the series. All of the compounds effectively lowered the body temperature of normal mice (Table III); the more active derivatives (**1**, **2**, **3**, and **5**) had about the same potency as thioridazine. Compounds **1**, **2**, **3**, and **5** were good antagonists of apomorphine-induced cage climbing and were about as active as thioridazine in this test. Two compounds (**1** and **4**) antagonized *d*-amphetamine-induced aggregation toxicity as effectively as thioridazine; the others were much less active in this test. Of particular significance was the inability of the subject compounds to produce catalepsy in mice at low doses, since it has been suggested that there may be a correlation between the production of catalepsy in animals and of extrapyramidal stimulation in man.[8] Both thioridazine and haloperidol are active in this test.

The most active member of the series, the 10-methoxy derivative (**3**), was about twice as active in the mouse behavior tests and had a much more favorable therapeutic index than thioridazine. Compound **4** was qualitatively different from the other members of the series. It did not cause loss of righting reflex or traction at the highest dose tested. It was only slightly active in the chimney and fighting behavior tests, and in antagonizing apomorphine cage climbing or potentiating EtOH and pentobarbital narcosis. It was, however, highly active in the dish and pedestal tests, in inducing ptosis, and in antagonizing *d*-amphetamine-induced aggregation toxicity and nicotine-induced TE and D.

It is interesting that, although the CNS activity of the compounds is qualitatively much different from that of the hexahydroazepino[4,3-*b*]indoles from which they were derived, the variation in potency with substitution on the indole nucleus seems to be similar. Methoxyl substitution at C-10 or methyl substitution at N-6 potentiated activity while substitution at other locations on the aromatic ring had little effect or decreased potency relative to the parent compound.

A comprehensive discussion of the pharmacology of **1** will be published at a later date.

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(8) S. Irwin, *Psychopharmacologia*, **9**, 259 (1966).

Analogs of α-Methylphenethylamine (Amphetamine). I. Synthesis and Pharmacological Activity of Some Methoxy and/or Methyl Analogs[1]

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A series of amphetamine derivatives substituted on the benzene ring with MeO and/or Me groups was synthesized. The pharmacological activity of these compounds was evaluated for toxicity, effects on barbiturate sleeping time, and ability to disrupt mouse behavior. Those which were active in behavioral disruption included 1-(2,5-dimethoxy-4-methylphenyl)-, 1-(2,4,5-trimethoxyphenyl)-, 1-(2,4-dimethoxy-3-methylphenyl)-, and 1-(3,4-methylenedioxyphenyl)-2-aminopropanes. In addition, 1-(3-methoxy-4-methylphenyl)-2-aminopropane, structurally resembling 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), was found to be just as active and long lasting as DOM. The amphetamine derivatives either diminished or prolonged the barbiturate sleeping time. 1-(3,4-Methylenedioxyphenyl)-2-aminopropane and DOM were equally effective in decreasing the sleeping time, while 1-(2,4,6-trimethylphenyl)- and 1-(3,5-dimethyl-4-hydroxyphenyl)-2-aminopropanes were the most active in the potentiation of the sleeping time.

For many years, there has been interest in the structure of some known hallucinogens. Smythies, *et al.*,[2] have studied the structure–action relationship of a number of mescaline analogs on the behavior of rats. Some ring-substituted amphetamine derivatives have been studied in humans by Shulgin,[3] and in animals by Smythies, *et al.*,[4] and Beaton, *et al.*[5] Snyder and Richelson[6] proposed a common configuration for the action of different classes of some hallucinogens on the basis of steric factors. A correlation between hallucinogenic activities of these different classes of compounds with the electronic properties of the phenyl or indole nucleus was also presented by Snyder and Merril.[7]

In this study, a series of compounds related to amphetamine (**1**) and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM or STP, **2**) was synthesized and their pharmacological activity was evaluated for their effect on barbiturate sleeping time and their ability to disrupt mouse behavior. It was hoped that evaluation of the compounds in this series would provide information as to which of the substituents on DOM is essential for its action. These compounds included 1-(2-methoxy-4-methylphenyl)-2-aminopropane (**3**), 1-(3-methoxy-4-methylphenyl)-2-aminopropane (**4**), and

(1) This work was supported by Grants MH-12959, U. S. Public Health Service, Bethesda, Md., and by the Britton Fund.

