145. Reinvestigation of the Classical Synthesis of Cinchona Alkaloids. I. A New Synthesis of Homomeroquinene and Quinotoxine[1])

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Zusammenfassung. Eine neue Synthese von N-benzoyl-homomerochinen-äthylester (**10b**) und dessen Überführung in Chinotoxin (**18**) wird beschrieben.

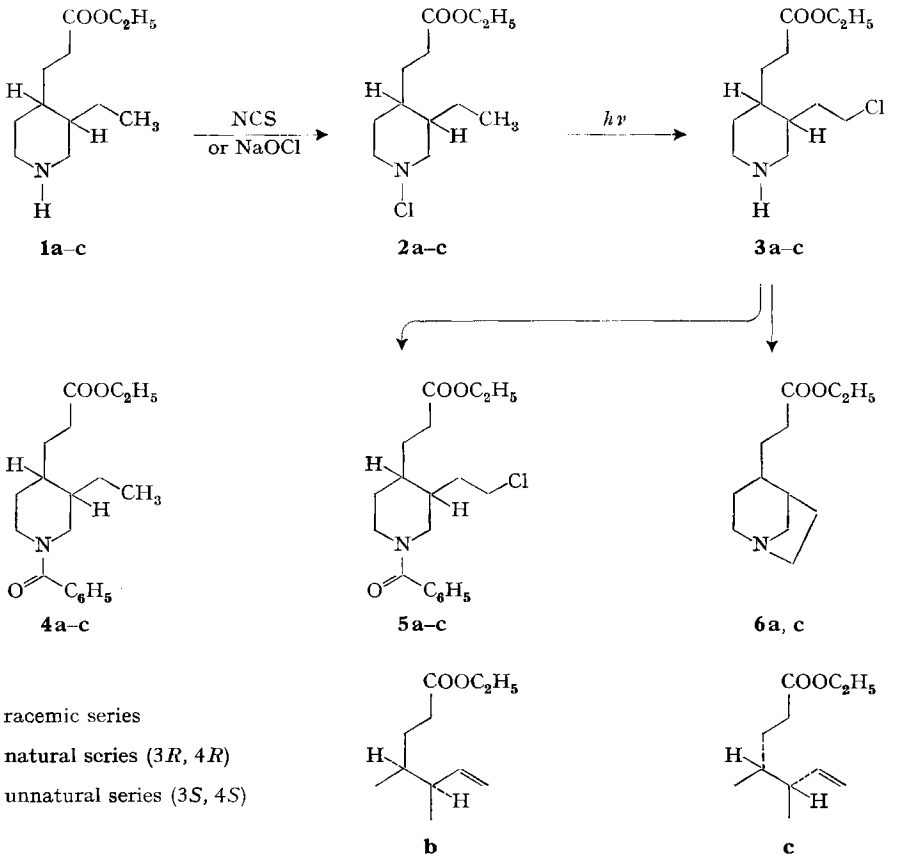
The classical synthesis of the *Cinchona* alkaloids, quinine and quinidine, was formulated by *Rabe* early in this century [1], [2] and is in part characterized by the assemblage of N-benzoyl-homomeroquinene ethyl ester (**10b**) and ethyl quininate (**14**) into the key intermediate quinotoxine (**18**), a process which was first carried out experimentally by *Prošťenik & Prelog* [3]. They made use of the optically active N-benzoyl-homomeroquinene obtained by degradation of cinchonine. Subsequently, *Woodward & Doering* [4] synthesized racemic N-benzoyl-homomeroquinene ethyl ester (**10a**) and quinotoxine, which was ultimately resolved. As one means of developing practical routes to the *Cinchona* alkaloids, we reinvestigated this classical synthesis. However, this undertaking required a more efficient synthesis of both homomeroquinene and quinotoxine. A successful solution to both these problems is described in this paper. The following paper deals with the conversion of quinotoxine to quinine and its naturally occurring diastereomers [5].

We turned our attention first to the synthesis of N-benzoyl-homomeroquinene ethyl ester (**10b**). In 1931 *Rabe* reported [2] an effecient stereoselective synthesis of the dihydro analog, homocincholoipon ethyl ester (**1b**), starting from readily available β-collidine. The conversion of the ethyl side chain of **1b** into the vinyl group of **10b** was therefore considered. Inspection of molecular models indicated that compound **1b** furnished all the requirements of the *Hofmann-Löffler-Freytag* reaction [6] for a facile β-chlorination of the ethyl side chain. The vinyl group would then be formed by dehydrochlorination [7].

These objectives were accomplished by the sequence of reactions shown in Schemes 1 and 2, and carried out with both optically active and racemic materials. N-Chlorination of amines **1a–c** proceeded equally well with N-chlorosuccinimide in ether or with sodium hypochlorite in a two-phase system (water/ether). Solutions of the crude N-chloramines **2a–c** in trifluoroacetic acid were subjected to photolysis by a 200 W *Hanovia* medium pressure mercury lamp below 15°; at temperatures above 15° considerable decomposition of the N-chloramine **2** occurred, resulting in the regeneration of starting amine **1**, isolated as the N-benzoyl derivative **4**. The pro-

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

Scheme 1



a: racemic series

b: natural series (3*R*, 4*R*)

