Biosynthesis of Phenanthroindolizidine Alkaloids from 6,7-Diphenylhexahydroindolizines

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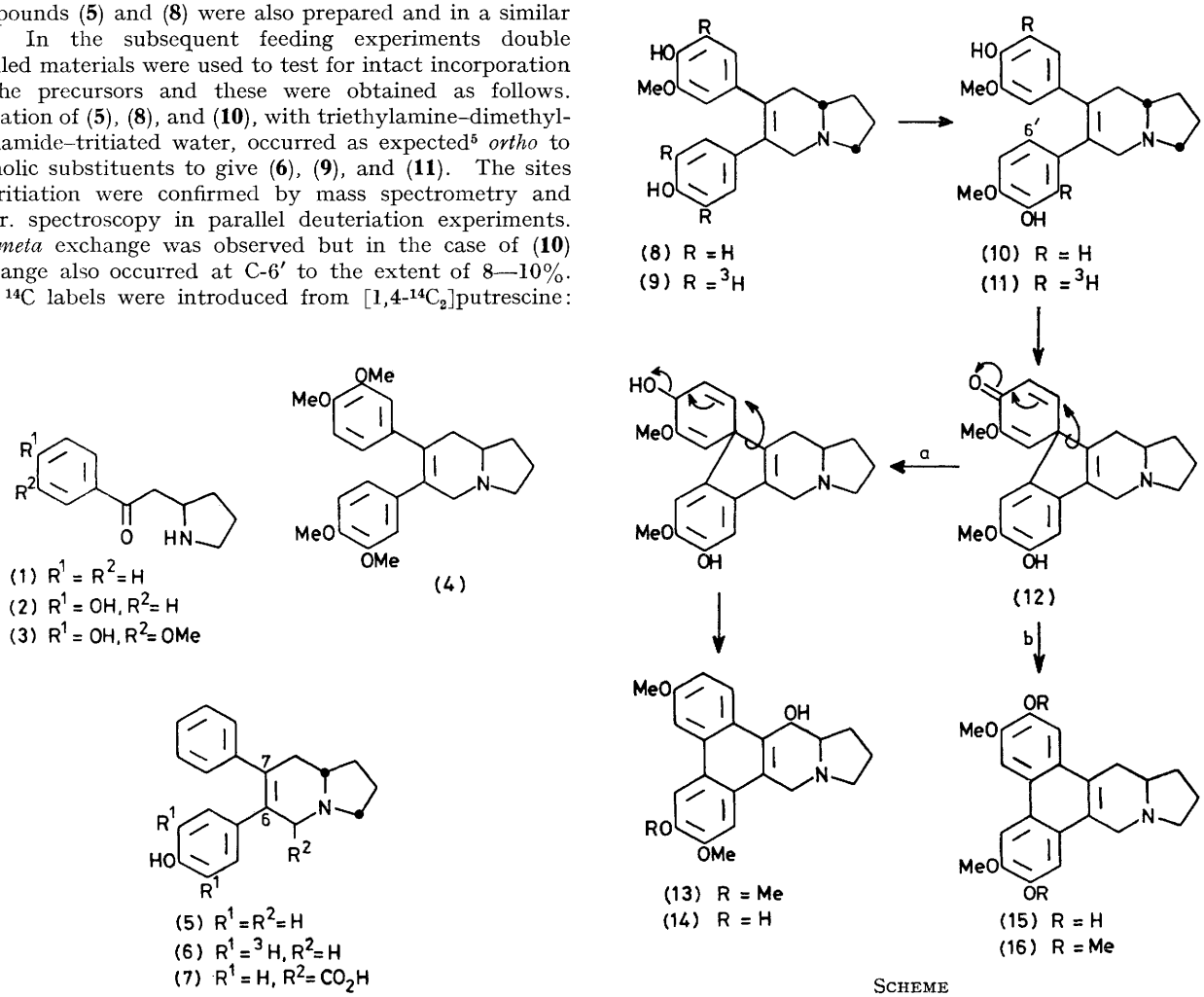
Summary Results of feeding experiments in *Tylophora asthmatica* with the 6,7-diphenylhexahydroindolizines (**5**), (**8**), and (**10**) allow definition of the biosynthesis of the phenanthroindolizidine alkaloids (**13**), (**14**), and (**16**) as being through (**8**), (**10**), and (**12**).

THE 2-phenacylpyrrolidines (**1**), (**2**), and (**3**) have been pin-pointed as important precursors for tylophorinine (**13**), and probably other phenanthroindolizidine alkaloids in *Tylophora asthmatica*.[1] These results and a consideration of the oxygenation pattern of the *T. asthmatica* bases in relation to possible biosynthesis by phenol oxidative coupling,[2] as well as the structure (**4**) for the alkaloid septicine,[3] suggested that (**10**) might be a key intermediate.[1]

The 6,7-diphenylhexahydroindolizine (**10**) was readily synthesized by adaptation of the biogenetically patterned route[4] to septicine (**4**); hydroxy-groups were protected as their benzyl ethers in the course of synthesis. The related compounds (**5**) and (**8**) were also prepared and in a similar way. In the subsequent feeding experiments double labelled materials were used to test for intact incorporation of the precursors and these were obtained as follows. Tritiation of (**5**), (**8**), and (**10**), with triethylamine–dimethylformamide–tritiated water, occurred as expected[5] *ortho* to phenolic substituents to give (**6**), (**9**), and (**11**). The sites of tritiation were confirmed by mass spectrometry and n.m.r. spectroscopy in parallel deuteriation experiments. No *meta* exchange was observed but in the case of (**10**) exchange also occurred at C-6′ to the extent of 8—10%. The ^{14}C labels were introduced from [1,4-$^{14}C_2$]putrescine: it was converted by diamine oxidase into Δ^1-pyrroline[6] which in the presence of suitable substituted benzoylacetic acids gave, in high yield, the appropriate radioactive 2-phenacylpyrrolidines. These compounds were then used for the synthesis of (**5**), (**8**), and (**10**) (● = ^{14}C) (*cf.* ref. **4**).

