J. Pharm. Pharmac., 1970, **22**, 270–278 *Received October* 6, 1969

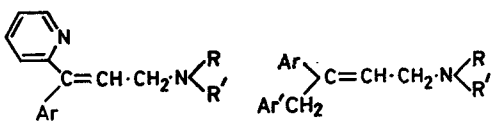
Stereochemical influences upon antihistamine activity. Further studies of isomeric 4-amino-1,2-diarylbutenes*

A. F. CASY AND R. R. ISON

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

The acid-catalysed dehydration of some 4-amino-1,2-diarylbutan-2-ols yields all four possible 4-amino-1,2-diarylbutenes. The structure and configuration of pure isomers have been established from spectroscopic data, and the ability of these compounds to anatagonize histamine-induced contractions of the guinea-pig ileum is reported. The most potent derivatives are all *cis*(H/Ar)-4-amino-1,2-diarylbut-2-enes. These results together with other data are discussed in terms of the possible structural and conformational requirements of histamine antagonists.

Geometrical configuration influences the antihistamine properties of 3-amino-1-aryl-1-pyrid-2′-ylprop-1-enes (I), the *cis*(H/pyrid-2-yl)-isomers being the more potent (Adamson, Barrett & others, 1957). The same dependence of activity upon stereochemistry is now reported for some antihistamine 4-amino-1,2-diarylbut-2-enes (II). The formation of 4-aminobutenes from the tertiary alcohols (III) by dehydration was first reported by Stoll, Morel & Frey (1950), but the products were not satisfactorily characterized either to double-bond position or to configuration (four isomers, two but-1-enes and two but-2-enes may result from the dehydration). The elimination of water from 4-dimethylamino-1,2-diphenylbutan-2-ol (III; R = R′ = Ph, X = NMe_2) was later investigated in detail (Casy & Pocha, 1967) and the most active antihistamine butene of Stoll & others (1950) was shown to be a ternary mixture, the *cis*(H/Ph)-but-2-ene (IV) being the most active component (Casy & Parulkar, 1969). In this paper, pharmacological data upon a further series of isomerically pure 4-aminobutenes are given and tentative structure-activity relations drawn from the results.



I II

III IV

• Presented in part at the 4th International Congress on Pharmacology, Basle, 1969.

CHEMISTRY

All the compounds tested as antihistamine agents were obtained by fractional crystallization of 4-aminobutene hydrohalide mixtures derived by dehydration of the corresponding tertiary alcohols (III); these mixtures comprised all four possible isomers, namely *cis*- and *trans*-but-1- (V) and -2-enes (VI), as was evident from the presence of four vinylic signals in the pmr spectrum of the total products of elimination. Amongst these isomers, but-1-enes were differentiated from but-2-enes by the multiplicities of their vinylic pmr signals (but-1-ene signals were singlets and but-2-ene signals were triplets, $J \sim 7$ Hz), whilst configurational assignments rested upon association of the lower field vinylic chemical shift with the more planar of the two isomers and upon ultraviolet absorption data (Casy & Parulkar, 1969); diagnostic spectral characteristics of the 4-amino-1,2-diarylbutenes are given in Table 1.

Table 1. *Spectral data of* 4-*amino*-1,2-*diarylbutenes*

CHR:CR′·CH_2·CH_2·X (V) CH$_2$R·CR′:CH·CH_2·X (VI)

