RESEARCH PAPERS

PHARMACOLOGY OF TREMOR-PRODUCING AMINO ALCOHOLS

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The pharmacological properties of a series of amino alcohols of the general formula $RCH(NH_2)\cdot(CH_2)_n\cdot C(OH)R_2$ have been studied The most striking action of these compounds is their ability to produce a sustained tremor, which is compared with those produced by other tremorogenic agents. The activities of various drugs as antagonists of the amino alcohol tremor are described.

IN recent years considerable attention has been directed to tremor-producing compounds because of their unusual central excitant activity, their usefulness in studying the phenomenon of tremor and for screening anti-Parkinsonian agents. Nicotine and eserine produce transient tremor often associated with clonic convulsion and anoxia. Tremor of short duration is also produced by aminothiols such as β-mercaptoethylamine[1], but drugs which evoke sustained tremor in experimental animals are rare. Harmine and harmaline produce tremor which lasts for 15–30 minutes in mice, while Tremorine, 1 : 4-di-(1-pyrrolidino)-2-butyne, produces severe tremor lasting for 1–3 hours in mice, and for 24 hours or more in dogs and monkeys[2]. Besides causing tremor, Tremorine also gives rise to salivation, lachrymation, diarrhoea and muscular weakness with rigidity.

The present paper reports the production of sustained tremor and ataxia in experimental animals by some amino alcohols recently synthesized in this department. The paper also presents a detailed pharmacological study of one typical representative of the tremor-producing amino alcohols.

In those amino alcohols containing an asymmetric carbon atom the tests described were made with the racemic compounds.

METHODS

Tremor producing activity. Albino mice weighing 18 to 30 g. were used. Doses were given on a mg./kg. basis. Solutions of the compounds in 0·1 N HCl were diluted with 0·9 per cent saline so that the required amount could be given intraperitoneally in a volume of 0·5 ml./25 g. Groups of 5 or 10 mice were used for each dose. As control 5 or 10 animals were injected with saline (0·5 ml./25 g.). The percentage of animals in each group showing tremor within a period of 3 hours after injection was noted. Only those animals which showed sustained tremor of head, body and limbs, and rigid erection of tail were assessed as positive responses. The Median Effective Dose (ED50) and its standard error were calculated for

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each compound by Irwin and Cheesman's modification[3] of Kärber's method[4]. Tests were repeated on the same group of animals after an interval of 7 to 10 days.

Influence of various substances on amino alcohol-induced tremor. Aqueous solutions of various substances were given subcutaneously to groups of five or ten albino mice at three or more dose levels. The drug concentration was adjusted to enable the volume injected in each case to be 0·25 ml. per 25 g. body weight. Thirty minutes later the animals were given an intraperitoneal injection of a tremor-producing dose (ED80) of an amino alcohol. In each group the fraction of the animals which showed tremor of the head, body and limbs within 3 hours was noted. As controls 5 or 10 animals were given the tremor-producing agent intraperitoneally.

Local anaesthetic activity. The intracutaneous weal test of Bülbring and Wajda[5] was employed. Each substance was tested in at least four guinea pigs. The dose of each compound corresponding to half the total number of stimuli was taken as the measure (ED50) of local anaesthetic activity. The relative potencies were derived from the dose-response curves.

Spasmolytic acitivity. Sections of ileum from freshly killed guinea pigs were suspended in a 2·5 ml. bath of Tyrode solution at 36°. After equilibration sufficient spasmogen (acetylcholine, histamine or nicotine) was added to the bath to evoke a submaximal response. The effect of amino alcohols on contractions produced by the above spasmogens was studied qualitatively.

The potency of two of the compounds as acetylcholine antagonists was quantitatively measured by determining pA_2 and pA_{10} values by Schild's method[6].

