291. The Stereoselectivity of Ketone Reduction with *Sporotrichum Exile*. Resolution of *cis*- and *trans*-2-Benzoyloctahydro-6(2*H*)-isoquinolones

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(8. X. 73)

Zusammenfassung. Das 4a(*S*), 8a(*R*)-Enantiomere des *cis*-2-Benzoyloctahydro-6(2*H*)-isochinolons wird durch *Sporotrichum exile* QM-1250 unter anaerobischen Bedingungen achtmal schneller reduziert als das 4a(*R*), 8a(*S*)-Enantiomere. Bei der entsprechenden *trans*-Verbindung wurde diese Stereospezifität nicht beobachtet.

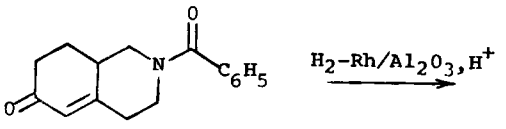
The *cis*- and *trans*-2-benzoyloctahydro-6(2*H*)-isoquinolones [1] have served as incipient materials in the preparation of *cis*- and *trans*-3-vinyl-4-piperidineacetic acids [2], which were utilized by us and other investigators in the total syntheses of cinchona [3] and heteroyohimbine alkaloids [4]. We now report the optical resolutions of these isoquinolones, which enabled us to synthesize several members of the forementioned alkaloid families in their natural enantiomeric forms.

The resolution in the *cis* series was effected by *Sporotrichum exile* QM-1250, which under anaerobic conditions reduced more rapidly the 4a(*S*),8a(*R*)-enantiomer (*Scheme 1*). After 4 hours of incubation a 1.6:1 mixture of the approximately 70% optically pure 4a(*S*),8a(*R*)-alcohol **3a** and 4a(*R*),8a(*S*)-ketone **4a** was obtained. Oxidation of alcohol **3a** with chromic acid gave the 4a(*S*),8a(*R*)-ketone **5a** of the same optical purity. Due to the greater solubility of racemic ketone **2** in benzene, the optically pure enantiomers **4** and **5** could be obtained by recrystallization of the partially resolved **4a** and **5a**. The optical purity of **5a** could also be improved by a repeated treatment with *Sporotrichum exile*, in which case, after oxidation of the intermediate alcohol **3b**, the 4a(*S*),8a(*R*)-ketone **5b** was obtained in 90% optical purity.

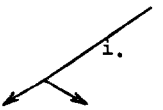
The 70% optical purity of the alcohol **3a** and the ketone **4a** obtained by single treatment with *Sporotrichum exile* indicated that the 4a(*S*),8a(*R*)-enantiomer **5** was reduced more rapidly than 4a(*R*),8a(*S*)-enantiomer **4**. The rates of reduction were obtained by reducing the pure enantiomers under the same conditions. This is illustrated in Figure 1. The individual points on the curves were obtained by removing aliquots at the indicated times, by extracting the substrates and products with methylene chloride and separating the alcohols and unreacted ketones by chromatography. The amounts of materials were determined spectroscopically. These results indicated that the initial velocity of reduction was 8 times greater for **5** than for **4**.

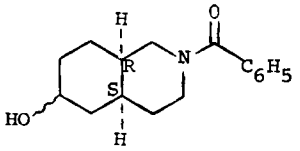
The 'steroidal' conformations of ketones **4** and **5** were indicated by their negative and positive ketone *Cotton* effects respectively, and by similarity of the optical rotatory dispersion curve of **4** in the 300 mμ region with that of 5β-androstan-17β-ol-3-one [5] (**6**, partial structure).

Scheme 1

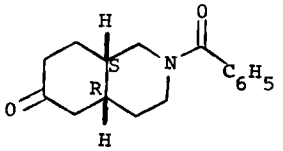


1 **2** racemic

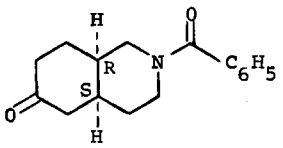




3a 70% optically pure

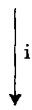


4a 70% optically pure



5a 70% optically pure

Optically pure **4**



3b 90% optically pure

5b 90% optically pure

Optically pure **5**

i = *Sporotrichum exile*
ii = oxidation with CrO_3
iii = recrystallization from benzene

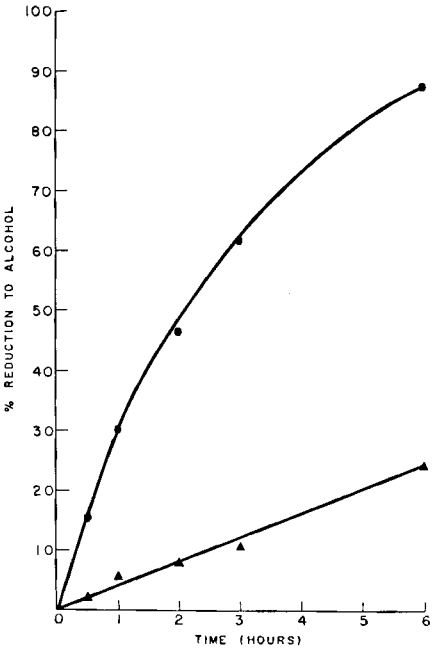
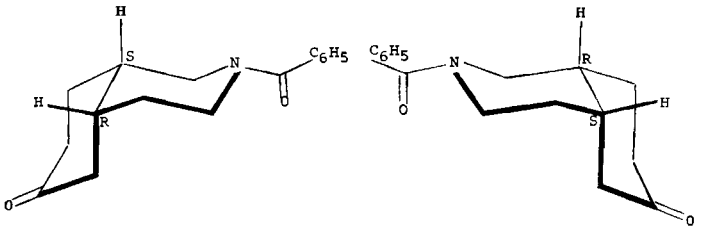
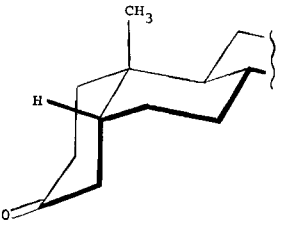


