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Analogues of Triprolidine: Structural Influences upon Antihistamine Activity

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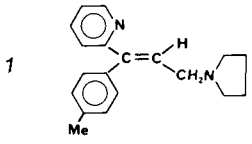
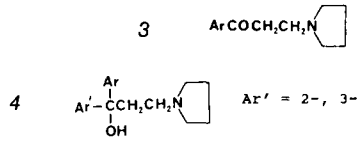
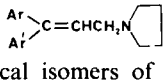
Abstract—The synthesis of some geometrical isomers related to triprolidine is reported. Previous configurational assignments, by UV and proton NMR, are validated by high field nuclear Overhauser enhancement methods and the isomeric purity of tested E- and Z-isomers was greater than 99.5% as assessed by an HPLC method developed for these compounds. Affinity constants for triprolidine (E and Z) in guinea-pig ileum showed a potency ratio of ~600 whereas at cerebellar sites this ratio was only ~100, suggesting that the H_1 receptor in these two tissues may not be identical. In-vivo tests using a lethal dose of compound 48/80 (a potent histamine-releasing agent) demonstrated that triprolidine itself was the most active compound to protect the animal among all the isomeric compounds tested: in all isomeric pairs the E-configuration possessed superior activity over Z. The disposition of the aryl groups in these geometrically constrained compounds mimics that seen in the structurally related chiral pheniramines which are sp^3 hybridized and whose absolute stereochemistry is known.



Triprolidine



The antihistamine, triprolidine (*1*) (which has the E configuration) and its corresponding Z-isomer provide a frequently quoted example of a geometrically isomeric pair whose members differ substantially in their biological potencies (Casy 1989). Aminopropenes of the triprolidine class are of special value as probes of the histamine H_1 receptor because of the rigid nature of much of their molecular framework which allows investigation of the requirements of the two aromatic binding sites proximal and distal, respectively, to the electrostatic site of the receptor. We report the chemistry



of some novel geometrical isomers of structure *2* (with application of modern methods of establishing configuration and isomeric purity) and present comparative biological data.

	Ar	Ar′
a	2-pyridyl	phenyl
b	2-pyridyl	4-methylphenyl
c	2-pyridyl	4-bromophenyl
d	2-pyridyl	4-chlorophenyl
e	2-pyridyl	4-ethylphenyl
f	3-pyridyl	phenyl
g	3-pyridyl	4-methylphenyl
h	4-pyridyl	phenyl

Chemistry

Isomeric mixtures (*2*) were obtained by the well-known route of treating a Mannich base (*3*) with a pyridyllithium reagent to give a tertiary alcohol (*4*) which was then dehydrated under acidic conditions of varying duration. Isomers were separated by fractional crystallization of hydrogen oxalate salts, progress of purification being monitored by ^{1}H NMR spectroscopy and HPLC (see below).

The configurational assignment of isomers (*2*) with Ar = 2-

Table 1. ^{1}H NMR and UV features of isomeric 1,1-diaryl-3-aminoprop-1-enes.

		^{1}H NMR[a]		
Compound	Configuration	Vinylic 2-H (t)	3-CH_2N (d)	UV[b] λ_{max}
2b HCl	E[c]	6·46 (7·01)[d]	3·86 (3·80)	229, 276[e]
	Z	6·24 (6·39)	3·78 (3·98)	258[f]
2a	E	6·69 (6·98)[g]	4·00 (3·26)	226, 276
Oxalate	Z	6·38 (6·35)	3·84 (3·20)	242
2c	E	6·69	4·00	230, 275
Oxalate	Z	6·35	3·84	260
2d	E	6·63	3·91	230, 274
Oxalate	Z	6·38	3·86	259
2e	E	6·63 (6·94)	3·99 (3·22)	229, 275
Oxalate	Z	6·33 (6·33)	3·83 (3·26)	260
5 HCl	E	6·47	3·89	232[i]
	Z[h]	6·51	3·90	260[f]
2f	E	6·43	3·97	226, 244
Oxalate	Z	6·38	3·90	no data
2g	E	6·38	3·98	227
Oxalate	Z	6·35	3·89	no data
2h	E	6·77	4·00	242[j]
Oxalate	Z	6·41	3·92	242

