(45) P. Hambright in ref 36, p 233; J. W. Buchler in ref 36, p 157.
(46) H. Scheer, U. Linsenmeier, and C. Krauss, *Hoppe-Seyler's Z. Physiol. Chem.*, **358**, 185 (1977).
(47) H. Scheer and J. J. Katz, to be published.
(48) L. L. Shipman, T. R. Janson, G. J. Ray, and J. J. Katz, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2873 (1975).
(49) G. Doring, G. Stiehl, and H. T. Witt, *Z. Naturforsch. G*, **22**, 639 (1967); G. Doring, G. Renger, J. Vater, and H. T. Witt, *ibid.*, **24**, 1139 (1967).

Total Synthesis of *Cinchona* Alkaloids. 1. Synthesis of Meroquinene

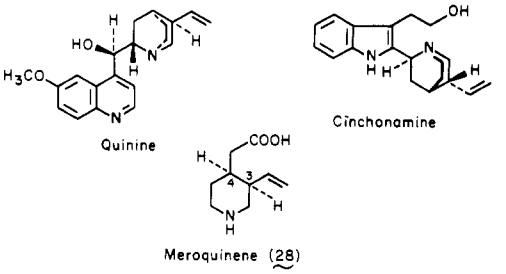
Milan R. Uskoković,* Thomas Henderson, Charles Reese, Hsi Lin Lee, Guenter Grethe, and Jürg Gutzwiller

Contribution from the Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received June 13, 1977*

Abstract: Meroquinene (**28**), the key intermediate in several total syntheses of *Cinchona* alkaloids, has been synthesized by three methods. Starting from *cis*-2-benzoyloctahydro-6(2*H*)-isoquinolone (**1**), the acetic acid and the vinyl side chains of **28** were formed by either Baeyer–Villiger oxidation, opening of the lactone **2** to the hydroxy ester **4**, and elimination, or by Schmidt rearrangement, nitrosation of the lactam **7**, and pyrolysis. A completely stereospecific synthesis of meroquinene (**28**) was effected by catalytic hydrogenation of 3-ethyl-4-pyridineacetic acid methyl ester (**21**), followed by conversion of the ethyl group of **23** into the vinyl group by Löffler–Freytag rearrangement and elimination.

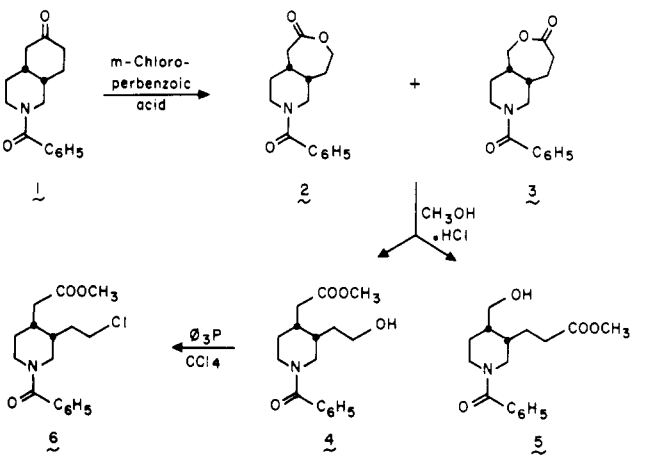
The medically important alkaloids quinine and quinidine have long been subjects of one of the most intensive structural and synthetic investigations in classical organic chemistry.[1] The original and quite elegant syntheses of these alkaloids[2-4] are unfortunately not amenable to large-scale preparation of various analogues. With such an aim in mind, we have investigated new synthetic routes to these alkaloids in the last few years. These investigations have led to several practical solutions which are reported in this paper and in the accompanying publications.

The quinuclidine ring with three chiral centers is the characteristic feature of the *Cinchona* alkaloids and elaboration of this ring system is the key for a successful total synthesis.[1,5] The two contiguous chiral centers at C-3 and C-4 have always controlled the selection of the synthetic precursors. In the classical synthesis[2] of these alkaloids, the quinuclidine ring was derived from 3(*R*)-vinyl-4(*S*)-piperidinepropionic acid (homomeroquinene), obtained by the degradation of cinchonine.[6] The first total synthesis of these alkaloids was formally achieved with the synthesis of homomeroquinene itself.[3,7] All recent syntheses of *Cinchona* alkaloids,[8-11] however, utilize the corresponding nor analogue, 3(*R*)-vinyl-4(*S*)-piperidineacetic acid (meroquinene), which is also a degradation product of cinchonine.[12] In this paper, we describe in full detail the synthesis of meroquinene in its racemic form as well as in both enantiomeric modifications.



In the designing stage of the meroquinene synthesis, we were primarily concerned with the cis configuration of the two side chains. Two approaches were explored, one starting from the preformed *cis*-isoquinolone (**1**),[13] and the other in which the cis configuration was to be achieved by the hydrogenation of a pyridine precursor. In the first case, the formation of meroquinene required an oxidative fragmentation of the cyclohexanone ring of **1** to produce the acetic acid and the vinyl side chains. Baeyer–Villiger oxidation was first examined for this purpose (Scheme I). Treatment of **1** with *m*-chloroperbenzoic acid yielded the desired lactone **2** and its isomer **3** as a mixture, which could not be separated. When stirred at room temperature in dilute methanolic hydrogen chloride, the lactones opened to give the hydroxy esters **4** and **5**, which could be separated by repeated column chromatography. However, the overall yield of the desired hydroxy ester **4** from **1** was only 35%, while the isomeric **5** was obtained in 57% yield. The ester **4** was converted in high yield to the corresponding chloro analogue **6**, which was then transformed into racemic *N*-benzoylmeroquinene (**13**) (Scheme V).

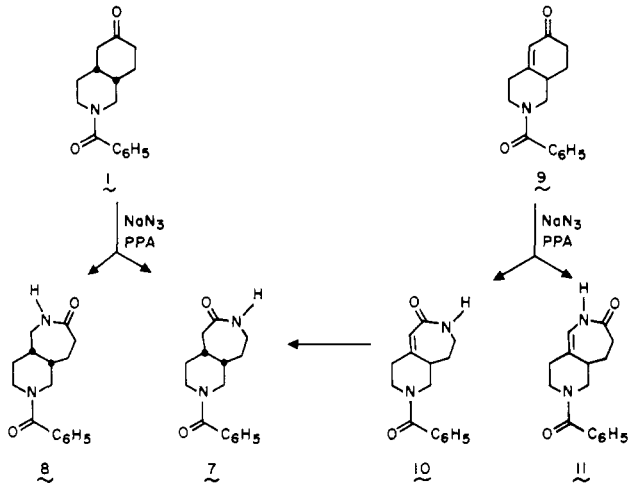
Scheme I



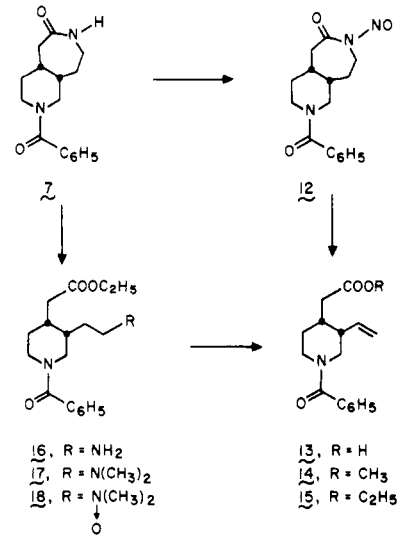
Since an opposite regioselectivity in the ring fragmentation of **1** was to be achieved, we turned our attention to the Schmidt rearrangement[14] (Scheme II). On exposure to sodium azide in polyphosphoric acid, the ketone **1** was transformed quantitatively to a 1:1 mixture of lactams **7** and **8**, which could be separated from each other by fractional crystallization. A further improvement in the desired regioselectivity was observed in the Schmidt rearrangement of the corresponding

