62. *Aminoalkyl Tertiary Carbinols and Derived Products. Part VII.* A New Synthesis of 1-Arylpyrrocolines.*

By P. A. Barrett.

The 3-(tertiary amino)-1-aryl-1-2′-pyridylalkan-1-ols (I) and (XII) and the 3-(tertiary amino)-1-aryl-1-2′-pyridylalkenes (II) and (XIII) cyclise on treatment with boiling acetic anhydride to the corresponding 1-arylpyrrocolines (III), (V), and (XIV). Under comparable conditions the *cis*-isomers of the alkenes (II) and (XIII) give higher yields of pyrrocoline than the corresponding *trans*-isomers. Simultaneously with cyclisation, the alkanols and alkenes undergo alternative degradations analogous to those suffered by the corresponding diphenyl-alkanols and -alkenes on treatment with acetic anhydride.

In Part V [1] it was shown that *cis*-1-*p*-chlorophenyl-1-2′-pyridyl-3-pyrrolidinoprop-1-ene † (*cis*-II*b*) was cyclised by acetic anhydride, with loss of the pyrrolidino-group, to 3-acetyl-1-*p*-chlorophenylpyrrocoline (III*b*), under conditions which gave none from the *trans*-isomer (*trans*-II*b*).

As mentioned in Part VI,[2] it has now been found that by using different experimental conditions the yield of acetylpyrrocoline (III*b*) from the *cis*-alkenylamine (II*b*) is greatly increased, and under these conditions the same pyrrocoline is obtained, though in lower yield, from the *trans*-isomer. This cyclisation is general. The alkenylamines [1,2] (II*a*—*i*) all gave pyrrocolines (III) or (V), and where both configurations have been examined a higher yield was obtained from the *cis*- than from the *trans*-isomers. From any alkenylamine (II) in which R^3 is methyl or phenyl, the product of cyclisation is the corresponding 3-methyl- or 3-phenyl-pyrrocoline (V*g*, *h*, and *i*). Thus, the alkenylamine (II*h*) on cyclisation gave 1-*p*-chlorophenyl-3-methylpyrrocoline (V*h*), whose constitution was confirmed by its identity with a sample prepared by the Scholtz–Chichibabin reaction [3,4] from 2-4′-chlorobenzylpyridine and propionic anhydride. From any alkenylamine (II) in which R^3 is hydrogen, the product of cyclisation is the corresponding 3-acetylpyrrocoline (III), formed by the acetylation, by the excess acetic anhydride always present, of the reactive 3-position of the pyrrocoline (V; $R^3 = H$), for the presence of which, as an intermediate in the reaction, evidence is adduced below. The invariable survival of the alkenylamine substituents R^2 and R^3, when these are methyl or phenyl, in the resultant pyrrocoline proves that it is the carbon atoms of the alkenylamine chain which compose the five-membered ring of the pyrrocoline, and that the latter is not derived from a molecule of acetic anhydride by reaction with a breakdown fragment of alkenylamine by a Scholtz–Chichibabin [3,4] type of reaction.

It has further been shown that the alcohols (I) also cyclise to the corresponding pyrrocolines on treatment with acetic anhydride, and evidence will be presented to show that the cyclisation of the alcohols (I) does not proceed through the alkenylamines (II).

The present paper deals with these reactions as new preparative routes to substituted pyrrocolines. The results as they are relevant to the stereochemistry of the alkenylamine isomers *cis*-(II) and *trans*-(II), were discussed in Part VI. The constitution of 3-acetyl-1-*p*-chlorophenylpyrrocoline (III*b*) was rigorously established earlier,[1] and that of 1-*p*-chlorophenyl-3-methylpyrrocoline (V*h*) is established above. The constitution of the other pyrrocolines is confirmed by their similar, highly characteristic ultraviolet absorption.

Reaction of the Alcohols (I) *with Acetic Anhydride.*—This reaction is complex and

* Part VI, preceding paper.

† As in earlier papers, *cis* and *trans* refer to the relation of the pyridyl and the aminoalkyl group.

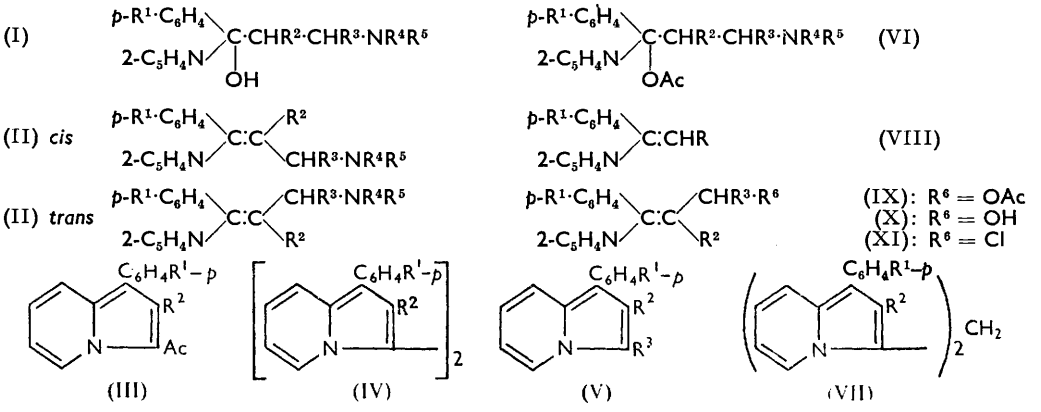
[1] Adamson, Barrett, Billinghurst, and Jones, *J.*, 1957, 2315.

[2] *Idem*, preceding paper.

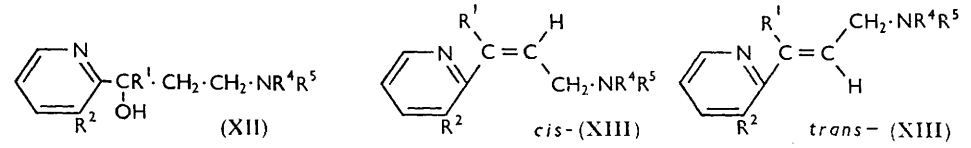
[3] Chichibabin and Stepanow, *Ber.*, 1929, **62**, 1068.

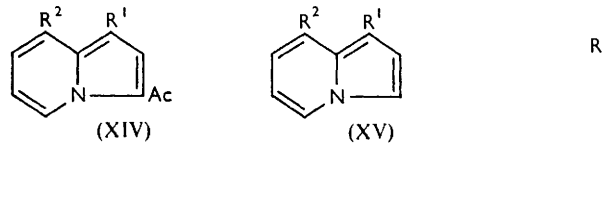
[4] Scholtz, *Ber.*, 1912, **45**, 734.

follows at least two paths. The alcohol (I*b*) is rapidly esterified to (VI*b*), which is intermediate in the rather slow reactions which occur on further boiling. After 3 hours' boiling some acetate (VI*b*) was recovered, but after 16 hours reaction was complete. In addition to the pyrrocoline (III*b*), there were isolated the dipyrrocolylmethane derivative (VII*b*) and the *p*-chlorophenylpyridylethylene (VIII*b*). It is apparent that the alcohol undergoes simultaneously both (i) ring closure to the pyrrocoline (V*b*), most of which is rapidly acetylated to (III*b*), and (ii) a degradation involving cleavage of the carbon chain similar



Compounds I—IX	R^1	R^2	R^3	R^4R^5
a	H	H	H	$<[CH_2]_4$
b	Cl	H	H	,,
c	H	Me	H	$<[CH_2]_5$
d	Cl	Me	H	,,
e	H	Ph	H	,,
f	Cl	Ph	H	$<[CH_2]_5$
g	H	H	Me	,,
h	Cl	H	Me	$<[CH_2]_4$
i	H	H	Ph	$<[CH_2]_5$





Compounds XII—XV	R^1	R^2	R^4R^5
a	*p*-MeO·C_6H_4	H	$<[CH_2]_4$
b	*p*-C_6H_4Me	H	,,
c	*o*-C_6H_4Me	H	,,
d	Ph	Me	,,
e	*p*-C_6H_4Cl	Me	$<[CH_2]_4$
f	5-Chloro-2-thienyl	H	,,
g	2-Pyridyl	H	Me_2

to that shown by Adamson [5] to occur with analogous diphenylpropanols. Degradation of the alcohol (I*b*) by the second route leads to *p*-chlorophenylpyridylethylene (VIII*b*), acetylpyrrolidine, and formaldehyde. The dipyrrocolylmethane (VII*b*) is clearly formed by condensation of the formaldehyde (produced by this second reaction) with pyrrocoline (V*b*) (simultaneously under production by the ring closure). Analogous products have

[5] Adamson, *Nature*, 1949, **164**, 500.

been isolated from several of the other examples examined. The reaction pattern is thus general, though the proportion of alcohol reacting by one or the other route varies considerably in examples containing different groups R^1, R^2, and R^3. Thus, the alcohol (I*i*) gave 60% of the pyrrocoline (V*i*) whereas the alcohol (I*g*) gave only 5% of the pyrrocoline (V*g*) and 60% of the phenylpyridylethylene (VIII*g*). The evidence available suggests that within the limited range ($NR^4R^5 = N < [CH_2]_4$, $N < [CH_2]_5$, or NMe_2) the nature of the amino-group used in conjunction with any given substituents R^1, R^2, and R^3 does not affect the course of the reaction. The course of the reaction was not markedly affected by addition of acetic acid or sodium acetate.

