50 ml of conc. HCl the mixture was kept at reflux for 20 h. The cooled solution was washed with ether, rendered alkaline by the addition of 6N NaOH, and extracted twice with an ether/benzene mixture. The combined extract was dried (Na_2SO_4) and evaporated to dryness. The residue (549 mg) was dissolved in a minimal amount of acetone and combined with a concentrated solution of 744 mg (0.0021 mol) of di-O-benzoyl-(+)-tartaric acid in acetone. The mixture was evaporated to dryness, the residue was washed with ether several times, and two crystallizations from acetone/methanol yielded 190 mg (15.7%) of the neutral *di-O-benzoyl-(+)-tartrate of quinotoxine* (**18**): m.p. 184.5–185.5°; $[\alpha]_D^{25} = -16.2°$ ($c = 1.00$, $CHCl_3/C_2H_5OH$ 2:1) [2]; mixed m.p. with authentic sample: 184.5–185.5°.

Quinotoxine (**18**) *from* **17**. A solution of 150 mg (0.35 mmol) of **17** in 15 ml of 2N KOH (CH_3OH/H_2O, 3:1) was kept at reflux temperature for 40 h, by when the starting material had disappeared. The reaction mixture was diluted with 30 ml of water and the methanol removed under reduced pressure. The remaining aqueous solution was extracted several times with dichloromethane. The combined extract was washed with water and extracted three times with 1N oxalic acid. The acidic solution was washed with ether, rendered alkaline by the addition of ammonium hydroxide and extracted several times with methylene chloride. The combined extract was dried (Na_2SO_4) and evaporated to dryness under reduced pressure to yield 101 mg of crude **18**. A solution of this material in 2 ml of acetone was added to a solution of 65 mg of di-O-benzoyl-(+)-tartaric acid [$[\alpha]_D^{25} = -115°$ ($c = 1.0$, CH_3OH)] in 2 ml of acetone. Sufficient methanol was added to the suspension to give a clear solution. Upon standing at room temperature, 57 mg of the yellow crystalline neutral *di-O-benzoyl-(+)-tartrate of quinotoxine* (**18**) were obtained, m.p. 180–183°. Recrystallization from methanol raised the m.p. to 184–185°; $[\alpha]_D^{25} = -19.7°$ ($c = 0.985$, $CHCl_3/C_2H_5OH$ 2:1); mixed m.p. with material obtained by method A, 184–185°.

REFERENCES

[1] *P. Rabe*, Ber. deutsch. chem. Ges. *44*, 2088 (1911); *P. Rabe & K. Kindler ibid. 51*, 466 (1918).
[2] *P. Rabe, W. Huntenberg, A. Schultze & G. Volger*, Ber. deutsch. chem. Ges. *64*, 2487 (1931).
[3] *M. Prošťenik & V. Prelog*, Helv. *26*, 1965 (1943).
[4] *R. B. Woodward & W. E. Doering*, J. Amer. chem. Soc. *65*, 860 (1950).
[5] *J. Gutzwiller & M. R. Uskoković*, Helv. *56*, 1494 (1973).
[6] *M. E. Wolff*, Chem. Rev. *63*, 55 (1963).
[7] *M. V. Rubtsov*, Ž. obšč. Chim. *30*, 1498 (1960).
[8] *M. Uskoković, C. Reese, H. L. Lee, G. Grethe & J. Gutzwiller*, J. Amer. chem. Soc. *93*, 5902 (1971).
[9] *W. v. Miller & G. Rohde*, Ber. deutsch. chem. Ges. *33*, 3214 (1900).

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146. Reinvestigation of the Classical Synthesis of *Cinchona* Alkaloids. II. The Synthesis of Quinine and its Naturally Occurring Diastereomers from Quinotoxine[1])

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(5. IV 73)

Zusammenfassung. Stereoselektive Synthesen der *Cinchona* Alkaloide Chinin (**6**) und seiner natürlich vorkommenden Diastereomeren **7**, **8** und **9**, ausgehend von Chinotoxin (**2**), werden beschrieben. Reduktion der Ketone **4** und **5** mit DIBAL ergibt ausschliesslich die C(8)–C(9)

[1]) Reported in part as a short communication: *G. Grethe, J. Gutzwiller, H. L. Lee & M. R. Uskoković*, Helv. *55*, 1044 (1972).

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

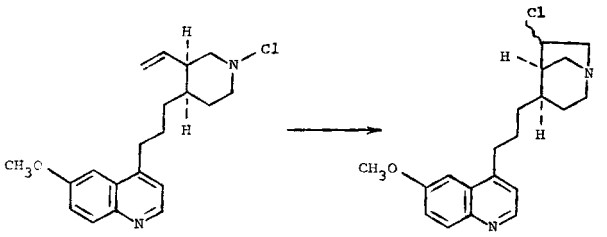
erythro-Verbindungen Chinin und Chinidin, während Reduktion von **5** mit Natriumborhydrid ausnahmslos zu den *epi*-Verbindungen **8** und **9** führt. Die letztgenannten Verbindungen werden selektiv auch auf einem anderen Weg über die *erythro*-Epoxide **20** und **21** erhalten.

Quinotoxine has played a key role in the history of *Cinchona* alkaloid syntheses [1]. In the course of the pioneering work of *Rabe* [2], methods were developed to convert quinotoxine to quinine and quinidine. Based on this conversion, quinotoxine later became the relay compound in the partial synthesis of quinine and quinidine by *Prelog* [3] and in the subsequent, total synthesis by *Woodward* [4]. In the preceding paper [5] we described a new synthetic route to quinotoxine. This paper deals with efficient, partially stereoselective methods for the conversion of quinotoxine either to quinine and quinidine, or to the minor *Cinchona* alkaloids 9-*epi*-quinine and 9-*epi*-quinidine.

