9, $J_{cis}$ = 11, $J_{trans}$ = 17 Hz, C$H$=CH$_2$), 7.36 (s, 5 H, C$_6$H$_5$); 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$_3$OH). 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$_6$H$_5$); 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$_3$OH). 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$_3$OH);

NMR (D$_2$O) δ 3.28 (m, 1 H, allylic methine proton), 3.80 (m, 4 H, C$H_2$NHC$H_2$), 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$_9$H$_{15}$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$_3$OH). Anal. (C$_9$H$_{16}$ClNO$_2$) C, H, N.

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

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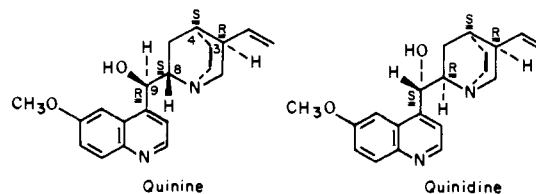
which is the subject of this publication, meroquinene was first combined with the quinoline component, and this was followed by cyclization to the quinuclidine ring. The second synthesis[3] described in the accompanying papers,[4] involves the conversion of meroquinene to a quinuclidine moiety, which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

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Scheme I
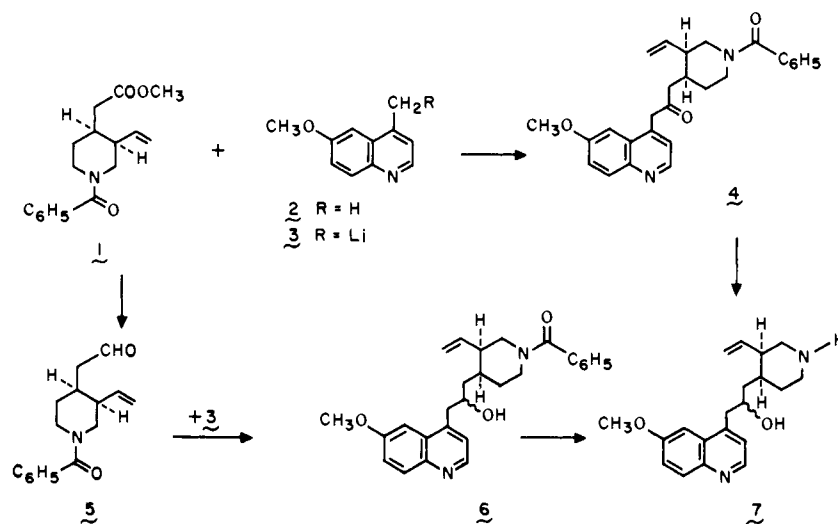
In order to assemble the skeleton of quinine and quinidine from meroquinene, we have used 6-methoxylepidine (**2**) as the complementary unit. This was an attractive choice owing to the ability of 6-methoxylepidyllithium (**3**) to act as a nucleophile. Compound **3** was prepared in situ by treatment of **2** with lithium diisopropylamide in tetrahydrofuran at −78 °C. A smooth acylation occurred on addition of *N*-benzoylmeroquinene methyl ester (**1**), affording the *N*-benzoyl ketone **4** in high yield (Scheme I). The benzylic protons of **4** gave rise to a characteristic singlet at δ 4.03 in the NMR spectrum.

Alternatively, meroquinene ester **1** was first reduced with diisobutylaluminum hydride to the aldehyde **5**, which upon reaction with **3** led to a mixture of epimeric *N*-benzoyl alcohols **6**. Removal of the *N*-benzoyl group was achieved by reduction with sodium aluminum hydride in tetrahydrofuran at room temperature. The resultant mixture of epimeric amino alcohols **7** was identical with the product of diisobutylaluminum hydride reduction of the *N*-benzoyl ketone **4**.

Formation of the quinuclidine ring and introduction of the hydroxy function at C-9 could be accomplished by three different methods. In the initial approach, the quinuclidine portion was constructed by the conjugative addition of the piperidine nitrogen to the preformed vinylquinoline moiety of the intermediate **9**. The C-9 hydroxy group was introduced subsequently by triplet oxygen oxidation (Scheme II). Thus, the epimeric amino alcohols **7** were O-acetylated by heating at 50 °C in acetic acid in the presence of boron trifluoride etherate. The ratio of the two epimeric acetates **8** was 3:2, as estimated by the intensities of the NMR signals at δ 2.01 and 2.05, which correspond to the acetoxy methyl protons. Cyclization via the vinylquinoline intermediate **9** was effected by heating the acetates **8** in benzene containing 5% glacial acetic acid and an excess of sodium acetate trihydrate. The crude reaction product was chromatographed on alumina to give a mixture of deoxyquinine (**10**) and deoxyquinidine (**11**) in 79% yield. On the basis of specific rotation measurements, the ratio of **10** to **11** in the mixture was approximately 43:57. For comparison purposes, pure deoxyquinine (**10**) and deoxyquinidine (**11**) were obtained from quinine and quinidine by a known procedure.[5,6] Individual treatment of **10** or **11** under the conditions of cyclization resulted in each case in a mixture of **10** and **11**, thus indicating that **9** → **10** + **11** is a reversible process.

Exposure of either pure deoxy compound **10** or **11**, as well as the mixture obtained by synthesis, to molecular oxygen in Me₂SO-*tert*-butyl alcohol (4:1) solution containing 0.5–2 equiv of potassium *tert*-butoxide resulted in a rapid con-