Reaction of the Alkenylamines (II) *with Acetic Anhydride.*—The yield of pyrrocoline (III) or (V) from the alkenylamines (II) is however very dependent on the experimental conditions. Ring closure by the method described in Part V gave *ca.* 10% of the pyrrocoline (III*b*) from the *cis*-allylamine (II*b*), and no isolable pyrrocoline from the *trans*-isomer. By the addition of acetic acid and anhydrous sodium acetate to the acetic anhydride, and employing slow addition (1½—2 hours) of the *cis*-allylamine (II*b*) to the reaction mixture the yield of (III*b*) was raised to *ca.* 50% and the production of tar substantially reduced. Under these conditions the *trans*-isomer (II*b*) gave (III*b*), but in consistently lower yield (*ca.* 25%). These preferred conditions were used for all subsequent examples. The yields of pyrrocoline obtained from the *cis*-alkenylamines in different examples were in the range of 25—50%.

As with the alcohols, the reaction of the alkenylamines (II) with acetic anhydride is complex, and a variety of products in addition to the pyrrocolines (III) or (V) has been isolated. Some of them occur only in isolated examples and are discussed below. A more general phenomenon is the formation of the acetoxy-compounds (IX). From all those alkenylamines where it has been sought (II*a*—*g*, *i*), evidence of their production was found. They are end-products, unchanged on further treatment with acetic anhydride. The esters (IX*c*, *e*, *f*) were isolated as crystalline solids; (IX*b*, *d*) were characterised by hydrolysis to the corresponding solid alkenols (X*b*, *d*). [The acetoxy-compound (IX*d*) was hydrolysed to the alkenol (X*d*) by boiling aqueous-alcoholic potassium hydroxide. Boiling concentrated hydrochloric acid converted the ester into the corresponding chloro-compound (XI*d*).] In the products of some cyclisations the acetoxy-compounds (IX) were accompanied by the corresponding alkenols (X*b*, *d*, *e*, *f*), the latter probably derived from the former during working up, since the acetoxy-compounds (IX) are very rapidly hydrolysed by 2N-hydrochloric acid. In four examples (II*b*, *c*, *d*, *e*) in which the acetoxy-compound was isolated from both separated isomers of the alkenylamine, that from the *trans*-isomer was identical with, and was obtained in higher yield than, that from the *cis*-isomer. Three of these examples were of the 2-substituted type (II; R^2 = Me or Ph) for which the absorption spectra are not diagnostic [2] of the stereochemical configuration, but in the fourth the absorption spectra showed that the single acetoxy-compound (IX*b*) formed both from *cis*- and *trans*-alkenylamines (II*b*), has the *trans*-configuration, and on hydrolysis gave the *trans*-alkenol (X*b*). It appears probable that all acetoxy-compounds (IX) and alkenols (X) isolated from the reactions have the *trans*-configuration.

The formation of both pyrrocoline (III) and *trans*-acetoxy-compound (IX) from both isomers, a higher proportion of the former from the *cis*-alkenylamine and of the latter from the *trans*-alkenylamine, is interpreted in terms of a fundamentally sharp distinction between the reactions undergone by the two forms, the *cis*-compound giving only pyrrocoline and the *trans*-isomer only *trans*-acetoxy-compound, confused by a slow isomerisation of each isomer to the other during the reaction. This sharp distinction has been realised in some pairs of alcohols, to be described in Part VIII, geometrically isomeric with respect to a *cyclo*alkane ring, in which the possibility of isomerisation is excluded.

Adamson [5] showed that 3-(tertiary amino)-1 : 1-diphenylprop-1-enes, when boiled with acetic anhydride, gave high yields of acetoxy-compounds analogous to those (IX) of the present series. The alcohols (I) and the alkenylamines (II) thus react with acetic

TABLE 1. 1-*Substituted* 3-*acetylpyrrocolines* (III) *and* (XIV) (*italicised wavelengths indicate inflections*).

				Absorption max. in EtOH											
				λ (mμ)						$10^{-3}\varepsilon$					
Compound	R^1	R^2	M. p.												
III*a*	H	H	82—83°	235	*248*	267	*285*	370	—	14	14·8	30	17·5	15	—
III*b*	Cl	H	173—174	220	—	265	285	369	—	18	—	26	18	15	—
III*c*	H	CH_3	127—128	225	*258*	274	—	355	373	13	16	23	—	8·9	12
III*d*	Cl	CH_3	154	225	245	273	—	363	377	21·2	15·2	25·5	—	14·5	12·2
III*e*	H	Ph	175—176	—	*247*	270	—	373	—	—	20	25	—	13	—
III*f*	Cl	Ph	181—182	*225*	—	267	—	371	—	20	—	24	—	12·5	—
XIV*a*	*p*-MeO·C_6H_4	H	122	239	—	272	—	366	—	18·5	—	34·5	—	13·7	—
XIV*b*	*p*-C_6H_4Me	H	133	*236*	—	269	—	373	—	14·5	—	30·5	—	14	—
XIV*c*	*o*-C_6H_4Me	H	65	*220*	—	266	—	367	*385*	12	—	20·5	—	9·6	7·5
XIV*d*	Ph	Me	100—101	224	*250*	270	—	365	—	14·5	13·9	24·2	—	14·5	—
XIV*e*	*p*-C_6H_4Cl	Me	112—113	223	—	264	—	370	—	22	—	28	—	15·2	—
XIV*f*	*	H	119	226	—	265	308	361	—	20	—	17·9	14·3	14·7	—
XIV*g*	2-Pyridyl	H	112	—	*248*	263	309	360 [a]	—	—	14·9	22·1	14·9	16·8	—

[a] Broad band. * 5-Chloro-2-thienyl.

		Found (%)				Required (%)			
Compound	Formula	C	H	N	Cl	C	H	N	Cl
III*a*	$C_{16}H_{13}ON$	81·1	5·3	6·0	—	81·7	5·6	6·0	—
III*b*	$C_{16}H_{12}ONCl$	71·4	4·8	4·9	13·0	71·2	4·5	5·2	13·2
III*c*	$C_{17}H_{15}ON$	81·6	6·0	5·6	—	81·9	6·0	5·6	—
III*d*	$C_{17}H_{14}ONCl$	72·2	5·2	5·1	12·1	71·9	4·9	4·9	12·5
III*e*	$C_{22}H_{17}ON$	84·9	5·5	4·8	—	84·9	5·5	4·5	—
III*f*	$C_{22}H_{16}ONCl$	76·6	4·3	4·0	10·3	76·5	4·6	4·1	10·3
XIV*a*	$C_{17}H_{15}O_2N$	76·9	5·6	5·2	—	77·0	5·7	5·3	—
XIV*b*	$C_{17}H_{15}ON$	82·0	6·0	5·5	—	81·9	6·0	5·6	—
XIV*c*	$C_{17}H_{15}ON$	82·4	6·2	6·1	—	81·9	6·0	5·6	—
XIV*d*	$C_{17}H_{15}ON$	81·8	5·6	6·1	—	81·9	6·0	5·6	—
XIV*e*	$C_{17}H_{14}ONCl$	72·1	5·0	5·0	12·5	71·9	4·9	4·9	12·5
XIV*f*	$C_{14}H_{10}ONClS$	61·0	3·5	11·5 [b]	13·2	61·0	3·6	11·6 [b]	12·9
XIV*g*	$C_{13}H_{12}ON_2$	76·3	5·3	11·7	—	76·3	5·1	11·9	—

[b] Sulphur analysis.

TABLE 2. 1-*Substituted pyrrocolines* (V) *and* (XV).

					Absorption max. in EtOH											
					λ (mμ)						$10^{-3}\varepsilon$					
Compound	R^1	R^2	R^3	M. p. (b.p./mm.)												
V*a*	H	H	H	67—68° [a]	236	—	*283*	305	—	362	23	—	8·6	12	—	3·4
V*b*	Cl	H	H	73 [a]	239	—	—	313	—	360	32	—	—	15	—	6
V*c*	H	Me	H	140—145/0·5	242	—	284	310	—	347	24	—	7·4	7·8	—	2·9
V*d*	Cl	Me	H	77 [a,b]	242	—	*285*	315	—	360	25	—	6·8	11	—	4·5
V*e*	H	Ph	H	112 [a]	250	264	—	305	—	360	32	24·5	—	9·2	—	5·6
V*f*	Cl	Ph	H	118 [b]	248	273	—	307	—	357	38	25	—	11·6	—	5·1
V*g*	H	H	Me	67—68 [a]	239	—	*280*	312	*355*	373	32	—	6	12	4·1	4·5
V*h*	Cl	H	Me	91—92 [a]	243	—	277	320	—	385	20	—	4·9	13	—	4·8
V*i*	H	H	Ph	115—116 [b]	238	—	274	309	*345*	*336*	28	—	20	19·5	10	4
XV*a*	*	H	—	72—73 [a,c]	240	—	277	305	—	367	25·6	—	10·5	12·4	—	4·25
XV*d*	Ph	Me	—	155—160/0·5	235	—	—	303	—	350	28	—	—	8·3	—	3·8

[a] From light petroleum (b. p. 40—60°). [b] From ethanol. [c] From light petroleum (b. p. 60—80°). * *p*-MeO·C_6H_4.

