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Asymmetric conversions of 10-bromo-10,11-dihydroquinines into 8-oxa-1-azabicyclo[4.3.0]nonane derivatives and related compounds

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Abstract—Some transformations of (10*R*)- and (10*S*)-bromo-10,11-dihydroquinine **2a** and **2b** have been investigated in order to obtain insights into their unexplored chirality. The (10*R*)-diastereomer **2a** converts stereoselectively into (4*S*)-(*E*-propenyl)-(6*S*,7*R*)-(6-methoxy-quinol-4-yl)-8-oxa-(1*R*)-azabicyclo[4.3.0]nonane **10**, which is the product of a novel rearrangement of the parent quinine **1** and displays the N(1)-(*S*)-configuration (**10a**) in the solid state. The (10*S*)-diastereomer **2b** afforded **10** and its (*Z*)-propenyl isomer **15** (in the ratio 55:45), as well as (*Z*)-3,10-didehydro-10,11-dihydro-quinine **19**. On treatment with acid the alkaloid **10** yields [(4*S*)-(*E*)-propenyl)-(2*S*)-piperidinyl]-6-methoxyquinoline-(α*R*)-methanol **12**. Closure of the oxazolidine ring in **12** gives **14**, the 9,9-dimethyl-derivative of **10**, with the N(1) configuration inverted. The molecular structures of **10a** and **14**, determined by X-ray diffraction, show their similar conformations except for the axial (*E*)-propenyl substituent, disordered in two orientations in **10a** and ordered in another position in **14**.

1. Introduction

Cinchona alkaloids have been intensively studied because of their role as versatile catalysts and ligands in a wide range of asymmetric processes. For example, the alkaloids participate in the dihydroxylation[1] and aminohydroxylation[2] of olefins as well as in phase-transfer reactions.[3,4] These alkaloids have been used as surface modifiers of catalysts for asymmetric hydrogenation,[5] they mediate enantioselective fluorination[6] and ring openings of prochiral cyclic *meso*-anhydrides.[7] Quinine also catalyzes the intramolecular oxo-Michael reaction and has been employed in syntheses of chiral anion exchangers.[8,9] These alkaloids are also used in the preparative resolution of racemic acids.[10] A review of about 250 original papers dealing with the numerous catalytic applications of the cinchona alkaloids and their applications in a wide variety of asymmetric syntheses has been recently published.[11]

In contrast to the above achievements, much less attention has been devoted to the asymmetric aspects of the stereochemistry of the alkaloids themselves. Brunner and co-workers synthesised 9-amino-epicinchonine and -epiquinine by inverting the C(9) configuration using Mitsunobu chemistry.[12] 9,10-Quinidine diols were stereospecifically converted into tricyclic *N*,*O*-acetals.[13] Stereospecific rearrangement of 9-chloro- and 9-bromo-epiquinine as well as 9-chloro-epiquinidine into the 1-azabicyclo[3.2.2]nonane derivatives enabled correction of the structure of hetero-cinchona alkaloids.[14] Hoffmann and collaborators found that acidic hydrolysis of quinine and quinidine mesylates proceeded with inversion of configuration at C(9), whereas the configuration at C(9) was retained for the same derivatives of epiquinine and epiquinidine after similar treatment.[15] Cook and his group synthesised (10*R*)- and (10*S*)-11-dihydroxy-10,11-dihydroquinine via the Sharpless osmylation process.[16]

The so far unexplored course of the reaction during which 10-halogeno-10,11-dihydrocinchona derivatives afford products deficient in one carbon atom[17] prompted us to study this reaction of 10-bromo-10,11-dihydroquinines.

2. Results and discussion

Addition of hydrogen bromide to the vinyl group of quinine **1** (**1**→**2**, Scheme 1) provides the diastereomeric 10-bromo-10,11-dihydroquinines **2a** and **2b**. Podlewski

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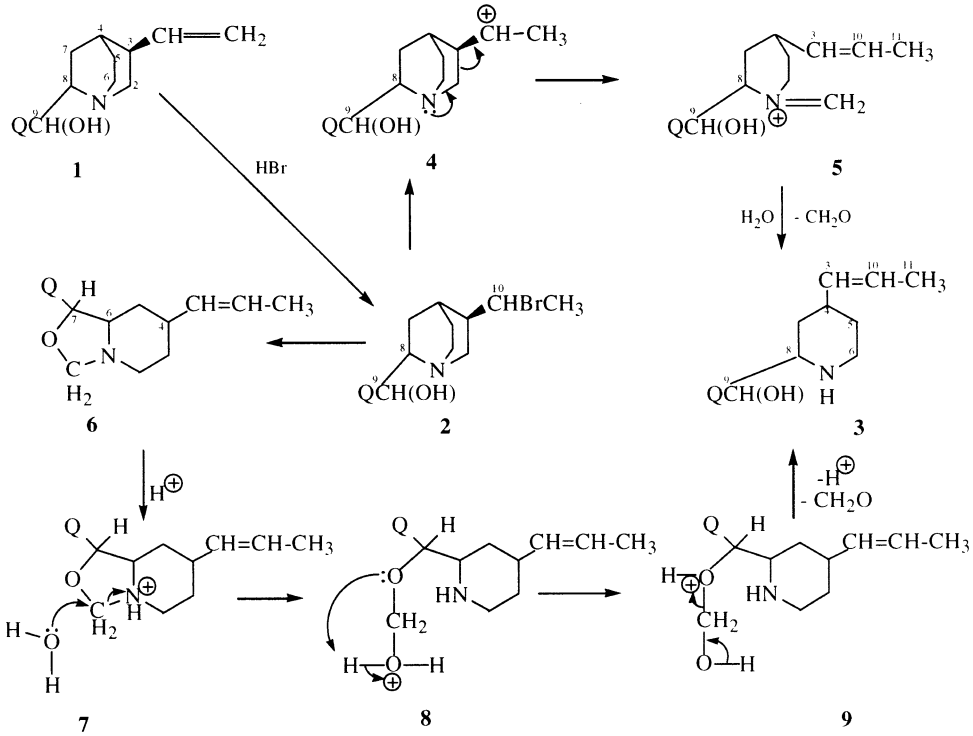


1 a) (8*R*,9*S*)-cinchonine
b) (8*S*,9*R*)-quinine
1a, 2c: Q = quinol-4-yl
1b, 2a, 2b: Q = 6-methoxyquinol-4-yl
6) (R_N,4*S*,6*R*,7*S*)

2a) (8*S*,9*R*,10*R*)-bromo-10,11-dihydroquinine
b) (8*S*,9*R*,10*S*)-bromo-10,11-dihydroquinine
c) (8*R*,9S)-10-bromo-10,11-dihydrocinchonine
3a) (8*R*,9*S*,4*S*)-nicinquine, isonicinquine

Scheme 1. Alternative reaction pathways along which the 10-bromo-10,11-dihydro-cinchona derivatives may lose their C(2) carbon atom as formaldehyde.

