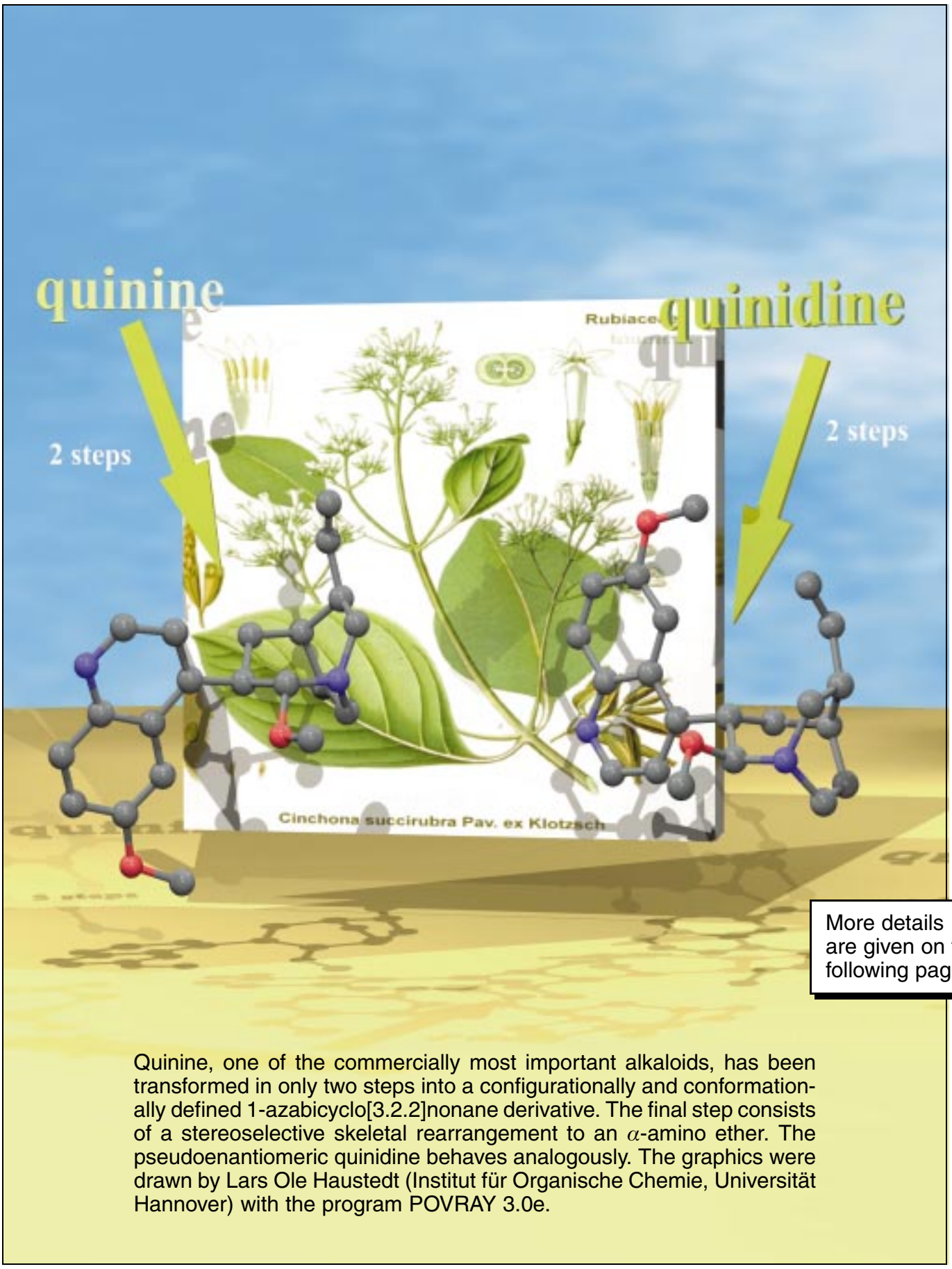

Quinine, one of the commercially most important alkaloids, has been transformed in only two steps into a configurationally and conformationally defined 1-azabicyclo[3.2.2]nonane derivative. The final step consists of a stereoselective skeletal rearrangement to an α-amino ether. The pseudoenantiomeric quinidine behaves analogously. The graphics were drawn by Lars Ole Haustedt (Institut für Organische Chemie, Universität Hannover) with the program POVRAY 3.0e.