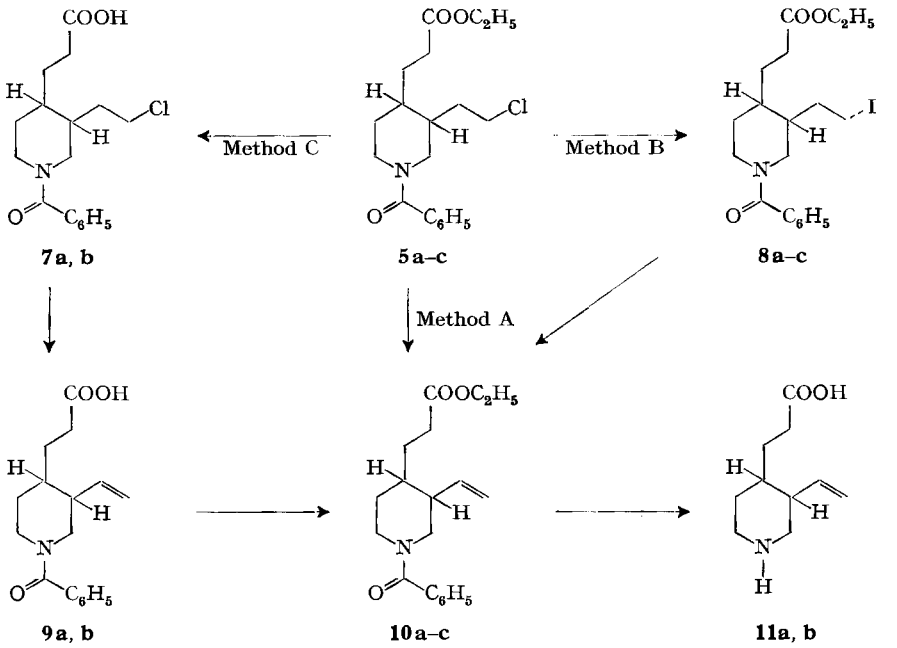
c: unnatural series (3*S*, 4*S*)

gress of the photolysis was monitored by the starch/iodine test for the presence of positive chlorine. After evaporation of the solvent at 30–35° under reduced pressure the resulting crude trifluoroacetates of **3a–c** were allowed to react under neutral conditions with benzoyl chloride to give **5a–c** in 70–90% yield after chromatography. The purity of these products was at least 95% (GLPC.). The racemic compound **5a** slowly crystallized on standing. Use of excess potassium carbonate in the benzoylation step effected cyclization of **3a–c** to the known 1-azabicyclo[3.2.1]-octane derivatives **6a–c** [7].

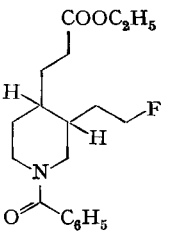
The formation of the double bond was accomplished by three different methods, of which pyrolysis of **5a** at 190° (0.025 Torr) (Method A) was the least satisfactory (17% yield).

When compounds **5a–c** were reacted with sodium iodide in methyl ethyl ketone and the crude iodides **8a–c** subsequently treated with silver fluoride in pyridine, N-benzoyl-homomeroquinene ethyl esters **10a–c** were formed in 40% yield (Method B). The products obtained by this method were hard to purify. Even when distilled, they contained small amounts of **4a–c** and varying quantities of **12a–c** and **13a–c**.

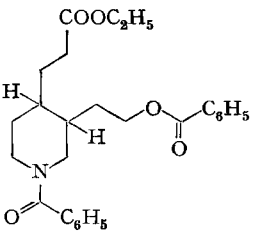
Scheme 2



These impurities were separeted from **10a–c** by chromatography on silica gel impregnated with silver nitrate, and from each other by a second silica gel chromatography.



12a–c



13a–c

The assignment of structure **13** is based on spectral evidence. This compound must have been formed from the corresponding alcohol[2]) during the benzoylation reaction. (Treatment of compounds **5** or **6** with benzoyl chloride under the conditions of the benzoylation failed to produce even traces of **13**).

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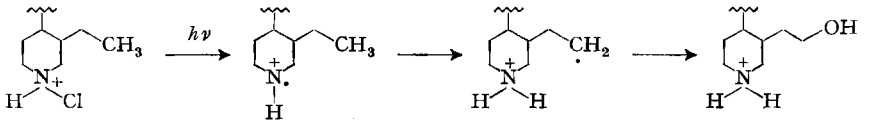
[2]) We assume that the alcohol was formed during photolysis by the possible sequence **i** → **iv**.

