THE EFFECT OF A NUMBER OF ARALKYLAMINES ON THE OXIDATION OF TYRAMINE BY AMINE OXIDASE[1]

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It has been suggested (Mann and Quastel, 1940) that the central stimulant action of *dl*-phenylisopropylamine is related to its inhibition of tyramine oxidation by amine oxidase. It appeared desirable to determine if a correlation exists between the central excitatory and amine oxidase inhibitory activity of a number of structurally related salts of benzylamine, beta-phenethylamine and aryl-2-aminopropane modifications.

A series of phenylaminobutane and phenylaminopentane compounds (Nos. 144, 68 and 145) are included in the study because they produced histopathological changes in the cerebrum, cerebellum and brain stem of animals, and it seemed pertinent to investigate their influence on amine oxidase activity.

METHODS. The method of Szymanski (1918) was used to secure inferential data on the action of the present compounds on the central nervous system of rats. Stimulation was inferred if motor activity increased after administration of a given compound. Effects noted after doses in excess of 25 mgm./kgm. were not considered significant because in many instances the behavior of the animals after higher doses suggested toxic effects. All compounds were injected intraperitoneally.

The following method was used to determine the effect of the present compounds on amine oxidase: The brains of three adult rats were washed free of blood, ground in a mortar with *M*/20 Na-K phosphate buffer at either pH 6.7 or 7.8 and squeezed through muslin. The final volume was 17.0 ml. One ml. of this suspension was placed in each 50 ml. Erlenmeyer flask and the volume made up to 2.0 ml. with buffer containing 3.7×10^{-3} *M* tyramine with or without 3.7×10^{-4} *M* concentration of the drug. The vessels were incubated 60 minutes at 37°C. in air. Each experiment was run in triplicate and each drug was tested at least four different times. At the end of the experiment 2.0 ml. of H_2O and 1.0 mgm. 20 per cent trichloracetic acid were added. The precipitated protein was centrifuged down and an aliquot of the supernatant was distilled from alkali into acid and the NH_3 estimated colorimetrically after Nesslerization. The results are expressed as the average percentage inhibition of the deamination of tyramine. There was no significant difference in these values at the two hydrogen ion concentrations used. Direct measurement of the inhibitory effect of these compounds on the oxidation of tyramine was not feasible since the oxidation product of the latter inhibits the oxygen uptake of brain.

DISCUSSION. In table 1 are shown data on compounds which were entirely devoid of or possessed only an insignificant central excitatory effect. The validity of the degree of tyramine oxidase inhibition obtained with the compounds

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TABLE 1

Compounds devoid of central excitatory effects

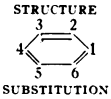
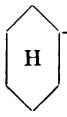
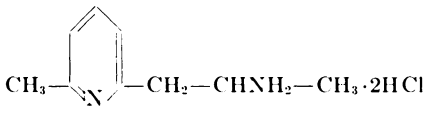
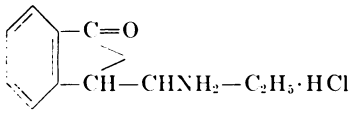
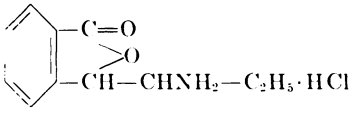
COMPOUND NO.	STRUCTURE  SUBSTITUTION	DOSE	EFFECT	INHIBITION
		mgm./kgm.		*Per cent*
143	1—CH_2—NH_2·HCl	25	No side effects	10
141	1—$CHNH_2$—CH_2CH_3·½ H_2SO_4	25	No side effects	0
27	1—CH_2—CH_2—NH_2·½ H_2SO_4	25	Depression	8
22	1—CH_2—CH_2—NH—CH_2—C_6H_5·HCl	10–25	Depression	11
14	1—CH_2—$CHNH_2$—CH_3·½ H_2SO_4 4—OH	10–25	No side effects—depression	30
45	1—CHOH—$CHNH_2$—CH_3 4—OH	25	No side effects	0
38	1—CH_2—$CHNH_2$—CH_3·HCl 3—OCH_3 4—OCH_3	15–25	No side effects—slight stimulation	12
20	1—CH_2—$CHNHCH_2CH_2OH$—CH_3·½H_2SO_4	10–25	No side effects—slight stimulation	3
88	1—CH_2—$CHNHC_4H_9$—CH_3·HBr 4—OH	10–25	No side effects—slight depression	0
138	1—CH_2—$CHCH_3$—NH—CH_2—$CHCH_3$—C_6H_5·HBr	25	Slight stimulation	9
41	1—CH_2—$CHCH_3$—NH—CH_2—C_6H_4—$COOC_2H_5$(p)·HCl	25	No side effects	6
90	1—CH_2—$CHCH_3$—$NCH_3CH_2CH_2$—$COOC_2H_5$·HCl	10–25	No side effects—very slight stimulation	1
86	1—CH_2—$CHN(CH_3)_2$—CH_3 4—OH	25	No side effects	2
48	1—CH_2—$CHNH_2$—C_2H_5 4—OH	12.5–25	No side effects—Depression	10
83	1—$CHNH_2$—CH_2—C_6H_4—OCH_3—(p) 4—OCH_3	15–25	Slight depression	20
16	 —CH_2—CH_2—NH_2·HCl	10–25	Depression	0

