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THE STEREOCHEMISTRY OF LYCORANE—III[1]

γ- AND δ-LYCORANE

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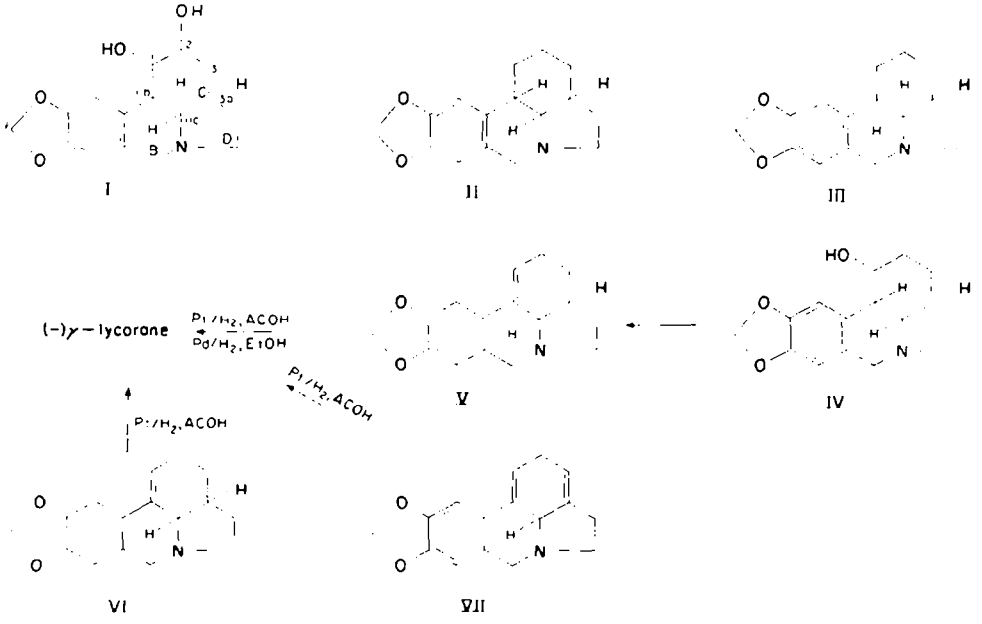
Abstract—Hydrogenation of α-anhydrodihydrocaranine (V) or anhydrocaranine (VII) with Adams catalyst in acetic acid or the Hauptmann reduction of α-dihydrocaranone (XX) yielded (−)γ-lycorane (XVII). Catalytic reduction of β-anhydrodihydrocaranine (IX) with palladium–carbon in ethanol gave (+)γ-lycorane (XVIII), while with Adams catalyst in acetic acid it afforded (+)δ-lycorane (XIX) along with (−)β-lycorane (III). Reduction of anhydrocaranine in ethanol gave (±)γ-lycorane which was also obtained by hydrogenation of anhydrolycorine (X). Based on these findings, the configurational structures of α-, β-, γ- and δ-lycorane were established and the configuration of dihydrolycorine was confirmed.

IN previous papers,[2] Takeda and Kotera have advanced the stereostructure I or its mirror image for dihydrolycorine. That the B/C ring juncture is *trans* in this compound, was based on the fact that α-dihydrocaranine (IV) readily lost a molecule of water to give α-anhydrodihydrocaranine (V) presumably due to a *trans* elimination of the hydroxyl group at C_1 and the hydrogen atom located at C_{11b}. However, there was encountered an occasion where the B/C rings might be supposed to be *cis*-fused, since



[1] Part II: K. Kotera, *Tetrahedron* **12**, 240 (1961).
[2] K. Takeda and K. Kotera, *Chem. & Ind.* 347 (1956); *Pharm. Bull.* **5**, 234 (1957).

the hydrogen atoms linked to C_{11b} and C_{11c} could be eliminated quite readily by selenium oxide.[3] In order to obtain confirmatory evidence for the configuration of the B/C ring juncture in dihydrolycorine and to establish the stereochemistry of lycoranes, which had been derived from the former or related compounds, the author has carried out a series of reactions which is the subject of the present paper.

Of the four possible stereoisomeric pairs of lycoranes, which contain three asymmetric centers, (−)α- and (−)β-lycorane were reported in the previous paper[1,4] and shown to represent the skeleton of dihydrolycorine or α-dihydrocaranine and that of β-dihydrocaranine, respectively. Isomeric lycoranes have been obtained from α-dihydrocaranine (IV) or β-dihydrocaranine (VIII) by the following procedure.

Hydrogenation of α-anhydrodihydrocaranine (V) with either Adams catalyst in acetic acid or palladium–carbon in ethanol gave a homogeneous oil which was convertible in good yield into its hydrochloride, $C_{16}H_{19}O_2N{\cdot}HCl$, m.p. 256° (decomp), $[\alpha]_D$ −15·0°. Although the melting point of this salt was very close to that of (−)α-lycorane hydrochloride, a mixed melting point and the infra-red spectra indicated clearly that they are not identical. The free base regenerated from its purified hydrochloride was not crystalline and its optical rotation $[\alpha]_D$ −17·1° and infra-red spectrum were distinctly different from those of (−)α-lycorane or (−)β-lycorane. It was certain, therefore, that with this compound the author had a new isomer of lycorane which was named (−)γ-lycorane. The same lycorane was also obtained by hydrogenation of anhydrodihydrolycorine (VI) or anhydrocaranine (VII)[5] in acetic acid over Adams catalyst.