Fig. 1. ● *4a*(S), *8a*(R)-*enantiomer* (**5**). ▲ *4a*(R), *8a*(S)-*enantiomer* (**4**)

Reduction of racemic *trans*-2-benzoyloctahydro-6(2*H*)-isoquinolone (**7**) with *Sporotrichum exile* under the same conditions proceeded at approximately the same rate as in the *cis* series. However, at 50% conversion the isolated unreacted ketone and alcohol exhibited only weak rotations, $[\alpha]_D^{25}$ +4.0° and −4.5° in methanol, respec-

Scheme 2

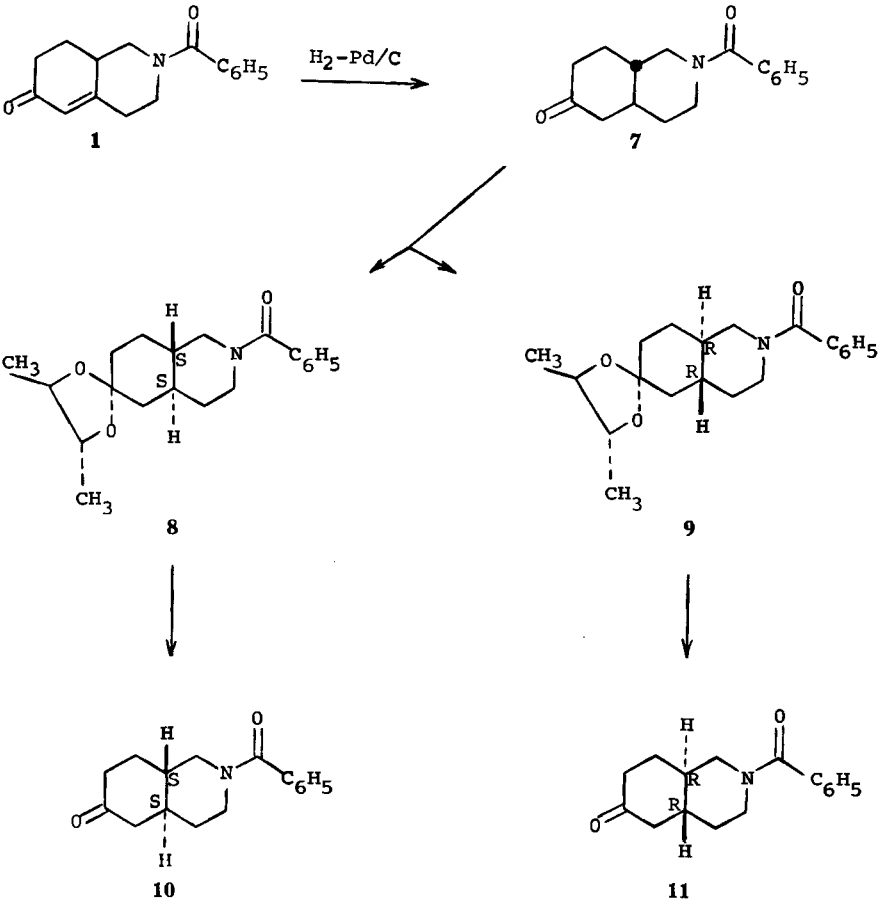




tively. This corresponds only to 6.5% optical purity. Therefore, in this case the reduction was not significantly stereoselective with respect to the enantiomeric form.

Resolution in the *trans* series was accomplished by the method of *Casanova & Corey* [6] (*Scheme 3*). The racemic *trans*-ketone **7** reacted with butane-2(*R*),3(*R*)-diol to give in high yield the diastereomeric 4a'(*S*),8a'(*S*)- and 4a'(*R*),8a'(*R*)-acetals, **8** and **9**, respectively. Separation of **8** and **9** was effected smoothly by crystallization from petroleum ether in which the acetal **8** is significantly more soluble than **9**. Hydrolysis in 70% acetic acid led to the optically pure 4a(*S*),8a(*S*)-**10** and 4a(*R*),8a(*R*)-enantiomer **11**. The absolute configurations of **10** and **11** were apparent from inspection of the ketone regions of their respective circular dichroism and optical rotatory dispersion curves. Enantiomer **10** exhibited a positive *Cotton* effect while that of **11** was negative.