The presence of the vinyl group in quinotoxine (**1**) significantly limits the use of halogenation reactions in the cyclization to quininone (**4**) and quinidinone (**5**). After extensive experimentation with different halogenating agents, we found that N-chloroquinotoxine (**3**) could be readily prepared by treatment with sodium hypochlorite. The N-chloramine **3** was cyclized by treatment with a strong non-nucleophilic mineral acid and subsequent work-up under basic conditions. This reaction presumably proceeds *via* intramolecular α-chlorination with the chloraminium ion **10** acting as a source of positive chlorine. A radical mechanism does not seem to be involved since the reaction is not catalyzed by light, not inhibited by hydroquinone and does not show the kinetic behavior of a radical chain reaction. Furthermore, no by-products were observed which would result from radical attack at the vinyl group[3]. That 8-chloroquinotoxine (**11**) is an intermediate is supported by effecting the cyclization using an external chloramine, N-chloro-diisopropylamine in concentrated phosphoric acid, followed by basic work-up.

A peculiarity of the *Cinchona* ketones is their extremely easy epimerisation, which causes their characteristic mutarotation[4]. Thus, in equilibrated solutions, ketones **4** and **5** exist as an approximately 1:1 mixture. However, essentially complete con-

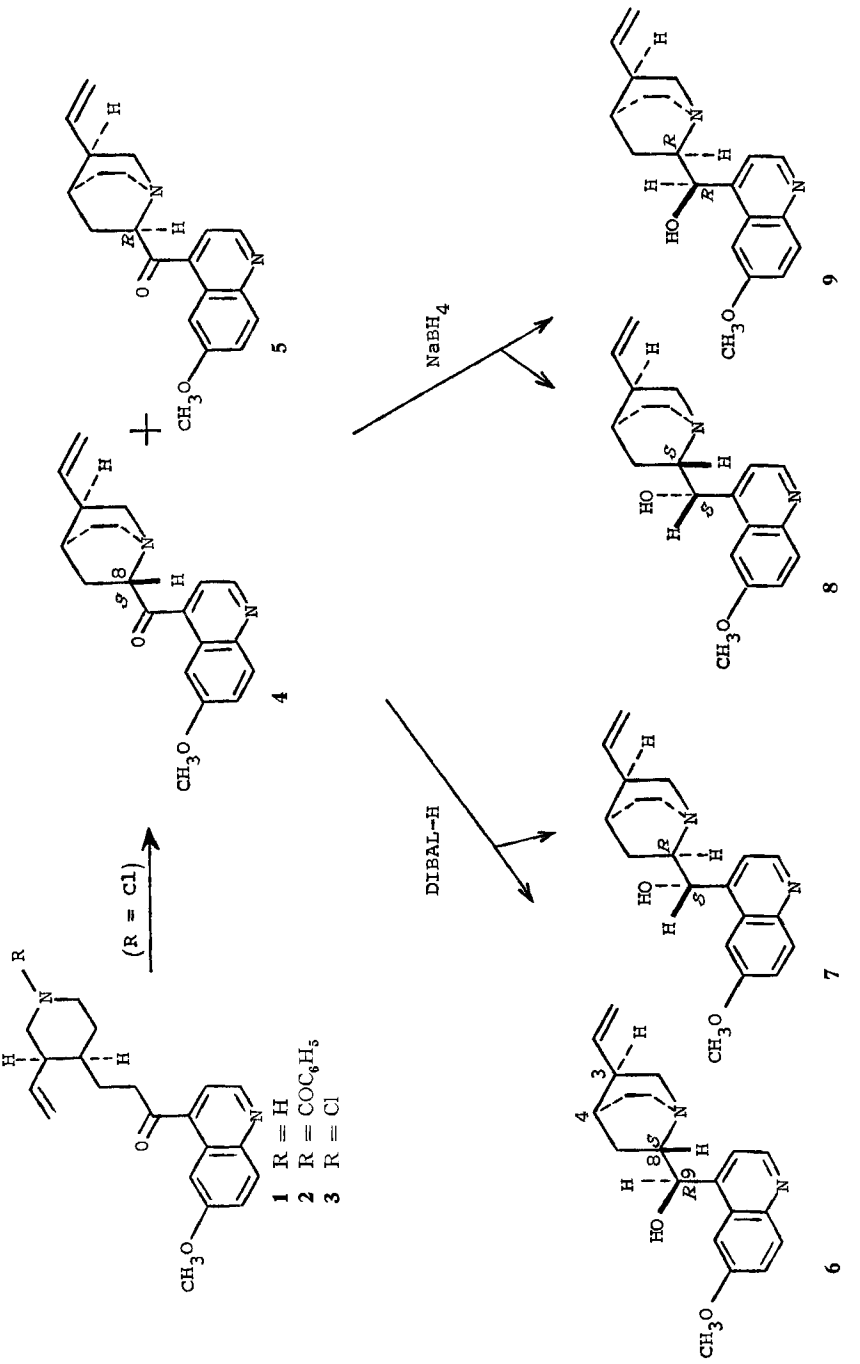
[3] When the deoxy-chloramine **i**, was heated at 45° in phosphoric acid in the presence of ferrous sulfate, a radical addition to the vinyl group occurred with cyclization to give the chloro compound **ii**.



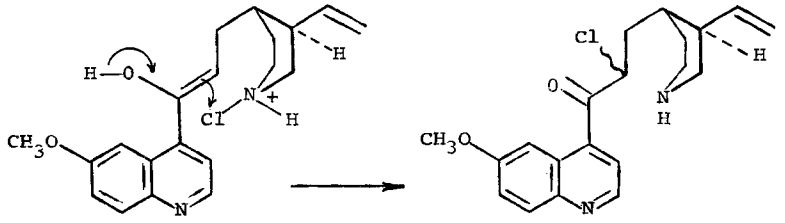
i **ii**

[4] The half-life of the equilibration of dihydroquinidinone, which is the epimer obtained in pure form by analogous crystallization in the dihydro series, was determined in various solvents. It ranged from 24 min in ethanol to 24 h in cyclohexane, as determined by measuring the rate of mutarotation.

