References and Notes

(1) M. R. Uskoković, T. Henderson, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) J. Gutzwiller and M. Uskoković, *J. Am. Chem. Soc.*, **92**, 204 (1970).
(3) G. Grethe, H. L. Lee, T. Mitt and M. R. Uskoković, *J. Am. Chem. Soc.*, **93**, 5904 (1971).
(4) G. Grethe, H. L. Lee, T. Mitt, and M. R. Uskoković, *J. Am. Chem. Soc.*, **100**, 581, 589 (1978).
(5) W. Koenigs, *Chem. Ber.*, **29**, 372 (1896).
(6) P. Rabe, E. Kullga, O. Marschall, W. Naumann, and W. F. Russell, *Justus Liebigs Ann. Chem.*, **373**, 85 (1910).
(7) G. L. Russell, E. G. Janzen, A. G. Bemis, E. J. Geels, A. J. Moye, S. Mak, and E. T. Strom, "Oxidation of Hydrocarbons in Basic Solutions", *Adv. Chem. Ser.*, **No. 51**, 112–171 (1965).
(8) G. Grethe, J. Gutzwiller, H. L. Lee, and M. R. Uskoković, *Helv. Chim. Acta*, **55**, 1044 (1972).
(9) J. Gutzwiller and M. R. Uskoković, *Helv. Chim. Acta*, **56**, 1494 (1973).
(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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Received June 13, 1977

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.

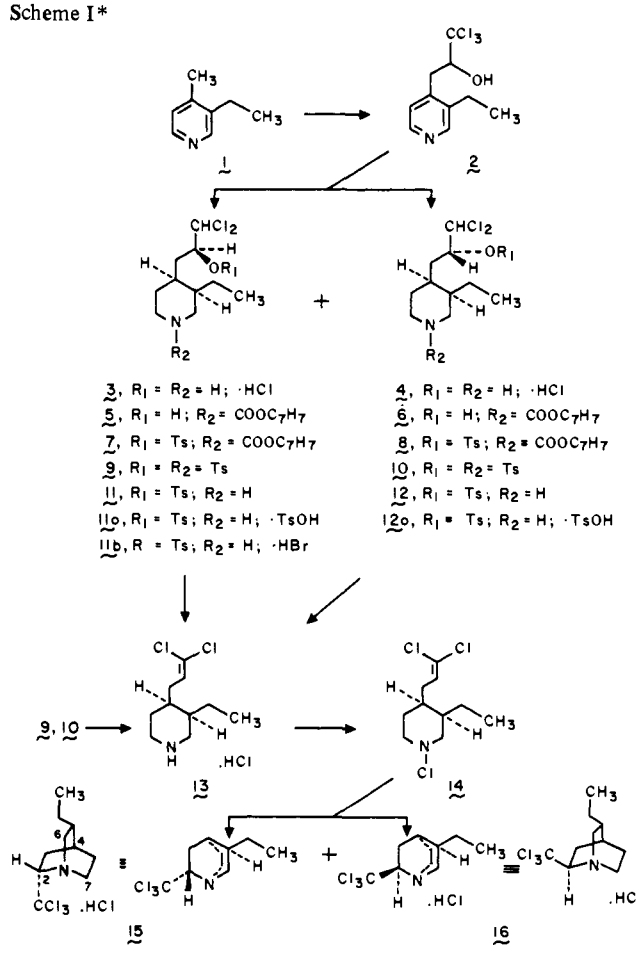
In preliminary form[1] we reported a new total synthesis of *Cinchona* alkaloids which features the use of quinuclidine derivatives properly substituted at C-2 and C-5. In this and a subsequent paper,[2] we describe in detail the preparation of these quinuclidines and their application to the synthesis 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*



*All compounds are racemic with the relative configuration indicated.

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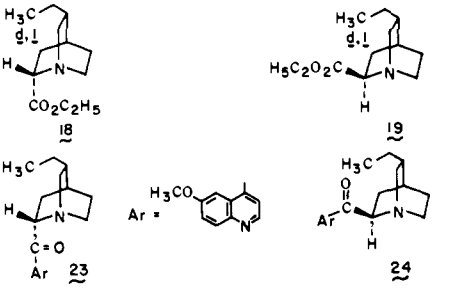
a sequence of reactions consisting of protection of the amino function, conversion of the alcohol group into a good leaving group, and removal of the N-protecting group with subsequent S_N2-type cyclization would lead to a quinuclidine derivative having a potential aldehyde function at C-2. N-Carbobenzoxylation of compounds **3** and **4** gave the urethanes **5** and **6**, respectively, which after treatment with tosic anhydride in pyridine yielded the derivatives **7** and **8** in an overall yield of 90%. These compounds, which were isolated as oils, could be used without further purification. Crystalline analytical samples were obtained by slow crystallization of the oils followed by recrystallization from ether–hexane. Although both compounds were nearly identical in their physical properties, a depression in the mixture melting point clearly showed that we were dealing with isomers. Removal of the N-protecting group was effected with 30% hydrobromic acid in glacial acetic acid[6] at room temperature. The hydrobromide **11b** crystallized from the reaction mixture after dilution with ether while the isomeric hydrobromide could not be obtained in crystalline form. All attempts to cyclize **11** or **12** under a variety of conditions failed. Treatment of either **11** or **12** with base resulted instead in the formation of the olefinic derivative **13.** The olefinic structure was confirmed spectroscopically in the NMR by a triplet at δ 5.91 and in the IR by an absorption at 870 cm^{-1}, characteristic for a trisubstituted double bond. When this reaction was carried out with potassium *tert*-butoxide in tetrahydrofuran, the olefin was obtained in 70% yield isolated in the form of its crystalline hydrochloride. The fact that both isomers (**11** and **12**) gave the same elimination product confirmed the assumption that the compounds of the two isomeric series differed only in their configuration at the carbon atom bearing the hydroxyl group. Since elimination occurred so readily, it was no surprise that **11** and **12** on standing at room temperature for several days gave a 1:1 mixture of **13** (as the free base) and the tosyl salts **11a** and **12a,** respectively. The crystalline salts were separated from the liquid olefin and after transformation into the free bases were subjected to the same procedure. Finally, compound **13** was also obtained from the crystalline *N,O*-ditosylates **9** and **10,** which in turn were prepared in 45% yield from **3** and **4,** respectively, on treatment with tosyl chloride in pyridine. Elimination of tosic acid and removal of the N-protecting group was effected by reacting **9** or **10** with potassium *tert*-butoxide in tetrahydrofuran and subsequently treating the crude reaction product with 30% hydrobromic acid in glacial acetic acid in the presence of phenol at 40 °C.[7] This procedure afforded **13** in 20–25% yield from **3** or **4** while the initial reaction sequence **3** (**4**) → **5** (**6**) → **7** (**8**) → **11** (**12**) → **13,** though involving more steps, gave the final product in 60% overall yield. On the basis of work carried out by Neale and co-workers[8] we hoped to achieve cyclization of this compound to a quinuclidine derivative by an intramolecular addition of an aminium radical generated conveniently from the *N*-chloramine **14** to the substituted olefin. The two chlorine atoms should favor this reaction greatly over an undesired electrophilic chlorination. Indeed, irradiation of a trifluoroacetic acid solution of the crude *N*-chloramine **14,** obtained from the free base of **13** with *N*-chlorosuccinimide in ether, at 20 °C with a Hanovia high-pressure mercury lamp (200 W) yielded a mixture of **15** and **16** in 72% yield. Surprisingly, the product resulting from a possible aminium radical rearrangement (Hofmann–Loeffler–Freitag)[9] could not be detected. The mixture contained **15** and **16** in a ca. 1:1 ratio as shown in the NMR by two triplets at δ 0.92 and 0.96 caused by the protons of the methyl groups of the two isomers. Separation of the isomeric hydrochlorides by fractional crystallization concurred with substantial losses in yield. The higher melting isomer **15** was obtained by crystallization of the mixture from ethanol–ether, while **16** could be isolated only after preparative thick layer chromatography of the mother liquors on silica gel.

The relative configuration of **15** and **16** as shown in Scheme I has been tentatively assigned on the basis of NMR studies using the lanthanide shift reagent $Yb(fod)_3$. The substrate solutions were 0.5 M in $CDCl_3$ and the reagent was added in increments of 10 mg. We assumed that the steric bulk of the trichloromethyl group would force the metal atom in the complex out of its axis passing through N and C-4, thereby causing nonequivalence of nearby protons. This effect was seen in the spectra of both compounds at a molar ratio of 0.36 of shift reagent to substrate (L/S = 0.36). In these spectra, the protons at C_2, C_6, and C_7 show the largest induced shifts as expected and give rise to three distinct resonances in a ratio of 1:3:1. The least shifted of these resonances is the triplet caused by the proton at C-2. Unfortunately, line broadening and bad resolution of these resonances did not allow us to make configurational assignments. This was, however, accomplished by an analysis of the induced shift of the methyl group signals. As a consequence of the steric effect of the trichloromethyl group, the distance between the methyl group and the metal atom should be larger in the cis isomer **16.** The difference in induced shifts resulting from this effect was demonstrated in the spectra of the free bases of **15** and **16** in $CDCl_3$ at L/S = 0.36. In the spectrum of the former, the methyl triplet is shifted from δ 0.92 to δ 1.26 while the triplet in the spectrum of the other isomer shows only a small induced shift (δ 0.95 to δ 1.00). On the basis of this and further evidence cited below, the trans configuration has been assigned to the higher melting isomer **15** and the cis configuration to compound **16.**