Isolated heart. An isolated frog heart attached to a Straub cannula was perfused with Ringer solution of the following composition: 0·65 NaCl, 0·01 KCl, 0·01 $CaCl_2$, 0·02 $NaHCO_3$ per cent (w/v) in distilled water. In most instances drug dilutions of 1×10^{-7}, 1×10^{-6}, 1×10^{-5} were tested. The pH of the drug solutions was adjusted to approximately 7. Between tests the perfusion was exchanged at least 3 times and a minimum of 10 minutes was allowed for recovery of the tissue.

Isolated rabbit auricles. The effect of amino alcohols on isolated rabbit auricles suspended in a 50 ml. bath of oxygenated Ringer solution at 29° was studied.

Isolated frog rectus abdominis muscle. The muscle was suspended in a 5 ml. bath of aerated frog Ringer solution. The stimulant effect of acetylcholine was recorded for 90 seconds every 5 minutes till consistent responses were obtained. The amino alcohol was then added to the bath 90 seconds before the next dose of acetylcholine. Its own effect on the muscle was also recorded for 90 seconds. The action of tubocurarine in modifying the stimulant effect of acetylcholine and amino alcohols was observed in the same way.

Blood pressure. The carotid blood pressure was recorded in cats anaesthetized with ether followed by chloralose 50 mg./kg., intravenously.

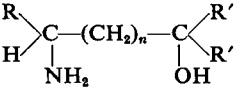
The amino alcohol was given in 0·9 per cent saline through a cannula in the femoral vein.

RESULTS

The chemical formulae of the twelve amino alcohols studied are shown in Table I together with their tremor-producing activity. Of these, nine compounds produced symptoms of central excitation which, at least in the dose range employed (15 to 30 mg./kg. i.p.), was the same qualitatively. As the first sign of excitation, the mouse showed motor unrest and frequent spasmodic forward movement. Some mice, particularly those treated

TABLE I

TREMOR PRODUCING ACTIVITY OF AMINO ALCOHOLS



Compound No.	Chemical formula			ED50 (Tremor) mg./kg. i.p.	Limits of ED50 mg./kg. i.p. P = 0·95
	R	R′	n		
1	C_6H_5	C_6H_5	0	45·24	42.77–48·26
2	C_6H_4	$C_6H_5CH_2$	0	49·64	41·85–58·7
3	C_6H_5	*o*-$MeOC_6H_4$	0	41·32	36·48–46·84
4	H	C_6H_5	0	30·32	26·16–35·17
5	CH_3	C_6H_5	0	36·18	30·5 –40·92
6	C_6H_5	C_6H_5	1	23·7	20·25–27·73
7	C_6H_5	$C_6H_5CH_2$	1	23·8	20·6 –27·38
8	C_6H_5	*p*-MeC_6H_4	1	—	—
9	C_6H_5	*m*-MeC_6H_4	1	28·64	24·43–32·7
10	C_6H_5	*o*-$MeOC_6H_4$	1	—	—
11	H	C_6H_5	1	>100	—
12	2-Furoyl	C_6H_5	1	35·36	30·4 –41·1

with aminoethanols, or the furyl-substituted aminopropanol (Compound 12) showed jumping and squeaking fits. These animals recovered from the fit within an hour, but showed marked reflex hyperexcitability.

Compounds No. 6, 7 and 9 produced a characteristic syndrome within the dose range of 20 to 40 mg./kg. intraperitoneally. The animals showed tremor of the head, body and limbs with rigid erection of the tail within 6 to 15 minutes after the injection. The tremor was continuous, severe, and sustained, lasting from 1 to 3 hours. With the tremor there was continuous struggling forward movement and frequent retropulsion or circling movement. At times the animal exhibited forward extensor spasm particularly when stimulated by sound or touch. Tremor was present at rest, but became more marked on movement. All four limbs, especially the forelimbs showed continuous irregular movements. These movements resembled neither the normal clonic convulsion nor the running movements provoked by nicotine. After 1 to 3 hours, the animals became more or less quiet showing occasional bursts of transient tremor. With higher doses (40–100 mg./kg. i.p.), the animals showed tremor which soon developed into clonic convulsion. Recovery followed or death occurred from respiratory paralysis.

