Lycoris Alkaloids. Part XXVIII. The Constitution of Lycorine and the Synthesis of its Degradation Products.*

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It has been shown that the initial action of alkali on lycorine methohydroxide produces anhydrolycorine methohydroxide which then undergoes either Hofmann or Emde degradation to give lycorine anhydromethine and lycorine anhydrohydromethine respectively. Anhydrolycorinium chloride has been converted into anhydrolycorine methiodide, and all of the principal degradation products of lycorine have now been synthesised. The structure of lycorine has been established and the course of its reactions explained.

Lycorine is an alkaloid of widespread occurrence among the Amaryllidaceae and, although the subject of much investigation (cf. Cook and Loudon, " The Alkaloids," Vol. II, edited by Manske and Holmes, Academic Press, New York, 1952, p. 331), the structure (I) (Kondo and Katsura, *Ber.*, 1940, **73**, 1424) has been open to doubt and some of the reactions and degradation products have hitherto remained obscure. It is now shown that the chemistry can be best expressed in terms of the modification (II) originally suggested by Cook and Loudon (*loc. cit.*).

Methylation of lycorine gives two diastereoisomeric methiodides (α- and β-), both of which undergo the Hofmann degradation with concomitant loss of two molecules of water to furnish the methine base, lycorine anhydromethine (IX), whose structure has been proved by degradation (Kondo and Uyeo, *Ber.*, 1935, **68**, 1756; 1937, **70**, 1087) and confirmed by synthesis of its dihydro-derivative (X) (Kelly, Thesis, New Brunswick, under the direction of Dr. K. Wiesner; cf. *J.*, 1953, 2094). In this remarkable reaction the presence of both the double bond and the quaternary nitrogen is necessary for the ready elimination of water, since under Hofmann conditions lycorine itself is stable, and dihydrolycorine methohydroxide is resistant, to degradation (Kondo and Katsura, *Ber.*, 1939, **72**, 2083). It was felt that the elimination of water and the Hofmann degradation might be separate processes and this question has now been answered (see below).

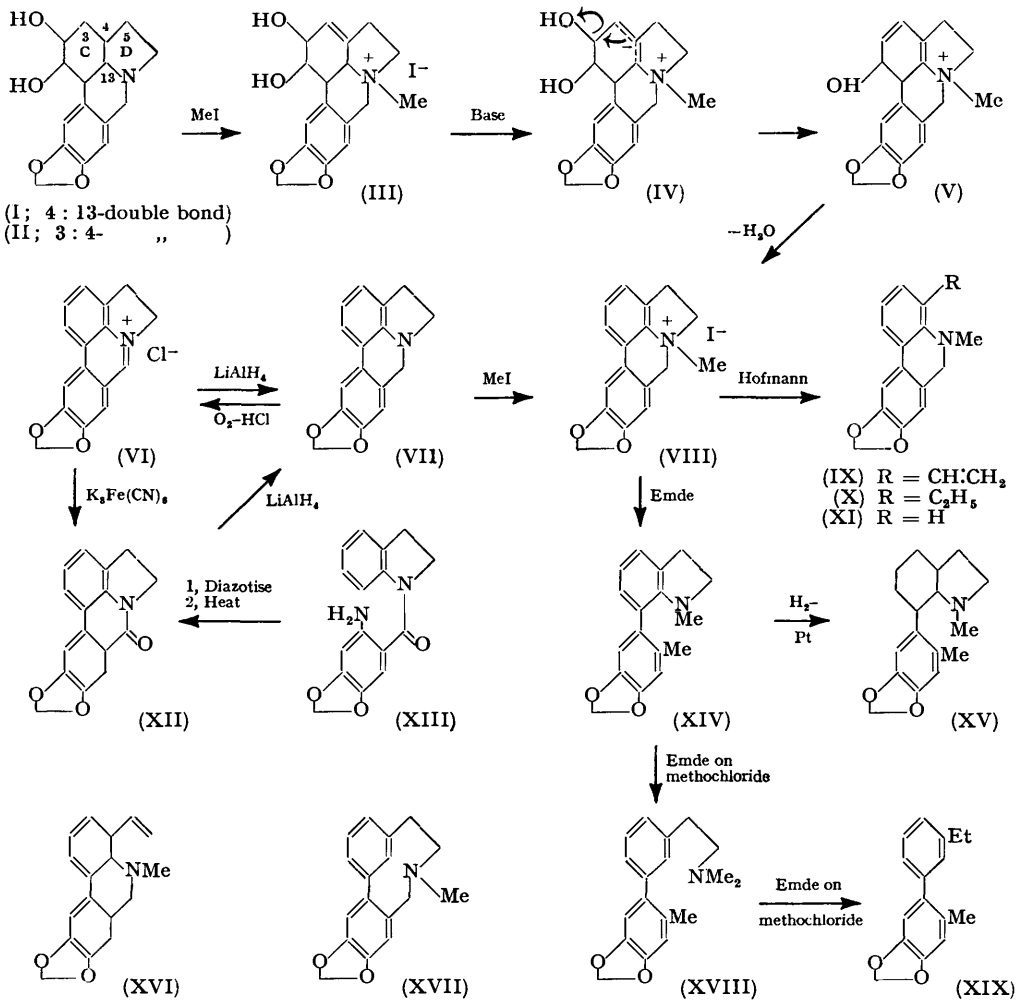
The starting point of the present study lies in the results reported by one of us (H. K.) for the Hofmann degradation of lycorine 26 years ago (Kondo and Tomimura, *J. Pharm. Soc. Japan*, 1928, **48**, 36, 223). It was found that when lycorine methohydroxide was heated with 20—30% sodium hydroxide it gave along with the methine base a compound " lycorine pseudomethohydroxide," to which was ascribed the formula $C_{16}H_{17}O_4N$,MeOH, m. p. 219° (decomp.). This substance gave, on heating, the methine base and " methyl-lycorine isomethine," $C_{16}H_{16}O_4N$·Me, m. p. 234° (decomp.). When either the latter compound or " lycorine pseudomethohydroxide " was heated with methyl iodide in a sealed tube they formed the same " methyl anhydrolycorine methiodide," $C_{16}H_{12}O_2N$·Me,MeI, m. p. 235° (decomp.). The " methyl anhydrolycorine methiodide " on treatment successively with silver oxide and hot sodium hydroxide appeared to undergo reversible hydration to yield " methyl-lycorine isomethine." These reactions, unusual if correct, have now been re-examined.

