SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF SOME DERIVATIVES OF *p*-AMINOPHENYLETHANOLAMINE

BY U. M. TEOTINO*, L. POLO FRIZ, G. STEIS* AND D. DELLA BELLA*

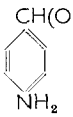
From the Research Department of the Laboratorio Bioterapico Milanese, Selvi & C., Milan

Received June 25, 1962

Synthesis of a series of *N*-alkyl derivatives of 2-amino-1-*p*-aminophenylethanolamine has been described, and the results of pharmacological screening reported. The antagonistic action exhibited at the adrenergic β-receptors by the *p*-nitro- and *p*-amino-*N*-isopropyl derivatives and the outstanding spasmolytic and bronchodilator activity of 1-*p*-aminophenyl-2-s-butylaminoethanol have been pointed out.

IN chemical and pharmacological investigations made in this laboratory on variously substituted phenylethanolamine derivatives, a series of *p*-nitrophenylamines was prepared (Teotino, Polo Friz, Steis and Della Bella, 1961).

In studying these compounds we prepared some hitherto unreported *p*-amino-derivatives of the structure I. These have received little attention



I Where R and R′ = H, Alkyl, Alkylaryl

from a biological point of view, although some interesting modifications of the pharmacological properties of sympathomimetic phenylalkylamines caused by the amino-group in the nucleus have been pointed out. Thus, in a comparison of bronchodilator activity in perfused guinea-pig lungs, *p*-aminoephedrine is reported to be twice as active as ephedrine and half as toxic (Tainter, 1933; Tainter and others, 1934), while *p*-aminophenethyldimethylamine was shown to be a hypertensive agent 10 times as potent as dimethylphenethylamine, but acting through a nicotinic mechanism (Bovet and Benoit, 1942).

Derivatives of 2-amino-1-*m*-aminophenylethanol have been investigated by Lands (1952), who reported that a pressor activity was exhibited by some derivatives, but no bronchodilator effects on guinea-pigs were observed with either the nor-derivative or 1-(*m*-aminophenyl)-2-isopropylaminoethanol.

A series of 2-alkylamino-1-(*m*- and *p*-aminophenyl)ethanols has been synthesised by Russian workers (Serghievskaja and Sventsitskaja, 1956) through 2-alkylbenzylamino-*m*- and *p*-nitroacetophenones. Catalytic hydrogenation of the latter compounds produced a simultaneous reduction of the nitro-group to an amino-group and of the keto-group to a secondary alcohol group as well as debenzylation of the original amino-group.

* Present address: Research Laboratories of Zambon S.p.A., Bresso-Milan.

Another Russian study (Syrneva, 1957) reports the activity of some alcohols of the structure: *m*- and *p*-$H_2N{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CH_2{\cdot}N(Me)R$ (R = from Me to C_5H_{11}). The sympathomimetic activity of these alcohols was shown to diminish on increasing R until when R = C_5H_{11} the derivative became sympatholytic.

We prepared the derivatives I (Table I) by reducing in ethanol the corresponding 2-mono- and -di-alkylamino-1-*p*-nitrophenylethanols at room temperature and atmospheric pressure using Pd over C as catalyst. The *p*-nitro-derivatives were obtained by reacting *p*-nitrostyrene oxide with primary or secondary amines (Teotino and others, 1961). The reduction usually proceeds quite rapidly (40–50 min.) until the theoretical quantity of hydrogen has been adsorbed. The corresponding monohydrochlorides of the aniline derivatives should be protected from air and light during isolation, to prevent excessive darkening.

The corresponding bases of the monoalkyl derivatives were obtained as solid substances readily purified by crystallisation from benzene; bases of dialkyl derivatives are mostly low-melting solids.

1-*p*-Aminophenyl-2-benzylaminoethanol monohydrochloride was obtained by reducing 2-benzylamino-1-*p*-nitrophenylethanol hydrochloride at room temperature and atmospheric pressure with Pd over C as catalyst; the product was subjected to hydrogenation again with Pd as catalyst and at 50–60° was debenzylated to give 2-amino-1-*p*-aminophenylethanol (Teotino and others, 1961).

The derivative of I where R = R′ = Me (1-*p*-aminophenyl-2-dimethylaminoethanol) was quaternised with ethyl iodide to obtain the corresponding ethiodide.

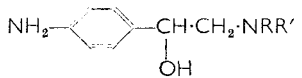
EXPERIMENTAL

*Reduction of 2-mono- and -di-alkylamino-*1-p-*nitrophenylethanols.* Reductions were effected at atmospheric pressure in a hydrogenation apparatus.

