The Constitutions of Erythratine and Erysodine and the Biosynthesis of the Erythrina Alkaloids

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IT has been proposed[1] that the *Erythrina* alkaloids [as (IV)] are constructed in Nature by the sequence (I) → (II) → (III) → (IV). The recently reported chemical conversion[2] of the diphenol (I) into the dienone (II) supports this idea. We now present chemical evidence for the later stages of erythraline (IV; R′R″ = CH_2) biosynthesis.

Erythratine[3] has usually been formulated as in (III; R=H), but with the ethylenic linkage in the 6(7)-position.[4] From the biogenetic point of view[1] a better formula would be (III; R=H), derived from the corresponding $\alpha\beta$-unsaturated ketone, itself formed from reduction of a dienone [as (II)]. We now report evidence which confirms the constitution (III, R=H) and also establishes the stereochemistry of the molecule.

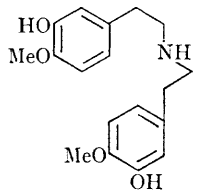
The n.m.r. spectrum ($CDCl_3$, 100 Mc./sec.) of erythratine and its benzoate (III; R=PhCO), supported by appropriate spin-decoupling studies, established the part structure, $R^1R^2R^3C{\cdot}CH_2{\cdot}CH(OMe){\cdot}CH(OH){\cdot}CH{=}CR^4R^5$ and confirmed the remaining structural features of the molecule (see Table). Oxidation of erythratine, with manganese dioxide in chloroform, gave the corresponding $\alpha\beta$-unsaturated ketone, m.p. 133·5—135·5°, ν_{max} 1675 cm.$^{-1}$ ($CHCl_3$), which was reduced with sodium borohydride to give a mixture of erythratine and its C-2 epimer, epierythratine, m.p. 147—150°, $[\alpha]_D$ +280° (*c*, 0·35 in EtOH). The infrared spectra (dilute CCl_4 solutions) of epierythratine and erythratine showed hydroxyl bands at ν_{max} 3556 and 3605 cm.$^{-1}$, respectively. The strong hydrogen bonding in epierythratine is consistent[5] only with a *cis*-arrangement of hydroxyl and methoxyl groups. Erythratine must therefore be the *trans*-isomer (III; R=H). The stereochemistry of the spiro-centre of asymmetry was defined by conversion of erythratine, with methanesulphonyl chloride in pyridine, into erythraline (IV; R′R″ = CH_2) of known[6] relative and absolute stereochemistry. Application of Mills's rule[7] to the optical rotations of erythratine ($[\alpha]_D$ + 145·5)[3] and epierythratine confirms the absolute configuration of erythratine as in (III). Whether erythratine or its epimer are indeed biological precursors of erythraline will depend, *inter alia*, on the stage at which formation of the methylenedioxy-group[8] and reduction of the 3(4)-double bond[9] occur in the plant. Feeding experiments are in hand to clarify these points.

Erysodine and erysovine (IV; R′ or R″=Me, R′ or R″=H) differ only in the relative positions of the methoxyl and hydroxyl groups in ring D.[10] The n.m.r. spectrum ($CDCl_3$) of erysodine showed aromatic singlets at τ 3·24 and 3·35. The high-field singlet was broadened relative to its low-field companion by long-range (benzylic) coupling. Thus, irradiation of the sample in the region (τ 7·25) corresponding to the benzylic methylene

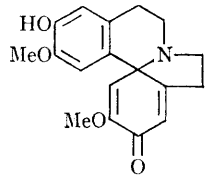
group caused sharpening of the high-field, but not of the low-field, aryl signal. The proton at C-17 [see (IV)] therefore absorbs at τ 3·35. Erysodine was heated at 118° in dimethylformamide containing D_2O for 4 days to give a monodeutero-derivative (*m/e* 300). The aryl signal at τ 3·35 had disappeared from the n.m.r. spectrum. Since exchange under these conditions is known[11] to take place only at positions *ortho* and *para* to phenolic hydroxyl groups erysodine must have the structure (IV; R′=H, R″=Me). The isomeric erysovine must therefore be (IV; R′=Me, R″=H).

Note added in proof:

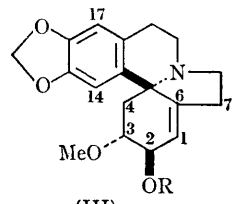
We have now identified the unsaturated ketone corresponding to (III) as a *new* alkaloid of *Erythrina crystagalli*.



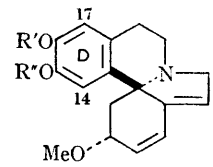
(I)



(II)



(III)



(IV)

TABLE

Nuclear magnetic resonance spectra

τ-values (in $CDCl_3$)

Proton	1	2	3	4*a**	4*e**	14	17†	OCH_2O	MeO
(III); R=H	4·44	5·72	6·40	8·37	7·70	3·27	3·45	4·15	6·72
(III); R=PhCO	4·31	4·31	6·06	8·17	7·66	3·20	3·45	4·13‡	6·74
Epierythratine	4·22	5·59	6·38	8·21	—	3·55	3·44	4·15	6·66

Coupling constants (c./sec.)

	Protons ij	12	23	34*a**	34*e**	4*a*4*e**
$\lvert J_{ij} \rvert$ in	(III); R=H	3·2	7·5	12·5	4·0	12·75
	(III); R=PhCO	—	—	12·0	5·0	12·5
	Epierythratine	—	3—4	12·0	4—5	12·0

* *a* and *e* represent axial and equatorial
† Identified by irradiation of benzylic methylene group (see text)
‡ Quartet, J = 1·4 c./sec.

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