sumption of 1 equiv of oxygen. A remarkable, highly stereospecific formation of the desired C₈,C₉-erythro alkaloids quinine (**12**) and quinidine (**13**) took place. From pure **10** only **12** was obtained, and from pure **11** only **13**, thus indicating that no epimerization of the deoxy compounds occurred under these conditions. This oxidation proceeds by a known mechanism.[7]
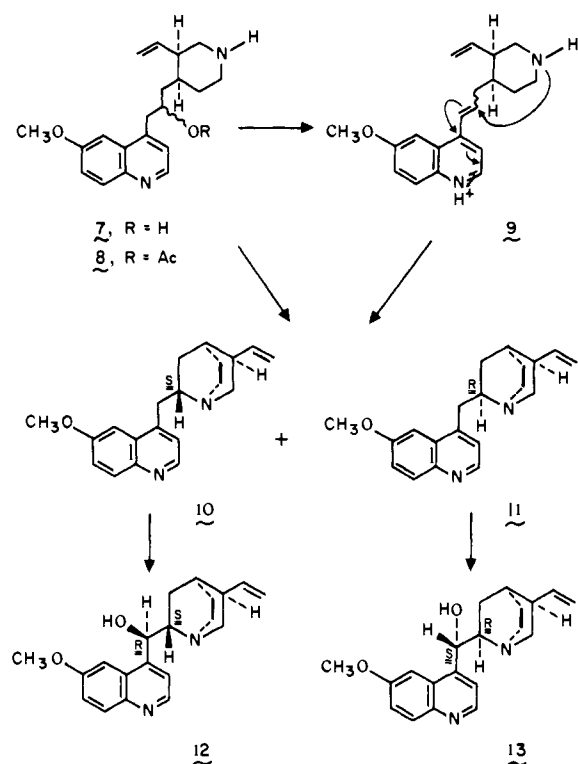
The observed high stereospecificity may be due to a preferred backside attack of the oxygen radical anion on the intermediate radicals **24** and **25** in order to avoid the repulsive force of the quinuclidino nitrogen free electron pair.

**24**     **25**
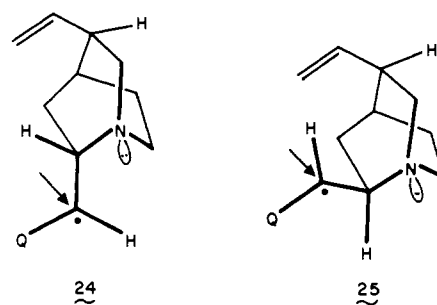
The second approach is based upon a simultaneous formation of the quinuclidine ring and introduction of a hydroxy function by an intramolecular opening of the epoxide **16** by the piperidino nitrogen (Scheme III). Bromination of the *N*-benzoyl ketone **4** with *N*-bromosuccinimide gave the α-bromo ketone **14**. The formation of the epoxide **15** occurred spontaneously after reduction of the keto group with sodium borohydride. Disappointingly, the overall yield from **4** was at best 40%, and the epoxide **15** was a mixture of all four possible diastereomers. The *N*-benzoyl group was removed reductively with diisobutylaluminum hydride at −78 °C, and the opening of the amino epoxide **16** was performed in boiling toluene with ethanol as a proton source. This reaction gave 13% of quinine (**12**), 24% of quinidine (**13**), 18% of *epi*-quinine (**17**), and 18% of *epi*-quinidine (**18**).

We reasoned then that a similar opening of the chloro epoxide **22**, should lead to the mixture **23** of quininone and quinidinone (Scheme IV). It was known from our previous work[8,9] that diisobutylaluminum hydride reduction of **23** gives exclusively quinine (**12**) and quinidine (**13**) in almost quantitative yield. Therefore, such an approach would provide another stereospecific synthesis of the desired erythro products. To this end, the *N*-benzoyl amide group of the intermediate **4** was hydrolyzed by hot 3 N sulfuric acid to give the amino ketone

Scheme II



7, R = H
8, R = Ac

9

10    +    11

12    13

Scheme III



4, X = H
14, X = Br

15, R = COC₆H₅
16, R = H

12, 8(S),9(R)
13, 8(R),9(S)
17, 8(S),9(S)
18, 8(R),9(R)

19, which was dichlorinated in 100% phosphoric acid solution with *N*-chlorodiisopropylamine. Reduction of the dichloro ketone **20** with sodium borohydride led to the dichlorohydrin **21**. The formation of the chloro epoxide and the subsequent rearrangement to the mixture **23** of quininone and quinidinone took place upon treatment of **21** with barium hydroxide. The overall yield of the mixture **23** from the amino ketone **19** was 34%. Fractional crystallization of these products from ether provided pure quinidinone (**23**, 8α-H). Quininone (**23**, 8β-H), which remained in the mother liquors, epimerized to an equilibrium with quinidinone (**23**, 8α-H). Subsequent crystallization gave more of the latter compound, totaling 80% of the original mixture.

The above described syntheses of quinine and quinidine have been used subsequently for the preparation of many analogues substituted differently in the benzene ring.