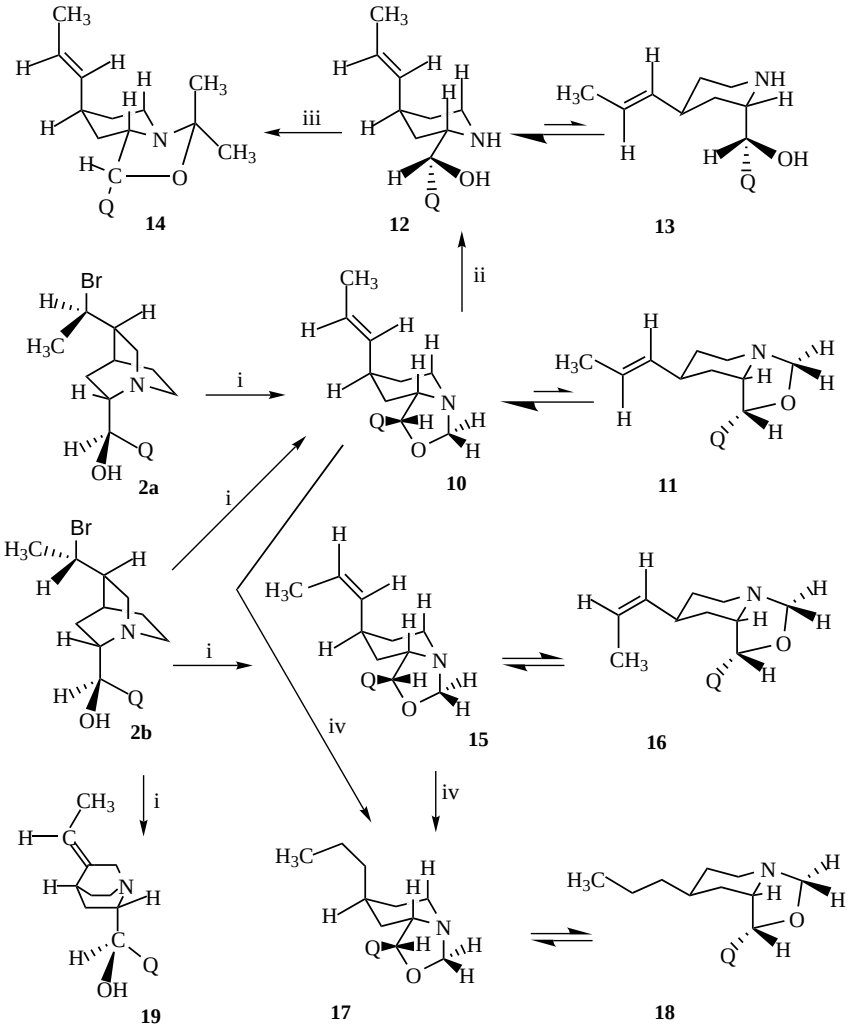
and Suszko[18] found that the more levo-rotatory diastereomer **2a** ($[\alpha]_D = -213.7$), with (10*R*)-configuration,[19] provided niquine on treatment with alkali, whereas the less levo-rotatory (10*S*)-isomer **2b** ($[\alpha]_D = -52$)[19] was transformed into β-isoquinine, a $\Delta^{3,10}$-isomer of **1**.

The formation of niquine, for which the 'planar' structure **3** was proposed by Solomon,[20] is accompanied by loss of the C(2) carbon as formaldehyde. According to Smith, the formation of niquine can be rationalised by the Grob fragmentation mechanism of γ-aminohalides **2→4→5→3** (Scheme 1).[21] However, for such a fragmentation to occur, the anti-parallel oriented nitrogen orbital containing the lone electron pair and the C(10)–Br bond from the N(1)–C(2)–C(3)–C(10)–Br group of the substrate **2** must adopt either an antiperiplanar, synperiplanar or synclinal position.[22] Meanwhile, despite the above stereoelectronic requirements, (10*R*)-bromo-10,11-dihydroquinine with an unfavourable anticlinal γ-haloamine group[22] underwent the fragmentation.[18] Analogous fragmentation products—nicinquine and isonicinquine **3a**—[23] arise from 10-bromo-10,11-dihydrocinchonine **2c**, which does not fulfil the stereoelectronic requirements either. However, in the latter case, it was discovered that the reaction may proceed via the intermediate product **6** (Scheme 1).[24] In turn, the intermediate loses its C(9) carbon atom (i.e. C(2) of the parent alkaloid) as formaldehyde according to the proposed reaction sequence **6→7→8→9→3** (Scheme 1).[24,25] Unfortunately, no stereochemical information concerning the formation of **6** could be acquired since the diastereomeric 10-bromo-10,11-dihydro-cinchonines were impossible to separate.

Therefore, the more easily separable 10-bromo-10,11-dihydroquinines seemed more promising not only for examining the scope of this novel rearrangement (**2→6**, Scheme 1) but also to investigate the stereochemistry of the reaction.

For the sake of comparison with the conversion of the cinchonine derivatives,[24] each of the diastereomers **2a** and **2b** was exposed to equimolar sodium bicarbonate in refluxing 80% aqueous ethanol. The (10*R*)-isomer **2a** provided an analogue of the compound **6** in which the propenyl side chain has (*E*)-configuration. The olefinic protons of this fragment have $J_{HH} = 15.4$ Hz and its methyl group exhibits $\delta_C = 18.01$.[24,26]

Since both (*E*)- and (*Z*)-isomers of **6** preserve the absolute configurations of C(4), C(8) and C(9) carbons of the parent cinchonine,[24] one could assume that these arrangements will be retained in the product derived from **2a**. Hence, *cis*- or *trans*-fusion between the pipe-



Scheme 2. Conversions of 10-bromo-10,11-dihydroquinines **2a** and **2b**. *Reagents and conditions*: (i) $NaHCO_3$, 80% aqueous EtOH, 11 h, reflux; (ii) $(COOH)_2$, 96% aqueous EtOH, 80 min, reflux; (iii) acetone, 8 weeks, rt; (iv) H_2, 4 atm, Adams PtO_2, 4.5 h, rt.

ridine and oxazolidine rings of the obtained alkaloid should be taken into consideration. The *cis*-junction would require the alkaloid to exist in a conformational equilibrium of **10** ⇆ **11** (Scheme 2). The C(4) proton of this compound has $\Sigma J = 18.5$ Hz. This result, precluding the 1,2-diaxial couplings with C(5)H and C(3)H, points to the equatorial disposition of the C(4) proton. Such a 1,2-diaxial interaction, however, occurs between C(6) and C(5) protons since their $^3J_{HH} = 9.4$ Hz. The axial C(6) and C(2) protons, apart from an NOE 1,3-diaxial enhancement, show an NOE with the propenyl C(1″) proton. In addition, the C(5) and C(3) axial protons exhibit NOEs with one of the C(9) protons appearing at $\delta_H = 4.96$ and revealing no NOE effect with C(7)H. The two NOEs exclude the possible *trans*-fusion between the six- and five-membered rings of **10**.

The above results not only confirm the axial position of the (*E*)-propenyl group but also allow us to indicate the conformer **10** to be predominant in the equilibrium mixture **10** ⇆ **11** (Scheme 2). A possible minor share of the other conformer **11** in the mixture should unnecessarily give rise to considerable averaging of the observed coupling constant between the C(5) and C(6) protons ($J = 9.4$ Hz) for which the calculated value of the $C(6)H_{AX}$–C(6)–C(5)–$C(5)H_{AX}$ dihedral angle is −147.5°.[27] This angle might be the result of deviation from the normal 1,2-diaxial position of hydrogens in the piperidine ring forced by its fusion with the five-membered ring, as is seen in *cis*-hydrindane.[28] It is worth adding here that when the five-membered moiety breaks (see the text below) the dihedral angle increases.

In order to examine structure **10** found in $CDCl_3$ solution, analysis in the solid state of the alkaloid derived from **2a** was carried out by X-ray diffraction analysis.

