849. *Alkaloids of Calabash-curare and* Strychnos *Species. Part III.*[1] *Structure and Absolute Stereochemistry of Macusine-A, Macusine-B, and Macusine-C.*

By A. R. Battersby and D. A. Yeowell.

Macusine-A, macusine-B, and macusine-C are degraded to bases which are correlated with substances of known structure and stereochemistry. This allows the constitution and absolute stereochemistry of macusine-B and macusine-C and also the absolute stereochemistry of macusine-A to be elucidated. The structure of the last alkaloid, determined by *X*-ray crystallography,[2] is supported by the chemical studies described.

Correlation of several α-indole alkaloids with normacusine-B allows the orientation of the ethylidene group in these bases to be determined; the configuration is the same as obtains for the β-indole alkaloids.

Preliminary accounts of part of this work have been published.[3,4]

Macusine-A and macusine-B are new quaternary alkaloids, the isolation of which from *Strychnos toxifera* bark was reported in Part II.[1] Further work has now shown that a third alkaloid, also quaternary and named macusine-C, accompanies macusine-B and can be separated from it with difficulty. Careful partition chromatography allows pure macusine-C to be isolated. The present Paper describes studies which lead to complete structures, including absolute stereochemistry, for all three alkaloids.

Analysis of many derivatives of macusine-B established the formula $C_{20}H_{25}N_2O^+$ for the alkaloid cation. The awkward properties of quaternary bases pointed against the use of macusine-B itself for further experiments; instead, the quaternary chloride was cleaved thermally at 320—325° in a high vacuum,[5] to afford the corresponding tertiary base normacusine-B, $C_{19}H_{22}N_2O$, in 77% yield; this base exhibits characteristic dimorphism. Quaternisation of normacusine-B with methyl iodide gave macusine-B iodide, which indicated the absence of any structural change in the pyrolysis step. Normacusine-B is a base (pK_a' 7·03) which has the ultraviolet absorption of a 2,3-disubstituted

[1] Part II, Battersby, Binks, Hodson, and Yeowell, *J.*, 1960, 1848.
[2] McPhail, Robertson, and Sim, *J.*, 1963, 1832.
[3] Battersby and Yeowell, *Proc. Chem. Soc.*, 1961, 17.
[4] McPhail, Robertson, Sim, Battersby, Hodson, and Yeowell, *Proc. Chem. Soc.*, 1961, 223.
[5] Bernauer, Berlage, von Philipsborn, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 2293.

indole; in 0·2N-acid the spectrum undergoes a hypsochromic shift of *ca.* 3 mμ and becomes superimposible upon that of macusine-B. The ultraviolet spectra of yohimbine (I) in neutral and in acidic solution are identical with those of normacusine-B and macusine-B, respectively, and the shift is undoubtedly a result of protonation (or quaternisation) at N(b). These spectral similarities indicated that normacusine-B is based upon the 1,2,3,4-tetrahydro-β-carboline system.

Normacusine-B contains one hydroxyl group and one imino-group, as shown by its infrared spectrum and by its ready acetylation to give *NO*-diacetylnormacusine-B which showed the ultraviolet and infrared spectra of an *N*-acylindole. Thus, the original imino-group in normacusine-B is that of the indole system, N(a). Hydrogenation of normacusine-B over platinum in acetic acid (0·95 mol. uptake) gave dihydronormacusine-B which could not be further reduced. In the absence of olefinic residues which resist hydrogenation, these data require normacusine-B to be pentacyclic, that is, to have three rings in addition to the indole residue. The ultraviolet spectrum of the dihydro-base is identical with that of normacusine-B; the chromophore and the reducable double-bond must, therefore, be out of conjugation.

Kuhn–Roth oxidation of normacusine-B gave 0·84 mol. of volatile acid (one *C*-methyl group), and the modified Kuhn–Roth method [6] showed this to contain only acetic acid. Dihydronormacusine-B, however, gave acetic and propionic acids. The ethyl group giving rise to the propionic acid must have been formed by reduction of an ethylidene or vinyl residue in normacusine-B. That the former is correct was shown by the presence in the n.m.r. spectrum of the unsaturated base (in trifluoroacetic acid) of a strong doublet at 8·23 which was coupled to a signal centred at τ 4·16; these signals correspond, respectively, to the methyl and olefinic protons of the ethylidene system.

The state of the hydroxyl group was examined as follows. Normacusine-B yielded an *O*-toluene-*p*-sulphonyl derivative which was reduced by lithium aluminium hydride [7] to deoxynormacusine-B. The small amount of this material precluded complete characterisation but it was shown spectroscopically to be an indolic base lacking a hydroxyl group and which underwent Kuhn–Roth oxidation to afford 1·45 mol. of acetic acid. Two *C*-methyl groups are clearly present in the deoxy-base, and the formation of a new one shows that the original hydroxyl group of normacusine-B is primary.

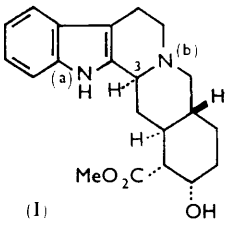
The foregoing results can now be summarised in partial structure (II) for normacusine-B.

