Tremor-Producing Aminopropanols

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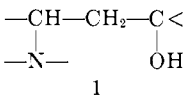
Twenty-one aminopropanols were prepared for testing as tremorogenic agents in mice. Efficiency of tremor detection by observation and by use of an electronic tremor detector were compared. The tremor detector made possible the quantitative detection of slight tremors which were not visually detectable. Time–activity data are presented for the aminopropanols, and data on antagonism studies with tremorine–scopolamine and tremorine–amphetamine are presented.

Tremor has been defined as oscillatory motion involving a part of the body that is moved by skeletal muscle.[1] This trembling or shaking may be regular or irregular, fine or gross, constant or periodic, and present at rest or with activity.[2] In humans, tremor is frequently associated with frontal lobe tumor, hysteria, Parkinson's disease, cerebellar abscess, multiple sclerosis, and hyperthyroidism. Tremors are known to be induced in experimental animals by a number of compounds including certain amino alcohols.[3,4] Conversely, some aminopropanols, including 3-dimethylamino-1-phenyl-1-(3-methoxyphenyl)propanol, have been patented as antispasmodics[5] and antiparkinsonism drugs.

A variety of aminopropanols of type **1** were prepared in this laboratory and their tremorogenic properties were evaluated in mice. These compounds were



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synthesized generally by treating an appropriate Grignard reagent with a 3-amino- or 3-substituted-aminopropionic ester. These esters were prepared either directly by the reaction of ethyl acrylate with an amine or by the reaction of substituted acrylic acids with hydroxylamine. In the final compounds the amine function was either primary, secondary, tertiary, or quaternary, acetylamino, carbamate, or, in one case, replaced by hydroxyl. The Grignard reagent used was phenyl-, benzyl-, or methylmagnesium halide. These compounds are listed in Table I and the new compounds are described in the Experimental Section.

A general behavioral screen with mice was used to determine the median lethal dose (LD_{50}) and the median effective dose (MED_{50}) for producing visually detectable tremors. These data are also listed in Table I. Tremors proved difficult to detect visually in the general screen and no distinction could be made between gross and fine tremors. Therefore, in order to rate the activities of our compounds and to differentiate between gross and fine tremors, all compounds were evaluated in mice using a tremor-detecting transducer. This transducer consisted of a pivotable inclined platform connected to a high-sensitivity, piezoelectric crystal (polarized barium titanate). A more detailed description of the tremor detector will be published elsewhere. An electrical signal related to tremor was generated when an animal was placed on the inclined platform. This signal was amplified (10^5), then filtered (20–40-cps bandpass) to diminish the nontremor components, and fed into two threshold detectors. These detectors were adjusted to trigger at two different voltages. As the threshold voltage of each detector was exceeded, a pulse was generated and recorded on a counter. The two counters thus reflected intensity and number of tremors for the 3-min test periods used.

In expt 1 the compounds were tested at 25 mg/kg ip at 10 min postinjection. The 10-min time period was determined as optimal from the tremor durations found in the general screen (Table I).

Of the 21 compounds evaluated in expt 1, ten were selected for further study. These ten compounds were tested at 25 mg/kg (expt 2) and at 15 mg/kg (expt 3) for 3-min durations at 5, 15, and 45 min postinjection. At each dosage level and time interval a blank, 0.1 *N* HCl, and tremorine [1,4-bis(1-pyrrolidino)-2-butyne][6] were also run as controls. The results are given in Tables II and III. In the tables, counter 1 and counter 2 data are presented both as percentages of the blank (0.1 *N* HCl) and of tremorine. Counter 1 measured the finer tremors while counter 2 measured the more coarse or gross tremors. Even at 25 mg, a near-toxic dose with some compounds, few of the mice exhibited well-defined, easily detectable, outward appearances of tremor. In these studies, usually only tremorine produced a tremor which could be readily detected visually.

