Structure and Mechanism in *Cinchona* Alkaloid Chemistry: Aqueous Hydrolysis Proceeds with Complete Inversion or Complete Retention of Configuration**

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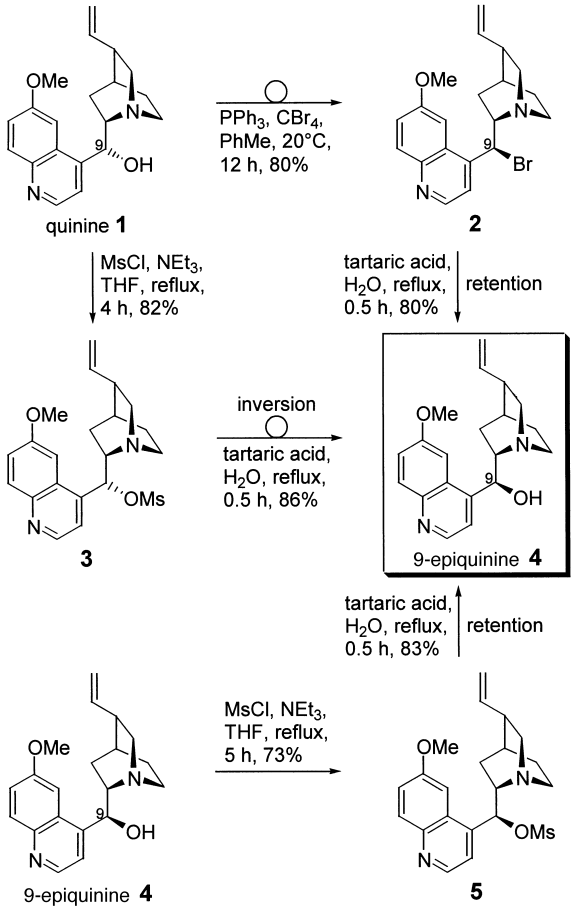
Solvolytic displacement reactions at saturated carbon centers are among the best known and most investigated reactions in organic chemistry. It is generally accepted that the steric course of solvolysis ranges from inversion of configuration to substantial and even complete racemization, dependent upon the stability and lifetime of any ion-pair and carbocation intermediates.[1]

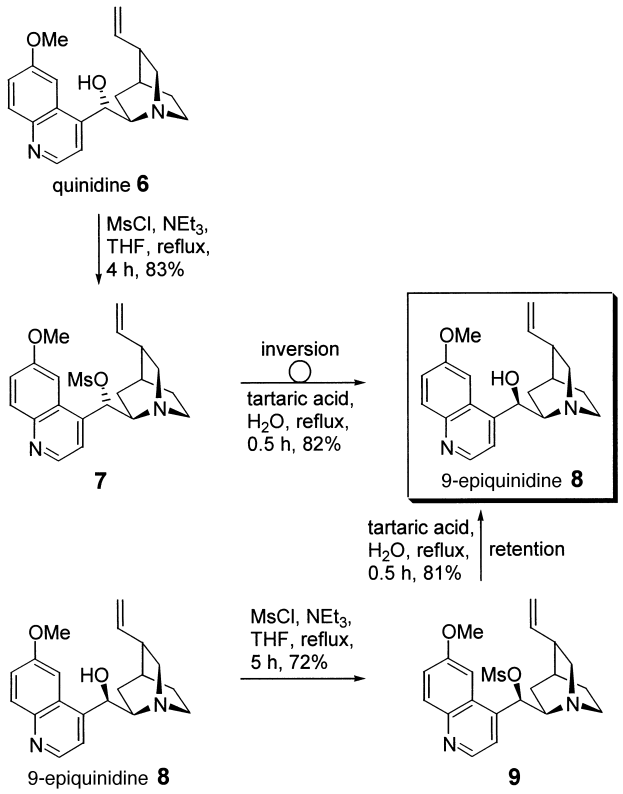
In the course of our work on *Cinchona* alkaloids we have investigated the hydrolysis of derivatives with a leaving group at carbon C9. Thus, quinine (**1**) was converted into the mesylate **3**, which dissolved readily in water in the presence of tartaric acid (1 equivalent) as a proton donor. On heating to 100 °C, the completely *inverted* 9-epiquinine (**4**) was obtained in good yield as the only product in a spot-to-spot reaction (Scheme 1).[2–4] Similarly, 9-epiquinine mesylate (**5**) was submitted to aqueous hydrolysis in the presence of two equivalents of tartaric acid at reflux. To our surprise, 9-epiquinine (**4**) was the only product and it was formed in a clean spot-to-spot reaction with complete *retention* of configuration.[4] In an analogous sequence, pseudo-enantiomeric quinidine (**6**) was converted into the mesylate **7** and hydrolysed, furnishing 9-epiquinidine (**8**) with complete *inversion* of configuration (Scheme 2). Hydrolysis of O-mesylated epiquinidine (**9**) proceeded with complete *retention* of configuration. The results from the quinidine series confirm the quinine work.

