

107. Synthesis of 9-*epi*-Quinine and 9-*epi*-Quinidine

Preliminary communication¹⁾

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Zusammenfassung. Die stereoselektive Synthese der beiden Cinchona-Nebenalkaloide 9-*epi*-Chinin (**14**) und 9-*epi*-Chinidin (**15**) wird beschrieben.

The minor cinchona alkaloids 9-*epi*-quinine (**14**) and 9-*epi*-quinidine (**15**) are characterized by their 8,9-*threo*^{2a)} configurations, *i.e.* 8*S*, 9*S* and 8*R*, 9*R* arrangements. They have been accessible in minute quantities from natural sources [1], or as the by-products in the synthesis of quinine and quinidine [2]. We now report a stereoselective synthesis of these two alkaloids.

As the precursor of the quinuclidine part of these alkaloids we have used the classical intermediate N-benzoyl-homomeroquinene (**6**) [2c], which was prepared *via* photolytic rearrangement of the N-chloramine derivative **2** of the known 3-(3*R*)-ethyl-4*R*-piperidinyl)-propionic acid ethyl ester (**1**) [3]. The photolysis was carried out in trifluoroacetic acid solution with a 200 W *Hanovia* high pressure mercury lamp. The resulting crude trifluoroacetate salt of **3** was allowed to react with benzoyl chloride in the presence of potassium carbonate which was added at such a rate as to maintain neutrality³⁾. Subsequent column chromatography on silica gel gave the pure amide **4⁴⁾** as an oil in 75% yield [b.p. 150°/0.02 Torr⁵⁾]; IR. (CHCl₃): 1730, 1628 cm⁻¹; mass spectrum (70 eV): *m/e* 351 (*M*⁺), 316 (*M* – Cl); [α]_D²⁵ = +20.2° (*c* = 1.09, CH₃OH). The introduction of the double bond was achieved by various routes. The most efficient one [4] consisted of a reaction sequence involving saponification of **4**, dehydrochlorination of the acid **5** with potassium *t*-butoxide in dimethylsulfoxide/benzene, and esterification of the resulting acid **6** to give the desired N-benzoyl-homomeroquinene ethyl ester⁶⁾ (**7**) in 70% overall yield [b.p. 115°/0.02 Torr⁷⁾]; IR. (CHCl₃): 1730, 1625, 1003, and 928 cm⁻¹; NMR. (CDCl₃): δ 5.12 (*m*, 2H, CH=CH₂),

¹⁾ Details will be published in J. org. Chemistry.

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^{2a)} Numbering according to Chemical Abstracts; following the IUPAC rules, the substituted carbon atom in α -position to the quinuclidine uitsagen would be number 2.

³⁾ Under alkaline conditions compound **3** cyclizes to (4*R*, 5*R*)-1-azabicyclo[3.2.1]octane-4-propionic acid ethyl ester.

