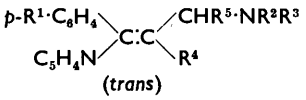
61. *Aminoalkyl Tertiary Carbinols and Derived Products. Part VI.*[1] *The Stereochemistry of Some* 1-*Phenyl*-1-2′-*pyridylprop*-1-*enes, and of Some* 3-(*Tertiary amino*)-1-*phenyl*-1-2′-*pyridylprop*-1-*enes carrying Additional Substituents.*

By D. W. Adamson, P. A. Barrett, J. W. Billinghurst, and T. S. G. Jones.

The spectra * of the *cis*- and *trans*-isomers of some 1-phenyl-1-2′-pyridylprop-1-enes resemble those of the corresponding 3-(tertiary amino)-compounds (VI) and (I).

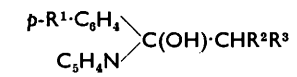
3-(Tertiary amino)-1-phenyl-1-2′-pyridylprop-1-enes carrying additional methyl or phenyl substituents have been prepared and separated into their geometrical isomers, and the latter have been assigned particular configurations. The spectra of the parent types (I) and (VI) are unaffected by the introduction of *meta*- or 3-substituents but are radically altered by *ortho*- or 2-substituents; the alterations are interpreted in terms of additional steric hindrance.

In Part V [1] we described the separation of a series of 3-(tertiary amino)-1-phenyl-1-2′-pyridylprop-1-enes into their *trans*- and *cis*-isomers (I) and (VI). The isomers were separated by displacement ion-exchange chromatography, the *trans*-isomer invariably being eluted first from the column. They differed significantly in their spectra,* the *cis*-isomers resembling styrene in giving a single peak in the neighbourhood of 250 mμ, and the *trans*-isomers resembling 2-vinylpyridine in giving two maxima, at *ca.* 240 and 280 mμ.

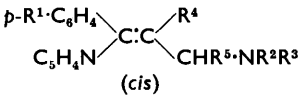


(*trans*)

(I): R^4, R^5 = H
(II): R^4 = Me, R^5 = H
(III): R^4 = Ph, R^5 = H
(IV): R^4 = H, R^5 = Me
(V): R^4 = H, R^5 = Ph



(XI): R^2 = Me, R^3 = H
(XII): R^2, R^3 = H
(XIII): R^2, R^3 = Me



(*cis*)

(VI): R^4, R^5 = H
(VII): R^4 = Me, R^5 = H
(VIII): R^4 = Ph, R^5 = H
(IX): R^4 = H, R^5 = Me
(X): R^4 = H, R^5 = Ph

(XIV): R^2 = Me, R^3 = H (*trans*)
(XV): R^2 = H, R^3 = Me (*cis*)
(XVI): R^2, R^3 = H
(XVII): R^2, R^3 = Me

From the spectra it was deduced that in the *trans*-isomer the pyridyl group is coplanar with the propene system to a degree sufficient to permit conjugation, and hence ultraviolet

* Throughout this paper " spectrum " is understood to mean ultraviolet absorption spectrum; *cis* and *trans* refer to the relation of the pyridyl and the (tertiary amino)methyl group.

[1] Adamson, Barrett, Billinghurst, and Jones, Part V, *J.*, 1957, 2315.

absorption of 2-vinylpyridine type, the phenyl group being forced out of the plane of the double bond by the steric effect of the aminomethyl group. A similar effect in the opposite sense determines the disposition of the *cis*-isomers.

We suggested that it was probably the methylene moiety of the aminomethyl group which effected this hindering and this has now been confirmed by the demonstration of similar spectral differences between isomers in which the tertiary amino-group is absent. The alcohols (XI; $R^1 = H$) and (XI; $R^1 = Cl$) gave, on dehydration, propenes which were separated by chromatography on alumina, or by ion-exchange chromatography, each into two isomers, one of each pair (XIV; $R^1 = H$ and Cl) showing (Fig. 1) the 2-vinylpyridine-like spectrum characteristic of the *trans*-isomers (I), and the other (XV; $R^1 = H$ and Cl) showing the styrene-like spectrum characteristic of the corresponding *cis*-isomers

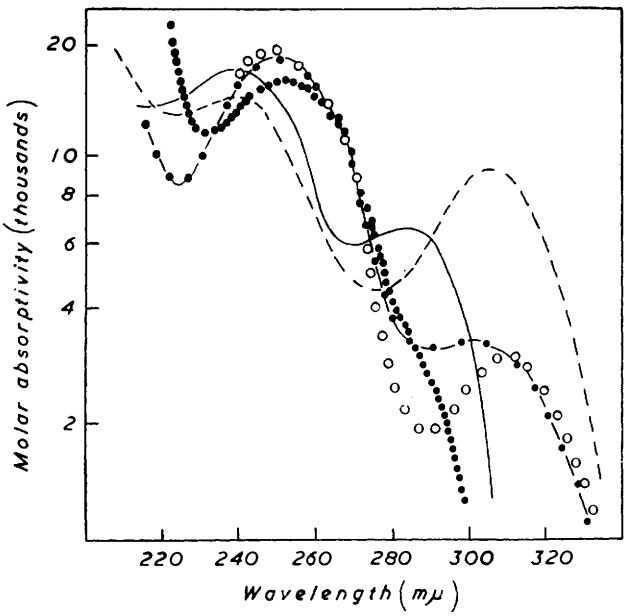
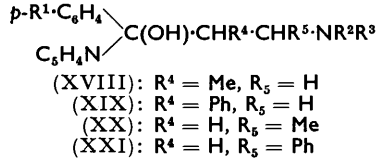
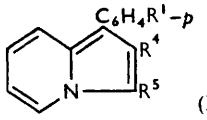


FIG. 1. trans-1-p-*Chlorophenyl*-1-2′-*pyridylprop*-1-*ene*:
—— *in* 0·1M-*ethanolic* NaOH;
– – – *in* 0·1M-*ethanolic* HCl.
cis-1-p-*Chlorophenyl*-1-2′-*pyridylprop*-1-*ene*:
. . . *in* 0·1M-*ethanolic* NaOH;
·—· *in* 0·1M-*ethanolic* HCl;
o o o *in* 5·5M-*aq.* HCl.

(VI). Both isomers show, in acid solution, the band at *ca.* 300 mμ characteristic of the *trans*-isomer (I) (ref. 1, Fig. 2, curve - - -) and of 2-vinylpyridine, but for (XV) it is much less intense than for (XIV). By analogy with the tertiary amino-isomers (I) and (VI), compounds (XIV) are designated *trans* and (XV) *cis*. In contrast with the tertiary amino-isomers, but in accordance with the pK_a values of their pyridyl nitrogen atoms,[2] the *cis*-propenes (XV) are eluted before the *trans*-propenes (XIV) in displacement ion-exchange chromatography. The corresponding phenylpyridylethylenes (XVI; $R^1 = H$ and Cl) prepared by dehydration of the alcohols (XII; $R^1 = H$ and Cl) were shown to be spectroscopically homogeneous by submission to ion-exchange or alumina chromatography. Their spectra (Fig. 2) were intermediate between those of the *trans*-isomers (I) and (XIV) and the *cis*-



(XVIII): R^4 = Me, R_5 = H
(XIX): R^4 = Ph, R_5 = H
(XX): R^4 = H, R_5 = Me
(XXI): R^4 = H, R_5 = Ph



(XXII)

isomers (VI) and (XV) in that they show (*a*) peaks at 230 and 235 mμ, (*b*) shoulders at 245 and 250 mμ, (*c*) a shelf at 280 mμ, and (*d*) a new peak at 300 mμ in acid solution.

[2] Everett and Jones, unpublished work.

We now describe geometrical isomers (II—V, VII—X) in which additional substituents are introduced into the parent types (I) and (VI) and assign them geometrical configurations, on the basis of their spectra where these retain the sharp distinction of those of the parent types. In those cases where substitution so alters the spectra as to make them inconclusive, two other criteria are employed, (i) the order of elution on ion-exchange chromatography, and (ii) the yield of the acetylpyrrocoline obtained on cyclisation. The *cis*-isomer (VI; $R^1 = Cl$, $NR^2R^3 = N < [CH_2]_4$) was shown [1] to cyclise on treatment with acetic anhydride to the acetylpyrrocoline (XXII; $R^1 = Cl$, $R^4 = H$, $R^5 = Ac$) under conditions which gave none from the *trans*-isomer (I), and this was offered as additional evidence of the correctness of the configurations assigned to these isomers. In Part VII (following paper) it is shown that cyclisation to the corresponding pyrrocoline (XXII) is general for all the *cis*-alkenylamines (VII—X) which have been examined. The use of different cyclisation conditions has greatly increased the yield of pyrrocoline over that previously reported, and under these conditions the corresponding *trans*-isomers

FIG. 2. FIG. 3.