## Experimental Section[10]

**6-Methoxy-4-[3-(1-benzoyl-3(*R*)-vinyl-4(*S*)-piperidyl)-2-oxopropyl]quinoline (4) from *N*-Benzoylmeroquinene Methyl Ester (1) and 6-Methoxylepidine (2).** To a solution of ca. 10.4 mmol of lithium diisopropylamide (prepared by addition of 2 mL of dry diisopropylamine in 7 mL of tetrahydrofuran to 5 mL of ca. 2.1 M phenyllithium in benzene-ether (7:3) at −78 °C under nitrogen) was added dropwise (10 min) with stirring a solution of 1.8 g (10.4 mmol) of 6-methoxylepidine (**2**) in 20 mL of tetrahydrofuran. The mixture was stirred at −78 °C for 10 min, and then a solution of 1.49 g (5.2 mmol) of *N*-benzoylmeroquinene methyl ester (**1**) in 30 mL of tetrahydrofuran was added dropwise (10 min). Stirring was continued at −78 °C for 10 min and at ambient temperature for 60 min. Water was added, and the aqueous layer was neutralized (pH ca. 8) with acetic acid, extracted thoroughly with ether, and worked up as usual. The residue (39 g) was adsorbed on 120 g of neutral alumina, activity II; after elution of starting materials with benzene, elution with benzene-ethyl acetate (9:1) and with dichloromethane-methanol (98:2) afforded 1.73 g (78%) of amorphous **4**: [α]²⁴_D + 27.3° (*c* 1.205, CHCl₃); IR (CHCl₃) 1715 (ketone), 1620 (amide), 1000 and 920 cm⁻¹ (vinyl); UV (EtOH) 219-220 nm (ε 48 600), 233 (53 200), 266 (5330) (sh), 278 (4270) (sh), 323 (5840) (sh), 331-332 (6430); NMR (CDCl₃) ε 3.92 (s, 3 H, OCH₃), 4.03 (s, 2 H, ArCH₂CO), ca. 5 (m, 2 H, CH=C*H*₂), ca. 5.7 (m, 1 H, C*H*=CH₂), 7.35 (s, 5 H, phenyl), ca.
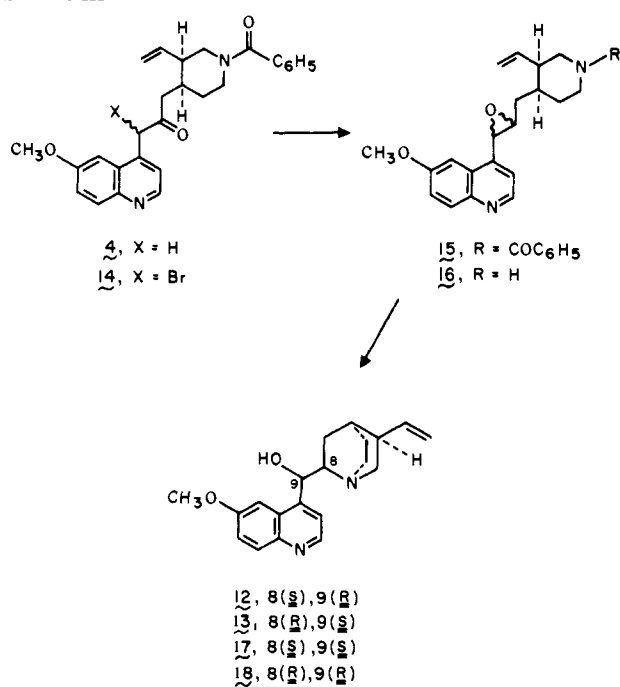
7.1-8.7 (5 H, aromatic); mass spectrum *m/e* 428 (M⁺). Anal. (C₂₇H₂₈N₂O₃) C, H, N.

**1-Benzoyl-3(*R*)-vinyl-4(*S*)-piperidineacetaldehyde (5) from 1.** To a dry ice cooled solution of 2.78 g (10 mmol) of 1-benzoyl-3(*R*)-vinyl-4(*S*)-piperidineacetic acid methyl ester (**1**) in 80 mL of anhydrous toluene was added dropwise (60 min) with stirring 15 mL of a 25% solution of diisobutylaluminum hydride in toluene. Stirring was continued for 3 h at −78 °C, then 3 mL of 50% aqueous methanol was added. The cooling bath was removed, 8 mL of 2 N aqueous K₂CO₃ and 7 g of anhydrous potassium carbonate was added followed by 1.5 mL of benzoyl chloride, and the mixture was stirred for 3 h at 20 °C. The inorganic solids were removed by filtration and washed with benzene, and the filtrate was washed with water, dried over sodium sulfate, and evaporated. The crude product (4.4 g) was distilled in a Kugelrohr (165-170 °C, 0.15 mm) to give 1.34 g (49%) of **5**: oil; [α]_D²⁵ +46.38° (*c* 1.110, CH₃OH); NMR (CDCl₃) δ ca. 5.15 (m, 2 H, CH=C*H*₂), ca. 5.80 (m, 1 H, C*H*=CH₂), 7.42 (s, 5 H, phenyl), 9.82 (s, 1 H, CHO). Anal. (C₁₆H₁₉NO₂) C, H, N.

**Epimeric 6-Methoxy-4-{3-[1-benzoyl-3(*R*)-vinyl-4(*S*)-piperidyl]-2ξ-hydroxypropyl}quinolines (6) from 5.** To a solution of ca. 5.5 mmol of lithium diisopropylamide (prepared in an atmosphere of dry nitrogen by addition of 0.8 mL of diisopropylamine to 2.6 mL of 2.14 M phenyllithium in hexane) was added with stirring a solution of 0.95 g (5.5 mmol) of 6-methoxylepidine (**2**) in 7 mL of benzene and 25 mL of tetrahydrofuran. After stirring at room temperature for 20 min, a solution of 0.95 g (3.7 mmol) of 1-benzoyl-3(*R*)-vinyl-4(*S*)-piperidineacetaldehyde (**5**) in 14 mL of tetrahydrofuran was added dropwise (30 min), and the resulting mixture was stirred at room temperature for 15 h. Water (50 mL) was added and the aqueous phase was extracted thoroughly with ether. Usual workup gave 2.4 g of crude product which was adsorbed on 100 g of neutral alumina, activity II. Elution with ethyl acetate-methanol (99:1) afforded 0.88 g (55%) of **6**: amorphous; IR (CHCl₃) 3600 (OH, free), 1620 (amide), 1000 and 920 cm⁻¹ (vinyl); NMR (CDCl₃) δ 3.88 (s, 3 H, OCH₃), ca. 5.2 (m, 2 H, CH=C*H*₂), ca. 5.9 (m, 1 H, C*H*=CH₂), 7.35 (s, 5 H, phenyl), ca. 7.1-8.3 (5 H, aromatic); mass spectrum *m/e* 430 (M⁺). Anal. (C₂₇H₃₀N₂O₃) C, H, N.