Yohimbine (I) and similar bases with a *trans*-quinolizidine system show sharp bands close to 2800 cm.$^{-1}$ in their infrared spectra.[8] Moreover, systems which are similar to yohimbine but which have the 3β-configuration (no 2800 cm.$^{-1}$ absorption) can be made to undergo inversion at the 3-position to afford the 3α-configuration (2800 cm.$^{-1}$ absorption appears) by treatment with pivalic acid in boiling xylene.[9] The infrared spectrum of normacusine-B shows no bands in the 2800 cm.$^{-1}$ region, and the base was not affected by hot pivalic acid. Attempted dehydrogenation of normacusine-B by mercuric acetate [10] or palladium black in aqueous maleic acid [11] did not change the chromophore. One possible explanation is that position 3 is fully substituted, though this was considered unlikely on biogenetic grounds. Also, a multiplet (1 proton) centred at 5·33 τ in the n.m.r. spectrum of normacusine-B is best assigned to a proton at position 3, for then its appearance at low field can be explained by a combination of the deshielding influence of the neighbouring indole system and the protonated tertiary nitrogen. The other possibility, shown to be correct in the sequel, is that normacusine-B possesses a structure which renders it sterically impossible for a 3-proton to epimerise or to be removed in dehydrogenation experiments.

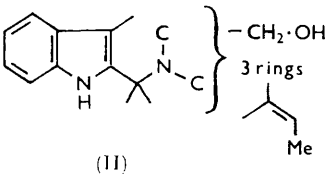
[6] Garbers, Schmid, and Karrer, *Helv. Chim. Acta*, 1954, **37**, 1336.
[7] Arnold, von Philipsborn, Schmid, and Karrer, *Helv. Chim. Acta*, 1957, **40**, 705.
[8] Bohlmann, *Angew. Chem.*, 1957, **69**, 641; *Chem. Ber.*, 1958, **91** 2157; Wenkert and Roychaudhuri, *J. Amer. Chem. Soc.*, 1956, **78**, 6417.
[9] Woodward, Bader, Bickel, Frey, and Kierstead, *Tetrahedron*, 1958, **2**, 1.
[10] Weisenborn and Diassi, *J. Amer. Chem. Soc.*, 1956, **78**, 2021.
[11] Wenkert and Roychaudhuri, *J. Amer. Chem. Soc.*, 1958, **80**, 1613.

A "caged" system is necessary, and thoughts on these lines were assisted by other developments.

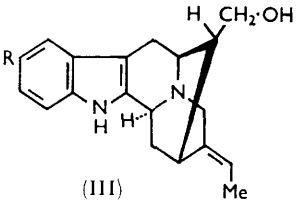
At the time of our work, structures based upon the system (III) had been proposed for sarpagine [12] (III; R = OH), lochnerine,[13] also called C-Alkaloid-T [7] (III; R = OMe), and lochneram which is the N(b)-metho-derivative of lochnerine.[14] These structure proposals, which did not include any of the stereochemical detail shown, rested on the chromophoric systems present, the functional groups and dehydrogenation products, and largely upon biogenetic argument; they were not established. Nevertheless, it was clear that if partial structure (II) is extended to structure (III; R = H) this could account for all the chemistry of normacusine-B. The basic strength and the infrared and n.m.r. spectra of sarpagine (pK_a' 7·18) and normacusine-B were very similar.



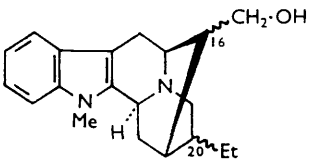
(I)



(II)



(III)



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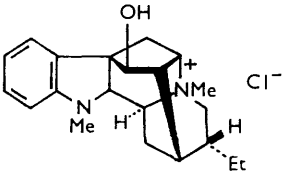
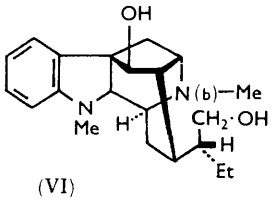


(V)



(VI)

The available quantity of macusine-B was too small to permit a determination of its structure by degradation, and we turned our attention to possible correlations with alkaloids of known constitution. It was fortunate that concurrent work by Taylor, Schlittler, Wenkert, and their co-workers [15] provided suitable materials of known structure and stereochemistry for this purpose. We selected the four alcohols (IV) corresponding to the two possible configurations at positions 16 and 20. If normacusine-B is in fact represented by the structure (III; R = H) then *N*(a)-methylation of dihydronormacusine-B should afford one of these four. They were obtained from ajmaline by the American workers' method,[15] except for the preparation of deoxyisoajmaline methochloride (V) by way of the *O*-toluene-*p*-sulphonyl derivative of dihydro-*N*-methylisoajmaline (VI); only this step is described in the Experimental section. Dr. W. I. Taylor kindly provided details of this work in advance of publication, and we are most grateful for this help.

