Studies of stereochemical influences upon anti-histaminic activity. The synthesis, configuration, and anti-histaminic properties of some isomeric aminobutenes[1]

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The acid-catalyzed dehydration of 4-dimethylamino-2-*p*-methoxyphenyl-1-phenylbutan-2-ol yields all four possible 4-amino-1,2-diarylbutenes. Pure samples of each isomer have been isolated, double bond positions and configurations being established from proton magnetic resonance and ultraviolet spectroscopic data. A stereoselective route to *cis* aminobut-1-enes has been further investigated. The anti-histaminic properties of the reported butenes together with some related compounds are given and structural influences upon activity discussed.

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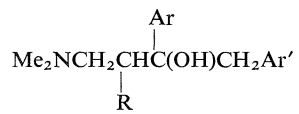
In 1950 Stoll and co-workers reported the anti-histaminic properties of some 4-amino-1,2-diarylbutenes formed by dehydration of 1,2-diaryl-4-*t*-aminobutan-2-ols (**1**), certain members having activities approaching that of Antergan (1). Since the aminobutenes were not characterized satisfactorily, the elimination of water from the butanols **1** has been further investigated and the double bond position and configuration of a series of so-derived isomeric aminobutenes established by spectroscopic means and the most active product of the Geigy workers shown to be a ternary mixture (2–4). In this paper further pharmacological data upon this mixture and upon a number of isomerically pure 4-aminobut-1-enes and -but-2-enes are given and tentative structure activity relationships drawn from the results.



1 R = (*a*), H; (*b*), Me.

$Me_2NCH_2CHMeCAr{=}CHAr^1$

2

$Me_2NCH_2CH{=}CArCH_2Ph$ $Me_2N(CH_2)_2CAr{=}CHPh$

Ar and H reference groups Ar and Ph reference groups

3 **4**

Ar = (*a*), Ph; (*b*), *p*-MeO·C_6H_4.

Chemistry

All the compounds tested (Tables II and III) were obtained by fractional crystallization of 4-aminobutene hydrochloride mixtures derived by acid-catalyzed elimination of the corresponding *t*-alcohols **1**. Those alcohols with 3-methyl substituents (**1***b*) gave but-1-enes exclusively (**2**) while the nor-analogues (**1***a*) gave all four possible isomers, namely *cis* and *trans* **3** and **4** (2, 3). An additional series of 2-*p*-methoxyphenylbutenes was synthesized by the sequence **5** through **8** and the four aminobutenes separated by fractional crystallization of their hydrochloride salts. Amongst these isomers, but-1-enes were differentiated from but-2-enes by the multiplicities of their vinylic proton magnetic resonance (p.m.r.) signals (but-1-ene signals were singlets and but-2-ene signals were triplets, $J = 7$ Hz), whilst configurational assignments rested upon association of the lower field vinylic chemical shift with the more planar of the two isomers (in both but-1-enes and but-2-enes the vinylic proton is subject to a greater degree of aromatic deshielding in the more planar isomer) (3, 4) (Table I). Models show the *trans* (Ph/Ar) but-1-ene **4***b* and the *cis* (Ar/H) but-2-ene **3***b* to be more planar forms. Ultraviolet (u.v.) data

TABLE I

Spectral data of 4-dimethylamino-2-*p*-methoxyphenyl-1-phenylbutenes

Butene	Chemical shift* vinylic signal	λ(ε)†
trans Ph/Ar **4***b*	411 Singlet	278 (18 300)
cis Ph/Ar **4***b*	397 Singlet	228 (21 200) 276 (13 130)
trans Ar/H **3***b*	353 Triplet, $J = 7$ Hz	239 (8 400)
cis Ar/H **3***b*	370 Triplet, $J = 7$ Hz	263 (14 600)

*Chemical shifts in Hz from tetramethylsilane (60 MHz operating frequency, Varian A-60 spectrometer), solvent $CDCl_3$.
†Solvent ethanol. λ is wavelength in mμ; extinction coefficient ε shown in parentheses.