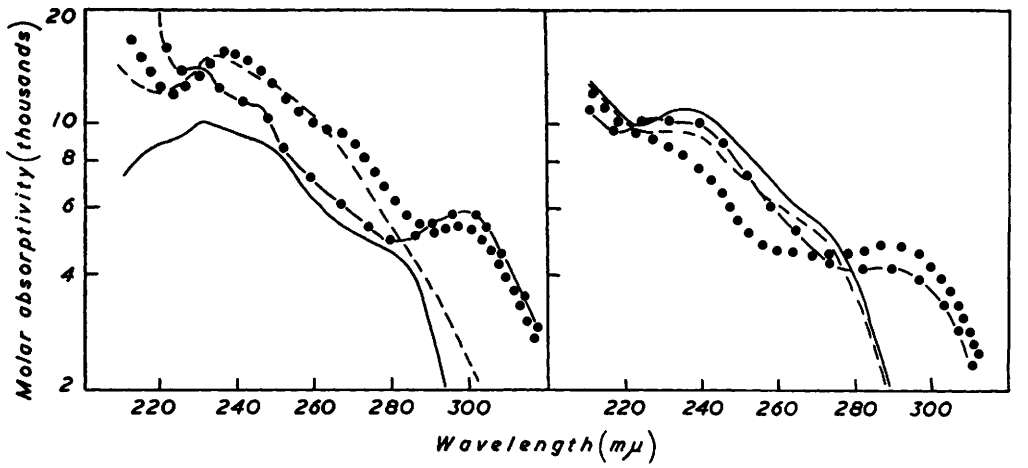


FIG. 2. 1-p-*Chlorophenyl*-1-2′-*pyridylethylene*: – – – *in* EtOH; . . . *in* 5M-*aq.* HCl. 1-*Phenyl*-1-2′-*pyridylethylene*: —— *in* EtOH; ·—· *in* 5M-*aq.* HCl.

FIG. 3. 2-*Methyl*-1-*phenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene*: (*a*) trans, —— *in* EtOH; ·—· *in* 5M-*aq.* HCl; (*b*) cis, – – – *in* EtOH, . . . *in* 5M-*aq.* HCl.

(II—V) also give pyrrocoline. Where the configuration of the isomers is defined by their spectra the yield of pyrrocoline obtained from the *trans*- is, however, always lower than that from the *cis*-isomer under the same conditions. When the spectra are not diagnostic, we therefore assign the *cis*-configuration to that isomer which gives the higher yield of pyrrocoline. The cyclisation experiments, the results of which are assumed here, are described in the following paper.

2-*Methyl Substituents*.—Four 2-methyl-substituted alcohols (Table 2) (XVIII*a*, *b*, *c*, and *d*) have been prepared and dehydrated to mixtures of the corresponding alkenylamines (II) and (VII) (Table 4), from which, in all cases, each pure isomer has been isolated. Separation was best effected by fractional crystallisation of the oxalates, the differential solubility being high in all cases. The isomers (II*a*), (VII*a*), (II*c*), and (VII*c*) were further purified by crystallisation as their solid bases. The depression of melting point shown by these pairs of isomers, together with the fact that in each case the higher-melting base was derived from the lower-melting, more soluble, oxalate, established their purity. Separation by base-exchange chromatography, which was used [1] for separation of the parent isomers of types (I) and (VI), is of less value here because, as discussed below, the

TABLE 1. *Aryl 2-(tertiary amino)ethyl ketone hydrochlorides* $R^1 \cdot CO \cdot CH_2 \cdot CH_2 \cdot NR^2R^3$,HCl.

					Found (%) [b]				Required (%)			
R^1	NR^2R^3	Yield (%)	M. p.[a]	Formula	C	H	N	Cl	C	H	N	Cl
2-C_6H_4Me	$N<C_4H_8$	40	134—135°	$C_{14}H_{20}ONCl$	66·5	7·9	5·3	14·3	66·3	7·9	5·5	14·0
3-C_6H_4Me	$N<C_4H_8$	55	131—132 *	,,	—	—	5·6	14·3	—	—	5·5	14·0
4-C_6H_4Me	NMe_2	68	168 *	$C_{12}H_{18}ONCl$	63·3	7·9	5·9	15·8	63·3	7·9	6·2	15·6
,,	$N<C_4H_8$	49	170	$C_{14}H_{20}ONCl$	66·2	7·6	5·6	14·0	66·3	7·9	5·5	14·0
,,	$N<C_5H_{10}$	61	177—178	$C_{15}H_{22}ONCl$	67·6	8·0	5·2	13·5	67·3	8·2	5·2	13·3
2 : 4-$C_6H_3Me_2$	$N<C_4H_8$	47	150—152	$C_{15}H_{22}ONCl$	66·9	8·3	5·1	13·3	67·3	8·2	5·2	13·3
2 : 5-$C_6H_3Me_2$	$N<C_4H_8$	45	140—141	$C_{15}H_{22}ONCl$	66·8	8·0	5·2	13·4	67·3	8·2	5·2	13·3
3 : 4-$C_6H_3Me_2$	$N<C_4H_8$	60	169—170	$C_{15}H_{22}ONCl$	67·3	8·2	5·0	13·6	67·3	8·2	5·2	13·3
4-C_6H_4Et	$N<C_4H_8$	53	118—120 *	$C_{15}H_{22}ONCl$	67·4	8·3	5·0	13·4	67·3	8·2	5·2	13·3
4-$C_6H_4Pr^i$	$N<C_4H_8$	57	167—168	$C_{16}H_{24}ONCl$	—	—	4·8	12·8	—	—	5·0	12·6
4-$C_6H_4Bu^t$	$N<C_4H_8$	60	157—158	$C_{17}H_{26}ONCl$	68·9	8·7	4·7	12·3	69·0	8·8	4·7	12·0

[a] After crystalln. from ethanol–ethyl acetate. With decomp. except those marked *. [b] Analytical samples were dried at 100° *in vacuo*.

TABLE 2. 1-*Aryl*-1-2′-*pyridylalkan*-1-*ols and* 3-(*tertiary amino*)-1-*aryl*-1-2′-*pyridylalkan*-1-*ols*.

					Found (%)				Required (%)			
Compound	R^1	R^2R^3	M. p.	Formula	C	H	N	Cl	C	H	N	Cl
XI*b*	Cl	H,Me	65° [a]	$C_{14}H_{14}ONCl$	67·9	5·8	6·0	13·4	67·9	5·7	5·7	14·3
XIII*a*	H	Me,Me	67—69 [a]	$C_{15}H_{17}ON$	78·8	7·5	—	—	79·3	7·5	—	—
XIII*b*	Cl	,,	115 [a]	$C_{15}H_{16}ONCl$	68·8	6·1	—	13·7	68·9	6·1	—	13·6
XVIII*a*	H	$<[CH_2]_5$	134	$C_{20}H_{26}ON_2$	77·4	8·1	9·4	—	77·4	8·4	9·0	—
XVIII*b*	Cl	,,	121	$C_{20}H_{25}ON_2Cl$	69·8	7·3	8·0	10·0	69·7	7·3	8·1	10·3
XVIII*c*	H	$<[CH_2]_4$	111	$C_{19}H_{24}ON_2$	77·3	8·1	9·6	—	77·0	8·1	9·5	—
XVIII*d*	Cl	,,	102	$C_{19}H_{23}ON_2Cl$	69·2	7·0	8·5	10·8	69·0	7·0	8·5	10·7
XIX*a*	H	$<[CH_2]_5$	146	$C_{25}H_{28}ON_2$	80·3	7·5	7·5	—	80·7	7·5	7·5	—
XIX*b*	Cl	$<[CH_2]_4$	158	$C_{24}H_{25}ON_2Cl$	73·4	6·4	7·0	8·7	73·4	6·4	7·1	9·0
XX*a*	H	$<[CH_2]_5$	86	$C_{20}H_{26}ON_2$	77·3	8·0	8·7	—	77·4	8·4	9·0	—
XX*b*	H	$<[CH_2]_4$	83 [a]	$C_{19}H_{24}ON_2$	77·0	8·0	9·3	—	77·0	8·1	9·5	—
XX*c*	Cl	,,	106 * [a]	$C_{19}H_{23}ON_2Cl$	68·5	6·8	8·4	10·5	69·0	7·0	8·5	10·7
,,	,,	,,	117 * [a]	,,	68·8	6·9	8·4	10·3	,,	,,	,,	,,
XXI*a*	H	$<[CH_2]_5$	124	$C_{25}H_{28}ON_2$	80·6	7·7	7·6	—	80·7	7·5	7·5	—
XXIX*a*	H	$<[CH_2]_4$	81 [a]	$C_{19}H_{24}ON_2$	77·0	7·8	9·3	—	77·0	8·1	9·5	—
XXIX*b*	Cl	,,	115	$C_{19}H_{23}ON_2Cl$	68·7	7·1	8·2	10·7	69·0	7·0	8·5	10·7

[a] Solvent light petroleum (b. p. 40—60°). Others from light petroleum (b. p. 60—80°). * Diastereoisomers (see text).