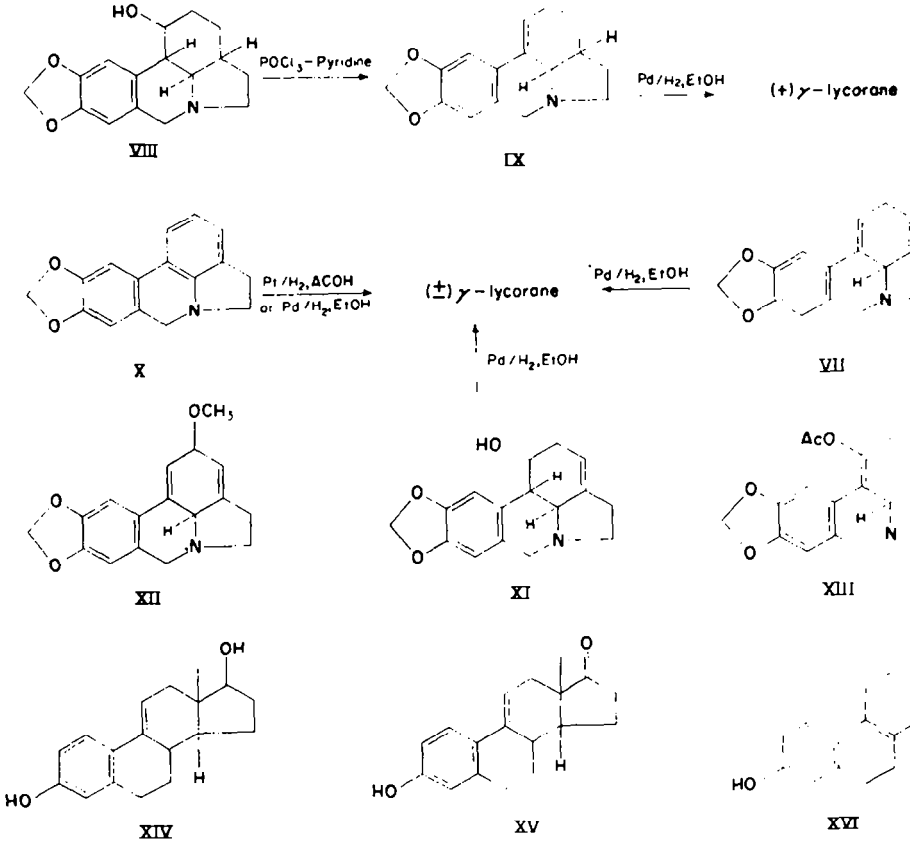
Next, the author investigated the hydrogenation of β-anhydrodihydrocaranine which was prepared from β-dihydrocaranine (VIII)[6] by the same method as used for the preparation of its α-isomer and assigned the analogous structure (IX). Treatment of β-anhydrodihydrocaranine with hydrogen and palladium–carbon in ethanol furnished an oil, $[\alpha]_D$ +16·2°, which was convertible in good yield into its hydrochloride, $C_{16}H_{19}O_2N{\cdot}HCl$, m.p. 255–256° (decomp), $[\alpha]_D$ +13·3°. The infra-red spectra of the free base as well as its hydrochloride were identical with those of (−)γ-lycorane and its hydrochloride, respectively. Since the optical rotations of the corresponding derivatives were almost the same in value but opposite in direction, it was highly probable that this hydrogenation product, (+)γ-lycorane, was an enantiomorph of (−)γ-lycorane. As expected, a mixture of equivalent weights of (−)γ-lycorane and (+)γ-lycorane yielded a racemate, (±)γ-lycorane, m.p. 101–102°, which showed no optical rotation. The same racemate was also obtained by hydrogenation of anhydrolycorine (X) in acidic or ethanol solution in the presence of Adams catalyst or palladium–carbon at a temperature not higher than 60°. Furthermore, hydrogenation of anhydrocaranine and even caranine (XI)[5,6] itself with palladium–carbon in ethanol furnished (±)γ-lycorane, albeit in a very small yield in the latter case.

Since convincing evidence has been accumulated[2,5,6] that α- and β-dihydrocaranine, IV and VIII, have the same stereostructure except for the configuration of ring C/D juncture, which is *cis* in the former and *trans* in the latter compound, and the location of the double bond in α- and β-anhydrodihydrocaranine is evidently at $C_1 - C_{11b}$ as shown in the Table 1, an essential feature of the hydrogenation of α- and

[3] H. M. Fales, L. D. Giuffrida and W. C. Wildman, *J. Amer. Chem. Soc.* **78**, 4145 (1956).
[4] K. Takeda, K. Kotera, S. Mizukami and M. Kobayashi, *Chem. Pharm. Bull.* **8**, 483 (1960).
[5] K. Takeda, K. Kotera and S. Mizukami, *J. Amer. Chem. Soc.* **80**, 2562 (1958).
[6] E. W. Warnhoff and W. C. Wildman, *Chem. & Ind.* 348 (1956); *J. Amer. Chem. Soc.* **79**, 2192 (1957).

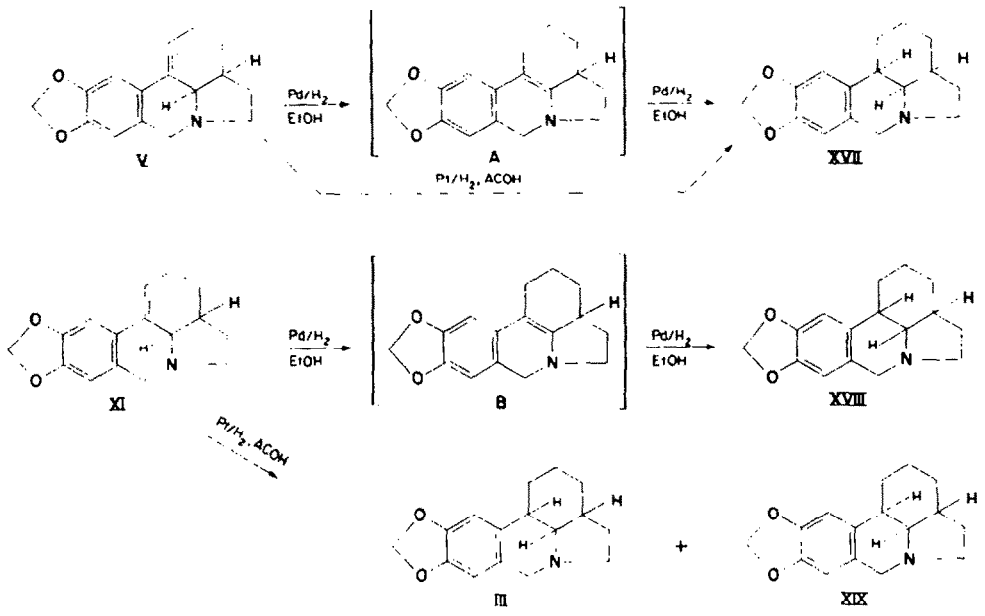
TABLE 1. DATA OF ULTRA-VIOLET SPECTRA OF ANHYDRODIHYDROCARANINES AND RELATED COMPOUNDS

Compound	log	mμ
α-Anhydrodihydrocaranine (V)[8]	4·12	263
β-Anhydrodihydrocaranine (IX)	4·17	266
Anhydrocaranine (VII)[5]	4·06	265
2-Methoxyanhydrocaranine (XII)[6]	4·08	266
α-Dihydrocaranone enolacetate (XIII)[6]	4·08	265
9-Dehydro-14-isoestradiol-17β (XIV)[7]	4·25	264
9-Dehydro-14-isoestrone (XV)[7]	4·26	264
8-Dehydro-14-isoestrone (XVI)[7]	4·32	275



β-anhydrodihydrocaranine, V and IX, is the formation of a pair of enantiomorphic compounds from diastereoisomers. In order to accommodate the experimental results as mentioned above, a migration of the double bond in one or both of the anhydrodihydrocaranines to the position between C_{11b} and C_{11c} followed by *cis*-addition of hydrogen atoms to the double bond from the back side of the ethylenic residue linked to ring C were necessary as shown in the following chart.

[7] L. F. Fieser and M. Fieser, *Steroids* p. 462. Reinhold, New York (1959).