The Hofmann degradation proceeded smoothly to the methine base if the methiodide was converted by pure silver oxide into the methohydroxide and this then heated *in vacuo*; but when silver oxide containing alkali was used the main product was a water-soluble, ether-insoluble compound which gave an optically inactive iodide, m. p. 228—229°, when treated with dilute hydriodic acid or heated on a water-bath with methyl iodide. The iodide gave analyses correct for $C_{17}H_{16}O_2NI$ and could not be extracted from basic solution by organic solvents, so was probably quaternary; it is now called anhydrolycorine methio-

* Part XXVII, Ann. Report, ITSUU Lab., 1954, **5**, 72.

dide and is apparently identical with " methyl anhydrolycorine methiodide," but a direct comparison was impossible as the original samples were lost during the war.

The action of 20% aqueous sodium hydroxide on lycorine α-methohydroxide gave the ether-soluble methine base and a water-soluble compound which by analysis and chemical properties was shown to be lævorotatory anhydrolycorine methocarbonate. This (—)-methocarbonate afforded with dilute hydrochloric acid or hydriodic acid, carbon dioxide and the corresponding (—)-methochloride, m. p. 219°, and (—)-methiodide respectively. From lycorine β-methohydroxide the same series of compounds could be prepared with identical melting points but with equal and opposite rotations. Combination of the respective enantiomorphs gave the racemates, and all of these compounds gave analyses



in good agreement with the general formula $C_{17}H_{16}O_2NX,yH_2O$ (X = $0{\cdot}5CO_3$, Cl, or I). " Lycorine pseudomethohydroxide," m. p. 219°, is apparently identical with *rac.*-anhydrolycorine methochloride, m. p. 219°, since Kondo and Tomimura (*loc. cit.*) heated the crude Hofmann product (a mixture of the methine base and *rac.*-anhydrolycorine methocarbonate) with chloroform, a procedure which we have now shown (see p. 4627) to convert the methocarbonate into the methochloride. It has not been possible in this work to find a

compound corresponding in its properties to " methyl-lycorine isomethine " or to confirm the postulated reversible hydration.

Intensive drying of anhydrolycorine methocarbonate at room temperature or drying it for a short period at 100° *in vacuo* gave the methine base (IX); the other salts, when refluxed with alkali, yielded as expected the same methine base.

The structure (VIII) for anhydrolycorine methiodide becomes obvious since it must differ from lycorine methiodide by the elements of two molecules of water; it should undergo the Hofmann degradation, readily yielding the methine base (IX), and have an asymmetric nitrogen atom since the enantiomorphs are formed from the diastereoisomeric α- and β-methiodides which differ only in the configuration about the quaternary nitrogen atom. The absorption spectrum agrees with this formulation and, as expected, closely resembles its open-chain analogue dihydrolycorine anhydromethine hydrochloride (see Fig. 1).

Further evidence in support of this view comes from the conversion of anhydrolycorinium chloride (VI) into *rac.*-anhydrolycorine methiodide (VIII) *via* (VII). Anhydroly-

FIG. 1.

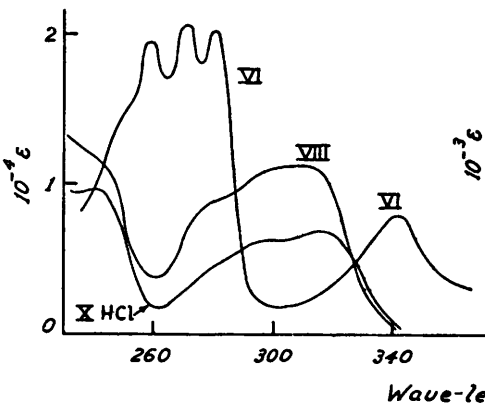


FIG. 2.

