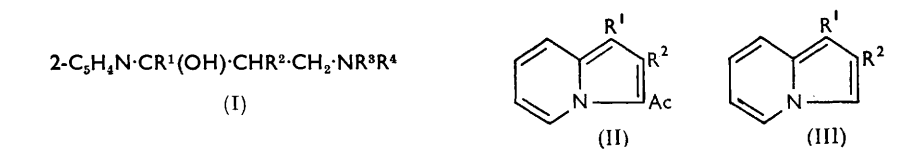
63. *Aminoalkyl Tertiary Carbinols and Derived Products. Part VIII.*[1] *Some* 1-*Alkyl- and* 1 : 2-cyclo*Alkano-pyrrocolines.*

By P. A. Barrett and (the late) K. A. Chambers.

1-(Tertiary amino)-3-2′-pyridylalkan-3-ols (I) and 1 : 5-di(tertiary amino)-3-2′-pyridylalkan-3-ols (V) have been cyclised to the corresponding 1-alkyl- and 1-2′-(tertiary amino)alkyl-pyrrocolines (II) and (VI). The analogous *cyclo*alkanols (X) are shown to be mixtures containing more than one of the possible steroisomers. The isomers present in larger amount give no pyrrocoline on cyclisation and are assigned the all-*trans*-configuration. The other isomers cyclise to the corresponding tricyclic 3-acetylpyrrocolines (XIV) and contain at least one *cis*-grouping.

In Part VII [1] was described a new synthesis of 1-arylpyrrocolines, *e.g.*, (II; R^1 = Ph, R^2 = H), from the corresponding 3-(tertiary amino)-1-aryl-1-2′-pyridylpropan-1-ols, *e.g.*, (I; R^1 = Ph, R^2 = H, NR^3R^4 = N<[CH_2]$_4$), in acetic anhydride. We now describe the extension of this reaction to the preparation of some 1-alkyl- and 1 : 2-*cyclo*alkano-pyrrocolines.

A series of alkanols (I; R^1 = alkyl, R^2 = H or alkyl) (Table 1) was prepared from 2-pyridyl-lithium and the appropriate 1-(tertiary amino)alkan-3-ones and cyclised by boiling acetic anhydride to the corresponding acetylpyrrocolines (II; R^1 = alkyl, R^2 = H or alkyl). Reaction was slower and cleaner, and the yield higher, than in the cyclisations to 1-arylpyrrocolines described in Part VII,[1] and formation of the corresponding



Compounds I—III	R^1	R^2	R^3R^4
a	Me	H	<[CH_2]$_5$
b	Et	Me	Me_2
c	Pr	Et	Me_2
d	Me	Me	Me_2
e	CMe_3	H	<[CH_2]$_5$

Compounds I—III	R^1	R^2	R^3R^4
f	Me	$CH_2·NEt_2$	Et_2
g	Me	$CH_2·N$<[CH_2]$_5$	<[CH_2]$_5$

dipyrrocolylmethanes has not been observed. It is concluded that the alkyl-carbinols undergo to a much smaller extent, if at all, reaction by the alternative route encountered [1] in the aryl series. The 3-acetyl-1-alkylpyrrocolines (II*a* and *d*) are stable yellow solids, hydrolysed to the 1-alkylpyrrocolines (III*a* and *d*), which, though readily obtained pure by vacuum-sublimation,[2] were markedly less stable to exposure than the corresponding 1-arylpyrrocolines. The alkylpyrrocolines (III*b*, *c*, and *e*) were oils.

Reaction of 2-pyridyl-lithium with the symmetrical 1 : 5-bisdimethylaminoalkan-3-ones (IV*a*) and (IV*b*) gave the 1 : 5-bisdimethylamino-3-2′-pyridylalkan-3-ols (V*a*) and (V*b*). These on cyclisation gave the 3-acetyl-1-dimethylaminoalkylpyrrocolines, one of which (VI*a*) was an oil, characterised as the hydrogen oxalate, and the other (VI*b*) was solid. The unsymmetrical 1 : 5-bisdimethylaminoalkan-3-ones (IV*c*) and (IV*d*) similarly gave the 2′-pyridylalkanols (V*c* and *d*), which on cyclisation gave high yields of the 3-acetyl-1-dimethylaminoalkylpyrrocolines (VI*c* and *d*): these pyrrocolines may be either of two isomers, or a mixture of both, depending on the relative proportions of the two non-equivalent amino-groups participating in the cyclisation. Analysis and ultraviolet absorption spectra confirm their formulation as (VI*c* and *d*) but attempts to separate them into pure isomers by base-exchange chromatography or by fractional crystallisation of

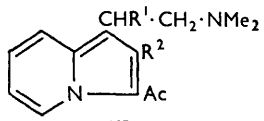
[1] Part VII, preceding paper.
[2] Cf. Holland and Naylor, *J.*, 1955, 1657.

their oxalates were unsuccessful. Regardless of which isomer preponderates in the mixture, the isolation of the pyrrocoline (VI*c*) in high yield establishes unequivocally as (IV*c*) the constitution of the di-Mannich base from ethyl methyl ketone, which has long been uncertain. Cardwell [3] rigorously proved the structure of the mono-Mannich base from ethyl methyl ketone and preferred, without proof, the structure (IV*c*) for the di-Mannich base. Haeussler and Schacht,[4] however, assigned the compound the structure (VIII*a*) on the basis of an iodoform reaction. Only if this compound has the constitution (IV*c*) can the derived 2-pyridylcarbinol give a pyrrocoline on cyclisation. The 2-pyridylcarbinol from (VIII*a*) would be precluded from doing so by the presence of the quaternary carbon atom.

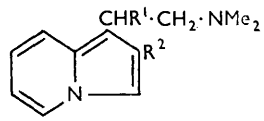
From one preparation of the pentanol (V*a*) of wide boiling range there was isolated after cyclisation, in addition to acetylpyrrocoline (II*a*), a compound to which on the basis of analysis and ultraviolet spectrum is assigned the constitution (II; R^1 = Me, R^2 = OAc). Presumably this was formed from unsymmetrical dipiperidinoalkanol (I*g*) present as a contaminant of the butanol (I*a*), with subsequent deamination. Analogous deamination during cyclisation has been encountered in the *cyclo*alkanol series (see below). However, after the cyclisation of the pure di(tertiary amino)alkanols (I*f*) and (I*g*) no pyrrocoline derivatives could be isolated.

$NMe_2 \cdot CH_2 \cdot CHR^1 \cdot CO \cdot CHR^2 \cdot CH_2 \cdot NMe_2$ (IV)

$NMe_2 \cdot CH_2 \cdot CHR^1 \cdot C(C_5H_4N\text{-}2)(OH) \cdot CHR^2 \cdot CH_2 \cdot NMe_2$ (V)



(VI)



(VII)

Compounds IV—VII	R^1	R^2		R^1	R^2
a	H	H			
b	Me	Me			
c	H	Me	*or*	Me	H
d	H	Et	*or*	Et	H

$Me \cdot CO \cdot CR^1(CH_2 \cdot NR^2R^3)_2$ (VIII): *a* R^1 = Me, R^2R^3 = Me_2
b R^1 = H, R^2R^3 =
c R^1 = H, R^2R^3 = Et_2

The present reaction is among the few pyrrocoline syntheses in which the complete carbon skeleton is present in one stable molecule before cyclisation. This permits the preparation of pyrrocoline derivatives, otherwise doubtfully accessible, which carry additional fused cyclic structures. The 2-pyridylcarbinol (X*b*), prepared from the *cyclo*hexanone Mannich base (IX*b*), on cyclisation (6 hr.) gave a low yield of the tricyclic pyrrocoline derivative (XIV*b*) and a high yield of the acetate (XI*b*). The alcohol (X*b*) derived from the latter by hydrolysis gave no pyrrocoline but was quantitatively reconverted into acetate (XI*b*) on treatment (12 hr.) with acetic anhydride. In Part VII [1] the difference in behaviour of *cis*- and *trans*-3-(tertiary amino)-1-aryl-1-2′-pyridylprop-1-enes * towards acetic anhydride was interpreted in terms of a sharp distinction between the *cis*-isomer giving pyrrocoline, and the *trans*-isomer giving none, confused by a slow isomerisation. In the present case we deduce that the recovered acetate (XI*b*) and the alcohol (X*b*) derived from it, neither of which gave pyrrocoline (XIV*b*) on treatment with acetic anhydride, have the *trans*-configuration, and that the alcohol (X*b*) as prepared was a mixture containing about 25% of the *cis*-isomer which was removed during the first treatment with acetic anhydride with formation of the pyrrocoline (XIV*b*). In contrast to the alkenylamines,[1] the difference in behaviour is sharp because the possibility of

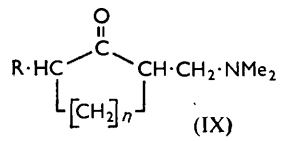
* *cis* and *trans* refer to the relation of the pyridine and the aminomethyl group.

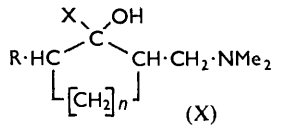
[3] Cardwell, *J.*, 1950, 1056.