The result was a surprise since the discussed alkaloid exhibited *trans*-fusion between the piperidine and oxa-

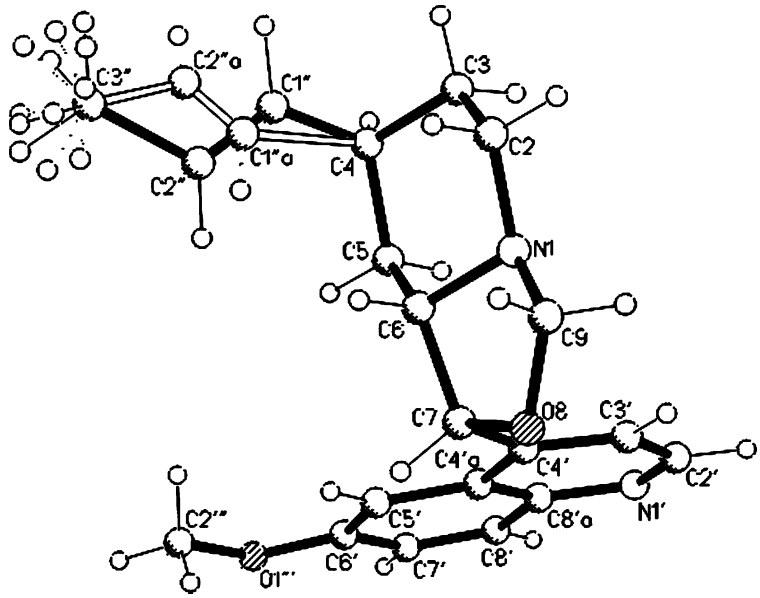


Figure 1. Drawing of molecule **10a** showing its absolute configuration and conformation as present in the crystal structure. Two sites of the disordered C(1″)=C(2″)–C(3″) 1-propenyl have been differentiated by the style of the bonds in the drawing: full bonds and full lines to H-atoms for one position, and open bonds and dotted lines to H-atoms in the other. The methyl hydrogens in methyl C(3″) are additionally disordered in four positions each.

zolidine rings shown in Fig. 1 as structure **10a** (discussed in detail later in the text). This crystal structure explains the appearance of the Bohlmann band on the IR spectrum. The X-ray structure of *trans*-**10a**, on the one hand, confirms the (4*S*,6*S*,7*R*)-configuration of **10**, but on the other hand, points to the pyramidal inversion of the N(1) nitrogen atom (see Table 1). Such an inversion is not an isolated phenomenon within structures comprising piperidine rings. For instance, bisquinolizidine alkaloids may change their N(16) chirality. In particular, lupanine, sparteine and 2-phenylsparteine, as free bases, feature the dominant conformer with 'chair–chair–boat–chair' rings,[29–31] whereas their perchlorates possess the 'all-chair' structure.[32–34] A thioanalogue of lupanine, (+)-2-thionosparteine, also shows dominance of the C-boat form over that of the 'all-chair' form in solution. Instead, asymmetric units of the crystals are composed of both forms in a 1:1 ratio.[35] Here the pyramidal inversion is due to crystal packing forces which are likely to give rise to *trans*-**10a**.

On treatment of **10** with acid, loss of the C(9) carbon (corresponding to C(2) of the parent **2a**) in the form of CH_2O occurs and niquine is formed. The eliminated formaldehyde was trapped as its condensation product with dimedone.

The formed niquine has the previously[20] undetermined (*E*)-propenyl side chain since it shows the olefinic $^3J_{HH}=15.4$ Hz and the methyl group resonates at $\delta_C=18.15$.[26] The propenyl substituent occupies an axial position because its C(1″) proton displays an NOE with C(6)H. The C(6) proton displays a 1,2-diaxial disposition with C(5)H; their coupling constant is 10.3 Hz and the $C(6)H_{AX}$–C(6)–C(5)–$C(5)H_{AX}$ dihedral calculated according to Altona amounts to −154°.[27] The NOE between C(1″)H and C(6)H and 1,2-diaxial coupling as well as C(4)H resonance (broadened singlet with $\Sigma J\approx$ 24 Hz) indicates not only that **12** is the dominant conformer in the equilibrium mixture **12** ⇆ **13** (Scheme 2) but also confirms retention of the (4*S*)- and (6*S*)-configurations of the substrate **10**. These spatial arrangements correspond to (4*S*)- and (8*S*)-configuration in the parent quinine **1**.[17,36]

The formation of niquine from **10** is not accompanied by its C(α)-epimer, inferring that the C(7)–*O* bond of the substrate **10** has remained unscathed, whereas the C(9)-*O* linkage should be broken. In such a case niquine should feature the unchanged (7*R*)-configuration of **10**, identical to C(9*R*) of quinine.[36] To verify this presumption, niquine was subjected to cyclisation via its reaction with acetone.[20] In the case of *cis*-fusion, the cyclisation product should feature an NOE between the methyl group appearing at $\delta_H=1.60$ and the C(5) axial proton. Instead, this group exhibits an NOE with the quinoline C(3′) proton, which in the *cis*-compound is more remote (model inspection) than the axial C(5)H. Occurrence of this Overhauser effect can be better explained by accepting the *trans*-fusion.

X-Ray diffraction analysis of the obtained isopropylidine derivative of niquine, **14** (Scheme 2) showed formation of the *trans*-junction between the piperidine and oxazolidine rings (see Fig. 2). This fusion arose due to inversion of configuration at N(1) in the restored 8-oxa-1-azabicyclo-[4.3.0]-nonane ring as compared with **10**. However, in accordance with the Cahn–Ingold-Prelog sequence rule,[37] N(1) has (*R*)-configuration, as in **10**. Both the X-ray analysis and NMR data also confirmed retention of the (4*S*,6*S*,7*R*)-configuration (see Fig. 2).

Table 1. Selected torsion angles (°) for **10a** and **14**

	10a	**14**
Piperidine ring		
C6–N1–C2–C3	−61.3(4)	−62.1(3)
N1–C2–C3–C4	56.8(5)	54.8(4)
C2–C3–C4–C5	−53.4(5)	−50.6(3)
C3–C4–C5–C6	52.2(4)	52.3(3)
C4–C5–C6–N1	−56.7(4)	−60.0(3)
C2–N1–C6–C5	62.7(4)	66.0(3)
Propenyl group		
C2–C3–C4–C1″	82.0(5)	74.1(3)
C2–C3–C4–C1″a	62.2(11)	
C3–C4–C1″–C2″	−128.3(8)	12.6(5)
C5–C4–C1″–C2″	1.3(11)	137.6(4)
C3–C4–C1″a–C2″a	103(2)	
C5–C4–C1″a–C2″a	−138(2)	
C4–C1″–C2″–C3″	−178.4(7)	−179.0(4)
C4–C1″a–C2″a–C3″	174.1(15)	
C1″–C4–C5–C6	−77.2(6)	
C1″a–C4–C5–C6	−69.8(9)	−76.4(3)
Oxazolidine ring		
N1–C6–C7–O8	35.5(3)	21.7(2)
C6–C7–O8–C9	−12.3(4)	2.2(3)
C7–O8–C9–N1	−16.7(5)	−25.2(3)
C6–N1–C9–O8	39.8(4)	40.2(3)
C9–N1–C6–C7	−46.0(3)	−38.5(2)
Piperidine–oxazolidine fusion		
C4–C5–C6–C7	−171.6(3)	−174.6(2)
C9–N1–C2–C3	−177.5(3)	174.7(2)
C9–N1–C6–C5	−173.5(3)	−164.6(2)
C2–N1–C6–C7	−169.8(3)	−167.9(2)
C5–C6–C7–O8	155.6(3)	140.7(2)
C2–N1–C9–O8	161.6(3)	165.5(2)
Oxazolidine–quinoline C(7)–C(4′) junction		
N1–C6–C7–C4′	−83.0(3)	−99.3(2)
C5–C6–C7–C4′	37.2(5)	19.7(3)
C4′–C7–O8–C9	109.3(4)	127.5(2)
O8–C7–C4′–C3′	−22.9(5)	−26.3(3)
C6–C7–C4′–C3′	91.5(4)	92.1(3)
O8–C7–C4′–C4′a	155.8(3)	152.5(2)
C6–C7–C4′–C4′a	−89.8(4)	−89.1(3)
Methoxyl orientation		
C5′–C6′–O1‴–C2‴	3.4(8)	2.6(5)
C7′–C6′–O1‴–C2‴	−177.7(5)	−177.7(4)

The conformations of **10a** and **14** are also shown in Figs. 1 and 2, and compared in Table 1. The conformations are similar despite their flexibility. The methyl substituents at C(9) induce little variation of the main molecular skeleton. The torsion angles about the single C(7)–C(4′) bond joining two moieties in the molecules are very similar. Some differences, of about 10°, are observed for the oxazolidine rings, but the piperidine rings are in the similarly distorted chair conformation. The main apparent difference is the conformation of the 1-propenyl substituent. In both compounds the propenyl group is situated axially at C(4), however, in **10a** it is disordered in two positions, none of which is observed in **14**. The orientation of the propenyl relative to the piperidine ring can be conveniently measured by torsion angles C(3)–C(4)–C(1″)–C(2″) and C(5)–C(4)–C(1″)–C(2″). The orientations of the disordered propenyl groups in **10a** differ by 230°, while the position assumed by the propenyl group in **14** is intermediate between the two orientations in **10a**. It is likely that these conformations are related to the packing of the molecules in the crystal lattices, rather than to the conformational properties of the molecules.