Trial methylations of normacusine-B with sodamide in liquid ammonia followed by methyl iodide [16] gave material which, though not fully characterised, corresponded in properties to the iodide (VII). Similarly, dihydronormacusine-B afforded *N*(a),*O*-dimethyldihydronormacusine-B methiodide, as shown by the quaternary nature, ultraviolet spectrum (*N*-methylindole), and composition of the product. Accordingly, *O*-acetyldihydronormacusine-B was methylated under carefully controlled conditions, to give a

[12] Stoll and Hofmann, *Helv. Chim. Acta*, 1953, **36**, 1143; Stauffacher, Hofmann, and Seebeck, *ibid.*, 1957, **40**, 508.

[13] Poisson, Le Men, and Janot, *Bull. Soc. chim. France*, 1957, 610; Mors, Zaltzman, Beereboon, Pakrashi, and Djerassi, *Chem. and Ind.*, 1956, 173.

[14] Arnold, Berlage, Bernauer, Schmid, and Karrer, *Helv. Chim. Acta*, 1958, **41**, 1505.

[15] Bartlett, Sklar, Taylor, Schlittler, Amai, Beak, Bringi, and Wenkert, *J. Amer. Chem. Soc.*, 1962, **84**, 622 and refs. therein to preliminary communications; Woodward and Schenker; *Angew. Chem.*, 1956, **68**, 13.

[16] Potts and Saxton, *J.*, 1954, 2641.

mixture from which deoxyisoajmalol-B (IX) was isolated. Thus, dihydronormacusine-B has the structure (X), and, at this stage in our work, (+)-*O*-acetyldeoxysarpagine (XII) became available. This base had been correlated [15] with ajmaline and was of known absolute configuration apart from position 19. It was found to be identical chemically and optically with *O*-acetylnormacusine-B. It follows that structure (XIII) is a complete expression for normacusine-B. Only the stereochemistry of the ethylidene system is left unknown by the foregoing work, and this has been proved to be as shown by correlation of normacusine-B with macusine-A (below). Macusine-B chloride therefore has the structure (VIII).

Since normacusine-B is identical with deoxysarpagine, the ethylidene configuration is proved to be as shown for sarpagine (III; R = OH), lochnerine (III; R = OMe), and the corresponding *N*(b)-metho-derivative, lochneram. More recently, tombozine [17] and vellosiminol [18] have been shown to be identical with normacusine-B which further has been isolated from *Aspidosperma polyneuron*.[19]

Hydrogenation of normacusine-B in our hands gave only one product (X) but later workers, using different conditions [20] or similar ones,[18] obtained a mixture of C-20 epimers. To examine this point further, *O*-acetylnormacusine-B (XII) was reduced under the conditions used for normacusine-B. Very slow hydrogenation occurred, to give a mixture in which only *O*-acetyldihydronormacusine-B (XI) and starting material could be detected.

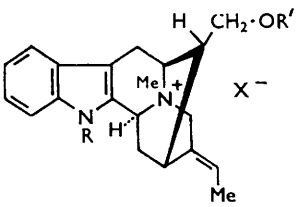
Chemical work on macusine-A, $C_{22}H_{27}N_2O_3^+$, was hampered by lack of material. However, it was shown that its ultraviolet spectrum corresponds to a 2,3-disubstituted indole and that acetylation of the alkaloid changes the spectrum to that of an *N*-acylindole. It follows that the imino-group of the alkaloid (infrared) is the indolic one; the second nitrogen atom is quaternary, and this carries one *N*-methyl group. One *O*-methyl group is also present. The infrared spectrum and composition also establish the presence of one methoxycarbonyl and one hydroxyl group. Modified Kuhn–Roth oxidation of the alkaloid gave only acetic acid, so that no group C–R is present where R is ethyl or a higher homologue. Information concerning the skeleton of macusine-A was sought by selenium dehydrogenation. This afforded a complex mixture from which was isolated a small yield of a base having the properties reported [21] for alstyrine (XVI). Only a minute amount was available but its characteristic ultraviolet spectrum showed it to be a 2-pyridylindole (cf. XVI), and its formation proved the relationship of the two nitrogen atoms in macusine-A. These results are summarised in partial structure (XVII) for macusine-A, and, at this stage, the remaining alkaloid was converted into the iodide for *X*-ray analysis. The work was kindly undertaken at the University of Glasgow, and the proof that macusine-A has the structure (XVIII) has already been published.[4,22] Only the absolute configuration remained to be defined. The availability of a further quantity of macusine-A enabled us to carry out this determination and to provide, as follows, independent chemical evidence for almost all the structural features of macusine-A.

It is convenient to consider macusine-C together with macusine-A since the two alkaloids are isomeric, $C_{22}H_{27}N_2O_3^+$. Moreover, macusine-C shows the same ultraviolet spectrum as macusine-A and a similar infrared spectrum (strongly bonded OH, and NH and CO_2R bands), and the two alkaloids are similarly acetylated by acetic anhydride in pyridine (see above).