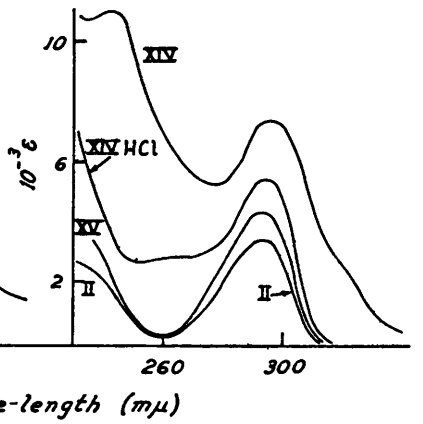


FIG. 1. (VI), *Anhydrolycorinium chloride.* (VIII), *Anhydrolycorine methochloride.* (X) HCl, *Dihydrolycorine anhydromethine hydrochloride.*

FIG. 2. (XIV), *Lycorine anhydrohydromethine.* (XIV) HCl, *Hydrochloride of* (XIV). (XV), *Hexahydrolycorine anhydrohydromethine.* (II), *Lycorine.*

corinium chloride, originally called isolycorine hydrochloride, was first prepared by Kondo and Tomimura (*loc. cit.*) by the action of phosphorus pentachloride or phosphorus oxychloride on lycorine and was recently reinvestigated (Kondo, Takeda, and Kotera, Ann. Report, ITSUU Lab., 1954, **5**, 66) and assigned the constitution (VI) mainly on the basis of the resemblance of its ultra-violet absorption spectrum (Fig. 1) to that of phenanthridinium salts.

Confirmation of these views has now been obtained by application of the Pschorr cyclisation. 1-(2-Amino-4 : 5-methylenedioxybenzoyl)-2 : 3-dihydroindole (XIII) afforded on cyclisation mainly 1-piperonyloylindole (this dehydrogenation is discussed below), with a smaller quantity of the desired phenanthridone (XII); on reduction by lithium aluminium hydride this gave synthetic anhydrolycorine (VII) whose methiodide was identical with *rac.*-anhydrolycorine methiodide (VIII) prepared as above. This also constitutes a synthesis of lycorine anhydromethine (IX). Anhydrolycorinium chloride (VI) was readily prepared in good yield by passing air through a solution of anhydrolycorine in dilute ethanolic hydrochloric acid. The synthetic phenanthridone (XII) was also shown to be identical with the product of the oxidation of (VI) with potassium ferricyanide (Kondo, Takeda, and Kotera, *loc. cit.*).

Until now the constitution of lycorine anhydrohydromethine formed by the Emde

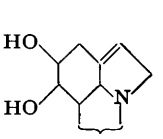
degradation of lycorine methochloride has not been clear. The double bond is essential for this reaction also, since the dihydro-compound is stable. The Emde base yielded formaldehyde with ozone and readily took up three mols. of hydrogen to give a hexahydrolycorine anhydrohydromethine (Kondo and Katsura, *Ber.*, 1940, **73**, 1424). Principally for these reasons it was supposed that the Emde base could best be represented by a formula such as (XVI) although, as pointed out by Cook and Loudon (*loc. cit.*), Groenewoud and Robinson (*J.*, 1934, 1692) had not been able to demonstrate this type of reduction in the Emde reduction of 2-diphenylyltrimethylammonium chloride.

It has now been found that *rac.*-anhydrolycorine methochloride undergoes the Emde reaction to give lycorine anhydrohydromethine. It would appear therefore that anhydrolycorine methohydroxide is an essential intermediate in this reaction and also that in both the Hofmann and the Emde degradation the first step is the elimination of two molecules of water from the quaternary salt by the action of base. Since the Emde product is not dihydrolycorine anhydromethine (X) it can only be (XIV). The remaining possibility (XVII) is eliminated since the Emde base shows a high percentage of *C*-methyl in the Kuhn–Roth determination and the absorption spectrum corresponds to that of a 2-diphenylylamine rather than to that of a non-basic diphenyl system and is strongly affected by acid (Fig. 2). Hexahydrolycorine anhydrohydromethine must be the octahydroindole (XV); the ultra-violet spectrum is as expected identical with that of lycorine (Fig. 2). Conjugation between the two aromatic rings in (XIV) must be largely inhibited since the absorption spectrum corresponds very approximately to a summation of the two independent chromophores. The further Emde degradation products of (XIV) (Kondo and Katsura, *loc. cit.*) can be readily interpreted as (XVIII) and (XIX) [cf. the Emde degradation of *N*-methyldihydroindole methiodide (von Braun and Neumann, *Ber.*, 1916, **49**, 1283)].

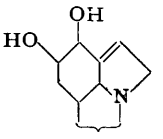
Repetition of the ozonolysis of the Emde base under standard conditions (Kondo and Katsura, *loc. cit.*) has confirmed the production of formaldehyde, but since dihydrolycorine anhydromethine also gives formaldehyde this most probably comes from the methylenedioxy-group. Similar results have been observed in other compounds without vinyl groups (Karrer and Kebrle, *Helv. Chim. Acta*, 1952, **35**, 862) so that care is necessary in the interpretation of such results.

