

The effect on spontaneous activity in mice is shown in Figure 1. The open-chain analogs, dextroamphetamine sulfate and (±)-2,5-dimethoxyamphetamine hydrochloride, were compared with the cyclic compounds at equimolar doses (20 μmol/kg). With the former compounds, a strong stimulant response began 10 min after injection. The latter compounds depressed the animals 5 min after injection. The 2-aminotetralin-treated animals attained control levels within 20 min while in those treated with the 5,8-ADT the effect was of longer duration. Neither compound caused a post-depression stimulation phase. The animals while under the effects of 2-AT and 5,8-ADT appeared to be capable of moving but simply did not.

Both 2-AT and 5,8-ADT are quite potent pressor agents in the anesthetized dog. The results are shown in Table I. Both agents required 20–40 min for the blood pressure to return to control level after administration of the compounds. The pressor responses produced by both compounds were blocked by phentolamine (2 mg/kg). Cocaine (5 mg/kg), administered intravenously, blocked completely the pressor response produced by 2-AT and reduced at least 75% of the pressor produced by 5,8-ADT. The pressor responses were enhanced by prior administration of hexamethonium bromide (5 mg/kg).

The Sidman avoidance schedule test has been useful in differentiating the stimulant and hallucinogenic components of various amphetamine derivatives.[22] The compounds (2-AT and 5,8-ADT) were administered at two dose levels in each of two highly trained rats and compared with (±)-amphetamine sulfate and saline control. The IRT data were multiplexed onto punched paper tape and classified, by computer, into the response categories. Table II shows this computed data. 2-Aminotetralin does not show a stimulant component but is probably hallucinogenic. 5,8-ADT has only stimulant properties identified by the marked increase

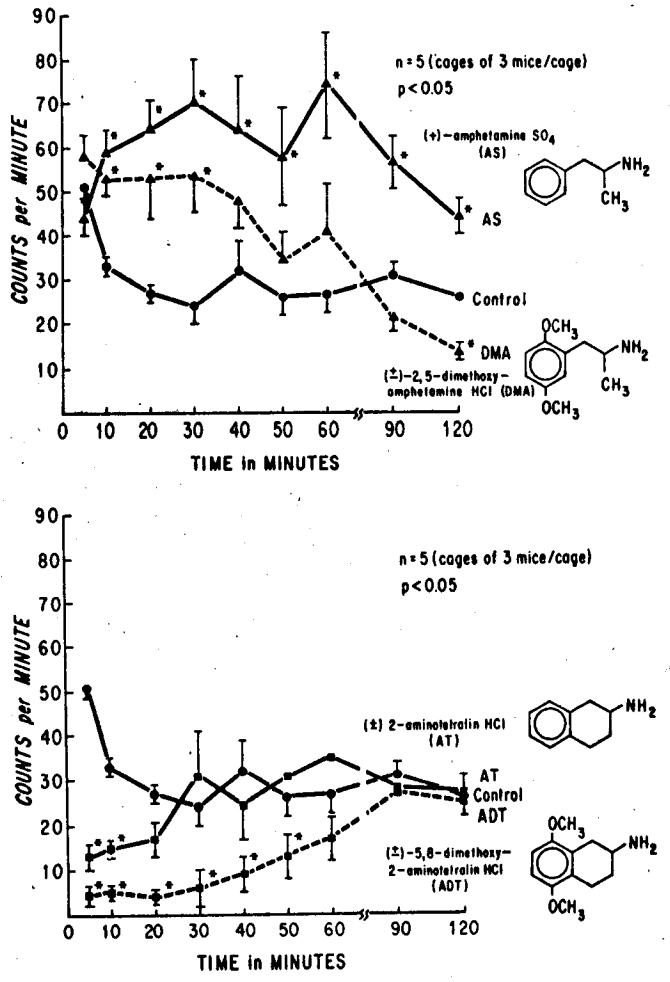


Figure 1. Spontaneous activity in mice at 20 μmol/kg.

