Synthesis of the Amaryllidaceae Alkaloid, Lycorine

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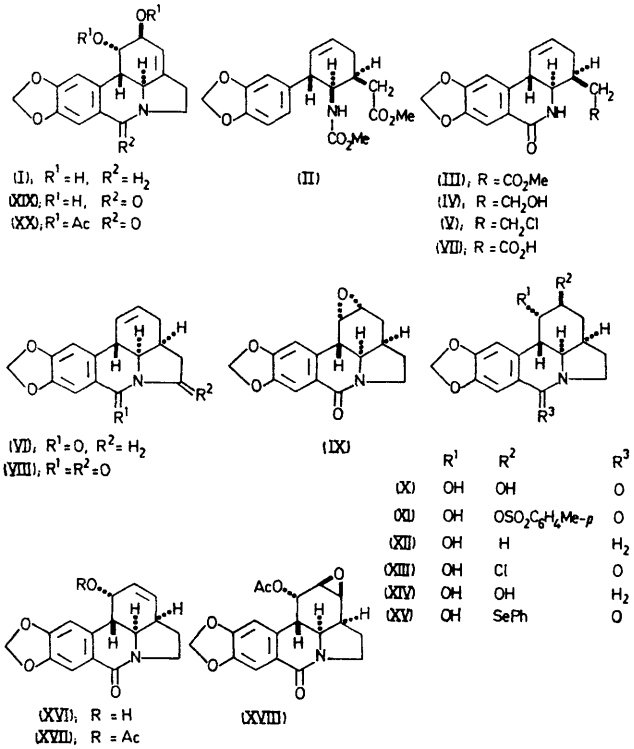
Summary A key intermediate for the total synthesis of lycorine has been prepared in racemic form; the optically pure form of this epoxylycorinane lactam, obtained from lycorine, has been reconverted into the alkaloid.

THERE have been many reports[1] on the synthesis of lycorine (I), the commonest alkaloid occurring in Amaryllidaceae plants. In connection with our synthetic work[2] on Amaryllidaceae alkaloids, we now report the synthesis of lycorine starting from the racemic urethane-ester (II).[2b]

Treatment of (II) with $POCl_3$ followed by $SnCl_4$ (1 mol. equiv.) in CH_2Cl_2 gave the lactam (III), 60%, m.p. 226—229 °C, ν_{max} 1660 and 1608 cm^{-1}, which was smoothly reduced to the alcohol (IV), 50%, m.p. 258—260 °C, with $LiAlH_4$ followed by $NaBH_4$ in tetrahydrofuran. An attempt to convert (IV) into its *O*-tosylate with tosyl chloride in pyridine gave instead the chloride (V), 85%, m.p. 233—234 °C. Treatment of (V) with triethyloxonium fluoroborate gave an imino-ether which cyclised on heating with Et_3N in $HCONMe_2$ at 130 °C for 6 h under argon to give the tetracyclic lactam (VI), 68%, ν_{max} 1640 cm^{-1}. Compound (VI) was also obtained by an alternative route in better yield: the lactam-ester (III) was hydrolysed by 5% HCl–AcOH to the acid (VII), m.p. 270—276 °C, which cyclised on heating with acetic anhydride to give the imide (VIII), 95% [from (III)], m.p. 260—262 °C, ν_{max} 1753, 1650, and 1608 cm^{-1}. Reduction of (VIII) with $LiAlH_4$ under strictly controlled conditions (Et_2O, 0 °C, 1 h) gave (VI), 80%. Oxidation of (VI) with *m*-chloroperbenzoic acid in CH_2Cl_2 gave the epoxide (IX), m.p. 252—253 °C, as the sole product.

The optically active oxide (IX) and the lactam (VI) were available in good quantities from natural lycorine. Thus, treatment of dihydrolycorine lactam (X) with tosyl chloride in pyridine gave the monotosylate (XI) which was smoothly converted by treatment with NaOAc into the α-epoxide (IX), m.p. 275—276 °C, $[\alpha]_D^{23}$ −216 ° (*c* 7·2 × 10^{-3} in $CHCl_3$), which was identical with the synthetic product (IX) in all respects except m.p. and optical rotation.



	R¹	R²	R³
(X)	OH	OH	O
(XI)	OH	$OSO_2C_6H_4Me$-p	O
(XII)	OH	H	H_2
(XIII)	OH	Cl	O
(XIV)	OH	OH	H_2
(XV)	OH	SePh	O

Compound (IX) was reduced with $LiAlH_4$ to give α-dihydrocaranine (XII),[3] m.p. 171—172 °C, thus confirming the configuration of epoxide ring and hence the structure of the oxidation product of the lactam (VI). When heated with 1·5% HCl in MeOH, the epoxide (IX) gave the chlorohydrin (XIII), which furnished the lactam (VI) on reduction with Zn and AcOH.

On treatment with 5% H_2SO_4 in dioxan the epoxide (IX) regenerated dihydrolycorine lactam (X) which was reduced with $LiAlH_4$ to dihydrolycorine (XIV).

Lycorine was synthesised from the optically active epoxide (IX). The oxide (IX) was treated with diphenyl diselenide and $NaBH_4$ in ethanol for 1 h to give the hydroxyselenide (XV), m.p. 240—242 °C, which was converted into the alcohol (XVI), 70% [from (IX)] m.p. 268—271 °C, by oxidation with $NaIO_4$ in place of the H_2O_2 reported originally.[4] Acetylation of (XVI) gave the acetate (XVII), m.p. 207—210 °C, which was oxidised with *m*-chloroperbenzoic acid to give the β-epoxide (XVIII), 80%, m.p. 141—142 °C. Treatment of the oxide (XVIII) with diphenyl diselenide, $NaBH_4$, and $NaIO_4$ in the same manner as in the case of the oxide (IX) furnished the lycorine lactam (XIX), 40%, m.p. 287—290 °C (decomp.), ν_{max} 1640 cm^{-1}; the acetyl group was hydrolysed during the reaction. Reduction of the diacetate (XX) with $LiAlH_4$ gave lycorine (I).

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