Both compounds **10** and **14** have (7*R*)-configuration, the C(7)–*O* bond of **10** could not be broken on treatment with acid. Thus, formation of niquine unnecessarily follows the Grob fragmentation pattern and may be rationalised by the alternative reaction pathway **2**→**6**→**7**→**8**→**9**→**3** (Scheme 1). In contrast to the highly stereoselective conversion of the (10*R*)-diastereomer (**2a**→**10**,Scheme 2) its (10*S*) counterpart provides a mixture of products.

The most abundant (40%) and, at the same time, the less polar component consists of two inseparable alkaloids. Fortunately their ^{1}H NMR signals overlapped only partially, so knowing the resonances of one (i.e. those of **10**), the signals of its (*Z*)-isomer **15** (Scheme 2) could be identified. Similarly the ^{13}C NMR resonances could be distinguished, especially those belonging to the C(4)- and C(3″)-carbons of **15**. The two characteristically differed from analogous resonances of the alkaloid **10**. The corresponding δ_C values of 28.77 and 12.28, as compared with 33.51 and 18.01 ppm, respectively, are due to alkene-2 γ-shielding occurring only in the (*Z*)-propenyl group.[24,26] The mixture of alkaloids **10** and **15**, with an *E*:*Z* ratio of 11:9 (^{1}H NMR integration), undergoes catalytic hydrogenation to give the compound with an *n*-propyl side chain (**17** ⇆ **18**, Scheme 2). This result confirms the structure **15**.

The alkaloid **15** features the C(2), C(5) and C(6) proton signals lacking the $^{3}J_{HH}$ values which would indicate 1,2-diaxial couplings. Moreover, the C(4) proton resonance shows $\Sigma J \approx 29$ Hz intermediate between 18.5 Hz, characteristic of equatorial positioning of the C(4)H in compound **10**, and 42 Hz corresponding to an axial C(4)H in the alkaloid **6**.[24] The above data are likely due to averaging of the resonances caused by the conformational equilibrium **15** ⇆ **16** (Scheme 2), which might be caused by repulsion between the methyl group and the axial C(2) and C(6) hydrogens, which hinders the rotation of the (*Z*)-propenyl chain about the C(1″)–C(4) bond. A similar equilibrium probably occurs in the hydrogenation product of the mixture of the alkaloids **10** and **15** (**17** ⇆ **18**, Scheme 2), since the C(2), C(5) and C(6) protons display no $^{3}J_{HH}$ values that would indicate 1,2-diaxial interactions within the piperidine fragment.

The next and less abundant (∼30%) product obtained from the (10*S*)-diastereomer **2b** is a $\Delta^{3,10}$-isomer of quinine featuring mp 182–185°C and $[\alpha]_D = -188.7$. These data are similar to those of β-isoquinine described by Suszko (mp 188°C; $[\alpha]_D = -191.45$)[38] and Henry (mp 183–185°C; $[\alpha]_D = -201.2$)[39] and also considered to be a $\Delta^{3,10}$-isomer of quinine. The discussed alkaloid showed the methine C(4) resonance at $\delta_C =$ 33.32, which on comparison with the model, 3-ethylidene-quinuclidine,[40] points to the previously undeter-

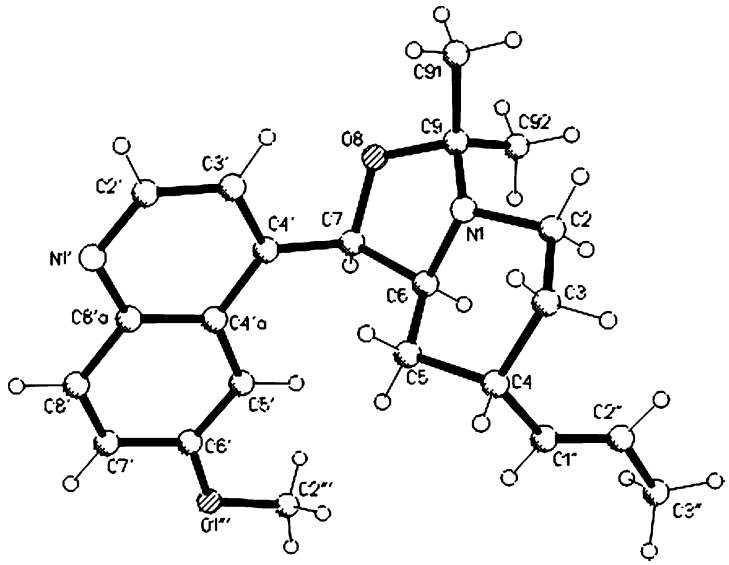
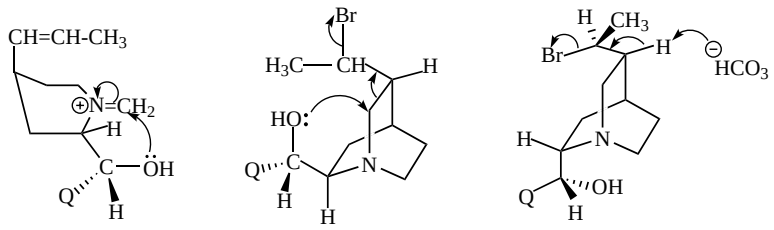


Figure 2. Drawing of molecule **14**, as present in the crystal structure showing its molecular conformation and absolute configuration.



20 **21** **22**

Scheme 3. Possible transition states for oxazolidine ring-closure during the rearrangement (**20**, **21**) and stereoselective elimination (**22**) discussed in the text. The formation of **20** may be preceded by the carbonium ion **4** of Scheme 1.

mined (*Z*)-configuration of the side chain (in the case of (*E*)-configuration, one would expect the C(4) signal to appear at $\delta_C = 26 \pm 1$). Moreover, NOEs between the C(4) and C(10) protons as well as between the C(2) methylene and C(11) methyl protons were observed (see **19**, Scheme 2).

The third component of the mixture obtained from **2b** is composed of niquine and its (*Z*)-isomer as it can be inferred from the ^{13}C NMR analysis. These alkaloids have been, at least partially, formed by the influence of alumina on the mixture of **10** and **15** during column chromatography. Two remaining minor components of the crude conversion product of **2b** were very difficult to separate.

Conversions of **2a** and **2b** shown in Scheme 2 clearly point out their chirality. This feature is most distinctly revealed by the diastereomer **2a**, which rearranges almost entirely into the alkaloid **10**. The rearrangement also occurs in the case of the isomer **2b** although with much lower stereoselectivity providing 55% of **10** versus 45% of **15**. Instead, high stereoselectivity in the elimination of HBr from **2b** has been observed (**2b**→**19**, Scheme 2).

