445. *Aminoalkyl Tertiary Carbinols and Derived Products. Part V.* Antihistamines. The Stereochemistry of* cis- *and* trans-3-*Phenyl*-3-*pyridylallylamines.*

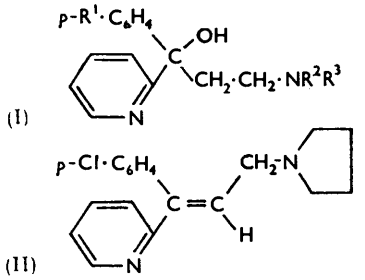
By D. W. Adamson, P. A. Barrett, J. W. Billinghurst, and T. S. G. Jones.

The allylamines prepared by sulphuric acid dehydration [1] of substituted 3-amino-1-phenyl-1-2′-pyridylpropan-1-ols have now been shown to be mixtures, separable by fractional crystallisation and base-exchange chromatography into pairs of isomers. Evidence, based partly on chemical reactions and partly on ultraviolet absorption spectra, is presented for the formulation of these pairs as *cis-trans*-isomers. The spectra indicate that the conjugated systems are different in the two isomers, the isomer designated *trans* having a spectrum similar to that of 2-vinylpyridine, and the spectrum of the isomer designated *cis* resembling that of styrene; these spectra are interpreted in terms of the co-planarity of one of the aryl groups with the ethylenic bond.

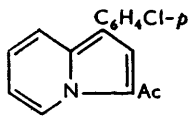
The conditions which determine the proportions in which the isomers are formed in the dehydration reaction have been investigated.

The synthesis of some 3-(tertiary amino)-1-aryl-1-2′-pyridylpropan-1-ols (I) and their dehydration by sulphuric acid to the corresponding allylamines, *e.g.*, (II), were described in Part III.[1] One of these allylamines (" 405C49 ") (II) was of especial interest for its very high antihistamine potency.[2,3]

As reported briefly,[4] it has been found that, in addition to " 405C49," another base is present under certain conditions. The new base is isomeric with " 405C49 " and is relatively inactive pharmacologically. It is now shown that the bases are geometrical isomers, " 405C49 " being *trans* (II) and the other being *cis* (III) in terms of the relative positions of the nitrogen-containing groups.

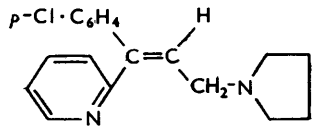


(I)



(IV)

(II)



(III)

The proportion of *trans*-isomer in the mixed allylamines is low when dehydration is carried out at room temperature, and increases with time and temperature of reaction and with increasing strength of sulphuric acid so that above a range of limiting conditions, defined in the Experimental section, it is the sole product of dehydration. The same conditions also quantitatively convert the *cis*- into the *trans*-isomers. Isomerisation is not, however, brought about by heat alone. On attempted distillation, a little *cis*-isomer distilled unchanged, but the bulk suffered gross decomposition.

Both isomers are oxidised by chromic acid in almost theoretical yield to 2-*p*-chlorobenzoylpyridine (identical with a specimen synthesised from 2-pyridyl-lithium and

* Part IV, *J.*, 1951, 52.

[1] Adamson and Billinghurst, *J.*, 1950, 1039.
[2] Bain, *Analyst*, 1951, **76**, 573.
[3] Green, *Brit. J. Pharmacol.*, 1953, **8**, 171.
[4] Adamson, Barrett, Billinghurst, Green, and Jones, *Nature*, 1951, **168**, 204.

p-chlorophenyl cyanide); potassium permanganate gave a lower yield of the ketone. Both isomers gave the same propylamine [1] in high yield when hydrogenated in the presence of palladised charcoal. These reactions are consistent with formulation of the compounds as *cis-trans*-isomers. Some evidence for the particular configurations of the isomers was furnished by the study of their reaction with acetic anhydride. The *trans*-isomer was recovered substantially unchanged after 30 minutes' boiling, whereas the *cis*-isomer was completely degraded, one of the products being the pyrrocoline derivative (IV), whose constitution was confirmed by identity with material prepared from 2-4'-chlorobenzylpyridine by acetic anhydride which, following Chichibabin's interpretation [5] of the reaction first studied by Scholtz,[6] will have the unequivocal structure (IV). This ring-closure supports the configuration assigned to the *cis*-isomer.

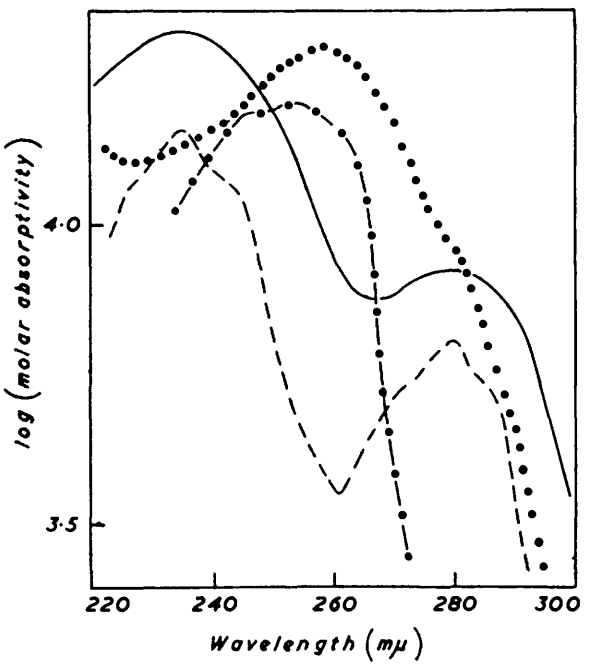


FIG. 1.

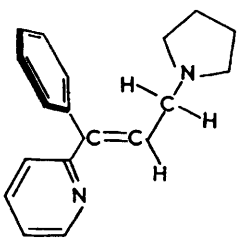
—— trans-1-p-*Chlorophenyl*-1-2'-*pyridyl*-3-*pyrrolidinoprop*-1-*ene* (*in* EtOH).
– – – 2-*Vinylpyridine* (*in* EtOH).
. . . cis-1-p-*Chlorophenyl*-1-2'-*pyridyl*-3-*pyrrolidinoprop*-1-*ene hydrobromide* (*in* H_2O).
·—· p-*Chlorostyrene* (*in* EtOH).

Professor R. Pepinsky, of Pennsylvania State College, recently provided final proof of the *cis*-structure by *X*-ray crystallographic studies of the analogous *p*-bromophenyl compound (personal communication); we are grateful to Professor Pepinsky for his interest in the problem.

