Total Synthesis of Hydrocinchonidine and Hydrocinchonine *via* Photo-oxygenation of an Indole Derivative

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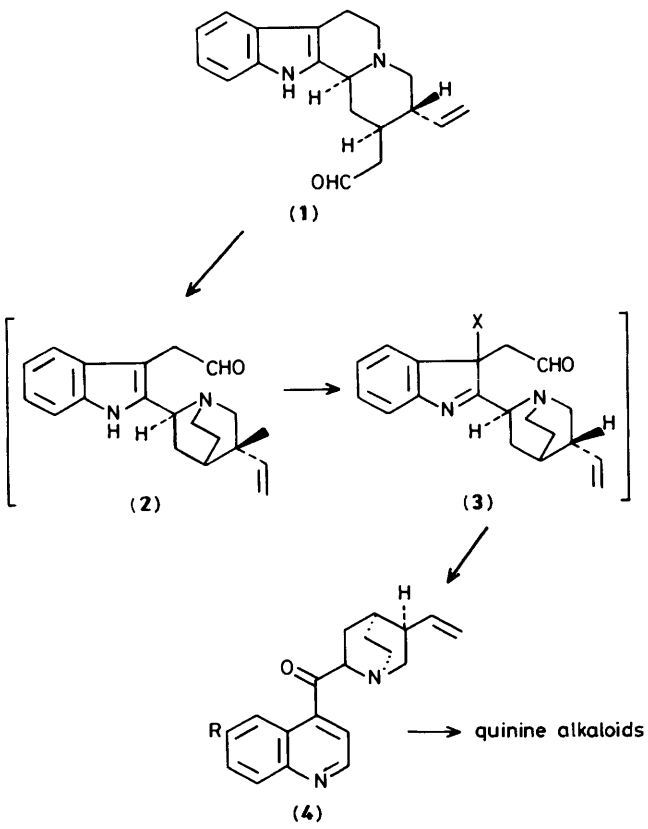
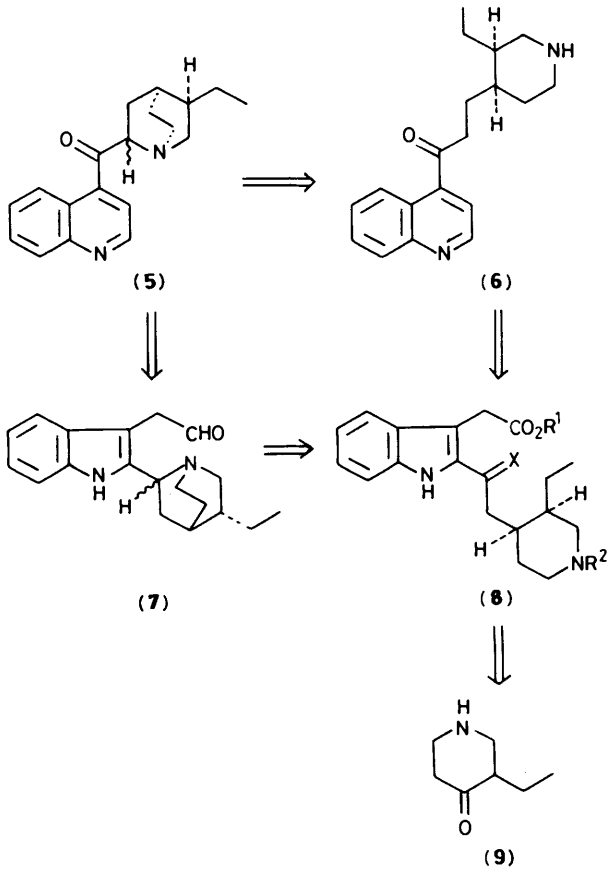
3-Ethylpiperidin-4-one (**9**) has been stereoselectively converted into (±)-2-{2-[(3*RS*,4*SR*)-*N*-benzyloxycarbonyl-3-ethyl-4-piperidyl]ethyl}-3-formylmethylindole (**20**), whose ring transformation *via* photo-oxygenation produced the 4-acylquinoline (**23**). Optical resolution of (±)-hydrocinchotoxine (**24**), derived from (**23**), led to a formal total synthesis of (+)-hydrocinchonine (**25**) and (−)-hydrocinchonidine (**26**).