**Epimeric-6-Methoxy-4-{3-[3(*R*)-vinyl-4(*S*)-piperidyl]-2ξ-hydroxypropyl}quinolines (7) from 4.** To a dry ice cooled (−78 °C) solution of 0.75 g (1.75 mmol) of 6-methoxy-4-{3-[1-benzoyl-3(*R*)-vinyl-4(*S*)-piperidyl]-2-oxopropyl}quinoline (**4**) in 50 mL of anhydrous toluene was added with stirring under nitrogen in portions a total of 2.6 mL of a ca. 25% solution of diisobutylaluminum hydride in toluene while the reaction was monitored by TLC. After 80 min, 2 mL of 50% aqueous methanol was added and the mixture was evaporated to dryness. The residue was partitioned between ether and 2 N aqueous

Scheme IV



4  R = COC₆H₅
19  R = H
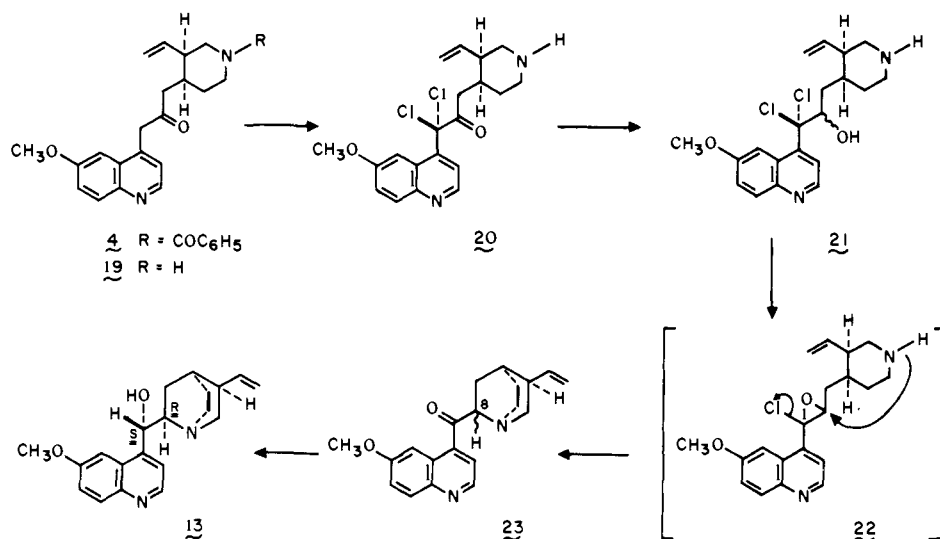
sulfuric acid, and the acidic phase rendered alkaline (pH <12) by addition of concentrated ammonium hydroxide and some potassium hydroxide, saturated with sodium chloride, and extracted thoroughly with dichloromethane. Usual workup gave 0.6 g of crude product which was crystallized in the presence of 0.3 g of dibenzoyl-(+)-tartaric acid from a concentrated solution of methanol-acetone (1:1) to give 0.754 g (85%) of the neutral dibenzoyl-(+)-tartrate of epimeric amino alcohols 7: mp 190–191.5 °C, after recrystallization from the same solvent mixture; $[\alpha]^{25}_D$ −27.0° (c 1.09, CH₃OH). Anal. [C₂₀H₂₆N₂O₂]₂·C₁₈H₁₄O₈] C, H, N.

The free base was obtained as a viscous, colorless oil: $[\alpha]^{25}_D$ +39.6° (c 1.425, CHCl₃); IR (CHCl₃) 3610 (OH, free), ca. 3400–3100 and ca. 2700–2500 (OH, bonded), 1620 (aromatic), 1000 and 920 cm⁻¹ (vinyl); UV (EtOH) 230 nm (ε 47 800), 270 (3930) (sh), 279 (4530), 289 (4090) (sh), 319 (5250), 331–332 (5900); NMR (CDCl₃) δ 3.93 (s, 3 H, OCH₃), ca. 5.2 (m, 2 H, CH=CH₂), ca. 6.1 (m, 1 H, CH=CH₂), ca. 7.1–8.7 (5 H, aromatic); mass spectrum m/e 326 (M⁺).

**Epimeric 6-Methoxy-4-{3-[3(R)-vinyl-4(S)-piperidyl]-2ξ-hydroxypropyl}quinolines (7) from 6.** To a solution of 0.145 g (0.33 mmol) of epimeric 6-methoxy-4-{3-[1-benzoyl-3(R)-vinyl-4(S)-piperidyl]-2ξ-hydroxypropyl}quinolines (6) in 20 mL of tetrahydrofuran was added 80 mg (15 mmol) of sodium aluminum hydride, and the mixture was stirred at room temperature for 80 min. Sodium hydroxide (20 mL, 1 N) was added, the aqueous phase was extracted thoroughly with ether, and the ethereal extracts were worked up as usual to give 0.11 g (over 90% yield) of crude 7.

**Epimeric 6-Methoxy-4-{3-[3(R)-vinyl-4(S)-piperidyl]-2ξ-acetoxypropyl}quinolines (8) from 7.** To a solution of 1.15 g (3.53 mmol) of epimeric 6-methoxy-4-{3-[3(R)-vinyl-4(S)-piperidyl]-2ξ-hydroxypropyl}quinolines (7) in 40 mL of glacial acetic acid was added 4 mL of freshly distilled boron trifluoride etherate and the solution was kept at 50 °C for 18 h. The acetic acid was stripped, ice-water was added to the residue, and the aqueous phase was rendered alkaline (pH ca. 9) by addition of 6 N sodium hydroxide. The ice-cold, alkaline phase was extracted thoroughly with dichloromethane, and the extracts were worked up as usual to give 1.241 g (96%) of TLC-pure 8: amorphous; $[\alpha]^{25}_D$ +21.4° (c 0.835, CHCl₃); IR (CHCl₃) 3700 (weak, N–H), 1730 (carbonyl), 1620 (aromatic), 1245 (acetate), 1000 and 920 cm⁻¹ (vinyl); UV (EtOH) 235 nm (ε 37 000), 270 (3680) (sh), 279 (4170), 287–288 (3440) (sh), 321 (4920), 333 (5400); NMR (CDCl₃) δ 2.01 and 2.05 (2 s, 3 H, ratio ca. 3:2, CH₃COO), 3.98 and 4.00 (2 s, 3 H, ratio ca. 3:2, OCH₃), ca. 5.1 (m, 2 H, CH=CH₂), ca. 5.25 (m, 1 H, CHOAc), ca. 5.85 (m, 1 H, CH=CH₂), ca. 7.1–8.65 (5 H, aromatic); mass spectrum m/e 368 (M⁺). Anal. (C₂₂H₂₈N₂O₃) C, H, N.