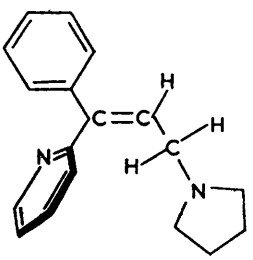
It is well known [7] that differences exist between the ultraviolet absorption spectra of some *cis*- and *trans*-isomers. The spectra are however usually similar in general character, there being only small differences in wavelength although the intensities may differ greatly. In contrast, the ultraviolet absorption spectra of the present isomers are highly distinctive.[4] The spectrum exhibited by the *trans*-isomer base in ethanol is very similar to that of 2-vinylpyridine in showing maximum absorption at 235 and 281 mμ (Fig. 1) while the *cis*-isomer has absorption bands closely resembling those of *p*-chlorostyrene in wavelength and intensity. These spectra may be interpreted in terms of the blocking effect of the component groups and of their relative spatial position about the double bond. It is impossible for a phenyl and a pyridyl ring joined to the same carbon atom to occupy

[5] Chichibabin and Stepanow, *Ber.*, 1929, **62**, 1068.
[6] Scholtz, *Ber.*, 1912, **45**, 734.
[7] Crombie, *Quart. Rev.*, 1952, **6**, 113.

the same plane, and the presence of the aminomethylene group on the β-carbon of the ethylene group must cause further steric hindrance. The hydrogen atoms of the methylene group are the cause of this hindrance, the tertiary nitrogen atom playing no part. It has long been postulated that for maximum conjugation in this type of structure co-planarity of the phenyl or of the pyridyl ring with the ethylene group is necessary. In view of the repulsive energy of the hindering hydrogen atoms, something less than complete overlap of the *p*-orbitals of each ring and the ethylene group will suffice. Recent studies [8] on derivatives of diphenyl have indicated that in this series large departures from co-planarity may be accommodated without loss of conjugation and of characteristic ultraviolet absorption. Nevertheless we believe that the ring more nearly occupying the plane of the ethylene group will be the more conjugated with the latter and we shall for brevity refer to these groups as co-planar. With this limitation in mind, it is possible to examine the detailed structures of the isomers in an attempt to interpret the spectra. The spectrum of the *trans*-isomer is so similar to that of 2-vinylpyridine that we deduce that the conjugated portions in the two molecules are also similar and that the pyridyl group and the ethylene group are nearly co-planar. The *p*-chlorophenyl group is then sufficiently inclined to the plane of the ethylene group to prevent conjugation with it and the contribution of the former to the near-ultraviolet absorption spectrum is small. Similarly[9] for the *cis*-isomer we deduce that the *p*-chlorophenyl group is the one in conjugation with the double bond. We therefore envisage the more detailed shapes of the molecules to be as illustrated diagrammatically in (V) and (VI).



(V)



(VI)

Since our preliminary communication,[4] Bauer and Lutz [9] have advanced a similar hypothesis to account for the difference in absorption spectra between some *cis*- and *trans*-dibenzoylstyrenes.

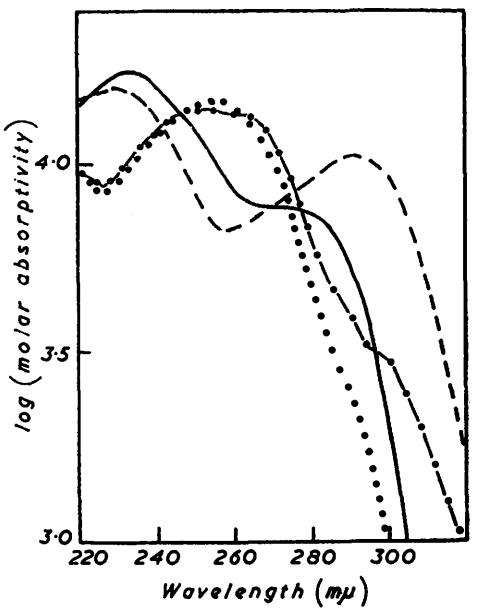
The ultraviolet absorption spectra of the isomers when determined in acid solution (Fig. 2) are also in accordance with the above hypothesis. In the first place the spectra of the *trans*-base and its monohydrochloride in water are indistinguishable. This is explicable if the nitrogen atom of the pyrrolidino-group does not interact with the double bond and is not itself hindered in salt formation by the rest of the molecule. The monohydrochloride must be formed exclusively through the pyrrolidino-group because of the great disparity in the strengths of the basic centres. In more strongly acid solution the peak at 281 mμ appears at progressively longer wavelengths and is increased in intensity. A similar difference is noted between the spectra of 2-vinylpyridine in neutral and in acid solution, presumably owing to an increase in the energy of the ground state of the salt relative to that of the excited state. In contrast, the spectrum of the *cis*-isomer in acid solution differs little from the styryl-like spectrum of the base, thereby confirming that the 2-pyridinium group of the salt, like the neutral 2-pyridyl group of the base, is not in conjugation with the double bond. It may be mentioned that the spectra of the isomers in acid

[8] Beavan, Hall, Lesslie, and Turner, *J.*, 1952, 854.
[9] Bauer and Lutz, *J. Amer. Chem. Soc.*, 1953, **75**, 5997.

solution dispose of the remote possibility (considered in the earlier stages of the work and not rigorously excluded by the evidence from the oxidation) that the isomers differed in respect of the position of the double bond, one isomer having the vinylamine group, $-CH{:}CH\cdot N$, since it has been shown [10] that compounds containing this group show a great diminution in ultraviolet light absorption on conversion from base into cation.

The strength of the two basic centres of each isomer is of interest in relation to the structures proposed, and a detailed investigation will be reported elsewhere (Everett and Jones). Not unexpectedly, the strength of the pyrrolidino-groups in the two isomers is almost identical [for (V) pK_a' was $9{\cdot}46 \pm 0{\cdot}03$ and for (VI) $9{\cdot}51 \pm 0{\cdot}07$, at 25° and ionic

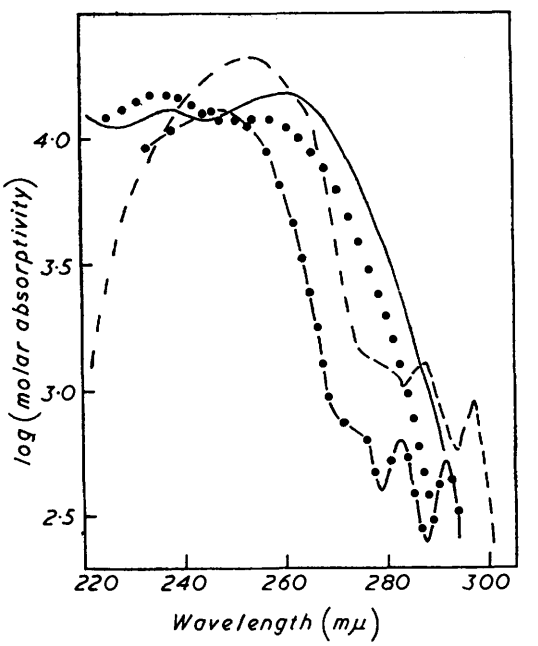
FIG. 2.



trans-1-p-*Chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene*:
—— *in* 0·05M-*aq.* NaOH.
– – – *in* 1·0M-*aq.* HCl.

cis-1-p-*Chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene*:
. . . *in* 0·1M-*aq.* NaOH.
·—· *in* 0·1M-*aq.* HCl.

FIG. 3.



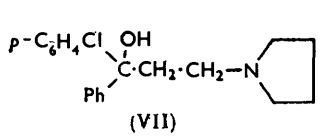
—— *Isomer* (VIII) *of* 1-p-*chlorophenyl*-1-*phenyl*-3-*pyrrolidinoprop*-1-*ene* (*in* EtOH)
– – – p-*Chlorostyrene* (*in* EtOH).
. . . *Isomer* (IX) *of* 1-p-*chlorophenyl*-1-*phenyl*-3-*pyrrolidinoprop*-1-*ene* (*in* EtOH).
·—· *Styrene* (*in hexane* [12]).

strength 0·05]. For the other (pyridyl) basic centres, the values found were: (V) 3·21 and (VI) 2·47 (at 25° and zero ionic strength). Reasons for this difference, and also for the unexpectedly low value, especially for (VI), will be advanced in the proposed publication.