Scheme 1



Scheme 2

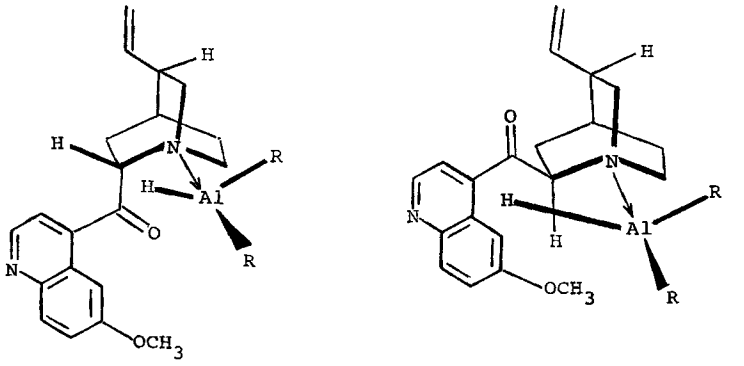


10 **11**

version to the less soluble epimer quinidinone (**5**) with 8(*R*)-configuration can be effected by crystallization [6].

The configuration of two [3(*R*),4(*S*)] of the four asymmetric carbon atoms of quinine (**6**) and its diastereomers **7**, **8**, **9** is determined by the configuration of the starting N-benzoyl-homomeroquinene ethyl ester [5], and the configuration of the two remaining centers C(8) and C(9) is fixed in the last step of this synthesis. Reduction of ketones **4** and **5** with diisobutylaluminum hydride (DIBAL-H) in anhydrous benzene leads selectively to the C(8)-C(9) *erythro* pair, quinine [**6**; 8(*S*),9(*R*)] and quinidine [**7**; 8(*R*),9(*S*)], respectively. This *Lewis* acid presumably first complexes with the quinuclidine nitrogen of **4** and **5**, and the resulting complexes in their most extended conformation (**12** and **13**) are responsible for the stereoselectivity of the subsequent reduction step.

Scheme 3



12 **13**

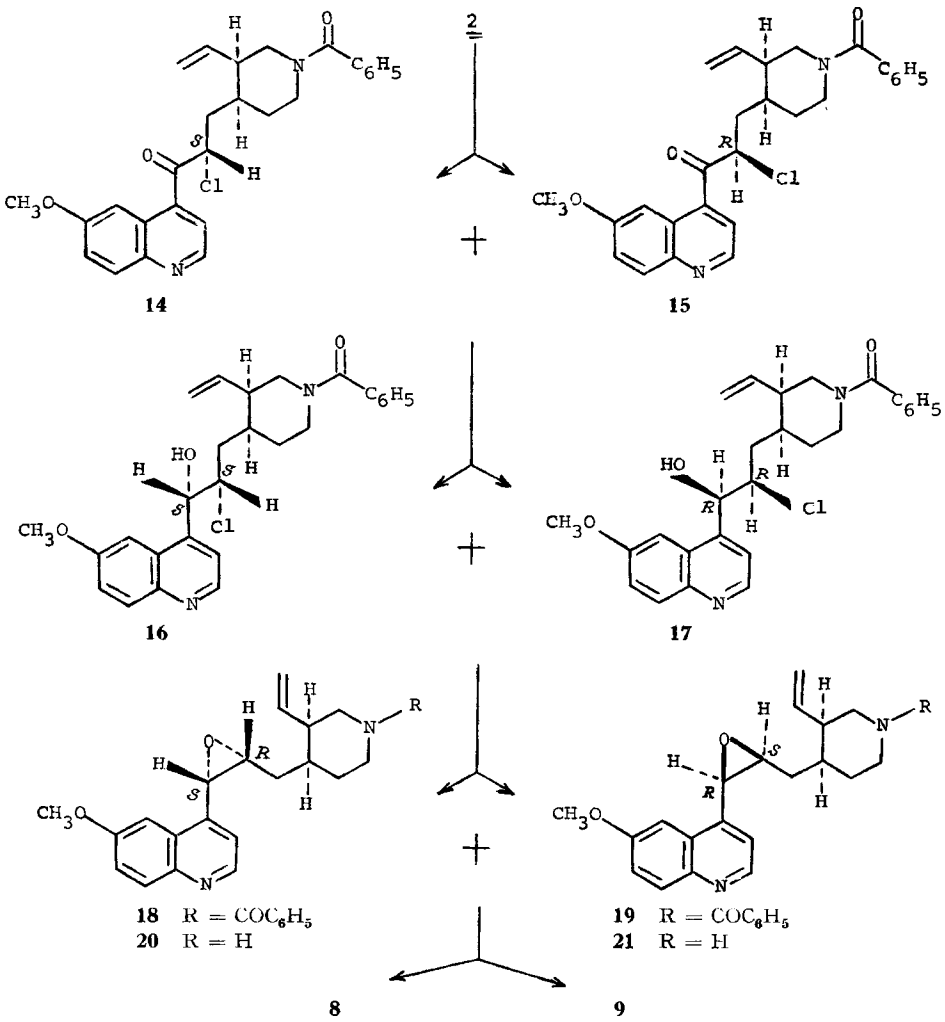
Thus, either pure quinidine (**7**) or a *ca.* 1:1 mixture of quinine (**6**) and quinidine (**7**) can be prepared by this method.

On the other hand, sodium borohydride reduction of quinidinone (**5**) in ethanol gives stereoselectively in high yield the C(8)-C(9) *threo* pair, 9-*epi*-quinine [**8**; 8(*S*),9(*S*)] and 9-*epi*-quinidine [**9**; 8(*R*),9(*R*)]. This indicates that under these conditions the ketone is first epimerized at C(8), and then reduced by hydride attack from the presumably less hindered side.

In an alternative synthesis [7], 9-*epi*-quinine (**8**) and 9-*epi*-quinidine (**9**) are formed by a simultaneous quinuclidine cyclization and ring opening of the *cis,erythro*-epox-

ides **20** and **21** (Scheme 4). Chlorination of N-benzoquinotoxine (**2**) with N-chlorodiisopropylamine in 100% phosphoric acid at room temperature in the dark gave smoothly the inseparable epimeric N-benzoyl-8-chloro-quinotoxines **14** and **15** in 80% yield. Reduction with sodium borohydride in ethanol at 0° or with lithium tri-(*t*-butoxy)-aluminum hydride in tetrahydrofuran at −78° afforded stereoselectively a mixture of the *threo*-chlorohydrins **16** and **17**. As was expected [8], the α-chloro-ketones reacted in the anti-parallel conformations **14a** and **15a** in which steric hindrance favored hydride attack from the side of the carbonyl group shielded by hydrogen (Scheme 5). Treatment of the chlorohydrins with aqueous potassium hydroxide at room temperature gave smoothly a mixture of the N-benzoyl-*cis,erythro*-epoxides **18** and **19**. The benzoyl group was removed reductively with diiso-

