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

Preliminary communication[1])

by **G. Grethe, J. Gutzwiller**[2]), **H. L. Lee** and **M. R. Uskoković**

Chemical Research Department, *Hoffmann-La Roche Inc.*,
Nutley, New Yersey 07110, USA

(11. II. 72)

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 neutrality[3]). Subsequent column chromatography on silica gel gave the pure amide **4**[4]) as an oil in 75% yield [b.p. 150°/0.02 Torr[5]); IR. ($CHCl_3$): 1730, 1628 cm^{-1}; mass spectrum (70 eV): *m/e* 351 (M^+), 316 ($M - Cl$); $[\alpha]_D^{22} = +20.2°$ ($c = 1.09$, CH_3OH)]. 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 ester[6]) (**7**) in 70% overall yield [b.p. 115°/0.02 Torr[7]); IR. ($CHCl_3$): 1730, 1625, 1003, and 928 cm^{-1}; NMR. ($CDCl_3$): δ 5.12 (*m*, 2H, $CH{=}CH_2$),

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

[2]) Present address: Chemische Forschungsabteilung der *F. Hoffmann-La Roche & Co. AG*, Basel.

[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.

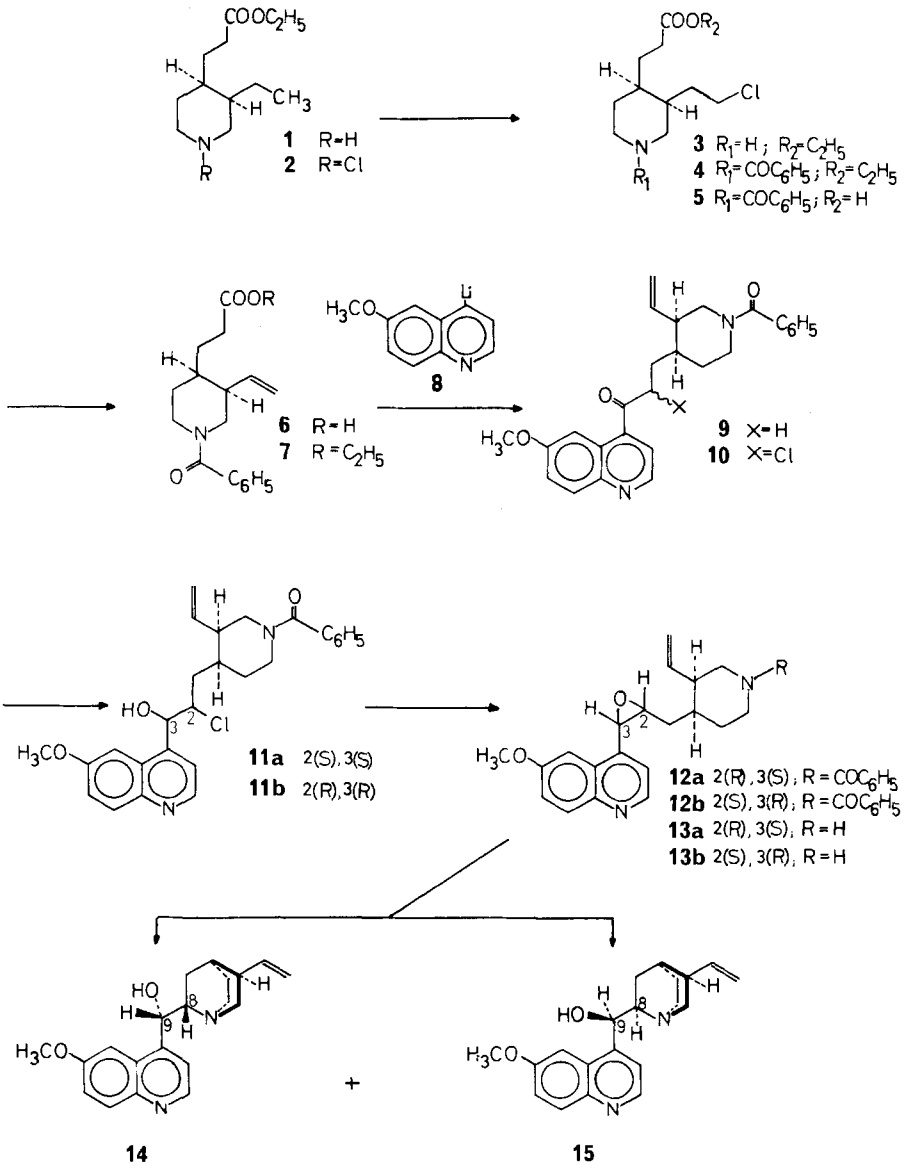
[4]) All new compounds gave satisfactory elemental analyses and the spectroscopic data were in agreement with the structures assigned.