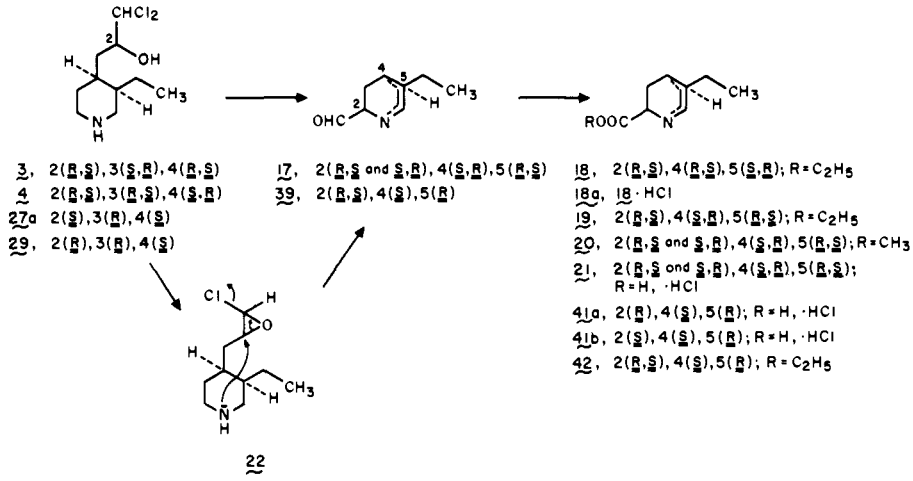
The trichloromethyl group of **15** or **16** proved to be stable under a variety of hydrolytic conditions. Attempts to transform these compounds into the desired ester or acid were unsuccessful. Therefore, we sought another route to these compounds, which is based on the opening of α-chloro epoxides[10] (Scheme II).

Treatment of the dichloropropanols **3** and **4** with methanolic potassium hydroxide or preferably with 2 N aqueous potassium hydroxide in a benzene suspension gave a mixture of the liquid epimeric quinuclidine-2-carboxaldehydes **17** in 60–70% yield. These compounds are presumably formed by an intramolecular nucleophilic reaction of the secondary amine at the epoxide ring[11] of the intermediate **22.** The aldehydes were found to be very labile compounds reverting on standing to a glassy polymer from which they could be partially recovered by vacuum distillation. However, the corresponding acids or esters which could be prepared readily proved to be stable. A mixture of **3** and **4** was treated with 3 equiv of methanolic potassium hydroxide and the resulting aldehydes **17** were oxidized in situ with freshly prepared silver oxide. Esterification of the crude epimeric acids **21** gave after distillation the epimeric methyl esters **20** or ethyl esters **18** and **19** in 60% overall yield from **3**



and **4** in a ratio of 1:1. Attempts to separate the esters **18** and **19** by fractional crystallization of their crystalline hydrochlorides failed. Treatment of the mixture of bases with phenoxyacetyl chloride[12] and crystallization of the reaction product afforded only isomer **18a** in pure form. However, separation of the esters **18** and **19** was accomplished by pre-

Scheme II

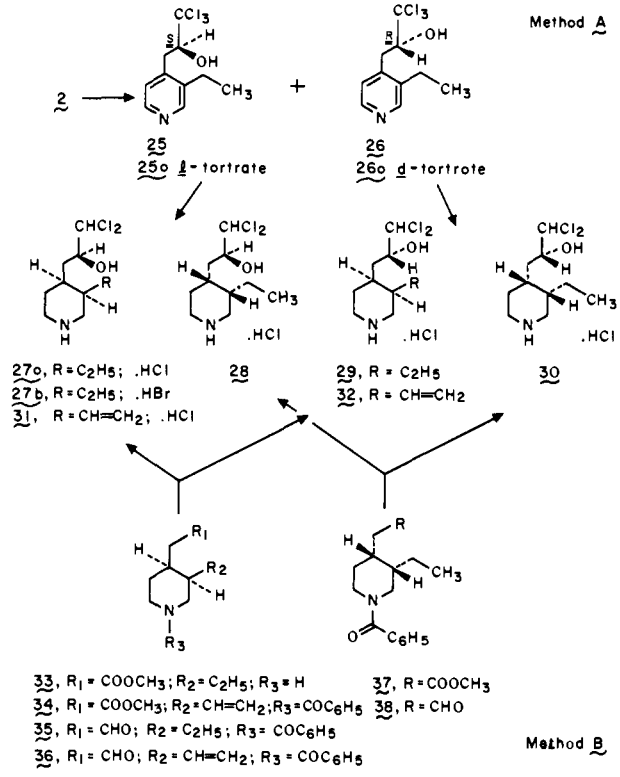


parative gas chromatography and the relative configuration at C-2 has been tentatively assigned as shown in the formulas on the basis of an analysis of their NMR spectra. The methyl groups of the ethyl side chain of **18** and **19** give rise to a triplet at δ 0.92 and 0.86, respectively. Similar chemical shifts have been observed for the methyl groups in dihydroquininone (**23**) (δ 0.92) and dihydroquinidinone (**24**) (δ 0.85) of known configuration. This also corroborates the assignments made for the trichloromethyl compounds **15** and **16**. The NMR spectra ($CDCl_3$) of all three trans compounds **15, 18,** and **23** exhibit a triplet at δ 0.92 while the chemical shift of the signal for the methyl group in the corresponding cis compounds varies slightly. This is to be expected if one assumes that in the trans compounds the nature of the substituent at C-2 should not affect the chemical shift of the methyl group signal. Furthermore, the trans derivatives are the more polar isomers as seen by higher retention times and low R_f values.

After we had shown the feasibility of preparing the desired quinuclidine derivatives in the racemic series, we turned our attention to the preparation of the optically active compounds required as starting material for the synthesis of *Cinchona* alkaloids. Two complementary methods were developed (Scheme III). In method A applicable only to the dihydro series, the trichloro derivative **2** was resolved with *l*- and *d*-tartaric acid into the enantiomers **25** and **26.** Analogous to the racemic series, hydrogenation of **25** and **26** gave in each case two diastereomers, separable by fractional crystallization. Again, none of the trans isomers were observed. The cis configuration of the products **27–30** was confirmed by an x-ray structure analysis of **27b**[13] and by the results obtained by method B. In this sequence, cincholoipon methyl ester (**33**),[4] its enantiomer **37**,[4] and *N*-benzoylmeroquinene methyl ester (**34**)[4] were used as the starting materials. Reduction of these compounds with diisobutylaluminum hydride in toluene at −70 °C and subsequent N-benzoylation of the crude reaction products gave in high yield the liquid aldehydes **35, 36,** and **38.**[14] A solution of aldehyde **35** in anhydrous tetrahydrofuran was treated at −70 °C with 2 equiv of dichloromethyllithium[15] to give the two diastereoisomers **27a** and **29.** Analogously, the enantiomeric aldehyde **38** afforded isomers **28** and **30.** The four products were identical in all aspects with specimens obtained by method A. Under the same reaction conditions the vinyl aldehyde **36** yielded a mixture of the diastereoisomeric dichloropropanols **31** and **32.** The configuration of these compounds was established by catalytic hydrogenation of **31** which gave the dihydro derivative **27a.**

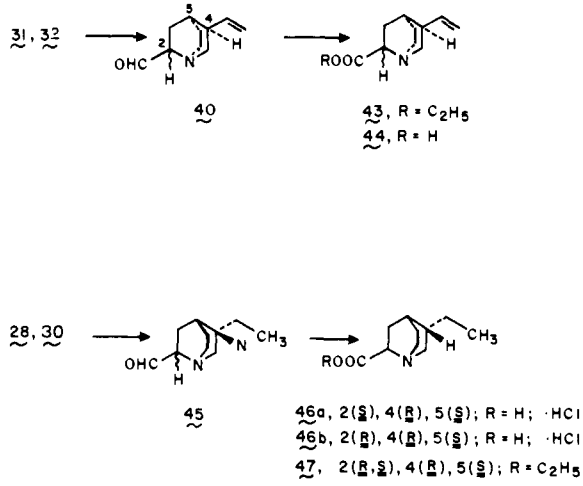
Transformation of the dichloropropanols into the quinuclidine aldehydes **39, 40,** and **45** or into the corresponding ethyl esters **42** (Scheme II), **43,** and **47** (Scheme IV) proceeded smoothly under the same reaction conditions described pre-

Scheme III



viously for the racemic series. At the same time that our work was completed, Augustine and Wanat[16] reported the preparation of the vinyl derivatives **43** from meroquinene by a different route. These workers compared their product with that obtained by degradation of quininone as described by Preobrazhenskii and co-workers.[17] Although the Russian group claims to have prepared the 2(*S*) isomer of **43** as indicated by conversion of this material to cinchonamine,[18] it seems more likely that under the acidic conditions used by both groups during the preparation of the ester they actually obtained the epimeric mixture **43.** Hydrolysis of a mixture of epimeric esters **42** (Scheme II) in 1 N hydrochloric acid at 90 °C afforded the corresponding acids **41a** and **41b** in a ratio of 1:1 as indicated by the signals for the methyl groups in the NMR spectrum at δ 0.92 and 0.98. Separation by fractional crystallization and recrystallization of the higher melting compound gave the pure 2(*R*) isomer **41a** which exhibited a triplet in the NMR spectrum at δ 0.92. The configuration at C-2 was determined by esterification of a ca. 2:1 mixture of **41b** and **41a** with diazomethane and subsequent NMR analysis of the reaction

Scheme IV



product. The spectrum exhibits two triplets at δ 0.92 and 0.86 in a 2:1 ratio, which allows us to assign the 2(R) configuration to **41a** and the 2(S) configuration to **41b**. Hydrolysis of the vinyl ester **43** in water yielded an epimeric mixture of the corresponding acids **44**. Immediately after dissolution in 1 N sodium hydroxide, **44** showed a rotation of $[\alpha]^{25}_{D}$ +93.2° which changed to $[\alpha]^{25}_{D}$ +80.8° after heating the solution for 16 h. The quinuclidinecarboxylic acid obtained by oxidative degradation of cinchonamine[19] showed after mutarotation in 1 N sodium hydroxide an identical rotation of $[\alpha]^{25}_{D}$ +81°. Acid hydrolysis of the esters **47** gave a mixture of the epimeric acids **46a** and **46b** from which the higher melting 2(S) isomer could be obtained in pure form by fractional crystallization.

