Phenol Oxidation and Biosynthesis. Part XXIII.[1] On the Benzyltetrahydroisoquinoline Origins of the *Erythrina* Alkaloids

By **Derek H. R. Barton, Christopher J. Potter,** and **David A. Widdowson,*** Chemistry Department, Imperial College, London SW7 2AY

The biogenetic precursor of the *Erythrina* alkaloids is shown not to be (±)-*N*-nor-reticuline or (+)-*N*-nororientaline.

We have previously demonstrated the specificity of (*S*)-*N*-norprotosinomenine (I) as a precursor of the *Erythrina* alkaloids [2] (Scheme 1). That this is also an exclusive precursor has been brought into question by the observation that *in vitro* 5'-methoxy-*N*-methylsulphonyl-*N*-nor-reticuline (II; $R^1 = R^4 = Me$, $R^2 = R^3 = H$, $R^5 = MeO$, $R^6 = SO_2Me$) can be converted into 14-methoxyerysodienone (III; R = OMe).[3]

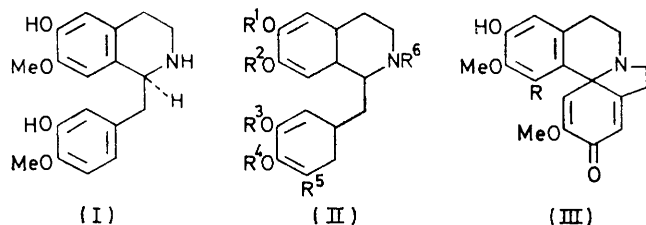
Conceivably, the isomers of *N*-norprotosinomenine,

[1] Part XXII, D. H. R. Barton, A. A. L. Gunatilaka, R. Letcher, A. M. F. T. Lobo, and D. A. Widdowson, *J.C.S. Perkin I*, 1973, 874.

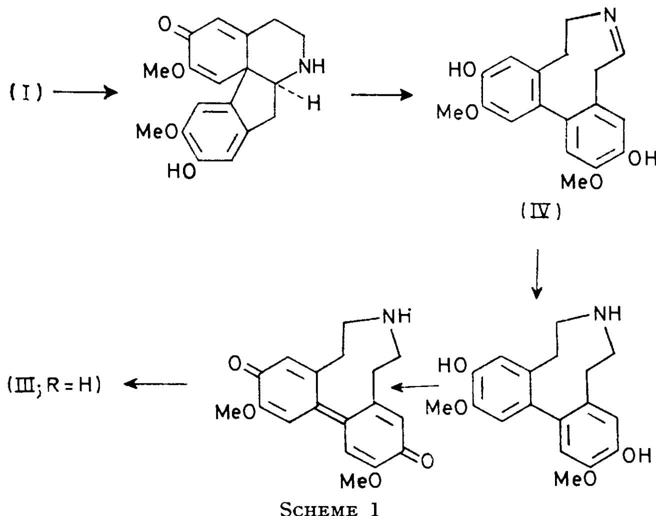
[2] D. H. R. Barton, R. B. Boar, and D. A. Widdowson, *J. Chem. Soc.* (*C*), 1970, 1213.

[3] B. Franck and V. Teetz, *Angew. Chem. Internat. Edn.*, 1971, **10**, 411.

N-nor-reticuline (II; $R^1 = R^4 = Me$, $R^2 = R^3 = R^5 = R^6 = H$) and N-nororientaline (II; $R^1 = R^3 = Me$,

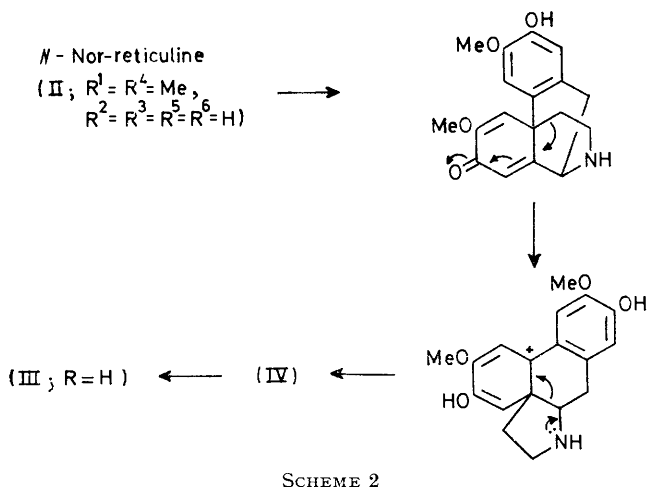


$R^2 = R^4 = R^5 = R^6 = H$), could act as *in vivo* precursors of the *Erythrina* system in an analogous manner, as shown in Schemes 2 and 3. The fourth isomer, thc