The medicinally important *Cinchona* alkaloids have been the targets of several synthetic schemes.[1–3] The tracer experiments on *Cinchona ledgeriana* by Battersby showed that *Cinchona* alkaloids were biosynthesized from an indole alkaloid, corynantheal (**1**), *via* the oxidation of cinchonaminal (**2**) to (**3**)[4] as depicted in Scheme 1. However no biomimetic approach from indole derivatives to *Cinchona* alkaloids has been reported. Recently we successfully carried out the transformation of indoles into quinolines through N(1)–C(2) fission by singlet oxygen[5] and have now carried out a synthesis of the *Cinchona* alkaloids *via* photo-oxygenation of the indole derivatives (**7**) or (**8**) derived from the known piperidone (**9**) as shown in Scheme 2. We now describe a synthesis of hydrocinchotoxine (**24**), and formal syntheses of hydrocinchonine (**25**) and hydrocinchonidine (**26**)[6] from the indole derivative (**8**).[7]



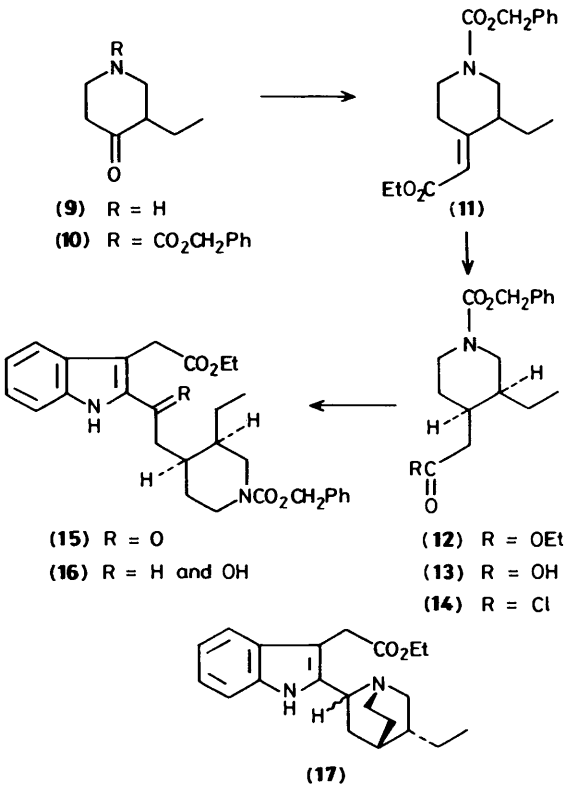
Scheme 1.



Scheme 2.

Protection of 3-ethylpiperidin-3-one (**9**)[8] with benzyl chloroformate gave the carbamate (**10**) in 87% yield. Reaction of (**10**) with triethyl phosphonoacetate in the presence of sodium hydride[9] produced quantitatively the α,β-unsaturated ester (**11**) as a single isomer. The *E*-structure (**11**) was tentatively assigned on the basis of mechanistic considerations. The α,β-unsaturated ester (**11**) was hydrogenated in the presence of Adams catalyst to afford the saturated ester (**12**), which was quantitatively obtained as a single stereoisomer. The *cis* configuration was assigned to it on mechanistic grounds and this was confirmed by its conversion into known natural products.

