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The binding of conformationally restricted antihistamines to histamine receptors

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Some 1,1-diaryl-3-aminoprop-1-enes and 1,2-diaryl-4-amino-but-1- and -2-enes, including isomers of triprolidine and pyrrobutamine, have been prepared, their geometrical configurations established by pmr spectroscopy, and their affinities for histamine receptors measured on the guinea-pig ileum. These isomers differed considerably in their affinities and a particularly large difference was observed with the isomers of triprolidine (1170:1). This is because the binding of 3-aminoprop-1-enes is enhanced when α-pyridyl and aminomethyl groups are *trans* to one another or when *p*-tolyl and aminomethyl groups are *cis*, whereas activity is reduced when these groups are in opposite configurations. There is also a considerable difference between the geometrical isomers of pyrrobutamine (*ca* 200:1) but the most active compounds all have the same configuration whether 3-aminoprop-1-enes or 4-aminobut-2-enes. For high activity it appears necessary to have a *trans* Ar.C:CH.CH_2.NC_4H_8 arrangement with the aromatic nucleus (α-pyridyl or phenyl) coplanar with the double bond, together with an aromatic function such as *p*-tolyl, benzyl or *p*-chlorobenzyl in a position *cis* to the aminomethyl group. All these compounds have restricted conformations so that the series serves as a useful model for the stereochemical requirements of the antihistamine receptor.

During the last 25 years there has been considerable interest in the antihistaminic properties of substituted 1,1-diaryl-3-aminoprop-1-enes, e.g. triprolidine (Fig. 1, R_1 = α-pyridyl, R_2 = *p*-tolyl) (Adamson, 1949; Adamson & Billinghurst, 1950; Adamson, Barrett & others, 1951, 1957, 1958; White, Green & Hudson, 1951; Green, 1953; Ison & Casy, 1971a) and 1,2-diaryl-4-aminobut-2-enes, e.g. pyrrobutamine (Fig. 1, R_1 = Ph, R_2 = *p*-Cl-$C_6H_4CH_2$) (Stoll, Morel & Frey, 1950; Lee, Anderson & Harris, 1952; Casy & Pocha, 1967; Casy & Parulkar, 1969; Casy & Ison, 1970; Ison & Casy, 1971b). The double bond present in both these structures

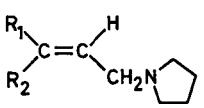

FIG. 1.

limits the number of possible conformational arrangements and gives rise to pairs of geometrical isomers which differ in activity. In triprolidine the α-pyridyl and pyrrolidinomethyl groups are *trans* (Green, 1953) and in pyrrobutamine the 2-phenyl group and the proton in the 3-position are *cis* (Casy & Ison, 1970). The structures

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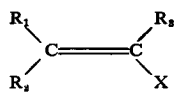
are therefore very similar (see Fig. 1), which suggests that they may be bound similarly at the histamine receptors and this paper describes an attempt to investigate this by measuring accurately their affinity for the receptors and the affinities of other compounds closely related to them (see Table 1). These include the supposedly less active isomers of triprolidine and pyrrobutamine, aminoprop-1-enes in which the aryl groups have been varied, and *cis* and *trans* aminobutenes in which the double-bond has been moved from the 2- to the 1-position. A further aim of the work has been to investigate the importance of the α-pyridyl group, present in triprolidine but not in pyrrobutamine.

Table 1. *Logarithms of the affinity constants for histamine receptors of the guinea-pig ileum at* 37°.