Compound No.	Isomer*	Alkene type	Structure R	R′	X	Chemical shift of vinylic signal† C–1	C–3	λ(ε)‡
2	*cis*	VI	Ph	Ph	NMe_2		378	241 (11,500)
3	*trans*	VI	Ph	Ph	NMe_2		358	end absorption
		V and VI mixture§	Ph	Ph	piperidine	408	371	—
						391	341	—
4	*cis*	V	Ph	Ph	piperidino	395	—	255 (17,100)
5	*trans*	V	Ph	Ph	piperidino	406	—	263 (20,000)
6	*cis*	VI	Ph	Ph	piperidino	—	382	241 (15,400)
		V and VI mixture§	Ph	Ph	pyrrolidin-1-yl	403	367·5	—
						386	337	—
7	*trans*	V	Ph	Ph	pyrrolidin-1-yl	415	—	261 (20,400)
8	*cis*	VI	Ph	Ph	pyrrolidin-1-yl	—	377	240 (12,700)
		V and VI mixture§	*p*-Cl·C_6H_4	Ph	pyrrolidin-1-yl	403·5	371	—
						388	341	
	cis	V	*p*-Cl·C_6H_4	Ph	pyrrolidin-1-yl	397·5	—	266 (15,800)
	trans	V	*p*-Cl·C_6H_4	Ph	pyrrolidin-1-yl	407·5	—	268 (19,200)
	cis	VI	*p*-Cl·C_6H_4	Ph	pyrrolidin-1-yl	—	368	241 (12,500)
	trans	VI	*p*-Cl·C_6H_4	Ph	pyrrolidin-1-yl	—	364	end absorption

* Configurational reference groups: R and R′ for V; R′ and H(α) for VI.
† Chemical shifts in Hz from tetramethylsilane (60 MHz operating frequency, Varian A-60 spectrometer), solvent $CDCl_3$; C–1 signal a singlet, C–3 a triplet $J \sim 7$ Hz. Pure isomers examined as hydrohalides.
‡ Solvent water. λ is wavelength in nm; extinction coefficient ε shown in parentheses.
§ Total base from corresponding t-alcohol III.

The *cis*-4-dimethylamino-1,2-diphenylbut-2-ene (IV; compound No. 2), obtained previously as a hydrochloride mixed with other isomers (Casy & Pocha, 1967) was isolated pure as a hydrobromide. Three isomerically pure butenes were separated from the mixture derived from the 4-piperidino-alcohol (III; R = R′ = Ph, X = piperidino) and two from the 1,2-diphenyl-4-pyrrolidin-1′-ylbutene mixture.

Although the antihistamine pyrrobutamine (1-*p*-chlorophenyl-2-phenyl-4-pyrrolidin-1′-ylbut-2-ene) is described in the patent literature as a 4-aminobut-2-ene (Lilly Patent, 1954), no evidence is given either for its double-bond position or configuration, hence its formation from the corresponding tertiary alcohol (III; R = *p*-Cl-C_6H_4, R′ = Ph, X = pyrrolidin-1-yl) has been included in the present study. The initial crop deposited from the dehydration mixture after acidification with ethanolic hydrogen chloride proved to be the pure *cis*(H/Ph)-but-2-ene hydrochloride. The pmr spectrum of this butene, as free base, was identical with that of the base derived from pyrrobutamine (marketed as a phosphate). Thus, pyrrobutamine is a *cis*-(H/Ph)-but-2-ene. The remaining isomers were isolated from the mother liquors

as hydrobromide salts; the pharmacological evaluation of all four isomers is in progress.

PHARMACOLOGICAL RESULTS

The antihistamine potencies of a series of 4-amino-1,2-diphenylbutenes, as measured by their ability to antagonize the histamine-induced contraction of the guinea-pig ileum are given in Table 2. Thanks are due to Drs. R. T. Brittain and R. G. W. Spickett of Allen and Hanburys, Ware, Herts, for arranging these tests. These data only allow semi-quantitative activity comparisons but it is clear that the three most effective compounds (No. 2, 6 and 8) are all *cis*(H/Ph)-4-amino-1,2-diphenylbut-2-enes. These are all active at a concentration of 0·01 μg/ml and cause 90% or greater inhibition 3 min after application and over 50% six min later. Both the *cis*-4-dimethylamino- and the *cis*-4-piperidino-but-2-enes (compound No. 2 and 6 respectively) are more potent than related isomers (*cf.* compound No. 1–3 and 4–6), while the 4-pyrrolidinyl isomers (compound No. 7 and 8), although initially of like potency, differ in duration of action, that of the *cis*-but-2-ene (compound No. 8) being the more prolonged. The *cis*-4-piperidino-but-2-ene (compound No. 6), the most active member of the series, has a pA_2 value of 8·76 comparable with that of antihistamines in clinical use (*cf.* chlorpheniramine pA_2 8·1 and mepyramine pA_2 8·71). Its *in vivo* specificity of action was demonstrated by the fact that it antagonized the effects of histamine but not those of acetylcholine, 4-hydroxytryptamine and bradykinin upon the guinea-pig lungs (Konzett & Rossler, 1940) (these spasmogens increase the resistance of the lungs to inflation). It potentiated hexobarbitone-induced sleeping times in mice and hence has undesirable CNS depressant properties in common with other antihistamine drugs such as mepyramine and diphenhydramine.