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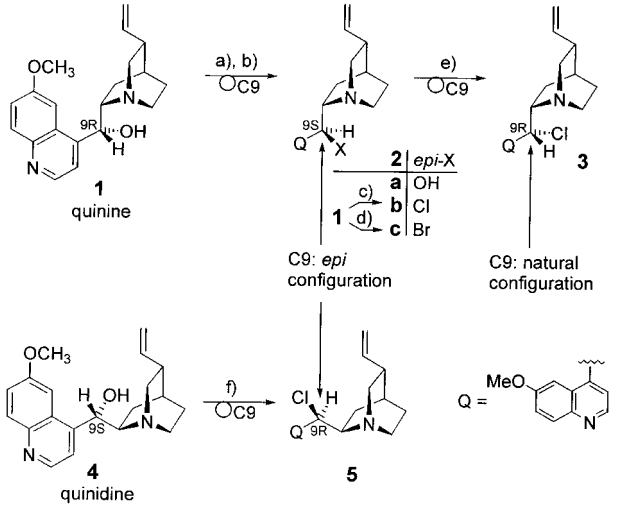
Structure and Mechanism in Cinchona Alkaloid Chemistry: Overturning a 50-Year-Old Misconception**

Wilfried M. Braje, Rudolf Wartchow, and H. Martin R. Hoffmann*

The cinchona alkaloids are commercially the most important alkaloid family. They are produced worldwide at an estimated 700 t per annum and are used in the pharmaceutical industry and in soft drinks. They are also versatile chiral auxiliaries for the separation of enantiomers through the formation of diastereomeric salts and for asymmetric syntheses, for example, for the Sharpless asymmetric dihydroxylation.[1] Cinchona alkaloids have been known and studied for over 350 years and a great deal of literature in diverse scientific journals and also in numerous patents has appeared.

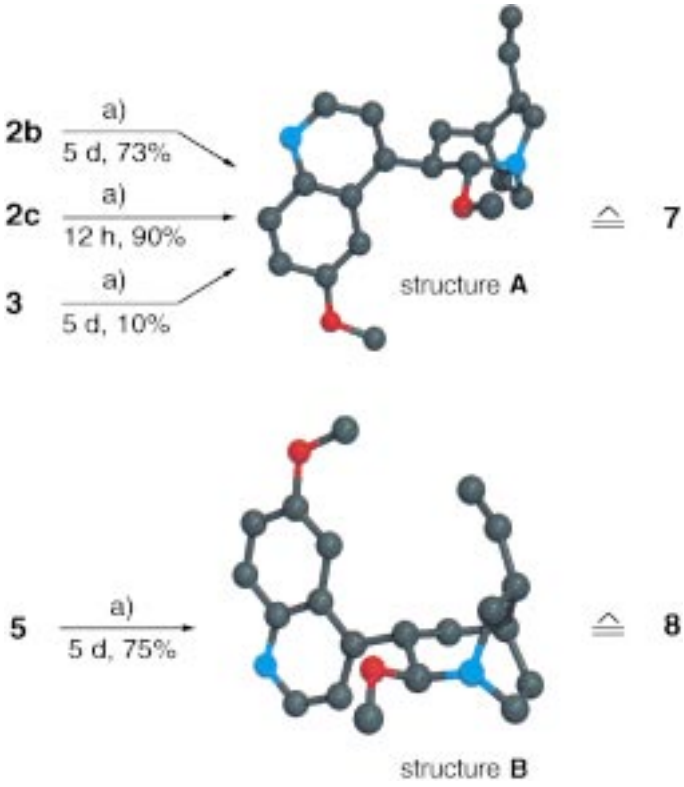
During our work on these alkaloids[2] we investigated the functionalization of the hydroxyl group at C9 through nucleophilic substitutions. To this end a number of leaving groups had to be introduced stereoselectively at C9. Although these reactions as a whole may seem straightforward they have, to the best of our knowledge, not been investigated in detail. They are described briefly here because they form the basis for the S_N1-type reactions reported below. Specifically, halogenation of quinine with $SOCl_2$ and with PBr_3/Br_2 afforded 9-*epi*-chloroquinine (**2b**) and 9-*epi*-bromoquinine (**2c**), respectively, in good to fair yield (Scheme 1). The preparation of 9-chloroquinine (**3**) with the natural configuration at C9 was less obvious. The starting material, 9-*epi*-quinine (**2a**) was prepared by converting quinine (**1**) into its mesylate, which was then refluxed with dilute aqueous acid to yield 9-*epi*-quinine (**2a**) in high yield. Halogenation of **2a** with $SOCl_2$ gave 9-chloroquinine (**3**). The corresponding 9-*epi*-chloroquinidine (**5**) was prepared by halogenation of quinidine (**4**) with PCl_5. Detailed NMR spectroscopic studies of the quinine derivatives showed coalescence effects for 9-*epi*-chloroquinine (**2b**) and 9-chloroquinine (**3**), with the protons H-2′, H-3′, H-5′, H-8, and H-9 appearing as broad lines in the ^{1}H NMR spectrum. The corresponding signals were very small in the ^{13}C NMR spectrum.[3] Interestingly, 9-*epi*-quinine (**2a**) showed no coalescence and 9-*epi*-bromoquinine (**2c**) very little.