0002-7863/78/1500-0571$01.00/0

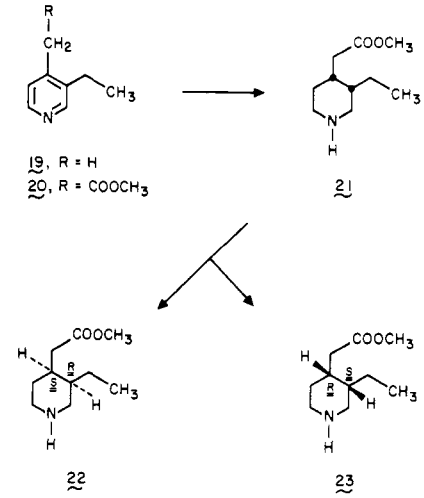
Scheme II



Scheme III



Scheme IV



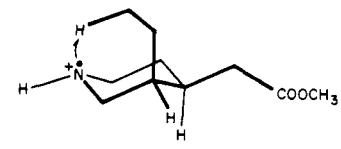
α,β-unsaturated isoquinolone **9.** In this case, the conjugated lactam **10** was isolated along with the isomeric enamine lactam **11** in a ratio of 5:1, respectively. These two products were clearly differentiated by their UV absorptions, **10** at 223–224 nm (ϵ 20 000) and **11** at 245 nm (ϵ 17 000), and by the resonance for the olefinic proton in the NMR spectra: a singlet at δ 5.87 for **10** and a doublet at δ 5.73 for **11.** Hydrogenation of **10** over rhodium on alumina catalyst gave exclusively the desired cis lactam **7.**

The lactam ring of **7** was converted into the vinyl and acetic acid side chains of racemic *N*-benzoylmeroquinene (**13**) by two methods. Treatment of **7** with nitrogen tetroxide gave quantitatively the corresponding *N*-nitroso lactam **12,** which underwent pyrolytic fragmentation when heated at 125 °C to give racemic *N*-benzoylmeroquinene (**13**) in 48% yield. After separation of **13** and treatment of the remaining product mixture with diazomethane, the hydroxy methyl ester **4** was isolated in 10% yield. Compound **4** is presumably derived by the opening of the lactone **2,** which in turn was formed in the pyrolysis of **12.**

Alternatively, lactam **7** was heated in 5% ethanolic hydrochloric acid at reflux to give the oily amino ester **16** in 65% yield. This amine was then, without purification of intermediates, converted into crystalline racemic *N*-benzoylmeroquinene ethyl ester (**15**) by N-dimethylation with formic acid and formaldehyde, *N*-oxide formation by aqueous hydrogen peroxide, and pyrolysis in vacuo, **16** → **17** → **18** → **15.** The overall yield of **15** from **16** was 85%.

Although an optical resolution of the starting isoquinolone **1** was later accomplished,[13] the above described synthesis was not employed in the preparation of optically active *N*-benzoylmeroquinene (**13a**) since a stereospecific synthesis[15] was developed at about the same time. Complete stereospecificity in the formation of the two cis side chains of meroquinene was achieved by catalytic hydrogenation of 3-ethyl-4-pyridineacetic acid methyl ester (**20**), prepared by an efficient carbomethoxylation of β-collidine (**19**).[16] This hydrogenation was carried out in 5% aqueous hydrochloric acid over platinum catalyst and afforded crystalline racemic cincholoipon methyl ester hydrochloride (**21**·HCl) in 88% yield (Scheme IV). None of the trans isomer was observed. Optical resolution of **21** was effected with *d*- and *l*-tartaric acids to give cincholoipon methyl ester (**22**) and its enantiomer **23.**

Our synthetic plan for the formation of the double bond in this case called for the functionalization of the ethyl side chain in **22** by the Löffler–Freytag rearrangement of the corresponding chloramine **25a.** This reaction was anticipated to go smoothly because its intermediate aminium radical ion in its most preferred conformation A has the side chain methyl group



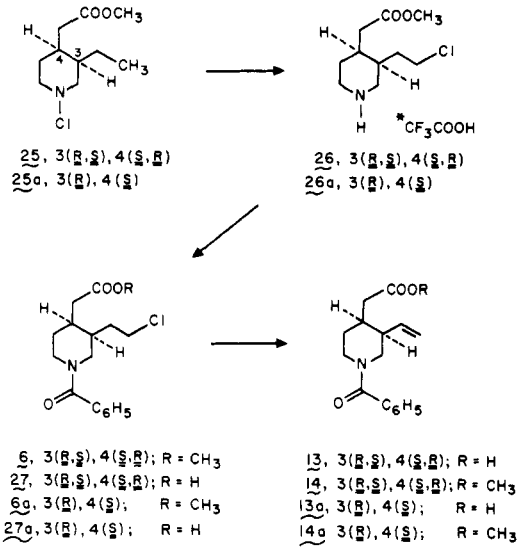
A

in close proximity to nitrogen, allowing for a ready abstraction of hydrogen.

This expectation was fully substantiated experimentally. Photolysis of the *N*-chloramine **25a** in trifluoroacetic acid solution with a 200-W Hanovia medium-pressure mercury lamp, followed by benzoylation of the crude photolysis product **26a,** led to the desired oily *N*-benzoyl chloroethyl derivative **6a** in 84% yield, after purification by column chromatography (Scheme V). The corresponding racemate **6,** obtained by the same method from **25,** was identical in all respects with a sample prepared from *cis*-*N*-benzoylisoquinolone (**1**) (Scheme I).

Completion of the synthesis of meroquinene by this route required the elimination of the elements of hydrogen chloride from the side chain. This was best accomplished by hydrolysis of the ester group of **6a** followed by treatment of the acid **27a** with potassium *tert*-butoxide in Me_2SO–benzene at 70 °C. The crystalline *N*-benzoylmeroquinene (**13a**) was obtained

Scheme V



in 87% overall yield from **6a** and was identical in all respects with an authentic sample obtained by the degradation of cinchonine.[13] The racemic and the (3*S*, 4*R*) enantiomeric series afforded analogous results. Esterification of **13a** gave the methyl ester **14a,** and hydrolysis yielded meroquinene (**28**), which was fully identified as its crystalline hydrochloride.

