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Structural influences upon antihistamine activity; 3-amino-1-aryl-1-(2-pyridyl)propenes and related compounds

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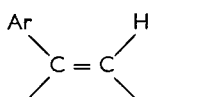
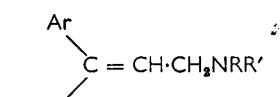
A series of 3-amino-1-aryl-1-(2-pyridyl)propenes and related compounds have been prepared by the dehydration of corresponding tertiary alcohols, and the configurations of geometrical isomeric derivatives established from spectroscopic data. The ability of the aminopropenes to antagonize histamine-induced contractions of the guinea-pig ileum is reported. These data allow various structure-activity relations to be discussed including stereochemistry (*cis* 2-pyridyl/H geometry is superior to *cis* substituted phenyl/H but not necessarily to *cis* phenyl/H), nature of the basic function (1-pyrrolidino is markedly superior to either dimethylamino or 1-piperidino) and the importance of the vinylic hydrogen atom (sharp falls in potency follow its replacement by methyl).

The work reported was carried out to extend knowledge of structure-activity relations in 1,1-diaryl-3-aminopropenes I with antihistamine properties such as triprolidine



I

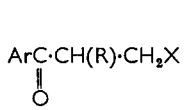


II

(I, Ar = 2-pyridyl, Ar' = *p*-Me·C_6H_4, X = 1-pyrrolidino). Data upon *cis-trans* pairs were sought in particular in view of previous reports upon the influence of geometrical configuration upon activity in isomeric 3-amino-1-aryl-1-(2-pyridyl)propenes (Adamson, Barrett & others, 1951) and 4-amino-1,2-diarylbut-2-enes II (Casy & Ison, 1970).

CHEMISTRY AND CONFIGURATION

Most of the synthetic work involved treating a Mannich base III with 2-pyridyl lithium to give a tertiary alcohol IV (Ar' = 2-pyridyl) which was then dehydrated under acid conditions to form the aminopropenes V (Ar' = 2-pyridyl). Isomers arose in cases where Ar ≠ Ar' and in most of these at least one form was isolated in a pure condition whilst the composition of mixtures was known from their pmr characteristics. The proportions of isomeric alkenes formed was dependent on



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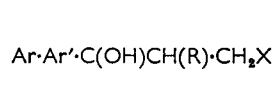
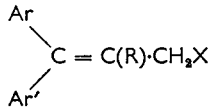


IV



V

(a) X = NMe_2 (b) X = 1-pyrrolidino (c) X = 1-piperidino

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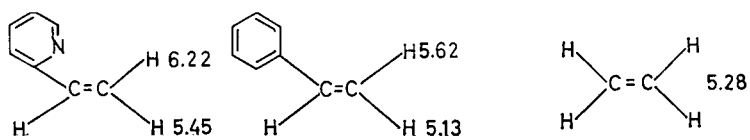
their equilibration rates since the conditions employed to dehydrate the precursors IV permitted isomerization. Thus, while a 2 h exposure of IVa (Ar= Ph, Ar′ = 2-pyridyl, R = H) to hot acid gave significant amounts of the two possible isomers V, that of IVb (Ar = *p*-Me·C_6H_4, Ar′ = 2-pyridyl, R = H) yielded a single aminopropene. Kinetic control of the last reaction was achieved by reducing the heating period to 15 min when approximately equal amounts of the two isomers formed. The accelerating effect of the *p*-tolyl group upon the equilibration of isomeric alkenes has previously been noted in studies of 4-aryltetrahydropyridines (Casy, Beckett & Iorio, 1967). Isomers were separated by fractional crystallization of the hydrogen oxalate salts of the total aminoalkenes V. progress of purification being monitored by pmr spectroscopy.

The configurational assignment of isomers derived from IVa (Ar = Ph, Ar′ = 2-pyridyl, R = H) and IVb (Ar = *p*-Me·C_6H_4, Ar′ = 2-pyridyl, R = H) was initially based on differences in their ultraviolet spectra as described by Adamson, Barrett & others (1957, 1958). In both pairs, the isomeric oxalate V having an ultraviolet spectrum similar to that of 2-vinylpyridine was assigned the *trans* 2-pyridyl/CH_2N configuration (Table 1). Differences in the pmr spectra of the same isomers V were also studied, (i) to seek further information about the preferred conformations of these molecules, and (ii) to investigate the scope of pmr spectroscopy in solving stereochemical problems in this series.

