Total Synthesis of Hydrocinchonidine and Hydrocinchonine from an Indole Derivative *via* Oxidation with Singlet Oxygen

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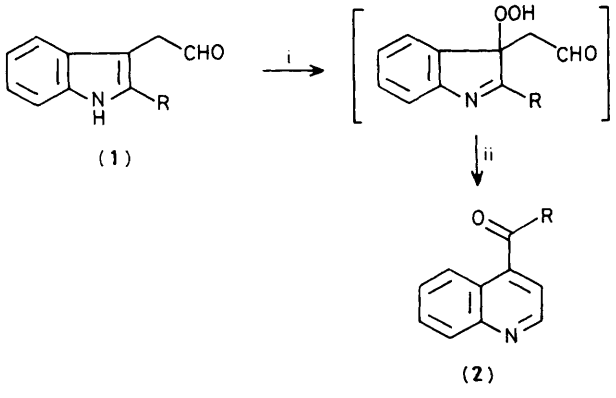
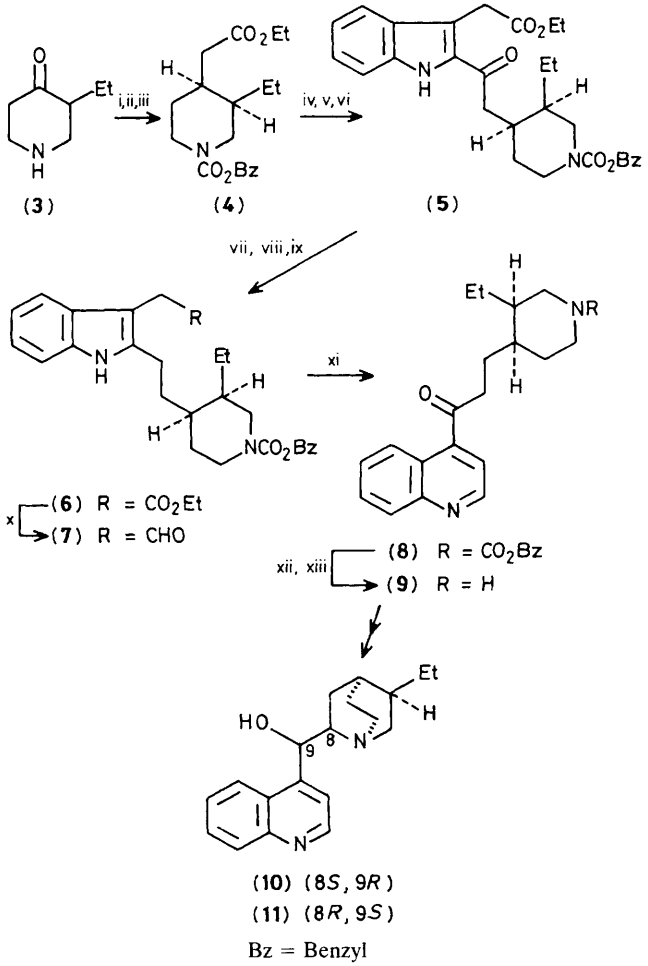
Hydrocinchotoxine (**9**), which has been converted into hydrocinchonidine (**10**) and hydrocinchonine (**11**), was synthesised *via* photo-oxygenation of the indole derivative (**7**) followed by treatment with dimethyl sulphide and dilute acetic acid.

It is well known that *Cinchona* alkaloids possessing important pharmacological activities are biosynthesised from indole alkaloids, such as corynantheal.[1] However no biomimetic synthesis of *Cinchona* alkaloids has been reported. Previously we described the conversion of indoles (**1**) into quinolines (**2**) through N(1)–C(2) fission by singlet oxygen.[2] We now report a novel synthesis of hydrocinchotoxine (**9**),[3] correlated to hydrocinchonidine (**10**) and hydrocinchonine (**11**), from an indole derivative (**7**) utilizing the above method.