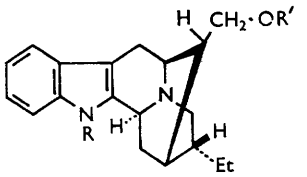
Pyrolysis of macusine-A chloride did not yield the expected nor-base but rather the ester (XIV), $C_{20}H_{22}N_2O_2$, formed by loss of formaldehyde in a retro-aldol reaction. The ultraviolet spectrum of this base was identical with that of normacusine-B (XIII) and

[17] Stauffacher, *Helv. Chim. Acta*, 1961, **44**, 2006.
[18] Rapoport and Moore, *J. Org. Chem.*, 1962, **27**, 2981.
[19] Antonaccio, Pereira, Gilbert, Vorbrueggen, Budzikiewicz, Wilson, Durham, and Djerassi, *J. Amer. Chem. Soc.*, 1962, **84**, 2161.
[20] Gosset, Le Men, and Janot, *Bull. Soc. chim. France*, 1961, 1033.
[21] Lee and Swan, *J.*, 1956, 771.
[22] McPhail, Robertson, and Sim, *J.*, 1963, 1832.

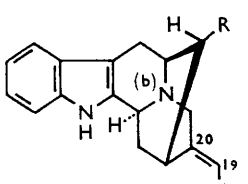
underwent the same hypsochromic shift in acid. Only the imino absorption (3170 cm.$^{-1}$) appeared in the OH,NH region of the infrared spectrum but the ester absorption was still



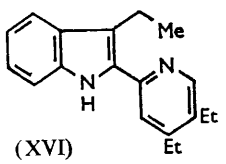
(VII: R = R′ = Me, X = I)
(VIII: R = R′ = H, X = Cl)



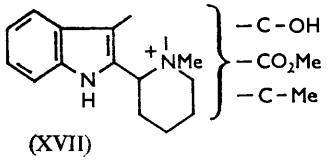
(IX: R = Me, R′ = H)
(X: R = R′ = H)
(XI: R = H, R′ = Ac)



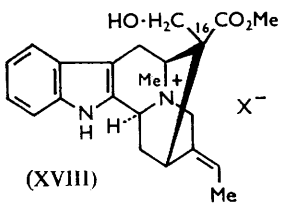
(XII: R = CH_2·OAc)
(XIII: R = CH_2·OH)
(XIV: R = CO_2Me)
(XV: R = CHO)



(XVI)



(XVII)



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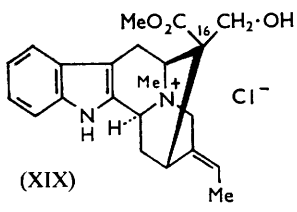


(XIX)

present. Palladium in boiling aqueous maleic acid left the deformo-base unchanged, thus indicating that the caged structure had not been opened. Finally, the molecular formula of this base was kindly confirmed by Dr. R. I. Reed (Glasgow) using mass spectrometry. Similar reverse aldol reactions under base catalysis have been observed previously, *e.g.*, for echitamine [23] and akumamidine,[24] and presumably the glass of the pyrolysis vessel acts as the base in our case.

Pyrolysis of macusine-C gave the same deformo-base (XIV) in admixture with *ca.* 20% of normacusine-C (tertiary base corresponding to XIX). The latter was detected by mass spectrometry of the mixture, when the parent ion (*m/e* **352**) of the true nor-base was readily detected together with an intense ion at *m/e* **322**. This corresponds to *ca.* 80% of the deformo-base, and the corresponding (P — 1) ion [25] also appeared strongly at **321**.

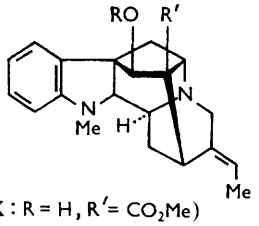
The total basic materials obtained by pyrolysis of macusine-A and macusine-C were reduced separately by lithium aluminium hydride, and normacusine-B (XIII) was isolated from both products. This proves the structure and absolute stereochemistry of the deformo-base. Further, it is established that macusine-C (XIX) is the C-16 epimer of macusine-A (XVIII) and that the absolute configuration of both alkaloids is as shown. The loss of formaldehyde from macusine-C is accompanied by a simple inversion at position 16. This work completes the correlation of a triad of alkaloids. Janot and his co-workers [26] assigned the same absolute stereochemistry to macusine-A on the basis of the sign of rotation of the *N*(b)-metho-derivative of polyneuridine (below).

The elucidation of these structures has assisted research on other alkaloids by direct correlation, or by way of degradation products, with normacusine-B; in some cases the

[23] Conroy, Bernasconi, Brook, Ikan, Kurtz, and Robinson, *Tetrahedron Letters*, 1960, No. 6, 1.
[24] Levy, Le Men, and Janot, *Compt. rend.*, 1961, **253**, 131.
[25] Clayton, Reed, and Wilson, *Tetrahedron*, 1962, **18**, 1449.
[26] Janot, Le Men, Gosset, and Levy, *Bull. Soc. chim. France*, 1962, 1079.

correlation has been with akuammidine which has itself been correlated [24] with normacusine-B. More recently, elucidation of the structure of akuammidine methiodide by *X*-ray analysis [27] has provided an independent starting point for correlations of structure.