Because of these structural uncertainties we elucidated the structure of **2c** by X-ray crystallography. Conformational analysis in solution ($CDCl_3$, NOE) indicated a *syn*,*open* conformation for the 9-*epi* derivatives,[4] similar to that seen in the crystal structure (see structure **C**).[5]



Scheme 1. a) MsCl, NEt_3, THF, reflux, 4 h, 82%; b) TsOH, H_2O, reflux, 30 min, 86%; c) $SOCl_2$, H_2O, reflux, 12 h, 80%; d) PBr_3, Br_2, $CHCl_3$, 45 °C, 2 h, 32%; e) PCl_5, $CHCl_3$, reflux, 2 h, 38%; f) PCl_5, $CHCl_3$, reflux, 2 h, 43%. Ms = methanesulfonyl, Ts = *p*-toluenesulfonyl.

We now had a series of alkaloids stereoselectively halogenated at C9 at hand and investigated their reactions under S_N1 conditions. Specifically, the reaction[6] of halides **2b** and also **2c** with silver benzoate in MeOH gave a new product **7** (m.p. 90 °C) in good to excellent yield (73–90%) in a spot-to-spot reaction. In contrast the reaction with the naturally configurated halide **3** gave only 10% yield of **7** after five days (Scheme 2).



Scheme 2. a) Silver benzoate, MeOH, reflux. The structures were determined by X-ray crystallographic analysis.