Table 2. *Inhibition of histamine-induced contractions of isolated guinea-pig ileum by some 4-amino-1-phenylbutenes*

$CHR{:}CR'{\cdot}CH_2{\cdot}CH_2{\cdot}X$ (V) $\qquad$ $CH_2R{\cdot}CR'{:}CH{\cdot}CH_2{\cdot}X$ (VI)

Compound No.	Structure: Alkene type (R = Ph)	R′	X	Concn μg/ml	% inhibition at time (in min): 3	6	9	12	15	18	21	24	27
1	V and VI mixture*	Ph	NMe_2	0·10	90	71	62	56	50	29	8	—	—
2	*cis*-VI	Ph	NMe_2	0·01	89	84	79	62	52	28	—	—	—
3	*trans*-VI	Ph	NMe_2	0·10	87	62	45	20	—	—	—	—	—
4	*cis*-V	Ph	piperidino	0·10	88	83	77	52	32	20	5	—	—
5	*trans*-V	Ph	piperidino	0·10	88	75	51	37	21	—	—	—	—
6	*cis*-VI	Ph	piperidino	0·01	100	99	97	90	76	72	64	42	26
7	*trans*-V	Ph	pyrrolidin-1-yl	0·10	92	87	76	76	70	62	44	30	24
				0·01	100	60	37	22	5	—	—	—	—
8	*cis*-VI	Ph	pyrrolidin-1-yl	0·01	96	74	52	37	26	14	10	—	—
9†	*trans*-V	But	NMe_2	0·10	81	50	20	5	—	—	—	—	—
10†	*cis*-VI	But	NMe_2	0·01	4	—	—	—	—	—	—	—	—
11†	*trans*-VI	But	NMe_2	0·10	91	81	64	36	26	24	7	—	—
12‡	*cis*-3-dimethylamino-1-phenyl-1-t-butylprop-1-ene			0·01	4	—	—	—	—	—	—	—	—
13§	1,2,5,6-tetrahydro-1-methyl-4-phenylpiperidine (XXI)			0·10	55	7	—	—	—	—	—	—	—
	mepyramine			0·001	81	50	20	5	—	—	—	—	—

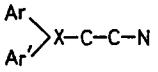
* Ternary mixture: *cis*- and *trans*-V (major) and *cis*-VI (minor component).
† Casy & Ison (1969).
§ Schmidle & Mansfield (1955).

These results emphasize the influence of steric factors upon activity among antihistaminic aminobutenes and show that the disposition of functions about the double bond in a *cis*(H/Ar)-1,2-diarylbut-2-ene are optimal for activity, in confirmation of

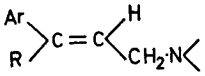
previous data upon isomeric 4-dimethylamino-2-*p*-methoxyphenyl-1-phenylbut-2-enes (Casy & Parulkar, 1969). It is further significant that pyrrobutamine (VI; R = *p*-Cl·C_6H_4, R′ = Ph, X = pyrrolidin-1-yl), a but-2-ene already marketed as an antihistamine agent, also has a *cis*(H/Ar)-configuration (see chemistry section).

