Biogenetic Synthesis of Cularine-type Compounds

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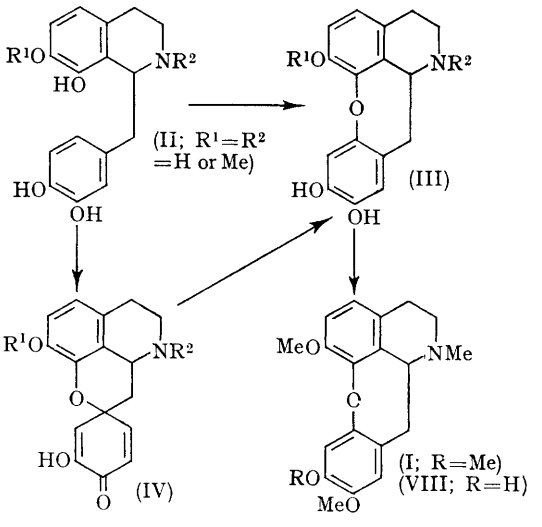
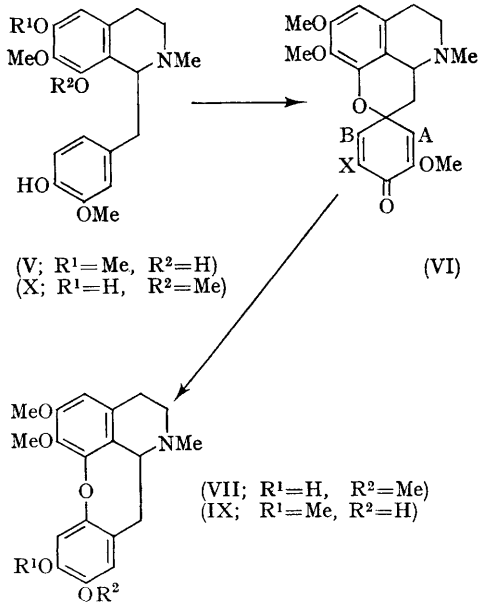
IN the biosynthesis of cularine (I)[1] and related alkaloids, the 1,2,3,4-tetrahydroisoquinoline derivative (II) could be an intermediate. Thus, oxidation of (II) would lead to either the cularine-type compound (III) or dienone (IV). Further conversion of the latter compound (IV) into (III) would involve unexceptional dienone–phenol rearrangement.



We now provide a laboratory analogy for the latter biogenetic route to cularine-type compounds. The oxidation of (V) was effected with potassium ferricyanide in the presence of ammonium acetate at room temperature by stirring for 3 hr. in a current of nitrogen. The product, m.p. 173—175° (3% yield as its hydrochloride), can be assigned the formula (VI)† on the basis of the following evidence. The i.r. [ν_{max} (in $CHCl_3$) 1675 (C=O), 1650 (C=C) cm.$^{-1}$] and u.v. [λ_{max} (MeOH) 231 mμ (log ϵ 4·42)] spectra were in accord with a dienone structure. The n.m.r. spectrum (in $CDCl_3$) revealed a singlet aromatic proton (τ 3·65), olefinic proton [(H_A; τ 4·08 doublet, J_{AB} = 2·5), (H_X; τ 3·90, doublet, J_{BX} = 12·5) and (H_B; τ 3·03, quartet, J_{AB} = 2·5, J_{BX} = 12·5 c./sec.)], *O*-methyl singlets (τ 6·25, 6·22, and 6·16), *N*-methyl singlet (τ 7·60), and broad multiplets of methylene groups (τ 6·50—7·30), unambiguously confirming the structure (VI). Although there should be two isomers produced in this oxidation, separation could not be effected.



† Satisfactory analyses were obtained for all new compounds described herein.

Rearrangement of (VI) with concentrated hydrochloric acid in glacial acetic acid by stirring at room temperature in a current of nitrogen gave the cularine-type isoquinoline (VII), m.p. 188—189°. This structure was tentatively assigned as (VII) by spectral methods as follows.

The i.r. spectrum showed ν_{max} (in $CHCl_3$) 3500 (OH) cm.$^{-1}$, and the n.m.r. (in $CDCl_3$) spectrum revealed three singlet aromatic protons (τ 3·82, 3·34 and 3·27), three *O*-methyl singlets (τ 6·21, 6·19 and 6·14), and an *N*-methyl singlet (τ 7·61). The chemical shifts of the 9- and 10-*O*-methyl groups in cularine and cularidine were assigned as τ 6·16 and 6·21 by spectral comparison with those of 6,10-*O*,*O*-didemethylcularine.[2] Since the chemical shift of the *O*-methyl groups of our product appeared at τ 6·21 and not at τ 6·16, the rearrangement product seems to be (VII) rather than (IX).

The above oxidation, followed by rearrangement with acid, showed a possible model for the biogenetic route to the cularine-type alkaloids, and another route leading directly to (III) from (II) is being studied.

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[1] R. H. F. Manke, *J. Amer. Chem. Soc.*, 1950, **72**, 55; T. Kametani and K. Kukumoto, *J. Chem. Soc.*, 1963, 4289; T. Kametani, S. Shibuya, S. Seino, and K. Fukumoto, *ibid.*, 1964, 4146; T. Kametani and S. Shibuya, *ibid.*, 1965, 5565.

[2] T. Kametani, S. Shibuya, C. Kibayashi, and S. Sasaki, *Tetrahedron Letters*, 1966, 3215; T. Kametani and S. Shibuya, *J. Pharm. Soc. Japan*, 1967, **87**, 198.