

238. Cinchona Alkaloids. Total Synthesis of Cinchonamine

Preliminary Communication¹⁾

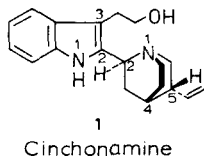
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Cinchona-Alkaloide. Totalsynthese von Cinchonamin. – *Zusammenfassung.* Zwei verschiedene Wege zur Totalsynthese des Cinchona-Alkaloids Cinchonamin (**1**) und seines C(2)-Epimers (**24**) werden beschrieben. Als Ausgangsmaterial diente synthetisch hergestelltes N-Benzoylmerochinen (**2**) oder sein Methylester **15**.

Cinchonamine (**1**)²⁾ was isolated as early as 1881 from the bark of *Remijia purdiena* [1], but the structure was elucidated only in 1950 [2] and the absolute configuration was established twenty years later [3]. A partial synthesis of **1** was reported by *Preobazhenskii et al.* [4]. The alkaloid and its C(2)-epimer **24** were also obtained by lithium aluminium hydride reduction of quinamine and *epi*-quinamine, respectively



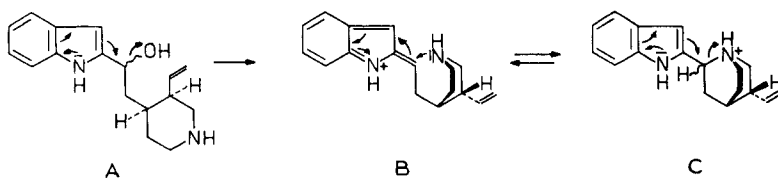
[5]. Recently [6], we described the total synthesis of dihydrocinchonamine by a route starting with optically active 5-ethylquinuclidine-2-carboxylate [7] and involving a *Madelung* reaction for the indole ring closure. Application of this reaction sequence to the synthesis of cinchonamine failed due to the lability of the vinyl group under the conditions of the *Madelung* reaction³⁾.

We now report the first total synthesis of cinchonamine (**1**) and 2-*epi*-cinchonamine(**24**), the main feature of which is the formation of the quinuclidine ring by cyclization of a conjugated iminium ion **B** which originates by thermal dehydration of the alcohol **A**. This key compound was prepared as an epimeric mixture **13** or as the individual diastereomers **20** and **21** by two methods outlined below.

¹⁾ A full account of this work will be published in the near future.

²⁾ According to Chemical Abstracts Systematic Nomenclature Cinchonamine is named 1*H*-Indole-3-ethanol, 2-(5-ethenyl-1-azabicyclo[2.2.2]oct-2-yl)-, [1*S*-(1 α , 2 α , 4 α , 5 β)], and the numbering refers to this name.

³⁾ Similar observations have been made by *Augustine et al.* in their detailed study on the *Madelung* reaction [8].



In the first approach, the 2-acylindole **10** was prepared from 2-nitrobenzaldehyde (**6**) and totally synthetic N-benzoylmeroquinene (**2**) [9] by a method reported recently for the synthesis of other 2-acyl-indoles[10]. N-Benzoylmeroquinene (**2**) was transformed in three steps to the α -bromoketone **5**⁴) [75%; oil; IR. (CHCl₃): 1715 cm⁻¹ (COCH₂Br); NMR. (CDCl₃): δ 3.80 (s, CH₂Br); MS. (*m/e*): 349 (*M*⁺), 105 (base peak)] without purification of the intermediate acid chloride **3** and the diazoketone **4**. Reaction of the sodium salt of the sulfonamide **7** [10] [11] with the α -bromoketone **5** gave in 70% yield the aldol product **8** which upon treatment with thionyl chloride in pyridine afforded the indole derivative **9** [55%; oil; MS (*m/e*): 526 (*M*⁺)]. Hydrolysis of the tosyl group occurred smoothly in boiling methanolic sodium hydroxide to give the expected acylindole **10** [65%; m.p. 152–153° (CH₃OH); IR. (CHCl₃): 3450 (NH), 1650 (CO), 1621 cm⁻¹ (CO–N); UV. (CH₃OH): λ_{max} 308 nm (ϵ 23,200)].