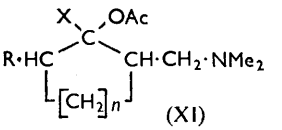
[4] Haeussler and Schacht, *Ber.*, 1950, **83**, 129.

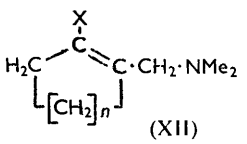
isomerisation is excluded. This interpretation is confirmed by additional examples described below. In connection with the relation between configuration and ability to cyclise it is noteworthy that neither 4-hydroxy-1-methyl-4-2'-pyridylpiperidine (XVI) nor the derived 1 : 2 : 5 : 6-tetrahydro-1-methyl-4-2'-pyridylpyridine (XVII), both of which may be regarded as extreme *trans*-forms of their respective types of isomerism, gave a pyrrocoline derivative on submission to cyclisation.

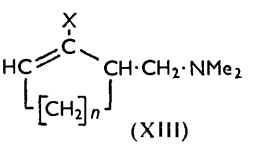
The *trans*-alcohol (X*b*) gave on dehydration a mixture of *cyclo*alkenes (XII*b*) and (XIII*b*) which was separated into a solid and a liquid fraction through the insolubility of the oxalate of the former. On treatment with acetic anhydride the solid was recovered unchanged, while the liquid fraction gave a 25% yield of the tricyclic pyrrocoline derivative (XIV*b*). It is concluded that the latter was substantially 2-dimethylaminomethyl-1-2'-pyridyl*cyclo*hex-1-ene (XII*b*) which, being a substituted *cis*-3-aminoprop-1-ene, should give a high yield of the corresponding pyrrocoline on cyclisation, and that the solid was the corresponding *cyclo*hex-6-ene (XIII*b*).

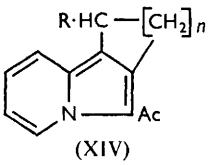

(IX)

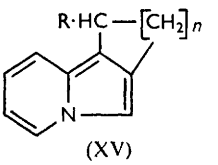

(X)


(XI)


(XII)


(XIII)


(XIV)


(XV)

X = 2-pyridyl

IX—XV	R	*n*
a	H	2
b	H	3
c	H	4
d	$CH_2 \cdot NMe_2$	2

IX—XV	R	*n*
e	$CH_2 \cdot NMe_2$	3
f	$CH_2 \cdot NMe_2$	4
g	$CH_2 \cdot OAc$	3
h	$CH_2 \cdot OAc$	4

Analogous behaviour was observed in the corresponding compounds from *cyclo*pentanone. Small yields of identical pyrrocoline (XIV*a*) were isolated on cyclisation both from the mixed isomeric *cyclo*pentanols (X*a*) and from the mixed *cyclo*pentenes (XII*a*) and (XIII*a*), the product of dehydration of the *trans*-alcohol obtained by hydrolysis of the *trans*-acetate (XI*a*) recovered from the cyclisation of the total alcohol. No attempt was made to separate the isomeric *cyclo*pentenes (XII*a*) and (XIII*a*).

The corresponding *cyclo*heptanol (X*c*) gave on cyclisation a small yield of non-basic oil, shown by ultraviolet absorption spectrum to contain some pyrrocoline (which was however not obtained pure) and the solid *trans*-acetate (XI*c*). Dehydration of the heptanol was not investigated.

The bis(dimethylaminomethyl)-2'-pyridyl*cyclo*alkanols (X*d*, *e*, and *f*) have been prepared from the corresponding bis(dimethylaminomethyl)*cyclo*alkanones (IX*d*, *e*, and *f*). The possibility that the latter are the unsymmetrical αα-disubstituted *cyclo*alkanones has not been rigorously disproved. However, no evidence was found to suggest that they were heterogeneous, and all the evidence available (cf. refs. 2, 5, 6, and see above) shows that aminomethylation occurs preferentially at a secondary rather than at a primary carbon atom, and at a primary rather than at a tertiary carbon atom. Further, the Mannich base from 2-methyl*cyclo*hexanone has been shown [7] to be 2-dimethylaminomethyl-6-methyl-*cyclo*hexanone and not the 2 : 2-compound. The bis(dimethylaminomethyl)*cyclo*alkanones are therefore assigned the constitution (IX), and the derived alcohols the constitution (X).

[5] Blicke in "Organic Reactions," Vol. I, Chapman and Hall, London, 1942, p. 303.
[6] Wilds and Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 469.
[7] de Feu, McQuillin, and Robinson, *J.*, 1937, 53.

TABLE 1. 1-(*Tertiary amino*)- *and* 1 : 5-*di*(*tertiary amino*)-3-2′-*pyridylalkan*-3-*ols* (I) *and* (V).

Compound	R^1	R^2	R^3R^4	B. p./mm.	M. p.[a]	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
I*a*	Me	H	$<[CH_2]_5$	120—122°/0·5	—	$C_{14}H_{22}ON_2$	71·5	9·5	12·2	71·8	9·4	12·0
I*b*	Et	Me	Me_2	99—100/0·2	—	$C_{13}H_{22}ON_2$	70·1	9·6	12·6	70·3	9·9	12·6
I*c*	Pr	Et	Me_2	125—128/0·5	—	$C_{15}H_{26}ON_2$	72·3	10·7	11·1	72·0	10·5	11·2
I*d*	Me	Me	Me_2	98—100/0·3	—	$C_{12}H_{20}ON_2$	69·0	9·6	13·2	69·2	9·6	13·5
I*d*	Me	Me	$<[CH_2]_5$	132—134/0·3	—	$C_{15}H_{24}ON_2$	72·0	9·6	11·3	72·5	9·7	11·3
I*e*	CMe_3	H	$<[CH_2]_5$	140—150/0·5	79—81°	$C_{17}H_{28}ON_2$	74·3	10·1	10·3	74·0	10·1	10·1
I*f*	Me	$CH_2{\cdot}NEt_2$	Et_2	150—155/1·5	—	$C_{18}H_{33}ON_3$	70·3	10·6	13·2	70·4	10·7	13·7
I*g*	Me	$CH_2{\cdot}N<[CH_2]_5$	$<[CH_2]_5$	186—190/0·2	—	$C_{20}H_{33}ON_3$	73·2	9·8	12·2	72·5	10·0	12·7
V*a*	H	H	—	138—142/0·5	73—74	$C_{14}H_{25}ON_3$	67·2	10·1	16·8	67·0	10·1	16·7
V*b*	Me	Me	—	130—140/0·4	98—99	$C_{16}H_{29}ON_3$	69·2	10·0	15·1	68·7	10·4	15·1
V*c*	Me	H	—	130—135/0·3 *	—	$C_{15}H_{27}ON_3$	68·4	9·9	14·6	67·9	10·2	15·8
V*d*	Et	H	—	130—132/0·2	—	$C_{16}H_{29}ON_3$	69·4	10·2	14·1	68·7	10·4	15·1
* Oxalate, recryst. from ethanol					156	$C_{19}H_{31}O_9N_3$	51·0	7·3	—	51·3	7·0	—

[a] After crystallisation from light petroleum (b. p. 40—60°).

TABLE 2. 3-*Acetyl*-1-*alkylpyrrocolines and* 3-*acetyl*-1-2′-(*tertiary amino*)*alkylpyrrocolines* (II *and* VI).

Compound	R^1	R^2	B. p./mm.	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
II*a*	Me	H	140—150°/0·2	100—101° [a]	$C_{11}H_{11}ON$	76·6	6·5	8·3	76·4	6·4	8·1
II*b*	Et	Me	140—148/0·1	82 [a]	$C_{13}H_{15}ON$	77·2	7·5	7·0	77·6	7·5	7·0
II*c*	Pr	Et	160—170/0·5	51—52 [b,c]	$C_{15}H_{19}ON$	78·6	8·4	6·1	78·6	8·3	6·1
II*d*	Me	Me	140—145/0·3	99—100 [a]	$C_{12}H_{13}ON$	77·3	6·8	7·6	77·0	7·0	7·5
II*e*	CMe_3	H	—	108—109 [b]	$C_{14}H_{17}ON$	78·0	8·0	6·3	78·2	7·9	6·5
VI*a*	H	H	165—175/0·5	—	—	—	—	—	—	—	—
,,	,,	,,	—	100 [d]	$C_{14}H_{18}ON_2,C_2H_2O_4,H_2O$	56·8	6·5	8·6	56·8	6·5	8·3
,,	,,	,,	—	176—177 [e]	$C_{14}H_{18}ON_2,C_2H_2O_4$	59·3	6·2	8·8	60·0	6·3	8·8
VI*b*	Me	Me	160—164/0·5	72 [b]	$C_{16}H_{22}ON_2$	74·7	8·3	11·0	74·5	8·5	10·9
,,	,,	,,	—	178 [f]	$C_{16}H_{22}ON_2,C_2H_2O_4$	62·2	6·7	8·1	62·1	6·9	8·1
VI*c*	H or Me	Me or H	152—158/0·1	—	$C_{15}H_{20}ON_2$	73·4	8·2	11·3	73·8	8·2	11·5
,,	,,	,,	—	175—177 [f]	$C_{15}H_{20}ON_2,C_2H_2O_4$	60·7	6·7	8·6	60·7	6·6	8·4
VI*d*	H or Et	Et or H	160—170/0·2	—	$C_{16}H_{22}ON_2$	—	—	10·8	—	—	10·9
,,	,,	,,	—	152—157 [f]	$C_{16}H_{22}ON_2,C_2H_2O_4$	62·4	7·0	8·2	62·1	6·9	8·1

[a, b] Cryst. from light petroleum ([a] b. p. 60—80°; [b] b. p. 40—60°). [c] Sublimed *in vacuo*. [d] Monohydrate (from H_2O). [e] Anhydr. (dried at 100°) Cryst. from EtOH–Et_2O.

