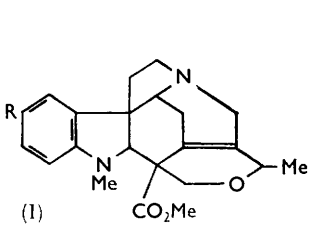
53. *Akuamma Alkaloids. Part V.* Akuammine and ψ-Akuammigine.*

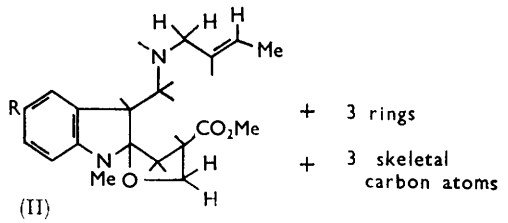
By J. A. Joule and G. F. Smith.

Akuammine and ψ-akuammigine are shown to differ only in the presence of a phenolic hydroxyl in the former. Several new reactions of akuammine and of ψ-akuammigine are described, which together lead to the proposal of partial structure (II; R = OH or H, respectively) for these bases, it being assumed that there is no skeletal rearrangement in their conversion by acid into the apo- bases.

Akuammine and ψ-akuammigine, two of the alkaloids of *Picralima klaineana*, were first isolated and characterised by Henry and Sharp.[1,2] Akuammine was given the molecular formula $C_{22}H_{28}N_2O_4$ and was found to contain one *N*-methyl group, one methoxyl group, and to form mono-acetyl and -benzoyl derivatives. The molecular formula was altered to $C_{22}H_{26}N_2O_4$ by Millson, Robinson, and Thomas,[3] who found one *C*-methyl group, one phenolic hydroxyl, an ester carbonyl, and isolated 3-ethylpyridine by zinc dust distillation. Vincamajoridine, isolated by Janot and Le Men [4] from *Vinca major*, was subsequently shown to be akuammine.[5] That the position of the hydroxyl group in akuammine is *para* to the aromatic nitrogen was proposed by Robinson and his co-workers on the basis of colour reactions and infrared spectroscopy [3] and by a comparison of the ultraviolet spectrum of akuammine with that of hexahydro-6-methoxy-9,11-dimethylcarbazole.[7] Janot and Le Men arrived at the same conclusion by comparison of the ultraviolet spectrum



(I)



(II)

of akuammine with that of eseroline.[4] We have found [8] that *O*-methylakuammine, prepared by the action of diozomethane on akuammine, has an ultraviolet spectrum almost identical with that of hexahydro-6-methoxycarbazole, and that an indolic degradation product of *O*-methylakuammine has an untraviolet spectrum almost identical with that of 1,2,3,4-tetrahydro-6-methoxycarbazole.

ψ-Akuammigine was found by Henry [2] to have the molecular formula $C_{22}H_{26}N_2O_3$. Robinson and his co-workers [3] found the infrared spectrum of this base to be very similar to that of akuammine and considered the base to be deoxyakuammine, in which the phenolic hydroxly has been replaced by hydrogen. Robinson and Thomas [6] found this alkaloid to have pK_a 7·35 (akuammine, 7·5) (in aqueous alcohol), not to form acyl derivatives, to be resistant to saponification and catalytic hydrogenation, and to be

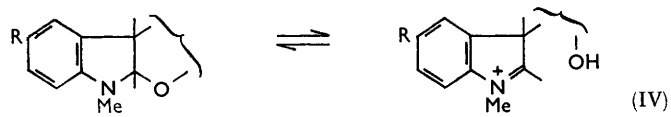
* Part IV, Edwards and Smith, *J.*, 1961, 1458.

[1] Henry and Sharp, *J.*, 1927, 1950.
[2] Henry, *J.*, 1932, 2759.
[3] Millson, Robinson, and Thomas, *Experientia*, 1953, **9**, 89.
[4] Janot and Le Men, *Compt. rend.*, 1954, **238**, 2550; 1955, **240**, 909.
[5] Janot, Le Men, Aghoramurthy, and Robinson, *Experientia*, 1955, **11**, 343.
[6] Robinson and Thomas, *J.*, 1954, 3522.
[7] Millson and Robinson, *J.*, 1955, 3362.
[8] Chalmers, Openshaw, and Smith, *J.*, 1957, 1115.

reduced by lithium aluminium hydride to ψ-akuammigol, for which they proposed the molecular formula $C_{21}H_{26}N_2O_2$. On the basis of colour reactions and the results of dehydrogenations they concluded that these alkaloids belong to the indoline group with a quaternary β-carbon and tentatively proposed structures (I; R = OH or H) for them.[6] We now wish to report our findings, which so far are best accounted for in terms of the partial structures (II; R = OH or H).

We have shown ψ-akuammigine in fact to be a deoxyakuammine by conversion of both ψ-akuammigine and *O*-tosylakuammine into the same base, $C_{22}H_{28}N_2O_3$, by the action of Raney nickel in boiling ethanol in an atmosphere of hydrogen. This was confirmed by a comparison of the mass spectra of ψ-akuammigine and *O*-methylakuammine kindly made by Dr. Biemann.

Robinson and Thomas [6] observed that ψ-akuammigine does not couple with benzenediazonium chloride, and ascribed this to a reduction in the basicity of N(*a*) by the close proximity of the methoxycarbonyl group in structure (I; R = H). We have found that, although the ultraviolet spectra of both ψ-akuammigine and *O*-methylakuammine do not change appreciably in dilute ethanolic hydrochloric acid, as would be expected of a very weakly basic N(*a*), they change radically in concentrated hydrochloric acid to give curves which correspond to the absorption of the Ph·N$^+$:C chromophore. That this change is not due to an acid-catalysed skeletal rearrangement was demonstrated by quantitative recovery on basification. These observations can only be accounted for in terms of the carbinolamine ether system (III). This, together with the proximity of protonated N(*b*), is sufficient to account for the reduced basicity of N(*a*). In incorporating an indoline ring and an *N*(a)-methyl group in (III) we are, for the sake of simplicity, anticipating evidence presented towards the end of this paper. The smooth reconversion of the ion (IV) into the original carbinolamine ether strongly suggests that the ether ring is five- or six-membered, but does not rigorously exclude a four- or a seven-membered ring. It is noteworthy that the *O*-methylakuammine begins to form a 3*H*-indolium ion at much



(III) (IV)

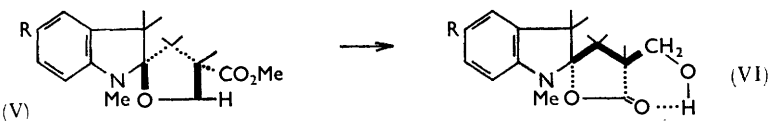
higher pH values than does ψ-akuammigine—ion formation is in fact nearly complete in N-aqueous hydrochloric acid: this may be ascribed to mesomeric electron release by the *para*-methoxyl group in (IV; R = OMe), tending to decrease the δ+ character of the 3*H*-indolium α-carbon atom, and thus to retard the change of (IV; R = OMe) into (III; R = OMe).