DISCUSSION

Most compounds which effectively antagonize histamine at low dose levels may be described by the general structure VII, where Ar is aryl (including heteroaryl), Ar′ is aryl or arylmethyl, and X is N, C–O or saturated C; X–C in VII may be replaced by C:C (Burger, 1960; Wilson & Gisvold, 1962; Barlow, 1964). The terminal nitrogen atom is part of a tertiary acyclic or alicylic basic grouping. If it be assumed that the aryl function(s) and the basic group are the essential pharmacodynamic moieties of these molecules, it is probable that their relative dispositions at the histamine receptor are similar in all potent derivatives if these antagonists have related modes of action. Some ideas upon the optimal arrangement may be gained



VII

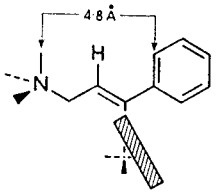


VIII

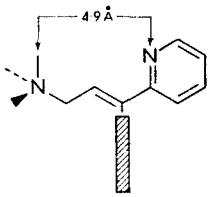
by examination of antihistamines in which the key features are attached to a C:C grouping. In these alkenes, the relative dispositions of molecular components are greatly restricted, especially in comparison with derivatives based on the general Structure VII itself. There are two groups of alkene derivatives with antihistamine properties, namely 3-aminopropenes such as triprolidine (I; Ar = *p*-Me·C_6H_4, NRR′ = pyrrolidin-1-yl) and the 4-aminobutenes presently described; the most active isomers of both groups possess the common structure VIII rigidly orientated in the same manner and it is proposed, in view of the high potency of these compounds and of the activity fall which follows a configurational change, that this unit is an optimal conformation for activity in antihistamine agents*. The overall shape of the more potent aminoalkene antihistamines will now be considered in terms of probable conformations.

In *cis*(H/Ar)-4-aminobut-2-enes of structure VIII (R = Ar′-CH_2), the Ar ring and the carbon–carbon double bond are approximately coplanar (physical evidence); to minimize non-bonded interactions, the plane of the second aryl group (Ar′) attached to the methylene group must lie at about 70° to the Ar–(C=C) plane and the net shape of the molecule in its preferred conformation, as indicated from examination of Catalin and Framework Molecular (FMM) models, is shown diagrammatically in IX. The planes of the two aromatic rings are thus nearly at right-angles, while all components of the Ar·C:CH·CH_2·N< grouping lie close to a mean plane. The distance between the nitrogen atom and an *ortho*-aromatic carbon atom shown in IX and X relates to the work of Kier (1968) on histamine, discussed later. In *trans* (H/Ar)-analogues of VIII (R = Ar′·CH_2), of much lower antihistamine potencies the Ar and carbon–carbon double-bond planes greatly diverge; conformers are

* In 3-aminoprop-1-enes (I), the structure VIII exists in either isomer (since, in VIII, R = Ar′ as well), and hence specificity in regard to the nature of the aryl group *cis* to $H_{(a)}$ must also obtain. This point will be discussed elsewhere.



IX



X

IX. Shaded rectangle represents the end-on view of aromatic ring in this, and other drawings; single lines represent features close to the plane of the paper, dotted lines, those below, and heavy lines those above the same plane.

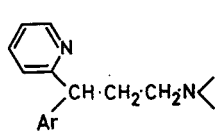
probable in which the benzyl aromatic ring lies in a similar plane to th C:CH·CH_2·N< grouping, but the comparable distance between the nitrogen atom and the aromatic carbon atom is at least 1 Å greater than that of a *cis*-isomer.

In isomeric 3-aminopropenes of the triprolidine type (I), only one of the aryl groups may be coplanar with the alkenic double bond. Models indicate that the aryl group *cis* to the hydrogen atom is more probable as the coplanar group and this is confirmed from physical data (Adamson & others, 1957, and unpublished pmr data). The preferred conformation of compounds containing structure X (see also Barlow, 1964) is thus very similar to that of the 4-aminobut-2-enes, the only difference between IX and X being the absence of an arylmethylene group in the latter. Pharmacological results upon the triprolidine isomers and related compounds show that a pyrid-2-yl group is preferred to phenyl and substituted phenyl groups as the aromatic member of the planar Ar·C:CH·CH_2:N< grouping.