SCHEME 1

wholly synthetic 1,2,3,4-tetrahydro-6-hydroxy-1-(4-hydroxy-3-methoxybenzyl)-7-methoxyisoquinoline, could only generate the required bridged biphenyl system (IV)



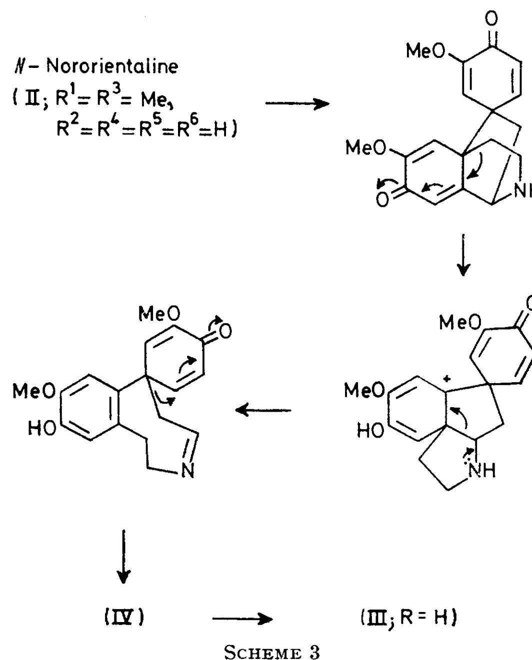
SCHEME 2

by the unlikely coupling to a four-membered ring bis-spirodienone intermediate, and on these grounds is discounted.

[4] (*a*) G. W. Kirby and L. Ogunkoya, *J. Chem. Soc.* (*C*), 1965, 6914; (*b*) D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *ibid.*, 1968, 1529.

Accordingly (±)-N-nor-reticuline and (+)-N-nororientaline [1] have been synthesised in radioactive form by tritiation of the free phenolic bases (self-catalysed exchange in tritiated water–dimethylacetamide at 118° during 3 days).[4] [5-^{3}H]-N-Norprotosinomenine was already available.[2]

The three bases, as their hydrochloride salts, together with a tyrosine reference, were fed in parallel to 5-month-old seedlings of *E. crista-galli* and *E. berteroana*.



SCHEME 3

The alkaloids (erythraline and erythroidines, respectively) were isolated and purified as before,[1,2] in the former case after 11 and in the latter after 33 days.[5] The results are given in the Table.

Feedings to *E. crista-galli* and *E. berteroana*

Precursor	Activity fed (disint. s^{-1} mg^{-1})	Incorporations (%) Erythraline [a]	Erythroidines [b]
(±)-[2-^{14}C]Tyrosine	1·92 × 10^5	0·18	
(±)-[2-^{14}C]Tyrosine	1·92 × 10^5		0·032
(±)-[5-^{3}H]-N-Norprotosinomenine	5·1 × 10^4	0·051	
(±)-[5-^{3}H]-N-Norprotosinomenine	5·0 × 10^5		0·060
(±)-[2′,6′,8-$^3H_3$]-N-Nor-reticuline	2·1 ± 10^5	0·001	
(±)-[2′,6′,8-$^3H_3$]-N-Nor-reticuline	2·55 × 10^5		0·008
(+)-[3′,5′,8-$^3H_3$]-N-Nororientaline	2·25 × 10^5	$<10^{-4}$	
(+)-[3′,5′,8-$^3H_3$]-N-Nororientaline	2·50 × 10^5		$<10^{-3}$

[a] From *E. crista-galli*. [b] From *E. berteroana*.

The incorporations for the reference tyrosine and the N-norprotosinomenine were comparable with those

[5] *Cf.* E. Leete and A. Ahmad, *J. Amer. Chem. Soc.*, 1966, **88**, 4722.

previously reported,[2] and were significantly higher than those of (+)-*N*-nororientaline and (±)-*N*-nor-reticuline.

It was noteworthy at the outset that *N*-nororientaline and orientaline had been detected in a number of *Erythrina* species [1,6] and this may have been indicative of a deeper involvement in the alkaloid biogenesis. In the event, (+)-*N*-nororientaline was consistently incorporated to the lowest extent of the potential precursors and may be a byproduct of a non-specific methylation of the (presumed) norlaudanosine precursor. This of course does not exclude the possible involvement of (−)-*N*-nororientaline in the biogenetic pathway. Indeed, this isomer corresponds stereochemically to the established norprotosinomenine precursor. The symmetry of the later biogenetic intermediates,[4b] however, removes the predictability of the stereochemical requirements for the benzyltetrahydroisoquinoline precursor.

