Total Synthesis of *Cinchona* Alkaloids. 4. Syntheses via Quinuclidine Precursors

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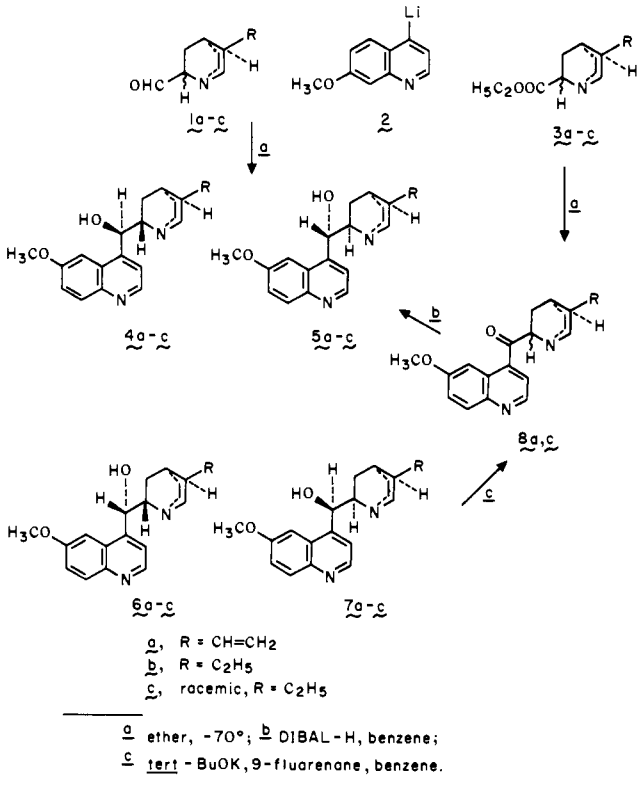
Abstract: *Cinchona* alkaloids of the quinoline as well as of the indole type have been synthesized by a method which involves combination of a preformed quinuclidine drivative with the respective aromatic moiety. Using this new approach, quinine (**4a**) and dihydroquinine (**4b**) and their stereoisomers have been prepared directly by condensation of the quinuclidine carboxaldehydes **1a** and **1b**, respectively, with 6-methoxy-4-quinolyllithium (**2**) or via the ketone intermediates **8** from the esters **3**. Quinuclidine ester **3b** also served as starting material for the first total synthesis of dihydrocinchonamine (**14b**). A practical result of this work is a four-step synthesis of racemic dihydroquinine (**4c**) and racemic dihydroquinidine (**5c**) from β-collidine.

In previous syntheses[1] of *Cinchona* alkaloids, the problem of forming the quinuclidine ring has been solved by cyclization of various piperidine derivatives late in the synthetic sequence. In two short communications[2] we reported initial results of a different synthetic approach to these alkaloids. This approach, described in detail in this paper, consists of combining synthetic quinuclidine derivatives of correct stereochemistry and proper functionalities with suitable aromatic derivatives to afford either the quinoline or the indole type of *Cinchona* alkaloids. The preparation of various quinuclidine derivatives suitable for this purpose was the subject of the preceding paper.[3]

Scheme I shows two complementary ways to synthesize

Scheme I



quinine, dihydroquinine, and their respective stereoisomers. Both methods utilize as the aromatic reactant 6-methoxy-4-quinolyllithium[4] (**2**) which was prepared by halogen–metal exchange from 4-bromo-6-methoxyquinoline and *n*-butyllithium in ether at −70 °C. It should be noted that appreciable decomposition of the lithium derivative **2** occurs at temperatures above −50 °C.

The first method leading directly to the alkaloids **4–7** involves condensation of the lithiated quinoline **2** with quinuclidine aldehydes **1a–c**.[3] For the preparation of quinine, a solution of freshly distilled aldehyde **1a** in ether was added slowly to the yellow suspension of equimolar amounts of lithiated quinoline to afford a mixture of the diastereoisomers **4a–7a**. Separation by a combination of chromatography and crystallization yielded 13% of quinine (**4a**), characterized as the neutral *d*-tartrate, 15% of quinidine **5a**, and 5% each of the two 9-epi isomers **6a** and **7a**, characterized as the acidic di-*O*-benzoyl-*d*-tartrate and the dihydrochloride, respectively. The synthetic products were identical in all aspects with authentic materials.[1c] Under the same reaction conditions, condensation of aldehyde **1b** with 6-methoxy-4-quinolyllithium (**2**) gave in comparable yields dihydroquinine (**4b**) and dihydroquinidine (**5b**), and a mixture of their 9-epi isomers **6b** and **7b**. From the last mixture, 9-*epi*-dihydroquinidine (**7b**) was isolated and characterized as its crystalline neutral dibenzoyl-*d*-tartrate.[5] The biologically inactive 9-epi compounds **6** and **7** can be transformed in high yield to the desired erythro isomers **4** and **5**. This transformation involves oxidation of a mixture of **6** and **7** to the ketones **8** and subsequent stereoselective reduction with diisobutylaluminum hydride[1d,e] to a mixture of **4** and **5**.

The racemic dihydro derivatives **4c–7c** were obtained from the quinuclidine derivative **1c** under conditions similar to the ones used in the optically active series. Since the aldehyde **1c** is easily prepared from β-collidine in three steps,[3] this sequence represents a short and practical synthesis of racemic dihydroquinine and dihydroquinidine. This method was very valuable for the preparation of a large number of derivatives. The only drawback in this otherwise attractive scheme is the low yield (ca. 30%) in the condensation step. Probably, this is caused by the presence of an acidic proton at C-2 of the quinuclidine molecule. All attempts to circumvent this problem by varying the reaction conditions (reverse addition, excess of lithium compounds, etc.) have failed thus far.