Magnetic influences governing the chemical shift of the vinylic protons in isomeric pairs of type VII, deduced chiefly from data upon 2-vinylpyridine, styrene and ethylene (see Scheme 1) and assuming the additivity of shielding effects (Tobey, 1969), are as follows:



SCHEME 1

Chemical shifts (ppm from TMS, δ scale) of vinylic protons in 2-vinylpyridine and styrene (Bhacca, Johnson & Shoolery, 1962) and ethylene (Tobey, 1969) in CCl_4 or $CDCl_3$.

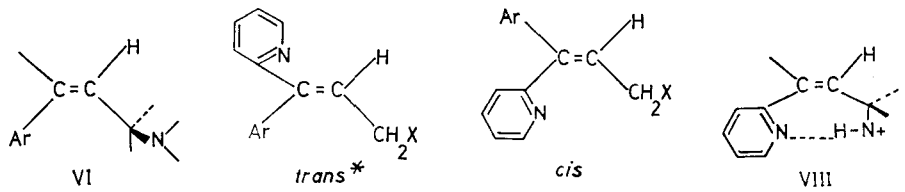
(1) The *cis* aryl groups—deshielding for both 2-pyridyl and benzenoid substituents but almost three fold greater in extent in the former case.

(2) The *trans* aryl groups—deshielding for 2-pyridyl, but shielding for benzenoid substituents.

Screening effects (1) and (2) will both be reduced the more the aryl group is turned out of the plane of the carbon-carbon double bond (Johnson & Bovey, 1958; Barbieux, Defay & others, 1964).

(3) The aminomethyl group—the greater the population of conformers VI with nitrogen close to the vinylic proton, the greater the deshielding of this proton. This population will depend on the extent of repulsive interactions between Ar and CH_2N substituents and is anticipated to be greater in the case of the alkene with *cis* 2-pyridyl and CH_2N groups on both steric and electronic grounds.

Because of the magnitudes of the field effects involved in (1), it follows that the vinylic signal of the *trans* isomer VII should be at lower field in the spectra of most isomeric pairs, but situations may be met (dependent on the extent of the Ar/CH_2N interaction) in which isomeric vinylic signals have very similar chemical shifts.



VII

(a) X = NMe_2; Ar = Ph (b) X = 1-pyrrolidino Ar = p-Me·C_6H_4

*[2-pyridyl and aminomethyl are the configurational reference groups as proposed by Adamson & others (1957)].

Such was the case, in fact, for the isomeric pair VIIa when the bases were examined in $CDCl_3$ (see Table 1).

In spectra of the corresponding acid oxalates in D_2O, however, the *trans* signal was distinctly lower field than the *cis* vinylic resonance. Solvation of the basic centres will increase steric interactions between the 2-pyridyl and CH_2X substituents in *cis* VII [and hence decrease deshielding factor (2)] while hydrogen bonding of the type VIII will reduce the population of conformers VI, and hence reduce factor (3). Both effects will result in the vinylic signal of *cis* VII being moved to *higher* field and account for the differences in vinylic signals observed in spectra of *cis* and *trans* VIIa under these conditions. In triprolidine (*trans*-VIIb) and its *cis* isomer, the *trans* vinylic signal was lower field in the spectra of both the free bases and the oxalate salts. The result for the bases is evidence that *cis* aryl/1-pyrrolidinomethyl interactions are greater than those of aryl and dimethylaminomethyl. Comparison of data for the *trans* pair VIIa and VIIb, and the corresponding *cis* pair (Table 1) shows that the *trans* vinylic signal suffers the greater change when NMe_2 is replaced by 1-pyrrolidino. In the *trans* isomers, more pronounced Ar/CH_2N interactions will cause the vinylic signal to move downfield on two counts (reduction of benzenoid shielding and elevation of CH_2N deshielding) but will not influence the vinylic signal of *cis* isomers so much because the increase in CH_2N deshielding will be offset by the decrease in 2-pyridyl deshielding.