TABLE 2. (*Continued.*)

Compound	Formula	Found (%) C	H	N	Cl	Required (%) C	H	N	Cl
V*a*	$C_{14}H_{11}N$	87·1	5·6	7·4	—	87·0	5·7	7·3	—
V*b*	$C_{14}H_{10}NCl$	73·9	4·5	6·1	15·3	73·8	4·4	6·2	15·6
V*c*	$C_{15}H_{13}N$ [d]	87·1	6·3	—	—	86·9	6·3	6·8	—
V*d*	$C_{15}H_{12}NCl$	74·7	5·3	6·1	14·2	74·6	5·0	5·8	14·7
V*e*	$C_{20}H_{15}N$	89·2	5·7	5·5	—	89·2	5·6	5·2	—
V*f*	$C_{20}H_{14}NCl$	78·7	4·9	4·7	11·6	79·1	4·6	4·6	11·7
V*g*	$C_{15}H_{13}N$	87·0	6·4	6·5	—	86·9	6·3	6·8	—
V*h*	$C_{15}H_{12}NCl$	74·6	4·9	5·9	14·3	74·6	5·0	5·8	14·7
V*i*	$C_{20}H_{15}N$	89·7	5·7	5·2	—	89·2	5·6	5·2	—
XV*a*	$C_{15}H_{13}ON$	80·7	5·8	6·5	—	80·7	5·9	6·3	—
XV*d*	$C_{15}H_{13}N$	87·0	6·4	7·0	—	86·9	6·3	6·8	—

[d] Chichibabin, *Ber.*, 1927, **60**, 1607.

anhydride in different ways, the ring closure to pyrrocoline, necessarily confined to compounds containing a pyridyl group, occurring simultaneously with more general methods of decomposition characteristic of the corresponding diphenyl-propanols and -alkenylamines. As no *trans*-acetoxy-compound (IX) could be found among the products from the alcohols (I) and acetic anhydride, it is concluded that this reaction does not involve initial dehydration to the alkenylamines (II).

Some Extensions of the Reaction.—A number of pyrrocolines have been prepared which extend the scope of the reaction described above. Three examples (XIV*a*, *b*, and *c*) containing substituted phenyl groups were prepared from the alcohols (XII) and the corresponding alkenylamines (XIII). Two 8-methylpyrrocolines (XIV*d* and *e*) were prepared from the picolylalkenylamines (XIII*d* and *e*). Pyrrocolines (XIV*c* and *e*) were prepared from each of the pure isomeric alkenylamines, the difference between the *cis*- and the *trans*-isomers being sharper than in earlier examples: the *cis*-isomers gave high yields of pyrrocoline, the *trans*-isomers gave none. It may be significant that both structures contain [2] highly hindering methyl groups. Two examples of pyrrocolines carrying heterocyclic substituents in the 1-position have also been prepared, (XIV*f*) from the alkenylamine, and (XIV*g*) from the alcohol (the corresponding alkenylamine is unknown). Earlier attempts [6] to dehydrate dipyridyl-alcohols were unsuccessful.

Other By-products of the Alkenylamine Cyclisations.—The acetylpyrrocolines (III*a* and *b*, and XIV*a*) were accompanied by smaller amounts of compounds which on the basis of analysis and ultraviolet spectra are believed to be the dipyrrocolyl compounds (IV*a*; IV*b*; and IV, R^1 = OMe, R^2 = H). The ultraviolet spectra show maxima corresponding in wavelength to those of the 1-arylpyrrocolines (V*a*; V*b*; and XV*a*) but with increased intensity. The dipyrrocolyls (IV*a* and *b*) have also been obtained from the hydrobromides of the alkenylamines (II*a* and *b*) by reaction with hot quinoline. The elements of acetic anhydride do not therefore participate in their formation. Their formulation as dipyrrocolyls appears certain, and it is more probable on mechanistic grounds that union should be in the 3- than in the 2-position.

Accompanying the 3-acetyl-1-*o*-tolylpyrrocoline (XIV*c*) in the cyclisation of the *cis*-alkenylamine (XIII*c*), and constituting the sole product from the *trans*-isomer, was a colourless basic compound (Q). An analogous compound (P) accompanied the acetoxy-compound (IX*b*) in the product of cyclisation of the *trans*-alkenylamine (II*b*), and was separated from it by base-exchange chromatography controlled by the absorption spectra of the fractions. Analysis suggested that both compounds were isomeric with the corresponding acetylpyrrocolines. In each, the single oxygen atom was not determinable as acetyl, and microreduction showed the presence of a double bond. The ultraviolet absorption spectra of compounds (P) and (Q) were almost identical and highly characteristic, each showing double peaks at 258 and 266 mμ (ε 4600), and at 320 and 330 mμ (ε *ca.* 300).

[6] Adamson and Billinghurst, *J.*, 1950, 1039.

The former peak so closely resembles the absorption of the corresponding alcohols, *e.g.*, (I*b*), and alkanes, as to exclude both the presence of αβ-unsaturation and the possibility that the compounds might be the appropriately substituted 1- or 3-2′-pyridylindenes. 3-2′-Pyridylindene has been prepared and shows a spectrum very similar to 2-vinylpyridine.[1] Indene shows [7] absorption closely resembling that of styrene, and 1-2′-pyridylindene would be unlikely to absorb less strongly. Chromic acid oxidation of compound (P) gave a compound which is probably α-*p*-chlorophenyl-α-2-pyridylacetic acid. Taken in conjunction with the spectral evidence, this supports the formulation of compounds (P) and (Q) as the substituted 1-phenyl-1-2′-pyridylpent-2-en-4-ones (XVI) and (XVII), though the analytical figures agree better with empirical formulæ containing two hydrogen atoms less, and final proof of structure is lacking. The ultraviolet absorption at 320—330 mμ is not only too intense to be referred to the crotonyl ketone chromophore, but the intensity is unaffected (though there is some alteration in $\lambda_{max.}$) on reduction of the ethylenic bond. My colleague, Dr. A. J. Everett, suggests that since the carbonyl frequency is normal (at 1700 cm.$^{-1}$) an interaction between the carbonyl-carbon atom and the pyridyl-nitrogen atom is responsible for the 320—330 mμ absorption.

From the ring closure of the γ-phenylalkenylamine (II*i*) there was isolated, in addition to 1 : 3-diphenylpyrrocoline (V*i*), a colourless, basic, unidentified isomer of the alkenylamine (II*i*). Its ultraviolet absorption spectrum was almost the same as that of the parent alcohol (I*i*). It does not, therefore retain the αβ-double bond of the alkenylamine (II*i*).

Hydrolysis of the Acetylpyrrocolines.—In many cases the 3-acetylpyrrocolines (III) and (XIV) have been hydrolysed to the parent pyrrocolines (V) and (XV) (Table 2), generally in high yield, by 5—10 minutes' boiling with concentrated hydrochloric acid. In a few cases (*e.g.*, III*b*) long boiling (1 hr.) was necessary to dissolve the sparingly soluble acetylpyrrocoline hydrochloride. The ultraviolet spectra of all the acetylpyrrocolines (III) and (XIV) (Table 1) are broadly similar, and differ sharply from those of the non-acetylated pyrrocolines (V) and (XV) (Table 2) which are again closely related. In both groups the similarity of the spectra confirms the constitutions.

Experimental

Italicised wavelengths represent inflections.