The successful preparation of quinuclidine derivatives containing the desired functionalities at C-2 and C-5 enabled us to achieve our goal of a new total synthesis of *Cinchona* alkaloids. The results of this work are described in the subsequent paper.

Experimental Section[20]

***rac*-1,1-Dichloro-3-[3(*R*)-ethyl-4(*S*)-piperidinyl]propan-2(*S*)-ol Hydrochloride (3) and *rac*-1,1-Dichloro-3-[3(*R*)-ethyl-4(*S*)-piperidinyl]propan-2(*R*)-ol Hydrochloride (4).** To a solution containing 26.85 g of ***rac*-1,1,1-trichloro-3-(3-ethyl-4-pyridinyl)propan-2-ol (2)** in 400 mL of 5% aqueous hydrochloric acid was added 4 g of platinum oxide and the mixture was hydrogenated at 60 °C and 67 atm. After cooling to room temperature, the catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. Crystallization of the residue from 70 mL of anhydrous ethanol gave 10.5 g (38%) of **3**, mp 200–205 °C. Recrystallization from ethanol gave analytically pure **3**: mp 205–209 °C; IR (KBr) 3390 (OH), 2450–2950 cm^{-1} (group of bands, NH_2^+); NMR (D_2O) δ 1.4 (3 H, t, J = 6 Hz, CH_3), 3.65 (4 H, m, $CH_2^+NH_2CH_2$), 4.53 (1 H, m, $CHOH$), 6.48 (1 H, d, J = 3 Hz, $CHCl_2$). Anal. ($C_{10}H_{19}Cl_2NO\cdot HCl$) C, H, N.

The combined mother liquors of the crystallization of **3** were concentrated to dryness under reduced pressure. Crystallization of the residue from 30 mL of acetone afforded 9.5 g (34.5%) of **4**, mp 123–129 °C. An analytical sample, after two recrystallizations from acetone, showed the following physical properties: mp 132–134 °C; IR (KBr) 3260 (OH), 2800–2960 cm^{-1} (group of bands, NH_2^+); NMR (D_2O) δ 1.4 (3 H, t, J = 6 Hz, CH_3), 3.62 (4 H, m, $CH_2^+NH_2CH_2$), 4.5 (1 H, m, $CHOH$), 6.49 (1 H, d, J = 3 Hz, $CHCl_2$); mass spectrum *m/e* (rel intensity) 238 (8), 210 (15), 204 (55), 168 (20), 156 (100), 126 (45), 112 (40). Anal. ($C_{10}H_{19}Cl_2NO\cdot HCl$) C, H, N.

***rac*-1,1-Dichloro-3-[1-benzyloxycarbonyl-3(*R*)-ethyl-4(*S*)-piperidinyl]propan-2(*S*)-ol (5).** To a suspension of 10.4 g of **3** in 190 mL of benzene was added 74 mL of 2 N potassium carbonate. The mixture was cooled in an ice bath and with stirring 11.2 g of benzyl chloroformate was added followed by the addition of 36 g of solid potassium carbonate. The mixture was stirred for an additional 3 h at room temperature. The benzene layer was separated and washed successively with 2 N potassium carbonate, water, 2 N hydrochloric acid, and water. The residue after workup was dissolved in 30 mL of ether and ca. 300 mL of petroleum ether was slowly added to the stirred solution. The crystalline precipitate was collected by filtration and washed thoroughly with petroleum ether to give 12.4 g (90%) of **5**, mp 91–92 °C. Recrystallization from ether–petroleum ether afforded analytically pure **5**: mp 92–95 °C; IR ($CHCl_3$) 3590 (OH), 1690 cm^{-1} (N-CO-O); NMR ($CDCl_3$) δ 5.15 (2 H, s, $OCH_2C_6H_5$), 5.68 (1 H, d, J = 4 Hz, $CHCl_2$); mass spectrum *m/e* (rel intensity) 373 (8), 337 (27), 328 (7), 294 (28), 282 (10), 266 (20), 258 (11), 246 (15), 238 (10), 91 (100); TLC (benzene–ethyl acetate, 8:2) R_f 0.58. Anal. ($C_{18}H_{25}Cl_2NO_3$) C, H, N.

***rac*-1,1-Dichloro-3-[1-benzyloxycarbonyl-3(*R*)-ethyl-4(*S*)-piperidinyl] propan-2(*R*)-ol (6).** Under the same conditions as described for the preparation of **5**, 10.4 g of **4** was reacted with benzyl chloroformate. The crude reaction product was chromatographed on 200 g of silica gel (Grace-Davison Grade 923) with 2 L of benzene and subsequently with 1 L of ethyl acetate as the solvent. The ethyl acetate eluate was evaporated to dryness under reduced pressure to afford 10.6 g (77%) of **6** as a liquid. An analytical sample was prepared by thick layer chromatography with benzene–ethyl acetate (8:2) as the solvent and subsequent bulb-to-bulb distillation of the eluate: bp 190–210 °C (0.010 mm); IR ($CHCl_3$) 3590 (OH), 1690 cm^{-1} (N-CO-O); NMR ($CDCl_3$) δ 5.30 (2 H, s, O-$CH_2C_6H_5$), 5.84 (1 H, d, J = 4.5 Hz, $CHCl_2$); TLC (benzene–ethyl acetate, 8:2) R_f 0.52. Anal. ($C_{18}H_{25}Cl_2NO_3$) C, H, N.

***rac*-1,1-Dichloro-3-[1-benzyloxycarbonyl-3(*R*)-ethyl-4(*S*)-piperidinyl]propan-2(*S*)-ol 4-Methylphenylsulfonate Ester (7).** To a stirred, ice-cold solution of 7.4 g of **5** in 200 mL of anhydrous pyridine was added in small portions 8 g of *p*-toluenesulfonic anhydride. After complete addition, the mixture was left standing at 3 °C for 70 h. The solution was diluted with methylene chloride and extracted three times with 3 N hydrochloric acid. Workup of the organic phase afforded 10.5 g of oily **7**. Part of this material (700 mg) crystallized on standing. The crystalline mass was separated from the remaining oil and washed thoroughly with hexane. Recrystallization from ether–hexane in the cold yielded 237 mg of analytically pure **7**: mp 89–91 °C; IR ($CHCl_3$) 1693 (N-CO-O), 1378, 1190, 1178 cm^{-1} (O-SO_2); NMR ($CDCl_3$) δ 2.43 (3 H, s, $C_6H_4CH_3$), 4.65 (1 H, m, $CHOTs$), 5.11 (2 H, s, $OCH_2C_6H_5$), 6.05 (1 H, d, J = 3 Hz, $CHCl_2$), 7.32 (5 H, s, phenyl); mass spectrum *m/e* (rel intensity) 527 (5), 428 (3), 454 (3), 436 (3), 420 (7), 392 (24), 328 (3), 320 (5), 312 (7), 276 (5), 248 (4), 220 (5), 200 (5), 91 (100). Anal. ($C_{25}H_{31}Cl_2NO_5S$) C, H, N.

***rac*-1,1-Dichloro-3[1-benzyloxycarbonyl-3(*R*)-ethyl-4(*S*)-piperidinyl]propan-2(*R*)-ol 4-Methylphenylsulfonate Ester (8).** Using the same method as described for the preparation of **7**, 10.6 g of **6** yielded 14.7 g of oily **8**. One gram of this material upon standing afforded 350 mg of crystalline **8**, mp 86–88 °C. Recrystallization from cold ether–hexane gave analytically pure **8**: mp 89–90 °C; mmp with **7**, 78–87 °C; IR ($CHCl_3$) 1695 (N-CO-O), 1378, 1192, 1178 cm^{-1} (O-SO_2); NMR ($CDCl_3$) δ 2.44 (3 H, s, $C_6H_4CH_3$), 4.64 (1 H, m, $CHOTs$), 5.12 (2 H, s, $OCH_2C_6H_5$), 6.01 (1 H, d, J = 3 Hz, $CHCl_2$), 7.32 (5 H, s, phenyl). Anal. ($C_{25}H_{31}Cl_2NO_5S$) C, H, N.

***rac*-1,1-Dichloro-3-{3(*R*)-ethyl-1[(4-methylphenyl)sulfonyloxy]-4(*S*)-piperidinyl}propan-2(*S*)-ol 4-Methylphenylsulfonate Ester (9).** To an aqueous solution of 2.8 g of **3** was added excess sodium hydroxide and the free base of **3** was extracted with methylene chloride. The oily free base was dissolved in 100 mL of anhydrous pyridine and 7.5 g of freshly prepared *p*-toluenesulfonyl chloride[21] was added to the solution of 0 °C. After standing at 3 °C for 7 days, the mixture was diluted with water and ether. The organic phase was separated and washed with 2 N hydrochloric acid. The residue after workup was treated with 50 mL of ether and the crystalline material was collected by filtration to give 2.5 g (45%) of **9**, mp 142–145 °C. Recrystallization from methanol (50 mL) afforded 1.96 g of analytically pure **9**: mp 145.5–146.5 °C; IR ($CHCl_3$) 1378, 1190, 1178 (O-SO_2), 1355, 1340, 1166 cm^{-1} (N-SO_2); NMR ($CDCl_3$) δ 2.42 and 2.48 (3 H each, 2 s, $C_6H_4CH_3$), 4.65 (1 H, m, $CHOTs$), 6.00 (1 H, d, J = 3 Hz, $CHCl_2$); mass spectrum *m/e* (rel intensity) 546 (1), 391 (55), 376 (30), 340 (35), 280 (10), 264 (40), 236 (15), 210 (20), 198 (15), 184 (25), 155 (100), 110 (50), 91 (100); TLC (benzene–ethyl acetate, 95:5) R_f 0.46. Anal. ($C_{24}H_{31}Cl_2NO_5S_2$) C, H, N.