The two hydroxyl groups in lycorine are vicinal and secondary [lead tetra-acetate fission (Kondo and Katsura, *Ber.*, 1940, **73**, 112) and stability to acid], and the double bond is not conjugated with the aromatic ring (ultra-violet absorption spectrum; Kondo and Katsura, *ibid.*, p. 1424) or αβ to the nitrogen atom (pK_a measurements). The slight change in the position of the peak at 293 mμ (ε 3500) in the absorption spectrum of lycorine when in acidic solution ($\lambda_{max.}$ 289 mμ, ε 5% lower) must be entirely due to the piperonyl residue since dihydrolycorine shows the same change. If the double bond is in ring C this leads at once to (II) as the only possible structure for lycorine.

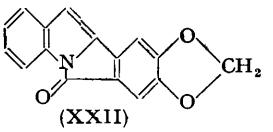
However, if the double bond should be in ring D two further structures (partial formulæ XX and XXI) must be examined, although the stability of lycorine to hot ethanolic sulphuric acid which would be expected to shift the double bond exocyclic to the six-membered ring into an endocyclic position constitutes strong evidence against this possibility (Brown, Brewster, and Schechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467). The structure



(XX)



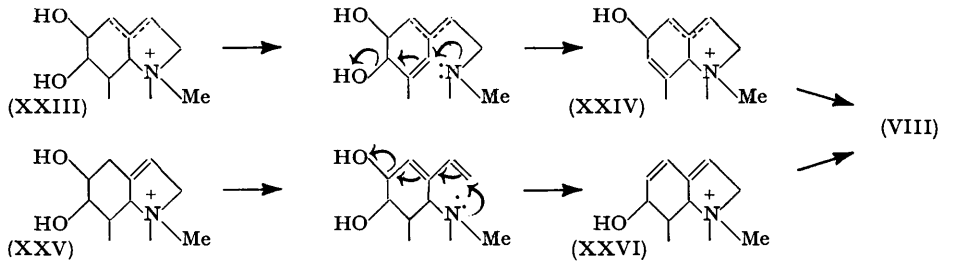
(XXI)



(XXII)

(XXI) cannot account for the formation of the anhydrolycorine methine (IX) and the anhydrolycorine metho-salts (cf. VIII) in the Hofmann degradation of the methohydroxide and can therefore be dismissed. Furthermore, in both remaining formulæ, reaction routes such as (XXIII) to (XXIV) or (XXV) to (XXVI) in which elimination of water is an integral part of a Hofmann reaction are excluded since they do not account for the retention of optical activity of the anhydrolycorine metho-salt.

An acceptable mechanism for the formation of the anhydrolycorine metho-salt that confirms the formula (II), which was deduced above from elementary considerations and is in agreement with biogenetic ideas (Wenkert, *Chem. and Ind.*, 1953, 1088), has previously



been advanced (Taylor, Thomas, and Uyeo, *Chem. and Ind.*, 1954, 929). The action of base on the quaternary salt removes a proton to give an " ylide " intermediate (IV) with the carbanion stabilised by the adjacent double bond. Decomposition *via* (V) generates

FIG. 3.

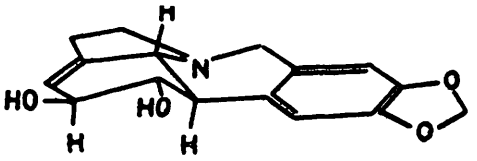


FIG. 4.

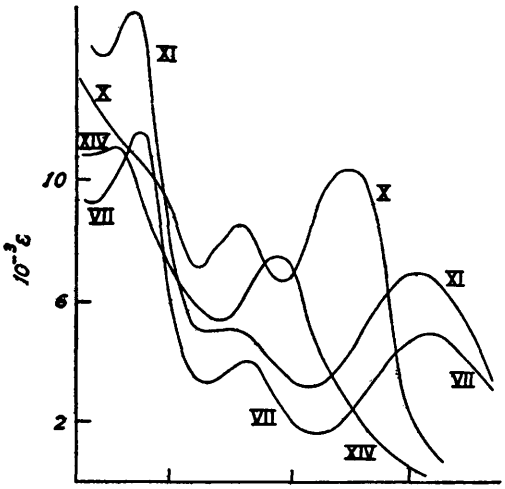


FIG. 4. (XI), 9 : 10-*Dihydro*-10-*methyl*-6 : 7-*methylenedioxyphenanthridine*. (VII), *Anhydrolycorine*. (X), *Dihydrolycorine anhydromethine*. (XIV), *Lycorine anhydrohydromethine*.

the anhydrolycorine metho-salt (VIII). The postulation of an " ylide "-type intermediate has suitable analogy in the literature such as the racemisation of (—)-nicotine bismethiodide by mild alkali which does not proceed *via* the methine base (Späth and Bobenberger, *Ber.*, 1944, **77**, 362; Wittig, Mangold, and Felletschin, *Annalen*, 1948, **560**, 116) and the ready racemisation of (—)-*sec.*-butylpyridine methiodide by weak base (Doering and Pasternak, *J. Amer. Chem. Soc.*, 1950, **72**, 143).

