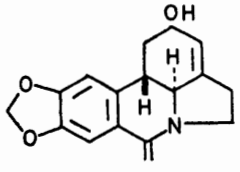
Total Synthesis of the Amaryllidaceae Alkaloids, Lycorine and Zephyranthine

By **Yoshisuke Tsuda,* Takehiro Sano, Jun'ichi Taga, Kimiaki Isobe,** and **Jun Toda,** Showa College of Pharmaceutical Sciences, Setagaya-ku, Tokyo, Japan
Shuzo Takagi,* Masae Yamaki, and **Mayumi Murata,** Faculty of Pharmaceutical Sciences, Mukogawa Women's University, Edagawa, Nishinomiya, Japan
Hiroshi Irie * and **Hirokazu Tanaka,** Faculty of Pharmaceutical Sciences, Kyoto University, Sakyo, Kyoto, Japan

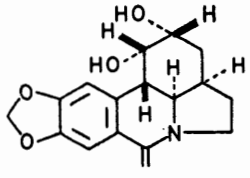
A synthesis of lycorine and zephyranthine was accomplished starting from 3,*r*-4,*c*-4a,5,6,*t*-10b-hexahydro-6-oxophenanthridine-4-carboxylic acid (VI). Homologation of the acid by the Arndt–Eistert reaction gave the homoester (VII), which was also obtained by cyclisation of methyl *c*-2-(*N*-methoxycarbonyl)-*t*-3-(3,4-methylenedioxyphenyl)cyclohex-4-enyl-*r*-acetate (VIII). Reduction of (VII) with lithium borohydride gave the alcohol (IX). After converting the alcohol function to the chloride and the lactam group to the imino-ether, the resulting imino-ether chloride was cyclised to *r*-3a,*c*-3b,4,5,7,*t*-11b-hexahydro-9,10-methylenedioxy-7-oxo-3*H*-pyrrolo-[3,2,1-*de*]phenanthridine (XI), which was alternatively obtained by lithium aluminium hydride reduction of 5,7-dioxo-3,*r*-3a,*c*-3b,4,5,*t*-11b-hexahydro-9,10-methylenedioxy-7*H*-pyrrolo[3,2,1-*de*]phenanthridine (XIV) under controlled conditions. Epoxidation of (XI) gave stereoselectively the α-oxide (XV). Repeated application of Sharpless' method to convert epoxide into allyl alcohol [using selenophenol on the 1,2-α-oxide (XV) and 1-acetyl-2,3-β-oxide (XXIV)] gave the lycorine lactam (XXV). Lithium aluminium hydride reduction of the diacetyllycorine lactam gave lycorine. Osmium tetraoxide treatment of (XI) gave two stereoisomeric glycols, one of which yielded, on lithium aluminium hydride reduction, zephyranthine.

THERE have been many reports [1] on the total synthesis of lycorine (Ia) [2] (a = optically active), the most abundant alkaloid of Amaryllidaceae species. We describe in detail our synthesis of this alkaloid and the related alkaloid, zephyranthine (II).[3]

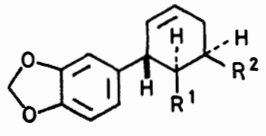
In a previous report,[4] we indicated that cyclisation of



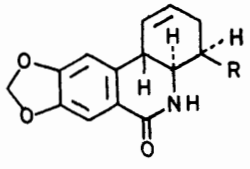
(I)



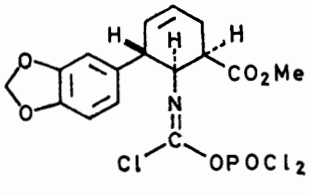
(II)



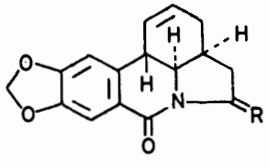
(III) R^1 = $NHCO_2Me$, R^2 = CO_2Me
(V) R^1 = N=C=O, R^2 = CO_2Me
(VIII) R^1 = $NHCO_2Me$, R^2 = CH_2CO_2Me



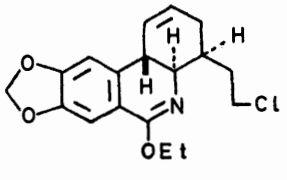
(IV) R = CO_2Me
(VI) R = CO_2H
(VII) R = CH_2CO_2Me
(IX) R = CH_2CH_2OH
(X) R = CH_2CH_2Cl
(XIII) R = CH_2CO_2H