[a] Chemical shifts, ppm ref. HDO (4·8) or TMS, of salts in D_2O unless otherwise stated; d = doublet, t = triplet. [b] Salts in ethanol, λ_{max} values in nm. [c] Triprolidine. [d] in $CDCl_3$. [e] c.f. 2-vinylpyridine λ_{max} 235 and 278 nm. [f] c.f. styrene λ_{max} 248 nm. [g] Base in $CDCl_3$ (and subsequent parentheses). [h] Zimeldine. [i] c.f. 3-vinylpyridine λ_{max} 238 and 278 nm. [j] c.f. 4-vinylpyridine λ_{max} 242 nm.

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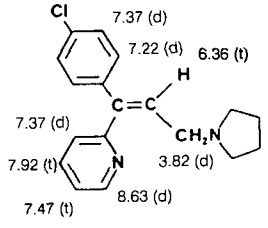
pyridyl was originally based on differences in UV spectra (Adamson et al 1957, 1958): spectra of E and Z isomers resembled those of 2-vinylpyridine and styrene respectively. Later ^{1}H NMR methods were applied which exploited isomeric differences in vinylic and CH_2N chemical shifts (Ison & Casy 1971). In this work, these methods were substantiated for the 2-pyridyl derivatives by nuclear Overhauser enhancement experiments run in the difference mode (NOED), a technique which proved essential for solving the stereochemistry of 2- and 4-pyridyl analogues where previous NMR (3-pyridyl) and UV (4-pyridyl) methods were ambiguous. Data of configurational value are presented in Table 1. NOED experiments were possible in all cases as a result of the ease of the necessary spectral assignments;

SCHEME 1. 400 MHz nuclear Overhauser enhancement (NOE) spectrum of triprolidine.



Position of irradiation (ppm)	Resonance assignment	Result
3·82	CH_2N	NOE at the vinylic CH (6·36 ppm)
6·36	Vinylic CH	NOE at Ar A_2B_2 (7·22 ppm) and CH_2N
7·2	Ar–A_2B_2	Large NOE at 7·37 ppm and NOE at vinylic CH (6·36 ppm)
7·47	H-5′ (pyridyl)	NOE at H-6′ (8·63 ppm) and H-4′ (7·92 ppm)

details of one example (triprolidine) are given (Scheme 1)—results for all others were similar.

Isomeric purity

Inspection of a ^{1}H NMR spectrum of an aminopropene sample in hydrogen oxalate form provided an approximate assessment of its isomeric purity in cases where E- and Z-vinylic signals were well resolved and capable of separate integration. However, because of the relative insensitivity of NMR techniques and the biological need for samples of high purity, an HPLC method of stereochemical analysis was developed using UV detection. The column chosen initially was a Hypersil 5 ODS (25 cm), but this resulted in chromatograms with very broad tailing peaks even after inclusion of ammonium acetate buffer (pH 6), an ion-pairing reagent and KCl in the mobile phase (25% tetrahydrofuran). A more polar column with a shorter (C_3) chain, Hypersil 5 CPS (10 cm), was therefore tested. In this cyanopropyl (CPS) column there are only propyl chains attached to the Si support. Since most silanol groups are capped, less tailing should occur because of the reduced likelihood of the analyte finding free polar groups. Use of a mobile phase of 20% tetrahydrofuran in water containing KCl (50 mM), hexanesulphonic acid (10 mM), and phosphoric acid (0·1%) led to

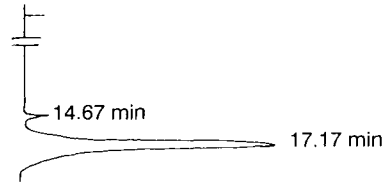


FIG. 1. HPLC trace of the Z-isomer of triprolidine showing 5% impurity of the E-isomer.

good separation of isomeric peaks. The isosbestic point was used as the wavelength for detection so as to assure equality of isomeric response. In the case of triprolidine and its isomer (detection wavelength 245 nm), a sample of the Z isomer supplied by the manufacturers proved to contain 5% of the E-form as an impurity (Fig. 1). One recrystallization of the mixture from ethanol gave a product whose chromatogram displayed a single peak at 17·5 min. A commercial sample of triprolidine proved to be isomerically pure (single peak, 13·28 min). Spiking experiments revealed that the HPLC system was capable of detecting down to 0·5% of isomeric impurity. In all cases reported here the retention time of an E-aminopropene (*2*) was less than that of the corresponding Z isomer.