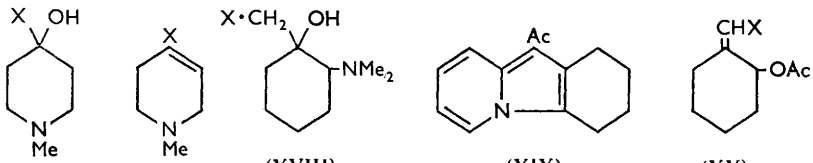
TABLE 2*a*.

Compound [a]	Absorption max. in EtOH λ (mμ)					ε				
II*a*	227	—	266	370	383	16,200	—	24,500	15,700	14,300
II*b*	231	256	275	370	382	21,900	12,200	24,000	13,900	12,800
II*c*	232	258	276	373	386	23,000	12,800	23,000	14,000	12,700
II*d*	230	255	275	372	384	20,000	11,500	24,000	13,700	12,800
II*e*	266	240 *	264	370	380	17,500	9,000	24,000	16,000	14,500
VI*a*	225	—	262	364	—	16,000	—	19,000	11,000	—
VI*b*	230	—	276	370	—	21,000	—	22,000	13,000	—
VI*c*	230	—	266	268	—	18,000	—	22,000	13,600	—
VI*d*	228	—	265	268	—	19,000	—	20,000	13,500	—

* Inflexion. [a] Examined as base, except (VI*a*) as anhydrous oxalate.

The substituted *cyclo*hexanol (X*e*), as prepared, was a mixture of isomers, one of which was isolated as its solid acetate (XI*e*). This gave no pyrrocoline on long boiling with acetic anhydride. The bulk was recovered unchanged though some deamination occurred with the production of the high-melting, well characterised, diacetate (XI*g*). Both these compounds are assigned the *trans-trans*-configuration. The oily residue left after separation of the solid acetate (XI*e*) gave on cyclisation a moderate yield of the dimethylaminomethylpyrrocoline (XIV*e*). This material therefore contained *cyclo*hexanol (X*e*) having some *cis*-configuration. From cyclisations carried out on the total alcohol, as prepared, the same three compounds have been isolated. The yields of pyrrocoline (XIV*e*) from different samples varied, however, suggesting variation in the proportion of stereoisomers in the *cyclo*hexanol (X*e*).

The substituted *cyclo*heptanol (X*f*) formed a semisolid mixture from which two of the three possible stereoisomers have been isolated, having m. p.s 84° and 82° respectively (mixed m. p. 56°). Both gave solid acetates (XI*f*) (m. p. 89° and 87° respectively; mixed m. p. 60°). The acetate (m. p. 87°) was recovered unchanged after long boiling with acetic anhydride, and is assigned the *trans-trans*-configuration. The acetate (m. p. 89°) gave on cyclisation a 50% yield of the dimethylaminomethylpyrrocoline (XIV*f*) and a



(XVI) (XVII) (XVIII) (XIX) (XX)

X = 2-pyridyl 2-$C_5H_4N{\cdot}CH_2{\cdot}CPh(OH){\cdot}CH_2{\cdot}N\langle[CH_2]_5$ (XXI)

5% yield of the acetoxymethylpyrrocoline (XIV*h*). This acetate is assigned the *cis-trans*-configuration. In all the alcohols examined the isomer having exclusively *trans*-configuration has been present in greater amount, and it seems probable that the isomer next in abundance will have the *cis-trans*- and not the *cis-cis*-configuration. In one experiment the solid portion of the crude alcohol gave the pure *cis-trans*-isomer. The solid isolated in later preparations was always a mixture of the two isomers. These were converted into the acetates (XI*f*), and the latter separated by fractional crystallisation of their oxalates.

The corresponding diamino*cyclo*pentanol (X*d*), submitted to cyclisation, gave material shown by the absorption spectrum to contain some pyrrocoline derivative, but this could not be characterised.

Cyclisation to a substituted pyrrocoline is not limited to 1-2′-pyridylpropan-1-ols but can occur with 1-2′-pyridylpropan-2-ols. This has been shown with 2-dimethylamino-1-(2′-pyridylmethyl)*cyclo*hexanol (XVIII) which on cyclisation gave 10-acetyl-1 : 2 : 3 : 4-tetrahydrobenzo[*b*]pyrrocoline (XIX). Deamination led simultaneously to a compound for which the analysis and ultraviolet spectrum suggest the constitution (XX). From the attempted cyclisation of 3-piperidino-2-phenyl-1-2′-pyridylpropan-2-ol (XXI), however, no pyrrocoline derivative could be isolated.

Experimental

Light-absorption data refer to EtOH solution.

Mono- and Di-β-(tertiary amino)alkanones.—Ketones were prepared by published methods,[3,7–10] except the following.

1-*Dimethylamino*-2-*ethylhexan*-3-*one*, prepared by the Mannich reaction[9] from di-*n*-propyl

[8] (*a*) Mannich and Hof, *Arch. Pharm.*, 1927, **265**, 589; (*b*) Hagemeyer, *J. Amer. Chem. Soc.*, 1949, **71**, 1119.

[9] Mannich, *Arch. Pharm.*, 1917, **255**, 261.

[10] Mannich and Hof, *ibid.*, 1926, **264**, 749.

ketone, had b. p. 104°/12 mm. (Found: C, 70·2; H, 12·1; N, 8·5. $C_{10}H_{21}ON$ requires C, 70·2; H, 12·3; N, 8·2%).

1 : 5-*Bisdimethylamino*-2-*ethylpentan*-3-*one*, prepared by the method of Mannich and Hof,[10] had b. p. 117—120°/12 mm. (Found: C, 65·7; H, 11·7; N, 13·5. $C_{11}H_{24}ON_2$ requires C, 66·0; H, 12·0; N, 14·0%). The *dihydrochloride* (from methanol) had m. p. 166—167° (Found: C, 48·0; H, 9·4; N, 10·1; Cl, 25·1. $C_{11}H_{26}ON_2Cl_2$ requires C, 48·4; H, 9·6; N, 10·3; Cl, 26·0%).

1 : 1-Bisdiethylaminomethylpropan-2-one (VIII*c*) was prepared by the method of Wilds and Shunk.[6] 1 : 1-*Bispiperidinomethylpropan*-2-*one* (VIII*b*), similarly prepared, had b. p. 175—180°/15 mm. (Found: C, 69·4; H, 11·2; N, 10·9. $C_{15}H_{28}ON_2$ requires C, 71·5; H, 11·2; N, 11·2%). An attempt to prepare the bisdimethylamino-analogue by this method failed.

2-*Dimethylaminomethyl*cyclo*alkanones*.—2-Dimethylaminomethyl*cyclo*hexanone was prepared by Frank and Pierle's method.[11] It was necessary to use slow addition and very vigorous stirring if substantial simultaneous production of the di-Mannich base (see below) was to be avoided.

2-*Dimethylaminomethyl*cyclo*pentanone*, prepared similarly from *cyclo*pentanone, had b. p. 95—96°/15 mm., n_D^{21} 1·4580 (Found: C, 68·2; H, 10·6; N, 9·7. $C_8H_{15}ON$ requires C, 68·1; H, 10·6; N, 9·9%). The *hydrochloride*, plates from ethanol–ether, had m. p. 147—148° (Found: C, 53·8; H, 8·9; N, 7·7; Cl, 20·7. $C_8H_{16}ONCl$ requires C, 54·0; H, 9·0; N, 7·9; Cl, 20·0%). The *methiodide*, prepared in acetone, sintered at 167—169° but was not completely melted at 200° (Found: C, 38·3; H, 6·4; N, 4·8; I, 45·2. $C_9H_{18}ONI$ requires C, 38·2; H, 6·4; N, 4·9; I, 44·9%). A small quantity, crystallised rapidly, separated unchanged from methanol as needles, but longer boiling led to decomposition with separation of trimethylammonium iodide, m. p. > 260° (Found: C, 20·8; H, 5·6; I, 67·2. Calc. for $C_3H_{10}NI$: C, 19·3; H, 5·4; I, 67·9%).

2-*Dimethylaminomethyl*cyclo*heptanone*, prepared similarly from *cyclo*heptanone, had b. p. 122—124°/16 mm., n_D^{21} 1·4700 (Found: C, 70·9; H, 11·0; N, 8·2. $C_{10}H_{19}ON$ requires C, 71·0; H, 11·2; N, 8·3%). The *methiodide*, prepared in acetone, separated only on addition of ether. After crystallisation from a little ethanol it formed prisms, m. p. 129—130° (decomp.) (Found: C, 42·4; H, 6·4; N, 4·6; I, 41·0. $C_{11}H_{22}ONI$ requires C, 42·1; H, 7·1; N, 4·5; I, 40·8%).