Example: 2-mono- or di-alkylamino-1-*p*-nitrophenylethanol hydrochloride (0·0735 mole) is dissolved or suspended in absolute ethanol (300 ml.). Pd over C (10 per cent 0·7 g.) is added and the mixture hydrogenated at room temperature. The reduction ceases when 0·218 mole of hydrogen has been absorbed. The catalyst is filtered off and the filtrate evaporated to dryness *in vacuo* in a current of nitrogen with protection from light. The residue solidifies on standing and is crystallised from a suitable solvent (Table I). Yield: 80–90 per cent of 2-mono- or di-alkylamino-1-*p*-aminophenylethanol monohydrochloride. The corresponding bases are obtained from aqueous solutions of the monohydrochlorides by the addition of alkali and successive extractions with a nonpolar solvent (diethyl ether or benzene).

1-p-*Aminophenyl-2-dimethylaminoethanol ethiodide.* 1-*p*-Aminophenyl-2-dimethylaminoethanol (1 g., 5·56 mmole) is dissolved in acetone (5 ml.). Ethyl iodide (0·86 g., 5·56 m mole) is added at room temperature. After about 10 min. crystals begin to separate. After 2 hr. the mixture is filtered: yield 1·4 g. (76 per cent), m.p. 195–6°. After recrystallisation from methanol m.p. rises to 198–9° (decomp.).

TABLE 1



R	R′	Derivative	Crystal solvent	m.p. °C	Found per cent				Formula	Required per cent				References
					C	H	Cl	N		C	H	Cl	N	
H	H	Monohydrochloride	Ethanol	150–2	50·81	6·81	18·64	14·75	$C_9H_{13}ClN_2O$	50·93	6·95	18·80	14·85	C.A., **48**, 10537 (1954)
H	Me	Base	Ethanol	124–5	64·90	8·41	—	16·70	$C_9H_{14}N_2O$	65·03	8·49	—	16·85	C.A., 51, 5047 (1957)
H	Et	Base	Isopropanol	134–5	66·55	8·89	—	15·61	$C_{10}H_{16}N_2O$	66·63	8·95	—	15·54	C.A., 51, 5047 (1957)
H	Pr^i	Base Monohydrochloride	Water Ethanol	138–9 157	67·54 57·34	9·37 8·22	— 15·27	14·37 12·31	$C_{11}H_{18}N_2O$ $C_{11}H_{19}ClN_2O$	68·00 57·25	9·34 8·30	— 15·37	14·42 12·14	C.A., 51, 5047 (1957)
H	Bu^n	Base		90	69·07	9·57	—	13·37	$C_{12}H_{20}N_2O$	69·19	9·68	—	13·45	C.A., 51, 5047 (1957)
*H	Bu^s	Base Monohydrochloride	Benzene Isopropanol	73–4 112–3	69·25 59·01	9·64 8·52	— 14·37	13·35 11·27	$C_{12}H_{20}N_2O$ $C_{12}H_{21}ClN_2O$	69·19 58·88	9·68 8·65	— 14·48	13·45 11·45	—
H	Bu^t	Monohydrochloride	Isopropanol	185–6	58·36	8·34	14·62	11·50	$C_{12}H_{21}ClN_2O$	58·88	8·65	14·48	11·45	—
H	$C_6H_5{\cdot}CH_2$	Monohydrochloride	Ethanol	155–6	64·53	6·61	12·31	10·54	$C_{15}H_{19}ClN_2O$	64·62	6·87	12·73	10·05	—
Me	Me	Ethiodide	Methanol	198–9	42·95	6·25	I=38·08	8·30	$C_{12}H_{21}IN_2O$	42·86	6·31	I=37·75	8·33	—
Et	Et	Monohydrochloride	Isopropanol	141–2	58·99	8·72	14·23	11·41	$C_{13}H_{21}ClN_2O$	58·88	8·65	14·48	11·45	—

* For this compound a patent application was filed in England under No. 23696/61 on June 30, 1961.

PHARMACOLOGICAL PROPERTIES OF THE COMPOUNDS EXAMINED

A preliminary screening of the pharmacological properties of the *p*-aminophenylethanolamines was effected *in vivo* on the blood pressure of the rat and cat, with simultaneous recording of nictitating membrane responses to electrical preganglionic stimulation, and *in vitro* on the rabbit and guinea-pig intestine responses to histamine, acetylcholine and barium chloride. At the same time the corresponding *p*-nitro-compounds (Teotino and others, 1961) were tested.