The observed ratio of **10** to **15** may indicate that the rearrangement of **2a** and **2b** proceeds via carbonium ion **4** (Scheme 1) the more so that 80% aqueous ethanol, being the reaction medium, exhibits good ionisation ability.[22,41] The cation **4** would then convert into the imminium cation **5** (Scheme 1), which enables an approach of C(2) to the oxygen at C(9) to close the oxazolidine rings of **10** and/or **15** (see **20**, Scheme 3). Because of the (8*S*)-configuration in **2a** and **2b**, formation of the oxazolidine moiety is unlikely to be a one-step process. On the other hand, such a concerted mechanism (**21**, Scheme 3) is conceivable for 10-bromo-10,11-dihydrocinchonine **2c** with (8*R*) arrangement.

The cation **4** could also be responsible for E1 elimination leading to the alkaloid **19**, which is energetically favourable over its (*E*)-isomer. In the latter compound, the distance between the (*E*)-methyl group and the C(4) hydrogen (model inspection) is smaller than that of the (*Z*)-methyl group from any of the C(2) protons in **19**. However, selective formation of the alkaloid **19** would be indicative of E2 elimination, since the (*Z*)-configuration might result from the preceding transition state **22** (Scheme 3).

3. Conclusion

In summary, the results presented demonstrate that the so far observed **2c→6** rearrangement not only extends to another cinchona alkaloid but also proceeds stereoselectively and is likely to involve a multi-stage mechanism. Another mechanism suggested for the acidic 'fragmentation' of the rearrangement product **10** has received firm support due to the retained (α*R*)-configuration in **12**. Stereoselectivity has also been observed during restoration of 8-oxa-1-azabicyclo-[4.3.0]nonane ring (**12→14**, Scheme 2) and elimination of HBr from **2b**. The origin of the asymmetry in the formation of **14**, **10** and **15** as well as further extending the scope of the rearrangement are still under investigation.

4. Experimental

4.1. General

Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 243B Polarimeter and are reported as follows: $[\alpha]_D$ (concentration g/100 mL, solvent). The IR spectra were recorded using FT-IR-Raman Nicolette-760 spectrometer. NMR spectra were obtained on a Varian Gemini 300 BB and Varian Mercury spectrometers at observation frequencies 75 and 300 MHz. ^{1}H NMR spectra were recorded in ppm (δ) related to tetramethylsilane and are reported as follows: chemical shift (multiplicity, integration, coupling constants in Hz, assignment). ^{13}C NMR spectra (δ, TMS) are presented as chemical shift (assignment). The NMR assignments were made by first-order analysis of the ^{1}H resonances and aided by DEPT, ^{1}H–^{1}H- and ^{13}C–^{1}H-cosy spectra. NOEs are reported as follows: δ_H irradiated (δ_H enhanced). MS spectra were performed on a AMD 402 instrument (AMD-INTECTRA Germany). Microanalyses were performed on an Euro EA-3000 (Euro Vector) apparatus.

4.2. (10*R*)-Bromo-10,11-dihydroquinine 2a

Quinine dihydrobromide (**1**·2HBr·3H_2O crystallised three times from water prior to use, 20 g, 37.04 mmol) was dissolved with cooling in 62% aqueous hydrobromic acid (100 mL, 1326 mmol). The mixture was placed in two sealed vials and kept for 9 h at 40°C. After cooling, the reaction mixture was poured onto ice (~200 g) and partially neutralised with sodium carbonate. The still acidic mixture was made alkaline using portions of ~20% aqueous sodium hydroxide while being vigorously shaken with diethyl ether (1350 mL).[18] The ethereal extract was dried over anhydrous potassium carbonate only for several minutes to avoid precipitation of the product, immediately decanted and left overnight to crystallise. The crystals were isolated by filtration and dried to afford **2a** (3.07 g, 21%). The mother liquor was concentrated to a volume of 400 mL to give second crop (2.33 g, 16%). Distilling off a further 200 mL of ether provided a third crop (3.76 g) and removal of the solvent gave a solid (1.86 g). The combined first and second crops were recrystallised twice from acetone. Mp (capillary method): 155–160°C shrinks and darkens, 166–167°C decomposes and melts; $[\alpha]_D = -213.7$ ($c = 1.015$, chloroform:ethanol/2:1 v/v). Reported:[18] mp 166–167°C decomp.; $[\alpha]_D = -200$ (solvent as above). Anal. calcd for $C_{20}H_{25}N_2O_2Br$ (405.336) C, 59.26; H, 6.22; N, 6.91; found: C, 59.78; H, 6.25; N, 6.95%.

The structure of **2a** was confirmed by X-ray diffraction analysis.[19]

4.3. (10*S*)-Bromo-10,11-dihydroquinine 2b

The aforementioned third crop and the residue from concentration of the final mother liquours were crystallised from benzene providing 3.85 and 0.96 g of **2b**, respectively. These fractions were combined and recrystallised from benzene (40 mL) giving **2b** (4.8 g, 27%). Mp (capillary method): 142.5–144°C shrinks, decomposes and melts; $[\alpha]_D = -51.95$ ($c = 1.0125$, chloroform:ethanol/2:1). Reported:[18] mp 160–162°C, decomp.; $[\alpha]_D = -50$ (solvent as above). Anal. calcd for $C_{20}H_{25}N_2O_2Br \cdot C_6H_6$ (483.1) C, 64.59; H, 6.46; N, 5.79; found: C, 64.47; H, 6.27; N, 5.53%.

X-Ray diffraction analysis[19] confirmed the structure of **2b**.

4.4. (4*S*)-(*E*)-propenyl)-(6*S*,7*R*)-(6-methoxyquinol-4-yl)-8-oxa-(1*R*)-azabicyclo[4.3.0]nonane 10

A mixture of **2a** (twice crystallised from acetone, 250 mg, 0.617 mmol) and 99.7% ethanol (16 mL) was added to a solution of sodium bicarbonate (52 mg, 0.619 mmol) in water (4 mL) and the mixture was heated under reflux for 11 h. Ethanol was then removed from the warm mixture and the remainder was exhaustively extracted with diethyl ether. The combined extracts were dried overnight with KOH in pellets. Removal of the solvent under reduced pressure yielded crystalline solid of **10** (197 mg), which was near-pure by ^{1}H NMR. Column chromatography (15 g of neutral alumina, Woelm, benzene 125 mL: 99.7% ethanol 1.25 mL; benzene 100 mL: 99.7% ethanol 5 mL; 99.7% ethanol 100 mL) of the product caused its partial decomposition giving **10** (110 mg, 55%) and contaminated niquine (~70 mg) (NMR: see Section 4.5).

Data for 10: Mp (Boetius) 142–145°C (recrystal. from diethyl ether); $[\alpha]_D = -220.8$ ($c = 1.07$; 99.7% ethanol). IR (KBr) 3032, 3003 (aromatic νC–H), 2952, 2930, 2855 (aliphatic νC–H), 2830, 2816, 2786, 2756, 2714 (Bohlmann band), 1621, 1592, 1507, 1433 (quinoline νC=C), 1472, 1461, 1383 (aliphatic δC–H), 1240, 1225 (νC–O–C) cm^{-1}. Anal. calcd for $C_{20}H_{24}N_2O_2$ (324.2) C, 74.04; H, 7.46; N, 8.63; found: C, 74.23; H, 7.49; N, 8.71%.