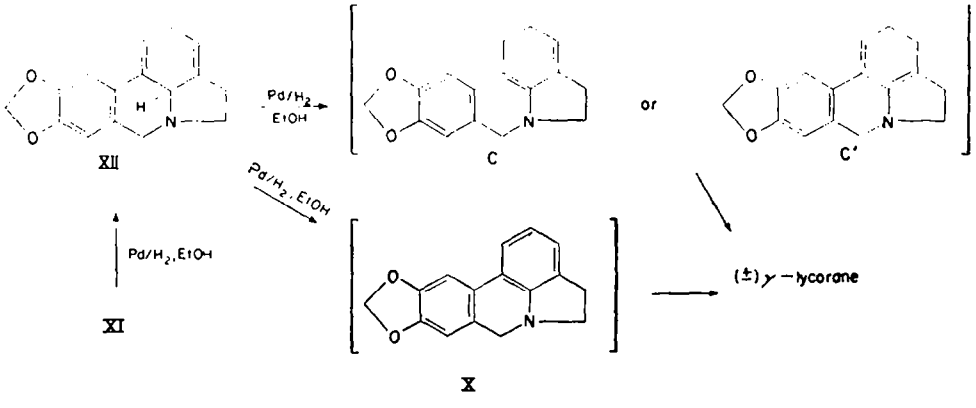
If the migration of the double bond in α- and β-anhydrodihydrocaranines to the 11b, 11c-position as in A or B did not precede the hydrogenation, the resulting lycoranes obviously are not enantiomeric, since the asymmetric centre at C_{11c} is in the same configuration while that at C_{3a} is enantiomeric in this pair of starting materials.

For the sake of convenience, the author would assume that the shift of the double bond took place in both anhydrodihydrocaranines giving enantiomeric A and B, as intermediates, then it would be readily conceivable that saturation of the respective double bonds gave rise to a pair of enantiomeric γ-lycoranes, whatever the mode of addition of hydrogen atoms may be. As to this, it has been accepted generally that *cis* addition is predominantly involved in the catalytic hydrogenation at low temperatures. Since the conditions used by the author for the preparation of these lycoranes were at room temperature or at temperatures not higher than 60°, it would be highly plausible that hydrogen added *cis* to A and B either from the back side or from the front side of the ethylenic residue linked to ring C. Of these possibilities, the front side attack of hydrogen to A and B can be ruled out experimentally based on the fact that anhydrocaranine gave optically active (−)γ-lycorane on hydrogenation in acetic acid. This reduction showed that no compound such as the product C or C′ of double bond migration or dehydrogenation product X is an intermediate and, most important, that C_{11c} in (−)γ-lycorane has the same configuration as in α- or β-dihydrocaranine or dihydrolycorine. Since hydrogenation of α-anhydrodihydrocaranine leading to the same lycorane did not affect the configuration of C_{3a} which is the same as that of α-dihydrocaranine or dihydrolycorine, even if the double bond migration took place during the reduction procedure, the hydrogen atoms at C_{3a} and C_{11c} in (−)γ-lycorane must have the same configuration as those in dihydrolycorine and are *cis* to each other. Accordingly it is clear that the hydrogen atoms is added to α-anhydrodihydrocaranine or to the intermediate A of double bond migration from the same α-side as that of the hydrogen atom attached at C_{3a} as in the case of anhydrocaranine. Since this must be

the case in the rearrangement product B of β-anhydrodihydrocaranine, the hydrogen atoms at C_{3a}, C_{11b} and C_{11c} in γ-lycoranes are most likely on the same side of ring C. Based on these discussions it was concluded that both rings B/C and C/D are very probably *cis*-fused in γ-lycoranes.

Although the shift of the double bond mentioned above is prerequisite for the conversion of β-anhydrodihydrocaranine into (+)γ-lycorane, it is not always necessary for the transformation of α-anhydrodihydrocaranine to (−)γ-lycorane, since the C/D rings are *cis*-fused in both of the latter compounds. In the latter case, an assumption that hydrogen atoms directly attacked α-anhydrodihydrocaranine from the rear side of the axial ethylenic side chain would be sufficient for explaining the path. The author considers, however, that α-anhydrodihydrocaranine was hydrogenated to give (−)γ-lycorane through the intermediate A in ethanol solution over palladium–carbon in an analogous manner as β-anhydrodihydrocaranine, while in acetic acid solution over Adams catalyst it was directly reduced like anhydrocaranine without precedence of any double bond shift. Supporting this view β-anhydrodihydrocaranine was catalytically reduced in acetic acid in the presence of Adams catalyst to give two compounds which were separated by chromatography into (−)β-lycorane and a new lycorane. (−)β-Lycorane thus obtained was characterized as its hydrochloride which was identical in all respects with an authentic sample of (−)β-lycorane hydrochloride reported in the preceding paper.[1] The other lycorane had m.p. 125–127°, $[\alpha]_D$ +48·0 and was analysed correctly for $C_{16}H_{19}O_2N$. Since this was not identical with any of the lycorane isomers so far obtained, it was designated as (±)δ-lycorane. If in this case the double bond migration took place during the hydrogenation, one of the products should be identical with (+)γ-lycorane.

The formation of (±)γ-lycorane from anhydrolycorine can be explained by assuming one-sided addition of hydrogen atoms to the aromatic ring C from either side of the ring, as considered highly probable in catalytic hydrogenation of benzenoid rings under mild conditions.[8]



Analogously the conversion of anhydrocaranine into (±)γ-lycorane by hydrogenation in a neutral medium would be explainable by assuming an intermediate C or

[8] R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, *J. Amer. Chem. Soc.* **64**, 1985 (1942).

C′ or through its dehydrogenation to anhydrolycorine, all of which lack any asymmetric centre and obviously give rise to racemic γ-lycorane on one-sided addition of hydrogen atoms to the double bonds.

The formation of (±)γ-lycorane in a very low yield from caranine would be interpreted as a result of dehydration of a small portion of the base during the hydrogenation under the conditions used by the author, affording anhydrocaranine as an intermediate.

Very recently Nakagawa and Uyeo[9] have established that the absolute configuration of the hydroxyl group attached to C_2 of lycorine or dihydrolycorine is β-oriented. Since the ethylenic residue attached to ring C in dihydrolycorine is on the same side as that of this hydroxyl and its configuration was obviously retained in (−)γ-lycorane as discussed above, the absolute configuration of (−)γ- and (+)γ-lycorane would be best represented by formulations XVII and XVIII, respectively.

It is remarkable that (−)γ-lycorane was also derived from α-dihydrocaranine by an alternative route. α-Dihydrocaranone[6] (XX) which was obtainable from α-dihydrocaranine by the modified Oppenauer oxidation was first converted into its thioketal XXI in the usual manner and then subjected to desulphurization by heating with Raney nickel. The resulting oil was found to be identical with (−)γ-lycorane. This result would be explainable only by assuming that an epimerization had taken place completely at the hydrogen atom attached to C_{11b} during the oxidation procedure to the ketone, as a result of keto-enol tautomerism especially in an alkaline solution.