αα′-*Bisdimethylaminomethyl*cyclo*alkanones*.—A mixture of *cyclo*hexanone (98 g.), dimethylamine hydrochloride (163 g.), and 37% aqueous formaldehyde (167 g.) was heated under reflux on the steam-bath with rapid stirring. A vigorous exothermic reaction took place (occasionally this required initiation by a few drops of concentrated hydrochloric acid). After being heated for a further ½ hr. the mixture was evaporated to dryness *in vacuo*. The residual solid was washed with hot ethanol and dried, to give 2 : 6-*bis*(*dimethylaminomethyl*)cyclo*hexanone dihydrochloride* (IX*e*) (200 g.), m. p. 165—166° raised to 169—170° on crystallisation from 95% aqueous ethanol (Found: C, 50·4; H, 9·0; N, 10·1; Cl, 24·9. $C_{12}H_{26}ON_2Cl_2$ requires C, 50·5; H, 9·1; N, 9·8; Cl, 24·9%). The *base* liberated with the theoretical quantity of sodium hydroxide and isolated in the usual way had b. p. 90—94°/0·4 mm. (Found: C, 67·6; H, 11·0; N, 13·4. $C_{12}H_{24}ON_2$ requires C, 67·9; H, 11·3; N, 13·2%). The *dioxalate*, prepared in ethanol, had m. p. 134° (Found: C, 48·4; H, 7·1; N, 6·9. $C_{16}H_{28}O_9N_2$ requires C, 48·8; H, 7·2; N, 7·2%). The *dimethiodide*, prepared in methanol, separated as needles, which sintered at 208—210° but were not completely melted at 240° (Found: C, 33·8; H, 6·2; N, 5·7; I, 51·4. $C_{14}H_{30}ON_2I_2$ requires C, 33·9; H, 6·1; N, 5·6; I, 51·3%).

2 : 5-*Bisdimethylaminomethyl*cyclo*pentanone dihydrochloride* (as IX*d*), similarly prepared, had m. p. 185—186° (from methanol) (Found: C, 48·4; H, 9·0; N, 10·0; Cl, 26·0. $C_{11}H_{24}ON_2Cl_2$ requires C, 48·7; H, 8·9; N, 10·3; Cl, 26·2%). The *base*, crystallised from light petroleum (b. p. 40—60°), had m. p. 44° (Found: C, 66·8; H, 11·2; N, 14·1. $C_{11}H_{22}ON_2$ requires C, 66·7; H, 11·1; N, 14·2%). The hygroscopic *dioxalate* (from ethanol–ether) had m. p. 120° (Found: C, 46·8; H, 6·9; N, 7·3. $C_{15}H_{26}O_9N_2$ requires C, 47·6; H, 6·9; N, 7·4%). The *dimethiodide* separated in granules from acetone and sintered above 155° (Found: C, 31·1; H, 5·9; N, 5·8; I, 52·6. $C_{13}H_{28}ON_2I_2$ requires C, 32·4; H, 5·8; N, 5·8; I, 52·7%); in boiling methanol it rapidly decomposed.

2 : 7-*Bisdimethylaminomethyl*cyclo*heptanone dihydrochloride* (as IX*f*), similarly prepared, had m. p. 170—171° (from ethanol) (Found: C, 52·7; H, 8·4; N, 9·3; Cl, 23·7. $C_{13}H_{28}ON_2Cl_2$ requires C, 52·2; H, 9·4; N, 9·4; Cl, 23·8%). The *base*, liberated at 0° with the theoretical quantity of sodium hydroxide, had b. p. 100—104°/0·5 mm. (Found: C, 68·3; H, 10·9; N, 12·5. $C_{13}H_{26}ON_2$ requires C, 69·0; H, 11·5; N, 12·4%). The *dioxalate*, prepared in ethanol and

[11] Frank and Pierle, *J. Amer. Chem. Soc.*, 1951, **73**, 724.

crystallised from methanol, formed needles, m. p. 140—141° (Found: C, 50·8; H, 7·3; N, 7·1. $C_{17}H_{30}O_9N_2$ requires C, 50·3; H, 7·4; N, 6·9%). The *dimethiodide*, prepared in acetone and crystallised from methanol, gave needles, m. p. 210—212° (decomp. from 180°) (Found: C, 35·4; H, 6·2; N, 5·4; I, 49·3. $C_{15}H_{32}ON_2I_2$ requires C, 35·3; H, 6·3; N, 5·5; I, 49·8%).

2-*Pyridyl-alcohols* (I) *and* (V).—The alcohols listed in Table 1 were prepared from 2-pyridyllithium and the corresponding ketone as described in Part III.[12]

3-*Acetyl*-1-*methylpyrrocoline*.—(i) 1-Piperidino-3-2′-pyridylbutan-1-ol (I*a*) (177 g.), b. p. 120—130°/0·5 mm., and acetic anhydride (1770 ml.) were boiled under reflux for 24 hr. After removal of excess of anhydride, the product was poured into water. The precipitated solid was filtered off, washed, dried, and distilled. The fraction (59 g.) having b. p. 140—150°/3·5 mm. recrystallised from light petroleum (b. p. 60—80°) (600 ml.), to give 3-acetyl-1-methylpyrrocoline (II*a*) (52 g., 40%), large yellow prisms, m. p. 100—101°.

(ii) The butanol (I*a*) (148 g.) and acetic anhydride (1480 ml.) were boiled under reflux for 6 hr. and worked up as in (i), to give the pyrrocoline (II*a*) (12 g.). The aqueous filtrate on basification and extraction gave an oil (96 g.) which was distilled, to give 1-*piperidino*-3-2′-*pyridylbutyl acetate* (82 g.), b. p. 140—150°/0·5 mm. (Found: C, 69·5; H, 8·8; N, 10·1; Ac, 14·9. $C_{16}H_{24}O_2N_2$ requires C, 69·3; H, 8·7; N, 10·1; Ac, 15·1%). The *oxalate* (from ethanol) had m. p. 169—170° (decomp.) (Found: C, 58·9; H, 7·4; N, 7·5; Ac, 11·6. $C_{18}H_{26}O_6N_2$ requires C, 59·0; H, 7·1; N, 7·7; Ac, 11·7%). The acetate (80 g.) was re-boiled with acetic anhydride (800 ml.) for 6 hr. and worked up, to give the pyrrocoline (II*a*) (18 g.) and recovered acetate (45 g.). The latter, after a third treatment with acetic anhydride for 18 hr. gave pyrrocoline (II*a*) (13 g.). The total yield of acetylpyrrocoline (II*a*), m. p. 98—100°, was 43 g.

(iii) A sample of the butanol (I*a*) (120 g.), having a boiling range 125—170°/0·5 mm., when cyclised and worked up as in (i) gave crude solid (21·5 g.) from which, in addition to acetylpyrrocoline (II*a*), there was isolated by fractional crystallisation from light petroleum (b. p. 40—60°) the less soluble 2-*acetoxymethyl*-3-*acetyl*-1-*methylpyrrocoline* (II; R^1 = Me, R^2 = CH_2·OAc) as fawn needles, m. p. 97° depressed on admixture with acetylpyrrocoline (II*a*) to 68—71° (Found: C, 69·1; H, 6·4; N, 5·8; Ac, 35·8. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1; N, 5·7; Ac, 35·2%), $\lambda_{max.}$ 230, 261, 267, and 378 mμ (ε 19,000, 14,000, 14,000, and 13,000).

3-*Acetyl*-1 : 2-*dialkylpyrrocolines*.—1-Dimethylamino-2-methyl-3-2′-pyridylpentan-3-ol (I*b*) (55 g.) and acetic anhydride (550 ml.) were boiled under reflux for 24 hr. After removal of excess of anhydride, the product was poured into water and extracted with ether. The ether layer was filtered (charcoal and kieselguhr) and evaporated. On addition of water the crude pyrrocoline solidified and was filtered off, washed, dried in the air, and distilled. The fraction having b. p. 140—148°/0·1 mm. solidified and after crystallisation from light petroleum (b. p. 60—80°) gave 3-*acetyl*-1-*ethyl*-2-*methylpyrrocoline* (II*b*) (27 g.), lemon-yellow prisms, m. p. 82°.

The *alkylyyrrocolines* (II*c–e*) (Table 2) were prepared similarly.

1-*Alkylpyrrocolines*.—3-Acetyl-1-methylpyrrocoline (5 g.) in concentrated hydrochloric acid (30 ml.) was boiled till the initial orange colour disappeared (*ca.* 2 min.). The mixture was cooled and basified with ammonia. The solid was filtered off, washed, dried, and sublimed at 70—80°/0·5 mm., to give 1-*methylpyrrocoline* (III*a*) (3·5 g.), cream-coloured, m. p. 44° (Found: C, 82·4; H, 6·7; N, 11·0. C_9H_9N requires C, 82·4; H, 6·9; N, 10·7%), $\lambda_{max.}$ 240, 280, 288, 300, and 360 mμ (ε 33,000, 2100, 3200, 4400, 2000 in EtOH). 1 : 2-Dimethylpyrrocoline (III*d*), similarly prepared, had m. p. 61—62° (Holland and Naylor [2] give m. p. 63°), $\lambda_{max.}$ 243, 284, 294, 305, 360 mμ (ε 28,000, 1800, 2350, 2700, 1900).