(2) J. R. Smythies, R. J. Bradley, V. S. Johnston, F. Benington, R. D. Morin, and L. C. Clark, Jr., *Psychopharmacologia*, **10**, 379 (1967).

(3) (a) A. T. Shulgin, *Experientia*, **20**, 366 (1964); (b) *Nature*, **201**, 1120 (1961).

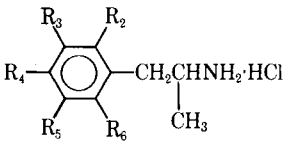
(4) J. R. Smythies, V. S. Johnston, R. J. Bradley, F. Benington, R. D. Morin, and L. C. Clark, Jr., *ibid.*, **216**, 128 (1967).

(5) J. M. Beaton, J. R. Smythies, F. Benington, R. D. Morin, and L. C. Clark, Jr., *ibid.*, **220**, 800 (1968).

(6) S. H. Snyder and E. Richelson, *Proc. Natl. Acad. Sci. U. S.*, **60**, 206 (1968).

(7) S. H. Snyder and C. R. Merril, *ibid.*, **54**, 258 (1965).

TABLE I
PHYSICAL CONSTANTS OF



No.	R_2	R_3	R_4	R_5	R_6	Yield,[a] %	Mp, °C	Formula	Analyses
3	OCH_3	H	CH_3	H	H	38	162–162.5[b]	$C_{11}H_{18}ClNO$	C, H, N
4	H	H	CH_3	OCH_3	H	58	182–183[b]	$C_{11}H_{18}ClNO$	C, H, N
5	OCH_3	H	H	OCH_3	H	26	111.5–112.5[c,d]		
9	OCH_3	H	OCH_3	OCH_3	H	40	188–190.5[e]		
10	H	OCH_3	OCH_3	OCH_3	H	36	216–217[f]	$C_{12}H_{20}ClNO_3$	C, H, N
11	H	OCH_3	OCH_3	H	H	22	147.5–148[g,h]		
12	H	OCH_3	H	OCH_3	H	32	160–161[g,i]	$C_{11}H_{18}ClNO_2$	C, H, N
13	OCH_3	OCH_3	H	H	H	46	154–156	$C_{11}H_{18}ClNO_2$	C, H, N
14	OCH_3	CH_3	OCH_3	H	H	25	163–164[g]	$C_{12}H_{20}ClNO_2$	C, H, N
15	H	CH_3	OCH_3	CH_3	H	20	255–257[g]	$C_{12}H_{20}ClNO$	C, H, N
16	H	CH_3	OH	CH_3	H	14	224–225[c]	$C_{11}H_{18}ClNO$	C, H, N
17	CH_3	H	CH_3	H	CH_3	18	269–271[c]	$C_{12}H_{20}ClN$	C, H, N
18	H	O_2CH_2		H	H	35	181–182[j]		

[a] Over-all yield. [b] Recrystallized from MeOH–Et_2O. [c] Recrystallized from *i*-PrOH–Et_2O. [d] R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, **62**, 161 (1940), reported mp 117.5°, prepared by the reaction of the corresponding benzaldehyde with diethyl malonate and subsequent conversion of this product into **9**. [e] Lit.[11] mp 187°. [f] Lit.[12] mp 208–209°, prepared by the reduction of 1-(3,4,5-trimethoxyphenyl)-2-nitropropene which was obtained from the reaction of 1-(3,4,5-trimethoxyphenyl)propene and $C(NO_2)_4$. [g] Recrystallized from EtOH–Et_2O. [h] Identified by its sulfate salt, mp 312–315°. A. W. Schrecker, *J. Org. Chem.*, **22**, 33 (1957), reported mp 313–315°, prepared by a Curtis or Schmidt rearrangement of α-methylhydrocinnamic acid. [i] T. A. Gorindachari and M. V. Lakshmikantham, *Proc. Indian Acad. Sci.*, **46A**, 406 (1957), reported mp 147°. [j] C. Mannich and W. Jacobsohn, *Ber.*, **43**, 189 (1910), reported mp 180–181°.

1-(2,5-dimethoxyphenyl)-2-aminopropane (**5**) which resulted from the systematic removal of substituents, one at a time, from DOM.