A composite score for each of the ten compounds was derived by averaging the highest tremor-detector scores achieved on either counter 1 or counter 2 at anytime during expt 1–3. The ten composite scores were then rank ordered in terms of tremorogenic activity. Four compounds (**2, 8, 3,** and **17** in order of rank) met an arbitrary criterion of 200% of blank, or better, which was used as a crude estimate of tremorogenic potency. Three of these potent amino alcohols were found also to be tremorogenic in the mouse general behavioral screen. The fourth, however (which ranked second in tremorogenic potency according to the tremor detector system), was not detected in the mouse screen (see Table I).

The four most active compounds were again evaluated at 15 mg in expt 4. Tremorogenic activity was measured at 5, 10, 15, 30, and 45 min postinjection.

(1) H. Wachs and B. Boshes, *Arch. Neurol.*, **4**, 66 (1961).
(2) H. Wachs, *Neurology*, **14**, 50 (1964).
(3) A. Ahmed, P. B. Marshall, and D. M. Shepherd, *J. Pharm. Pharmcol.*, **10**, 672 (1958).
(4) J. P. Ayton and P. B. Marshall, *ibid.*, **15**, 217 (1963).
(5) M. Ose and H. Kaneko, Japanese Patent 14,728 (1963); *Chem. Abstr.*, **60**, 455 (1964).
(6) G. M. Everett, L. E. Blockus, and I. M. Shepperd *Science*, **124**, 79 (1956).

Table I

Chemical and Biological Data

$$RCHCH_2C\lessgtr^{R_1}_{R_2}$$

X OH

No.	No.	X	R_1	R_2	Ref for prepn or mp, °C	Visual tremor detection in mouse general behavioral screen[a] LD_{50}, mg/kg iv	No. affected	Tremor MED_{50}, mg/kg iv	Tremor duration, min
1	2-Furyl	NH_2	C_6H_5	C_6H_5	*b*	25	2/2	10	3–27
2	C_6H_5	NH_2	C_6H_5	C_6H_5	*b–d*	45	2/2	3.16	3–27
							2/2	10	15–45
3	2-Thiophenyl	NH_2	C_6H_5	C_6H_5	160–161	25	1/2	3.16	3–12
							2/2	10	3–27
4	4-Anisyl	NH_2	C_6H_5	C_6H_5	*e*	25	0/2	20[f]	
5	C_6H_5	NH_2	$C_6H_5CH_2$	$C_6H_5CH_2$	*b*	18	2/2	3.16	3–12
6	C_6H_5	OH	C_6H_5	C_6H_5	*d*	>100	0/2	10[g]	
7	4-Anisyl	$NHCOCH_3$	C_6H_5	C_6H_5	*c*	>200	0/2	31.6	
8	H	NHC_2H_5	C_6H_5	C_6H_5	*h*	56	0/2	50	
9	H	$N(C_2H_5)_2$	C_6H_5	C_6H_5	*h*	44	1/2	31.6	3–12
10	H	$N^+(C_2H_5)_2CH_3I^-$	C_6H_5	H	*h*	14	0/2	12.6	
11	C_6H_5	NH_2	H	H	*c*	>90	0/2	100[i]	
12	H	NH_2	C_6H_5	H	*c*	>100	0/2	100	
13	H	$N^+(C_2H_5)_2CH_3Cl^-$	C_6H_5	C_6H_5	*h*	2	1/2	3.16	3–15
14	H	$N(C_2H_5)CO_2CH_3$	C_6H_5	C_6H_5	83–84	>100	2/2	100	15–120
15	4-Anisyl	NHC_2H_5	C_6H_5	C_6H_5	242	35	0/2	3.16	
16	C_6H_5	$NHCOCH_3$	C_6H_5	C_6H_5	*c*	10	1/2	10	15–120
17	C_6H_5	NHC_2H_5	C_6H_5	C_6H_5	102	32	2/2	3.16	3–30
18	C_6H_5	$N(C_2H_5)COCH_3$	C_6H_5	C_6H_5	197–198	100	0/2	100	
19	C_6H_5	$N(C_2H_5)_2$	C_6H_5	C_6H_5	249 dec	80	0/2	79	
20	C_6H_5	$N^+(C_2H_5)_2CH_3Cl^-$	C_6H_5	C_6H_5	244–245	57	0/2	56	
21	C_6H_5	NH_2	CH_3	CH_3	75	56	0/2	56	

