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TOTAL SYNTHESIS OF (±)-LYCORICIDINE

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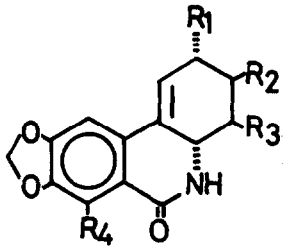
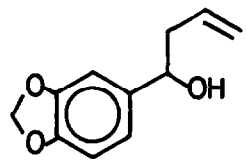
Lycoricidine[1] (margetine[2,3]) and narciclasine[4,5] (lycoricidinol[1], 2), the non-basic constituents of Amaryllidaceae plants, are of biological interest because of their antimitotic activity. Although the plane formula of lycoricidine is reported as 1, the configuration of the hydroxyl groups are not fully established. However, the stereostructure 1 is presumed to be correct since the reported nmr spectrum of lycoricidine triacetate corresponds very well with that of lycoricidinol tetraacetate, whose structure has already been determined by X-ray analysis. We wish to report the first total synthesis of racemic 1.

Reaction of 3,4-methylenedioxyphenyl allyl carbinol (3)[7] with ethyl acrylate at 80° gave a diastereomeric mixture of ethyl 2-(3,4-methylenedioxyphenyl)-cyclohex-3-ene-1-carboxylate in the ratio of 1 : 1. After treatment of the mixture with sodium ethoxide in ethanol, followed by alkaline hydrolysis, the trans-acid (mp 103°, 4) was obtained. This acid was converted by the modified Curtius reaction[8] to the corresponding isocyanate which was cyclized to the lactam (mp above 285° dec., 5, 88.5 %) using boron trifluoride etherate at room temperature. (This new cyclization technique was found to be applicable to several substituted phenethylisocyanates.)

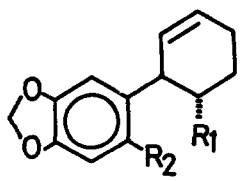
When the lactam (5) was heated with acetic anhydride—pyridine and a resulting product (N-acetylimide, mp 158°) was hydrolysed with n-potassium hydroxide in aqueous methanol (70°), the carboxylic acid (mp 201°, 6, methyl ester mp 175°) was obtained (67.8 % yield from imide). Treatment of the acid (6) with N-bromosuccinimide in tetrahydrofurane yielded the bromolactone (mp 272°, 7) which was converted to the olefinic lactone (mp 267°, 8) by refluxing it in pyridine. Hydrolysis and recyclization of the lactone (8) with aqueous sodium hydroxide at 90°



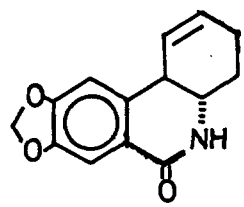
(1) $R_1=R_2=R_3=OH$, $R_4=H$
(2) $R_1=R_2=R_3=R_4=OH$
(17) $R_1=OAc$, $R_2=R_3=R_4=H$
(22) $R_1=OAc$, $R_2,R_3=$  $R_4=H$
(23) $R_1=R_2=R_3=OAc$, $R_4=H$



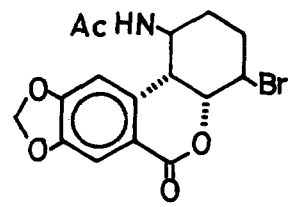
(3)



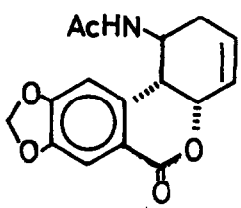
(4) $R_1=COOH$, $R_2=H$
(6) $R_1=NHAc$, $R_2=COOH$



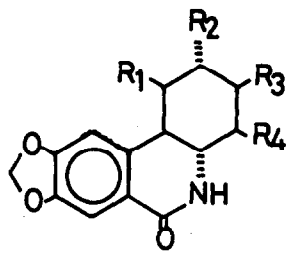
(5)



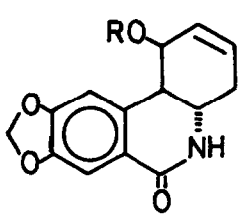
(7)



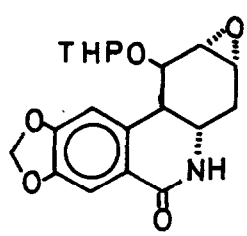
(8)



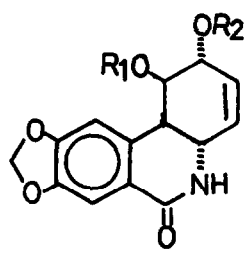
(11) $R_1=OAc$, $R_2=R_3=R_4=H$
(16) $R_1=OH$, $R_2=OAc$ $R_3=R_4=H$
(18) $R_1=Br$, $R_2=OAc$ $R_3=R_4=H$
(19) $R_1=R_3=R_4=H$, $R_2=OAc$
(20) $R_1=R_3=R_4=OH$, $R_2=OAc$
(21) $R_1=OH$, $R_2=OAc$ $R_3=R_4=$