Pharmacology Results and Discussion

The binding and compound 48/80 protection data were prepared by Dr J. M. Young and Mrs Wendy Gibson (University of Cambridge, UK) and Mr K. Schellekens (Janssen Pharmaceutica, UK), respectively.

Previous comparisons of the antihistaminic potencies of triprolidine and its corresponding Z-analogue on the isolated guinea-pig ileum by the classical gut-bath procedure utilized samples of isomeric purity based on NMR evidence (Ison & Casy 1971; Ison et al 1973). Results for samples of isomeric purity of at least 99·5% assessed by the more sensitive HPLC procedure reported here, are given in Table 2. Slopes of plots

Table 2. Logarithms of the affinity constants of triprolidine and its Z-isomer for histamine receptors of the guinea-pig ileum at 37°C[a].

Isomer	Concn (nM)	log K_b
E	1	9·973 ± 0·055 (6)
	2	10·067 ± 0·027 (4)
	5	9·982 ± 0·071 (6)
	10	10·088 ± 0·021 (2)
	50	10·089 ± 0·081 (8)
	Mean	10·034 ± 0·011 (26)[b]
	Concn (μm)	
Z	1	7·436 ± 0·022 (7)
	5	7·195 ± 0·021 (7)
	25	7·137 ± 0·039 (7)
	Mean	7·256 ± 0·029 (21)[c]

[a] Measured using an automated apparatus (Edinburgh Staff 1970; Mercer 1989). Histamine was the agonist used in doses of 1 and 2×10^{-7} M, and contractions were measured isotonically. The antagonist effects of E and Z (*2b*) were slow in onset and equilibrium required 15–45 min for completion. Number of experiments indicated in parentheses. [b] Ison et al (1973) reported 9·945 ± 0·047 (6). [c] Ison et al (1973) reported 6·878 ± 0·059 (20).

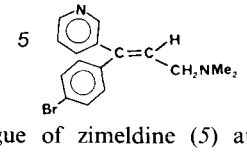
Table 3. Affinity constants (K_a M^{-1}) of isomeric 1,1-diaryl-3-aminoprop-1-enes (*2*) for guinea-pig cerebellum sites at 30°C[a].

Compound	Affinity constant (K_a M^{-1})
E-*2b* (4-Me)[b]	$1{\cdot}2\pm0{\cdot}1\times10^9$ ($1{\cdot}09\pm0{\cdot}05$)[c]
	$1{\cdot}9\pm0{\cdot}1\times10^9$ ($1{\cdot}00\pm0{\cdot}03$)
Z-*2b*[d]	$6{\cdot}2\pm0{\cdot}3\times10^7$ ($0{\cdot}94\pm0{\cdot}05$)
	$2{\cdot}0\pm0{\cdot}2\times10^7$ ($0{\cdot}95\pm0{\cdot}07$)
E-*2b*	$2{\cdot}3\pm0{\cdot}2\times10^9$ ($0{\cdot}95\pm0{\cdot}06$)
	$2{\cdot}3\pm0{\cdot}1\times10^9$ ($1{\cdot}02\pm0{\cdot}06$)
Z-*2b*[f]	$1{\cdot}7\pm0{\cdot}2\times10^7$ ($1{\cdot}08\pm0{\cdot}09$)
	$2{\cdot}0\pm0{\cdot}1\times10^7$ ($1{\cdot}19\pm0{\cdot}05$)
E-*2c* (4-Br)	$6{\cdot}61\pm0{\cdot}54\times10^8$ (2)[e]
E-*2d* (4-Cl)	$8{\cdot}99\pm0{\cdot}61\times10^8$ (1)
Z-*2d* (4-Cl)	$3{\cdot}95\pm0{\cdot}18\times10^7$ (2)
E-*2e* (4-ethyl)	$1{\cdot}84\pm0{\cdot}16\times10^9$ (2)
E-*2g* (4-methyl)	$3{\cdot}46\pm0{\cdot}21\times10^9$ (2)
Z-*2h*	$4{\cdot}52\pm1{\cdot}27\times10^7$ (2)