Compound **10** was transformed to the desired mixture of epimeric alcohols **13** by two alternative routes, **10** $\rightarrow$ **11** $\rightarrow$ **13** or **10** $\rightarrow$ **12** $\rightarrow$ **13**. In the first route, removal of the N-benzoyl group was effected in 70% yield by heating a solution of **10** in 5*N* potassium hydroxide (methanol/water 4:1) at the reflux temperature for three days. The resulting derivative **11** was subsequently reduced with sodium borohydride in methanol at 0° to give the epimeric mixture **13**⁵) in good yield. In the preferred route, compound **10** was first reduced with sodium borohydride to afford in 90% yield the epimeric mixture **12** from which the major isomer **12a** (2*R*) was obtained by fractional crystallization [m.p. 167–169°, (CH₃OH/ether); [α]_D²⁵ = +73° (*c* = 0.90, CH₃OH); IR. (CHCl₃): 3600 cm⁻¹ (OH); NMR. (CDCl₃): δ 6.19 (s, (H–C(3))); 8.97 (s, NH)]. Reductive N-debenzoylation of the mixture **12** with diisobutyl aluminium hydride in tetrahydrofuran at –70° gave in 60% yield the desired derivatives **13**.

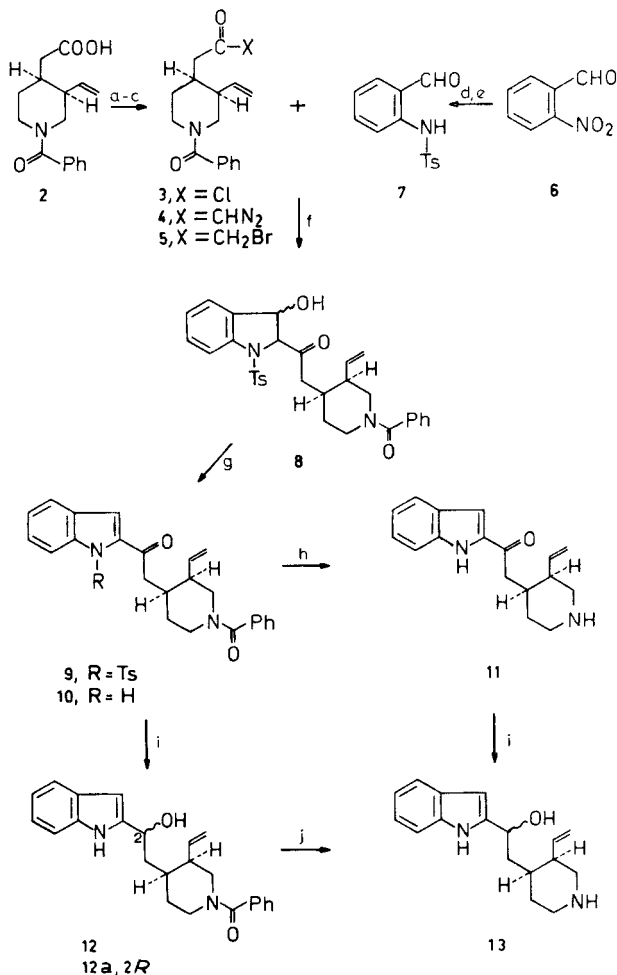
The same mixture of epimeric hydroxy compounds was obtained by an alternative and more efficient synthesis (Scheme 2). Lithiation of 1-benzenesulfonylindole (**16**) with *n*-butyllithium [12] and reaction of the lithio derivative *in situ* with readily available N-benzoylmeroquinene aldehyde (**17**) [7] gave in 85% yield a crystalline mixture of **18** and **19** in an approximate ratio of 3:1. Because of its insolubility in methanol the major 2*R*-isomer⁶) **18** [m.p. 188–189° (CH₂Cl₂/ether); [α]_D²⁵ = +159.8°

4) All new compounds gave combustion analyses and/or mass spectra and other spectral data consistent with assigned structures. NMR. spectra were recorded 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.

5) The 2*R*-isomer **20** could be isolated from this mixture by fractional crystallization from methylene chloride/ether.

6) The configuration of the newly generated chiral center was established by an X-ray crystal structure analysis of the hydrochloride of its hydrolysis product **20a**. We are indebted to Dr. F. Blount of these laboratories for carrying out this analysis.