[a] In conducting the research reported herein, the investigators adhered to the "Guide for Laboratory Animals Facilities and Care," U. S. Public Health Service Publication No. 1024, Revised 1965. [b] Reference 3. [c] Reference 4. [d] I. A. McKenzie and A. C. Richardson, *J. Chem. Soc.*, **123,** 90 (1923). [e] J. English and A. D. Bliss, *J. Am. Chem. Soc.*, **78,** 4060 (1956). [f] In the cases where no animals were affected, the MED_{50} values are the highest dosages tried. [g] Injected as a suspension in propylene glycol. [h] D. W. Adamson, *J. Chem. Soc.*, 8-146 (1949). [i] Injected as a suspension in DMSO.

Table II

Biological Tremor Detector Data for Expt 2[a]

No.	Test compd counts as % blank 5 min	15 min	45 min	Test compd counts as % tremorine 5 min	15 min	45 min
	Counter 1 (Fine Tremors)					
2	157	242	282	20	24	11
3	162	210	218	17	23	40
6	53	63	75	11	9	18
8	74	226	146	22	45	85
9	182	203	103	30	34	16
15	90	126	136	17	26	31
16	81	80	94	13	10	15
17	244	220	141	31	22	21
18	94	131	107	7	11	15
21	115	182	79	12	19	9
	Counter 2 (Gross Tremors)					
2	183	344	26	20	20	72
3	167	202	173	36	37	81
6	63	64	87	17	9	44
8	47	232	137	22	68	228
9	205	214	106	52	40	50
15	162	86	191	27	22	50
16	109	91	122	23	16	7
17	266	197	199	32	20	54
18	183	152	50	10	14	15
21	148	130	86	21	19	12

[a] The compounds were administered in a dose of 25 mg/kg ip.

Table III

Biological Tremor Detector Data Expt 3[a]

No.	Test compd counts as % blank 5 min	15 min	45 min	Test compd counts as % tremorine 5 min	15 min	45 min
	Counter 1 (Fine Tremors)					
2	121	264	218	26	43	46
3	205	185	229	21	24	44
6	110	99	26	18	13	11
8	65	127	120	23	27	153
9	123	170	149	49	65	32
15	82	99	113	15	15	34
16	92	96	111	14	14	20
17	188	185	132	18	24	36
18	45	110	47	18	15	7
21	179	156	171	40	20	30
	Counter 2 (Gross Tremors)					
2	164	461	208	36	110	72
3	213	126	165	48	31	68
6	109	107	9	21	20	7
8	39	71	76	44	19	245
9	110	163	135	107	131	34
15	86	102	138	20	17	53
16	142	112	108	27	20	49
17	191	217	119	31	49	109
18	130	64	21	28	20	6
21	214	131	296	85	26	92

[a] The compounds were administered in a dose of 15 mg/kg ip.

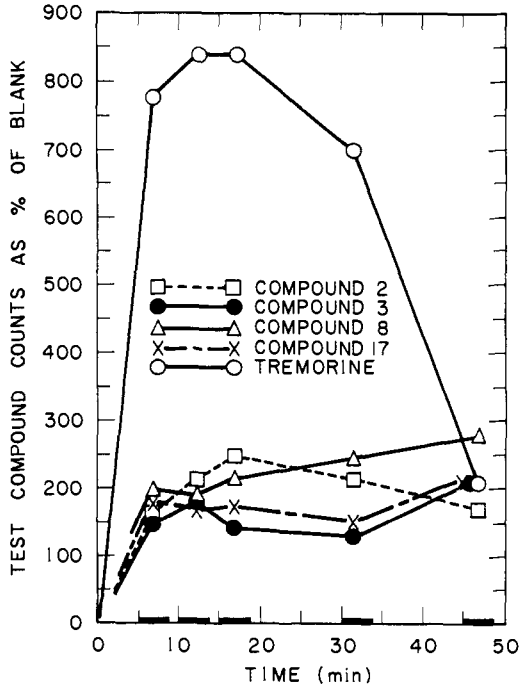

Figure 1.—The counts on counter 1 for the test compounds (15 mg/kg) and tremorine (15 mg/kg) as compared to a blank are graphed at the different time periods. Data from expt 4.