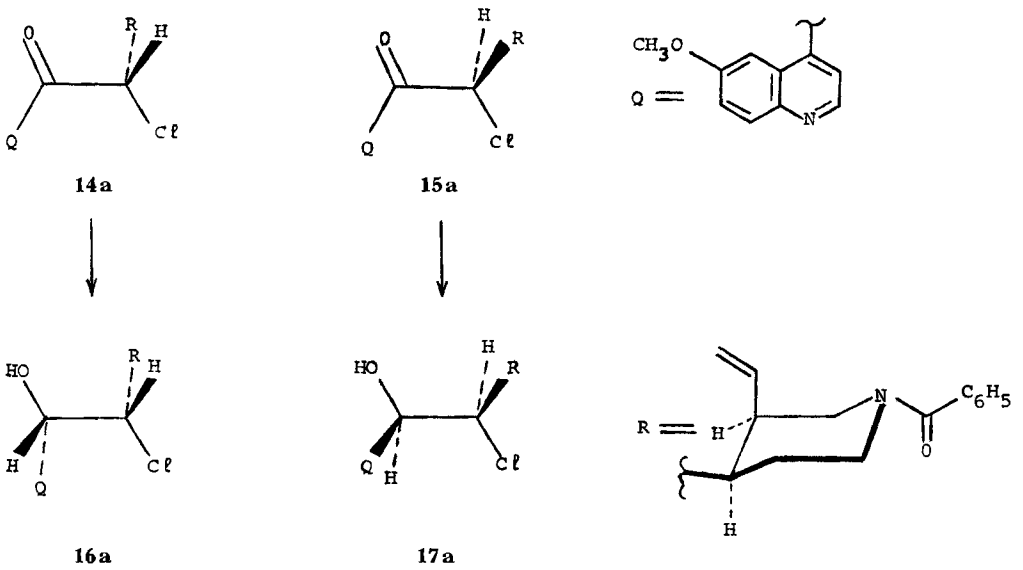
Scheme 4



butylaluminum hydride in toluene at $-78°$ to give the amino epoxides **20** and **21**, which were cyclized in refluxing toluene/methanol 100:1. This reaction led to 9-*epi*-quinine (**8**) and 9-*epi*-quinidine (**9**) in a ratio of 2:1 after chromatographic purification. The overall yield of **8** and **9** from the chlorohydrins **16** and **17** was 50%. Only traces of the *erythro* products quinine and quinidine were observed. The conversion of **16** and **17** to the same 2:1 mixture of **8** and **9** was also accomplished by a single operation. Thus, treatment of the *threo*-chlorohydrins in boiling methanolic aqueous potassium hydroxide effected epoxide formation, hydrolytic debenzoylation and cyclization to give 9-*epi*-quinine (**8**) and 9-*epi*-quinidine (**9**) in 57% yield.

The four diastereomeric alkaloids can be identified on the basis of their TLC. Rf values, the *erythro* pair being more polar than the *threo* pair. Separation by crystallization [9] and partial separation by chromatography [10] is described in the literature. Quinine (**6**) was crystallized as the neutral (+)-tartrate hydrate, which lost its water of crystallization on prolonged drying. Quinidine (**7**) crystallized as an ethanolate from ethanol, and the solvent was lost after prolonged drying. The two *erythro* bases, **6** and **7**, are best identified by their characteristic ORD. data and specific rotations. The *threo* diastereomers **8** and **9** were separated by preparative TLC. Their main spectral characteristic is the NMR. absorption of 9-H, a doublet at *ca.* δ 5 with J value of *ca.* 10 Hz. 9-*epi*-Quinidine (**9**) can be obtained in crystalline form, and the amorphous 9-*epi*-quinine (**8**) was fully characterized in the form of either its acidic or neutral di-O-benzoyl-(+)-tartrate.

Scheme 5



Experimental Part

M.p. were taken on a *Kofler* hot stage or on a *Thomas-Hoover* melting point apparatus and are not corrected. IR. spectra were determined either on a *Beckman* IR-9 or IR-12 spectrophotometer. The UV. spectra were recorded on a *Cary* 14M spectrophotometer, the NMR. spectra on a *Varian*

A-60 or HA-100 spectrophotometer using TMS as internal standard. The mass spectra were taken with a CEC 21–110 mass spectrometer at 70 eV using a direct insertion probe. *Merck* silica gel GF_{254} was used as sorbent for preparative layer (2 mm) chromatography. Usual work-up means washing the organic phase with water or brine solution, drying over anhydrous sodium sulfate for chloroform or dichloromethane, or over anhydrous magnesium sulfate for ethereal solutions, and evaporation to dryness *in vacuo*.

Quininone (**4**) *and Quinidinone* (**5**) *from Quinotoxine* (**1**). To a solution of 2,6 g (8 mmol) of quinotoxine (**1**) in 100 ml of dichloromethane were added 15 ml of a *ca.* 17% aqueous sodium hypochlorite solution, and the mixture was stirred vigorously at 20° for 80 min. The organic phase was separated and worked up as usual to give 2.8 g of N-chloroquinotoxine (**3**). This crude chloramine was dissolved in 10 ml of dichloromethane, 30 ml of 100% phosphoric acid were added and the organic solvent was removed under a stream of nitrogen. The homogeneous, viscous solution was kept at 20° for 20 h, water was added, and the aqueous phase rendered alkaline by addition of conc. ammonium hydroxide. After 15 min, the aqueous phase was extracted thoroughly with dichloromethane, and the organic extracts were worked up as usual to give 2,6 g of crude **4** and **5**. This product, in dichloromethane, was filtered through 30 g of neutral alumina, activity II, and finally crystallized from its concentrated ether solution; 1,62 g (62,3%) of *quinidinone* (**5**) were obtained; m.p. 99–100,5°; $[\alpha]_D^{25} = +72{,}6°$ ($c = 0{,}99$, ethanol; after standing in solution for 18 h at 20°); spectroscopically identical with authentic quinidinone. IR. ($CHCl_3$): 1700 cm^{-1} (ketone), 1620 (aromatic), 1000 and 920 (vinyl). UV. max (EtOH): 212/3 nm (ε 38 900); 240 (infl) (16000), 260 (infl) (7100), 343 (4950). NMR. ($CDCl_3$, 60 MHz): δ 3,96 (*s*, 3H, OCH_3); 4,15 (*m*, 1H, 8-*H*); *ca.* 5,1 (*m*, 2H, $=CH_2$); *ca.* 6,0 (*m*, 1H, $-CH=$); 7,41 (*dd*, 1H, $J = 10$ and 3 Hz, 7′—*H*); 7,71 (*m*, 2H, 3′—*H* and 5′—*H*); 8,05 (*d*, 1H, $J = 10$ Hz, 8′—*H*); 8,76 (*d*, 1H, $J = 4.5$ Hz, 2′—*H*).