TABLE 3. 3-(*Tertiary amino*)-1-*aryl*-1-2′-*pyridylpropan*-1-*ols* (XXIII) *and* (XXIV).

Compound	R^1	R^4	R^5	NR^2R^3	Yield (%)	Derivative	M. p.[b]	Solvent for recrystn.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
XXIII*a*	H	H	Me	N<C_4H_8	53	Base	106—107°	EtOH	$C_{19}H_{24}ON_2$	76·7	8·0	9·3	77·0	8·1	9·5
						Oxalate	181—182	MeOH	$C_{21}H_{26}O_5N_2$	65·1	6·7	—	65·3	6·7	—
XXIV*a*	H	Me	H	N<C_4H_8	56	Base	54—55	*	$C_{19}H_{24}ON_2$	77·2	8·2	9·5	77·0	8·1	9·5
						Oxalate	155—156	EtOH	$C_{21}H_{26}O_5N_2$	65·4	6·5	—	65·3	6·7	—
XXIV*b*	Me	H	H	NMe_2	60	Base	86—87	EtOH	$C_{17}H_{22}ON_2$	75·5	8·0	10·2	75·6	8·1	10·4
						Oxalate	163—164	MeOH	$C_{19}H_{24}O_5N_2$	63·3	6·5	—	63·3	6·7	—
XXIV*c*	Me	H	H	N<C_4H_8	80	Base	119—120	EtOH	$C_{19}H_{24}ON_2$	77·0	7·8	9·4	77·0	8·1	9·5
						Oxalate	148—119	EtOH–EtOAc	$C_{21}H_{26}O_5N_2$	65·3	6·8	—	65·3	6·7	—
XXIV*d*	Me	H	H	N<C_5H_{10}	54	Base	85—86	EtOH	$C_{20}H_{26}ON_2$	77·7	8·3	9·0	77·4	8·4	9·0
						Oxalate	146—147	MeOH	$C_{22}H_{28}O_5N_2$	65·6	6·9	—	66·0	7·0	—
XXIII*b*	Me	H	Me	N<C_4H_8	69	Base	111—112	EtOH	$C_{20}H_{26}ON_2$	77·2	8·5	9·3	77·4	8·4	9·0
						Oxalate	175—176	MeOH	$C_{22}H_{28}O_5N_2$	65·9	6·8	—	66·0	7·0	—
XXIII*c*	H	Me	Me	N<C_4H_8	58	Base	107—108	EtOH	$C_{20}H_{26}ON_2$	77·3	8·4	8·7	77·4	8·4	9·0
						Oxalate[a]	196	MeOH	$C_{23}H_{29}O_7N_2$	62·2	6·6	—	62·0	6·5	—
XXIV*e*	Me	Me	H	N<C_4H_8	67	Base	104—105	EtOH	$C_{20}H_{26}ON_2$	76·9	8·4	8·9	77·4	8·4	9·0
						Oxalate	142—143	EtOH	$C_{22}H_{28}O_5N_2$	66·0	6·8	—	66·0	7·0	—
XXIV*f*	Et	H	H	N<C_4H_8	65	Base	112—113	EtOH	$C_{20}H_{26}ON_2$	77·4	8·4	9·0	77·4	8·4	9·0
						Oxalate	147—149	EtOH	$C_{22}H_{28}O_5N_2$	65·8	6·9	—	66·0	7·0	—
XXIV*g*	Pr^i	H	H	N<C_4H_8	74	Base	83—84	EtOH	$C_{21}H_{28}ON_2$	77·4	8·5	8·8	77·8	8·6	8·6
						Oxalate	146—147	EtOH–EtOAc	$C_{23}H_{30}O_5N_2$	66·8	7·1	—	66·7	7·2	—
XXIV*h*	Bu^t	H	H	N<C_4H_8	80	Base	120—121	EtOH	$C_{22}H_{30}ON_2$	78·1	8·8	7·9	78·1	8·9	8·3
						Oxalate	127—128	$CHCl_3$–EtOAc	$C_{24}H_{32}O_5N_2$	67·1	7·6	—	67·3	7·5	—

[a] Sesquioxalate. [b] The oxalates melted with decomp. * Light petroleum (b. p. <40°).

TABLE 4. 1-*Aryl*-1-2′-*pyridylalk*-1-*ene and* 3-(*tertiary amino*)-1-*aryl*-1-2′-*pyridylalk*-1-*ene isomers* (cf. Table 4*a*).

Compound	R^1	R^2R^3	Isomer	Derivative	M. p. or b. p./mm.	Ultraviolet absorption max.[c] Base[d] λ		$10^{-3}\varepsilon$		Salt[e] λ		$10^{-3}\varepsilon$		Cation[f] λ		$10^{-3}\varepsilon$	
XVI*a*	H	H,H	—	Base	120—122°/0·5	232	*275*	9·8	*4·9*	—	—	—	—	230	300	13·8	5·9
,,	,,	,,	—	Hydrochloride	186—187 [a]	—	—	—	—	—	—	—	—	—	—	—	—
XVI*b*	Cl	H,H,	—	Hydrochloride	192—193 [b]	232	—	16·2	—	—	—	—	—	237	297	15·6	5·4
XIV*a*	H	H,Me	*trans*	Hydrochloride	138 [a]	242	286	12·6	5·9	—	—	—	—	242	303	11·3	6·6 [g]
XV*a*	,,	,,	*cis*	Base	110/0·5	244	—	13·7	—	—	—	—	—	241	304	14·9	3·4 [g]
XIV*b*	Cl	,,	*trans*	Hydrochloride	197—199	240	286	17·9	6·4	—	—	—	—	240	307	14·6	9·3 [g]
XV*b*	,,	,,	*cis*	Base	150—152/0·5	253	—	16·0	—	—	—	—	—	248	300	18·3	3·4 [g]
XVII*a*	H	Me,Me	—	Base	126—128/0·5	241	*270*	11·2	*5·0*	—	—	—	—	234	305	10·7	4·8 [g]
XVII*b*	Cl	,,	—	Base	150—152/0·5	245	—	14·1	—	—	—	—	—	244	310	15·0	5·7
II*a*	H	$<[CH_2]_5$	*trans*	Base	85—86	230	*265*	10·1	*5·8*	225	*270*	10·7	*5·6*	—	—	—	—
,,	,,	,,	*trans*	Oxalate	175—176	—	—	—	—	—	—	—	—	—	—	—	—
VII*a*	,,	,,	*cis*	Base	100—102	240	*270*	11·2	*4·7*	225	*268*	20·0	*7·9*	—	—	—	—
,,	,,	,,	*cis*	Oxalate	125	—	—	—	—	—	—	—	—	—	—	—	—
II*b*	Cl	,,	*trans*	Oxalate	201—202	—	—	—	—	240	283	13·0	5·8	—	—	—	—
VII*b*	,,	,,	*cis*	Oxalate	75—77	—	—	—	—	232	—	13·4	—	—	—	—	—
II*c*	H	$<[CH_2]_4$	*trans*	Base	55	235	*265*	9·8	*5·8*	—	—	—	—	*230*	290	*9·0*	4·8
,,	,,	,,	*trans*	Oxalate	158—159	—	—	—	—	—	—	—	—	—	—	—	—
VII*c*	,,	,,	*cis*	Base	69—70	237	*270*	11·1	*6·0*	—	—	—	—	235	290	10·5	4·3
II*d*	Cl	,,	*trans*	Oxalate	216	238	—	10·2	—	231	—	14·0	—	232	*290*	14·1	*5·7*
VII*d*	,,	,,	*cis*	Oxalate	134—135	246	—	14·0	—	235	*280*	15·5	*7·2*	242	*290*	15·6	*7·6*
III*a* or VIII*a*	H	$<[CH_2]_5$	—	Base	91—92	270	—	10·0	—	—	—	—	—	244	—	13·0	—
III*b*	Cl	$<[CH_2]_4$	*trans*	Base	104—105	231	259	15·6	11·1	—	—	—	—	240	*295*	14·7	*9·1*
,,	,,	,,	*trans*	Oxalate	151—152	—	—	—	—	—	—	—	—	—	—	—	—
VIII*b*	,,	,,	*cis*	Base	110	240	*280*	14·8	*11·9*	—	—	—	—	243	*310*	17·0	*4·3*
,,	,,	,,	*cis*	Oxalate	147—148	—	—	—	—	—	—	—	—	—	—	—	—
IV*a*	H	$<[CH_2]_5$	*trans*	Base	—	240	*282*	13·0	*6·0*	—	—	—	—	—	—	—	—
IX*a*	,,	,,	*cis*	Base	—	248	—	11·2	—	—	—	—	—	—	—	—	—
IV*b*	,,	$<[CH_2]_4$	*trans*	Base	—	—	—	—	—	—	—	—	—	240	282	12·1	6·2
IX*b*	,,	,,	*cis*	Base	—	—	—	—	—	—	—	—	—	245	—	12·5	—
IV*c*	Cl	,,	*trans*	Base	—	—	—	—	—	233	262	16·0	7·4	—	—	—	—
,,	,,	,,	*trans*	Oxalate	159—160	—	—	—	—	—	—	—	—	—	—	—	—
IX*c*	,,	,,	*cis*	Base	200—204/0·3	—	—	—	—	245	—	16·0	—	—	—	—	—
X*a*	H	$<[CH_2]_5$	*cis*	Base	77—79	253	—	17·9	—	—	—	—	—	255	*291*	14·0	*3·84*
XXX*a*	,,	$<[CH_2]_4$	*trans*	Oxalate	158—160	250	—	13·5	—	—	—	—	—	260	—	14·0	—
XXXI*a*	,,	,,	*cis*	Oxalate	152	242	255	11·2	11·2	—	—	—	—	250	—	10·0	—
XXX*b*	Cl	,,	*trans*	Oxalate	140—141	260	—	15·5	—	—	—	—	—	217	265	14·0	18·0
XXXI*b*	,,	,,	*cis*	Oxalate	175—176	250	—	11·9	—	—	—	—	—	217	265	14·0	12·0