In the second method, the quinuclidine esters **3**[3] are used instead of the aldehydes **1** in the condensation step. The esters have the advantage that they can be stored indefinitely while the labile aldehydes have to be prepared freshly for each run. Condensation of **3c**[3] with 6-methoxy-4-quinolyllithium in ether at −70 °C gave a crystalline mixture (**8c**) of racemic dihydroquininone and racemic dihydroquinidinone after purification by chromatography on silica gel. For our purpose, the crude reaction product which contained 30–40% of **8**[7] could be used for the next step without purification. Reduction with diisobutylaluminum hydride in benzene[1d,e] gave, after chromatographic separation, racemic dihydroquinine (**4c**) and racemic dihydroquinidine (**5c**) in about 20% total yield (based on **3c**). Quinine (**4a**) and quinidine (**5a**) were obtained analogously from the unsaturated ester **3a**.

Thus, two new methods based on the use of quinuclidine precursors have been developed for the preparation of *Cin-*

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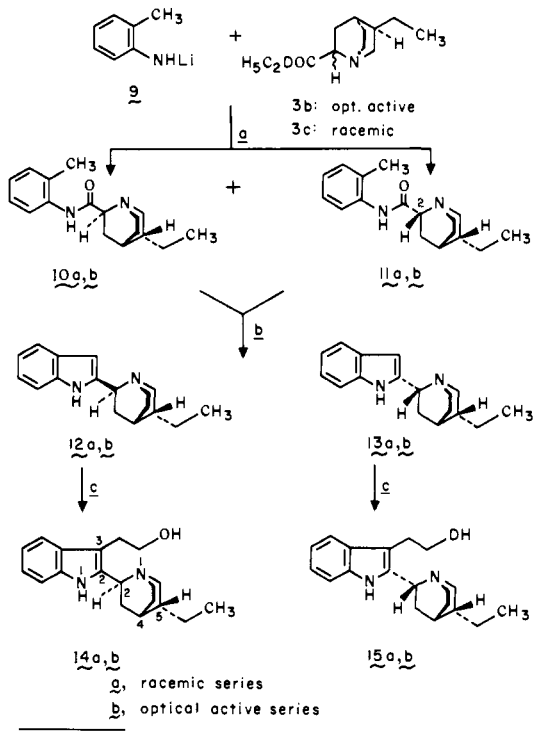
chona alkaloids of the quinoline type. The same principle also was applied to the first total synthesis of the minor indole *Cinchona* alkaloid dihydrocinchonamine (**14b**) (Scheme II).

Scheme II



[a] THF, reflux; [b] $NaNH_2$, 235°; [c] CH_3MgI, $(CH_2)_2O$.

Preobrazhenskii and co-workers previously synthesized cinchonamine[8] from ethyl 5(*R*)-vinyl-4(*S*)-quinuclidine-2(*S*)-carboxylate[3] obtained by degradation of quininone.[9] While these workers formed the indole part of the molecule by a Fischer synthesis, we applied the Madelung cyclization[10] for this purpose. This required the preparation of the intermediates **10** and/or **11**. Two equivalents of the lithium derivative **9** prepared in situ from *o*-toluidine and *n*-butyllithium in tetrahydrofuran[11] was heated with the quinuclidine ester **3** at 90 °C with slow removal of the solvent to afford after distillation in 90% yield the two epimeric toluidides **10** and **11**. Separation into the pure compounds by chromatography on silica gel was carried out in the racemic series only. The configurational assignment at the epimeric center (C-2) is based on the chemical shifts of the methyl protons of the ethyl group. In the more polar epimer **11a**, the triplet is shifted upfield by 7 Hz to 0.83 ppm. An inspection of Dreiding models of **10** and **11** reveals that shielding of the methyl protons caused by the anisotropic effect of the benzene ring is more likely to happen in **11**.

Cyclization of either **10** or **11** or more conveniently of a mixture of both was accomplished with 3 equiv of sodamide under the conditions of the Madelung indole synthesis.[12] Best results (ca. 80%) were obtained by heating a mixture of the reactants in either with slow distillation of the solvent to 235 °C within 50 min and by keeping the mixture at this temperature for an additional 40 min. These conditions are very critical and any change resulted in a lower yield of products. Separation of the mixture in which **13** was slightly prevalent was achieved by a combination of crystallization from methanol followed by chromatography of the mother liquors. In the racemic series, epimer **12a** was obtained by crystallization while in the optically active series **13b** crystallized first. Again, the stereochemistry at the epimeric center was determined by NMR spectroscopy taking into account the effect of the indole ring on the chemical shift of the terminal methyl group (0.91 ppm for **12b** and 0.78 ppm for **13b**). This assignment was corroborated by the reported chemical shifts of the terminal methyl groups in 10-methoxydihydrocinchonamine and its epimer[13] (0.92 and 0.83 ppm, respectively) and by the transformation of epimer **12b** into dihydrocinchonamine (**14b**). For this purpose, the indolemagnesium iodide, prepared by the portionwise addition of crystalline **12b** to a tenfold excess of methylmagnesium iodide, was reacted at 0 °C with an ethereal solution of ethylene oxide (20 equiv). This reaction gave crystalline dihydrocinchonamine (**14b**) in 30% yield identical in all aspects with natural material.[14] The major component in the remaining crude product was unreacted starting material **12b** which could be easily recycled. Under identical conditions, compound **13b** afforded crystalline 2-*epi*-dihydrocinchonamine (**15b**). Analogous results were obtained in the racemic series.

In summary, quinuclidine derivatives properly substituted and possessing the correct stereochemistry have served as common precursors for the preparation of *Cinchona* alkaloids of the quinoline type as well as of the indole type.