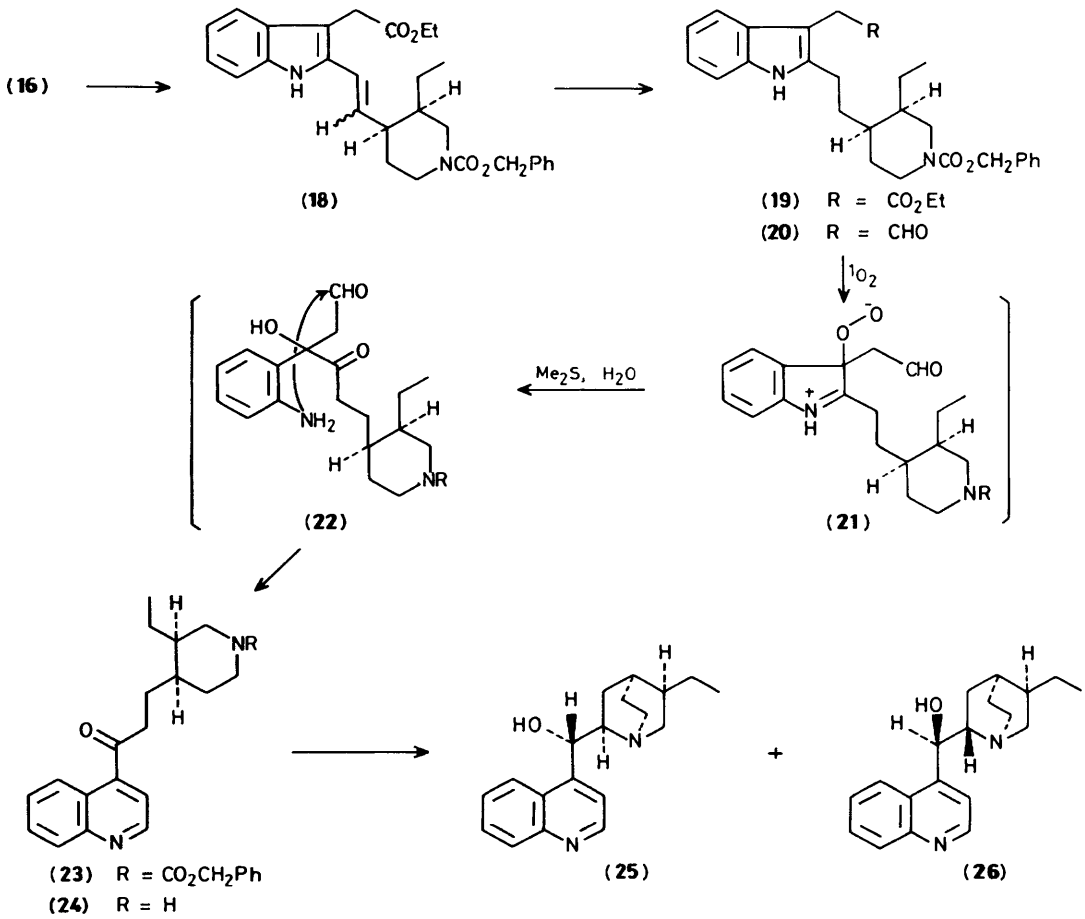
Introduction of the 4-piperidylacetyl group into the C-2 position of ethyl indol-3-ylacetate was achieved by condensation with the acid chloride in the presence of tin(IV) chloride.



Scheme 3.

Hydrolysis of the ester (**12**) using lithium hydroxide, followed by chlorination of the resulting acid (**13**) with oxalyl chloride yielded the corresponding acid chloride (**14**). A mixture of ethyl indol-3-ylacetate and the acid chloride (**14**) in diethyl ether was treated with tin(IV) chloride for 5 min with ice-cooling. Work-up furnished the desired ketone (**15**) in 71% overall yield from the ester (**12**). The condensation when carried out in methylene dichloride gave a less satisfactory result. When boron trifluoride–diethyl ether was utilised as a condensing agent, the ketone (**15**) was obtained in only 22% yield. Next construction of the quinuclidine (**17**) from (**15**) was examined by several reaction sequences, including reductive amination; all, however, proved fruitless. Therefore our attention turned to the ring transformation of the piperidylethyl derivative (**8**). Reduction of the ketone group in (**15**) to give (**19**) was performed in the following three steps. Thus reduction of (**15**) with sodium borohydride, followed by dehydration of the resulting epimeric alcohols (**16**) by heating in a mixture of acetic acid and benzene, and the subsequent hydrogenation of the olefin (**18**) using Adams catalyst produced the ester (**19**) in 84% overall yield. Reduction of the ester (**19**) with di-isobutylaluminium hydride, carried out at −78 °C in a mixture of dimethoxyethane and methylene dichloride, gave the substrate (**20**) for the photo-oxygenation in 69% yield.