[a] From chloroform–ether. [b] From chloroform–ethyl acetate. [c] Values italicised are for inflexions and are approximate. [d] Base dissolved in EtOH, or salt made alkaline in EtOH. [e] Salt dissolved in EtOH. [f] Salt or base dissolved in 5N-HCl, except [g] where solvent was 0·1N-HCl in EtOH.

ultraviolet spectra of these isomers are so nearly identical as to be useless for controlling the progress of the separation. The method was used for examples (*a*) and (*c*) in which both isomeric bases were solid, and determination of mixed m. p.s of the fractions gave a satisfactory, if tedious, control of the separation. The isomer giving the sparingly soluble oxalate was eluted first on ion-exchange chromatography and that giving the more soluble oxalate gave a substantially higher yield of pyrrocoline. The *trans*-configuration (II) is therefore assigned to the former and the *cis*-configuration (VII) to the latter isomer in each case. The isomers (II) and (VII) differ from the parent types (I) and (VI) in that their spectra are almost identical (Fig. 3) and take the form of a rather broad curve with a single peak at *ca.* 240 mμ, showing a distinct shoulder at 270 mμ. In acid solution, both isomers give a peak at 290 mμ. The form of the curves, being a hybrid of those of styrene and 2-vinylpyridine, and their similarity, are readily interpreted in steric terms. The presence of the 2-methyl group in (II) and (VII) in addition to the aminomethyl group introduces a steric symmetry lacking in (I) and (VI). It is to be expected that in each isomer both aryl groups, being equally hindered, have an equal opportunity to attain the necessary degree of co-planarity and will contribute equally to the spectrum.

TABLE 4*a*.

		Found (%)				Required (%)			
Compound	Constitution	C	H	N	Cl	C	H	N	Cl
XVI*a*	$C_{13}H_{11}N$	85·8	5·6	7·7	—	86·2	6·1	7·7	—
,,	$C_{13}H_{11}N,HCl$	71·4	5·6	6·1	—	71·7	5·5	6·4	—
XVI*b*	$C_{13}H_{10}NCl,HCl$	62·3	4·4	5·6	27·8	61·9	4·4	5·6	28·2
XIV*a*	$C_{14}H_{13}N,HCl$	72·0	5·8	6·0	15·6	72·6	6·0	6·0	15·3
XV*a*	$C_{14}H_{13}N$	86·0	6·6	7·0	—	86·2	6·7	7·2	—
XIV*b*	$C_{14}H_{12}NCl,HCl$	63·7	4·9	—	26·9	63·2	4·9	—	26·7
XV*b*	$C_{14}H_{12}NCl$	72·6	5·4	5·6	15·6	73·2	5·2	6·1	15·5
XVII*a*	$C_{15}H_{15}N$	85·9	7·2	6·6	—	86·1	7·2	6·7	—
XVII*b*	$C_{15}H_{14}NCl$	73·0	5·8	5·7	14·5	73·9	5·7	5·7	14·6
II*a*	$C_{20}H_{24}N_2$	81·8	8·0	9·9	—	82·2	8·2	9·6	—
,,	$C_{20}H_{24}N_2,C_2H_2O_4$	69·0	7·0	7·2	—	69·1	6·8	7·3	—
VII*a*	$C_{20}H_{24}N_2$	82·1	8·1	9·4	—	82·2	8·2	9·6	—
,,	$C_{20}H_{24}N_2,C_2H_2O_4$	68·8	7·1	7·3	—	69·1	6·8	7·3	—
II*b*	$C_{20}H_{23}N_2Cl,C_2H_2O_4$	63·2	6·0	6·5	8·5	63·4	6·0	6·7	8·5
VII*b*	$C_{20}H_{23}N_2Cl,C_2H_2O_4$	62·9	6·2	—	8·5	63·4	6·0	6·7	8·5
II*c*	$C_{19}H_{22}N_2$	81·5	7·4	10·2	—	82·0	7·9	10·1	—
,,	$C_{19}H_{22}N_2,C_2H_2O_4$	68·3	6·4	7·5	—	68·5	6·5	7·6	—
VII*c*	$C_{19}N_{22}N_2$	81·4	7·7	11·1	—	82·0	7·9	10·1	—
II*d*	$C_{19}H_{21}N_2Cl,C_2H_2O_4$	62·6	5·7	7·0	8·9	62·6	5·7	7·0	8·8
VII*d*	$C_{19}H_{21}N_2Cl,C_2H_2O_4$	62·2	5·7	6·9	9·0	62·6	5·7	7·0	8·8
III*a* or VIII*a*	$C_{25}H_{26}N_2$	84·7	7·3	7·7	—	84·7	7·3	7·9	—
III*b*	$C_{24}H_{23}N_2Cl$	76·5	5·9	7·6	9·6	76·9	6·1	7·5	9·5
,,	$C_{24}H_{23}N_2Cl,C_2H_2O_4$	67·5	5·5	6·1	7·2	67·2	5·4	6·0	7·6
VIII*b*	$C_{24}H_{23}N_2Cl$	76·9	6·2	7·5	9·5	76·9	6·1	7·5	9·5
,,	$C_{24}H_{23}N_2Cl,C_2H_2O_4$	67·3	5·4	6·2	7·6	67·2	5·4	6·0	7·6
IV*a*	$C_{20}H_{24}N_2$	81·9	8·1	9·4	—	82·2	8·2	9·6	—
IX*a*	$C_{20}H_{24}N_2$	82·0	7·6	9·3	—	82·2	8·2	9·6	—
IV*b*	$C_{19}H_{22}N_2$	81·7	7·9	10·0	—	82·0	7·9	10·1	—
IX*b*	$C_{19}H_{22}N_2$	81·9	7·7	10·2	—	82·0	7·9	10·1	—
IV*c*	$C_{19}H_{21}N_2Cl$	73·1	6·5	8·7	11·5	73·0	6·7	9·0	11·4
,,	$C_{19}H_{21}N_2Cl,1\frac{1}{2}C_2H_2O_4$	58·7	5·4	6·2	7·9	59·0	5·4	6·3	7·9
IX*c*	$C_{19}H_{21}N_2Cl$	72·5	6·7	8·8	11·5	73·0	6·7	9·0	11·4
X*a*	$C_{25}H_{26}N_2$	84·8	7·4	7·9	—	84·7	7·3	7·9	—
XXX*a*	$C_{19}H_{22}N_2,C_2H_2O_4$	68·0	6·4	7·7	—	68·5	6·5	7·6	—
XXXI*a*	$C_{19}H_{22}N_2,C_2H_2O_4$	68·2	6·5	7·6	—	68·5	6·5	7·6	—
XXX*b*	$C_{19}H_{21}N_2Cl,C_2H_2O_4$	62·8	6·1	6·4	8·5	62·6	5·7	7·0	8·8
XXXI*b*	$C_{19}H_{21}N_2Cl,C_2H_2O_4$	62·5	6·0	6·6	8·6	62·6	5·7	7·0	8·8