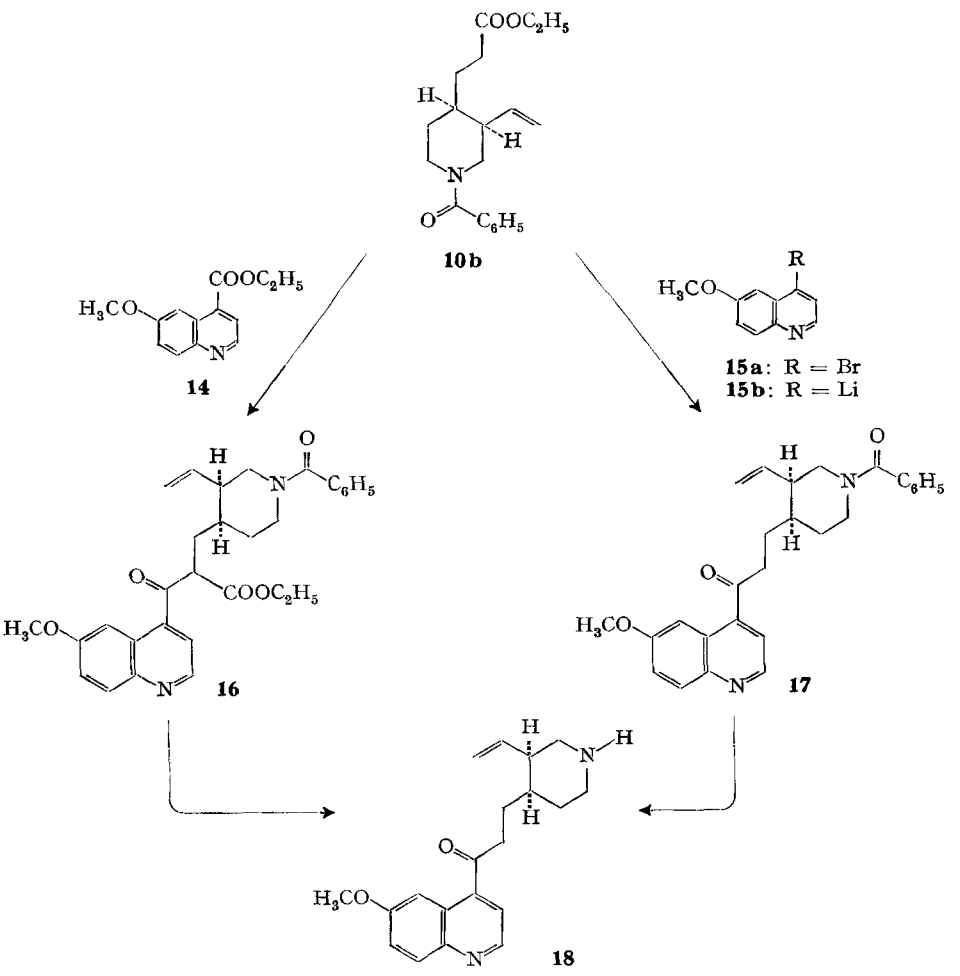


i **ii** **iii** **iv**

The cumbersome purification necessary in Method B was avoided in the third process (Method C), which consisted of saponification of **5a, b**, dehydrochlorination of **7a, b** with potassium *t*-butoxide in DMSO, and esterification of **9a, b**. Distillation of the reaction products in this case yielded N-benzoyl-homomeroquinene ethyl ester (**10a, b**) of 95–97% purity in 75–80% yield[3]). The analytical data of compounds **10a–c** are in agreement with the assigned structures. Racemic homomeroquinene (**11a**) was obtained by acid hydrolysis of **10a**, and the known crystalline natural homomeroquinene (**11b**) [2] by the hydrolysis of **10b** in boiling methanolic potassium hydroxide.

Previously [3] [4], quinotoxine (**18**) was synthesized by *Claisen* condensation of **10b** with ethyl quininate (**14**) followed by hydrolysis and decarboxylation of the

Scheme 3



[3]) The same method for the conversion of an ethyl into a vinyl group was used in the synthesis of 3-vinyl-4-piperidineacetic acids [8].

β-keto ester **16**. By employing 6-methoxy-4-quinolyllithium (**15b**) instead of the ester **14**, the loss of one carbon inherent in the original procedure could be avoided. The condensation of **10b** with **15b**, obtained from the bromo derivative **15a**, afforded crystalline N-benzoylquinotoxine (**17**), which upon hydrolysis yielded quinotoxine (**18**). The product was identical with quinotoxine obtained by degradation of quinine [9].

To sum up, an efficient synthesis of N-benzoyl-homomeroquinene ethyl ester, combined with a modification of the condensation reaction, considerably improved the preparation of quinotoxine and thus the *Rabe-Woodward* synthesis of *Cinchona* alkaloids.

Experimental Part

All melting and boiling points are uncorrected. The m.p. were taken in open capillary tubes with a *Thomas-Hoover* melting point apparatus. Distillations were carried out in a short-path distillation apparatus, the temperatures given are heating block temperatures. Infrared spectra (IR.) were determined with a *Beckman* Infrared, Model IR-9, spectrophotometer. Optical rotations were measured on a *Perkin-Elmer* polarimeter, Model 141. NMR. spectra were recorded on a *Varian* Associates, Model A-60 or HA-100, spectrophotometer. The mass spectra were taken with a *CEC* 21–110 mass spectrometer at 70 eV using a direct insertion probe. Analytical gas chromatograms were obtained using a F+M Model 810R-19 instrument. For preparative gas chromatography (GLPC.) a *Varian* Aerograph, Model 700, instrument was employed.

Racemic cis-*3-(1-chloro-3-ethyl-4-piperidyl)-propionic acid ethyl ester* (**2a**) *from* **1a**. – *A.* To a solution of 1.064 g (0.005 mol) of racemic *cis*-3-(3-ethyl-4-piperidyl)-propionic acid ethyl ester (**1a**), in 30 ml of ether, were added 30 ml of a 16.9% aqueous solution of sodium hypochlorite. The mixture was shaken at room temperature, and at 1 h intervals, the aqueous layer was separated and fresh sodium hypochlorite solution (30 ml) was added to the ethereal phase. After 4.5 h, 100 ml of benzene was added to the mixture. The organic layer was separated, washed successively with water, 3N aqueous hydrochloric acid and water, and dried (Na_2SO_4). Concentration afforded 0.90 g (73%) of liquid **2a**.

B. To a stirred suspension of 11 g (0.082 mol) of N-chlorosuccinimide, in 200 ml of anhydrous ether, was added, in a nitrogen atmosphere, a solution of 15 g (0.070 mol) of **1a** in 100 ml of anhydrous ether. After continued stirring for 1 h at room temperature, the mixture was successively washed with water, 2.5N aqueous sulfuric acid, and water. The ethereal solution was dried (Na_2SO_4) and evaporation of the solvent under reduced pressure gave 18 g (100%) of liquid **2a**.

