A Total Synthesis of Dihydrolycorine, Hydrogenation Product of the Alkaloid Lycorine

By HIROSHI IRIE, YASUHIRO NISHITANI, MINORU SUGITA, and SHOJIRO UYEO*

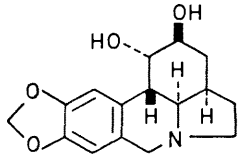
(*Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan*)

Summary The total synthesis of dihydrolycorine, a hydrogenation product of the alkaloid lycorine, is reported.

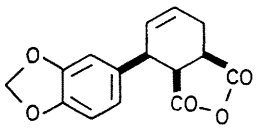
IN connection with our work on synthesising compounds related to alkaloids of the *Amaryllidaceae*, we have now synthesised a racemic form of dihydrolycorine (I), the sole hydrogenation product of lycorine[1] which is an alkaloid from *Lycoris radiata* Herb.[2] and a wide variety of species of the same family.[3]

1,2,3,6-Tetrahydro-3-(3,4-methylenedioxyphenyl)phthalic anhydride(II)[4] was heated under reflux in methanol to give a mixture of two half-esters (III and IV) which were not separated at this stage, but directly subjected to the Friedel–Crafts cyclisation by treatment with phosphorus pentachloride followed by stannic chloride in methylene chloride to give a mixture consisting of the indanone-ester (V) [ν_{max} ($CHCl_3$) 1698 cm.$^{-1}$] and the tetralone-ester (VI) [ν_{max} ($CHCl_3$) 1660 cm.$^{-1}$].

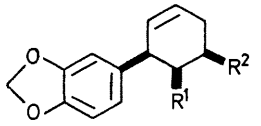
Cyclisation of (II) or the corresponding diacid under Friedel–Crafts conditions afforded exclusively the tetralone-carboxylic acid (VII) and not the indanone-carboxylic acid



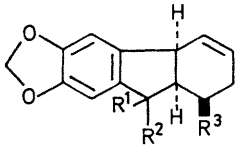
(I)



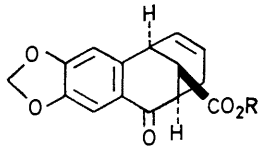
(II)



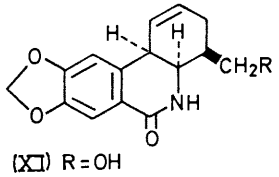
(III) $R^1 = CO_2H$; $R^2 = CO_2Me$
(IV) $R^1 = CO_2Me$; $R^2 = CO_2H$



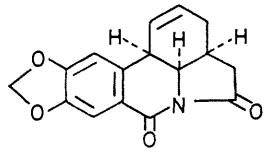
(V) $R^1, R^2 = O$; $R^3 = CO_2Me$
(VIII) $R^1, R^2 = O$, $R^3 = CO_2H$
(IX) $R^1 = H, R^2 = OH$, $R^3 = CH_2OH$
(X) $R^1, R^2 = O$; $R^3 = CH_2OH$



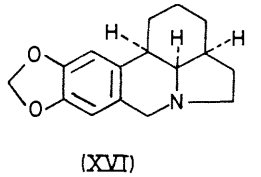
(VI) R = Me
(VII) R = H



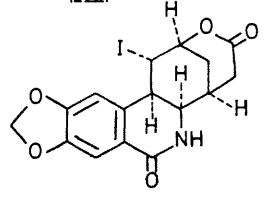
(XI) R = OH
(XII) R = OTs
(XIII) R = CN
(XIV) R = CO_2H



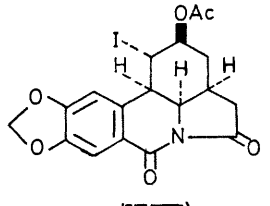
(XV)



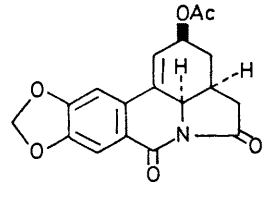
(XVI)



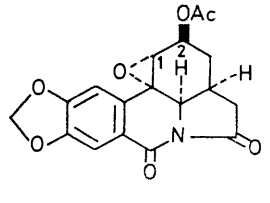
(XVII)



(XVIII)



(XIX)



(XX)