These correlations prove that the ethylidene configuration found in macusines-A, -B, and -C is also present in polyneuridine [19] (normacusine-A), in voachalotine [28] [*N*(a)-methyl-

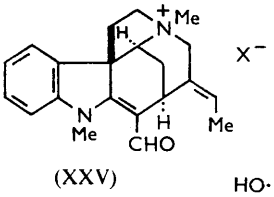


(XX: R = H, R′ = CO_2Me)

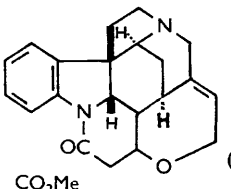
(XXI: R = Ac, R′ = CO_2Me)

(XXII: R = R′ = H)

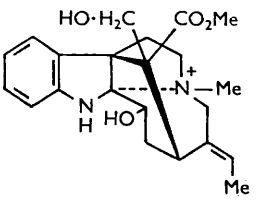
(XXIII: R = 3,4,5-$(MeO)_3C_6H_2\cdot CO$; R′ = H)



(XXV)



(XXVI)



(XXIV)

normacusine-A], and in vellosimine [18] (XV), the aldehyde corresponding to normacusine-B. The ajmaline-like bases, vincamajine [20] (XX) and vincamedine [20] (XXI) also possess this same configuration, and it seems probable that the ethylidene group of tetraphyllicine [15,29] (XXII) and rauvomitine [15,29] (XXIII) are also so arranged. This is the case for the modified α-indole alkaloid echitamine (XXIV), as shown by *X*-ray analysis.[30]

Thus, all the α-indole alkaloids of known stereochemistry about the ethylidene system possess the same configuration found in the β-series, *e.g.*, for fluorocurarine [31] (XXV) and the many other calabash curare alkaloids.[32,33] Strychnine (XXVI) shows the same configuration for an oxidised ethylidene system. It will be of interest to determine how this stereochemical control is achieved in the biosynthesis of the α- and β-indole alkaloids.

Experimental

For general directions, see Part II.[1]

Isolation of Macusine-C (XIX).—Impure macusine-B chloride (2·2 g.), obtained by direct crystallisation as in Part II,[1] was further fractionated in two equal portions on a cellulose column (160 g., 85 × 2·7 cm.) with methyl ethyl ketone saturated with water as the solvent. Two major fractions which overlapped slightly were obtained. The faster-moving fraction yielded *macusine-C chloride* which crystallised from ethanol–ether to give the pure alkaloid (0·1 g.), m. p. 260—261° (decomp. 264—265°) (Found: C, 65·6; H, 6·9. $C_{22}H_{27}ClN_2O_3$ requires C, 65·6; H, 6·8%), $[\alpha]_D^{24}$ −60·8 ± 0·5° (*c* 2·13 in H_2O), $\lambda_{max.}$ 222, 272, 278, 289, $\lambda_{min.}$ 241, 276, 287 mμ (log ε 4·63, 3·88, 3·87, 3·76, 3·38, 3·86, 3·68) (in water).

A solution of macusine-C chloride in acetic anhydride (1 ml.) and pyridine (0·5 ml.) was heated at 60° for 10 min. and evaporated to dryness. The residue in ethanol was passed first through alumina and then through Amberlite IRA-400 resin in the chloride phase. Evaporation of the percolate left a residue which showed $\nu_{max.}$ (Nujol) 1710 (N·CO), 1740 (CO_2Me), and 1749 $cm.^{-1}$ (O·COMe), and an ultraviolet spectrum corresponding to an *N*(a)-acylindole chromophore with some contribution from an unchanged indolic chromophore.

Macusine-C iodide was precipitated from an aqueous solution of the alkaloid chloride (51 mg.) by potassium iodide and was recrystallised from ethanol–ether (64 mg.), m. p. 285°

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(decomp.) (Found: C, 51·0, 51·3; H, 5·3, 5·4; N, 5·45. $C_{22}H_{27}IN_2O_3,H_2O$ requires C, 51·55; H, 5·7; N, 5·5%).

The slower-moving fraction from the column afforded pure macusine-B, already described.[1]

Normacusine-B (XIII).—Macusine-B chloride (0·1 g.) was evenly spread from a methanolic solution over the lower half of four glass bulbs (100 ml.) each with a right-angled neck containing a glass-wool plug. After the bulbs had been evacuated to *ca.* 10^{-4} mm., they were half-immersed in a metal-bath at 320—325° for 30—40 sec. The combined sublimate, in chloroform, was passed through alumina (10 g.), and the percolate was evaporated to a resin which crystallised from methanol to yield *normacusine-B* as needles (66 mg., 77%), m. p. 275—276°. Rhombic crystals, m. p. 245°, were obtained when ether was the solvent, and these were converted into the form of higher m. p. by recrystallisation from methanol (Found: C, 77·4; H, 7·3; *C*-Me, 4·3%; Equiv., 301. $C_{19}H_{22}N_2O$ requires C, 77·5; H, 7·5; *C*-Me, 5·1%; Equiv., 294), pK_a' 7·03 (80% methylcellosolve–water), $[\alpha]_D^{21}$ +38° (*c* 0·67 in methanol), $\lambda_{max.}$ 226, 275, 282, 290, $\lambda_{min.}$ 247, 277, 289 mμ (log ε 4·58, 3·86, 3·88, 3·79, 3·30, 3·85, 3·77 (in ethanol).