The ring transformation was conducted in a three-step one-pot reaction.[5] Irradiation of a solution of the aldehyde (**20**) in the presence of Rose Bengal and oxygen in methanol at −20 °C using a 200-W halogen lamp for 1 h, followed by reduction using dimethyl sulphide and the subsequent treatment using dilute acetic acid in tetrahydrofuran afforded the quinoline derivative (**23**) in 69% overall yield. The reaction process could be



Scheme 4.

explained as follows. Oxidation of the indole (**20**) with singlet oxygen formed the zwitterion (**21**), which was hydrolysed to the keto aldehyde (**22**) after reduction. Recondensation followed by aromatization *via* dehydration produced the 4-acylquinoline (**23**).

The benzyloxycarbonyl group of (**23**) was removed by the action of trimethylsilyl iodide[10] in acetonitrile giving (±)-hydrocinchotoxine (**24**) in 73% yield. All properties of the synthetic compound (**24**) were identical with those of the authentic compound, prepared from cinchonine,[11] except the optical rotation. Optical resolution was achieved by fractional recrystallization of the salt with (−)-di-*p*-toluoyl-L-tartaric acid. (+)-Base (**24**), $[\alpha]_D^{30}$ +1.15° (*c* 0.202, methanol), was identical with the authentic specimen in all respects. Since (+)-hydrocinchotoxine (**24**) has been transformed into (+)-hydrocinchonine (**25**) and (−)-hydrocinchonidine (26),[6] a formal total synthesis of these *Cinchona* alkaloids has been accomplished.

Experimental

General Methods.—M.p.s were determined on a Yanaco micro-melting point apparatus and are uncorrected. U.v. spectra were taken by a Hitachi 124 spectrophotometer. I.r. spectra were recorded in $CHCl_3$ solution on a Hitachi 260-10 spectrophotometer. N.m.r. spectra were measured on a JEOL JNM-PMX-60 or a JEOL-PS-100 spectrometer in $CDCl_3$. Chemical shifts are reported as δ_H values relative to internal $SiMe_4$. Ordinary mass spectra were taken on a Hitachi M-52G machine, and accurate mass spectra with a JEOL-JMS-01SG-2 spectrometer. All new compounds described in the Experimental section were homogeneous on t.l.c. All reactions except hydrogenation and oxygenation were run under an atmosphere of dry nitrogen and magnesium sulphate was used to dry extracts unless otherwise stated. Optical rotations were measured on a JASCO-DIP-340 polarimeter.

(±)-N-*Benzyloxycarbonyl-3-ethyl-4-piperidone* (**10**).—Sodium hydroxide (1.16 g, 26.0 mmol) was added to a solution of the piperidine hydrochloride (**9**)[8] (4.26 g, 26.0 mmol) in water (10 ml) with ice-cooling. After further addition of sodium hydrogen carbonate (4.37 g, 52.3 mmol) and benzene (30 ml), benzyl chloroformate (5.58 ml, 39 mmol) was slowly added to the mixture with vigorous stirring. After being stirred for 3.5 h at room temperature, the mixture was extracted with benzene and the extract was washed with brine, dried, and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with ethyl acetate–hexane (3:17, v/v) afforded the *carbamate* (**10**) (5.91 g, 87%) as an oil (Found: C, 68.6; H, 7.35; N, 4.95. $C_{15}H_{19}NO_3$ requires C, 68.95; H, 7.35; N, 5.35); $\delta_{max.}$ 1 697 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.92 (3 H, br t, *J* 8 Hz, Me), 1.10—1.90 (2 H, m, CH_2), 2.15—2.50 (3 H, m, CH_2 and CH), 3.01—4.20 (4 H, m, 2 × CH_2), 5.16 (2 H, s, OCH_2), and 7.28—7.32 (5 H, br s, Ph); *m/z* 261 (M^+).