Experimental Section

General.[15] For preparative thin layer chromatography, the following solvent mixtures were used: solvent A, chloroform–triethylamine–methanol (85:10:5); solvent B, chloroform–triethylamine (95:5); solvent C, benzene–ethyl acetate–ammonium hydroxide (90:10:0.3); solvent D, benzene–ethyl acetate–triethylamine (50:50:5).

Quinine (4a) and Quinidine (5a) from 1a. To 30 mL of anhydrous ether was added 2.74 mL (4.4 mol) of a 1.62 M solution of *n*-butyllithium in hexane. The resulting solution was cooled to −68 °C and subsequently a solution of 1.08 g (4.5 mmol) of **4-bromo-6-methoxyquinoline** in 30 mL of anhydrous tetrahydrofuran was added dropwise to the stirred solution under a nitrogen atmosphere. After complete addition, stirring was continued for 0.5 h at −68 °C followed by the slow addition of 0.748 g (4.5 mmol) of **1a** dissolved in 15 mL of anhydrous ether. The mixture was stirred for 2 h, hydrolyzed with water, and allowed to warm to room temperature. The aqueous layer was separated and washed twice with ether. Workup of the organic layers afforded a brown oil which was purified by preparative thick layer chromatography (solvent A). Three major bands were eluted with chloroform–methanol (1:1) to give as crude products 300 mg (20%) of **4a**, 340 mg (23%) of **5a**, and 330 mg (22%) of a mixture of **6a** and **7a**. The solution of crude **4a** in ethanol was added to an ethanolic solution of 68.3 mg of *d*-tartaric acid. Recrystallization of the precipitate from ethanol gave 220 mg (13%) of the neutral *d*-tartrate of **4a**: mp 209–210 °C; mmp with authentic material[1c] 208–209 °C; $[\alpha]^{25}_D$ −159.5° (*c* 1.00, CH_3OH). Recrystallization of crude **5a** from ethanol afforded 215 mg (15%) of pure **5a**: mp 172–173 °C; mmp with natural quinidine, 171–172.5 °C; $[\alpha]^{25}_D$ +265.6° (*c* 1.07, 95% EtOH). The mixture of epi isomers (240 mg) was separated by preparative thick layer chromatography (solvent B) in the order of increasing polarity into 71 mg of **7a** and 62 mg of **6a**. A solution of **6a** in acetone was combined with a solution of di-*O*-benzoyl-*d*-tartrate (34 mg) to give, after crystallization from ethanol–ether, the acidic di-*O*-benzoyl-*d*-tartrate monohydrate of **6a**, mp and mmp with authentic material[1c] 154–157 °C. Treatment of **7a** with ethanolic hydrogen chloride and recrystallization of the crude product from ethanol–ether afforded pure dihydrochloride of **7a**: mp 185–188 °C evacuated capillary); mmp with an authentic specimen[1c] 185–188 °C; $[\alpha]^{25}_D$ +55.4° (*c* 0.99, MeOH). Anal. ($C_{20}H_{24}N_2O_2 \cdot 2HCl \cdot 0.5H_2O$) C, H, Cl, N, H_2O.

Dihydroquinine (4b) and Dihydroquinidine (5b) from 1b. Using the same conditions described for the preparation of **4a** and **5a**, 538 mg of quinuclidine aldehyde **1b** was reacted with 6-methoxy-4-quinolyllithium (prepared from 760 mg of the bromo compound). The crude product (1.14 g) was purified by preparative thick layer chromatography (solvent A). Elution of the lowest major band with chloroform–methanol (1:1) gave 138 mg (13%) of **dihydroquinine (4b)**: mp 170–171 °C after recrystallization from chloroform–ether; mmp with natural material 170–171 °C; $[\alpha]^{25}_D$ −144.5° (*c* 0.9350, 95% ethanol); IR ($CHCl_3$) 3605 cm^{-1} (OH); UV (EtOH) 231 nm (ε 27 000), 280 (3100), 333 (4200); NMR ($CDCl_3$) δ 0.79 (3 H, t, *J* = 6.5 Hz, $CH_2C\underline{H}_3$), 3.84 (3 H, s, OCH_3), 5.07 (1 H, broad, CHO*H*), 5.44 (1

H, d, J = 3 Hz, C*H*OH), 7.22 (2 H, cp, CH-5′ and CH-7′), 7.41 and 8.43 (2 H, AB, J = 4.5 Hz, CH-3′ and CH-2′), 7.85 (1 H, d, J_o = 9 Hz, CH-8′). Elution of the next higher band with chloroform–methanol (1:1) gave 210 mg of an oil which was dissolved in ethanol. Upon standing, crystalline **dihydroquinidine (5b)** separated: mp 169–170 °C; mmp with natural material 169–170 °C; $[\alpha]^{25}_D$ +222° (*c* 0.970, EtOH); IR ($CHCl_3$) 3605 cm^{-1} (OH); UV (EtOH) 233 nm (ϵ 32 300), 279 (4000), 320 (4500), 332 (5100); NMR ($CDCl_3$) δ 0.86 (3 H, t, J = 6.5 Hz, CH_2CH_3), 3.83 (3 H, s, OCH_3), 5.04 (1 H, broad, CHO*H*), 5.53 (1 H, d, J = 5 Hz, C*H*OH), 7.18 (1 H, d, J_m = 3 Hz, CH-5′), 7.21 (1 H, dd, J_m = 3 Hz, J_o = 9 Hz, CH-7′), 7.47 and 8.49 (2 H, AB, J = 4.5 Hz, CH-3′ and CH_2-2′), 7.88 (1 H, d, J_o = 9 Hz, CH-8′). Elution of the third major band with chloroform–methanol (1:1) afforded 87 mg of a mixture of **dihydro-*epi*-quinine (6b)** and **dihydro-*epi*-quinidine (7b)**. The mixture was dissolved in benzene and treated with a solution of 48 mg of dibenzoyl-*d*-tartaric acid in benzene–acetone. The solvents were evaporated to dryness and the residue, after recrystallization from benzene, yielded the neutral dibenzoyl-*d*-tartrate of **7b:** mp 168–170 °C; mmp with authentic material[5] 169–170 °C; $[\alpha]^{25}_D$ −13.7° [*c* 0.970, EtOH–$CHCl_3$ (4:1)]. Anal. $[(C_{20}H_{26}N_2O_2)_2 \cdot C_{18}H_{14}O_8]$ C, H, N.