Compounds	Salt	R_1	R_2	R_3	X	Mean log K_B ± s.e. (number of results). Reported pA_2 values in parentheses
3-Aminopropenes						
I (triprolidine)	oxalate	α-pyridyl	*p*-tolyl	H	$CH_2NC_4H_8$	9·945 ± 0·047 (6) (9·0[1])
II	HCl	*p*-tolyl	α-pyridyl	,,	,,	6·878 ± 0·059 (20)
III	oxalate	α-pyridyl	Ph	,,	,,	8·658 ± 0·047 (5)
IV	,,	Ph	α-pyridyl	,,	,,	7·688 ± 0·035 (8)
V	,,	α-pyridyl	*p*-Cl-C_6H_4	,,	,,	8·611 ± 0·063 (9)
VI	,,	*p*-Cl-C_6H_4	α-pyridyl	,,	,,	7·777 ± 0·065 (9)
VII	,,	α-pyridyl	Ph	,,	CH_2NMe_2	7·548 ± 0·021 (6) 6·3[3]
VIII[2]	,,	Ph	α-pyridyl	,,	,,	
IX	,,	,,	,,	Me	,,	6·047 ± 0·085 (6)
X	HCl	,,	Ph	H	$CH_2NC_4H_8$	8·149 ± 0·047 (8) (>9[1])
XI	,,	*p*-tolyl	*p*-tolyl	,,	,,	7·662 ± 0·054 (10)
XII	,,	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	,,	,,	8·004 ± 0·037 (6)
XIII[4]	,,	Ph or *p*-tolyl	*p*-tolyl or Ph	,,	,,	— (8·5[1])
XIV	,,	Ph	*p*-Cl-C_6H_4	,,	,,	8·451 ± 0·052 (6) 7·3[6]
XV[5]	,,	*p*-Cl-C_6H_4	Ph	,,	,,	
4-Aminobutenes						
XVI	HBr	Ph	$PhCH_2$	H	CH_2NMe_2	8·448 ± 0·023 (6)
XVII	HCl	,,	,,	,,	$CH_2NC_5H_{10}$	8·700 ± 0·061 (7) (8·76[7])
XVIII	,,	,,	,,	,,	$CH_2NC_4H_8$	9·640 ± 0·022 (6)
XIX (pyrrobutamine)	$2H_3PO_4$	,,	*p*-Cl-$C_6H_4CH_2$	,,	,,	10·343 ± 0·059 (8)
XX	HBr	*p*-Cl-$C_6H_4CH_2$	Ph	,,	,,	— (7·97[1])
XXI	HCl	H	,,	Ph	$CH_2CH_2NC_5H_{10}$	7·501 ± 0·021 (10)
XXII	,,	,,	,,	,,	$CH_2CH_2NC_4H_8$	8·164 ± 0·018 (5)
XXIII	HBr	,,	*p*-Cl-C_6H_4	,,	,,	8·119 ± 0·067 (6) (7·4[1])
XXIV	HCl	Ph	H	,,	$CH_2CH_2NC_5H_{10}$	6·973 ± 0·036 (6)
XXV	HBr	*p*-Cl-C_6H_4	,,	,,	$CH_2CH_2NC_4H_8$	8·650 ± 0·039 (4)
Standards						
Diphenhydramine hydrochloride						7·950 ± 0·052 (6) (7·45,[8] 8·02,[9] 8·14[10])
Phenindamine tartrate						8·590 ± 0·028 (8) (7·76,[8] 8·46,[10] 8·8[11])
Chlorpheniramine maleate						9·039 ± 0·052 (9) (8·05,[8] 8·82[10])
Mepyramine maleate						9·394 ± 0·077 (8) (8·41,[8] 9·32,[11] 9·36,[10] 9·47[9])

[1] Ison & Casy, 1971a (2 min contact time).
[2] 9:1 mixture of VIII:VII (pmr integral data).
[3] Value calculated from the mean log K_B = 6·3736 ± 0·052 (6) for the 9:1 mixture and K_B for VII assuming that the isomers act competitively.
[4] 1:1 mixture of the *cis* and *trans* isomers (pmr integral data).
[5] 7·3:2·7 mixture of XV:XIV (pmr integral data).
[6] Value calculated from the mean log K_B = 7·956 ± 0·042 (6) for the 7·3:2·7 mixture and K_B for XIV assuming that the isomers act competitively.
[7] Casy & Ison, 1970 (2 min contact time).
[8] Schlichtegroll, 1957 (2 min contact time).
[9] Schild, 1947 (14 min contact time).
[10] Marshall, 1955 (10 min contact time).
[11] Reuse, 1948 (15 min contact time).
[12] Augstein, Ham & Leeming, 1972.

The results make it possible to see not only the difference between the binding of the various geometrical isomers but also the effects on binding of particular changes in structure and the extent to which these vary in different compounds; they should also indicate the compounds which are likely to have particularly high activity. The affinity for histamine receptors was measured by methods in which the compounds were allowed to come into equilibrium with the tissues (Edinburgh Staff, 1970). With some of them this took up to 30 min and the results obtained in this work are therefore likely to be higher (and more accurate) than values previously reported for some of the compounds from estimates of pA_2 (Schild, 1947), even though $pA_2 = \log$ affinity constant.