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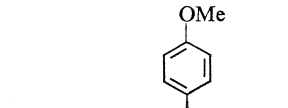
$$\underset{\mathbf{5}}{\mathrm{ArCOMe}} \xrightarrow[\mathrm{CH_2O}]{\mathrm{NHMe_2}} \underset{\mathbf{6}}{\mathrm{ArCO(CH_2)_2NMe_2}}$$

$$\xrightarrow{\mathrm{PhCH_2MgCl}} \underset{\mathbf{7}}{\mathrm{Me_2N(CH_2)_2C(Ar)(OH)CH_2Ph}} \xrightarrow{\mathrm{HCl—HAc}} \underset{\mathbf{8}}{\text{butene mixture}}$$

$\mathrm{Ar} = p\text{-MeO}\cdot\mathrm{C_6H_4}$

supports these assignments, the absorption maxima and extinction coefficients of *trans* **4***b* and *cis* **3***b* being at longer wavelengths and more intense respectively than those of the corresponding *cis* and *trans* isomers (Table I). These spectral results are in accord with data obtained for related isomers (3). The *cis* but-1-ene **4***b* showed an additional wavelength band (peak at 228 mμ) apparent only as a shoulder near 227 mμ in the *trans* isomer, the more complex *cis* spectrum resembling those of the 3-methyl congeners **9** (*trans*, maxima at 232 mμ, ε 17 200 and 256 mμ, ε 12 130; *cis* broad band between 222 mμ, ε



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14 600 and 263 mμ, ε 10 990) (4). The butenes *cis* **4***b* and *cis* and *trans* **9** are all highly crowded molecules in which no single chromophore is likely to be favored and this may be the reason why they give u.v. spectra that are more complex than those of the *trans* but-1-ene **4***b* and the but-2-enes **3** where favored planar conformations are clear upon inspection of models.

An alternative route to but-1-enes, exemplified by the sequence **10** through **13**, has previously been shown to lead to a *cis* isomer (3). Further study shows these reactions to be stereoselective respecting:

$$\underset{\mathbf{10}}{\mathrm{PhCH_2COPh}} \xrightarrow[\mathrm{NaNH_2}]{\mathrm{RCl}} \underset{\mathbf{11}}{\mathrm{PhCH(R)COPh}} \xrightarrow{\mathrm{LAlH_4}} \underset{\mathbf{12}}{\mathrm{PhCH(R)CHOHPh}}$$

$$\xrightarrow{\mathrm{KHSO_4}} \underset{\mathbf{13}}{\mathrm{RCPh{=}CHPh}} \quad \underset{\mathbf{14}}{\mathrm{PhCH{=}C(OR)Ph}}$$

$\mathrm{R} = \mathrm{Me_2N(CH_2)_2}$

(*a*) reduction of the ketone **11**. The p.m.r. spectrum of the total alcoholic product in $CDCl_3$ displayed sharp signals for the 1-methine, 2-methine, and NMe_2 protons (doublet $J = 7$, quartet $J = 7$, and singlet at 283, 177, and 121 Hz from TMS respectively) indicative of the preponderance of one diastereoisomer, and

(*b*) the dehydration step **12** to **13**. The p.m.r. spectrum of the total product of elimination showed vinylic signals at 390 and 407 Hz (from TMS) characteristic of *cis* and *trans* **13** respectively (3), present in the ratio of approximately 2 to 1 (cf. the same elimination of the α-ethyl analogue of **11** which led chiefly to *trans* α-ethylstilbene) (4).

Both *C*- and *O*-alkylated products were isolated upon alkylation of desoxybenzoin with 2-dimethylaminoethyl chloride in benzene, the enol ether **14** being characterized by its vinylic p.m.r. signal (a sharp singlet near 350 Hz) and infrared (i.r.) (doublet, 1670 and 1635 cm^{-1}) and u.v. (λ_{max} 287 mμ; ε 27 540; hydrochloride in ethanol) features typical of conjugated enol ethers (5, 6). The ratio of *O*- to *C*-alkyl product was about 7 to 1.5, a result in contrast with alkylation experiments upon desoxybenzoin using simple alkyl halides in which only minor amounts of *O*-alkylated products were detected (4). The proportion of the *C*-alkyl derivative **11** was raised when the reaction was repeated using dimethylsulfoxide as solvent, the total alkylation product consisting of about 40% **11**, 50% **14**, and 10% starting material as assessed from p.m.r.

