505. *The Indole Alkaloids. Part IV.*[1] *The Structure of Henningsamine*

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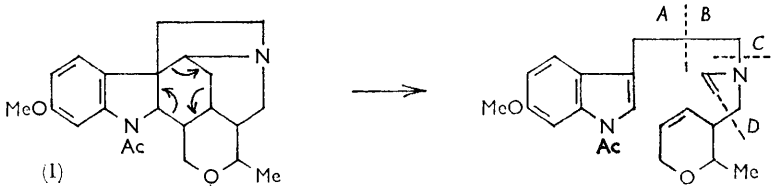
Mass-spectrometric studies of henningsamine and its derivatives and related compounds lead to the structure as diacetyl Wieland–Gumlich aldehyde A, which is confirmed by hydrolysis to, and synthesis from, Wieland–Gumlich aldehyde. Acetylation of diaboline gives diacetyl Wieland–Gumlich aldehyde B.

Henningsamine, $C_{23}H_{26}N_2O_4$, was isolated from *Strychnos henningsii* Gilg.[1] in very small quantities which precluded extensive chemical studies.

The mass spectrum of henningsamine (Figure) confirmed the molecular weight (394) of this alkaloid and accurate mass-determination on the molecular ion using a high-resolution mass spectrometer gave the value 394·18941 in support of the composition $C_{23}H_{26}N_2O_4$ (Calc. 394·18925). The mass spectra of dihydroindoles have been determined and discussed previously,[2–4] and the spectrum of henningsamine showed, in fact, considerable similarity to those of demethoxycarbonyldihydroakuammicine [2,3] or strychnospermine (I),[3] for example, which may fragment as follows:

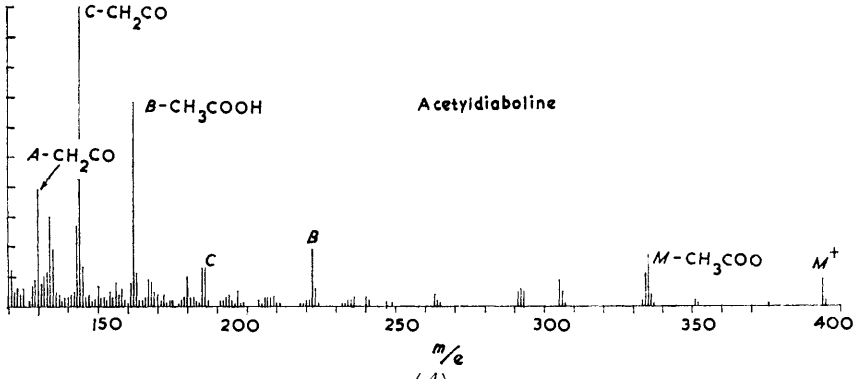


[1] Part III, J. S. Grossert, J. M. Hugo, M. E. von Klemperer, and F. L. Warren, preceding Paper. This Paper also forms Part XXVIII of Application of Mass Spectrometry to Structure Problems, Part XXVII, K. Biemann, and J. J. Watson, *Monatsh Chem.*, 1965, **95**, in the press.

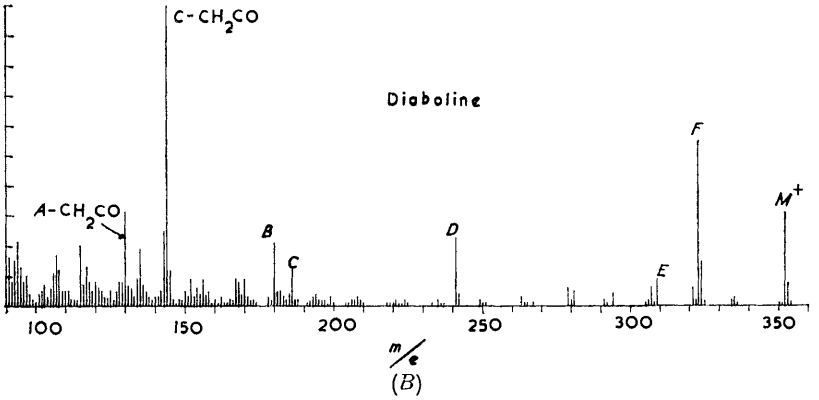
[2] K. Biemann, M. Friedmann-Spiteller, and G. Spiteller, *Tetrahedron Letters*, 1961, 485.

[3] K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill, New York, 1962, ch. 8.