Racemic Dihydroquinine (4c) and Racemic Dihydroquinidine (5c) from 1c. Using the same reaction conditions described above, 1.67 g of aldehyde **1c** was reacted with 6-methoxy-4-quinolyllithium (prepared from 2.38 g of the bromo compound). The crude reaction product (3.25 g) was purified by preparative thick layer chromatography (solvent A). Elution of the lowest band gave 1.11 g (34%) of a mixture of **4c** and **5c.** From the next higher band, 319 mg (9.8%) of a mixture of the two 9-epimers **6c** and **7c** was obtained identical on TLC (solvent B, R_f 0.25) with authentic specimens. The crude mixture of **4c** and **5c** was dissolved in a minimal amount of ethanol and, upon cooling, 130 mg of crystalline **5c** was obtained, mp 147–149 °C after drying at 100 °C (0.1 mm). The mother liquor was concentrated to dryness under reduced pressure and the residue was applied to five preparative thick layer plates. The plates were developed three times in solvent A. Crystallization of the eluate of the higher major band from ethanol afforded additional 34 mg of **5c**, total 164 mg, 5.2%. Recrystallization from ethanol and drying of the crystalline material at 100 °C (0.1 mm) to constant weight yielded pure **5c:** mp 150–152 °C; mmp with authentic material 149–150 °C; IR ($CHCl_3$) 3610 (OH, free), 3400–3100 cm^{-1} (OH, bonded); UV (EtOH) 231 nm (ϵ 32 800), 279 (3800), 320 (4400), 332 (4990); NMR ($CDCl_3$) δ 0.76 (3 H, t, J = 6.5 Hz, CH_2CH_3), 3.87 (3 H, s, OCH_3), 5.38 (1 H, broad, CHO*H*), 5.69 (1 H, d, J = 3 Hz, C*H*OH), 7.27 (1 H, d, J_m = 2.5 Hz, CH-5′) 7.30 (1 H, dd, J_m = 2.5, J_o = 9 Hz, CH-7′), 7.55 and 8.63 (2 H, AB, J = 4.5 Hz, CH-3′ and CH-2′), 7.99 (1 H, d, J_o = 9 Hz, CH-8′). Anal. ($C_{20}H_{26}N_2O_2$) C, H, N.

Elution of the lower major band with methylene chloride, washing of the organic solution with aqueous potassium carbonate and water, drying over sodium sulfate, and evaporation to dryness gave crude **4c** as an oil. The residue was dissolved in the minimal amount of acetone and upon standing crystalline **4c** was obtained: mp 168–169 °C; mmp with authentic material 168–169 °C; IR ($CHCl_3$) 3600 (OH, free), 3500–3100 (OH, bonded); UV (EtOH) 232 nm (ϵ 34 260), 280 (3900), 321 (4550), 333 (5140); NMR ($CDCl_3$) δ 0.74 (3 H, t, J = 6.5 Hz, CH_2CH_3), 3.85 (3 H, s, OCH_3), 5.66 (1 H, d, J = 5 Hz, C*H*OH), 5.90 (1 H, broad, CHO*H*), 7.26 (1 H, d, J_m = 2.5 Hz, CH-5′), 7.30 (1 H, dd, J_m = 2.5, J_o = 9 Hz, CH-7′), 7.97 (1 H, d, J_o = 9 Hz, CH-8′), 7.53 and 8.61 (2 H, AB, J = 4.5 Hz, CH-3′ and CH-2′). Anal. ($C_{20}H_{26}N_2O_2$) C, H, N.

***rac*-Dihydroquinine (4c) and *rac*-Dihydroquinidine (5c) from 3c.** To a stirred solution of 4.15 mL of 1.6 M *n*-butyllithium in hexane in 50 mL of anhydrous ether was added in an atmosphere of nitrogen at −70 °C 1.6 g of 6-methoxy-4-bromoquinoline dissolved in 50 mL of anhydrous ether. The mixture was stirred at this temperature for another 15 min. After a solution of 750 mg of 1,4-diazabicyclo[2.2.2]octane (Dabco) in 50 mL of anhydrous ether was added, stirring was continued for 2 h at −70 °C. Subsequently, 1.1 g of ester **3c** dissolved in 50 mL of ether was added slowly. After complete addition, the mixture was stirred for 30 min and then quenched by the addition of water. The mixture was allowed to warm to room temperature. The aqueous layer was separated and extracted three times with ether. Workup of the combined organic solution gave 2.2 g of crude product which by UV analysis[7] contained ~35% of **8c.** Crude product from another run was purified by preparative thick layer chromatography with ether as solvent. The plates were developed three times. Elution of the major band with methanol and crystallization of the eluate from Skellysolve B afforded the mixture **8c** of ***rac*-dihydroquininone** and ***rac*-dihydroquinidinone:** mp 86–90 °C; IR ($CHCl_3$) 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.85 and 0.91 (3 H, 2 t, J = 7 Hz, ratio ~1:1, CH_2CH_3); 3.91 (3 H, s, OCH_3), 7.38 (1 H, dd, J_o = 9, J_m = 2.5 Hz, CH-7′), 7.63 and 7.72 (1 H, 2 d, J_m = 2.5 Hz, CH-5′), 7.62 and 8.83 (~1 H, AB, J = 4.5 Hz, CH-3′ and CH-2′ of ***rac*-dihydroquinidinone**), 7.72 and 8.85 (~1 H, AB, J = 4.5 Hz, CH-3′ and CH-2′ of ***rac*-dihydroquininone**), 8.01 (1 H, J_o = 9 Hz, CH-8′); UV (2-propanol) 212 nm (ϵ 38 700), 344 (5100); mas spectrum *m/e* (rel intensity) 324 (100), 309 (30), 295 (25), 281 (5), 267 (20), 186 (15), 172 (12), 158 (28), 138 (60). Anal. ($C_{20}H_{24}N_2O_2$) C, H, N.