It has not been possible to epimerise (*a*) the secondary alcoholic groups in either lycorine or dihydrolycorine by potassium pentyloxide at 170° (cf. Barton, *Experientia*, 1950, **6**, 316) or (*b*) the allylic hydroxyl group in lycorine by 10% ethanolic sulphuric acid (cf. Ruzicka, Prelog, and Tagmann, *Helv. Chim. Acta*, 1944, **27**, 1149). The absence of ready elimination of the allylic hydroxyl group or of the hydroxyl group β to the aromatic nucleus, coupled with the stability of the nitrogen atom of the heterocyclic ring to elimination under Hofmann conditions, indicates rather strongly that none of these groups has adjacent *trans*-coplanar hydrogen atoms, that is, all four hydrogen atoms concerned have an axial configuration, in so far as the term may be applied to a *cyclo*hexene ring (cf. Barton,

Cookson, Klyne, and Shoppee, *Chem. and Ind.*, 1954, 21). Lycorine must therefore have the structure and configuration shown in Fig. 3 or its mirror image.

It is of interest that although the absorption spectrum of anhydrolycorine (VII) and 9 : 10-dihydro-10-methyl-6 : 7-methylenedioxyphenanthridine (XI) are closely similar, there is a marked change in the position of the long-wave-length maximum in dihydrolycorine anhydromethine (X); apparently this is a steric effect of the ethyl group (Fig. 4).

In the Pschorr cyclisation mentioned above most of the product was the 1-piperonyloylindole, the intermediate free radical abstracting initially a hydrogen atom from position 2 of the dihydroindole nucleus. Dehydrogenation with concomitant removal of the *N*-methyl group becomes important in Pschorr condensations of *o*-substituted benzanilides (Hey and Turpin, *Chem. and Ind.*, 1954, 221).

As a by-product of this work diazotised 1-(2-amino-4 : 5-methylenedioxybenzoyl)-indole was heated and afforded, as expected, the product (XXII). This compound showed a carbonyl band at 1712 cm.$^{-1}$, which is at a rather higher frequency than normal, owing to ring strain in the lactam system.

Added in Proof.—Wenkert (*Chem. and Ind.*, 1954, 1175), who has communicated his papers to us before publication, has deduced a structure for lycorine, in which one of the vicinal hydroxyl groups is tertiary. This conclusion was influenced by a novel interpretation of the von Braun degradation of diacetyldihydrolycorine and a revised biogenetic scheme for alkaloids of this group (Wenkert and Hansen, *ibid.*, 1954, 1262). In a forthcoming publication it will be shown that Wenkert's ideas require modification. Two of us (W. I. T. and B. R. T.) acknowledge valuable discussions on these topics with Dr. E. Wenkert.

Experimental

Absorption spectra were taken in 95% ethanol.

Lycorine.—The base was recovered unchanged after 4 hours' heating either with 10% ethanolic sulphuric acid under reflux or at 170° in *sec.*-amyl alcohol containing a large excess of the sodium alkoxide. Titration in methanol–water gave pK_a 6·8 for lycorine and 8·8 for dihydrolycorine (cf. Wiesner, Taylor, and Uyeo, *Chem. and Ind.*, 1954, 46).

(−)-*Anhydrolycorine Metho-salts.*—An excess of freshly prepared silver oxide was added with shaking to lycorine α-methiodide (0·5 g.) in water (8 ml.) and after a short while the mixture was filtered. The clear solution was heated on a water-bath for 1 hr. with sodium hydroxide (2 g.), becoming turbid, and after a further 12 hr. at room temperature the now semi-solid precipitate (0·4 g.) was filtered off and taken up in water–ether. Extraction of the ethereal layer with dilute hydrochloric acid and concentration of the acidic solution gave lycorine anhydromethine hydrochloride (50 mg.), m. p. 209° (decomp.) (lit., 214—215°) (Found : C, 67·7, 67·8; H, 5·4, 5·6. Calc. for $C_{17}H_{15}O_2N$,HCl : C, 67·7; H, 5·3%). The free base after recrystallisation from ether–light petroleum had m. p. and mixed m. p. 97° (Found : C, 76·6; H, 5·4. Calc. for $C_{17}H_{15}O_2N$: C, 77·0; H, 5·7%). The aqueous layer was concentrated and cooled in ice to yield (−)-*anhydrolycorine methocarbonate* (0·1 g.), m. p. 88—91°, $[\alpha]_D$ −49° (*c*, 2·5 in H_2O), after recrystallisation from water [Found : in air-dried material, C, 55·5, 55·7; H, 5·9, 5·9; in material dried at room temperature over $CaCl_2$ to m. p. 153° (decomp.), C, 60·3; H, 5·8. $C_{34}H_{32}O_4N_2,CO_3,9H_2O$ requires C, 55·6; H, 6·7. $C_{34}H_{32}O_4N_2,CO_2,6H_2O$ requires C, 59·9; H, 6·3%]. An aqueous solution of the salt afforded carbon dioxide on treatment with hydrochloric acid, and barium carbonate on addition of barium hydroxide. The methocarbonate, dissolved in a small volume of hot 3% hydrochloric acid, gave, on cooling, the corresponding *methochloride*, m. p. 79—81°, $[\alpha]_D$ −63° (*c*, 1·9 in H_2O) [Found : in a sample dried in air, C, 53·7; H, 6·0; in a sample dried *in vacuo* at room temperature to m. p. 162° (decomp.), C, 61·7; H, 5·9. $C_{17}H_{16}O_2NCl,4·5H_2O$ requires C, 53·4; H, 6·5. $C_{17}H_{16}O_2NCl,1·5H_2O$ requires C, 62·0; H, 5·8%]. The methochloride was also prepared in quantitative yield by refluxing the methocarbonate in chloroform for 20 hr. The *methiodide* was prepared from the methocarbonate by addition of hydriodic acid or refluxing with methyl iodide or addition of potassium iodide to a solution of the methochloride, and had m. p. 226° (decomp.), $[\alpha]_D$ −56° (*c*, 2·5 in H_2O) (Found : C, 50·1, 50·2; H, 4·5, 4·4. $C_{17}H_{16}O_2NI,H_2O$ requires C, 49·7; H, 4·4%).