(±)-*Ethyl* (N-*Benzyloxycarbonyl-3-ethyl-4-piperidylidene*)*acetate* (**11**).—Triethyl phosphonoacetate (15.3 ml, 77.3 mmol) was added to a suspension of 60% sodium hydride (2.8 g, 70.8 mmol) in dry tetrahydrofuran (150 ml) at room temperature. The mixture was stirred for 0.5 h after which a solution of the above ketone (**10**) (16.8 g, 64.4 mmol) in dry tetrahydrofuran (50 ml) was added dropwise with ice-cooling. The mixture was stirred for 2 h at room temperature after which most of the solvent was evaporated and the mixture was then poured into 10% aqueous ammonium chloride. The resulting mixture was extracted with methylene dichloride and the extract was washed with brine, dried, and evaporated to give a residue, which was chromatographed on silica gel. Elution with methylene dichloride afforded the α,β-*unsaturated ester* (**11**) (21.3 g, 100%) as an oil, $\nu_{max.}$ 1 696 (C=O) and 1 650 cm^{-1} (C=C); δ_H 0.87 (3 H, br t, *J* 8 Hz, CH_2Me), 1.28 (3 H, t, *J* 7.4 Hz, OCH_2Me), 1.42—3.85 (9 H, m, 4 × CH_2 and CH), 4.14 (2 H, q, *J* 7.4 Hz, OCH_2Me), 5.13 (2 H, s, OCH_2Ph), 5.69 (1 H, br s, CH=), and 7.27—7.41 (5 H, br s, Ph); *m/z* 331 (M^+) (Found: M^+, 331.1764. $C_{19}H_{25}NO_4$ requires *M*, 331.1782).

(±)-(3RS,4SR)-*Ethyl* (N-*Benzyloxycarbonyl-3-ethyl-4-piperidyl*)*acetate* (**12**).—A mixture of platinum oxide (700 mg) and ethanol (100 ml) was stirred for 15 min under a hydrogen atmosphere before addition of a solution of the α,β-unsaturated ester (**11**) (19.6 g, 59.2 mmol) in ethanol (200 ml). The mixture was then stirred for 14 h under the hydrogen atmosphere at ambient temperature. After further addition of platinum oxide (300 mg), the mixture was stirred for 6 h under the same conditions. The catalyst was filtered off, and the filtrate was evaporated to give a residue, which was chromatographed on alumina (grade III). Elution with chloroform afforded the *ester* (**12**) (19.7 g, 100%) (Found: C, 68.5; H, 8.2; N, 3.8. $C_{19}H_{27}NO_4$ requires C, 68.45; H, 8.15; N, 4.2%); $\nu_{max.}$ 1 720 and 1 684 cm^{-1} (C=O); δ_H 0.62—1.01 (3 H, m, CH_2Me), 1.25 (3 H, t, *J* 7.1 Hz, OCH_2Me), 1.10—1.60 (5 H, m, 2 × CH_2 and CH), 2.02—2.32 (3 H, m, CH_2 and CH), 2.80—3.93 (4 H, m, 2 × CH_2), 4.12 (2 H, q, *J* 7.1 Hz, OCH_2Me), 5.10 (2 H, s, OCH_2Ph), and 7.26—7.51 (5 H, br s, Ph); *m/z* 333 (M^+).