The crude mixture of **8c** (2 g) was dissolved in 50 mL of azeotropically distilled benzene and 6.5 mL of a 1.5 N solution of DIBAL-H in toluene was added slowly. After stirring for an additional 1 h at room temperature, the mixture was cooled in an ice bath and quenched by the addition of 10 mL of methanol–water (1:1). The precipitate was collected by filtration and thoroughly washed with methanol. The combined filtrate was evaporated to dryness under reduced pressure. The solid residue was dissolved in chloroform and washed with 1 N NaOH and water. Workup afforded 1.8 g of yellow oil. Purification of the crude product by preparative thick layer chromatography (solvent A) gave 374 mg (11% based on **3c**) of **5c** (mp 150–152 °C after crystallization from ethanol; mmp with authentic material 151–153 °C) and 279 mg (8% based on **3c**) of **4c** (mp 171–173 °C after crystallization from acetone; mmp with an authentic specimen 172–173 °C).

Quinine (4a) and Quinidine (5a) from 3a. Using the same reaction conditions described above, but omitting the addition of Dabco, 2.1 g of ester **3a** was reacted with 6-methoxy-4-quinolyllithium (prepared from 4.76 g of the bromo compound) followed by reduction of the crude reaction product with DIBAL-H. Separation of the crude product by preparative thick layer chromatography (solvent A) afforded 285 mg (9%) of quinine (**4a**), crystallized as the neutral *d*-tartrate, and 311 mg (10%) of quinidine (**5a**): mp 170–172 °C; mmp with natural material 170–172 °C; $[\alpha]^{25}_D$ +261° (*c* 0.995, EtOH).

***rac*-5(*R*)-Ethyl-*N*-(*o*-tolyl)-4(*S*)-quinuclidine-2(*S*)-carboxamide (10a) and *rac*-5(*R*)-Ethyl-*N*-(*o*-tolyl)-4(*S*)-quinuclidine-2(*R*)-carboxamide (11a).** To a stirred solution of 16.1 g of *o*-toluidine in 60 mL of anhydrous tetrahydrofuran was added at 15 °C in a nitrogen atmosphere 94 mL of a 1.6 M solution of *n*-butyllithium in hexane. This was followed after 10 min by the addition of 21.1 g of **3c** dissolved in 40 mL of anhydrous tetrahydrofuran. The mixture was kept at reflux temperature for 15 h and after removal of ~80 mL of solvent, the residual mixture was heated at 90 °C for another 15 h. Addition of 100 mL of water–tetrahydrofuran (1:1) to the cooled mixture was followed by extraction with ether (twice). Workup of the combined extract and removal of impurities by bulb-to-bulb distillation (85 °C, 0.05 mm) gave 25 g (91.3%) of liquid residue consisting of an epimeric mixture of **10a** and **11a.** Part of the mixture (3.9 g) was separated by preparative thick layer chromatography (solvent C, four times). Elution of the less polar material gave 1.6 g of an oil, which on treatment with pentane and recrystallization from the same solvent afforded analytically pure **10a:** mp 65–67 °C; IR ($CHCl_3$) 3325 (NH), 1690 and 1530 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 6.5 Hz, CH_2CH_3), 2.21 (3 H, s, $C_6H_4CH_3$), 3.41 (1 H, t, J = 9 Hz, CH-2), 9.10 (1 H, b, NH); UV (CH_3OH) 241 nm (ϵ 8800); mass spectrum *m/e* (rel intensity) 272 (100), 243 (20), 215 (20), 166 (10), 162 (15), 138 (30), 124 (6), 120 (5), 110 (65), 107 (18), 91 (6), 82, (60), 55 (15); R_f 0.25 (solvent C). Anal ($C_{17}H_{24}N_2O$) C, H, N.

Treatment of an ethanolic solution of **10a** with excess ethanolic hydrogen chloride, removal of the solvent, and crystallization of the residue from acetone–ether afforded pure **10a**·HCl: mp 172–173 °C; NMR ($CDCl_3$) δ 0.81 (3 H, t, J = 6.5 Hz, CH_2CH_3), 2.36 (3 H, s, $C_6H_4CH_3$), 4.76 (1 H, m, CH-2); UV (CH_3OH) 233 nm (ϵ 6800). Anal. ($C_{17}H_{24}N_2O$·HCl) C, H, N.

Elution of the more polar material from the plates yielded 1.7 g of oil which upon trituration with pentane gave pure **11a:** mp 80–82 °C; IR ($CHCl_3$) 3310 (NH), 1690 and 1530 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 6.5 Hz, CH_2CH_3), 2.23 (3 H, s, $C_6H_4CH_3$), 3.42 (1 H, t, J = 9 Hz, CH-2), 9.32 (1 H, b, NH); UV (CH_3OH) 242 nm (ϵ 8800); R_f 0.18 (solvent C). Anal. ($C_{17}H_{24}N_2O$) C, H, N.