**Mixture of Deoxyquinine (10) and Deoxyquinidine (11). A. From Amino Acetates 8.** To a solution of 1.241 g (3.38 mmol) of the epimeric 6-methoxy-4-{3-[3(R)-vinyl-4(S)-piperidyl]-2ξ-acetoxypropyl}quinolines (8) in 150 mL of benzene was added 7.5 mL of glacial acetic acid and 17 g of sodium acetate trihydrate, and the mixture was heated under gentle reflux with stirring for 14 h. After

cooling, 100 mL of ice-water was added, and the resulting mixture was rendered alkaline by addition of 6 N sodium hydroxide. The aqueous phase was extracted thoroughly with ether and the ethereal extracts were worked up as usual to give 1.028 g of crude product which was adsorbed on 30 g of neutral alumina, activity II. Elution with ethyl acetate afforded 0.85 g (79%) of a mixture of 10 and 11: coloress, viscous oil; $[\alpha]^{25}_D$ +76.3° (c 1.21, CHCl₃; suggests a ratio of 10 to 11 of ca. 43:57); IR (CHCl₃) 1620 (aromatic), 1000 and 920 cm⁻¹ (vinyl); UV (EtOH) 231 nm (ε 35 300), 268 (3320) (sh), 279 (3880), 290 (3240) (sh), 321 (4250), 333 (4790); NMR (CDCl₃) δ 3.94 (s, 3 H, OCH₃), ca. 5.2 (m, 2 H, CH=CH₂), ca. 5.9 (m, 1 H, CH=CH₂), 7.2–8.4 (5 H, aromatic); mass spectrum m/e 308 (M⁺). Anal. (C₂₀H₂₄N₂O) C, H, N.

**B. From Amino Alcohols 7.** A solution of 0.350 g (1.08 mmol) of epimeric 6-methoxy-4-{3-[3(R)-vinyl-4(S)-piperidyl]-2ξ-hydroxypropyl}quinolines (7) in 50 mL of benzene-acetic acid (4:1) was heated under gentle reflux for 29 h. After the addition of water (ca. 50 mL), the aqueous phase was rendered alkaline by addition of 6 N sodium hydroxide and extracted thoroughly with ether and the ethereal extracts were worked up as usual. The crude product (0.285 g) was separated by preparative thin layer chromatography (chloroform-triethylamine, 9:1) to give 85 mg (26%) of a mixture of 10 and 11 and 163 mg (47%) of starting material. The latter was again heated under reflux in 40 mL of benzene-acetic acid (4:1) for 60 h to give, after the same workup, another 63 mg (total yield 45%) of a mixture of deoxyquinine (10) and deoxyquinidine (11) in a ratio of ca. 1:1 (as estimated by TLC).

**Quinine (12) and Quinidine (13) from 10 and 11.** The reaction was run in a 100-mL three-neck flask connected with a gas buret and equipped with a gas outlet, an Erlenmeyer flask attached by means of a piece of Gooch rubber tubing, and a magnetic stirrer. A solution of 0.275 g (0.895 mmol) of a mixture of deoxyquinine (10) and deoxyquinidine (11) (ratio ca. 43:57) in 40 mL of dimethyl sulfoxide–tert-butyl alcohol (4:1) was stirred in the above apparatus in an atmosphere of dry oxygen at 20 °C for ca. 10 min (no O₂ uptake was observed). To the equilibrated solution was added 0.15 g (ca. 1.5 molar equiv) of dry potassium tert-butoxide, and the resulting red-brown solution was stirred at 20 °C for 9 min, when 22.0 mL of oxygen was consumed. The reaction was quenched by addition of water and neutralized by addition of acetic acid. The solvents were stripped in vacuo (0.1 mm), and the residue was dissolved in dichloromethane, washed with 0.5 N sodium hydroxide, and worked up as usual. The crude product (0.3 g) was crystallized from a concentrated solution in ethanol to give 54 mg of quinidine (13). The mother liquor was separated by preparative thin layer chromatography (chloroform-triethylamine-methanol, 87.5:10:2.5) to give 93 mg (32%) of quinine (12) and 63 mg (totally 117 mg, 40%) of quinidine (13).

Quinidine (13), after crystallization from ethanol and drying at 90 °C (0.1 mm): mp and mmp with authentic quinidine 170–171.5 °C; $[\alpha]^{25}_D$ +261.6° (c 0.85, EtOH); IR (CHCl₃) 3625 (OH, free), ca. 3400–3100 (weak, OH, bonded), 1000 and 920 cm⁻¹ (vinyl); UV

(EtOH) 229 nm ($\epsilon$ 33 500), 269 (3500) (sh), 278–279 (4020), 288 (3500) (sh), 319–320 (4630), 331–332 (5280); NMR (CDCl$_3$) $\delta$ 3.79 (s, 3 H, OCH$_3$), ca. 5.0 (m, 2 H, CH=CH$_2$), 5.61 (d, 1 H, $J$ = 4 Hz, C$H$OH), ca. 6.0 (m, 1 H, C$H$=CH$_2$), ca. 7.2–8.5 (5 H, aromatic); mass spectrum $m/e$ 324 (M$^+$), 136 (base peak). Anal. (C$_{20}$H$_{24}$N$_2$O$_2$) C, H, N.

Quinidine (12) was crystallized as its neutral (+)-tartrate monohydrate: mp and mmp with an authentic sample 207–209 °C (dec >200 °C); [$\alpha$]$^{25}$D −156.1° ($c$ 1.01, CH$_3$OH) authentic sample [$\alpha$]$^{25}$D −155.5° ($c$ 0.81, CH$_3$OH); IR (KBr) identical with the spectrum of an authentic sample. Anal. (C$_{20}$H$_{24}$N$_2$O$_2$·C$_4$H$_6$O$_6$·H$_2$O) C, H, N.

The amorphous free base was spectroscopically identical with an authentic sample: IR (CHCl$_3$) 3620 (OH, free), ca. 3400–3100 (OH bonded), 995 and 915 cm$^{-1}$ (vinyl); UV (EtOH) 230 nm ($\epsilon$ 30 200), 268 (3200) (sh), 278 (3540), 289 (3100) (sh), 319 (4150), 331 (4610); NMR (CDCl$_3$) $\delta$ 3.83 (s, 3 H, OCH$_3$), ca. 4.9 (m, 2 H, CH=CH$_2$), ca. 5.25 (b, 1 H, OH), 5.54 (d, 1 H, $J$ = ca. 4 Hz, CHOH), ca. 5.7 (m, 1 H, C$H$=CH$_2$), ca. 7.2–8.4 (5 H, aromatic); mass spectrum $m/e$ 324 (M$^+$), 136 (base peak).