Except for the nor and *N*-methyl derivatives, which exhibited a slight hypertensive activity (1,000 to 1,500 times less potent than adrenaline), the *N*-alkylated derivatives with a higher alkyl substituent were all shown to possess some degree of hypotensive activity. This activity of both *p*-nitro- and *p*-amino- compounds increases as follows: propyl < iso-propyl < t-butyl < n-butyl < s-butyl; the *p*-amino-derivatives proved, however, much more active than the corresponding *p*-nitro derivatives.

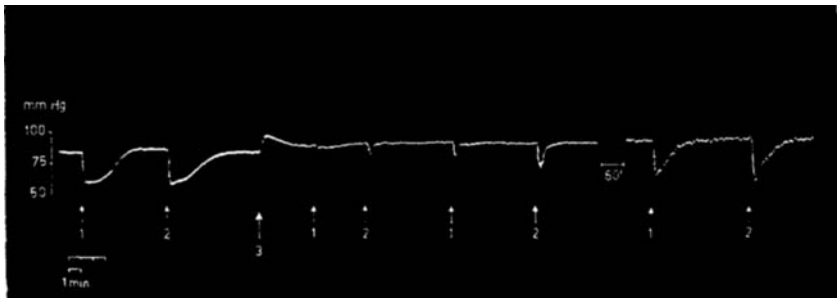


FIG. 1. Rat, 220 g., amylobarbitone anaesthesia (200 mg./kg., i.p.). Carotid blood pressure. Pretreatment (60 min. before) with 5 mg./kg. of phentolamine, intravenously. It can be seen that the characteristic hypotensive responses to adrenaline (0·25 μg./kg.) at (1) and to isoprenaline (0·16 μg./kg.) at (2), are abolished after administration of 10 mg./kg. of the *p*-nitro-*N*-isopropyl derivative intravenously at (3).

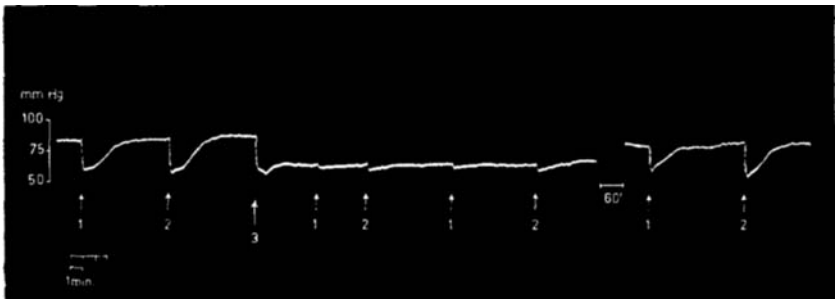


FIG. 2. Rat, 250 g., amylobarbitone anaesthesia (200 mg./kg., i.p.). Carotid blood pressure. Pretreatment (60 min. before) with 5 mg./kg. of phentolamine, intravenously. It can be seen that the characteristichypotensive responses to adrenaline (0·25 μg./kg.) at (1) and to isoprenaline (0·16 μg./kg.) at (2) are abolished after administration of 10 mg./kg. of *p*-amino-*N*-isopropyl derivative intravenously at (3).

The hypotensive property of the derivatives was not affected by pretreatment of the test preparation with atropine. The response of the nictitating membrane was not appreciably influenced by any of the compounds tested, and its response to both adrenaline and noradrenaline remained practically unmodified.

The pressor responses to *N*-ethyl derivatives were inconsistent, being hypertensive in some experiments and hypotensive in others. Of particular interest were the results obtained with the two *N*-isopropyl compounds, which exhibited an antagonistic action at the adrenergic β-receptor level. This property, illustrated in Figs. 1 and 2, was shown by both the *p*-amino- and the *p*-nitro-compounds in equal degrees: they inhibited both the reversed response to adrenaline after phentolamine and the response to isoprenaline. An experiment with dichloroisoprenaline effected under the same experimental conditions has also been reported for comparison (Fig. 3).

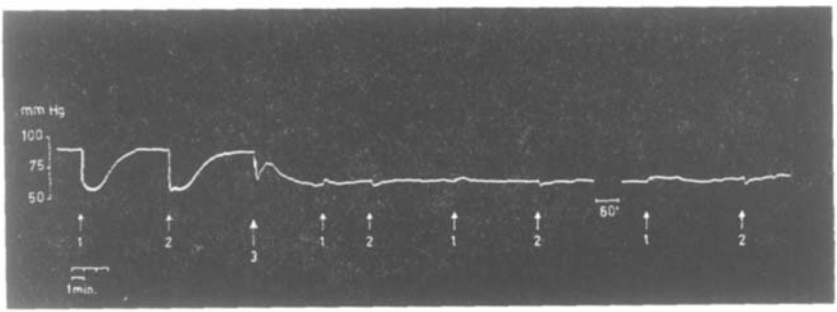


FIG. 3. Rat, 205 g., amylobarbitone anaesthesia (200 mg./kg., i.p.). Carotid blood pressure. Pretreatment (60 min. before) with 5 mg./kg. of phentolamine, intravenously. It can be seen that the characteristic hypotensive responses to adrenaline (0·25 μg./kg.) at (1) and to isoprenaline (0·16 μg./kg.) at (2) are abolished after administration of 10 mg./kg. of dichloroisoprenaline intravenously at (3).