The very low incorporation of *N*-nor-reticuline rules out any significant involvement in *Erythrina* alkaloid biogenesis; the extent that it is incorporated may represent a degree of transmethylation to *N*-norprotosinomenine rather than the coupling process of Scheme 2.

N-Norprotosinomenine is thus shown, with the possible exception of (−)-*N*-nororientaline, to be the specific *and* exclusive precursor of the erythrinan system.

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. N.m.r. spectra were run for solutions in deuteriochloroform. T.l.c. was carried out on alumina GF plates.

N-*Nor-reticuline*.—This was prepared by the method of Battersby and his co-workers,[7] as the monohydrate, m.p. (from $MeOH-Et_2O$) 160—163° (lit.,[7] 165—166°), τ 3·26br (3H, s, aryl H), 3·45br (2H, s, aryl H), 5·57 (3H, m, OH and NH), 5·90 (1H, m, H-1), 6·15 (6H, s, OMe), and 6·7—7·5 (6H, m, CH_2 envelope); *m/e* 315 (M^+), 178 (100%), 163, and 137.

(±)-[2′,6′,8-$^3H_3$]-N-*Nor-reticuline*.—Inactive (±)-*N*-nor-reticuline (15 mg) in redistilled dimethylacetamide (1 ml) containing tritiated water (0·3 ml; 5 Ci ml^{-1}) was heated in a sealed tube at 118° for 3 days. The solvents were removed *in vacuo* and the crude residue fractionated by t.l.c. (eluant 5% $CHCl_3$–MeOH) to give (±)-[2′,6′,8-$^3H_3$]-*N*-nor-reticuline (9 mg, 51%) of activity 2·36 × 10^5 disint. s^{-1} mg^{-1}.

(+)-[3′,5′,8-$^3H_3$]-N-*Nororientaline*.— (+)-*N*-Nororientaline, isolated from *E. poeppigiana* Walp.,[1] was treated similarly. The tritiated product was isolated as the hydrochloride salt, m.p. (from $MeOH-Et_2O$) 247—249° (lit.,[1] 249—250°), activity 7·70 × 10^4 disint. s^{-1} mg^{-1}.

(±)-[5-^3H]-N-*Norprotosinomenine*.—This was available from previous work.[2] The sample was repurified and then had m.p. (from $MeOH-Et_2O$) 240—242° (lit.,[2] 240—241°), activity 2·45 × 10^4 disint. s^{-1} mg^{-1}.

Feeding Experiments with E. crista-galli.—The precursors were fed by the cotton-wick method as previously described.[2] It has been shown that winter-germinated seeds fed at 5 months old during the month of June give optimum incorporations.[8] These conditions were again applied.

Each hydrochloride salt (*ca.* 2 mg) was dissolved in water (1 ml) and the solution was divided between two plants. The plants were lifted after 11 days and macerated in 0·06M-hydrochloric acid. The macerated materials were stirred for 6 days at ambient temperature then filtered through Celite pads. Inactive erythraline hydrobromide (14 mg) was added to each filtrate and the solutions were basified ($NaHCO_3$) and extracted with chloroform (6 × 50 ml). The extracts were dried (Na_2SO_4) and evaporated and the residues fractionated by p.l.c. (eluant 50% EtOAc–C_6H_6) to give erythraline, which was recrystallised to constant activity as the hydrobromide salt. The results are given in the Table.

Feeding to E. berteroana.—The precursors were fed by the cotton-wick method. A lengthy feeding time is necessary,[5] and again feeding in June to young (5-month) plants gave optimum incorporations.

The precursors (*ca.* 2 mg) were fed as before during 33 days each to one seedling. The plants were macerated and extracted with 0·06M-hydrochloric acid for 6 days. Radioinactive α-erythroidine hydrochloride (*ca.* 14 mg) was added to each filtered extract and the extracts were worked up for the unresolved mixture of α- and β-erythroidines. After p.l.c. the bases were converted into the hydrochloride salts and crystallised (the mixture crystallises without separation of the components) to constant activity. The results are given in the Table.

We thank the S.R.C. for a studentship (to C. J. P.). We also thank Dr. V. Boekelheide for the samples of erythroidines and Professor B. Franck for helpful correspondence.

[3/1732 *Received*, 16*th August*, 1973]

[6] S. Ghosal, A. Chakraborti, and R. S. Srivastava, *Phytochemistry*, 1972, **11**, 2101; K. Ito, H. Furukawa, and H. Tanaka. *Chem. Comm.*, 1970, 1076.

[7] A. R. Battersby, R. Binks, R. J. Francis, D. J. McCaldin, and H. Ramuz, *J. Chem. Soc.*, 1964, 3600.

[8] R. B. Boar, Ph.D. Thesis, London 1970.