3-*Acetyl*-1-p-*Chlorophenylpyrrocoline* (III*b*).—(a) *From the alcohol.* (i) The alcohol [6] (I*b*) (30 g.) and acetic anhydride (300 ml.) were boiled under reflux for 3 hr. Excess of anhydride was removed *in vacuo* and the residue treated with water (1 l.). The sticky solid (A) was filtered off and washed with water. The filtrate was basified with ammonia. The oil was isolated with ether, and solidified (13 g.). Recrystallisation from light petroleum (b. p. 40—60°) gave 1-p-*chlorophenyl*-1-2′-*pyridyl*-3-*pyrrolidinoprop*-1-*yl acetate* (VI*b*), m. p. 82—83° (Found: C, 66·8; H, 6·4; N, 7·7; Cl, 9·9; Ac, 12·2. $C_{20}H_{23}O_2N_2Cl$ requires C, 66·9; H, 6·4; N, 7·8; Cl, 9·9; Ac, 12·0%), $\lambda_{max.}$ 225, 255, and 262 mμ (ε 12,800, 3900, 4200 in EtOH). The material (A) was washed with ether, which removed dark oil and left friable solid (B). The ether filtrate was extracted twice with 2N-hydrochloric acid. The aqueous layer was basified with ammonia, and the oil (2·0 g.) isolated with ether and converted into hydrochloride (by ethereal hydrogen chloride) which solidified when seeded and on crystallisation from a small volume of ethanol gave 1-*p*-chlorophenyl-1-2′-pyridylethylene hydrochloride (VIII*b*) (0·5 g.), m. p. 195—197°, unchanged on admixture with an authentic specimen [2] (Found: C, 62·2; H, 4·2; N, 5·4; Cl, 27·8. Calc. for $C_{13}H_{11}NCl_2$: C, 61·9; H, 4·4; N, 5·6; Cl, 28·2%). The solid (B) was boiled with ethanol [420 ml.; sufficient to dissolve the material had it all been (III*b*)] and filtered from undissolved solid (C). The filtrate deposited 3-acetyl-1-*p*-chlorophenylpyrrocoline [1] (III*b*) (4·7 g.), m. p. 173—174°. The solid (C) (1·7 g.), on recrystallisation from pyridine, gave *di*-(1-p-*chlorophenyl*-3-*pyrrocolyl*)*methane* (VII*b*) as straw-coloured needles, m. p. 255°,

[7] Morton and de Gouveia, *J.*, 1934, 911.

unchanged on admixture with an authentic specimen from 1-*p*-chlorophenylpyrrocoline (V*b*) and formaldehyde prepared earlier by my colleague, Dr. N. Whittaker (Found: C, 74·2; H, 3·9; N, 6·0; Cl, 15·1. $C_{29}H_{20}N_2Cl_2$ requires C, 74·5; H, 4·3; N, 6·0; Cl, 15·2%).

(ii) The alcohol (20 g.) and acetic anhydride (400 ml.) were boiled for 16 hr. and worked up as in (i). The aqueous layer gave, on basification, only 1·0 g. of brown oil which did not solidify on being seeded with the acetate (VI*b*). The ether-insoluble solid, on crystallisation, gave acetylpyrrocoline (III*b*) (9·1 g., 50%) and dipyrrocolylmethane (VII*b*) (0·9 g.).

(iii) The alcohol (5 g.) and acetic anhydride (25 ml.) were heated till just boiling and excess of anhydride immediately removed *in vacuo*. Working up as in (i) gave the acetate (VI*b*) (4·2 g.), m. p. and mixed m. p. 82—83°.

(b) *From the alkenylamine.* The alkenylamine (II*b*) used in the following experiments (i)—(vi) was prepared by dehydration of the alcohol (I*b*) in concentrated sulphuric acid at 0—10° for 2 hr. Such material has been shown [1] to be predominantly *cis*-isomer.

(i) Acetic anhydride (250 ml.), acetic acid (150 ml.), and sodium acetate (freshly fused and ground; 250 g.) were boiled under reflux (oil-bath), alkenylamine (II*b*) (25 g.) in acetic acid (100 ml.) was added during 1½ hr., and the mixture boiled for a further 1½ hr. The solvent was removed *in vacuo* and the residue treated with water (2 l.). After being kept overnight, the sticky black solid was filtered off and washed with water, then ether (60 ml. in portions) which removed much dark oil and left friable greyish-yellow material (14·8 g.). One crystallisation from ethanol (900 ml.) [with filtration from material (A)] gave acetylpyrrocoline (III*b*), pale yellow needles (12·0 g., 53%), m. p. 173—174°, raised on further crystallisation to 175—176°. Two similar experiments gave yields of 52% and 54%. The insoluble material (A) (0·9 g.) was crystallised from pyridine, to give *di*-(1-p-*chlorophenyl*-3-*pyrrocolyl*), deep yellow needles, m. p. 288—290° (Found: C, 74·2; H, 3·9; N, 6·3; Cl, 15·7. $C_{28}H_{18}N_2Cl_2$ requires C, 74·1; H, 4·0; N, 6·2; Cl, 15·7%), $\lambda_{max.}$ 238, 315, and 375 mμ (ε 35,000, 36,500, and 10,000 in dioxan).

(ii) Omitting the sodium acetate, (iii) reducing or (iv) omitting the acetic acid and (v) adding the alkenylamine all at once reduced the yields of acetylpyrrocoline to (ii) 35%, (iii) 44%, (iv) 33%, and (v) 45%.

(vi) Isolation of by-products. Alkenylamine (II*b*) (100 g.) was cyclised as described under (i). After the addition of water (2 l.) the sticky solid (A) was filtered off and washed with water. The aqueous layer was basified with ammonia and extracted with ether, to give oil (B) (9·0 g.). The solid (A) was washed with ether (180 ml. in portions), and on crystallisation from ethanol gave acetylpyrrocoline (III*b*) (47·8 g.: m. p. 170—172°). The ether washings gave black oil (31 g.) which was extracted with boiling light petroleum (b. p. 60—80°) (3 × 400 ml.) with filtration from tar. The combined light petroleum extracts on evaporation gave a light brown oil (24 g.). This was dissolved in ether and extracted with successive 100 ml. portions of 2N-hydrochloric acid. The aqueous acid extracts were combined and basified with ammonia, and the oil isolated with ether, combined with (B), and distilled, to give a colourless oil (15·9 g.), b. p. 185—190°/0·2 mm. This oil (8·2 g.) was separated by ion-exchange chromatography, controlled by the ratio of the optical densities at 265 mμ and 282 mμ (referred to below as O.D.R.). The material eluted first, having O.D.R. 10, gave on distillation a *compound* (P) (2·1 g.) as a viscous, amber oil, b. p. 175—180°/0·1 mm. (Found: C, 71·3; H, 4·2; N, 5·2; Cl, 12·6; Ac, 1·4%; microreduction, 1·04 double bonds, calculated on *M* 270. $C_{16}H_{12}ONCl$ requires C, 71·3; H, 4·5; N, 5·2; Cl, 13·2%), $\lambda_{max.}$ 223, 257, 263, 315, and 320 mμ (ε 17,600, 4600, 4650, 300, and 260 in EtOH) [cf. the acetate (VI*b*) above]. The material eluted next (O.D.R. 1) was distilled, to give an oil (2·4 g.), b. p. 200—205°/0·1 mm. (Found: Ac, 11·3. $C_{16}H_{14}O_2NCl$ requires Ac, 15·0%), presumed from the acetyl determination to contain a substantial proportion of the acetoxy-compound (IX*b*), probably associated with some propenol (X*b*) (see below). It was hydrolysed for 2 hr. with 2N-hydrochloric acid (50 ml.) at 100°. Basification gave an oil which solidified and was filtered off, washed, dried, and recrystallised from ethanol and then from light petroleum (b. p. 80—100°), to give trans-3-p-*chlorophenyl*-3-2′-*pyridylprop*-2-*en*-1-*ol* (X*b*) as colourless plates (1·8 g.), m. p. 98° (Found: C, 68·8; H, 5·0; N, 5·9; Cl, 14·5. $C_{14}H_{12}ONCl$ requires C, 68·4; H, 4·9; N, 5·7; Cl, 14·5%), $\lambda_{max.}$ 235 and 277 mμ (ε 17,000 and 6500 in EtOH).

In a cyclisation of alkenylamine (II*b*) (400 g.) worked up similarly, the fraction having O.D.R. 1 deposited crystals when kept for several days. These were filtered off and crystallised to give propenol (X*b*) (6·6 g.), m. p. and mixed m. p. 97—98°.

(vii) Pure *trans*-1-*p*-chlorophenyl-1-2′-pyridyl-3-pyrrolidinoprop-1-ene [1] (II*b*) (44 g.) was treated as in (vi), giving acetylpyrrocoline (III*b*) (10·4 g., 26%), and a basic oil, b. p.

175—180°/0·1 mm. (17·1 g.), 10 g. of which were separated by ion-exchange chromatography into compound (P) (2·5 g.), having O.D.R. 10 (Found: C, 71·0; H, 4·5%), and the *acetoxy-compound* (IX*b*) (3·0 g.) having O.D.R. 1 (Found: Ac, 14·8. $C_{16}H_{14}O_2NCl$ requires Ac, 15·0%), $\lambda_{max.}$ 232 and 272 mμ (ε 18,500 and 6500 in EtOH). This material did not solidify but was hydrolysed, as described in (vi), to propenol (X*b*) (2·1 g.), m. p. 97—98°, not depressed on admixture with the sample described under (viii).

(viii) Pure *cis*-1-*p*-chlorophenyl-1-2′-pyridyl-3-pyrrolidinoprop-1-ene (II*b*) (freed from *trans*-isomer by ion-exchange chromatography as described in Part V [1]) (70 g.) was cyclised and worked up as in (vi), to give acetylpyrrocoline (III*b*) (38·5 g., 61%), m. p. 171—172°, and a basic oil (9·8 g.), b. p. 185—190°/0·2 mm. From the latter by ion-exchange chromatography no material having an O.D.R. of 10 was isolated. The material having O.D.R. 1, after working up and hydrolysis as described in (vi), gave the propenol (X*b*) (1·2 g.), m. p. 97—98°, not depressed on admixture with the sample described under (vii).