The three double labelled compounds (**6**), (**9**), and (**11**) (● = ^{14}C) were assimilated as aqueous solutions through wicks in the stems of *T. asthmatica*. The isolated alkaloids tylophorine (**16**), tylophorinine (**13**), and tylophorinidine (**14**) showed similar levels of incorporation for a particular precursor (Table), indicating a close biosynthetic relationship between the alkaloids. The changes in isotope ratio (Table) were consistent with the necessary tritium loss from sites in (**6**) and (**9**) which become hydroxylated in the course of biosynthesis, and from C-6′ in (**11**) during phenol coupling. It follows that (**6**), (**9**), and (**11**) are intact precursors for (**16**), (**13**), and (**14**) but the much lower



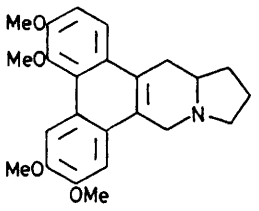
SCHEME

TABLE. Incorporation of precursors into *T. asthmatica* alkaloids.

Precursor (● = ^{14}C)	Administered $^{3}H/^{14}C$	% Incorporation[a] ($^{3}H/^{14}C$) Tylophorine (**16**)		Tylophorinine (**13**)		Tylophorinidine (**14**)		Total
(**11**)	8·0	0·12	(8·0)[b]	0·15	(8·2)[b]	0·13	(8·0)[b]	0·4
(**9**)	10·1	0·10	(10·3)[c]	0·04	(10·5)[c]	0·05	(10·1)[c]	0·2
(**6**)	12·7	0·003	(11·7)[d]	0·002	(12·1)[d]	0·003	(12·0)[d]	0·008

[a] Based on ^{14}C values. [b] Loss of 8% tritium from C-6′ allowed for. [c] Loss of one third of the tritium allowed for. [d] Loss of half the tritium allowed for.

incorporation of (**6**) suggests that it can only be utilized along a minor pathway. The major pathway to (**10**) must be (**1**)→(**2**)→(**3**)→(**8**)→(**10**). The hexahydroindolizine (**10**) can only give (**13**), (**14**), and (**16**) through the dienone (**12**), alternative courses of rearrangement (path b; Scheme), and reduction and rearrangement (path a) affording the three alkaloids after further minor modification. It is to be noted that the dienone (**12**) (and the dienol derived from it) provides a unique opportunity, in the rearrangement of such systems in alkaloid biosynthesis, for the migration of a stryryl as opposed to an aryl residue, a course which must be taken in the biosynthesis of (**13**) and (**14**), and may well be taken also in the formation of (**16**), with (**15**) as an intermediate. Isotylocrebrine (**17**) is a minor alkaloid of *T. asthmatica*.[7] Perhaps significantly its formation from (**10**) would involve aryl migration in the rearrangement of (**12**). The hexahydroindolizine (**10**) can, on paper, provide almost all the other known phenanthroindolizidine alkaloids by variation of the routes discussed above. Whether this is correct remains to be examined, as does the generation of tylophorine (**16**) from (**10**) in plants other than *T. asthmatica*.



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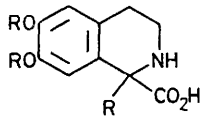

(18)

Amino-acids of the type (**18**) are important intermediates in the biosynthesis of isoquinoline alkaloids.[8] Synthesis[9] of the related hexahydroindolizine (**7**) by simple adaptation of the route[4] to septicine (**4**) opens the way for the examination of suitably substituted analogues of (**7**) as intermediates in phenanthroindolizidine biosynthesis between phenacylpyrrolidines [as (**3**)] and diphenylhexahydroindolizines [as (**8**)].

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[1] R. B. Herbert, F. B. Jackson, and I. T. Nicolson, *J.C.S. Chem. Comm.*, 1976, 865.
[2] D. H. R. Barton and T. Cohen, in 'Festschrift Dr. A. Stoll,' Birkhäuser, Basle, 1957, p. 117; A. R. Battersby, in 'Oxidative Coupling of Phenols,' eds. W. I. Taylor and A. R. Battersby, Arnold, London, 1967, p. 119.
[3] J. H. Russel, *Naturwiss.*, 1963, **50**, 443.
[4] R. B. Herbert, F. B. Jackson, and I. T. Nicolson, *J.C.S. Chem. Comm.*, 1976, 450.
[5] G. W. Kirby and L. Ogunkoya, *J. Chem. Soc.*, 1965, 6914.
[6] A. J. Clarke and P. J. G. Mann, *Biochem. J.*, 1959, **71**, 596.
[7] T. R. Govindachari, N. Viswanathan, J. Radhakrishnan, B. R. Pai, S. Natarajan, and P. S. Subramaniam, *Tetrahedron*, 1973, **29**, 891.
[8] G. J. Kapadia, G. S. Rao, E. Leete, M. B. E. Fayez, Y. N. Vaishnav, and H. M. Fales, *J. Amer. Chem. Soc.*, 1970, **92**, 6943; M. L. Wilson and C. J. Coscia, *ibid.*, 1975, **97**, 431; A. R. Battersby, R. C. F. Jones, and R. Kazlauskas, *Tetrahedron Letters*, 1975, 1873.
[9] R. B. Herbert and F. B. Jackson, unpublished work.

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