(A)



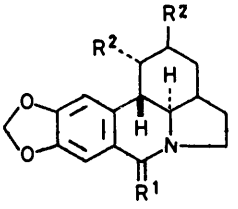
(XI) R = H_2
(XIV) R = O

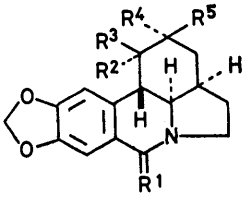


(XII)

the isocyanate (V) with tin(IV) chloride in methylene chloride gave the lactam (IV) in acceptable yield when the reaction was carried out on a small scale. However, the reaction did not always give reproducible results on a large scale. On the other hand, treatment of the urethane-ester (III) with phosphoryl chloride followed by tin(IV) chloride in methylene chloride gave the lactam (IV) in 60% yield. From checking the cyclisation mixture by t.l.c. before adding tin(IV) chloride, we realised that the isocyanate (V) [4] was formed. This suggested that phosphoryl chloride played an important part in the cyclisation of the urethane-ester not only as the reagent for elimination of methanol from the urethane to give the isocyanate but also as a reagent for the formation of an intermediate easily cyclised to the lactam on treatment with tin(IV) chloride. When the isocyanate (V), derived from the half-ester (VI) under Curtius condition,[4] was treated with tin(IV) chloride in the presence of phosphoryl chloride, the lactam (IV) was obtained in reproducible and good yield even on a large scale. We propose the intermediate (A) as a plausible activated species.[5] Hydrolysis of the lactam (IV) gave the corresponding acid (VI). Attempts to convert the acid into the lactam-homoester (VII) under Arndt–Eistert conditions did not give reproducible results because the acid chloride and the diazo-ketone derived from the acid were weakly soluble in the usual solvent for the homologation reaction. However, cyclisation of the urethane-homoester (VIII) [6] with phosphoryl chloride followed by tin(IV) chloride as for cyclisation of the urethane-ester (III) yielded the lactam-homoester (VII) smoothly.

The lactam-homoester (VII) was transformed into the alcohol (IX) by treatment with lithium borohydride in 90% yield. Attempts to obtain the tosylate of the alcohol (IX) in the usual manner resulted in formation of the chloride (X). The chloride was quantitatively obtained by treatment of the alcohol (IX) with thionyl chloride. Attempts to convert the chloride to the tetracyclic lactam (XI) were unsuccessful, despite trials with several bases, sodium hydride, potassium t-butoxide, *etc.*, under a variety of conditions. In contrast to these disappointing results, the cyclisation was eventually accomplished by treatment of the imino-ether chloride (XII), obtained from the chloride by treatment with a Meerwein reagent, with triethylamine in dimethylformamide giving the required tetracyclic lactam (XI) in good yield. After this successful synthesis we found an alternative and convenient route to the same compound from the lactam-homoester (VII). Hydrolysis of the lactam-homoester (VII) in acetic acid and dilute hydrochloric acid gave the acid (XIII), which was easily cyclised to the imide (XIV) with acetic anhydride. Lithium aluminium hydride reduction of the imide in ether at 0° for 1 h furnished the tetracyclic lactam (XI) in 75% yield. Although prolongation of the reaction time and elevation of the reaction temperature did not give good results, the reaction was a convenient method for preparation of the tetracyclic lactam (XI), when the reaction conditions were strictly controlled.





(XXV) $R^1 = O; R^2 = OH$
(XXVI) $R^1 = O; R^2 = OAc$
(XXVII) $R^1 = H_2; R^2 = OAc$

(XVI) $R^1 = O; R^3 = R^4 = H; R^2 = R^5 = OH$
(XVII) $R^1 = O; R^3 = R^4 = H; R^2 = OH; R^5 = OTs$
(XVIII) $R^1 = H_2; R^3 = R^4 = R^5 = H; R^2 = OH$
(XIX) $R^1 = O; R^3 = R^4 = H; R^2 = OH; R^5 = Cl$
(XX) $R^1 = H_2; R^3 = R^4 = H; R^2 = R^5 = OH$
(XXI) $R^1 = O; R^3 = R^4 = H; R^2 = OH; R^5 = SePh$
(XXVIII) $R^1 = O; R^2 = R^4 = OH; R^3 = R^5 = H$
(XXIX) $R^1 = O; R^2 = R^4 = H; R^3 = R^5 = OH$
(XXX) $R^1 = O; R^2 = R^4 = OAc; R^3 = R^5 = H$
(XXXI) $R^1 = O; R^2 = R^4 = H; R^3 = R^5 = OAc$

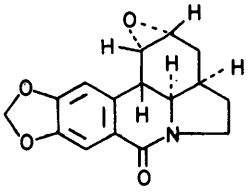
Oxidation of the tetracyclic lactam (XI) with *m*-chloroperbenzoic acid in methylene chloride gave the oxide (XV) as the sole product.