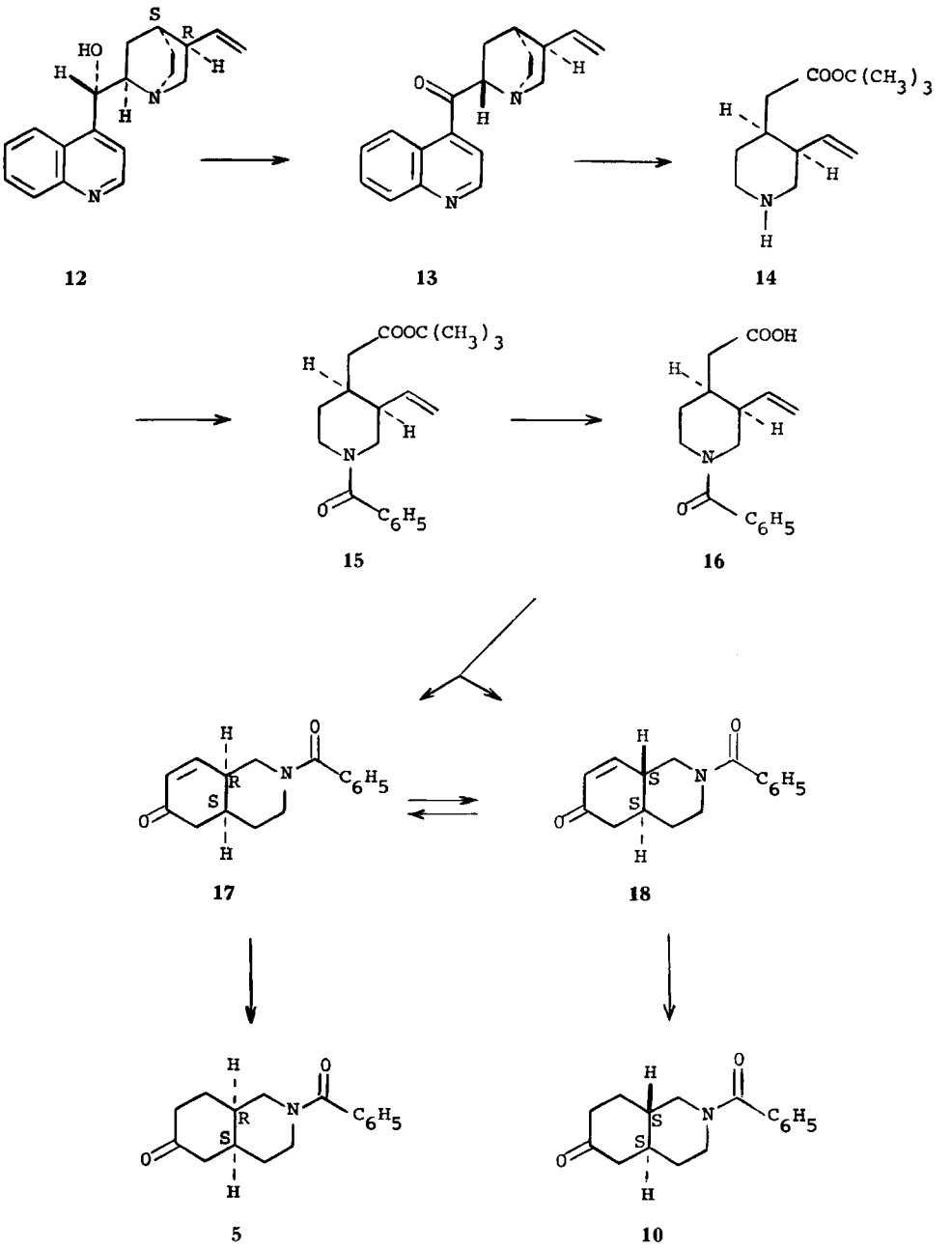
Scheme 3



The absolute configurations and optical purity of the isoquinolones **4**, **5**, **10** and **11** were further confirmed by obtaining the *cis*-4a(*S*),8a(*R*)-enantiomer **5** and the *trans*-4a(*S*),8a(*S*)-enantiomer **10** from naturally occurring cinchonine (**12**) *via* meroquinene

t-butyl ester (**14**), both of known absolute configurations. The sequence of reactions employed did not affect the configuration at the center corresponding to C(4a) of **5** and **10** (*Scheme 4*).

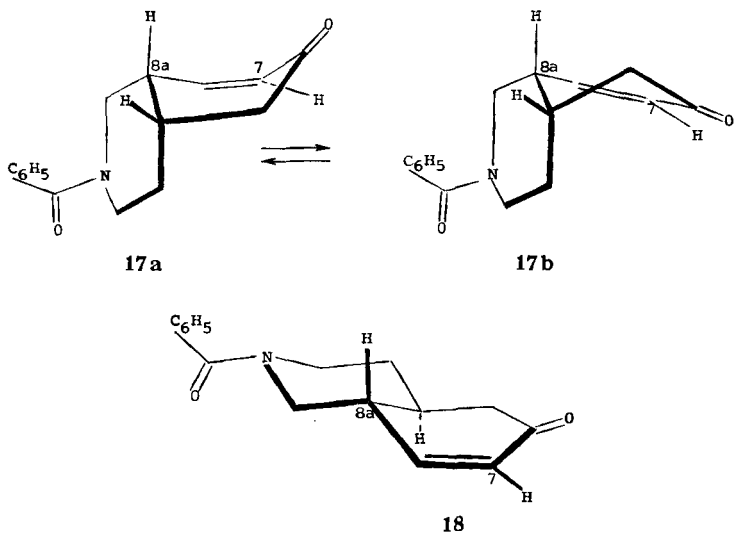
Scheme 4



Cinchonidinone (**13**) was obtained in high yield by oxidation of **12** with benzophenone in the presence of potassium *t*-butylate [7]. Subsequent oxidation of the potassium enolate of **13** in *t*-butylalcohol with molecular oxygen [8] then led to meroquinene *t*-butyl ester (**14**), which was purified *via* its D-tartrate salt. Benzoylation and hydrolysis then gave N-benzoylmeroquinene (**16**). Polyphosphoric acid promoted cyclization at room temperature took more than five days to come to near completion. An approximately 1:2.4 mixture of the *cis*- and *trans*-α,β-unsaturated ketones **17** and **18** was obtained, which were separated by chromatography. In separate experiments, the pure ketones **17** and **18** epimerized under the reaction conditions described above to the same equilibrium mixture as obtained in the cyclization of **16**.

The unsaturated isoquinolones were differentiated by their circular dichroism in 350 nm region [9]. The *cis*-isomer **17** exhibited a positive *Cotton* effect ($[\Theta]^{324}_{sh}$ + 740° and $[\Theta]^{330}_{max}$ + 760°) indicating a counter-clockwise chirality of the skew enone moiety. This is compatible with a *cis* ring-junction. Molecular models reveal that the 'non-steroidal' half-boat conformation **17a** accommodates the skew enone, while the corre-

Scheme 5



sponding half-chair conformation **17b** would require a planar enone. The low intensity of the *Cotton* effect is probably due to an equilibrium of these two conformations. That only 'non-steroidal' conformations are being considered is due to the NMR. evidence which shows the coupling (6.06, J = 2 Hz) of H(7) by allylic H(8a). This coupling requires that H(8a) be axial to the carbocyclic ring.

The *trans*-α,β-unsaturated ketone **18** exhibited a negative *Cotton* effect ($[\Theta]^{334}_{min}$ – 1720° and $[\Theta]^{344}_{min}$ – 1730°) in agreement with clockwise chirality of its enone moiety.

Catalytic hydrogenation of **17** and **18** gave the optically pure 4a(*S*),8a(*R*)-octahydroisoquinolone **5** and 4a(*S*),8a(*S*) analog **10**, respectively, which were identical with the same compounds obtained by resolution.