Table 1. *Spectral data of some 3-amino-1-1,diarylprop-1-enes.*

Compound	Chemical shift* vinylic H†	CH_2X‡	λ(ε)**
trans-VIIa	6·33(6·63)	3·05(3·87)	245(7800), 283(5700)
cis-VIIa	6·33(6·37)	3·17(3·77)	252(10,000)
trans-VIIb	6·92(6·65)	3·21(4·02)	238(14,700), 283(6650)
cis-VIIb	6·27(6·45)	3·24(3·95)	244(14,100), 258(14,500)
trans-IX	6·87(6·83)	2·87(3·76)	233(14,600), 282(7500)
cis-IX	5·98(6·03)	3·42(3·93)	spectrum of pure isomer not available

* ppm(δ), base in $CDCl_3$ (TMS standard); values in parenthesis refer to acid oxalates in D_2O (DSS standard).

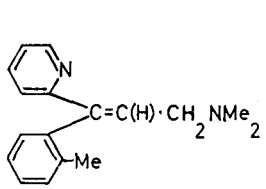
† triplet, $J \sim 7$Hz

‡ doublet, $J \sim 7$Hz

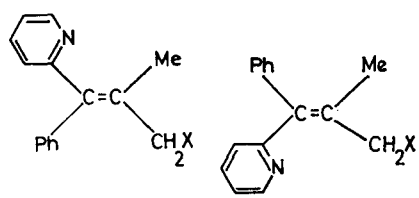
** Oxalate in ethanol. λ is wave length in nm; extinction coefficient ε shown in parenthesis. Adamson & others (1957, 1958) report; *trans*-VIIa, 238(20 900) 280(10 700; *cis*-VIIa, 247(22 400) oxalates in chloroform–ethanol; *trans*-VIIb, 233(16 200) 283(8200); *cis*-VIIb, 233(13 600) 260(13 800), oxalates in ethanol.

Shielding considerations (1) and (2) also apply to the CH_2X protons. In the pairs VIIa and VIIb, examined as bases, the *cis* signals had the lower field position as expected from the proximity of CH_2X to 2-pyridyl. In spectra of the oxalates in D_2O, however, the *trans* signals were lower field. This result is again attributed to enhanced steric interactions between 2-pyridyl and CH_2X when the basic centres of *cis* isomers are solvated; in consequence, deshielding due to factor (1) is reduced to a level where it is surpassed by deshielding factors (1) and (2) operating in the *trans* isomers. The larger steric demands of 1-pyrrolidinomethyl over CH_2NMe_2 are again revealed by the smaller differences in CH_2X chemical shifts in the spectra of *cis* and *trans* VIIb as compared with those of VIIa. Differences in ultraviolet and pmr characteristics similarly allowed the stereochemical characterization of the 1-*o*-tolyl analogues IX. In this pair, the CH_2X signal was at lower field in the spectra of both free base and oxalate of the *cis* member (Table 1); this result is attributed to the very large interaction between *o*-tolyl and CH_2X substituents in the *trans* isomer which forces the aromatic group well out of the plane of the carbon-carbon double bond whereby the CH_2X protons are shielded rather than deshielded by the *o*-tolyl group.

Reaction of the Mannich bases III a-c (Ar = Ph, R = Me) with 2-pyridyl lithium was essentially stereospecific since the pmr spectra of the products IV a-c (Ar = Ph, Ar′ = 2-pyridyl, R = Me) displayed no duplication of signals as would be typical of a diastereoisomeric mixture. Dehydration of the alcohols IV a-c (Ar = Ph, Ar′ = 2-pyridyl, R = Me) gave an approximately equal mixture of *cis-trans* alkenes X in each case; fractional crystallization of corresponding oxalates yielded one isomerically pure form of Xa and mixtures of Xb and Xc of known composition. Configurational assignments were based on the *cis* 2-pyridyl/CH_2X isomers having the lower field CH_2X and higher field = C·Me resonances. Differences in the latter signals were small and were only revealed in the case of the 3-piperidino analogue Xc when the spectrum of a mixture was recorded in benzene, the result being a further example of the ASIS effect (Laszlo, 1967). Several non-isomeric 1,1-diaryl-3-aminopropenes V which did not contain the 2-pyridyl moiety were also prepared and tested (details in Table 2). The aminoalkene Vb (Ar = Ph, Ar′ = *p*-Me·C_6H_4, R = H) was isolated as a 50:50 mixture of geometrical isomers, as shown by the duplication of the aryl Me and CH_2N signals in the pmr spectrum of the product.