MS *m*/*z* 324 (M^+, 1.29), 137 (100), 122 (28.59), 116 (5.87), 108 (10.92), 94 (21.51); HRMS calcd for $C_{20}H_{24}N_2O_2$: 324.18378; found 324.18535. ^{1}H NMR ($CDCl_3$): 8.77 (d, 1H, $^3J = 4.4$, H-2′), 7.57 (dd, 1H, $^3J = 4.4$, $^4J \approx 0.5$, H-3′), 7.13 (d, 1H, $^4J = 2.8$, H-5′), 7.37

(dd, 1H, $^3J=9.2$, $^4J=2.9$, H-7′), 8.04 (d, 1H, $^3J=9.1$, H-8′), 4.96 (d, 1H, $^2J=3.0$, H-9), 4.24 (d, 1H, $^2J=3.0$, H-9), 5.73 (dd?, 1H, $^3J=7.9$, H-7), 3.27 (ddd, 1H, $^3J=9.4$, $^3J=7.8$, $^3J=3.6$, H-6), 1.04 (ddd, 1H, $^2J=13.6$, $^3J=9.2$, $^3J=4.5$, H-5), 1.49 (dddd, 1H, $^2J=13.3$, $^3J=4.8$, $^3J=3.7$, $^4J=1.0$, H-5), 1.95 (m, 1H, $\Sigma J=18.5$, H-4), 1.64 (tt, 1H, $^2J=^3J=10.2$, $^3J=4.4$, H-3), 1.48 (m, 1H, H-3), 2.97 (ddd, 1H, $^2J=11.0$, $^3J=4.9$, $^3J=4.4$, H-2), 2.56 (ddd, 1H, $^2J=11.0$, $^3J=10.2$, $^3J=3.3$), 3.94 (s, 3H, OMe), 5.37 (ddq, 1H, $^3J=15.4$, $^3J=6.3$, $^4J=1.4$, H-1″), 5.21 (dqd, 1H, $^3J=15.4$, $^3J=6.3$, $^4J=1.4$, H-2″), 1.61 (dt, 3H, $^3J=6.1$, $^4J=1.4$, H-3″). ^{13}C NMR ($CDCl_3$): 147.87 (C-2′), 119.67 (C-3′), 143.99 (C-4′), 126.96 (C-4′a), 101.79 (C-5′), 157.34 (C-6′), 120.86 (C-7′), 131.79 (C-8′), 144.73 (C-8′a), 86.71 (C-9), 77.16 (C-7), 60.28 (C-6), 30.73 (C-5), 33.51 (C-4), 29.02 (C-3), 44.64 (C-2), 55.55 (OMe), 133.53 (C-1″), 124.85 (C-2″), 18.01 (C-3″). NOE: 1.04 (1.49, 1.95, 3.27, 4.96, 5.73, 7.13, 7.57); 2.56 (5.37, 5.21, 4.96, 4.24, 2.97, 3.27, 1.48, 7.57); 3.27 (5.73, 5.37, 5.21, 4.24, 1.49, 1.04); 4.96 (2.97, 2.56, 7.57, 4.24, 1.64, 1.04).

4.5. [(4*S*)-(1*E*)-Propenyl)-(2*S*)-piperydynyl]-6-methoxyquinoline-(α*R*)-methanol—'niquine' 12

A solution of almost pure **10** (1.115 g, 3.44 mmol, obtained as above from 1.47 g of **2a** twice recrystallised from acetone) in 96% aqueous ethanol (10 mL) and a solution of oxalic acid $(COOH)_2{\cdot}2H_2O$ (0.44 g, 3.49 mmol) in the same solvent were heated under reflux for 80 min. No formaldehyde was detected while forcing the vapours through a gas-washing bottle filled with water solution of dimedone. Ethanol was removed in vacuo and the remaining syrup, giving off an odour of formaldehyde, was dissolved in 99.7% ethanol (25 mL). The solvent was again distilled off in vacuo. The residue was heated under reflux for 10 min with a solution of oxalic acid (0.44 g, 3.49 mmol) in ethanol (25 mL) and left overnight to isolate niquine by precipitating it as its acid oxalate.[18,20] The salt was filtered off washed with ethanol and air dried to afford **12** (1.04 g, 58%).

Niquine acid oxalate (0.66 g, 1.17 mmol) were dissolved in 2N aqueous HCl, made alkaline with ~20% aqueous KOH and exhaustively extracted with diethyl ether (300 mL and 3×50 mL). The combined extracts were dried overnight with KOH in pellets. After removal of the solvent the crude niquine was crystallised from acetone to afford pure **12** (155 mg, 42%). Mp (Boetius) 136.5–138°C; $[\alpha]_D=-128.65$ ($c=1.02$, ethanol 99.7%). IR (KBr) 3500–2500 (νO–H, N–H), 3023 (aromatic νC–H), 2945, 2916, 2884, 2840 (aliphatic νC–H), 1620, 1592, 1509, 1433 (quinoline νC=C), 1470, 1363 (aliphatic δ C–H), 1255, 1242 (νC–O and C–O–C) cm^{-1}. Anal. calcd for $C_{19}H_{24}N_2O_2$ (312.413) C, 73.05; H, 7.74; N, 8.97; found: C, 72.56; H, 7.78; N, 8.84%. MS m/z 311 (M^+–H, 0.18), 189 (100), 174 (11.0), 160 (12.74), 145 (6.61), 124 (58.0), 117 (10.43) 89 (4.86) 56 (45.57); MSFAB m/z 313.1 (M+H^+, 23); HRMS.FAB calcd for $C_{19}H_{25}N_2O_2$: 313.19159; found 313.19302. ^{1}H NMR (acetone-d_6): 8.70 (d, 1H, $^3J=4.2$, H-2′), 7.58 (dd, 1H, $^3J=4.5$, $^4J\approx0.7$, H-3′), 7.55 (d, 1H, $^4J=2.7$, H-5′), 7.38 (dd, 1H, $^3J=9.1$, $^4J=2.7$, H-7′), 7.96 (d, 1H, $^3J=9.1$, H-8′), 4.85 (N-H), 5.37 (dd?, 1H, $^3J=4.9$, H-α), 3.35 (ddd, 1H, $^3J=10.3$, $^3J=4.9$, $^3J=3.0$, H-2), 1.41 (m, 1H, H-3), 1.74 (ddd, 1H, $^2J=13.3$, $^3J=10.3$, $^3J=4.9$, H-3), 2.50 (bs, 1H, $\Sigma J\approx24$, H-4), 5.51 (ddq, 1H, $^3J=15.5$, $^3J=6.6$, $^4J=1.5$, H-1″), 5.26 (dqd, 1H, $^3J=15.4$, $^3J=6.3$, $^4J=1.5$, H-2″), 1.52 (dt, 3H, $^3J=6.3$, $^4J=1.4$, H-3″), 3.93 (s, 3H, OMe), 1.65 (m, 1H, H-5), 1.44 (m, 1H, H-5), 2.82 (m, 2H, H-6); ^{13}C NMR (acetone-d_6): 148.28 (C-2′), 120.29 (C-3′), 147.68 (C-4′), 103.18 (C-5′), 158.23 (C-6′), 121.74 (C-7′), 132.39 (C-8′), 145.43 (C-8′a), 127.99 (C-4′a), 73.09 (C-α), 56.24 (C-2), 31.84 (C-3), 34.98 (C-4), 32.31 (C-5), 42.42 (C-6), 55.91 (OMe), 135.21 (C-1″), 124.73 (C-2″), 18.15 (C-3″). NOE: 3.35 (5.51, 2.82, 5.26, 1.41, 1.74, 5.37, 7.58, 7.55), 5.51 (5.26, 3.35, 2.82, 2.50, 1.52).

4.5.1. 2,2′-Methylene-di-(5,5-dimethylcyclohexan-1,3-dione). The above ethanolic distillates were added to a solution of dimedone (1 g) in water (125 mL) yielding the condensation product (181 mg). Mp (Boetius) 189–192°C (reported:[20] 190–192°C). MS m/z 292 (M^+ 80.50), 277 (13.54), 233 (11.46), 208 (14.87), 191 (15.59), 180 (22.83), 177 (10.97), 165 (100), 152 (28.51), 140 (24.00), 137 (19.47), 124 (33.47), 112 (21.17), 97 (25.37). HRMS calcd for $C_{17}H_{24}O_4$: 292.16745; found 292.16806.