Chemistry.—The amines were prepared by the condensation of nitroethane with the corresponding aldehyde followed by $LiAlH_4$ reduction of the resulting phenylnitropropene. No attempt was made to purify the intermediate phenylnitropropenes. The aldehyde required for the preparation of **4** was obtained from 3-methoxy-*p*-toluic acid. Treatment of the acid with $SOCl_2$ afforded the acid chloride, which was then reduced to 3-methoxy-*p*-tolualdehyde.

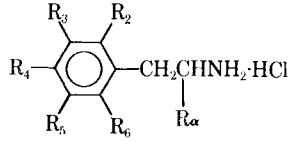
Synthesis of **3** was carried out as shown in Scheme I. The carbonyl group of 2-methoxy-*p*-tolualdehyde (**8**) was derived by replacement of the bromine atom of 3-methoxy-4-bromotoluene (**6**). The Grignard reagent from **6** was treated with triethyl orthoformate to give the acetal **7**. Acid hydrolysis of this acetal freed the carbonyl group affording the aldehyde **8**. The incomplete conversion of **6** to the Grignard reagent resulted in a low yield of **8**. The steric hindrance on the Br atom caused by the *o*-OMe substituent could account for this, although electronic factors could also be important. The use of triethyl orthoformate for the preparation of aldehydes has been reported.[8] This method would have been satisfactory if the Grignard reagent could have been prepared in a higher yield.

Table I lists physical constants of the substituted amphetamines.

Pharmacological Studies.—The ability of compounds to disrupt mouse behavior was determined by a swim maze test. At a comparative dose of 50 μmoles/kg, compounds which were active in our swim test were 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, **2**), 1-(3-methoxy-4-methylphenyl)-2-aminopropane (**4**), 1-(2,4,5-trimethoxyphenyl)-2-aminopropane (**9**), 1-(2,4-dimethoxy-3-methylphenyl)-2-aminopropane (**14**), 1-(3,4-methylenedioxyphenyl)-2-aminopropane (**18**), and 3,4,5-trimethoxyphenethylamine (mescaline, **19**) (Table II). This dose appeared to be the optimum for DOM, as in our test system doses below 50 μmoles/kg did not have a distinctive effect and no obvious increase in behavioral disruption was observed for those above 50 μmoles/kg. Of the above mentioned compounds, **2**, **9**, and **19** have been reported to cause hallucinations in humans.[3] Furthermore, the behavior-disrupting activity of **9** and **19** has been demonstrated on animals using the Sidman avoidance schedule.[2,4] It seems, therefore, that as a qualitative measurement of the disruption of animal behavior our swim maze test is applicable. Our data showed that the action of **2** and **18** were relatively long, whereas that of **19** was rather transient. In the latter case, the demethylation of one or both OMe groups and the subsequent conjugation of the resulting phenolic OH would probably account for its short action. It was rather interesting to find **14** so active, although its action was very short. Even more interesting were the data obtained from **4**. This compound not only possessed behavior-disrupting activity comparable to that of **2**, but the duration of its effect was also shown to be as long. Since **4** was derived from the removal of 2-OMe from **2**, and, in addition, the two 2-methoxylated compounds **3** and **5** were not active, the presence of 2-OMe in **2** did not seem to be responsible for the activity of **2**. In addition, judging from the finding that 1-(3,4-dimethoxyphenyl)-2-aminopropane (**11**), which differed from **4** only by the *para* substituent, was devoid of activity, the *p*-methyl group of **2** appeared to be essential for its action. This *p*-Me could be envisioned to do at least one of the

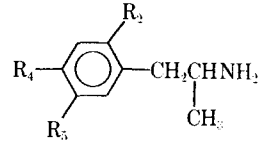
(8) G. B. Bachman, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 323.