Is the retentive hydrolysis of mesylates **5** and **9** triggered by an unusual fission of the sulfur–oxygen bond, perhaps assisted by intramolecular participation of the basic bridgehead nitrogen? N,O-Acyl and N,O-sulfonyl shifts have previously been encountered in *Cinchona* alkaloid chemistry.[5] We therefore changed the leaving group from methanesulfonate to bromide. 9-Epibromoquinine (**2**) was subjected to the usual hydrolysis conditions and, again, the only product formed was 9-epiquinine (**4**) (Scheme 1).

Does retention of configuration involve an aziridinium ion intermediate and hence double inversion? Examples of neighboring nitrogen participation in 1,2-amino halides and



Scheme 1. Hydrolyses which lead to 9-epiquinine (**4**) through inversion or retention of configuration. Ms = Methanesulfonyl.



Scheme 2. Analogous hydrolysis reactions in the quinidine series.

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mesylates are well known.[6] However, aziridinium ion participation has previously been ruled out in the silver benzoate mediated reaction of 9-epibromoquinine (**2**) with methanol as the solvent.[7, 8]

We assume that the contrasting stereochemical results are due to conformational control in the ground and transition states,[7] as well as hydrogen bonding in the solvent water. A clear picture of the preferred conformation of our starting material in the ground state was provided by NOE studies and X-ray crystal diffraction. The mesylate **3** is in an *anti*, *closed* conformation (Figure 1 a).[9] Attack of water proceeds in S_N2-like fashion and is thought to be assisted by local hydrogen bonding involving the (protonated) bridgehead nitrogen atom.

In contrast, 9-epibromoquinine (**2**) and also mesylated 9-epiquinine (**5**) are structurally and conformationally very similar and adopt the *syn*, *open* conformation.[11] Note that this conformation has a hydrophobic face (Figure 1 b), which probably disfavors attack by water on this side. Reaction with water is thought to proceed with a change of mechanism.[12, 13]

In conclusion, there is little doubt that simple secondary aliphatic halides and sulfonates, which have usually been studied as model substrates and discussed in textbooks, are solvolysed with overall inversion of configuration, accompanied by varying amounts of racemization. In the case of the *Cinchona* alkaloids and especially with water as a solvent, the well-defined rotamer population of the natural product, combined with molecular recognition of the hydrophilic binding pocket, is thought to play a critical role.[14] Two distinct reactions are observed with water as the solvent. The duality of the steric course highlights the special role of *Cinchona* alkaloids in asymmetric synthesis.[15] The transformations reported for the three substrates **2**, **5**, and **9** are to our knowledge the first examples of hydrolysis reactions which proceed with complete retention of configuration. After the puzzle of the hetero-*Cinchona* rearrangement,[7] a further facet of quinine – quinidine chemistry[16] has now been elucidated.