***rac*-1,1-Dichloro-3-{3(*R*)-ethyl-1[(4-methylphenyl)sulfonyloxy]-4(*S*)-piperidinyl}propan-2(*R*)-ol 4-Methylphenylsulfonate Ester (10).** Using the same procedure as described for the preparation of **9**, 20 g of **4** afforded 16.7 g (42%) of **10**, mp 138–143 °C after crystalliza-

tion from methanol. A sample was recrystallized from methanol to yield analytically pure **10:** mp 148–151 °C; mmp with **9**, 128–131 °C; IR ($CHCl_3$) 1380, 1194, 1180 (O-SO_2), 1359, 1340, 1170 cm^{-1} (N-SO_2); NMR ($CDCl_3$) δ 2.43 and 2.46 (3 H each, 2 s, $C_6H_4CH_3$), 4.66 (1 H, m, C*H*OTs), 5.90 (1 H, d, J = 3 Hz, $CHCl_2$); TLC (benzene–ethyl acetate, 95:5) R_f 0.49. Anal. ($C_{24}H_{31}Cl_2NO_5S_2$) C, H, N.

***rac*-1,1-Dichloro-3-[3(*R*)-ethyl-4(*S*)-piperidinyl]propan-2(*S*)-ol 4-Methylphenylsulfonate Ester Hydrobromide (11b).** A solution of 9.8 g of oily **7** in 50 mL of 33% hydrobromic acid in glacial acetic acid was kept at room temperature for 20 h. During this time a crystalline precipitate formed. Ether (300 mL) was added to the mixture, and the crystalline material was collected by filtration, thoroughly washed with ether, and air dried to afford 8.2 g (93%) of **11b**, mp 152–155 °C (hot plate). An analytical sample was prepared from **11** obtained in another run. Addition of excess ethanolic hydrobromic acid to a solution of 211 mg of **11** in ether gave 217 mg of crystalline **11b**, mp 148–150 °C. Recrystallization from methanol–ether yielded analytically pure **11b:** mp 150–152 °C (hot plate); IR (KBr) 2790, 1600 ($^+NH_2$), 1385, 1195, 1177 cm^{-1} (O-SO_2). Anal. ($C_{17}H_{25}ClNO_3S$·HBr) C, H, N.

***rac*-1,1-Dichloro-3-[3(*R*)-ethyl-4(*S*)-piperidinyl]propan-2(*S*)-ol 4-Methylphenylsulfonate Ester 4-Methylphenylsulfonic Acid Salt (11a).** A suspension of 7.7 g of **11b** in water was basified by the addition of excess ammonium hydroxide. The free base **11** was extracted with three portions of methylene chloride. The liquid residue (6.25 g) after workup was left standing at room temperature for 6 days during which time partial crystallization occurred. The mixture was treated with ether and the crystalline material was collected by filtration to give 4.468 g (50%) of **11a.** A sample (468 mg) was recrystallized from methanol and subsequently twice from ethanol to yield 114 mg of analytically pure **11a:** mp 193.5–194 °C; IR ($CHCl_3$) 2820 (broad, $^+NH_2$), 1380, 1195, 1180 (O-SO_2), 1210 (broad), 1035, 1010 cm^{-1} ($-SO_3^-$); NMR ($CDCl_3$) δ 0.78 (3 H, t, J = Hz, CH_2CH_3), 2.36 and 2.41 (3 H, each, 2 s, $C_6H_4CH_3$), 4.60 (1 H, m, C*H*OTs), 5.96 (1 H, d, J = 3 Hz, $CHCl_2$); TLC (CH_3CN–NH_4OH, 9:1) R_f 0.74. Anal. ($C_{17}H_{25}Cl_2NO_3S$·$C_7H_8SO_3$) C, H, N.

***rac*-1,1-Dichloro-3-[3(*R*)-ethyl-4(*S*)-piperidinyl]-1-propene Hydrochloride (13). A.** Crystalline **11a** (4 g) was transformed into the free base **11** (2.57 g) as described above and after standing at room temperature for 3 days the oil was separated from crystalline **11**a and combined with the liquid obtained in the previous experiment. This material was dissolved in a small amount of ethanol and the solution was treated with excess 2-propanolic hydrogen chloride, and upon addition of ether, 1.774 g (42%) of crystalline **13,** mp 132–134 °C, was obtained. An analytical sample after recrystallization from ethanol–ether melted at 137–139 °C; IR ($CHCl_3$) 2800, 2760, 1595 ($^+NH_2$), 1627, 870 cm^{-1} (CH=CCl_2); NMR ($CDCl_3$) δ 0.97 (3 H, t, J = 7 Hz, CH_2CH_3), 5.81 (1 H, t, J = 7 Hz, CH=CCl_2); mass spectrum *m/e* (rel intensity) 221 (15), 206 (5), 192 (15), 186 (35), 110 (100); TLC (CH_3CN–NH_4OH, 9:1) R_f 0.7. Anal. ($C_{10}H_{17}Cl_2N$·HCl) C, H, N.

B. A suspension of 16.6 g of **11b** in water was rendered alkaline by the addition of excess 6 N sodium hydroxide and extracted twice with methylene chloride. The combined extract was washed with water. Workup afforded 12.8 g of liquid free base **11.** This material was dissolved in 250 mL of anhydrous tetrahydrofuran, the solution was cooled to 0 °C, and with stirring 3.85 g of potassium *tert*-butoxide was added portionwise. The mixture was stirred for an additional 1 h at 0 °C, then diluted with water and extracted three times with methylene chloride. Workup of the organic extract gave 7 g of oil. The residue was dissolved in 20 mL of ethanol and excess dry hydrochloric acid passed through the solution. Addition of ether precipitated crystalline material which was collected by filtration to afford 6.5 g (72%) of **13,** mp 135–137.5 °C.

C. To a stirred solution of 1.6 g of **9** in 60 mL of anhydrous tetrahydrofuran cooled to 0 °C was added 350 mg of potassium *tert*-butoxide and the mixture was allowed to stir for 2 h at 0 °C. After diluting with water, the mixture was extracted twice with methylene chloride. Workup yielded a liquid residue which was dissolved in 10 mL of 30% hydrobromic acid in glacial acetic acid. Phenol (550 mg) was added and the mixture was kept at 40 °C for 65 h. After the addition of 150 mL of ether, the mixture was left overnight in the refrigerator and the crystalline precipitate (610 mg) was collected by filtration. Conversion of this material into the free base of **13** by the addition of excess sodium hydroxide and extraction with methylene chloride and subsequent formation of the hydrochloride as described under method B gave 363 mg (48%) of **13,** mp 137–140 °C, after recrystallization from ethanol–ether.

Using the same conditions as described in method C, 15.7 g of **10** gave 4 g (54%) of **13,** mp 132–135 °C.

***rac*-1,1-Dichloro-3-{3(*R*)-ethyl-1[(4-methylphenyl)sulfonyloxy]-4(*S*)-piperidinyl}propan-2(*R*)-ol 4-Methylphenylsulfonate Ester Methylphenylsulfonic Acid Salt (12a).** A solution of 4.5 g of crude **8** prepared from 3.2 g of **6** was dissolved in 25 mL of 33% hydrobromic acid in glacial acetic acid. The solution was left at room temperature for 70 h, diluted with ether, and extracted three times with water. The aqueous phase was rendered alkaline by the addition of 6 N sodium hydroxide and extracted with chloroform. Workup afforded 2.28 g (67% from **6**) of liquid **12,** which was kept at room temperature for 4 days. Analogous to the preparation of **13,** method A, the separation of the crystalline material and transformation into the free base followed by storing at room temperature was repeated several times. The combined liquid fraction was dissolved in ethanolic hydrogen chloride and addition of ether afforded 602 mg (40%) of crystalline **13:** mp 137–139 °C; mmp with an analytical sample of **13,** 137–139 °C.

Part of the crystalline material from the separation procedure was recrystallized from ethanol–ether and subsequently from ethanol to give analytically pure **12a:** mp 187–188 °C; mmp with **11a** 172–180 °C: IR ($CHCl_3$) 2820–3025 ($^+NH_2$), 1380, 1200, 1185 (O-SO_2), 1235 (broad), 1030, 1020 cm^{-1} ($-SO_3^-$); NMR ($CDCl_3$) δ 0.81 (3 H, t, J = 7 Hz, CH_2CH_3), 2.36 and 2.41 (3 H each, 2 s, $C_6H_4CH_3$), 4.65 (1 H, m, C*H*OTs), 5.98 (1 H, d, J = 3 Hz, $CHCl_2$); TLC (CH_3CN–NH_4OH, 9:1) R_f 0.8. Anal. ($C_{17}H_{25}Cl_2NO_3S$·$C_7H_8SO_3$) C, H, N.