TABLE II
PHARMACOLOGICAL PROPERTIES OF



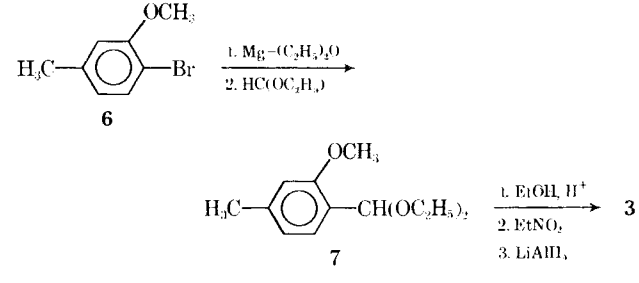
								Sleeping time[a]					Swim maze test									
													10 min					30 min				
							Mouse			Recovery			Completion		Error			Completion		Error		
No.	R_α	R_2	R_3	R_4	R_5	R_6	LD_{50} ± SE, mg/kg	Mean ± SE, min	p	Dissociation	Potentiation	time[b] sec	Grade[c] X	E[d]	Y[e]	$X+2Y$	time[b] sec	Grade[c] X	E[d]	Y[e]	$X+2Y$
1	CH_3	H	H	H	H	H		18.4 ± 2.4	<0.001	1		−1	3−	1.0	1+	1−	−1	3−	1.0	1+	1−
2	CH_3	OCH_3	H	CH_3	OCH_3	H	89 ± 4.2	31.0 ± 1.9	<0.001	3		42	3+	3.6	3+	9+	28	1+	3.1	3+	7+
3	CH_3	OCH_3	H	CH_3	H	H	92 ± 4.2	59.0 ± 6.2	NS[f]	NC[g]	NC	11	1−	1.9	1+	1+	4	2−	1.7	1+	0
4	CH_3	H	H	CH_3	OCH_3	H	96 ± 3.6	36.1 ± 6.6	NS	NC	NC	33	2+	3.7	3+	8+	48	3+	4.2	4+	11+
5	CH_3	OCH_3	H	H	OCH_3	H	135 ± 7.9	51.8 ± 7.0	NS	NC	NC	2	2−	1.5	1+	0	9	2−	2.4	2+	2+
9	CH_3	OCH_3	H	OCH_3	OCH_3	H	180 ± 13.3	36.8 ± 1.9	<0.02	6		30	2+	3.3	3+	8+	1	2−	1.8	1+	0
10	CH_3	H	OCH_3	OCH_3	OCH_3	H	250 ± 14.6	34.6 ± 2.4	<0.01	5		21	1+	2.1	2+	5+	21	1+	1.8	1+	3+
11	CH_3	H	OCH_3	OCH_3	H	H	210 ± 9.7	47.3 ± 4.0	NS	NC	NC	4	2−	1.8	1+	0	6	2−	2.1	2+	2+
12	CH_3	H	OCH_3	H	OCH_3	H	155 ± 9.3	50.0 ± 4.7	NS	NC	NC	12	1−	2.1	2+	3+	20	1+	2.5	2+	5+
13	CH_3	OCH_3	OCH_3	H	H	H	108 ± 7.9	64.6 ± 5.6	<0.05		5	28	1+	2.9	2+	5+	19	1−	1.9	1+	1+
14	CH_3	OCH_3	CH_3	OCH_3	H	H	160 ± 29.7	69.4 ± 2.2	<0.001		3	25	1+	3.8	3+	7+	0	2−	1.0	1+	0
15	CH_3	H	CH_3	OCH_3	CH_3	H	78 ± 7.4	31.8 ± 4.3	<0.02	4		25	1+	2.8	2+	5+	10	1−	2.4	2+	3+
16	CH_3	H	CH_3	OH	CH_3	H	174 ± 15.8	72.0 ± 2.9	<0.001		2	7	2−	2.4	2+	2+	6	2−	2.1	2+	2+
17	CH_3	CH_3	H	CH_3	H	CH_3	138 ± 7.1	80.5 ± 3.4	<0.001		1	6	2−	1.9	1+	0	7	2−	2.1	2+	2+
18	CH_3	H	O_2CH_2		H	H	65 ± 9.2	26.1 ± 3.0	<0.001	2		31	2+	4.1	4+	10+	22	1+	3.3	3+	7+
19	H	H	OCH_3	OCH_3	OCH_3	H	315 ± 20.5	34.4 ± 2.1	<0.01	5		27	1+	4.0	4+	9+	8	2−	2.3	2+	2+
20	H	H	OCH_3	OCH_3	H	H	380 ± 17.1	67.0 ± 6.2	<0.02		4	15	1−	3.0	3+	5+	13	1−	2.6	2+	3+

[a] Sleeping time for control group is 47.6 ± 3.5 min. [b] Time for completion of swimming task (after subtraction of 5 sec necessary for control animals to complete swim). [c] X: above 40, 3+; 30-39, 2+; 20-29, 1+; 10-19, 1−; 0-9, 2−; −1 and below, 3−. [d] $E = \bar{x}^1 + (\bar{x} + 1)^{\frac{1}{2}}$, where $\bar{x}$ is the mean number of errors. [e] Y: above 1.0, 4+; 3.0-3.9, 3+; 2.0-2.9, 2+; 1.0-1.9, 1+. [f] p value larger than 0.05 was considered to be not significant (NS). [g] No change.