Racemic cis *3-[1-benzoyl-3-(2-chloroethyl)-4-piperidyl]-propionic acid ethyl ester* (**5a**) *from* **2a**. 15 g (0.060 mol) of **2a** were dissolved in 150 ml of trifluoroacetic acid at 0°. The resulting clear solution was transferred to a quartz flask, purged with dry nitrogen for 30 min, and then irradiated at 10° with a 200 W-*Hanovia* medium pressure mercury lamp. Samples were removed at intervals and the reaction was continued until a negative starch-iodine test was obtained. After 5 h the solvent was removed at 35° under reduced pressure. Benzene was added to the residue and evaporated under reduced pressure, to give crude **3a**.

To a stirred solution of 40 g of this crude trifluoroacetate of racemic *cis*-3-[3-(2-chloroethyl)-4-piperidyl]-propionic acid ethyl ester (**3a**) and 26 g of benzoyl chloride in 400 ml of benzene, was added, over a period of 2 h, a saturated aqueous solution of potassium carbonate until the pH reached 9. Stirring was continued for 1 h. After the addition of 200 ml of benzene the mixture was washed successively with 6N aqueous sodium hydroxide, water, 3N aqueous hydrochloric acid, and water, dried (Na_2SO_4) and evaporated to dryness. The oily residue (30 g) was chromatographed on 650 g of silica gel (*Grace, Davison Chemical*, Grade 923) with benzene/ethyl acetate 9:1 as the liquid phase to give 22.3 g (91%) of **5a** of 96.3% purity (GLPC.)[4]). On standing at room temperature for two months, the oily **5a** slowly crystallized. Washing of the crystalline mass with pentane/

[4]) GLPC. analyses were run on a 15 ft. × 0.25 inch column of 1% Apiezon-L on GC-2 at 150–250° (6°/min) with a nitrogen flow rate of 100 ml/min. The following retention times were observed: **4**, 15.8 min; **5**, 20.4 min; **10**, 16.2 min; **12**, 17.1 min.

ether afforded analytically pure **5a**: m.p. 53–55°. IR. ($CHCl_3$): 1740 cm^{-1} (cster C=O), 1640 (C=O). NMR. ($CDCl_3$): δ 1.25 (*t*, 3H, $J = 7$ Hz, CH_2—CH_3), 4.15 (*q*, 2H, $J = 7$ Hz, CH_2—CH_3), 7.49 (*s*, 5H, phenyl). MS.: *m/e* (rel. intensity) 351 (25), 316 (100), 288 (18), 246 (10), 188 (5), 105 (100), 77 (100).

$C_{19}H_{26}ClNO_3$ (351.88) Calc. C 64.85 H 7.45 N 3.98% Found C 64.80 H 7.36 N 3.94%

3-[1-Benzoyl-3(R)*-(2-chloroethyl)-4*(R)*-piperidyl]-propionic acid ethyl ester* (**5b**) *from* **1b**. The mono-(+)-tartrate of 3-[3(*R*)-ethyl-4(*R*)-piperidyl]-propionic acid ethyl ester (**1b**) (15 g, 0.041 mol) was treated with excess 2N aqueous potassium carbonate, and the liberated free base was extracted into dichloromethane. The combined organic extract was dried (Na_2SO_4) and evaporated to dryness to give 8.8 g (0.041 mol) of **1b**. Transformation of **1b** into the chloroamine **2b** was effected with N-chlorosuccinimide in water/ether as described above for **2a** (Method B). Photolysis of a solution of 9 g (0.036 mol) of **2b** in 150 ml of trifluoroacetic acid was carried out as described before and afforded 22 g of crude trifluoroacetate of 3-[3(*R*)-(2-chloroethyl)-4(*R*)-piperidyl]-propionic acid ethyl ester (**3b**). Benzoylation and subsequent chromatography of the crude product (18 g) on 650 g of silica gel (*Grace, Davison Chemical*, Grade 923) yielded 11.1 g (76%) of liquid **5b**. An analytical sample was obtained by distillation: b.p. 150°/0.018 Torr; $[\alpha]_D^{22} = +20.2°$ ($c = 1.09$, CH_3OH).

$C_{19}H_{26}ClNO_3$ (351.88) Calc. C 64.85 H 7.45 N 3.98% Found C 64.59 H 7.76 N 4.02%

3-[1-Benzoyl-3(S)*-(2-chloroethyl)-4*(S)*-piperidyl]-propionic acid ethyl ester* (**5c**) *from* **1c.** Analogous to the preparation of the enantiomer **5b**, 8.9 g (0.025 mol) of the mono-(−)-tartrate of 3-[3(*S*)-ethyl-4(*S*)-piperidyl]-propionic acid ethyl ester (**1c**) yielded 5.95 g (72%) of the liquid 3*S*,4*S*-isomer **5c**. Two distillations afforded an analytical sample: b.p. 160°/0.015 Torr; $[\alpha]_D^{22} = -20.0°$ ($c = 0.99$, CH_3OH).