The animals showed no salivation or lachrymation, but sometimes passed faeces and urine frequently.

TABLE II

INFLUENCE OF VARIOUS DRUGS ON TREMOR INDUCED BY COMPOUND 6 (1 : 1 : 3-TRIPHENYL-3-AMINOPROPAN-1-OL)

Drug	Control: No. showing tremor/No. injected	Treated: Dose mg./kg. s.c.	Treated: No. showing tremor/No. injected
Atropine sulphate	7/10	5	9/10
		10	9/10
		20	9/10
Hyoscine hydrobromide	4/5	5	4/5
		10	4/5
		20	4/5
	4/5	5	5/5
		10	5/5
		20	5/5
	16/20	2·5	8/10
		5	7/10
		10	10/10
		20	9/10
Benzhexol	8/10	1·25	7/10
		2·5	8/10
		10	8/10
		20	9/10
Caramiphen	9/10	2·5	9/10
		5	10/10
		10	9/10
		20	8/10
Chlorpromazine	17/20	2·5	8/10
		5	4/10
		10	2/10
Morphine Sulphate	4/5	2·5	4/5
		5	5/5
		10	4/5
		20	4/5
Apomorphine HCl	4/5	5	5/5
		10	3/5
Mephenesin	16/20	20	8/10
		100	4/5
		200	2/5
		300	2/6
S.K.F. 525A	3/5	200	5/5
		400	5/5
Meprobamate	4/5	50	5/5
		100	5/5
		200	5/5
Pentobarbitone sodium	5/5	60	9/10
		100	0/5
Phenytoin sodium	8/10	10	10/10
		20	9/10
Trimethadione	4/5	500	3/5
		1000	3/5
Tubocurarine chloride	4/5	2·5	4/5
Magnesium sulphate	9/10	1000	4/7
Calcium gluconate	4/5	2500	5/5
5-HT	3/4	10	4/5
		20	4/5
		40	3/5
Reserpine	3/5	10	4/5
		20	5/5
		40	3/5
Bulbocapnine	4/5	10	5/5
		20	5/5
		40	5/5
LSD	4/5	2	4/5
Hexamethonium bromide	4/5	10	5/5
1 : 1-Di-(*p*-tolyl)-3-phenyl-3-amino-propan-1-ol (Compound 8)	8/10	25	8/10
		50	4/5
1 : 1-Di-(o-anisyl)-3-phenyl-3-amino-propan-1-ol (Compound 10)	8/10	40	10/10
		80	6/6
1 : 2-diphenyl-2-aminoethanol	4/5	25	4/5
		50	5/5
		100	4/5

In higher doses compounds 1 to 5 produced tremor and convulsion, but ataxia was not evident.

Compounds 8 and 10 caused no tremor or convulsion even in doses of 100 mg./kg. intraperitoneally. This dose, however, killed the animals.

TABLE III

LOCAL ANAESTHETIC ACTIVITY OF THE AMINO ALCOHOLS ASSAYED BY GUINEA PIG WEAL METHOD

Compound	Median effective dose (ED50) mg.	Local anaesthetic activity (Procaine = 1)
1	0·125	5·9
2	0·089	8·3
3	0·1	7·4
4	0·162	4·5
5	0·125	5·9
6	0·081	9·1
7	0·085	8·7
8	0·055	13·4
9	0·062	12·0
10	0·05	14·8
11	0·199	3·7
12	0·14	5·3
Procaine	0·74	1
Cocaine	0·1	7·4
Cinchocaine	0·066	11·2

Compound 11 caused slight tremor in mice after injection of 100 mg./kg. intraperitoneally.

After the tremor induced by the first injection of 30 mg./kg. intraperitoneally had subsided, a second injection of Compound 6 produced more severe tremor within a few minutes. This indicated that no tachyphylaxis occurred.

