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Enantioselective Catalysis 98.[1]

Preparation of 9-Amino(9-deoxy)cinchona Alkaloids

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Abstract: Cinchonine and quinine were allowed to react with hydrazoic acid in a Mitsunobu reaction to yield the corresponding azides with inversion of configuration at C9. *In situ* reduction of these azides provided 9-amino(9-deoxy)epicinchonine and 9-amino(9-deoxy)epiquinine, respectively. The structures were confirmed by CD-spectroscopy and X-ray crystallography.

The cinchona alkaloids are known to be suitable optically active bases for the separation of racemates by fractional crystallisation[2]. They are also catalysts or co-catalysts in a variety of enantioselective reactions. The asymmetric dihydroxylation of olefins (ADH) is probably the best known reaction in which derivatives of quinine or quinidine give diols in high enantiomeric excess[3]. It is also phase transfer[4] and base catalysed[5] reactions that can be performed in high enantioselectivity by using these alkaloids as chiral transmitters. Their good performance in part is due to their β-aminoalcohol substructure, that can act as a binding site for a metal or for hydrogen bonding to a substrate[6].

It is well known that for catalysis with low valent transition metals, e.g. Rh^{I}, backbonding from the metal to the coordinated co-catalyst is an important factor for complex stability and enantioselectivity. In order to provide the cinchona alkaloids with such properties we decided to introduce an amino function into the alkaloids at C9 (Scheme 1). This group could then be converted into an imine, which qualifies for backbonding.

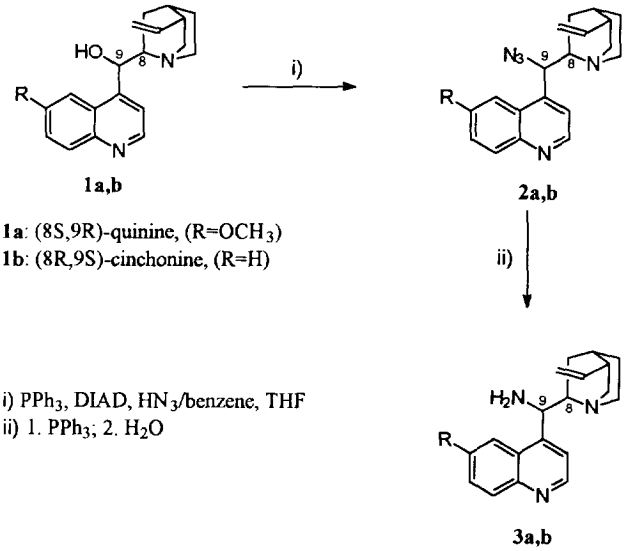
Results and discussion

An earlier published synthesis[7] of 9-amino(9-deoxy)cinchona alkaloids via reduction of cinchoninone oxime or quininone oxime may be questioned since the products showed very little optical rotation and thus probably were a mixture of the possible diastereomers.

The substitution of the tosylate in cinchonine-tosylate by potassium benzoate led to a ring expanded hetero-cinchonine derivative with an azabicyclo[2.2.3]nonane system instead of the quinuclidine moiety[8].

Our synthesis of the desired amines is based on the Mitsunobu reaction[9]. For preliminary investigations we chose cinchonine and quinine as representatives of the cinchona alkaloid family. When quinine was reacted with hydrazoic acid in THF/benzene at room temperature in the presence of triphenylphosphine and diisopropylazodicarboxylate (DIAD), a slightly yellow solution was obtained. In order to avoid isolation of the azide the reduction was performed with an excess of triphenylphosphine according to Staudinger[10]. Hydrolysis of the intermediate aminophosphorane and chromatographic work-up gave the free base in 60% yield. In the case of cinchonine a single recrystallisation of the amine hydrochloride salt was sufficient for purification.

Scheme 1:



1a,b

2a,b

1a: (8S,9R)-quinine, (R=OCH_3)
1b: (8R,9S)-cinchonine, (R=H)

ii)

i) PPh_3, DIAD, HN_3/benzene, THF
ii) 1. PPh_3; 2. H_2O

3a,b

3a: (8S,9S)-9-amino(9-deoxy)epiquinine
3b: (8R,9R)-9-amino(9-deoxy)epicinchonin

The reaction sequence can be carried out as a one-pot-synthesis. The formation of the intermediate azides may be monitored by IR-spectroscopy as under the reaction conditions hydrazoic acid exhibits an N_3-vibration at 2055 cm^{-1} and the azides **2a,b** at 2040 cm^{-1}.

The main question was to establish the stereochemistry of the products. On the one hand, the Mitsunobu reaction in general takes place with inversion of configuration by an S_N2 mechanism[9], on the other hand, the bicyclic quinuclidine moiety in connection with the benzylic β-aminoalcohol substructure gives rise to a variety of rearrangements when treated with acids or during substitution reactions[11]. Several spectroscopic methods verified the proposed structure.

Figure 1: CD-spectra (ethanol, conc. in g/l): **3a** = ● (0.70), epiquinine = ○ (0.30) and **3b** = △ (0.27).