The ψ-akuammigine and *O*-methylakuammine ammonium ions are stable under more vigorous acid conditions, for both bases were quantitatively recovered after 3 hr. at 80° in dry methanolic hydrochloric acid. The resistance of ψ-akuammigine to alkaline hydrolysis [6] is paralleled by the observation that prolonged heating of the base in dry *ethanolic* hydrochloric acid does not lead to any detectable transesterification. However, on being heated in aqueous 3N-hydrochloric acid at 80° for 8 hr. ψ-akuammigine is converted into apo-ψ-akuammigine, $C_{21}H_{24}N_2O_3$, and *O*-methylakuammine into *O*-methylapoakuammine, $C_{22}H_{26}N_2O_4$. Both compounds have lost the ester-methoxyl group and are hydroxy-lactones. Apo-ψ-akuammigine shows a carbonyl stretching frequency of 1746 cm.$^{-1}$, its monoacetyl derivative shows two (1747 and 1773 cm.$^{-1}$), and the tetrahydropyranyl ether one, at 1775 cm.$^{-1}$. Mild acid-catalysed hydrolysis of the latter ether smoothly regenerates apo-ψ-akuammigine. These results show apo-ψ-akuammigine to be a γ-lactone, the carbonyl stretching frequency of which is lowered by intramolecular

hydrogen bonding. *O*-Methylapoakuammine behaves in an analogous manner, with a peak at 1756 cm.$^{-1}$, changed to 1778 cm.$^{-1}$ and 1751 cm.$^{-1}$ in the acetyl derivative.

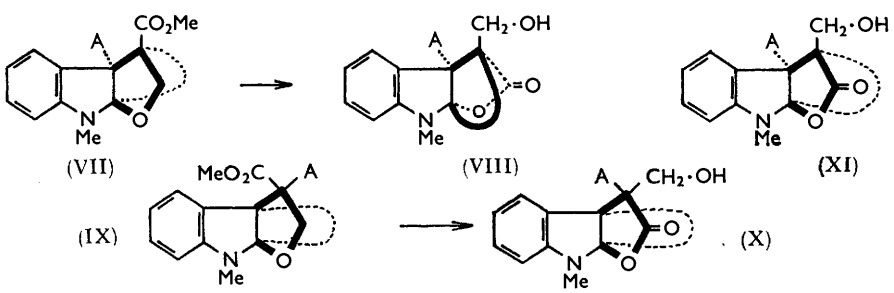
Janot, Le Men, and Levy[9] have demonstrated the presence of the system $HO{\cdot}CH_2{-}\overset{\backslash\ /}{C}{-}CO_2Me$ in the indoline derived by reduction of the ψ-akuammigine ammonium ion (IV; R = H). This arrangement rules out the possibility of lactone formation between the alcoholic hydroxyl and carboxyl group and leads to the conclusion that the lactone ring closes on to the indoline α-carbon atom. If skeletal rearrangement is assumed not to have occurred in the conversion of ψ-akuammigine into apo-ψ-akuammigine, the partial structures of the alkaloids can be extended to (V; R = OMe or H), and those of the apo-bases to (VI; R = OMe or H).* We have so far not been able to establish conclusively the absence of skeletal rearrangement in the change (V) ⟶ (VI). No trace of ψ-akuammigine was produced by the action of dry methanolic hydrochloric acid on apo-ψ-akuammigine, or by the action of diazomethane under various conditions. Attempts to reduce apo-ψ-akuammigine to afford even traces of ψ-akuammigol with lithium aluminium hydride failed, the main product being in all cases a mixture of indolic bases.

The other possible way of accounting for a γ-lactone grouping in the apo-bases is illustrated in formulæ (VII) ⟶ (XI). As is evident from these formulæ, for the conversions to occur without skeletal rearrangement, group A in (VII) and (VIII) must not



be attached to the carbocyclic ring carrying the ester group, and in (IX) and (X) it must not be attached to the ring shown going into the plane of the paper. These limitations we believe rule out partial structures (VII) and (IX) for ψ-akuammigine. One could visualise an epimerisation at the carbon atom carrying the ester and hydroxymethyl groups by reversible fission of the bond between that carbon atom and the indoline β-carbon atom, leading, for example, from (VII) to (XI): this we also believe to be very unlikely.

The change from ψ-akuammigine to the apo-base is accompanied by a marked bathochromic shift of the two bands in the ultraviolet spectrum. This may well be due to a change in stereochemistry of the ring junction at the indoline α- and β-carbons, such as the one shown in formulæ (V) and (VI). This is supported by the fact that the ultraviolet absorption spectra of the ammonium ions derived from ψ-akuammigine and from



the apo-base are identical. Another important difference between ψ-akuammigine and its dihydromethine (see below) on the one hand, and the corresponding apo-bases on the

* Absolute stereochemistry is not implied by these or other formulæ in this paper. The epimerisation involved in the change (V) ⟶ (VI) is discussed later in the paper.

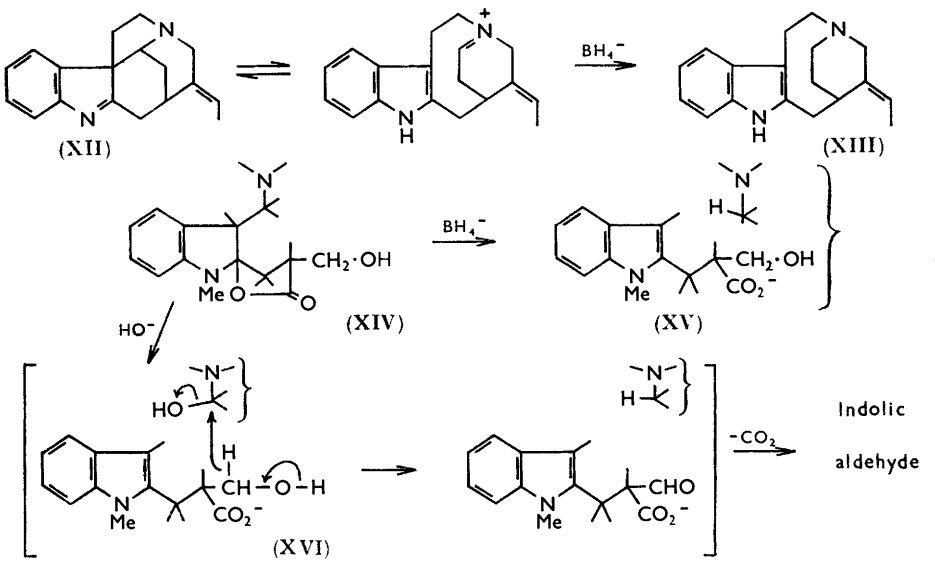
[9] Janot, Le Men, and Levy, personal communication, September, 1960.

other, lies in the pK_a values, which in the former pair are 7·15 and 7·1, and in the latter pair 5·6 and 5·8, respectively. The reason for this difference is not clear, for both pairs, on ultraviolet spectroscopic evidence, contain the Ph·N·C·O chromophore. The explanation might involve the relative closeness of the carbonyl-carbon atom to N(*b*) in the two series: if these atoms were appreciably closer in the apo-series, the result would be a weakening of the basicity by a field effect.

Both *ψ*-akuammigine and *O*-methylakuammine are completely resistant to the action of aqueous-alcoholic alkali at 80°. This indicates a high degree of steric hindrance round the methoxycarbonyl group. That this group is probably attached to a quaternary carbon is shown by the failure of sodium ethoxide in *O*-deuteroethanol at 100° to introduce a deuterium atom into the molecule.

In sharp contrast with this is the lability of apo-*ψ*-akuammigine in alkali. Even at room temperature, opening of the lactone ring is accompanied by the appearance of indolic ultraviolet absorption. Acidification followed by neutralisation fails to regenerate apo-*ψ*-akuammigine, or indeed to yield any ether-soluble material. At 80° in aqueous-alcoholic alkali, or alkali in aqueous dioxan, however, apo-*ψ*-akuammigine is converted in 60% yield into an ether-soluble base, $C_{20}H_{24}N_2O$, corresponding to the simple loss of carbon dioxide. This base has an indolic spectrum, and the single oxygen forms part of a carbonyl group (1726 cm.$^{-1}$). That this carbonyl group is probably aldehydic is indicated by the disappearance of a band at 2705 cm.$^{-1}$ (aldehyde CH) on reduction with methanolic borohydride, and by the presence of nitrile stretching absorption at 2240 cm.$^{-1}$ in the total product of the action of acetic anhydride on the oxime.