Experimental Section

Illustrative hydrolysis procedure: Quinine mesylate **3** (350 mg, 0.87 mmol) and tartaric acid (136 mg, 0.90 mmol) were dissolved in water (4 mL) and refluxed at 100 °C for 30 minutes. The solution was cooled to RT and sat. $NaHCO_3$ solution (10 mL) was added. The mixture was extracted several times with $CHCl_3$. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromato-

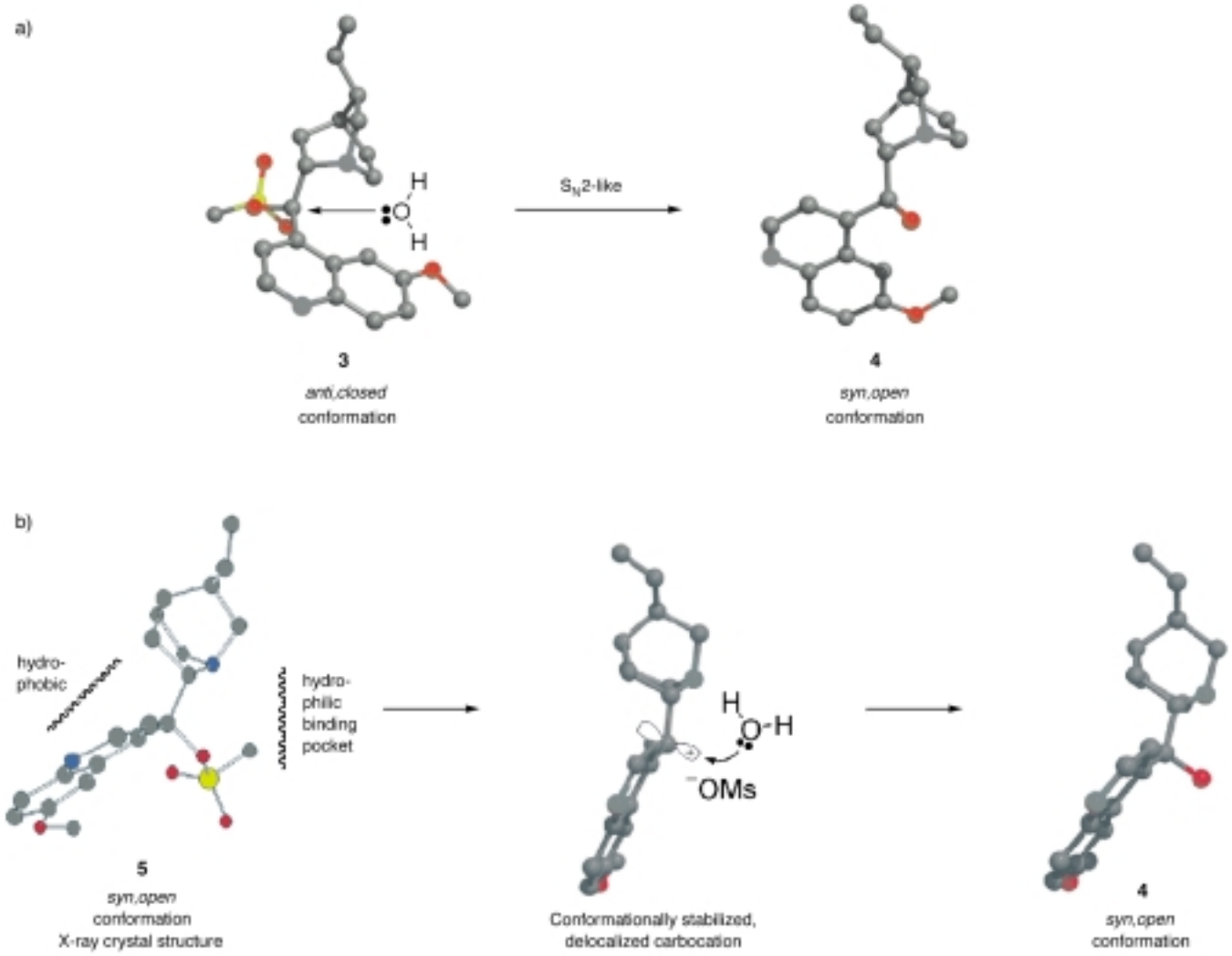

Figure 1. a) Postulated course[10] of the hydrolysis of quinine mesylate (**3**) with natural configuration at C9: Inversion of configuration. b) Postulated course of hydrolysis of 9-epiquinine mesylate (**5**). Retention of configuration and front-side hydration are favoured by the *syn*, *open* conformation.