Oxidation of Compound (*P*).—The compound (2·0 g.), dissolved in acetic acid (60 ml.), was heated on the steam-bath for 10 min. with chromium trioxide (24 g.) in water (18 ml.) and acetic acid (100 ml.). The mixture was cooled, poured on ice, basified by aqueous sodium hydroxide, and extracted with ether. The aqueous layer was just acidified with hydrochloric acid (litmus). Extraction with ether gave oil which, after addition of a little water to dissolve acetic acid, deposited gum (0·8 g.) which, separated by decantation, crystallised from water to give α-p-*chlorophenyl*-α-2-*pyridylacetic acid*, colourless needles (0·5 g.), m. p. 116—117° (Found: C, 63·5; H, 4·3; N, 5·3; Cl, 13·6. $C_{13}H_{10}O_2NCl$ requires C, 63·0; H, 4·0; N, 5·7; Cl, 14·3%).

3-*Acetyl*-1-*phenylpyrrocoline* (III*a*).—(i) *From the alcohol.* 1-Phenyl-1-2′-pyridyl-3-pyrrolidinopropan-1-ol [6] (I*a*) (8 g.) and acetic anhydride (100 ml.) were boiled for 6 hr. After removal of excess of anhydride and addition of water, the separated oil was taken into ether, and the ether solution was washed with 2N-hydrochloric acid and evaporated to give a brown oil (2 g.), which solidified. Distillation gave a yellow oil, which after crystallisation from light petroleum (b. p. 60—80°) gave acetylpyrrocoline (III*a*) (1·2 g.), m. p. 81—82°, not depressed on admixture with the sample described under (iii).

(ii) 3-Dimethylamino-1-phenyl-1-2′-pyridylpropan-1-ol [6] [as (I*a*) but with $NR^4R^5 = NMe_2$] (5 g.), similarly treated, gave (III*a*) (0·5 g.), m. p. 82—83°.

(iii) *From the alkenylamine.* Alcohol (I*a*) (36 g.) was dehydrated by dissolution in 400 ml. of 85% sulphuric acid at 0° and storage for 4 hr. 1-Phenyl-1-2′-pyridyl-3-pyrrolidinoprop-1-ene (33 g.) was cyclised as described above. Addition of water gave a dark oil, which was extracted with ether. The aqueous layer was basified and the oil (A) isolated with ether. This ether extract was filtered (charcoal) and extracted with 2N-hydrochloric acid (5 × 200 ml.). The combined acid extracts were united and basified, and the oil was collected in ether, united with (A) (total, 10·2 g.), and distilled (b. p. 159—162°/0·2 mm.), to give a colourless mobile oil (7·5 g.) [Found: Ac, 11·8. Calc. for $C_{16}H_{15}O_2N$ (IX*a*): Ac, 17·0%]. This material was presumed to be a mixture, substantially acetoxy-compound (IX*a*), but containing probably propenol (X*a*) and/or the analogue of compound (P). The ether layer was evaporated to a brown oil (20 g.), which rapidly solidified. Distillation (b. p. 194—200°/0·2 mm.) gave 17 g. of a yellow oil which solidified and recrystallised from light petroleum (b. p. 60—80°), to give 3-*acetyl*-1-*phenyl-pyrrocoline* (III*a*) (14 g.), yellow prisms, m. p. 82—83°. The residue in the distillation flask solidified on addition of a few drops of light petroleum. It was lixiviated with a little chloroform, filtered, and recrystallised from light petroleum (b. p. 60—80°) to give *di*-(1-*phenyl*-3-*pyrrocolyl*) (IV*a*) (0·8 g.), deep yellow needles, m. p. 198—200° (Found: C, 87·5; H, 4·7; N, 7·1%; *M*, 386. $C_{28}H_{20}N_2$ requires C, 87·5; H, 5·2; N, 7·3%; *M*, 384), $\lambda_{max.}$ 236, 308, and *358* mμ (ε 37,500, 33,000, and 10,500 in dioxan).

3-*Acetyl*-2-*methyl*-1-*phenylpyrrocoline* (III*c*).—(i) *From the alcohol.* 2-Methyl-1-phenyl-3-piperidino-1-2′-pyridylpropan-1-ol [2] (I*c*) (22 g.) and acetic anhydride (250 ml.) were boiled for 6 hr. After removal of excess of anhydride, addition of water gave a black viscous oil which partly solidified. This was extracted with boiling ether, leaving much black tar undissolved. The residue on evaporation of the ether was similarly extracted successively with light petroleum (b. p. 80—100°) and light petroleum (60—80°), with filtration each time (charcoal) from resin. The solid so obtained was recrystallised several times from light petroleum (b. p. 60—80°), to give acetylpyrrocoline (III*c*) (4·2 g.), m. p. 127—128°.

(ii) *From the alkenylamine.* The alcohol (I*c*) (60 g.) was dehydrated by storage in cold

concentrated sulphuric acid for 2 hr., and the alkenylamine separated [2] *via* the oxalates into pure *trans*-2-methyl-1-phenyl-3-piperidino-1-2′-pyridylprop-1-ene, *trans*-(II*c*), and substantially pure *cis*-(II*c*).

(a) The *trans*-alkenylamine (II*c*) (8·5 g.) was cyclised as described above. Addition of water gave an oil which solidified and was filtered off. The filtrate was basified and the liberated oil (A) isolated with ether. The solid was dissolved in ether, extracted several times with 2N-hydrochloric acid, and recovered as solid (B). The combined acid extracts were basified and the liberated oil was isolated with ether, combined with (A) (total, 5·5 g.) and distilled, the fraction having b. p. 142—150°/0·2 mm. being collected (3·7 g.). This solidified and recrystallised from light petroleum (b. p. 40—60°), to give 2-*methyl*-3-*phenyl*-3-2′-*pyridylallyl acetate* (IX*c*) (2·5 g.), colourless plates, m. p. 64—65°, unchanged on admixture with the sample prepared from the *cis*-isomer (Found: C, 76·1; H, 6·3; N, 5·2; Ac, 16·1. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4; N, 5·2; Ac, 16·1%). The solid (B) on crystallisation from light petroleum (b. p. 60—80°) gave 3-*acetyl*-2-*methyl*-1-*phenylpyrrocoline* (III*c*), large pale-yellow prisms, m. p. 127—128°. The acetate (IX*c*), on hydrolysis with 2N-hydrochloric acid and crystallisation of the crude product from light petroleum (b. p. 80—100°), gave 2-*methyl*-3-*phenyl*-3-2′-*pyridylprop*-2-*en*-1-*ol* (X*c*), colourless needles or jagged prisms, m. p. 120° (Found: C, 80·0; H, 6·6; N, 6·0. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·7; N, 6·2%).

(b) Alkenylamine (II*c*) (substantially *cis*-isomer) (42 g.), cyclised as in (a), gave the acetoxy-compound (IX*c*) (7·8 g.), m. p. 64—65°, unchanged on admixture with the sample prepared from the *trans*-isomer above, and acetylpyrrocoline (III*c*) (26·8 g.), m. p. 127—128°.

3-*Acetyl*-1-p-*chlorophenyl*-2-*methylpyrrocoline* (III*d*).—(i) *From the alcohol.* 1-*p*-Chlorophenyl-2-methyl-3-piperidino-1-2′-pyridylpropan-1-ol [2] (I*d*) (20 g.) and acetic anhydride (400 ml.) were boiled for 16 hr. Removal of excess of anhydride and addition of water gave a black tar (A) which was filtered off. The aqueous filtrate, on basification, gave an oil which was isolated with ether and distilled, to give 1-*p*-chlorophenyl-1-2′-pyridylprop-1-ene [1] (VIII*d*) (3·3 g.), b. p. 120—122°/0·1 mm. (Found: C, 72·5; H, 5·2; Cl, 15·7. Calc. for $C_{14}H_{12}NCl$: C, 73·2; H, 5·2; Cl, 15·5%). The solid (A) was cautiously washed free from black oil with acetone, and the solid residue crystallised from acetone to give acetylpyrrocoline (III*d*) (2·1 g.), m. p. 154°.