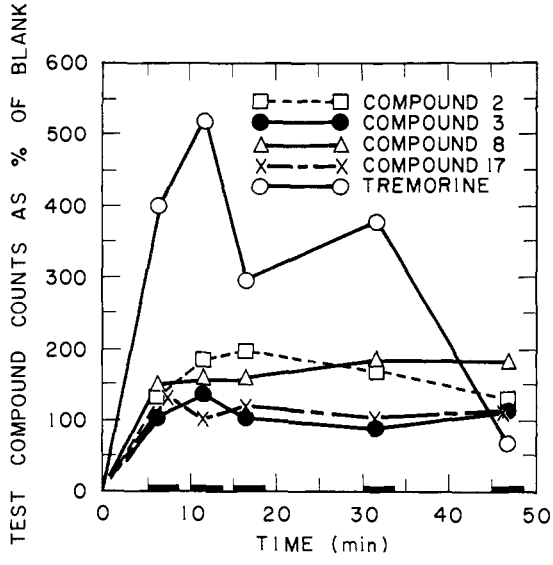

Figure 2.—The counts on counter 2 for the test compounds (15 mg/kg) and tremorine (15 mg/kg) as compared to a blank are graphed at the different time periods. Data from expt 4.

The results are graphed in Figures 1–3. Figure 1 shows the counter 1 data; Figure 2, counter 2 data; and Figure 3, counter 3 data. (A third counter was added to the tremor-detector system for these experiments and measured the most gross tremors.)

Further studies were undertaken to determine whether the neuromuscular vibrations recorded on the electronic detecting and counting apparatus were actually tremor. Frommel and associates[7] studied the effect of scopolamine (1 mg/kg sc) and tremorine (20 mg/kg sc) simultaneously injected into mice. After

(7) E. Frommel, C. Fleury, I. v. Lederbur, M. Beguin, and S. Family, *Arzneimittel-Forsch.*, **13**, 855 (1963).

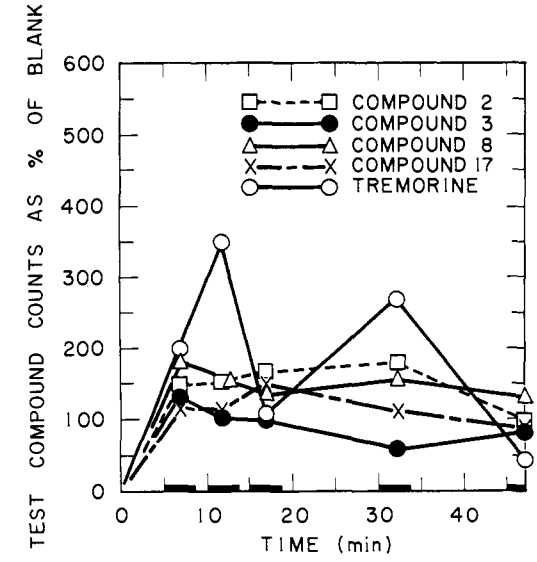

Figure 3.—The counts on counter 3 for the test compounds (15 mg/kg) and tremorine (15 mg/kg) as compared to a blank are graphed at the different time periods. Data from expt 4.

30, 60, and 120 min, the tremors were evaluated visually and arbitrarily scored as follows: no tremor = 0, moderate tremor = 5, and acute tremor = 10. The unchallenged tremorine controls averaged 150 points, whereas the mice in the scopolamine–tremorine experiment were rated at 15 points. In a similar experiment, mice simultaneously injected with amphetamine at 10 mg/kg sc and tremorine at 20 mg were rated at 60 points by these experimenters.