***rac*-5(*R*)-Ethyl-2(*S*)-trichloromethyl-4(*S*)-quinuclidine Hydrochloride (15) and *rac*-5(*R*)-Ethyl-2(*R*)-trichloromethyl-4(*S*)-quinuclidine Hydrochloride (16).** Four grams of **13** upon treatment with 6 N sodium hydroxide and extraction with methylene chloride gave 3.5 g of free base which was dissolved in 80 mL of anhydrous ether. The solution was added slowly to a stirred suspension of 2.2 g of *N*-chlorosuccinimide in 130 mL of ether. After stirring for an additional 1 h, the mixture was successively washed with water (twice), 2.5 N sulfuric acid (twice), and water (twice). Workup afforded 3.75 g of an oil which was dissolved in 150 mL of trifluoroacetic acid. After purging thoroughly with nitrogen, the solution was irradiated in a quartz apparatus at 15 °C for 2.5 h with a 200-W Hanovia high-pressure mercury lamp. The solvent was removed under reduced pressure at 40 °C and the residue was dissolved in 150 mL of benzene. Benzoyl chloride (3 mL) was added to the solution followed by the dropwise addition of a saturated solution of potassium carbonate to adjust the pH to 10. The organic layer was separated, washed successively with 2 N sodium hydroxide (twice) and water (twice), and extracted three times with 2 N hydrochloric acid. The combined acidic extract was washed with benzene, rendered alkaline by the addition of 12 N sodium hydroxide and solid potassium carbonate, and extracted with methylene chloride to give after workup 2.9 g (72%) of a colorless, liquid mixture of the free bases of **15** and **16.** Upon treatment with excess ethanolic hydrogen chloride and ether, a crystalline precipitate was obtained which after recrystallization from ethanol–ether gave 650 mg of **15,** mp 170–174 °C. An analytical sample was obtained after several recrystallizations from ethanol–ether: mp 174–175 °C; NMR ($CDCl_3$) δ 0.92 (3 H, t, J = 7 Hz, CH_2CH_3), 4.41 (1 H, pair of triplets, J = 9 and 1.5 Hz, $CHCCl_3$); mass spectrum *m/e* (rel intensity) 255 (10), 240 (5), 220 (100), 138 (60), 82 (15), 55 (55); TLC (ether–petroleum ether, 3:7, developed three times) R_f 0.48. Anal. ($C_{10}H_{16}Cl_3N$·HCl) C, H, Cl, N.

The combined mother liquors were evaporated to dryness under reduced pressure. The residue was treated with a saturated aqueous solution of potassium carbonate. The mixture of free bases (2 g) obtained by extraction with ether was separated by preparative thick layer chromatography on 15 plates with petroleum ether–ether (8:2) as the solvent. The plates were developed five times. Two main zones overlapping each other were detected by spraying with Dragendorff reagent. Three bands were extracted with ethyl acetate. The lower one gave 205 mg of an oil which upon treatment with ethanolic hydrogen chloride afforded 157 mg of crystalline **15,** mp 174–175 °C. The middle band gave 710 mg of a mixture of epimers and the upper band yielded 320 mg of a liquid. Treatment of the latter with ethanolic hydrogen chloride, removal of the solvent under reduced pressure, and trituration of the residue with acetone gave 156 mg of **16,** mp 150–151 °C. Recrystallization from acetone afforded analytically pure **16:** mp

156–158 °C; NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7 Hz, CH_2CH_3), 4.65 (1 H, pair of triplets, J = 12 and 3.5 Hz, $CHCCl_3$); TLC (ether–petroleum ether, 3:7, developed three times) R_f 0.53. Anal. ($C_{10}H_{16}Cl_3N$·HCl) C, H, Cl, N.

***rac*-5(*R*)-Ethyl-4(*S*)-quinuclidine-2ξ-carboxaldehydes (17). A.** To 5.45 g of **3** dissolved in 40 mL of methanol was added 31.6 mL of a methanolic solution containing 3.36 g of potassium hydroxide. The mixture was stirred at room temperature for 55 h. The precipitate formed in the reaction mixture was removed by filtration and the filtrate was evaporated to dryness under reduced pressure at a temperature not exceeding 30 °C. The residue was dissolved in 300 mL of ether, insoluble material was removed by filtration, and evaporation of the filtrate gave 4.12 g of an oily residue. A solution of the residue in 100 mL of ether was added to a solution containing 2.5 g of sodium bisulfite in 8 mL of water. After removal of the solvents under reduced pressure, the residue was dissolved in 10 mL of water. Addition of ethanol and ether precipitated 3.4 g of solid addition product, which was added to 50 mL of a saturated aqueous solution of sodium carbonate. The suspension was heated at 40 °C until a clear solution was obtained. After an additional 5 min at 40 °C, the mixture was cooled and extracted three times with ether. The combined ether extract was dried over potassium carbonate and evaporated to dryness under reduced pressure to afford 950 mg (29%) of liquid aldehydes **17**. An analytical sample of **17** was prepared by bulb-to-bulb distillation: bp 60–85 °C (0.4 mm); IR ($CHCl_3$) 2820, 2720, 1722 cm^{-1} (CHO); NMR ($CDCl_3$) δ 0.83 and 0.92 (3 H, 2 t, J = 7 Hz, ratio ca. 1:1, CH_2CH_3), 9.80 (1 H, s, CHO); mass spectrum *m/e* (rel intensity) 167 (84), 152 (5), 138 (100), 124 (44), 110 (67), 96 (40), 82 (52), 55 (70). Anal. ($C_{10}H_{17}NO$) C, H, N.

B. A solution containing 1.39 g of **4** in 25 mL of water was combined with 150 mL of benzene. The stirred mixture was cooled in an ice bath and 8.56 mL of 1.75 N potassium hydroxide was added slowly. Stirring at room temperature was continued under an atmosphere of nitrogen for 20 h. The aqueous layer was separated and extracted with benzene. The combined organic layer was dried and evaporated under reduced pressure at 30 °C. Bulb-to-bulb distillation of the residue at 60–85 °C (0.3 mm) afforded 600 mg (72%) of liquid **17**.

***rac*-Ethyl 5(*R*)-Ethyl-4(*S*)-quinuclidine-2(*S*)-carboxylate (18), Hydrochloride 18a, and *rac*-Ethyl 5(*R*)-Ethyl-4(*S*)-quinuclidine-2(*R*)-carboxylate (19).** To a solution containing 8.3 g of **3** in 600 mL of methanol cooled to 0 °C was added dropwise with stirring a solution of 5.04 g of potassium hydroxide in 234 mL of methanol. After completed addition, the temperature of the mixture was allowed to rise to room temperature and stirring was continued overnight. Insoluble material was removed by filtration and the filtrate was added to a mixture of 11.7 g of silver nitrate and 4.8 g of sodium hydroxide in 200 mL of water. The reaction mixture after stirring for 3 h at room temperature was filtered through Celite Filter Aid and the filtrate was saturated with hydrogen sulfide. The precipitate was removed by filtration through Celite Filter Aid and the filtrate was evaporated to dryness. The residue was treated with 500 mL of ethanol and the mixture was refluxed for 3 h. After filtration, the filtrate was saturated with anhydrous hydrogen chloride and refluxed for 15 h. The precipitate was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The yellow oil obtained was treated with 300 mL of a saturated aqueous solution of sodium carbonate and the mixture was extracted five times with ether. Workup and bulb-to-bulb distillation of the residue afforded 3.81 g (60% from **3**) of a mixture of the two epimers **18** and **19**: bp 101 °C (0.5 mm); IR ($CHCl_3$) 1730 cm^{-1} ($COOC_2H_5$); NMR ($CDCl_3$) δ 0.86 and 0.92 (3 H, 2 t, ratio 1:1, J = 7 Hz, CH_2CH_3), 1.29 (3 H, t, J = 7 Hz, OCH_2CH_3), 3.45 (1 H, m, NCH), 4.23 (2 H, q, J = 7 Hz, OCH_2CH_3); mass spectrum *m/e* (rel intensity) 211 (53), 196 (13), 182 (65), 168 (5), 154 (18), 138 (100), 124 (15), 110 (39), 96 (5), 82 (35), 43 (23); GLC [90 cm × 2 mm glass, 5% PEG 20M on Gas Chrom Z (60/80), 150 °C] t_0 23 and 25 min, ratio 1:1. Anal. ($C_{12}H_{21}NO_2$) C, H, N.

Separation by preparative gas chromatography (200 × 1 cm column, 10% PEG 20M on Gas Chrom Z; 160 °C; N_2 250 mL/min) afforded **18** [t_0 25 min; NMR ($CDCl_3$) δ 0.92 (3 H, t, J = 7 Hz, CH_2CH_3)] and **19** [t_0 23 min; NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 7 Hz, CH_2CH_3)].

To a solution of 4.66 g of a mixture of **18** and **19** in benzene was added 3.12 mL of phenoxyacetyl chloride.[12] The solvent was removed under reduced pressure and the residue was crystallized from acetone–ether. Recrystallization from acetone–ether gave 1.2 g of **18a**: mp 168–169 °C after drying at 60 °C (0.01 mm) for 15 h; IR ($CHCl_3$) 2450 (broad, $^+$NH), 1755 cm^{-1} ($COOC_2H_5$); NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7 Hz, CH_2CH_3), 1.36 (3 H, t, J = 7 Hz, OCH_2CH_3), 4.22 (1 H, m, NCH), 4.40 (2 H, q, J = 7 Hz, OCH_2CH_3). Anal. ($C_{12}H_{21}NO_2$·HCl) C, H, N.