FIG. 1. *Guinea pig ileum.* 2·5 ml. bath. Interval 3 min. H, histamine 0·05 μg.; A, acetylcholine chloride 0·1 μg.; N, nicotine 5 μg. The white line indicates the period in which the bath contained Compound 6 (1×10^{-6}).

Influence of various substances on amino alcohol-induced tremor. To determine whether pretreatment with various substances could protect animals against the tremorogenic action, Compound 6, the most potent of the amino alcohols shown in Table I, was used to elicit the tremor. The results, which are presented in Table II, indicated that parasympatholytic drugs, anti-Parkinson agents, ganglion-blocking agents, neuromuscular blocking agents (curare), analgesics, anticonvulsants, and sedatives could not protect the animal from the tremor induced by Compound 6. Serpasil, 5-hydroxytryptamine (5-HT) and bulbocapnine also had no antagonistic effect in the doses used. The amino alcohols which did not themselves cause tremor (Compounds 8 and 10) were examined as possible antagonists of the tremor produced by Compound 6, but these

proved to be ineffective. The amino alcohol 1 : 2-diphenyl-2-aminoethanol, the pharmacology of which has been studied by Downman[7], neither evoked tremor itself nor did it antagonise tremor due to Compound 6.

The agents which significantly reduced the tremor were chlorpromazine, mephenesin and pentobarbitone sodium. Animals under ether anaesthesia showed no tremor, but during recovery tremor re-appeared.

S.K.F. 525 A (β-diethylaminoethyl diphenylpropylacetate[8]) and bulbocapnine in the doses used seemed to augment the tremor, as the animals pretreated with these substances showed marked tremor and clonic convulsion, while the control animals showed only moderate tremor without convulsions.

Local anaesthetic activity. Table III shows the activity of the twelve amino alcohols relative to procaine, cocaine, and cinchocaine as assessed

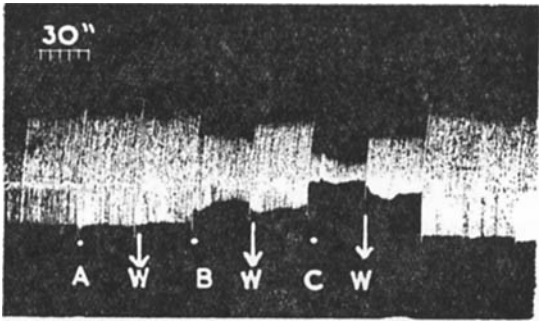


FIG. 2. *Isolated frog heart perfused through a Straub cannula.* At A, B and C the frog Ringer solution contained 1×10^{-7}, 1×10^{-6} and 1×10^{-5} of Compound 6 respectively. At W the perfusion fluid was exchanged 4 times. Note the marked depression in the presence of 1×10^{-5}, from which the heart recovered after 1 hour.

by the guinea pig intracutaneous weal method. All the compounds proved to be more potent local anaesthetics than procaine. The potency of three compounds was found to be greater than that of cinchocaine. In general 1 : 3-amino alcohols showed higher local anaesthetic activity than 1 : 2-amino alcohols.

Spasmolytic action. All the compounds showed a spasmolytic effect on guinea pig ileum. Figure 1 shows the effect of Compound 6 on histamine, acetylcholine and nicotine contractions. No attempt was made to assess the relative anticholinergic, antihistaminic and antinicotinic activity of all these compounds on guinea pig ileum. Estimation of anticholinergic activity of Compounds 6 and 10, by Schild's method, after 14 minutes' contact gave the following results:

Compound 6 $pA_2 = 5{\cdot}43$; $pA_{10} = 5{\cdot}09$; $(pA_2 - pA_{10}) = 0{\cdot}34$

Compound 10 $pA_2 = 5{\cdot}60$; $pA_{10} = 5{\cdot}08$; $(pA_2 - pA_{10}) = 0{\cdot}52$

According to the criterion of Marshall[9] these compounds are non-competitive antagonists of acetylcholine, as the $(pA_2 - pA_{10})$ difference is significantly less than 0·96. This was confirmed by determining

concentration-action curves for acetylcholine in the presence and absence of the antagonists. In the presence of either Compound 6 or 10, the curve was not parallel to that for acetylcholine alone.