In order to have substantial supplies of the oxide and to confirm the stereochemistry of the oxide ring, a synthesis of compound (XVa) from lycorine was performed. Tosylation of dihydrolycorine lactam (XVIa) gave the monotosylate (XVIIa). Treatment of the tosylate with sodium acetate [7] in methanol resulted in removal of toluene-*p*-sulphonic acid to give the oxide (XVa) whose n.m.r. and i.r. spectra were identical with those of the racemic oxide (XV). Hydrolysis of the oxide (XVa) with dilute sulphuric acid in aqueous dioxan regenerated dihydrolycorine lactam [8] and lithium aluminium hydride reduction resulted in formation of α-dihydrocaranine (XVIIIa),[9] indicating an α-configur-

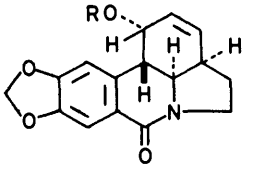
ation of the oxide ring in (XV) and (XVa). When the oxide (XVa) was treated with hydrogen chloride, it yielded the chlorohydrin (XIXa). Reduction of the chlorohydrin with zinc in acetic acid gave the lactam (XIa). This lactam (XIa) was spectroscopically identical with the racemic lactam (XI). Ring c is compelled to have a boat conformation. Stereoselective formation of the α-oxide by oxidation with peracid can be rationalised as due to steric interference by the two allylic axial β-hydrogens of the approach of the peracid.

Lithium aluminium hydride reduction of dihydrolycorine lactam (XVI), derived from the racemic oxide (XV) by treatment with dilute sulphuric acid, afforded (±)-dihydrolycorine (XX), providing an efficient synthetic route of this compound.

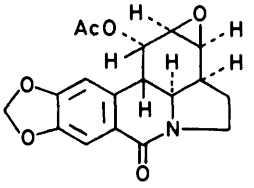
Now, we were in a position to complete the alignment of the functional groups in ring c of lycorine. The required arrangement of a glycol and an olefinic bond in lycorine was introduced by the method of Sharpless and his co-workers.[10] Thus, the oxide (XVa) was subjected to nucleophilic ring opening with diphenyl diselenide and sodium borohydride to give the hydroxy-selenide (XXIa). Oxidative removal of the phenylseleno-group was accomplished by oxidation with sodium periodate, which gave, in this case, a better yield of the alcohol (XXIIa) than did hydrogen peroxide, the reagent used in the original report. Acetylation of the alcohol (XXIIa) gave the acetate (XXIIIa) which was subjected



(XV)



(XXII) R = H
(XXIII) R = Ac



(XXIV)

sequentially to oxidation, selenide formation, and oxidative elimination. Thus, oxidation of the acetate (XXIIIa) with *m*-chloroperbenzoic acid gave the β-oxide (XXIVa) as the sole product. The β-configuration of the oxide ring in (XXIVa) was predicted from the steric interference by the acetoxy-group of the reagent and ultimately proved by our success in synthesising lycorine. The oxide (XXIVa) was treated with diphenyl diselenide and sodium borohydride followed by sodium periodate to give lycorine lactam (XXVa) in 40% yield. During the course of these reactions, the *O*-acetyl group at C-1 was hydrolysed. Since the newly formed glycol system in lycorine lactam has a *trans*-diaxial orientation, sodium periodate had no effect on this system in the short period of the reaction. Acetylation of lycorine lactam gave diacetyl-lycorine lactam (XXVIa) which was identical in all respects with diacetyl-lycorine lactam derived from diacetyl lycorine (XXVIIa) by a carefully controlled oxidation with potassium permanganate. Lithium aluminium hydride reduction of the diacetate (XXVIa) in tetrahydrofuran furnished lycorine, accomplishing a total synthesis of this alkaloid. After we had completed the relay synthesis, we repeated the sequence using the racemic oxide (XV). Since the final product, (±)-lycorine was barely soluble in the usual organic solvents, our success in the synthesis of (±)-lycorine (I) was confirmed by i.r. spectral comparison of its diacetate (XXVII) with diacetyl-lycorine (XXVIIa).

