THE PHARMACOLOGY OF COMPOUNDS RELATED TO β-2,5-DIMETHOXY PHENETHYL AMINE

I. The Ethyl, Isopropyl and Propyl Derivatives

AXEL M. HJORT[1], LOWELL O. RANDALL and EDWIN J. DE BEER

From the Wellcome Research Laboratories, Tuckahoe, New York

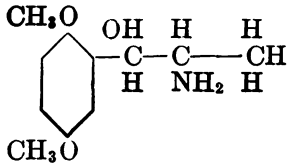
Received for publication October 24, 1947

Introduction. The following paper presents the results of a systematic study of a series of phenethylamine derivatives. The individual members were examined for toxicity, circulatory effects, mydriatic action and action on the isolated intestine and uterus. The data obtained were analyzed with respect to (a) absolute potencies, (b) the relationship of pharmacological action to chemical structure, and (c) correlations between various pharmacological effects and pressor activity, which is the outstanding, although not the common, feature of the group.

Discussion will be confined solely to the data presented in this paper since it frequently happens that relationships between chemical structure and physiological action are limited to a given series. Reviews such as that by Hartung (1) may be consulted for the broader aspects of this problem.

The conclusions drawn are dependent upon the precision and accuracy of the data in question; therefore, every effort was made to reduce error by careful experimentation and by the use of as many experimental animals as was practicable. All physiological measurements were standardized and each was carried out by the same operator insofar as possible. All 24 compounds were synthesized and analyzed in these laboratories (2, 3, 4).

The plan of the series is as follows: the 24 members possess as a common feature an amino or quaternary nitrogen linked through a two-carbon chain to a 2,5-dimethoxyphenyl group so that the latter is in a beta-position, with respect to the nitrogen group. The 18 amine hydrochlorides consist of the primary, secondary and tertiary derviatives of the following 6 alkyl side chains: ethyl, isopropyl, propyl, β-hydroxyethyl, β-hydroxyisopropyl and β-hydroxypropyl. For purposes of discussion it is sometimes convenient to regard the propyl derivatives as β-methylethyl compounds. In addition, the quaternary ammonium chlorides, which are different chemically and often physiologically from the amines, also were prepared for each of the side chains. The structural formula for No. 839, β-(2,5-dimethoxyphenyl)-β-hydroxyisopropylamine is given below as a typical example:



[1] Now of 14 Fernway Road, Scarsdale, New York.

TABLE 1

Action on mice

COMP. NO.	ALKYL CHAIN	N GROUP	PILOMOTOR	EXOPHTHALMOS	SALIVATION	OTHER SYMPTOMS	LD_{50} mgm/kgm.	NO. OF MICE	SLOPE	LIMITS OF ERROR AS %
831	β—hydroxyethyl	pri	long	long	long	Depression	131	20	10	87–114
832	OH	sec	long	long	long	Depression	94	35	11	91–110
833	|	ter	long	long	long	Depression	200	30	32	96–105
834	R—CH—CH_2	quat	none	none	none	Fine tremors	41	27	26	97–103
	|								
	X									
839	β—hydroxyisopropyl	pri	long	long	long	Depression	92	40	10	91–109
840	OH	sec	long	long	long	Depression	96	27	20	92–108
841	|	ter	long	long	long	Depression	131	27	14	91–110
842	R—CH—CH—CH_3	quat	none	brief	none	Fine tremors	22	36	25	94–106
	|									
	X									
835	β—hydroxypropyl	pri	brief	brief	none	Depression	206	47	36	97–103
836	OH	sec	brief	brief	none	Fine tremors	147	22	11	88–114
837	|	ter	none	brief	none	Fine tremors	164	24	20	93–107
838	R—C—CH_2	quat	none	brief	none	Fine tremors	67	39	14	93–107
	| \								
	CH_3 X									
819	ethyl	pri	long	long	none	Fine tremors	161	27	55	97–103
820	R—CH_2—CH_2	sec	long	long	none	Coarse tremors	124	30	31	95–106
821	|	ter	long	brief	none	Coarse tremors	134	69	44	97–103
822	X	quat	brief	brief	none	Fine tremors	49	72	25	97–104
827	isopropyl	pri	brief	brief	none	Depression	135	37	31	96–104
828	R—CH_2CH—CH_3	sec	brief	brief	none	Depression	116	37	20	94–106
829	|	ter	brief	brief	none	Fine tremors	125	25	58	97–103
830	X	quat	brief	brief	none	Fine tremors	26	34	21	94–106
823	propyl	pri	brief	none	none	Coarse tremors	107	42	23	95–105
824	R—CH—CH_2	sec	brief	none	none	Coarse tremors	98	27	27	95–105
825	| |	ter	brief	brief	none	Coarse tremors	101	32	16	92–108
826	CH_3 X	quat	brief	brief	none	Fine tremors	36	40	10	90–111

