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THE AMARYLLIDACEAE ALKALOIDS

ABSOLUTE CONFIGURATIONS OF DIASTEREOISOMERIC METHIODIDES IN THE LYCORINE-TYPE ALKALOIDS[1]

K. KOTERA, Y. HAMADA and R. MITSUI
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan

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Abstract—On the basis of the conformations and the established absolute configurations of lycorine (I) and dihydrolycorine (IX), discussions on quaternization of the alkaloids permit the assignment of the absolute configurations of lycorine α- and β-methiodide, (II and III), and dihydrolycorine methiodide (X), respectively. In diastereoisomeric methiodides of the lycorine-type alkaloids, their chemical correlations, and comparisons of the optical rotations and the UV spectra lead to the conclusion that the N-Me groups in the methiodides designated previously as α-series have β-absolute configuration and those of β-series have α-configuration. This conclusion is also supported by the results of CD and ORD studies.

IN PREVIOUS papers,[2,3] conclusive evidence for conformations and absolute configurations of lycorine and related compounds was based on physical methods using NMR, CD and ORD spectroscopies. Furthermore, Koyama *et al.*[4] carried out the X-ray analysis of dihydrolycorine hydrobromide, showing that the stereochemistry and the absolute configuration were correct.[5,6]

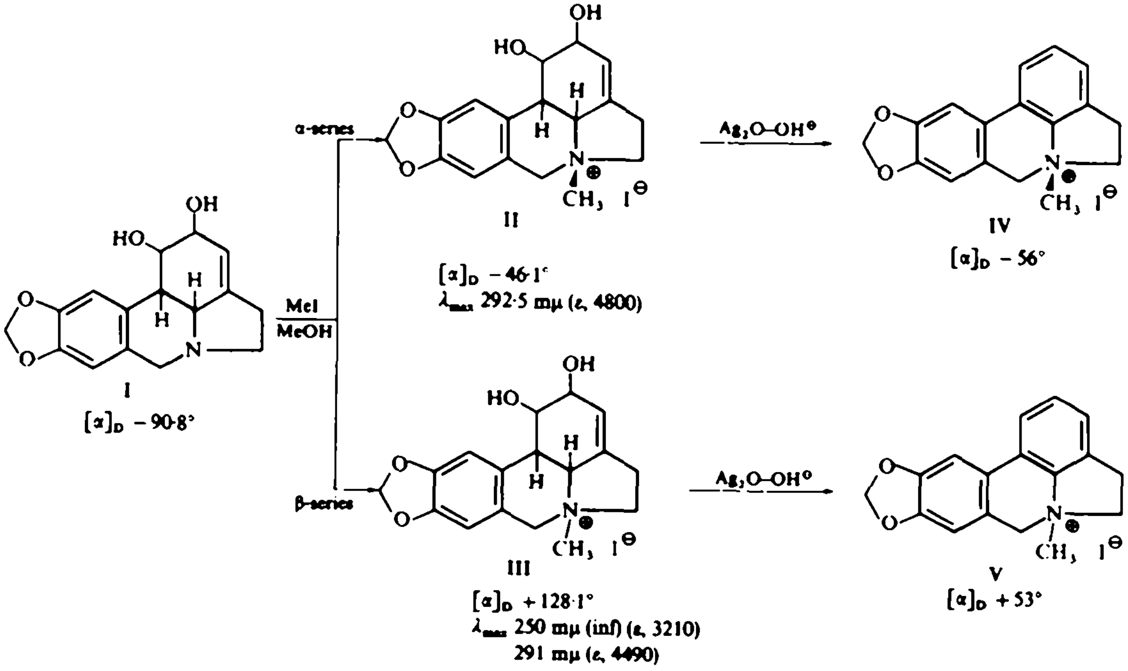


CHART 1

In 1938 Kondo *et al.*[7] found that quaternization of lycorine (I) with methyl iodide in refluxing methanol gave two diastereoisomeric methiodides, named α- and β-methiodides. In 1954 Uyeo *et al.*[8] converted these two methiodides by treatment with silver oxide in an alkaline medium into the corresponding (−)- and (+)-anhydrolycorine methiodides, which differ only in the configuration about the quaternary N atom. Subsequently, in caranine[9] (XV) and pluviine[10] (XXIII) two isomeric methiodides were also found. The absolute configurations in diastereoisomeric methiodides of the lycorine-type alkaloids have still remained undetermined.

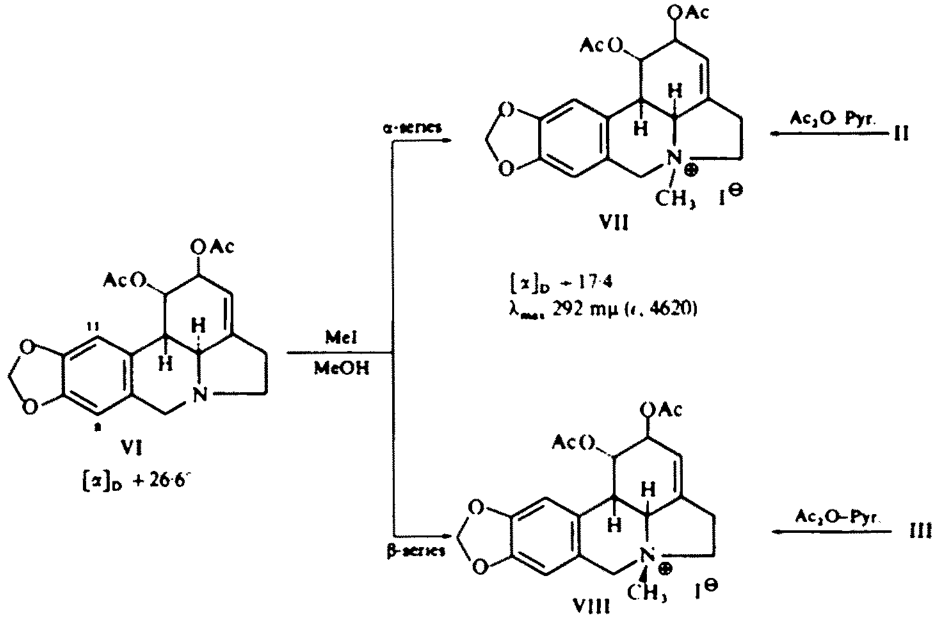


Chart 2

$[\alpha]_D$ +165·1
λ_{max} 250 mμ (inf) (ε, 3600)
291·5 mμ (ε, 4760)

This paper provides conclusive evidence which establishes absolute configurations of isomeric methiodides, e.g. lycorine α- and β-methiodides, (II and III), and (−)- and (+)-anhydrolycorine methiodides, (IV and V).

Diacetyllycorine (VI) was quaternized with methyl iodide in refluxing methanol for 2·5 hr, affording two diastereoisomeric methiodides, VII and VIII, m.p. 235–236° (dec), $[\alpha]_D$ +17·4°, λ_{max} 292 mμ (ε 4620) and m.p. 243–243·5° (dec), $[\alpha]_D$ +165·1°, λ_{max} 250 (inf), 291·5 mμ (ε 3600, 4760). The two isomers were also obtained by acetylation of lycorine α- and β-methiodides, II and III, respectively. The α-methiodides of lycorine and diacetyllycorine exhibit absorption maxima only near 290 mμ in the UV spectra, whereas the β-methiodides show characteristic inflexions near 250 mμ in addition to slight hypsochromic shifts at α-bands near 290 mμ (Figs 1 and 2), and the optical rotatory values of α-methiodides are more laevo-rotatory than those of β-methiodides.