As a further part of our studies of the synthesis of Amaryllidaceae alkaloids, we performed a straightforward synthesis of (±)-zephyranthine (II) using as the key intermediate, the lactam (XI); zephyranthine (IIa) has also been obtained from lycorine by Ozeki.[3] Treatment of the lactam (XI) with osmium tetraoxide in pyridine gave two stereoisomeric glycols (XXVIII) and (XXIX) in 35 and 15% yield, respectively, both of which were isolated as their diacetates (XXX) and (XXXI). The mass spectra of the two acetates were virtually identical, indicating that they were stereoisomeric. The major product (XXX) gave (±)-zephyranthine (II) on lithium aluminium hydride reduction in tetrahydrofuran. N.m.r. and i.r. spectra of the latter were superimposable upon those of the natural product.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto microscopic hot-stage apparatus and uncorrected. Unless otherwise stated i.r. spectra were measured for dispersions in Nujol using a Shimazu IR-27G spectrometer and n.m.r. spectra were recorded in deuteriochloroform with tetramethylsilane as an internal reference with a Varian A-60 spectrometer. Mass spectra were taken with a Hitachi RMU-60M spectrometer with a heated direct inlet system.

Arndt–Eistert Reaction of the Lactam Acid (VI).—A solution of the lactam acid (VI) (2 g) and thionyl chloride (4 ml) in benzene (60 ml) was heated under reflux for 2 h. Removal of the solvent under reduced pressure gave a residue. A suspended solution of the residue in benzene (80 ml) was added to an ethereal solution of diazomethane [prepared from *N*-methyl-*N*-nitroso-*p*-tosyl amide (40 g)] and the whole was stirred overnight. Evaporation of the solvent gave a residue which was taken up in methanol (80 ml). Silver oxide (4 g) was added to the solution at 40° and the mixture was stirred overnight and filtered. The filtrate was concentrated to dryness to leave an oily residue which was chromatographed on silica gel in chloroform. Elution with the same solvent gave *methyl 8,9-methylenedioxy-6-oxo-3,4,4a,5,6,10b-tetrahydrophenanthridin-4-yl-acetate* (VII) (1.4 g, 64%) which crystallised from chloroform–methanol as leaflets, m.p. 227—230°, $\nu_{max.}$ 3 400, 1 740, and 1 640 cm^{-1} (Found: C, 64.7; H, 5.3; N, 4.2%; M^+, 315. $C_{17}H_{17}NO_5$ requires C, 64.8; H, 5.4; N, 4.2%; M^+, 315).

Cyclisation of the Urethane-homoester (VIII).—A mixture of the urethane-homoester (VIII) (1 g) and phosphoryl chloride (3 ml) was refluxed for 2 h and cooled to 0°, and to the mixture was added tin(IV) chloride (0.34 ml) and the whole was stirred for 1 h, and evaporated to dryness to leave a residue which was taken up in chloroform. The chloroform solution was washed with water, dried, and evaporated to dryness to give the lactam-homoester (VII) (870 mg, 96%), m.p. 230—231°, identical with the sample of (VII) obtained from the lactam acid (VI).

Reduction of the Lactam-homoester (VII).—Lithium borohydride (1.5 g) was added to a solution of the lactam-homoester (VII) (2.4 g) in tetrahydrofuran (600 ml) and the mixture was heated under reflux with stirring. The usual work-up gave the *alcohol* (IX) (2 g, 92%) which crystallised from chloroform–methanol as needles, m.p. 258—260°, $\nu_{max.}$ 3 400 and 3 150 (NH and OH) and 1 660 cm^{-1} (CO) (Found: C, 66.6; H, 6.0; N, 4.8%; M^+, 287. $C_{16}H_{17}NO_4$ requires C, 66.9; H, 6.0; N, 4.9%; M^+, 287).