To a solution of **11a** in ether was added excess ethanolic hydrogen chloride. The precipitate was collected by filtration and recrystallized

from acetone–ethanol to afford analytically pure **11a**·HCl: mp 179–181 °C (after drying for 5 days at 80 °C, 0.01 mm); NMR ($CDCl_3$) δ 0.84 (3 H, t, J = 7 Hz, $CH_2C\underline{H}_3$), 2.38 (3, H, s, $C_6H_4C\underline{H}_3$), 4.95 (1 H, m, CH-2); UV (CH_3OH) 239 nm (ϵ 8300). Anal. ($C_{17}H_{24}N_2O$·HCl) C, H, N.

4(*S*),5(*R*)-Ethyl-2(*S*)-(2-indolyl)quinuclidine (12b) and 4(*S*),5(*R*)-Ethyl-2(*R*)-(2-indolyl)quinuclidine (13b). The crude mixture (12.1 g, 0.044 mol) of **10b** and **11b** prepared from 10.5 g of **3b** as described for the racemic compounds was dissolved in 15 mL of anhydrous ether. To this solution was added under a blanket of nitrogen 4.8 g (0.132 mol) of sodamide. The reaction mixture was heated up to 235 °C in 50 min and kept at this temperature for an additional 40 min. After cooling to room temperature, the mixture was diluted with 10 mL of 95% ethanol and subsequently with 100 mL of water. This mixture was stirred at 80 °C for 30 min and then extracted repeatedly with ether. Workup of the combined organic extract afforded 10.5 g (83% based on **3b**) of a mixture of **12b** and **13b**. Crystallization from methanol yielded 2.7 g (21%) of **12b**: mp 128–129 °C; $[\alpha]^{25}_D$ +52.02° (c 0.9401, 95% C_2H_5OH); ORD (c 0.2472, CH_3OH) $[\alpha]_{293}$ +1415° (pk), $[\alpha]_{290}$ 0°, $[\alpha]_{288}$ −2830° (tr), $[\alpha]_{285}$ −1801° (pk), $[\alpha]_{279}$ −3087° (tr), $[\alpha]_{268}$ 0°, $[\alpha]_{222}$ +18 007° (pk), $[\alpha]_{210}$ 0°, $[\alpha]_{200}$ −24 438°; CD (c 0.2472, CH_3OH) $[\theta]_{300}$ 0, $[\theta]_{290}$ +2881, $[\theta]_{288}$ 0, $[\theta]_{285}$ −617, $[\theta]_{264}$ −6688, $[\theta]_{232}$ −1132, $[\theta]_{229}$ 0, $[\theta]_{214}$ +24 181, $[\theta]_{200}$ +13 891; IR ($CHCl_3$) 3450 cm^{-1} (NH); NMR ($CDCl_3$) δ 0.91 (3 H, t, J = 6.5 Hz, $CH_2C\underline{H}_3$), 4.06 (1 H, t, J = 8.5 Hz, CH-2), 6.40 (1 H, s, CH-3); UV (CH_3OH) 218 nm (ϵ 40 000), 269–272 (9500), 280–282 (8800), 290 (6100); mass spectrum *m/e* ((rel intensity) 254 (100), 239 (5), 225 (45), 211 (5), 197 (35), 157 (37), 143 (50), 130 (25); R_f 0.50 (solvent D). Anal. ($C_{17}H_{22}N_2$) C, H, N.

Concentration of the mother liquor and separation of the mixture by preparative thick layer chromatography (25 plates, solvent D) yielded an additional 0.7 g of crystalline **12b** (total 3.4 g, 27%) from the eluate of the higher band. Elution of the more polar material (4.5 g, 36%) and recrystallization from ethanol gave 2.2 g of pure **13b**: mp 113–114 °C; $[\alpha]^{25}_D$ +101.61° (c 1.1046, 95% C_2H_5OH); IR ($CHCl_3$) 2460 cm^{-1} (NH); NMR ($CDCl_3$) δ 0.78 (3 H, t, J = 6.5 Hz, $CH_2C\underline{H}_3$), 4.04 (1 H, t, J = 9 Hz, CH-2), 6.39 (1 H, s, CH-3), 9.35 (1 H, b, NH); UV (CH_3OH) 218 nm (ϵ 37 800), 267–269 (8600), 281 (7800), 289 (5500); R_f 0.25 (solvent D). Anal. ($C_{17}H_{22}N_2$) C, H, N.

***rac*-4(*S*),5(*R*)-Ethyl-2(*S*)-(2-indolyl)quinuclidine (12a) and *rac*-4(*S*),5(*R*)-Ethyl-2(*R*)-(2-indolyl)quinuclidine (13a).** Cyclization of 18.4 g of a mixture of **10a** and **11a** under the condition described above afforded 17 g (98%) of a mixture of **12a** and **13a**. Crystallization of the crude material from methanol and recrystallization of the crystalline fraction (8.5 g) from the same solvent gave 6.5 g (38%) of pure **13a**: mp 134–135 °C; R_f 0.15 (solvent B). Anal. ($C_{17}H_{22}N_2$) C, H, N.

The combined mother liquors of the crystallization of **13a** were concentrated and the mixture was separated by preparative thick layer chromatography (40 plates, developed twice, solvent B). Elution of the lower band and crystallization of the material from methanol afforded an additional 3.5 g of **13a** (total 10 g, 58%). Crystallization of the eluate (5 g) of the higher major band from methanol gave 4 g (23%) of **12a**: mp 125–126 °C; R_f 0.25 (solvent B). Anal. ($C_{17}H_{22}N_2$) C, H, N.