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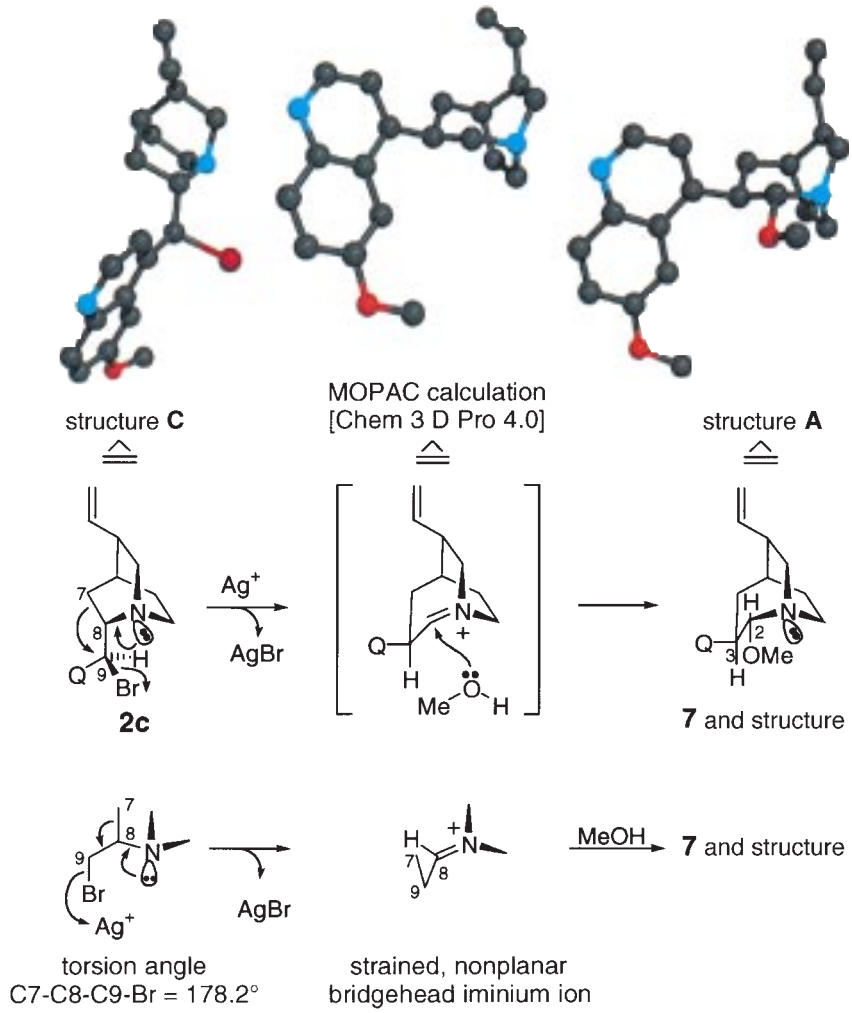
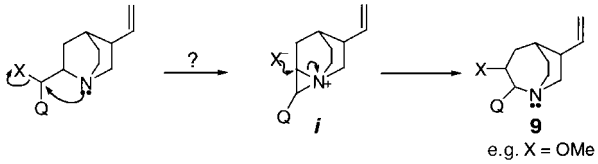
The pseudo-enantiomeric quinidine series behaved similarly. Again, 9-*epi*-chloroquinidine (**5**) and $PhCO_2Ag$ afforded only one product **8** of low polarity. Detailed NMR spectroscopic investigations suggested the formation of a 1-azabicyclo[3.2.2]nonane moiety. Yet the position and stereochemistry of the quinoline residue and the methoxy group were inconsistent with all constitutional isomers proposed previously. Unlike other cinchona alkaloid derivatives that we have studied, the hetero bases crystallized readily. The structures of the rearranged products of the two series were confirmed by X-ray crystallography and are shown in Scheme 2 (**A** and **B**).

The hetero-cinchona bases were formulated previously as **9** by Rabe,[6] one of the pioneers of cinchona alkaloid chemistry.[7] The mechanism of the hetero-cinchona rearrangement and structure **9** were also discussed at length by Woodward and Turner[8] following a landmark total synthesis of quinine.[9] The hetero-cinchona rearrangement has been interpreted further by Warnhoff and others.[10a,b]

Irrespective of the stereochemical detail, our structures (Scheme 2) do not agree with the literature reports (Scheme 3).[6, 8, 10, 11] In view of the known chemistry of β-amino alcohols the literature structure may seem plausible. In fact, examples for aziridinium ion participation in activated β-amino alcohols are legion, and continue to appear.[12]



Scheme 4. Mechanism of the rearrangement. See text for further details.

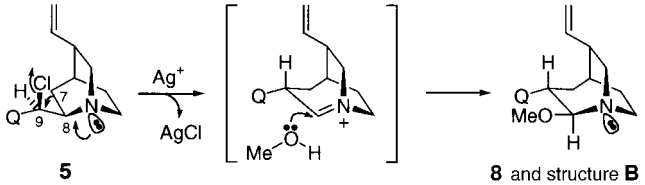


Scheme 3. Supposed involvement of an aziridinium ion ***i*** in the hetero-cinchona rearrangement.