NO-*Diacetylnormacusine-B*.—A solution of normacusine-B (17 mg.) in pyridine (2 ml.) and acetic anhydride (1·5 ml.) was heated in an evacuated sealed tube at 80° for 20 hr. The solution was evaporated, and the base, recovered in ether as usual, was converted into NO-*diacetylnormacusine-B picrate* (16 mg.), m. p. 220—221° (from methylene chloride–ether) (Found: C, 55·75; H, 4·75. $C_{29}H_{29}N_5O_{10},H_2O$ requires C, 55·7; H, 5·0%). Recovery of the base, by passing a solution of the picrate in chloroform over neutral alumina, afforded *NO*-diacetylnormacusine-B, $\lambda_{max.}$ 240, (sh. 262), 290, 299, $\lambda_{min.}$ 222, 286, 295 mμ (log ε 4·19, 3·99, 3·70, 3·66, 4·08, 3·68, 3·62 (in ethanol), $\nu_{max.}$ 1707 (CO·N), 1748 $cm.^{-1}$ (CO_2R).

O-*Acetylnormacusine-B* (XII).—Normacusine-B (65 mg.) was added to pyridine (0·48 ml.) and acetic anhydride (0·98 ml.), and the solution was kept at 20° for 5¼ hr. The product, isolated as above, gave O-*acetylnormacusine-B* (60 mg.), m. p. 219—220° (from ether) (Found: C, 75·1; H, 7·3. $C_{21}H_{24}N_2O_2$ requires C, 75·0; H, 7·2%), $[\alpha]_D^{25}$ +9·1 (*c* 1·85 in methanol), ultraviolet spectrum of a 2,3-disubstituted indole.

Dihydronormacusine-B (X).—Normacusine-B (5·8 mg.) was added to a suspension of 5% platinum–charcoal catalyst (30 mg., previously equilibrated with hydrogen) in glacial acetic acid (5 ml.). The mixture was shaken with hydrogen; slow uptake (0·95 mol.) occurred. After removal of the catalyst, the solution was evaporated, and the residue in methanol was treated with a few drops of 0·1N-aqueous sodium hydroxide. Recrystallisation of the product from aqueous methanol gave *dihydronormacusine-B* (5 mg.), m. p. 189—190° (Found: C, 76·8; H, 7·9. $C_{19}H_{24}N_2O$ requires C, 77·0; H, 8·15%), $\lambda_{max.}$ 226, 275, 282, 290, $\lambda_{min.}$ 247, 278, 288 mμ (in ethanol).

On a larger scale (134 mg.), the hydrogenation was still slower, and repeated treatments with fresh catalyst and hydrogen were required to give the dihydro-derivative (95 mg.).

Deoxynormacusine-B.—Normacusine-B (61 mg.), toluene-*p*-sulphonyl chloride (42 mg., 1·05 equiv.) and pyridine (2 ml.) were kept under nitrogen for 4 days and the solution was then evaporated to dryness. That part of the residue which was insoluble in boiling light petroleum (b. p. 60—80°; 3 × 25 ml.) was dissolved in methylene chloride–ether (9 : 1 v/v) and shaken with aqueous sodium hydrogen carbonate. Evaporation of the organic layer left *O*-(toluene-*p*-sulphonyl)normacusine-B (92 mg.). This, in tetrahydrofuran (4 ml.) at 40°, was added to a solution of lithium aluminium hydride (360 mg.) in tetrahydrofuran (10 ml.) at 40°. The mixture was then heated under reflux for 5 hr., treated with saturated aqueous sodium potassium tartrate (30 ml.), and extracted with ether–methylene chloride (1 : 5 v/v; 3 × 50 ml.). The gum (95 mg.) so obtained was chromatographed on alumina in 1 : 1 benzene–chloroform. The initial band (4 mg.) was rejected, and chloroform then eluted a semicrystalline material (37 mg.). This was converted into the hydrochloride and further fractionated on cellulose powder (30 g.) in solvent system " C " containing 1% methanol.[1] The main fraction yielded a base which, after further chromatography on alumina, crystallised from methylene chloride and light-petroleum (b. p. 60—80°) to give deoxynormacusine-B (6 mg.), m. p. 268°, after change of form at 260° (Found: *C*-Me, 7·8. 2*C*-Me in $C_{19}H_{22}N_2$ requires 11·1%), $\nu_{max.}$ 3160 $cm.^{-1}$ only (NH), ultraviolet spectrum of a 2,3-disubstituted indole.

Action of Pivalic Acid on Normacusine-B.—A solution of normacusine-B (12·8 mg.) in pivalic acid–xylene (1 : 9 v/v; 0·5 ml.) was heated under reflux in nitrogen for 15 hr. Evaporation of the solution and chromatography of the residue on alumina (1 g.) gave normacusine-B (11 mg.) identified by m. p., mixed m. p., and infrared spectrum.