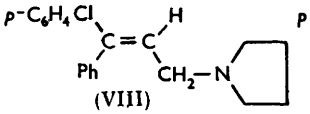
The occurrence of geometrical isomerism has been observed also in the related series of diphenylallylamines in which the phenyl groups are dissimilarly substituted, and the spatial configuration of the isomers may be deduced from their spectra in the same way as in the pyridyl series. The phenomenon is thus general and not dependent on a feature peculiar to the 2-pyridyl group. Dehydration of the alcohol (VII) gave a mixture from which two pure, sharply defined allylamines, differing in their pharmacological activities, were isolated. The ultraviolet absorption spectra of the isomers, although similar, revealed

[10] Bowden, Braude, Jones, and Weedon, *J.*, 1946, 49.

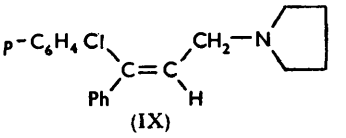
differences in the wavelengths and intensity of their main absorption peaks of the same magnitude as the differences observed between *p*-chlorostyrene and styrene (Fig. 3). It is



(VII)



(VIII)



(IX)

therefore concluded that in one isomer the *p*-chlorophenyl group is co-planar with the double bond and *trans* to the aminomethylene group (VIII) while in the other, (IX), the unsubstituted phenyl group is *trans* to the aminomethylene group.

We have re-examined the dehydration of the other analogous alcohols (I; $R^1 = H$ or Cl; $NR^2R^3 = NMe_2$, NEt_2, $N<C_4H_8$, $N<C_5H_{10}$, $N<C_5H_8>O$) listed in Table 2 of

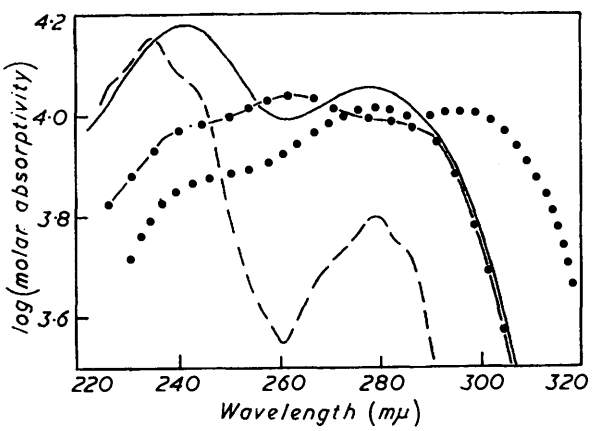
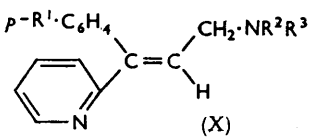


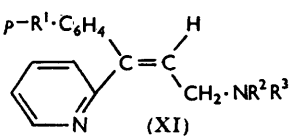
FIG. 4.

—— trans-1-2′-*Pyridyl*-1-(5-*chloro*-2-*thienyl*)-3-*pyrrolidinoprop*-1-*ene*.
– – – 2-*Vinylpyridine*.
. . . cis-1-2′-*Pyridyl*-1-(5-*chloro*-2-*thienyl*)-3-*pyrrolidinoprop*-1-*ene*.
·—·· 1 : 1-*Di*-2′-*thienylprop*-1-*ene*.
All in EtOH.

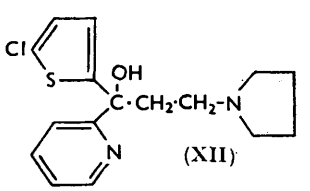
Part III [1] and of some new *p*-substituted-phenylcarbinols (I; $R^1 = F, Br, MeO$; $NR^2R^3 = N < C_4H_8$) and a thienyl analogue (XII). The majority of the alcohols, when heated with 85—98% sulphuric acid at 100° for 10—30 min., gave mixtures of the allylamines



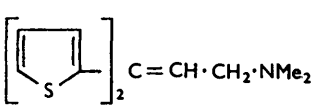
(X)



(XI)



(XII)



(XIII)

which were separated into *cis-trans*-isomers (X) and (XI). More dilute sulphuric acid was required in the cases of the more sensitive compounds (I; $R^1 = MeO$) and (XII). The more stable isomer (X) of each pair, like (II), exhibited the characteristic 2-vinylpyridine-like ultraviolet absorption and was the *trans*-isomer, and the other less stable isomer (XI), like (III), gave a spectrum similar to that of styrene or of the corresponding *para*-substituted styrene, and was the *cis*-isomer.

The isomeric allylamines derived from (XII) were of interest as examples in which

neither of the chromophoric groups was phenyl. In conformity with the hypothesis one isomer (*trans*) showed the " orthodox " 2-vinylpyridine-like spectrum (Fig. 4), whereas the other (*cis*) exhibited a distinctive ultraviolet absorption spectrum similar to that of the 3 : 3-di-2′-thienylallylamines (*e.g.*, XIII),[11] and to that of 1 : 1-di-2′-thienylprop-1-ene.

A further example of isomerism of this type has recently been provided by Cymerman-Craig and Harrisson,[12] who separated the isomeric *cis*- and *trans*-3-(4-methyl-1-piperazino)-1-phenyl-1-2′-thienylprop-1-enes and compared their ultraviolet absorption spectra with those of known compounds possessing analogous chromophores.

TABLE 1. *Aryl* 2-(*tertiary amino*)*ethyl ketones*, $R^1{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NR^2R^3$.

No.	R^1	NR^2R^3	Compound	M. p.	Solvent for crystn.
1	*p*-C_6H_4F	$N<[CH_2]_4$	Base	55—56°	Pet †
2	,,	,,	Hydrochloride	153	EtOH–EtOAc
3	*p*-C_6H_4Br	$N<[CH_2]_4$	Base	79—80	EtOH
4	,,	,,	Hydrochloride	197—198	EtOH
5	*p*-MeO·C_6H_4	$N<[CH_2]_4$	Hydrochloride	183—183·5	EtOH
6	2-(5-Cl·C_4H_2S)	$N<[CH_2]_4$ [a]	Hydrochloride	189 *	EtOH
7	*p*-C_6H_4Cl	NMeEt	Base	13—14	—
8	,,	,,	Hydrochloride	148·5—150	EtOH–EtOAc

		Found (%)					Required (%)				
No.	Formula	C	H	N	Cl	Br/F/S	C	H	N	Cl	Br/F/S
1	$C_{13}H_{16}ONF$	70·4	7·0	6·2	—	8·2	70·6	7·2	6·3	—	8·6
2	$C_{13}H_{16}ONF,HCl$	—	—	—	14·0	7·7	—	—	—	13·8	7·4
3	$C_{13}H_{16}ONBr$	55·6	5·6	—	—	28·6	55·3	5·7	—	—	28·4
4	$C_{13}H_{16}ONBr$	—	—	—	11·4	—	—	—	—	11·1	—
5	$C_{14}H_{19}O_2N,HCl$	62·3	7·5	5·2	13·5	—	62·3	7·4	5·2	13·2	—
6	$C_{11}H_{14}ONS,HCl$	—	—	5·3	25·5	11·4	—	—	5·0	25·4	11·4
7	$C_{12}H_{16}ONCl$	63·6	6·8	6·4	15·3	—	63·9	7·1	6·2	15·7	—
8	$C_{13}H_{16}ONCl,HCl$	—	—	—	27·2	—	—	—	—	27·1	—

* Decomp. † Light petroleum (b. p. <40°). [a] The reaction solvent was glacial acetic acid.