Experimental Section

General. Melting points were taken in capillaries with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined with a Beckman infrared spectrophotometer. Model IR-9 or Model IR-12. The UV spectra were recorded on a Cary recording spectrophotometer, Model 14M. Rotatory dispersion curves were measured at 23 °C with a Durrum-Jasco spectrophotometer, Model 5, using 1-cm, 0.1-cm, or 0.1-mm cells. Specific rotations are given for the highest and lowest wavelengths measured, for intersections, and for peaks and troughs. Circular dichroism curves were measured on the same instrument and they are recorded in molecular ellipticity units [θ]. Optical rotations were measured on a Perkin-Elmer polarimeter, Model 141. Nuclear magnetic resonance spectra were obtained on a Varian Associates spectrophotometer, Model A-60 or HA-100, and chemical shifts are reported in δ using tetramethylsilane as internal reference (δ 0). The mass spectra were taken with a CEC 21-110 mass spectrometer at 70 eV using a direct insertion probe. GLC was carried out on a Becker 409 instrument (analytical) or a Perkin-Elmer 801 instrument (preparative). Silica gel F_{254} Merck was used for analytical thin layer chromatography and 20 × 20 × 0.2 cm plates of silica gel F_{254} Brinkmann were employed for preparative purposes. For evaporative bulb-to-bulb distillation, a Büchi Kugelrohrofen was used. The temperatures given as those of the bath. Anhydrous tetrahydrofuran was prepared by passing through aluminum oxide and subsequently distilling over lithium aluminum hydride. Workup of organic layers consisted of washing with water or brine, drying over sodium sulfate or magnesium sulfate, and evaporating to dryness under reduced pressure.

Racemic *cis*-1-Benzoyl-3-(2-hydroxyethyl)-4-piperidineacetic Acid Methyl Ester (4) from Racemic *cis*-2-Benzoyl-octahydro-6(2*H*)-isoquinolone (1). To a solution of 4.3 g (0.0167 mol) of the cis isoquinolone **1** in 70 mL of methylene chloride was added 5.75 g (~28 mmol) of 95% *m*-chloroperbenzoic acid and 8.6 g (102 mmol) of sodium bicarbonate. The reaction mixture was stirred in the dark at room temperature for 24 h, followed by addition of 30 mL of 10% sodium sulfite. After the starch-iodide paper test became negative, the reaction mixture was diluted with 200 mL of methylene chloride and extracted sequentially with 100 mL each of 5% aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was chromatographed on a 1300-g silica gel column with ethyl acetate to give 4.3 g (94%) of a mixture of racemic *cis*-1-benzoyl-3-(β-ethanol)-4-piperidineacetic acid lactone (**2**) and 1-benzoyl-4-methanol-3-piperidine-β-propionic acid lactone (**3**)

A solution of this mixture in 200 mL of 0.07% methanolic hydrogen chloride was stirred overnight and then evaporated to dryness. The residue was separated by repeated chromatography on a silica gel column with hexane–chloroform–*tert*-butyl alcohol (6:2:2) eluent giving 1.56 g (35.6%) of **4,** and 2.7 g (57%) of racemic *cis*-1-benzoyl-4-methanol-3-piperidine-β-propionic acid methyl ester (**5**).

An analytical sample of **4** was obtained as an oil by further purification by preparative thin layer chromatography: IR ($CHCl_3$) 3630 (OH), 1730 ($COOCH_3$), 1625 cm^{-1} ($NCOC_6H_5$); NMR ($CDCl_3$) δ 3.65 (s, 3 H, $COOCH_3$), 7.36 (s, 5 H, C_6H_5); mass spectrum *m/e* 305 (M^+). Anal. ($C_{17}H_{23}NO_4$) C, H, N.

Racemic *cis*-1-Benzoyl-3-(2-chloroethyl)-4-piperidineacetic Acid Methyl Ester (6). To a solution of 0.443 g (1.45 mmol) of the hydroxy ester **4** in 13.9 mL of dimethylformamide was added 0.455 g (1.7 mmol) of triphenylphosphine and 0.292 g (1.64 mmol) of carbon tetrachloride. The mixture was stirred in the dark at room temperature for 18 h, at which time 0.16 mmol of carbon tetrachloride was added. The mixture was stirred for an additional 3 h and then evaporated to dryness. The crude product was chromatographed on thick layer silica gel plates with ethyl acetate go give 0.381 g (18%) of oily **6.** An analytical sample was prepared by high vacuum distillation: oil; IR ($CHCl_3$) 1735 ($COOCH_3$), 1630 cm^{-1} ($NCOC_6H_5$); NMR ($CDCl_3$) δ 2.31 (broad s, 2 H, CH_2COOCH_3), 3.66 (s, 3 H, $COOCH_3$), 7.41 (s, 5 H, C_6H_5); mass spectrum *m/e* 323 (M^+). Anal. ($C_{17}H_{22}ClNO_2$) C, H, Cl, N.

***cis*-7-Benzoyldecahydro-2*H*-pyrido[3,4-*d*]azepin-2-one (7) and *cis*-7-Benzoyldecahydro-3*H*-pyrido[4,3-*c*]azepin-3-one (8) from *cis*-2-Benzoyloctahydro-6(2*H*)-isoquinolone (1).** To a suspension of 20.6 g (0.08 mol) of the finely ground cis isoquinolone **1** in 800 g of polyphosphoric acid was added 10.0 g (0.16 mol) of sodium azide, and the mixture was stirred for 16 h at 55–60 °C. After cooling to room temperature, the reaction mixture was poured onto crushed ice, and the resulting solution was made alkaline by the addition of solid sodium carbonate at 0 °C. The alkaline solution was extracted thoroughly with dichloromethane and the organic phase was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness in vacuo. The residue, 24.8 g of oil, which crystallized on trituration with acetone, was shown by TLC to be composed of **7** and **8.** The exhaustive fractional crystallization of the crude product from acetone gave 6.33 g (29%) of **7,** which after one recrystallization from absolute ethanol and three recrystallizations from acetone had mp 167–168.5 °C; IR ($CHCl_3$) 3420 (N-H), 1664 (lactam), 1625 cm^{-1} (amide); mass spectrum *m/e* 272 (M^+). Anal. ($C_{16}H_{20}N_2O_2$) C, H, N.