(+)-*Anhydrolycorine Metho-salts.*—In a similar manner, lycorine β-methohydroxide (0·5 g.) gave with alkali lycorine anhydromethine and (+)-*anhydrolycorine methocarbonate* (100 mg.), m. p. 87—90° (from water), $[\alpha]_D$ +48° (*c*, 2·6 in H_2O) [Found : in an air-dried sample, C, 55·0;

H, 6·1; in a sample dried over $CaCl_2$ to m. p. 152° (decomp.), C, 60·3; H, 6·2%]. The *methochloride* had m. p. 79—81°, $[\alpha]_D$ +64° (*c*, 1·4 in H_2O) [Found : in material dried in air, C, 53·7; H, 6·5; in material dried at 100° to m. p. 163° (decomp.), C, 61·7; H, 5·8%]. The *methiodide* had m. p. 226° (decomp.), $[\alpha]_D$ +53° (*c*, 3·4 in H_2O) (Found : C, 50·0; H, 3·9%).

rac.-*Anhydrolycorine Metho-salts* (VIII).—Lycorine (0·5 g.) was converted into the methiodide and without separation of the α- and β-methiodides degraded by the procedure described above, yielding, besides lycorine anhydromethine, rac.-*anhydrolycorine methocarbonate* (0·25 g.), m. p. 120—121°, $[\alpha]_D$ ±0°, after recrystallisation from water [Found : in a sample dried in air, C, 55·5; H, 6·0; in a sample dried over calcium chloride to m. p. 177—179° (decomp.), C, 62·3; H, 5·8; N, 4·5. $C_{34}H_{32}O_4N_2,CO_3,4H_2O$ requires C, 62·9; H, 6·0; N, 4·2%]. The *methochloride* prepared from the *rac.*-methocarbonate or by mixing the enantiomorphs had m. p. 84° (Found : in air-dried material, C, 53·4; H, 6·3; in material dried *in vacuo* at 105° for 3 hr. to m. p. 219° (decomp.), C, 64·2; H, 5·5; N, 4·7. $C_{17}H_{16}O_2NCl,H_2O$ requires C, 63·8; H, 5·7; N, 4·4%). The *methiodide* prepared by the usual methods and also by racemisation of the (+)- or (−)-enantiomorph by means of iodine or potassium iodide–iodine in aqueous solution, had m. p. 228° (decomp.) (from water) (Found : C, 52·0; H, 4·2; N, 3·6. $C_{17}H_{16}O_2NI$ requires C, 52·0; H, 4·1; N, 3·6%). The *rac.*-methiodide was recovered unchanged after 5 hr. at 100° in ethanol or acetic acid saturated with hydrogen chloride. When treated with silver oxide it gave the *rac.*-methohydroxide which, with carbon dioxide, furnished the *rac.*-methocarbonate, m. p. 120—121°, undepressed by the compound obtained directly from lycorine methiodide.

Conversion of Anhydrolycorine Metho-salts into Lycorine Anhydromethine (IX).—When either (+)- or (−)-anhydrolycorine methocarbonate was dried *in vacuo* at room temperature for 7 days it was converted in almost quantitative yield into water-insoluble lycorine anhydromethine (IX). The solid *rac.*-methocarbonate was more stable but when heated at 100° for 5 hr. also gave the methine base.

A solution of *rac.*-anhydrolycorine methohydroxide, prepared from *rac.*-anhydrolycorine methiodide (0·2 g.), was evaporated to dryness and heated at 100° for 30 min. *in vacuo*. The residue, extracted with ether, yielded an oil (0·1 g.) which crystallised from light petroleum to give the methine base, m. p. 97° which was further characterised as its picrolonate, m. p. 180° (decomp.) (from ethanol) (Found, on a sample dried for 4 hr. at 100° over P_2O_5 : C, 58·7, 59·0; H, 5·2, 5·1. Calc. for $C_{17}H_{15}O_2N,C_{10}H_8O_5N_4,H_2O$: C, 59·2; H, 4·6%).