The Figs. 1 and 2 show also the different pressor effects induced by the two derivatives after pretreatment of the test preparation with an adrenergic blocking agent: with the *p*-amino-derivative a constant hypotension is observed, while the hypotensive effect of the *p*-nitro-compound in the whole animal is reduced or even reversed. A more detailed study of the properties of the two compounds, which seem very similar to those of dichloroisoprenaline, will be reported. No significant effects were noted in the study of the *NN*-dialkyl derivatives. The quaternary ethiodide of the *NN*-dimethyl derivative, assayed on the rabbit isolated intestine with intact sympathetic nerve supply according to Finkleman, lacked any adrenergic nerve blocking activity. The *in vitro* experiments on the guinea-pig intestine response to histamine, acetylcholine and barium revealed that among the compounds tested those with a higher alkyl substituent were capable of antagonistic action. No appreciable differences were observed in this test between the *p*-amino- and the

p-nitro-compounds, but the compounds with a higher alkyl substituent, for example the *N*-isopropyl derivatives, and above all the *N*-butyl isomers, proved more active.

The influence of these latter derivatives on the isolated intestine of the rabbit is worthy of note. Among the *p*-amino-*N*-butyl-substituted isomers, only the s-butyl isomer exhibited a marked spasmolytic property. The corresponding *p*-nitro-derivatives instead proved effective stimulants of the rhythmic activity of the isolated organ. Figs. 4 and 5 show the qualitative as well as the quantitative differences observed between the two series of compounds.

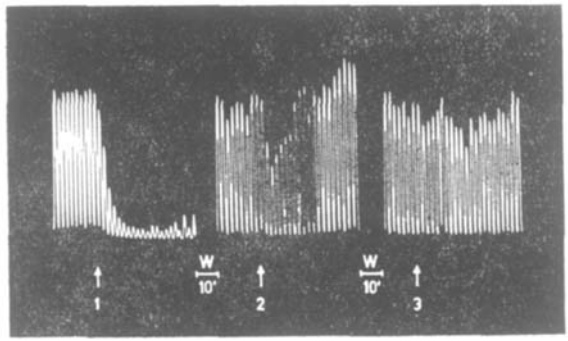


FIG. 4. Isolated rabbit duodenum in Tyrode solution. Differences in the influence exerted by *N*-butyl isomers of the *p*-amino-substituted series are shown. While the *N*-s-butyl derivative at (1), at a concentration of 5 μg./ml. (time of contact 2 min.), markedly inhibits the motor activity, both the *N*-t-butyl at (2) and the *N*-n-butyl derivative at (3), at concentrations of 10 μg./ml., proved almost inactive.

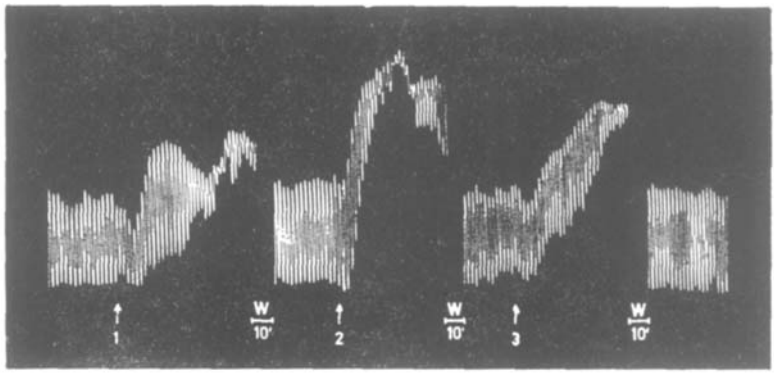


FIG. 5. Isolated rabbit duodenum in Tyrode solution. The properties of the *N*-butyl isomers of the *p*-nitro-substituted series were found to be different from the properties of the isomers of the *p*-amino-substituted series. The *N*-s-butyl at (1), the *N*-n-butyl at (2) and the *N*-t-butyl derivative at (3), at a concentration of 10 μg./ml., proved effective stimulants of intestinal motility.