$C_{19}H_{26}ClNO_3$ (351.88) Calc. C 64.85 H 7.45 N 3.98% Found C 64.74 H 7.50 N 3.90%

Racemic cis-*1-azabicyclo[3.2.1]octane-4-propionic acid ethyl ester acidic oxalate* [**6a**. $(COOH)_2$] *from* **3a**. A benzene solution of the crude trifluoroacetate of **3a**, obtained from 18 g (0.084 mol) of **1a** by the method described above, was stirred with excess 6N sodium hydroxide. The benzene layer was separated and the aqueous phase extracted twice with dichloromethane. The combined organic extract was washed twice with brine, dried (Na_2SO_4), and evaporated to dryness to give 9.1 g of crude **6a**. The aqueous phase was evaporated to dryness and extracted with 300 ml of hot benzene. Solid potassium carbonate (30 g) was added to the clear benzene solution and the mixture was stirred 3 h at reflux temperature.

The mixture was filtered through Celite Filter-Aid and evaporation of the filtrate gave 7.8 g of liquid **6a**. The two fractions of **6a** were combined and transformed into the oxalate by combining acetone solutions of the free base and of oxalic acid. The acetone was removed and the residue was crystallized from ethanol/ether to give, in several fractions, a total of 11.6 g (45%) of the oxalate of **6a**, m.p. 120–125°. A sample was recrystallized from ethanol/ether to afford analytically pure oxalate of **6a**: m.p. 123–125°. NMR. (CD_3OD): δ 1.25 (*t*, 3H, $J = 7$ Hz, —OCH_2CH_3), 2.38 (*t*, 2H, $J = 7$ Hz, —CH_2—CO—), *ca.* 3.35 (complex, 6H, CH_2—α to N, partly hidden beneath CH_3OH-peak), 4.15 (*q*, 2H, $J = 7$ Hz, CH_2—CH_3). MS.: *m/e* (rel. intensity) 211 (95), 196 (15), 182 (13), 160 (85), 110 (100), 96 (20), 82 (100), 57 (60), 42 (100).

$C_{12}H_{21}NO_2 \cdot C_2H_2O_4$ (301.34) Calc. C 55.80 H 7.69 N 4.65% Found C 55.78 H 7.78 N 4.63%

4(S),*5*(S)*-1-Azabicyclo[3.2.1]octane-4-propionic acid ethyl ester acidic oxalate* [**6c**. $(COOH)_2$] *from* **3c**. This compound was obtained by the preceeding procedure, but starting from **1c**. Recrystallization from ethanol/ether afforded pure oxalate of **6c**: m.p. 127–128°; $[\alpha]_D^{24} = -80.4°$ ($c = 1.02$, CH_3OH).

$C_{12}H_{21}NO_2 \cdot C_2H_2O_4$ (301.34) Calc. C 55.80 H 7.69 N 4.65% Found C 55.80 H 7.84 N 4.77%

Addition of an equivalent amount of sodium ethoxide to an ethanolic solution of the oxalate afforded, after evaporation to dryness and extraction of the residue with benzene, the *free base* **6c** as a clear liquid: IR. ($CHCl_3$): 1743 cm^{-1} (C=O); NMR. ($CDCl_3$): δ 1.29 (*t*, 3H, $J = 7$ Hz, CH_2—CH_3). 4.16 (*q*, 2H, $J = 7$ Hz, CH_2—CH_3).

Racemic cis-*3-(1-benzoyl-3-vinyl-4-piperidyl)-propionic acid ethyl ester* (**10a**) *from* **5a**. – *Method B*. A solution of 3.5 g (0.01 mol) of **5a** and 2.3 g (0.015 mol) of sodium iodide in 120 ml of methyl

ethyl ketone was kept at reflux temperature for 44 h. The mixture, in which a precipitate had formed, was diluted with 50 ml of water and 100 ml of ether. The organic layer was separated, washed with water, diluted with benzene (100 ml), dried (Na_2SO_4), and evaporated to dryness to give 4 g (90%) of liquid racemic *cis*-3-[1-benzoyl-3-(2-iodoethyl)-4-piperidyl]-propionic acid ethyl ester (**8a**). This material was dissolved in 120 ml of anhydrous pyridine, and after the addition of 2.5 g (0.020 mol) of silver fluoride the mixture was stirred at room temperature for 24 h. Ether (800 ml) was added and the black precipitate removed by filtration. The filtrate was washed with 3N aqueous hydrochloric acid and water, dried (Na_2SO_4), and evaporated to dryness. The residue was distilled at 120–150°/0.015 Torr to give 1.6 g of a liquid. GLPC. analysis[4]) indicated that the distillate contained, in addition to 7% of racemic N-benzoyl-homocincholoipon ethyl ester (**4a**), 78% of the desired product **10a** and 10% of the fluoro derivative **12a**. Purification by preparative GLPC.[5]) afforded first *analytically pure* **10a**: IR. ($CHCl_3$): 1730 cm^{-1} (ester C=O), 1627 (C=O), 1000, 928 (vinyl). NMR. ($CDCl_3$): δ 1.23 (*t*, 3H, J = 7 Hz, CH_2–CH_3), 4.09 (*q*, 2H, J = 7 Hz, CH_2–CH_3), *ca.* 5.12 (*m*, 2H, CH=CH_2), *ca.* 5.85 (*m*, 1H, CH=CH_2), 7.34 (*s*, 5H, phenyl). MS.: *m/e* (rel. intensity) 315 (20), 274 (4), 270 (5), 242 (2), 228 (8), 214 (6), 210 (10), 148 (6), 105 (100), 77 (30).