1, $R_2 = R_4 = R_5 = H$
2, $R_2 = R_5 = OCH_3$; $R_4 = CH_3$
3, $R_2 = OCH_3$; $R_4 = CH_3$; $R_5 = H$
4, $R_2 = H$; $R_4 = CH_3$; $R_5 = OCH_3$
5, $R_2 = R_5 = OCH_3$; $R_4 = H$

SCHEME I



following: (a) it could increase the solubility of **2** and thus facilitate its entering into the CNS, or (b) it may have changed the electronic property of the benzene ring and made it bind better to the receptor.

Both diminution and potentiation of barbitrate sleeping time were observed among the 15 amphetamine derivatives. At an equimolar dose, **18** was nearly as good as amphetamine (**1**) in shortening the sleeping time (Table II). This reversal effect on the sleeping time as also found with DOM (**2**). Apparently, the 3,4-dimethoxy groups of **11** did not provide the compound with any effect on the sleeping time, and this effect could only be obtained by changing the 3,4-dimethoxy groups of a 1-phenyl-2-aminopropane molecule to a 3,4-methylenedioxy linkage (see **18**). 1-(3,4,5-Trimethoxyphenyl)-2-aminopropane (**10**) and mescaline (**19**) were equally active in shortening the sleeping time. The compound found to be the most active in prolongation of the sleeping time was 1-(2,4,6-trimethylphenyl)-2-aminopropane (**17**). 1-(3,5-Dimethyl-4-hydroxyphenyl)-2-aminopropane (**16**) had an effect approaching that of **17**. Replacement of 4-OH by OMe resulted in a compound (**15**) of opposite effect. The absence or presence of a third OMe in the two phenethylamine derivatives **19** and **20** also gave opposite effects. This, however, was not observed in the amphetamine series (see **10** and **11**).

Several amphetamine derivatives, most of which decreased the sleeping time, were rather toxic (Table II). A nearly threefold increase in toxicity was observed when the 4-OMe of **10** was replaced by Me to give **2**, and more than a twofold decrease in LD_{50} when the 4-OH of **16** was replaced by OMe (**15**).

Experimental Section[9]

Substituted Phenylnitropropenes. Condition 1 (HOAc, $EtNO_2$, or EtOH as Solvent).—The substituted phenylnitropropenes were prepared by the condensation of the appropriate aldehyde with $EtNO_2$ in the presence of NH_4OAc. In the preparation of the intermediate nitropropenes of **15–17**, HOAc was used as the solvent,[10] and the corresponding amines **15–17** were obtained by LAH reduction.

Using $EtNO_2$ as solvent the following compounds were isolated: 1-(2,4,5-trimethoxyphenyl)-2-nitropropene, mp 100–101.5° (84%) (lit.[11] mp 101°), 1-(3,4,5-trimethoxyphenyl)-2-nitropropene, mp 96–97° (63%) (lit.[12] mp 94°), 1-(2,3-dimethoxyphenyl)-2-nitropropene, mp 76.5–78.5°, and 1-(3,4-dimethoxyphenyl)-2-nitropropene, mp 72.5–74°.

In the preparation of 1-(3,5-dimethoxyphenyl)-2-nitropropene, mp 87.5–88.5° (EtOH), EtOH was used as solvent. *Anal.* ($C_{11}H_{13}NO_4$) C, H, N.

Condition 2 (Azeotropic Distillation).—1-(2-Methoxy-3-methylphenyl)-2-nitropropene was prepared by refluxing a mixture of 25 mmoles of 3-methoxy-*p*-tolualdehyde, 10 ml of $EtNO_2$, 1 g of NH_4OAc, and 60 ml of C_6H_6 for 18 hr, with continuous removal of H_2O into a Dean–Stark tube. After evaporation of the solvent the residue was distilled under reduced pressure to yield 40% of yellow oil, bp 113° (0.1 mm), which solidified upon standing to give bright yellow needles, mp 48–50°. Recrystallization from MeOH gave prisms, mp 48–51°. *Anal.* ($C_{11}H_{13}NO_3$) C, H, N.

