Biosynthesis of Cularine

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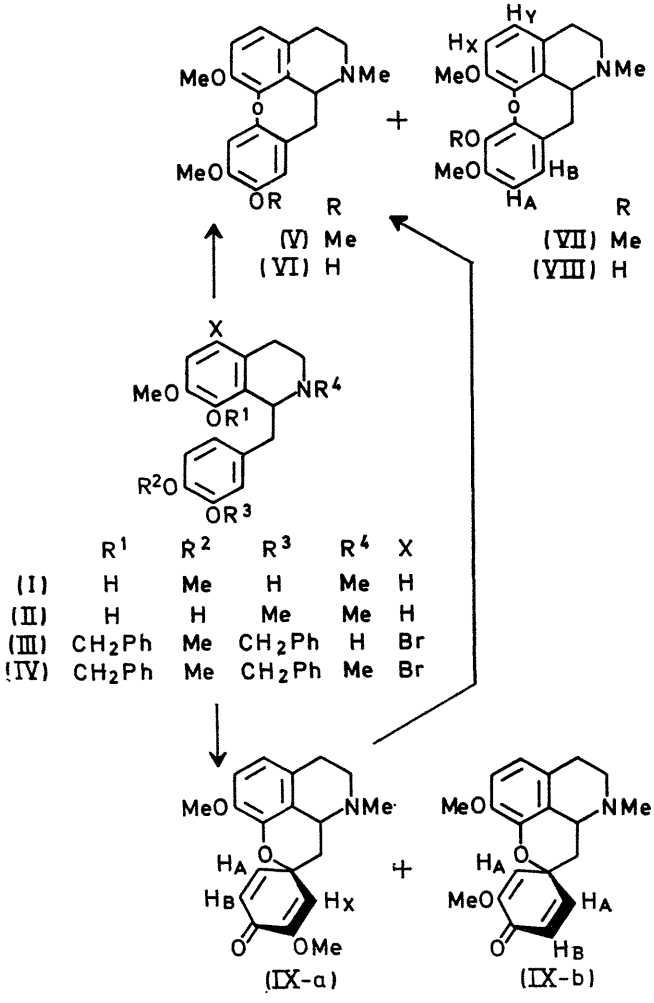
Summary Phenolic oxidative coupling of the diphenolic isoquinoline (**I**), followed by *O*-methylation, gave cularine (**V**) and cancentrine type compound (**VII**) while the same reaction of the isoquinoline (**II**) gave the dienones (**IXa**) and (**IXb**).

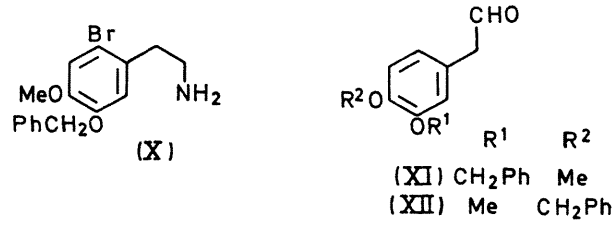
CULARINE (**V**) and related alkaloids can be biosynthesised from the 1,2,3,4-tetrahydroisoquinoline derivatives (**I**) and (**II**).[1] Oxidative coupling of (**I**), followed by *O*-methylation, gives either cularine (**V**) or compouud (**VII**).[2] Phenolic oxidation of (**II**) gives the dienone (**IX**), which can be converted into cularine by dienone–phenol rearrangement. We report a biosynthesis of cularine by the former route.