Parallel with the easy decomposition of apo-*ψ*-akuammigine by alkali into indolic material is the reduction by methanolic potassium borohydride in good yield to an amino-acid, $C_{21}H_{26}N_2O_3$, the ultraviolet spectrum of which shows it also to be an indole. These reactions strongly resemble the reduction of decarbomethoxyakuammicine (XII) to the



indole (XIII) by way of a reverse Mannich reaction.[10] We believe that a similar reaction sequence is called into play in the alkaline decomposition and in the borohydride reduction of apo-*ψ*-akuammigine.

The simplest interpretation of the formation of the indolic aldehyde might be that the

[10] Smith and Wróbel, *J.*, 1960, 792.

immediate product of the reverse Mannich reaction, the indolic carbinolamine (XVI), or the corresponding enamine, undergoes an internal hydride shift as shown, which results in the reduction of the carbinolamine system and oxidation of the CH_2·OH group to an aldehyde group. The loss of carbon dioxide then follows quite rationally.

The borohydride reduction of apo-ψ-akuammigine to the indolic amino-acid (XV) is more straightforward. That the *N*(b)-electrons play a part in the reduction to an indole is shown by the reduction of apo-ψ-akuammigine methiodide by borohydride, not to an indole, but to an indoline betaine.

These observations prove the presence in apo-ψ-akuammigine of an indoline ring-system, and the separation of N(*b*) from the indoline β-carbon atom by only one carbon atom. Furthermore the formation of an amino-acid under very mild alkaline conditions supports the view that the lactone ring closes on the indoline α-carbon, for then indole formation involves an elimination of the lactone group directly as carboxylate anion.

The amino-acid is not esterified by methanolic hydrochloric acid, which is indicative of a still considerable degree of steric hindrance, and it is not decarboxylated under vigorously acidic or alkaline conditions at higher temperatures, which suggests that the carboxyl group is not attached to a carbon adjacent to the indole α-position.

Zinc dust dehydrogenation failed to yield a homogeneous product: no indoles and only very small quantities of carbazoles and pyridines could be detected by ultraviolet spectroscopical examination of chromatographic fractions. This is in sharp contrast with the dehydrogenation of base (XIII), which gave 3-ethylpyridine and 3-ethyl-2-methylindole in relatively good yields, and is very likely to indicate the absence of a preformed piperidine ring in the amino-acid.

Whereas ozonolysis of ψ-akuammigine and of the apo-base gave good yields of acetaldehyde (24% and 20%, respectively, as the *p*-nitrophenylhydrazone), the amino-acid gave none. That the ethylidene group is nevertheless still present is indicated by the failure of the modified Kuhn–Roth oxidation to yield even a trace of propionic acid (by paper chromatography), which rules out reduction or double-bond migration, and is proved by the nuclear magnetic resonance spectrum (see below).

Robinson and Thomas [6] reported the reduction of the ester group in ψ-akuammigine by lithium aluminium hydride, to afford ψ-akuammigol, $C_{21}H_{26}N_2O_2$. We have found that this alcohol reacts with acetone by acid catalysis to give a crystalline isopropylidene derivative, $C_{24}H_{32}N_2O_2$, which shows no absorption in the hydroxyl stretching region and is smoothly hydrolysed back to ψ-akuammigol. This indicates that the reduction has split the carbinolamine ether function, and that ψ-akuammigol is an indoline containing two alcoholic groups. The molecular formula of the alcohol has accordingly to be changed to $C_{21}H_{28}N_2O_2$, which is consistent with the elemental analyses of the base, the isopropylidene derivative, and the methiodide. ψ-Akuammigol does not react with periodic acid, so the hydroxyl groups are likely to be in a 1,3-relationship, in full accord with the findings of Janot *et al.*[9] ψ-Akuammigol is a remarkably weak indoline base, for it is not appreciably protonated on N(*a*) in dilute ethanolic hydrochloric acid, an effect that may well be due to steric hindrance to solvation of protonated N(*a*). It is, however, nearly completely protonated on N(*a*) in concentrated hydrochloric acid.

O-Methylakuammine is also reduced by lithium aluminium hydride to *O*-methylakuamminol, $C_{22}H_{30}N_2O_3$, which forms an amorphous isopropylidene derivative showing no absorption in the hydroxyl stretching region.

Reduction of ψ-akuammigine with sodium in ethanol yields neo-ψ-akuammigol, $C_{21}H_{26}N_2O_2$: this base still contains the carbinolamine ether system, for it retains indoline absorption in dilute acid and it shows 3*H*-indolium absorption in concentrated hydrochloric acid. The infrared spectrum shows a broad, strongly hydrogen-bonded hydroxyl band. The structure of this compound is almost certainly that of ψ-akuammigine with CO_2Me replaced by CH_2·OH.

As has already been mentioned, ψ-akuammigine and *O*-tosylakuammine are both

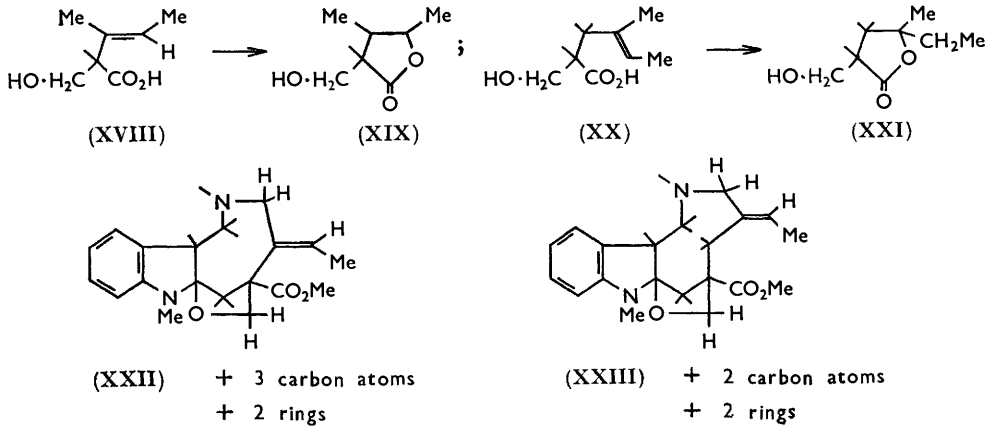
reduced by Raney nickel in boiling ethanol to dihydroiso-ψ-akuammigine, $C_{22}H_{28}N_2O_3$. This base still contains the methoxycarbonyl group and in addition a hydroxyl group ($\nu_{max.}$ in $CHCl_3$, 3620 cm.$^{-1}$); it is resistant to the action of 10% aqueous-alcoholic alkali at 80°. The most interesting feature of this base is that its ultraviolet absorption (see Experimental section) corresponds to that of the *gem*-diamino-system, Ph·N·C·N, present in the calycanthaceous alkaloids,[11] in echitamine,[12] and in eserine. The formation of dihydroiso-ψ-akuammigine must therefore involve hydrogenolysis of a C–N(*b*) bond, with subsequent replacement by N(*b*) of the carbinolamine ether oxygen atom, which thus appears as the alcoholic hydroxyl group.

Although the thermal decomposition of ψ-akuammigine methohydroxide (Hofmann degradation) regenerates the pure alkaloid, hydrogenolysis of the methiodide leads, by the uptake of one mol. of hydrogen, to the crystalline dihydromethine, $C_{23}H_{30}N_2O_3$. Hydrogenolysis of apo-ψ-akuammigine methiodide likewise leads to the corresponding dihydromethine, $C_{22}H_{28}N_2O_3$. Both these dihydromethines still contain the ethylidene group, for ozonolysis yields acetaldehyde (25% and 19% yield, respectively, as the *p*-nitrophenylhydrazone), and they both contain two *C*-methyl groups (Kuhn–Roth).