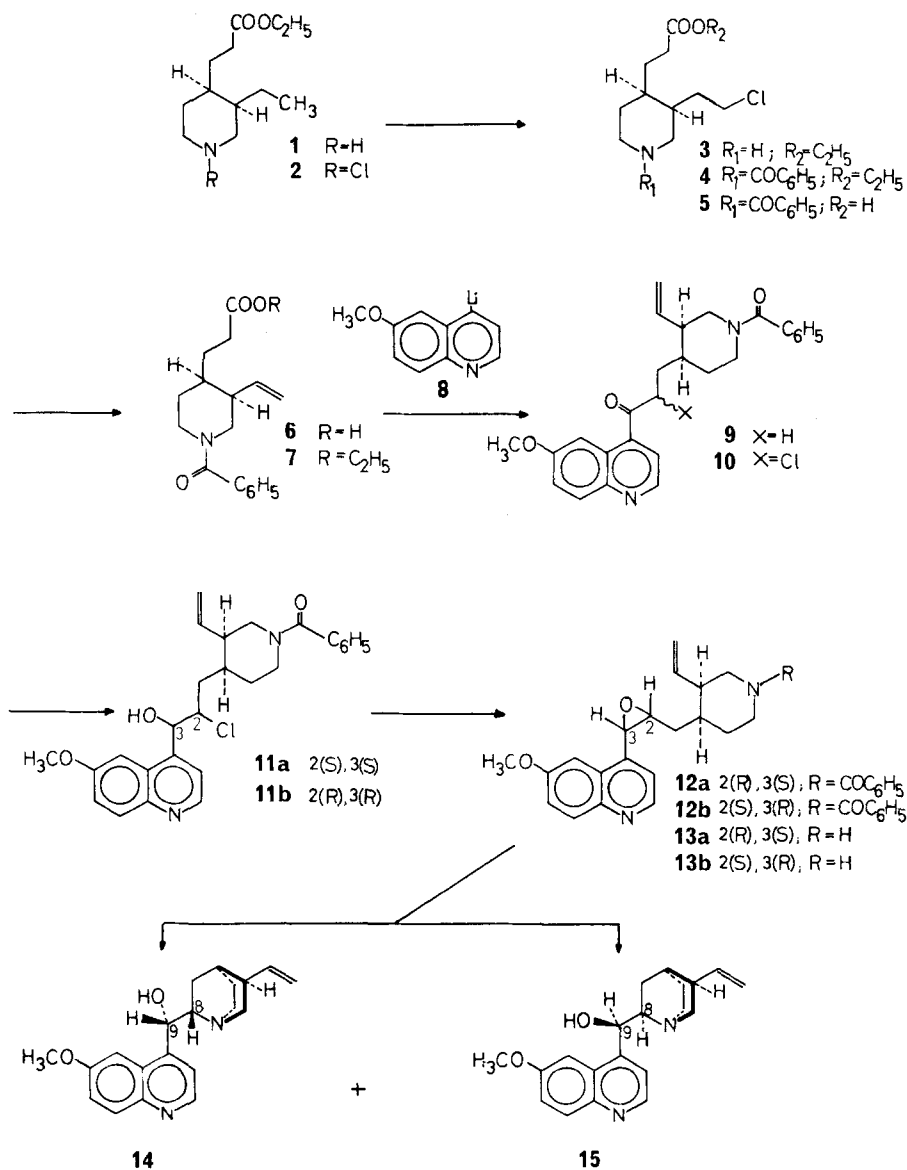
⁴⁾ All new compounds gave satisfactory elemental analyses and the spectroscopic data were in agreement with the structures assigned.

⁵⁾ Distillations were carried out in a molecular distillation apparatus; the temperatures given are heating block temperatures.

⁶⁾ Other methods consisted of the pyrolysis of **4** to **7**, and of the dehydrohalogenation *via* the iodo derivative **4** (I instead of Cl).

⁷⁾ *R. B. Woodward & W. E. Doering* [2c] reported b.p. 134–145°/0.08 Torr for the racemic compound.

Scheme 1



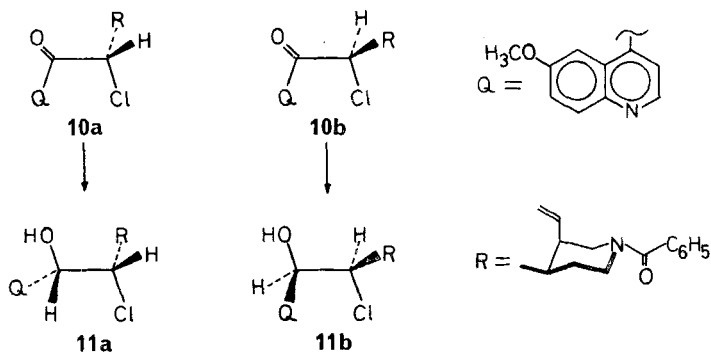
ca. 5.85 (*m*, 1H, $CH=CH_2$); mass spectrum (70 eV): m/e 315 (M^+); $[\alpha]_D^{25} = +35.8^\circ$ ($c = 0.97$, CH_3OH)⁸⁾. Hydrolysis of the ester and N-benzoyl groups with potassium hydroxide in boiling methanol yielded crystalline homo-meroquinene [m.p. 210–211° from methanol/acetone; $[\alpha]_D^{25} = +43.6^\circ$ ($c = 1.052$, H_2O)⁹⁾.