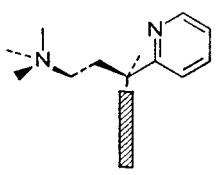
Formally less rigid antihistamine agents will now be examined to establish whether or not they are likely to adopt conformations in which their aryl group and CH_2·N< grouping are disposed in a similar fashion to the aminoalkene conformations IX and X.

Pheniramines

These compounds have the general formula XI and may be regarded as alkane analogues of the 3-aminopropenes I. Models of XI of shape close to that of the 4-aminobutenes IX seem to be very reasonable conformations, as they appear to entail no serious non-bonded interactions (see XII). In these models, the pyrid-2-yl group is made the aryl group most nearly coplanar with the alkylamine chain by analogy with the 3-aminopropene results. In XII the dihedral angle* between the



XI



XII

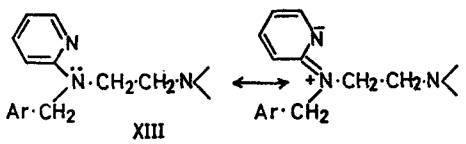
aromatic rings is not far removed from 90°, as in IX. A model in which the near-planar Ar·CH·CH_2·CH_2·N< grouping is maintained may also be made when the

* Defined as the angle between planes containing (*a*) C–1 and C–2 of one aryl group and (*b* C–1 and C–2 of the other aryl group, with the quaternary carbon atom common to both.

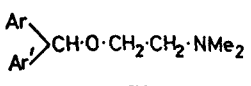
inter-aryl dihedral angle is greater than 90° ("butterfly" arrangement of Ar_2CH), but non-bonded interactions are judged to be greater in this conformation.

Ethylene diamines

The compounds, general formula XIII (the pyrid-2-yl group is replaced by a phenyl group in some derivatives, e.g., Antergan), have an aryl group and an aryl-methyl group linked to one of the diamine nitrogen atoms; restricted rotation about the N–Ar bond is probable as a result of resonance interactions as shown. Once again it is possible to construct a model of XIII that is very similar to the 4-amino-but-2-ene conformation IX except that $CH_2{\cdot}N<$ (planar nitrogen) replaces C=C. This form is probable on the grounds of minimum steric interactions and also maximum operation of N–Ar resonance effects.



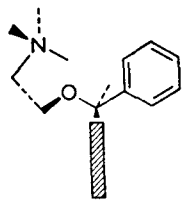
XIII



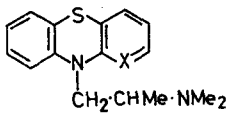
XIV

Diphenhydramines

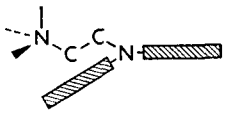
The variant of the general structure VII in which X is C–O and the terminal carbon atom carries two aromatic groups (e.g., diphenhydramine (XIV; Ar = Ar′ = Ph) similarly yields a strain-free model XV, akin to the 4-aminobutenes IX, in which the ether-oxygen bonds lie close to the plane of one of the aromatic rings with an inter-aryl dihedral angle near 90°. Nauta, Rekker & Harms (1966) have proposed an "active" diphenhydramine conformation similar to XV and have infrared and ultraviolet spectroscopic evidence for the coplanarity of the oxygen atom and the *p*-tolyl group in *p*-methyldiphenhydramine (XIV, Ar = Ph, Ar′ = *p*-Me·C_6H_4).



XV



XVI



XVII

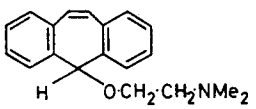
XVII. Molecule viewed along a line joining the hetero-atoms of the phenothiazine nucleus; the sulphur atom is obscured by the nitrogen atom.