[a] vs [^{3}H]mepyramine using a particulate fraction of guinea-pig cerebellum (Aceves et al 1985). [b] Substituent of 1-phenyl group. [c] Hill coefficient. [d] Contains 15% of E-isomer by HPLC analysis c.f. K_a of pure sample shown below. [e] Number of experiments (and subsequent parentheses). [f] Sample examined concurrently with pure Z-*2b*.

of log (dose ratio -1) against agonist concentration (Schild plots) did not differ significantly from unity, but data points were not sufficient to establish the antagonistic mode as one of pure competition. The E:Z potency ratio of 600 after a 15–45 min contact time compares favourably with the reported value of 1170 (Ison et al 1973) when allowance is made for variations in the experimental conditions, and confirms the high degree of selectivity of the H_1 receptor for triprolidine over its Z-analogue. This ratio exceeds that exhibited towards related E/Z pairs of aminopropenes by up to two orders of magnitude (Casy 1978). It is of interest that optical antipodes of chlorpheniramine, a reduced analogue of triprolidine, exhibit a similar ratio of activity (608) under the same experimental conditions (Mercer 1989).

The abilities of triprolidine and some of its analogues to displace [^{3}H]mepyramine from membrane fractions of guinea-pig brain (cerebral cortex) are given in Table 3. Triprolidine bound strongly to guinea-pig cerebral cortex and its affinity constant was about 100 times that of its Z-congener. The E:Z affinity constant ratio for triprolidine and its geometrical isomer is one-sixth to one-tenth those values recorded in the gut-bath experiments, a result which may suggest that H_1-receptor sites of guinea-pig ileum and cerebellum are not identical. The affinity constant ratio of another pair of geometrical isomers, namely the E- and Z-4-chlorophenyl derivatives, *2d*, (samples pure by HPLC) was 44, a value inferior to that of the triprolidine pair as a result of the relatively greater affinity of the halogenated Z isomer. In the E-series (*2*), replacement of 4-methyl by 4-ethyl had little influence upon affinity, while small falls were observed following substitution by chlorine or bromine. Replacement of 2-pyridyl of triprolidine by 3-pyridyl led to a product of a remarkably high affinity, exceeding that of the parent. This result is surprising in view of the low potency of the E-



E-analogue of zimeldine

analogue of zimeldine (*5*) at guinea-pig ileum and rat cerebellum sites (5–6% that of (+)-brompheniramine) (Hall & Ogren 1984), although the potency-raising influence of pyrrolidino (as in *2g*) over dimethylamino is well known (Ison & Casy 1971). The Z-4-pyridyl (*2h*) analogue, like other geometrical isomers of this configuration, had a K_a value in the 10^7 M^{-1} range rather than 10^9 as found for E-congeners.

Table 4. Number of rats (out of 2 tested) that survived, the 48/80 lethality test[a].

	Dose of test compound (mg kg^{-1} s.c.)				
Compound	10	5	2·5	1·5	0·63
Triprolidine (E-*2b*)	2	—	2	—	1
E-*2c* (4-Br)[b]	2	0	0	—	—
E-*2d* (4-Cl)	2	1	0	—	—
Z-*2d*	0	—	0	—	—
E-*2e* (4-ethyl)	2	—	—	1	—
E-*2g* (4-methyl)	2	2	1	—	—
Z-*2h*	1	—	0	—	—

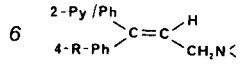
[a] Compound 48/80 injected at a challenge dose of 0·5 mg kg^{-1}, intravenously. Test compounds were assumed to be active if the animals have a survival time >240 min (Niemegeer et al 1978). [b] Substituent of 1-phenyl group.