IX



X

(a) X = NMe_2
(b) X = 1-pyrrolidino
(c) X = 1-piperidino

PHARMACOLOGICAL RESULTS AND DISCUSSION

The antihistamine potencies of the 3-amino-1,1-diarylprop-1-enes and related compounds, as measured by their ability to antagonize the histamine-induced con-

Table 2. *Inhibition of histamine-induced contractions of isolated guinea-pig ileum by some 3-amino-1-aryl-1-(2-pyridyl)propenes and related compounds*.*

Compound No.	Configuration†	Structure Text formula	Basic substituent	Concn µg/ml	% inhibition at time (in min) :3	:6	:9	:12	:15	:18	:21	:24
1	*trans*	VIIa	NMe_2	0·10	32	30	23	0	—	—	—	—
2	*cis*	VIIa	NMe_2	0·10	40	32	0	—	—	—	—	—
	Mepyramine			0·001	49	36	27	25	19	15	—	—
3	*trans*	VIIb	1-pyrrolidino	1·0	100	100	72	83	63	—	—	—
				0·01	59	45	24	14	0	—	—	—
4	*cis*	VIIb	1-pyrrolidino	1·0	61	54	25	29	25	21	18	11
	Mepyramine			0·001	50	32	22	15	10	9	4	—
5	*trans*	IX	NMe_2	0·10	100	85	65	50	40	25	15	15
				0·01	63	31	13	0	0	—	—	—
6	*cis*(50):*trans*(50)	IX	NMe_2	1·0	100	90	56	27	27	8	0	—
	Mepyramine			0·001	94	77	47	31	15	0	—	—
7	*cis*	Xa	NMe_2	0·10	33	24	14	5	—	—	—	—
8	*cis*(30):*trans*(70)	Xa	NMe_2	0·10	19	19	10	19	19	10	10	—
	Mepyramine			0·001	49	36	27	25	19	15	—	—
9	*cis*(85):*trans*(15)	Xb	1-pyrrolidino	1·0	48	8	4	—	—	—	—	—
10	*cis*(50):*trans*(50)	Xc	1-piperidino	1·0	32	0	—	—	—	—	—	—
	Mepyramine			0·001	100	96	76	57	38	27	13	13
11	Va(Ar=Ar′=Ph,R=H)		NMe_2	0·10	60	40	15	0	—	—	—	—
12	Va(Ar=Ar′=Ph,R=Me)		NMe_2	0·10	0	—	—	—	—	—		—
13	3-Dimethylamino-3-methyl-1,1-diphenylpropene		NMe_2	0·10	32	25	17	—	—	—	—	—
	Mepyramine			0·001	49	36	27	25	19	15	—	—
14	Vb(Ar=Ar′=Ph,R=H)		1-pyrrolidino	0·01	100	90	47	47	42	32	26	26
				0·001	88	50	44	19	0	0	—	—
15	Vb(Ar=Ar′=*p*-Me·C_6H_4, R=H)		1-pyrrolidino	0·01	48	33	29	19	24	14	14	—
	Mepyramine			0·001	91	91	86	77	73	64	64	60
16	*cis*(50):*trans*(50)Vb(Ar=Ph, Ar′=*p*-Me·C_6H_4,R=H)		1-pyrrolidino	1·0	100	100	100	100	—	—	—	—
				0·01	39	21	11	14	7	—	—	—
	Mepyramine			0·001	50	32	22	15	10	9	4	—
17	*trans*(H/Ph)-1-*p*-Chlorophenyl-2-phenyl-4-(1-pyrrolidino)but-2-ene			0·10	82	75	46	57	45	45	38	—
				0·001	24	19	14	9	0	—	—	—
18	*trans*(Ar/Ar′)-1-*p*-Chlorophenyl-2-phenyl-4-(1-pyrrolidino)but-1-ene‡			0·01	69	65	62	53	56	25	16	37
19	*cis*(Ar/Ar′)-1-*p*-Chlorophenyl-2-phenyl-4-(1-pyrrolidino)but-1-ene			0·01	45	41	28	17	0			
	Mepyramine			0·001	49	36	27	19	15			