The above experiments were repeated in our laboratories at the same drug dosages. Instead of detecting tremor visually, however, the tremor detector was used. Scopolamine (1 mg/kg sc), amphetamine (10 mg/kg sc), tremorine (20 mg/kg sc), and blank (0.1 *N* HCl) each were administered to ten mice and the neuromuscular effects were recorded for 3 min at 30 min postinjection. Other groups of animals were given simultaneous doses of scopolamine–tremorine and amphetamine–tremorine. Figure 4 graphically illustrates the results; each compound and combination are charted according to total counts on each counter for 3 min. The blank value was reasonably constant on all three counters and scopolamine showed little or no tremorogenic effect at this dosage. Amphetamine produced a characteristic graph with the counts on counters 1 and 3 being higher than those on counter 2. Counters 1 and 3 were approximately 250% of blank, while counter 2 was nearly 200%. Tremorine was the most tremorogenic and showed its characteristic properties by producing more fine than gross tremors. The tremors induced by 20 mg of tremorine were effectively reduced by 1 mg of scopolamine; the fine tremors on counter 1 were reduced by 57%, the tremors on counter 2 reduced 69%, and those on counter 3 by 78%. The coarse tremors sensed on counter 3 were actually 66% lower than blank. Amphetamine at 10 mg did not decrease the amount of tremorine-induced tremor as effectively as scopolamine. The fine tremors were reduced by 14% and the moderate tremors by 13%. The coarse tremors were increased by 60% showing that the strong effect of amphetamine in producing gross or coarse tremors was prevalent.

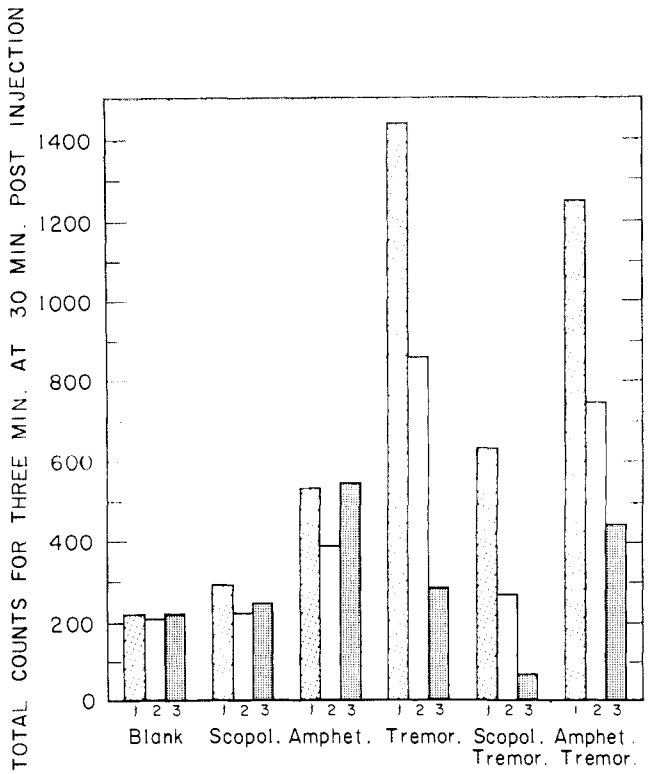

Figure 1.—The total counts for 3 min at 30 min postinjection are graphed for blank (0.1 *N* HCl), scopolamine (1 mg/kg), amphetamine (10 mg/kg), tremorine (20 mg/kg), scopolamine–tremorine, and amphetamine–tremorine; counters 1-3 are shown.