Certain of the compounds were examined in-vivo by measuring their ability to protect rats against a lethal dose of compound 48/80 (a mixture of oligomers obtained by condensation of *p*-methoxy-*N*-methylphenethylamine and formaldehyde, recognized as a potent histamine-releasing agent (Niemegeer et al 1978). The test compounds were assumed to be active if the animals had a survival time of >240 min. Table 4 shows the results and records the number of rats that survived; each compound and dose of compound was tested on two animals.

Triprolidine stands out as the most effective protecting agent. 4-Ethyl, 4-bromo, 4-chloro and 3-pyridyl analogues were all effective at a dose of 10 mg kg^{-1}; of these only the 3-pyridyl derivative (*2g*) was effective at 2·5 mg kg^{-1}. All these derivatives belong to the E configuration series; the Z analogue (*2d*) was ineffective at 10 mg kg^{-1}. The Z-4-pyridyl analogue (*2f*), although of similar (low) affinity to Z-*2d* at central sites (Table 4), proved the more effective protecting agent. These data are in reasonable accord with the in-vitro potency findings.

General comments

Studies of dissymmetric chiral antihistamines provide ample evidence of the stereoselective nature of H_1 histamine receptors in regard to ligands which block these sites (Casy 1989; Mercer 1989). Such work has established the importance of the configuration of a chiral centre close to the diaryl unit of the molecule. Receptor sensitivity to the disposition of the two aryl groups about a benzylic carbon is also apparent in antihistamines of the aminopropene type, exem-



plified by previous and current results. Isomers of structure *6* (configuration E for 2-pyridyl, Z for phenyl) have higher affinities than corresponding Z(2-pyridyl) or E(phenyl) isomers, while receptor stereoselectivities are maintained in the less potent 3-pyridyl analogues. It is significant that chiral

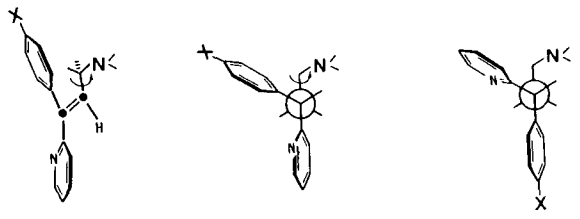


FIG. 2. Triprolidine-pheniramine steric comparisons.

Table 5. Preparative, HPLC and purity details of some isomeric aminopropenes (*2*).

Compound	Isomer	Conditions[a]	R_t (min)[b]	Purity (%)[c]
2e	E	120°C, 1 h	20	100
	Z	120°C, 10 min	29	92
2a	E	120°C, 4 h	8	90
	Z	100°C, 10 min	11	60
		120°C, 1 h		68
2c	E	120°C, 4 h	24	100
	Z	100°C, 30 min	32	70
2f[d]	E	120°C, 1 h	7·8	91
	Z		10·0	Not isolated
2g	E	120°C, 30 min	e	96
2h	E	120°C, 4 h		90
	Z	100°C, 1 h	e	100

[a] Dehydration of precursor *t*-alcohol with 85% H_2SO_4. [b] Retention times in the described HPLC system. [c] From chromatograms of recrystallized hydrogen oxalate salts. [d] R_f values for zimeldine 24 min and corresponding E-isomer (*5*) 14·7 min. [e] Not recorded.

and geometrical configurational relationships correspond (Fig. 2). Thus antipodal pheniramines corresponding to the arrangement A of the constrained isomer triprolidine have the configuration B(*S*), while their mirror images C are equivalent to the weakly active Z-analogue of the aminopropene. When the alkenic double bond of triprolidine is hydrogenated, the relative orientations of the aromatic pair and aminoalkyl chain alter because of hybridization changes at C-1 and C-2, but overall gross relationships must be maintained in the *S* antipode because H_1 affinities of *S*-antipodes and triprolidine are of the same order. From structural features of most agents which block H_1 receptors of histamine, it is evident that ligand-receptor interactions involve the dual aromatic and protonated amino features of the molecules. Of the two active sites which accommodate the aromatic groups, one prefers unsubstituted phenyl (or 2-pyridyl) and the other a *p*-substituted aryl group, as established by the present and previous stereochemical investigations. It also follows from work on the aminopropenes that the anionic site of the receptor (which associates with $^+$NH of the antagonist) is proximate to the more extended aromatic feature of the ligand.