TABLE II

Inhibition of histamine-induced contractions of isolated guinea-pig ileum by some aminobutenes (series 1)

Number	Structure	Ar	Ar′	Dose μg/ml	Percentage inhibition
1	*trans* **4***a*	Ph	Ph	1.0	62
2	*trans* **3***a*	Ph	Ph	1.0	49
				5.0	74
3	Ternary mixture (*cis* **3***a*, *cis* and *trans* **4***a*)	Ph	Ph	1.0	100
4	*trans* **2**	Ph	Ph	1.0	45
				5.0	71
5	*trans* **2**	Ph	*p*-MeC_6H_4	1.0	52
6	*trans* **2**	Ph	2-pyridyl	1.0	24
7	*trans* **2**	Ph	*o*-MeC_6H_4	1.0	5
				10.0	32
8	*cis* **2**	Ph	*o*-MeC_6H_4	1.0	11
				10.0	59
9	*trans* **2**	2-Thienyl	Ph	1.0	65
10	*trans* **2**	*p*-$MeOC_6H_4$	Ph	1.0	2.5
				10.0	68
11	*cis* **2**	*p*-$MeOC_6H_4$	Ph	1.0	43

TABLE III

Inhibition of histamine induced contractions of isolated guinea-pig ileum by some aminobutenes (series 2)

Number	Structure	Dose μg/ml	Percentage inhibition at time (in min)								
			3	6	9	12	15	18	21	24	27
1	*trans* **2** (Ar = Ar′ = Ph)	0.1	95	47	14	0					
2	*trans* **2** (Ar′ = *o*-F·C_6H_4, Ar = Ph)	0.1	53	24	7	0					
3	*trans* **2** (Ar′ = *o*-Cl·C_6H_4, Ar = Ph)	0.1	7	0	0						
4	*trans* **4***b*	0.1	100	95	64	58	30	20	13	8	2
5	*cis* **4***b*	0.1	16	10	0						
6	*trans* **3***b*	0.1	0	0							
7	*cis* **3***b*	0.1	100	95	90	78	52	60	38	40	36
8	Mepyramine	0.001	99	97	91	82	71	70	38	19	23

integrals of characteristic signals. The configuration of the *O*-alkyl derivative **14** is unknown but is probably *trans* Ph/Ph on the grounds of its very intense u.v. absorption band.

Preliminary Pharmacological Results and Discussion

The anti-histaminic potencies of a series of aminobutenes, as measured by their ability to antagonize the histamine-induced contraction of the guinea-pig ileum, are given in Tables II and III. Thanks are due to Drs. R. T. Brittain and R. G. W. Spickett of Allen and Hanburys, Ware, U.K. for arranging these tests. Tentative structure–activity relationships drawn from results of the initial series (Table II) are as follows:

First, amongst the diphenylbutene samples (Table II, Nos. 1–3) the ternary mixture is by far the most active; it has a pA_2 value of 9.4 comparable with those of highly active anti-histaminic agents (7). This mixture is composed of the *cis* and *trans* but-1-enes **4***a* and the *cis* but-2-ene **3***a*, and since the but-1-enes are much less active than the mixture [the *cis* isomer **4***a*, not included in these tests, has previously been shown to have a low order of activity (8)], it may be deduced (assuming

synergism is not operative in the mixture) that the *cis* but-2-ene **3***a* is the most active of the four isomers derived from the butanol **1***a* (Ar = Ar′ = Ph). Pure *cis* **3***a*, unavailable at the time of these tests, has now been isolated and a study of its anti-histaminic properties is in hand.

Secondly, a 3-methyl substituent reduced activity in *trans* but-1-enes (Table I, Nos. 1 and 4). In the same series the 1, 2-diphenyl and 1-*p*-tolyl, 2-phenyl members have comparable activities (Nos. 4 and 5) while the 1-2(2-pyridyl) and 1-(*o*-tolyl) analogues are of significantly reduced potency (Nos. 6 and 7). Replacement of 2-phenyl in No. 4 by 2-thienyl is advantageous (No. 9) but substitution of 2-phenyl by *p*-methoxyphenyl gives a less potent compound (No. 10).

Thirdly, among the two but-1-ene pairs Nos. 7/8, and 10/11, the *cis* member is more potent than the *trans* isomer.

These initial results indicative of the antagonism of histamine by aminobutene derivatives being stereoselective in nature, encouraged us to examine a second series, data for which (Table III) is summarized below:

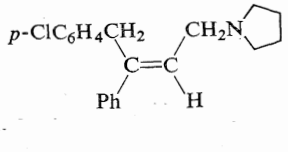
First, *o*-fluoro and particularly *o*-chloro substituents in the phenyl group at C-1 of *trans* **2** (Ar = Ar′ = Ph) reduce activity (Table III, No. 1–3); cf. similar influence of *o*-methyl in previous series (Table II, Nos. 4 and 7).