Is an aziridinium ion such as ***i*** (Scheme 3) involved in the hetero-cinchona rearrangement? Cation ***i*** would have to be highly strained. Moreover, we obtained no evidence for a self-quaternization of the series of activated cinchona alkaloids containing leaving groups at C9, including **2b**, **2c, 3**, and **5**. We suggest that the hetero-cinchona rearrangement is stereoelectronically favorable and entails a nucleophilic C7 to C9 shift with formation of a strained, nonplanar bridgehead iminium ion.[13] The C7–C8 and C9–X bonds in **2b**, **2c**, and **5** are antiperiplanar as are the C7–C8 bond and the lone pair of electrons on the nitrogen atom (see arrows in Scheme 5), as evident from the crystal structure of the starting material **2c** (structure **C**). In both hetero bases **7** and **8** the methoxy group and the bulky 4′-quinoline group adopt a quasi equatorial position. The corresponding hydrogen atoms H2 and H3 are quasi-*trans* diaxial (torsion angle for **7** H2-C2-C3-H3 = 168.5°; Scheme 4).

The well-known diminished basicity of hetero-cinchona alkaloids is also more easily understood by the presence of the α-methoxyamine group as in **A** and **B** (see Scheme 2).

Why do the 9-*epi* derivatives **2b** and **2c** rearrange much more readily than the diastereomeric **3**, which has the natural configuration at C9 (Scheme 2)? The required conformation with antiperiplanar arrangement of C7–C8 and C9–X (Scheme 5) is not readily attainable in the natural series.[4b] The rearrangement of **3** proceeds in a spot-to-spot reaction in poor yield and the starting material could be recovered almost quantitatively. The Curtin–Hammett principle[14] does not apply here. In contrast, C9–X bond breaking in the 9-*epi* series is probably concerted with C7–C8 migration, even though σ-bond migration may lag behind ionization of the C–X bond.



Scheme 5. Formation of **8** from **5**.

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More than half a century has passed since the hetero-cinchona bases were first isolated and introduced into the literature. We have fully elucidated the structure of the hetero-cinchona bases **7** and **8** and have revised supposedly established results. Since the constitution and conformation of the hetero-cinchona bases have now been clarified and corrected, earlier mechanistic interpretations[6, 8, 10a,b] of the hetero-cinchona rearrangement must also be abandoned.

Experimental Section

The numbering of the alkaloids follows the conventional nomenclature of Rabe.[15] The hetero-cinchona bases are numbered according to the IUPAC-Autonom. Quinine and quinidine (>99% purity) were obtained from Chininfabrik Buchler GmbH, Braunschweig, Germany.

Crystal structure analysis of **2c**:[16] $C_{20}H_{23}BrN_2O$, $M_r = 387.32$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 8.507(1)$, $b = 9.056(1)$, $c = 23.646(2)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 1821.7(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.412$ g cm^{-3}, $F(000) = 800$, crystal size $0.48 \times 1.7 \times 0.41$ mm, $T = 300$ K, $\mu(Mo_{K\alpha}) = 22.7$ cm^{-1}. Data collection: diffractometer Stoe IPDS (Imaging Plate), graphite-monochromated $Mo_{K\alpha}$ radiation (fine-focus sealed tube, $\lambda = 0.71073$ Å), 2Θ range = 4.8–48.1°, data set h,k,l −9:9, −10:10, −26:26, total data 9746, unique data 2811, observed data 2202 with $I > 2\sigma(I)$, $R_{int} = 0.055$. Structure solution by SHELXS-86 and refinement by SHELXL-93, hydrogen atoms in geometrically calculated positions, max./min. residual electron density 0.30/−0.24 e Å^{-3}, $R(F^1) = 0.0304$ based on 2202 reflections with $F_o > 4\sigma(F_o)$, $wR2 = 0.0416$, $wR2$ based on F^2 of 2811 reflections, Flack parameter −0.01(1).

General procedure for preparation of **7** and **8**: Freshly prepared silver benzoate (150 mg, 0.65 mmol) was added to a solution of **2b** (200 mg, 0.58 mmol) in MeOH (5 mL). and the mixture was refluxed for 5 d. An aqueous solition of $NaHCO_3$ was added and the organic phase extracted ($CHCl_3$). Column chromatography on silica gel (EtOAc/MeOH 10/1) afforded **7** (144 mg, 73%), as a colorless solid. Compound **8** was prepared from **5** by the same procedure.