CHEMISTRY

The 3-aminopropenes were synthesized by dehydration of the appropriate tertiary alcohols in acid. The *cis/trans* isomers were separated by fractional crystallization where necessary (Adamson & others, 1957) and their configurations assigned by pmr spectroscopy (Ison & Casy, 1971a). The alcohols were usually prepared by treatment of a Mannich base with an organolithium or Grignard reagent. Di-*p*-chlorphenyl-3-(1-pyrrolidino)propan-1-ol was prepared by the reaction of *p*-chlorophenylmagnesium bromide with ethyl β-pyrrolidinopropionate. This ester was treated with α-pyridyl lithium and formed the Mannich base, 1-(α-pyridyl)-3-(1-pyrrolidino)propan-1-one (Fig. 2a). In a similar reaction ethyl β-dimethylaminopropionate and α-pyridyl lithium gave the corresponding dimethylamino compound (Fig. 2b). Adamson (1950) obtained 3-(1-piperidino)-1-(α-thienyl)propan-1-one in a comparable manner from ethyl β-piperidinopropionate and α-thienylmagnesium bromide.

The pyrrolidino α-pyridyl Mannich base (Fig. 2a) was treated with α-pyridyl

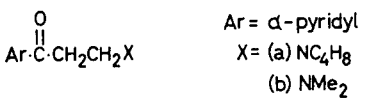


FIG. 2

lithium to form 1-(di-α-pyridyl)-3-(1-pyrrolidino)propan-1-ol but attempts to dehydrate this alcohol to prepare the corresponding *di*-α-pyridylprop-1-ene failed.

The 4-aminobut-1- and -2-ene isomers were obtained by fractional crystallization of the 4-component hydrohalide mixtures derived by dehydration of the corresponding 4-amino-1,2-diarylbutan-2-ols. Pure isomers were identified and configurations assigned by pmr spectroscopy (Casy & Pocha, 1967).

PHARMACOLOGY

Method

The affinity constants were measured on the guinea-pig isolated ileum at 37° using an automated apparatus as previously described (Abramson & others, 1969; Edinburgh Staff, 1970). Histamine was the agonist and the contractions of the muscle were recorded isotonically. The effects of the antihistamines were slow in onset and equilibrium was complete only after 15 to 30 min (depending on the concentration of the antagonist) when the responses became constant. A fresh piece of ileum was used for each experiment.

Approximate dose ratios were chosen for each concentration of antagonist so that the responses produced by the mixed histamine and antihistamine solutions were about the same as those of the control histamine solutions (usually 5×10^{-8} and 1×10^{-7}M). The dose-ratio produced by one particular concentration of antagonist was calculated by comparing the concentrations of histamine used in the presence and absence of the antagonist and taking into account the actual size of the responses (Edinburgh Staff, 1970). The affinity constant was calculated from the dose ratio and the concentration of antagonist according to the Gaddum-Schild equation (Schild, 1949). Every antagonist was tested at several concentrations so that the dose-ratios usually ranged up to 1000 and sometimes higher. The results obtained for each compound were consistent with competitive antagonism.

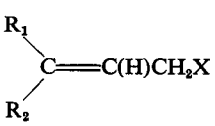
Results

Table 1 shows the logarithms of the affinity constants of the diarylamino-olefins for the histamine receptors of the guinea-pig ileum at 37°. Mean values are given together with the standard error and number of estimates. Previously reported pA_2 values are given in parentheses.

DISCUSSION

The results for standard compounds included in Table 1 confirm that triprolidine and pyrrobutamine are amongst the most active antihistamine drugs. The differences between the affinities of the pairs of 3-aminoprop-1-ene isomers and the *cis* and *trans* forms of pyrrobutamine are shown in Table 2a. It is remarkable that the ratios

Table 2a. *Comparative affinities of the* 3-*aminoprop*-1-*ene and pyrrobutamine isomers.*



	R_1	R_2	X	Δ log K_B	Ratio of affinities
I/II (triprolidine)	α-pyridyl	*p*-tolyl	NC_4H_8	3·067	1170
III/IV	,,	phenyl	,,	0·970	9·33
V/VI	,,	*p*-Cl–C_6H_4	,,	0·834	6·82
VII/VIII	,,	phenyl	NMe_2	1·2*	16*
XIV–XV	phenyl	*p*-Cl–C_6H_4	NC_4H_8	1·1*	13*
XIX/XX Pyrrobutamine	,,	*p*-Cl–$C_6H_4CH_2$	,,	2·3†	200*