(VIII) as claimed by previous authors.[4] The indanone (V), which was separated from the mixture by fractional crystallisations from benzene, was submitted to the conditions of the Schmidt reaction (with sodium azide in trichloroacetic acid) without success. Then the indanone-ester (V) was reduced by lithium aluminium hydride in tetrahydrofuran to give the diol (IX), which was re-oxidised to the keto-alcohol (X) with activated manganese dioxide in methylene chloride, and again subjected to the Schmidt reaction with sodium azide in trichloroacetic acid. The product was a mixture [ν_{max} (Nujol) 1762 (trichloroacetate CO), 1651, and 1633 cm.$^{-1}$ (amide CO)] which, after elimination of the trichloroacetyl group by hydrolysis, yielded two isomeric lactams, m.p. 205—208° [ν_{max} ($CHCl_3$) 3575, 3400 (OH and NH), and 1651 cm^{-1} (amide CO); λ_{max} (MeOH) 224·5, 264, and 305 nm (ϵ 33,800, 4100, and 5900)] and m.p. 195—196° [ν_{max} (Nujol) 3350 (OH and NH), and 1633 cm^{-1} (amide CO); λ_{max} (MeOH) 224, 266, 304 nm (ϵ 31,000, 8100, and 7500)]. Although the structure of the latter compound is still under investigation, the former has been shown to be represented by the formula (XI), as expected. Thus, the compound (XI) was tosylated and the tosylate (XII) was converted into the cyano-lactam (XIII) by treatment with potassium cyanide in acetonitrile. Hydrolysis of the nitrile (XIII) in hydrochloric acid–acetic acid gave the corresponding carboxylic acid (XIV) in good yield. Cyclisation of the carboxylic acid took place readily with acetic anhydride to yield the imide (XV) which, on treatment with lithium aluminium hydride followed by catalytic reduction in the presence of Adams catalyst, furnished (±)-γ-lycorane,[5] m.p. 102—104° (XVI), whose stereochemistry has been established. The carboxylic acid (XIV) with the established structure and stereochemistry was treated with iodine–potassium iodide in aqueous sodium hydrogen carbonate to give the iodo-lactone (XVII) [ν_{max} (KBr) 3350 (NH), 1745, and 1664 cm.$^{-1}$ (CO)] which was rather unstable and easily converted into the iodo-acetyl-imide (XVIII) with acetic anhydride and acetic acid. The structure of (XVIII) was confirmed by its spectral properties [ν_{max} (KBr) 1765, 1745—1725, and 1665 (CO); λ_{max} (EtOH) 233, 279, and 312 nm (ϵ 26,600, 6000, and 8960)], and combustion values. Dehydrohalogenation of (XVIII) was achieved by heating it under reflux with lithium chloride in dimethylformamide under nitrogen. The resulting olefin (XIX), which showed the expected spectral properties [ν_{max} ($CHCl_3$) 1758, and 1670 (CO); λ_{max} (EtOH) 251, 298, and 330 nm (ϵ 35,000, 5580, and 5950); τ ($CDCl_3$) 2·44 (1H, s, Ar-H), 3·10 (1H, s, Ar-H), 3·80 (1H, broad s, olefinic H), 3·92 (2H, s, methylenedioxy), 4·53 (1H, m, AcO–C*H*), 5·37 (1H, m, N–C*H*), and 7·88 (3H, s, OAc)], was treated with *m*-chloroperbenzoic acid in chloroform at room temperature for 2 days to give the oxide (XX). The α-configuration of the oxide ring was inferred from the steric effect of the adjacent acetoxy-moiety and strongly supported by its n.m.r. spectrum showing a signal of the proton on C-1 (bearing the oxide oxygen) as a singlet, indicating that the dihedral angle between the protons at C-1 and C-2 is about 90°.

The final step to dihydrolycorine was reductive cleavage of the oxide ring to yield a secondary alcohol. We have found (eventually) that a mixture of lithium aluminium hydride and zinc chloride is effective for this purpose, though the yield of dihydrolycorine was only 5% based on the oxide.

The synthetic (±)-dihydrolycorine, m.p. 248—250° was identical with natural dihydrolycorine in the n.m.r.

(CD_3SOCD_3) and mass spectra and on t.l.c. using different solvent systems. The i.r. spectrum ($CHCl_3$) of the *OO'*-diacetyl derivative of this synthetic compound, m.p. 179—181°, was superimposable on the spectrum of diacetyldihydrolycorine from natural sources.

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