$C_{19}H_{25}NO_3$ (315.42) Calc. C 72.35 H 7.99 N 4.44% Found C 72.27 H 8.28 N 4.16%

The second fraction contained *racemic* cis-*3-[1-benzoyl-3-(2-fluoroethyl)-4-piperidyl]-propionic acid ethyl ester* (**12a**): MS.: *m/e* (rel. intensity) 335 (40), 288 (15), 274 (5), 262 (3), 248 (6), 230 (15), 188 (7), 140 (5), 105 (100), 77 (25).

In another run, 4.4 g of crude **10a** were purified by preparative TLC. on silica gel [20 plates, 20 × 20 mm; silica gel *Camag* DSF-5 impregnated with 10% $AgNO_3$, 2 mm thickness, mobile phase: benzene/ethyl acetate 3:2]. Two zones detectable by UV.-light were removed from the plates and each was eluted with benzene/ethyl acetate 1:1. The silica gel was removed by filtration and the filtrates were concentrated to give 2.01 g of pure **10a** from the lower zone and 1.61 g of a mixture of compounds from the upper zone. Part of this mixture (0.8 g) was again chromatographed on silica gel [4 plates, 20 × 20 mm, silica gel F_{254} *Merck*, 2 mm thickness, mobile phase: ethyl acetate/petroleum ether 4:6]. The plates were developed several times until separation into three zones was achieved. Each zone was eluted with ethyl acetate, the silica gel removed by filtration, and the filtrates were evaporated to dryness. From the first zone (highest R_f value) were obtained 155 mg of **4a**. The middle zone afforded 208 mg of the fluoro compound **12a** and the lowest zone yielded 242 mg of liquid *racemic* cis-*3-[1-benzoyl-3-(2-benzoyloxyethyl)-4-piperidyl]-propionic acid ethyl ester* (**13a**): IR. ($CHCl_3$): 1715 cm^{-1} (ester C=O), 1620 (amide C=O), 1275 and 1112 (C–O-benzoate). NMR. ($CDCl_3$): δ 1.25 (*t*, 3H, J = 7 Hz, CH_2–CH_3), 4.16 (*q*, 2H, J = 7 Hz, CH_2–CH_3), 7.42 (*s*, 5H, phenyl), *ca.* 7.8 (complex, 5H, phenyl). MS.: *m/e* (rel. intensity) 437 (40), 392 (7), 350 (4), 332 (18), 316 (20), 302 (2), 288 (20), 210 (12), 105 (100), 77 (80).

Method A. A mixture of 0.5 g (0.0014 mol) of **5a** and glass powder was heated at 190°/0.025 Torr for 5 h. The black reaction mixture was dissolved in dichloromethane, the glass powder removed by filtration, and the filtrate evaporated to dryness. The residue (350 mg) was distilled at 150°/0.015 Torr to give 99 mg of **10a** of 78% purity (GLPC.)[4]).

Method C. A solution of 41.9 g (0.119 mol) of **5a** in 600 ml of methanol was combined with 600 ml of 1N sodium hydroxide and left standing at room temperature for 36 h. The methanol was removed, the residue treated with 3N hydrochloric acid, and the mixture extracted with dichloromethane. The combined extract was dried (Na_2SO_4) and evaporated to give 39.5 g (100%) of *cis*-3-[*1-benzoyl-3-(2-chloroethyl)-4-piperidyl*]-*propionic acid* (**7a**). A solution of 39.5 g (0.119 mol) of **7a** in 600 ml of anhydrous benzene was added to a solution of 29 g (0.258 mol) of potassium *t*-butoxide in 600 ml of anhydrous DMSO. The mixture was stirred in a nitrogen atmosphere for 15 h at 70°. After removal of benzene under reduced pressure, 500 ml of 1N sodium hydroxide were added and the mixture was extracted with dichloromethane. The aqueous solution was acidified with conc. hydrochloric acid and extracted three times with an ether/benzene mixture. The combined extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue (crude **9a**) was dissolved in 320 ml of anhydrous ethanol, 4.8 ml of conc. sulfuric acid were added, and the solution was refluxed for 18 h. The solution was concentrated under reduced pressure to about 100 ml, diluted with water, and extracted three times with ether/benzene. The combined extract was washed successively with water, saturated aqueous sodium

hydrogencarbonate solution and water, dried (Na_2SO_4), and evaporated under reduced pressure to give 31.3 g of crude **10a**. Low-boiling impurities were removed by distillation at 40°/0.2 Torr to afford 27.5 g (75%) of pure **10a**.

3-[1-Benzoyl-3(R)-vinyl-4(R)-piperidyl]-propionic acid ethyl ester (**10b**) *from* **5b**. By using Method B (above), 1.8 g (0.005 mol) of **5b** yielded 880 mg (55%) of **10b**; b.p. 100–115°/0.015 Torr. Preparative GLPC.[5]) afforded analytically pure **10b**: $[\alpha]_D^{25} = +35.8°$ ($c = 0.97$, CH_3OH).

$C_{19}H_{25}NO_3$ (315.42) Calc. C 72.35 H 7.99 N 4.44% Found C 72.54 H 8.05 N 4.37%

Following the procedure outlined under Method C, 10.9 g (0.031 mol) of **5b** afforded 6.9 g (79%) of *3-[1-benzoyl-3(R)-vinyl-4(R)-piperidyl]-propionic acid* (**9b**); m.p. 131–133°. An analytical sample was recrystallized from ether: m.p. 132–134°; $[\alpha]_D^{25} = +64.3°$ ($c = 1.019$, CH_3OH). IR. ($CHCl_3$): 1718 cm^{-1} (acid C=O), 1628 (amide C=O), 1005 and 930 (vinyl). NMR. ($CDCl_3$): δ *ca.* 5.10 (*m*, 2H, $CH=CH_2$), 5.85 (*m*, 1H, $CH=CH_2$), 7.34 (*s*, 5H, phenyl), 10.33 (broad, 1H, COO*H*). MS.: *m/e* (rel. intensity) 287 (15), 228 (5), 214 (5), 182 (10), 148 (5), 122 (4), 105 (100), 77 (30).