***rac*-Methyl 5(*R*)-Ethyl-4(*S*)-quinuclidine-2ξ-carboxylate (20).** Under the same conditions described for the preparation of **18,** 5.53 g of **3** was cyclized and oxidized. The crude mixture of epimeric acids was dissolved in 350 mL of methanol. Concentrated sulfuric acid (5 mL) was added and the mixture was refluxed overnight. After the addition of another 2 mL of concentrated sulfuric acid, refluxing was continued for another 15 h. The volume of the solution was reduced to ca. 30 mL by evaporation under reduced pressure. The residue was rendered alkaline with a saturated aqueous solution of sodium carbonate and diluted with methylene chloride. Insoluble material was removed by filtration and dissolved in the minimal amount of water. The aqueous phase was extracted three times with methylene chloride. Workup of the combined organic solution gave after distillation 2.33 g (59% from **3**) of **20**: bp 84–85 °C (0.35 mm); NMR ($CDCl_3$) δ 0.85 and 0.89 (3 H, 2 t, J = 7 Hz, CH_2CH_3, ratio 1:1), 3.73 (3 H, s, $COOCH_3$); GLC (6 ft × 0.25 in.; 4% PEG 4000 MS on Gas Chrom Z; 150°) t_0 7.3 and 7.7 min.

***rac*-5(*R*)-Ethyl-4(*S*)-quinuclidine-2ξ-carboxylic Acid Hydrochloride (21).** A solution of 2.15 g of a mixture of **18** and **19** in 100 mL of 1 N hydrochloric acid was left standing at room temperature for 10 days. The solution was washed with ether and evaporated to dryness under reduced pressure. Complete dryness was ensured by repeatedly adding toluene to the residue and removing the solvent under reduced pressure. Crystallization of the residue from ethanol–ether gave 429 mg of an epimeric mixture of **21** in a ratio of 2:1, mp 239–242 °C. Repeating the above procedure twice more afforded an additional 500 mg of crystalline **21**. An analytical sample of the mixture was obtained by recrystallization from ethanol–ether and drying at 100 °C (0.01 mm) for 20 h: mp 240–242 °C; IR (KBr) 1740 cm^{-1} (COOH); NMR (CD_3OD) δ 0.92 and 0.96 (3 H, 2 t, J = 7 Hz, CH_2CH_3, ratio 2:1) Anal. ($C_{10}H_{17}NO_2$·HCl) C, H, N.

1,1,1-Trichloro-3-(3-ethyl-4-pyridinyl)propan-2(*R*)-ol (26) and *d*-Monotartrate (26a). A solution of 53.72 g of **2** in ethanol was combined with an ethanolic solution of 32.9 g of *d*-tartaric acid. The solvent was removed under reduced pressure. Fractional crystallization of the residue from acetone afforded analytically pure *d*-tartrate **26a**: mp 176–177.5 °C; $[\alpha]^{25}_D$ +30.7° (*c* 0.960, C_2H_5OH). Anal. ($C_{10}H_{12}Cl_3NO$·$C_4H_6O_8$) C, H, Cl, N.

An aqueous solution of 12.6 g of **26a** was rendered alkaline by the addition of a saturated aqueous solution of sodium carbonate. The aqueous mixture was extracted four times with methylene chloride. The crystalline residue obtained after workup was recrystallized from ether to afford 5.6 g of analytically pure **26**: mp 132–134 °C; $[\alpha]^{25}_D$ +45.1° (*c* 1.025, ethanol); ORD (*c* 0.318, 95% C_2H_5OH) $[\alpha]_{700}$ +89, $[\alpha]_{589}$ +122, $[\alpha]_{256}$ +2420 (pk), $[\alpha]_{242}$ +2140 (tr), $[\alpha]_{218}$ +16890 (pk); CD (*c* 0.268, 95% C_2H_5OH) $[\theta]_{270}$ 0, $[\theta]_{257}$ +520, $[\theta]_{226}$ +150, $[\theta]_{219}$ +1920; UV (C_2H_5OH) 261 nm (ϵ 2890), 268 (2350); IR ($CHCl_3$) 3600 cm^{-1} (OH); NMR (Me_2SO-d_6) δ 1.2 (3 H, t, J = 7 Hz, CH_2CH_3), 2.72 (2 H, q, J = 7 Hz, CH_2CH_3), 4.25 (1 H, m, CHOH), 6.8 (1 H, d, J = 7 Hz, CHO*H*), 7.28 and 8.13 (2 H, AB pattern, J = 6 Hz, CH-5 and CH-6), 8.18 (1 H, s, CH-2). Anal. ($C_{10}H_{12}Cl_3NO$) C, H, Cl, N.

1,1,1-Trichloro-3-(3-ethyl-4-pyridinyl)propan-2(*S*)-ol (25) and *l*-Monotartrate (25a). The mother liquors from the fractional crystallization of **26** were combined and evaporated to dryness. The residue (45.5 g) was dissolved in water, insoluble material was removed by filtration, and the filtrate was rendered alkaline by the addition of 6 N sodium hydroxide. Extraction with methylene chloride (three times) and workup of the extract gave 28.5 g of residue. An ethanolic solution of this material was combined with 15.9 g of *l*-tartaric acid in ethanol and the mixture was evaporated to dryness under reduced pressure. Fractional crystallization from acetone gave 12.3 g of **25a,** $[\alpha]^{25}_D$ −30.0° (*c* 1.063, C_2H_5OH). An analytical sample of **25a** showed mp 177–178 °C; $[\alpha]^{25}_D$ −30.3° (*c* 1.065, C_2H_5OH). Anal. ($C_{10}H_{12}Cl_3NO$·$C_4H_6O_8$) C, H, Cl, N.

The tartrate **25a** (7.8 g) was transformed into the free base **25** as described for the preparation of **26.** Recrystallization from ether afforded 3.6 g of analytically pure **25**: mp 132–134 °C; $[\alpha]^{25}_D$ −45.5° (*c* 1.020, C_2H_5OH); ORD (*c* 0.268, 95% C_2H_5OH) $[\alpha]_{700}$ −84° $[\alpha]_{589}$ −112, $[\alpha]_{256}$ −2400 (tr), $[\alpha]_{240}$ −2000 (pk), $[\alpha]_{218}$ −14000 (pk); CD (*c* 0.268, 95% C_2H_5OH) $[\theta]_{275}$ 0, $[\theta]_{258}$ −470, $[\theta]_{226}$ −130,

$[\theta]_{218}$ −2000. Anal. ($C_{10}H_{12}Cl_3NO$) C, H, N.

Hydrogenation of 25. Hydrogenation of 2.7 g of **25** as described previously for **2** afforded, after crystallization from 20 mL of ethanol, 600 mg (22%) of **1,1-dichloro-3-[3(*R*)-ethyl-4(*S*)-piperidinyl]propan-2(*S*)-ol hydrochloride (27a)**, mp 227–229 °C. Several recrystallizations from ethanol yielded analytically pure **27a**: mp 232–233 °C; $[\alpha]^{25}_D$ −28.3° (*c* 1.0237, CH_3OH); IR (KBr) 3345 (OH), 2470–2960 cm^{-1} (group of bands, $^+NH_2$); NMR (D_2O) δ 1.41 (3 H, t, *J* = 7 Hz, CH_2CH_3), 3.62 (4 H, m, $CH_2{}^+NH_2CH_2$), 4.52 (1 H, m, CHOH), 6.49 (1 H, d, *J* = 3 Hz, $CHCl_2$). Anal. ($C_{10}H_{19}Cl_2NO{\cdot}HCl$) C, H, N.

The free base obtained from **27a** on treatment with aqueous potassium carbonate and extraction with methylene chloride was combined with ethanolic hydrogen bromide to give after several recrystallizations from ethanol analytically pure **27b**: mp 223–224 °C; $[\alpha]^{25}_D$ −24.77° (*c* 0.9486, CH_3OH). Anal. ($C_{10}H_{19}Cl_2NO{\cdot}HBr$) C, H, N.

The mother liquors from the crystallization of **27a** were combined and concentrated under reduced pressure. The residue was triturated with acetone and the crystalline material was recrystallized from acetone to afford 729 mg (26%) of **1,1-dichloro-3-[3(*S*)-ethyl-4(*R*)-piperidinyl]propan-2(*S*)-ol hydrochloride (28)**. Recrystallization from acetone yielded analytically pure **28**: mp 169.5–171.5 °C; $[\alpha]^{25}_D$ −25.15° (*c* 0.9306, CH_3OH); IR (KBr) 3345 (OH), 2460–2980 cm^{-1} (group of bands, $^+NH_2$); NMR ($CDCl_3$) δ 1.43 (3 H, t, *J* = 7 Hz, CH_2CH_3), 3.64 (4 H, m, $CH_2{}^+NH_2CH_2$), 4.54 (1 H, m, CHOH), 6.52 (1 H, d, *J* = 3 Hz, $CHCl_2$). Anal. ($C_{10}H_{19}Cl_2NO{\cdot}HCl$) C, H, N.

Hydrogenation of 26. Under the same conditions described above, hydrogenation of 2.7 g of **26** afforded 600 mg (22%) of **1,1-dichloro-3-[3(*S*)-ethyl-4(*R*)-piperidinyl]propan-2(*R*)-ol hydrochloride (30)**, mp 228–230 °C. Recrystallization from 30 mL of ethanol yielded analytically pure **30**: mp 232–233 °C; $[\alpha]^{25}_D$ +29.63° (*c* 1.0942, CH_3OH). Anal. ($C_{10}H_{19}Cl_2NO{\cdot}HCl$) C, H, N.

The combined mother liquors were concentrated under reduced pressure and the residue, after crystallization from acetone, afforded analytically pure **1,1-dichloro-3-[3(*R*)-ethyl-4(*S*)-piperidinyl]propan-2(*R*)-ol hydrochloride (29)**: mp 168–170 °C; $[\alpha]^{25}_D$ +25.25° (*c* 1.0140, methanol). Anal. ($C_{10}H_{19}Cl_2NO{\cdot}HCl$) C, H, N.