**Quinine (12) from 10.** 9-Deoxyquinine (10) (0.20 g, 0.65 mmol) [neutral (+)-tartrate dihydrate: mp 137–138 °C, [$\alpha$]$^{25}$D −51.7° ($c$ 0.89, methanol); prepared from natural quinine according to the literature[5,6]] was hydroxylated as described above. Chromatographically pure, amorphous quinine (12, 0.144 g, 69%) was isolated which was characterized as its neutral (+)-tartrate after recrystallization from ethanol and drying at 110 °C (0.1 mm): mp and mmp with an authentic sample 211–212.5 °C; [$\alpha$]$^{25}$D −157.8° ($c$ 0.99, methanol). Anal. (C$_{20}$H$_{24}$N$_2$O$_2$·C$_4$H$_6$O$_6$) C, H, N.

The free base [[$\alpha$]$^{25}$D −160.4° ($c$ 1.05, ethanol)] was spectroscopically identical with authentic quinine.

**Quinidine (13) from 11.** 9-Deoxyquinidine (11) (200 mg, 0.65 mmol) [mp 67–68 °C; [$\alpha$]$^{25}$D +209.3° ($c$ 1.00, ethanol); prepared from natural quinidine according to the literature[5,6]] was hydroxylated as described above to give 0.155 g (74%) of chromatographically pure quinidine (13): mp 170–171 °C, after recrystallization from ethanol and subsequent drying; [$\alpha$]$^{25}$D +261.8° ($c$ 0.99, ethanol); spectroscopically identical with an authentic sample. Anal. (C$_{20}$H$_{24}$N$_2$O$_2$) C, H, N.

**Epimeric 6-Methoxy-4-{3-[1-benzoyl-3($R$)-vinyl-4($S$)-piperidyl]-1$\xi$-bromo-2-oxopropyl}quinolines (14) from 4.** To a solution of 3.0 g (7 mmol) of ketone 4 in 300 mL of dry carbon tetrachloride in a 500-mL Pyrex flask were added 1.72 g (9.7 mmol) of solid $N$-bromosuccinimide and a few crystals of dibenzoyl peroxide, and the mixture was irradiated by means of a 250-W IR-heating lamp with stirring. After irradiating for 90 min, the refluxing mixture was cooled and filtered, the filter cake was washed with carbon tetrachloride, and the combined filtrates were evaporated to dryness to give 3.9 g of a crude amorphous mixture of epimeric bromo ketones 14.

**Diastereomeric 6-Methoxy-4-{3-[1-benzoyl-3($R$)-vinyl-4($S$)-piperidyl]-1$\xi$,2$\xi$-oxapropyl}quinolines (15) from 14.** To a solution of 3.9 g of the crude $\alpha$-bromo ketones 14 in 300 mL of methanol was added an excess of solid sodium borohydride. The solution was stirred at room temperature for 30 min, 50 mL of water was added, and stirring was continued for 12 h. The methanol was evaporated, the aqueous residue was extracted thoroughly with dichloromethane, and the organic extracts were washed (H$_2$O), dried (Na$_2$SO$_4$), and evaporated to give 2.7 g of crude product which was absorbed on 90 g of neutral alumina, activity II. Elution with benzene containing 10–50% of ethyl acetate afforded 1.4 g (40% calculated on the basis of ketone 4) of an amorphous, inseparable mixture of the diastereomeric $N$-benzoyl epoxides 15: [$\alpha$]$^{25}$D +12.4° ($c$ 1.33, CHCl$_3$); IR (CHCl$_3$) 1620 (amide), 1000 and 920 cm$^{-1}$ (vinyl); UV (EtOH) 222 nm ($\epsilon$ 37 000), 231–232 (38 100), 268–270 (3800), 278 (3800), 290 (3220) (infl), 323 (4350) (infl), 333–334 (4930); NMR (CDCl$_3$) $\delta$ 3.90 (s, 3 H, OCH$_3$), ca. 3.6, 4.15, and 4.45 (2 H, epoxide, indicating mixture), ca. 5.1 (m, 2 H, CH=CH$_2$), ca. 5.7 (b, 1 H, C$H$=CH$_2$), 7.34 and 7.38 (2 s, 5 H, phenyl), ca. 5.1–8.8 (5 H, aromatic); mass spectrum $m/e$ 428 (M$^+$). Anal. (C$_{27}$H$_{28}$N$_2$O$_3$) C, H, N.

**Diastereomeric 6-Methoxy-4-{3-[3($R$)-vinyl-4($S$)-piperidyl]-1$\xi$,2$\xi$-oxapropyl}quinolines (16) from 15.** To a stirred, dry ice cold solution of 1.2 g (2.8 mmol) of the $N$-benzoyl epoxides 15 in 100 mL of dry toluene in an atmosphere of dry nitrogen was added 2 mL of a ca. 1.5 M solution of diisobutylaluminum hydride in toluene. Stirring was continued for 45 min at −78 °C, 5 mL of methanol–water (1:1) was added, and the mixture was stirred for 90 min at 20 °C. The precipitate was filtered off and washed with methanol, and the com-

bined filtrates were evaporated to dryness. The crude product (1.1 g) was separated by preparative thin layer chromatography (chloroform–triethylamine–methanol, 85:10:15) to give 0.578 g (63% yield) of an amorphous, inseparable mixture of the diastereomeric amino epoxides 16: IR (CHCl$_3$) 3700 (weak, N-H); 1010 and 930 cm$^{-1}$ (vinyl); UV (EtOH) 231 nm ($\epsilon$ 28 370), 279 (3190), 290 (2750) (infl), 320 (3870) (sh) 333 (4410); NMR (CDCl$_3$) $\delta$ 3.98 (s, 3 H, OCH$_3$), ca. 4.3 (m, 2 H, epoxide), ca. 5.15 (m, 2 H, CH=CH$_2$), ca. 6.0 (m, 1 H, C$H$=CH$_2$), ca. 7.2–8.7 (5 H, aromatic); mass spectrum $m/e$ 324 (M$^+$), 136 (base peak).