* tested as hydrogen oxalates or hydrohalides
† reference groups are 2-pyridyl and aminomethyl unless otherwise stated
‡ pA_2 7·4

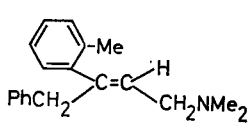
traction of the guinea-pig ileum are given in Table 2. Thanks are due to Dr. R. T. Brittain of Allen and Hanburys, Ware, Herts., for arranging these tests. The compounds were tested in groups on separate occasions and corresponding responses of the tissue to the standard drug mepyramine are included in the Table. Apart from cases where pA_2 values were measured, these data only allow semi-quantitative activity comparisons. Nevertheless certain trends in structure-activity relations are discernible, as discussed below.

(1) Comparison of data for the pairs No. 1/3 and No. 11/14 shows that a pronounced enhancement of potency follows replacement of dimethylamino by 1-pyrolidino in 3-amino-1-aryl-1-(2-pyridyl)propenes. A similar observation was made for a series of antihistaminic 3-amino-1,1-diphenylpropenes (White, Green & Hudson, 1951). These results are somewhat surprising in view of the similar basic properties and gross dimensions of the two amino functions (see later). Related 1,2-diaryl-4-(1-pyrrolidino)butenes also possess significant antihistamine potencies and there appears to be a diminished stereospecific dependence upon activity amongst 4-(1-pyrrolidino)butenes compared with that found for 4-dimethylamino and 4-piperidino analogues (Casy & Ison, 1970). Thus both the *cis* and *trans* but-1-enes (Nos. 18 and 19) are moderately potent while the *trans* but-2-ene (No. 17) has a pA_2 approaching 8. Pyrrobutamine,

the *cis* analogue of the last compound, which is in clinical use is confirmed as a very potent antihistamine agent but its pA_2 value could not be determined because it had a non-competitive mechanism of action.

(2) *Stereospecificity.* Adamson & others (1951) have made the general statement that for drugs of the triprolidine class I "high and specific antihistamine activity was shown only by isomers having the α-pyridylethylene type of structure (i.e. *trans* 2-pyridyl/CH_2N isomers), the other isomer of each pair invariably being considerably less active in this respect". Particular examples were limited to the isomeric pair I (Ar = 2-pyridyl, Ar′ = *p*-Cl·C_6H_4, X = 1-pyrrolidino), the *trans* (2-pyridyl/CH_2N) member being reported as highly potent and 80 times as active as the corresponding *cis* isomer. The data of Table 2 now provides information on a further two pairs of isomers of this class. Triprolidine itself (No. 3) is highly potent (pA_2 9·0) and is more active than the corresponding *cis* isomer (No. 4); the potency difference appears to be of a lower order, however, than that anticipated from the 80 fold difference reported for 1-(2-pyridyl)-1-*p*-chlorophenyl analogues. Both *cis* and *trans* 1-(2-pyridyl)-1-phenyl derivatives (Nos. 1 and 2) have feeble antihistamine activities of short duration and there is no noticeable difference in their potencies. These results raise the question of the general superiority (from a pharmacological point of view) of 2-pyridyl over phenyl and substituted phenyl as the aryl group *trans* to aminomethyl in antihistamines of structure I. This appears to be true when the choice is between 2-pyridyl and *p*-chlorophenyl or *p*-tolyl but is less certain in the case of phenyl itself in view of results on 1,1-diphenyl-3-pyrrolidinoprop-1-ene (No. 14). This compound, although short acting has a high potency with a pA_2 (after a 2 min contact time) determined as well above the value 9 established for triprolidine (*cf.* White & others, 1951). The significant potency of the *cis-trans* mixture No. 16 (pA_2 8·5) further demonstrates that non-yyridyl containing analogues of I retain pronounced antihistamine properties while the lower activity of No. 15 compared with No. 14 shows that phenyl is preferred to *p*-tolyl as the aromatic group *trans* to CH_2N in I. A clear decision regarding the relative efficacies of phenyl and 2-pyridyl in this respect must await the pharmacological evaluation of *cis* and *trans* 1-phenyl-1-(2-pyridyl)-3-pyrrolidinoprop-1-ene.