These results demonstrate the presence, in both ψ-akuammigine and the apo-base, of the allylamine system N(*b*)·CH_2·C=CHMe, the hydrogenolysis involving fission of the allylammonium C–N^+ bond. This finds many precedents, *e.g.*, the hydrogenolysis of isocalebassine.[13]

ψ-Akuammigine dihydromethine methiodide is resistant to catalytic hydrogenolysis and to Hofmann degradation. It is noteworthy that ψ-akuammigol methiodide is also, and unexpectedly, resistant to catalytic hydrogenolysis.

The carbonyl stretching frequency in apo-ψ-akuammigine dihydromethine is at 1773 cm.$^{-1}$ in spite of the presence of a free hydroxyl group: that this indicates that the hydroxyl group no longer forms a hydrogen bond with the carbonyl oxygen is suggested by the considerably higher hydroxyl stretching frequency (3620 cm.$^{-1}$) than for apo-ψ-akuammigine (3490 cm.$^{-1}$). *O*-Methylapoakuammine dihydromethine behaves similarly, with bands at 1787 and 3610 cm.$^{-1}$.



Whereas apo-ψ-akuammigine dihydromethine is completely unaffected by 3N-aqueous hydrochloric acid at 80°, ψ-akuammigine dihydromethine is converted, not into the corresponding apo-base, but into a new type of compound, probably $C_{22}H_{26}N_2O_2$, whose ultraviolet spectrum resembles that of the akuammicine chromophore, Ph·N·C=C·CO_2Me.

[11] Hodson and Smith, *J.*, 1957, 1877.
[12] Birch, Hodson, and Smith, *Proc. Chem. Soc.*, 1959, 224.
[13] Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1957, **40**, 731.

That this resemblance is probably spurious is suggested by the normal infrared frequency of the ester-carbonyl group (1726 cm.$^{-1}$) (in akuammicine [14] it is 1675 cm.$^{-1}$), and by the stability of the compound in 3N-aqueous hydrochloric acid at 80°, conditions which lead to hydrolysis and decarboxylation of akuammicine.[14]

ψ-Akuammigine dihydromethine, like the parent alkaloid, is completely resistant to saponification, and is reduced by lithium aluminium hydride to a diol which must be the equivalent of ψ-akuammigol, for it is protonated on N(*a*) in concentrated hydrochloric acid. This diol surprisingly does not form an isopropylidene derivative: the reason for this is very probably related to the absence of hydrogen-bonding in the apo-dihydromethines.

The dihydromethines parallel the parent bases in their behaviour with borohydride: ψ-akuammigine dihydromethine was unaffected by this reagent, whereas apo-ψ-akuammigine dihydromethine was reduced to an indolic amino-acid which, though it could not be isolated as such, was converted by methanolic hydrochloric acid into an ether-soluble indolic hydroxy-lactone, $C_{22}H_{30}N_2O_3$, with maxima at 1761, 1726, and 3460 cm.$^{-1}$ in Nujol. The tetrahydropyranyl ether shows a single carbonyl stretching frequency in CCl_4 at 1768 cm.$^{-1}$, clearly corresponding to a γ-lactone. In this compound lactonisation can only have occurred at one or other of the olefinic carbon atoms, which limits the relationship between the carboxyl group and the double bond to two possibilities, (XVIII) and (XX), and allows the expansion of partial structure (II) to structures (XXII) or (XXIII).

Dehydrogenation of ψ-akuammigine or apo-ψ-akuammigine with zinc dust, palladium–charcoal, or soda-lime failed to yield a homogeneous product. In each case chromatography of total dehydrogenation products and careful ultraviolet spectroscopical analysis of each fraction showed the complete absence of β-carbolines and alstyrine-like compounds. This seems to rule out an " α-indole " type skeleton [that is, where N(*b*) is separated by one carbon from the α-carbon of the indoline ring] for these alkaloids. The only chromophores observed were indole, pyridine, and carbazole, in keeping with a " β-indole " type of skeleton.

The annexed Table shows the more easily recognisable bands in the nuclear magnetic resonance spectra of the six bases listed. These are largely in agreement with conclusions already reached. The main difficulty is provided by ψ-akuammigine dihydromethine: the olefinic proton resonance, two bands centred at 4·87 τ, corresponds in intensity to 1·6

	Olefinic H	Ester OMe	Indolic *N*-Me	Arom. *N*-Me	Aliph. *N*-Me	Olef. *C*-Me	Aliph. *C*-Me
ψ-Akuammigine	4·61	6·23		7·18		8·50	
Apo-ψ-akuammigine	4·57			7·09		8·32	
ψ-Akuammigine dihydromethine	(4·87)	6·32		7·10	7·65	?	8·92
Apo-ψ-akuammigine dihydromethine	4·71			7·26	7·58	8·27	
Indolic amino-acid	4·71		6·68			8·47	
Indolic lactone			6·36		7·53		8·83

protons instead of to one; there does not appear to be the usual olefinic *C*-methyl absorption at 8·3—8·5 τ, but instead a *C*-methyl peak at 8·92 τ, which is in the saturated region. In spite of this, however, the base gives a 25% yield of acetaldehyde, isolated as the *p*-nitrophenylhydrazone, one of the highest yields in this series.

The presence of an olefinic proton and an olefinic methyl group is clearly indicated in the spectrum of the indolic amino-acid, which gives no acetaldehyde on ozonolysis. This anomalous behaviour is paralleled by echitamine base which, although shown by nuclear magnetic resonance spectroscopy to contain an ethylidene group,[15] gives no acetaldehyde on ozonolysis in non-hydroxylic solvents.[16]

The indolic lactone, as expected, contains no ethylidene group. The spectrum, however, does not allow a decision to be made between formulæ (XIX) and (XXI).

[14] Aghoramurthy and Robinson, *Tetrahedron*, 1957, **1**, 172.
[15] Conroy, Bernasconi, Brook, Ikan, Kurtz, and Robinson, *Tetrahedron Letters*, 1960, No. 6, 1.
[16] Birch, Hodson, Moore, Potts, and Smith, *Tetrahedron Letters*, 1960, No. 19, 36.

Finally, positive proof of the presence of a methyl group on N(*a*) excludes structures in which N(*a*) is common to two rings, as in mavacurine [17] and hunterine.[18]

By mutual agreement, we are submitting this paper for publication simultaneously with the submission by Janot, Le Men, and Levy to *Bull. Soc. chim. France* of a paper on akuammine and ψ-akuammigine. The work in the two laboratories was carried out independently.

Experimental

ψ-Akuammigine.—This base was isolated from seeds of *Picralima klaineana* essentially by the method described by Henry.[2] The base crystallised from ethanol as irregular prisms, m. p. 162—164° (lit.,[2] 165°) (Found: C, 72·2; H, 7·2; N, 7·3%; *M*, by mass spectroscopy, 366. Calc. for $C_{22}H_{26}N_2O_3$: C, 72·1; H, 7·15; N, 7·65%; *M*, 366); pK_a in 50% aqueous ethanol was 7·15 (lit.,[6] 7·35), $\lambda_{max.}$ 245, 291 mμ in EtOH (ε 11,000, 4000), 242, 288 mμ in 0·2N-ethanolic HCl (ε 11,000, 4000), 241, 245, 306 mμ in concentrated HCl (ε 3400, 3500, 4000), 240, 245, 310 mμ in concentrated H_2SO_4 (ε 5400, 5600, 7250), $\nu_{max.}$ (in CCl_4) 1737 cm.$^{-1}$ (C=O str.).