$C_{20}H_{22}N_2O_2$ (322,41) Calc. C 74,51 H 6,88 N 8,69% Found C 74,73 H 7,04 N 8,59%

Evaporation of mother liquors to dryness gave 0.23 g (9%) of TLC.-pure *mixture of* **4** *and* **5**.

Quinidine (**7**) *from* **5**. To a freshly prepared solution of 0,50 g (1,55 mmol) of quinidinone (**5**) in 30 ml of anhydrous benzene were added 1,4 ml of a *ca.* 25% solution of diisobutylaluminum hydride (DIBAL-H) in toluene in batches while the reaction was monitored by TLC. The reaction was stirred at 20° under nitrogen for 90 min, 2 ml of water/methanol were added, and the mixture was evaporated *in vacuo*. The residue was dissolved in chloroform, washed with 1N sodium hydroxide and brine solution, dried over sodium sulfate and evaporated to give 0,54 g of crude product. Crystallization from ethanol afforded 0,335 g (after drying at 100°/0,1 Torr) of **7**. The mother liquor was separated by prep. TLC. to give an additional 0,140 g (total yield 94%) of **7**; m.p. and mixed m.p. with authentic quinidine 170–171,5°; $[\alpha]_D^{22} = +263{,}6°$ ($c = 0{,}96$; ethanol).

$C_{20}H_{24}N_2O_2$ (324,41) Calc. C 74,04 H 7,46 N 8,64% Found C 74,20 H 7,52 N 8,46%

Quinine (**6**) *and Quinidine* (**7**) *from* **4** *and* **5**. A solution of 1,3 g (4 mmol) of quinidinone (**5**) in 50 ml of methanol was kept at 20° for 3 h. The solvent was stripped, the residue azeotroped with benzene. The amorphous epimeric mixture of quininone (**4**) and quinidinone (**5**) thus obtained was dissolved in 100 ml of anhydrous benzene, and 5,4 ml of a *ca.* 25% solution of DIBAL-H in toluene was added batchwise (60 min) while the reaction was monitored by TLC. 10 ml of water were added, the precipitate removed by filtration, washed thoroughly with methanol, and the combined filtrates were evaporated to dryness. The residue was dissolved in dichloromethane, washed with 1N sodium carbonate, and worked up as usual. The mixture was separated by crystallization into 0,505 g (39%) of *quinidine* (**7**) [crystallized as the free base from ethanol; m.p. and mixed m.p. 170–171,5° (after drying at 100°/0,1 Torr for 90 min); $[\alpha]_D^{25} = +261{,}5°$ ($c = 0{,}845$; ethanol)] and 0,43 g (33%) of *quinine* (**6**), which was crystallized as the less soluble neutral (+)-tartrate monohydrate from ethanol. After drying at 110°/0,1 Torr for 18 h, the anhydrous salt was obtained: m.p. 211–212,5°; $[\alpha]_D^{25} = -156{,}4°$ ($c = 0{,}97$; CH_3OH).

$(C_{20}H_{24}N_2O_2)_2 \cdot C_4H_6O_6$ (800,96) Calc. C 65,98 H 7,05 N 7,00% Found C 65,86 H 7,05 N 6,94%

9-epi-*Quinine* (**8**) *and* 9-epi-*Quinidine* (**9**) *from* **4** *and* **5**. A solution of 0,500 g (1,55 mmol) of quinidinone (**5**) in 50 ml of ethanol was kept at 20° for 18 h. The equilibrated solution was cooled in an ice bath, 0,1 g of sodium borohydride was added with stirring, and the mixture was stirred at 0° for 15 min. The reaction was quenched by addition of 1 ml of acetic acid, 10 ml of 2N sodium carbonate were added, and the ethanol was evaporated. Water was added to the residue and

extracted thoroughly with dichloromethane. The organic extracts were washed with 2N sodium carbonate and worked up as usual. The crude product was separated by preparative layer chromatography (chloroform/triethylamine 19:1) in the order of increasing polarity into 195 mg (ca. 38.5%) of 9-*epi*-quinidine (**9**), 228 mg (ca. 45%) of 9-*epi*-quinine (**8**), 34 mg (ca. 7%) of quinidine (**7**) and 22 mg (ca. 4%) of quinine (**6**).

9-epi-*Quinidine* (**9**): After recrystallization from ether, m.p. 111–112°; $[\alpha]_D^{25} = +108°$ ($c = 1{,}00$; ethanol). IR. ($CHCl_3$): *ca.* 3450–3250 cm^{-1} (OH bonded), 1620 (aromatic), 1000 and 920 (vinyl). UV. max (EtOH): 231 nm ($\varepsilon = 44\,100$), 272 (infl) (4320), 281 (4850), 292 (infl) (4200), 323/5 (sh) (5750), 334 (6280). NMR. ($CDCl_3$): δ 1,81 (*m*, 1H, 4-*H*); 2,85–3,05 (*m*, 5H, N—CH_2, N—C*H*); 3,90 (*s*, 3H, OCH_3); 4,65 (*b*, 1H, O*H*); *ca.* 5,09 (*d*, 1H, $J = 10$ Hz, *H*—C—OH); ca. 5,1 (*m*, 2H, =CH_2); *ca.* 5,9 (*m*, 1H, —C*H*=); 7,35 (*dd*, 1H, $J = 10$ and 2,5 Hz, 7′—*H*); 7,45 (*d*, 1H, $J = 4{,}5$ Hz, 3′—*H*); 7,58 (*d*, 1 H, $J = 2{,}5$ Hz, 5′—*H*); 8,01 (*d*, 1H, $J = 10$ Hz, 8′—*H*); 8,73 (*d*, 1H, $J = 4.5$ Hz, 2′—*H*). MS.: M^+ *m/e* 324, *m/e* 136 (base peak).