(±)-(3RS,4SR)-(N-*Benzyloxycarbonyl-3-ethyl-4-piperidyl*)-*acetic Acid* (**13**).—A mixture of the above ester (**12**) (4.47 g, 13.4 mmol), lithium hydroxide monohydrate (1.67 g, 40.2 mmol), methanol (27 ml), and water (13 ml) was stirred for 2 h at ambient temperature and then concentrated under reduced pressure. The residue was taken up into water (150 ml) and the solution washed with ether. The aqueous solution was acidified by slow addition of 5% hydrochloric acid and extracted with chloroform. The chloroform solution was dried and evaporated to give the *acid* (**13**) (4.09 g, 100%); $\nu_{max.}$ 2 850—2 600 (OH) and 1 695 cm^{-1} (C=O); δ_H 0.75—1.00 (3 H, m, CH_2Me), 1.10—1.55 (5 H, m, 2 × CH_2 and CH), 1.95—2.35 (3 H, m, CH_2 and CH) 2.85—4.05 (4 H, m, 2 × CH_2), 5.09 (2 H, s, OCH_2Ph), 7.22—7.36 (5 H, br s, Ph), and 7.70 (1 H, br s, CO_2H); *m/z* 305 (M^+) (Found: M^+, 305.1615. $C_{11}H_{23}NO_4$ requires *M*, 305.1626).

(±)-2-[(3RS,4SR)-N-*Benzyloxycarbonyl-3-ethyl-4-piperidyl-acetyl*]-3-*ethoxycarbonylmethylindole* (**15**).—Oxalyl chloride (0.66 ml, 6.90 mmol) was added to a solution of the above acid (**13**) (2.11 g, 6.90 mmol) in dry methylene dichloride (30 ml) and the mixture was stirred for 12 h at ambient temperature. After addition of dry benzene (30 ml), the mixture was evaporated to give the acid chloride (**14**) as an oil, which was subsequently used in the following reaction.

Tin(IV) chloride (2.46 ml, 20.7 mmol) was added to a mixture of the acid chloride (**14**) and ethyl indol-3-ylacetate (1.68 g, 8.28 mmol) in dry diethyl ether (60 ml) with ice-cooling. After being stirred for 5 min, the resulting mixture was poured into ice–water. The mixture was extracted with benzene and the extract was washed with saturated aqueous sodium hydrogen carbonate and brine, dried, and evaporated. The residue was purified by silica gel column chromatography eluting with ethyl acetate–methylene dichloride (1:4, v/v) to afford the *ketone* (**15**) (2.39 g, 71%1) as a syrup (Found: C, 68.4; H, 6.5; N, 5.3. $C_{29}H_{34}N_2O_5 \cdot H_2O$ requires C, 68.6; H, 6.9; N, 5.3%); $\nu_{max.}$ 3 460 (NH) and 1 738 and 1 690 cm^{-1} (C=O); δ_H 0.75—1.05 (3 H, m, CH_2Me), 1.26 (3 H, t, *J* 6.9 Hz, OCH_2Me), 1.20—1.65 (5 H, m, 2 × CH_2 and CH), 2.20—2.60 (1 H, m, CH), 2.75 (2 H, d, *J* 7 Hz, $COCH_2$), 2.85—4.00 (4 H, m, 2 × CH_2), 4.11 (2 H, s, CH_2CO_2), 4.17 (2 H, q, *J* 6.9 Hz, OCH_2Me), 5.09 (2 H, s,

OCH_2Ph), 7.01—7.70 (9 H, m, 9 × ArH), and 9.15 (1 H, br s, NH); *m/z* 490 (M^+).