Pyrrocolines (III*b*), (III*c*), and (III*e*) formed pale yellow fluorescent oils. All had the strong naphthalene-like smell characteristic of alkylpyrrocolines, and decomposed rapidly in air.

3-*Acetyl*-1-2′-(*tertiary amino*)*alkylpyrrocolines*.—1 : 5-Bis(dimethyl amino)-2 : 4-dimethyl-3-2′-pyridylpentan-3-ol (V*b*) (69 g.) and acetic anhydride (700 ml.) were boiled under reflux for 24 hr. After removal of excess of anhydride the product was poured into water and extracted with ether. The ether layer was discarded. The aqueous layer was basified by 5N-sodium hydroxide and extracted with ether. After removal of the ether the oil was distilled. The fraction (25 g.) having b. p. 160—164°/0·5 mm. solidified and after crystallisation from light petroleum (b. p. 40—60°) gave 3-*acetyl*-1-(2-*dimethylamino*-1-*methylethyl*)-2-*methylpyrrocoline* (VI*b*) (18 g.) as pale yellow prisms, m. p. 72°. The colourless *oxalate* (from ethanol) had m. p. 178°. The colourless *methiodide*, prepared in acetone, had m. p. 201° (Found: C, 50·9; H, 6·5; N, 6·9; I, 32·1. $C_{17}H_{25}ON_2I$ requires C, 51·0; H, 6·25; N, 7·0; I, 31·8%).

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

The *aminoalkylpyrrocolines* (VI*a*, *c*, and *d*) (Table 2) were prepared similarly.

1-(2-*Dimethylamino*-1-*methylethyl*)-2-*methylpyrrocoline*.—The acetylpyrrocoline (11 g.) and concentrated hydrochloric acid (50 ml.) were boiled till the initial deep yellow colour disappeared (*ca.* 2 min.). The mixture was cooled, basified with ammonia, and extracted with ether, and the ether evaporated to give the pyrrocoline (VII*b*) as a yellow oil, $\lambda_{max.}$ 243, 280, 290, 301, and 350 mμ (ε 29,600, 2000, 2700, 3000, 2300). The colourless *oxalate*, prepared in ethanol–ether, had m. p. 138—140° (Found: C, 62·5; H, 7·1; N, 9·4. $C_{16}H_{22}O_4N_2$ requires C, 62·8; H, 7·2; N, 9·2%). The *methiodide*, prepared in ethanol–ether, had m. p. 177° (Found: C, 50·3; H, 6·2; I, 35·4. $C_{15}H_{23}N_2I$ requires C, 50·3; H, 6·4; I, 35·5%).

Attempted Preparation of 2-(*Tertiary amino*)*methylpyrrocolines*.—When the amino-2-pyridylalkanols (I*f*) and (I*g*) were submitted to cyclisation as described above, no pyrrocoline derivative could be detected in the products by ultraviolet spectroscopy.

4-*Acetyl*-2 : 3-*dihydro*-1H-cyclo*penta*[a]*pyrrocoline* (XIV*a*).—2-Dimethylaminomethyl*cyclo*pentanone (58 g.) was treated with 2-pyridyl-lithium as described in Part III,[12] to give mixed isomers of 2-*dimethylaminomethyl*-1-2′-*pyridyl*cyclo*pentanol* (X*a*) (46 g.), b. p. 112—118°/0·2 mm. (Found: C, 72·0; H, 9·0; N, 12·0. $C_{13}H_{20}ON_2$ requires C, 70·9; H, 9·1; N, 12·7%). The *cyclo*pentanol and acetic anhydride (460 ml.) were boiled for 6 hr. After removal of excess of anhydride the product was poured into water and extracted with ether. The ether layer was washed with 0·5N-hydrochloric acid (2 × 75 ml.) and evaporated. The residue, on crystallisation from light petroleum (b. p. 40—60°), gave the cyclo*penta*[a]*pyrrocoline* (XIV*a*) (0·9 g.) as straw-coloured prisms, m. p. 109—110° (Found: C, 78·5; H, 6·6; N, 7·4. $C_{13}H_{13}ON$ requires C, 78·5; H, 6·6; N, 7·1%), $\lambda_{max.}$ 230, 256, 275, 371, and 383 mμ (ε 21,500, 12,200, 25,700, 13,600, and 12,200). The aqueous filtrate and acid washings were combined and basified. The oil was extracted with ether, and the ether evaporated. The residue (27 g.) and acetic anhydride were boiled for 6 hr. On working up as above, no further pyrrocoline was isolated. The basic oil (22 g.) (Found: Ac, 4·3%) was hydrolysed by boiling with 2N-hydrochloric acid (100 ml.) for 2 hr., and on working up gave the *trans*-alcohol (X*a*) (19 g.), b. p. 108—110°/0·4 mm. (Found: C, 71·0; H, 9·0; N, 11·5%). The *trans*-alcohol (19 g.) was heated in concentrated sulphuric acid (190 ml.) on the steam-bath for ¼ hr. After pouring on ice and working up in the usual way there was obtained a mixture of 2-dimethylaminomethyl-1- (XII*a*) and 3-dimethylamino-2-2′-pyridyl*cyclo*pentene (XIII*a*) (15 g.) (Found: C, 76·7; H, 8·9; N, 13·7. Calc. for $C_{13}H_{18}N_2$: C, 77·2; H, 9·0; N, 13·9), $\lambda_{max.}$ 250 and 284 (ε 9500 and 6800). Cyclisation by the method described in Part VII [1] afforded the pyrrocoline (XIV*a*) (1·5 g.), m. p. and mixed m. p. 109—110°, and recovered *cyclo*pentene (XIII*a*), (9 g.) b. p. 98—108°/0·5 mm. (Found: C, 77·0; H, 8·7%).

6-*Acetyl*-7 : 8 : 9 : 10-*tetrahydrobenzo*[a]*pyrrocoline* (XIV*b*).—(i) 2-Dimethylaminomethyl-*cyclo*hexanone (39 g.) with 2-pyridyl-lithium gave mixed isomers of 2-*dimethylaminomethyl*-1-2′-*pyridyl*cyclo*hexanol* (X*b*) (42 g.), b. p. 140—144°/2·5 mm. (Found: C, 71·9; H, 9·3; N, 11·5. $C_{14}H_{22}ON_2$ requires C, 71·8; H, 9·4; N, 12·0%), $\lambda_{max.}$ 260 mμ (ε 3400). The *oxalate* (from ethanol) had m. p. 174—176° (Found: C, 59·5; H, 7·4; N, 8·5. $C_{14}H_{22}ON_2,C_2H_2O_4$ requires C, 59·3; H, 7·4; N, 8·7%). The hexanol (X*b*) (50 g.) and acetic anhydride (500 ml.) were boiled for 6 hr. Working up as described above gave a non-basic solid (4·0 g.) which on crystallisation from light petroleum (b. p. 60—80°) gave 6-*acetyl*-7 : 8 : 9 : 10-*tetrahydrobenzo*-[a]*pyrrocoline* (XIV*b*) (1·2 g.), yellow prisms, m. p. 117° (Found: C, 78·8; H, 6·9; N, 6·5. $C_{14}H_{15}ON$ requires C, 78·9; H, 7·1; N, 6·6%), $\lambda_{max.}$ 230, 276 and 370 mμ (ε 19,000, 21,000, and 13,000). The filtrate and washings afforded a basic oil (49 g.), which was boiled for a further 6 hr. with acetic anhydride (500 ml.). Working up gave the pyrrocoline (XIV*b*) (0·4 g.) and a basic oil (46 g.). The oil was boiled for a third period of 6 hr. with acetic anhydride. Working up gave a basic oil (42 g.), but no isolable pyrrocoline. The oil, when distilled, gave trans-2-*dimethylaminomethyl*-1-2′-*pyridyl*cyclo*hexyl acetate* (XI*b*) (38 g.), b. p. 136—138°/0·5 mm. (Found: C, 69·7; H, 8·7; N, 9·5; Ac, 15·0. $C_{16}H_{24}O_2N_2$ requires C, 69·6; H, 8·7; N, 10·1; Ac, 15·6%). The acetate was hydrolysed for 2 hr. with boiling 2N-hydrochloric acid (200 ml.). The recovered *trans*-alcohol (31 g.) on dehydration gave mixed *cyclo*alkenes (XII*b*) and (XIII*b*) (19 g.) [$\lambda_{max.}$ 242, 276 mμ (ε 7800, 5000)], which were separated and behaved on cyclisation as described below.