Treatment of diacetyldihydrolycorine (XI) with methyl iodide gave a sole product, diacetyldihydrolycorine methiodide (XII), m.p. 245–246° (dec), $[\alpha]_D$ +24·8°, λ_{max} 250 (inf), 292 mμ (ε 3480, 4850) which was identical with the product obtained by

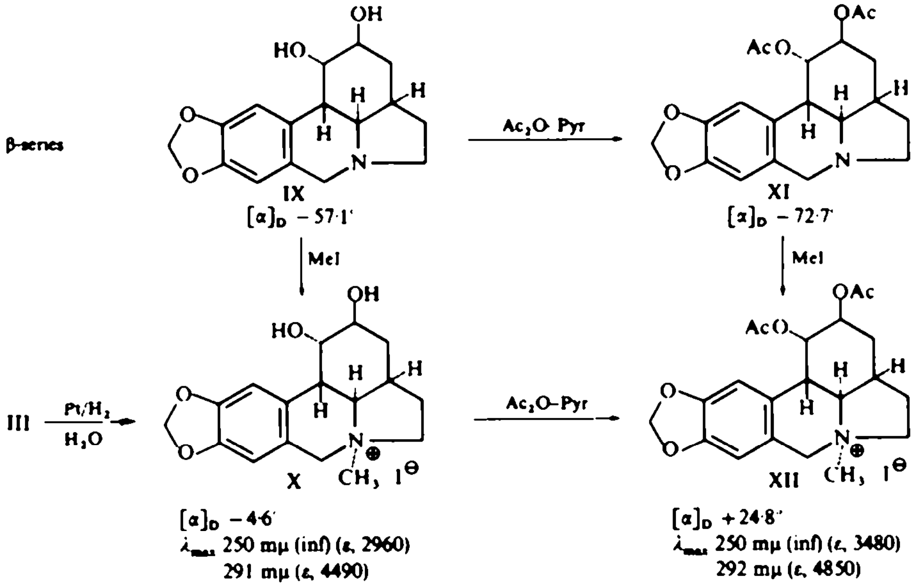


CHART 3

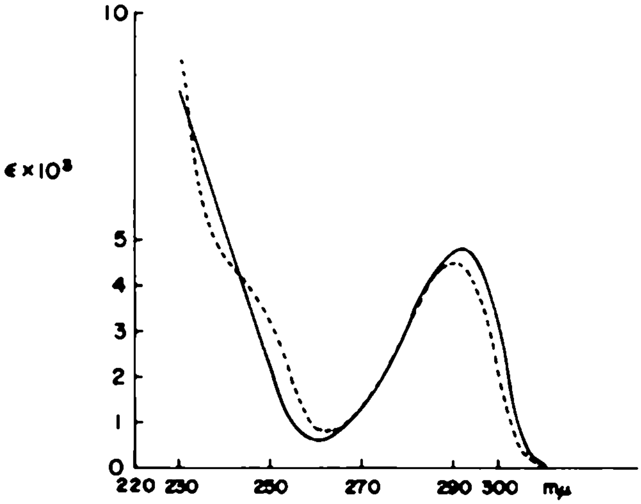


FIG. 1 The UV spectra of diastereoisomeric methiodides of lycorine (I) in 95% EtOH.
——— lycorine α-MeI (II)
lycorine β-MeI (III).

acetylation of dihydrolycorine methiodide (X). Two methiodides, X and XII, are found to be the β-series as shown in the UV spectra. This was confirmed from the result that lycorine β-methiodide was readily hydrogenated in water with Adams' catalyst within 1 hr, yielding dihydrolycorine methiodide (X) in good yield. However, hydrogenation of diacetyllycorine β-methiodide (VIII) to diacetyldihydrolycorine methiodide was unsuccessful, probably owing to the steric effect of the bulky acetoxyl groups.

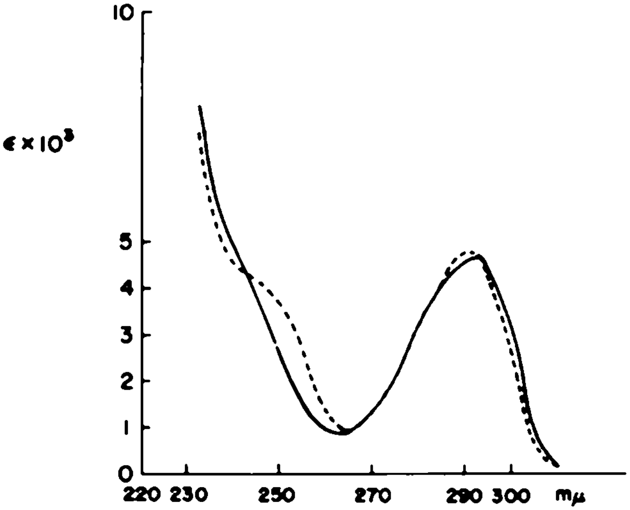
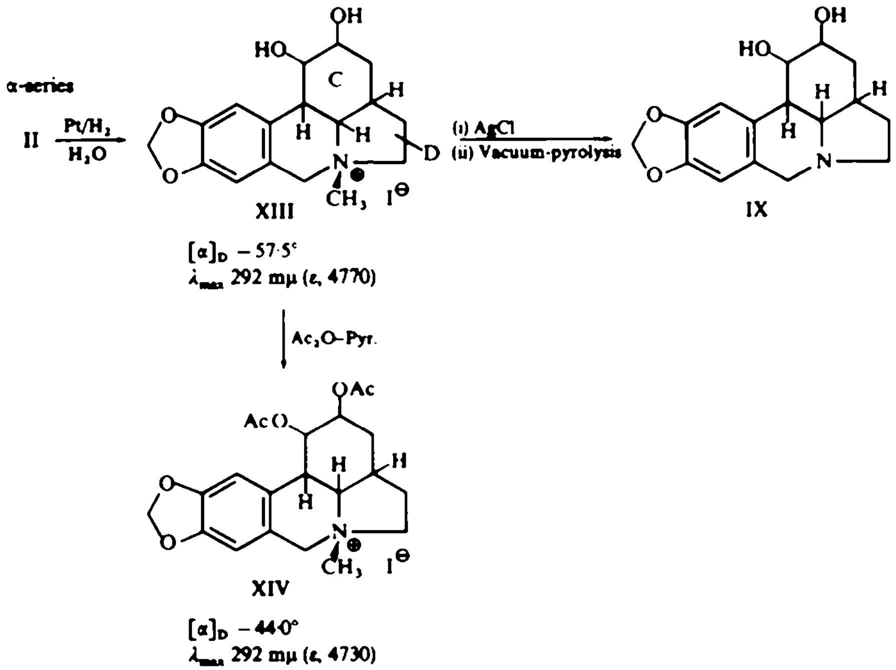


FIG. 2 The UV spectra of diastereoisomeric methiodides of diacetyl lycorine (VI) in 95% EtOH.
——— diacetyl lycorine α-MeI (VII)
- - - - diacetyl lycorine β-MeI (VIII).



XIII

$[\alpha]_D$ −57·5°
λ_{max} 292 mμ (ε, 4770)

IX

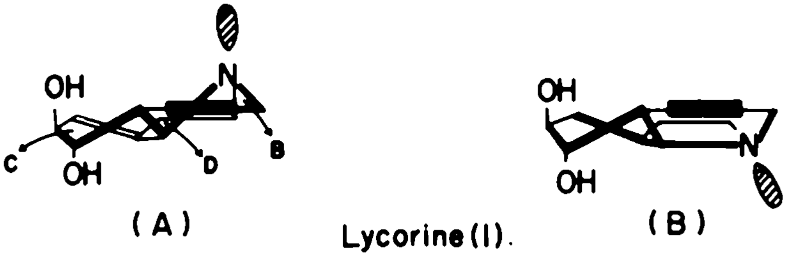
XIV

$[\alpha]_D$ −44·0°
λ_{max} 292 mμ (ε, 4730)

CHART 4

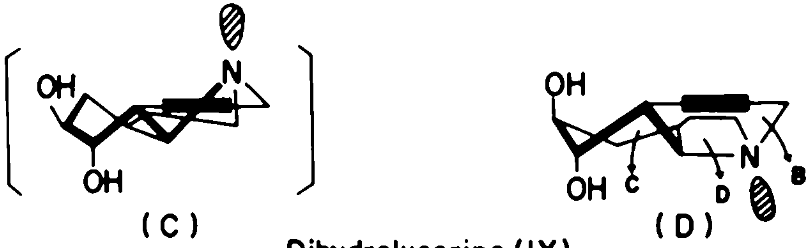
Hydrogenation of lycorine α-methiodide (II) with Adams' catalyst in water for 7 hr afforded with a considerable resistance the product, m.p. 260·5° (dec), $[\alpha]_D$ $-57·5°$, λ_{max} 292 mμ (ε 4770), which was converted to dihydrolycorine by vacuum-pyrolysis of its methochloride. Thus, the hydrogenation product is assigned as the structure XIII resulted from the attack of hydrogen from the rear side of the molecule in the same manner as the cases of lycorine and lycorine β methiodide. Acetylation of XIII gave diacetyldihydrolycorine α-methiodide (XIV), m.p. 234·5° (dec), $[\alpha]_D$ $-44·0°$, λ_{max} 292 mμ (ε 4730). The compounds, XIII and XIV, are indicated from the UV spectra to be the α-methiodides, diastereoisomeric to X and XII, respectively. Hydrogenation of diacetyllycorine α-methiodide to XIV also failed.