Table I. Pressor Responses of AT and ADT in the Anesthetized Dog

Compd	Dose, μg/kg	mm rise ± S.E.
AT	50	15 ± 3
	100	52 ± 8
	200	112 ± 10
ADT	50	42 ± 7
	100	50 ± 11
	200	63 ± 12

Table II. Sidman Avoidance Testing in the Rat[a]

Drug	Dosage, mg/kg	B	P	E	L	Conditioned stimulus 1	2	3	4	5	6	7	8	9	10
						A. Rat 8									
Saline		13	9	240	12	5	17	41	58	39	29	21	18	8	4
AS	2	87	69	128	11	21	33	23	13	11	10	8	5	2	2
2-AT	2	28	53	145	57	10	33	40	36	12	4	2	2	2	4
2-AT	5	46	83	126	82	11	23	26	20	18	16	6	2	2	2
5,8-ADT	2	41	50	177	18	18	39	32	24	17	19	15	8	3	2
5,8-ADT	5	84	54	147	17	17	30	21	26	12	11	13	8	7	2
5,8-ADT	10	103	167	81	53	11	21	12	13	9	6	3	2	2	2
Saline		12	11	211	15	5	17	53	61	27	21	14	8	3	2
						B. Rat 9									
Saline		10	7	227	19	4	18	32	48	47	35	21	11	7	4
AS	2	53	74	142	6	27	39	24	19	13	8	7	2	1	2
2-AT	2	38	58	152	46	8	17	36	33	26	16	7	4	3	2
2-AT	5	69	53	134	90	5	22	37	38	11	10	2	3	3	3
5,8-ADT	2	8	12	193	20	8	44	35	25	27	25	16	5	5	3
5,8-ADT	5	26	49	163	36	28	37	38	27	15	6	7	3	0	2
5,8-ADT	10	48	108	119	76	36	32	18	12	10	5	2	1	1	2
Saline		5	9	221	16	3	15	30	49	44	37	18	14	8	3

[a] Absolute number of responses for each 100-min session, classified as Burst (B), Premature (P), Efficient (E), and Late (L), followed by the interresponse time distribution within the conditioned stimulus.

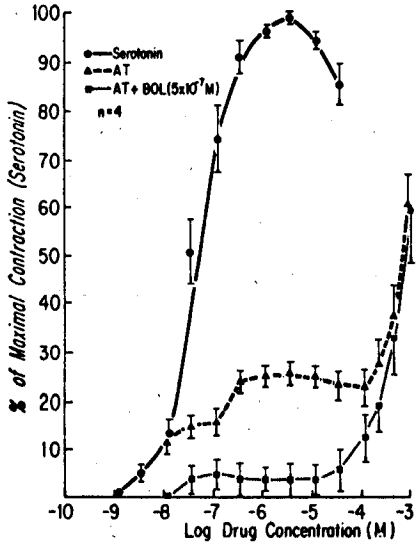


Figure 2. Rat fundus strips. A comparison of the dose-response curves of serotonin, AT, and AT in the presence of 2-bromolysergic acid diethylamide (BOL). Note the biphasic nature of the AT dose-response curve.

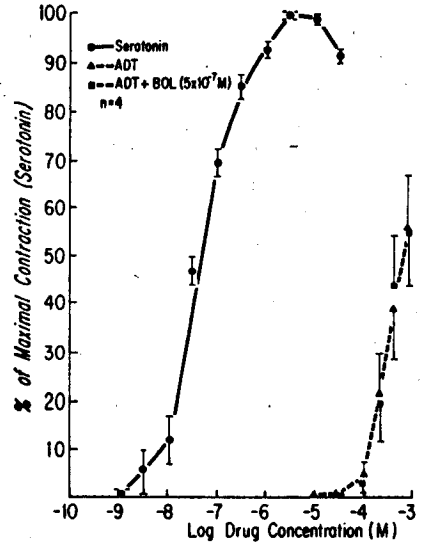


Figure 3. Rat fundus strips. A comparison of the stimulant action of serotonin, ADT, and ADT in the presence of 2-bromolysergic acid diethylamide (BOL). Note that BOL does not antagonize responses to ADT.

in burst and premature responses. 2,5-Dimethoxyamphetamine was not included in this Sidman avoidance study, since it is a psychotomimetic in man but elicits only a stimulant response in rats.