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graphy (EtOAc/MeOH 4/1, then MeOH) to give **4** as a colorless solid (243 mg, 0.75 mmol) in 86% yield.

Preparation of 9-*epi*-bromoquinine (**2**): Quinine **1**, PPh_3 (2 equiv) CBr_4 (1.1 equiv) were stirred in toluene at RT for 12 h. Workup by extraction with dilute hydrochloric acid, neutralization of aqueous extract (sat. $NaHCO_3$ solution) and back-extraction with $CHCl_3$ (ca. 5 ×). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (EtOAc, then EtOAc/MeOH 4/1) gave **2**, colorless solid, yield 80% (X-ray structure data in ref. [7]).

Crystal structure analysis of 9-epiquinine mesylate (**5**):[17] $C_{21}H_{26}N_2O_4S_1$, $M_r = 402.51$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 8.408(1)$, $b = 9.950(2)$, $c = 23.954(3)$ Å, $V = 2004.0(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.334$ g cm^{-3}, $F(000) = 856$, crystal size $0.48 \times 0.14 \times 0.20$ mm, $T = 300$ K, $\mu(Mo_{K\alpha}) = 1.9$ cm^{-1}. Data collection: Stoe IPDS diffractometer, graphite monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), 2-Θ range = 3.4–41.7°, data set h, k, l −8:8; −9:9; −23:23, 7204 measured reflections, 2084 independent reflections, 1351 observed reflections with $I > 2\sigma(I)$, $R_{int} = 0.0945$. Structure solution with SHELXS-86 and refinement with SHELXL-93, hydrogen atoms in geometrically calculated positions, max./min. residual electron density 0.22/−0.23 e Å^{-3}, $R(F^1) = 0.0482$ based on 1351 reflections with $F_o > 4\sigma(F_o)$, $wR2 = 0.0814$, $wR2$ based on F^2 with 2084 reflections, Flack parameter −0.1(2).

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[1] a) J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, **1992**, pp. 292–307; b) F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry*, 4th ed., Plenum Press, New York, **1993**; c) A. Streitwieser *Chem. Rev.* **1956**, *56*, 571; A. Streitwieser, *Solvolytic Displacement Reactions*, McGraw–Hill, New York, **1962**; d) R. Brückner, *Reaktionsmechanismen*, Spektrum, Heidelberg, **1996**, p. 56.

[2] Naturally occurring carboxylic acids other than tartaric acid were also investigated, but gave some minor side products. The order of decreasing selectivity was: tartaric acid > malic acid, succinic acid, citric acid > mandelic acid > lactic acid, *p*-toluenesulfonic acid, sulfuric acid.

[3] See also: J. Susko, F. Szelag, *Bull. Int. Acad. Pol. Sci. Lett. Cl. Sci. Math. Nat. Ser. A* **1936**, 403.

[4] Thin layer chromatography was performed on silica gel plates (60 F_{254}, Merck). Detection with UV light and bromocresol green and purification by columm cromatography on silica gel showed no product other than 9-epiquinine (**4**). Diastereomeric quinine (**1**) was never observed.

[5] a) T. G. Waddell, T. Rambalakos, K. R. Christie, *J. Org. Chem.* **1990**, *55*, 4765; b) H. M. R. Hoffmann, O. Schrake, *Tetrahedron: Asymmetry* **1998**, *9*, 1051.

[6] a) J. Cossy, C. Dumas, D. G. Pardo, *Eur. J. Org. Chem.* **1999**, 1693; further recent examples: b) J. Wilken, M. Kossenjans, W. Saak, D. Haase, S. Pohl, J. Martens, *Liebigs Ann.* **1997**, 573.