Chemistry Preparative Work

Melting points are uncorrected. IR (Unicam SP 1025), UV, and NMR (^{1}H, ^{13}C, Jeol GX 270 and GX 400) spectroscopic and MS (VG 7070E, 70 eV EI) data supported structures in all cases; details relevant to configuration are included (Table 1), others may be obtained from the authors on request. HPLC data are quoted as retention times (min) measured from chromatograms of a 10 cm Hypersil (5 μM) CPS column, using a mobile phase of 20% tetrahydrofuran in water containing 50 mM KCl, 10 mM hexanesulphonic acid, and 0·1% H_3PO_4. The detection wavelength was the appropriate isosbestic point.

Mixtures of 1,1-diaryl-3-pyrrolidinoprop-1-enes (*2*) were obtained by heating *t*-alcohol precursors (*4*) with 85%

Table 6. Melting points and microanalytical data for aminopropenes (*2*) and their precursors.

Compound	Configuration	Melting point (°C)	Molecular formula	Microanalysis (%) Required C	H	N	Found C	H	N
3 HCl (Ar = 4-ethylphenyl	—	151	$C_{15}H_{21}NO \cdot HCl$	67·3	8·2	5·2	67·5	8·1	5·05
4 (Ar = 2-pyridyl, Ar′ = 4-ethylphenyl)	—	108–109	$C_{20}H_{26}N_2O$	77·4	8·4	9·0	77·8	8·6	8·8
2e $C_2H_2O_4$	E	149–150	$C_{20}H_{24}N_2\ C_2H_2O_4$	69·1	6·8	7·3	69·0	6·8	7·4
3 HCl (Ar = 4-bromophenyl)	—	190	$C_{13}H_{16}BrNO \cdot HCl$	49·1	5·3	4·4	49·1	5·5	4·4
2c $C_2H_2O_4$	E	176–178	$C_{18}H_{19}BrN_2\ C_2H_2O_4$	55·4	4·9	6·5	55·6	4·9	6·4
	Z	181–182						a	
4 (Ar = 3-pyridyl, Ar′ = phenyl)	—	141	$C_{18}H_{22}N_2O$	76·6	7·85	9·9	77·2	8·25	9·6
2f $C_2H_2O_4$	E	165–166	$C_{18}H_{20}N_2\ C_2H_2O_4$	67·8	6·2	7·9	68·0	6·3	7·9
4 (Ar = 3-pyridyl, Ar′ = 4-methylphenyl)	—	112	$C_{19}H_{24}N_2O$	77·0	8·2	9·45	77·4	8·4	9·5
2g $C_2H_2O_4$	E	194–195	$C_{19}H_{22}N_2\ C_2H_2O_4$	68·5	6·6	7·6	68·9	6·6	7·6
4 (Ar = 4-pyridyl, Ar′ = phenyl)	—	155–156	$C_{18}H_{22}N_2O$	76·6	7·85	9·9	77·0	7·85	9·7
2h $C_2H_2O_4$	Z	189–191	$C_{18}H_{20}N_2\ C_2H_2O_4$	67·8	6·2	7·9	68·1	6·3	7·95

a = Insufficient for microanalysis.

sulphuric acid over a 100–120°C temperature range (Ison & Casy 1971). Variation of reaction time led to different ratios of E:Z isomers, as judged by HPLC analysis. Mixtures were isolated in free base form and separated by crystallization of their hydrogen oxalate salts (obtained by treating bases with excess of acetone saturated with oxalic acid) from ethanol. Details of dehydration conditions, HPLC retention times, and isomeric purity are given in Table 5, while data characterizing novel products and their precursors are presented in Table 6. 3-Pyridyllithium (Gilman & Spatz 1951) and its 4-pyridyl congener were prepared by addition of the appropriate bromopyridine to *n*-butyllithium in ether at −50°C. Compounds E- and Z-*2a* (oxalates, both mp 166°C) were prepared as previously described (Ison et al 1973). Samples of the isomeric pair *2d*, kindly supplied by Dr Ison, were shown to be pure by HPLC after one recrystallization from EtOH.

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