The X-ray analysis of dihydrolycorine hydrobromide[4] has proved that the lone pair electrons on the nitrogen atom of dihydrolycorine are oriented towards the rear side of the molecule. Based on this finding, quaternization of lycorine and dihydrolycorine is discussed.



(A) (B)

Lycorine (I).



(C) (D)

Dihydrolycorine (IX)

CHART 5 ▬ : Benzene Ring

The reason why quaternization of lycorine affords two diastereoisomeric α- and β-methiodides, whereas dihydrolycorine gives the only β-methiodide, may be explained by considering the difference between the transition states of lycorine- and dihydrolycorine-methiodides. Model inspections suggest that lycorine exists as the conformation A and/or B as shown in Chart 5. Although in the previous communication[1] we supposed an equilibrium between the two forms in solution, no evidence for supporting this assumption was obtained even by extensive NMR studies. If lycorine in solution is fixed in the A form having the half-chair B-ring, on quaternization, methyl iodide will be accessible to the molecule with almost equal chance from both of the upper and the rear sides. The access of the reagent from the rear side, however, should cause conformational change of the B-ring from half-chair to twisted boat without conformational changes of the other rings, and the transition state derived from the B form will be less stable than that of the half-chair from the A form. Thus, the formation of the α-methiodide from the A form seems to be more preferable than the β-methiodide from the B form. This assumption may be supported by the fact that the yield of the α-methiodide increases with decrease of the reaction temperature. The product ratios of α- and β- methiodides are about 4:3 in refluxing methanol, 3:1 at room temperature and 5:1 at 0° in the refrigerator.* On the other hand, the conformation of dihydrolycorine is fixed only in the D form as indicated distinctly by the X-ray analysis[4] and the NMR study.[2] In this conformation, approach of the reagent from the rear side must be much more favourable compared with that from the upper side. If the reagent approaches from the upper side, remarkable conformational changes should occur in both the C- and D-rings together with in the B-ring, and the intermediate should take the form resemble to the unfavourable C form. For this reason, dihydrolycorine would afford only the β-methiodide from the D form. However, as mentioned above, hydrogenation of lycorine α-methiodide (II) yielded dihydrolycorine α-methiodide (XIII) being related to the C form, and the considerable resistance observed on the reduction seems to be attributable to compulsive formation of the unfavourable conformation. Consequently, the N-methyl group of lycorine α-methiodide would have α-configuration as shown in the formula II, and those of lycorine β-methiodide and dihydrolycorine methiodide β-configurations as portrayed in the formulae, III and X, respectively. From the above-mentioned chemical relations, it may be concluded that the methiodides belonging to the α-series have β-configurations of the N-Me groups and those of β-series α-configuration. This conclusion was also supported by comparison of the ORD and CD curves of (−)- and (+)-anhydrolycorine methiodides, (IV and V), with those of nuciferine and nantenine, which belong to the aporphine alkaloids.[1,3,11] Recently, Craig and Roy[12] reported that the absolute configuration of aporphine alkaloids may simply be determined from the sign of their high-amplitude Cotton effect centered at 235–245 mμ and that the positive Cotton effect corresponds to (S)-configuration of a twisted biphenyl system as in nantenine and the negative Cotton effect is ascribed to (R)-configuration as nuciferine. As shown in Figs 3 and 4, the CD curves of (−)- and (+)-anhydrolycorine methohalogenides near 240 mμ correspond to those of nuciferine and nantenine, respectively. These results show that (−)- and (+)-anhydrolycorine methiodides should have the respective absolute configuration of the N-Me group as shown in the formulae, IV and V. This conclusion agrees with that from the above discussions for lycorine α- and β-methiodides.

In the same manner as for lycorine, the α- and β-methiodides of caranine[9] (XV) are assigned as XVI and XVII, respectively, from the optical rotatory values and UV spectra. It is well known[9] that hydrogenation of caranine afforded α-dihydrocaranine (XXI) and β-dihydrocaranine (XVIII) which were epimeric on the C_{3a} configuration. From conformational analogies between lycorine or caranine and β-dihydrocaranine, and between dihydrolycorine and α-dihydrocaranine, it is expected that quaternization of β-dihydrocaranine will give two isomeric methiodides

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* Separation of two diastereoisomeric methiodides was carried out by repeated recrystallization from ethanol or water. No interconversion between the isomeric methiodides was observed in refluxing methanol or water.

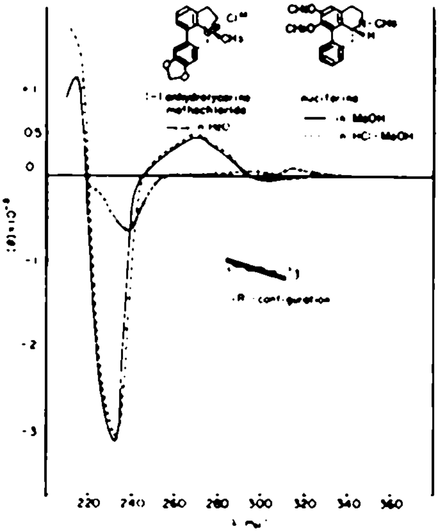

FIG. 3 The CD curves of nuciferine and ( )-anhydrolycorine methochloride.

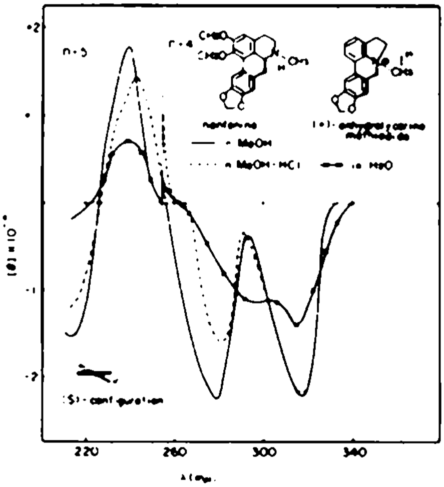

FIG. 4 The CD curves of nantenine and (+)-anhydrolycorine methiodide (V).

and that of α-dihydrocaranine only β-methiodide. As expected, β-dihydrocaranine gave the α-methiodide XIX, m.p. 295° (dec), $[\alpha]_D$ −119·5° and the β-methiodide XX, m.p. 298° (dec), [α] +29·4°, whereas α-dihydrocaranine afforded only the β-methodide XXII, m.p. 310° (dec), $[\alpha]_D$ −14·6°. The UV spectra of these methiodides are also in good agreement with the findings mentioned above.