Experimental Part

General Remarks. The data of UV.-, IR.- and NMR.-Spectra are given in nm (ε), cm^{-1} and δ, respectively.

Racemic cis-*2-Benzoyloctahydro-6(2H)-isoquinolone* (**2**). To a solution of 151 g (0.595 mol) of rac-2-benzoyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolone (**1**) in 3000 ml of abs. ethanol were added 300 ml of 3N aqueous hydrochloric acid and 30 g of 5% rhodium on alumina catalyst. The mixture was hydrogenated at room temp. and atmospheric pressure until the uptake of hydrogen ceased (1.5 h). Catalyst was separated by filtration and washed thoroughly with ethanol. The filtrate was evaporated to a small volume *in vacuo*, diluted with 3500 ml of dichloromethane and washed with 3N aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate and sodium chloride solutions. The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness to yield 155 g of crude crystalline product. Gas chromatographic analysis indicated that it contained 61.9% of rac-*cis*-2-benzoyloctahydro-6(2*H*)-isoquinolone (**2**) and 13% of corresponding *trans* analog. This product was recrystallized twice from benzene to give 75.5 g (49.5%) of **2**, m.p. 146–148°. The analytical sample had m.p. 147–148.5°. – IR. ($CHCl_3$): **1713** (ketone), 1625 (amide), 1299.

$C_{16}H_{19}NO_2$ (257.32) Calc. C 74.68 H 7.44 N 5.44 Found C 74.30 H 7.44 N 5.47

4a(R), *8a*(S)-*2-Benzoyloctahydro-6*(2H)-*isoquinolone* (**4**) *and 4a*(S), *8a*(R)-*2-Benzoyloctahydro-6*(2H)-*isoquinolone* (**5**). The bioconversion medium contained 20 g of Edamin (*Sheffield Chemical Co.*), 3 g of cornsteep liquor (*Corn Products Co.*), and 50 g of dextrose per liter (distilled water) adjusted to pH 5.0. In a typical fermentation 500 ml of the sterilized medium in a 2 l cotton-plugged Erlenmeyer flask was inoculated with 20 ml of a 72 h vegetative growth of *Sporotrichum exile* QM 1250, and incubated at 28° on a rotary shaker. After 48 h of growth, a solution of 500 mg of rac-2-benzoyloctahydro-6(2*H*)-isoquinolone (**2**) in 10 ml of ethanol was added. The cotton plug was replaced with a rubber stopper and incubation was continued as before for an additional 4 h period. The whole broth was then extracted twice with one liter portions of methylene chloride. Extracts from 10 such fermentations were combined, dried over anhydrous sodium sulfate and evaporated. Chromatography on silica-gel with 95:5 chloroform/methanol gave 1.5 g of crystalline 4a(*R*), 8a(*S*)-2-benzoyloctahydro-6(2*H*)-isoquinolone (**4a**), with $[\alpha]_D^{25} = +44°$ (c = 1.0, CH_3OH), and 2.41 g of oily 4a(*S*),8a(*R*)-2-benzoyldecahydro-6-isoquinolol (**3a**) with $[\alpha]_D^{24.3} = -53.9°$ (c = 1.0, CH_3OH). To the solution of product **3a** in 250 ml of methylene chloride was added 66 ml of 2% chromium trioxide in 95% acetic acid, and stirred at room temp. for 20 h. It was then washed with diluted sodium hydrogen sulfite solution, 2N sodium carbonate, and water, dried over anhydrous sodium sulfate and evaporated. It gave 1.9 g of crystalline 4a(*S*), 8a(*R*)-2-benzoyloctahydro-6(2*H*)-isoquinolone (**5a**), with $[\alpha]_D^{25.3} = -40.6°$ (c = 0.955, CH_3OH).

The ketone **5a** (1.9 g) was subjected to the action of *Sporotrichum exile* QM 1250 as described above. The same type of work-up procedure afforded a mixture, which after chromatography gave 0.3 g of crystalline 4a(*R*), 8a(*S*)-ketone **4b**, with $[\alpha]_D^{25.4} +13.7°$ (c = 1.1, CH_3OH), and 1.38 g of oily 4a(*S*), 8a(*R*)-isoquinolol **3b**, with $[\alpha]_D^{25.2} -71.9°$ (c = 0.95, CH_3OH). Oxidation of **3b** gave 1.1 g of crystalline 4a(*S*), 8a(*R*)-ketone **5b**, with $[\alpha]_D^{25.2} = -54°$ (c = 0.97, CH_3OH).

The partially resolved ketone **4a** (1.5 g) was recrystallized twice from 5 ml of benzene at room temp. to give 1.1 g (22%) of optically pure 4a(*R*), 8a(*S*)-2-benzoyloctahydro-6(2*H*)-isoquinolone (**4**). The analytical sample had m.p. 183.5–185.5°, $[\alpha]_D^{25} = +61.15°$ (c = 1.045, CH_3OH). – ORD. (c = 0.2574, CH_3OH): $[\Phi]^{589} +157°$, $[\Phi]^{332}_{max} +626°$, $[\Phi]^{317}_{min} +547°$, $[\Phi]^{253}_{max} +3999°$. – CD. ($c$ = 0.2574, CH_3OH): $[\Theta]^{293}_{min} -1060°$.

$C_{16}H_{19}NO_2$ (257.335) Calc. C 74.68 H 7.44 N 5.44 Found C 74.68 H 7.72 N 5.31

The partially resolved ketone **5b** (1.1 g) was recrystallized twice from benzene to give 0.95 g (19%) of optically pure 4a(*S*), 8a(*R*)-2-benzoyloctahydro-6(2*H*)-isoquinolone (**5**); m.p. 182.5–185°, $[\alpha]_D^{25} -61.15°$ (c = 1.04, CH_3OH). – ORD. (c = 0.2574, CH_3OH): $[\Phi]^{589} -162°$, $[\Phi]^{333}_{min} -622°$, $[\Phi]^{318}_{max} -547°$, $[\Phi]^{253}_{min} -5249°$. – CD. ($c$ = 0.2574, CH_3OH): $[\Theta]^{293}_{max} +1040°$.