The effects of 2-AT and 5,8-ADT on the isolated rat fundus strips are shown in Figures 2 and 3 in comparison with serotonin (5-HT) (Figure 4). Only 2-AT contracted the fundus strip in low concentrations. There appeared to be two components involved in the contractions elicited by 2-AT, one at low concentrations and another at high concentrations. Only the contractions at lower concentrations appeared to be sensitive to antagonism by 2-bromolysergic acid diethylamide (BOL). High concentrations of 5,8-ADT contracted the fundus strip, and these were not antagonized by BOL. Also, 2-AT ($1.1 \times 10^{-4} M$) antagonized responses to 5-HT from three- to tenfold but did not antagonize responses to acetylcholine (three experiments). The complex nature of the 2-AT dose-response curve suggests that at low concentrations it may be acting as a partial agonist on 5-HT receptors. While 5,8-ADT did not function as an agonist at low concentrations, concentrations of 8.4 X

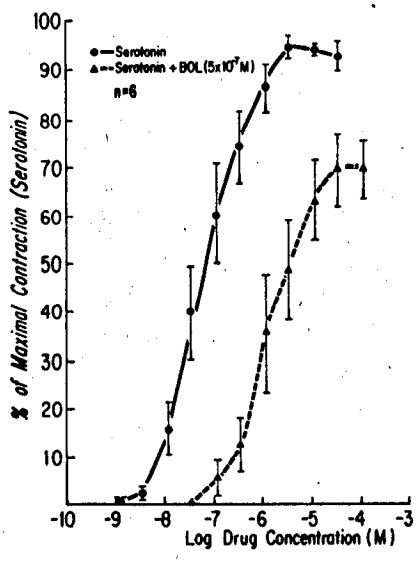


Figure 4. Rat fundus strips. A comparison of the stimulant action of serotonin alone and in the presence of 2-bromolysergic acid diethylamide (BOL).

10^{-5} *M* antagonized responses to both serotonin and acetylcholine greater than 30-fold (three experiments).

Discussion

5,8-ADT has a complex profile of effects as demonstrated by the data presented. The apparent conflict in results between the effect on spontaneous motor activity and the effect on Sidman avoidance is rationalized on the basis of the differences in responses measured and the species used. Whether or not 5,8-ADT is psychotomimetic in man like its open-chain analog, 2,5-dimethoxyamphetamine, cannot be answered by these studies. The fact that both 2-AT and 5,8-ADT release norepinephrine from adrenergic nerve terminals and that 5,8-ADT has some direct α-adrenergic stimulatory activity in the anesthetized dog is consistent with the results from the Sidman avoidance studies. Phentolamine blocks direct α effects, while cocaine inhibits indirect acting agents. The contention of hallucinogenic activity for 2-AT based on the Sidman avoidance studies is consistent with the results on serotonin receptors. The effect observed with psychotomimetics related to LSD and mescaline can be blocked by serotonin antagonists. 2-AT exhibits agonistic effects at low concentrations. The psychotomimetic effects of DOM, 2,5-dimethoxy-4-methylamphetamine, are also blocked by serotonin antagonists.[23] Pharmacological studies on 2-AT and 5,8-ADT are continuing in order to understand the mechanisms by which they cause their varied effects.

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Isoquinolines. 3.[1] 3-Aminoisoquinoline Derivatives with Central Nervous System Depressant Activity†

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A series of novel 3-amino-4-arylisoquinoline (2) and 3-amino-4-benzylisoquinoline derivatives 3 was synthesized and evaluated primarily for their CNS effects. The method used for the synthesis of the 3-aminoisoquinolines 2 and 3 involved the alkylation of the appropriate α-cyano-*o*-tolunitrile 4 followed by an acid-catalyzed cyclization to yield the 4-aryl- or 4-benzyl-substituted isoquinolines 2 and 3. Two compounds in this series, 3-amino-4-(*p*-aminophenyl)isoquinoline (10) and 4-(*p*-acetamidophenyl)-3-aminoisoquinoline (11), were shown to have similar and marked central nervous system activity, characterized by general CNS depression and anticonvulsant activity.

In the course of a routine pharmacological screen of 3-amino-4-methylisoquinoline (1) primarily prepared as a potential antimalarial drug,[2] we observed considerable CNS activity in the primary mouse screen.[3] In order to assess the effect of 4-phenyl and 4-benzyl substitution in this series, the novel 3-amino-4-phenylisoquinoline (2) and 3-amino-4-benzylisoquinoline (3) derivatives were synthesized and evaluated. This communication presents the synthesis and pharmacological evaluation of this series of compounds.

Chemistry. The method used for the synthesis of the 3-aminoisoquinolines reported in Tables II and III involved the alkylation of α-cyano-*o*-tolunitrile (4) followed by

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