(3) Results from compounds Nos. 7–10 establish the importance of having a vinylic hydrogen atom *cis* to an aromatic group in antihistamines based on I. Since the aryl substituents are phenyl and 2-pyridyl, the activities of these compounds should not be greatly dependent upon configuration (see 2 above) and the uniformly low orders of potency observed emphasizes the detrimental effect of an increase in the bulk of the substituent *cis* to Ar in I. The same trend is apparent in Nos. 11 and 12. A possible explanation of this result may be the less favoured nature of a coplanar Ar·C = C conformation in 2-methyl analogues of I as a result of *cis* Ar/Me interactions. An essentially coplanar Ar·C = C·C·N arrangement has previously been advanced as an important requirement for antihistamine activity in 1,1-diarylprop-1-enes and 1,2-diarylbut-2-enes (Casy & Ison, 1970). Another result in support of this view and appropriate to this section is the reduced activity of the 2-*o*-tolylbut-2-



XI

ene XI (in which a coplanar Ar·C = C conformation is likewise unfavoured) as compared with the 2-phenyl analogue (Ison, 1970).

(4) In contrast with the 2-methyl analogues of I, compound No. 5 is an example in which an increased divergence of the aryl group Ar′ from the double bond plane is achieved as is evident from models and physical evidence already discussed. Although direct comparison of Nos. 5/6 and the unsubstituted phenyl analogues Nos. 1/2 is not possible because the two sets of isomers were tested on separate occasions, it is clear that (i) both the *trans* and *cis*/*trans* mixture (Nos. 5 and 6) are significantly active, (ii) the *trans* derivative (No. 5) is more potent than the *cis* isomer (No. 6), and (iii) the *trans* *o*-tolyl derivative (No. 5) is more potent than the phenyl congener (No. 1). These results suggest that factors which increase the deviation of the Ar′ and C = C planes in antihistamines of structure I have an advantageous effect upon potency either in terms of association of Ar′ at the receptor or because of a concomitant increase in the population of planar Ar·C = C conformers. In crowded molecules there is evidence that the steric requirements of pyrrolidino are significantly greater than those of dimethylamino, piperidino and morpholino (Munk & others, 1968) (see also pmr discussion). Hence the potency raising power of the pyrrolidino group in antihistamines of structure I may lie in its influence upon the orientation of the adjacent aromatic substituent (Ar′).

EXPERIMENTAL CHEMISTRY

Tertiary alcohols (IV). The following *2-pyridyl carbinols* were prepared by treatment of the appropriate Mannich ketones (III) (all previously described) with 2-pyridyl lithium at −50° under N_2 according to the method of Adamson & Billinghurst (1950) (yields in parenthesis): IVa (Ar = Ph, Ar′ = 2-pyridyl, R = H), (53%), m.p. 97–99° from ethanol, reported m.p. 99–100° (Adamson & Billinghurst, 1950); IVb (Ar = *p*·Me·C_6H_4, Ar′ = 2-pyridyl, R = H), (28%), m.p. 116–117° from ethanol, reported m.p. 119–120° (Adamson & others, 1958); IVa (Ar = *o*-Me·C_6H_4, Ar′ = 2-pyridyl, R = H), (11%), m.p. 96° from ethanol (Found: C, 75·8; H, 8·4. $C_{17}H_{22}N_2O$ requires: C, 75·5; H, 8·2%); IVa (Ar = Ph, Ar′ = 2-pyridyl, R = Me), (49%), m.p. 74–75° from ethanol (Found: C, 75·6; H, 8·0; N, 10·1. $C_{17}H_{22}N_2O$ requires: C, 75·5; H, 8·2%;) IVb (Ar = Ph, Ar′ = 2-pyridyl, R = Me), (9%), m.p. 112° from hexane, reported m.p. 111° (Adamson & others, 1958); IVc (Ar = Ph, Ar′ = 2-pyridyl, R = Me), (18%), m.p. 125–126° from hexane reported m.p., 134° (Adamson, & others, 1958) (Found: C, 77·4; H, 8·4: N, 9·3. $C_{20}H_{26}N_2O$ requires: C, 77·4; H, 8·4; N, 9·0%).