Isolated frog heart. Compound 6 was the only amino alcohol tested on this and the following tissues. In a concentration of 1×10^{-7} it had no

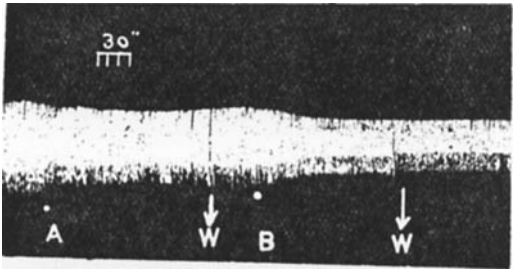


FIG. 3. *Isolated rabbit auricle.* 50 ml. bath. At A 50 μg. and at B 500 μg. of Compound 6 was added to the bath. At W the solution was changed.

appreciable effect on frog heart. Higher concentrations, 1×10^{-6} or 1×10^{-5}, progressively depressed the amplitude and rate of contraction, the depression gradually worsening with the time of contact. The heart, however, recovered after repeated washing (Fig. 2).

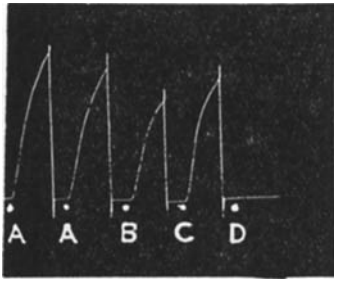


FIG. 4. *Isolated frog rectus abdominis muscle.* 5 ml. bath.

A, contraction due to 0·5 μg. of ACh for 90 seconds.

B, contraction due to 300 μg. of Compound 6 for 90 seconds.

C, contraction due to 300 μg. of Compound 6 in the presence of 50 μg. of tubocurarine chloride.

D, contraction due to 0·5 μg. of ACh in the presence of 50 μg. of tubocurarine chloride.

Isolated rabbit auricle. A dose of 0·5 mg. of Compound 6 in a 50 ml. bath depressed the amplitude of contraction without changing the rate. Smaller doses had little or no effect on the amplitude or rate (Fig. 3). The preparation required about 30 minutes to recover from the depression produced by Compound 6.

Isolated frog rectus muscle. 50 to 100 μg. of Compound 6 added to the 5 ml. bath produced no effect itself on the muscle, but depressed the stimulant action of acetylcholine. Higher doses (300–500 μg.) produced contracture which was not antagonized by curare (Fig. 4). When the dose was increased to 1 mg., the muscle showed an irreversible contracture.

Action on blood pressure. Doses from 0·5 to 2 mg./kg. of Compound 6 intravenously caused a fall in blood pressure.

DISCUSSION

Nine of the twelve amino alcohols reported here have the common property of producing symptoms of central excitation characterised by restlessness, tremor, ataxia, and reflex hyperexcitability. Sustained

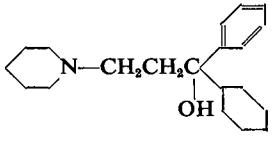
tremor without convulsion and death is a rare phenomenon. The compounds produce a profound and sustained tremor of the head, body and limbs accompanied by continuous struggling forward movements, and retropulsion or circling movements. Retropulsion is not seen during harmine or harmaline tremor, although the tremor produced by these alkaloids is sometimes associated with difficulty in walking. The amino alcohols do not cause parasympathetic stimulation, and in larger doses they produce convulsion. In these respects they resemble harmine.