Scheme 1

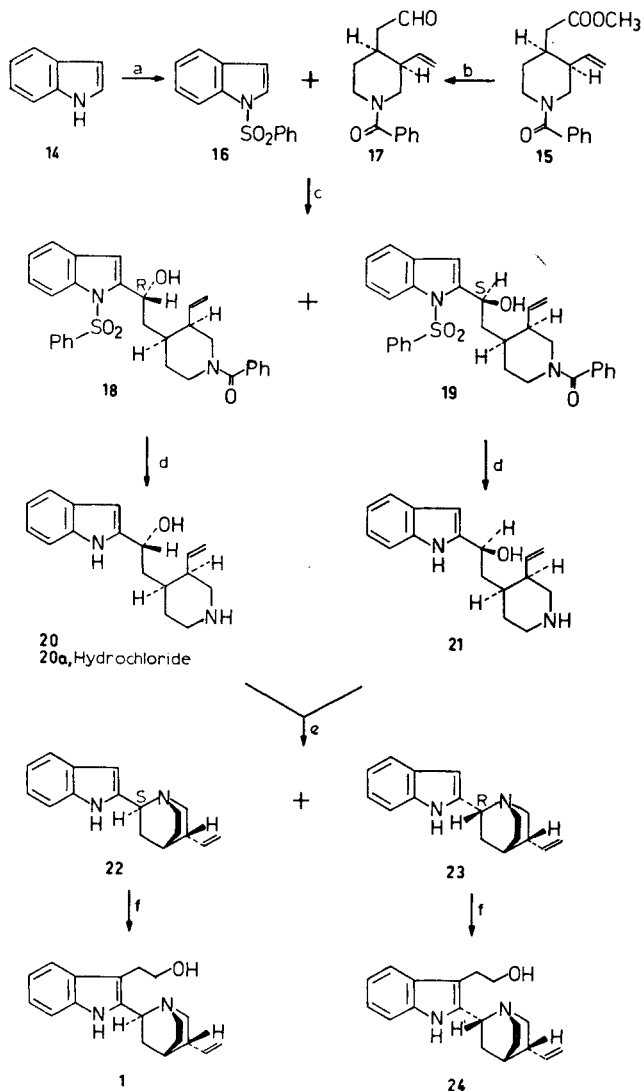


- a) SOCl₂, benzene, 1 h, Δ; b) 2% CH₂N₂ in ether, 0°; c) 48% HBr/ether; d) FeSO₄, NH₄OH; e) *p*-TsCl, pyridine, CH₂Cl₂, 0°; f) NaH, DMF; g) SOCl₂, pyridine; h) 5N KOH (CH₃OH/H₂O 4:1); i) NaBH₄; j) DIBAL-H, -70°, THF.

(*c* = 1.00, CHCl₃); IR. (CHCl₃): 3570 (OH), 1620 (CO-N), 1445 and 1170 (SO₂), and 925 cm⁻¹ (CH=CH₂); NMR. (CDCl₃ + DMSO-d₆): δ 4.18 (*d*, *J* = 5.5 Hz, OH); 6.69 (*s*, H-C(3)); MS. (*m/e*): 514 (*M*⁺), 105 (base peak)] was readily separated⁷⁾ from its diastereomer **19** [m.p. 161–162° (CH₂Cl₂/ether); [α]_D²⁵ = -37.8° (*c* = 1.05, CHCl₃); NMR. (CDCl₃ + DMSO-d₆): δ 3.76 (*d*, *J* = 5.5 Hz, OH); 6.71 (*s*, H-C(3)), MS. (*m/e*) 514 (*M*⁺), 105 (base peak)]. Upon heating in refluxing 1N potassium hydroxide (CH₃OH/H₂O, 4:1) each isomer gave the corresponding hydrolysis product in 90% yield: **18** → **20** [m.p. 128–129° (CH₂Cl₂/ether); [α]_D²⁵ = +66.7° (*c* = 0.52, CH₃OH); IR.

⁷⁾ This separation only served analytical purposes, for continuation of the synthesis, the mixture of isomers was used.

Scheme 2



a) NaH, DMSO, $\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$; b) DIBAL-H, -70° , toluene; c) *n*-BuLi, TMEDA, THF; d) 1N KOH ($\text{CH}_3\text{OH}/\text{H}_2\text{O}$ 4:1); e) *o*-dichlorobenzene, 155° ; f) CH_3MgI , ethylene oxide.