Ring-Substituted 1-Phenyl-2-aminopropanes Hydrochlorides.—To a stirred suspension of 0.15 mole of LAH in 100–150 ml of THF was added dropwise a solution of 0.05 mole of the appropriate substituted nitrostyrene in 100 ml of THF. The mixture was refluxed with stirring for 1 hr, excess LAH was decomposed (H_2O), and the solid was removed by filtration. The filter cake was washed with hot THF (three 50-ml portions). The combined filtrate and washings were evaporated *in vacuo* to give the crude amine, generally as an oil. When an ethereal solution of the amine was mixed with Et_2O–HCl, the hydrochloride salt precipitated. See Table I.

In cases where a hygroscopic HCl salt resulted, it was redissolved in H_2O, extracted with CH_2Cl_2 to remove impurities, and made basic with 2 *N* NaOH ($NaHCO_3$ was used for **16**). The free amine was extracted into C_6H_6, and the combined C_6H_6 extracts, after washing with H_2O, were dried (Na_2SO_4), concentrated *in vacuo*, diluted with anhydrous Et_2O, and mixed with Et_2O–HCl. After this treatment the HCl salt usually was obtained as a solid.

The reduction of 1-(3-methoxy-4-methylphenyl)-2-nitropropene with LAH was carried out in boiling anhydrous Et_2O for 5 hr. Excess LAH was decomposed with a few drops of 2 *N* NaOH and filtered. The filtrate was mixed with Et_2O–HCl to precipitate the HCl salt. Extraction of the filter cake with Et_2O and treatment of the Et_2O extracts with Et_2O–HCl gave an additional crop of the hydrochloride. The combined crude hydrochloride salts were recrystallized from MeOH–Et_2O yielding **4**.

3-Methoxy-*p*-tolualdehyde.—A solution of 7.3 g (0.044 mole) of 3-methoxy-*p*-toluic acid in 25 ml of $SOCl_2$ was refluxed for 1 hr, then evaporated *in vacuo* to remove the excess $SOCl_2$. The residue of crude acid chloride was dissolved in 25 ml of diglyme, cooled to Dry Ice temperature, and added dropwise to 80 ml (*ca.* 0.045 mole) of $LiAlH(O\text{-}t\text{-}Bu)_3$ in diglyme; the addition required about 1 hr. The mixture was stirred for 2 hr while being allowed to reach room temperature, then poured with stirring onto 600 g of ice. The solid was collected on a filter and extracted with 95% EtOH (four 200-ml portions). The combined EtOH extracts were evaporated *in vacuo* leaving a mixture of pale yellow oil and a trace amount of another immiscible liquid. The oil, after being separated, was dissolved in a small amount of MeOH, and H_2O was added until turbid. Chilling the solution gave 41 g. (62%) of solid, mp 35–38°. Subsequent recrystallization from aqueous MeOH gave needles: mp 40–41°; λ_{max} (KBr) 5.90, 5.95 (C=O), 6.24, 6.31 μ (C=C). *Anal.* ($C_9H_{10}O_2$) C, H.

When the mother liquor of the crude aldehyde was evaporated *in vacuo* and the residue was distilled under reduced pressure, 0.9 g (13%) of an oily liquid, bp 72° (0.5 mm), was obtained. This liquid, which appeared to be the 3-methoxy-4-methylbenzyl alcohol, showed absorption peaks a 3.01 (OH) and 9.6 μ (C–O), but was not further purified.

Lithium tri-*t*-butoxyaluminohydride was prepared in the following manner. To 2.7 g (0.071 mole) of LAH in 200 ml of anhydrous Et_2O was added dropwise dried *t*-BuOH until H_2 evolution ceased. (The requirement of 15.6 ml (0.168 mole) of *t*-BuOH indicated formation of 0.056 mole (79%) of $LiAlH(O\text{-}t\text{-}Bu)_3$.) The product precipitated as a fine white solid. After the removal of Et_2O and *t*-BuOH *in vacuo*, the solid was dissolved in 100 ml of diglyme.