Discussion

Production of a sustained tremor without convulsion and death is rare. None of the ten most active aminopropanols caused death at 15 mg/kg ip, and at least four (**2**, **3**, **8** and **17**, Table I) produced both both gross and fine tremors for a sustained period. Of 21 compounds studied in the mouse general behavioral screen in which tremor was detected visually, **1**, **2**, **3**, **5**, and **17** were found to be active at 3.16–10 mg/kg iv and **3** and **13** to be active in one of two mice at 3.16 mg. Of these, however, only **2**, **3**, and **17** were active at 25 mg/kg ip using the tremor detector. Ahmed[3] tested three of the compounds which were also prepared and tested in our study. He found **2** and **5** to be active at 25 mg/kg ip, and **1** to be active at 35 mg. These relative activities agree with the results of our general screen using visual detection, but, by using the tremor detector, a quantitative measure of tremor was possible, and **2** and **5** were not equally potent. At 25 mg and 10 min postinjection, the rank of activity using the detector was **8**, **3**, **2**, **10**, and **9**. Compounds **10** and **9**, however, had little or no activity in the general mouse screen and **5** and **1** which were active in the general screen proved to be inactive when tremor was detected electronically. In more exhaustive experiments at 25 mg, **2** showed good activity in producing fine tremors. However, its activity in producing gross tremors declined rapidly after maxima at 15 min postinjection.

Compound **8** was the most active compound at the lower dosage of 15 mg in producing both fine and gross tremors as shown in Figures 1 and 2. These graphs show that the activity of **8** was still strong at 45 min, whereas again **2** had peak activity at 15 min. Figure 3 shows data from counter 3 which tabulated counts from a detector set to measure only the most gross tremors. Compounds **2** and **8** were nearly equal in activity, whereas **3** and **17** were ineffective.

The tremorogenic actions of scopolamine and amphetamine were studied. At the dosages used, scopolamine produced negligible tremors and amphetamine was weakly active. Amphetamine produced a high porportion of gross and fine tremors but fewer moderate tremors. This type of gross, high-frequency, neuromuscular effect occurs often in mice treated with amphetamine. Tremorine showed a characteristic activity pattern by producing a high proportion of fine tremors in comparison to the moderate and gross tremors. In tremorine-antagonism studies, fine, moderate, and gross components of tremor were detected and charted. Scopolamine greatly reduced the action of tremorine on all three counters; the gross tremors on counter 3 were actually lower than control, indicating a possible sedative effect. The tremorine-produced fine and moderate tremors were only slightly diminished by amphetamine while the gross tremors were slightly elevated, indicating the production of coarse vibrations by amphetamine.

From our work, we infer that tremorine is more effective in mice at 15 than at 25 mg/kg ip, and that maximum tremorogenic activity occurs at 10–13 min postinjection. Possibly the most interesting aminopropanol studied was **8** which at 15 mg consistently produced tremors beyond 45 min. Since this compound produced no visually detectable tremors in mice at doses to 50 mg/kg iv, in the mouse general behavioral screen, the presumption is that the tremors were so fine as to be undetectable by visual scanning only. Our results argue strongly for the use of a quantitative, tremor-detection apparatus for the detection and quantification of tremorogenic compounds.

Experimental Section

All melting points were taken on a Fisher-Johns melting block and are uncorrected.

Chemical. 3-Amino-3-(2-thiophenyl)propionic Acid.—3-(2-Thiophenyl)acrylic acid and hydroxylamine, according to the procedure of Ahmed and co-workers[3] for the furyl isomer, gave 23% of product, mp 210–212°. Russian workers[8] recorded mp 207–208° (different method of preparation).

3-Amino-1,1-diphenyl-3-(2-thiophenyl)-1-propanol (3). 3-Amino-3-(2-thiophenyl)propionic acid was esterified by refluxing in ethanolic HCl. After distillation (bp 106°, 1.0 mm) a 65% yield was obtained. The oil and phenylmagnesium bromide, according to the method of Ahmed, *et al.*,[3] gave **3** in 8% yield, mp 160–161° (from butyl chloride).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 73.8; H, 6.19; N, 4.53. Found: C, 73.6; H, 6.28; N, 4.29.