TABLE 1—*Continued*

COMPOUND NO.		DOSE	EFFECT	INHIBITION
		mgm./kgm.		*Per cent*
217		25	No side effects	11
103 A		25	No side effects	0
103 B		25	No side effects	5
124		25	No side effects	1

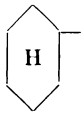
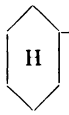
in table 1, with the exception of para-hydroxyphenyl-2-aminopropane (No. 14) and 1-amino-1,2-di(para-methoxyphenyl)-ethane (No. 83) is questionable because it is within the limits of experimental error of the method. Although the enzyme was obtained from rat brain tissue, the high inhibitory value noted for No. 14 may be referable to its marked pressor activity. There is no apparent explanation for the high inhibitory activity of No. 83.

Table 2 contains data on those aryl-2-aminopropane derivatives which exhibited effects suggestive of pronounced stimulation of the central nervous system in doses of 25 mgm./kgm. or less. All of these agents produced a significant inhibition of the deamination of tyramine. A 32 per cent inhibition of the amine oxidase was shown by *dl*-phenylisopropylamine (No. 1) which produced slight to marked stimulation in doses of 1.5 to 3.0 mgm./kgm. The central excitatory as well as the amine oxidase inhibitory activity of *dl*-phenylisopropylamine (No. 1) was less than that of its dextrorotatory isomer (No. 2) but greater than that of its levo isomer (No. 3). This is in contrast to the report by Beyer (1946) that no consistent difference in enzymatic behavior could be detected for the optical forms of *dl*-phenylisopropylamine. He used, however, liver preparations. The effect on the central nervous system and on depression of brain respiration *in vitro* of *dl*-N-methylphenylisopropylamine (No. 4) and *d*-N-methylphenylisopropylamine (No. 4-a) is of the same magnitude as their corresponding primary amino analogues, Nos. 1 and 2. In spite of the fact that *dl*-cyclohexyl-2-aminopropane (No. 10) and its N-methyl modification (No. 25) are only one-

tenth as potent motor activity stimulants as their corresponding phenyl modifications (Nos. 1 and 4), the decreased amount of tyramine deamination of Nos. 10 and 25 is entirely comparable with Nos. 1 and 4. Of all the compounds in table 2, para-methylphenylisopropylamine (No. 42) manifested the highest de-

TABLE 2

Compounds causing marked uncomplicated central nervous system stimulation at 25mgm./kgm.

COMPOUND NO.	STRUCTURE SUBSTITUTION	DOSE	EFFECT	INHIBITION
		mgm./kgm.		*Per cent*
1	1— CH_2—$CHNH_2$—$CH_3 \cdot \frac{1}{2} H_2SO_4$ (dl)	1.5–3.0	Slight stimulation—marked stimulation	32
2	1—CH_2—$CHNH_2$—$CH_3 \cdot \frac{1}{2} H_2SO_4$(d)	2.0	Marked stimulation	49
3	1—CH_2—$CHNH_2$—$CH_3 \cdot \frac{1}{2} H_2SO_4$ (l)	2.5–10	No side effects—marked stimulation	21
4	1—CH_2—$CHNHCH_3$—$CH_3 \cdot HCl$ (dl)	1.5–3.0	Slight stimulation—marked stimulation	25
4a	1—CH_2—$CHNHCH_3$—$CH_3 \cdot HCl$ (d)	2.0	Marked stimulation	36
42	1—CH_2—$CHNH_2$—$CH_3 \cdot \frac{1}{2} H_2SO_4$ 4-CH_3	10–20	Slight stimulation—marked stimulation	65
5	1—CH_2—$CHNH_2$—$CH_3 \cdot HCl$ 3,4-CH_2O_2	1.0–10	Slight stimulation—marked stimulation	14
149a	1—CH_2—$CHNH_2$—$C_2H_5 \cdot \frac{1}{2} H_2SO_4$	5.0–20	Slight stimulation—marked stimulation	20
10	 —CH_2—$CHNH_2$—$CH_3 \cdot HCl$	10–20	Slight stimulation—marked stimulation	32
25	 —CH_2—$CHNHCH_3$—$CH_3 \cdot HCl$	10–20	Slight stimulation—marked stimulation	33