TABLE 2. 1-*Aryl*-1-2′-*pyridyl*-3-(*tertiary amino*)*propan*-1-*ols*, $C_5H_4N{\cdot}CR^1(OH){\cdot}CH_2{\cdot}CH_2{\cdot}NR^2R^3$.

No.	R^1	NR^2R^3	Yield (%)	Compound	M. p.	Solvent for crystn.
1	*p*-C_6H_4F	$N<[CH_2]_4$	69	Base	91·5—93°	EtOH
2	,,	,,	—	Oxalate	154—155 *	MeOH–EtOH
3	*p*-C_6H_4Br	$N<[CH_2]_4$	72	Base	143·5—145	EtOH
4	*p*-MeO·C_6H_4	$N<[CH_2]_4$	71	Base	82—83	EtOH
5	,,	,,	—	Oxalate	142·5—143 *	EtOH–EtOAc
6	2-(5-Cl·C_4H_2S)	$N<[CH_2]_4$	51	Base	90—90·5	EtOH
7	,,	,,	—	Oxalate	149—150·5 *	EtOH–EtOAc
8	*p*-C_6H_4Cl	NMeEt	—	Base	46—47	Pet †
9	,,	,,	—	Oxalate	160—162 *	MeOH

		Found (%)					Required (%)				
No.	Formula	C	H	N	Cl	Br/F/S	C	H	N	Cl	Br/F/S
1	$C_{18}H_{21}ON_2F$	71·9	6·8	9·5	—	6·5	72·0	7·0	9·3	—	6·3
2	$C_{18}H_{21}ON_2F,C_2H_2O_4$	61·3	5·7	—	—	5·1	61·5	5·9	—	—	4·9
3	$C_{18}H_{21}ON_2Br$	59·9	5·7	7·8	—	22·6	59·8	5·8	7·8	—	22·2
4	$C_{19}H_{24}O_2N_2$	73·2	7·7	9·0	—	—	73·1	7·7	9·0	—	—
5	$C_{19}H_{24}O_2N_2,C_2H_2O_4$	62·5	6·2	—	—	—	62·7	6·5	—	—	—
6	$C_{16}H_{19}ON_2ClS$	59·6	5·7	8·8	11·3	9·6	59·5	5·9	8·7	11·0	9·9
7	$C_{16}H_{19}ON_2ClS,C_2H_2O_4$	52·4	5·3	—	—	—	52·4	5·1	—	—	—
8	$C_{17}H_{21}ON_2Cl$	66·9	6·8	8·9	11·2	—	67·0	6·9	9·2	11·7	—
9	$C_{17}H_{21}ON_2Cl,\frac{1}{2}C_2H_2O_4$	61·4	6·0	—	—	—	61·8	6·3	—	—	—

*† See Table 1.

Dehydration of the alcohols (I; R^1 = halogen) under more severe conditions led, as in the example discussed in detail above, to the exclusive production of the *trans*-isomer

[11] Adamson, Part II, *J.*, 1950, 885.
[12] Cymerman-Craig and Harrisson, *Austral. J. Chem.*, 1955, **8**, 378.

(X; R^1 = halogen). The course of the dehydration of alcohols (I; R^1 = H or MeO) or (XII) was less clear-cut since the product was unstable to sulphuric acid at higher temperatures (*e.g.*, complete breakdown occurred rapidly at 200°). In these cases, use of lower temperatures was successful for the preparation of the pure *trans*-isomers, though in low yield. The *trans*- were more stable than the *cis*-isomers to the action of boiling acetic anhydride as in the case of (II) and (III), but again the difference in stability was more pronounced when the phenyl group was substituted by *p*-halogen than when it was unsubstituted.

We conclude from a re-examination of the allylamine salts described in Table 2 of Part III [1] that, despite their apparent homogeneity, with the exception of "405C49," they were mixtures of *cis-trans*-isomers in proportions which varied greatly, depending on the conditions of their formation and purification.

Fractional crystallisation of the neutral oxalates from ethanol generally separated the isomers (Table 3). Three bases were crystalline. This property apparently bears no simple relation to geometrical configuration, since two of the solids (X; R^1 = Cl and Br; $NR^2R^3 = N{<}C_4H_8$) were *trans* and one (XI; R^1 = Cl, $NR^2R^3 = NMe_2$) was the *cis*-isomer.

Chromatography on alumina gave only partial separation of two examples (Table 3, *g* and *l*).

Ion-exchange chromatography, which was not introduced until the later stages of the work, gave sharp separation with good recovery of the pure isomers.[13] The material selected was a sulphonated polystyrene resin (nominal cross-linking, 2·25%) in bead form, kindly supplied by the Chemical Research Laboratory, Teddington. The crude dehydration product was absorbed on the resin column and displaced with aqueous-alcoholic ammonia. The identity of the fractions and the point at which one isomer gave place to the other were established by ultraviolet spectroscopy.

The customary criteria of purity (*i.e.*, analysis, sharp m. p. unchanged on further crystallisation) are not adequate in all cases to make it certain that any given isomer has been obtained free from its partner. It is possible to be confident of the purity of the *trans*-isomers for several reasons, *viz.*: the relative insolubility of their oxalates in ethanol; the formation of identical material by different methods of separation and by treatment with acetic anhydride or concentrated sulphuric acid; and the specific nature of the absorption spectrum. The evidence for the purity of the *cis*-isomers is less clear. The absorption spectra are less characteristic and do not reveal contamination by a small proportion of the *trans*-isomer. On the other hand, the antihistamine potency of the *cis*-isomer is considerably lower (in some examples, nearly one hundred times) than that of the *trans*-isomer. It is concluded that in some cases physical evidence (*e.g.*, a crystalline base, or relatively insoluble salt) indicated a very high degree of purity, and in the others contamination by no more than a few per cent. of the *trans*-isomer is presumptive.

The compounds have been examined for their antihistamine and other biological effects by Mr. A. F. Green of the Pharmacology Laboratory. The relation between the structure of these and related compounds and their biological activities will be discussed elsewhere.

Experimental

M. p.s of salts are all with decomposition.

Dehydration of 1-p-*Chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinopropan*-1-*ol* (Part III; [1] VI*g*).—The alcohol (20 g.) in concentrated sulphuric acid (100 ml.) was heated on the steam-bath for 15 min., cooled, poured on ice, and basified with aqueous ammonia, and the liberated oil was extracted into ether. Removal of the solvent by distillation gave a mixture of the isomeric allylamines (II = X*g* and III = XI*g*) as a pale brown oil (18 g., 95%).

[13] Jones, *Analyst*, 1952, **77**, 962; "Ion Exchange and Its Applications" (Report of Symposium), Soc. Chem. Ind., London, 1955, p. 164.