(ii) *From the alkenylamine.* The alcohol (I*d*) (88 g.) was dehydrated in concentrated sulphuric acid (500 ml.) for 2 hr. and the 1-*p*-chlorophenyl-2-methyl-3-piperidino-1-2′-pyridylprop-1-ene (II*d*) (85 g.) separated [2] *via* the oxalate into pure *trans*-(II*d*) (20 g.) and substantially pure *cis*-alkenylamines (II*d*) (68 g.). (*a*) The *trans*-isomer (20 g.) was cyclised by the standard method. Addition of water gave a sticky black solid. The aqueous filtrate was basified and the oil (A) (3 g.) isolated with ether. The black solid was washed with ether to give a friable solid (B). The ether filtrate was extracted several times with 2N-hydrochloric acid, the combined extracts were basified, and the separated oil was isolated with ether and freed from resinous material by dissolution in boiling light petroleum (b. p. 60—80°). The petroleum extract was evaporated to an oil (10 g.) which deposited some crystals. Filtration and washing with, followed by crystallisation from, light petroleum (b. p. 60—80°) gave colourless needles of the alkenol (X*d*) (1·3 g.), m. p. 113°, unchanged on admixture with the sample described below (Found: C, 69·1; H, 5·0; N, 5·5; Cl, 13·8%). The filtrate was combined with the oil (A) (total 11 g.) and distilled. The fraction having b. p. 175—180°/0·1 mm. (10 g.) was substantially the *acetoxy-compound* (IX*d*) (Found: Ac, 13·7. $C_{17}H_{16}O_2NCl$ requires Ac, 14·3%). It did not solidify and was hydrolysed by 2 hours' boiling with potassium hydroxide (22 g.) in water (22 ml.) and ethanol (100 ml.). Removal of the ethanol gave a crude solid which when washed and twice crystallised from light petroleum (b. p. 80—100°) gave 3-p-*chlorophenyl*-2-*methyl*-3-2′-*pyridylprop*-2-*en*-1-*ol* (X*d*) (6·5 g.), colourless needles, m. p. 113—114°, unchanged on admixture with the sample prepared from the *cis*-isomer (Found: C, 69·7; H, 5·4; N, 5·4; Cl, 13·7. $C_{15}H_{14}ONCl$ requires C, 69·4; H, 5·4; N, 5·4; Cl, 13·7%). The solid (B) on crystallisation from ethanol gave 3-*acetyl*-1-p-*chlorophenyl*-2-*methylpyrrocoline* (III*d*) (3·2 g.), cream-coloured needles, m. p. 155—156°. (*b*) The *cis*-isomer (68 g.) was cyclised as described above, to give: (i) the alkenol (X*d*) (0·6 g.), m. p. 113°; (ii) an oil, b. p. 180—184°/0·2 mm. (8 g.) (Found: Ac, 11·9%), which on hydrolysis gave the alkenol (X*d*) (3·5 g.), m. p. 113—114°, unchanged on admixture with the sample described above from the *trans*-isomer; and (iii) acetylpyrrocoline (III*d*) (45 g.), m. p. 153—154°, not depressed on admixture with the sample from the *trans*-isomer.

3-*Acetyl*-1 : 2-*diphenylpyrrocoline* (III*e*).—(i) *From the alcohol.* 1 : 2-Diphenyl-3-piperidino-1-2′-pyridylpropan-1-ol [2] (I*e*) (20 g.) and acetic anhydride (200 ml.) were boiled for 4 hr. Removal of acetic anhydride and addition of water gave a solid which was filtered off, washed with water and ethanol, and dried (13 g.). It was boiled with ethanol [520 ml.; sufficient to have dissolved the material had it all been acetylpyrrocoline (III*e*)] and filtered from material (A). The filtrate deposited crystals (10·2 g.) which after one further crystallisation from ethanol (charcoal) gave 3-acetyl-1 : 2-diphenylpyrrocoline (III*e*) (8·0 g.), straw-coloured needles, m. p. 175—176°. The solid (A) (2·5 g.) was recrystallised from acetone to give *di*-(1 : 2-*diphenyl*-3-*pyrrocolyl*)*methane* (VII*e*) (1·8 g.), fine pale needles, m. p. 250° (decomp.) (Found: C, 89·5; H, 5·4; N, 4·9. $C_{41}H_{30}N_2$ requires C, 89·5; H, 5·5; N, 5·1%).

(ii) *From the alkenylamine.* The alcohol (I*e*) (100 g.) was dehydrated in concentrated sulphuric acid (1 l.) at 0—10° for 24 hr. The 1 : 2-diphenyl-3-piperidino-1-2′-pyridylprop-1-ene (II*e*) (92 g.), crystallised from light petroleum (b. p. 40—60°) as described in Part VI,[2] gave a pure solid isomer (II*e*) (52 g.), m. p. 92—94°, and a semi-solid residue of mixed isomers.

(*a*) The solid isomer (II*e*) (50 g.) was cyclised by the standard method. After addition of water, a dark purple solid separated and was filtered off, washed, and dried (A; 45 g.). The aqueous filtrate was basified with ammonia, and the liberated oil isolated in ether. Evaporation of the ether gave oil (2·2 g.) which rapidly solidified. Crystallisation from light petroleum (b. p. 40—60°) gave two kinds of crystal. By repeated crystallisation (seeding in two places with the two sorts of crystal), separation of the deposited crystals by hand-picking, and recrystallisation of the separated fractions, were obtained a somewhat impure specimen of the acetoxy-compound (IX*e*) described below, compact prisms, m. p. 110—112°, and recovered alkenylamine (II*e*), rosettes of pointed prisms, m. p. and mixed m. p. 92—94° (Found: C, 84·7; H, 7·3; N, 7·7. Calc. for $C_{25}H_{26}N_2$: C, 84·7; H, 7·3; N, 7·9%). The solid A was lixiviated with cold ethanol (100 ml.) and recrystallised twice from boiling ethanol, to give acetylpyrrocoline (III*e*) (16 g.), m. p. 174—175°. The combined alcoholic filtrates were evaporated to a dark oil, which was dissolved in excess of 2N-hydrochloric acid, and filtered (charcoal); basification with ammonia gave oil which solidified and was filtered off, washed, and dried (23 g.). From this, after a prolonged series of crystallisations, were isolated: (i) 2 : 3-*diphenyl*-3-2′-*pyridylprop*-2-*en*-1-*ol* (X*e*) (7·4 g.), very soluble in ethanol and very sparingly soluble in hot light petroleum (b. p. 60—80°), but crystallising well from light petroleum (b. p. 80—100°), as needles, m. p. 120°, when crystallisation commenced while the solution was hot (Found: C, 83·9; H, 5·9; N, 4·8. $C_{20}H_{17}ON$ requires C, 83·6; H, 5·9; N, 4·9%) or jagged prisms, m. p. 126°, when crystallisation did not commence till the solution was cold (Found: C, 83·6; H, 5·9; N, 4·9%) (mixed m. p. of the two forms, 126°); (ii) 2 : 3-*diphenyl*-3-2′-*pyridylallyl acetate* (IX*e*) (9·8 g.), large prisms {from light petroleum (b. p. 60—80°) or from a small volume of ethanol [the latter effectively removing traces of the alkenol (X*e*)]}, m. p. 118° (Found: C, 80·1; H, 5·6; N, 4·6; Ac, 13·7. $C_{22}H_{19}O_2N$ requires C, 80·2; H, 5·8; N, 4·3; Ac, 13·1%).

(*b*) The residual mixed isomers (40 g.), cyclised as described under (*a*), gave acetylpyrrocoline (III*e*) (16·6 g.), m. p. 175—176°, the acetoxy-compound (IX*e*) (4·5 g.), m. p. 116—117° unchanged on admixture with the sample described above, and the alkenol (X*e*) (3·5 g.), a mixture of needles and prisms as described above.

Conversion of the Acetoxy-compound (IX*e*) *into the Chloro-compound* (XI*e*).—The acetoxy-compound (IX*e*) (2·0 g.) was heated in concentrated hydrochloric acid (30 ml.) on the steam-bath for 3 hr. Basification with ammonia and extraction with chloroform gave 3-*chloro*-1 : 2-*diphenyl*-1-2′-*pyridylprop*-1-*ene*, large prisms [from light petroleum (b. p. 60—80°)], m. p. 123—124° (Found: C, 78·6; H, 5·3; N, 4·5; Cl, 11·6. $C_{20}H_{16}NCl$ requires C, 78·6; H, 5·2; N, 4·6; Cl, 11·6%).

3-*Acetyl*-1-p-*chlorophenyl*-2-*phenylpyrrocoline* (III*f*).—(i) 1-*p*-Chlorophenyl-2-phenyl-3-piperidino-1-2′-pyridylpropan-1-ol [2] (I*f*) (110 g.) was dehydrated in concentrated sulphuric acid at 0° for 24 hr., to give mixed isomers of 1-*p*-chlorophenyl-2-phenyl-3-piperidino-1-2′-pyridylprop-1-ene (II*f*) (102 g.). This (50 g.) was cyclised by the standard method. Addition of water gave a dark solid which was washed with ether and recrystallised twice from a large volume of ethanol (charcoal), to give 3-*acetyl*-1-p-*chlorophenyl*-2-*phenylpyrrocoline* (III*f*) (21 g.), straw-coloured needles, m. p. 181—182°. The ether washings were extracted several times with 2N-hydrochloric acid, the combined acid extracts were basified with ammonia, and the liberated oil was isolated in ether and combined with the oil liberated from the original aqueous filtrate on basification. The ether layer, on evaporation, gave black tar (9·0 g.) which did not

solidify when seeded with (III*f*) and was discarded. The basic oil (7·0 g.) rapidly solidified and was extracted several times with 200 ml. portions of boiling light petroleum (b. p. 60—80°). The combined extracts were evaporated to small volume and deposited crystals which, after further crystallisation from ethanol, followed by light petroleum (b. p. 60—80°), gave 3-p-*chlorophenyl*-2-*phenyl*-3-2′-*pyridylallyl acetate* (IX*f*) (4·5 g.), colourless rectangular prisms, m. p. 122° (Found: C, 72·4; H, 5·0; N, 4·0; Cl, 10·0; Ac, 11·8. $C_{22}H_{18}O_2NCl$ requires C, 72·6; H, 5·0; N, 3·9; Cl, 9·8; Ac, 11·8%).