The Pictet–Spengler reaction of compound (**X**)[3] with the phenylacetaldehyde (**XI**)[4] gave the 1,2,3,4-tetrahydroisoquinoline (**III**), *N*-methylation of which, followed by hydrogenolysis of the resulting *N*-methylisoquinoline (**IV**), afforded the diphenolic isoquinoline (**I**). Compound (**I**) was

oxidised with potassium ferricyanide in the presence of 1N-ammonium acetate and chloroform by stirring for 3·5 h at room temperature. Separation by silica-gel chromatography, using chloroform–methanol (99 : 1) as eluant, gave the cularine system (**VIII**) (5%) by *ortho–ortho* coupling and *O*-demethylcularine (**VI**) (2·5%). The former (**VIII**), $C_{19}H_{21}NO_4$ (M^+, 327), showed a hydroxy-group in its i.r. spectrum [ν_{max} ($CHCl_3$) 3480 cm^{-1}] and, in its n.m.r. spectrum ($CDCl_3$), four aromatic protons [τ 3·48 (1H, d, J_{AB} 8·5 Hz, H_A), 3·37 (d, 1H, H_B), 3·25 (1H, d, J_{XY} 8·5 Hz, H_X), and 3·07 (1H, d, H_X)] and a methine proton (τ 5·49, 1H, q, J 4·5 and 12·0 Hz). Compounds (**VIII**) and (**VI**) were methylated by diazomethane into the cancentrine type compound (**VII**) and cularine (**V**) which was identical with an authentic sample in spectroscopic comparisons. The structure of compound (**VII**), $C_{20}H_{23}NO_4$ (M^+ 341), was assigned on the basis of its n.m.r. spectrum, which showed four methyl resonances [τ 7·44 (3H), 6·15 (6H) and 5·95 (3H)], one methine proton τ 5·68 (1H, q, J 4·5 and 11·5 Hz)] and four aromatic protons [τ 3·42 (1H, d, J_{AB} 8·5 Hz, H_A), 3·24 (1H, d, H_B), 3·24 (1H, d, J_{XY} 8·5 Hz, H_X), and 3·11 (1H, d, H_Y)].



SCHEME 1



SCHEME 2

In order to synthesise cularine *via* the dienone (**IX**) the diphenolic isoquinoline (**II**) was prepared from the phenylacetaldehyde (**XII**)[5] [as (**I**) had been obtained from (**XI**)] and oxidised similarly with potassium ferricyanide, into a mixture of two dienones that differ in configuration at the spiro-centre. They were separated by silica gel chromatography using chloroform-methanol (99 : 1). Dienone-A (**IXa** or **IXb**) (2·5%), $C_{19}H_{21}NO_4$(M^+, 327), m.p. 132—133°, showed a typical cross-conjugated dienone system in its i.r. (ν_{max} 1680, 1645, and 1620 cm^{-1}) and u.v. spectra [λ_{max} (EtOH) 236·5 and 284 nm (log ϵ 4·11 and 3·56)]. The n.m.r. spectrum revealed two aromatic [τ 3·25 (2H, s)] and three olefinic protons [τ 3·98 (1H, d, J_{AX} 3 Hz, H_X), 3·73 (1H, d, J_{AB} 10 Hz, H_B), 3·03 (1H, q, H_A)] with expected three methyl resonances (τ 7·59, 6·34, and 6·18). Similarly, dienone-B (**IXa** or **IXb**) (3·85%), $C_{19}H_{21}NO_4$ (M^+, 327), m.p. 137—138·5°, showed a dienone system in its i.r. (ν_{max} 1680, 1650, and 1620 cm^{-1}) and u.v. spectra [λ_{max} (EtOH) 236·5 and 286·0 nm (log ϵ 4·32 and 3·65)] and an n.m.r. spectrum showed three methyl signals (τ 7·61, 6·30, and 6·20), two aromatic protons (τ 3·25, 2H, d) and three olefinic protons [τ 4·17 (1H, d, J_{AX} 3·0 Hz, H_X), 3·77 (1H, d, J_{AB} 10 Hz, H_B), and 2·84 (1H, q, H_A)]. The acid-catalysed rearrangement of the dienones did not give cularine-type compounds under conditions tried so far.

(*Received, January 18th*, 1971; *Com.* 091.)

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