$C_{16}H_{19}NO_2$ (257.335) Calc. C 74.68 H 7.44 N 5.44 Found C 74.77 H 7.49 N 5.44

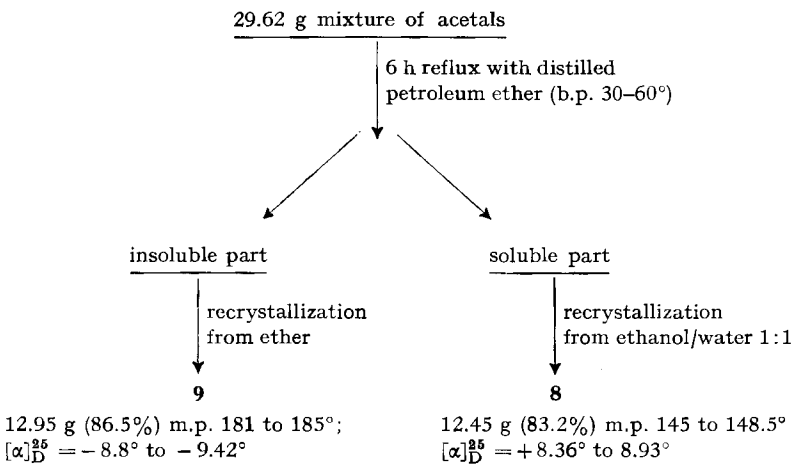
Reduction of pure Enantiomers **4** *and* **5**. Culture growth for determination of the relative rates of reduction of **4** and **5** was prepared as described for reduction of **2**. Immediately before addition of substrate, the culture was diluted with an equal volume of sterile distilled water, giving a cell

concentration of 0.42 g dry weight per liter, and 100 ml portions were dispensed into two 500 ml Erlenmeyer flasks. Fifty mg of **4** or **5** in 2 ml ethanol were added separately to flasks, the flasks were purged with nitrogen gas, rubber stoppers were inserted, and incubation was continued as above. One ml samples at various times were extracted twice with 2 ml of methylene chloride. The solvent fractions were pooled and evaporated to a dry residue, which was redissolved in 0.5 ml methylene chloride, and duplicate 100 μl samples spotted on *Brinkmann* SG_{254} TLC plates. The plates were developed for 15 cm in benzene/methanol 90:10. The shortwave UV. absorbing spots were scraped and eluted in 5 ml of ethanol, and their extinctions read at 230 nm on a *Gilford* 2400-S spectrophotometer, averaged, and compared to a standard curve of known concentrations of **4** and **5**. The results are summarized graphically in Fig. 1.

Rac-trans-*2-Benzoyloctahydro-6(2*H)-*isoquinolone* (**7**). To a solution of 51.0 g (0.20 mol) of rac-2-benzoyl-1,3,4,7,8,8a-hexahydro-6(2*H*)-isoquinolone (**1**) in 2 l of 95% ethanol was added 5 g of Pd/C (10%) and hydrogenated at room temp. and 3 atm pressure. The reaction ceased after one mol-equiv. of hydrogen was taken up. Catalyst was removed by filtration through Celite and washed well with chloroform. The combined filtrates were evaporated *in vacuo* to give 53.4 g of crude product. Fractional crystallization from 95% ethanol gave 13.14 g of rac-*trans*-2-benzoyl-octahydro-6(2*H*)-isoquinolone (**7**), m.p. 158–160°. The mother liquors were chromatographed on 190 *Brinkmann* silica gel preparative plates with 2-propanol to give additional 7.63 g of **7**, together 20.77 g (40%). – IR. ($CHCl_3$): 1715 (ketone); 1630 (amide); 1445, 1327, 1105.

$C_{16}H_{19}NO_2$ (257.32) Calc. C 74.68 H 7.44 N 5.44 Found C 74.73 H 7.57 N 5.26

2'-Benzoyl-4(R), *5*(R)*-dimethyl-1',2',3',4',4a'*(S), *7',8',8a'*(S)*-octahydrospiro[1,3-dioxolane-2,6'* (*5'*H)*-isoquinoline*] (**8**) *and 2'-Benzoyl-4*(R), *5*(R)*-dimethyl-1',2',3',4',4a'*(R), *7',8',8a'*(R)*-octahydrospiro[1,3-dioxolane-2,6'* (*5'*H)*-isoquinoline*] (**9**). To a solution of 23.4 g (0.0909 mol) of rac-*trans*-2-benzoyloctahydro-6(2*H*)-isoquinolone (**7**) in 2 l of anhydrous benzene was added 2.24 g of *p*-toluenesulfonic acid and 9.83 g (0.109 mol) of (–)-butane-2(*R*), 3(*R*)-diol. The resulting solution was refluxed for 3 h and the water formed in the reaction (*ca.* 1.7 ml) was collected in a *Dean-Stark* water separator. After the addition of 18 ml of pyridine, the mixture was diluted to 4 l with benzene, washed 4 times with 100 ml of water, dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The last traces of pyridine were removed by co-distillation with toluene *in vacuo*. The crystalline residue, 29.62 g was fractionally crystallized by repeating several times the following system:



Analytical sample of 2-benzoyl-4(*R*), 5(*R*)-dimethyl-1',2',3',4',4a'(*S*), 7',8',8a'(*S*)-octahydrospiro[1,3-dioxolane-2,6'(5*H*)-isoquinoline] (**8**): m.p. 147–148.5°, $[\alpha]_D^{25} = +9.95°$ ($c = 1.005$, CH_3OH). – IR. ($CHCl_3$): 1618 (amide), 1440, 1370, 1310, 1285, 1237, 1083, 1040, 978, 950, 923, 862, 837. – NMR. ($CDCl_3$): 1.25 (*d*, $J = 6$ Hz, CH_3); 3.64 (*m*, C*H*); 7.38 (*s*, phenyl).