$C_{20}H_{24}N_2O_2$ (324,41) Calc. C 74,04 H 7,46 N 8,64% Found C 73,92 H 7,45 N 8,58%

9-epi-*Quinine* (**8**): Amorphous; $[\alpha]_D^{25} = +43{,}8°$ ($c = 1{,}20$; ethanol). IR. ($CHCl_3$) no free OH, *ca.* 3450–3250 cm^{-1} (OH bonded), 1620 (aromatic), 1000 and 920 (vinyl). NMR. ($CDCl_3$): δ 3,91 (*s*, 3H, OCH_3); 4,70 (*b*, 1H, O*H*); 5,07 (*d*, 1H, $J = 10$ Hz, 8-*H*); *ca.* 5,0 (*m*, 2H, =CH_2); *ca.* 5,65 (*m*, 1H, —C*H*=), 7,25–7,40 (*m*, 2H, 7′—*H* and 3′—*H*); 7,62 (*d*, 1H, $J =$ *ca.* 3 Hz, 5′—*H*); 8,00 (*d*, 1H, $J = 10$ Hz, 8′—*H*); 8,72 (*d*, 1H, 2′—*H*); MS.: M^+ *m/e* 324, *m/e* 136 (base peak).

Acidic di-O-benzoyl-(+)-tartrate monohydrate of **8**: recrystallized from ethanol/ether, m.p. 154–157°; $[\alpha]_D^{22} = -36{,}9°$ ($c = 1{,}15$; methanol).

$C_{20}H_{24}N_2O_2 \cdot C_{18}H_{14}O_8 \cdot H_2O$	Calc.	C 65,13	H 5,75	N 4,00	H_2O 2,57%
(700,72)	Found	,, 65,29	,, 5,52	,, 4,01	,, 2,60%

Epimeric N-Benzoyl-8-chloro-quinotoxines (**14** *and* **15**) *from* **2**. To a solution of 1,15 g (2,7 mmol) of N-benzoylquinotoxine (**2**) in 3 ml of dichloromethane were added 15 ml of 99% phosphoric acid, and the mixture was stirred under a nitrogen stream until it was homogeneous. A total of 0,45 ml (ca. 1,2 molar equiv.) of N-chloro-diisopropylamine was added and the resulting viscous solution was stirred in the dark at 20° in an open flask for 16 h. The reaction mixture was then poured into ice-water, the resulting solution was rendered alkaline (pH *ca.* 9) by addition of conc. ammonium hydroxide, and extracted thoroughly with chloroform. Usual work-up gave 1,27 g of crude product which was separated by prep. TLC. (benzene/ethyl acetate 1:3) into 88 mg (6%) of the corresponding α,α-dichloroketone and 1,04 g (83%) of an amorphous mixture of **14** and **15**; $[\alpha]_D^{25} = +45{,}8°$ ($c = 1{,}0$; $CHCl_3$). IR. ($CHCl_3$): 1710 cm^{-1} (ketone), 1620 (amide), 1000 and 930 (vinyl). UV. max (EtOH): 209 nm ($\varepsilon = 47\,700$), 248 (4300). NMR. ($CDCl_3$): δ 3,90 (*s*, 3H, OCH_3); *ca.* 5,2 (*m*, 3H, =CH_2 and *H*—C—Cl); *ca.* 5,9 (*m*, 1H, —C*H*=); 7,35 (*s*, 5H, phenyl); *ca.* 7,3–8,8 (5 aromatic H, two sets of peaks). MS.: *m/e* 426 ($M^+ -$ HCl).

$C_{27}H_{27}ClN_2O_3$ (462,98) Calc. C 70,05 H 5,80 N 6,05% Found C 70,37 H 5,84 N 5,87%

threo-4-[3-(1-*Benzoyl-3*(R)-*vinyl-4*(S)-*piperidyl*)-2-*chloro-1-hydroxypropyl*]-6-*methoxy-quinolines* (**16** *and* **17**) *from* **14** *and* **15**. To a solution of 1,43 g (3,1 mmol) of epimeric N-benzoyl-8-chloro-quinotoxines (**14** and **15**) in 80 ml of tetrahydrofuran was added at −78°, with stirring, 1 g (ca. 1,25 molar equiv.) of solid lithium tri-(*t*-butoxy)-aluminum hydride. The solution was stirred for 2 h at −78°, and then at ambient temperature for 2 h. The solvent was evaporated, the residue partitioned between dichloromethane and 1N sodium hydroxide, and the organic phase worked up as usual. The crude product, in ethyl acetate, was filtered through 10 g of neutral alumina, activity II, to give 1,31 g (91%) of amorphous *threo*-chlorohydrins **16** and **17**. An analytical sample was obtained by prep. TLC.; $[\alpha]_D^{25} = +52{,}0°$ ($c = 1{,}04$; $CHCl_3$). IR. ($CHCl_3$): 3600 cm^{-1} (weak, OH free), *ca.* 3500–3200 (OH bonded), 1620 (amide). NMR. ($CDCl_3$, 60 MHz): δ 3,90 (*s*, 3H, OCH_3); 7,30 (*s*, 5H, phenyl); *ca.* 7,2–8,7 (5H aromatic). MS.: *m/e* 428 ($M^+ -$ HCl).