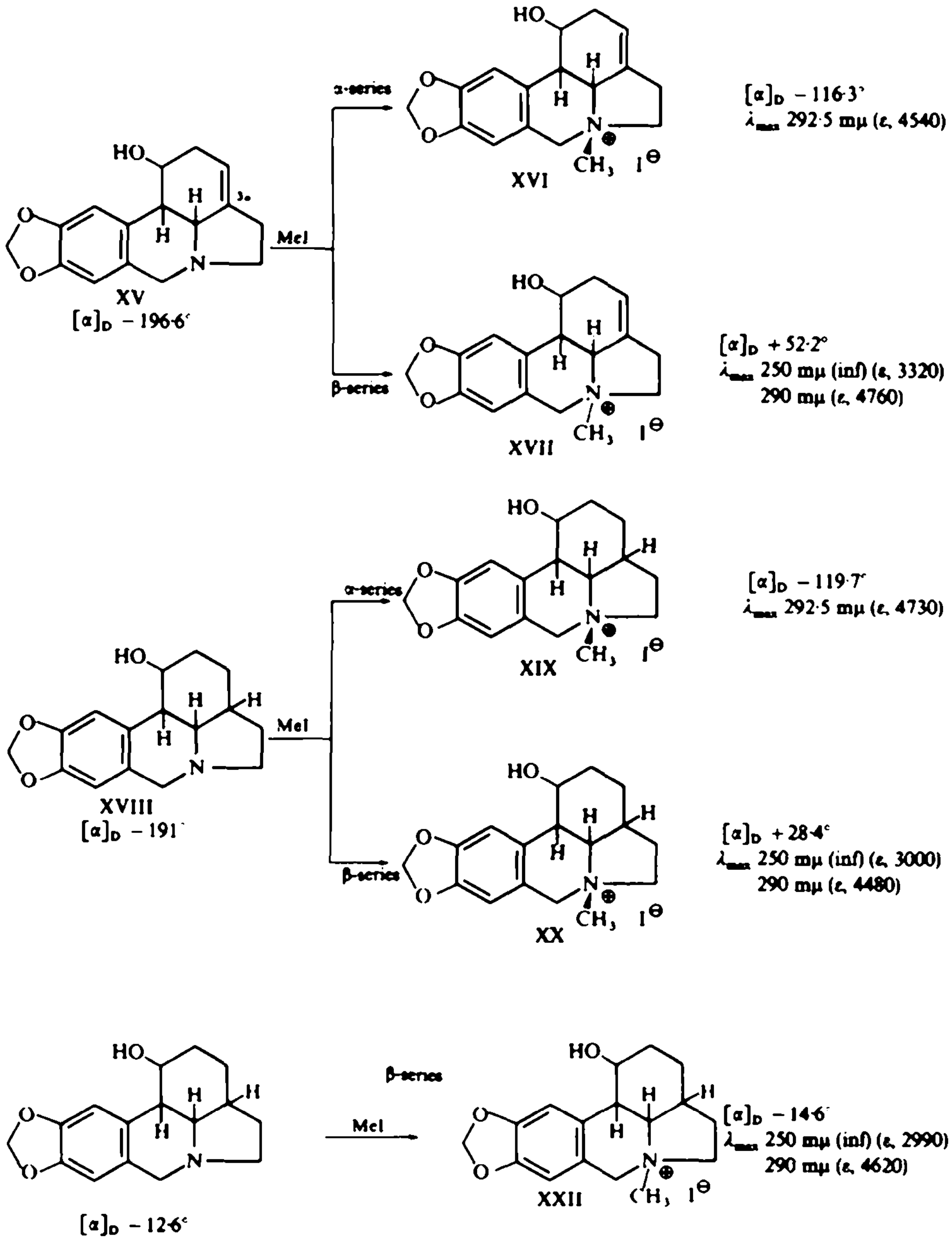
HO
H
H
N
XV
[α]D − 196·6°
MeI
α-series
β-series
XVI
CH3 I⊖
[α]D − 116·3°
λmax 292·5 mμ (ε, 4540)
XVII
[α]D + 52·2°
λmax 250 mμ (infl) (ε, 3320)
290 mμ (ε, 4760)
XVIII
[α]D − 191°
XIX
[α]D − 119·7°
λmax 292·5 mμ (ε, 4730)
XX
[α]D + 28·4°
λmax 250 mμ (infl) (ε, 3000)
290 mμ (ε, 4480)
[α]D − 12·6°
β-series
MeI
XXII
[α]D − 14·6°
λmax 250 mμ (infl) (ε, 2990)
290 mμ (ε, 4620)

Chart 6

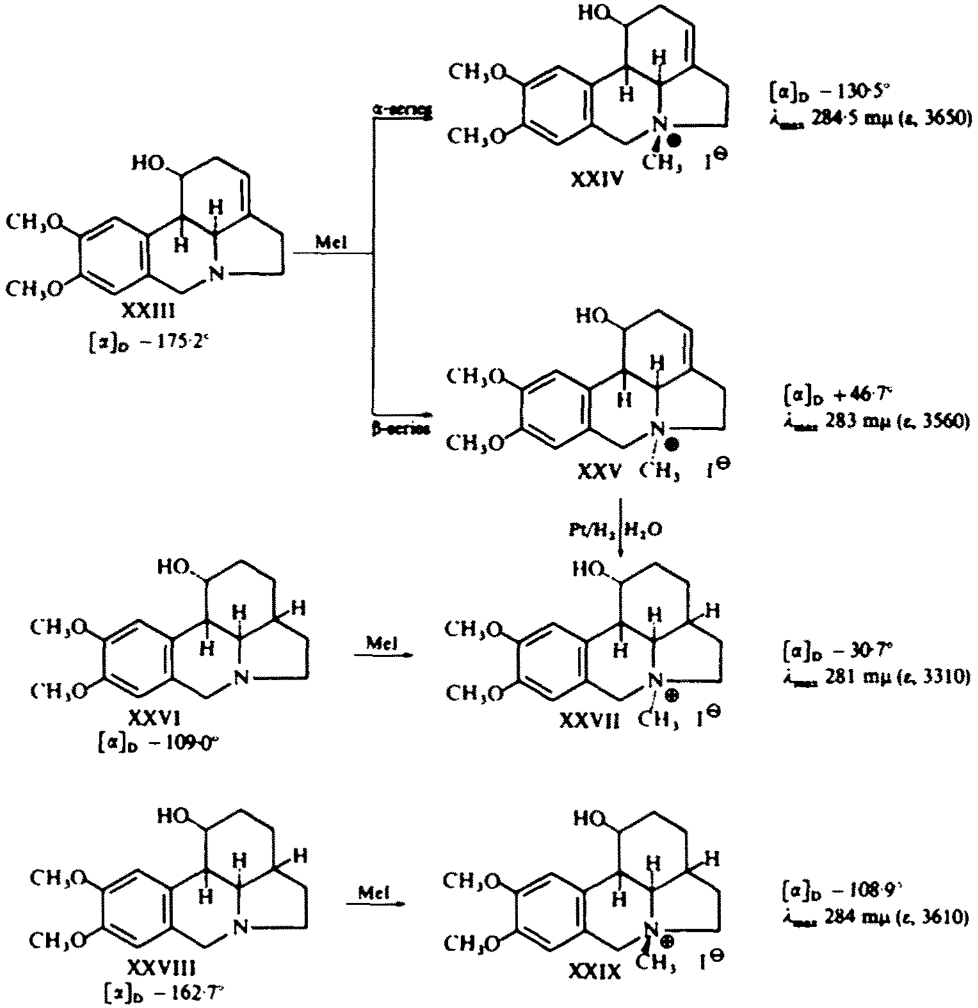

Chart 7

Boit *et al.*[10] isolated pluviine α-methiodide (XXIV), m.p. 259–260° (dec), $[\alpha]_D$ −129° by direct quaternization of pluviine (XXIII). Uyeo *et al.*[10] obtained another pluviine β-methiodide (XXV), m.p. 231–233°, $[\alpha]_D$ +38·2° by transformation from lycorenine (XXXIIa). However, the absolute configurations of these methiodides have not determined yet. Reinvestigation of quaternization of pluviine with methyl iodide in refluxing methanol afforded the above two isomeric methiodides. From the rotatory values, their structures are assigned as XXIV and XXV, respectively. Hydrogenation of pluviine β-methiodide (XXV) with Adams' catalyst gave α-dihydropluviine β-methiodide (XXVII), m.p. 135–136°, $[\alpha]_D$ −31·2°, which was also obtained by quaternization of α-dihydropluviine (XXVI). β-Dihydropluviine (XXVIII) was refluxed with methyl iodide in methanol for 2 hr to give β-dihydropluviine α-methiodide

(XXIX), m.p. 230–231°, $[\alpha]_D$ −108·9°, but the anticipated β-methiodide[10] was not obtained, probably because of the small quantity of β-dihydropluviine used. Thus, the absolute configurations of diastereoisomeric methiodides in the lycorine-type alkaloids have wholly been determined.

Previously, Uyeo *et al.*[10] reported conversions of hippeastrine (XXX) and lycorenine (XXXIIa) or homolycorine (XXXIIb) into lycorine β-methiodide (III) and pluviine β-methiodide (XXV) *via* the respective intermediates, XXXI and XXXIII, as shown in Chart 8. The stereochemistry and the absolute configurations of hippeastrine,[10, 13] lycorenine and homolycorine[10, 14] have been established except the configurations of the N-Me groups. It seems reasonable to suppose that the alkaloids of this type have β-configuration of the N-Me group, owing to a severe non-bonded interaction between the aromatic C_{11} hydrogen and α-N-Me group.* Model inspections suggest that on the conversions to lycorine-type methiodides, the rotation around the C_{11a}–C_{11b} bond in the intermediates, XXXI and XXXIII, and subsequent ring-closure may occur favourably with the retention of the configuration of N-Me group, resulting in the formation of only β-methiodides.