Emde Degradation of rac.-*Anhydrolycorine Methochloride*.—Sodium amalgam (1 g.; 4%) was added to *rac.*-anhydrolycorine methochloride (0·1 g.) in water (4 ml.), and the mixture heated on a water-bath for 2 hr. The resulting oil was taken up in ether, dried (K_2CO_3), and concentrated to give a compound (50 mg.), m. p. 69—70°, prisms from methanol, identical with a sample of the Emde base, lycorine anhydrohydromethine (XIV) prepared directly from lycorine methochloride (Found : C, 76·9; H, 6·3; *C*-Me, 3·4, 3·6. Calc. for $C_{17}H_{17}O_2N$: C, 76·5; H, 6·3; 1 *C*-Me, 5·6%). The *rac.*-anhydrolycorine methochloride was recovered unchanged after attempted reductive splitting with 20% palladium–charcoal or Adams platinum oxide in acetic acid. The Emde base was unchanged after being kept at 100° for 2·5 hr. in the presence of hydrogen chloride in ethanol.

Conversion of Anhydrolycorinium Chloride into rac.-*Anhydrolycorine Methiodide*.—Powdered anhydrolycorinium chloride (0·12 g.) was added during 40 min. to lithium aluminium hydride (50 mg.) in dry ether (50 ml.) under nitrogen and stirred for 2 hr. at room temperature. The product was methylated with methyl sulphate and potassium carbonate to yield the methosulphate, m. p. 224—225°, which was converted into *rac.*-anhydrolycorine methiodide, m. p. 226—228°.

Ozonolyses.—Micro-determination of vinyl groups was carried out according to Doeuvre's method following Karrer and Kebrle (*loc. cit.*). Oxygen containing 1% of ozone passed into a solution of the sample at a rate of 30 ml./min. gave the following yields (%) of formaldehyde after 5 min. and, in parentheses, 15 min. Quinine, 55; lycorine anhydrohydromethine 15·4 (33·4); dihydrolycorine anhydromethine, 1·5 (63·7); lycorine anhydromethine, 39 (100).

2 : 3-*Dihydro*-1-*piperonyloylindole*.—Condensation of piperonyloyl chloride with dihydroindole in the presence of pyridine gave the *amide*, m. p. 116—117°, $\lambda_{max.}$ 295 mμ (ε 15,000) (Found : C, 71·8; H, 5·1; N, 5·2. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9; N, 5·2%).

2 : 3-*Dihydro*-1-(4 : 5-*methylenedioxy*-2-*nitrobenzoyl*)*indole*.—2 : 3-Dihydroindole (1 g.) in chloroform (5 ml.) and pyridine (5 ml.) was added to a solution of excess of 4 : 5-methylenedioxy-2-nitrobenzoyl chloride in chloroform. The chloroform was distilled off and the residue kept at 100° for 30 min. Aqueous ethanol was then added and the precipitate was chromatographed in chloroform over alumina. The yellow band, on elution, afforded the pure *nitro-amide*,

yellow prisms m. p. 217—218° (from chloroform–ethanol) (Found: C, 61·0, 61·1; H, 3·8, 3·9; N, 9·1. $C_{16}H_{12}O_5N_2$ requires C, 61·5; H, 3·9; N, 8·9%).

1-(2-*Amino*-4 : 5-*methylenedioxybenzoyl*)-2 : 3-*dihydroindole* (XIII).—Reduction of the nitro-amide in ethyl acetate–ethanol in presence of Raney nickel, followed by addition of excess of hydrochloric acid, gave the *amino-amide hydrochloride*, m. p. 244—246° (decomp.) (from 95% ethanol) (Found: C, 60·0; H, 4·9; N, 8·9. $C_{16}H_{15}O_3N_2Cl$ requires C, 60·3; H, 4·7; N, 8·8%). The *amino-amide* (XIII) crystallised in prisms, m. p. 142—143°, from ethyl acetate (Found: C, 67·8; H, 5·1. $C_{16}H_{14}O_3N_2$ requires C, 68·1; H, 5·0%).

Pschorr Cyclisation of the Amino-amide.—The amino-amide (1 g.), diazotised in 5% sulphuric acid (30 ml.), was set aside at room temperature for 1 hr., then at 75° for 2 hr., and finally at 100° for a further hour. The dried chloroform extract was chromatographed over alumina. From the first fractions 1-*piperonyloylindole* (300 mg.) was isolated and, crystallised from ethanol, had m. p. 92—93°, $\lambda_{max.}$ 306 and 250 mμ (ε 8500 and 11,000) (Found: C, 72·4; H, 4·2; N, 5·3. $C_{16}H_{11}O_3N$ requires C, 72·5; H, 4·2; N, 5·3%). Alkaline hydrolysis gave indole, m. p. and mixed m. p. 42°, and piperonylic acid, m. p. and mixed m. p. 224—227°. Further elution with chloroform removed a yellow band which gave 6 : 7-*methylenedioxypyrrolino*-(3′ : 2′ : 1′-1 : 10a : 10)*phenanthridone* (XII) (100 mg.), m. p. 232—234° (from chloroform–ethanol), $\lambda_{max.}$ 342, 274, and 242 mμ (ε 4000, 13,000, and 30,000) (Found: C, 72·5; H, 4·2; N, 5·3. $C_{16}H_{11}O_3N$ requires C, 72·5; H, 4·2; N, 5·3%). The ultra-violet absorption spectrum was identical with that of the anhydrolycorine lactam obtained from anhydrolycorinium hydrochloride and it gave an undepressed mixed m. p.