Separation of the trans- *and* cis-*Isomers of* 1-p-*Chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene* (Table 3; Xg and XIg).—(a) *By fractional crystallisation of oxalates* (Table 3, method A). The mixture of bases (18 g.) was dissolved in ethanol (50 ml.), and oxalic acid dihydrate (7·6 g., 1 mol.) in a little ethanol was added. The mixed oxalates rapidly crystallised and were collected, washed with ethanol and ether, and dried (21 g.; m. p. 148—155°). Numerous crystallisations from ethanol gave the *trans*-isomer oxalate (X*g*), needles, m. p. 184° (5·8 g., 23%) [Part III [1] (VII*g*) gives m. p. 177°]. The earlier filtrates were concentrated and allowed to crystallise, the crude *cis*-isomer oxalate separating as plates (m. p. 151—152°). It was freed from a little *trans*-isomer by crystallisation from chloroform to give prismatic needles, m. p. 156—157°, which, after drying in the air, contained 1 mol. of chloroform, lost on drying at 100° [Found: C, 49·7; H, 4·3; Cl, 24·6; loss at 100°, 22·4; Cl (after drying), 9·4. $C_{18}H_{19}N_2Cl,C_2H_2O_4,CHCl_3$ requires C, 49·6; H, 4·3; Cl, 27·9; loss, 23·6; Cl (after drying), 9·1%]. The chloroform was removed by crystallisation from ethanol, cis-1-p-*chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene oxalate* (XI*g*) being obtained as plates (8·5 g., 34%), m. p. 156—157°.

The trans-*isomer base*, liberated from the oxalate by alkali, distilled without decomposition (b. p. 180—182°/0·2 mm.). It solidified and after crystallisation from light petroleum (b. p. 40—60°) formed prisms, m. p. 61—62°, n_D^{19} 1·603 (supercooled) (Found: C, 72·3; H, 6·3; N, 9·1; Cl, 11·4. $C_{18}H_{19}N_2Cl$ requires C, 72·4; H, 6·3; N, 9·4; Cl, 11·9%). Light absorption in 4×10^{-4}M-solution in EtOH: max. 235, 281 mμ (log ε 4·33, 3·93); in 4×10^{-5}M-solution in 5·5M-HCl: max. 227, 293 mμ (log ε 4·14, 4·00).

The cis-*isomer base* (5 g.), liberated from the oxalate, distilled without decomposition to give a colourless oil, b. p. 172—176°/0·1 mm., n_D^{19} 1·600 (Found: C, 72·4; H, 6·3; N, 9·2; Cl,

TABLE 3. 3-(*Tertiary amino*)-1-*aryl*-1-2′-*pyridylprop*-1-*ene isomers* (X *and* XI).

Compound [a]		R¹	NR²R³	Separation [b]	Salt [c]	M. p. [d]	Mixed M. p. [d]	Peak ultraviolet light absorption [e] λ	log ε	λ	log ε
X*a*	H		NMe_2	A, D, E	Oxalate	179°	168—171°	238	4·32	280	4·03
XI*a*	,,		,,	A	,,	180—181		247	4·35	—	—
X*b*	H		NEt_2	A, B, D	,,	130—131	130—132	235	4·13	281	3·86
XI*b*	,,		,,	B	,,	163		252	4·10	—	—
X*c*	H		$N<[CH_2]_4$	B, D, E	,,	164—165	154—156	237	4·21	280	3·95
XI*c*	,,		,,	B	,,	169—170		251	4·18	—	—
X*d*	H		$N<[CH_2]_5$	A, D	,,	173—174	168—170	237	4·16	281	3·82
XI*d*	,,		,,	A	,,	175—176		256	4·30	—	—
X*e*	Cl		NMe_2	A, D, E	,,	182—183	167—169	237	4·44	280	4·11
XI*e*	,,		,,	A, F	,,	174—175		255	4·45	—	—
,,	,,		,,		Base [f]	61—62 *		—	—	—	—
X*f*	Cl		NEt_2	A, D	Oxalate [g]	130—131	120—125	235	4·26	281	3·88
XI*f*	,,		,,	A	,,	155—156		257	4·32	—	—
X*g*	Cl		$N<[CH_2]_4$	A, B, C,	Base [f]	61—62 *	—	235	4·33	281	3·93
,,	,,		,,	D, E, F	HCl [h]	180—182		234	4·34	273	4·01 ‡
,,	,,		,,		HBr [h]	183—184		229	4·40	273	4·04 ‡
,,	,,		,,		Oxalate	184		235	4·31	280	3·93
XI*g*	Cl		$N<[CH_2]_4$	A, C	HBr [h]	135—136	153—154	258	4·36	—	— ‡
,,	,,		,,		Oxalate [g]	157		258	4·33	—	— ‡
X*h*	Cl		$N<[CH_2]_5$	A, D, E	,,	175—176	162—165	234	4·26	280	3·91
XI*h*	,,		,,	A	,,	173—174		257	4·33	—	—
X*i*	Cl		$N<[CH_2]_4>O$	A, D	,,	187	160—161	236	4·29	281	3·94
XI*i*	,,		,,	A	,,	164—165		255	4·20	—	—
X*j*	Cl		NMeEt	D	,, [j]	161—162	148—150	235	4·25	280	3·86
XI*j*	,,		,,	A	,,	157		257	4·29	—	—
X*k*	F		$N<[CH_2]_4$	B	,, [f]	184—185	—	238	3·90	281	3·67
XI*k*	,,		,,	B	,,	166—167		252	3·90	280	3·67
X*l*	Br		$N<[CH_2]_4$	B, C, E,	Base [f]	90—91 *	—	238	4·28	280	3·86
,,	,,		,,	F	HCl [h]	179—180		232	4·28	265	3·89 ‡
,,	,,		,,		HBr [h]	186—188		235	4·30	280	3·90
,,	,,		,,		Oxalate [f]	182—183		—	—	—	—
XI*l*	,,		,,	B, C	HBr [h]	159—160	—	259	4·29	—	—
,,	,,		,,		Oxalate	163—164		259	4·30	—	—
X*m*	MeO		$N<[CH_2]_4$	B	Oxalate [f]	179—180	—	233	4·28	277	3·99
XI*m*				B	,,	140—142		237	4·18	270	4·13
X*n*	2-(5-Cl·C_4H_2S)[k]		$N<[CH_2]_4$	B, F	,, [f]	148—149	142—143	241	4·15	278	4·06
XI*n*				B	,,	155—156			(see Fig. 3)		

TABLE 3. (*Continued.*)