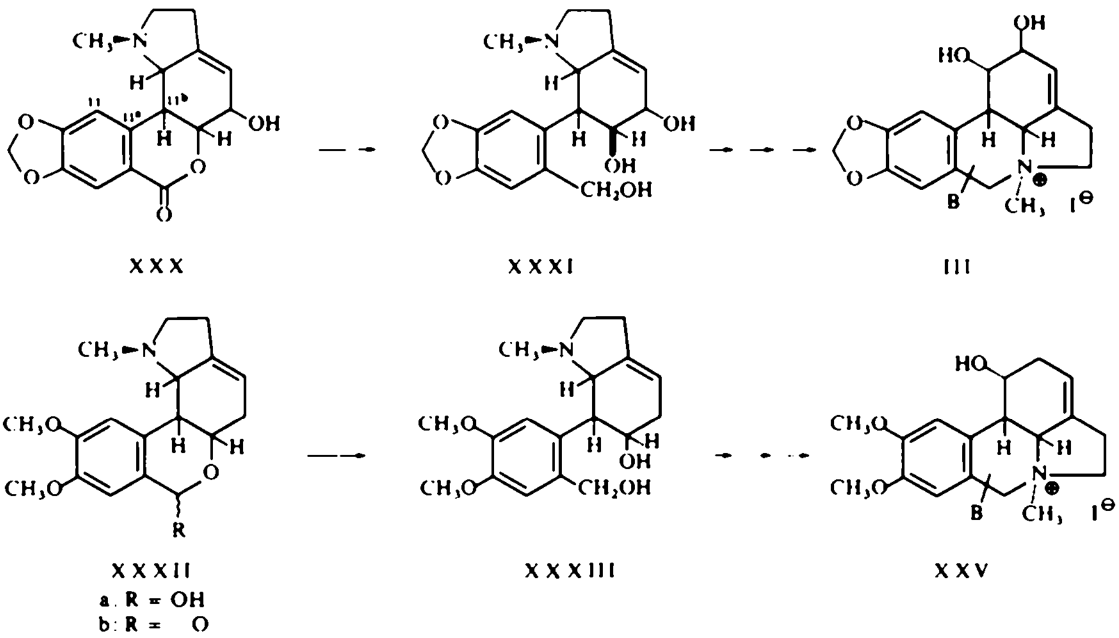

Chart 8

Recently, our group[3] investigated the optical rotatory behaviour of lycorine and related compounds, and proposed an empirical rule, like the octant rule, for the sign and the magnitude of the Cotton effects due to an aromatic α-band. In terms of this rule, the absolute configurations of diastereoisomeric methiodides in both lycorine (I) and caranine (XV) were discussed.[3]

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* It seemed difficult to rationalize the configurations of N-Me groups from the results of NMR studies.[15]

TABLE 1. CD DATA FOR METHIODIDES OF LYCORINE-TYPE ALKALOIDS.

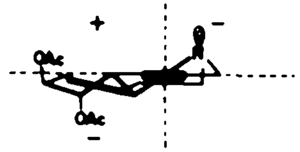
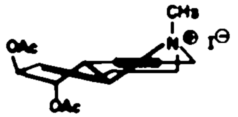
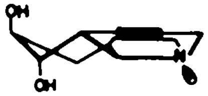
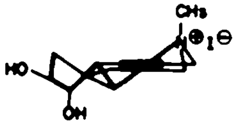
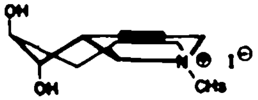
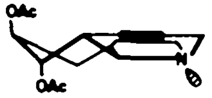
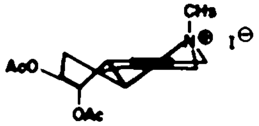
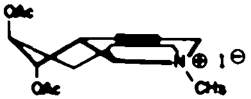
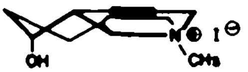
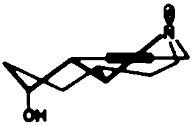
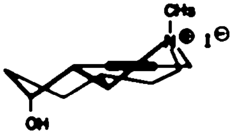
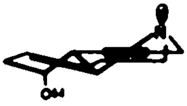
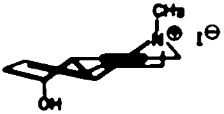
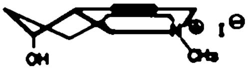
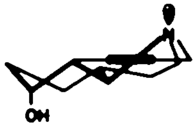
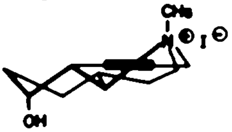
No	Compound	1st Cotton E. $[\theta]_{max}$ (λ, mμ)	2nd Cotton E. $[\theta]_{max}$ (λ, mμ)	Projection
VI	Diacetyllycorine	−6200 (291)	+4900 (239)	
VII	Diacetyllycorine α-MeI	−6610 (290·5)	+5370 (240)	
VIII	Diacetyllycorine β-MeI	*a*	−2300 (250)	
IX	Dihydrolycorine	−5317 (297)	+4667 (241)	
XIII	Dihydrolycorine α-MeI	−2683 (290)		
X	Dihydrolycorine β-MeI	*b*	*b*	
XI	Diacetyldihydrolycorine	−5380 (294)	+7650 (240)	
XIV	Diacetyldihydrolycorine α-MeI	−6090 (291·5)	+5200 (242·5) +4630 (240)	
XII	Diacetyldihydrolycorine β-MeI	*c*	*c*	
XXI	α-Dihydrocaranine	[d] −4060 (296)	+3030 (243)	
XXII	α-Dihydrocaranine β-MeI	*a*	−1722 (240)	

TABLE 1.—*continued*

No.	Compound	1st Cotton E. $[\theta]_{max}$ (λ, mμ)	2nd Cotton E. $[\theta]_{max}$ (λ, mμ)	Projection
XVIII	β-Dihydrocaranine	[d] −7610 (293)	+6310 (242)	
XIX	β-Dihydrocaranine α-MeI	−5220 (295)	+1430 (246) + 740 (240)	
XX	β-Dihydrocaranine β-MeI	−2009 (292)		
XXIII	Pluviine	−4030 (285)	+2680 (252·5)	
XXIV	Pluviine α-MeI	−3800 (286)		
XXV	Pluviine β-MeI	+1200 (289)	−7230 (242)	
XXVI	α-Dihydropluviine	−1433 (276)		
XXVII	α-Dihydropluviine β-MeI	*a*	−7100 (241)	
XXVIII	β-Dihydropluviine	−5400 (280)		
XXIX	β-Dihydropluviine α-MeI	−3890 (282)		

a The $[\theta]_{max}$ values of the first Cotton effects were obscure, but they may be estimated at 0 ± 500.

b The measurements of both CD and ORD curves were impossible.

c The measurement of CD curve was impossible and the ORD data showed $[\phi]_{400}$ +1580, $[\phi]_{300}$ +3690, $[\phi]_{254}$ +5060 and $[\phi]_{235}$ +14340.

d These data were cited from the list of our previous paper (see, Ref. 3).

As shown in Table 1, the first Cotton effects corresponding to the aromatic α-bands of the methiodides, which are concerned with the present study, also show comparably reasonable $[\theta]_{max}$-values as expected from the respective projections.

EXPERIMENTAL

All m.ps determined in capillary tubes were uncorrected. Specific rotations were measured with Rudolf Photoelectric Polarimeter Model 200. NMR spectra were taken in D_2O soln containing dioxan as an internal standard using a Varian A-60 spectrophotometer. UV spectra were determined with a Hitachi EPS-2 recording spectrophotometer and IR spectra with a Nippon Bunko DS-201B spectrometer.

Quaternization of diacetyllycorine (VI) *with methyl iodide in refluxing* MeOH

A mixture of VI (500 mg) and MeI (0·88 ml) in abs MeOH (12·5 ml) was heated under reflux for 1 hr. Additional MeI (0·22 ml) was added and the soln refluxed for further 1·5 hr. The mixture was evaporated to dryness under reduced press to leave a yellowish oil (715 mg). Trituration with acetone gave a solid (95 mg) which was crystallized from acetone–MeOH to yield VII (49 mg) as colourless needles, m.p. 230–231° (dec). A pure sample, obtained by repeated recrystallization from acetone–MeOH had a m.p. of 233·5–234° (dec). This was identical with VII prepared by acetylation of II in the m.p., mixed m.p., optical rotations and IR spectra. The mother liquor was evaporated and the residue crystallized from acetone-Et_2O to give crystals which on repeated recrystallization from acetone afforded colourless prisms (13·3 mg), m.p. 237° (dec). Further recrystallization from acetone–MeOH afforded colourless prisms, m.p. 243–243·5° (dec) which was identified as VIII from comparison of m.p., mixed m.p. and IR spectra.