(ii) Mixed isomeric hexanols (X*b*) (40 g.) were dehydrated in concentrated sulphuric acid (200 ml.) on the steam-bath for ¼ hr., affording an oil (29 g.), which partially solidified. The solid (10 g.) was filtered off and crystallised from light petroleum (b. p. 40—60°), to give

3-*dimethylaminomethyl*-2-2′-*pyridyl*cyclo*hexene* (XIII*b*), m. p. 43—45° (Found: C, 77·7; H, 9·2; N, 12·9. $C_{14}H_{20}N_2$ requires C, 77·8; H, 9·3; N, 13·0%), $\lambda_{max.}$ 243 and 280 mμ (ε 9000 and 7800); the *oxalate* (from ethanol) had m. p. 190—191° (Found: C, 62·9; H, 7·2; N, 8·7. $C_{16}H_{22}O_4N_2$ requires C, 62·8; H, 7·2; N, 9·2%). The oily filtrate (19 g.) was converted into its oxalate in ethanol (200 ml.) and next morning the oxalate of (XIII*b*) (12·8 g.) was filtered off (m. p. and mixed m. p. 189—191°). On basification it gave the base (8·2 g.), m. p. and mixed m. p. 42—44°. The filtrate from the oxalate preparation was evaporated to dryness, and the residue converted into a base, which was distilled to give an oil (9·0 g.), b. p. 108—114°/0·1 mm., substantially 2-dimethylaminomethyl-1-2′-pyridyl*cyclo*hexene (XII*b*), $\lambda_{max.}$ 242 and 280 mμ (ε 8500 and 7500). On cyclisation by the usual method it gave acetylpyrrocoline (XIV*b*) (2·4 g.), m. p. and mixed m. p. 116—117°. The *cyclo*hexene (XIII*b*) (42 g.), submitted to the usual cyclisation procedure,[1] was recovered unchanged (38 g.; m. p. and mixed m. p. 42—44°).

6-*Acetyl*-8 : 9 : 10 : 11-*tetrahydro*-7-cyclo*hepta*[a]*pyrrocoline* (XIV*c*).—(i) 2-Dimethylaminomethyl*cyclo*heptanone (85 g.) with 2-pyridyl-lithium gave 2-*dimethylaminomethyl*-1-2′-*pyridyl*-cyclo*heptanol* (X*c*) (117 g.), b. p. 140—143°/0·4 mm. (Found: C, 72·4; H, 9·4; N, 11·5. $C_{15}H_{24}ON_2$ requires C, 72·6; H, 9·7; N, 11·3%). The *oxalate* (from ethanol) had m. p. 162—164° (Found: C, 60·3; H, 7·8; N, 7·8. $C_{17}H_{26}O_5N_2$ requires C, 60·4; H, 7·7; N, 8·3%). The *methiodide*, prepared in acetone and crystallised from methanol, had m. p. 210—211° (decomp.) (Found: C, 49·2; H, 7·0; N, 7·0; I, 32·4. $C_{16}H_{27}ON_2I$ requires C, 49·2; H, 7·0; N, 7·2; I, 32·6%). The *cyclo*heptanol (50 g.) was cyclised as described above for the *cyclo*pentanol (X*a*) to give (i) a non-basic oil (2·5 g.), substantially the acetylpyrrocoline (XIV*c*), $\lambda_{max.}$ 232, 268, 276, and 374 mμ (ε 16,000, 13,000, 14,000, and 7000), from which the pure compound was not isolated, and (ii) a basic oil which was distilled (b. p. 140—150°/0·6 mm.) (36 g.) and recrystallised from light petroleum (b. p. 40—60°) to give trans-2-*dimethylaminomethyl*-1-2′-*pyridyl*cyclo*heptyl acetate* (XI*c*) (17 g.), m. p. 52—54° (Found: C, 70·2; H, 8·8; N, 9·5; Ac, 15·1. $C_{17}H_{26}O_2N_2$ requires C, 70·4; H, 8·9; N, 9·6; Ac, 14·8%). (ii) The *cyclo*heptanol (X*c*) (19 g.) was dehydrated in concentrated sulphuric acid at 100° for ¼ hr. Working up gave substantially the mixed (or a pure) *cyclo*heptenes (XII*c* and/or XIII*c*) (7 g.), $\lambda_{max.}$ 244 and 277 mμ (ε 9400 and 7500). On cyclisation no pyrrocoline was isolated.

7 : 8 : 9 : 10-*Tetrahydrobenzo*[a]*pyrrocoline*.—The acetylpyrrocoline (XIV*b*) was hydrolysed as described above, and the crude product sublimed *in vacuo* to give the colourless *pyrrocoline* (XV*b*), m. p. 59—60° depressed on admixture with the parent acetyl compound to 42—45° (Found: C, 84·4; H, 7·4; N, 8·4. $C_{12}H_{13}N$ requires C, 84·2; H, 7·6; N, 8·2%), $\lambda_{max.}$ 244, 250, 287, 296, 308, and 360 mμ (ε 29,000. 30,000, 2300, 3000, 4200, 2100).

4-*Acetyl*-1-*dimethylaminomethyl*-2 : 3-*dihydro*-1H-cyclo*penta*[a]*pyrrocoline* (XIV*d*).—The diamino-ketone (IX*d*) (44 g.) was treated with 2-pyridyl-lithium to give 2 : 5-*bisdimethylaminomethyl*-1-2′-*pyridyl*cyclo*pentanol* (31 g.), b. p. 135—137°/0·5 mm. (Found: C, 69·6; H, 9·5; N, 14·7. $C_{16}H_{27}ON_3$ requires C, 69·4; H, 9·8; N, 15·2%). This (30 g.) was cyclised as described above. After removal of excess of anhydride the product was poured into water. The aqueous layer was decanted from tar and basified, and the oil isolated with ether and extracted with boiling light petroleum (b. p. 40—60°). The light petroleum extracts were evaporated to give an oil (3·5 g.) shown by light absorption [$\lambda_{max.}$ 230, 270, and 370 mμ (ε 5400, 5500, and 1200)] to contain *ca.* 10% of acetyl-pyrrocoline, probably (XIV*d*).

6-*Acetyl*-10-*dimethylaminomethyl*-7 : 8 : 9 : 10-*tetrahydrobenzo*[a]*pyrrocoline* (XIV*e*)—(i) 2 : 6-Bisdimethylaminomethyl*cyclo*hexanone (80 g.) with 2-pyridyl-lithium gave mixed isomers of 2 : 6-*bisdimethylaminomethyl*-1-2′-*pyridyl*cyclo*hexanol* (X*e*) (55 g.), b. p. 140—155°/0·5 mm. (Found: C, 70·1; H, 9·8; N, 14·1. $C_{17}H_{29}ON_3$ requires C, 70·1; H, 10·0; N, 14·4%). This (52 g.) was boiled with acetic anhydride (500 ml.) for 6 hr. After removal of excess of anhydride the product was poured into water. The solution was filtered (charcoal) from tar and basified. The liberated oil (26 g.) was isolated with ether and distilled, three fractions being collected: (i) 150—160°/0·5 mm. (11 g.), (ii) 160—190°/0·5 mm. (8 g.), and (iii) 190—195°/0·5 mm. (3·9 g.). The orange, viscous fraction (iii) solidified after several days and crystallised from light petroleum (b. p. 40—60°), to give 6-*acetyl*-10-*dimethylaminomethyl*-7 : 8 : 9 : 10-*tetrahydrobenzo*[a]*pyrrocoline* (XIV*e*) (1·7 g.) as cream-coloured crystals, m. p. 70—71° (Found: C, 75·2; H, 8·3; N, 10·6. $C_{17}H_{22}ON_2$ requires C, 75·5; H, 8·2; N, 10·4%), $\lambda_{max.}$ 230, 275, 370, and 382 mμ (ε 19,000, 20,000, 11,500, and 10,400). The sparingly soluble *oxalate* separated as a gel from cold ethanol, but became crystalline on boiling. It had m. p. 240—241° (Found: C, 63·3; H, 6·6; N, 7·7. $C_{19}H_{24}O_5N_2$ requires C, 63·4; H, 6·7; N, 7·8%). The cream-coloured

methiodide, prepared in acetone and crystallised from methanol, had m. p. 265° (decomp.) (Found: C, 52·7; H, 6·2; N, 6·7; I, 31·0. $C_{18}H_{25}ON_2I$ requires C, 52·4; H, 6·1; N, 6·8; I, 30·8%), $\lambda_{max.}$ 229, 272, and 363 mμ (ε 31,000, 24,000, and 12,600). Fraction (i) solidified and, crystallised from light petroleum (b. p. 40—60°), gave trans-trans-2 : 6-*bisdimethylaminomethyl*-1-2′-*pyridyl*cyclo*hexyl acetate* (XI*e*) (4·2 g.), prisms, m. p. 76—78° (Found: C, 68·8; H, 9·2; N, 12·3; Ac, 14·8. $C_{19}H_{31}O_2N_3$ requires C, 68·5; H, 9·3; N, 12·6; Ac, 12·9%). The colourless *dioxalate* (from ethanol) had m. p. 185—186° (Found: C, 52·8; H, 7·2; N, 7·7. $C_{23}H_{35}O_{10}N_3$ requires C, 53·8; H, 6·8; N, 8·2%). The residues from the crystallisation of fraction (i) were combined with fraction (ii) and converted into the oxalate in ethanol. The precipitated mixed oxalates of the pyrrocoline (XIV*e*) and *cyclo*hexyl acetate (XI*e*) were filtered off. The filtrate was evaporated and the residue dissolved in water, basified, and extracted three times with ether. The ether was evaporated to an oil which was distilled. The fraction having b. p. 150—165°/0·2 mm. solidified after several days and, crystallised from light petroleum (b. p. 60—80°), gave trans-trans-2-*acetoxymethyl*-6-*dimethylaminomethyl*-1-2′-*pyridyl*-cyclo*hexyl acetate* (XI*g*) (2·3 g.), prisms, m. p. 100° (Found: C, 65·6; H, 8·3; N, 8·0; Ac, 24·2. $C_{19}H_{28}O_4N_2$ requires C, 65·6; H, 8·0; N, 8·0; Ac, 24·8%).