Protection of 3-ethylpiperidin-4-one (**3**)[4] with benzyl chloroformate, followed by Emmons reaction[5] of the carbamate and catalytic hydrogenation using Adams catalyst, afforded in highly stereoselective manner the *cis*-ester (**4**) in 76% yield from (**3**). The ester (**4**) was hydrolysed with LiOH in H_2O–MeOH and then chlorinated with $(COCl)_2$ in CH_2Cl_2 to give the corresponding acid chloride, which was condensed with ethyl indole-3-acetate in the presence of $SnCl_4$ in Et_2O at 0 °C for 10 min. Reduction of the 2-acylindole (**5**), obtained in 71% yield from (**4**), with $NaBH_4$, followed by dehydration of the alcohol with AcOH in hot benzene and catalytic hydrogenation produced the indole derivative (**6**) in 84% yield from (**5**).



Scheme 1. i, $^1O_2$; ii, Me_2S then dilute AcOH.



Scheme 2. *Reagents:* i, BzOCOCl, $NaHCO_3$; ii, $(EtO)_2POCH_2CO_2Et$, NaH; iii, H_2, PtO_2; iv, LiOH; v, $(COCl)_2$; vi, ethyl indole-3-acetate, $SnCl_4$; vii, $NaBH_4$; viii, AcOH, heat; ix, H_2, PtO_2; x, DIBAL; xi, $^1O_2$; Me_2S; dil. AcOH; xii, Me_3SiI; xiii, (−)-di-*p*-toluoyl-L-tartaric acid.

Reduction of (**6**) with Bu^i_2AlH (DIBAL) in a mixture of CH_2Cl_2 and dimethoxyethane (DME) at −78 °C gave the aldehyde (**7**), $\nu_{max.}$ ($CHCl_3$) 3470 (NH), 1725 and 1690 cm^{-1} (C=O), δ_H ($CDCl_3$) 3.61(2H, d, *J* 3 Hz, CH_2CHO) and 9.63(1H, t, *J* 3 Hz, CHO), in 69% yield. Transformation of (**7**) into (±)-*N*-protected hydrocinchotoxine (**8**) was carried out as previously:[2] irradiation of the solution of (**7**) in MeOH in the presence of Rose Bengal with a 200 W halogen lamp in a flow of oxygen at −10 °C for 1 h, accompanied by the subsequent reactions, reduction with Me_2S at −20 °C for 1 h and treatment with AcOH in a mixture of H_2O and tetrahydrofuran (THF) at 25 °C for 10 h. The desired 4-acylquinoline (**8**), $\lambda_{max.}$ (MeOH) 316(ε 3 870), 305(3 750), 238(10 700), and 232 nm (11 800), $\nu_{max.}$ ($CHCl_3$) 1695 cm^{-1} (C=O), was obtained in 64% yield after purification by chromatography on silica gel. Deprotection of (**8**) with trimethylsilyl iodide[6] in MeCN furnished (±)-hydrocinchotoxine (**9**) in 73% yield. Optical resolution of the racemate (**9**) was achieved by recrystallisation of the di-*p*-toluoyl-L-tartrate, m.p. 150.5—151.5 °C, $[\alpha]_D^{26}$ −57.9° (*c* 0.202, MeOH) from Pr^iOH. U.v.(MeOH), i.r.($CHCl_3$), n.m.r.($CDCl_3$), and mass spectra and t.l.c. behaviour of the (+)-free base (**9**), $[\alpha]_D^{30}$ +1.15° (*c* 1.39, EtOH) {lit.,[7] $[\alpha]_D$ +1.0° (EtOH)}, were identical with those of the authentic sample prepared from cinchonine.[7] Since the base (**9**) has been converted into hydrocinchonidine (**10**) and hydrocinchonine (**11**),[8] a formal total synthesis of these *Cinchona* alkaloids has been accomplished.

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