Diacetyllycorine β-methiodide (VIII)

A mixture of III (200 mg) and Ac_2O (1 ml) in dried pyridine (8 ml) was heated on a steam-bath for 3·5 hr. The solvent was then evaporated completely under reduced press leaving a brown gum which was crystallized from acetone to give VIII as colourless prisms (168 mg), m.p. 243° (dec). Evaporation of the mother liquor and crystallization of the residue from acetone gave an additional product (25 mg) of VIII. A pure sample for analysis was obtained by recrystallization from acetone–MeOH as prisms m.p. 243–243·5 (dec), $[\alpha]_D^{21\cdot5}$ +165·1 (c = 0·962, MeOH). λ_{max}^{MeOH} 250 (infl), 291·5 mμ (ε 3600, 4760). (Found: C, 49·29; H, 5·00; N, 2·44; O, 18·80; I, 24·46. $C_{21}H_{24}O_6NI$ requires: C, 49·13; H, 4·71; N, 2·73; O, 18·70; I, 24·72%.)

Diacetyllycorine α-methiodides (VII)

Compound II (150 mg) in dried pyridine (15 ml) was treated with Ac_2O (1 ml) and the soln heated on a steam-bath for 3·5 hr. Working up in the usual manner, the acetate VII was obtained as colourless needles, m.p. 231–232 (dec) from acetone–MeOH. An analytical sample from acetone–MeOH had a m.p. of 236° (dec) as colourless needles. $[\alpha]_D^{22}$ +17·4° (c = 1·069, MeOH). λ_{max}^{EtOH} 292 mμ (ε 4600). (Found: C, 49·32; H, 4·68; N, 2·47; O, 18·50; I, 24·91. $C_{21}H_{24}O_6NI$ requires: C, 49·13; H, 4·71; O, 18·70; N, 2·73; I, 24·72%.)

Diacetyldihydrolycorine β-methiodide (XII) *from diacetyldihydrolycorine* (XI)

MeI (200 mg) was added to a soln of XI (50 mg) in abs MeOH (2 ml). After refluxing for 2 hr, the reaction mixture was evaporated to dryness under reduced press. Trituration of the residue (72 mg) with EtOH afforded crystals (52 mg) which showed OH absorption band in the IR spectrum. An analytical sample obtained by recrystallization from EtOH had a m.p. of 245–246° (dec). $[\alpha]_D^{22\cdot5}$ +24·8° (c = 0·961, H_2O). λ_{max}^{EtOH} 250 (infl), 292 mμ (ε 3480, 4850). A mixed m.p. determination with XII obtained by direct acetylation of X showed no depression and the IR spectra were superimposable. (Found: C, 48·25; H, 5·35; N, 2·79: $C_{21}H_{26}O_6NI \cdot \frac{1}{2}H_2O$ requires: C, 48·09; H, 5·19; N, 2·67%.)

Catalytic reduction of lycorine β-methiodide (III) *over* PtO_2

Compound III (100 mg) in EtOH (12 ml) was hydrogenated over Adams' catalyst prepared from PtO_2 (100 mg) in EtOH (1·2 ml). After H_2 uptake was complete (1 hr), the catalyst was removed by filtration and the filtrate evaporated to dryness under reduced press. Crystallization of the residue (89 mg) from EtOH afforded X (33 mg) as prisms, m.p. 283° (dec). $[\alpha]_D^{18}$ −4·6° (c = 1·50, H_2O). λ_{max}^{EtOH} 250 (infl), 291 mμ (ε 2960, 4490). NMR τ: 2·93 (1H, S, H_{11}), 3·03 (1H, S, H_8), 4·02 (2H, S, $-OCH_2O-$), 7·00 (3H, S, NME). This was identified by comparison of its m.p., mixed m.p. and IR spectrum with that of X obtained by quaternization of IX with MeI in abs MeOH.

Acetylation of dihydrolycorine β-methiodide (X) *with* Ac_2O *and pyridine*

A mixture of X, Ac_2O (0·5 ml) and dried pyridine (5 ml) was allowed to stand at room temp for 7 day and then heated at 100° for 3·5 hr. Concentration of the solvent gave a solid, m.p. 244–245° (dec) which was recrystallized from H_2O to yield the diacetate XII as plates, m.p. 245° (dec), which was identical in all respects with the product obtained by direct quaternization of diacetyldihydrolycorine with MeI.

Catalytic reduction of lycorine α-methiodide (II) *over* PtO_2

A soln of II (500 mg) in H_2O (25 ml) was shaken in the presence of Adams' catalyst (250 mg) in an atom of H_2. After H_2 uptake was complete (6·5 hr), the catalyst was removed by filtration and the filtrate was concentrated to a small volume under reduced press. The first crop isolated was filtered and washed with H_2O giving the residue (180 mg) as prisms. The filtrate and washings were combined and concentrated to give an additional product (110 mg). The combined crystalline product was recrystallized from MeOH to give XIII (215 mg) as colourless prisms, m.p. 257·5° (dec). An analytical sample recrystallized from MeOH had a m.p. of 260·5° (dec) as colourless prisms. $[\alpha]_D^{22}$ −57·5° (c = 1·061, EtOH). λ_{max}^{EtOH} 292 mμ (ϵ 4770). NMR τ: 2·97 (1H, S, H_{11}), 3·25 (1H, S, H_8), 4·03 (2H, S, –OCH_2O–), 7·00 (3H, S, NMe). (Found: C, 47·35; H, 5·14; N, 3·23. $C_{16}H_{19}O_4N \cdot MeI$ requires: C, 47·34; H, 5·14; N, 3·24%.)

Acetylation of dihydrolycorine α-methiodide (XIII)

Ac_2O (1 ml) was added to a suspension of XIII (100 mg) in dried pyridine (8 ml) and the mixture warmed on a steam-bath for 5 hr. Working up in the usual manner, the product had a m.p. of 234·5° (dec) as prisms after recrystallization from EtOH. $[\alpha]_D^{22}$ −44·0° (c = 0·698, MeOH). λ_{max}^{EtOH} 292 mμ (ϵ 4730). (Found: C, 49·08; H, 5·29; N, 2·93. $C_{21}H_{26}O_6NI$ requires: C, 48·93; H, 5·08; N, 2·71%.)

Attempted catalytic reduction of diacetyllycorine α-methiodide (VII) *over* PtO_2 *in* AcOH

Compound XII (5 mg) in AcOH was hydrogenated over Adams' catalyst (85 mg) for 12 hr. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced press. Trituration of the residue (88 mg) with acetone-MeOH afforded the starting material perfectly

Attempted catalytic reduction of diacetyllycorine β-methiodide (VIII) *over* PtO_2 *in* AcOH

Compound VIII (50 mg) in AcOH was hydrogenated over Adams' catalyst (40 mg) for 2 hr. No absorption of H_2 occurred. Worked up in the usual way, the product crystallized from acetone was proved by comparison of m.p., mixed m.p. and IR spectrum to be the starting material.

Vacuum-pyrolysis of dihydrolycorine-β-methiodide (X)

A soln of X (100 mg) in H_2O (5 ml) was shaken with freshly prepared AgCl (250 mg) for 30 min, and then the mixture allowed to stand at room temp for 1 hr. After the salt was removed by filtration and washed with H_2O. The filtrate and H_2O washings were combined and evaporated to dryness under reduced press. The residue was distilled at 200–240° in a metal-bath at a highly reduced press (0·02–0·003 mm/Hg) to give a partially solidified distillate, which was washed with MeOH giving colourless prisms (10 mg), m.p. 230–235° (dec). A mixed m.p. determination with authentic IX showed no depression and the IR spectra were superimposable.

Vacuum-pyrolysis of dihydrolycorine α-methiodide (XIII)

A soln of XIII (100 mg) in H_2O (3 ml) was shaken with freshly prepared AgCl (200 mg) for 30 min, and then the mixture left at room temp for 1 hr. Working up in the manner similar to the case of dihydroloy-corine β-methiodide, distillation of the residue at 195–240° in a metal-bath under high vacuum (0·003–0·02 mm/Hg) afforded pale yellowish crystals, m.p. 228–231° (dec), which was identical from comparison of its m.p., mixed m.p. and IR spectrum with authentic IX.