**Quinine (12), Quinidine (13), *epi*-Quinine (17), and *epi*-Quinidine (18) from 16.** A solution of 0.356 g (1.1 mmol) of diastereomeric amino epoxides 16 in 50 mL of toluene and 2 mL of ethanol was heated under gentle reflux for 24 h. The solvent was evaporated, and the residue (0.35 g) was separated by preparative thin layer chromatography to give 0.049 g (13%) of quinine (12) [neutral $d$-tartrate: mp 207–209 °C, dec >200 °C; [$\alpha$]$^{25}$D −153.3° ($c$ 0.90, CH$_3$OH)]; 0.087 g (24%) of quinidine (13) [mp 171–172 °C; [$\alpha$]$^{25}$D +256.0° ($c$ 0.82, EtOH)]; 0.068 g (18%) of *epi*-quinine (17) [neutral dibenzoyl-$d$-tartrate: mp 187–189 °C; [$\alpha$]$^{25}$D +67.7° ($c$ 0.93, EtOH-CHCl$_3$, 3:2)]; and 0.065 g (18%) of *epi*-quinidine (18) [neutral dibenzoyl-$d$-tartrate: mp 167–168 °C; [$\alpha$]$^{25}$D +2.4° ($c$ 0.90, EtOH-CHCl$_3$ 4:1)].

**6-Methoxy-4-{3-[3($R$)-vinyl-4($S$)-piperidyl]-2-oxopropyl}quinoline (19).** A solution of 0.388 g (0.91 mmol) of 6-methoxy-4-{3-[1-benzoyl-3($R$)-vinyl-4($S$)-piperidyl]-2-oxopropyl}quinoline (4) in 50 mL of 3 N aqueous sulfuric acid was heated under gentle reflux for 24 h. The solution was rendered alkaline by addition of concentrated ammonium hydroxide and extracted thoroughly with dichloromethane. Usual workup gave 0.28 g of crude amino ketone, which was chromatographed on a silicia gel column with chloroform–methanol–ammonia (89:10:1) to give 0.22 g (75%) of crystalline 19: mp 58–60 °C from ethyl acetate-ether; [$\alpha$]$^{25}$D +47.2° ($c$ 1.03, CH$_3$OH); IR (CHCl$_3$) 1715 (ketone), 1000 and 920 cm$^{-1}$ (vinyl); UV (EtOH) 234 nm ($\epsilon$ 35 030), 270 (3320) (sh), 278 (3720), 290 (3260) (sh), 323 (4520) (sh), 332 (4950); (0.1 N HCl) 248 (32 200), 314 (4890), 344 (5240); NMR (CDCl$_3$) $\delta$ 3.90 (s, 3 H, OCH$_3$), 4.01 (s, 2 H, Ar-C$H_2$CO), ca. 4.9 (m, 2 H, CH=CH$_2$), ca. 5.96 (m, 1 H, C$H$=CH$_2$), 7.1–8.7 (5 H, aromatic); mass spectrum $m/e$ 324 (M$^+$). Anal. (C$_{20}$H$_{24}$N$_2$O$_2$) C, H, N.

**Quinidinone (23, 8$\alpha$-H) from 19.** To a solution of 0.25 g (0.77 mmol) of 6-methoxy-4-{3-[3($R$)-vinyl-4($S$)-piperidyl]-2-oxopropyl}quinoline (19) in 1 mL of dichloromethane was added 1 mL of 100% phosphoric acid, and the organic solvent was removed under a stream of nitrogen. To the resulting viscous solution was added 0.25 mL (2.2 molar equiv) of $N$-chlorodiisopropylamine, and the viscous mixture was stirred slowly until it was homogeneous. After standing at 20 °C in the dark for 24 h, 40 mL of ice-water was added, the ice-cold solution was carefully neutralized (pH ca. 9) by addition of concentrated ammonium hydroxide, and a solution of 0.3 g of sodium borohydride in 20 mL of methanol and 30 mL of tetrahydrofuran was added. After stirring for 20 min at 20 °C, the aqueous phase was saturated with sodium chloride and extracted thoroughly with ether, and the ethereal extracts were washed with brine, dried (magnesium sulfate), and evaporated. The crude dichlorohydrin 21 (0.2 g) was dissolved in 50 mL of methanol, 0.28 g (ca. 0.8 mmol) of barium hydroxide octahydrate in 30 mL of water was added, and the solution was kept under nitrogen at 20 °C for 18 h. The methanol was stripped, and the residue dissolved in dichloromethane and worked up as usual. The crude product (0.2 g) was separated by preparative TLC (CHCl$_3$-MeOH-NH$_4$OH, 94.5:5:0.5) to give 0.080 g (34%) of an amorphous mixture of quininone and quinidinone (23). Crystallization from ether afforded 0.064 g of quinidinone (23, 8$\alpha$-H): mp 100–102 °C; [$\alpha$]$^{25}$D +73.8° ($c$ 1.01, EtOH, after standing at 20 °C for 2.5 days); IR (CHCl$_3$) 1700 (ketone), 1000 and 920 cm$^-$ (vinyl); UV (EtOH) 210 nm ($\epsilon$ 45 400), 240 (infl) (17 400), 261 (infl) (7200), 295 (infl) (2180), 343 (5020); NMR (CDCl$_3$) $\delta$ 3.97 (s, 3 H, OCH$_3$), 4.21 (t, 1 H, $J$ = 10 Hz, COCH), 5.06 (m, 2 H, CH=CH$_2$), 6.04 (m, 1 H, C$H$=CH$_2$), 7.44 (dd, 1 H, $J$ = 10 and 3 Hz, Ch-7′), 7.70 (d, 1 H, $J$ = 4.5 Hz, Ch-3′), 7.71 (d, 1 H, $J$ = 3 Hz, CH-5′), 8.08 (d, 1 H, $J$ = 10 Hz, CH-8′), 8.91 (d, 1 H, $J$ = 4.5 Hz, CH-2′); mass spectrum $m/e$ 322 (M$^+$), 136 (base peak). Anal. (C$_{20}$H$_{22}$N$_2$O$_2$) C, H, N.

