238. Cinchona Alkaloids. Total Synthesis of Cinchonamine

Preliminary Communication[1])

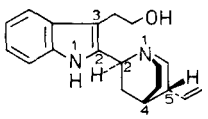
by **G. Grethe, H. L. Lee,** and **M. R. Uskoković**

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

(8. VII. 76)

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



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Cinchonamine

[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* reaction[3]).

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.

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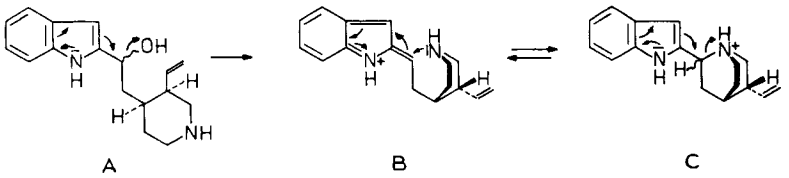
[1]) A full account of this work will be published in the near future.

[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*-(1α,2α,4α,5β)], 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].



A B C

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. ($CHCl_3$): 1715 cm^{-1} ($COCH_2Br$); NMR. ($CDCl_3$): δ3.80 (*s*, CH_2Br); 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° (CH_3OH); IR. ($CHCl_3$): 3450 (NH), 1650 (CO), 1621 cm^{-1} (CO–N); UV. (CH_3OH): λmax 308 nm (ε23,200)].

Compound **10** was transformed to the desired mixture of epimeric alcohols **13** by two alternative routes, **10** → **11** → **13** or **10** → **12** → **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°, (CH_3OH/ether); $[\alpha]_D^{25} = +73°$ ($c = 0.90$, CH_3OH); IR. ($CHCl_3$): 3600 cm^{-1} (OH); NMR. ($CDCl_3$): 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*-isomer[6] **18** [m.p. 188–189° (CH_2Cl_2/ether); $[\alpha]_D^{25} = +159.8°$

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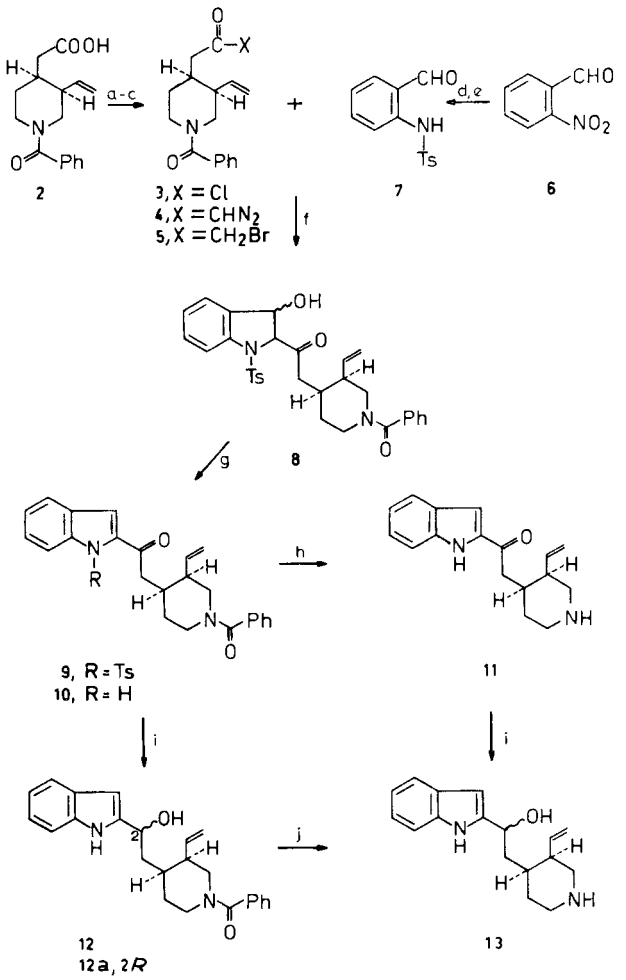
4) All new compounds gave combustion analyses and/or mass spectra and other spectral data consistent with assigned structures. NMR. spectra were recorded on a *Varian* A-60 or HA-100 spectrophotometer, using TMS as internal standard. The mass spectra were taken with a *CEC* 21-110 mass spectrometer at 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