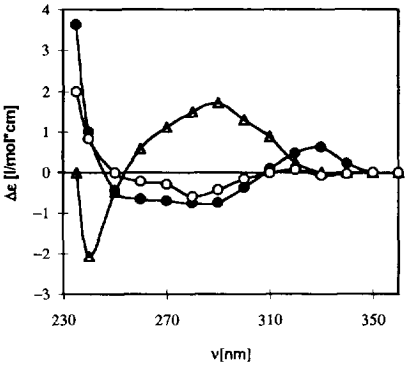
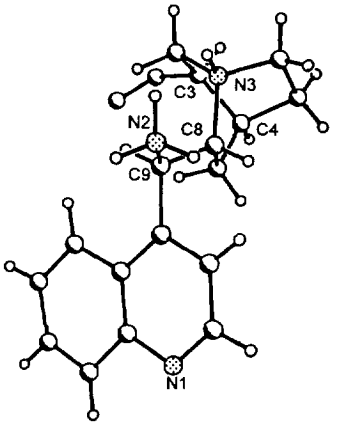


Figure 2: ORTEP-plot of the trihydrochloride of **3b** (chloride ions and water are left out).



Mass spectroscopy (EI) shows the typical fragmentation for the cinchona alkaloid system. The UV-spectra exhibit the same absorption bands as the parent alkaloids[12]. This result is not surprising since the chromophoric system of the cinchona alkaloids includes only the aromatic quinoline ring. Hence absorption at longer wavelenghts is neither affected by the hydroxyl group nor the amino group. The CD-spectra (Figure 1) show the same shape and the same signs of Cotton effects for **3a** and for epiquinine[13], which has (8S,9S) configuration like **3a**. **3b** exhibits inverse signs. Former investigations revealed that the CD-spectra of cinchona alkaloid isomers can be correlated to their stereochemistry at C8 and C9[12]. Thus, the similar spectra for **3a** and epiquinine and the mirror image spectrum for **3b** confirm the expected configurations. That means, starting from the natural erythro bases our synthesis yielded the threo bases with (8R,9R) or (8S,9S) configuration.

It was possible to characterise the trihydrochloride salt of **3b** structurally by X-ray diffraction analysis (Figure 2). Appropriate crystals were obtained from methanol/ether and contain one molecule of water per trihydrochloride of **3b**. The absolute configuration at C8 and C9 could be assigned by comparison with the configurations at C3 and C4, which are the same for all cinchona alkaloids and were not changed during the reaction procedure.

Our further efforts will concentrate on the synthesis of the erythro forms and their catalytic activity in enantioselective reactions.

Preparation of the 9-amino(9-deoxy)cinchona alkaloids

9-Amino(9-deoxy)epicinchonine **3b**: to a well stirred mixture of cinchonine (2.94 g, 10 mmol), triphenylphosphine (3.15 g, 12 mmol) and hydrazoic acid/benzene[14] (12 ml, 4%, 12 mmol) in 50 ml of THF is slowly added DIAD (2.16 ml, 11 mmol) in 10 ml of THF at 5°C. The mixture is stirred for 3 h at room temperature. Then triphenylphosphine (2.62 g, 10 mmol) in 10 ml of THF is added in one portion. The mixture is heated at 40°C until the gas evolution has ceased. 1 ml of water is added and the solution is stirred for another 3 h. Solvents are removed *in vacuo* and the residue is dissolved in CH_2Cl_2 and 2n hydrochloric acid (1:1, 100 ml). The aqueous phase is washed with CH_2Cl_2 (3 x 50 ml). The water is

removed under reduced pressure and the amine trihydrochloride recrystallised from methanol. Colourless crystals, mp. 199°C (decomp.), $[\alpha]_D$ = +62 (c = 3.6, 1n HCl, 25°C).

Free base **3b**: colourless oil, $[\alpha]_D$ = +105 (c = 1.0, $CHCl_3$, T = 25°C), yield 61%. - ^1H nmr ($CDCl_3$, i-TMS, 400 MHz): δ = 0.87-1.59 (m, 5H, quinuclidine), 2.10 (s, 2H, $-NH_2$), 2.23 (m, 1H, quinuclidine), 3.00 (m, 5H, quinuclidine), 4.75 (d, 1H, J = 10.1 Hz, C9-H), 5.07 (m, 2H, $-CH=CH_2$), 5.87 (m, 1H, $-CH=CH_2$), 7.57-8.37 (m, 5H, quinoline), 8.90 (d, 1H, J = 4.6 Hz, quinoline-2-H). - MS (EI): m/z (%) = 293 M^+ (83), 157 (86), 136 (100), 95 (18), 108 (50).

9-Amino(9-deoxy)epiquinine **3a** (free base): slightly yellow oil, $[\alpha]_D$ = +80 (c = 1.1, $CHCl_3$, 25°C). - ^1H nmr ($CDCl_3$, i-TMS, 250 MHz): δ = 0.79 (m, 1H, quinuclidine), 1.25-1.63 (m, 4H, quinuclidine), 2.06 (s, 2H, $-NH_2$), 2.27 (m, 1H, quinuclidine), 2.79 (m, 2H, quinuclidine), 3.02-3.32 (m, 3H, quinuclidine), 3.96 (s, 3H, $-OCH_3$), 4.57 (d, 1H, J = 10.1 Hz, C9-H), 4.98 (m, 2H, $-CH=CH_2$), 5.79 (m, 1H, $-CH=CH_2$), 7.35-8.05 (m, 4H, quinoline), 8.75 (d, 1H, J = 4.6 Hz, quinoline-2-H). - MS (FAB): m/z (%) = 324 MH^+ (100), 207 (15), 188 (28), 136 (38).

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