[7] W. M. Braje, R. Wartchow, H. M. R. Hoffmann, *Angew. Chem.* **1999**, *111,* 2698; *Angew. Chem. Int. Ed.* **1999**, *38,* 2540.

[8] With neutral water as a solvent, 9-epibromoquinine (**2**) and silver benzoate also yield 9-epiquinine (**4**) as the only product with complete retention of configuration. However, the 1-azabicyclo[3.2.2] skeletal rearrangement[7] is strongly solvent dependent. This ring expansion involves fission of two σ-bonds and takes place, for example, with silver benzoate in methanol or with silver benzoate in anhydrous acetone.

[9] For a definition of *syn*, *anti* and *open*, *closed* conformations, see: a) G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Markó, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 8069; b) G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, *J. Org. Chem.* **1990**, *55*, 6121.

[10] See also: H. B. Bürgi, J. D. Dunitz, J. M. Lehn, G. Wipff, *Tetrahedron* **1974**, *30*, 1563.

[11] The conformation of 9-epiquinine mesylate (**5**) and 9-epibromoquinine (**2**)[7] was determined in the solid state (X-ray crystallography[17]) as well as in solution (NOE studies, solvent $CDCl_3$) as *syn*, *open* (Figure 1b).

[12] Generation of a stabilized intermediate carbocation seems facile, because the π electron cloud of the quinoline moiety is oriented correctly for overlap with the vacant p orbital at C9 (Figure 1b). Hydration of the (protonated) bridgehead nitrogen and of the leaving group in the *syn*, *open* conformation is thought to favor nucleophilic attack of the carbocation from the front. Nonetheless, since the intermediate cation is delocalized and comparatively long-lived, the stereochemical outcome, that is complete retention of configuration, is remarkable.

[13] 1-Phenylethyl halides (PhCH(Me)–X; X = Cl, Br), which may be considered as models for our O-mesyl cinchonanes and **2**, have been reported to solvolyse in aqueous ethanol with substantial racemization and up to 27% inversion of configuration. See: C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd ed., Cornell University Press, Ithaca, **1969**, p. 521, Table 33–1.

[14] X-ray crystal structure of the protonated quinine tartrate hemihydrate and conformation of the hydrogen tartrate ion: C. Ryttersgaard, S. Larsen, *Acta Crystallogr. Sect. C* **1998**, *54*, 1698.

[15] Selected recent examples for applications in asymmetric catalysis: Asymmetric dihydroxylation: a) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483; b) ion-pairing and asymmetric phase transfer catalysis: E. J. Corey, F.-Y. Zhang, *Angew. Chem.* **1999**, *111*, 2057; *Angew. Chem. Int. Ed.* **1999**, *38*, 1931; c) B. Lygo, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **1999**, *40*, 8671; d) M. J. O'Donnell, F. Delgado, R. S. Pottorf, *Tetrahedron* **1999**, *55*, 6347; e) D. Martyres, *Synlett* **1999**, *9*, 1508, and references therein.

[16] Further recent works in the field of *Cinchona* alkaloids: a) W. M. Braje, J. Frackenpohl, O. Schrake, R. Wartchow, W. Beil, H. M. R. Hoffmann, *Helv. Chim. Acta* **2000**, *83*, 777; b) S. Röper, J. Frackenpohl, O. Schrake, R. Wartchow, H. M. R. Hoffmann, *Org. Lett.* **2000**, *2*, in press; c) J. Frackenpohl, H. M. R. Hoffmann, *J. Org. Chem.* **2000**, *65*, in press.

[17] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-115799 (**5**) and -115802 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

P_6 Manganocene and P_3 Cymantrene: Consequences of the Inclusion of Phosphorus Atoms in Mn-Coordinated Cyclopentadienyl Ligands**

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Dedicated to Professor Karl-Heinz Thiele on the occasion of his 70th birthday.

The phosphorus-rich analogue of the cyclopentadienyl ligand 3,5-di(*tert*-butyl)-1,2,4-triphospholyl (**1**) can either be

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