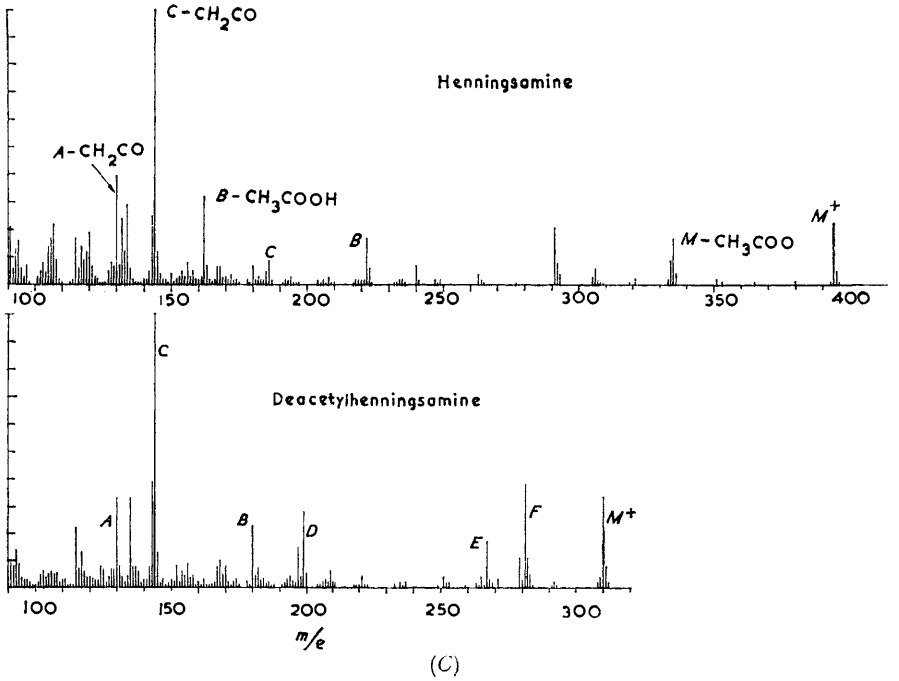
[4] H. Budzikiewicz, J. M. Wilson, C. Djerassi, J. Levy, J. LeMen, and M.-M. Janot, *Tetrahedron*, 1963, **19**, 1265.



(*A*)



(*B*)



(*C*)

Mass spectrum of acetyldiaboline, diaboline, henningsamine, and deacetylhenningsamine

The species of mass 334 and 335 can be shown to result from the loss of $C_2H_3O_2$ and $C_2H_4O_2$, respectively,* indicating the presence of an acetoxy-group which is confirmed by the spectra of deacetylbis(trideuteroacetyl)henningsamine discussed below.

Some of the fragments of lower mass, namely 130 (C_9H_8N) and 144 ($C_{10}H_{10}N$) are indicative of unsubstituted dihydroindoles or their *N*-acyl derivatives with at least one α-hydrogen in the acyl group which is generally eliminated as keten,[3] or as a substituted keten. An intense peak at *m/e* 43 is in agreement with the assumption of an *N*-acetyl moiety and the elemental composition of species *C* (*m/e* 186), $C_{12}H_{12}NO$, in fact corresponds to the species of mass 144 with the retention of the acetyl group. These conclusions regarding the aromatic part of henningsamine are in agreement with the ultraviolet, infrared, and nuclear magnetic resonance (n.m.r.) spectra.

The pair of peaks at *m/e* 222 ($C_{12}H_{16}NO_3$) and 162 ($C_{10}H_{12}NO$) differ by $C_2H_4O_2$ which requires that these represent the alicyclic moiety of henningsamine including the acetoxy-group (eliminated as acetic acid in the formation of the entity of *m/e* 162).

These conclusions, namely that henningsamine is an *N*-acetyldihydroindole derivative with a non-indolic part consisting of eleven carbon atoms, one nitrogen, one oxygen, and an acetoxy-group are confirmed by the mass spectrum (Figure) of deacetylhenningsamine (II; R = R′ = H) (obtained on acid hydrolysis) and the product (II; R = R′ = $CO{\cdot}CD_3$) of its reacetylation with [$^2H_6$]acetic anhydride. These reactions lead to a loss of 84 mass units (394 ⟶ 310) corresponding to the replacement of two acetyl groups by two hydrogen atoms which are in turn replaced by two trideuteroacetyl groups. The spectrum of (II; R = R′ = $CO{\cdot}CD_3$) (peaks at *m/e* 131, 145, 162, 189, 225, 337, 338, and 400) is in agreement with the above postulate as *m/e* 335 and 222 shift to *m/e* 338 and 225, respectively (retention of one trideuteroacetyl group in each of these), and *m/e* 144 and 130 shift to *m/e* 145 and 131, respectively, as expected on transfer of hydrogen and deuterium, respectively, from the acetyl groups to the indole nitrogen. The ion at *m/e* 162 remains unchanged in the spectrum of the deuterated compound as none of the acetyl groups remain in this fragment. The infrared bands at 5·74 and 6·04 μ and the δ values at 2·08 and 2·39 correspond to the *O*-acetyl and *N*-acetyl groups, respectively.