2-[1-Benzoyl-3(*R*)-ethyl-4(*S*)-piperidinyl]acetaldehyde (35). The hydrochloride of **33** (6.5 g) was treated with a slight excess of a saturated potassium carbonate solution. The aqueous solution was diluted with 500 mL of methylene chloride and the mixture was dried over solid potassium carbonate. After filtration, the organic solution was evaporated to dryness under reduced pressure and the residual clear liquid (5.1 g) was dissolved in 200 mL of anhydrous toluene (azeotropically distilled). The solution was cooled to −70 °C and 39 mL of a 1.5 M solution of diisobutylaluminum hydride in toluene was added dropwise within 2 h in an atmosphere of nitrogen. After completed addition, the mixture was stirred for an additional 1 h at −70 °C and then hydrolyzed by the dropwise addition of 6 mL of a methanol–water mixture (1:1). After the cooling bath was removed and 10 mL of 2 N potassium carbonate and 27 g of solid potassium carbonate were added to the mixture, 5.6 g (4.6 mL) of benzoyl chloride was added dropwise. The mixture was stirred at room temperature for 3 h and workup yielded 6.1 g (80%) of liquid **35** after bulb-to-bulb distillation at 180 °C (0.001 mm). An analytical sample was prepared by preparative thick layer chromatography with benzyl–ethyl acetate (1:1) as the solvent. The eluate from the major band after washing with dilute sodium carbonate and bulb-to-bulb distillation afforded analytically pure **35**: bp 180 °C (0.001 mm); $[\alpha]^{25}_D$ +2.14° (*c* 1.1230, CH_3OH); IR ($CHCl_3$) 2730 and 1722 (CHO), 1620 cm^{-1} (N-CO-C_6H_5); NMR ($CDCl_3$) δ 7.33 (5 H, s, C_6H_5), 9.76 (1 H, s, CHO); mass spectrum *m/e* (rel intensity) 259 (15), 230 (30), 214 (5), 202 (20), 188 (5), 105 (100), 77 (30). Anal. ($C_{16}H_{21}NO_2$) C, H, N.

2-[1-Benzoyl-3(*S*)-ethyl-4(*R*)-piperidinyl]acetaldehyde (38). Reduction of 25.2 g of crude **37** (obtained from 50 g of the *l*-monotartrate of **37**) as described above for the preparation of **35** gave after bulb-to-bulb distillation at 160–170 °C (0.001 mm) 27.96 g (72%) of liquid **38**. Preparative thick layer chromatography with benzene–ethyl acetate (8:2) as the solvent (developed twice) afforded after distillation of the eluate of the major band analytically pure **38**: bp 150–160 °C (0.001 mm); $[\alpha]^{25}_D$ −1.57° (*c* 1.0215, CH_3OH). Anal. ($C_{16}H_{21}NO_2$) C, H, N.

Preparation of 27a and 29 from 35. A solution containing 22.6 mL of methylene chloride in 800 mL of anhydrous tetrahydrofuran was cooled to −90 °C. Under an atmosphere of dry nitrogen, 150 mL of a 1.62 M solution of *n*-butyllithium in hexane was added to the stirred solution at such a rate as to maintain the low temperature (2 h). After stirring at the same temperature for 30 min, the mixture was allowed to warm to −70 °C, followed by the dropwise addition of a solution of 29.2 g of **35** in 300 mL of anhydrous tetrahydrofuran. After 30 min, the reaction was quenched by the addition of 150 mL of water and 800 mL of ether. The mixture was allowed to warm to room temperature, the aqueous layer was separated, and the organic layer was washed with ether. The combined ether solution was extracted with three 100-mL portions of 3 N hydrochloric acid. The acidic solution was washed with two 100-mL portions of ether and evaporated to complete dryness under reduced pressure. The residue was crystallized from acetone to give in three crops 17.5 g (56%) of a mixture of **27a** and **29**. Fractional crystallization from ethanol followed by recrystallization of the combined fractions from ethanol afforded pure **27a**: mp 232–233 °C; mmp with an authentic sample 232–233 °C; $[\alpha]^{25}_D$ −28.6° (*c* 1.005, CH_3OH). The combined mother liquors were evaporated to dryness and crystallized from acetone to afford pure **29**: mp 172–173 °C; mmp with an analytical specimen 172–173 °C; $[\alpha]^{25}_D$ +25.2° (*c* 1.000, CH_3OH).

Preparation of 31 and 32 from 36. To a solution containing 1.15 mL of methylene chloride in 20 mL of anhydrous tetrahydrofuran cooled to −70 °C was added over a period of 30 min 8.8 mL of a 1.65 M solution of *n*-butyllithium in hexane under an atmosphere of nitrogen. Stirring of the mixture at the same temperature was continued for 20 min, followed by the dropwise addition of 1.52 g of **2-[1-benzoyl-3(*R*)-vinyl-4(*S*)-piperidinyl]acetaldehyde (36)**[14] dissolved in 8 mL of anhydrous tetrahydrofuran. After 30 min, the reaction was quenched by the addition of 10 mL of water and 30 mL of ether. The mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous phase was extracted three times with ether. The combined organic extract was washed with water, dried, and filtered. Addition of excess ethanolic hydrogen chloride to the filtrate gave 1.2 g (74%) of a crystalline mixture of the two diastereomers **31** and **32**. Fractional crystallization from ethanol followed by recrystallization of the combined fractions from ethanol gave analytically pure **1,1-dichloro-3-[3(*R*(-vinyl-4(*S*)-piperidinyl]propan-2(*S*)-ol hydrochloride (31)**: mp 225–225.5 °C; $[\alpha]^{25}_D$ −13.3° (*c* 1.02, CH_3OH); IR (KBr) 3395 (OH), 2810, 2640, 2550, 2465, 1610, and 1597 ($^+NH_2$), 938 cm^{-1} ($CH{=}CH_2$); NMR (Me_2SO-d_6) δ 5.12 and 5.17 (2 H, m, $CH{=}CH_2$), 5.75 (1 H, m, CHOH), 5.90 (1 H, m, $CH{=}CH_2$), 6.09 (1 H, d, *J* = 3 Hz, $CHCl_2$); mass spectrum *m/e* (rel intensity) 237 (10), 220 (8), 210 (12), 204 (80), 168 (25), 156 (55), 136 (10), 124 (40), 110 (30), 82 (85), 57 (60), 44 (100). Anal. ($C_{10}H_{17}Cl_2NO{\cdot}HCl$) C, H, N.

The mother liquors were combined and evaporated to dryness. Recrystallization of the residue from acetone gave pure **1,1-dichloro-3-[3(*R*)-vinyl-4(*S*)-piperidinyl]propan-2(*R*)-ol hydrochloride (32)**: mp 165–167 °C; $[\alpha]^{25}_D$ +30.7° (*c* 1.00, CH_3OH); IR (KBr) 3330 (OH), 2815, 2640, 2560, 2475, 1600, 1582 ($^+NH_2$), 935 cm^{-1} ($CH{=}CH_2$). Anal. ($C_{10}H_{17}Cl_2NO{\cdot}HCl$) C, H, N.

Hydrogenation of 31. To a solution of 220 mg of **31** in 20 mL of 1 N hydrochloric acid was added 65 mg of platinum oxide. The mixture was hydrogenated using Brown's method.[22] The apparatus was first flushed with nitrogen and then 5 mL of 1 N sodium borohydride solution was injected. The reaction mixture was stirred at room temperature. After 24 h, the uptake of 0.01 N sodium borohydride had ceased (12 mL). The catalyst was removed by filtration and the filtrate was evaporated to dryness. Complete dryness was ensured by repeated addition and removal of an ethanol–benzene mixture to the residue. Crystallization of the residue from ethanol gave 173 mg (79%) of **27a**: mp 234–235 °C; mmp with an authentic specimen 233–234 °C; $[\alpha]^{25}_D$ −29.9° (*c* 1.03, CH_3OH).

5(*R*)-Ethyl-4(*S*)-quinuclidine-2ξ-carboxaldehyde (39). This compound was obtained from **27a** by method B described for the preparation of **17**. Evaporative bulb-to-bulb distillation at 80 °C (0.1 mm) yielded analytically pure **39**: liquid; $[\alpha]^{25}_D$ +102.61° (*c* 1.168, CH_3OH); IR ($CHCl_3$) 2820, 2730, 1730 cm^{-1} (CHO); NMR ($CDCl_3$) δ 0.83 and 0.91 (3 H, 2 t, ratio 1:1, *J* = 7 Hz, CH_2CH_3), 9.80 (1 H, s, CHO). Anal. ($C_{10}H_{17}NO$) C, H, N.

Utilizing the same procedure, 42 g of a mixture of **27a** and **29** afforded, after bulb-to-bulb distillation at 100 °C (0.2 mm), 17.3 g (68%) of liquid **39**.

5(*R*)-Vinyl-4(*S*)-quinuclidine-2ξ-carboxaldehyde (40). Using the

same procedure described for the preparation of **17** (method B), 16.2 g of a mixture of **31** and **32** afforded, after bulb-to-bulb distillation, 5.6 g (57%) of **40**: liquid; bp 70–75 °C (0.3 mm); $[\alpha]^{25}_D$ +123.61° (*c* 1.6220, CH_3OH); IR ($CHCl_3$) 2955, 2880, 1732 (CHO), 2820, 2730 (Bohlmann bands), 996, 923 cm^{-1} ($CH{=}CH_2$); NMR ($CDCl_3$) δ 5.04 (2 H, m, $CH{=}CH_2$), 5.87 (1 H, m, $CH{=}CH_2$), 9.77 (1 H, s, CHO); mass spectrum *m/e* (rel intensity) 165 (15), 136 (100), 122 (10), 108 (9), 94 (15), 81 (20), 70 (23), 55 (17), 42 (30).