"R" stands for the 2,5-dimethoxy phenyl grouping and "X" for the nitrogen containing group. "pri", "sec", "ter", and "quat" are abbreviations for primary, secondary, tertiary and quarternary respectively. The figures in the column headed "Slope" give the slopes of the various log dosage-probit response curves. The "Limits of error give the range within which the LD_{50} values may be expected to fall 19 out of 20 times. The figures given are expressed as percentages and are to be applied to the corresponding LD_{50}.

Reports on the pharmacological activity of two members of this series have been published previously. Hjort (5) discussed No. 820, β-2,5-dimethoxyphenylethylmethylamine and Graham and Cartland (6) described No. 823, β-2,5-dimethoxyphenylpropyl amine.

TOXICITY. The LD_{50} values for albino mice were determined by a procedure previously described (7). The precision of these figures is relatively high as is shown by the limits of error in Table 1, but the absolute values may be modified by such factors as environment, diet, etc. (8, 9).

With a few exceptions, the compounds of this series were neither very toxic nor were they innocuous. With respect to chemical structure, the amines were decidedly less toxic than were the corresponding quaternary compounds. The presence of a β-hydroxy group seemed to reduce toxicity in the propylamine group, but was without definite effect in the other two groups. Pilomotor action and exophthalmic effects either were absent or were weak, with the quaternary compounds, and with the propyl and the β-hydroxypropyl chains. Fine tremors generally were observed with these groups. Depression commonly was observed with the β-hydroxy amines, while signs of central nervous stimulation were frequent with the non-hydroxy amines.

As for correlations between pharmacological observations, the more toxic of the amines were also the more potent pressors. The pressors also produced the most pronounced pilomotor actions and exophthalmic effects. The duration of these effects appeared to be proportional to the duration of the pressor action. Salivation, when it occurred, was found with those β-hydroxy compounds which were also pressors. The presence of these three signs, pilomotor action, exophthalmic effects and salivation, usually served to predict pressor properties, and the duration of the phenomena appeared to be directly correlated with the duration of pressor activity. Exceptions to this rule are No. 833 and No. 841.

CIRCULATORY EFFECTS. Circulatory effects were studied in dogs treated with 'Dial'. Blood pressure was measured with a mercury manometer. All drugs were given intravenously. Details of the procedure have been described previously (7).

It may be stated that measurements were reasonably consistent, although numerical estimates of their precision were not obtained. The maximum rise or fall in blood pressure may be readily obtained, but the duration of such effects is difficult to measure when the return of the blood pressure to the initial level is gradual and when sufficient time has elapsed to allow other extraneous factors possibly to affect the level. Heart rates were obtained from blood pressure records. Tachyphylaxis was always found to be associated with prolonged pressor activity. Each drug was tested on at least two, and frequently on more than two, dogs. Results are given in Table 2.