7: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.72$ (d, $J = 4.5$ Hz, 1H; H-2′), 8.01 (d, $J = 9.2$ Hz, 1H; H-8′), 7.41 (d, $J = 2.6$ Hz, 1H; H-5′), 7.36 (dd, $J = 2.6$, 9.2 Hz, 1H; H-7′), 7.23 (d, $J = 4.8$ Hz, 1H; H-3′), 5.89 (ddd, $J = 6.8$, 10.5, 17.2 Hz, 1H; H-10), 5.11 (ddd, $J = 1.5$, 1.5, 5.9 Hz, 1H; H-11_{cis}), 5.07 (ddd, $J = 1.5$, 1.5, 12.5 Hz, 1H; H-11_{trans}), 4.19–4.13 (m, 1H; H-2), 3.95 (s, 3H; H-11′), 3.74–3.64 (m, 1H; H-3), 3.54 (dd, $J = 9.4$, 14.7 Hz, 1H; H-7_{exo}), 3.40–3.31 (m, 1H; H-8_{endo}), 3.12 (s, 3H; H-12), 2.91 (ddd, $J = 2.0$, 7.8, 10.2 Hz, 1H; H-7_{endo}), 2.78 (ddd, $J = 4.8$, 8.8, 15.1 Hz, 1H; H-8_{exo}), 2.52–2.44 (m, 1H; H-6), 2.09 (br s, 1H; H-5), 2.03–1.93 (m, 1H; H-9_{endo}), 1.88–1.72 (m, 3H; H-4_{endo}, H-4_{exo}, H-9_{exo}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 157.51 (C, C-6′), 148.60 (C, C-4′), 147.71 (CH, C-2′), 144.68 (C, C-10′), 141.10 (CH, C-10), 131.65 (CH, C-8′), 128.50 (C, C-9′), 120.83 (CH, C-7′), 118.00 (CH, C-3′), 114.75 (CH_2, C-11), 102.13 (CH, C-5′), 101.34 (CH, C-2), 55.40 (CH_3, C-11′), 54.74 (CH_3, C-12), 52.27 (CH_2, C-7), 43.64 (CH, C-6), 41.60 (CH, C-3), 37.96 (CH_2, C-8), 32.54 (CH, C-5), 31.11 (CH_2, C-4), 27.96 (CH_2, C-9); IR ($CHCl_3$): $\tilde{\nu} = 2935$ (s), 2870 (m), 1621 (m), 1589 (w), 1510 (s), 1473 (m), 1432 (m), 1255 (m), 1230 (m), 1176 (w), 1075 (s), 1034 (m) cm^{-1}; MS (130 °C): *m/z* (%): 339 (6.6) [M^++1], 338 (31.2) [M^+], 323 (100.0), 307 (7.4), 296 (1.5), 264 (1.3), 250 (1.1), 210 (1.8), 196 (2.1), 186 (3.8), 168 (4.5), 137 (10.2); HRMS: $C_{21}H_{26}N_2O_2$ requires 338.1994; found: 338.1994. Crystal structure analysis:[16] $C_{21}H_{26}N_2O_2$, $M_r = 338.45$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 8.398(1)$, $b = 9.038(1)$, $c = 24.936(2)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 1892.7(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.188$ g cm^{-3}, $F(000) = 728$, crystal size $0.74 \times 0.41 \times 0.37$ mm, $T = 300$ K, $\mu(Mo_{K\alpha}) = 0.8$ cm^{-1}. Data collection as for **2c**, 2Θ range = 4.7–48.0°, data set h,k,l −9:9; −10:8; −28:28, total data 9067, unique data 2912, observed data 1743 with $I > 2\sigma(I)$, $R_{int} = 0.041$. Structure solution and refinement as for **2c**, max./min. residual electron density 0.17/−0.13 e Å^{-3}, $R(F^1) = 0.0340$ based on 1743 reflections with $F_o > 4\sigma(F_o)$, $wR2 = 0.0638$, $wR2$ based on F^2 of 2912 reflections, Flack parameter −0.07(148).