$C_{20}H_{27}NO_3$ (329.43) Calc. C 72.92 H 8.26 N 4.25 Found C 72.98 H 8.32 N 4.33

Analytical sample of 2′-benzoyl-4(*R*), 5(*R*)-dimethyl-1′,2′,3′,4′,4a′(*R*), 7′,8′,8a′(*R*)-octahydrospiro[1,3-dioxolane-2,6′(5′*H*)-isoquinoline] (**9**): m.p. 182–184°, $[\alpha]_D^{25} = -8.75°$ (*c* = 0.96, CH_3OH). – IR. ($CHCl_3$): 1618 (amide), 1442, 1375, 1312, 1290, 1240, 1092, 1045, 983, 958, 932, 905, 840. – NMR. ($CDCl_3$): 1.24 (*d*, *J* = 6 Hz, CH_3); 3.62 (*m*, CH); 7.40 (*s*, phenyl).

$C_{20}H_{27}NO_3$ (329.43) Calc. C 72.92 H 8.26 N 4.25 Found C 73.08 H 8.36 N 4.24

4a(S), *8a*(S)-*2-Benzoyloctahydro-6*(2H)-*isoquinolone* (**10**). A solution of 2.5 g (0.076 mol) of 2′-benzoyl-4(*R*), 5(*R*)-dimethyl-1′,2′,3′,4′,4a′(*S*), 7′,8′,8a′(*S*)-octahydrospiro[1,3-dioxolane-2,6′(5′*H*)-isoquinoline] (**8**) in 100 ml of 70% acetic acid was heated at 100–105° for 1.5 h. The reaction mixture was evaporated *in vacuo* to a small volume (*ca.* 5 ml), diluted with 1 l of benzene, washed with 100 ml of 2N aqueous sodium carbonate and 3 times with 100 ml of water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. It gave 1.96 g (100%) of 4a(*S*), 8a(*S*)-2-benzoyloctahydro-6(2*H*)-isoquinolone (**10**), m.p. 151–153° (from abs. ethanol); $[\alpha]_D^{25} = +61.8°$ (*c* = 1.01, $CHCl_3$). – ORD (*c* = 0.2574, CH_3OH); $[\Phi]^{589} + 130°$, $[\Phi]^{309}_{max} + 3120°$, $[\Phi]^{290}$ 0°, $[\Phi]^{267}_{min} - 3400°$. – CD. (*c* = 0.2574, CH_3OH): $[\Theta]^{291}_{max} + 4818°$.

$C_{16}H_{19}NO_2$ (257.32) Calc. C 74.68 H 7.44 N 5.44 Found C 74.94 H 7.48 N 5.44

4a(R), *8a*(R)-*2-Benzoyloctahydro-6*(2H)-*isoquinolone* (**11**). A solution of 0.329 g (0.001 mol) of 2′-benzoyl-4(*R*), 5(*R*)-dimethyl-1′,2′,3′,4′,4a′(*R*), 7′,8′,8′a(*R*)-octahydrospiro[1,3-dioxolane) 2,6′(5′*H*)-isoquinoline] (**9**) in 50 ml of 70% acetic acid was heated at 100–105° for 4 h and 40 min. The reaction mixture was evaporated *in vacuo* to a small volume (*ca.* 2 ml), diluted with 500 ml of benzene, washed with 50 ml of 2N aqueous sodium carbonate and 3 times with 50 ml of water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. It gave 0.256 g (100%) of 4a(*R*), 8a(*R*)-2-benzoyloctahydro-6(2*H*)-isoquinolone (**11**), m.p. 151–153° (from abs. ethanol); $[\alpha]_D^{25} = -62.60°$ (*c* = 1.005, $CHCl_3$). – ORD. (*c* = 0.2248, CH_3OH): $[\Phi]^{589} - 146°$, $[\Phi]^{307}_{min} - 3307°$, $[\Phi]^{288}$ 0°, $[\Phi]^{264}_{max} + 3891°$. – CD. (*c* = 0.0087 M, CH_3OH): $[\Theta]^{290}_{min} - 5690°$.

$C_{16}H_{19}NO_2$ (257.32) Calc. C 74.68 H 7.44 N 5.44 Found C 74.72 H 7.49 N 5.59

Cinchonidinone (**13**). To a solution of 84 g (0.75 mol) of potassium *t*-butoxide in 400 ml of dry benzene was added a suspension of 88.3 g (0.3 mol) of cinchonine (**12**) and 245 g (1.35 mol) of benzophenone in 600 ml of dry benzene, and the mixture was then heated under gentle reflux for 20 h, with stirring, in an atmosphere of dry nitrogen. To the cooled, reddish-brown mixture was added 1 l of 10% aqueous hydrochloric acid, and the two-phase mixture was stirred until all the enolate had dissolved. The yellow aqueous layer was separated and washed with 250 ml of ether. The organic phases were extracted four additional times with 200 ml portions of 10% hydrochloric acid and the combined aqueous phases were neutralized to pH *ca.* 9 with conc. ammonium hydroxide and extracted thoroughly with methylene chloride. The organic extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was crystallized from ether to give 74.5 g (85% yield) of yellowish cinchonidinone (**13**) m.p. 128–130°. After recrystallization from ethanol, an analytical sample had m.p. 133–134°, $[\alpha]_D^{28} = +80.5°$ (*c* = 1.52, in ethanol; after equilibration of the ethanolic solution for 20 h at 22°).