(9) R= H
(10) R= Ac
(12) R= THP



(13)



(14) $R_1=THP$, $R_2=H$
(15) $R_1=H$, $R_2=Ac$

produced the olefinic lactam (mp 280°, 9) in 90 % yield. The O-acetate (mp 272°, 10), which was prepared by heating the olefinic lactam (9) with acetic anhydride —pyridine, was hydrogenated over platinum oxide to give a dihydro derivative (mp 257°) which was assumed to have the structure 11 on the basis of the nmr spectrum (in DMSO-d_6 δ5.67 ppm : W/2 of >C<u>H</u>OCOCH$_3$ = 8 Hz). The olefinic lactam (9) was converted to the tetrahydropyranyl ether (mp ca. 270°, 12) by refluxing it in chloroform with 2,3-dihydropyrane and p-toluenesulfonic acid. The ether (12) was oxydised with m-chloroperbenzoic acid in chloroform to give the α-epoxide (mp 217°, 13) which was converted to the allylic alcohol (mp 232°, 14) in 63 % yield according to the Sharpless's procedure[9] using diphenyl diselenide, sodium borohydride and hydrogene peroxide. The allyl alcohol (14) was acetylated, then hydrolyzed to the diol monoacetate (mp 250°, 15) using p-toluenesulfonic acid.

In order to determine the relative configuration between the substituents in the ring-C, the diol monoacetate (15) was hydrogenated over platinum oxide to give the saturated diol monoacetate(mp 288°, 16). When the acetate was heated with boron trifluoride etherate in acetic acid, the allyl alcohol acetate (mp 290°, 17) was obtained. The uv spectrum of (17) was similar to that of lycoricidine (1). This olefinic alcohol acetate (17) was also produced by dehydrobromination of the bromohydrine acetate (mp 213°, 18) which was synthesized by the treatment of the lactam (5) with N-bromosuccinimide in acetic acid. Furthermore, the bromohydrine acetate(18) was hydrogenated over Raney nickel to give the acetate (mp 256°, 19) and the configuration of C_2-acetoxyl group of (19) was assigned as α-axial on the basis of the nmr spectrum (in DMSO-d_6 δ5.12 ppm : W/2 of >C<u>H</u>OCOCH$_3$ = 8 Hz).

Oxydation of the olefinic diol monoacetate (15) with osmium tetroxide in pyridine gave the tetraol monoacetate (mp 258°, 20) in 87.2 % yield since the oxydation was considered to occur predominantly from the less hindered β-side of the molecule. The acetonide (mp 258°, 21) was obtained from the tetraol monoacetate (20) with 2,2-dimethoxypropane—N,N-dimethylform amide (1 : 1) and p-toluenesulfonic acid as catalyst in 83.5 % yield, and the acetonide (21) was dehydrated to the racemic lycoricidine derivative (mp 205°, 22) by thionyl chloride in pyridine at 0° in 57.8 % yield. 22 : ir (KBr) 3300, 1740, 1677 cm^{-1} ; uv (95% ethanol)

247.5, 308 nm ; nmr (DMSO-d_6) δ7.97 (broad, 1H), 7.38 (s, 1H), 7.37 (s, 1H), 6.45 (broad, 1H), 6.11 (s, 2H), 5.38 (m, 1H), 4.4 - 4.13 (m, 3H),2.14 (s, 3H), 1.33 ppm (s, 3H). The compound 22 was hydrolysed with p-toluenesulfonic acid in aqueous methanol—chloroform and acetylation of the product with acetic anhydride—pyridine gave the racemic lycoricidine triacetate (mp 235°, 23) : mass spectrum m/e 417 (M^+), 255 (base peak) ; ir (chloroform) 3320, 1750, 1667, 1230 cm^{-1} ; uv (95% ethanol) 244.5, 306 nm ; nmr ($CDCl_3$) δ7.51 (s, 1H), 7.43 (broad, 1H), 7.00 (s , 1H), 6.25 - 6.0 (complex m, 3H), 5.55 - 5.17 (m,3H),4.65 (broad, 1H), 2.17 (s, 3H), 2.11 (s, 3H), 2.10 ppm (s, 3H). The mass, ir, uv and nmr spectra of the acetate (23) were in good agreement with those of the natural lycoricidine triacetate. The acetate (23) was hydrolysed with ammonia in methanol at room temperature to give the racemic lycoricidine (mp 230° dec., 1) : ir (KBr) 2400 - 3600, 1650 cm^{-1} ; uv (95% ethanol) 243.5, 305 nm.[10]

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10) The elemental analysis data of the all compounds in this communication were satisfactory to the assigned structures in the figure.