**References and Notes**

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(10) The general conditions are the same as described in the preceding paper.[1]

# Total Synthesis of *Cinchona* Alkaloids. 3. Syntheses of Quinuclidine Intermediates

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**Abstract:** Quinuclidines containing an ethyl or vinyl side chain at C-5 and a trichloromethyl group, an aldehyde, or an ester function at C-2 have been synthesized by three different routes starting from β-collidine, meroquinene, or cincholoipon. Key intermediates in these reaction sequences are the 1,1-dichloro-3-piperidinylpropan-2-ols, **3**, **4**, and **27–32**. In the racemic dihydro series, compounds **3** and **4** were converted to the 1,1-dichloro olefin **13** which as the *N*-chloramine **14** on photolysis afforded the trichloromethyl quinuclidines **15** and **16**. On the other hand, base-catalyzed chlorohydrin rearrangement of the dichloropropanols and subsequent intramolecular reaction of the intermediate α-chloro epoxides afforded the quinuclidine aldehydes **17**, **39**, **40**, or **45**. These compounds were transformed into the corresponding acids or esters by standard procedures. Configurational assignments were made on the basis of physicochemical properties of the compounds.
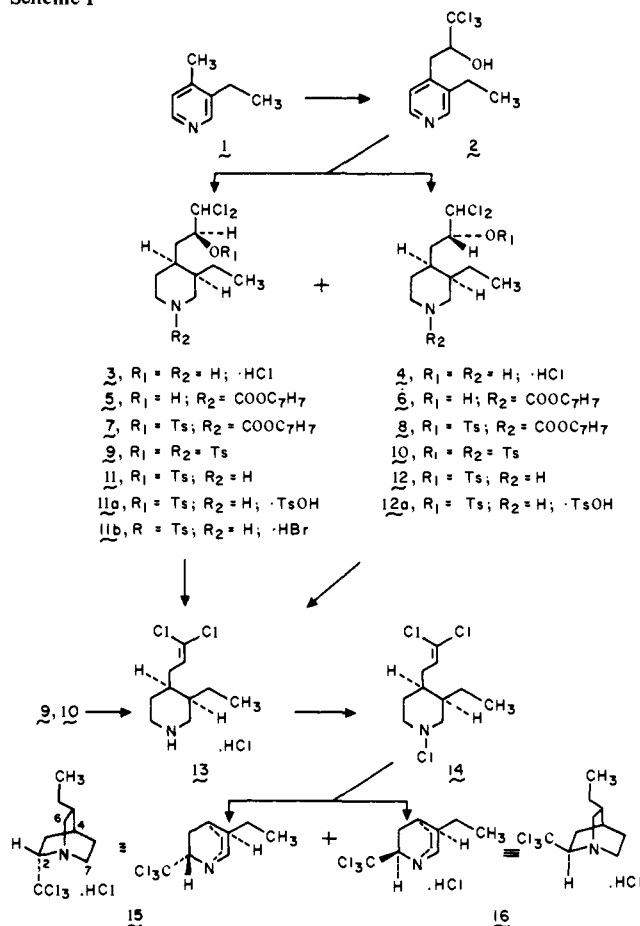
In preliminary form[1] we reported a new total synthesis of *Cinchona* alkaloids which features the use of quinuclidine derivatives properly substituted at C-2 and C-5. In this and a subsequent paper,[2] we describe in detail the preparation of these quinuclidines and their application to the synthesis of *Cinchona* alkaloids.

Since an economic synthesis of these alkaloids was desirable, we decided on the readily available β-collidine[3] as starting material. This compound already possesses the required two-carbon side chain at C-3 and an activated methyl group at C-4, which can be utilized for a two-carbon homologation. Transformation of an ethyl side chain into a vinyl group has been described by us,[4] and, based on previous results, we anticipated that hydrogenation of the pyridine ring would lead to the required cis configuration of the two side chains. The propyl side chain should contain a functional group at C-2 to allow for cyclization to the quinuclidine derivative and the terminal carbon atom should be part of a functional group which can later be used for the combination with the aromatic portion of the alkaloids.

Condensation of β-collidine (1) with chloral gave the crystalline alcohol 2.[5] Selective cis hydrogenation of the pyridine ring and reductive removal of one chlorine from the side chain of 2 was accomplished simultaneously using a platinum catalyst in 5% aqueous hydrochloric acid. After fractional crystallization, the two diastereomeric hydrochlorides 3 and 4 were obtained in a ca. 1:1 rato in 70% yield. These compounds differ only in their configuration at C-2 as evidenced from subsequent transformations. None of the trans isomers could be detected. The relative configuration as indicated in compounds 3 and 4 was established by a combination of x-ray analysis and chemical transformations in the optically active series (vide infra).

The 1,1-dichloro-3-piperidinylpropan-2-ols are the key intermediates in the preparation of the desired quinuclidine derivatives. In our initial approach (Scheme I), we hoped that

**Scheme I***



3, $R_1 = R_2 = H$; ·HCl
5, $R_1 = H$; $R_2 = COOC_7H_7$
7, $R_1 = Ts$; $R_2 = COOC_7H_7$
9, $R_1 = R_2 = Ts$
11, $R_1 = Ts$; $R_2 = H$
11a, $R_1 = Ts$; $R_2 = H$; ·TsOH
11b, $R = Ts$; $R_2 = H$; ·HBr

4, $R_1 = R_2 = H$; ·HCl
6, $R_1 = H$; $R_2 = COOC_7H_7$
8, $R_1 = Ts$; $R_2 = COOC_7H_7$
10, $R_1 = R_2 = Ts$
12, $R_1 = Ts$; $R_2 = H$
12a, $R_1 = Ts$; $R_2 = H$; ·TsOH

*All compounds are racemic with the relative configuration indicated.