Chlorination of the Alcohol (IX).—A solution of the alcohol (IX) (2 g), thionyl chloride (6 ml), and pyridine (1 ml) in benzene (500 ml) was heated under reflux for 40 min. Removal of the solvent under reduced pressure gave a residue which was taken up in chloroform. The chloroform solution was washed with dilute hydrochloric acid, aqueous sodium carbonate, and water, dried, and concentrated to dryness to give a residue which was chromatographed on silica gel in chloroform. Elution with the same solvent gave the chloride (X) (1.5 g, 70%) as needles (from acetone), m.p. 237—240°, $\nu_{max.}$ 3 140 (NH) and 1 670 cm^{-1} (CO) (Found: C, 62.5; H, 5.3; N, 4.4%; M^+, 305. $C_{16}H_{16}ClNO_3$ requires C, 62.8; H, 5.3; N, 4.6%; M^+, 305).

Cyclisation of the Chloride (X) *to the Tetracyclic Lactam* (XI).—A mixture of the chloride (X) (1.2 g) and triethyloxonium fluoroborate (Meerwein reagent) (1 mol equiv.) in dry methylene chloride (100 ml) was refluxed for 4 h and the solution was washed with 5N-potassium carbonate and water, dried, and evaporated to dryness to leave a residue (1.4 g). A solution of the residue and triethylamine (2 ml) in dimethylformamide (50 ml) was refluxed under nitrogen for 2 h. The solution was poured into water and extracted with methylene chloride. The extract was washed with water, dried, and evaporated to dryness to leave a residue which was chromatographed on alumina in methylene chloride. Elution with the same solvent gave 3a,3b,4,5,7,-11b-*hexahydro*-9,10-*methylenedioxy*-7-*oxo*-3H-*pyrrolo*[3,2,1-de]*phenanthridine* (XI) (740 mg, 83%) as needles (from ethanol), m.p. 126—128°, $\nu_{max.}$ 1 640 cm^{-1} (CO), δ 5.98 (2 H, s, OCH_2O), 6.23 (2 H, m, olefinic H), 6.86 and 7.50 (1 H each, s, aromatic H) (Found: C, 71.3; H, 5.5; N, 5.0%; M^+, 269. $C_{16}H_{15}NO_3$ requires C, 71.4; H, 5.6; N, 5.2%; M^+, 269).

Imide (XIV) *from the Lactam-homoester* (VII).—A solution of the lactam-homoester (VII) (2.12 g) in 5% hydrochloric acid (30 ml) and acetic acid (30 ml) was refluxed for 20 min and evaporated. The resulting residue was, without further purification, heated in acetic anhydride (50 ml) on a water-bath for 2 h. Removal of the solvent gave a residue which was chromatographed on silica gel in benzene. Elution with chloroform gave the *imide* (XIV) (1.56 g, 82%) which crystallised from chloroform–methanol as needles, m.p. 263—264°, $\nu_{max.}$ 1 750 and 1 650 cm^{-1} (CO) (Found: C, 67.7; H, 4.4; N, 4.9%; M^+, 283. $C_{16}H_{13}NO_4$ requires C, 67.8; H, 4.6; N, 5.0%; M^+, 283).

Partial Reduction of the Imide (XIV) *with Lithium Aluminium Hydride*.—A suspended solution of the imide (XIV) (150 mg) and lithium aluminium hydride (150 mg) in ether (300 ml) was stirred at 0° for 1 h. The usual work-up gave a residue which was chromatographed on alumina in benzene. Elution with methylene chloride gave the tetracyclic lactam (XI) (105 mg) identical with the tetracyclic lactam obtained from the chloride (X).

Oxidation of the Tetracyclic Lactam (XI) *with* m-*Chloroperbenzoic Acid*.—A solution of the tetracyclic lactam (XI) (250 mg) and *m*-chloroperbenzoic acid (320 mg) in methylene chloride (30 ml) was stirred at 5° overnight. The solution was washed with 5% potassium carbonate and water, dried, and evaporated to dryness to leave the α-*epoxide* (XV) (251 mg) which crystallised from methylene chloride–acetone as needles, m.p. 254—255°, $\nu_{max.}$ 1 640 cm^{-1} (CO), δ 6.01 (2 H, s, OCH_2O) and 7.00 and 7.53 (1 H, each, s, aromatic H) (Found: C, 67.4; H, 5.5; N, 4.9%; M^+, 285. $C_{16}H_{15}NO_4$ requires C, 67.4; H, 5.3; N, 4.9%; M^+, 285).