gree, 65 per cent, of inhibition of the amine oxidase, but its central excitatory activity is only one-fifth that of No. 1. It is to be noted that the interference with oxidation of tyramine by 2-amino-1-phenylbutane (No. 149-A) and 2-amino-1-(3,4-methylenedioxyphenyl)-propane (No. 5) was far less than No. 42. As indicated in table 2 the doses necessary to produce central stimulation with

No. 5 or No. 149-A varied over a range of 1 to 10 mgm./kgm. and 5 to 20 mgm./kgm., respectively

All of the 1-phenyl-3-aminobutane and -4-aminopentane modifications which were included in the present studies were found to manifest a significant inhibi-

TABLE 3

1-Phenyl-3-Amino-Butane or 4-Amino-Pentane Modifications

COMPOUND NO.	STRUCTURE 3 2 4 1 5 6 SUBSTITUTIONS	DOSE	EFFECTS	INHIBITION
		mgm./kgm.		*Per cent*
144	1—CH_2—CH_2—$CHNH_2$—CH_3·½ H_2SO_4	15–25	No side effects—very slight stimulation	67
63	1—CH_2—CH_2—$CHNH_2$—CH_3·HBr 4—OH	25	No side effects	27
172	1—CH_2—CH_2—$CHNH_2$—CH_3·½ H_2SO_4 4—CH_3	5–25	No side effects—convulsions (death)	77
67	1—CH_2—CH_2—$CHNH_2$—C_2H_5·HCl 4—OCH_3	1–10	Depression—convulsions (death)	47
64	1—CH_2—CH_2—$CHNH_2$—CH_3·HCl 3, 4—CH_2O_2	10–25	Slight stimulation—tremors	18
68	1—CH_2—CH_2—$CHNH_2$—CH_3·HCl 3—OCH_3 4—OCH_3	25	No side effects	17
145	1—CH_2—CH_2—CH_2—$CHNH_2$—CH_3·½ H_2SO_4	20–25	Slight stimulation	34
71	1—CH_2—CH_2—CH_2—$CHNH_2$—CH_3·HBr 4—OH	25	No side effects	21
72	1—CH_2—CH_2—CH_2—$CHNH_2$—CH_3·HCl 4—OCH_3	10–25	Depression—convulsions	38

tory action on amine oxidase (table 3). Either no effect or only a slight stimulant action on the central nervous system was observed after the para-hydroxyphenyl- (No. 63) and 3,4-dimethoxyphenyl-butane derivatives as well as their unsubstituted phenyl parent compounds (No. 144) or 4-amino-1-phenylpentane (No. 145) and its para-hydroxyphenyl analogue (No. 71). Although outstand-

ing effects were not noted on gross observations of the animals receiving these derivatives, it is to be recalled that chronic administration of No. 144, 68 and 145 produced histopathologically demonstrable damage of the central nervous system of animals. It is to be noted that 3-amino-1-para-methylphenylbutane (No. 172), -1-(3,4-methylenedioxyphenyl-3-aminobutane (No. 64), -1-para-methoxyphenylpentane (No. 67) and 4-amino-1-para-methoxyphenyl-3-amino-pentane (No. 72) produced such toxic effects as tremors or convulsions after 25 mgm./kgm. or less.

SUMMARY

In the present experiments determinations were made of the effect on motor activity in rats and on tyramine oxidation by amine oxidase of 39 benzylamine, beta-arylethylamine and aryl-2-aminopropane modifications. In many instances there was observed an excellent positive correlation between the effect of these derivatives on motor activity and amine oxidase inhibition. There were, however, notable exceptions which may be explained by permeability and distribution factors which can markedly influence *in vivo* results. In other experiments it was found that injection of several 3-amino-1-phenylbutane and 4-amino-1-phenylpentane derivatives in animals produced histopathologically demonstrable damage of the central nervous system. Since enzymatic data on these types of compounds were not available, it appeared desirable to include them in the present studies. All of these agents also exhibited a significant amine oxidase inhibitory effect.

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