To establish a relative basis for comparison, the dose required to produce a rise of 50 mm. of Hg is given for all pressor compounds, except for 3 of the less potent drugs. Depressor effects were feeble and transient, and for this type of compound the effects produced by a constant dose of 0.008 mM. per kgm. are given in the table.

The outstanding feature of this study was the discovery of several very powerful, long-acting pressor compounds. Four of these, the primary and secondary β-hydroxyethyl derivatives, No. 831 and No. 832, and the primary and secondary β-hydroxyisopropyl compounds, No. 839 and No. 840, were effective for an hour

or more, at doses equal to or less than 0.001 mM. per kgm. No. 839, in particular, is a remarkable drug and will be the subject of a separate communication.

TABLE 2

	PRIMARY	SECONDARY	TERTIARY	QUATERNARY
β-hydroxyethyl	No. 831 0.001 mM/kgm. P50, 60 min. Rate −, T Ep 0, ACh −	No. 832 0.0005 mM/kgm. P50, 60 min. Rate −, T Ep 0, ACh −	No. 833 0.008 mM/kgm. D12, 1 min. Rate 0 Ep +, ACh −	No. 834 0.008 mM/kgm. D18, 2 min. Rate 0 Ep 0, ACh 0
β-hydroxy-isopropyl	No. 839 0.0006 mM/kgm. P50, 120 min. Rate −, T Ep +, ACh 0	No. 840 0.001 mM/kgm. P50, 90 min. Rate −, T Ep +, ACh −	No. 841 0.008 mM/kgm. D16, 1 min. Rate 0 Ep +, ACh −	No. 842 0.008 mM/kgm. D22, 2 min. Rate − Ep +, ACh 0
β-hydroxypropyl	No. 835 0.008 mM/kgm. D24, 1 min. Rate 0 Ep 0, ACh 0	No. 836 0.008 mM/kgm. D15, 1 min. Rate 0 Ep 0, ACh 0	No. 837 0.008 mM/kgm. D5, 1 min. Rate 0 Ep 0, ACh 0	No. 838 0.008 mM/kgm. D25, 5 min. Rate 0 Ep +, ACh 0
ethyl	No. 819 0.0025 mM/kgm. P50, 24 min. Rate −, T Ep 0, ACh 0	No. 820 0.002 mM/kgm. P50, 20 min. Rate −, T Ep −, ACh 0	No. 821 0.003 mM/kgm. P50, 15 min. Rate −, T Ep R, ACh 0	No. 822 0.008 mM/kgm. P30, 5 min. Rate −, T Ep +, ACh 0
isopropyl	No. 827 0.008 mM/kgm. P37, 15 min. Rate −, T Ep 0, ACh 0	No. 828 0.008 mM/kgm. D30, P10, 10 min. Rate −, T Ep −, ACh 0	No. 829 0.008 mM/kgm. D35, 1 min. Rate 0 Ep 0, ACh 0	No. 830 0.008 mM/kgm. D10, 1 min. Rate 0 Ep +, ACh 0
propyl	No. 823 0.008 mM/kgm. D10, 2 min. Rate − Ep 0, ACh 0	No. 824 0.008 mM/kgm. D22, 2 min. Rate 0 Ep 0, ACh 0	No. 825 0.008 mM/kgm. D50, 5 min. Rate − Ep 0, ACh −	No. 826 0.008 mM/kgm. D24, 2 min. Rate − Ep +, ACh 0

"P" stands for an increase in systolic pressure, "D" for a decrease in diastolic pressure and the succeeding numeral indicates the extent of change in mm. of Hg. The duration of the effects are given in minutes. "T" stands for tachyphylaxis. "Rate" stands for he art rate. "Ep" and "ACh" are abbreviations for epinephrine and for acetylcholine, respectively. "+" means enhancement, "−" means diminution, and "0" means no change. "R" indicates a reversal of the pressor action of epinephrine.

Pressor activity was not a universal attribute of this series. Only 10 of the 24 compounds were pressors, while the rest were transient depressors.