Cyclic derivatives

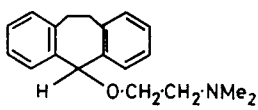
These are formed when the two aryl groups of VII are fused at *o*-positions to a sulphur or carbon atom. In phenothiazine derivatives, e.g., promethazine (XVI; X = CH) a model can be made in which the 2-aminoethyl side-chain attached to ring nitrogen atom and one of the aromatic rings lie more or less in one plane with the second aromatic ring removed from this dimension (XVII). However, the angle between the two aromatic rings is obtuse rather than acute as in the 4-aminobutenes

IX, as a result of the rings being constrained to a "butterfly" conformation by their linkages to the heterocyclic atoms (the alternative "butterfly" conformation is unlikely on account of steric interactions between the 2-aminoethyl side-chain and adjacent aromatic hydrogen atoms). Similar considerations of molecular shape apply to isothipendyl (XVI; X = N).

In the fused-ring derivatives XVIII and XIX, the angle between the two aromatic planes is less than that in the phenothiazines and models of these compounds closely resemble IX in having a nearly planar Ph·C·O·CH_2·CH_2·N< grouping with the second ring approximately at right-angles to this feature (Nauta & others, 1966). These derivatives may be regarded as analogues of diphenhydramine and both are significantly more active than the parent compound in which the two rings are unconstrained. The recently introduced antihistamine cyproheptadine XX has a molecular shape similar to XVIII and XIX, except that the planes of the aminoalkyl group and one aromatic ring do not coincide so closely, as they are held apart by the double-bond linkage.

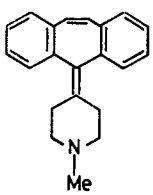


XVIII

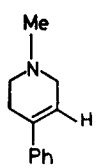


XIX

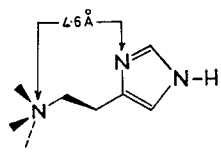
The preceding account has demonstrated that many antihistamine drugs in clinical use may adopt conformations similar to those of the model aminoalkene antihistamine IX and X without serious non-bonded interactions being generated. If the overall molecular arrangement typified in IX and X is accepted as specially conducive to the blockade of histamine receptors, it appears most reasonable to postulate that the near-planar aminoalkyl-aryl moiety of the antagonist molecule occupies the histamine receptor itself, as this unit has a similar shape to, and dimensions of, the histamine molecule (see below). It is assumed that histamine sites occupied by the protonated NH_2 group and the imidazole ring of the agonist probably interact with the protonated side-chain nitrogen atom and the aryl groups respectively of the antagonist. The second aromatic feature of the antagonist (antiplanar



XX



XXI



XXII

with the rest of the molecule) is assumed to occupy an additional receptor area which is not implicated in the uptake of histamine itself (the concept of antagonists utilizing more receptor sites than the molecules which they antagonize has been discussed by Ariëns & Simonis, 1964). Speculations along these lines have previously been made by Nauta & others (1966) about *p*-methyldiphenhydramine. The importance of

having two aromatic groups in an antihistamine agent is emphasized by the low activity of the tetrahydropyridine XXI (Table 2, compound No. 13), a molecule which contains the near-planar Ar·C:CH·CH_2·N< grouping of the potent amino-alkenes, while results upon the t-butyl derivatives (Table 2, compounds No. 9–12) emphasize the importance of the planar feature itself. In these derivatives, all of low potency, coplanarity of the aromatic and double-bond planes is seriously distributed by the bulky t-butyl group.

Kier (1968) has proposed favoured *anti-* and *gauche-*($\overset{+}{N}H_3$/Ar)-conformations for histamine based on molecular orbital calculations and has suggested that the similar N–N interatomic distances of the *anti*-conformer XXII and of triprolidine X may be of significance regarding the latter compound's antagonistic properties. It is of interest that the distances between the side-chain nitrogen atom and an aromatic *ortho*-atom (N or C) comprising the near-planar feature of conformations proposed for the antihistamine agents of structure I, *cis* VI, XI, XIII and XIV are all close to the histamine N–N distance specified above and this observation shows how the shape and dimensions of the histamine molecule may be reproduced in anti-histamine agents.