Further crystallization of the mother liquors gave 5.72 g (26.5%) of **8,** which after one recrystallization from acetone and one from absolute ethanol had mp 188–190 °C; IR ($CHCl_3$) 3422 (N-H), 1670 (lactam), 1630 cm^{-1} (amide); mass spectrum *m/e* 272 (M^+). Anal. ($C_{16}H_{20}N_2O_2$) C, H, N. The remaining mother liquors were shown by TLC to be composed almost exclusively of **7** and **8.**

2-Benzoyl-1,2,3,4,7,8,9,9a-octahydro-6*H*-pyrido[3,4-*d*]azepin-6-one (10) and 2-Benzoyl-1,2,3,4,6,8,9,9a-octahydro-7*H*-pyrido[4,3-*c*]azepin-7-one (11) from 2-Benzoyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolone (9). To a suspension of 1.02 g (0.004 mol) of the finely ground conjugated ketone **9** in 40 g of polyphosphoric acid was added 0.5 g (0.008 mol) of sodium azide and the reaction mixture was stirred at 120 °C for 30 min. After cooling to room temperature, ice was added and the resulting solution was made alkaline by the addition of saturated aqueous sodium carbonate at 0 °C and extracted with dichloromethane. The dichloromethane extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The crude product was crystallized by trituration with acetone to give 0.415 g (38.5%) of **10,** mp 199–212 °C. The mother liquors were chromatographed on preparative thick layer plates to yield 0.259 g (24%) of **10** and 0.135 g (12.5%) of **11.** An analytical sample of **10** was prepared in a separate experiment by three recrystallizations of the crude crystalline product from acetone: mp 219–221 °C; IR ($CHCl_3$) 3422 (N-H), 1663 (lactam), 1630 cm^{-1} (amide); UV (2-propanol) 223–224 nm (ϵ 20 600); NMR ($CDCl_3$) δ 5.87 (s, 1 H, C=CH), 7.40 (s, 5 H, phenyl); mass spectrum *m/e* 270 (M^+). Anal. ($C_{16}H_{18}N_2O_2$) C, H, N.

An analytical sample of **11** was prepared by chromatography of the combined mother liquors of several experiments. Compound **11** was eluted from a silica gel column with 5% methanol in ethyl acetate and crystallized from acetone: mp 194–196 °C; IR ($CHCl_3$) 3410 (N-H),

1670 (lactam), 1625 cm^{-1} (amide); UV (2-propanol) 245 nm (ϵ 17 000); NMR ($CDCl_3$) δ 5.73 (d, 1 H, J = 6 Hz, C=CH), 7.40 (s, 5 H, phenyl), 7.70 (d, 1 H, J = 6 Hz, NH). Anal. ($C_{16}H_{18}N_2O_2$) C, H, N.

***cis*-7-Benzoyldecahydro-2*H*-pyrido[3,4-*d*]azepin-2-one (7).** To a solution of 5.4 g (0.02 mol) of **10** in 450 mL of absolute ethanol was added 10 mL of 3 N aqueous hydrochloric acid and 5.4 g of 5% rhodium on alumina catalyst, and the reaction mixture was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased (1.25 h). The catalyst was separated by filtration and washed thoroughly with ethanol. The filtrate was neutralized with 2 N aqueous sodium carbonate and evaporated to a small volume in vacuo. The residue was extracted with 1000 mL of dichloromethane. The extract was washed with water, dried with anhydrous sodium sulfate, and evaporated to dryness. The noncrystalline crude product (5.54 g, theory 5.42 g) exhibited an IR spectrum identical with that of pure **7** and TLC indicated besides **7** only traces of impurities. Recrystallized twice from acetone: mp 162–165 °C. Anal. ($C_{16}H_{20}N_2O_2$) C, H, N.

***cis*-1-Benzoyl-3-(2-aminoethyl)-4-piperidineacetic Acid Ethyl Ester (16).** A solution of 2.8 g (ca. 0.01 mol) of **7** in 500 mL of 5% ethanolic hydrochloric acid was refluxed for 100 h. The solvent was removed by evaporation in vacuo. The residue was taken up in 1200 mL of dichloromethane, and the resulting solution was shaken with a solution of 0.53 g (0.005 mol) of sodium carbonate in 10 mL of water, dried over anhydrous sodium sulfate, and evaporated. This procedure gave 2.1 g (65%) of oily **16.** (The TLC indicated a trace of starting material as impurity.)

***cis*-1-Benzoyl-3-vinyl-4-piperidineacetic Acid Ethyl Ester (Racemic *N*-Benzoylmeroquinene Ethyl Ester) (15).** A mixture of 1.91 g (0.006 mol) of **16,** 1.38 g (0.030 mol) of formic acid, and 1.05 g (0.13 mol) of 37% formaldehyde was heated for 1 h at 100 °C. A vigorous evolution of gas occurred and stopped during this time. After cooling to room temperature, 3.5 mL of concentrated hydrochloric acid was added and the mixture thus obtained was evaporated to dryness in vacuo. The residue was dissolved in 50 mL of water, and this solution was washed by shaking with ether, then made alkaline to ca. pH 8 with 2 N sodium carbonate and extracted thoroughly with dichloromethane. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness in vacuo to give 1.7 g of crude oily *cis*-1-benzoyl-3-(2-dimethylaminoethyl)-4-piperidineacetic acid ethyl ester (**17**). To the stirred solution of this product in 10 mL of methanol was added at 0 °C 2 mL of 30% aqueous hydrogen peroxide. The reaction mixture was warmed to room temperature and stirred for 16 h. The excess of hydrogen peroxide was decomposed by addition of platinum black and stirring for 1 h at 0 °C. Platinum black was separated by filtration and washed with methanol. The filtrate was evaporated to dryness in vacuo to yield 1.86 g of crude *cis*-1-benzoyl-3-(2-dimethylaminoethyl)-4-piperidinacetic acid ethyl ester *N*-oxide (**18**) as an oil. Heating of this product in vacuo at rising temperature from 90 °C to 125 °C over a period of 25 min gave, after chromatographic purification, 1.54 g (85%) of **15:** mp 66–68 °C (from hexane); IR ($CHCl_3$) 1730 (ester), 1625 (amide), 1000 and 930 cm^{-1} (vinyl); NMR ($CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz, CH_2CH_3), 4.15 (q, 2 H, J = 7 Hz, CH_2CH_3), 4.80–5.30 (m, 2 H, CH=CH_2), 5.90 (m, 1 H, CH=CH_2), 7.39 (s, 5 H, phenyl); mass spectrum *m/e* 301 (M^+). An analytical sample, mp 67–68 °C, was prepared by repeated recrystallizations from hexane. Anal. ($C_{18}H_{23}NO_3$) C, H, N.

***cis*-7-Benzoyl-1-nitrosodecahydro-2*H*-pyrido[3,4-*d*]azepin-2-one (12).** To a solution of 5.521 g (0.06 mol) of nitrogen tetroxide in 360 mL of carbon tetrachloride at −70 °C was added 9.84 g (0.012 mol) of anhydorous sodium acetate. The mixture was allowed to warm to 0 °C and a solution of 10.88 g (0.04 mol) of **7** in 40 mL of dichloromethane was added with stirring. After 30 min at 0 °C, the mixture was poured into a slurry of ice and water. The resulting mixture was placed in a separatory funnel and the organic phase was separated. The aqueous phase was extracted thoroughly with ice-cold dichloromethane and the combined organic phases were washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness at 0 °C in vacuo. The yellow oily **12** was obtained in a quantitative yield, and was identified by its IR spectrum.