Dihydrocinchonamine (14b).[16] Solid **12b** (0.7 g, 2.75 mmol) was added portionwise to 10 mL of a 2.79 M ethereal solution of methylmagnesium iodide at room temperature in a nitrogen atmosphere. After completed addition, the reaction mixture was refluxed for 2 h and then cooled down to 0 °C. A solution of 1.8 g (41 mmol) of ethylene oxide in 20 mL of anhydrous ether was added slowly to the cooled mixture and stirring was continued at 0 °C for 2 h. Then, additional ethylene oxide (0.7 g in 8 mL of ether) was added and the reaction mixture was kept at 4 °C overnight. After ether was removed by passing nitrogen over the mixture, dichloromethane (30 mL) and water were added cautiously to the residue. The organic layer was separated and the aqueous phase was extracted twice with dichloromethane. The residue obtained after workup was treated with ethanolic hydrogen chloride. The resulting solid was washed thoroughly with ether andtreated with saturated aqueous K_2CO_3. Extraction with ether and workup of the organic extract afforded 258 mg (31%) of **14b**: mp 162–163 °C (after recrystallization from CH_2Cl_2); $[\alpha]^{25}_D$ +118.4° (c 1.02, 95% C_2H_5OH); CD (c 0.027%, CH_3OH) $[\theta]_{320}$ 0, $[\theta]_{297}$ +3205, $[\theta]_{290}$ +4200, $[\theta]_{274}$ +4642, $[\theta]_{251}$ 0, $[\theta]_{230}$ −48 630, $[\theta]_{220}$ 0, $[\theta]_{210}$ +30 946; IR ($CHCl_3$) 3480 cm^{-1} (NH); UV (CH_3OH) 222 nm (ϵ 43 000), 283 (9750), 292 (7900); NMR ($CDCl_3$) δ 0.92 (3 H, t, J = 6.5 Hz, $CH_2C\underline{H}_3$), 4.14 (1, H, t, J = 8 Hz, CH-2), 8.49 (1 H, b, NH); mass spectrum *m/e* (rel intensity) 298 (30), 280 (23), 268 (25), 253 (6), 241 (10), 223 (10), 211 (5), 201 (7), 187 (7), 169 (13), 156 (30), 144 (20), 123 (100), 110 (25); R_f 0.6 (solvent B). Anal. ($C_{19}H_{26}N_2O$) C, H, N.

***rac*-Dihydrocinchonamine (14a)** was obtained in 37% yield from **12a** by the procedure described above, mp 177–178 °C after recrystallization from methanol. Anal. ($C_{19}H_{26}N_2O$) C, H, N.

Recrystallization of the crude hydrochloride obtained during the workup from ethanol–ether afforded analytically pure **14a**·HCl: mp 243–244 °C; NMR (Me_2SO-d_6) δ 0.95 (3 H, t, J = 6.5 Hz, $CH_2C\underline{H}_3$), 5.01 (1 H, t, J = 8 Hz, CH-2). Anal. ($C_{19}H_{26}N_2O$·HCl) C, H, N.

3-*epi*-Dihydrocinchonamine (15b). Following the procedure for the preparation of **14b**, the crude product obtained from 1 g of **13b** was purified by preparative thick layer chromatography (eight plates, solvent B). Elution of the major band gave 0.59 g of crude **15b** (51%). Crystallization from dichloromethane–acetone afforded 159 mg (15%) of **15b**: mp 166–168 °C (after recrystallization from dichloromethane–ether); $[\alpha]^{25}_D$ +24.51° (c 1.0455, 95% C_2H_5OH); IR ($CHCl_3$) 3490 cm^{-1} (NH); NMR ($CDCl_3$) δ 0.85 (3 H, t, J = 6.5 Hz, $CH_2C\underline{H}_3$), 4.12 (1 H, t, J = 9 Hz, CH-2), 8.63 (1 H, b, NH); UV (CH_3OH) 225 nm (ϵ 38 600), 285 (8400), 293 (7610); R_f 0.6 (solvent B). Anal. ($C_{19}H_{26}N_2O$) C, H, N.

The mother liquor of the crystallization of **15b** was concentrated and the residue was treated with ethanolic hydrogen chloride, and upon addition of ether the crystalline hydrochloride of **15b** precipitated. Recrystallization from ethanol–ether gave 188 mg (14%) of **15b**·HCl, mp 225–226 °C

***rac*-3-*epi*-Dihydrocinchonamine (15a).** The crude product obtained from 5.08 g of **13a** under the reaction conditions described for the preparation of **14b** was purified by preparative thick layer chromatography (developed twice, solvent B). Elution of the more polar major band gave 1.3 g of starting material **13a**. The eluate of the other major band after concentration was crystallized from methanol to afford 1.1 g (25%, based on recovered **13a**) of pure **15a**·0.15H_2O, mp 167–169 °C. Anal. ($C_{19}H_{26}N_2O$·0.15H_2O) C, H, N. H_2O.

Treatment of **15a** with ethanolic hydrogen chloride and recrystallization of the product from ethanol–ether gave analytically pure **15a**·HCl: mp 234–235 °C; NMR ($MeSO$-d_6) δ 0.89 (3 H, t, J = 6.5 Hz, $CH_2C\underline{H}_3$), 5.06 (1 H, t, J = 8 Hz, CH-2). Anal. ($C_{19}H_{26}N_2O$·HCl) C, H, N.