Ethyl 5(*R*)-Ethyl-4(*S*)-quinuclidine-2ξ-carboxylate (42). The mixture of epimeric esters was prepared analogously to the synthesis of **18** and **19**. A mixture of **27a** and **29** (14 g) afforded, after bulb-to-bulb distillation at 100 °C (0.5 mm), 6.7 g (63%) of **42**: liquid; $[\alpha]^{25}_D$ +76.5° (*c* 1.06, CH_3OH). An analytical sample was prepared by preparative thick layer chromatography with chloroform–methanol (95:5) as the solvent followed by bulb-to-bulb distillation of the eluate: bp 95–97 °C (0.05 mm); $[\alpha]^{25}_D$ +77.32° (*c* 1.0489, CH_3OH); IR ($CHCl_3$) 1730 cm^{-1} ($COOC_2H_5$); NMR ($CDCl_3$) δ 0.85 and 0.90 (3 H, 2 t, ratio 1:1, J = 7 Hz, CH_2CH_3), 1.29 (3 H, t, J = 7 Hz, OCH_2CH_3), 3.45 (1 H, m, NCH), 4.22 (2 H, q, J = 7 Hz, OCH_2CH_3); GLC [3 m × 3 mm glass, 10% OV-101 on Gas Chrom Q (100/120), 70 °C for 10 min, 2.5 °C/min] t_0 126 and 128.5 min. Anal. ($C_{12}H_{21}NO_2$) C, H, N.

5(*R*)-Ethyl-4(*S*)-quinuclidine-2(*R*)-carboxylic Acid Hydrochloride (41a). A solution of 4 g of **42** in 200 mL of 1 N hydrochloric acid was heated at 90 °C for 20 h. The solvent was removed under reduced pressure. Fractional crystallization of the residue from ethanol and subsequently from acetone afforded 2.6 g (63%) of a mixture of epimeric acids. The lower melting fractions (200–210 °C) were suspended in hot acetone and insolubles were removed by filtration. Evaporation of the filtrate and crystallization of the residue from acetone yielded 580 mg (12%) of material consisting mainly (90%, vide NMR) of the 2(*S*) epimer **41b**: mp 210–212 °C; NMR (CD_3OH) δ 0.98 (3 H, t, J = 7 Hz, CH_2CH_3), 1.58 (2 H, m, CH_2CH_3), 4.37 (1 H, m, NCH). The insoluble material was combined with the higher melting fractions (260–270 °C) and recrystallized several times from ethanol to afford 1.42 g (34%) of pure **41a**: mp 270–271 °C; $[\alpha]^{25}_D$ +123.94° (*c* 1.0900, CH_3OH); IR (KBr) 1742 cm^{-1} (COOH); NMR (CH_3OD) δ 0.92 (3 H, t, J = 7 Hz, CH_2CH_3), 1.45 (2 H, m, CH_2CH_3), 4.35 (1 H, m, NCH). Anal. ($C_{10}H_{17}NO_2$·HCl) C, H, Cl, N.

Ethyl 5(*R*)-Vinyl-4(*S*)-quinuclidine-2ξ-carboxylate (43). Utilizing the procedure described previously, 5.19 g of aldehyde **36** was transformed into **31** and **32**. The mixture of free bases thus obtained (3.38 g) was reacted as described for the preparation of **18** and **19**. The esterification was carried out in refluxing 4% ethanolic hydrogen chloride (20 h) to afford 1.61 g (54%; 38% from **36**) of a mixture of liquid esters **43** after bulb-to-bulb distillation at 74–80 °C (0.03 mm), $[\alpha]^{25}_D$ + 78.2° (*c* 1.05, 95% C_2H_5OH). An analytical sample of **43** was prepared by preparative thick layer chromatography with chloroform–methanol (95:5) as the solvent followed by bulb-to-bulb distillation of the eluate: bp 70 °C (0.04 mm); $[\alpha]^{25}_D$ + 82.10° (*c* 1.0743, CH_3OH); IR ($CHCl_3$) 1732 ($COOC_2H_5$), 1040, 920 cm^{-1} ($CH{=}CH_2$); NMR ($CDCl_3$) δ 1.27 (3 H, t, J = 7 Hz, OCH_2CH_3), 4.20 (2 H, q, J = 7 Hz, OCH_2CH_3), 5.02 (2 H, m, $CH{=}CH_2$), 5.88 (1 H, m, $CH{=}CH_2$); mass spectrum *m/e* (rel intensity) 209 (20), 195 (2), 180 (8), 168 (3), 154 (2), 136 (100), 108 (5), 95 (2), 86 (5), 81 (8), 55 (8), 42 (13); GLC [3 m × 3 mm glass, 10% OV-101 on Gas Chrom Q (100/120), 20 min at 70 °C then 2.5 °C/min] t_0 124 and 125.5 min, ratio 1:1. Anal. ($C_{12}H_{19}NO_2$) C, H, N.

5(*R*)-Vinyl-4(*S*)-quinuclidine-2ξ-carboxylic Acid (44). A solution of 310 mg of **43** in 10 mL of water was left standing at room temperature for 10 days. The solvent was completely removed under reduced pressure. Sublimation of the residue at 165 °C (0.15 mm) afforded 210 mg of hygroscopic acid **44**: $[\alpha]^{25}_D$ +78.4° (*c* 0.72, $CHCl_3$); $[\alpha]^{25}_D$ +93.2° (*c* 0.87, 1 N NaOH). After heating a solution of **44** in 1 N NaOH on the steam bath for 16 h: $[\alpha]^{25}_D$ +80.8° (*c* 0.87, 1 N NaOH).

5(*S*)-Ethyl-4(*R*)-quinuclidine-2ξ-carboxaldehyde (45). By the same method described for the preparation of **17** (method B), 1.34 g of **28** afforded after bulb-to-bulb distillation, 558 mg (68%) of liquid **45**: bp 100 °C (0.3 mm); $[\alpha]^{25}_D$ −85.56° (*c* 1.0682, CH_3OH). Anal. ($C_{10}H_{17}NO$), C, H, N.

5(*S*)-Ethyl-4(*R*)-quinuclidine-2(*S*)-carboxylic Acid Hydrochloride (46a). Analogous to the preparation of **18** and **19**, 4.8 g of a mixture of the crude free bases of **28** and **30** (obtained from 27.4 g of **38**) yielded 1.56 g (37%) of the epimeric mixture of ethyl **5(*S*)-ethyl-4(*R*)-quinuclidine-2ξ-carboxylates (47)**: bp 85 °C (0.15 mm); $[\alpha]^{25}_D$ −42.1° (*c* 1.125, CH_3OH). By the same method described for the preparation of **41a**, hydrolysis of the esters **47** afforded 752 mg (47%) of a mixture of **46a** and **46b**. Fractional crystallization from ethanol yielded analytically pure **46a**: mp 269–270 °C; $[\alpha]^{25}_D$ −126.49° (*c* 1.0712, CH_3OH). Anal. ($C_{10}H_{17}NO_2$·HCl) C, H, Cl, N.

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

References and Notes

(1) G. Grethe, H. L. Lee, T. Mitt, and M. R. Uskoković, *J. Am. Chem. Soc.*, **93**, 5904 (1971).
(2) G. Grethe, H. L. Lee, T. Mitt, and M. R. Uskoković, *J. Am. Chem. Soc.*, following paper in this issue.
(3) An efficient three-step synthesis of β-collidine has been developed in these laboratories (unpublished results).
(4) M. R. Uskoković, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *J. Am. Chem. Soc.*, **93**, 5902 (1971); M. R. Uskoković, T. Henderson, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *ibid.*, **100**, 571 (1978).
(5) E. Koenigs and W. Ottmann, *Chem. Ber.*, **54**, 1343 (1921).
(6) D. Ben-Ishai, *J. Org. Chem.*, **19**, 62 (1954).
(7) J. Rudinger, K. Poduska, and M. Zaoral, *Collect. Czech. Chem. Commun.*, **25**, 2022 (1960).
(8) R. S. Neale, *J. Org. Chem.*, **32**, 3263 (1967); R. S. Neale and N. L. Marcus, *ibid.*, **32**, 3273 (1967).
(9) M. E. Wolff, *Chem. Rev.*, **63**, 55 (1963).
(10) A. Kirrmann, P. Duhamel, and R. Nouri-Bimorghi, *Bull. Soc. Chim. Fr.*, 3264 (1964).
(11) P. Duhamel, L. Duhamel, and J. Gralak, *Bull. Soc. Chim. Fr.*, 3641 (1970).
(12) G. V. Kaiser, E. W. Ashbrook, and J. E. Baldwin, *J. Am. Chem. Soc.*, **93**, 2342 (1971).
(13) We are indebted to Dr. J. F. Blount of these laboratories for carrying out the x-ray analysis.
(14) J. Gutzwiller and M. R. Uskoković, *J. Am. Chem. Soc.*, **100**, 576 (1978).
(15) G. Köbrich, K. Flory, and W. Drischel, *Angew. Chem.*, **76**, 536 (1964), and subsequent papers; G. Köbrich, *Bull. Soc. Chim. Fr.*, **9**, 2712 (1969).
(16) R. L. Augustine and S. F. Wanat, *Synth. Commun.*, **1**, 241 (1971).
(17) R. P. Evstigneeva, Ch'en Ch'an-pai, and N. A. Preobrazhenskii, *J. Gen. Chem. USSR (Engl. Transl.)*, **30**, 495 (1960).
(18) Ch'en Ch'an-pai, R. P. Evstigneeva, and N. A. Preobrazhenskii, *Dokl. Akad. Nauk. SSSR*, **123**, 707 (1958).
(19) R. Goutarel, M. M. Janot, V. Prelog, and W. I. Taylor, *Helv. Chim. Acta*, **33**, 150 (1950).
(20) The general conditions are the same as described in the first paper.[4]
(21) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 1179.
(22) C. A. Brown and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 2829 (1962).