* Approximate value based on an estimated log K_B for one of the two isomers (see Table 1).
† Approximate value based upon the pA_2 value for XX (see Table 1).

of the affinities of the *trans*:*cis* isomers of triprolidine and the *cis*:*trans* isomers of pyrrobutamine are very high (1167 and *ca* 200:1 respectively), compared with ratios of only about 10:1 for the other pairs. These must be regarded as lower limits, because it is possible that the isomers were not completely separated although the compounds had been carefully crystallized and the pmr spectra indicated that they were pure. Even if it is supposed that the presence of 5% of one geometrical isomer could not be detected by pmr spectroscopy, the low ratios would not, however, be

greatly altered and it is quite clear that the combination of substituents in triprolidine and pyrrobutamine is critical.

The results for the isomers of the triprolidine-like compounds, which contain an α-pyridyl group, confirm that the compounds in which this is *trans* to the aminomethyl group are more active than their *cis* isomers (Adamson & others, 1951). The effects upon activity of various substitutions in the 3-aminoprop-1-ene series are summarized in Table 2b which shows the strong influence of the α-pyridyl nucleus. In all cases

Table 2b. *Effects of substitution in* 3-*aminoprop*-1-*enes* (*I–XV*).

		Δ log K_B	
		*trans**	*cis*
Replacement of phenyl by α-pyridyl	X → III; X → IV	+0·51	−0·46
	XIV → V; XV → VI	+0·16	+0·5†
Replacement of *p*-tolyl by α-pyridyl	XI → I; XI → II	+2·28	−0·78
Replacement of *p*-chlorophenyl by α-pyridyl	XII → V; XII → VI	+0·61	−0·23
	XV → III; XIV → IV	+1·4†	−0·76
Replacement of phenyl by *p*-tolyl	IV → II; III → I	−0·81	+1·29
Replacement of phenyl by *p*-chlorophenyl	IV → VI; III → V	+0·09	−0·05
	X → XV; X → XIV	−0·8†	+0·30
Replacement of pyrrolidino by dimethylamino	III → VII	−1·11	
	IV → VIII		−1·4†

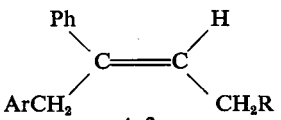
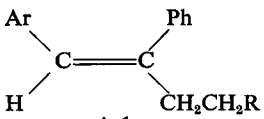
* Configuration relative to the aminomethyl group.
† Approximate value based on an estimated log K_B for one of the two isomers (see Table 1).

the introduction of an α-pyridyl group in the *trans* position leads to higher activity than that of the corresponding compounds which lack the heterocyclic ring whereas in the *cis* position an α-pyridyl group almost always reduces activity. The effects of the *p*-tolyl group are opposite; in the *trans* position it reduces activity and in the *cis* position it enhances potency. With the phenyl and *p*-chlorophenyl groups the effects are much less. The large difference between the triprolidine isomers appears therefore to be due to both the α-pyridyl and *p*-tolyl groups being in favourable positions relative to the aminomethyl group in the active isomer (*trans*), but being in unfavourable positions in the less active compound (*cis*). This combination of effects produces a ratio of affinity (*trans*: *cis*) of 1170 which indicates a difference in the free energy of binding of 17·72 kJ mol^{-1} (4·24 kcal mol^{-1}).

The results with the 4-aminobut-1- and -2-enes confirm that the most active compounds have the *cis* (H/Ph) but-2-ene configuration found in pyrrobutamine (Fig. 1; R_1 = Ph) (Casy & Ison, 1970). The ratios of the affinities of the *cis* but-2-enes compared with those of their isomers are high (see Table 2c), particularly in the case of pyrrobutamine. As in the 3-aminopropene series the pyrrolidino compounds had higher affinity than the dimethylamino and piperidino compounds which suggests that, within these isomers, the pyrrolidino group is an ideal size for fitting the receptors.