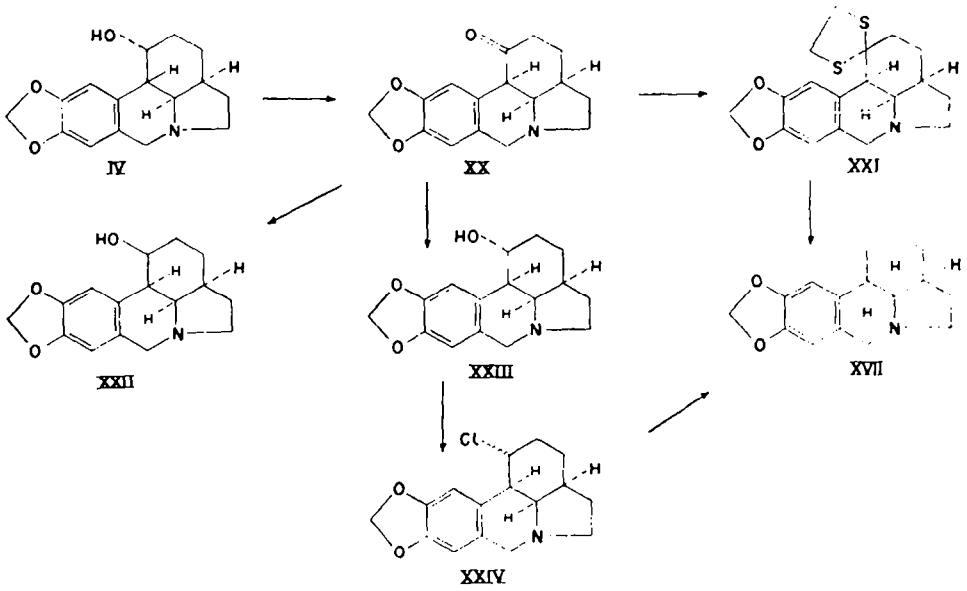
Supporting this view, α-dihydrocaranone showed only one spot (*Rf* 0·58) by paper chromatography using butanol–acetic acid–water (10:1:5) as a solvent system. Furthermore, treatment of this with lithium aluminium hydride gave two isomeric compounds D and E, $C_{16}H_{19}O_3N$, which had m.p.s. 110–111° and 150–151° respectively, and were also characterized as the respective acetates, $C_{18}H_{21}O_4N$, m.p.s 95–96° and 85–86°.

These two compounds were also obtained by catalytic reduction of α-dihydrocaranone with Adams catalyst in acetic acid. On reduction with sodium in ethanol, on the other hand, the only isolatable product was compound E. Neither compound D nor E was identical with α-dihydrocaranine which would be expected to occur in the reduction mixture, if the initial oxidation product of α-dihydrocaranine did not undergo any epimerization.

These results indicated that the ketone XX is, in contrast to β-dihydrocaranone,[1] homogeneous and not an equilibrium mixture, and the reduction products are epimers only with respect to the asymmetric centre at C_1. The mode of reduction of the ketone and the fact that compound D was more easily eluted than compound E on chromatography over alumina suggested that the configuration of the hydroxyl group in compound D is probably axial, while that in compound E equatorial. Compounds D and E were named, therefore, 1-epi-γ-dihydrocaranine and γ-dihydrocaranine and assigned configurational structures XXII and XXIII, respectively. Conversion of 1-epi-γ-dihydrocaranine into a lycorane was not successful, but the treatment of γ-dihydrocaranine with thionyl chloride gave a chloro-compound XXIV which afforded on catalytic reduction with Adams catalyst in ethanol, as expected, (−)γ-lycorane.

With the configuration of (−)γ- and (+)γ-lycorane established, the author can now deduce the stereochemistry of (−)α-, (−)β- and (+)δ-lycorane.

[9] Y. Nakagawa and S. Uyeo, *J. Chem. Soc.* 3736 (1959).



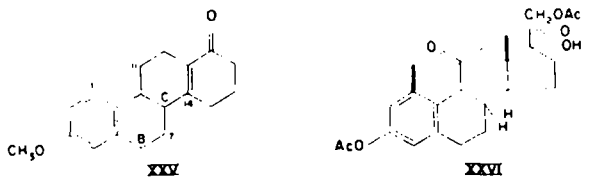
Since in the course of transformations of α-dihydrocaranine to (−)γ-lycorane by the route mentioned above, any inversion cannot be expected to take place at the asymmetric centres other than that at C_{11b} and (−)α-lycorane no doubt retains original configurations of the skeleton of α-dihydrocaranine as reported previously,[4] two lycoranes are different stereochemically only in the configuration at C_{11b}. Based on the established configuration of (−)γ-lycorane it can be concluded, therefore, that (−)α-lycorane has a *trans*-B/C and a *cis*-C/D junction, as formulated as II, and it is clear that the stereochemistry of dihydrolycorine is I, supporting the previous view.[2]

It has been shown previously that α- and β-dihydrocaranine are stereoisomers with respect to the asymmetric centre at C_{3a}. Since (−)β-lycorane is comparable in configurations to the skeleton of β-dihydrocaranine, it can only be represented by III, having a *trans*-B/C and a *trans*-C/D ring junction.

As to the stereochemistry of (+)δ-lycorane, it is obvious that it is an epimer of (−)β-lycorane with respect to the configuration at C_{11b}, as represented by the formula XIX. Thus the author has established the stereochemistry of all of the possible lycorane isomers, α-, β-, γ- and δ-lycorane.

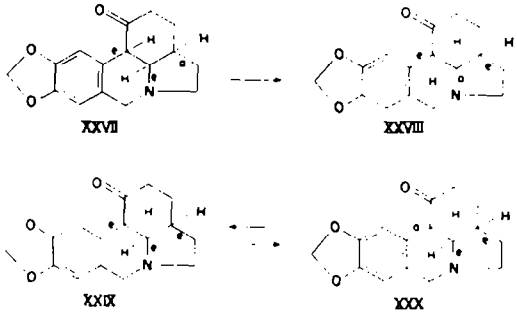
Finally, the author would like to discuss briefly some problems which were encountered during the course of the present studies. First the fact that α-anhydrodihydrocaranine gave on hydrogenation with Adams catalyst in acetic acid solely (−)γ-lycorane, while β-anhydrodihydrocaranine furnished under the similar conditions two hydrogenation products, (−)β-lycorane and (+)δ-lycorane, may be explained by assuming that the hydrogenation occurred preferently on the α-face of the former compound due to serious shielding effect of the β-oriented axial ethylenic bond attached to ring C. In contrast to this, β-anhydrodihydrocaranine is nearly planar and neighbouring hydrogen atoms can therefore attack the double bond from both sides of the molecule, giving a pair of epimeric dihydro-compounds.

The second problem is concerned with the configurational assignment of α- and β-dihydrocaranone. As to the stability of the B/C ring jucture in such a hydrophenanthridine ring system containing an aromatic ring A, little is known so far. It has



XXV XXVI

recently been reported,[10,11] however, that compounds XXV and XXVI having B/C *cis* structures are more stable than the B/C *trans* isomers or at least of similar stability due to more serious non-bonded interactions between C_1 and C_{11} and between C_7 and C_{14} in the latter than in the former. If this is also the case in α- and β-dihydrocaranone, the non-bonded interaction may have caused an epimerization of the hydrogen atom attached to C_{11b} under the alkaline conditions of the Oppenauer method giving rise predominantly to compounds having B/C *cis* configuration, since the starting materials leading to these ketones had *trans*-fused B/C rings. Experimental results have indicated that α-dihydrocaranone has *cis*-fused B/C rings, while the β-isomer is an equilibrium mixture consisting of epimers having B/C rings in *cis* and *trans* configuration.