Secondly, amongst the *p*-methoxyphenyl derivatives (Table III, Nos. 4–7), the *trans* but-1-ene **4***b* and the *cis* but-2-ene **3***b* are far more active than corresponding geometrical isomers, the duration of action of *cis* **3***b* being particularly prolonged. *Cis* **3***b* (pA_2 6.94) is substantially less potent than the standard drug mepyramine (pA_2 8.67).

These results further emphasize the influence of steric factors upon activity among anti-histaminic aminobutenes and confirm that the disposition of functions about the double bond in a *cis* (Ar/H) 1,2 diarylbut-2-ene appear to be optimal for activity. It is significant that pyrrobutamine, an aminobut-2-ene already marketed as an anti-histaminic agent (9), has the same *cis* configuration **15** (unpublished p.m.r. results).

Differences in the anti-histaminic properties of geometrical isomers have previously been reported for Triprolidine **16** and its *trans* (2-pyridyl/H) analogue (10). The former compound and the *cis* but-2-enes **3***a*, **3***b*, and **15** possess the common structural feature **17** rigidly orientated in the same manner and it is attractive to postulate that their histamine-blocking actions are of like nature involving similar drug-receptor association modes.

Kier (11) has recently proposed favored *anti* and gauche $\overset{+}{N}H_3$/Ar conformations for histamine based on molecular orbital calculations, and has suggested that the similar N to N interatomic distances of the *anti* conformer and triprolidine may be of significance regarding the latter compound's antagonistic properties. The present demonstration of stereospecific action among anti-histaminic agents which lack a pyridine substituent, suggests that the distance between the side chain nitrogen atom and the center of the aromatic ring attached to C-1 more truly represents the critical parameter for activity in these compounds. The problem of explaining the activity difference between triprolidine and its *trans* Ph/H isomer remains (since both forms may satisfy the aryl–nitrogen distance requirement), and further structure–activity data upon triprolidine analogues and related aminobutenes are being sought to provide more evidence upon this question.



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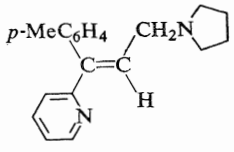

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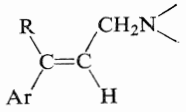

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Experimental

The proton magnetic resonance (p.m.r.) spectra were recorded on a Varian A-60 spectrometer using $CDCl_3$, CCl_4, or D_2O as solvent. Chemical shifts are expressed in Hz from the TMS standard.

β-*Dimethylamino-p-methoxypropiophenone*

A mixture of *p*-methoxyacetophenone (22.5 g), dimethylamine hydrochloride (15.75 g), paraformaldehyde (5.8 g), concentrated hydrochloric acid (0.4 ml), and ethanol (38 ml) was heated under reflux for 20 h. The cooled product was diluted with acetone (150 ml) when the *hydrochloride* of the β-*aminoketone* **6** (36 g), m.p. 186–186.5° separated.

Anal. Calcd. for $C_{12}H_{18}ClNO_2$: C, 59.1; H, 7.45; N, 5.7. Found: C, 58.7; H, 7.2; N, 5.3.

4-Dimethylamino-2-p-methoxyphenyl-1-phenylbutan-2-ol and its Elimination

The β-aminoketone **6** (24.5 g) in ether (50 ml) was added to benzylmagnesium chloride in ether (125 ml) prepared from benzyl chloride (29.7 g) and magnesium (6.7 g), the mixture heated under reflux for 3 h, and then decomposed with NH_4Cl–ice. The organic layer was dried (Na_2SO_4) and evaporated to give the impure butanol **7** (29 g), characterized as the *hydrochloride*, m.p. 195–196° from ethanol–ether.

Anal. Calcd. for $C_{19}H_{26}ClNO_2$: C, 67.9; H, 7.8; N, 4.2. Found: C, 67.6; H, 7.7; N, 4.0.