With regard to structure and circulatory effects, pressor action, with a few exceptions, was limited to the ethyl and isopropyl primary and secondary amines. Within these limits the presence of a β-hydroxy group enhanced pressor potency and duration. By contrast, pressor properties were never found for compounds containing a β-methyl group; i.e. the propyl compounds. (Graham and Cartland (6) report that β-2,5-dimethoxyphenylpropylamine is a weak pressor.) With the exceptions of the 2 ethyl derivatives, No. 821 and No. 822, the presence of a tertiary or quaternary nitrogen atom also appeared to be adverse to pressor activity.

The heart rate frequently was reduced temporarily. This was always the case with the pressor members of the series, when it might be expected to be associated with the sharp rise in blood pressure, but it was also noted with about one-third of the depressor compounds.

All β-hydroxyisopropyl derivatives enhanced the pressor action of epinephrine. While this may have contributed to the pressor properties of the primary and secondary members, No. 839 and No. 840, it may be pointed out also that many depressors, such as No. 841 and all of the quaternary compounds, which with one exception were depressors, also enhanced the pressor action of epinephrine. Furthermore, No. 821, the tertiary ethyl derivative, combined pressor properties with the ability to reverse the action of epinephrine. Of the remaining members of the series, none had an effect on epinephrine action, except No. 820 and No. 828, which decreased it.

The ability to diminish the depressor action of acetylcholine was shown by the primary, secondary and tertiary β-hydroxyethyl compounds and the secondary and tertiary β-hydroxyisopropyl compounds; No. 839, the primary β-hydroxyisopropyl derivative being the exception. The property was absent from all compounds containing a quaternary nitrogen atom or a β-methyl group or lacking a β-hydroxy group; No. 825, the tertiary propyl derivative, was the single exception.

MYDRIATIC ACTIVITY. Solutions of the drugs were instilled into the conjunctival sacs of albino rabbits. The diameter of the pupil was measured at systematic intervals with a millimeter rule. An X-ray viewing screen furnished a constant source of light. Log concentration-response graphs were plotted and the concentrations that were required to produce 50 per cent increases in pupil diameters in 30 minutes were read from the graphs. This value, which we have called "MC_{50}" (mydriatic $concentration_{50}$) for the sake of convenience, affords a means for the comparison of relative intensities of action. It was possible to achieve a fair degree of precision, approximately ±20 per cent, by using 4 rabbits for each of 3 concentration levels. Values were quite reproducible. Species differences were pronounced. Some of the drugs were highly potent in rabbits, but all were ineffective in cats. The results are given in Table 3.

When mydriasis was produced it was prompt in onset, reached a maximum in 15 to 30 minutes and lasted for 2 to 4 hours. According to these experiments, some members of this series were highly potent mydriatics. No. 839, β-(2,5-dimethoxyphenyl)-β-hydroxyisopropylamine, No. 831, β-(2,5-dimethoxy-

phenyl)-β-hydroxyethylamine, and No. 832, β-(2,5-dimethoxyphenyl)-β-hydroxyethylmethylamine, were effective in concentrations as low as 0.02 per cent. Under the same conditions, the MC_{50} for ephedrine was 4.1 per cent.

With respect to structural relationships, the presence of a β-hydroxy-group generally enhanced activity, but the β-methyl group, i.e., propyl and β-hydroxypropyl derivatives, was associated with inactive compounds. All but one tertiary compound and all quaternary compounds were inactive.