(±)-2-[(3RS,4SR)-N-*Benzyloxycarbonyl*-3-*ethyl*-4-*piperidylethyl*]-3-*ethoxycarbonylmethylindole* (**19**).—Sodium borohydride (145 mg, 15.4 mmol) was added in small portions at ambient temperature to a solution of the above ketone (**15**) (754 mg, 1.54 mmol) in methanol (20 ml). After the mixture had been stirred for 30 min the solvent was evaporated off. The residue was partitioned between water and chloroform. The chloroform solution was separated, dried, and evaporated to give the crude alcohol (**16**) (760 mg) as a syrup, $\nu_{max.}$ 3 460 (NH) and 1 720 and 1 690 cm^{-1} (C=O); δ_H 0.85—1.00 (3 H, m, CH_2Me), 1.25 (3 H, t, *J* 7.0 Hz, OCH_2Me), 3.65 (2 H, s, CH_2CO_2), 4.06 (2 H, q, *J* 7.0 Hz, OCH_2Me), 5.02 (2 H, s, OCH_2Ph), and 8.90 (1 H, br s, NH), which was used in the following reaction without further purification.

The above alcohol (**16**) (760 mg) dissolved in a mixture of acetic acid and benzene (1:4, v/v; 20 ml) was refluxed for 4 h. After evaporation of the solvents, the residue was dissolved in ethanol (30 ml) and the solution added to a suspension of platinum oxide (63 mg) in ethanol (30 ml), which had been stirred for 5 min under a hydrogen atmosphere; the resulting mixture was stirred for 2 h at room temperature under hydrogen. The mixture was then filtered to remove the catalyst and the filtrate evaporated to give a residue which was subjected to chromatography on silica gel. Elution with methylene dichloride afforded the *ester* (**19**) (616.5 mg, 84%) as a pale yellow oil (Found: C, 73.25; H, 7.6; N, 5.4. $C_{29}H_{36}N_2O_4$ requires C, 73.1; H, 7.6; N, 5.9%); $\nu_{max.}$ 3 497 (NH) and 1 730 and 1 687 cm^{-1} (C=O); δ_H 0.75—1.02 (3 H, m, CH_2Me), 1.22 (3 H, t, *J* 6.9 Hz, OCH_2Me), 1.31—1.70 (8 H, m, 3 × CH_2 and 2 × CH), 2.50—3.05 (4 H, m, 2 × CH_2), 3.63 (2 H, s, CH_2CO_2), 3.60—3.95 (2 H, m, CH_2), 4.09 (2 H, t, *J* 6.9 Hz, OCH_2Me), 5.09 (2 H, s, OCH_2Ph), 7.00—7.55 (9 H, m, 9 × ArH), and 7.96 (1 H, m, NH); *m/z* 476 (M^+).

(±)-N-*Benzyloxycarbonylhydrocinchotoxine* (**23**).—1M Diisobutylaluminium hydride in hexane (0.40 ml, 0.4 mmol) was added slowly to a solution of the ester (**19**) (175 mg, 0.368 mmol) in a mixture of dry dimethoxyethane and dry methylene dichloride (1:1, v/v; 10 ml) at −78 °C and the mixture was stirred for 10 min. After addition of methanol (0.5 ml), the resulting mixture was stirred for 10 min and poured into 3% hydrochloric acid. The mixture was thoroughly extracted with methylene dichloride and the extract was washed with water, dried, and evaporated to give a residue, which was purified by silica gel column chromatography. Elution with methylene dichloride afforded the aldehyde (**20**) (109.4 mg, 69%) as a rather unstable oil, $\nu_{max.}$ 3 480 (NH) and 1 728 and 1 690 cm^{-1} (C=O); δ_H 0.70—0.98 (3 H, m, CH_2Me), 3.61 (2 H, d, *J* 2.5 Hz, CH_2CHO), 5.02 (2 H, s, OCH_2Ph), 8.03 (1 H, br s, NH), and 9.54 (1 H, t, *J* 2.5 Hz, CHO).