Racemic *cis*-1-Benzoyl-3-vinyl-4-piperidineacetic Acid (13). The nitroso compound **12** from the previous experiment was placed in a round-bottom flask fitted with a reflux condenser and heated under nitrogen in an oil bath maintained at 125 °C. After ca. 10 s, a relatively violent reaction occurred which was accompanied by a dense cloud of white smoke and change in color from the characteristic yellow-green of the starting material to a dark brown. Heating was continued for 1 h. The residue was taken up in 50 mL of 1 N potassium hydroxide, diluted with 50 mL of water, and washed by shaking with ether. The aqueous phase was neutralized with 50 mL of 1 N hydrochloric acid and extracted with ether. The ether phase was then washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness, yielding 5.29 g (48.5%) of **13** as an oil. An analytical sample was prepared by preparative thin layer chromatography followed by molecular distillation: IR ($CHCl_3$) 1713 (carboxyl), 1625 (amide), 1000 and 930 cm^{-1} (vinyl); NMR ($CDCl_3$) δ 4.90–5.30 (m, 2 H, CH=CH_2), 5.80 (m, 1 H, CH=CH_2), 7.38 (s, 5 H, phenyl), 10.20 (s, 1 H, COOH); mass spectrum *m/e* 273 (M^+). Anal. ($C_{16}H_{19}O_3$) C, H, N.

The aqueous phase, which remained after the separation of **13,** was reextracted with dichloromethane. This gave 3.81 g (32%) of a mixture containing racemic *cis*-1-benzoyl-3-(2-hydroxyethyl)-4-piperidineacetic acid as the major component and a trace of **13.** To the stirred solution of this mixture in ether was added 0.8 g of diazomethane in 40 mL of ether, and the stirring was continued for 15 min. The excess of diazomethane was destroyed by dropwise addition of glacial acetic acid until the yellow color disappeared. The reaction mixture was then diluted to 1000 mL with ether, washed with 2 N sodium carbonate and water, dried over anhydrous magnesium sulfate, and evaporated to dryness. This gave 1.55 g of crude *cis*-1-benzoyl-3-(2-hydroxyethyl)-4-piperidineacetic acid methyl ester (**4**). An additional 0.74 g of crude **4** was obtained by reextraction of the aqueous phase with dichloromethane. These products were combined (2.29 g) and purified by chromatography on 21 Brinkmann silica gel F preparative plates with ethyl acetate to yield 1.28 g (10.5% from **7**) of pure **4.** An analytical sample was obtained by molecular distillation: IR ($CHCl_3$) 3615 (-OH), 1735 (ester), 1625 cm^{-1} (amide); NMR ($CDCl_3$) δ 3.63 (s, 3 H, OCH_3), 7.37 (s, 5 H, phenyl); mass spectrum *m/e* 305 (M^+). Anal. ($C_{17}H_{23}NO_4$) C, H, N.

3-Ethyl-4-pyridineacetic Acid Methyl Ester (20). To a three-neck 5-L round-bottom flask equipped with a Teflon blade stirrer, addition funnel, and inlet of nitrogen and flushed with nitrogen was added 1060 mL of approximately 1.6 M (1.7 mol) of *n*-butyllithium in hexane. Under a moderate stream of nitrogen and with stirring, the flask was placed then in an acetone–dry ice bath. At −60 °C, 182 g (1.8 mol) of diisopropylamine was added dropwise over a 9-min period. Then, 100 g (0.827 mol) of β-collidine (**19**), dissolved in enough anhydrous tetrahydrofuran to make 1 L of solution, was added over a 30-min period, and the reaction mixture was stirred for an additional 30 min. This was followed by addition of 120 g (2 mol) of dimethyl carbonate, dissolved in anhydrous tetrahydrofuran to make 1 L of solution, over a 30-min period. A large red precipitate was formed during the last addition. Stirring was continued at −60 °C for another 30 min; then the dry ice bath was removed and the reaction was allowed to warm up for 2 h with stirring. One liter of benzene was added, followed by 100 mL of saturated aqueous sodium sulfate solution. Stirring was continued until the organic precipitate was dissolved, and the solution was then dried over anhydrous sodium sulfate. Sodium sulfate was removed by filtration, and the filtrate evaporated to give 163 g of crude **20,** approximately 80% pure as determined by gas chromatography. This corresponds to a 88% yield. The above described reaction was repeated once more. The combined crude product (307 g) was dissolved in 1 L of benzene; this solution was shaken first with 200 mL of ice–water and 170 mL of concentrated hydrochloric acid, and then two times with 200 mL of 1 N hydrochloric acid. The aqueous acidic layer was neutralized with concentrated ammonium hydroxide at ice temperature and extracted with dichloromethane (3 × 500 mL). The extract was dried over anhydrous sodium sulfate, filtered, and evaporated to give 257 g of 90% pure **20.** This product was further purified by distillation through a short Vigreux column to yield 206 g of 99% pure **20:** bp 98 °C (0.04 mm); IR ($CHCl_3$) 1730 (carbonyl), 1590, 1560, and 1490 (aromatic), 1160 cm^{-1} (C–O–C); UV (CH_3OH) 263 nm (ϵ 2980), 270 (2400) (sh); NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 2.64 (q, 2 H, J = 7.5 Hz, CH_2CH_3), 3.64 (s, 2 H, CH_2), 3.67 (s, 3 H, OCH_3), 7.13 (d, 1 H, J = 5 Hz, CH-5), 8.38 (d, 1 H, J = 5 Hz, CH-6), 8.43 (s, 1 H, CH-2); mass spectrum *m/e* 179 (M^+). Anal. ($C_{10}H_{13}NO_2$) C, H, N.

The ester **20** was treated with an excess of 5% methanolic hydrogen chloride in an ice bath. Methanol was partially evaporated and on cooling crystalline 3-ethyl-4-pyridineacetic acid methyl ester hydrochloride was obtained, mp 167–168 °C (from methanol). Anal.

($C_{10}H_{14}ClNO_2$) C, H, Cl, N.

Racemic *cis*-3-Ethyl-4-piperidineacetic Acid Methyl Ester Hydrochloride (21). To the solution of 33.4 g (0.155 mol) of the hydrochloride of **20** in 900 mL of 5% aqueous hydrochloric acid was added 0.3 g of platinum dioxide, and the mixture was hydrogenated at 70 atm and 60 °C. The catalyst was removed by filtration, and the filtrate was evaporated to dryness in vacuo and azeotropically with benzene. The residue was dissolved in 1 L of 4.3% methanolic hydrogen chloride, and the solution was refluxed for 5 h and evaporated to dryness. The last operation was repeated once more. Crystallization from acetone gave 28.34 g (82%) of racemic **21** (a four times larger experiment gave **21** in 88% yield). An analytical sample was obtained by recrystallization from acetone: mp 133–135 °C; IR (KBr) 2750 (NH_2^+), 1730 (carbonyl), 1230 and 1170 cm^{-1} (C–O–C); NMR (D_2O) δ 1.40 (t, 3 H J = 7 Hz, CH_2CH_3), 1.83 (q, 2 H, J = 7 Hz, CH_2CH_3), 2.30 (m, 3 H, CH_2 + CH), 2.94 (broad s, 3 H, CH_2 + CH), 3.62 (m, 4 H, CH_2NCH_2), 4.18 (s, 3 H, OCH_3); mass spectrum *m/e* 185 (M^+). Anal. ($C_{10}H_{20}ClNO_2$) C, H, Cl, N.