$C_{17}H_{21}NO_3$ (287.35) Calc. C 71.05 H 7.37 N 4.87% Found C 71.25 H 7.46 N 4.86%

A solution of 6.4 g (0.022 mol) of **9b** in 100 ml of 4% ethanolic hydrogen chloride was left standing at room temperature for 15 h. The solvent was removed under reduced pressure and the residue again treated with 100 ml of 4% ethanolic hydrogen chloride at room temperature overnight. After repeating this procedure once more, evaporation of the solvent under reduced pressure and removal of low boiling impurities by distillation at 35°/0.1 Torr afforded 5.9 g (84%) of **10b** of 94% purity (GLPC.)[4]).

3-[1-Benzoyl-3(S)-vinyl-4(S)-piperidyl]-propionic acid ethyl ester (**10c**) *from* **5c**. Prepared in 30% yield from **5c** by Method B above. An analytical sample of **10c** was obtained by preparative GLPC.[5]): $[\alpha]_D^{25} = -35.4°$ ($c = 1.12$, CH_3OH).

$C_{19}H_{25}NO_3$ (315.42) Calc. C 72.35 H 7.99 N 4.44% Found C 72.02 H 8.14 N 4.43%

Racemic homomeroquinene (**11a**) *from* **10a**. A suspension of 1.52 g (0.0048 mol) of **10a** in 30 ml of 3N hydrochloric acid was kept at reflux for 50 h. After removal of the solvent, an aqueous suspension of freshly precipitated silver oxide was added to the residue. The mixture was stirred for 1 h, the solids were removed by filtration, the filter cake was washed thoroughly with methanol, and the filtrate evaporated to dryness. The residue was washed with ether and crystallized from methanol/acetone to yield 510 mg (58%) of **11a**, m.p. 213–215°. Recrystallization from the same solvent mixture afforded analytically pure **11a**: m.p. 214–216°. IR. (KBr): 2500 cm^{-1} (broad, $\overset{+}{N}H_2$), 1565, 1390 (COO^-), 990 and 925 (vinyl). MS.: *m/e* (rel. intensity) 183 (30), 166 (1), 155 (1), 142 (4), 138 (15), 124 (28), 110 (15), 82 (100), 70 (15), 57 (25), 44 (30).

$C_{10}H_{17}NO_2$ (183.24) Calc. C 65.54 H 9.35 N 7.64% Found C 65.33 H 9.31 N 7.46%

Homomeroquinene (**11b**) *from* **10b**. A solution of 873 mg (0.0028 mol) of **10b** in 50 ml of a 4:1 mixture of 5N aqueous potassium hydroxide and methanol was kept at reflux for 18 h. The methanol was removed by distillation and the aqueous solution rendered acidic by the addition of conc. hydrochloric acid. The solvent was removed under reduced pressure, and to ensure complete dryness of the residue, benzene was added several times and removed by distillation. The residue was extracted with hot ethanol and the extract evaporated to dryness. An aqueous solution of the residue was treated with freshly precipitated silver oxide. After removal of the solids by filtration, hydrogen sulfide was passed through the filtrate, and the precipitate was filtered. The filtrate was evaporated to dryness and the residue crystallized from methanol/acetone to afford 244 mg (48%) of **11b**. Two recrystallizations from methanol/acetone yielded pure **11b**: m.p. 210–211°, mixed m.p. with material obtained by degradation [2]: 211–212°; $[\alpha]_D^{24} = +43.55°$ ($c = 1.05$, H_2O)[6]).

N-Benzoylquinotoxine (**17**) *from Quinine*. A solution of 22 g (0.052 mol) of quinine sulfate (*Maarssen*) in 100 ml of 90% acetic acid was heated at reflux temperature for 8 h. The solvent was removed under reduced pressure and the residue dissolved in water. The aqueous solution was rendered alkaline by the addition of 6N NaOH and extracted with dichloromethane. The

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[5]) Preparative GLPC. was carried out on a 10 ft. × 0.375 inch column of 20% SE-30 on Anakrome A at 220° with a nitrogen flow rate of 150 ml/min.

[6]) Lit. [2] reports $[\alpha]_D^{20} = +50.4°$ ($c = 1.91$, H_2O).

extract was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to give 20 g of crude *quinotoxine* (**18**). To a solution of this product in 600 ml of benzene were added 25 g of wet potassium carbonate and 7.2 ml of benzoyl chloride. The mixture was stirred at room temperature for 3 days. The organic layer was separated, washed with a dilute solution of sodium hydroxide and extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to afford 31 g of crude benzoylation product. Purification was achieved by chromatography on 1 kg of silica gel (*Merck* 70–320) with ethyl acetate as the eluent. After initial fractions totalling 5 l, which gave 6.5 g of impurities after evaporation, the next five cuts of 1000 ml each were combined and evaporated to dryness to yield 17.4 g of a yellow solid. Treatment with ethanolic hydrogen chloride and crystallization of the product from ethanol/ether afforded 13.9 g (58%) of the *hydrochloride of* N-*benzoylquinotoxine* (**17**): m.p. 199–201°. Recrystallization from ethanol yielded analytically pure hydrochloride of **17** as light yellow crystals: m.p. 202–204° (dec.); $[\alpha]_D^{25} = +45.38°$ (c = 0.985, CH_3OH). IR. (KBr): 1975–2270 cm^{-1} (series of bands, $\overset{+}{N}H$), 1710 (C=O), 1635 (amide C=O). NMR. (DMSO-d_6): δ 3.89 (*s*, 3H, OCH_3), *ca.* 5.18 (*m*, 2H, $CH=CH_2$), 5.81 (*m*, 1H, $CH=CH_2$), 7.37 (*s*, 5H, phenyl), 7.64 (*s*, 1H, C*H*-5'), 7.69 and 8.35 (*AB*-pattern, 2H, J = 10 Hz, C*H*-7' and C*H*-8'), 8.21 (*d*, 1H, J = 5 Hz, C*H*-3'), 9.12 (*d*, 1H, J = 5 Hz, C*H*-2').