The *diphenyl carbinols* IVa and IVb (Ar = Ar′ = Ph, R = H) (Adamson, 1949), IVa (Ar = Ar′ = Ph, R = Me) and 3-dimethylamino-1,2-diphenyl-1- methylpropan-1-ol (Kjaer & Peterson, 1951) were all prepared using phenyl lithium as the aryl organometallic reagent.

The *p-tolyl carbinols* IVb (Ar = Ph, Ar′ = *p*-Me·C_6H_4, R = H) and IVb (Ar = Ar′ = *p*-Me·C_6H_4, R = H) were prepared by treatment of the aminoketone IIIb (Ar = *p*-Me·C_6H_4, R = H) with phenyl lithium in toluene and *p*-tolyl lithium in ether respectively, followed by the normal workup. Thus were obtained IVb (Ar = Ph, Ar′ = *p*-Me·C_6H_4, R = H) *hydrochloride*, (16%), m.p. 167–168° from ethanol ether (Found: C, 72·2; H, 8·05. $C_{20}H_{25}NO$·HCl requires- C, 72·4; H, 7·9%) and IVb (Ar = Ar′ = *p*-Me·C_6H_4, R = H) *free base*, (60%), m.p. 131–132° from ethanol (Found: C, 81·6; H, 8·6. $C_{21}H_{27}NO$ requires: C, 81·5; H, 8·8%).

The 3-amino-1,1-diarylpropenes (V) were prepared by acid-catalysed dehydration of the appropriate tertiary alcohols. In the case of derivatives containing the 2-pyridyl group, the dehydrating medium used was 85% sulphuric acid as previously reported (Adamson & Billinghurst, 1950) with 2 h reaction times at 100–110° being used except in the case of IVb (Ar = *p*-Me·C_6H_4, Ar′ = 2-pyridyl, R = H) (see main text). The liberated free base mixtures were acidified with ethanolic oxalic acid and fractional crystallization produced either pure salts or isomer mixtures (pmr evidence). The remaining carbinols were dehydrated using an acetic acid and concentrated hydrochloric acid mixture according to the method of Casy, Myers & Pocha (1966). Thus were obtained the following compounds and isomeric mixtures (all recrystallized from ethanol–ether): trans-VIIa *hydrogen oxalate*, m.p. 176°, reported m.p. 179° (Adamson & others, 1957) (Found: C, 65·6; H, 6·3; N, 8·4. $C_{18}H_{20}N_2O_4$ requires: C, 65·8; H, 6·1; N, 8·5%); cis-VIIa *hydrogen oxalate*, m.p. 178–179°, reported m.p. 180–181° (Adamson & others, 1957) (Found: C, 65·8; H, 6·0; N, 8·7%); trans VIIb *hydrogen oxalate*, m.p. 171°, reported m.p. 173–174° (Adamson & others, 1958); cis VIIb *hydrogen oxalate*, m.p. 147–148°, reported m.p. 149–150° (Adamson, & others, 1958); trans IX *hydrogen oxalate*, m.p. 160° (Found: C, 66·6; H, 6·5; N, 8·1. $C_{19}H_{22}N_2O_4$ requires: C, 66·65; H, 6·5; N, 8·2%).

The pure oxalate of *cis* IX could not be isolated but its pmr characteristics were noted from various mixed oxalate crops (see Table 1). Liberation of the bases from these samples and reacidification with ethanolic hydrogen bromide led to the isolation of a 50:50 mixture (pmr integral data) of the cis *and* trans *IX dihydrobromides*, m.p. 213–214° (d.) (Found: C, 49·1; H, 5·5. $C_{17}H_{20}N_2$·2HBr requires: C, 49·3; H, 5·4%) which was used in pharmacological testing (compound 6, see Table 2).

cis Xa *Hydrogen oxalate*, m.p. 184–185° (Found: C, 66·8; H, 6·6; N, 8·1. $C_{19}H_{22}N_2O_4$ requires: C, 66·65; H, 6·5; N, 8·2%). Pmr characteristics in ppm (δ), base in $CDCl_3$ (TMS), values in parenthesis refer to hydrogen oxalates in D_2O (DSS): CH_2N, 2·97 (3·87) (singlet), = C·Me, 1·85 (1·80) (singlet). Also isolated was a 70:30 mixture (pmr integral data) of the trans *and* cis Xa *hydrogen oxalates*, m.p. 158° (compound 8, Table 2), from which the following pmr characteristics were obtained for the *trans* isomer CH_2N, 2·47 (3·72) (singlet), = C·Me 1·90 (1·84) (singlet).