XXVII XXVIII

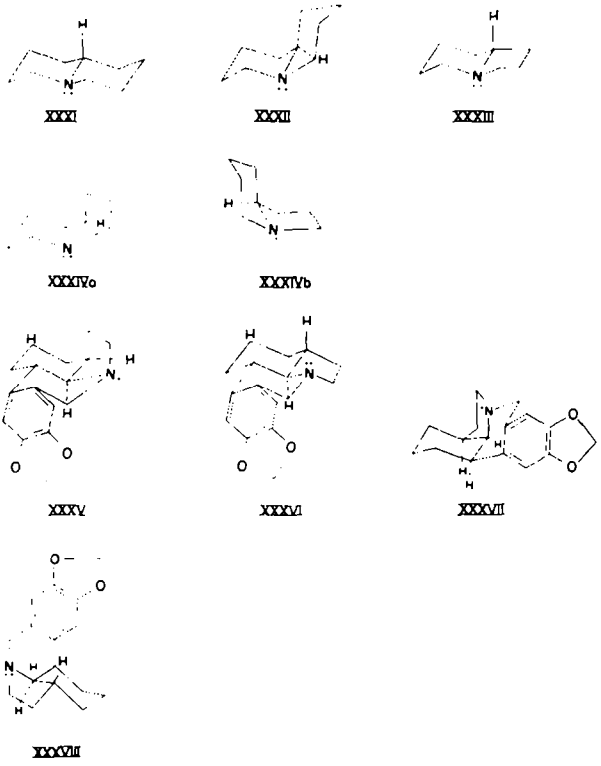
XXIX XXX

In α-dihydrocaranone, the benzene ring can take up the stable equatorial even after the epimerization at C_{11b} took place to decrease the non-bonded interaction between C_1 and C_{11}, since ring C and D are *cis*-fused and ring conversions are free. The *cis-trans* equilibrium of the B/C ring juncture is therefore greatly in favour of the *cis*-form (XXVIII) and not the *trans*-form (XXVII). On the other hand, in β-dihydrocaranone, conversion of ring C is not possible, ring C and D being *trans*-fused. If epimerization occurred in this, the benzene ring which was originally equatorial with respect to ring C will have to take up an axial position, the steric effect of which will unfavourably affect the epimerization at C_{11b}, resulting in existence of a pair of epimers, XXIX and XXX, in equilibrium in solutions.

The last problem to be discussed is the infra-red spectra of four lycoranes, isolated by the author. Recently Bohlmann[12] found that the *trans*-quinolizidine (XXXI) showed characteristic bands in the 2700–2800 cm^{-1} region which were lacking in the *cis*-quinolizidine (XXXII). This finding has been confirmed in a variety of alkaloids

[10] W. Johnson, I. David, H. Dehm, R. Height, E. Wannhoff, W. Wood, and E. Johnes, *J. Amer. Chem. Soc.* **80**, 661 (1958).
[11] J. Elks, J. E. Oughton and L. Stephenson, *Proc. Chem. Soc.* 6 (1959).
[12] F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958); F. Bohlmann and C. Arndt, *Ibid.* **91**, 2167 (1958); F. Bohlmann, W. Weise, D. Rahtz and C. Arndt, *Ibid.* **91**, 2176 (1958); F. Bohlmann, E. Winterfeldt and H. Brackel, *Ibid.* **91**, 2194 (1958).

and also applied to the other alkaloids for establishment of their stereochemistry. Since lycoranes have a pyrrocolidine ring system in the molecule in place of a quinolizidine, it seemed to be interesting to examine whether Bohlmann's rule is applicable to the steric structures of lycoranes proposed by the author, infra-red spectra of four



lycoranes in carbon disulphide were compared with one another especially in the 2700–2800 cm^{-1} region. As shown in Fig. 1, it was found that both (−)β-lycorane (XXXVI) and (−)γ-lycorane (XXXVII), having a *trans*-pyrrocolidine ring XXXIII, exhibited characteristic bands in the 2700–2800 cm^{-1} region, but (±)δ-lycorane (XXXVIII), having *cis*-pyrrocolidine XXXIVa or XXXIVb, did not show bands in the corresponding region. It appeared abnormal that (−)α-lycorane (XXXV) showed a band at 2783 cm^{-1}, since this should have a *cis*-pyrrocolidine ring in the molecule.

EXPERIMENTAL[13]

(−)*γ-Lycorane* (XVII)

(a) *From α-anhydrodihydrocaranine* (V). Hydrogenation of α-anhydrodihydrocaranine (100 mg) over Adams catalyst (20 mg) in acetic acid (7 ml) was complete in 2 hr after 0·9 equivalent of hydrogen had been taken up. The hydrogenation product was chromatographed on alumina (5 g), and pet ether eluate gave (−)*γ-lycorane* (XVII, 65 mg) as an oil which was dried in a vacuum to a constant weight. $[\alpha]_D^{30°}$ −17·1° (*c* 0·25, ethanol). (Found: C, 74·90; H, 7·44; N, 5·20. $C_{16}H_{19}O_2N$ requires: C, 74·68, H, 7·44; N, 5·44%).

[13] All m.p.s are uncorrected. Unless otherwise stated, the ultra-violet spectra were taken in 95% ethanol using a Beckman Model DU spectrophotometer. Alumina used for chromatography in this experiment was Merck's Reagent Grade standardized according to the method of Brockmann. The infra-red absorption spectra were determined with a Perkin-Elmer Model 12C Single-beam Infra-red Spectrophotometer.

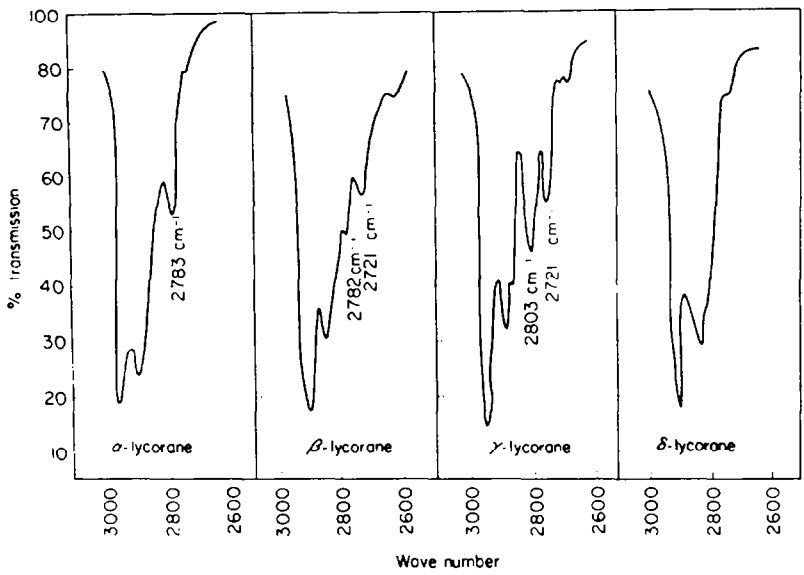


FIG. 1. Infra-red spectra of four isomeric lycoranes at 3000–2600 cm^{-1} in carbon disulphide solution.