The preceding discussion shows that the highest antihistaminic activity is shown by those isomers with the same configuration as triprolidine and pyrrobutamine. This provides some support to the view that a *trans* Ar.C: $CH{\cdot}CH_2{\cdot}NC_4H_8$ arrangement, in which the coplanar aromatic group with the double bond is α-pyridyl or phenyl, is important for activity, because *trans* 1,1-diarylprop-1-enes and *cis* (H/Ph) 1,2-diarylbut-2-enes such as triprolidine and pyrrobutamine are likely to exist in this this conformation (Casy & Ison, 1970; Ison & Casy, 1971a). Moreover, the 2-methyl

Table 2c. *Ratios of the affinities of the* cis *(H/Ph) but-2-enes with their isomers.*

 *cis*-2-ene	*trans*-2-ene	 *cis*-1-ene	*trans*-1-ene
XIX (pyrrobutamine) Ar = *p*-Cl–C_6H_4 R = NC_4H_8	200* (XIX:XX)	50·0 (XIX:XXV)	166 (XIX:XXII)
XVIII Ar = Ph R = NC_4H_8	—	—	30·2 (XVIII:XXII)
XVII Ar = Ph R = NC_5H_{10}	—	53·7 (XVII:XXIV)	15·9 (XVII:XXI)

* Approximate value based on a pA_2 value for XX (see Table 1).

triprolidine-like compound (IX), in which a conformation of this type is less favoured, has very low affinity. It is also significant that the less active *cis*- and *trans*-but-1-ene and *trans*-but-2-ene isomers of the *cis* (H/Ph) 1,2-diarylbut-2-enes (see Table 2c) cannot adopt the coplanar structure because of their stereochemical structures. This type of spatial arrangement is not the only factor for high activity, however, because the *cis* triprolidine-like isomers (II, IV and VI) have low affinity even though they can take up the coplanar conformation. It seems therefore that it is also necessary to have an appropriate aromatic function such as *p*-tolyl, benzyl or *p*-chlorobenzyl in a *cis* position to the aminomethyl group. It has previously been noted that the plane of this second aryl group will probably be at about 90° to the Ar—(C=C) plane (Casy & Ison, 1970; Ison & Casy, 1971a).

Although it has been suggested that antihistamines may exert their actions at sites other than the receptors for histamine (Witiak, 1970), the conformationally restricted compounds described in this work can still serve as a useful model for the stereochemical requirements of the antihistamine receptor and for the design of new compounds. It would be particularly interesting to measure the affinities of some *cis* (α-pyridyl/H)-1-aryl-2-(α-pyridyl)-4-aminobut-2-enes.

EXPERIMENTAL CHEMISTRY

The preparations and pmr parameters of the following isomers in Table 1 have been previously reported: I, IX, X and XI (Ison & Casy, 1971a), XVI, XVII, XVIII, XXI, XXII, XXIII, XXIV and XXV (Casy & Ison, 1970).

The samples of II (m.p. 179–180°), pmr characteristics in ppm (δ), hydrochloride in D_2O(DSS): =C.H, 6·50 (triplet, J7), CH_2N, 4·05 (doublet, J7), and XIX were gifts from the Wellcome Research Laboratories and Eli Lilly and Company (Canada) Ltd. respectively.

The following 3-aminopropenes were prepared by dehydration of the appropriate alcohols (Adamson & Billinghurst, 1950) in 85% sulphuric acid (Adamson & others, 1957), fractionally crystallizing the oxalates from ethanol-ether (values in parentheses indicate m.p.'s recorded by Adamson & others, 1957): III. *oxalate*, m.p. 165–166° (164–165°) (Found: C, 67·9; H, 6·3. $C_{20}H_{22}N_2O_4$ requires: C, 67·8; H, 6·2%); IV. *oxalate*, m.p. 165–166° (169–170°) (Found: C, 67·6: H, 6·2%); V. *oxalate*, m.p. 176–

177° (184°); VI. *oxalate*, m.p. 159–160° (156–157°); VII. *oxalate*, m.p. 174–176° (179°); VIII. *oxalate* (9:1 mixture with VII, see Table 1), m.p. 177–178° (180–181°).