The correlation between mydriatic action and pressor properties was strong. Mydriatic action was shown only by pressor compounds and all pressor compounds, save the quaternary substance, No. 822, were mydriatics. Mydriatic

TABLE 3

The mydriatic effects on the albino rabbit

ALKYL SIDE-CHAIN	PRIMARY $-NH_2$	SECONDARY $-NHCH_3$	TERTIARY $-N(CH_3)_2$	QUATERNARY $-N(CH_3)_3Cl$
β-hydroxyethyl	No. 831 MC50 0.023	No. 832 MC50 0.019	No. 833 MC50 i	No. 834 MC50 i
β-hydroxyisopropyl	No. 839 MC50 0.017	No. 840 MC50 0.054	No. 841 MC50 i	No. 842 MC50 i
β-hydroxypropyl	No. 835 MC50 i	No. 836 MC50 i	No. 837 MC50 i	No. 838 MC50 i
ethyl	No. 819 MC50 0.603	No. 820 MC50 0.347	No. 821 MC50 1.128	No. 822 MC50 i
isopropyl	No. 827 MC50 0.692	No. 828 MC50 i	No. 829 MC50 i	No. 830 MC50 i
propyl	No. 823 MC50 i	No. 824 MC50 i	No. 825 MC50 i	No. 826 MC50 i

"MC50" stands for per cent concentration required to increase diameter of the pupil by 50 per cent.

"i" indicates inactivity.

potency was proportional to pressor potency, and the more potent pressors possessed the greater mydriatic activity. Mydriasis was abolished by 0.5 per cent physostigmine, but pilocarpine was ineffective at 2 per cent levels. It is interesting to note that 3 of the most powerful mydriatics were antagonistic toward the ability of acetylcholine to depress blood pressure (see Table 3). However, the most powerful mydriatic of the group, No. 839, did not inhibit the action of acetylcholine, and 3 tertiary compounds which were inhibitors failed to produce mydriasis. No relationship was apparent between the occurrence of mydriatic properties and the ability of certain members of the group to enhance epinephrine activity.

ACTION ON ISOLATED TISSUE. Table 4 shows the effects of the members of

this series on the tone of smooth muscle (segments of the small intestine and the uterus of virgin adult rabbits, and the whole uterine horn of virgin adult guinea pigs). The sections of tissue were suspended in Van Dyke-Hastings solution (10), which was aerated with a mixture of 94 per cent air and 6 per cent carbon

TABLE 4

Action on isolated smooth muscle

ALKYL SIDE-CHAIN	PRIMARY	SECONDARY	TERTIARY	QUATERNARY
β-hydroxyethyl	No. 831 g.u. 0.03 (+) r.u. 0.03 (+) r.i. 0.03 (−)	No. 832 g.u. 0.06 (+) r.u. 0.06 (+) r.i. 0.06 (−)	No. 833 g.u. 0.06 (+) r.u. 0.06 (+) r.i. 0.06 (−)	No. 834 g.u. 0.12 (+) r.u. 0.12 (+) r.i. 0.12 (−)
β-hydroxyisopropyl	No. 839 g.u. 0.015(+) r.u. 0.015(+) r.i. 0.015(−)	No. 840 g.u. 0.03 (+) r.u. 0.03 (+) r.i. 0.03 (−)	No. 841 g.u. 0.04 (+) r.u. 0.04 (+) r.i. 0.04 (−)	No. 842 g.u. 0.06 (+) r.u. 0.06 (+) r.i. 0.06 (−)
β-hydroxypropyl	No. 835 g.u. 0.12 (+) r.u. 0.12 (+) r.i. 0.12 (−)	No. 836 g.u. 0.12 (+) r.u. 0.12 (+) r.i. 0.12 (−)	No. 837 g.u. 0.12 (+) r.u. 0.12 (+) r.i. 0.12 (−)	No. 838 g.u. 0.12 (+) r.u. 0.12 (+) r.i. 0.12 (−)
ethyl	No. 819 g.u. 0.015(+) r.u. 0.015(+) r.i. 0.015(−)	No. 820 g.u. 0.015(+) r.u. 0.015(+) r.i. 0.015(−)	No. 821 g.u. 0.015(+) r.u. 0.015(+) r.i. 0.015(−)	No. 822 g.u. 0.06 (+) r.u. 0.06 (+) r.i. 0.06 (−)
isopropyl	No. 827 g.u. 0.12 (+) r.u. 0.12 (+) r.i. 0.06 (−)	No. 828 g.u. 0.12 (+) r.u. 0.12 (+) r.i. 0.06 (−)	No. 829 g.u. 0.12 (+) r.u. 0.12 (+) r.i. 0.06 (−)	No. 830 g.u. 0.12 (+) r.u. 0.12 (+) r.i. 0.12 (−)
propyl	No. 823 g.u. 0.06 (+) r.u. 0.06 (+) r.i. 0.06 (−)	No. 824 g.u. 0.06 (+) r.u. 0.06 (+) r.i. 0.06 (−)	No. 825 g.u. 0.06 (+) r.u. 0.06 (+) r.i. 0.06 (−)	No. 826 g.u. 0.12 (+) r.u. 0.12 (+) r.i. 0.12 (−)