The spectra of the non-aminated *iso*butenes (XVII; R^1 = H and Cl) are similar to those of the isomers (II) and (VII), and consist of single bands with peaks at 242 and 246 mμ respectively and only slight indication of submerged peaks at 270 mμ. In acid solution they show well-defined peaks at 320 mμ.

2-Phenyl Substituents.—Two 2-phenyl-substituted alcohols (Table 2) (XIX*a* and *b*)

TABLE 5. 3-(*Tertiary amino*)-1-*aryl*-1-2′-*pyridylprop*-1-*enes* (XXV), (XXVII), (XXVI), and (XXVIII) (cf. Table 5*a*).

Compound	R^1	R^4	R^5	NR^2R^3	Deriv.	M. p.[a]	Solvent for recrystn.	Ultraviolet absorption max.[c] Salt in EtOH λ		Salt in EtOH $10^{-3}\varepsilon$		Cation in H_2O[d] λ				Base in EtOH[e] λ			
														$10^{-3}\varepsilon$				$10^{-3}\varepsilon$	
XXV*a*	H	H	Me	N<C_4H_8	Oxalate	160—161°	EtOH	237	281	13·7	7·3	237	294	9·0	11·0	240	288	13·2	6·0
XXVII*a*	,,	,,	,,	,,	Oxalate	169—170	EtOH	231	277	11·8	5·9	270	290	6·8	6·1	233	277	13·0	5·2
XXVI*a*	H	Me	H	N<C_4H_8	Oxalate	147—148	EtOH	241	282	14·0	8·6	—	—	—	—	238	284	14·4	7·3
XXVIII*a*	,,	,,	,,	,,	Oxalate	182—183	MeOH	250	*282*	12·0	*6·0*	—	—	—	—	250	—	13·7	—
XXVI*b*	Me	H	H	NMe_2	Oxalate	173—174	EtOH	235	280	13·3	7·0	—	—	—	—	—	—	—	—
XXVIII*b*	,,	,,	,,	,,	Oxalate	181—182	MeOH	234	260	13·4	12·3	—	—	—	—	—	—	—	—
XXVI*c*	Me	H	H	N<C_4H_8	Base	59—61 *	Pet †	—	—	—	—	—	—	—	—	236	285	15·3	6·8
,,	,,	,,	,,	,,	Oxalate	173—174	MeOH	233	283	16·2	8·2	—	—	—	—	238	285	12·5	5·8
,,	,,	,,	,,	,,	HCl[b]	116—118 *	H_2O	235	283	15·0	7·4	—	—	—	—	—	—	—	—
,,	,,	,,	,,	,,	HBr[b]	119—121 *	H_2O	230	275	15·5	8·1	—	—	—	—	—	—	—	—
XXVIII*c*	,,	,,	,,	,,	Oxalate	149—150 *	EtOH	233	260	13·6	13·8	—	—	—	—	252	—	14·0	—
XXVI*d*	Me	H	H	N<C_5H_{10}	Oxalate	164—165	MeOH	233	283	13·0	6·0	292	—	9·0	—	237	285	12·0	5·2
XXVIII*d*	,,	,,	,,	,,	Oxalate	167—169	EtOH	262	—	13·5	—	255	—	16·0	—	250	—	13·0	—
XXV*b*	Me	H	Me	N<C_4H_8	Oxalate	168—169	EtOH	237	281	15·0	8·1	290	—	9·0	—	*235*	*280*	*11·5*	*5·4*
XXVII*b*	,,	,,	,,	,,	Oxalate	175—176	EtOH	230	273, 281	16·0	8·4, 8·1	—	—	—	—	238	285	12·1	6·4
XXV*c*	H	Me	Me	N<C_4H_8	Oxalate	156—157	EtOH	237	282	13·8	8·0	235	295	8·2	11·0	242	284	13·0	8·0
XXVII*c*	,,	,,	,,	,,	Oxalate	176—177	EtOH	235	*280*	12·5	*6·9*	270	*290*	6·6	*5·8*	232	271	12·0	6·4
XXVI*e*	Me	Me	H	N<C_4H_8	Oxalate	160—161	EtOH	235	281	16·1	8·3	—	—	—	—	238	282	14·5	7·0
XXVIII*e*	,,	,,	,,	,,	Base	57—58 *	Pet †	—	—	—	—	—	—	—	—	252	—	14·8	—
,,	,,	,,	,,	,,	Oxalate	174—175	EtOH	*235*	261	*14·5*	13·5	—	—	—	—	254	—	14·4	—
XXVI*f*	Et	H	H	N<C_4H_8	Oxalate	153—154	EtOH–EtOAc	235	282	12·0	5·5	—	—	—	—	—	—	—	—
XXVI*g*	*i*-Pr	H	H	N<C_4H_8	Oxalate	166—167	EtOH–EtOAc	235	282	12·1	5·7	—	—	—	—	235	285	14·0	6·4
XXVIII*g*	,,	,,	,,	,,	Oxalate	168	EtOH–EtOAc	235	260	14·0	14·0	—	—	—	—	260	—	15·0	—
XXVI*h*	*t*-Bu	H	H	N<C_4H_8	Oxalate	164	EtOH–EtOAc	230	280	13·6	6·6	—	—	—	—	237	283	12·5	5·2
XXVIII*h*	,,	,,	,,	,,	Oxalate	174	EtOH–EtOAc	235	262	15·0	15·0	—	—	—	—	240	—	11·3	—

[a] With decomp. except those marked *. [b] Monohydrate: the analytical sample was dried at 100° *in vacuo*. [c] Values italicised are for inflexions and are approximate. [d] Base or salt dissolved in aq. HCl (0·1N or stronger). [e] Base dissolved in EtOH or salt dissolved in EtOH containing 0·1N-NaOH. † Light petroleum (b. p. 40—60°).

have been prepared and dehydrated to mixtures of the alkenylamines (III) and (VIII) (Table 4). The alcohol (XIX*b*) gave on dehydration a mixture of alkenylamines from which two pure solid isomers (III*b*) and (VIII*b*) were isolated by ion-exchange chromatography, controlled by the m. p.s and mixed m. p.s of the fractions. The isomers were also separated, less satisfactorily, by fractional crystallisation of the oxalates. The yield of pyrrocoline from the isomer which was eluted first was lower than from that eluted second. The former is therefore assigned the *trans*- and the latter the *cis*-configuration. The spectra of the diphenylpropenes (III*b*) and (VIII*b*) are similar and, except for some extension towards the red, resemble the *trans*-alkenylamine type: both show the characteristic absorption at 300—320 mμ in acid solution, the *trans*-isomer absorbing the more intensely.

The alcohol (XIX*a*) gave, on dehydration, a semi-solid mixture from which one solid isomer (III*a*) or (VIII*a*) has been isolated by crystallisation and by base-exchange chromatography. The later fractions of the column gave oil which presumably consisted substantially of the second isomer. However, as both the solid and the liquid fractions gave approximately equal yields of pyrrocoline, there are insufficient grounds for assigning configurations.

3-*Methyl Substituents.*—Three 3-methyl-substituted alcohols [Table 2; (XX*a*), (XX*b*), and (XX*c*)] have been prepared and dehydrated to mixtures, each of which was separated by base-exchange chromatography into the *trans*- and the *cis*-alkenylamines (IV) and (IX). As expected, their absorption spectra resembled those of the unsubstituted types (I) and (VI) and served to control the separations.