No pure isomers could be isolated from either of the elimination products derived from the IVb or IVc (Ar = Ph, Ar′ = 2-pyridyl, R = Me) carbinols. However, the following enriched mixtures were obtained: An 85:15 mixture of the cis *and* trans Xb *hydrogen oxalates*, m.p. 154–155° (compound 9, Table 2), (Found: C, 68·2; H, 6·4. $C_{21}H_{24}N_2O_4$ requires: C, 68·45; H, 6·6%). Pmr characteristics in ppm (δ), bases in $CDCl_3$ (TMS), values in parenthesis refer to hydrogen oxalates in D_2O (DSS): *cis* isomer, CH_2N, 3·18 (3·97) (singlet), = C·Me, 1·92 (1·89) (singlet); *trans* isomer, CH_2N, 2·94 (3·83) (singlet), = C·Me, 1·94 (1·89) (singlet).

A 50:50 mixture of the cis *and* trans Xc *oxalates*, m.p. 159–160° (compound 10, Table 2), (Found: C, 69·25; H, 6·8. $C_{22}H_{26}N_2O_4$ requires: C, 69·1; H, 6·85%). Pmr characteristics (specified above) of the mixture: CH_2N, 2·95 (3·70 and 3·87) (singlets), = C·Me, 1·87 (1·88) (singlets). Separation of the superimposed isomeric signals (see above) was achieved by running a pmr spectrum of the free base mixture in benzene (TMS) which revealed the following resonance absorptions: CH_2N, 3·03 and 3·13, = C·Me, 2·02 and 2·12 ppm (δ).

The following aminopropenes were prepared from the appropriate tertiary alcohols using an acetic acid and concentrated hydrochloric acid dehydration medium (see

earlier): Va (Ar = Ar′ = Ph, R = H) hydrochloride, m.p. 168°, reported m.p. 168–170° (Adamson, 1949); Va (Ar = Ar′ = Ph, R = Me) hydrochloride, m.p. 190°, reported m.p. 191° (Kazaryan & Nazarov, 1957); Vb (Ar = Ar′ = Ph, R = H) hydrochloride, m.p. 163°, reported m.p. 165–167° (Adamson, 1949); 1,1-diphenyl-3-methyl-3-dimethylaminoprop-1-ene (cmp. 13, Table 2) hydrochloride, m.p. 161°, reported 162–163° (Casy, Beckett & Armstrong, 1961); 50:50 mixture of *cis* and *trans* Vb (Ar = Ph, Ar′ = *p*-Me·C_6H_4, R = H) *hydrochlorides* (cmp. 16, Table 2), m.p. 143–144° from ethanol–ether (Found: C, 76·5; H, 7·8. $C_{20}H_{23}N$·HCl requires: C, 76·3; H, 7·7%), pmr characteristics in ppm (δ), bases in $CDCl_3$ (TMS), values in parenthesis refer to hydrochlorides in $CDCl_3$ (TMS): = C·H, 6·22 (6·45) (superimpose triplets, *J*7), CH_2N, 3·15 and 3·18 (hydrochloride masked by pyrrolidino bands) Ar·Me, 2·30 and 2·36 (2·32 and 2·38) (singlets); Vb (Ar = Ar′ = *p*-Me·C_6H_4, R = H) *hydrochloride*, m.p. 217° from ethanol–ether (Found: C, 76·8; H, 8·0. $C_{21}H_{25}N$·HCl requires: C, 76·9; H, 8·0%) pmr characteristics (specified above): = C·H, 6·23 (6·46) (triplet), *J*7), CH_2N, 3·27 (3·75) (doublet, *J*7), Ar·Me, 2·32 and 2·38 (2·33 and 2·40) (singlets).

The pyrrobutamine isomers (compounds 17, 18 and 19, Table 2) and pyrrobutamine itself have been previously described (Casy & Ison, 1970).

Pmr spectra were recorded on a Varian A-60D instrument and ultraviolet spectra on a Beckmann DK-2 recording spectrophotometer.

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