(CHCl_3): 3600 (OH) and 3460 cm^{-1} (NH); MS. (m/e): 270 (M^+), 143 (base peak); **20a**: m.p. $200\text{--}201^\circ$ (CH_2Cl_2 /ether/ CH_3OH); $[\alpha]_{\text{D}}^{25} = +43.49^\circ$ ($c = 1.099$, CH_3OH); IR. (KBr): 2860 and 2760 cm^{-1} (NH_2) and **19** $\rightarrow$ **21** [MS. (m/e): 270 (M^+), 143 (base peak)]. Hydrolysis of the N-benzenesulfonyl group under the above cited conditions was completed within 10 h while debenzoylation took at least four days.

The crucial part of the synthesis is the formation of the quinuclidine ring. The ring closure was achieved in 40% yield by heating a solution of the quinuclidine ring.

of the diastereomeric mixture **13** in *o*-dichlorobenzene at 155° for a period of 10–15 days. In each case, we obtained a 1:1 mixture of the two epimeric indolylquinuclidines **22** [m.p. 148–149° (CH₃OH), $[\alpha]_D^{25} = +61.9^\circ$ ($c = 0.64$, CH₃OH); NMR. (CDCl₃): δ 4.11 (*t*, $J = 9$ Hz, H–C(2)); *ca.* 5.08 (*m*, CH=CH₂); 6.00 (*m*, CH=CH₂); 6.41 (*s*, H–C(3)); 9.13 (*br.*, *NH*); MS. (*m/e*): 252 (*M*⁺), 143 (*base peak*)] and **23** [m.p. 92–93° (petroleum ether); $[\alpha]_D^{25} = +98.1^\circ$ ($c = 0.52$, CH₃OH); NMR. (CDCl₃): δ 4.06 (*t*, $J = 9$ Hz, H–C(2)); *ca.* 4.96 (*m*, CH=CH₂); 5.83 (*m*, CH=CH₂); 6.39 (*s*, H–C(3)); 8.96 (*br.*, *NH*)].

Under cyclization conditions, either isomer was transformed within *ca.* twelve days into a 1:1 mixture of both isomers. The results of the cyclization and the isomerization can only be explained by assuming the intermediacy of a conjugated iminium ion B.

The configuration at C(2) of **22** and **23** was determined by NMR-spectroscopy on the basis of the chemical shifts of the methylene protons of the vinyl group (δ *ca.* 5.08 for **22** and *ca.* 4.96 for **23**). In analogy to results obtained in the dihydro-cinchonamine series [6] shielding of the vinyl protons due to the anisotropic effect of the indole ring is more likely in **23**. The configurational assignment was supported by the results of an ¹³C-NMR.-analysis of both isomers⁸⁾ and by the transformation of **22** and **23** into cinchonamine (**1**) and 2-*epi*-cinchonamine (**24**), respectively. For this purpose, the indole magnesium iodides, prepared by the addition of crystalline **22** or **23** to a ten-fold excess of methyl magnesium iodide, were reacted at 0° with an ethereal solution of ethylene oxide to afford in 40% yield cinchonamine (**1**) [m.p. 185–186° (CH₂Cl₂/ether), lit. 186° [2]; $[\alpha]_D^{25} = +128^\circ$ ($c = 0.3$, abs. EtOH), lit. 123° [2]; IR. (CHCl₃): 3460 (NH) and 915 cm⁻¹ (CH=CH₂); NMR. (CDCl₃): δ 4.20 (*d* × *d*, $J = 7.5$ and 10 Hz, H–C(2)); 8.30 (*br.*, *NH*); UV. (CH₃OH); $\lambda_{\max}$ 284 nm (ϵ 8440); MS. (*m/e*): 296 (*M*⁺), 156 (*base peak*)] and 2-*epi*-cinchonamine (**24**), respectively [m.p. 168–169° (CH₂Cl₂/ether), lit. 168° [5]; $[\alpha]_D^{25} = +46.5^\circ$ ($c = 0.4$, abs. EtOH), lit. 48° [5]; NMR. (CDCl₃): δ 4.15 (*d* × *d*, $J = 8$ and 10 Hz, H–C(2)); 8.26 (*br.*, *NH*)].

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⁸⁾ We thank Mr. R. Pitcher of these laboratories for the ¹³C-NMR. data which will be published in the full paper.