Quaternization of lycorine (I) *with methyl iodide in refluxing* MeOH

MeI (2·5 ml) was added to a suspension of I (1·245 g) in abs MeOH (8·8 ml), and the soln refluxed for 2 hr The mixture was evaporated to dryness and the residue (2·008 g) was crystallized from abs EtOH to yield 1·033 g of II. A portion was recrystallized from abs EtOH and had a m.p. of 250–251° (dec); $[\alpha]_D^{20}$ −43·5° (c = 0·370, MeOH); λ_{max}^{EtOH} 292·5 mμ (ϵ 4800); NMR τ: 2·98 (1H, S, H_{11}), 3·25 (1H, S, H_8), 4·03 (2H, S, –OCH_2O–), 7·13 (3H, S, NME). The residue from the mother liquor was crystallized from H_2O to give 0·72 g of III. A pure sample from H_2O had a m.p. of 281° (dec) as colourless rods. $[\alpha]_D^{20}$ +127·0° (c = 1·058, MeOH); λ_{max}^{EtOH} 250 (inf), 291 mμ (ϵ 3210, 4490).

Quaternization of lycorine (I) *with methyl iodide at about 25° at room temp*

A soln of I (100 mg) and MeI (100 mg) in abs MeOH (30 ml) was left at about 25° for 1 day. The mixture was worked up in the same manner as mentioned above to give II (92 mg) and III (30 mg), respectively.

Quaternization of lycorine (I) *with methyl iodide at 0° in a refrigerator*

MeI (400 mg) was added to a soln of I (100 mg) in cold abs MeOH (50 ml) and the mixture stored in a refrigerator for 3 day. Since examination of the mixture on TLC showed the presence of the starting material, MeI (200 mg) was added and the soln left in the refrigerator for further 4 day. Working up in a similar manner, there were obtained 89 mg of II and 17 mg of III.

Attempted isomerization of lycorine α-methiodide (II) *in refluxing* MeOH *or* H_2O

Compound II was refluxed in MeOH for 5 hr or in H_2O for 25 hr. The product was examined by comparison of m.p., mixed m.p. and optical rotation with those of the starting material, showing no isomerization of II to III.

Attempted isomerization of lycorine β-methiodide (III) *in refluxing* MeOH *or* H_2O

In the similar manner to the case of II, attempted isomerization of III was examined. As a result, it was proved that no isomerization of III to II occurred.

Quaternization of α-dihydrocaranine (XXI) *with methyl iodide*

MeI (0·5 ml) was added to a soln of XXI (100 mg) in abs MeOH (1 ml). After warming at 55–60° for 4 hr, the mixture was cooled to room temp. The resulting crystalline product was filtered and washed with MeOH giving 139 mg of a white solid, m.p. 305° (dec). The filtrate and MeOH washings were combined and then evaporated to dryness under reduced press. Crystallization of the residue (15 mg) from MeOH gave an additional product (9 mg), m.p. 305° (dec). A portion of XXII thus obtained was recrystallized twice from MeOH and had a m.p. of 310° (dec) after drying at 95° under reduced press for 2 hr; $[\alpha]_D^{22}$ $-14{\cdot}6$ ($c = 0{\cdot}329$, MeOH); λ_{max}^{EtOH} 250 (infl), 290 mμ (ε 2990, 4620) (Found: C, 49·08; H, 5·36; N, 3·29. $C_{16}H_{19}O_3N{\cdot}CH_3I$ requires: C, 49·16; H, 5·34; N, 3·37%.)

Quaternization of β-dihydrocaranine (XVIII) *with methyl iodide*

A soln of XVIII (500 mg) in abs MeOH (1 ml) was heated with MeI (0·25 ml) on a steam-bath. After refluxing 3 min, a crystalline product began to separate. On further refluxing for 1·5 hr and allowing to stand at room temp, crystalline products (65 mg) were separated by filtration and recrystallized from a large amount of MeOH to give crude crystals (5·4 mg) as plates which gave on recrystallization from MeOH pure XX, m.p. 298° (dec) as plates: $[\alpha]_D^{22}$ $+28{\cdot}4$ ($c = 0{\cdot}197$ H_2O-dimethylformamide (1·1); λ_{max}^{EtOH} 250 (infl), 290 mμ (ε 2990, 4480). (Found: C, 49·34; H, 5·04; N, 3·38. $C_{16}H_{19}O_3N{\cdot}CH_3I$ requires: C, 49·16; H, 5·34; N, 3·37%.) The mother liquors were concentrated to a small volume giving crude another product (23 mg) as prisms which afforded on recrystallization from EtOH pure XIX (8 mg), m.p. 291° (dec) as leaflets; $[\alpha]_D^{24}$ $-119{\cdot}7$ ($c - 0{\cdot}564$, MeOH); λ_{max}^{EtOH} 292·5 mμ (ε 4730). (Found: C, 49·30; H, 5·21; N, 3·42. $C_{16}H_{19}O_3N{\cdot}CH_3I$ requires: C, 49·16; H, 5·34; N, 3·37%.)

Quaternization of pluviine (XXIII) *with methyl iodide*

MeI (0·5 ml) was added to a soln of pluviine (50 mg) in abs MeOH (3 ml) and the mixture refluxed for 1·5 hr. Evaporation of the solvent gave 79 mg of a crystalline product, $[\alpha]_D^{24}$ $-83{\cdot}8°$ ($c = 0{\cdot}5$, H_2O), which was recrystallized from abs EtOH giving XXIV (44 mg), m.p. 259–260° (dec) as prisms. $[\alpha]_D^{22{\cdot}5}$ $-130{\cdot}5°$ ($c = 0{\cdot}410$, H_2O); λ_{max}^{MeOH} 284·5 mμ (ε 3650); (Ref 10, m.p. 260–261° (dec), $[\alpha]_D^{23}$ $-129°$). The mother liquor was evaporated to dryness under reduced press and the residue, $[\alpha]_D^{24}$ $+26{\cdot}7°$ ($c = 0{\cdot}5$, H_2O) was crystallized from acetone to give crude XXV (16 mg) as prisms, m.p. 225–227°. A pure sample recrystallized from MeOH had a m.p. of 230–232° as prisms; $[\alpha]_D^{22{\cdot}5}$ $+46{\cdot}7°$ ($c = 0{\cdot}960$, H_2O); λ_{max}^{MeOH} 283 mμ (ε 3570); (Ref. 10, m.p. 231–233°, $[\alpha]_D$ $+38{\cdot}2°$).

Quaternization of α-dihydropluviine (XXVI) *with methyl iodide*

Compound XXVI (23 mg), $[\alpha]_D$ $-109{\cdot}0°$ (Ref. 10, $[\alpha]_D$ $-87{\cdot}2°$) was refluxed in abs MeOH (0·5 ml) with MeI (0·8 ml) for 8 hr. Working up in a usual manner, trituration of the residue (34 mg), $[\alpha]_D$ $-28{\cdot}9°$ with MeOH and recrystallization from MeOH gave XXVII (24 mg), m.p. 138–140°. $[\alpha]_D^{24}$ $-31{\cdot}2°$ ($c = 0{\cdot}494$, H_2O); λ_{max}^{EtOH} 281 mμ (ε 3310); [Ref. 10, m.p. 136–139° (with H_2O), m.p. 231–233° (with ½ H_2O),

$[\alpha]_D$ −43·2°, −45·5°]. Moreover, Uyeo *et al.*[10] reported that reaction of XXVI with MeI gave another product, α-dihydropluviine α-methiodide, m.p. 223–224°, $[\alpha]_D$ −74·4°, but we could not obtain this product so far examined.

Catalytic reduction of pluviine β-methiodide (XXV) *over* PtO_2

Pluviine β-methiodide (50 mg) was hydrogenated in H_2O over Adams' catalyst for 2·5 hr. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced press. The residue (53 mg) was recrystallized twice from MeOH giving XXVII (26 mg), m.p. 140–141° as rods; $[\alpha]_D^{24}$ −30·7° (*c* = 0·920, H_2O). This was identical in all respects with XXVII obtained by direct quaternization of α-dihydropluviine.

