Biosynthesis of Quinine from Loganin

By A R BATTERSBY† and E S HALL

(*Robert Robinson Laboratories, University of Liverpool, Liverpool* L69 3BX)

Summary Experiments *in vivo* demonstrate the specific incorporation of [5-^{3}H]loganin into quinine

THE suggestion[1] that the quinoline alkaloids of *Cinchona* (XI—XIV) are biosynthesised from indolic precursors was supported by the specific incorporation of tryptophan into quinine[2] (XIV) Further, the close structural relation of the C_9-unit of quinine [that portion to right of the 2,3- bond (XIV)] to the C_{9-10}-unit of the *Corynanthe* alkaloids [thickened bonds in corynantheine aldehyde (V)] can be rationalised if the quinoline bases are formed by late modification of (V) or of a near relative[3] In the indole series, the C_{9-10}-unit is derived from geraniol (I) by way of loganin[4] (II), secologanin[5] (III), and vincoside[6] (IV) and if the *Cinchona–Corynanthe* relationship holds, then the same sequence should obtain for quinine (XIV) Earlier work[7,8] confirmed that geraniol is incorporated into quinine in the expected way and we now outline experiments with loganin

[5-^{3}H]Loganin[9] (II) was administered to *Cinchona ledgeriana* plants which, after 9 days, were worked for alkaloids with quinine (XIV) and cinchonine (XI) added as carriers The isolated quinine was active (0·015% incorp) and the cinchonine was inactive Radiochemical purity of the quinine was established by conversion of the base, purified to constant activity, first into the sulphate and then into the hydrochloride with recrystallisation of both salts, the molar activity was constant throughout Finally, the base recovered from the hydrochloride was converted into the *O*-benzoyl derivative which was fractionated by t l c again without change of molar activity

If the pathway outlined above from loganin to the indole alkaloids is also followed for the bases of *Cinchona*, then the ^{3}H-quinine should be labelled[10] at C-3 This was tested by modified Oppenauer oxidation of the active quinine and work-up with D_2O–DCl The isolated quinidinone (X) was radio-inactive and contained in different runs, 20—30% monodeuterioquinidinone ‡

These results lead to the following conclusions (a) loganin is a specific precursor of quinine, (b) the loss of ^{3}H from quinine on conversion into quinidinone is in keeping with the expected location of ^{3}H at C-3, (c) the lack of label in cinchonine (XI) may obviously be because (XI) was not

† Present address University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW

‡ Oxidation is accompanied by inversion[11] at C-3 Further, the isomers (VIII) and (X) interconvert in solution which accounts for loss of deuterium during the purification

being formed at the time of this experiment or this result may be an important clue to the mechanism of the late biosynthetic stages, thus, loganin could have been incorporated but with loss of the label as a consequence of the inversion step which generates the opposite configuration at C-3 in (XI) Experiments concerning this aspect and the use of vincoside (IV) and corynantheine aldehyde (V) as precursors of quinine are in progress

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