Compound	Formula	Found (%) C	H	N	Cl	Br/F/S	Required (%) C	H	N	Cl	Br/F/S
X*a*	$C_{16}H_{18}N_2,C_2H_2O_4$	65·8	6·0	8·6	—	—	65·8	6·1	8·5	—	—
XI*a*	,,	65·7	5·9	8·3	—	—	,,	,,	,,	—	—
X*b*	$C_{18}H_{22}N_2,C_2H_2O_4$	67·7	6·7	7·8	—	—	67·4	6·7	7·9	—	—
XI*b*	,,	67·6	6·8	7·9	—	—	,,	,,	,,	—	—
X*c*	$C_{18}H_{20}N_2,C_2H_2O_4$	67·7	6·1	8·1	—	—	67·8	6·2	7·9	—	—
XI*c*	,,	67·7	6·1	8·1	—	—	,,	,,	,,	—	—
X*d*	$C_{19}H_{22}N_2,C_2H_2O_4$	68·2	6·4	7·4	—	—	68·5	6·5	7·6	—	—
XI*d*	,,	68·3	6·4	7·5	—	—	,,	,,	,,	—	—
X*e*	$C_{16}H_{17}N_2Cl,C_2H_2O_4$	59·3	5·0	7·7	9·9	—	59·6	5·2	7·7	9·8	—
XI*e*	,,	59·8	5·1	8·1	10·0	—	,,	,,	,,	,,	—
,,	$C_{16}H_{17}N_2Cl$	70·4	6·2	10·3	13·1	—	70·4	6·3	10·3	13·0	—
X*f*	$C_{18}H_{21}N_2Cl,C_2H_2O_4$	61·6	5·7	7·2	—	—	61·4	5·9	7·2	9·1	—
XI*f*	,,	61·4	5·7	7·1	—	—	,,	,,	,,	,,	—
X*g*	$C_{18}H_{19}N_2Cl$	72·3	6·3	9·1	11·4	—	72·4	6·3	9·4	11·9	—
,,	$C_{18}H_{19}N_2Cl,HCl$	—	—	—	21·0	—	—	—	—	21·2	—
,,	$C_{18}H_{19}N_2Cl,HBr$	—	—	—	—	21·1	—	—	—	—	21·1
,,	$C_{18}H_{19}N_2Cl,C_2H_2O_4$	61·9	5·5	7·1	9·3	—	61·8	5·4	7·2	9·1	—
XI*g*	$C_{18}H_{19}N_2Cl,HBr$	—	—	—	—	20·8	—	—	—	—	21·1
,,	$C_{18}H_{19}N_2Cl,C_2H_2O_4$	61·5	5·2	7·1	9·2	—	61·8	5·4	7·2	9·1	—
X*h*	$C_{19}H_{21}N_2Cl,C_2H_2O_4$	63·0	5·7	6·7	8·7	—	62·6	5·7	7·0	8·8	—
XI*h*	$C_{19}H_{21}N_2Cl,C_2H_2O_4$	62·4	5·7	7·0	8·2	—	,,	,,	,,	,,	—
X*i*	$C_{18}H_{19}ON_2Cl,C_2H_2O_4$	59·5	5·3	7·1	8·7	—	59·3	5·2	6·9	8·8	—
XI*i*	,,	59·2	5·4	6·7	8·9	—	,,	,,	,,	,,	—
X*j*	$C_{17}H_{19}N_2Cl,C_2H_2O_4$	60·8	5·7	7·2	9·1	—	60·6	5·6	7·4	9·4	—
XI*j*	,,	61·1	5·9	7·1	9·0	—	,,	,,	,,	,,	—
X*k*	$C_{18}H_{19}N_2F,C_2H_2O_4$	64·6	5·5	7·7	—	4·7	64·5	5·6	7·5	—	5·1
XI*k*	,,	64·7	5·6	7·2	—	5·5	,,	,,	,,	—	,,
X*l*	$C_{18}H_{19}N_2Br$	63·0	5·4	7·9	—	23·2	63·0	5·5	8·2	—	23·3
,,	$C_{18}H_{19}N_2Br,HCl$	—	—	—	9·3	—	—	—	—	9·4	—
,,	$C_{18}H_{19}N_2Br,HBr$	—	—	—	—	37·6	—	—	—	—	37·7
,,	$C_{18}H_{19}N_2Br,C_2H_2O_4$	55·3	5·0	—	—	—	55·4	4·8	—	—	—
XI*l*	$C_{18}H_{19}N_2Br,HBr$	—	—	—	—	37·8	—	—	—	—	37·7
,,	$C_{18}H_{19}N_2Br,C_2H_2O_4$	55·3	4·7	—	—	—	55·4	4·8	—	—	—
X*m*	$C_{19}H_{22}ON_2,C_2H_2O_4$	65·5	6·1	7·4	—	—	65·6	6·3	7·3	—	—
XI*m*	,,	66·1	6·5	7·4	—	—	,,	,,	,,	—	—
X*n*	$C_{16}H_{17}N_2ClS,C_2H_2O_4$	54·7	4·7	7·2	9·3	8·0	54·7	4·8	7·1	9·0	8·1
XI*n*	,,	—	—	7·1	9·3	8·5	—	—	7·1	9·0	8·1

[a] Examples *a*—*i* correspond to examples *a*—*i* of Part III,[1] Table 3.

[b] A, Fractional crystallisation of oxalates from ethanol. B, Base exchange chromatography. C, Chromatography on alumina. D, Preferential destruction of *cis*-isomer by treatment with acetic anhydride. E, Dehydration by hot sulphuric acid to give pure *trans*-isomer. F, Crystallisation of solid base.

[c] Solvent ethanol except when otherwise indicated. [d] All with decomp. except those marked *. [e] Solvent chloroform, followed by ethanol. [f] Solvent methanol. [g] Solvent ethyl acetate. [h] Solvent ethanol–ethyl acetate. [i] Solvent light petroleum (b. p. 40—60°). [j] Solvent methanol–ethanol. [k] Replaces the group R^1Ph. [l] In ethanol, except where indicated by ‡ when the solvent is water.

11·5%). Light absorption in 4×10^{-4}M-solution in EtOH: max. 255 mμ (log ε 4·35); in 4×10^{-5}M-solution in 5·5M-HCl: max. 249 mμ (log ε 4·15).

(b) *By alumina chromatography of bases* (*Table* 3, *method* C). The mixture of bases (10 g.), dissolved in light petroleum (b. p. 40—60°; 100 ml.), was adsorbed on alumina (400 g.; column 5 cm. in diam.) and eluted with benzene, the eluate being collected in 2-l. portions. The progress of the separation was followed by absorption spectrum and m. p. of the oxalate of the separate portions. From the head fractions (1—3) was obtained pure *cis*-isomer oxalate (1·3 g.). After elution with 20 l. of benzene, the column was stripped with chloroform to give base (4·2 g.) from which, after two crystallisations, pure *trans*-isomer oxalate (2·3 g.) was obtained.

Oxidation of cis- *and* trans-1-p-*Chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene*.—(i) *cis*-Isomer oxalate (5 g.), in glacial acetic acid (150 ml.), was added to a mixture of chromium trioxide (36 g.), water (25 ml.), and glacial acetic acid (240 ml.), and the whole heated on the steam-bath for 5 min. The mixture was poured on ice, basified with ammonia, and extracted thrice with ether. Evaporation of the ether gave a colourless solid (2·7 g., 96%). Crystallisation from light petroleum (b. p. 40—60°) gave 2-p-*chlorobenzoylpyridine* (1·9 g., 68%), m. p. 64°

(Found: C, 66·2; H, 3·5; N, 6·6; Cl, 16·6. $C_{12}H_8ONCl$ requires C, 66·2; H, 3·7; N, 6·4; Cl, 16·4%); its p-*nitrophenylhydrazone* formed needles (from ethanol), m. p. 186° (Found: C, 61·5; H, 3·8; Cl, 10·4. $C_{18}H_{13}O_2N_4Cl$ requires C, 61·3; H, 3·7; Cl, 10·1%). This was identical (m. p. and mixed m. p. as base and as *p*-nitrophenylhydrazone) with a synthetic specimen prepared by reaction of pyridyl-lithium with *p*-chlorobenzonitrile.

(ii) Oxidation of *trans*-isomer base (1·0 g.) by the same method gave the same ketone (0·62 g., 85%), m. p. and mixed m. p. 63—64° (*p*-nitrophenylhydrazone, m. p. and mixed m. p. 186°).