(±)-*Dihydrolycorine* (XX).—A solution of the α-epoxide (XV) (50 mg) in 10% sulphuric acid (3 ml) and dioxan (3 ml) was heated under reflux for 30 min. After cooling, the crystals deposited were recrystallised from methanol to give dihydrolycorine lactam (XVI) (30 mg) as needles, m.p. 270°. Lithium aluminium hydride reduction of dihydrolycorine lactam (25 mg) in tetrahydrofuran (10 ml) gave dihydrolycorine (XX) (10 mg) as prisms (from acetone), m.p. 249—253°. Its diacetate, m.p. 177—180°, was identical (i.r.) with an authentic sample derived from lycorine (Ia).

(±)-α-*Dihydrocaranine* (XVIII).—A mixture of the foregoing α-epoxide (XV) (30 mg) and lithium aluminium hydride (30 mg) in tetrahydrofuran (10 ml) was refluxed for 2 h. The usual work-up gave (±)-α-dihydrocaranine (XVIII) (15 mg) as prisms (from acetone), m.p. 182°, identical with an authentic sample.[9]

α-*Epoxide* (XVa) *from Dihydrolycorine Lactam* (XVIa).—Dihydrolycorine lactam (XVIa) (445 mg) in pyridine (40 ml) was treated with toluene-*p*-sulphonyl chloride (2.2 g) for 19 h at room temperature. The solvent was removed under reduced pressure and a residue was taken up in methylene chloride. The solution was washed with 5% hydrochloric acid and water, dried, and evaporated to yield the monotosylate (XVIIa). Without further purification, the monotosylate was treated with anhydrous sodium acetate (2 g) in methanol (40 ml) under reflux for 1 h. After evaporation of the solvent, the residue was extracted with methylene chloride and the extract was washed with water, dried, and evaporated to yield the α-epoxide (XVa) (250 mg), m.p. 275—276°, identical with the racemic α-epoxide (XV). Treatment of the α-epoxide (XVa) (30 mg) with 10% sulphuric acid (6 ml) and dioxan (6 ml) gave dihydrolycorine lactam.

Lactam (XIa) *from the* α-*Epoxide* (XVa).—A solution of the α-epoxide (XVa) (100 mg) in 10% hydrochloric acid (10 ml) and methanol (60 ml) was heated under reflux for 30 min. The solvent was evaporated to leave the chlorohydrin (XIXa). To a boiling solution of the crude chlorohydrin in acetic acid (15 ml) was added zinc powder (4 g) in four portions over 40 min. After refluxing for 1 h, the mixture was cooled and filtered. The filtrate was evaporated to dryness to give a residue which was taken up in methylene chloride. The solution was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated to leave a residue (115 mg) which was chromatographed on alumina in benzene. Elution with the same solvent gave the lactam (XIa), m.p. 125—130°, spectro-

scopically identical with the racemic lactam (XI). The lactam (XIa) was reconverted into the α-epoxide (XVa) by oxidation with *m*-chloroperbenzoic acid.

Conversion of the α-Epoxide (XVa) *to the Allyl Alcohol* (XXIIa).—To a suspension of the α-epoxide (XVa) (100 mg) and diphenyl diselenide (655 mg) in ethanol (15 ml), sodium borohydride (20 mg) was, with stirring, added under argon. The mixture was refluxed for 1 h, cooled, and filtered. The filtrate was evaporated to leave the hydroxy-selenide (XXIa) (135 mg). The crude hydroxy-selenide (65 mg) was treated with sodium periodate (57 mg) in ethanol (5 ml) at room temperature, then warmed at 40—45° for 2 h, and filtered. The filtrate was warmed at 50° for a further 6 h and evaporated. The residue was dissolved in methylene chloride. The solution was washed with 10% sodium hydrogencarbonate and water, dried, and concentrated to leave a residue which was chromatographed on alumina. Elution with methylene chloride gave the allyl alcohol (XXIIa) (36 mg) as needles, m.p. 268—271° (from methanol), $\nu_{max.}$ 3 280 (OH) and 1 640 cm^{-1} (CO). Treatment of the allyl alcohol with acetic anhydride–pyridine gave the acetate (XXIIIa) as prisms, m.p. 205—206° (from methanol), δ 2.02 (3 H, s, $COCH_3$), 6.05 (2 H, s, OCH_2O), 6.17 (2 H, m, olefinic H), and 6.62 and 7.55 (1 H each, s, aromatic H). The *acetate* (XXIII) forms prisms, m.p. 198—200° (from methanol), $\nu_{max.}$ 1 730 and 1 640 cm^{-1} (CO) (Found: C, 65.8; H, 5.2; N, 4.1%; M^+, 327. $C_{18}H_{17}NO_5$ requires C, 66.1; H, 5.2; N, 4.3%; M^+, 327).