The hydrochloride formed needles from water, m.p. 255–256° (decomp), $[\alpha]_D^{20°}$ −15·0° (*c* 1·00, ethanol), λ_{max} 290 mμ (log ε 3·70). (Found: C, 65·56; H, 6·89; N, 4·89. $C_{16}H_{19}O_2N$·HCl requires: C, 65·39; H, 6·86; N, 4·77%).

The infra-red spectra of (−)γ-lycorane (XVII) and (−)α-lycorane in carbon disulphide solution were not identical. The mixed m.p. of the hydrochlorides of (−)γ-lycorane and (−)α-lycorane was depressed to 237–247° (decomp).

Hydrogenation of α-anhydrodihydrocaranine (100 mg) in ethanol (100 ml) with 10% palladium-charcoal (150 mg) was complete in 7 hr when 1·2 equivalent of hydrogen had been taken up. The catalyst was removed by filtration and most of the solvent was evaporated. The residue was dissolved in dil HCl, filtered, made alkaline with Na_2CO_3 and extracted with pet ether. Concentration of the dried extract gave an oil (71 mg), identical with (−)γ-lycorane (XVII) by comparison of the infra-red spectra in carbon disulphide solution. Furthermore, the hydrochloride, m.p. 255–256° (decomp), was also identical with that of (−)γ-lycorane in m.p., mixed m.p. and infra-red spectrum.

(b) *From anhydrocaranine* (VII). A solution of anhydrocaranine (300 mg) in acetic acid (30 ml) was shaken in hydrogen in the presence of Adams catalyst (180 mg) at 50–60°. Theoretical amounts of hydrogen were absorbed in 11 hr. After evaporation of acetic acid under reduced press, the residue was dissolved in water, filtered, basified with 10% Na_2CO_3 and extracted with benzene. The benzene extract was shaken with 5% HCl and the aqueous acidic layer made alkaline with 10% Na_2CO_3 and extracted again with benzene. Concentration of the dried extract gave an oil (240 mg) which was chromatographed over alumina (20 g). Pet ether eluate gave an oil (150 mg) which was identical in infra-red spectrum in carbon disulphide solution with (−)γ-lycorane (XVII) obtained above. The hydrochloride, m.p. 255–256° (decomp), was also identical in m.p., mixed m.p. and infra-red spectrum with that of XVII.

(c) *From anhydrodihydrolycorine* (VI). A solution of anhydrodihydrolycorine (20 mg) in acetic acid (1 ml) was shaken in hydrogen in the presence of Adams catalyst (2 mg). Hydrogenation was complete in 5 hr after 1 mole of hydrogen was absorbed. The hydrogenation product was worked up in the usual manner and an oil (14 mg) was obtained, whose infra-red spectrum was identical with that of (−)γ-lycorane (XVII). The hydrochloride, m.p. 255–256° (decomp), was also identical with that of XVII in m.p., mixed m.p. and infra-red spectrum.

Dehydration of β-dihydrocaranine (VIII). To a cooled mixture of phosphorous oxychloride (1 g) and pyridine (3 ml) was added β-dihydrocaranine (350 mg) in portions. After being kept in a refrigerator for 13 hr, the mixture was poured into ice to destroy the excess of phosphorous oxychloride,

basified with 10% Na_2CO_3 and extracted with ether. Concentration of the dried extract afforded crude *β-anhydrodihydrocaranine* (IX, 205 mg) which was dissolved in pet ether and passed through a column of alumina (10 g). 2:1 Pet ether–benzene eluate was crystallized from pet ether to give prisms (130 mg), m.p. 124–126°, $[\alpha]_D^{24}$ −155·3° (*c* 0·13, ethanol), λ_{max} 266, 312 mμ (log ε 4·20, 3·85). (Found: C, 74·91: H, 6·56: N, 5·32. $C_{16}H_{17}O_2N$ requires: C, 75·25; H, 6·71: N, 5·48%).

Hydrogenation of β-anhydrodihydrocaranine (IX) *in ethanol with palladium–carbon*

A mixture of β-anhydrodihydrocaranine (100 mg) and 10% palladium–carbon (100 mg) in ethanol (15 ml) took up 1 mole of hydrogen in 6 hr. Filtration of the catalyst and evaporation of the filtrate gave an oil (85 mg). This was chromatographed in pet ether on alumina (6 g). 3:1 Pet ether–benzene eluate gave (+)*γ-lycorane* (XVIII) (47 mg), $[\alpha]_D^{20°}$ +16·3° (*c* 0·30, ethanol).

The infra-red spectrum was identical with that of (−)γ-lycorane (XVII). *The hydrochloride* had m.p. 255–256° (decomp) and $[\alpha]_D^{22°}$ +13·3° (*c* 0·64, ethanol). (Found: C, 65·11; H, 7·09; N, 4·55. $C_{16}H_{19}O_2N$·HCl requires: C, 65·41; H, 6·86; N, 4·77%).

An aqueous solution of the hydrochloride (3·405 mg) of (−)γ-lycorane (XVII) and that (3·411 mg) of (±)γ-lycorane (XVIII) was basified with aqueous Na_2CO_3 and extracted with pet ether. Concentration of the dried solution gave (±)γ-lycorane (4 mg), which on crystallization from pet ether, formed prisms, m.p. 101–102°, $[\alpha]_D$ 0°, identical with (±)γ-lycorane as obtained below.

Hydrogenation of β-anhydrodihydrocaranine (IX) *with Adams catalyst in acetic acid*

β-Anhydrodihydrocaranine (150 mg) in acetic acid (5 ml) was shaken in hydrogen with Adams catalyst (55 mg) for 5 hr (hydrogen uptake: 13 ml, calc. for 1 H_2: 13 ml). After removal of the catalyst the filtrate was evaporated to dryness *in vacuo*, the residue was dissolved in water, filtered, made alkaline with Na_2CO_3 and extracted with pet ether. The extract was evaporated and the residue (115 mg) chromatographed in pet ether over alumina (4 g). Elution with light petroleum–benzene (5:1, 2:1, and 1:1) gave an oil (51 mg) which was converted into the hydrochloride (20 mg), m.p. 272–273 (decomp), needles (from ethanol), identical with an authentic specimen of (−)β-lycorane hydrochloride in m.p., mixed m.p. and infra-red spectrum. Elution with benzene and benzene–ether (10:1, 5:1) gave (+)*δ-lycorane* (XIX, 35 mg), 125–127, prisms (from light petroleum), $[\alpha]_D^{18°}$ +48·0° (*c* 0·65 ethanol), λ_{max} 291 mμ (log ε 3·68). (Found: 74·74; H, 7·52; N, 5·11. $C_{16}H_{19}O_2N$ requires: C, 74·68; H, 7·44; N, 5·44%).