Attempted Dehydrogenations.—(a) *With mercuric acetate.* Mercuric acetate (14·8 mg.) was added to a solution of normacusine-B (3·2 mg.) in 5% aqueous acetic acid, and the solution was heated at 100° for 3·5 hr. After removal of the metallic ions by hydrogen sulphide, the solution was evaporated to a few ml. and the ultraviolet spectrum recorded. It was identical with that of starting material.

(b) *With palladium black.* Normacusine-B (3·5 mg.), maleic acid (7·7 mg.), palladium black (2·6 mg.), and water (1 ml.) were heated under reflux for 18 hr. After removal of the catalyst, the ultraviolet spectrum was found to be that of normacusine-B.

Deformonormacusine-A and sarpagine behaved similarly, whereas the product from yohimbine showed the spectrum of 3,4,5,6-tetradehydroyohimbine.

Deoxyisoajmaline Methochloride (V).—Dihydro-*N*-methylisoajmaline [15] (0·57 g.) was heated at 78° in pyridine (10 ml.) with toluene-*p*-sulphonyl chloride (0·35 g.) in an evacuated sealed tube for 12 hr. Evaporation of the mixture then left a residue which in methanol was passed over Amberlite IRA-400 resin in the chloride phase. The percolate was evaporated and the residue was dissolved in N-hydrochloric acid, extracted with ether, basified, and again extracted with ether. Evaporation of the acidified solution left a residue from which deoxyisoajmaline methochloride (0·43 g.), m. p. 298°, was extracted with chloroform; it was identified by comparison with authentic material.[15]

N(a),O-*Dimethyldihydronormacusine-B Methiodide.*—Sodium (8·5 mg.) was dissolved in liquid ammonia (10 ml.), to give a blue colour which just persisted; more sodium (20 mg.) was then added, followed by dihydronormacusine-B (50 mg.). After 15 min., the base had dissolved and methyl iodide (1 ml.) was then added. Evaporation of the solution left a residue which was dissolved in N-hydrochloric acid and extracted with 1 : 1 ether–methylene chloride, to afford a resin (88 mg.). This was chromatographed on alumina in 2 : 1 ethanol–methylene chloride, and the product from the main band (50 mg.) crystallised from ethanol to give needles (25 mg.), m. p. 286—287°. Recrystallisation twice from ethanol gave NO-*dimethyldihydronormacusine-B methiodide*, m. p. 298—299° after sintering at 292° (Found: C, 56·8; H, 6·7; OMe, 6·5; *N*-Me, 5·0. $C_{22}H_{31}IN_2O$ requires C, 56·65; H, 6·7; OMe, 6·65; *N*-Me, 6·45%), $\lambda_{max.}$ 223, 276, 282, (sh. 291), $\lambda_{min.}$ 246, 278 mμ (log ε 4·73, 3·87, 3·88, 3·78, 3·05, 3·86) (in ethanol).

O-*Acetyldihydronormacusine-B.*—(*a*) A solution of dihydronormacusine-B (30 mg.) in pyridine (0·22 ml.) and acetic anhydride (0·45 ml.) was kept at 20° for 5 hr. and then worked up as for *O*-acetylnormacusine-B (above) to give a crude resin. This was chromatographed on neutral alumina in chloroform, and the main band crystallised from ether, to give O-*acetyldihydronormacusine-B* as needles (29 mg.), m. p. 219—220° after sintering at 210° (Found: C, 75·1; H, 8·05. $C_{21}H_{26}N_2O_2$ requires C, 74·5; H, 7·7%), ultraviolet spectrum of a 2,3-disubstituted indole, $\nu_{max.}$ 1743 (OAc), 3160 cm.$^{-1}$ (NH).

(*b*) *O*-Acetylnormacusine-B (28 mg.) in glacial acetic acid (7 ml.) was shaken with hydrogen and 10% platinum–charcoal catalyst for 5 days at room temperature and pressure. The solution was then filtered and the filtrate was shaken with fresh catalyst (120 mg.) and hydrogen, as before, for 4 days. Filtration and evaporation of the solution left a residue which was fractionally crystallised from ethanol, to give starting material (5 mg.) and *O*-acetyldihydronormacusine-B (15 mg.) identical with the sample under (*a*).

N(a)-*Methyldihydronormacusine-B* (*Deoxyisoajmalol-B*) (IX).—Liquid ammonia was distilled through soda-lime on to a small crystal of dry ferric nitrate, and sodium (3·5 mg.) was added. A solution of *O*-acetyldihydronormacusine-B (43·5 mg.) in anhydrous tetrahydrofuran (2·5 ml.) was then added, and after 2 min., a solution of methyl iodide (2·25 mg.) in ether (1 ml.) was run in. The mixture was evaporated to dryness and a solution of the residue in methanol (2 ml.) and aqueous 2N-sodium hydroxide (0·2 ml.) was warmed to 60° for 25 min. After being kept at room temperature for 6 hr., the solution was diluted with water (20 ml.) and extracted with ether, to afford a resin (37 mg.). Chromatography of this material in chloroform on alumina, and re-chromatography of the overlapping bands, gave many fractions; the high-melting ones were combined and recrystallised from ethanol, to give *N*(a)-methyldihydronormacusine-B (3·5 mg.), m. p. 248—250°, shown by m. p., mixed m. p., and infrared spectrum to be identical with deoxyisoajmalol-B.