$C_{27}H_{29}ClN_2O_3$ (465,0) Calc. C 69,74 H 6,29 N 6,02% Found C 69,69 H 6,31 N 6,02%

The same result was obtained from the reduction of **14** and **15** with sodium borohydride in ethanol at 0°.

cis, erythro-4-[3-(1-*Benzoyl-3*(R)-*vinyl-4*(S)-*piperidyl*)-1, 2-*epoxypropyl*]-6-*methoxy-quinolines* (**18** *and* **19**) *from* **16** *and* **17**. To a solution of 0,21 g (0,45 mmol) of *threo*-4-[3-(1-benzoyl-3(*R*)-vinyl-

4(*S*)-piperidyl)-2-chloro-1-hydroxy-propyl]-6-methoxy-quinolines (**16** and **17**) in 8 ml of methanol were added 5 ml of 2N aqueous potassium hydroxide. After standing at 20° for $2^1/_2$ days, the methanol was evaporated, more water added, and the aqueous phase extracted thoroughly with dichloromethane. Usual work-up and subsequent purification by prep. TLC. gave 0,173 g (90%) of amorphous **18** and **19**; $[\alpha]_D^{25} = +57.3°$ (c = 0,956; $CHCl_3$). IR. ($CHCl_3$): no OH, 1620 (amide). NMR. ($CDCl_3$, 60 MHz): δ *ca.* 3,6 (*m*, 1H, —O—C*H*—CH_2); 3,95 (*s*, 3H, OCH_3); *ca.* 4,5 (*m*, 1H, arom-C*H*—O); *ca.* 5,0 (*m*, 2H, =CH_2); *ca.* 5,8 (*m*, 1H, —C*H*=); 7,35 (*s*, 5H, phenyl); *ca.* 7,2–8,4 (5H aromatic). MS.: M^+ *m/e* 428.

$C_{27}H_{28}N_2O_3$ (428,51) Calc. C 75,67 H 6,59 N 6,54% Found C 75,60 H 6,82 N 6,48%

cis, erythro-*6-Methoxy-4-[3-(3*(R)*-vinyl-4*(S)*-piperidyl)-1, 2-epoxypropyl]-quinolines* (**20** *and* **21**) *from* **18** *and* **19**. To an anhydrous solution of 2,74 g (6,4 mmol) of *cis,erythro*-4-[3-(1-benzoyl-3(*R*)-vinyl-4(*S*)-piperidyl)-1,2-epoxypropyl]-6-methoxy-quinolines (**18** and **19**) in 80 ml of toluene was added with stirring at –78° a total of 5.8 ml of a ca. 25% solution of DIBAL-H in toluene while the reaction was monitored by TLC. The reaction was quenched and thoroughly extracted with 2N sulfuric acid. The aqueous phase was rendered alkaline by addition of conc. ammonium hydroxide and extracted thoroughly with chloroform. Usual work-up afforded 2,2 g of crude product which was adsorbed on 23 g of silica gel *Merck*, 0,05–0,2 mm. Elution with ethyl acetate gave 0,61 g (21%) of the starting N-benzoyl epoxides, elution with chloroform/methanol/triethylamine 8:1:1 afforded 1,62 g (78%) of the amorphous amino-*cis*-epoxides **20** and **21**. NMR. ($CDCl_3$): *ca.* 3,5 (*m*, 1H, $\overset{O}{\diagdown\!\!\diagup}$C*H*—$CH_2$—); 3,91 (*s*, 3H, O$CH_3$); *ca.* 4,4 (*m*, 1H, arom-C*H*$\overset{O}{\diagdown\!\!\diagup}$); *ca.* 5,0 (*m*, 2H, =$CH_2$); *ca.* 5,9 (*m*, 1H, —C*H*=); 7,0 (*b*, 1H, N—*H*); *ca.* 7,15–8,7 (5H aromatic, 2 sets of peaks). MS.: M^+ *m/e* 324, *m/e* 136 (base peak, indicating thermal cyclization to end products).

9-epi-*Quinine* (**8**) *and 9*-epi-*Quinidine* (**9**). – a) *From* cis *amino epoxides* **20** *and* **21** *in toluene/methanol.* A solution of 0,347 g (1,07 mmol) of *cis,erythro*-6-methoxy-4-[3-(3(*R*)-vinyl-4(*S*)-piperidyl)-1,2-epoxypropyl]-quinolines **20** and **21** in 49,5 ml of toluene and 0,5 ml of methanol was heated under gentle reflux under nitrogen for 20 h. The crude product obtained after removal of the solvent was separated by prep. TLC. (chloroform/triethylamine 95:5, 3 times developed) in order of increasing polarity into 74 mg (22%) of 9-*epi*-quinidine (**9**), 127 mg (36%) of 9-*epi*-quinine (**8**) and 0,1 g (ca 28%) of a mixture of methanolysis products containing traces of quinine and quinidine.

9-epi-*Quinidine* (**9**): after recrystallization from ether, m.p. 111–113°; $[\alpha]_D^{25} = +107,8°$ (c = 1,02; ethanol). IR. ($CHCl_3$): no free OH, *ca.* 3500–3200 cm^{-1} (OH bonded), 1620 (aromatic), 1000 and 920 (vinyl). UV. max (EtOH): 231 nm (ε = 44 100), 272 (infl) (4320), 281 (4850), 292/3 (infl) (4200), 323/5 (sh) (5750), 334 (6280). NMR. ($CDCl_3$, 60 MHz): δ 2,3 (*m*, 1H, bridgehead methine); *ca.* 3 (*m*, 5H, C*H*—N—(CH_2)$_2$); 3,91 (*s*, 3H, OCH_3); 4,38 (*s*, 1H, O*H*); 5,08 (*d*, 1H, J = *ca.* 10 Hz, *H*—C—OH); *ca.* 5,1 (*m*, 2H, =CH_2); 5,97 (*m*, 1H, —C*H*=); 7,39 (*dd*, 1H, J = 9 and 2 Hz, 7′—*H*); 7,56 (*d*, 1H, J = 4 Hz, 3′—*H*); 7,62 (*d*, 1H, J = 2 Hz, 5′—*H*); 8,06 (*d*, 1H, J = 9 Hz, 8′—*H*); 8,78 (*d*, 1H, J = 4 Hz, 2′—*H*). MS.: M^+ *m/e* 324, *m/e* 136 (base peak).

$C_{20}H_{24}N_2O_2$ (324,41) Calc. C 74,04 H 7,46 N 8,64% Found C 73,88 H 7,54 N 8,48%

Neutral di-O-benzoyl-(+)-tartrate monoethanolate of **9**: m.p. 165–167° (dec.) (crystals shrink >140°), after recrystallization from ethanol/acetone; $[\alpha]_D^{25} = +1°$ (c = 1,02; EtOH/$CHCl_3$ 4:1), –5° (c = 0,98; MeOH).