A sample of *di*-p-*chlorophenyl*-3-(1-*pyrrolidino*)*propan*-1-*ol*, m.p. 137–138° (ethanol) (found: C, 64·9; H, 5·9. $C_{19}H_{21}Cl_2NO$ requires: C, 65·2; H, 6·0%), was prepared from *p*-chlorophenylmagnesium bromide and ethyl β-pyrrolidinopropionate (Adamson, 1949) by a previously described method (Ison & Casy, 1971b). This alcohol was dehydrated with a mixture of acetic and hydrochloric acids by the method of Casy & others (1966) to form XII. *hydrochloride*, m.p. 240–241° (ethanol) (found: C, 61·8; H, 5·3. $C_{19}H_{19}Cl_2N{\cdot}HCl$ requires: C, 61·9; H, 5·5%). Similarly, 1-*p*-chlorophenyl-1-phenyl-3-(1-pyrrolidino)propan-1-ol (Adamson & others, 1957) was dehydrated and fractional crystallization of hydrochloride mixtures from ethanol-ether gave XIV. *hydrochloride*, m.p. 216–217°, reported m.p. 219–221° (Adamson & others, 1957), and a 7·3:2·7 mixture of XV:XIV. *hydrochlorides* (see Table 1), m.p. 166–167°.

The pmr characteristics of the above 3-aminoprop-1-enes are given in Table 3.

Table 3. *Pmr parameters of some* 3-*amino*-1,1-*diarylprop*-1-*enes*.

Compound		Chemical shift[a] vinylic H[b]	CH_2X[c]
III	oxalate	6·79	4·05
IV	„	6·50	3·95
V	„	6·75	4·02
VI	„	6·58	4·08
VII	„	6·82	4·04
VIII	„	6·51[d]	3·92[d]
XII	HCl	(6·56)	(3·76)
XIV	„	(6·52)	(3·76)
XV	„	(6·54)[d]	(3·75)[d]

[a] ppm (δ), in D_2O (DSS standard); values in parentheses refer to $CDCl_3$ solutions (TMS standard).
[b] Triplet, $J \sim 7$Hz.
[c] Doublet, $J \sim 7$Hz.
[d] Data derived from enriched mixtures (see Table 1).

Treatment of β-pyrrolidinopropionate (Adamson, 1949) (80 g) with α-pyridyl lithium prepared from a slight excess of ethereal *n*-butyl lithium (Fieser & Fieser, 1967) and α-bromopyridine (78 g) at −50° under N_2 according to the method of Adamson & Billinghurst (1950), gave the Mannich base, 1-(α-*pyridyl*)-3-(1-*pyrrolidino*)-*propan*-1-*one oxalate* (Fig. 2a), 65 g (47%), m.p. 146–147° (ethanol) (found: C, 57·0; H, 6·3. $C_{14}H_{18}N_2O_5$ requires: C, 57·1; H, 6·2%). A similar treatment of β-dimethylaminopropionate (Adamson, 1949) (20 g) with α-pyridyl lithium gave 1-(α-*pyridyl*)-3-*dimethylaminopropan*-1-*one oxalate* (Fig. 2b), 10·7 g (33%), m.p. 167° (ethanol/water) (found: C, 53·9; H, 6·1. $C_{12}H_{16}N_2O_5$ requires: C, 53·7; H, 6·0%).

The above pyrrolidino Mannich base (Fig. 2a) (6·4 g) was reacted with α-pyridyl lithium prepared from ethereal *n*-butyl lithium and α-bromopyridine (12·9 g) in the usual way to form 1-(*di*-α-*pyridyl*)-3-(1-*pyrrolidino*)*propan*-1-*ol oxalate* (5·3 g), m.p. 205–206° (ethanol/water) (found: C, 61·3; H, 6·2. $C_{19}H_{23}N_3O_5$ requires: C, 61·1 H, 6·2%). Attempts to dehydrate this alcohol with concentrated sulphuric acid at 150°, phosphorus pentoxide in boiling xylene, and by treatment with phosphorus tribromide followed by methanolic potassium hydroxide, all resulted in the recovery

of unchanged alcohol. When a base catalysed elimination was tried using a mixture of thionyl chloride and pyridine, decomposition occurred.

Pmr spectra of all the 3-aminopropene and 4-aminobutene isomers used in the pharmacological testing were recorded on a Varian HA-100 instrument and indicated that the samples were isomerically pure (see main text). The solvents used were deuterium oxide or deuterochloroform with DSS or TMS as internal reference standards.

Melting points were recorded on a Mettler FPI instrument connected to a pen recorder using a heating rate of 2° per minute.

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