Dehydrogenation of Macusine-A.—An intimate mixture of finely powdered macusine-A chloride (50 mg.) and selenium (65 mg.) was heated in a small glass bulb with a long neck (4 in.); the temperature was raised from 160 to 300° during 7 min. Two further dehydrogenations were carried out on the same scale and the distillate (10 mg.) was reserved. After the

residue in the bulb had been ground with sand, it was extracted continuously with ether for 7 hr., to yield a gum (48 mg.), and with chloroform for 12 hr., to give a dark brown gum (130 mg.). Extraction of these three fractions with benzene gave a clear gum (75 mg.) which was chromatographed on alumina, first with benzene and later with increasingly rich mixtures of chloroform in benzene. The fractions showing the 2-pyridylindole chromophore were combined (5·4 mg.) and treated in ethanol with picric acid. A partly crystalline picrate separated (4·7 mg.), and this was converted back into the free base by passing a solution of it in benzene–chloroform over alumina. Careful chromatography of this base, as before, gave a crystalline base, m. p. 110°, which afforded a picrate, m. p. 218—220° (lit.,[21] for alstyrine, m. p. 110—111°; picrate m. p. 218—221°), $\lambda_{max.}$ 325, $\lambda_{min.}$ 274 mμ (in ethanol) which changed to $\lambda_{max.}$ 255, 309, 375, $\lambda_{min.}$ 242, 277, 329 mμ in acidified ethanol (cf. lit. spectrum in acid [34]).

Pyrolysis of Macusine-A Chloride.—Macusine-A chloride (0·1 g.) was distributed in five bulbs and pyrolysed for 50 sec. as for macusine-B chloride above. The methanol-soluble material was worked up as usual for basic material (42 mg.) which was chromatographed on alumina in chloroform. Combination of the semicrystalline fractions (18 mg.), and conversion of them into the picrate in methanol, yielded, after recrystallisation from the same solvent, deformonormacusine-A picrate (19 mg.), m. p. 239—241° (decomp.) (Found: C, 57·3; H, 4·7. $C_{26}H_{25}N_5O_9$ requires C, 56·6; H, 4·6%). *Deformonormacusine-A* itself was recovered from the picrate by passing the salt in chloroform over alumina; the base crystallised from methanol as needles, m. p. 240—241°. A dimorphic form had m. p. 228°, and the melt resolidified and melted again at the higher temperature [Found: *M* (mass spectrum), 322. $C_{20}H_{22}N_2O_2$ requires *M*, 322], $\nu_{max.}$ (Nujol) 1740 (CO_2Me), 3170 cm.$^{-1}$ (NH), $\lambda_{max.}$ 230, 275, 280, 290, $\lambda_{min.}$ 247, 277, 288 mμ (log ε 4·34, 3·87, 3·87, 3·79, 3·43, 3·87, 3·77 (in ethanol).

Pyrolysis of Macusine-C Chloride.—This was carried out as above with the salt (114 mg.) distributed in six bulbs; the pyrolysis period was 30—45 sec. In this case, the methanol-soluble material was passed, in chloroform, over alumina, and the residue (56 mg.) from the percolate was worked up for base (44 mg.). This was converted into the picrate (35 mg.) in methanol, m. p. 225—226° (decomp.), shown below to be the picrate of deformonormacusine-A together with that of normacusine-C.

The base, recovered from the picrate on alumina as above, was crystallised from ether, to afford slightly impure deformonormacusine-A, m. p. 217—222°, undepressed on admixture with the foregoing sample; the infrared spectra were indistinguishable. The mass spectrum of the sample showed all the peaks corresponding to deformonormacusine-A, with a strong peak at *m/e* 322 together with others, particularly a parent peak at *m/e* 352 ($C_{21}H_{24}N_2O_3$ requires 352; $C_{20}H_{22}N_2O_2$ requires 322).

Correlation of Macusine-A and Macusine-C with Normacusine-B.—Macusine-A chloride (0·2 g.) was pyrolysed as above, and a solution of the total basic products (74 mg.), in anhydrous ether (32 ml.), was heated under reflux with lithium aluminium hydride (44 mg.) for 4·5 hr. The cooled solution was treated with an excess of saturated aqueous sodium potassium tartrate and the ether layer together with the ethereal extracts from the aqueous layer were dried and evaporated to leave a gum (31 mg.). This was chromatographed on alumina in chloroform, and the fractions corresponding to normacusine-B (by thin-layer chromatography) were combined and crystallised from methanol, to give normacusine-B (10 mg.), identified by m. p., mixed m. p. (269—273°), and infrared spectrum; $[\alpha]_D^{20}$ +34° (*c* 0·58 in methanol).

The total basic material (43 mg.) from macusine-C chloride (76 mg.) was treated in the same way, to afford normacusine-B (8·5 mg.), identified by m. p. (269—274°), mixed m. p. (271—276°), and infrared spectrum; $[\alpha]_D^{20}$ +35·2° (*c* 0·60 in methanol).

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[34] Prasad and Swan, *J.*, 1958, 2024.