⁸⁾ The same sequence of reactions was also carried out in the racemic and enantiomeric series. The racemic chloro derivative **4** crystallized on standing, m.p. 53–55° from pentane/ether.

⁹⁾ M. Proštenik & V. Prelog [2b] reported m.p. 211–212° and $[\alpha]_D^{20} = +50.4^\circ$ ($c = 1.906$, H_2O).

It was anticipated that the formation of the 8,9-*threo* alkaloids 9-*epi*-quinine (**14**) and 9-*epi*-quinidine (**15**) could be achieved stereospecifically from the *cis* epoxides **13** (2*R*,3*S*, and 2*S*,3*R*) by forming the quinoclidine ring with simultaneous epoxide opening. The synthesis of these compounds required the preparation of the *threo* chlorohydrins **11a** (2*S*,3*S*) and **11b** (2*R*,3*R*), which were to be obtained by reduction of the epimeric α -chloro-ketones **10a** (2*S*) and **10b** (2*R*). It was expected [5] that the α -chloro-ketones would react largely in the antiparallel conformations **10a** and **10b**, and that steric hindrance would favor hydride attack from the side of the carbonyl group shielded by hydrogen.

Scheme 2



The required N-benzoyl-quinotoxine **9** [m.p. 109–110° (ether); $[\alpha]_D^{25} + 42.44^\circ$ ($c = 0.382$, CH_3OH); IR. (CHCl_3): 1693, 1622, 998, and 928 cm^{-1} ; mass spectrum (70 eV) m/e 428 (M^+), 105 (base peak)] was obtained in 30–35% yield by condensation of N-benzoyl-homomeroquinene ethyl ester (**7**) and 6-methoxy-4-quinollythium (**8**). α -Keto chlorination, without attack at the vinyl group or at the aromatic rings, was accomplished utilizing N-chlorodiisopropylamine [6] in 100% phosphoric acid in the dark. This gave an amorphous mixture of the epimeric α -chloro-ketones **10** [IR. (CHCl_3): 1726, 1610, 1003 and 935 cm^{-1} ; $[\alpha]_D^{25} = +45.8^\circ$ ($c = 1.0$, CHCl_3)] in 80% yield. Reduction with sodium borohydride (ethanol, 0°C) or with lithium tri-*t*-butoxyaluminum hydride (tetrahydrofuran, -78° to 20°) afforded stereoselectively a mixture of the *threo* chlorohydrins **11** [amorphous; $[\alpha]_D^{25} = +52.0^\circ$ ($c = 1.04$, CHCl_3)]. Treatment of **11** with aqueous potassium hydroxide at 20° gave smoothly a mixture of the *erythro*-N-benzoylepoxides **12** [amorphous; $[\alpha]_D^{25} = +57.3^\circ$ ($c = 0.956$, CHCl_3); mass spectrum (70 eV) m/e 428 (M^+)]. The benzoyl group was removed reductively with diisobutylaluminum hydride in toluene at -78° to give the amino epoxides **13** [mass spectrum (70 eV) m/e 324 (M^+), m/e 136 (base peak)] which were cyclized in refluxing toluene/methanol 100:1. This reaction yielded 9-*epi*-quinine (**14**) [7] [neutral dibenzoyl-*d*-tartrate hydrate, m.p. 155–158° (dec.); $[\alpha]_D^{25} = -24.3^\circ$ ($c = 0.93$, $\text{C}_2\text{H}_5\text{OH}$)] and 9-*epi*-quinidine (**15**) [7] [m.p. 111–113°; $[\alpha]_D^{25} = +107.8^\circ$ ($c = 1.02$, $\text{C}_2\text{H}_5\text{OH}$)] in a ratio of 2:1 after chromatographic purification. The overall yield of **14** and **15** from **11** was 50%. Only traces of the *erythro* products quinine and quinidine were observed.

Alternatively, the same 2:1 mixture of 9-*epi*-quinine (**14**) and 9-*epi*-quinidine (**15**) could be obtained in 57% yield upon exposure of the chlorohydrins **11** to hot aqueous methanolic potassium hydroxide.

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