A mixture of the butanol **7** hydrochloride (9.5 g), concentrated hydrochloric acid (25 ml), and glacial acetic acid (70 ml) was heated under reflux for 4 h. The product was concentrated under reduced pressure and the free base recovered as usual. The p.m.r. spectrum of the total butene mixture in $CDCl_3$ displayed 4 vinylic signals (2 broad singlets and 2 triplets) and 4 closely placed OMe and NMe_2 singlets near 225 and 183 Hz from TMS respectively. Fractional crystallization of the base hydrochloride from ethanol–ether gave the following isomers (listed in order of separation):

The *trans but-1-ene* **4***b hydrochloride* (800 mg), m.p. 227–228°.

Anal. Calcd. for $C_{19}H_{24}ClNO$: C, 71.8; H, 7.6; N, 4.5. Found: C, 72.2; H, 7.8; N, 4.2.

The *trans but-2-ene* **3***b hydrochloride* (290 mg), m.p. 186.5–187.5°. Found: C, 72.05; H, 8.1.

The *cis but-2-ene* **3***b hydrochloride* (320 mg), m.p. 203–204°. Found: C, 71.9; H, 7.4.

The *cis but-1-ene* **4***b hydrochloride* (400 mg), m.p. 178.5–179.5°. Found: C, 71.9; H, 7.8.

Alkylation of Desoxybenzoin with 2-Dimethylaminoethyl Chloride

Sodamide (2.5 g) was added to desoxybenzoin (10.8 g) in benzene (20 ml) and the mixture heated under reflux for 3 h, cooled, and treated with 2-dimethylaminoethyl chloride (6.75 g), freshly liberated from the hydrochloride. After a further reflux period of 16 h, the reaction mixture was cooled, filtered, and concentrated *in vacuo*. The residue gave a distillate (13.1 g), b.p. 145–172°/1.2 mm and its p.m.r. spectrum in CCl_4 showed it to consist of about 70% of the *O*-alkyl-derivative **14** (integral of the vinylic singlet at 361 Hz), 15% of the *C*-alkyl isomer **11** (integral of the methine triplet at 283 Hz), and 15% desoxybenzoin (integral of the methylene singlet at 244 Hz). The total product in cold ether was acidified with ethereal HCl, and the precipitated salt collected, washed with ether, and fractionally crystallized from ethanol to give the *C-alkylamine* **11** *hydrochloride* (1 g), m.p. 250–253°.

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.2; H, 7.25; N, 4.6. Found: C, 70.8; H, 7.15; N, 4.3.

The *O-alkylisomer* **14** *hydrochloride* (7.2 g), m.p. 185–185.5°. Found: C, 71.2; H, 7.2; N, 4.4. Characteristic p.m.r. signals in D_2O: singlet 345 Hz (vinylic proton) and deformed, object–mirror image, triplets centered at 214 Hz (OCH_2) and 190 Hz (NCH_2) (in the base, CCl_4 solvent, these methylene signals are approximate first order triplets, $J = 7$ Hz). Repetition of the alkylation reaction with dimethyl sulfoxide as solvent (sodio derivative of desoxybenzoin formed as before then solvent benzene replaced by DMSO) and a heating period of 16 h at 80°, gave the *C*- and *O*-alkyl isomers in a ratio of 4:5.

Acknowledgment

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1. W. G. Stoll, Ch. J. Morel, and Ch. Frey. Helv. Chim. Acta, **33**, 1194 (1950).
2. A. F. Casy, J. L. Myers, and P. Pocha. Tetrahedron, **22**, 1001 (1966).
3. A. F. Casy and P. Pocha. Tetrahedron, **23**, 633 (1967).
4. A. F. Casy, A. Parulkar, and P. Pocha. Tetrahedron, **24**, 3031 (1968).
5. A. L. Nussbaum, E. Yuan, D. Dincer, and E. P. Oliveto. J. Org. Chem. **26**, 3925 (1961).
6. H. Rosenkrautz and M. Gut. Helv. Chim. Acta, **36**, 1000 1953.
7. R. B. Barlow. Introduction to chemical pharmacology. 2nd ed. Methuen and Co., Ltd., London. 1964. p. 357.
8. W. G. Stoll, Ch. Frey, and Ch. J. Morel. Helv. Chim. Acta, **33**, 1208 (1950).
9. U.S. Patent No. 2,655,509 (1953); Chem. Abstr. **48**, 13726*c* (1953).
10. D. W. Adamson, P. A. Barrett, J. W. Billinghurst, and T. S. G. Jones. J. Chem. Soc. 2315 (1957).
11. L. B. Kier. J. Med. Chem. **11**, 441 (1968).