Further Investigations

The results of preliminary *in vivo* and *in vitro* experiments reported prompted us to investigate further the properties of 1-*p*-aminophenyl-2-s-butylaminoethanol.

Acute toxicity. This derivative proved of low toxicity: the LD50 in rats was about 120 mg./kg. i.v. and 650 mg./kg. orally. On oral administration of 25 mg./kg. daily for 90 days there was no evidence of weight loss in the animals nor observable morphological changes in the blood or parenchymal organs (liver, kidney, spleen, bone marrow and gastric mucosa) were noted. Doses ranging from 5 to 50 mg./kg. i.v., in a single dose, produced in rats and cats a slight hypotension (10–20 mm. Hg at higher doses) of some duration.

Autonomic actions. No appreciable modifications have been observed on vagal and sympathetic peripheral synapses. The pressor responses to both adrenaline and noradrenaline remained unmodified and the responses to acetylcholine were slightly reduced. In the rabbit the electrocardiographic tracing, recorded at the moment of intravenous introduction of 10–20 mg./kg. of the compound, remained within normal limits and no change in pulse frequency was observed. The compound antagonised the effects of both acetylcholine and histamine on the guinea-pig intestine and also inhibited the motility of the rabbit intestine (Fig. 4). The responses to barium were abolished at a concentration of 20–30 μg./ml. of the compound. The responses of guinea-pig tracheal rings to histamine and acetylcholine were inhibited by the compound.

Spasmolytic activity. This derivative was successively tested for spasmolytic activity *in vivo* by observing its influence on the intestinal transit of wood charcoal introduced by a gastric tube and also on the

TABLE II

EFFECT OF INTRAPERITONEAL 1-*p*-AMINOPHENYL-2-S-BUTYLAMINOETHANOL, OF PAPAVERINE AND OF EPHEDRINE ON THE INTESTINAL TRANSIT OF WOOD CHARCOAL IN THE RAT

Treatment and dose, mg./kg.	No. of rats	Per cent of inhibition
Controls	10	0
Papaverine 10	10	49
Ephedrine 10	8	41
1-*p*-Aminophenyl-2-s-butylaminoethanol 25	12	42
,, ,, 50	12	59

TABLE III

TIME OF BRONCHOSPASM ONSET INDUCED BY AN AEROSOL OF A SOLUTION CONTAINING ACETYLCHOLINE (0·06 PER CENT), HISTAMINE (0·03 PER CENT) AND 5-HT (0·03 PER CENT) IN GUINEA-PIGS PRETREATED, ORALLY, BY 1-*p*-AMINOPHENYL-2-S-BUTYLAMINOETHANOL, EPHEDRINE AND DIPROPHYLLINE

(Mean results obtained in groups of 6 guinea-pigs are indicated)

Treatment and dose, mg./kg.		Time of bronchospasm onset after aerosol given A, 60, B 120 and C 240 min. after treatment with drug		
		A	B	C
Controls	45″			
Ephedrine 10		2′	1′ 40″	50″
Diprophylline 100		1′ 27″	1′ 53″	53″
1-*p*-Aminophenyl-2-s-butylaminoethanol		1′ 40″	3′ 14″	over 5′

onset of bronchospasm induced in the guinea-pig by an aerosol of a solution containing acetylcholine, histamine and 5-hydroxytryptamine. The effects of the compound upon the speed of peristalsis in the rat are illustrated in Table II. The results obtained with papaverine and ephedrine are shown for comparison.

Table III shows the results of experiments made to study protection against bronchospasm induced by an aerosol. As can be seen, the compound possessed an evident protective action, even more marked than that obtained by corresponding doses of diprophylline[7-(2,3-dihydroxypropyl)theophylline] and by ephedrine.

REFERENCES

Bovet, D. and Benoit, G. (1942). *C.R. Soc. Biol., Paris*, **136**, 328–329.
Lands, A. M. (1952). *J. Pharmacol.*, **104**, 474–477.
Serghievskaja, S. I. and Sventsitskaja, L. E. (1956). *Zhur. Obscei. Khim.*, **26**, 1967–1976; 2077–2081.
Syrneva, Yu. J. (1957). *Farmakol. i Toksikol.*, **20**, No. 4, 7–14.
Tainter, M. L. (1933). *Arch. int. Pharmacodyn.*, **46**, 192–232.
Tainter, M. L., Padden, J. R. and Jones, M. (1934). *J. Pharmacol.*, **51**, 371–386.
Teotino, U. M., Polo Friz, L., Steis, G. and Della Bella, D. (1961). *Il Farmaco, Ed. Sci.*, XVII, 252–264.