(ii) The *cyclo*hexanol (X*e*) (59 g.) was heated in acetic anhydride (500 ml.) till just boiling, and the excess of anhydride then immediately removed *in vacuo*. The residue was poured into water and cautiously basified with ammonia. The liberated oil (59 g.) was isolated by 3 extractions with ether and substantially solidified. Recrystallisation from light petroleum (b. p. 40—60°) gave the *trans-trans*-acetate (XI*e*) (40 g.), m. p. and mixed m. p. 76—78°. The residual mixed isomeric acetates (21 g.) on cyclisation behaved as described under (i).

(iii) The *trans-trans-cyclo*hexyl acetate (XI*e*) (20 g.), submitted to cyclisation, was substantially recovered unchanged (15 g.); m. p. and mixed m. p. 183—185°. There was also isolated the diacetate (XI*g*) (1·3 g.), m. p. and mixed m. p. 99—100°.

6-*Acetyl*-11-*dimethylaminomethyl*-8 : 9 : 10 : 11-*tetrahydro*-7H-cyclo*hepta*[a]*pyrrocoline* (XIV*f*).—(i) *Cyclisation of the mixed* cyclo*heptanols* (X*f*). 2 : 7-Bisdimethylaminomethyl-*cyclo*heptanone (IX*f*) (68 g.) with 2-pyridyl-lithium gave mixed isomers of 2 : 7-*bisdimethylaminomethyl*-1-2′-*pyridyl*cyclo*heptanol* (X*f*) (42 g.), b. p. 152—156°/0·4 mm. (Found: C, 71·2; H, 10·3; N, 13·7. $C_{18}H_{31}ON_3$ requires C, 70·8; H, 10·2; N, 13·8%). This material was boiled with acetic anhydride (420 ml.) for 6 hr. The excess of anhydride was removed and the residue dissolved in water, basified with ammonia, and extracted with ether,[6] tar being filtered off. The ether was evaporated to an oil (36 g.), which was freed from resin by dissolution in hot light petroleum (b. p. 40—60°). The light petroleum extracts were evaporated to an oil (30 g.) which was converted into the oxalate in ethanol. The precipitated oxalate was filtered off, washed, dried (13 g.; m. p. 210°), and crystallised from methanol, to give 6-*acetyl*-11-*dimethylaminomethyl*-8 : 9 : 10 : 11-*tetrahydro*-7H-cyclo*hepta*[a]*pyrrocoline oxalate* (cf. XIV*f*) (10 g.) as fawn-coloured needles, m. p. 210° (Found: C, 64·3; H, 7·0; N, 7·5. $C_{18}H_{24}ON_2,C_2H_2O_4$ requires C, 64·2; H, 7·0; N, 7·5%), $\lambda_{max.}$ 230, 272, and 366 mμ (ε 27,000, 21,000, and 11,500). The base formed an amber oil. The *methiodide*, prepared in acetone and crystallised from ethanol, formed almost colourless prisms, m. p. 242—244° (decomp.) (Found: C, 53·6; H, 6·9; N, 6·0; I, 27·2; loss at 100° *in vacuo*, 8·7. $C_{19}H_{27}ON_2I,C_2H_5{\cdot}OH$ requires C, 53·4; H, 7·0; N, 5·9; I, 27·0; loss, 9·7. Found, on a dried sample: C, 54·1; H, 6·3; N, 6·6; I, 29·7. $C_{19}H_{27}ON_2I$ requires C, 53·5; H, 6·4; N, 6·6; I, 29·8%), $\lambda_{max.}$ 232, 262, and 366 mμ (ε 31,000, 21,000, and 11,000). The filtrate from the oxalate preparation was evaporated. To the residue water and ether were added and the whole was basified by aqueous ammonia. The ether was evaporated and the residual oil (16 g.) was distilled. The fraction having b. p. 190—210°/0·5 mm. (10 g.) was dissolved in ether and washed several times with N-hydrochloric acid. The residue (5 g.) left on evaporation of the ether layer was recrystallised several times from light petroleum (b. p. 60—80°), to give 11-*acetoxymethyl*-6-*acetyl*-8 : 9 : 10 : 11-*tetrahydro*-7H-cyclo*hepta*[a]*pyrrocoline* (XIV*h*) (3·7 g.), pale yellow prisms or needles, m. p. 112° (Found: C, 72·2; H, 6·9; N, 4·6; Ac, 29·0. $C_{18}H_{21}O_3N$ requires C, 72·3; H, 7·0; N, 4·7; Ac, 28·8%), $\lambda_{max.}$ 231, 274, 368, and 383 (infl.) (ε 26,000, 23,000, 13,000, and 11,600).

(ii) *Separation of* cis-trans- *and* trans-trans-cyclo*heptanols* (X*f*) via *the* cyclo*heptyl acetate oxalates* (XI*f*). A second preparation of mixed *cyclo*heptanols (X*f*) (133 g.) (b. p. 160—170°/0·5 mm.) substantially solidified and, recrystallised from light petroleum (b. p. 40—60°) at *ca.* −20°, gave a solid mixture (A) of *cis-trans-* and *trans-trans-cyclo*heptanol (X*f*) (74 g.), m. p. 45—55°, and non-crystallisable residues (B; 62 g.). The solid (A) was heated in acetic anhydride (300

ml.) till just boiling, the excess of anhydride immediately removed *in vacuo*, and the acetate isolated by basification and ether-extraction (four times). The mixed acetates were converted into the oxalate in ethanol with anhydrous oxalic acid (50 g.), precipitation being initiated by addition of a little ether. After 4 hr., the oxalate was filtered off (filtrate C), washed with ethanol and ether (40 g.; m. p. 180—185°), and recrystallised from methanol, to give cis-trans-2 : 7-bisdimethylaminomethyl-1-2′-pyridyl*cyclo*hexyl acetate oxalate (as XI*f*) (32 g.), prisms, m. p. 195—196°. It was dissolved in a little water and basified. The solid base was filtered off, washed, dried, and crystallised from light petroleum (b. p. 40—60°) to give cis-trans-2 : 7-*bisdimethylaminomethyl*-1-2′-*pyridyl*cyclo*heptyl acetate* (XI*f*) (18 g.), m. p. 87—89°, depressed to 56—62° on admixture with the *trans-trans*-isomer described below (Found: C, 69·7; H, 9·7; N, 12·1; Ac, 12·5. $C_{20}H_{33}O_2N_3$ requires C, 69·2; H, 9·5; N, 12·1; Ac, 12·4%). Hydrolysis with 2N-hydrochloric acid on the steam-bath for 2 hr. and crystallisation of the crude product from light petroleum (b. p. 40—60°) gave cis-trans-2 : 7-*bisdimethylaminomethyl*-1-2′-*pyridyl*-cyclo*heptanol* (X*f*), m. p. 84—86°, depressed to 58—61° on admixture with the *trans-trans*-isomer described below (Found: C, 70·8; H, 9·6; N, 14·0. $C_{18}H_{31}ON_3$ requires C, 70·8; H, 10·2; N, 13·8%).

The filtrate C was evaporated and the residue converted into a base, which slowly solidified and, recrystallised from light petroleum (b. p. 40—60°) at *ca.* −20°, gave trans-trans-2 : 7-*bisdimethylaminomethyl*-1-2′-*pyridyl*cyclo*heptyl acetate* (XI*f*) (25 g.), m. p. 86°, depressed to 53—60° on admixture with the *cis-trans*-isomer (Found: C, 68·7; H, 9·3; N, 11·4; Ac, 13·0%). The oxalate separated from a small volume of ethanol only on addition of ether. It was difficult to recrystallise and was not obtained pure. The *trans-trans*-acetate (XI*f*) (2 g.) and 2N-hydrochloric acid (20 ml.) were heated on the steam-bath for 2 hr., cooled, and basified. The oil solidified and was filtered off, washed, dried, and recrystallised from light petroleum (b. p. 40—60°) at *ca.* −20°, to give trans-trans-2 : 7-*bisdimethylaminomethyl*-1-2′-*pyridyl*cyclo*heptanol* (X*f*), m. p. 82°, depressed to 56—61° on admixture with the *cis-trans*-heptanol described above (Found: C, 70·6; H, 10·0; N, 14·0. $C_{18}H_{31}ON_3$ requires C, 70·8; H, 10·2; N, 13·8%). The non-crystallisable residue (B) (62 g.), acetylated and separated as described above, gave *cis-trans*-acetate oxalate (as XI*f*) (10 g.), m. p. 194°, and *trans-trans*-acetate (XI*f*), m. p. and mixed m. p. 86—87°.