Methyl 1-(N-Ethyl-3-hydroxy-3 3-diphenylpropyl)carbamate (14).—3-Ethylamino-1,1-diphenyl-1-propanol (**8**, 1.0 g, 4.0 mmoles) and 25 ml of $CHCl_3$ were stirred with 1.2 g (30.0 mmoles) of NaOH in 25 ml of water. To this cooled mixture, 0.57 g (6.0 mmoles) of methyl chloroformate was added. This mixture was stirred in an ice bath for 0.5 hr, kept at 25° overnight, acidified with dilute HCl, and shaken well. The organic layer was separated, dried, and concentrated to yield 1.24 g of yellow oil which soon solidified and was recrystallized from butyl chloride; mp 83–84°.

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.8; H, 7.40; N, 4.47. Found: C, 73.2; H, 7.42; N, 4.41.

3-Ethylamino-3-(4-anisyl)-1,1-diphenyl-1-propanol (15). 3-Acetamido-3-(4-anisyl)-1,1-diphenyl-1-propanol (**7**, 1.0 g, 2.7

(8) V. P. Mamaev, N. N. Savorov, and E. M. Rokhlin, *Dokl. Akad. Nauk. SSSR*, **101**, 269 (1955).

mmoles) was reduced with $LiAlH_4$ (0.3 g, 8.0 mmoles) in 30 ml of tetrahydrofuran (THF) by refluxing for 24 hr. The yellow oil (quantitative yield) was converted to the **hydrochloride salt** (6 *N* HCl), mp 242° (from ethyl alcohol).

Anal. Calcd for $C_{24}H_{27}NO_2 \cdot HCl$: C, 72.6; H, 7.12; N, 3.52. Found: C, 72.5; H, 7.03; N, 3.86.

3-Ethylamino-1,1,3-triphenyl-1-propanol (**17**).—3-Acetamido-1,1,3-triphenyl-1-propanol (**16**, 20.0 g, 0.06 mole) was refluxed with $LiAlH_4$ (0.18 mole) in THF for 24 hr. The product was isolated by ether extraction and recrystallized from cyclohexane to yield 13.9 g (74%), mp 102°. Witting, *et al.*,[9] gave mp 104–105° for material obtained from the reaction of phenyllithium and 3-ethylimino-1-hydroxy-1,1-diphenylpropane.

3-(N-Ethylacetamido)-1,1,3-triphenyl-1-propanol (**18**).—Compound **17** (11.7 g, 0.037 mole) was heated for 2 hr at 50° with acetic anhydride (0.066 mole) and acetic acid (0.033 mole). The product crystallized from the hot mixture and was isolated and recrystallized from ethanol to yield 11.4 g (83%), mp 195°. An analytical sample, mp 197–198°, was obtained by further recrystallizations from ethanol.

Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.4; H, 7.29; N, 3.75. Found: C, 80.3; H, 7.31; N, 3.73.

3-(N,N-Diethylamino)-1,1,3-triphenyl-1-propanol (**19**).—Compound **18** (9.1 g, 0.025 mole) was refluxed overnight with $LiAlH_4$ in THF. The free base was isolated as a yellow oil in 93% yield. The **hydrochloride salt** was prepared with hot 6 *N* HCl and purified by recrystallization from dilute ethanol; mp 249° dec.

Anal. Calcd for $C_{25}H_{29}NO \cdot HCl$: C, 75.8; H, 7.64; N, 3.54. Found: C, 75.5; H, 7.87; N, 3.68.

Methyldiethyl-(3-hydroxy-1,3,3-triphenylpropyl)ammonium Chloride (**20**).—Base **19** (3.0 g, 8.4 mmoles), 3 ml (80 mmoles) of methyl iodide, and 10 ml of ethanol were heated for 4 hr at 100° in a steel bomb. The solution was concentrated, and the gum was triturated with isopropyl alcohol to give a solid. One recrystallization from isopropyl alcohol yielded the yellow iodide salt, 1.15 g, mp 185–187° dec. It was stirred for 3 hr with Dowex 2 (chloride) resin in 100 ml of methanol. The mixture was then filtered and concentrated, and the chloride salt was recrystallized from isopropyl alcohol–water. The analytical sample had mp 244–245.°

Anal. Calcd for $C_{26}H_{32}ClNO \cdot 0.5H_2O$: C, 74.5; H, 7.76; N, 3.34. Found: C, 74.8; H, 7.79; N, 3.28.