TABLE 5*a*.

		Found (%)			Required (%)		
Compound	Formula	C	H	N	C	H	N
XXV*a*	$C_{21}H_{24}O_4N_2$	68·3	6·3	7·6	68·5	6·5	7·6
XXVII*a*	$C_{21}H_{24}O_4N_2$	68·1	6·2	7·4	68·5	6·5	7·6
XXVI*a*	$C_{21}H_{24}O_4N_2$	68·8	6·7	7·8	68·5	6·5	7·6
XXVIII*a*	$C_{21}H_{24}O_4N_2$	68·5	6·4	7·6	68·5	6·5	7·6
XXVI*b*	$C_{19}H_{22}O_4N_2$	66·9	6·2	8·2	66·7	6·4	8·2
XXVIII*b*	$C_{19}H_{22}O_4N_2$	66·8	6·4	8·2	66·7	6·4	8·2
XXVI*c*	$C_{19}H_{22}N_2$	—	—	9·9	—	—	10·1
,,	$C_{21}H_{24}O_4N_2$	68·5	6·2	7·6	68·5	6·5	7·6
,,	$C_{19}H_{23}N_2Cl$	—	—	11·3 [a]	—	—	11·3 [a]
,,	$C_{19}H_{23}N_2Br$	—	—	22·0 [a]	—	—	22·3 [a]
XXVIII*c*	$C_{21}H_{24}O_4N_2$	68·2	6·3	7·4	68·5	6·5	7·6
XXVI*d*	$C_{22}H_{26}O_4N_2$	69·2	6·8	7·2	69·1	6·8	7·3
XXVIII*d*	$C_{22}H_{26}O_4N_2$	69·2	6·8	7·5	69·1	6·8	7·3
XXV*b*	$C_{22}H_{26}O_4N_2$	69·1	6·8	7·3	69·1	6·8	7·3
XXVII*b*	$C_{22}H_{26}O_4N_2$	68·8	7·0	7·1	69·1	6·8	7·3
XXV*c*	$C_{22}H_{26}O_4N_2$	69·2	6·8	7·3	69·1	6·8	7·3
XXVII*c*	$C_{22}H_{26}O_4N_2$	68·6	6·7	7·1	69·1	6·8	7·3
XXVI*e*	$C_{22}H_{26}O_4N_2$	69·0	7·0	7·3	69·1	6·8	7·3
XXVIII*e*	$C_{20}H_{24}N_2$	82·2	8·2	9·6	82·2	8·2	9·6
,,	$C_{22}H_{26}O_4N_2$	68·9	6·9	7·3	69·1	6·8	7·3
XXVI*f*	$C_{22}H_{26}O_4N_2$	68·8	6·8	7·2	69·1	6·8	7·3
XXVI*g*	$C_{23}H_{28}O_4N_2$	69·6	6·9	6·9	69·7	7·1	7·1
XXVIII*g*	$C_{23}H_{28}O_4N_2$	69·8	6·9	6·8	69·7	7·1	7·1
XXVI*h*	$C_{24}H_{30}O_4N_2$	69·7	7·3	6·6	70·2	7·3	6·8
XXVIII*h*	$C_{24}H_{30}O_4N_2$	70·2	6·9	6·7	70·2	7·3	6·8

[a] Halogen analysis.

3-*Phenyl Substituents.*—The 3-phenyl alcohol (XXI*a*) (Table 2) showed unusual lability to sulphuric acid, perhaps associated with the fact that the compound is a substituted benzylamine, and did not survive dehydration under any but the mildest conditions. It was perhaps a consequence of this that the derived alkenylamine (X*a*) (Table 4) was found on ion-exchange chromatography to contain only *cis*-isomer. The *trans*-isomer has not been prepared. The configuration of the *cis*-isomer is defined by its styrene-like

spectrum and confirmed by the high yield of 1 : 3-diphenylpyrrocoline obtained on ring closure.

Methyl Substituents in the Phenyl Group.—Three alcohols [Table 3; (XXIII*a*), (XXIII*b*), and (XXIII*c*)] containing an *o*-methyl substituent in the phenyl group have been prepared and on dehydration gave mixtures which were separated by base-exchange chromatography into the isomeric alkenylamines (XXV) and (XXVII) (Table 5). In each case the spectrum (Fig. 4) of the *trans*-isomer (XXV) is of normal vinylpyridine type. The spectrum of the *cis*-isomer (XXVII) shows little trace of the styryl type of absorption, but only a broad shelf (ε ~5000) in the 260—280 mμ region. In this isomer, in addition to the normal hindering of the pyridyl group by the aminomethylene group, the hindering effect of the *o*-methyl group is so considerable that the phenyl group too is prevented from conjugating efficiently with the double bond. The spectrum is therefore a hybrid one though closer to the vinylpyridine than to the styrene type. In acid solution, a typical peak at 300 mμ is given by the *trans*-isomer and a lower, broader shelf by the *cis*-form.

The configurations of the isomers to which the spectra are referred are confirmed by the

FIG. 4. FIG. 5.

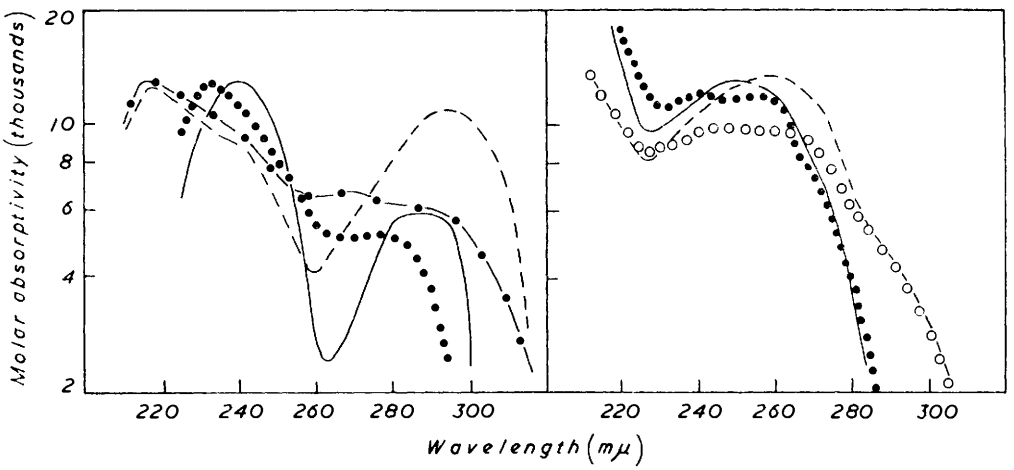


FIG. 4. 1-2′-*Pyridyl*-3-*pyrrolidino*-1-*o*-*tolylprop*-1-*ene oxalate*: (*a*) trans, —— *in* 0·1M-*ethanolic* NaOH, – – – *in* 5M-*aq.* HCl; (*b*) cis, . . . *in* 0·1M-*ethanolic* NaOH, ·—· *in* 5M-aq. HCl.

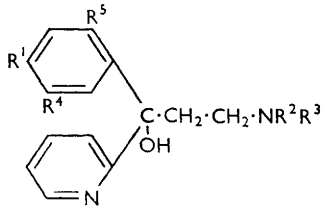
FIG. 5. 1-(3-*Methyl*-2-*pyridyl*)-1-*phenyl*-3-*pyrrolidinoprop*-1-*ene oxalate*: (*a*) trans, . . . *in* 0·1M-*ethanolic* NaOH, o o o *in* 5M-*aq.* HCl; (*b*) cis, —— *in* 0·1M-*ethanolic* NaOH, – – – *in* 5M-*aq.* HCl.

order of elution and by cyclisation experiments which were unusually conclusive in that the *cis*-isomer gave a high yield of pyrrocoline and the *trans*-isomer gave none.

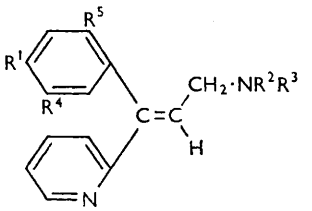
Several alcohols [Table 3; (XXIV)] carrying *m*- or *p*-alkyl substituents in the phenyl group have been prepared and dehydrated to the corresponding alkenylamines, and the isomers (Table 5) separated by ion-exchange chromatography. As expected, the isomers (XXVI) and (XXVIII) showed ultraviolet absorption spectra resembling those of the parent types (I) and (VI).