$C_{19}H_{20}N_2O$ (292.39) Calc. C 78.05 H 6.98 N 9.68 Found C 78.03 H 7.01 N 9.58

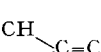
Meroquinene t-butyl ester (**14**). A solution of 9.4 g (0.24 mol) of potassium in 400 ml of dry *t*-butyl alcohol was saturated with dry oxygen by bubbling the dry gas through the solution for 15 min at room temp. and atmospheric pressure. The 35 g (0.12 mol) of cinchonidinone (**13**) was then added as a slurry in 200 ml of purified *t*-butyl alcohol. The reaction mixture was stirred without external heating while oxygen was bubbled through at a moderate rate. A gradual rise of temperature to *ca.* 40° was observed while the originally reddish color was discharged and a yellowish solid gradually precipitated. After $4^1/_2$ h, when the temperature of the reaction mixture had dropped to 22° and TLC. showed no longer any cinchonidinone, the solution was neutralized with acetic acid, and evaporated *in vacuo* almost to dryness. Water was added, the pH was adjusted to *ca* 9 by addition of concentrated ammonium hydroxide, and the aqueous phase was extracted thoroughly with ether; the ethereal phase was washed twice with 2N sodium carbonate, then dried over anhydrous magnesium sulfate and evaporated to dryness. It gave 14.5 g of crude meroquinene *t*-butyl ester (**14**), which could be purified by distillation (although with considerable losses due to pyrolysis), b.p. 94–96°/0.35 Torr, $n^{22} = 1.4674$, $[\alpha]_D^{25} = +44°$ (*c* = 1.125, EtOH).

Instead, the crude product (14.5 g) was dissolved in 50 ml of abs. ethanol, and added to a solution of 9.9 g of D-tartaric acid in 50 ml of abs. ethanol. The crystals formed upon refrigeration overnight were separated by filtration and washed with cold acetone to give 17.4 g (38% yield) of meroquinene *t*-butyl ester D-tartrate, m.p. 165–166° after drying at 50° *in vacuo*. After three recrystallizations from methanol/petroleum ether, an analytical sample had m.p. 178°, $[\alpha]_D^{25} = +30.2°$ ($c = 1.19$, H_2O).

$C_{13}H_{23}NO_2 \cdot C_4H_6O_6$ (375.43) Calc. C 54.39 H 7.79 N 3.73 Found C 54.39 H 7.84 N 3.81

N-Benzoylmeroquinene t-butyl ester (**15**). A solution of 10 g (0.027 mol) of meroquinene *t*-butyl ester D-tartrate in 1200 ml of chloroform was shaken twice with 100 ml of 1N aqueous sodium hydroxide. The alkaline aqueous layers were back-washed with 200 ml of chloroform and the combined chloroform solutions were dried over anhydrous sodium sulfate, filtered and evaporated to yield 6.10 g (0.027 mol) of meroquinene *t*-butyl ester (**14**). To the solution of **14** and 5.2 g benzoyl chloride in 150 ml of benzene was added dropwise 5N aqueous potassium carbonate until a pH of *ca.* 9 was reached. The reaction mixture was stirred vigorously for 1 h, then diluted with 2850 ml of benzene, washed three times with 100 ml of 6N sodium hydroxide, three times with 100 ml of water, two times with 100 ml of 3N hydrochloric acid, and finally to neutrality with water. After drying over anhydrous sodium sulfate, it was evaporated to dryness. The residue was dissolved in methanol, refluxed for 1 h, filtered and evaporated. It gave 9.4 g of crude product, which was chromatographed on a 800 g silica gel column with 1:1 benzene/ethyl acetate eluent. It gave 6.44 g (72.4% yield) of crystalline N-benzoyl-meroquinene *t*-butyl ester (**15**), m.p. 65–67° after recrystallization from ether; $[\alpha]_D^{25} = +42.12°$ ($c = 1.0$, CH_3OH). – NMR. ($CDCl_3$): 1.43 [*s*, $COOC(CH_3)_3$]; 2.20 [bs, $-CH_2-COOC(CH_3)_3$]; 4.83–5.33 (*m*, $-CH=CH_2$); 5.83 (*m*, $-CH=CH_2$); 7.37 (*s*, phenyl).

$C_{20}H_{27}NO_3$ (329.445) Calc. C 72.92 H 8.26 N 4.25 Found C 72.95 H 8.11 N 4.17

N-Benzoylmeroquinene (**16**). To a solution of 5.19 g (0.0157 mol) of N-benzoylmeroquinene *t*-butyl ester (**15**) in 150 ml of methanol was added 150 ml of 1N aqueous sodium hydroxide, and then it was stirred at room temp. for 72 h. After evaporation of the methanol, the aqueous mixture was acidified with 3N hydrochloric acid and extracted 8 times with 200 ml of methylene chloride. The extract was dried over anhydrous sodium sulfate, filtered and evaporated. The residue was taken up in 0.1N aqueous sodium hydroxide and washed with ether to remove unreacted ester. The alkaline layer was made acidic with 0.1N aqueous hydrochloric acid and extracted 5 times with 300 ml of methylene chloride. The extract was dried over anhydrous sodium sulfate, filtered and evaporated to give 4.14 g (96.5% yield) of N-benzoylmeroquinene (**16**), m.p. 114–117° after recrystallization from methylene chloride/ether; $[\alpha]_D^{25} = +46.07°$ ($c = 1.0$, CH_3OH). – NMR. ($CDCl_3$): 2.28 (bs, $-CH_2-COOH$); 5.08 ($d \times d$, $J_{gem} = 2$ Hz, $J_{trans} = 16.5$ Hz, ); 5.18 ($d \times d$, $J_{gem} = 2$ Hz, $J_{cis} = 10.5$ Hz, ); 5.87 ($d \times d \times d$, $J_{vic} = 8.5$ Hz, $J_{cis} = 10.5$ Hz, $J_{trans} = 16.5$ Hz, ); 7.38 (*s*, phenyl); 10.75 (*s*, COO*H*).