Bulbocapnine distinctly inhibits the harmine tremor[10] while Zetler[11] has reported that lysergic acid diethylamide (LSD) and 5-HT are effective antagonists of harmine tremor. However, bulbocapnine, LSD and 5-HT did not antagonize the amino alcohol induced tremor. It is of interest that 1 : 1-di-(*p*-tolyl)-3-aminopropan-1-ol (Compound 8) and 1 : 1-di-(ortho-anisyl)-3-aminopropan-1-ol (Compound 10), which were not themselves tremorogenic, were incapable of antagonizing the tremor produced by Compound 6. Tremorine tremor is accompanied by marked parasympathetic stimulation and lack of movement. The animals do not exhibit the spasmodic forward extensor movement or retropulsion observed during the amino alcohol tremor. Tremorine tremor is specifically antagonized by anti-Parkinson drugs which are ineffective against the amino alcohol-induced tremor.

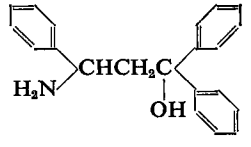
From the above facts it appears that the mechanism of production of tremor by the amino alcohols is quite different from that of harmine or Tremorine.

The tremor is not due to nicotinic-like action, as there is no evidence of tachyphylaxis, and it is not antagonized by hexamethonium which antagonizes nicotine convulsions[12]. Chlorpromazine, however, in 10 mg./kg. dosage, significantly reduced the tremor. In large doses pentobarbitone sodium and mephenesin also antagonized the amino alcohol tremor.

Tremor may be evoked by drugs having a variety of chemical structures. Although nicotine, harmaline and Tremorine all contain a five-membered ring of the pyrrole type, it is unlikely that this structure is responsible for the production of tremor, since so many pyrrole derivatives are known which do not cause tremor. The amino alcohols themselves neither possess a pyrrole ring, nor do they appear likely to give rise to one under physiological conditions. The failure of benzhexol to antagonize amino alcohol tremors is interesting in view of its close structural relationship to the amino alcohols in general and to Compound 6 in particular; it is in fact itself an amino alcohol:



Benzhexol



Compound 6

The principal difference between benzhexol and Compound 6 is in the environment of the nitrogen atom which is free in the latter, but is part of

a piperidine ring in the former. Thus it would not be surprising if the extra bulk around the nitrogen atom of benzhexol prevented it from combining with the tremor receptor. If this were true, then, taken in conjunction with the fact that benzhexol antagonizes nicotine and Tremorine tremors, it would indicate that the amino alcohols act on a different receptor from nicotine or Tremorine. The fact that benzhexol is a satisfactory anti-Parkinson drug also supports our view that the tremor produced by amino alcohols is essentially different from the tremor of Parkinson's disease, and that amino alcohols of the type described here are unsuitable for eliciting tremor in the testing of anti-Parkinson drugs. They may, however, be useful tools for further study of the mechanism of tremor production.

The effects of the compounds on heart, intestine and blood pressure are probably caused by direct depression of muscles resulting from local anaesthetic actions. The muscular contracture which occurs in the frog rectus abdominis when exposed to a high concentration of the drug may be due to a toxic action on the muscle proteins.

Synthesis of Amino Alcohols

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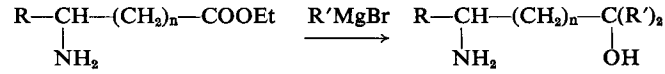
The amino alcohols were prepared from esters of suitable α- or β-amino acids according to the general equation



Ethyl phenylamino-acetate was prepared as described by Marvel and Noyes[13].

Ethyl β-phenyl-β-aminopropionate was prepared as described by McKenzie and Richardson[14].