1-(2-Methoxy-4-methylphenyl)-2-aminopropane Hydrochloride (3).—Freshly distilled triethyl orthoformate (29.6 g, 0.20 mole) was added dropwise to the Grignard reagent prepared from 30.2 g (0.15 mole) of 4-bromo-3-methoxytoluene (**6**) and 3.8 g (0.16 g-atom) of Mg turnings in 125 ml of Et_2O. After the addition was complete, the mixture was refluxed for 4.5 hr. H_2O (25 ml) was slowly added, followed by enough 10% H_2SO_4 to make the mixture acidic (*ca.* pH 2). This mixture was then refluxed with stirring for 1 hr. The aqueous layer was separated from the organic layer and extracted with Et_2O (three 50-ml portions). The combined Et_2O extracts were dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Distillation of the residue gave 16 g of a mixture of 2-methoxy-*p*-tolualdehyde (**8**) and the unreacted 4-bromo-3-methoxytoluene, bp 64–66° (0.15 mm), which could not be separated by fractional distillation. This mixture was then used directly in the preparation of 1-(2-methoxy-4-methylphenyl)-2-nitropropene.

For characterization, the above mixture was mixed with a solution of 2,4-dinitrophenylhydrazine in aqueous EtOH–H_2SO_4. The 2,4-dinitrophenylhydrazone was collected on a filter and recrystallized from absolute EtOH, mp 222–225° dec. *Anal.* ($C_{15}H_{14}N_4O_5$) C, H, N.

A mixture of 6.0 g of the impure aldehyde, 7.5 g of $EtNO_2$, 1 g of NH_4OAc, and 75 ml of C_6H_6 was refluxed for 10 hr, while the

(9) Melting points are corrected and were taken on a Fisher-Johns or Mel-Temp apparatus. Where analyses are indicated only by symbols of the elements or function, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(10) A. T. Shulgin, *J. Med. Chem.*, **11**, 186 (1968).

(11) V. Bruckner, *J. Prakt. Chem.*, **138**, 268 (1933), prepared from the treatment of the corresponding phenylpropene with $NaNO_2$ in HOAc.

(12) A. T. Shulgin, *Experientia*, **20**, 366 (1964), prepared from the treatment of the corresponding phenylpropene with $C(NO_2)_4$.

H_2O from the reaction was continuously removed by a Dean–Stark tube. The resulting solution, after cooling, was washed with 10 ml of H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. During distillation of the residue, two fractions were collected. The first fraction, 3.5 g, bp 55° (0.15 mm), was identified by ir as the 3-methoxy-4-bromotoluene. The second fraction, which weighed 2.5 g, was a bright yellow, viscous oil, bp 132° (0.4 mm). Its ir spectrum showed the absence of an absorption peak due to C=O.

The above oil, with no further purification, was dissolved in 50 ml of Et_2O and was added dropwise to a suspension of 1.5 g of LAH in 75 ml of Et_2O, while the temperature was maintained between 0 and 5°. The mixture was refluxed for 4 hr, and H_2O and 10% NaOH were added successively to decompose excess LAH. The inorganic solids were removed by filtration, and the filtrate was evaporated *in vacuo* leaving a light yellow oil. A solution of this oil in 50 ml of Et_2O was saturated with HCl to precipitate the HCl salt. Recrystallization from MeOH–Et_2O gave 1.4 g (38% over-all, based on the recovered 3-methoxy-4-bromotoluene) of 1-(2-methoxy-4-methylphenyl)-2-aminopropane hydrochloride.

Pharmacology. Swim Maze Test.—The H-shaped swim maze,[13,14] constructed of galvanized metal sheet, has an over-all dimension of 80 × 60 × 15 cm, three swim channels 6 cm in width, and a landing strip 30 × 6 cm with a 10-cm projection at 40° angle. An 8-cm level of H_2O was maintained at 37° by several straps of heating tape placed underneath the tank.

Prior to the administration of drugs, mice were trained to swim the maze for 2 consecutive days (at intervals of 2 hr). They were placed in the H_2O at one end of the tank and the swimming time was recorded as the time from placement in the tank until exit at the landing strip. The trained animals were able to complete the two-right-turn swimming task in an average of 5 sec and with an average of less than one error. During the training period, those that did not show good performance were excluded from the study. The animals in groups of ten were injected intraperitoneally with 50 μmoles/kg of compounds in 30% aqueous propylene glycol. The control group was given only propylene glycol. The swim tests were performed at both 10 and 30 min after the injection. The results were expressed as (a) the completion time for swimming (X), and (b) number of errors (Y) during that time. With the emphasis on Y, the disruption of mouse behavior was evaluated as $X + 2Y$.