Quaternization of β-dihydropluviine (XXVIII) *with methyl iodide*

A soln of XXVIII (50 mg) and MeI (0·25 ml) in abs MeOH (2 ml) was refluxed for 1·5 hr. Evaporation of the solvent gave 79 mg of white solid, $[\alpha]_D^{20}$ −99·4 (*c* = 1·04, MeOH), which was recrystallized several times from MeOH to give XXIX (30 mg) as prisms, m.p. 230–231° (dec); $[\alpha]_D^{20}$ −108·9° (*c* = 0·989, MeOH); λ_{max}^{EtOH} 284 mμ (ε 3610). (Found: C, 49·39; H, 5·89; N, 2·96. $C_{18}H_{26}O_3NI\cdot\frac{1}{2}H_2O$ requires: C, 49·09; H, 6·18; N, 3·18%.) Uyeo *et al.*[10] obtained β-dihydropluviine β-methiodide, m.p. 265–267°, $[\alpha]_D$ −30·7°, from β-dihydrolycorenine, but this could not be obtained in this reaction.

ORD, CD and UV spectra were measured with a JASCO model ORD/UV-5 instrument of the Japan Spectroscopic Co. Ltd., in MeOH soln using a cell of 1 mm width, unless otherwise stated. CD data are collected in Table 1.

Diacetyllycorine (VI)

ORD; $[\phi]_{400}$ +550°, $[\phi]_{302\cdot5}$ −2780° tr, $[\phi]_{270}$ +9260°, $[\phi]_{240}$ +19,200° sh, $[\phi]_{225}$ +35,630°. UV λ_{max} (ε); 292 (4760) and 237·5 mμ (3620).

Diacetyllycorine α-methiodide (VII). ORD; $[\phi]_{400}$ +120°, $[\phi]_{355}$ +200°, $[\phi]_{300}$ −2040° tr, $[\phi]_{260}$ +6650° pk, $[\phi]_{240}$ +4390°. UV λ_{max} (ε); 290 (5520) and 241 (infl) mμ (6700).

Diacetyllycorine β-methiodide (VIII). ORD; $[\phi]_{400}$ +1550°, $[\phi]_{294}$ +6790° pk, $[\phi]_{282}$ +5550° tr, $[\phi]_{261}$ +10,070° sh, $[\phi]_{235}$ +29,640°, $[\phi]_{220}$ +56,200°. UV λ_{max} (ε); 290 (4890) and 245 (infl) mμ (4600).

Dihydrolycorine (IX). ORD; $[\phi]_{400}$ −859°, $[\phi]_{325}$ −1969°, $[\phi]_{302}$ −4655° tr, $[\phi]_{278}$ −680° pk, $[\phi]_{259}$ −1862° tr, $[\phi]_{251}$ −1396° pk, $[\phi]_{230}$ −14,322° tr, $[\phi]_{225}$ −12,102°. UV λ_{max} (ε); 290·5 mμ (4730).

Dihydrolycorine α-methiodide (XIII). ORD in EtOH; $[\phi]_{350}$ −1220°, $[\phi]_{302}$ −4675° tr, $[\phi]_{295}$ −2846°, $[\phi]_{279}$ +1423° pk, $[\phi]_{260}$ +813° sh, $[\phi]_{240}$ −4736°.

Diacetyldihydrolycorine (XI). ORD; $[\phi]_{400}$ −1080°, $[\phi]_{303}$ −4800° tr, $[\phi]_{275}$ +1400° sh, $[\phi]_{260}$ +1000°, $[\phi]_{250}$ +1300° pk, $[\phi]_{233}$ −13,100° tr, $[\phi]_{220}$ −7090°. UV λ_{max} (ε); 292 (4930) and 233 (infl) mμ (4330).

Diacetyldihydrolycorine α-methiodide (XIV). ORD; $[\phi]_{400}$ −1460°, $[\phi]_{301}$ −5630 tr, $[\phi]_{274}$ +1620° pk, $[\phi]_{266}$ +1310° tr, $[\phi]_{257}$ +1790° pk, $[\phi]_{240}$ −6000°. UV λ_{max} (ε); 291 (5130), 240 (infl) (6400) and 220 mμ (18,980).

α-*Dihydrocaranine* (XXI). ORD; $[\phi]_{440}$ −340°, $[\phi]_{301\cdot5}$ −2790° tr, $[\phi]_{280}$ 0° pk, $[\phi]_{260-254}$ −840° sh, $[\phi]_{233\cdot5}$ −10,640° tr, $[\phi]_{218}$ −2570° pk, $[\phi]_{212}$ −10,000°.

α-*Dihydrocaranine β-methiodide* (XXII). ORD; $[\phi]_{380}$ −750°, $[\phi]_{325}$ −1174° tr, $[\phi]_{300}$ −864° pk, $[\phi]_{255}$ −2708° tr, $[\phi]_{235}$ −1370°. UV λ_{max} (ε); 288 mμ (5056).

β-*Dihydrocaranine* (XVIII). ORD; $[\phi]_{440}$ −210°, $[\phi]_{302}$ −6000° tr, $[\phi]_{275\cdot5}$ +3980° pk, $[\phi]_{248\cdot5}$ +4350° pk, $[\phi]_{233\cdot5}$ −8100° tr, $[\phi]_{221\cdot5}$ −750° pk, $[\phi]_{216}$ −3500°. UV λ_{max} (ε); 291·5 (4940) and 233 (sh) mμ (4000).

β-*Dihydrocaranine α-methiodide* (XIX). ORD; $[\phi]_{380}$ −1845°, $[\phi]_{301}$ −6270° tr, $[\phi]_{277}$ −896° pk, $[\phi]_{266\cdot5}$ −1765°, $[\phi]_{256}$ −2292° sh, $[\phi]_{245}$ −7273°, $[\phi]_{225}$ −16,140°. UV λ_{max} (ε); 290 mμ (4930).

β-*Dihydrocaranine β-methiodide* (XX). CD; $[\theta]_{307}$ 0°, $[\theta]_{292}$ −2009°, $[\theta]_{215}$ 0°. UV λ_{max} (ε); 289 (3284) and 220 mμ (11,279).

Pluviine (XXIII). ORD; $[\phi]_{380}$ −2535 , $[\phi]_{293\cdot5}$ −8576 tr, $[\phi]_{273}$ −4176 pk, $[\phi]_{240}$ −12,380 tr, $[\phi]_{227}$ −4030° pk, $[\phi]_{215}$ −16,830

Pluviine α-methiodide (XXIV). ORD; $[\phi]_{400}$ −260°, $[\phi]_{300}$ −3130°, $[\phi]_{294}$ −4340° tr, $[\phi]_{267}$ 0° pk, $[\phi]_{258}$ −1830° tr, $[\phi]_{240}$ +7110°. UV λ_{max} (ε); 285 mμ (4020).

Pluviine β-methiodide (XXV). ORD; $[\phi]_{400}$ +430°, $[\phi]_{290\cdot5}$ +3500° pk, $[\phi]_{274}$ +1170° tr, $[\phi]_{253}$ +2750° sh, $[\phi]_{230}$ +14,840°. UV λ_{max} (ε); 282·5 mμ (3620).

α-Dihydropluviine (XXVI). ORD; $[\phi]_{400}$ −837°, $[\phi]_{293}$ −3111° tr, $[\phi]_{247}$ 0° pk, $[\phi]_{225}$ −8201°. UV λ_{max} (ε); 282·5 mμ (4240).

α-Dihydropluviine β-methiodide (XXVII). ORD; $[\phi]_{400}$ −320°, $[\phi]_{305}$ −730° tr, $[\phi]_{291}$ −330° pk, $[\phi]_{260}$ −2260°, $[\phi]_{251}$ −3290 tr, $[\phi]_{240}$ 0°. UV λ_{max} (ε); 282·5 mμ (3870).

β-Dihydropluviine (XXVIII). ORD; $[\phi]_{400}$ −1060°, $[\phi]_{300}$ −5140°, $[\phi]_{295}$ −6400° tr, $[\phi]_{270}$ +900° pk, $[\phi]_{241}$ −7300° tr, $[\phi]_{225}$ 0° (a cell of 0·2 mm width).

β-Dihydropluviine α-methiodide (XXIX). ORD; $[\phi]_{400}$ −1260°, $[\phi]_{300}$ −3430°, $[\phi]_{293}$ −5160° tr, $[\phi]_{266}$ −3210° pk, $[\phi]_{255}$ −4300° tr, $[\phi]_{250}$ −3560°.

(−)-Anhydrolycorine methochloride. ORD in H_2O; $[\phi]_{270}$ −15,600°, $[\phi]_{248\cdot5}$ −3800° tr, $[\phi]_{229}$ +48,400° pk, $[\phi]_{220}$ +36,100°.

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