$(C_{20}H_{24}N_2O_2)_2 \cdot C_{18}H_{14}O_8 \cdot C_2H_5OH$ (1053,24) Calc. C 68,42 H 6,51 N 5,32%
Found ,, 68,45 ,, 6,29 ,, 5,40%

9-epi-*Quinine* (**8**), neutral di-O-benzoyl-(+)-tartrate monoethanolate: after recrystallization from ethanol/ether; m.p. 155–158° (dec.) (crystals collapse >140°); $[\alpha]_D^{25} = -24,3°$ (c = 0,93; ethanol).

$(C_{20}H_{24}N_2O_2)_2 \cdot C_{18}H_{14}O_8 \cdot C_2H_5OH$ (1053,24) Calc. C 68,42 H 6,51 N 5,32%
Found ,, 68,31 ,, 6,19 ,, 5,40%

The *free base* is amorphous: IR. ($CHCl_3$): *ca.* 3500–3200 cm^{-1} (OH bonded), 1620 (aromatic), 1000 and 920 (vinyl). NMR. ($CDCl_3$): δ 3,92 (*s*, 3H, OCH_3); 4,50 (*b*, 1H, O*H*); 5,05 (*d*, 1H, J = *ca.* 10 Hz, *H*—C—OH); *ca.* 5,0 (*m*, 2H, =CH_2); 5,75 (*m*, 1H, —C*H*=); 7,36 (*dd*, 1H, J = 9 and 3 Hz, 7′—*H*); 7,39 (*d*, 1H, J = 4 Hz, 3′—*H*); 7,65 (*d*, 1H, J = 3 Hz, 5′—*H*); 8,02 (*d*, 1H, J = 9 Hz, 8′—*H*); 8,72 (*d*, 1H, J = 4 Hz, 2′—*H*). MS.: M^+ *m/e* 324, *m/e* 136 (base peak).

b) *From* cis-*amino epoxides* **20** *and* **21** *in dimethylformamide.* A solution of 1,53 g of **20** and **21** in 50 ml of anhydrous dimethylformamide was heated at 155° for 80 min. The solvent was evaporated, the residue dissolved in ether, washed with water and worked up as usual. The crude product (1,45 g) was separated as described above into 0,374 g (25%) of 9-*epi*-quinidine (**9**), 0,67 g (43%) of 9-*epi*-quinine (**8**), 0,164 g (11%) of quinidine (**7**) and 0,054 g (4%) of quinine (**6**).

c) *From* threo-*chlorohydrins* **16** *and* **17**. To a solution of 0,50 g (1,08 mmol) of *threo*-4-[3-(1-benzoyl-3(*R*)-vinyl-4(*S*)-piperidyl)-2-chloro-1-hydroxy-propyl]-6-methoxy-quinolines (**16** and **17**) in 50 ml of methanol was added a solution of 1,12 g (20 mmol) of potassium hydroxide in 70 ml of water, and the resulting solution was heated under gentle reflux under nitrogen for 40 h. The methanol was evaporated, the aqueous residue extracted thoroughly with dichloromethane, and the organic phase worked up as usual to give 0,37 g of crude product. Separation by prep. TLC., as described above, gave in the order of increasing polarity 31 mg (6%) of starting material, 63 mg (18%) of 9-*epi*-quinidine (**9**), and 137 mg (39%) of 9-*epi*-quinine (**8**).

REFERENCES

[1] *R. B. Turner & R. B. Woodward,* 'The Chemistry of the *Cinchona* Alkaloids', in 'The Alkaloids' (*R. H. F. Manske & H. L. Holmes,* Eds.), Vol. 3, Chap. 16, Academic Press, New York 1953.
[2] *P. Rabe,* Ber. deutsch. chem. Ges. *44,* 2088 (1911); *P. Rabe & K. Kindler, ibid. 51,* 466 (1918).
[3] *M. Prošteník & V. Prelog,* Helv. *26,* 1965 (1943).
[4] *R. B. Woodward & W. E. Doering,* J. Amer. chem. Soc. *67,* 860 (1945).
[5] *G. Grethe, H. L. Lee, T. Mitt & M. R. Uskoković,* Helv. *56,* 1485 (1973).
[6] *R. B. Woodward, N. L. Wendler & F. J. Brutschy,* J. Amer. chem. Soc. *67,* 1425 (1945) and references cited therein.
[7] *G. Grethe, J. Gutzwiller, H. L. Lee & M. R. Uskoković,* Helv. *55,* 1044 (1972).
[8] *J. W. Cornforth, R. H. Cornforth & K. M. Mathew,* J. chem. Soc. *1959,* 112, 2539.
[9] *P. Rabe,* Liebigs Ann. Chem. *492,* 242 (1931).
[10] *H. Auterhoff & K. Kalpathy,* Pharmac. Acta Helv. *38,* 491 (1963).

147. Modellreaktionen zur Biosynthese von Verbindungen der Damascon-Reihe und ihre präparative Anwendung

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(14. III. 73)

Summary. We report a new general synthesis of damascones. In the presence of acids, 7,8-dehydro-β-ionole (**10**) or the related diols **11** are converted into a mixture of β-damascone (**2**) and the 7,8-dehydrotheaspiranes (**19**). In the same way the 6-hydroxy-7,8-dehydro-α-ionoles **12** are transformed into a mixture of β-damascenone (**3**) and the 8-oxatheaspiranes (**20**). The reaction provides access to damascone derivatives **4–7** which have been found in nature.

These synthetic experiments lend support to our hypotheses concerning the biogenesis of damascones from suitable carotenoids or their metabolites.

Kulturen von *Phycomyces blakesleeanus* werden durch die Anwesenheit von β-Jonon zur Carotinogenese angeregt, ohne dass diese Verbindung in β-Carotin inkorporiert wird [1]. Es ist zu vermuten, dass die in der Natur bisher aufgefundenen Jonon-Derivate nicht direkt aus dem Isopentenylpyrophosphat-Stoffwechsel stam-