Picolylalkenylamines.—Two (3-picolyl)carbinols [Table 2; (XXIX*a*) and (XXIX*b*) have been prepared and dehydrated to mixtures, each of which was separated by fractional crystallisation of the oxalates into the isomeric alkenylamines (XXX) and (XXXI) (Table 4). The pattern of their spectra (Fig. 5) is the reverse of that discussed above for the *o*-tolyl isomers (XXV) and (XXVII). The spectrum of the *cis*-isomer is of normal styrene type, and that of the *trans*-isomer is of modified styrene type, taking the form of a broad, flattened peak extending from 240 to 260 mμ, but showing traces of the vinylpyridine absorption—a peak at 240 mμ and a shoulder at 280 mμ of relatively high (ε ~8000) intensity. In acid solution, both isomers give spectra of the *cis*-type—a low

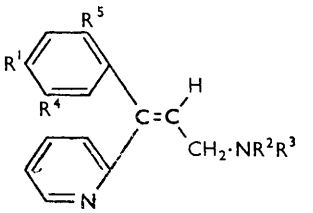
shoulder in the 300 mμ region (ref. 1, Fig. 2, curve – · – · –). The spectra of the *trans*-isomers are interpreted as showing that the hindering effect of the 3-methyl substituent is so considerable that, despite the presence of the *cis*-aminomethyl group, it is easier for



(XXIII) : R^5 = Me
(XXIV) : R^5 = H



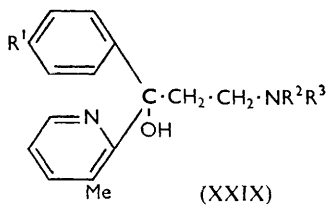
(XXV) : R^5 = Me
(XXVI) : R^5 = H



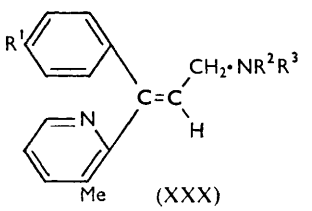
(XXVII) : R^5 = Me
(XXVIII) : R^5 = H

the phenyl than for the picolyl group to assume coplanarity with the propene system, and the former makes the greater contribution to the spectrum. The configurations of the isomers to which these spectra are referred are again confirmed by the order of elution and by cyclisation.

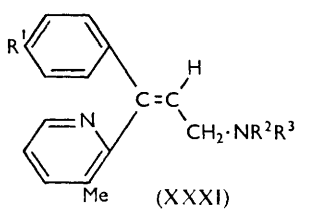
All the substituted alkenylamines described were prepared primarily for examination as antihistamines; many were found by Mr. A. F. Green of these Laboratories to show high activity, one of the most active [3] being (XXVIc) (" Actidil ").



(XXIX)



(XXX)



(XXXI)

Experimental

Ketones.—The following ketones, and those listed in Table 1, were prepared by the Mannich reaction as described in Part III: [4] p-*chloro*-α-*methyl*-β-*piperidinopropiophenone*, m. p. 36—37° [from light petroleum (b. p. 40—60°)] (Found: C, 67·6; H, 7·5; N, 5·3; Cl, 13·2. $C_{15}H_{20}ONCl$ requires C, 67·8; H, 7·5; N, 5·3; Cl, 13·4%) [*hydrochloride*, m. p. 175—176° (from ethanol) (Found: C, 59·4; H, 7·0; N, 4·4; Cl, 22·7. $C_{15}H_{20}ONCl,HCl$ requires C, 59·6; H, 6·9; N, 4·6; Cl, 23·5%)]; α-*methyl*-β-*pyrrolidinopropiophenone hydrochloride*, m. p. 149—150° [from acetone–ethanol (3 : 1)] (Found: C, 65·6; H, 7·8; N, 5·4; Cl, 13·8. $C_{14}H_{19}ON,HCl$ requires C, 66·3; H, 7·9; N, 5·5; Cl, 14·0%); p-*chloro*-α-*methyl*-β-*pyrrolidinopropiophenone*, b. p. 152—156°/0·1 mm. (Found: C, 66·1; H, 7·0; N, 5·5; Cl, 13·9. $C_{14}H_{18}ONCl$ requires C, 66·7; H, 7·1; N, 5·6; Cl, 14·1%).

4-*Chloro*-α-*phenyl*-β-*pyrrolidinopropiophenone* was prepared from benzyl *p*-chlorophenyl ketone [5] by the method used by Mannich and Lammering [6] for α-phenyl-β-piperidinopropiophenone, and after crystallisation from light petroleum (b. p. 60—80°) had m. p. 97° (Found: C, 72·7; H, 6·0; N, 4·9; Cl, 11·4. $C_{19}H_{20}ONCl$ requires C, 72·7; H, 6·4; N, 4·5; Cl, 11·3%).

β-*Piperidinobutyrophenone* was prepared from crotonophenone [7] by the method used by Stobbe and Rosenburg [8] for β-phenyl-β-piperidinopropiophenone, and after crystallisation from light petroleum (b. p. 40—60°) had m. p. 38° (Found: N, 6·0. $C_{15}H_{21}ON$ requires N, 6·1%).

β-*Pyrrolidinobutyrophenone*, similarly prepared, had b. p. 126—130°/0·4 mm. (Found: N, 6·8. $C_{14}H_{19}ON$ requires N, 6·5%).

[3] Green, *Brit. J. Pharmacol.*, 1953, **8**, 171.
[4] Adamson and Billinghurst, *J.*, 1950, 1039.
[5] Jenkins, *J. Amer. Chem. Soc.*, 1934, **56**, 682.
[6] Mannich and Lammering, *Ber.*, 1922, **55**, 3510.
[7] Dufraisse and Demontoignier, *Bull. Soc. chim. France*, 1927, **41**, 843.
[8] Stobbe and Rosenburg, *J. prakt. Chem.*, 1912, **86**, 230.

p-*Chlorocrotonophenone*, prepared by the method used by Dufraisse and Demontoignier [7] for crotonophenone, had b. p. 160—164°/16 mm. (Found: C, 66·3; H, 4·6; Cl, 19·9. $C_{10}H_9OCl$ requires C, 66·6; H, 5·0; Cl, 19·7%). β-Piperidino-*p*-chlorobutyrophenone was prepared from it by Stobbe and Rosenburg's method,[8] but on attempted distillation it decomposed; it was therefore used for reaction with pyridyl-lithium (see below) without further purification.

2-*Pyridyl-alcohols*.—1-Phenyl-1-2′-pyridylethan-1-ol (XII*a*),[9] 1-*p*-chlorophenyl-1-2′-pyridylethan-1-ol (XII*b*),[3] 1-phenyl-1-2′-pyridylpropan-1-ol (XI*a*),[9] and the alcohols listed in Tables 2 and 3 were prepared from the corresponding ketones by reaction with 2-pyridyl-lithium as described in Part III.[4] The 2-3′-picolyl-alcohols (XXIX*a* and *b*) were similarly prepared, from 2-bromo-3-picoline.

Dehydration of the Alcohols to the Mixed Isomeric Alkenylamines.—The alcohols listed in Tables 2 and 3 were, with exceptions noted below, dehydrated to the mixed isomeric alkenylamines by heating them in sulphuric acid (85% v/v) (10 parts) at 100° for ¼ hr. and working up as described previously.[4] The oxalates of the mixed alkenylamines, prepared in hot ethanol by addition of 1·1 mol. of anhydrous oxalic acid, usually crystallised on cooling but occasionally separated only on the addition of ether or ethyl acetate.

Separation of the Diasteroisomers of 1-p-*Chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinobutan*-1-*ol* (XX*c*).—The crude alcohol (59 g.), which did not solidify, was converted into its oxalate with oxalic acid (22·5 g.) in a small volume of ethanol. After 12 hr. the solid oxalate (25 g.) was filtered off and washed with ethanol and ether, then was converted into the base, which solidified and after crystallisation from light petroleum (b. p. 60—80°) gave one *isomer* (9·0 g.) as prisms, m. p. 115—117°. The mother-liquors from the oxalate preparations were evaporated to dryness. The oxalate was converted into the base, which was distilled (25 g.; b. p. 170—200°/0·2 mm.). This solidified and after recrystallisation from a small volume of light petroleum (b. p. 40—60°) gave the second *isomer* (14 g.) as prisms, m. p. 105—106°, depressed to m. p. 80—85° on admixture with the first. Each isomer gave the same alkenylamine isomers on dehydration.