ψ-Akuammigine methiodide crystallised from ethanol as plates, m. p. 273—275° (lit.,[2] 275°) (Found: C, 54·4; H, 5·7; N, 5·7. Calc. for $C_{22}H_{26}N_2O_3,CH_3I$: C, 54·3; H, 5·7; N, 5·5%), $\lambda_{max.}$ 240, 287 mμ in EtOH (ε 7000, 2200), 239, 310 mμ in concentrated HCl (ε 6600, 3900), $\nu_{max.}$ (in Nujol) 1736 cm.$^{-1}$ (C=O str.).

ψ-Akuammigine Betaine.—A solution of ψ-akuammigine (215 mg.) in dry methanol (2 c.c.) was heated in an evacuated sealed tube at 155° for 7 hr. The methanol was then boiled off and the residue partitioned between water and ether. The aqueous phase gave *ψ-akuammigine betaine* as a hygroscopic resin (202 mg.) (Found, in material dried at 90° at 0·05 mm.; C, 66·0; H, 7·6. $C_{22}H_{26}N_2O_3,2H_2O$ requires C, 65·65; H, 7·5%), $\lambda_{max.}$ 241, 286 mμ in EtOH (ε 7100, 2500) unchanged by acid. The betaine (50 mg.) was refluxed with methyl iodide (2 c.c.) for 2 hr. The product crystallised from ethanol to give plates (67 mg.), m. p. 271—275° alone or mixed with ψ-akuammigine methiodide.

Octahydro-ψ-akuammigine Methiodide.—A solution of ψ-akuammigine (150 mg.) in glacial acetic acid (10 c.c.) and concentrated hydrochloric acid (0·1 c.c.) was hydrogenated over Adams catalyst (75 mg.). After 18 hr. hydrogen uptake ceased at about 4 mol. The product was worked up for ether-soluble basic material, which was obtained as a colourless syrup (137 mg.), $\nu_{max.}$ (in CCl_4) 1725 cm.$^{-1}$ (C=O str.); this had no ultraviolet absorption >220 mμ. This base formed a *monomethiodide* at room temperature, which crystallised from ethanol as square plates, m. p. 243—246° (slight decomp.) (Found: C, 52·55; H, 6·9. $C_{22}H_{34}N_2O_3,CH_3I,0·5H_2O$ requires C, 52·55; H, 7·25%).

ψ-Akuammigine Dihydromethine.—A solution of ψ-akuammigine methiodide (980 mg.) in ethanol (50 c.c.) was hydrogenated (uptake 1 mol.) over Adams catalyst (210 mg.) in the presence of anhydrous potassium carbonate (500 mg.). The mixture was worked up for ether-soluble basic material, which was obtained as a colourless gum (723 mg.) which slowly crystallised. Recrystallisation from pentane gave *ψ-akuammigine dihydromethine* as prisms, m. p. 123—125°, with slight sintering from 113° (Found: C, 71·8; H, 7·8; N, 7·45; *C*-Me, 3·7. $C_{23}H_{30}N_2O_3$ requires C, 72·2; H, 7·9; N, 7·3; 1*C*-Me, 4·0%), pK_a in 50% aqueous ethanol, 7·1, $\lambda_{max.}$ 246, 295 mμ in EtOH (ε 9100, 2900), 240, 290 mμ in 0·2N-ethanolic HCl (ε 8500, 2700), 241, 244, 309 mμ in concentrated HCl (ε 4700, 4900, 5700), $\nu_{max.}$ (in CCl_4) 1732 cm.$^{-1}$ (C=O str.).

The *picrate* crystallised from ethanol as square plates m. p. 196—199° (Found: C, 57·15; H, 5·4; *C*-Me, 2·88. $C_{23}H_{30}N_2O_3,C_6H_3N_3O_7$ requires C, 56·95; H, 5·45; 2*C*-Me, 4·9%). The *methiodide*, prepared in the usual way at room temperature, crystallised from ethanol as needles, m. p. 234—235° (Found: C, 53·1; H, 6·7; *C*-Me, 3·3. $C_{23}H_{30}N_2O_3,CH_3I,H_2O$ requires C, 53·15; H, 6·45; 2*C*-Me, 5·6%), $\lambda_{max.}$ 237, 289 mμ in EtOH (ε 10,000, 2900), 245 (infl.), 315 mμ in concentrated HCl (ε 10,500, 8700); $\nu_{max.}$ (in Nujol) 3504, 3453 (OH str.), 1732 cm.$^{-1}$ (C=O str.).

Base X.—A solution of ψ-akuammigine dihydromethine (236 mg.) in 3N-aqueous hydrochloric acid (5 c.c.) was heated in an evacuated sealed tube at 80° for 8 hr. Basification and ether extraction gave a yellow resin (197 mg.), chromatography of which on a cellulose column (6 g.) loaded with phosphate–citrate buffer (1·5 c.c.; pH 3·0), with wet ether as eluant, yielded

[17] Bickel, Schmid, and Karrer, *Helv. Chim. Acta*, 1955, **38**, 649.
[18] Bartlett, Taylor, and Hamet, *Compt. rend.*, 1959, **249**, 1259.

base X (18 mg.) in the first 8 c.c.: subsequent fractions showed increasing contamination with indolic material. Neither base X nor its salts crystallised, although the infrared and ultraviolet spectra indicated a fair degree of homogeneity; the base (Found: C, 75·95; H, 7·8. $C_{22}H_{26}N_2O_2$ requires C, 75·4; H, 7·45%) had $\lambda_{max.}$ 228, 305, 342 mμ in EtOH (ε 6100, 5850, 10,800) unchanged in 0·2N- ethanolic HCl, 235, 319 mμ in concentrated H_2SO_4, and $\nu_{max.}$ (in Nujol) 1728 cm.$^{-1}$ (C=O str.).

Apo-ψ-akuammigine.—A solution of ψ-akuammigine (1·20 g.) in 3N-aqueous hydrochloric acid (8 c.c.) was heated in an evacuated sealed tube at 80° for 8 hr. The resulting pale yellow solution was basified and extracted with ether (3 × 100 c.c.). The dried ether extracts yielded a pale yellow gum (1·10 g.) which crystallised from ethanol, to give *apo-ψ-akuammigine* as colourless rods, m. p. 148—152° (Found: C, 71·45; H, 6·6; OMe, 1·4; *C*-Me, 3·1%; *M*, by mass spectroscopy, 352. $C_{21}H_{24}N_2O_3$ requires C, 71·6; H, 6·9; OMe, 0·0; 1*C*-Me, 4·3%; *M*, 352), pK_a in 50% aqueous ethanol 5·6, $\lambda_{max.}$ 248, 303 mμ in EtOH (ε 11,500, 4900) unchanged in 0·2N-ethanolic HCl, 241, 302 mμ in concentrated HCl (ε 3400, 1900), 240, 245, 310 mμ in concentrated H_2SO_4 (ε 5050, 5150, 6000), $\nu_{max.}$ (in CCl_4) 3490 (OH str.), 1746 cm.$^{-1}$ (C=O str.).

Apo-ψ-akuammigine Tetrahydropyranyl Ether.—To a solution of apo-ψ-akuammigine (80 mg.) in 1 : 1 redistilled dihydropyran–dry chloroform (20 c.c.) was added one drop of concentrated hydrochloric acid. After 24 hr. at room temperature the solution was poured with vigorous swirling into ether (30 c.c.) and ice-cold 10% aqueous sodium hydroxide (30 c.c.). The ether layer was separated, combined with a further ether extract (30 c.c.) of the aqueous phase, dried, and evaporated, finally in a high vacuum. The colourless resin (91 mg.) was chromatographed on alumina. The tetrahydropyranyl ether was eluted by 1 : 1 benzene–ether as a colourless resin (52 mg.) which showed no absorption in the OH stretching region and a maximum at 1781 cm.$^{-1}$ (C=O str.) (in CCl_4). Mild acidic hydrolysis regenerated apo-ψ-akuammigine in high yield.