An earlier preparation of mixed *cyclo*heptanols (X*f*) (b. p. 155—160°/0·5 mm.) (149 g.) partially solidified during several days and crystallised at *ca.* −20° from light petroleum (b. p. 40—60°) (300 ml.); washing with cold solvent gave the pure *cis-trans-cyclo*heptanol (X*f*) (60 g.), m. p. 82°, not depressed on admixture with the sample described above. In all subsequent preparations the solid *cyclo*heptanol proved to be a mixture of the *cis-trans-* and *trans-trans*-forms as described above.

(iii) *Cyclisation of the* cis-trans-*acetate* (XI*f*). The acetate (14 g.) and acetic anhydride (150 ml.) were boiled for 6 hr. Working up as described under (i) gave acetylpyrrocoline oxalate (cf. XIV*f*) (8 g.), m. p. and mixed m. p. 209°, a non-basic oil (3·8 g.) which partially solidified when seeded with acetoxymethylpyrrocoline (XIV*h*), and a basic oil (2 g.) which did not solidify when seeded with either of the isomeric acetates (XI*f*).

(iv) *Cyclisation of the* trans-trans-*acetate* (XI*f*). The acetate (20 g.) and acetic anhydride (200 ml.) were boiled for 6 hr. After removal of excess of anhydride the product was poured into water, basified and extracted three times with ether. The ether extracts on evaporation gave solid (15 g.) which was distilled. The fraction having b. p. 150—160°/0·5 mm. (11 g.) crystallised from light petroleum (b. p. 40—60°), to give recovered *trans-trans*-acetate (XI*f*) (9·2 g.), m. p. and mixed m. p. 86—87°. The residue in the distillation flask gave no solid oxalate when treated in ethanol with oxalic acid.

11-*Dimethylaminomethyl*-8 : 9 : 10 : 11-*tetrahydro*-7H-cyclo*hepta*[a]*pyrrocoline* (XV*f*).—The acetyl compound (XIV*f*) was hydrolysed as described above, and the crude product sublimed at 130°/0·5 mm., to give the colourless *pyrrocoline* (XV*f*), m. p. 82—83°. The compound also crystallised well from light petroleum (b. p. 40—60°) as large colourless prisms (Found: C, 79·2; H, 9·0; N, 11·5. $C_{16}H_{22}N_2$ requires C, 79·4; H, 9·1; N, 11·6%), $\lambda_{max.}$ 243, 283, 292, 303, and 360 mμ (ε 31,000, 2000, 2500, 2800, and 2300). The almost colourless *oxalate*, crystallised from ethanol, had m. p. 175—178° (decomp.) (Found: C, 64·4; H, 7·3; N, 8·2. $C_{18}H_{24}O_4N_2$ requires C, 65·0; H, 7·3; N, 8·4%). The fawn *methiodide*, prepared in methanol, had m. p. 175—180° (decomp.) (Found: C, 53·4; H, 6·5; I, 32·7. $C_{17}H_{25}N_2I$ requires C, 53·2; H, 6·5; I, 33·1%).

10-*Acetyl*-1 : 2 : 3 : 4-*tetrahydrobenzo*[b]*pyrrocoline* (XIX).—2-Dimethylamino*cyclo*hexanone [13] (36 g.) with 2-pyridylmethyl-lithium [14] by the usual method gave 2-*dimethylamino*-1-2′-*pyridylmethyl*cyclo*hexanol* (XVIII) (31 g.), b. p. 140—150°/0·5 mm. (Found: C, 72·4; H, 8·9; N, 11·5. $C_{14}H_{22}ON_2$ requires C, 71·8; H, 9·4; N, 12·0%). This was boiled with acetic anhydride (300 ml.) for 6 hr. After removal of excess of anhydride the product was poured into water. A viscous oil separated which partially solidified. The aqueous layer (A) was decanted and the semi-solid was lixiviated with a little ether and filtered off. It crystallised from ethanol, to give the pyrrocoline (XIX) (3·5 g.), yellow needles, m. p. 154° (Arata [15] gives m. p. 152°) (Found: C, 79·0; H, 7·1; O, 7·6. Calc. for $C_{14}H_{15}ON$: C, 78·9; H, 7·1; O, 7·5%), $\lambda_{max.}$ 237, 274, 283, 364, and 380 (infl.) mμ (ε 26,000, 4400, 4000, 14,000, and 11,000). The aqueous layer (A) was basified and the liberated oil extracted with ether and distilled, the fraction having b. p. 125—132°/0·5 mm. being collected (Found: N, 6·3; Ac, 16·7. $C_{14}H_{17}O_2N$ requires N, 6·1; Ac, 18·5%), $\lambda_{max.}$ 242, 270, and 278 mμ (ε 8000, 5900, 5600).

4-*Hydroxy*-1-*methyl*-4-2′-*pyridylpiperidine* (XVI).—*N*-Methylpiperidone [16] (57 g.) reacted with 2-pyridyl-lithium in the usual way, giving a solid (47 g.), which, by crystallisation from light petroleum (b. p. 40—60°) and then from acetone, gave the *alcohol* (XVI) (35 g.) as large prisms, m. p. 84—85° (Found: C, 68·7; H, 7·9; N, 14·5. $C_{11}H_{16}ON_2$ requires C, 68·8; H, 8·3; N, 14·6%), $\lambda_{max.}$ 258 mμ (ε 3000). This (5 g.) and acetic anhydride (50 ml.) were boiled for 6 hr. After removal of the excess of anhydride the product was dissolved in water, basified, and extracted with ether three times, affording a solid (4·5 g.) which on crystallisation from light petroleum (b. p. 40—60°) gave 1-*methyl*-4-2′-*pyridylpiperidin*-4-*yl acetate*, rods, m. p. 88—89°, depressed to 58—72° on admixture with the alcohol (Found: C, 67·2; H, 7·7; N, 11·9. $C_{13}H_{18}O_2N_2$ requires C, 66·7; H, 7·7; N, 12·0%). The product was very clean, and no pyrrocoline was detected by ultraviolet spectroscopy.

1 : 2 : 5 : 6-*Tetrahydro*-1-*methyl*-4-2′-*pyridylpyridine* (XVII).—Thionyl chloride (4·7 g.) in benzene (5 ml.) was added dropwise to the hydroxy-piperidine (XVI) (5 g.) in benzene (16 ml.) at 0°, and the mixture then boiled under reflux for 2 hr. Excess of thionyl chloride was removed *in vacuo*, and the residue treated with water, filtered, and evaporated *in vacuo*. The residue, recrystallised from ethanol, gave the tetrahydropyridine hydrochloride (4·5 g.), m. p. 200—202°. Analysis suggested that this was a mixture of mono- and di-hydrochlorides. The *base* had b. p. 148—151°/10 mm., m. p. 36—38° (Found: C, 75·6; H, 7·7; N, 16·5. $C_{11}H_{14}N_2$ requires C, 75·9; H, 8·0; N, 16·1%), $\lambda_{max.}$ 240 and 270 mμ (ε 7800 and 4300). After its submission to the usual cyclisation procedure, no pyrrocoline was detected in the product.

2-*Phenyl*-3-*piperidino*-1-2′-*pyridylpropan*-2-*ol*.—ω-Piperidinoacetophenone [17] (70 g.) with 2-pyridylmethyl-lithium [14] gave an oily undistillable propanol (103 g.). This was dissolved in ethanol (250 ml.) and treated with hydrogen chloride till just acid to Congo-red. Sufficient ether was added to produce a slight permanent turbidity, and the mixture left overnight. The solid (73 g.) was filtered off and recrystallised from ethanol, to give the *dihydrochloride* (63 g.), m. p. 188° (decomp.) (Found: C, 61·3; H, 7·5; N, 7·3; Cl, 18·7. $C_{19}H_{26}ON_2Cl_2$ requires C, 61·8; H, 7·1; N, 7·6; Cl, 19·3%). The *base*, crystallised from light petroleum (b. p. 40—60°), had m. p. 59—60° (Found: C, 77·1; H, 8·2; N, 9·4. $C_{19}H_{24}ON_2$ requires C, 77·1; H, 8·1; N, 9·5%), $\lambda_{max.}$ 259 (infl.), 263, and 267 (infl.) mμ (ε 4650, 5200, and 4250). After submission to cyclisation by the usual method, no pyrrocoline could be isolated from the product.

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[13] Mousseron, Jullien, and Canet, *Compt. rend.*, 1950, **231**, 479.
[14] Goldberg, Barkley, and Levine, *J. Amer. Chem. Soc.*, 1951, **73**, 4301.
[15] Arata, *J. Pharm. Soc. Japan*, 1955, **75**, 265.
[16] McElvain and Rorig, *J. Amer. Chem. Soc.*, 1948, **70**, 1820.
[17] Dufraisse and Moureu, *Bull. Soc. chim. France*, 1927, **41**, 472.