[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



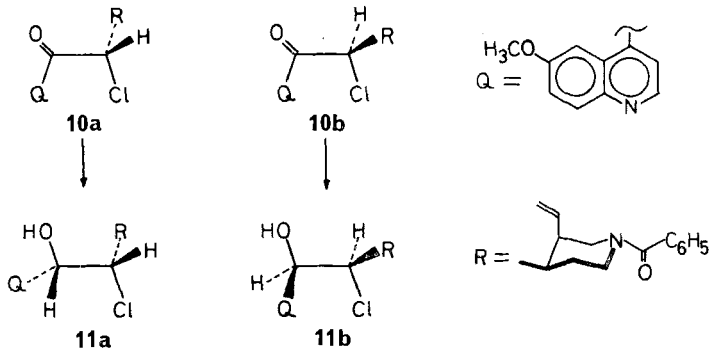
ca. 5.85 (*m*, 1H, C*H*=CH$_2$); mass spectrum (70 eV): *m/e* 315 (M^+); $[\alpha]_D^{25} = +35.8°$ ($c = 0.97$, CH_3OH)][8]). Hydrolysis of the ester and N-benzoyl groups with potassium hydroxide in boiling methanol yielded crystalline homo-meroquinene [m.p. 210–211° from methanol/acetone; $[\alpha]_D^{25} = +43.6°$ ($c = 1.052$, 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. Prošťenik & V. Prelog* [2b] reported m.p. 211–212° and $[\alpha]_D^{20} = +50.4°$ ($c = 1.906$, 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 quinuclidine 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); $[\alpha]_D^{25} + 42.44°$ ($c = 0.382$, 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-quinolyllithium (**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}; $[\alpha]_D^{25} = +45.8°$ ($c = 1.0$, $CHCl_3$)] in 80% yield. Reduction with sodium borohydride (ethanol, 0°C) or with lithium tri-*t*-butoxyaluminium hydride (tetrahydrofuran, −78° to 20°) afforded stereoselectively a mixture of the *threo* chlorohydrins **11** [amorphous; $[\alpha]_D^{25} = +52.0°$ ($c = 1.04$, $CHCl_3$)]. Treatment of **11** with aqueous potassium hydroxide at 20° gave smoothly a mixture of the *erythro*-N-benzoylepoxides **12** [amorphous; $[\alpha]_D^{25} = +57.3°$ ($c = 0.956$, $CHCl_3$); mass spectrum (70 eV) *m/e* 428 [M^+)]. The benzoyl group was removed reductively with diisobutylaluminium 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.); $[\alpha]_D^{25} = -24.3°$ ($c = 0.93$, C_2H_5OH)] and 9-*epi*-quinidine (**15**) [7] [m.p. 111–113°; $[\alpha]_D^{25} = +107.8°$ ($c = 1.02$, C_2H_5OH)] 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.

BIBLIOGRAPHY

[1] *P. Rabe*, Ber. deutsch. chem. Ges. *74*, 725 (1941).
[2] a) *P. Rabe & K. Kindler*, Ber. deutsch. chem. Ges. *51*, 466 (1918); b) *M. Prošťenik & V. Prelog*, Helv. *26*, 1965 (1943); c) *R. B. Woodward & W. E. Doering*, J. Amer. chem. Soc. *67*, 860 (1945); d) *M. Uskoković, J. Gutzwiller & T. Henderson, ibid. 92*, 203 (1970); *J. Gutzwiller & M. Uskoković, ibid. 92*, 204 (1970); e) *M. Gates, B. Sugaranam & W. L. Schreiber, ibid. 92*, 205 (1970); f) *G. Grethe, H. L. Lee, T. Mitt & M. R. Uskoković, ibid. 93*, 5904 (1971).
[3] *P. Rabe, W. Huntenberg, A. Schultze & G. Volger*, Ber. deutsch. chem. Ges. *64*, 2487 (1931).
[4] *M. Uskoković, C. Reese, H. L. Lee, G. Grethe & J. Gutzwiller*, J. Amer. chem. Soc. *93*, 5902 (1971).
[5] *J. W. Cornforth, R. H. Cornforth & K. M. Mathew*, J. chem. Soc. *1959*, 112, 2539.
[6] *N. C. Deno, R. Fishbein & J. C. Wyckoff*, J. Amer. chem. Soc. *93*, 2065 (1971).
[7] The Merck Index, 8th edition, *P. G. Stecher*, Ed., p. 411, 412, Merck & Co., Inc., Rahway, N.J., 1968.

Nato Advanced Institute on Chemistry of Insects

Villa Monastero, Varenna (Lago di Como) Italy, 14–19 September 1972

Eight Plenary Lectures on Insect Chemistry. To write to *Prof. Dr. M. Viscontini*, Organisch-chemisches Institut der Universität, CH–8001 Zürich, Rämistrasse 76

Preis des Schweizerischen Chemiker-Verbandes

Verleihung anlässlich des I. Internationalen Symposiums über Säulen-Flüssigchromatographie, Interlaken, 2., 3. und 4. Mai 1973, für eine hervorragende Arbeit auf dem Gebiet der

Chromatographie

Auskünfte + Bewerbungen bis spätestens 30. September 1972 mit zweifacher Ausführung der Arbeiten an *Prof. Dr. W. Simon*, ETH, Laboratorium für Organische Chemie, Universitätsstrasse 6/8, 8006 Zürich.