Total Synthesis of the Alkaloids Clivonine and Clividine

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Summary (±)-Clivonine and (±)-clividine, lactonic alkaloids in *Amaryllidaceae* plants, have been synthesised.

In connection with our synthetic work[1] on *Amaryllidaceae* alkaloids, we report here the synthesis of the lactonic alkaloids clivonine (I)[2] and clividine (II),[3] which occur in *Clivia miniata* Regel (*Amaryllidaceae*).

Cycloaddition of fumaric acid and 3,4-methylenedioxyphenyl allyl carbinol[4] in boiling acetic anhydride for 4 h gave a small amount of the anhydride (III)† and two stereoisomeric anhydrides (IV) (ν_{max} 1860 and 1790 cm^{-1}) and (V) (ν_{max} 1855 and 1785 cm^{-1}). Hydrolysis of (IV) and (V) with aqueous sodium hydroxide gave the corresponding acids (VI) and (VII). Re-cyclisation of the acids with acetic anhydride under reflux for 12 h furnished stereospecifically the same *trans-cis*-anhydride (III)‡ (ν_{max} 1850 and 1775 cm^{-1}). Confirmation of the structures of all the anhydrides was provided from the synthesis of α-, β-, and δ-lycorane[5] from the anhydrides, (III)—(V), respectively.§

Treatment of (III) with anhydrous methanol (1 equiv.) in benzene gave the regio-isomeric half esters (VIII) [δ ($CDCl_3$) 3·51 (OMe) and 11·15 (CO_2H)] and (IX) [δ 3.51, (OMe) and 8·78, (CO_2H)] in a ratio of 7:3. Treatment of the former with thionyl chloride followed by sodium azide gave the azide (X) [ν_{max} ($CHCl_3$) 2140 cm^{-1}] which was heated in benzene to give the isocyanate (XI) [ν_{max} ($CHCl_3$) 2260 cm^{-1}]. The isocyanate was converted into the urethane (XII) [δ 3·64 and 3·60, (2 -OMe), ν_{max} 3350, 1733, and 1690 cm^{-1}] with methanol which was hydrolysed to the acid (XIII) by treatment with hydrochloric acid in acetic acid.

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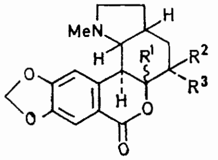
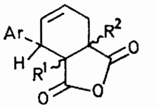
† Satisfactory elemental analyses and mass spectra were obtained for all the compounds cited here and i.r. spectra were determined for KBr disc unless otherwise indicated.

‡ The same type of epimerisation has been reported by R. D. Haworth and F. H. Slinger, *J. Chem. Soc.*, 1940, 1321.

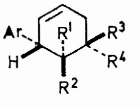
§ The synthesis of lycoranes will be reported in the full paper.

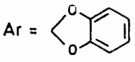


(I) R^1 = —H, R^2 = H, R^3 = OH
(II) R^1 = ---H, R^2 = OH, R^3 = H

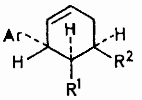


(III) R^1 = ---H, R^2 = ---H
(IV) R^1 = ---H, R^2 = —H
(V) R^1 = —H, R^2 = ---H

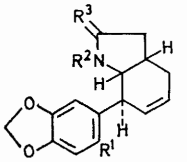




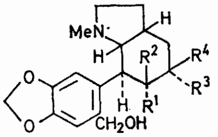
(VI) $R^1=R^3=H$; $R^2=R^4=CO_2H$
(VII) $R^1=R^3=CO_2H$; $R^2=R^4=H$



(VIII) $R^1 = CO_2H$; $R^2 = CO_2Me$
(IX) $R^1 = CO_2Me$; $R^2 = CO_2H$
(X) $R^1 = CON_3$; $R^2 = CO_2Me$
(XI) $R^1 = N{=}C{=}O$; $R^2 = CO_2Me$
(XII) $R^1 = NH{-}CO_2Me$; $R^2 = CO_2Me$
(XIII) $R^1 = NH{-}CO_2Me$; $R^2 = CO_2H$
(XIV) $R^1 = NH{-}CO_2Me$; $R^2 = CH_2CO_2Me$
(XV) $R^1 = NH{-}CO_2Me$; $R^2 = CH_2CO_2H$



(XVI) $R^1 = H$; $R^2 = CO_2Me$; $R^3 = O$
(XVII) $R^1 = CH_2OAc$; $R^2 = CO_2Me$; $R^3 = O$
(XVIII) $R^1 = CH_2OH$; $R^2 = Me$; $R^3 = H_2$



(XIX) $R^1 = R^3 = OH$; $R^2 = R^4 = H$
(XX) $R^1 = R^3 = H$; $R^2 = R^4 = OH$

When the diazoketone derived from the acid (XIII) in the usual manner was treated with silver oxide in methanol, the methyl ester (XIV) was obtained (55%), though attempts to obtain the homo-acid (XV) by carrying out the Wolff rearrangement in aqueous solution have not given any acceptable results. Hydrolysis of the ester (XIV) under acidic condition gave the corresponding acid (XV) which was easily cyclised to the oxoindole (XVI) [δ 3·50 (OMe), ν_{max} 1780 and 1730 cm^{-1}] (72%) with acetic anhydride.

Treatment of (XVI) with chloromethyl methyl ether in acetic acid in the presence of zinc chloride followed by silver acetate in acetic anhydride and acetic acid furnished the acetate (XVII) [δ 2·05, (CO–Me), 3·45 (OMe), and 5·02 (s, benzylic CH_2)] (58%). Reduction of (XVII) with lithium aluminium hydride in ether gave the amino-alcohol (XVIII) [δ 1·83 (N–Me)] (65%), which was characterised as its picrate, m.p. 188—189°. Oxidation of (XVIII) with osmium tetroxide in ether gave the stereoisomeric triols (XIX), m.p. 180—183° and (XX), m.p. 230—232° (20·2 and 22·2% respectively), after separation on an alumina column. The faster running triol (XIX) was treated with manganese dioxide in chloroform to give (±)-clivonine (I), m.p. 223—225° which was identical with clivonine¶ in the n.m.r. ($CDCl_3$), i.r. ($CHCl_3$), and mass spectra. The slower running triol (XX) was also oxidised with the same reagent in chloroform and tetrahydrofuran to give (±)-clividine (II), m.p. 170—172° (although without direct comparison with the natural source).

Since clivonine has been converted into dihydrohippeastrine, our synthesis means the total synthesis of dihydrohippeastrine in a formal sense.

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