3(*R*)-Ethyl-4(*S*)-piperidineacetic Acid Methyl Ester (22) and 3(*S*)-Ethyl-4(*R*)-piperidineacetic Acid Methyl Ester (23). To the solution of 460 g (2.132 mol) of racemic cis methyl ester **21** hydrochloride in 500 mL of ice-water was added 370 mL of 6 N aqueous sodium hydroxide and the mixture was extracted with 2 × 500 mL of chloroform. The chloroform extract was dried, filtered, and evaporated to give 389 g (100%) of racemic *cis*-3-ethyl-4-piperdineacetic acid methyl ester (**21**). The free base **21** and 315.4 g of *l*-tartaric acid were dissolved in 3.5 L of hot methanol and cooled to room temperature. On successive addition of acetone and stirring at room temperature, several crops of 3(*S*)-ethyl-4(*r*)-piperidineacetic acid methyl ester (**23**) mono-*l*-tartrate were obtained. After four recrystallizations from methanol–acetone the yield was 238.3 g (28.7%): mp 143–143.5 °C; $[\alpha]^{25}_D$ −5.5° (*c* 1.0, CH_3OH). Anal. ($C_{14}H_{25}NO_8$) C, H, N.

3(*S*)-Ethyl-4(*R*)-piperidineacetic acid methyl ester (**23**) hydrochloride: mp 174.5–175 °C after recrystallization from methanol–acetone; $[\alpha]^{25}_D$ +8.4° (*c* 1.0, CH_3OH). Anal. ($C_{10}H_{20}ClNO_2$) C, H, Cl, N.

The *l*-tartrate mother liquors were converted into the free base, which was then reacted with equimolar amounts of *d*-tartaric acid in methanol. After successive addition of acetone, several crops of 3(*R*)-ethyl-4(*S*)-piperidineacetic acid methyl ester (**22**) mono-*d*-tartrate were obtained. After recrystallization from methanol–acetone the yield was 206.8 g (25%): mp 143–143.5 °C; $[\alpha]^{25}_D$ +5.4° (*c* 1.0, CH_3OH). Anal. ($C_{14}H_{25}NO_8$) C, H, N.

3(*R*)-Ethyl-4(*S*)-piperidineacetic acid methyl ester (**22**) hydrochloride: mp 174.5–175.5 °C after recrystallization from methanol–acetone; $[\alpha]^{25}_D$ −8.3° (*c* 1.0, CH_3OH). Anal. ($C_{10}H_{20}ClNO_2$) C, H, Cl, N.

The remainder of the racemic free base **21** was regenerated from *d*-tartrate mother liquors, and was used in subsequent resolution experiments.

3(*R*)-Ethyl-4(*S*)-piperidineacetic acid (24) hydrochloride was obtained by alkaline hydrolysis of the methyl ester **22,** followed by treatment with methanolic hydrogen chloride: mp 192–194 °C; $[\alpha]^{25}_D$ −44.63° (*c* 1.0082, CH_3OH). Anal. ($C_9H_{18}ClNO_2$) C, H, Cl, N.

Racemic *cis*-1-Chloro-3-ethyl-4-piperidineacetic Acid Methyl Ester (25). To the stirred suspension of 4.8 g (0.036 mol) of *N*-chlorosuccinimide in 120 mL of anhydrous ether under nitrogen was added 5.55 g (0.03 mol) of racemic *cis*-3-ethyl-4-piperidineacetic acid methyl ester (**21**) and the reaction mixture was stirred for 1 h. After dilution with 1 L of ether, the reaction mixture was washed in sequence with 3 × 100 mL of water, 2 × 100 mL of 5 N aqueous potassium carbonate, 2 × 100 mL of water, 2 × 100 mL of 2.5 N aqueous sulfuric acid, and 2 × 100 mL of water. The ethereal solution was then dried over anhydrous magnesium sulfate, filtered, and evaporated to give 5.6 g (92%) of TLC pure oily **25** which was immediately used in the next step.

1-Chloro-3(*R*)-ethyl-4(*S*)-piperidineacetic Acid Methyl Ester (25a). By the same method starting from 3(*R*)-ethyl-4(*S*)-piperidineacetic acid methyl ester (**22**), crude 1-chloro-3 (*R*)-ethyl-4(*S*) -piperi - dineacetic acid methyl ester (**25a**) was obtained.

1-Chloro-3(*S*)-ethyl-4(*R*)-piperidineacetic Acid Methyl Ester (25b). By the same method starting from 3(*S*)-ethyl-4(*R*)-piperidineacetic acid methyl ester (**23**) crude 1-chloro-3(*S*)-ethyl-4(*R*)-piperidineacetic acid methyl ester (**25b**) was obtained.

Racemic *cis*-1-Benzoyl-3-(2-chloroethyl)-4-piperidineacetic Acid Methyl Ester (6). The solution of 5.6 g (0.0255 mol) of **25** in 150 mL of trifluoroacetic acid in a quartz flask was flushed with nitrogen and cooled in an ice bath for 30 min. Under a continuous stream of nitrogen and with cooling, the solution was irradiated with a 200-W Hanovia lamp for 50 min when TLC and negative potassium iodide starch test indicated the absence of starting material **25.** Evaporation in vacuo gave crude racemic *cis*-3-(2-chloroethyl)-4-piperidineacetic acid methyl ester trifluoroacetate (**26**). To the stirred solution of this salt in 450 mL of benzene was added first 5.94 g (0.0425 mol) of benzoyl chloride and then dropwise slowly 5 N aqueous potassium carbonate until pH ~9 was reached. Stirring was then continued for 2 h. The reaction mixture was diluted with 3 L of benzene and extracted in sequence with 3 × 100 mL of 6 N aqueous sodium hydroxide, 3 × 100 mL of water, 2 × 100 mL of 3 N aqueous hydrochloric acid, and water. The benzene solution was dried over anhydrous sodium sulfate and evaporated. The residue was dissolved in methanol, refluxed for 15 min, and evaporated. The product thus obtained was chromatographed on silica gel plates in a 1:1 ether–petroleum ether system, and eluted with a 3:1 chloroform–methanol mixture. This gave 7.01 g (84%) of oily **6:** NMR ($CDCl_3$) δ 2.30 (broad s, 2 H, CH_2COOCH_3), 3.65 (s, 3 H, OCH_3), 7.37 (s, 5H, C_6H_5). Anal. ($C_{17}H_{22}ClNO_3$) C, H, N; Cl: calcd, 10.95; found, 10.28.