(iii) *trans*-Isomer base (4 g.) was dissolved in water (20 ml.) by the dropwise addition of 2N-hydrochloric acid till just acid to Congo-red, and potassium permanganate (4·25 g.) in water (250 ml.) was added with stirring during 1 hr. The mixture was distilled in steam. The ketone solidified in the distillate and after filtration and drying (1·4 g., 48%) had m. p. and mixed m. p. 63°.

(iv) *cis*-Isomer base (4·0 g.), similarly oxidised, gave the ketone (0·9 g., 31%), m. p. and mixed m. p. 63—64°.

Hydrogenation of cis- *and* trans-1-p-*Chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene*.—(i) *trans*-Isomer base (5 g.) in glacial acetic acid (50 ml.) was hydrogenated in the presence of palladium–charcoal (1·0 g.). Absorption (400 ml.) ceased after 48 hr. After filtration and removal of the solvent *in vacuo*, the gummy acetate was converted into base and thence into oxalate (5·6 g., 84%), m. p. 144—145°. After two crystallisations from ethanol the 1-*p*-chlorophenyl-1-2′-pyridyl-3-pyrrolidinopropane oxalate (4·8 g., 72%) had m. p. 146—147° [Part III,[1] (VIII*g*), gives m. p. 148—149°]. The oily base prepared from it had n_D^{19} 1·570.

(ii) *cis*-Isomer base (5 g.), similarly reduced with palladium–charcoal (2 g.), absorbed hydrogen (430 ml.) for 24 hr. The crude oxalate (5·5 g., 82%) had m. p. 143—144°, raised on crystallisation to m. p. 146—147°, unchanged on admixture with previous sample; the base had n_D^{19} 1·570.

1-*Aryl*-1-2′-*pyridyl*-3-(*tertiary amino*)*propan*-1-*ols* (I and XII).—Five alcohols (Table 2) not previously described were prepared by the method give in Part III [1] from the corresponding aryl 2-pyrrolidinoethyl ketones (Table 1).

Dehydration of the Alcohols (I) *to Mixtures of the* trans- *and* cis-1-*Aryl*-1-2′-*pyridyl*-3-(*tertiary amino*)*prop*-1-*enes* (X and XI).—With some exceptions noted below, dehydration of the alcohols (I) to mixtures of the *trans*- and *cis*-allylamines (X and XI) was effected by 5 times the weight of aqueous sulphuric acid (85% v/v) at 100° for 15—20 min. and working up as previously described,[1] except that the oily mixtures of isomeric allylamines were not distilled. Examples (*g*) and (*l*) (Table 3) were similarly prepared by using concentrated sulphuric acid, and examples (*m*) and (*n*) by aqueous sulphuric acid (65% v/v) at 120° and 105° respectively.

Separation of the trans-(X) *and* cis-(XI) *Isomers* (Table 3).—(a) *By fractional crystallisation* (Table 3, method A). Examples (*d*), (*h*), and (*i*) were separated by direct fractional crystallisation of the oxalates from ethanol as described above for example (*g*), the *trans*-isomer being less soluble. The isomers of example (*i*) resembled those of example (*g*) in showing a large difference in solubility and the recovery of separated pure isomers was high. The isomers of examples (*d*) and (*h*) did not differ greatly in solubility, and recovery of separated isomers was low. Examples (*a*) and (*f*) were separated similarly, the *cis*-isomer being the less soluble. Example (*e*) was separated by the following procedure: a cold saturated alcoholic solution of the mixed isomeric oxalates was evaporated to half volume and allowed to cool somewhat. While still warm a crop of plates separated and was filtered off. The filtrate shortly deposited a mass of needles which was collected. The plates were recrystallised to give pure cis-*isomer oxalate*, m. p. 174—175° [base, m. p. 61—62° after crystallisation from light petroleum (b. p. 40—60°)], and the needles to give pure trans-*isomer oxalate*, m. p. 182—183°. Examples (*b*), (*c*), and (*j*) resisted separation by crystallisation.

Crystalline form was a reliable guide to the course of separation in some cases, *e.g.*, the separation of examples (*e*), (*g*), and (*i*), in all of which the *trans*-form crystallised in needles and the *cis*-form in plates, but in other cases was unhelpful or misleading. Many of the isomer oxalates were found to be dimorphous, *e.g.*, (XI*e*) could be obtained at will as needles or plates, depending on whether it was left to crystallise in the presence or absence of a trace of undissolved solid. Separations were more reliably followed by m. p. and ultraviolet spectrum.

(b) *By base-exchange chromatography* (Table 3, method B). Examples (*b*), (*c*), (*g*), (*k*), (*l*), (*m*), and (*n*) were separated on columns of sulphonated polystyrene of low cross-linkage in aqueous ethanol by displacement development using aqueous-ethanolic ammonia.[13]

(c) *By chromatography on alumina* (Table 3, method C). Example (*l*) was separated by this method, as described above for example (*g*), the eluates being light petroleum (b. p. 40—60°), and light petroleum (b. p. 40—60°) containing chloroform in increasing proportion (up to 25% v/v).

Behaviour towards Acetic Anhydride of cis- *and* trans-1-p-*Chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*ene.*—(i) *trans*-Isomer base (1·0 g.) was boiled in acetic anhydride (15 ml.) for ½ hr. The excess of reagent was distilled off *in vacuo*, the oily residue was dissolved in water, the base was liberated with ammonia and taken into ether, and the ether was removed. The oily base (0·8 g.) solidified on seeding and gave oxalate (0·9 g.), m. p. 184°, unchanged on admixture with *trans*-isomer oxalate.

(ii) *cis*-Isomer base (2·0 g.), similarly treated, gave, after removal of the excess of reagent, a viscous dark oil from which pale yellow needles separated. These were filtered off and washed with ether. From the dark filtrate, treated as in (i), no solid oxalate separated or could be isolated by dilution with ether. The yellow needles (0·4 g.) after crystallisation from ethanol gave 3-*acetyl*-1-p-*chlorophenylpyrrocoline* as pale yellow needles, m. p. 173—174°, not depressed on admixture with authentic material prepared as described below [Found: C, 71·4; H, 4·7; N, 5·0; Cl, 13·0; Ac, 15·5%; *M* (Rast), 276. $C_{16}H_{12}ONCl$ requires C, 71·3; H, 4·5; N, 5·2; Cl, 13·2; Ac, 16·0%; *M*, 269·5].

3-*Acetyl*-1-p-*chlorophenylpyrrocoline* (IV).—A mixture of 2-4′-chlorobenzylpyridine [15] (10 g.) and acetic anhydride (60 ml.) was heated (pressure tube) at 280° for 7 hr. The dark crystalline product (9 g.) was filtered from excess of anhydride and distilled. The yellow distillate (b. p. 215—235°/0·1 mm.) solidified and after crystallisation from ethanol gave the compound (IV) (5·2 g.), m. p. 172—173° not depressed on admixture with the sample described above.

Differential Acetic Anhydride Degradation of Mixed Isomers (X) *and* (XI) *with Isolation of* trans-*Isomer* (X) (Table 3, method D).—*Examples*: (i) A mixture of (X*g*) and (XI*g*) oxalates (10 g.) was boiled under reflux with acetic anhydride (160 ml.) for ½ hr. After working up as above, solid oxalate (2·8 g.) was obtained by dilution with ether, and after one crystallisation from ethanol (2·3 g.) had m. p. 184°, unchanged on admixture with (X*g*) oxalate.