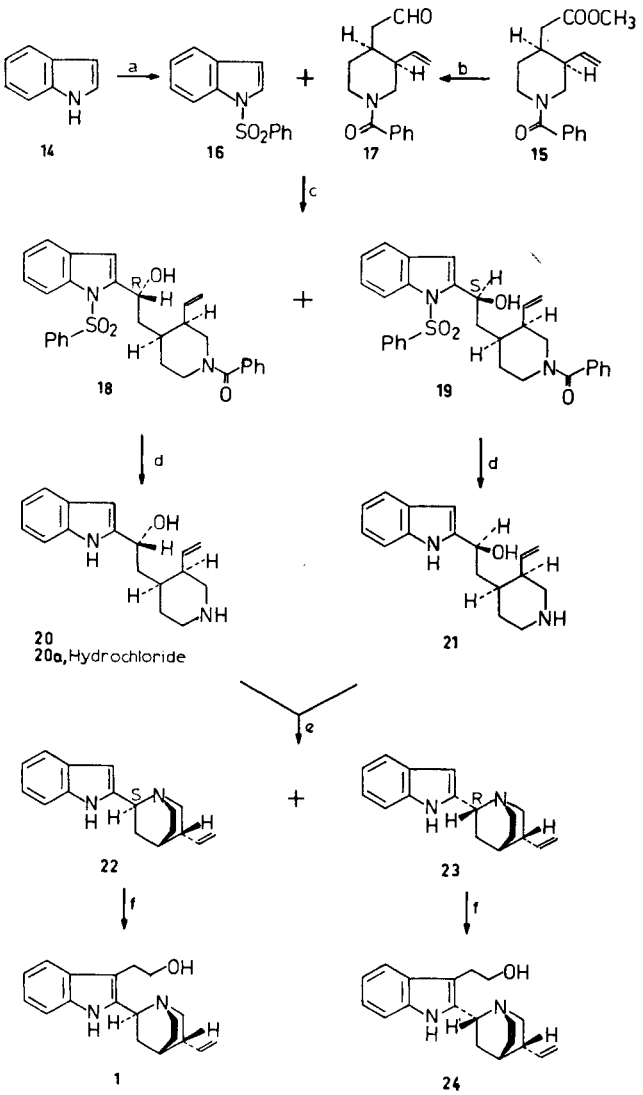


a) $SOCl_2$, benzene, 1 h, Δ; b) 2% CH_2N_2 in ether, 0°; c) 48% HBr/ether; d) $FeSO_4$, NH_4OH; e) *p*-TsCl, pyridine, CH_2Cl_2, 0°; f) NaH, DMF; g) $SOCl_2$, pyridine; h) 5N KOH (CH_3OH/H_2O 4:1); i) $NaBH_4$; j) DIBAL-H, −70°, THF.

(c = 1.00, $CHCl_3$); IR. ($CHCl_3$): 3570 (OH), 1620 (CO–N), 1445 and 1170 (SO_2), and 925 cm^{-1} ($CH{=}CH_2$); NMR. ($CDCl_3$ + DMSO-d_6): 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 separated[7]) from its diastereomer **19** [m.p. 161–162° (CH_2Cl_2/ether); $[\alpha]_D^{25} = -37.8°$ (c = 1.05, $CHCl_3$); NMR. ($CDCl_3$ + DMSO-d_6): 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 (CH_3OH/H_2O, 4:1) each isomer gave the corresponding hydrolysis product in 90% yield: **18** → **20** [m.p. 128–129° (CH_2Cl_2/ether); $[\alpha]_D^{25} = +66.7°$ (c = 0.52, CH_3OH); IR.

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

Scheme 2



a) NaH, DMSO, $C_6H_5SO_2Cl$; b) DIBAL-H, $-70°$, toluene; c) *n*-BuLi, TMEDA, THF; d) 1N KOH (CH_3OH/H_2O 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. 200–201° (CH_2Cl_2/ether/CH_3OH); $[\alpha]_D^{25} = +43.49°$ ($c = 1.099$, CH_3OH); IR. (KBr): 2860 and 2760 cm^{-1} ($\overset{+}{N}H_2$)] and **19** → **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 isomers **20** or **21** or

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° (CH_3OH), $[\alpha]_D^{25} = +61.9°$ ($c = 0.64$, CH_3OH); NMR. ($CDCl_3$): δ 4.11 (t, $J = 9$ Hz, H–C(2)); *ca.* 5.08 (m, CH=CH_2); 6.00 (m, CH=CH_2); 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); $[\alpha]_D^{25} = +98.1°$ ($c = 0.52$, CH_3OH); NMR. ($CDCl_3$): δ 4.06 (t, $J = 9$ Hz, H–C(2)); *ca.* 4.96 (m, CH=CH_2); 5.83 (m, CH=CH_2); 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 dihydrocinchonamine 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 ^{13}C-NMR.-analysis of both isomers[8]) 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° (CH_2Cl_2/ether), lit. 186° [2]; $[\alpha]_D^{25} = +128°$ ($c = 0.3$, abs. EtOH), lit. 123° [2]; IR. ($CHCl_3$): 3460 (NH) and 915 cm^{-1} (CH=CH_2); NMR. ($CDCl_3$): δ 4.20 ($d \times d$, $J = 7.5$ and 10 Hz, H–C(2)); 8.30 (br., NH); UV. (CH_3OH); λmax 284 nm (ε 8440); MS. (m/e): 296 (M^+), 156 (base peak)] and 2-*epi*-cinchonamine (**24**), respectively [m.p. 168–169° (CH_2Cl_2/ether), lit. 168° [5]; $[\alpha]_D^{25} = +46.5$ ($c = 0.4$, abs. EtOH), lit. 48° [5]; NMR. ($CDCl_3$): δ 4.15 ($d \times d$, $J = 8$ 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 ^{13}C-NMR. data which will be published in the full paper.