(ii) Repetition of experiment (i) gave acetylpyrrocoline (III*f*) (16·0 g.), non-basic dark material (13 g.) from the ether layer after extraction with 2N-hydrochloric acid, and a dark basic oil (11·4 g.), which only partly solidified. From the latter, by repeated crystallisation from light petroleum (b. p. 80—100°) was obtained, not the acetoxy-compound (IX*f*), but 3-p-*chlorophenyl*-2-*phenyl*-3-2′-*pyridylprop*-2-*en*-1-*ol* (X*f*) (3·8 g.), colourless needles, m. p. 120° [mixed with (IX*f*), m. p. 100—108°] (Found: C, 75·1; H, 5·2; N, 4·2; Cl, 11·5. $C_{20}H_{16}ONCl$ requires C, 74·6; H, 5·0; N, 4·3; Cl, 11·0%).

3-*Methyl*-1-*phenylpyrrocoline* (V*g*).—(i) *From the alcohol.* 1-Phenyl-3-piperidino-1-2′-pyridylbutan-1-ol [2] (I*g*) (20 g.) and acetic anhydride (400 ml.) were boiled for 16 hr. After removal of excess of anhydride and addition of water, the separated oil was extracted with ether, and the ether layer washed several times with 2N-hydrochloric acid and evaporated to dryness. The residue was distilled, to give a yellow oil (2·6 g.), b. p. 160—175°/0·1 mm., which partially solidified, and on crystallisation from light petroleum (b. p. 40—60°) gave the pyrrocoline (V*g*) (0·8 g.), m. p. 67—68°, not depressed on admixture with the sample described below. The combined acid extracts on basification and ether-extraction gave an oil (9·8 g.) which, after distillation, was converted into its hydrochloride by ethereal hydrogen chloride. Crystallisation from chloroform–ether then gave 1-phenyl-1-2′-pyridylethylene hydrochloride [2] (VIII*g*), m. p. and mixed m. p. 187° (Found: C, 71·5; H, 5·5; N, 6·4; Cl, 16·0. Calc. for $C_{13}H_{12}NCl$: C, 71·7; H, 5·5; N, 6·4; Cl, 16·3%).

(ii) *From the alkenylamine.* The alcohol (I*g*) (50 g.) was dehydrated in concentrated sulphuric acid (500 ml.) at 0° for 6 hr. The 1-phenyl-3-piperidino-1-2′-pyridylbut-1-ene (II*g*) (42 g.) was cyclised by the standard method. Removal of excess of solvent and addition of water gave a brown oil which was extracted into ether, washed with dilute ammonia solution (to remove acetic acid), with water, and then with 2N-hydrochloric acid (4 × 200 ml.). The ether layer was evaporated and the residue (26 g.), crystallised from light petroleum (b. p. 40—60°), gave 3-*methyl*-1-*phenylpyrrocoline* (V*g*) (24 g.), golden-yellow plates, m. p. 67—68°. The combined acid extracts were basified, the oil isolated by means of ether, combined with the oil obtained by basifying the original aqueous filtrate, and distilled, to give a product (5·2 g.), b. p. 130—154°/0·2 mm., which was substantially the acetoxy-compound (IX*g*) (Found: Ac, 13·75. Calc. for $C_{17}H_{17}O_2N$: Ac, 16·1%).

1-p-*Chlorophenyl*-3-*methylpyrrocoline* (V*h*).—(i) *From the alkenylamine. cis*-1-*p*-Chlorophenyl-1-2′-pyridyl-3-pyrrolidinobut-1-ene (II*h*) (10 g.), separated from its *trans*-isomer by ion-exchange chromatography,[2] was cyclised by the standard method. After addition of water, yellow crystals separated which were filtered off, washed, and dried (7 g.), and on crystallisation from light petroleum (b. p. 40—60°) (charcoal) gave 1-p-*chlorophenyl*-3-*methylpyrrocoline* (V*h*) (4·5 g.), greenish-yellow lath-like plates, m. p. 91—92°. (ii) *From* 2-p-*chlorobenzylpyridine.* 2-*p*-Chlorobenzylpyridine [8] (10 g.) and propionic anhydride (60 ml.) were heated in a pressure tube at 280° for 8 hr. The liquid product was decanted from a little black solid, excess of anhydride removed *in vacuo*, and the residual oil washed with water and 2N-sodium hydroxide. Distillation gave 1-*p*-chlorophenyl-3-methylpyrrocoline (V*h*) (7·9 g.), b. p. 180—195°/0·5 mm., which solidified on being seeded and, crystallised from light petroleum (b. p. 40—60°), formed greenish-yellow plates (3·8 g.), m. p. and mixed m. p. 91°.

1 : 3-*Diphenylpyrrocoline* (V*i*).—(i) *From the alcohol.* 1 : 3-Diphenyl-3-piperidino-1-2′-pyridylpropan-1-ol [2] (I*i*) (5·0 g.) and acetic anhydride (50 ml.) were boiled for 6 hr. Removal of excess of anhydride and addition of water gave the pyrrocoline (V*i*) (2·1 g.), m. p. 115—116° (from ethanol). (ii) *From the alkenylamine.* The alcohol (I*i*) (50 g.) was dehydrated in ice-cold concentrated sulphuric acid (500 ml.) for 3 hr. The 1 : 3-diphenyl-3-piperidino-1-2′-pyridylprop-1-ene (II*i*) (47 g.) was cyclised by the standard method. 1 : 3-*Diphenylpyrrocoline* (V*i*) (26 g.) formed deep yellow needles, m. p. 115—116°, from alcohol. The aqueous filtrate from the reaction gave, on basification, an oil which after isolation by means of ether solidified

[8] Panizzon, *Helv. Chim. Acta*, 1944, **27**, 1748.

and on crystallisation from light petroleum (b. p. 40—60°) gave a *compound* (0·9 g.) as colourless prisms, m. p. 140—141° (Found: C, 84·9; H, 7·1; N, 7·7%; *M*, 341. $C_{25}H_{26}N_2$ requires C, 84·7; H, 7·3; N, 7·9%; *M*, 354), $\lambda_{max.}$ 260 and 265 mμ (ε 4800 and 4900 in EtOH). 1 : 3-Diphenyl-3-piperidino-1-2′-pyridylpropan-1-ol has $\lambda_{max.}$ 258 and 262 mμ (ε 4000 and 4000 in EtOH).

3-*Acetyl*-1-p-*methoxyphenylpyrrocoline* (XIV*a*).—1-*p*-Methoxyphenyl-1-2′-pyridyl-3-pyrrolidinopropan-1-ol [6] (XII*a*) (20 g.) was dehydrated in ice-cold 85% sulphuric acid (200 ml.) for 2 hr. The propene (XIII*a*) (16·5 g.) was cyclised by the standard method. Addition of water gave black, semi-solid material which was isolated, washed by decantation, and extracted with boiling light petroleum (b. p. 60—80°) (2 × 500 ml.). The petroleum-insoluble residue (A) consisted of yellow crystals mixed with much black tar. The petroleum filtrates were evaporated to give a yellow solid. A second extraction with light petroleum (b. p. 60—80°) (charcoal) and several crystallisations from ethanol and from acetone gave 3-*acetyl*-1-p-*methoxyphenylpyrrocoline* (XIV*a*) (4·5 g.), orange prisms, m. p. 122°. The material (A) was lixiviated with a little acetone, filtered off, and crystallised from pyridine, giving *di*-(1-p-*methoxyphenyl*-3-*pyrrocolyl*), yellow needles, m. p. 225°, $\lambda_{max.}$ 245, 266, 304, and *370* (ε 37,000, 31,000, 34,000, and 9000 in dioxan). No pyrrocoline was isolated when the alcohol (XII*a*) was boiled with acetic anhydride.

3-*Acetyl*-1-p-*tolylpyrrocoline* (XIV*b*).—The alcohol [2] (XII*b*) (40 g.) was dehydrated in ice-cold 85% sulphuric acid (400 ml.) for 3 hr. The propene (XIII*b*) (38 g.) was cyclised by the standard method. Addition of water gave dark solid which, on crystallisation from ethanol–light petroleum (b. p. 80—100°), afforded 3-*acetyl*-1-p-*tolylpyrrocoline* (XIV*b*), yellow plates, m. p. 133°. The original aqueous filtrate was basified with ammonia and extracted with ether, to give oil (5·0 g.) which was distilled; impure 3-2′-pyridyl-3-*p*-tolyl-allyl acetate (IX; R^1 = Me, R^2, R^3 = H) had b. p. 170—172°/0·5 mm. (Found: C, 77·5; H, 6·6; N, 4·9; Ac, 15·9. Calc. for $C_{17}H_{17}O_2N$: C, 76·4; H, 6·4; N, 5·2; Ac, 16·1%).