Henningsamine on hydrogenation over platinum in ethanol gives dihydrohenningsamine (dihydro-II; R = R′ = Ac) (*M*, 396) showing the presence of one reducible double bond in the molecule. Hydrogenation of deacetylhenningsamine (II; R = R′ = H), however, gives a mixture of compounds with molecular weights of 314 (III; X = OH) (absorption of 2 moles of hydrogen) and 298 (III; X = H) (hydrogenolytic loss of oxygen). Fractional vaporisation of the sample into the ion-source of the spectrometer showed that this reduction product is indeed a mixture of two components, the one of molecular weight 314 becoming more apparent at higher temperature. It also indicated that the most prominent peak of the 298 species is at *m/e* 168, whilst the 314 component has a very intense peak at *m/e* 184. These observations suggest the presence of an allylic oxygen atom and two double bonds.

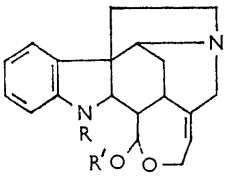
Such a system is reminiscent of various dihydroindole alkaloids with the carbon skeleton of Wieland–Gumlich aldehyde, most of which have been isolated from *Strychnos* species. In the case of henningsamine, the ions of type *B* (*m/e* 222 and 162) are less abundant than the corresponding ones at *m/e* 136 and 166 in demethoxycarbonyldihydroakuammicine and strychnospermine (I).[3]

To confirm this hypothesis the spectrum of diaboline (II; R = Ac; R′ = H) (Figure) was determined. There also the ion *B* (*m/e* 180) is of low abundance, and must therefore be due to the presence of the unsaturated seven-membered ether ring and also to the *N*-acetyl group, because on hydrolysis the intensity of the peak at *m/e* 180 increases.

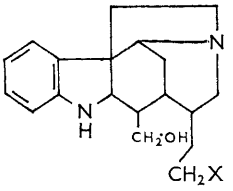
Comparison of the mass spectra of deacetyldiaboline and Wieland–Gumlich aldehyde (II; R = R′ = H) with deacetylhenningsamine clearly indicate that these compounds

* All the assigned elemental formulæ mentioned here and later, have been determined from the high-resolution mass spectrum of henningsamine.

have the same carbon skeleton; and this receives confirmation from a similar comparison of the mass spectra of their reacetylated products, acetyldiaboline (Figure) and diacetyldeacetylhenningsamine.



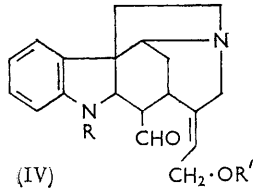
(II)



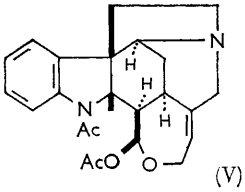
(III)

Various preparations of deacetylhenningsamine give mass spectra varying somewhat in the relative intensity, particularly in the abundance of ion *B* (*m/e* 180), some of them being practically identical with a " standard sample " of Wieland–Gumlich aldehyde. Similar phenomena might be the reason for the difficulties in comparing deacetyldiaboline with Wieland–Gumlich aldehyde.[5] There are some small differences in the intensities in the spectra of deacetylhenningsamine, deacetyldiaboline, and Wieland–Gumlich aldehyde as well as henningsamine and acetyldiaboline. This is best attributed to epimerism (*cf.* Deyrup, Schmid, and Karrer [6]). Treatment with hot pyridine eliminates these differences.