9 : 10-*Dihydro*-6 : 7-*methylenedioxypyrrolino*(3′ : 2′ : 1′-1 : 10a : 10)*phenanthridine* (*Anhydrolycorine*) (VII).—The above phenanthridone (120 mg.) was extracted into excess of lithium aluminium hydride in boiling ether. The product was crystallised from 95% ethanol to yield the *dihydrophenanthridine* (VII) (60 mg.), m. p. 111—112°, $\lambda_{max.}$ 345, 287, and 250 mμ (ε 5000, 4500, and 12,000) (Found: C, 76·4; H, 5·3; N, 5·8. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%). The synthetic base showed identical m. p. and ultra-violet absorption spectrum on comparison with anhydrolycorine prepared from anhydrolycorinium chloride (Kondo, Takeda, and Kotera, *loc. cit.*). In ethanolic hydrochloric acid the absorption spectrum changed rapidly to that of the anhydrolycorinium salt. The methiodide, m. p. 232—235° (Found: C, 52·3; H, 4·1; N, 3·6%), was identical in m. p., mixed m. p., and ultra-violet and infra-red spectra with *rac.*-anhydrolycorine methiodide.

Preparation of Anhydrolycorinium Chloride from the Dihydrophenanthridine.—The dihydrophenanthridine (30 mg.) was dissolved in ethanol (2 ml.), one drop of concentrated hydrochloric acid was added, and air was bubbled through the solution for 1 hr. The product, crystallised from ethanol, gave *anhydrolycorinium chloride*, decomp. 280—285°, $\lambda_{max.}$ 341, 280, 270, and 258 mμ (ε 7000, 22,000, 23,000, and 22,000) (Found: C, 62·6; H, 4·6. $C_{16}H_{12}O_2NCl,1{\cdot}33H_2O$ requires C, 62·6; H, 4·8%).

9 : 10-*Dihydro*-10-*methyl*-6 : 7-*methylenedioxyphenanthridine* (XI).—The corresponding phenanthridone (Forrest, Haworth, Pinder, and Stevens, *J.*, 1949, 1311) was reduced with lithium aluminium hydride in boiling ether to the *dihydrophenanthridine* (XI), m. p. 84—85°, $\lambda_{max.}$ 339, 280, and 249 mμ (ε 7500, 5500, and 17,000) (Found: C, 75·3; H, 5·6; N, 5·9. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·5; N, 5·9%). In ethanolic hydrochloric acid the absorption spectrum has max. at 319 and 278 mμ (ε 7500 and 10,000).

1-(4 : 5-*Methylenedioxy*-2-*nitrobenzoyl*)*indole*.—4 : 5-Methylenedioxy-2-nitrobenzoyl chloride (from 2·6 g. of acid) in acetone (25 ml.) was added dropwise to a stirred solution of indole (1 g.), potassium hydroxide (1·7 g.) in water (2·5 ml.) and acetone (15 ml.) at 10°. After addition of more potassium hydroxide (1 g.) and 1½ hours' stirring the precipitated potassium 4 : 5-methylenedioxy-2-nitrobenzoate was filtered off, and the solution concentrated to dryness, then dissolved in chloroform–water. The chloroform extract yielded the *nitro-amide* (0·7 g.), m. p. 132—133°, yellow needles from ethanol (Found: C, 62·1; H, 3·2. $C_{16}H_{10}O_5N_2$ requires C, 62·0; H, 3·3%).

1-(2-*Amino*-4 : 5-*methylenedioxybenzoyl*)*indole*.—The nitro-amide (0·5 g.) in acetone (25 ml.) was hydrogenated in the presence of 15% palladium–charcoal (0·3 g.). to give the *amino-amide* (0·3 g.), m. p. 139—140° (from ethanol), $\lambda_{max.}$ 372 and 251 mμ (ε 9000 and 25,000) (Found: C, 68·7; H, 4·7; N, 10·1. $C_{16}H_{12}O_3N_2$ requires C, 68·6; H, 4·4; N, 10·0%).

Pschorr Cyclisation.—The amino-amide (0·1 g.) was diazotised at 0° in 3% methanolic sulphuric acid (12 ml.). After 30 min. at room temperature, copper bronze was added and after a further 30 min. the mixture was heated on a water-bath for a short period, filtered, and taken to dryness. The solid was extracted with chloroform and chromatographed on alumina,

giving the tetracyclic lactam (XXII) (20 mg.), m. p. 214—216°, yellow needles from ethanol (Found : C, 73·0; H, 3·6. $C_{16}H_9O_3N$ requires C, 73·0; H, 3·6%), $\lambda_{max.}$ 365, 352, 314, 301, 274 and 248 mμ (ε 6000, 6000, 28,000, 26,000, 30,000 and 22,500).

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