"g.u.", "r.u." and "r.i." are abbreviations for guinea pig uterus, rabbit uterus and rabbit intestine respectively. The figures give the average millimolar concentration required to produce a slight stimulation (+), or a slight relaxation (−).

dioxide. The precision of this type of experiment is low and only grossly quantitative results can be obtained.

All 24 members of the group relaxed the intestine and stimulated both kinds of uterine tissue. Some of the compounds were quite active. No. 839, β-(2,5-dimethoxyphenyl)-β-hydroxyisopropylamine, was effective in concentrations as low as 1:333,333. The less potent compounds required concentrations of about 1:33,333. With regard to chemical structure, the only generalization which

could be drawn is that the quaternary compounds almost always were less potent than their homologs.

SUMMARY

A systematic study of a series of 24 β-2,5-dimethoxyphenylalkyl amine and quaternary compounds resulted in the discovery of several powerful, long-acting pressor substances of which No. 839, β-2,5-dimethoxyphenyl-β-isopropyl-amine, is outstanding.

Pressor activity generally was restricted to the primary and the secondary amines of the ethyl and the isopropyl series. Within these limits, the presence of a β-hydroxy group increased pressor activity. The β-methyl group, as manifested by the propyl compounds, always was inhibitory to pressor action. Tertiary and quaternary nitrogen derivatives usually were inactive. The β-hydroxyisopropylamines and compounds containing quaternary nitrogen enhanced epinephrine activity. The depressor effect of acetylcholine was decreased by certain compounds. All compounds contracted the isolated guinea pig and the isolated rabbit uterus, and all relaxed the isolated rabbit intestine.

Pressor activity was correlated strongly with mydriatic potency. Exophthalmos, salivation and pilomotor effects in the mouse usually, but not always, were associated with pressor properties.

REFERENCES

(1) HARTUNG, W. H.: Ind. and Eng. Chem., **37**: 126, 1945.
(2) BALTZLY, R., AND BUCK, J. S.: J. Am. Chem. Soc., **62**: 161, 1940.
(3) BALTZLY, R., AND BUCK, J. S.: J. Am. Chem. Soc., **62**: 164, 1940.
(4) BALTZLY, R., AND BUCK, J. S.: J. Am. Chem. Soc., **64**: 3040, 1942.
(5) HJORT, A. M.: THIS JOURNAL, **52**: 101, 1934.
(6) GRAHAM, B. E., AND CARTLAND, G. F.: THIS JOURNAL, **81**: 360, 1944.
(7) HJORT, A. M., DE BEER, E. J., BUCK, J. S., AND RANDALL, L. O.: THIS JOURNAL, **76**: 64, 1942.
(8) DE BEER, E. J., HJORT, A. M., AND COOK, C. A.: THIS JOURNAL, **65**: 46, 1939.
(9) HJORT, A. M., DE BEER, E. J., AND FASSETT, D. W.: THIS JOURNAL, **65**: 79–88, 1939.
(10) VAN DYKE, H. B., AND HASTINGS, A. B.: Am. J. Physiol., **83**: 563, 1927–1928.