8: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.71$ (d, $J = 4.8$ Hz, 1H; H-2′), 7.99 (d, $J = 9.0$ Hz, 1H; H-8′), 7.34 (dd, $J = 2.5$, 9.0 Hz, 1H; H-7′), 7.31 (d, $J = 2.5$ Hz, 1H; H-5′), 7.21 (d, $J = 4.8$ Hz, 1H; H-3′), 6.12 (ddd, $J = 5.4$, 10.9, 16.1 Hz, 1H; H-10), 5.28 (d, $J = 17.6$, 1H; H-11_{trans}), 5.22 (d, $J = 10.7$ Hz, 1H; H-11_{cis}), 4.25 (d, $J = 9.7$ Hz, 1H; H-2), 3.94 (s, 3H; H-11′), 3.73–3.64 (m, 1H; H-3), 3.35 (dd, $J = 6.7$, 14.7 Hz, 1H; H-7_{endo}), 3.23–3.05 (m, 6H; H-12, H-8_{endo}, H-8_{exo}, H-7_{exo}), 2.56–2.48 (m, 1H; H-6), 2.32–2.25 (m, 1H; H-4_{exo}), 2.09–2.05 (m, 1H; H-5), 1.95–1.86 (m, 1H; H-9_{exo}), 1.80–1.71 (m, 1H; H-9_{endo}), 1.43–1.34 (m, 1H; H-4_{endo}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.67$ (C, C-6′), 149.11 (C, C-4′), 147.68 (CH, C-2′), 144.69 (C, C-10′), 141.20 (CH, C-10), 131.55 (CH, C-8′), 128.65 (C, C-9′), 121.62 (CH, C-7′), 117.69 (CH, C-3′), 114.15 (CH_2, C-11), 101.35 (CH, C-5′), 98.86 (CH, C-2), 55.44 (CH_3, C-11′), 54.38 (CH_3, C-12), 46.48 (CH_2, C-8), 45.04 (CH_2, C-7), 40.74 (CH, C-3), 39.66 (CH, C-6), 37.48 (CH_2, C-4), 33.01 (CH_2, C-9), 32.57 (CH, C-5); IR ($CHCl_3$): $\tilde{\nu} = 2934$ (s), 2875 (w), 1621 (m), 1510 (m), 1473 (m), 1433 (w), 1237 (m), 1074 (s), 1034 (w), 843 (m) cm^{-1}; MS (60 °C): *m/z* (%): 339 (9.6) [M^++1], 338 (36.7) [M^+], 323 (100.0), 307 (11.1), 264 (3.9), 224 (3.8), 214 (3.8), 196 (5.4), 186 (9.3), 169 (9.0), 153 (10.6), 138 (17.8), 122 (60.6), 105 (69.8), 84 (70.7) 77 (45.2); HRMS: $C_{21}H_{26}N_2O_2$ requires 338.1994; found: 338.1993. Crystal structure analysis:[16] $C_{21}H_{26}N_2O_2$, $M_r = 338.45$, monoclinic, space group $P2_1$ (No. 4), $a = 7.877(1)$, $b = 7.246(1)$, $c = 16.359(2)$ Å, $\alpha = 90$, $\beta = 101.59(2)$, $\gamma = 90°$, $V = 914.7(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.229$ g cm^{-3}, $F(000) = 364$, crystal size $0.41 \times 0.74 \times 0.48$ mm, $T = 300$ K, $\mu(Mo_{K\alpha}) = 0.8$ cm^{-1}. Data collection as for **2c**, 2θ range = 5.2–47.9°, data set h, k, l −8:8, −8:8, −18:17, total data 3158, unique data 2409, observed data 1678 with $I > 2\sigma(I)$, $R_{int} = 0.029$. Structure solution and refinement as for **2c**, max./min. residual electron density 0.11/−0.09 e Å^{-3}, $R(F^1) = 0.0307$ based on 1678 reflections with $F_o > 4\sigma(F_o)$, $wR2 = 0.0591$, $wR2$ based on F^2 of 2409 reflections, Flack parameter 0.3(15).