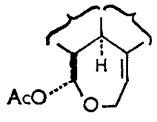
The structure of henningsamine can then be written as (II; R = R′ = Ac). It does not seem to have the " open structure " (IV; R = R′ = Ac) because of the absence of an aldehydic proton signal in its n.m.r. spectrum and the absence of an *M* − 29 (loss of CHO) ion in its mass spectrum. Furthermore, the absorption of one mole of hydrogen over platinum gives a single product, whilst reduction of the olefinic double bond and the aldehyde group, if not also hydrogenolysis of the allyl acetate, would be expected of the open form. That these reductions are observed in part in the case of deacetylhenningsamine implies that the oxepin form is in equilibrium with the open hydroxy-aldehyde, (II ⇌ IV; R = R′ = H).



(IV)



(V)



(VI)

The absolute configuration is (V) since the melting point of henningsamine was undepressed with diacetyl Wieland–Gumlich aldehyde A,[5] m. p. 204·5—205·5°, obtained by direct acetylation of Wieland–Gumlich aldehyde.

It is significant that henningsamine has $[\alpha]_D$ −43°, whilst diacetyl Wieland–Gumlich aldehyde A is reported [6] as having $[\alpha]_D$ −33° and our diacetyl compound showed $[\alpha] \gtrsim -23°$.

Deyrup *et al.*[6] acetylated Wieland–Gumlich aldehyde to give diacetyl Wieland–Gumlich aldehyde A, m. p. 203—204°, and in smaller quantity amorphous diacetyl Wieland–Gumlich aldehyde B (picrate, m. p. 214—215°). Acetylation of diaboline (II; R = Ac, R′ = H) reported [5] to give an amorphous diacetate, has, in our hands, yielded a crystalline product, m. p. 92—94·5°, having $[\alpha]_D^{21}$ +51·2° and a picrate corresponding to diacetyl Wieland–Gumlich aldehyde B.

It seems that the acetylation of diaboline is influenced by the presence of the N–Ac grouping to give predominantly the diacetyl-B (VI), whilst in the case of Wieland–Gumlich aldehyde (II; R = R′ = H) the *O*-acetylation is unhindered and can give both forms.

[5] F. E. Bader, E. Schlittler, and H. Schwarz, *Helv. Chim. Acta*, 1953, **36**, 1256.
[6] J. A. Deyrup, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, 1962, **45**, 2266.

Experimental

The various derivatives required for the mass-spectrometric investigation were prepared on a scale of 1—2 mg., using the conditions stated in the text. The spectra were determined on the isolated product without further purification.

Henningsamine.—This had $\lambda_{max.}$ 208, 252 mμ (log ε 4·52, 4·18), $\lambda_{infl.}$ 280 mμ (log ε 3·61), pK_a, 6·6, $\lambda_{max.}$ (KBr), 5·74 (CO), 6·03 (amide CO), 6·27 μ (aromatic); δ ($CDCl_3$), 2·08 (singlet, OAc), 2·39 (singlet, NAc).

Acetylation of Diaboline.—Diaboline acetylated with acetic anhydride and pyridine for 36 hr. and the product crystallised from ethyl acetate–light petroleum gave acetyldiaboline (diacetyl Wieland–Gumlich aldehyde B) crystals, m. p. 92—94·5°, $[\alpha]_D^{21}$ +51·2° (*c* 1 in chloroform) {lit.,[6] $[\alpha]_D^{22}$ +48·6° ± 4° (chloroform) for the amorphous compound}, $\lambda_{max.}$ ($CHCl_3$), 5·72 (CO), 6·02 μ (amide CO); δ ($CDCl_3$), 2·09 (singlet, OAc), 2·41 (singlet, N–Ac). Crystallisation from ethyl acetate–light petroleum took place with water of solvation which was not readily removed (Found: C, 67·8; H, 7·0. $C_{23}H_{26}N_2O_4,\frac{3}{4}H_2O$ requires: C, 67·7; H, 6·8. Found, after drying at 80°/0·6 mm.: C, 68·6; H, 6·7. $C_{23}H_{26}N_2O_4,\frac{1}{2}H_2O$ requires C, 68·5; H, 6·7%). Crystallised from ethyl acetate and dried at 80°/0·6 mm. (Found: C, 69·3; H, 6·9. $C_{23}H_{26}N_2O_4$ requires C, 70·0; H, 6·6%). Picrate, from ethanol, gave crystals, m. p. 212·5—214° (lit.,[6] 214—215°) (Found: C, 55·95; H, 4·8. Calc. for $C_{29}H_{29}N_5O_{11}$: C, 55·9; H, 4·7%). *Hydrochloride*, m. p. 230° (decomp.) (Found: C, 63·7; H, 6·6. $C_{23}H_{27}ClN_2O_4$ requires C, 64·1; H, 6·3%).

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