(9) G. W. Witting, H. J. Schmidt, and H. Renner, *Chem. Ber.*, **95**, 2377 (1962).

3-Amino-1,1-dimethyl-3-phenyl-1-propanol (**21**).—Ethyl 3-amino-3-phenylpropionate[3] (3.8 g, 0.02 mole) was refluxed with methylmagnesium bromide (3 *M* in ether, 27 ml, 0.08 mole) in ether overnight. The reaction was worked up and the resulting oil was stirred with 4 ml of 2.5 *N* NaOH for 1 hr and left at 25° in order to hydrolyze a small amount of starting ester. The alkaline mixture was extracted with ether, which was dried and concentrated to give 1.5 g (42%) of an oil which crystallized. This material showed no ester carbonyl in the infrared. An analytical sample, mp 75°, was prepared by recrystallization from butyl chloride.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.7; H, 9.56; N, 7.81. Found: C, 73.6; H, 9.66; N, 7.84.

Biological.—For testing purposes, all aminopropanols were dissolved either in 0.1 *N* HCl or suspended (**6**, **16**, and **18**) by homogenizing with 0.1 *N* HCl and 2 drops of Tween 80. These solutions or suspensions were administered to male, albino mice (18–25 g) either intravenously *via* the tail vein (general behavioral screen, LD_{50}, MED_{50}) or intraperitoneally (tremor detector). The animals were periodically tested and observed in the behavioral screen at 3, 15, 30, and 60 min following injection. Two animals per dose level (0.1 log intervals) were used for LD_{50} determinations.

In the initial tremor-detector experiments carried out at 10 min postinjection and at a dosage of 25 mg/kg ip (expt 1) ten animals were used per compound and ten each for control (tremorine) and blank (0.1 *N* HCl). In expt 2 and 3 at 5, 15, and 45 min postinjection and at dosages of 25 and 15 mg/kg ip, five animals per compound for each of the time periods were used; four test compounds, tremorine, and a blank were evaluated each day for 5 days. The tremorine values at each time period are means of 50 mice. In expt 4, 15 mice per time period in a regimen of three mice per day for 5 days were used. The tremorine and blank controls were evaluated in ten mice per time period. In all experiments, a different group of animals was used for each time period to avoid acclimatization and no animal was used more than once. In expt 1–4, drug concentrations were adjusted for an injection of 0.5 ml/animal. In the antagonism studies, 0.2 ml of drug solution was administered.

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Aryloxyalkylaminoguanidines. Their Synthesis and Biological Properties[1]

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Proton magnetic resonance has been used to show that the products of guanylation of aryloxyethylhydrazines are (aryloxyethylamino)guanidines. Several such aminoguanidines containing chlorine and methyl substituents in the aromatic ring have been shown to possess adrenergic neuron blocking properties and to inhibit dopamine β-oxidase *in vitro*.

There is a striking similarity about certain features of the structure–activity patterns displayed by several series of compounds which affect the functioning of the adrenergic system. Thus, in a series of biologically

$$\underset{\text{I}}{Ar(CH_2)_nB} \qquad \underset{\text{II}}{ArY(CH_2)_nB}$$

B = a, NR_2; b, $^+NR_3$; c, $NHC\lesssim^{NR}_{NHR}$; d, $\overset{+}{N}R_2NH_2$

active bases of general formula I where extension of the chain by one methylene group leads to loss of activity, chain extension by introduction of a group Y (see II), where Y can represent O, S, NH, or CH=CH, frequently allows retention of activity.

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