O-*Acetylapo-ψ-akuammigine.*—A solution of apo-ψ-akuammigine (95 mg.) in 1 : 1 acetic anhydride–triethylamine (2 c.c.) was left at room temperature for 24 hr. The solvents were then removed under reduced pressure, and the residue worked up for basic material. This was a colourless resin (94 mg.) which crystallised from ether to give *acetylapo-ψ-akuammigine* as blades, m. p. 161—163° (Found: C, 70·35; H, 6·3. $C_{23}H_{26}N_2O_4$ requires C, 70·05; H, 6·65%), $\lambda_{max.}$ 249, 304 mμ in EtOH (ε 8900, 3500), $\nu_{max.}$ (in CCl_4) 1773, 1747 cm.$^{-1}$ (C=O str.).

Apo-ψ-akuammigine Dihydromethine.—A solution of apo-ψ-akuammigine (237 mg.) and methyl iodide (0·5 c.c.) in benzene (20 c.c.) was left at room temperature for 24 hr. The solvents were then boiled off. The methiodide (332 mg.) did not crystallise and was hydrogenated (uptake 1 mol.) in ethanol (50 c.c.) over Adams catalyst (107 mg.) in the presence of anhydrous potassium carbonate (500 mg.). Working up for basic material gave a crystalline *dihydromethine* that recrystallised from ether as prisms, m. p. 170—172° (Found: C, 71·45; H, 7·45; *C*-Me, 4·3. $C_{22}H_{28}N_2O_3$ requires C, 71·7; H, 7·65; 2*C*-Me, 8·2%), pK_a in 50% aqueous ethanol, 5·8, $\lambda_{max.}$ 252, 303 mμ in EtOH (ε 10,000, 4100), 250, 304 mμ in 0·2N- ethanolic HCl (ε 10,300, 3900), $\nu_{max.}$ (in CCl_4) 3620 (OH str.), 1773 cm.$^{-1}$ (C=O str.).

The *tetrahydropyranyl ether*, prepared as above, was a colourless resin (69% yield), $\nu_{max.}$ (in CCl_4) 1783 cm.$^{-1}$, no OH stretching band.

Indolic Amino-acid.—Potassium borohydride (40 mg.) was added in small portions during 2 hr. to a solution of apo-ψ-akuammigine (126 mg.) in methanol (10 c.c.) at room temperature. Water (10 c.c.) was then added, and the methanol removed under reduced pressure. The pH of the solution was brought to 7 by the cautious addition of dilute hydrochloric acid; the *amino-acid* then crystallised as nodules, presumably needles (107 mg.). Recrystallisation could only be effected by dissolution in one equivalent of aqueous sodium hydroxide, followed by neutralisation with hydrochloric acid. The compound decomposed above 280° (Found: C, 69·0; H, 7·55. $C_{21}H_{26}N_2O_3,0{\cdot}5H_2O$ requires C, 69·4; H, 7·45%), $\lambda_{max.}$ 225, 286 mμ (ε 30,900, 8300), $\lambda_{infl.}$ 278, 294 mμ (ε 7800, 7100) in 0·2N- ethanolic HCl, $\lambda_{max.}$ 360, $\lambda_{infl.}$ 260 mμ in concentrated H_2SO_4 (ε 5150, 2800), $\nu_{max.}$ (in Nujol) 3400 (OH str.), 2150 (NH^+ str.), 1613 cm.$^{-1}$ (CO_2^-).

Indolic Aldehyde.—A solution of apo-ψ-akuammigine (150 mg.) in ethanol (3 c.c.) and 60% aqueous potassium hydroxide (0·5 c.c.) was heated at 80° in an evacuated sealed tube for 4·5 hr. The ethanol was then removed under reduced pressure, water (15 c.c.) was added, and the product extracted with ether (3 × 20 c.c.). The extracts yielded an orange-yellow gum which crystallised (91 mg.) from a small volume of ethanol. Recrystallisation from ethanol yielded the *aldehyde* as leaflets, m. p. 137—139° (Found: C, 77·4; H, 7·95. $C_{20}H_{24}N_2O$ requires C,

77·9; H, 7·85%), $\lambda_{max.}$ 224, 286 mμ (ε 31,500, 7900), $\lambda_{infl.}$ 275, 292 mμ (ε 7300, 7750) in EtOH, $\nu_{max.}$ (in CCl_4) 2705 (aldehyde CH str.), 1726 cm.$^{-1}$ (C=O str.).

With hydroxylamine in refluxing ethanol this afforded an amorphous oxime, $\nu_{max.}$ (in CCl_4) 3630, 3270 cm.$^{-1}$ (OH str.) (no C=O absorption). Boiling acetic anhydride converted this into an amorphous base, $\nu_{max.}$ (in CCl_4) 2240 cm.$^{-1}$ (CN stretching) (no OH absorption).

Indolic Lactone.—Potassium borohydride (250 mg) was added during 3 hr. to a refluxing solution of apo-ψ-akuammigine dihydromethine (312 mg.) in methanol (30 c.c.), the methanol was then boiled off, water (20 c.c.) was added, and the aqueous solution washed with ether (3 × 10 c.c.). The aqueous solution was evaporated under reduced pressure and the residue dissolved in dry methanolic hydrogen chloride. This solution was refluxed for 1 hr., then evaporated to dryness under reduced pressure, and the residue was partitioned between aqueous potassium carbonate (50 c.c.) and ether (50 c.c.). The aqueous phase was further extracted with ether (2 × 25 c.c.). The combined ether extracts yielded crystals (93 mg.); recrystallisation from acetone yielded the *lactone* as plates, m. p. 230—233° (Found: C, 70·45; H, 7·8; N, 7·6; OMe, 0·0; *C*-Me, 6·5. $C_{22}H_{30}N_2O_3$ requires C, 71·3; H, 8·1; N, 7·6; OMe, 0·0; 2*C*-Me, 8·1%), $\lambda_{max.}$ 225, 286 mμ (ε 26,000, 7100), $\lambda_{infl.}$ 279, 292 mμ (ε 5900, 6200) in EtOH, unchanged in concentrated HCl, $\nu_{max.}$ (in CCl_4) 3460 (OH str.), 1761, 1726 cm.$^{-1}$ (C=O str.). The *tetrahydropyranyl ether* crystallised from ether as needles, m. p. 205—225° (Found: C, 70·2; H, 7·95. $C_{28}H_{38}N_2O_4$ requires C, 71·3; H, 8·35%), $\nu_{max.}$ (in CCl_4) 1768 cm.$^{-1}$ (C=O str.).

ψ-Akuammigol.—This base was prepared by Robinson and Thomas's method [6] as needles (from chloroform–ether), m. p. 201—204° (lit., 201°), pK_a in 50% aqueous ethanol 8·1 (lit.,[6] 8·2), $\lambda_{max.}$ 250, 295 mμ in EtOH (ε 10,000, 2200), 247, 292 mμ in 0·2N-ethanolic HCl (ε 10,000, 2200), 260, 268 mμ in concentrated HCl (ε 370, 330). Its *methiodide*, prepared in the usual way at room temperature, crystallised from ethanol as polyhedra, m. p. 275—277° (decomp.) (Found: C, 54·65; H, 6·45. $C_{21}H_{28}N_2O_2,CH_3I$ requires C, 54·8; H, 6·45%), $\lambda_{max.}$ 247, 291 mμ in EtOH (ε 7250, 2350), $\lambda_{max.}$ 261, 268 mμ in concentrated HCl (ε 390, 320).