$C_{27}H_{28}N_2O_3 \cdot HCl$ (464.98) Calc. C 69.74 H 6.29 N 6.02% Found C 69.67 H 6.47 N 5.90%

16 ml. of a 0.128 N methanolic solution of sodium methoxide were added to 954 mg (0.002 mol) of **17**. HCl. The solution was evaporated to dryness under reduced pressure, the residue repeatedly extracted with ether, and the extract filtered through Celite Filter-Aid. The filtrate was evaporated to dryness. The residue crystallized on standing at room temperature. Recrystallization from ether yielded 420 mg (50%) of analytically pure *N-benzoylquinotoxine* (**17**); m.p. 112–113°; $[\alpha]_D^{25} = +40.59°$ (c = 1.003, CH_3OH). IR. ($CHCl_3$): 1693 cm^{-1} (C=O), 1622 (amide C=O), 1030, 998 and 927 (vinyl). UV. max (CH_3OH): 210 nm (ε = 53 100), 240 (sh) (21 200), 255 (sh) (11 500), 344–345 (4600). NMR. ($CDCl_3$): δ 3.89 (*s*, 3H, OCH_3), *ca.* 5.12 (*m*, 2H, $CH=CH_2$), 5.90 (*m*, 1H, $CH=CH_2$), 7.35 (*s*, 5H, phenyl), 7.38 (*dd*, 1H, J_o = 10 Hz, J_m = 2 Hz, C*H*—7'), 7.54 (*d*,1H, J = 5 Hz, C*H*—3'), 7.80 (*d*, 1H, J_m = 2 Hz, C*H*—5'), 8.01 (*d*, 1H, J_o = 10 Hz, C*H*—8'), 8.82 (*d*, 1H, J = 5 Hz, C*H*—2'). MS.: *m/e* (rel. intensity) 428 (15) M^+, 323 (20), 295 (10), 259 (5), 214 (20), 202 (10), 186 (45), 173 (30), 160 (50), 158 (55), 149 (15), 105 (100), 77 (100).

$C_{27}H_{28}N_2O_3$ (428.51) Calc. C 75.67 H 6.59 N 6.54% Found C 75.95 H 6.62 N 6.54%

N-Benzoylquinotoxine (**17**) *from* **10b**. To 50 ml of a stirred ethereal solution containing 2.12 ml of a 1.6 N solution of butyllithium in hexane was added, at −70° under nitrogen, a solution of 810 mg (0.034 mol) of 4-bromo-6-methoxy-quinoline (**15a**) in 50 ml of anhydrous ether, followed by 790 mg (0.068 mol) of freshly distilled tetramethylethylenediamine (from CaH_2) in 50 ml of anhydrous ether, and finally by 1.072 g (0.034 mol) of **10b** in 50 ml of anhydrous ether. During and between the additions, at intervals of 30 min, the temperature of the mixture was maintained strictly at −70°. After the additions were completed, the mixture was stirred at −70° for 3 days. Then 10 ml of water and 200 ml of ether were added to the reaction mixture and the temperature was allowed to rise to 20°. The ethereal layer was separated, washed with 50 ml of water, dried (Na_2SO_4) and evaporated under reduced pressure to yield 2.77 g of a yellow oil. Purification of the reaction product was accomplished by column chromatography on 200 g of silica gel (*Merck* 0.2–0.05 mesh, column inner diameter 20 mm) with ethyl acetate as eluent. Fractions of 50 ml were collected and the progress of the chromatography was monitored by TLC. [silica gel F_{254} (*Merck*); ethyl acetate]. Fractions 7–17 were combined, the solvent was removed under reduced pressure and the resulting N-benzoylquinotoxine (**17**) (456 mg, 34.5%) was crystallized twice from ether to yield pure **17**: m.p. 111–112°; $[\alpha]_D^{25} = +41.6°$ (c = 0.975, CH_3OH); mixed m.p. with material obtained *via* method A: 111–112°.

Quinotoxine (**18**) *from* **10b**. A solution of 631 mg (0.002 mol) of **10b** in 10 ml of anhydrous tetrahydrofuran was added dropwise in an atmosphere of nitrogen to a refluxing solution of 532 mg (0.0023 mol) of ethyl quininate (**14**) and 448 mg (0.004 mol) of potassium *t*-butoxide in 15 ml of anhydrous tetrahydrofuran. The mixture was kept at reflux for 3 h. The solvent was subsequently removed and the residue dissolved in 50 ml of 1N NaOH. The aqueous solution was washed with benzene and rendered acidic by the addition of 50 ml of conc. HCl. After the addition of a further

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°.

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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).

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