1-Benzoyl-3(*R*)-(2-chloroethyl)-4(*S*)-piperidineacetic Acid Methyl Ester (6a). Starting from 1-chloro-3(*R*)-ethyl-4(*S*)-piperidineacetic acid methyl ester (**25a**), the same sequence of reactions gave **6a:** oil; $[\alpha]^{25}_D$ +30.47° (*c* 0.9123, CH_3OH); NMR ($CDCl_3$) δ 1.20–4.60 (m, 12 H, CH + CH_2), 2.35 (broad s, 2, $-CH_2COOCH_3$), 3.67 (s, 3 H, OCH_3), 7.38 (s, 5 H, C_6H_5); mass spectrum *m/e* 323 (M^+). Anal. ($C_{17}H_{22}ClNO_3$) C, H, N; Cl: calcd 10.95; found, 10.31.

1-Benzoyl-3(*S*)-(2-chloroethyl)-4(*R*)-piperidineacetic Acid Methyl Ester (6b). Starting from 1-chloro-3(*S*)-ethyl-4(*R*)-piperidineacetic acid methyl ester (**25b**), the same sequence of reactions gave **6b:** oil; $[\alpha]^{25}_D$ −32.46° (*c* 1.029, CH_3OH). Anal. ($C_{17}H_{22}ClNO_3$) C, H, Cl, N.

Racemic *cis*-1-Benzoyl-3-(2-chloroethyl)-4-piperidineacetic Acid (27). To the solution of 7.24 g (0.02235 mol) of **6** in 112 mL of methanol was added 112 mL of 1 N aqueous sodium hydroxide and the mixture was stirred at room temperature for about 17 h. Methanol was removed by distillation, and the residue was made acidic with 3 N aqueous hydrochloric acid and extracted with 8 × 200 mL of dichloromethane. The extract was dried over anhydrous sodium sulfate, filtered, and evaporated to give 6.85 g (99%) of crystalline **27:** mp 121–124 °C after recrystallization from ether; IR ($CHCl_3$) 3500 and 1715 (acid), 1625 cm^{-1} (amide); mass spectrum *m/e* 309 (M^+). Anal. ($C_{16}H_{20}ClNO_3$) C, H, Cl, N.

1-Benzoyl-3(*R*)-(2-chloroethyl)-4(*S*)-piperidineacetic Acid (27a). Starting from 1-benzoyl-3(*R*)-(2-chloroethyl)-4(*S*)-piperidineacetic acid methyl ester (**6a**), hydrolysis under the same conditions gave **27a:** mp 162–163.5 °C from dichloromethane–ether; $[\alpha]^{25}_D$ +26.45° (*c* 1.0245, CH_3OH); NMR ($CDCl_3$) δ 1.20–4.60 (m, 12 H, CH + CH_2), 2.32 (broad s, 2 H, CH_2COOH), 7.37 (s, 5 H, C_6H_5), 10.52 (s, 1 H, COOH); mass spectrum *m/e* 309 (M^+). Anal. ($C_{16}H_{20}ClNO_3$) C, H, Cl, N.

1-Benzoyl-3(*S*)-(2-chloroethyl)-4(*R*)-piperidineacetic Acid (27b). Starting from 1-benzoyl-3(*S*)-(2-chloroethyl)-4(*R*)-piperidineacetic acid methyl ester (**6b**), hydrolysis under the same conditions gave **27b:** mp 162–163 °C from methylene chloride–ether; $[\alpha]^{25}_D$ −27.14° (*c* 1.042, CH_3OH). Anal. ($C_{16}H_{20}ClNO_3$) C, H, Cl, N.

Racemic *cis*-1-Benzoyl-3-vinyl-4-piperidineacetic Acid (13). To the solution of 5.44 g (0.0176 mol) of **27** in 82.5 mL of anhydrous benzene was added 3.99 g (0.0356 mol) of potassium *tert*-butoxide in 82.5 mL of dimethyl sulfoxide, and the reaction mixture was stirred and heated at 70 °C under nitrogen for 7 h. Benzene was removed by distillation, and after addition of 82.5 mL of 1 N aqueous sodium hydroxide, the residue was extracted with 5 × 100 mL of dichloromethane. The aqueous phase was made acidic with concentrated hydrochloric acid and extracted with 5 × 200 mL of ether–benzene, 1:1. The last extract was dried over anhydrous sodium sulfate, filtered, and evaporated to afford 5.15 g of oily **13,** the spectra of which were identical with those of **13** prepared as described above.

1-Benzoyl-3(*R*)-vinyl-4(*S*)-piperidineacetic Acid (13a). Starting from 1-benzoyl-3(*R*)-(2-chloroethyl)-4(*S*)-piperidineacetic acid (**27a**), elimination under the same conditions gave **13a** in 87.5% yield after chromatography: mp 115–117 °C (dichloromethane–ether); $[\alpha]^{25}_D$ +49.77° (*c* 1.0368, CH_3OH); NMR ($CDCl_3$) δ 2.22 (broad s, 2 H, CH_2COOH), 4.90–5.3 (m, 2 H, $CH{=}CH_2$), 5.84 (ddd, 1 H, J_{vic} =

9, J_{cis} = 11, J_{trans} = 17 Hz, C*H*=CH_2), 7.36 (s, 5 H, C_6H_5); mass spectrum *m/e* 273 (M^+), 105 (base peak). Anal. ($C_{16}H_{19}NO_3$) C, H, N.

1-Benzoyl-3(*S*)-vinyl-4(*R*)-piperidineacetic Acid (13b). Starting from 1-benzoyl-3(*S*)-2-chloroethyl)-4(*R*)-piperidineacetic acid (**27b**), elimination under the same conditions gave **13b**, mp 114–115 °C, after two recrystallizations from ether, $[\alpha]^{25}_D$ −48.85° (*c* 0.9315, CH_3OH). Anal. ($C_{16}H_{19}NO_3$) C, H, N.

Racemic *cis*-1-Benzoyl-3-vinyl-4-piperidineacetic Acid Methyl Ester (14). To the solution of 5.15 g of **13** in 90 mL of methanol was added 48 mL of diazomethane solution (~3 g/100 mL, ethanol–ether) and the mixture was stirred for 90 min. This was followed by addition of several drops of glacial acetic acid and by evaporation to dryness to give 5.53 g of crude **14**, which was chromatographed on 54 preparative silica gel plates with ethyl acetate and eluted with chloroform–methanol (1:1). This gave 2.52 g (46.5%) of **14**, which crystallized from cold ether: mp 57–58 °C; IR ($CHCl_3$) 1735 and 1178 ($COOCH_3$), 1636 (CON<), 1012 and 933 cm^{-1} (CH=CH_2); NMR ($CDCl_3$) δ 3.65 (s, 3 H, OCH_3), 4.9–6.2 (m, 3, CH=CH_2), 7.37 (s, 5, C_6H_5); mass spectrum *m/e* 287 (M^+). Anal. ($C_{17}H_{21}NO_3$) C, H, N.