Effects on Barbiturate Sleeping Time.—Mice in groups of ten were injected intraperitoneally with 50 μmoles/kg of compounds in 30% propylene glycol. After 5 min, sodium pentobarbital (40 mg/kg) in saline was given *via* the same route. Controls were first given 30% propylene glycol, then pentobarbital in saline. The presleeping time and sleeping time (loss of the righting reflex) were recorded and treated statistically.

Acute Toxicity.—All compounds dissolved in 30% propylene glycol (10 mg/kg) were administered intraperitoneally to groups of ten male albino Yale–Swiss mice weighing 17–23 g. The LD_{50} within a 24-hr period was determined graphically according to the method of Miller and Tainter.[15]

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(13) M. E. Kosman, *Proc. Soc. Exptl. Biol. Med.*, **115**, 728 (1964).

(14) C. A. Buehler, S. F. Thames, L. G. Abood, and J. H. Biel, *J. Med. Chem.*, **8**, 643 (1965).

(15) L. D. Miller and M. L. Tainter, *Proc. Soc. Exptl. Biol. Med.*, **57**, 261 (1944).

Pharmacologic and Metabolic Studies with Deuterated Zoxazolamine[1]

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The synthesis of deuteriozoxazolamine-4,6-d_2 is described. Nmr data on the deuterated drug and related derivatives are discussed. The deuterated drug exhibits a kinetic deuterium isotope effect in *in vitro* metabolism. No increased duration of pharmacologic action with the deuterated drug was observed.

In our continuing work on the biological consequences of deuterium substitution on drugs, we studied the effects of the muscle relaxant zoxazolamine. The results of those studies are reported herein.

We previously reported[2] that the barbiturate butethal induced a twofold increase in sleeping time of mice when D atoms were substituted on the penultimate C of the butyl side chain, which is the site of metabolic deactivation. The biological isotope effect of $k_H/k_D \cong 2$ was attributed to a slower rate of metabolism of the deuterated drug. Evidence for this conclusion was also obtained from the slower rate of metabolism observed with the deuterated species in *in vitro* studies with the liver microsomal enzymes.

Conney, *et al.*,[3] have reported that zoxazolamine is metabolized in man by two routes. A minor pathway involves hydrolytic deamination to a pharmacologically active metabolite, 5-chloro-2-hydroxybenzoxazole. Both biologically active benzoxazole derivatives are metabolically deactivated by a ring hydroxylation pathway at C-6 to yield the respective 5-chloro-6-hydroxybenzoxazole derivatives. Since the specific site of metabolic deactivation of zoxazolamine is at the C-6 position, our goal was the preparation of the drug labeled with D at this position, and the study of its effect on the rate of metabolism.

Our inital attempt at the direct introduction of D into zoxazolamine involved acid-catalyzed exchange of the drug with D_2O at 100°. The material obtained from this reaction consisted solely of the hydrolytic deamination product, 5-chloro-2-hydroxybenzoxazole (**1**), with no evidence of incorporation of D in the aromatic ring.

Successful introduction of D atoms into the benzene ring was achieved by an acid-catalyzed exchange reaction of 2-amino-4-chlorophenol with D_2O at 100°. The intermediate deuterated phenol was condensed directly with BrCN in EtOH to yield zoxazolamine.[4] Combustion analysis indicated the incorporation of two D atoms into zoxazolamine prepared in this way. To

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(2) J. Soboren, D. M. Yasuda, M. Tanabe, and C. Mitoma, *Fed. Proc.*, **24**, 427 (1965); M. Tanabe, D. Yasoda, S. LeValley, and C. Mitoma, *Life Sci.*, **8**, 1123 (1969).

(3) A. H. Conney, N. Tronsot, and J. J. Burns, *J. Pharmacol. Exptl. Therap.*, **128**, 333 (1960).

(4) T. Negano, M. Itoh, and K. Matsumora, *J. Am. Chem. Soc.*, **75**, 2570 (1953).