Diacetyl-ψ-akuammigol Methiodide.—A solution of ψ-akuammigol (41 mg.) in 1 : 1 acetic anhydride–triethylamine (4 c.c.) was left at room temperature overnight. After removal of the solvents, the residue was worked up for basic ether-soluble material. This was obtained as a gum, $\nu_{max.}$ 1752 cm.$^{-1}$ (C=O str.) (no OH absorption). It was left with methyl iodide (0·5 c.c.) ether (10 c.c.) for 24 hr. at room temperature: several crystallisations from acetone gave *diacetyl-ψ-akuammigol methiodide* as prisms, m. p. 241—244° (decomp.) (Found: C, 54·05; H, 6·1; OAc, 13·5. $C_{25}H_{32}N_2O_4,CH_3I,0{\cdot}25H_2O$ requires C, 54·25; H, 6·25; OAc, 14·9%), $\lambda_{max.}$ 244, 292 mμ in EtOH (ε 11,000, 4100), $\nu_{max.}$ (in Nujol) 3490 (OH str.), 1742, 1735 cm.$^{-1}$ (C=O str.).

Isopropylidene-ψ-akuammigol.—A solution of ψ-akuammigol (105 mg.) in benzene (10 c.c.) and dry acetone (10 c.c.) was brought to the boil, two drops of concentrated hydrochloric acid were added, and the mixture was slowly distilled for 5 min. The remaining solvent was then removed under reduced pressure and the residue partitioned between ether (20 c.c.) and aqueous potassium carbonate (10 c.c.) at 0°. The ether solution was evaporated and the residue chromatographed on alumina with benzene as the eluant; crystals were obtained (41 mg.), recrystallisation of which from pentane yielded *isopropylidene-ψ-akuammigol* as polyhedra, m. p. 131—133° (Found: C, 75·5; H, 8·25. $C_{24}H_{32}N_2O_2$ requires C, 75·75; H, 8·5%), $\lambda_{max.}$ 250, 295 mμ in EtOH (ε 9300, 3300), 248, 293 mμ in 0·2N-ethanolic HCl (ε 8900, 3100) (no OH absorption) (in CCl_4).

Iso-ψ-akuammigol.—ψ-Akuammigol (144 mg.) was heated in 3N-aqueous hydrochloric acid (5 c.c.) in an evacuated sealed tube for 7 hr. A deep blue colour was produced. The solution was basified and extracted with ether. There was ether- and water-insoluble material which had a blue colour. The ether-soluble material (21 mg.) was partially crystalline. Several recrystallisations from acetone gave *iso-ψ-akuammigol* as prisms, m. p. 242—245° (Found: C, 72·2; H, 8·1. $C_{21}H_{28}N_2O_2$ requires C, 72·15; H, 8·3. $C_{21}H_{28}N_2O_2,C_3H_6O$ requires C, 72·35; H, 8·6%), $\lambda_{max.}$ 257, 310 mμ in EtOH, 247, 298 mμ in 0·2N- ethanolic HCl, 277 mμ in concentrated H_2SO_4, $\nu_{max.}$ (in Nujol) 3433, 3280 (OH str.), 1706 (C=O str., weak).

ψ-Akuammigol Dihydromethine.—Lithium aluminium hydride (40 mg.) was added to a solution of ψ-akuammigine dihydromethine (59 mg.) in dry ether (10 c.c.), and the mixture left at room temperature for 2 hr. The excess of reagent was decomposed with water, and the ether phase evaporated, yielding a resin (50 mg.) which crystallised from benzene to give *ψ-akuammigol dihydromethine* as blades, m. p. 243—244° (decomp. from 100°) (Found: C, 73·5,

72·95; H, 9·0, 8·75; *C*-Me, 5·6. $C_{22}H_{32}N_2O_2$,0·25H_2O requires C, 73·2; H, 9·0; 2*C*-Me, 8·4%), $\lambda_{max.}$ 251, 296 mμ in EtOH (ε 8900, 2900), 246, 291 mμ in 0·2N-ethanolic HCl (ε 8400, 2750), 261, 269 mμ in concentrated HCl (400, 295), $\nu_{max.}$ (in Nujol) 3560, 3145 cm.$^{-1}$ (OH str.).

Neo-ψ-akuammigol.—Sodium (400 mg.) was added in small portions during 0·5 hr. to a refluxing solution of ψ-akuammigine (239 mg.) in ethanol (30 c.c.). The ethanol was then removed under reduced pressure, and the residue treated with water (100 c.c.) and extracted with ether (3 × 50 c.c.). The extracts yielded a gum (217 mg.), chromatography of which on alumina, with 2 : 3 ether–benzene as eluant, gave crystals (98 mg.); recrystallisation from acetone yielded *neo-ψ-akuammigol* as prisms, m. p. 207—208° (Found: C, 74·1; H, 7·6. $C_{21}H_{26}N_2O_2$ requires C, 74·5; H, 7·75%), $\lambda_{max.}$ 246, 293 mμ in EtOH (ε 8700, 3500), 242, 290 mμ in 0·2N- ethanolic HCl (ε 9350, 3700), 241, 246, 306 mμ in concentrated HCl (ε 8900, 8300, 9300), $\nu_{max.}$ (in CCl_4) 3080 cm.$^{-1}$ (OH str.) (no C=O absorption).

Isodihydro-ψ-akuammigine.—A solution of ψ-akuammigine (105 mg.) in ethanol (20 c.c.) containing freshly prepared Raney nickel (*ca.* 1 g. of sludge) was refluxed for 45 min. with concurrent bubbling of hydrogen through the solution. The solution was then filtered through Hiflo-supercel and the ethanol removed under reduced pressure. The partly crystalline residue of *isodihydro-ψ-akuammigine* crystallised from acetone as leaflets, m. p. 264—267° (61 mg.) (Found: C, 71·3, 71·1; H, 7·65, 7·35; N, 7·35; OMe, 8·05; *C*-Me, 3·2%; *M*, by mass spectroscopy, 368. $C_{22}H_{28}N_2O_3$ requires C, 71·7; H, 7·65; N, 7·6; OMe, 8·4; 1*C*-Me, 4·1%; *M*, 368), pK_a 6·1 in 50% aqueous ethanol, $\lambda_{max.}$ 257, 314 mμ in EtOH (ε 9600, 3300), 246, 299 mμ in 0·2N-ethanolic HCl (ε 9100, 2900), 245, 299 mμ in concentrated HCl (ε 3200, 1200), 280 mμ in 70% perchloric acid (ε 6000), $\nu_{max.}$ (in $CHCl_3$) 3620 (OH str.), 1725 cm.$^{-1}$ (C=O str.).

Attempted Preparation of Henry's "Hydrated Akuammine."—A solution of akuammine (1·24 g.) in 10% aqueous-methanolic potassium hydroxide (3·5 c.c.) was sealed in an evacuated tube and left at room temperature for 14 days. The solvents were removed under reduced pressure and a slight excess of hydrochloric acid added. The crystalline precipitate was filtered off and dried (1·17 g.). It had m. p. 215—218° (decomp.) alone or mixed with akuammine hydrochloride of the same m. p.

O-*Tosylakuammine.*—Akuammine (195 mg.) in dry pyridine (10 c.c.) was treated with toluene-*p*-sulphonyl chloride (101 mg.) and left at room temperature for 1 hr. Water (100 c.c.) was added and the solution extracted with ether (3 × 50 c.c.). The alkali-washed ether extracts gave crystals which, recrystallised twice from ether containing a trace of ethanol, afforded *O*-tosylakuammine as plates, m. p. 237—239° (lit., 235—237°) (135 mg.), $\lambda_{max.}$ 251, 295 mμ in EtOH (ε 8900, 2800) unchanged by acid.