1-Benzoyl-3(*R*)-vinyl-4(*S*)-piperidineacetic Acid Methyl Ester (14a). Starting from pure 1-benzoyl-3(*R*)-vinyl-4(*S*)-piperidineacetic acid (**13a**) esterification under the same conditions gave oily **14a** in 92% yield. An analytical sample was purified by sublimation, $[\alpha]^{25}_D$ +49.72° (*c* 0.9955, CH_3OH). Anal. ($C_{17}H_{21}NO_3$) C, H, N.

3(*R*)-Vinyl-4(*S*)-piperidineacetic Acid (Meroquinene) (28). To a stirred solution of 8.2 g (0.03 mol) of **13a** in 100 mL of methanol was added 63 mL of 1 N aqueous sodium hydroxide and the reaction mixture was heated at reflux for 17 h. It was then cooled in an ice bath and neutralized by addition of 1 N hydrochloric acid. After evaporation to dryness, the solid residue was extracted with 4 × 200 mL of hot absolute ethanol. The ethanol extract was filtered and evaporated to a small volume. On cooling, two crops of crystalline **28** were obtained, 2.2 g of mp 217–223 °C and 1.25 g of mp 221–222 °C (67% yield). An analytical sample was obtained by recrystallization from absolute ethanol: mp 222–225 °C; $[\alpha]^{25}_D$ +25.05° (*c* 0.998, CH_3OH); NMR (D_2O) δ 3.28 (m, 1 H, allylic methine proton), 3.80 (m, 4 H, CH_2NHCH_2), 5.70 (d, 1 H, J_{trans} = 16 Hz, HC=CH_2), 5.80 (d, 1 H, J_{cis} = 11 Hz, HC=CH_2), 6.40 (ddd, 1 H, J_{trans} = 16, J_{cis} = 11, J_{vic} = 7.5 Hz, C*H*=CH_2); mass spectrum *m/e* 169 (M^+). Anal. ($C_9H_{15}NO_2$) C, H, N.

3(*R*)-Vinyl-4(*S*)-piperidineacetic acid (**28**) hydrochloride: mp 147–149 °C after recrystallization from ethanol–acetone; $[\alpha]^{25}_D$ +30.97° (*c* 1.0213, CH_3OH). Anal. ($C_9H_{16}ClNO_2$) C, H, N.

Acknowledgment. We are thankful to the staff of our Physical Chemistry Department for spectra and analyses.

References and Notes

(1) R. B. Turner and R. B. Woodward in "The Alkaloids", Vol. III, R. H. F. Manske and H. L. Holmes, Ed., Academic Press, New York, N.Y., 1953, Chapter 16.
(2) P. Rabe and K. Kindler, *Chem. Ber.*, **51**, 466 (1918).
(3) R. B. Woodward and W. van E. Doering, *J. Am. Chem. Soc.*, **66**, 849 (1944), **67**, 860 (1945).
(4) R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945).
(5) M. R. Uskoković and G. Grethe in "The Alkaloids", Vol. XIV, R. H. F. Manske, Ed., Academic Press, New York, N.Y., 1973, Chapter 5.
(6) M. Prošťenik and V. Prelog, *Helv. Chim. Acta*, **26**, 1965 (1943).
(7) G. Grethe, H. L. Lee, T. Mitt, and M. R. Uskoković, *Helv. Chim. Acta*, **56**, 1485 (1973).
(8) J. Gutzwiller and M. Uskoković, *J. Am. Chem. Soc.*, **92**, 204 (1970).
(9) M. Gates, B. Sugavanam, and W. L. Schreiber, *J. Am. Chem. Soc.*, **92**, 205 (1970).
(10) G. Grethe, H. L. Lee, T. Mitt, and M. R. Uskoković, *J. Am. Chem. Soc.*, **93**, 5904 (1971).
(11) E. C. Taylor and S. F. Martin, *J. Am. Chem. Soc.*, **94**, 6218 (1972); **96**, 8095 (1974).
(12) W. E. Doering and J. D. Chanley, *J. Am. Chem. Soc.*, **68**, 586 (1946).
(13) M. R. Uskoković, D. L. Pruess, C. W. Despreaux, S. Shiuey, G. Pizzolato, and J. Gutzwiller, *Helv. Chim. Acta*, **56**, 2834 (1973).
(14) M. R. Uskoković, J. Gutzwiller, and T. Henderson, *J. Am. Chem. Soc.*, **92**, 203 (1970).
(15) M. Uskoković, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *J. Am. Chem. Soc.*, **93**, 5902 (1971).
(16) J. A. W. Gutzwiller and M. R. Uskoković, U.S. Patent 3 663 554 (May 16, 1972), (preparation of β-collidine).

Total Synthesis of *Cinchona* Alkaloids. 2. Stereoselective Total Syntheses of Quinine and Quinidine

Jürg Gutzwiller and Milan R. Uskoković*

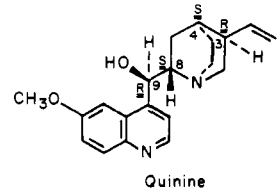
Contribution from the Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received June 13, 1977*

Abstract: Quinine (**12**) and quinidine (**13**) are synthesized from totally synthetic *N*-benzoylmeroquinene methyl ester (**1**) and 6-methoxylepidine (**2**). Two of the three syntheses described in this paper are stereoselective by virtue of producing only the 8,9-erythro diastereomers **12** and **13**. The third synthesis produced in addition to **12** and **13** the undesired 8,9-threo isomers, 9-*epi*-quinine (**17**) and 9-*epi*-quinidine (**18**).

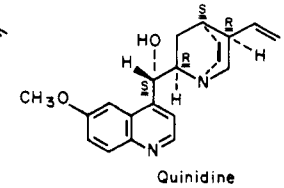
In the preceding paper[1] we described the preparation of 3(*R*)-vinyl-4(*S*)-piperidineacetic acid or meroquinene, a reasonable synthon for the construction of the quinuclidine ring of quinine and quinidine. The two chiral centers of this precursor are destined to become the C-3 and C-4 centers of the alkaloids.

The configurations at the third and fourth chiral centers, C-8 and C-9, are erythro, 8(*S*), 9(*R*) in quinine and 8(*R*), 9(*S*) in quinidine. Since the 8,9-threo isomers, *epi*-quinine and *epi*-quinidine, are not active in either the antimalarial or antiarrhythmia test, the stereoselectivity of all new syntheses is qualified by the formation of erythro products.

Two different approaches from meroquinene to quinine and quinidine have been pursued in our laboratory. In the first one,[2]



Quinine



Quinidine

which is the subject of this publication, meroquinene was first combined with the quinoline component, and this was followed by cyclization to the quinuclidine ring. The second synthesis[3] described in the accompanying papers,[4] involves the conversion of meroquinene to a quinuclidine moiety, which was subsequently linked to the quinoline synthon.

0002-7863/78/1500-0576$01.00/0