EXPERIMENTAL

4-Amino-1,2-diarylbutenes. The butan-2-ol III hydrochlorides were dehydrated with a mixture of acetic acid and concentrated hydrochloric acid by the previously reported method (Casy, Myers & Pocha, 1966), and the isomers in the dehydration mixture separated by fractional crystallization from ethanol-ether of the hydrohalides. Isomers are listed in their order of separation.

Dehydration of 4-dimethylamino-1,2-diphenylbutan-2-ol (15 g) gave cis-4-*dimethylamino*-1,2-*diphenylbut*-2-*ene* (compound No. 2) *hydrobromide* (2·3 g), m.p. 179–180° (Found: C, 64·7; H, 6·6; N, 3·9. $C_{18}H_{22}BrN$ requires: C, 65·0; H, 6·7; N, 4·2%). The other isomers have been previously reported (Casy & Pocha, 1967).

Dehydration of 1,2-*diphenyl*-4-*pyrrolidin*-1′*ylbutan*-2-*ol hydrochloride* (13·5 g), m.p. 163° from ethanol-ether (Found: C, 72·0; H, 7·8; N, 4·2. $C_{20}H_{26}ClNO$ requires: C, 72·3; H, 7·9; N, 4·2%) gave cis-1,2-*diphenyl*-4-*pyrrolidin*-1′-*ylbut*-2-*ene* (compound No. 8) *hydrochloride* (0·77 g), m.p. 198° (Found: C,76·6; H, 7·5. $C_{20}H_{24}ClN$ requires: C, 76·3; H, 7·7%) and the corresponding trans-*but*-1-*ene hydrochloride* (1·53 g), m.p. 160–162° (Found: C, 76·3; H, 7·8%).

Dehydration of 1-*p*-chlorophenyl-2-phenyl-4-pyrrolidin-1′-ylbutan-2-ol (Lilly Patent, 1954) (12 g) gave the *cis*-1-*p*-chlorophenyl-2-phenyl-4-pyrrolidin-1′-ylbut-2-ene hydrochloride (1·73 g), m.p. 227–228°, reported m.p. 227–228° (Lilly Patent, 1954); the base formed a *methiodide*, m.p. 117°, from acetone-ether (Found: C, 55·6; H, 5·65. $C_{21}H_{25}ClIN$ requires: C, 55·6; H, 5·55%). Acidification of the residual bases in the dehydration mixture with ethanolic hydrogen bromide gave the corresponding cis-*but*-1-*ene hydrobromide* (1·3 g), m.p. 184–185° (Found: C, 61·4; H, 6·2; N, 3·3. $C_{20}H_{23}BrClN$ requires: C, 61·15; H, 5·9; N, 3·6%), the corresponding trans-*but*-1-*ene hydrobromide* (2·01 g), m.p. 191° (Found: C, 61·2; H, 6·0; N, 3·7%), and the corresponding trans-*but*-2-*ene hydrobromide* (0·44 g), m.p. 152–153° (Found: C, 61·0; H, 6·0; N, 3·7%).

Dehydration of 1,2-diphenyl-4-piperidinobutan-2-ol (Pohland & Sullivan, 1953) (10 g) gave the cis-1,2-*diphenyl*-4-*piperidinobut*-2-*ene* (compound No. 6) *hydrochloride* (1·54 g), m.p. 248–249° (Found: C, 76·6; H, 8·1. $C_{21}H_{26}ClN$ requires:

C, 76·9; H, 8·0%), the corresponding trans-*but*-1-*ene* (compound No. 5) *hydrochloride* (1·42 g), m.p. 195° (Found: C, 76·7; H, 8·0%) and the corresponding cis-*but*-1-*ene* (compound No. 4) *hydrochloride* (0·67 g), m.p. 160–161° (Found: C, 77·0; H, 8·0%). The *cis*-but-2-ene gave a *methiodide*, m.p. 163–164° from acetone-ether (Found: C, 61·2; H, 6·8. $C_{22}H_{28}IN$ requires: C, 60·95; H, 6·5%).

Acknowledgements

The authors thank Eli Lilly and Company (Canada) Limited for a sample of pyrrobutamine phosphate, and the Medical Research Council of Canada for financial support.

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