Conversion of O-Tosylakuammine into Isodihydro-ψ-akuammigine.—*O*-Tosylakuammine (103 mg.) in ethanol (30 c.c.) containing freshly prepared Raney nickel (*ca.* 1·5 g. of sludge) was refluxed for 2 hr. with concurrent passage of a stream of hydrogen. The solution was then filtered through Hiflo-supercel, and the solvent removed under reduced pressure. The product was crystallised twice from acetone, to yield leaflets, m. p. 263—267° (37 mg.), undepressed when mixed with isodihydro-ψ-akuammigine. The infrared spectra of the two specimens in Nujol were identical.

O-*Methylakuammine.*—A solution of akuammine (3·00 g.) in 1 : 1 chloroform–methanol (140 c.c.) containing ethereal diazomethane (0·35 g.) was left at 0° for 24 hr. More ethereal diazomethane (0·35 g.) was added, and after 24 hr. at 0°, a third portion (0·35 g.). The solution was left for 48 hr. at 0°, and the solvents were then removed *in vacuo*. The product, a brown gum, was worked up for basic, non-phenolic material (2·15 g.). This was chromatographed in 1 : 1 benzene–ether (100 c.c.) on alumina (30 g.). The column was eluted with ether (250 c.c.). The combined eluates afforded O-*methylakuammine* that crystallised from acetone as needles, m. p. 242—243° (1·90 g.) (Found: C, 70·0; H, 6·9%; *M*, by mass spectroscopy, 396. $C_{23}H_{28}N_2O_4$ requires C, 69·7; H, 7·1%; *M*, 396), $\lambda_{max.}$ 244, 308 mμ in EtOH (ε 11,500, 4200), 243, 306 mμ in 0·2N-ethanolic HCl (ε 12,000, 4100), 258, 348 mμ in N-aqueous HCl (ε 5750, 6200), 261, 356 mμ in concentrated HCl (ε 8500, 9300), $\nu_{max.}$ (in Nujol) 1727 cm.$^{-1}$ (C=O str.).

O-*Methylakuammine methiodide*, prepared in the usual way at room temperature, crystallised from ethanol as polyhedra, m. p. 244—248° (decomp.) (Found: C, 53·55; H, 5·6. $C_{23}H_{28}N_2O_4$,CH_3I requires C, 53·55; H, 5·75%), $\lambda_{max.}$ 241, 307 mμ in EtOH (ε 10,200, 3400), 260, 363 mμ in concentrated HCl (ε 9500, 8900), $\nu_{max.}$ (in Nujol) 1724 cm.$^{-1}$ (C=O str.).

O-*Methylakuammine Dihydromethine*.—The above methiodide (214 mg.) in ethanol (35 c.c.) was hydrogenated (uptake 1 mol. in 30 min.) over Adams catalyst (100 mg.) in the presence of anhydrous potassium carbonate (500 mg.). The ether-soluble basic product was the gummy dihydromethine, $\lambda_{max.}$ 245, 313 mμ in EtOH (ε 9500, 3100), 242, 310 mμ in 0·2N-ethanolic HCl (ε 9800, 3400), 262, 361 mμ in concentrated HCl (ε 6300, 5000), $\nu_{max.}$ (in CCl_4) 1734 cm.$^{-1}$ (C=O str.). The *methiodide* crystallised from acetone as blades, m. p. 152—155° (Found: C, 55·1; H, 6·75. $C_{24}H_{32}N_2O_4,CH_3I,C_3H_6O$ requires C, 54·9; H, 6·7%), $\lambda_{max.}$ 240, 310 mμ in EtOH (ε 8000, 2700), $\nu_{max.}$ (in Nujol) 1740, 1708 cm.$^{-1}$ (C=O str.).

O-*Methylapoakuammine*.—*O*-Methylakuammine was heated (207 mg.) in 3N-aqueous hydrochloric acid (20 c.c.) at 80° for 12 hr. in an evacuated sealed tube. The solution was then basified and extracted with ether (3 × 60 c.c.). The dried extracts yielded crystals (191 mg.); recrystallisation from ethanol yielded O-*methylapoakuammine* as prisms, m. p. 171—176° (Found: C, 69·1; H, 6·7. $C_{22}H_{26}N_2O_4$ requires C, 69·1; H, 6·85%), $\lambda_{max.}$ 247, 322 mμ in EtOH (ε 7800, 4200) unchanged in 3N-aqueous HCl, 258, 283, 345 mμ in concentrated HCl (ε 4200, 1900, 3000), $\nu_{max.}$ (in Nujol) 3120 (OH str.), 1756 cm.$^{-1}$ (C=O str.). The *acetyl derivative*, prepared by use of acetic anhydride and triethylamine at room temperature, crystallised from ether as rectangular plates, m. p. 167—171° (Found: C, 67·1; H, 6·3. $C_{24}H_{28}N_2O_5$ requires C, 67·9; H, 6·6%), $\lambda_{max.}$ 250, 324 mμ in EtOH (ε 8500, 3700), $\nu_{max.}$ (in CCl_4) 1778, 1751 cm.$^{-1}$ (C=O str.).

O-*Methylapoakuammine methiodide*, prepared in the usual way, crystallised from ethanol as needles, melting gradually and with decomposition from 88° to 190° (Found: C, 50·7; H, 5·8. $C_{22}H_{26}N_2O_4,CH_3I$ requires C, 50·7; H, 5·7%), $\lambda_{max.}$ 245, 323 mμ in EtOH (ε 9600, 4000), $\lambda_{max.}$ 351 mμ, $\lambda_{infl.}$ 252, 285 mμ in concentrated HCl (ε 2700, 9800, 4800), $\nu_{max.}$ (in Nujol) 3460 (OH str.) 1766 cm.$^{-1}$ (C=O str.).

O-*Methylapoakuammine Dihydromethine*.—A solution of the above methiodide (174 mg.) in ethanol (50 c.c.) was hydrogenated (uptake 1 mol.) over Adams catalyst (74 mg.). The basic ether-soluble material afforded *O-methylapoakuammine dihydromethine* as a viscous liquid (125 mg.), $\lambda_{max.}$ 250, 321 mμ in EtOH (ε 9800, 4000), 258, 355 mμ in concentrated H_2SO_4 (ε 6800, 5600), $\nu_{max.}$ (in CCl_4) 3610 (OH str.), 1787 cm.$^{-1}$ (C=O str.).

Action of Potassium Borohydride on O-*Methylapoakuammine*.—A solution of *O*-methylapoakuammine (103 mg.) in methanol (15 c.c.) was treated at room temperature with potassium borohydride (65 mg.) during 2 hr. The methanol was removed under reduced pressure, water (15 c.c.) was added, and the solution washed with ether (2 × 15 c.c.). The aqueous phase was brought to pH 7 by dilute hydrochloric acid, and the solution extracted with chloroform. The chloroform extract yielded a colourless resin (6 mg.), $\lambda_{max.}$ in 0·2N-ethanolic HCl 225, 284 mμ (ε 25,700, 7400), $\lambda_{infl.}$ 304, 313 mμ (ε 5500, 4100). The aqueous solution had the same ultraviolet absorption.

O-*Methylakuamminol*.—*O*-Methylakuammine (212 mg.) in dry ether (100 c.c.) was treated with lithium aluminium hydride (115 mg.) and left at room temperature for 2 hr. The excess of reagent was then decomposed with the minimum of water. The ether phase gave O-*methylakuamminol* that crystallised from acetone as prisms, m. p. 114—115° (180 mg.) (Found: C, 71·1; H, 8·2. $C_{22}H_{30}N_2O_3,0{\cdot}25C_3H_6O$ requires C, 70·95; H, 8·2%), $\lambda_{max.}$ 248, 310 mμ in EtOH (ε 8500, 3800) unchanged in dilute acid, 275, 281 mμ in concentrated HCl (ε 1700, 1550), $\nu_{max.}$ (in Nujol) 3370 (OH str.), 1704 (C=O str.).

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