(ii) A mixture of (X*c*) and (XI*c*) bases (30 g.) was boiled under reflux with acetic anhydride (150 ml.) for 15 min. and worked up as above. Dilution with ether gave a semisolid oxalate which after two crystallisations from ethanol gave (X*c*) oxalate (7·5 g.), m. p. 164—165°.

(iii) A mixture of (X*b*) and (XI*b*) oxalates (partially separated by crystallisation and having m. p. 135—140°) (2 g.) and acetic anhydride (30 ml.) was treated as above. After crystallisation from ethanol (X*b*) oxalate (1·2 g.), m. p. 130—131°, was obtained.

(iv) A mixture of (X*j*) and (XI*j*) crude bases (4·8 g.) and acetic anhydride (40 ml.) was boiled under reflux for 10 min. and worked up as above. The basic product (2·3 g.) was distilled and the fraction boiling at 134—136°/0·02 mm. (1·5 g.) was converted into the oxalate. Crystallisation from methanol–ethanol gave (X*g*) oxalate (1·0 g.), m. p. 162—163°.

Effect of Temperature and Strength of Sulphuric Acid on the Proportions of cis- *and* trans-*Isomers obtained from* 1-p-*Chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinopropan*-1-*ol.*—*Examples*: (i) The alcohol (10 g.) was dissolved in concentrated sulphuric acid (100 ml.) below 10°. After a further 2 hr. below 10°, the mixture was worked up as described above. The oily base (9·0 g., 95%) did not crystallise on being seeded with *trans*-isomer base, and was converted into crude oxalate (9·8 g., 78%) (m. p. 148—152°), which after numerous crystallisations gave pure *trans*-isomer oxalate (1·7 g., 13·5%), m. p. 184°.

(ii) The alcohol (10 g.) was added during 5 min. to concentrated sulphuric acid (100 ml.) at 200°, and the mixture was held at 200° for a further 5 min. After working up as in (i), solid *trans*-isomer base (9·2 g., 98%), m. p. 55—58°, was obtained, which gave *trans*-isomer oxalate (10·2 g., 81%), m. p. 184°.

(iii) The alcohol (5 g.) was heated similarly with concentrated sulphuric acid (25 ml.) at 250°. On working up as in (i), solid *trans*-isomer base (2·3 g.) was obtained [oxalate (2·2 g., 35%), m. p. 184°].

(iv) *cis*-Isomer base (9 g.) was heated in concentrated sulphuric acid (50 ml.) at 160° for 10 min. After working up as in (i), there was obtained solid *trans*-isomer base (9·0 g.) [oxalate (9·8 g.), m. p. 183—184°].

Numerous similar experiments were carried out for periods of heating of 10 min. and 3 hr.,

[14] Houben-Weyl, "Methoden der Organischen Chemie," 4th edn., 1955, Vol. III, Part 2, p. 667.
[15] Panizzon, *Helv. Chim. Acta*, 1944, **27**, 1748.

the temperature being varied by intervals of 20°, and the strength of the sulphuric acid by 20% decrements. The results are tabulated as the limiting temperatures (with a possible −20° error) above which exclusive formation of *trans*-isomer occurs, the criteria for exclusive formation being (i) the crude base forming a hard solid, and (ii) the crude oxalate having m. p. >180°.

H_2SO_4 (%)	100	80	60
Limiting temp. : 10 min.	160°	180°	200° (superheated)
3 hr.	120°	140°	160°

A second set of experiments defined approximately the time necessary to effect complete conversion into *trans*-isomer in concentrated sulphuric acid at different temperatures.

Temp.	200°	160°	120°	100°	80°
Time of 100% conversion	<2 min.	<10 min.	1 hr.	>3, <6 hr.	>21 hr.

Behaviour of Other Alcohols on Vigorous Sulphuric Acid Treatment (Table 3, method E).—(i) The alcohol (I; $R^1 = H$, $NR^2R^3 = N<[CH_2]_4$) (5 g.) was heated with concentrated sulphuric acid (25 ml.) at 200° for 10 min., poured on ice, and treated with excess of ammonia; no insoluble material separated.

(ii) The alcohol (I; $R^1 = H$, $NR^2R^3 = N<[CH_2]_4$) (2 g.) was heated in concentrated sulphuric acid (10 ml.) at 150° for 5 min. Working up as above gave (X*c*) oxalate (0·5 g.), m. p. and mixed m. p. 163—164°.

(iii) The alcohol (I; $R^1 = Cl$, $NR^2R^3 = NMe_2$) (8·0 g.) was heated with concentrated sulphuric acid (50 ml.) at 180° for 10 min. It gave pure (X*e*) oxalate (6·0 g.), m. p. and mixed m. p. 182—183°.

(iv) The alcohol (I; $R^1 = H$, $NR^2R^3 = NMe_2$) (3 g.), heated with concentrated sulphuric acid (20 ml.) at 140° for 5 min., gave (X*a*) oxalate (1·3 g.), m. p. and mixed m. p. 178—179°.

(v) The alcohol (I; $R^1 = Br$, $NR^2R^3 = N<[CH_2]_4$) (10 g.) was heated in concentrated sulphuric acid (20 ml.) at 185° for 10 min. Working up gave an oil which on crystallisation from light petroleum (b. p. 60—80°) gave the compound (X*l*) (6·5 g.), m. p. 90—91°.

(vi) The alcohol (XII) (2·0 g.) was heated in aqueous sulphuric acid (85% v/v; 6 ml.) on the steam-bath for 6 min. On working up, this gave (X*n*) oxalate (1·1 g.), m. p. 149°.

Geometrical Isomers of 1-p-*Chlorophenyl*-1-*phenyl*-3-*pyrrolidinoprop*-1-*ene*.—1-p-*Chlorophenyl*-1-*phenyl*-3-*pyrrolidinopropan*-1-*ol* (VII) was prepared by the reaction of phenylmagnesium bromide with 4-chloro-β-pyrrolidinopropiophenone [1] and after crystallisation from light petroleum (b. p. 60—80°) had m. p. 118—120° (Found: C, 72·2; H, 7·0; N, 4·3; Cl, 11·2. $C_{19}H_{22}ONCl$ requires C, 72·3; H, 7·0; N, 4·4; Cl, 11·3%). The alcohol (10 g.) was dehydrated by boiling concentrated hydrochloric–glacial acetic acid as described in Part I.[16] The crude hydrochloride obtained on evaporation to dryness crystallised from ethanol–ethyl acetate, then from ethanol, to give that *isomer* (IX) of 1-p-*chlorophenyl*-1-*phenyl*-3-*pyrrolidinoprop*-1-*ene hydrochloride* showing a styrene-like spectrum (Fig. 3) (3·6 g.; m. p. 219—221°) (Found: Cl, 20·9. $C_{19}H_{21}NCl_2$ requires Cl, 21·3%). The ethanol–ethyl acetate filtrate, after concentration, deposited crystals which, after several recrystallisations from ethanol–ethyl acetate, gave that *isomer* (VIII) showing a *p*-chlorostyrene-like spectrum (Fig. 3) [3·0 g.; m. p. 165—167° (decomp.)] (Found: Cl, 21·7%).

The authors thank Mr. P. R. W. Baker and Mr. A. Bennett for the microanalyses.

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[*Received, December 14th*, 1956.]

[16] Adamson, *J.*, 1949, S144.