4.5.2. (4*S*)-(*E*)-Propenyl)-(6*S*,7*R*)-(6-methoxyquinol-4-yl)-9,9-dimethyl-8-oxa-(1*R*)-azabicyclo-[4.3.0]nonane—'isopropylidene-niquine' 14. A solution of niquine **12** (90 mg, 0.288 mmol) in acetone (5 mL) was kept for 8 weeks at ambient temperature in a stoppered flask. The progress of the reaction was monitored by TLC (alumina, Merck 5581; benzene:99.7% ethanol/9:1 v/vol). Slow evaporation of the solvent gave a resin, which began to solidify after freezing in liquid nitrogen. The partially solidified product was left for 72 h in a dessiccator and the obtained solid was crystallised from acetone yielding **14** (50 mg, 44%). Mp (Boetius) 149–154°C decomp.; $[\alpha]_D=-115.3$ ($c=1.084$, 99.7% ethanol). IR (KBr) 3092, 3078, 3022 (aromatic νC–H), 2957, 2920, 2898, 2852 (aliphatic νC–H), 1619, 1591, 1504, 1430 (quinoline νC=C), 1470, 1455 (aliphatic δC–H), 1381, 1367 (geminal dimethyl groups), 1234, 1224 (νC–O and/or νC–O–C). MS m/z 352 (M^+, 7.08), 337 (19.37), 295 (30.68), 166 (14.99), 165 (100), 150 (35.28), 110 (24.39). HRMS calcd for $C_{22}H_{28}N_2O_2$: 352.21509; found 352.21410. ^{1}H NMR ($CDCl_3$): 8.75 (d, 1H, $^3J=4.4$, H-2′), 7.56 (dd, $^3J=4.4$, $^4J\approx0.7$, H-3′), 7.18 (d, 1H, $^4J=3.0$, H-5′), 7.35 (dd, 1H, $^3J=9.1$, $^4J=2.8$, H-7′), 8.02 (d, 1H, $^3J=9.3$), 5.77 (d, 1H, $^3J=8.0$, H-7), 3.50 (ddd, 1H, $^3J=11.6$, $^3J=8.4$, $^3J=2.8$, H-6), 1.39 (dtd, 1H, $^2J=12.7$, $^3J=2.5$, $^4J=1.1$, H-5), 0.75 (ddd, 1H, $^2J=12.6$, $^3J=11.8$, $^3J=4.9$, H-5), 2.27 (bs, 1H, $\Sigma J\approx21$, H-4), ~1.61 (m, 1H, H-3), ~1.65 (m, 1H, H-3), 2.74 (dt, 1H, $^2J=10.7$, $^3J=3.6$, H-2), 2.50 (td, 1H, $^2J=^3J=10.6$, $^3J=4.7$, H-2), 1.60 (d, 3H, $^4J\approx0.4$, α-Me at C-9), 1.31 (d, 3H, $^4J\approx0.4$, β-Me at C-9), 3.93 (s, 3H, OMe), 5.54 (ddq, 1H, $^3J=15.4$, $^3J=6.4$, $^4J=1.4$, H-1″), 5.37 (dqd, 1H, $^3J=15.4$, $^3J=6.2$, $^4J=1.4$, H-2″), 1.68 (dt, 3H, $^3J=6.0$, $^4J=1.4$, H-3″). ^{13}C NMR ($CDCl_3$); 147.73 (C-2′), 119.90 (C-3′), 143.82

(C-4′), 127.10 (C-4′a), 101.79 (C-5′), 157.11 (C-6′), 120.81 (C-7′), 131.54 (C-8′), 144.79 (C-8′a), 75.56 (C-7), 57.11 (C-6), 32.40 (C-5), 33.56 (C-4), 29.68 (C-3), 41.41 (C-2), 94.85 (C-9), 133.27 (C-1″), 124.95 (C-2″), 18.26 (C-3″), 55.61 (OMe), 18.74 (C-9 α-Me), 26.04 (C-9 β-Me). NOE: 3.50 (5.77, 5.54, 2.50, 1.39, 1.31, 5.37), 0.75 (2.27, 1.61, 1.39, 7.56), 2.50 (5.54, 5.37, 3.50, 2.74, 1.60, 1.31), 5.54 (5.37, 3.50, 2.50, 2.27, 1.68, 1.39), 7.56 (8.75, 5.77, 1.60, 0.75).

4.6. Reaction of 2b with sodium bicarbonate

A mixture of **2b** (600 mg, 1.23 mmol—the equivalent of 500 mg of benzene-free **2b**), $NaHCO_3$ (103 mg, 1.23 mmol), water (10 mL) and 99.7% ethanol (40 mL) were heated under reflux for 11 h. Ethanol was removed under reduced pressure and the residue was exhaustively extracted with diethyl ether. The combined ethereal extracts were dried over anhydrous potassium carbonate. Removal of the solvent under reduced pressure gave a foamy solid (436 mg), which on TLC (see above) showed the spots A, B, C, D, E marked in accordance with their decreasing polarity. Column chromatography (40 g neutral alumina partially deactivated by treatment with water (1.2 mL); benzene 100 mL: 99.7% ethanol 0.5 mL; benzene 400 mL: 99.7% ethanol 4 mL; benzene 100 mL: 99.7% ethanol 10 mL; 99.7% ethanol 100 mL) yielded 163 mg of the alkaloids E (**10**, **15**), ~5 mg of D (with unreadable ^{1}H NMR spectrum), 31 mg of the alkaloids D+C (aproximately 1:1), 51 mg of C contaminated by D, 41 mg of C (alkaloid **19**), 17 mg of predominantly C+B, 70 mg of the alkaloids A contaminated by B and C. The alkaloids A consist of **12** (^{13}C NMR see: Section 4.5) and its (*Z*)-counterpart showing the δ_C values of 72.95, 56.25, 31.83, 29.85, 133.69, 123.61, 12.92, 32.13 as well as 6-methoxyquinol-4-yl resonances common with those of **12**.

4.6.1. (4*S*)-(*Z*)-Propenyl)-(6*S*,7*R*)-(6-methoxyquinol-4-yl)-8-oxa-(1*R*)-azabicyclo[4.3.0]nonane 15. This alkaloid makes 45% of the above 163 mg fraction. ^{1}H NMR ($CDCl_3$): 8.78 (d, 1H, ^3J=4.6, H-2′), 7.64 (dd, 1H, ^3J=4.4, $^4J\approx$0.7, H-3′), 7.09 (d, 1H, ^4J=2.5, H-5′), 7.37 (dd, 1H, ^3J=9.2, ^4J=2.5, H-7′), 8.04 (d, 1H, ^3J=9.2, H-8′), 5.67 (d, 1H, ^3J=8.2, H-7), 4.96 (d, ^2J=3.3, H-9), 4.35 (d, ^2J=3.8, H-9), 3.92 (s, 3H, OMe), 3.46 (td, 1H, ^3J=7.8, ^3J=4.4, H-6), 1.38 (m, 1H, H-5), 1.22 (ddd, 1H, ^2J=13.6, ^3J=7.7, ^3J=4.2, H-5), 2.03 (m, 1H, $\Sigma J\sim$29, H-4), 1.37 (m, 1H, H-3), 1.57 (m, 1H, H-3), 3.04 (ddd, 1H, ^2J=11.0, ^3J=7.1, ^3J=3.8, H-2), 2.68 (ddd, 1H, ^2J=11.1, ^3J=8.1, ^3J=3.2, H-2), ~5.28 (m, 1H, H-1″), ~5.24 (m, 1H, H-2″), 1.03 (d, ^3J=4.9, H-3″). ^{13}C NMR ($CDCl_3$): 147.77 (C-2′), 119.37 (C-3′), 144.04 (C-4′), 126.88 (C-4′a), 101.67 (C-5′), 157.22 (C-6′), 121.00 (C-7′), 131.68 (C-8′), 145.09 (C-8′a), 86.98 (C-9), 76.66 (C-7), 60.68 (C-6), 30.52 (C-5), 28.77 (C-4), 29.83 (C-3), 45.65 (C-2), 55.57 (OMe), 132.66 (C-1″), 124.81 (C-2″), 12.28 (C-3″).