A solution of the above aldehyde (**20**) (33.3 mg, 0.077 mmol) and Rose Bengal (10 mg) in methanol (30 ml) was irradiated for 1 h with a 200-W halogen lamp through a Pyrex filter at −20 °C with oxygen bubbling through the solution. Dimethyl sulphide (1.5 ml) was added to the resulting mixture which was then stirred for 1 h at the same temperature without bubbling of oxygen. After evaporation, a mixture of acetic acid, water, and tetrahydrofuran (1:1:2, v/v/v; 20 ml) was added to the residue and the mixture was stirred for 10 h at room temperature and then concentrated under reduced pressure. The resulting solution was poured into 10% aqueous sodium hydroxide and the mixture was extracted with benzene. The extract was washed with water, dried, and evaporated to give a residue, which was chromatographed on silica gel. Elution with ethyl acetate–methylene dichloride (1:9, v/v) afforded the *quinoline derivative* (**23**) (23.0 mg, 69%) as a syrup (Found: C, 75.1; H, 6.85; N, 6.05. $C_{27}H_{30}N_2O_3$ requires C, 75.3; H, 7.0; N, 6.5%); $\lambda_{max.}$(MeOH) 232 (11 810), 238 (10 650), 305 (3 750), and 315 nm (3 870); $\nu_{max.}$ 1 690 cm^{-1} (C=O); δ_H 0.75—1.05 (3 H, m, CH_2Me), 1.10—1.90 (8 H, m, 3 × CH_2 and 2 × CH), 2.80—3.10 (4 H, m, 2 × CH_2), 3.80—4.18 (2 H, m, CH_2), 5.08 (2 H, s, OCH_2Ph), 7.24—7.38 (5 H, br s, Ph), 7.40—8.30 (5 H, m, 5 × ArH), and 8.85—9.02 (1 H, m, ArH); *m/z* 430 (M^+).

(±)-*Hydrocinchotoxine* (**24**).—Trimethylsilyl iodide (0.136 ml, 0.956 mmol) was slowly added to a solution of the above carbamate (**23**) (102.9 mg, 0.239 mmol) in dry acetonitrile (5 ml) with ice-cooling and the mixture was stirred for 30 min at the same temperature and then concentrated under reduced pressure. The residue was poured into 10% hydrochloric acid with ice-cooling and the mixture was washed with ether. The aqueous solution was basified by addition of 10% aqueous potassium hydroxide and the liberated base was thoroughly extracted with methylene dichloride. The extract was washed with water, dried (K_2CO_3), and evaporated to yield a residue, which was subjected to column chromatography on alumina. Elution with methanol–chloroform (1:5, v/v) gave (±)-hydrocinchotoxine (**24**) (48.4 mg, 73%) as a yellowish syrup, whose i.r., n.m.r., and mass spectra were identical with those of the authentic compound, prepared from cinchonine.[11]

(+)-*Hydrocinchotoxine* (**24**).—Ether was added to a solution of the above racemate (**24**) (144.5 mg, 0.488 mmol) and di-*p*-toluoyl-L-tartaric acid monohydrate (197.1 mg) in methylene dichloride. The resulting crystals were repeatedly recrystallised from isopropyl alcohol to give the salt (111 mg) as fine needles, m.p. 144—146 °C, $[\alpha]_D^{26}$ −64.28° (*c* 0.112, methanol). The salt (111 mg, 0.161 mmol) was partitioned between 10% ammonia and chloroform. The chloroform layer was washed with water, dried, and evaporated to give (+)-hydrocinchotoxine (**24**) (47 mg) as a syrup, $[\alpha]_D^{30}$ +1.15° (*c* 1.39, ethanol) {lit.,[11] $[\alpha]_D$ +1.0° (ethanol)}, whose properties were identical with those of the authentic compound in all respects.

Acknowledgments

We thank Mr. K. Kawamura, Miss K. Mushiake, Miss E. Koike, and Mrs. H. Nagai of this Institute for microanalysis, spectral measurements, and preparation of the manuscript.

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Received 15*th June* 1987; *Paper* 7/1052