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Keywords: alkaloids · nitrogen heterocycles · rearrangements · stereoelectronic control · structure elucidation

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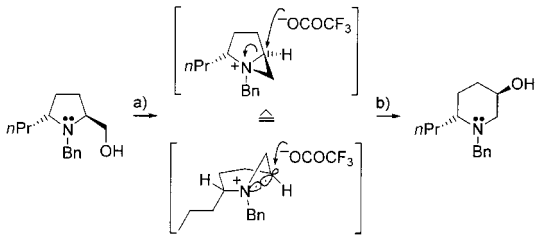
F. Eiden, *Pharm. Unserer Zeit* **1998**, 257, in particular Figure 28 on p. 269.
[11] Structure **9** appears in electronic data bases: Beilstein Commander 4.0, search March **1999**.
[12] Cossy and her co-workers have reported the ring enlargement of an L-proline derivative in the synthesis of (−)-pseudoconhydrine (Scheme 6):



Scheme 6. Top: inside-flap attack, bottom: S_N2-type attack; a) $(CF_3CO)_2O$, then Et_3N; b) NaOH.

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[16] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data centre as supplementary publication nos. CCDC-115800 (**7**), -115801 (**8**), and 115802 (**2c**). 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).

A Small-Molecule Guanidinium Receptor: The Arginine Cork**

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Individual arginine residues are critical to the function of many nucleotide-binding proteins.[1, 2] Small-molecule receptors capable of binding the *N*-alkylguanidinium moiety of arginine could be used in numerous ways, such as antiviral drugs and molecular probes for arginine-rich proteins. Reported herein is a designed, small-molecule receptor that binds *N*-alkylguanidinium cations. Binding selectivity for arginine, relative to lysine, is observed in water and methanol solvents. The solid-state structure of its complex with two *N*-alkylguanidinium cations suggests that it should have a special affinity for the dipeptide ArgArg, and this prediction has been confirmed by microcalorimetric titration in water.

The amino acid arginine is a critical component of many RNA-binding proteins that mediate a wide range of biological processes.[1, 2] While the "basic-domain" class of RNA-binding proteins contain arginine-rich sequences of 10–15 amino acids, highly conserved arginine residues often make specific electrostatic contacts with phosphate groups in the polyribonucleotide backbone. Two examples of such proteins that regulate important steps in the replication of the human immunodeficiency virus type I (HIV-1) are the transcriptional activator Tat[1–4] and the Rev protein.[1, 2, 5] The recently determined structure of the HIV-1 nucleocapsid protein bound to the genomic Ψ-RNA recognition element[6] displays a specific arginine–base interaction (Arg32−A8). RNA recognition processes have become important targets for the development of antiviral and antibiotic drugs.[7, 8] Small molecules tailored to bind specifically to arginine residues could lead to novel pharmaceuticals, as well as molecular probes that could facilitate the characterization of RNA-binding proteins.

There have been a few reports of artificial receptors that bind arginine or arginine derivatives,[9–11] but what is the best design for the recognition of the arginine side chain in peptides? To be useful for biological applications, such a receptor must be reasonably soluble in water, it must have high affinity for the *N*-alkylguanidinium moiety, and it must display selectivity relative to other cations, particularly versus the *N*-alkylammonium side chain of lysine. We can recognize arginine by means of a hydrogen-bond array that either imitates one of the natural patterns or seeks to improve on nature by de novo design. By following the former biomimetic route Schrader[11] synthesized "molecular tweezers" containing two phosphonate groups capable of binding guanidinium cations by four hydrogen bonds (Figure 1a). The structure of the resulting complex resembles that of the critical arginine residue of Tat (Arg52) bound to phosphodiesters P22 and P23 of HIV-1 TAR RNA, a feature dubbed the "arginine fork" (Figure 1b) by Frankel et al.[3] Despite the presence of electrostatic interactions between the guanidinium cation and two anionic phosphonate groups of molecular tweezer **2**, only modest binding was observed, even in methanol ($K_d \approx$ 2 mM). This can be attributed to incomplete preorganization of the hydrogen-bond acceptor sites in **2**.

Most receptors designed for the guanidinium cation are flexible crown ether derivatives.[9, 12–16] Our approach to recognition of small, planar molecules is to construct a relatively rigid, planar array of hydrogen-bonding groups by fusing together a series of six-membered rings.[17–23] Nearly perfect host–guest complementarity results from registry between the N−N and N−O hydrogen bond distances and the

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