Hydrogenation of anhydrolycorine (X)

(a) A solution of anhydrolycorine (800 mg) in acetic acid (15 ml) was added to a suspension of reduced platinum oxide (1 g) in acetic acid (15 ml). The mixture was shaken in hydrogen at 60° for 28 hr. The catalyst was removed by filtration, the acetic acid evaporated under reduced press. The residue was dissolved in water, filtered, basified with 10% Na_2CO_3 and extracted with benzene. Concentration of the dried extract gave the product (500 mg) which was chromatographed on alumina (25 g). Elution with pet ether and crystallization of the eluate from the same solvent yielded (±)*γ-lycorane* (200 mg), prisms, m.p. 101–102°, $[\alpha]_D^{24}$ 0° (*c* 0·88 ethanol), λ_{max} 292 mμ (log ε 3·68). The infra-red spectrum was identical with those of (−)γ-lycorane (XVII) and (+)γ-lycorane (XVIII) in carbon disulphide solution. (Found: C, 74·97; H, 7·48; N, 5·45. $C_{16}H_{19}O_2N$ requires: C, 74·68; H, 7·44; N, 5·44%).

The hydrochloride formed needles from water, m.p. 256° (decomp), $[\alpha]_D^{22°}$ 0° (*c* 1·26 ethanol). (Found: C, 65·76; H, 6·89; N, 4·63. $C_{16}H_{19}O_2N$·HCl requires: C, 65·39; H, 5·86; N, 4·77%).

The aqueous layer separated from benzene extract mentioned above was made more basic with 10% NaOH and extracted with benzene. Concentration of the dried extract gave anhydrolycorinone (50 mg). From the alkaline aqueous solution, anhydrolycorinium chloride[6] (100 mg) was isolated through its reineckate.

(b) A solution of anhydrolycorine (250 mg) in ethanol (50 ml) was shaken in hydrogen in the presence of 10% palladium–carbon (250 mg) as catalyst at room temp. The reduction stopped in 28 hr after 2·0 mole equivalents of hydrogen were absorbed. The mixture was worked up in the usual manner to give (±)γ-lycorane (20 mg) and anhydrolycorinone (80 mg).

Hydrogenation of anhydrocaranine (VII) *in ethanol with palladium–carbon*

A solution of anhydrocaranine (200 mg) in ethanol (20 ml) was shaken in hydrogen in the presence of 10% palladium-on-charcoal (250 mg) at 40–45°. After approximately 1 mole equiv. of hydrogen

had been taken up, the reduction stopped in 22 hr. The mixture was worked up in the usual manner and there was obtained (±)γ-lycorane (70 mg), m.p. 101–102°.

Hydrogenation of caranine (XI) *in ethanol with palladium–carbon*

A solution of caranine (300 mg) in ethanol (20 ml) was stirred under hydrogen in the presence of 10% palladium-on-charcoal (300 mg). The reduction stopped in 14 hr after approximately 1 mole of hydrogen had been absorbed. The catalyst was removed by filtration and the ethanol was evaporated. The residue was dissolved in benzene and chromatographed on alumina (20 g). The first eluate with benzene gave (±)γ-lycorane (11 mg). Further elution with 4:1 benzene–ether afforded β-dihydrocaranine (VIII, 145 mg), prisms from ethyl acetate, m.p. 164–168°, identical in m.p., mixed m.p. and infra-red spectrum with an authentic sample.[14]

Further elution with 1:1 benzene–ether gave α-dihydrocaranine (IV, 30 mg), prisms from ethyl acetate, m.p. and mixed m.p. 169–170°.

Modified Oppenauer oxidation of α-dihydrocaranine (IV)

This reaction was carried out independently before the details[6] of a similar reaction has been published by Warnhoff and Wildman. Although the conditions used by us were somewhat different from those employed by the named authors, the product was apparently identical and the yield almost the same as those reported in their paper.

In an atmosphere of nitrogen, metallic potassium (150 mg) was dissolved in t-butyl alcohol (15 ml) which was freshly distilled over metallic sodium. To the solution was added under stirring benzophenone (900 mg) and powdered α-dihydrocaranine (300 mg) and the mixture was refluxed under nitrogen for 3 hr. The colour changed gradually from yellow to yellowish red. The excess of t-butyl alcohol was evaporated under reduced press and the residue extracted with 5% HCl (50 ml) and benzene (20 ml). The benzene layer was extracted twice with 10% HCl (10 ml) and then washed with water (10 ml). The combined aqueous layers were basified with 10% Na_2CO_3 and extracted with benzene (50 ml). Concentration of the dried benzene solution gave a crystalline product (265 mg) which was dissolved in benzene (30 ml) and chromatographed over alumina (10 g). Elution with benzene (180 ml) gave α-dihydrocaranone (XX, 180 mg), which formed needles on recrystallization from ethanol, m.p. 144–146°, $[\alpha]_D^{23°}$ 0° (*c* 1·075, chloroform), $[\alpha]_D^{24°}$ +3·4° (*c* 1·083, ethanol), λ_{max} 290 mμ (log ε 3·66); λ_{max}^{Nujol} 5·87 μ, $\lambda_{max}^{CS_2}$ 5·81 μ (>C=O). (Found: C, 71·11; H, 6·54; N, 5·27. Calc. for $C_{16}H_{17}O_3N$: C, 70·83; H, 6·32; N, 5·16%).

Further elution with benzene–ether (1:1) recovered the starting material (IV, 60 mg) unchanged.

The paper chromatography of α-dihydrocaranone by an ascending method using butanol–acetic acid–water (10:1:5) gave one spot (*Rf* 0·58) by Dragendorff's reagent.

Thioketalization of α-dihydrocaranone (XX)

A mixture of α-dihydrocaranone (100 mg), ethanedithiol (0·3 ml) and 47% boron fluoride–etherate (0·3 ml) was kept at room temp for 42 hr. After addition of water (5 ml) and 10% NaOH (4 ml), the mixture was extracted with ether (50 ml) and the ethereal extract washed 5 times with 2 ml portions of 10% NaOH and then with water, concentrated and chromatographed on alumina (5 g). Elution with 1:1 benzene–pet ether afforded a product which was crystallized from ethanol to give *the thioketal* (XXI, 80 mg) as needles, m.p. 131–132°, $[\alpha]_D$ −31·4° (*c* 0·32, chloroform), λ_{max} 294 mμ (log ε 3·68). (Found: C, 62·20; H, 6·22; N, 3·85; S, 17·80. $C_{18}H_{21}O_2NS_2$ requires: C, 62·21; H, 6·09; N, 4·03; S, 18·46%).

Desulphurization of the thioketal (XXI)

A solution of the thioketal (60 mg) in methanol (10 ml) was refluxed with freshly prepared Raney nickel[15] (600 mg) for 6 hr. Filtration from the catalyst and concentration of the filtrate afforded an oil (40 mg) which was converted into its hydrochloride. Crystallization from water gave needles (20 mg),

[14] The author is indebted to Dr. W. C. Wildman of the National Heart Institute, Bethesda, Md. for an authentic sample of β-dihydrocaranine.