Oxidation of the Acetate (XXIIIa).—The acetate (XXIIIa) (350 mg) was treated with *m*-chloroperbenzoic acid (735 mg) in chloroform (30 ml) at room temperature for 5 days. Work-up in the same manner as for the α-epoxide (XVa) gave the β-epoxide (XXIVa) (337 mg) as prisms, m.p. 141—142° (from acetone), δ 2.07 (3 H, s, $COCH_3$), 6.00 (2 H, s, OCH_2O), and 6.55 and 7.47 (1 H each, s, aromatic H). The *epoxide* (XXIV) forms prisms, m.p. 240—241° (from acetone), $\nu_{max.}$ 1 740 and 1 640 cm^{-1} (CO) (Found: C, 63.1; H, 5.0; N, 4.0%; M^+, 343. $C_{18}H_{17}NO_6$ requires C, 63.0; H, 5.0; N, 4.1%; M^+, 343).

Lycorine Lactam (XXVa) *from the β-Epoxide* (XXIVa).—Treatment of the β-epoxide (XXIVa) (135 mg) with diphenyl diselenide (74 mg) and sodium borohydride (20 mg) followed by sodium periodate (422 mg) as for the α-epoxide gave lycorine lactam (XXVa) (53 mg) as prisms, m.p. 275° (from ethanol). The diacetate (XXVIa) forms prisms from methanol, m.p. 114 and >300°, $\nu_{max.}$ 1 745, 1 735, and 1 645 cm^{-1} (CO), δ 2.02 and 2.08 (3 H, each, s, $COCH_3$), 5.25 (1 H, m, C*H*OAc), 5.55 (1 H, m, olefinic H), 5.68 (1 H, m, C*H*OAc), 5.95 (2 H, s, OCH_2O), and 6.60 and 7.45 (1 H, each, s, aromatic H). spectroscopically identical with an authentic specimen (see below). Compounds (XXV) and (XXVI) form prisms, m.p. 275 and 197°, respectively.

Diacetyl-lycorine Lactam (XXVIa) *from Diacetyl-lycorine* (XXVIIa).—A suspended solution of diacetyl-lycorine (XXVIIa) (100 mg), magnesium sulphate (100 mg), and potassium permanganate (200 mg) in acetone (40 ml) and water (20 ml) was stirred at room temperature for 40 s. The solution was poured into aqueous sodium hydrogensulphite and extracted with methylene chloride. The extract was washed with water, dried, and evaporated to dryness to leave a residue which was chromatographed on alumina in chloroform. Elution with the same solvent gave diacetyl-lycorine lactam (XXVIa) (10 mg) as prisms, m.p. 114 and >300°, *m/e* 385 (M^+).

Lycorine (Ia).—Diacetyl-lycorine lactam (XXVIa) (47 mg) was refluxed with a large excess of lithium aluminium hydride in tetrahydrofuran. The usual work-up gave lycorine (Ia) (15 mg), which gave diacetyl-lycorine (XXVIIa), m.p. 207—213°. Compound (I) forms prisms, m.p. 245—247° (from ethanol), and (XXVII) forms needles, m.p. 233—235° (from methanol), $\nu_{max.}$ 1 735 cm^{-1} (CO), δ 1.93 and 2.06 (3 H, each, s, $COCH_3$), 3.51 and 4.16 (1 H, each, d, *J* 15 Hz, benzylic H), 5.30 (1 H, m, C*H*OAc), 5.53 (1 H, m, olefinic H), 5.75 (1 H, m, C*H*OAc), 5.93 (2 H, s, OCH_2O), 6.60 and 6.78 (1 H, each, s, aromatic H) (Found: C, 64.4; H, 5.7; N, 3.6%; M^+, 371. $C_{20}H_{21}NO_6$ requires C, 64.7; H, 5.7; N, 3.8%; M^+, 371).