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Heavy Metal Nucleotide Interactions. 11. Stereochemical and Electronic Effects in the Electrophilic Attack of *cis*- and *trans*-Diammineplatinum(II) on 5′-Guanosine Monophosphate and Polyguanylate in Aqueous Solution[1,2]

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Abstract: *cis*- and *trans*-$(H_3N)_2Pt^{II}$ react in acidic solution with 5′-GMP to produce mono and bis complexes with GMP bound via N(7). As the pH is increased for solutions with r (Pt(II):phosphate) = 0.5, proton transfer from the phosphate occurs from pH 5 to 7 (D_2O) and from the N(1)–H above pH 9. The decrease in pK, N(1)–H, which is a measure of the inductive effect of the platinum(II) complex, is 0.3, 0.6 log unit for *cis*- and *trans*-$(H_3N)_2Pt^{II}$, respectively. This is much smaller than ΔpK for N(7) methylation, 2.5 log units. N(7) platination has a much smaller effect on the electron distribution and chemical reactivity of 5′-GMP than either protonation or methylation. The use of Raman spectra to assign binding sites is outlined. As the r value is increased above 0.5, pH ≥7, quite different reactions are observed for the cis and trans isomers. *trans*-$(H_3N)_2Pt^{II}$ appears at r = 1 to form primarily a mononuclear complex with N(7) binding. At pH >9, the principal species is *trans*-$[(H_3N)_2Pt(OH)(GMPH_{-1})]^{2-}$. When r = 2, $[\{trans\text{-}(H_3N)_2Pt(OH)\}_2GMPH_{-1}^{-}]$ with N(1)–N(7) binding is produced. *cis*-$(H_3N)_2Pt^{II}$ or $enPt^{II}$ at r = 1 causes a large decrease in the N(1)–H pK, >2.8 log units, as has been observed to occur also with inosine. Solubility is much lower than in the trans system. Possible structures for the product of this unique *cis*-$(H_3N)_2Pt^{II}$ interaction are discussed. A cooperative process involving deprotonation, the formation of N(1), N(7) or O(6) interactions, and a rather high degree of polymerization is suggested for the product $[cis\text{-}(H_3N)_2Pt(GMPH_{-1})^{-}]_n$. The data indicate that N(7) is a strong nucleophile for platinum(II), but because $(H_3N)_2Pt(OH)_2$, a poor electrophile, is produced at high pH, attack on deprotonated GMP at N(7) is not favorable and at N(1) it is even less so. Reactions of *cis*-$(H_3N)_2Pt^{II}$ with poly(rG) at 37 °C are very slow because of the multistranded, strongly hydrogen-bonded structure of poly(rG). The *cis*-$(H_3N)_2Pt^{II}$ appears to be strongly hydrogen bonded to the polymer via the ammine ligands.

A number of experiments have indicated that the guanine base is probably the preferred site of electrophilic attack by *cis*-$[PtCl_2(NH_3)_2]$ on native polynucleotides. Mansy[4] reported that the rate of reaction with DNAs increased with increasing G + C content, Stone et al.[5] found that the increase in buoyant density upon reaction was proportional to G + C content, and Munchausen and Rahn[6] found, using ^{195m}Pt, an increase in platinum binding with increasing G + C content.

Because different experiments have pointed to the guanine base as the preferred binding site for platinum(II) complexes, considerable attention has been focused on the mode of binding. The two isomers, *cis*- and *trans*-$[PtCl_2(NH_3)_2]$, exhibit quite different physiological effects,[7] although the only chemical experiment of which we are aware that shows a difference is the DNA binding study of Grant et al.[8] where cis but not trans binding was observed. Although there are many possible explanations for the different physiological behavior of these two isomers, almost all attention has been directed to potential stereochemical differences in their binding to the guanine base. Lately, there have been several publications that suggest the important difference is the ability of *cis*-$(H_3N)_2Pt^{II}$ to form an intramolecular N(7)–O(6) chelate in its binding to the guanine base,[9-11] thereby altering interbase hydrogen bonding. It would be very interesting if the physiological difference between these isomers has its origin in such a simple stereochemical effect.

Although metal ion chelation involving the guanosine or inosine N(7)–O(6) atoms has been proposed many times, it generally has been rejected on steric grounds.[12] Recently, Szalda, Kistenmacher, and Marzilli[13] synthesized a theophyllinato-Cu^{II} complex in which such an interaction was forced. The crystal structure showed a Cu–N(7) distance of 1.956 (3) Å, while the Cu–O(6) distance was much longer, 2.919 (3) Å. Chelation has been suggested both with the neutral guanosine and in some cases for the N(1) deprotonated conjugate base. In a detailed spectroscopic study of the *cis*-$(H_3N)_2Pt^{II}$–inosine reaction in dilute aqueous solution, we found no evidence for such an intramolecular interaction at any pH.[14] In the case of the binding of *cis*-$(H_3N)_2Pt^{II}$, the evidence presented for N(7)–O(6) chelation appears to be summarizable as follows.

(1) The N(7)–O(6) chelation was first proposed for $(H_3N)_2Pt^{II}$ and the neutral guanine by Goodgame et al.[9] in a paper dealing with the structure of $[Pt(NH_3)_2(5'\text{-}IMP)_2]^{2-}$. It should be noted that the crystal structure showed *only* interaction at N(7) of inosine.

(2) The oxygen 1s binding energy is reported to be 532.7 eV for DNA, 532.3 eV for DNA + *trans*-$[PtCl_2(NH_3)_2]$ (r = 0.82), and 531.7 eV for DNA + *cis*-$[PtCl_2(NH_3)_2]$ (r = 0.82).[10a] The decrease in binding energy of ca. 1.0 eV was attributed to a "chelation of Pt with the N(7) Gua and O(6) Gua sites". It should be noted that the guanine O(6) would be expected to contribute approximately 4% of the intensity of the oxygen 1s envelope, since this is due to the phosphate diester oxygens plus those on cytosine and thymine as well as guanine O(6). Consequently, a shift in the oxygen binding energy does not seem to point to a specific interaction with the guanosine O(6).

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