Separation of the Mixed Isomeric Alkenylamines (*Table* 4): cis- *and* trans-2-*Methyl*-1-*phenyl*-3-*piperidino*-1-2′-*pyridylprop*-1-*ene* (II*a*) *and* (VII*a*).—(i) Fractional crystallisation of the mixed isomeric oxalates from ethanol gave the sparingly soluble trans-*oxalate* as colourless needles, m. p. 175—176°. The corresponding *base* had m. p. 85—86°. The oxalate recovered from the mother-liquors was converted into the base, which solidified and after several crystallisations from light petroleum (b. p. 40—60°) gave pure cis-*base* as prisms, m. p. 100—102°, depressed on admixture with *trans*-base to 75—79°. The cis-*oxalate* formed prisms, m. p. 125°. (ii) Mixed isomeric bases (3 g.) were submitted to ion-exchange chromatography as described in Part V.[1] The eluate was collected in fourteen fractions, all of which deposited crystalline material. Samples of solid were removed from every third fraction and dried on porous tile. The m. p.s and mixed m. p.s showed fractions 1—7 to contain pure *trans*-isomer, m. p. 83—85°, and fractions 10—14 to contain pure *cis*-isomer, m. p. 98—101°.

cis- *and* trans-1-p-*Chlorophenyl*-2-*methyl*-3-*piperdino*-1-2′-*pyridylprop*-1-*ene* (II*b*) *and* (VII*b*).—The sparingly soluble trans-*oxalate* crystallised from ethanol as rods, m. p. 201—202°. The oxalate recovered from the mother-liquors was converted into the base and submitted to ion-exchange chromatography, 42 fractions being collected. Although the ultraviolet absorption spectra of the two isomers determined photoelectrically were almost identical, the Holiday cam-plate [10] of the *trans*-isomer showed well-defined fine structure, a feature present in fractions 1—10 and absent in fractions 12—42. The latter were therefore collected and converted into cis-*oxalate*, plates (from ethanol–ether), m. p. 75—77° depressed to 68—71° on admixture with *trans*-oxalate.

cis- *and* trans-2-*Methyl*-1-*phenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene* (II*c*) *and* (VII*c*).—The sparingly soluble trans-*oxalate* crystallised from ethanol as needles, m. p. 158—159°. The corresponding base had m. p. 55°. The oxalate recovered from the mother-liquors was converted into the base and submitted to base-exchange chromatography, twenty-two fractions being collected all of which deposited crystals. Fractions 1—6 contained *trans*-isomer, m. p. 52—54°. Fractions 12—22 had m. p.s in the range 65—70°, and were united and worked up to give pure cis-*base*, m. p. 69—70°, depressed on admixture with *trans*-isomer to 45—47°.

cis- *and* trans-1-p-*Chlorophenyl*-2-*methyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene* (II*d*) *and*

[9] Tilford, Shelton, and Van Campen, jun., *J. Amer. Chem. Soc.*, 1948, **70**, 4004.
[10] Holiday, *J. Sci. Instr.*, 1937, **14**, 166.

(VII*d*).—The mixed isomeric oxalates were crystallised several times from ethanol, to give trans-*oxalate*, needles, m. p. 216°. The mother-liquors were evaporated, the residual oxalate was dissolved in boiling ethyl acetate and filtered from a little *trans*-oxalate, and the ethyl acetate filtrate evaporated to small volume. On cooling, crystals separated and after crystallisation from ethanol–ether gave cis-*oxalate*, m. p. 134—135°. The isomers were also separated by base-exchange chromatography as described above for the piperidino-analogue.

cis- *and* trans-1-p-*Chlorophenyl*-2-*phenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene* (III*b*) *and* (VIII*b*).—(i) The alcohol (10 g.) was dehydrated by solution in 98% sulphuric acid (100 ml.) at room temperature for 3 hr. The mixed isomeric alkenylamines (9·2 g.) solidified. They were converted into the oxalates, which were separated by fractional crystallisation from ethanol and ethanol–ether into the less soluble trans-*oxalate*, m. p. 151—152°, and the more soluble cis-*oxalate*, m. p. 147—148°. The trans-*base* had m. p. 104—105° and the cis-*base* had m. p. 110°, depressed on admixture with *trans*-isomer to 82—88°. (ii) The mixed bases were separated by base-exchange chromatography into forty fractions, from each of which crystals separated. On the basis of the m. p.s and mixed m. p.s, fractions 5—22 were united and worked up to give *trans*-isomer, m. p. 44—45°, and fractions 26—40 similarly gave *cis*-base, m. p. 110°, depressed on admixture with the *trans*-isomer to 83—87°.

Isomeric 1 : 2-*Diphenyl*-3-*piperidino*-1-2′-*pyridylprop*-1-*ene* (III*a*) *and* (VIII*a*).—The alcohol (20 g.), similarly dehydrated, gave mixed alkenylamines (18 g.) which partly solidified. The solid portion (11 g.), filtered from the oil, recrystallised from light petroleum (b. p. 40—60°) to give an *isomer*, m. p. 91—92°. Separation of the mixed isomers by base-exchange chromatography gave the same solid isomer, m. p. 91—92°, in the head fractions, and oil in the tail fractions, whence no solid hydrochloride or oxalate was obtained.

cis-1 : 3-*Diphenyl*-3-*piperidino*-1-2′-*pyridylprop*-1-*ene* (X*a*).—The alcohol (10 g.), similarly dehydrated, gave alkenylamine (8·4 g.), which slowly solidified. This was separated by ion-exchange chromatography into 35 fractions, of similar spectrum ($\lambda_{max.}$ 250 mμ). The material crystallised from light petroleum, to give the cis-*base*, m. p. 77—79°. From alcohol dehydrated in 85% sulphuric acid at 100° for ¼ hr. no water-insoluble product was recovered.

cis- *and* trans-1-(3-*Methyl*-2-*pyridyl*)-1-*phenyl*-3-*pyrrolidinoprop*-1-*ene* (XXX*a*) *and* (XXXI*a*).—The mixed oxalates were separated by fractional crystallisation from ethanol and ethanol–ether into the less soluble trans-*oxalate*, m. p. 158—160°, and the more soluble cis-*oxalate*, prisms, m. p. 152°.

cis- *and* trans-1-p-*Chlorophenyl*-1-(3-*methyl*-2-*pyridyl*)-3-*pyrrolidinoprop*-1-*ene* (XXX*b*) *and* (XXXI*b*).—(i) The isomeric oxalates were separated by fractional crystallisation from ethanol and ethanol–ether into the less soluble cis-*oxalate*, plates, m. p. 175—176°, and the more soluble trans-*oxalate*, m. p. 140—141°. (ii) Mixed bases were submitted to base-exchange chromatography. The spectra of the fractions were not sufficiently dissimilar to define the transition from *trans*- to *cis*-isomer. However, on an arbitrary basis the first third of the fractions was worked up to give pure *trans*-oxalate, m. p. 140°, and the last third of the fractions to give pure *cis*-oxalate, m. p. 175°.

cis- *and* trans-1-2′-*Pyridyl*-3-*pyrrolidino*-1-o-*tolylprop*-1-*ene* (XXV*a*) *and* (XXVII*a*).—The mixed isomeric bases were separated [11] by base-exchange chromatography, controlled spectroscopically, the ratio of the optical densities at 290 and 270 mμ being used (Figs. 2 and 3 of ref. 11 refer to the separation of this pair of isomers).

cis- *and* trans-1-(2 : 4-*Dimethylphenyl*)-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene* (XXV*b*) *and* (XXVII*b*), *and* cis- *and* trans-1-(2 : 5-*Dimethylphenyl*)-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene* (XXV*c*) *and* (XXVII*c*).—In each case the isomeric bases were separated by ion-exchange chromatography, controlled by the cam-plate method.[10]

The two examples lacking the tertiary amino-group [Table 4, (XIV) and (XV), *a* and *b*], the three γ-methyl-substituted examples [Table 4, (IV) and (IX), *a*, *b*, and *c*] and all the alkyl substituted examples in Table 5 not containing an *o*-methyl substituent were separated by base-exchange chromatography controlled by the ultraviolet absorption spectra of the fractions.

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[11] Jones in " Ion Exchange and Its Applications " (Report on Symposium), Soc. Chem. Ind., London, 1955, p. 164.