(±)-*Diacetylzephyranthine Lactam* (XXX).—A solution of the lactam (XI) (800 mg) and osmium tetraoxide (1 g) in pyridine (50 ml) was stirred at room temperature overnight. Sodium hydrogensulphite (2.25 g), pyridine (25 ml), and water (66 ml) were added to the mixture. The whole was stirred for 1 h and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated under reduced pressure to leave a residue which was, without further purification, treated with acetic anhydride and pyridine. The usual work-up gave a residue which was chromatographed on silica gel in chloroform. The first elution with the same solvent gave a crystalline residue. Fractional recrystallisation of the residue from chloroform–methanol gave (±)-diacetylzephyranthine lactam (XXX) (110 mg) as needles, m.p. >300°, $\nu_{max.}$ 1 740 and 1 640 cm^{-1} (CO), δ 2.03 and 2.06 (3 H each, s, $COCH_3$), 5.08 and 5.91 (1 H each, m, C*H*OAc), 6.00 (2 H, s, OCH_2O) 6.58 and 7.43 (1 H each, s, aromatic H) (Found: C, 61.8; H, 5.3; N, 3.5%; M^+, 387. $C_{20}H_{21}NO_7$ requires C, 62.0; H, 5.5; N, 3.6%; M^+, 387), identical with authentic specimen obtained from natural zephyranthine in n.m.r. spectrum comparison. From the mother liquor of the above recrystallisation, the isomer (XXXI) (10 mg) was obtained as prisms, m.p. 243—250°, M^+, 387.

(±)-*Zephyranthine* (II).—A suspended solution of diacetylzephyranthine lactam (XXX) (95 mg) and lithium aluminium hydride (120 mg) in tetrahydrofuran (20 ml) was refluxed for 3 h. The product was chromatographed on silica gel. Elution with chloroform–methanol (1 : 1) gave (±)-zephyranthine (II) (45 mg) as needles, m.p. 224—225°, $\nu_{max.}$ 3 500—3 100 cm^{-1} (OH), *m/e* 285 (M^+), identical n.m.r. spectrum with that of zephyranthine (IIa). Its diacetate formed needles, m.p. 143—145° (from acetone) (Found: C, 64.0; H, 6.1; N, 3.7%; M^+, 373. Calc. for $C_{20}H_{23}NO_6$: C, 64.3; H, 6.2; N, 3.8%; M^+, 373), also identical with diacetylzephyranthine (IIa) in i.r. and n.m.r. spectra and t.l.c. behaviour.

[8/1178 *Received*, 26*th June*, 1978]

REFERENCES

[1] J. B. Hendrickson, R. W. Alder, D. R. Dalton, and D. G. Hey, *J. Org. Chem.*, 1969, **34**, 2667; H. Irie, Y. Nishitani, M. Sugita. and S. Uyeo, *Chem. Comm.*, 1970, 1313; H. Irie, Y. Nishitani, M. Sugita, and S. Uyeo, *J. Pharm. Soc. Japan*, 1976, **96**, 631; B. Ganem, *Tetrahedron Letters*, 1971, 4105; S. F. Dyke, M. Sainsbury. and J. R. Evans, *Tetrahedron*, 1973, **29**, 213; K. Torssell, *Tetrahedron Letters*, 1974, 723; H. Iida. S. Aoyagi, and C. Kibayashi. *J.C.S. Chem. Comm.*, 1974. 499; B. Umezawa, O. Hoshino, S. Sawaki. S. Sato. and N. Numao. *J. Org. Chem.*, 1977, **42**, 4272.

[2] W. C. Wildman, 'The Alkaloids,' ed. R. H. F. Manske. Academic Press, New York, 1968, vol. XI, p. 307.

[3] S. Ozeki. *Chem. Pharm. Bull. Japan*, 1964, **12**, 253; *J. Pharm. Soc. Japan*, 1964, **89**, 1194; 1965, **85**, 200.

[4] H. Tanaka, Y. Nagai, H. Irie. S. Uyeo, and A. Kuno, *J.C.S. Perkin I*, 1979, 874.
[5] Y. Tsuda, K. Isobe, J. Toda, and J. Taga, *Heterocycles*. 1976, **5**, 157.
[6] H. Tanaka, H. Irie, S. Baba, S. Uyeo, A. Kuno, and Y. Ishiguro, *J.C.S. Perkin I*, 1979, 535.
[7] K. Takada, K. Kotera, S. Mizukami, and M. Kobayashi, *Chem. Pharm. Bull. Japan*, 1960, **8**, 483 (these authors used potassium acetate in the place of sodium acetate).
[8] K. Wiesner, W. I. Taylor, and S. Uyeo, *Chem. and Ind.*, 1954, 46.
[9] E. W. Warnhoff and W. C. Wildman, *J. Amer. Chem. Soc.*, 1957, **79**, 2192.
[10] K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, 1973, **95**, 2697.