3-*Acetyl*-1-o-*tolylpyrrocoline* (XIV*c*).—1-2′-Pyridyl-3-pyrrolidino-1-*o*-tolylpropan-1-ol [2] (XII*c*) (26 g.) was dehydrated in 85% sulphuric acid (260 ml.) on the steam-bath for 20 min. The propene (19 g.) was separated [2] by ion-exchange chromatography into the *trans*- (XIII*c*) (8·1 g.) and the *cis*-isomer (XIII*c*) (10·2 g.). (i) The *trans*-isomer (8·1 g.) was cyclised by the standard method. Addition of water gave a dark oil which was isolated with ether and distilled (b. p. 158—162°/0·1 mm.) as an oil (3·5 g.). This, on crystallisation from light petroleum (b. p. 60—80°), gave a *compound* (Q) (1·2 g.) as large colourless prisms, m. p. 114° (Found: C, 81·9; H, 6·0; O, 6·7; N, 5·7%; Ac, 0; reduction, 1·05 double bond calc. on *M* 250. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·0; O, 6·4; N, 5·6%), $\lambda_{max.}$ 258, 264, 321, and 330 mμ (ε 4610, 4660, 261, 266 in EtOH); after reduction $\lambda_{max.}$ were at 263, *268*, 296, and 305 (ε 4300, 3500, 270, and 280 in EtOH). (ii) The *cis*-isomer (10·2 g.), on cyclisation and addition of water, gave an oil, b. p. 180—184°/0·2 mm. (7·1 g.), which set to a glass. Crystallisation from light petroleum (b. p. 60—80°) gave a mixture (5·7 g.) of colourless and pale yellow crystals from which the colourless material was eluted in 2N-hydrochloric acid. The insoluble yellow 3-*acetyl*-1-o-*tolylpyrrocoline* (XIV*c*) crystallised from light petroleum (b. p. 40—60°) as pale yellow prisms (4·4 g.), m. p. 65°. From the acid washings, by basification and crystallisation from light petroleum (b. p. 60—80°), was obtained compound (Q) (0·4 g.), m. p. 112—113°.

3-*Acetyl*-8-*methyl*-1-*phenylpyrrocoline* (XIV*d*).—1-(3-Methyl-2-pyridyl)-1-phenyl-3-pyrrolidinoprop-1-ene [2] (XIII*d*) (5·5 g.) was cyclised by the standard method. Addition of water gave a dark oil which was extracted into ether. The ether layer was washed with 2N-hydrochloric acid, water, and dilute aqueous ammonia, filtered (charcoal), and evaporated (3·0 g.). Crystallisation from light petroleum (b. p. 40—60°) gave 3-*acetyl*-8-*methyl*-1-*phenylpyrrocoline* (XIV*d*), large straw-coloured prisms (2·2 g.), m. p. 100—101°.

3-*Acetyl*-1-p-*chlorophenyl*-8-*methylpyrrocoline* (XIV*e*).—1-*p*-Chlorophenyl-1-(3-methyl-2-pyridyl)-3-pyrrolidinopropan-1-ol [2] (XII*e*) (30 g.) was dehydrated in 85% sulphuric acid (150 ml.) on the steam-bath for 10 min. The propene (XIII*e*) was separated [2] *via* the oxalates into *cis*- (XIII*e*) (16 g.) and substantially pure *trans*-propene (XIII*e*) (12 g.).

The *cis*-propene (16 g.) was cyclised by the standard method. Addition of water precipitated a dark solid (14·8 g.) which, on crystallisation from acetone, then from light petroleum (b. p. 60—80°), gave the *pyrrocoline* (XIV*e*) (10·6 g.), as large, almost colourless prisms, m. p. 112—113°. The *trans*-isomer (12 g.) gave no pyrrocoline.

3-*Acetyl*-1-(5-*chloro*-2-*thienyl*)*pyrrocoline* (XIV*f*).—1-(5-Chloro-2-thienyl)-1-2′-pyridyl-3-pyrrolidinopropan-1-ol [6] (XII*f*) (5 g.) was dehydrated in 65% sulphuric acid on the steam-bath

for 15 min. The propene (XIII*f*) (4·5 g.) was cyclised by the standard method. Addition of water gave a semisolid black mass, which was filtered off and extracted with ether (Soxhlet). Evaporation of the ether gave a dark solid (2·5 g.), then by two crystallisations from light petroleum (b. p. 60—80°) yellow crystals. Two crystallisations from ethanol [with filtration the first time from yellow material (A)] gave 3-*acetyl*-1-(5-*chloro*-2-*thienyl*)*pyrrocoline* (XIV*f*) as rosettes of yellow needles, m. p. 119°. The material (A), m. p. 217—220°, was probably di-[1-(5-chloro-2-thienyl)-3-pyrrocolyl], $\lambda_{max.}$ 234, *250*, 330, *370* (ε 26,000, 23,500, 25,900, 11,000 in EtOH). Heating the alcohol (XII*f*) with acetic anhydride gave no pyrrocoline.

3-*Acetyl*-1-2′-*pyridylpyrrocoline* (XIV*g*).—3-Dimethylamino-1 : 1-di-2′-pyridylpropan-1-ol [6] (XII*g*) (10 g.) and acetic anhydride (200 ml.) were boiled for 6 hr. After removal of anhydride, addition of water precipitated a black solid which, after several crystallisations from light petroleum (b. p. 60—80°), gave 3-*acetyl*-1-2′-*pyridylpyrrocoline* (XIV*g*), yellow plates, m. p. 112°.

Di-(1-*phenyl*-3-*pyrrocolyl*).—The alkenylamine (II*a*) (10 g.) was dissolved in chloroform, and 50% aqueous hydrobromic acid (4·4 ml.) was added. The chloroform was removed. The hydrobromide crystallised and was heated with quinoline (50 ml.) at 160° for 3 hr. The quinoline was removed by distillation and steam-distillation and the dark residue dissolved in ether; Filtration, evaporation, and storage overnight afforded crystals. These were washed with acetone and recrystallised from light petroleum (b. p. 60—80°), to give the dipyrrocolyl (IV*a*) (0·2 g.), m. p. and mixed m. p. 189—192°, $\lambda_{max.}$ 236, 310, and *358* (ε 35,100, 30,800, and 9600 in dioxan).

Di-(1-p-*chlorophenyl*-3-*pyrrocolyl*).—(i) The *trans*-alkenylamine (II*b*) (10 g.), quinoline (40 ml.), and 50% aqueous hydrobromic acid (5 ml.) were heated at 160° for 3 hr. During three days' storage crystals separated and were filtered off, washed with ethanol, and dried (1·2 g.). Crystallisation from pyridine gave the dipyrrocolyl (IV*b*), m. p. and mixed m. p. 285—288°. (ii) The *cis*-alkenylamine (II*b*) (10 g.) similarly reacted to give the dipyrrocolyl (IV*b*) (1·1 g.).

1-2′-*Pyridylindan*-1-*ol*.—Indan-1-one was treated with pyridyl-lithium as described in Part III,[6] to give 1-2′-*pyridylindan*-1-*ol*, b. p. 158—165°/0·3 mm., prisms from light petroleum (b. p. 40—60°), m. p. 78—79° (Found: C, 79·9; H, 6·2; N, 6·4. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·2; N, 6·6%), $\lambda_{max.}$ 262 (ε 5400 in EtOH).

3-2′-*Pyridylindene*.—The indanol (2 g.) was dehydrated in 85% sulphuric acid (20 ml.) at 0° for 2 hr. Crystallisation from light petroleum (b. p. 40—60°) gave the *indene* as colourless needles or prisms, m. p. 80—82° (depressed to 55—58° on admixture with the indanol) (Found: C, 87·3; H, 5·7; N, 7·1. $C_{14}H_{11}N$ requires C, 87·0; H, 5·7; N, 7·3%), $\lambda_{max.}$ 235 and 280 (ε 21,000 and 6500 in EtOH).

1-*Arylpyrrocolines*.—3-Acetyl-1-phenylpyrrocoline (III*a*) (2·6 g.) was boiled with concentrated hydrochloric acid (30 ml.) till the initial orange colour disappeared (*ca.* 5 min.). The mixture was cooled and basified, and the liberated oil extracted with ether and distilled. The fraction boiling at 155—160°/0·3 mm. crystallised from light petroleum (b. p. 40—60°), to give 1-*phenylpyrrocoline* (V*a*), pale yellow prisms, m. p. 68°. The 1-*arylpyrrocolines* given in Table 2 were prepared similarly. They decomposed rapidly on exposure to air and light. Analytical samples were prepared in most cases by sublimation at 0·1—0·5 mm.

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