$C_{16}H_{19}NO_3$ (273.336) Calc. C 70.31 H 7.01 N 5.13 Found C 70.59 H 7.13 N 5.07

4a(S), *8a*(R)-*2-Benzoyl-1,3,4,4a,5,8a-hexahydro-6*(2H)-*isoquinolone* (**17**) *and 4a*(S), *8a*(S)-*2-Benzoyl-1,3,4,4a,5,8a-hexahydro-6*(2H)-*isoquinolone* (**18**). A mixture of 5.4 g (0.0193 mol) of N-benzoylmeroquinene (**16**) and 100 g of polyphosphoric acid was stirred at room temp., and monitored by TLC. using benzene/ethyl acetate/acetic acid 60:35:5. After five days only a minor amount of starting material was present. The reaction mixture was cooled to 0°, and 150 ml of water was added. When all polyphosphoric acid was hydrolyzed, the aqueous mixture was extracted three times with 200 ml of methylene chloride. The extract was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude product, 4.9 g, was dissolved in 200 ml of methylene chloride and washed with 150 ml of 2N potassium carbonate. The aqueous alkaline layer was back-washed with 3 × 200 ml of methylene chloride. The combined extract was dried over anhydrous sodium sulfate, filtered and evaporated. The residue, 4 g, was chromatographed on a 800 g silica gel column with ethyl acetate/hexane 1:1. This gave, as the less polar

component, 1.9 g (38.5% yield) of 4a(*S*), 8a(*S*)-2-benzoyl-1,3,4,4a,5,5a-hexahydro-6(2*H*)-isoquinolone (**18**), m.p. 127–128° after recrystallization from benzene/ether; $[\alpha]_D^{22} = +51.5°$ (c = 1.01, CH_3OH). – IR. ($CHCl_3$): 1681 (conj. ketone), 1630 (amide). – UV. (C_2H_5OH): 221–222 (19,600). – ORD. (*c* = 0.2554, CH_3OH): $[\Phi]^{589} +126°$, $[\Phi]^{396}$ 0°, $[\Phi]^{384}_{infl} -195°$, $[\Phi]^{366}_{min} -474°$, $[\Phi]^{349}$ 0°, $[\Phi]^{326}_{infl} +1724°$, $[\Phi]^{312}_{max} +2124°$. – CD. (*c* = 0.2554, CH_3OH): $[\Theta]^{344}_{min} -1740°$, $[\Theta]^{333}_{min} -1720°$. – NMR. ($CDCl_3$): 6.05 (*d*×*d*, J_{cis} = 10 Hz, $J_{allylic}$ = 1.5 Hz, –CH=C*H*–CO–); 6.68 (b*d*, J_{cis} = 10 Hz, –C*H*=CH–CO–); 7.40 (*s*, phenyl). – MS.: *m/e* 255 (M^+).

$C_{16}H_{17}NO_2$ (225.32) Calc. C 75.27 H 6.71 N 5.49 Found C 75.43 H 6.85 N 5.43

In addition, 0.8 g (16.2% yield) of 4a(*S*), 8a(*R*)-2-benzoyl-1,3,4,4a,5,8a-hexahydro-6(2*H*)-isoquinolone (**17**) was obtained as the more polar product; m.p. 150–152°, after recrystallizations from benzene/ether and benzene; $[\alpha]_D^{22} = -260°$ (*c* = 1.0, CH_3OH). – IR. ($CHCl_3$): 1682 (conj. ketone), 1630 (amide). – UV. (C_2H_5OH): 217–218 (18,200). – CD. (*c* = 0.2554, CH_3OH): $[\Theta]^{330}_{max} +760°$, $[\Theta]^{324}_{max} +740°$. – NMR. ($CDCl_3$): 2.50 (b*s*, –C*H*$_2$–CO–); 2.79 (*m*, H-8a); 6.06 (*d*×*d*, J_{cis} = 10 Hz, $J_{allylic}$ = 2 Hz, –CH=C*H*–CO–); 6.81 (b*d*, J_{cis} = 10 Hz, –C*H*=CH–CO–); 7.37 (*s*, phenyl). – MS.: *m/e* 255 (M^+).

$C_{16}H_{17}NO_2$ (255.32) Calc. C 75.27 H 6.71 N 5.49 Found C 75.40 H 6.81 N 5.46

4a(S), *8a*(R)-*2-Benzoyloctahydro-6*(2H)-*isoquinolone* (**5**). To a solution of 0.255 g (0.001 mol) of 4a(*S*), 8a(*R*)-2-benzoyl-1,3,4,4a,5,8a-hexahydro-6(2*H*)-isoquinolone (**17**) in 10 ml of 95% ethanol was added 50 mg of Pd/C (10%) and then it was hydrogenated at room temp. and atmospheric pressure for 1.5 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to dryness to give 0.257 g (100% yield) of 4a(*S*), 8a(*R*)-2-benzoyloctahydro-6(2*H*)-isoquinolone (**5**), m.p. 182.5–183.5° (from benzene); $[\alpha]_D^{22} = -61.8°$ (*c* = 1.0, CH_3OH). – ORD. (*c* = 0.2454, CH_3OH): $[\Phi]^{589} -152°$, $[\Phi]^{332}_{min} -655°$, $[\Phi]^{318}_{max} -577°$, $[\Phi]^{255}_{min} -4719°$. – CD. (*c* = 0.2454, CH_3OH): $[\Theta]^{296}_{max} +1049°$.

$C_{16}H_{19}NO_2$ (257.33) Calc. C 74.68 H 7.44 N 5.44 Found C 74.98 H 7.54 N 5.21

4a(S), *8a*(S)-*2-Benzoyloctahydro-6*(2H)-*isoquinolone* (**10**). To a solution of 0.255 g (0.001 mol) of 4a(*S*), 8a(*S*)-2-benzoyl-1,3,4,4a,5,8a-hexahydro-6(2*H*)-isoquinolone (**18**) in 10 ml of 95% ethanol was added 50 mg of Pd/C (10%) and then it was hydrogenated at room temp. and atmospheric pressure for 1.5 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to dryness to give 0.257 g (100%) of 4a(*S*), 8a(*S*)-2-benzoyloctahydro-6(2*H*)-isoquinolone (**10**), m.p. 155–156° (from 95% ethanol); $[\alpha]_D^{22} = +62.2°$ (*c* = 1.0, $CHCl_3$). – ORD. (*c* = 0.2888, CH_3OH): $[\Phi]^{589} +120°$, $[\Phi]^{311}_{max} +3297°$, $[\Phi]^{293}$ 0°, $[\Phi]^{271}_{min} -2896°$. – CD. (*c* = 0.2888, CH_3OH): $[\Theta]^{293}_{max} +5704°$.

$C_{16}H_{19}NO_2$ (257.33) Calc. C 74.68 H 7.44 N 5.44 Found C 74.61 H 7.50 N 5.36

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