Ethyl β-(2-furyl)-β-aminopropionate

β-(2-furyl)-β-aminopropionic acid was prepared by a modification of the method described by Posner[15]. To a cold solution of sodium ethoxide (30 g. sodium dissolved in 1000 ml. absolute ethanol) was added a solution of 93 g. hydroxylamine hydrochloride in 65 ml. water. The precipitated sodium chloride was filtered off, and 90 g. furylacrylic acid was added to the filtrate. The clear solution was refluxed for 17 hours, solid beginning to separate after 15 hours. Filtration of the cold reaction mixture gave β-(2-furyl)-β-aminopropionic acid (19 g.), m.p. 202° to 206°.

Esterification of the acid with alcoholic hydrogen chloride gave the ethyl ester (12·5 g.), b.p. 60° to 64°/0·1 mm. Found C, 59·0; H, 7·3; N, 7·6. $C_9H_{13}O_3N$ requires C, 59·0; H, 7·1; N, 7·7.

The following example illustrates the method of applying the Grignard reaction to the preparation of amino alcohols from the above esters.

Preparation of 1 : 1-*di*-(m-*tolyl*)-3-*phenyl*-3-*aminopropan*-1-*ol*

An ethereal solution of ethyl β-phenyl-β-aminopropionate (9·6 g.; 0·05 mol.) was added to a cooled ethereal solution of the Grignard reagent

prepared from *m*-bromotoluene (51 g.; 0·3 mol.). After standing for 30 minutes at room temperature the reaction mixture was refluxed for 30 minutes. The resulting solution was cooled in a freezing mixture, and the organo-metallic complex was decomposed by addition of saturated ammonium chloride solution (1 litre) together with solid ammonium

TABLE IV

AMINO ALCOHOLS

No.		M.pt.°C	Formula	Found per cent			Required per cent			Ref.
				C	H	N	C	H	N	
1	1:1:2-Triphenyl-2-amino-ethanol	154	$C_{20}H_{19}NO$							14
2	1:3-Diphenyl-2-benzyl-3-amino-propan-2-ol	125	$C_{22}H_{23}NO$							16
3	1:1-Di-(*o*-anisyl)-2-phenyl-2-aminoethanol	160	$C_{29}H_{29}NO_3$	75·5	6·5	3·8	75·7	6·6	4·0	
4	1:1-Diphenyl-2-aminoethanol	110	$C_{14}H_{15}NO$							17
5	1:1-Diphenyl-2-aminopropan-1-ol	103	$C_{15}H_{17}NO$							18
6	1:1:3-Triphenyl-3-amino-propan-1-ol	149	$C_{21}H_{21}NO$							14
7	1:4-Diphenyl-2-benzyl-4-amino-butan-2-ol	125	$C_{23}H_{25}NO$	83·6	7·6	3·9	83·4	7·6	4·2	
8	1:1-Di-(*p*-tolyl)-3-phenyl-3-aminopropan-1-ol	147	$C_{23}H_{25}NO$	83·4	7·8	4·1	83·4	7·6	4·2	
9	1:1-Di-(*m*-tolyl)-3-phenyl-3-aminopropan-1-ol	139	$C_{23}H_{25}NO$	83·2	7·8	4·1	83·4	7·6	4·2	
10	1:1-Di-(*o*-anisyl)-3-phenyl-3-aminopropan-1-ol	160	$C_{23}H_{25}NO_3$	75·2	6·8	3·6	76·0	6·9	3·9	
11	1:1-Diphenyl-3-amino-propan-1-ol	143	$C_{15}H_{17}NO$							19
12	1:1-Diphenyl-3-(2-furyl)-3-aminopropan-1-ol	123	$C_{19}H_{19}NO_2$	78·0	6·5	4·9	77·8	6·5	4·8	

chloride (50 g.) to maintain saturation. The aqueous layer was extracted several times with chloroform. The chloroform extracts, combined with the original ether layer, were washed with water, dried and distilled. As the residual oil did not crystallize on trituration with ether, it was steam distilled to remove by-products of the diphenyl type; after isolation by chloroform extraction the oil gradually solidified on treatment with ether. The amino alcohol crystallized from ethanol as colourless prisms m.p. 139° to 140°. (3·2 g).

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