[15] *Organic Synthesis*, **21**, 15 (1945).

m.p. 255–256° (decomp), $[\alpha]_D^{20°}$ −14·3° (*c* 0·75, ethanol), identical in m.p., mixed m.p., infra-red spectrum and optical rotation with (−)*γ*-lycorane hydrochloride. The free base regenerated from the hydrochloride showed the identical infra-red spectrum and optical rotation as those of (−)*γ*-lycorane (XVII).

Reduction of α-dihydrocaranone (XX)

(a) *With Adams catalyst in acetic acid.* A solution of α-dihydrocaranone (200 mg) in acetic acid (9 ml) was shaken in hydrogen with Adams catalyst (70 mg) for 3 hr. Hydrogen uptake was 21 ml (calc. for 1 H_2: 17 ml). After removal of the catalyst the filtrate was evaporated to dryness and the residue dissolved in water, filtered, basified and extracted with benzene. The dried benzene was evaporated, the residue (190 mg) dissolved in benzene (15 ml) and passed through a column of alumina (10 g). Elution with benzene–ether (10:1) gave crude *1-epi-γ-dihydrocaranine* (XXII, 144 mg) which was recrystallized from a small amount of acetone to give a pure sample (90 mg) as cubes, m.p. 110–111°, $[\alpha]_D^{25°}$ +70·0° (*c* 0·937, ethanol), λ_{max} 291 mμ (log ε 3·68); λ_{max}^{Nujol} 3·02 μ (−OH). (Found: C, 70·50; H, 7·20; N, 5·05. $C_{16}H_{19}O_3N$ requires: C, 70·31; H, 7·01; N, 5·13%).

The acetate prepared with acetic anhydride and pyridine, formed prisms, m.p. 95–96°, (from n-pentane–methanol), $[\alpha]_D^{26°}$ −10·6° (*c* 1·019 ethanol), λ_{max} 291 mμ (log ε 3·58); ν_{max}^{Nujol} 1727, 1269, 1248 cm^{-1} (CH_3COO—). (Found: C, 68·40; H, 6·71; N, 4·46. $C_{18}H_{21}O_4N$ requires: C, 68·55; H, 6·88; N, 4·44%).

The acetate gave 1-epi-*γ*-dihydrocaranine on hydrolysis.

The eluate with benzene–ether (3:1, 2:1, 1:1) gave crude *γ-dihydrocaranine* (XXIII, 29·0 mg) which on recrystallization with methanol afforded a pure sample (19 mg) as prisms, m.p. 150–151°, $[\alpha]_D^{62°}$ −80·9° (*c* 0·989, ethanol), λ_{max} 291 mμ (log ε 3·65); λ_{max}^{Nujol} 3·08 μ (−OH). (Found: C, 70·55; H, 7·18; N, 4·99. $C_{16}H_{19}O_3N$ requires: C, 70·31; H, 7·01; N, 5·13%).

The acetate formed prisms from n-pentane–methanol, m.p. 85–87°, $[\alpha]_D^{25°}$ −36·6° (*c* 1·134 ethanol), λ_{max} 291 mμ (log ε 3·61); ν_{max}^{Nujol} 1731, 1256, 1238 cm^{-1} (CH_3COO—). (Found: C, 68·27; H, 6·75; N, 4·30. $C_{18}H_{21}O_4N$ requires: C, 68·55; H, 6·88; N, 4·44%).

The acetate gave *γ*-dihydrocaranine on hydrolysis.

(b) *With lithium aluminium hydride.* To a suspension of lithium aluminium hydride (80 mg) in dry ether (20 ml) was added dropwise under stirring α-dihydrocaranone (150 mg) in dry ether (20 ml) over a period of 20 min, and the mixture refluxed for a further 3 hr. The excess of lithium aluminium hydride was destroyed gradually by addition of water (15 ml), the ethereal layer separated, and the aqueous layer extracted with benzene. The combined organic layers were dried over sodium sulphate and evaporated to dryness under reduced press. The residue (125 mg) was dissolved in benzene and chromatographed over alumina (7 g). Elution with benzene–ether (10:1, 5:1) gave 1-epi-*γ*-dihydrocaranine (XXII, 65 mg), m.p. and mixed m.p. 110–111°. The eluate with benzene–ether (3:1, 2:1) gave *γ*-dihydrocaranine (XXIII, 7 mg), identical in m.p., mixed m.p. and infra-red spectrum with an authentic specimen.

(c) *With metallic sodium and ethanol.* To a hot solution of α-dihydrocaranone (118 mg) in dry ethanol (30 ml) was added in portions metallic sodium (1·2 g) over a period of 20 min and the mixture was refluxed under nitrogen for 2 hr. The ethanol was evaporated *in vacuo* in an atmosphere of nitrogen, water (50 ml) was added to the residue, the whole extracted with benzene (150 ml) and the dried extract was evaporated to dryness under reduced press. The residue (89 mg) was dissolved in benzene (10 ml) and chromatographed over alumina (5 g).

Elution with benzene–ether (9:1) gave α-dihydrocaranone (13 mg), m.p. and mixed m.p. 143–145°, The eluate with benzene–ether (3:1) afforded on crystallization from ether *γ*-dihydrocaranine (XXIII, 27 mg) as prisms, m.p. and mixed m.p. 150–151°.

Reaction of γ-dihydrocaranine (XXIII) *with thionyl chloride*

A solution of *γ*-dihydrocaranine (88 mg) in thionyl chloride (4 ml) was allowed to stand overnight. The excess of thionyl chloride was completely removed and ice-cold water was added. The mixture was filtered, basified with Na_2CO_3 and extracted with pet ether. The dried extract was evaporated and the residue gave on twice recrystallization from ethanol *a chloro-compound* (XXIV, 46 mg) as needles, m.p. 140–141°, $[\alpha]_D^{31°}$ +38·4° (*c* 0·628, chloroform), λ_{max} 291 mμ (log ε 3·54). The infra-red spectrum did not show a band corresponding to the hydroxyl group and Beilstein test was positive. (Found: C, 65·87; H, 6·29; N, 4·95. $C_{16}H_{18}O_3NCl$ requires: C, 65·85; H, 6·22; N, 4·80%).

Hydrogenation of a chloro-compound (XXIV) *with Adams catalyst in ethanol*

A solution of a chloro-compound (20 mg) in ethanol (3 ml) was shaken in hydrogen for 3 hr. Hydrogen uptake was 1·6 ml (calcd. for 1 H_2: 1·52 ml). After removal of the catalyst the ethanol was evaporated to dryness under reduced press and the residue dissolved with dil HCl, filtered, basified with Na_2CO_3 and extracted with pet ether. The dried extract was evaporated to dryness and the residue (13 mg) chromatographed over alumina (1 g). Elution with benzene–pet ether (10:1) gave an oil (9 mg), identical in infra-red spectrum and optical rotation with (−)γ-lycorane (XVII).

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