NMR data for the 55% component **10**, see Section 4.4.

4.6.2. (*Z*)-3,10-Didehydro-10,11-dihydroquinine, '(*Z*)-Δ^{3,10}-isoquinine' 19. The above 41 mg fraction gave **19** (31 mg) on crystallisation from benzene. Mp (Boetius) 182–185°C; $[\alpha]_D$=−188.7 (*c*=0.5125, 99.7% ethanol). IR (KBr): 3690–2350 broad absorption with extrema at 3347, 3125, 2737, 2591 (hydrogen bonded *ν*OH), 3090, 3040, 3008 (*ν*C–H aromatic), 2952, 2929, 2895, 2860 (*ν*C–H aliphatic), 1622, 1591, 1566, 1511 (quinoline *ν*C=C), 1458, 1382 (*δ*C–H aliphatic), 1261, 1242 (*ν*C–O and/or *ν*C–O–C) cm^{-1}. MS *m*/*z* 324 (M$^+$, 89.96), 309 (19.25), 189.0 (56.43), 188 (34.29), 172 (27.65), 160 (23.18), 137 (67.88), 136 (100), 122 (25.34), 117 (25.17), 108 (22.06), 81 (26.75), 68 (31.80), 56 (25.50). HRMS calcd for $C_{20}H_{24}N_2O_2$ 324.18378; found 324.18282. ^{1}H NMR ($CDCl_3$): *δ* 8.57 (d, 1H, ^3J=4.4, H-2′), 7.49 (d, 1H, ^3J=4.5, H-3′), 7.22 (d, 1H, ^4J=2.7, H-5′), 7.29 (dd, 1H, ^3J=9.0, ^4J=2.7, H-7′), 7.94 (d, 1H, ^3J=9.3, H-8′), 5.61 (d, 1H, ^3J=3.7, H-9), 3.09 (td, 1H, ^3J=8.8, ^3J=3.8, H-8), 1.95 (ddd, 1H, ^2J=12.2, ^3J=8.6, ^3J=1.2, H-7), 1.38 (dm, 1H, ^2J=12.4, H-7), 3.57 (m, 1H, H-6), 2.70 (dd?, 1H, ^2J=13.1, ^3J=9.6, H-6), 1.77 (m, 1H, H-5), 1.55 (m, 1H, H-5), 2.33 (bs, 1H, ΣJ=9, H-4), 3.45 (dbs, 1H, ^2J=17.3, H-2), 3.34 (dbs, 1H, ^2J=17.0, H-2), 5.16 (qt, 1H, ^3J=6.7, ^4J=2.5, H-10), 1.43 (dt, 3H, ^3J=6.8, ^5J=1.4, H11), 3.88 (s, 3H, OMe), ~4.6 (OH). ^{13}C NMR ($CDCl_3$): *δ* 147.42 (C-2′), 118.38 (C-3′), 147.82 (C-4′), 101.33 (C-5′), 157.58 (C-6′), 121.33 (C-7′), 131.38 (C-8′), 126.48 (C-9′), 144.00 (C-10′), 71.81 (C-9), 60.74 (C-8), 28.04 (C-7), 43.93 (C-6), 27.82 (C-5), 33.32 (C-4), 140.82 (C-3), 56.70 (C-2), 114.56 (C-10), 12.36 (C-11), 55.64 (OMe). NOE: 3.39 (1.43, 3.09, 2.70), 2.33 (5.16, 1.95), 5.16 (2.33, 1.43).

4.7. (4*S*)-Propyl-(6*S*,7*R*)-(6-methoxyquinol-4-yl)-8-oxa-(1*R*)-azabicyclo[4.3.0]nonane 17

A mixture of **10** and **15** (61 mg, 0.188 mmol, from the above 163 mg fraction of the alkaloids E) was dissolved in 99.7% ethanol (10 mL) and hydrogenated by shaking with Adams catalyst (PtO_2, 10 mg, 0.044 mmol) under hydrogen (4±2 atm) at room temperature for 4.5 h. The catalyst was then removed by filtration and the solvent was evaporated under reduced pressure. The remainder was dissolved in diethyl ether and filtered. Removal of the ether from the filtrate yielded non-crystalline **17** (53 mg, 87%). $[\alpha]_D$=−216.8 (*c*=0.505, 99.7% ethanol). MS *m*/*z* 326 (M$^+$, 2.44), 189 (8.38), 159 (4.74), 153 (11.41), 139 (100), 124 (7.22), 110 (8.91), 96 (28.04), 69 (8.27). HRMS calcd for $C_{20}H_{26}O_2N_2$: 326.19943; found 326.20066. ^{1}H NMR ($CDCl_3$): 8.73 (d, 1H, ^3J=4.6, H-2′), 7.61 (dd, 1H, ^3J=4.6, $^4J\approx$0.8, H-3′), 7.10 (d, 1H, ^4J=2.7, H-5′), 7.38 (dd, 1H, ^3J=9.2, ^4J=2.6, H-7′), 8.03 (d, 1H, ^3J=9.3, H-8′), 4.92 (d, 1H, ^2J=3.8, H-9), 4.34 (d, 1H, ^2J=4.1, H-9), 5.64 (d, 1H, ^3J=8.0, H-7), 3.45 (td, 1H, ^3J=7.9, ^3J=4.7, H-6), 1.38 (ddd, 1H, ^2J=13.6, ^3J=6.6, ^3J=4.7, H-5), 1.23 (m, 1H, H-5), 0.92 (m, 1H, H-4), 1.51 (m, 1H, H-3), 1.25 (m, 1H, H-3), 2.96 (ddd, 1H, ^2J=11.0, ^3J=7.4, ^3J=3.8, H-2), 2.63 (ddd, 1H, ^2J=11.1, ^3J=8.1, ^3J=3.2, H-2), 1.05 (m, 2H, H-1″), 0.86 (m, 2H, H-2″), 0.60 (t, 3H, ^3J=7.0, H-3″). ^{13}C NMR ($CDCl_3$): 147.60 (C-2′), 119.23 (C-3′), 143.78 (C-4′), 126.81 (C-4′a), 101.63 (C-5′), 157.11 (C-6′), 120.93 (C-7′), 131.53 (C-8′), 145.26 (C-8′a), 45.67 (C-2), 29.46 (C-3), 30.39 (C-4), 29.94 (C-5), 60.45 (C-6), 76.58 (C-7), 86.82 (C-9), 35.69 (C-1″), 19.88 (C-2″), 13.88 (C-3″), 55.55 (OMe).

Table 2. Crystal data and structure refinement for **10a** and **14**

	10a	**14**
Empirical formula	$C_{20}H_{24}N_2O_2$	$C_{22}H_{28}N_2O_2$
Formula weight	324.41	352.46
Crystal system/ space group	Orthorhombic/ $P2_12_12_1$	Orthorhombic/ $P2_12_12_1$
Unit cell dimensions		
a (Å)	7.8441(7)	8.190(2)
b (Å)	8.0804(7)	15.134(3)
c (Å)	28.183(2)	16.076(3)
Volume (Å^3)	1786.3(3)	1992.6(7)
Z	4	4
Calculated density (g/cm^3)	1.206	1.175
$F(000)$	696	760
Reflections collected	17662	14047
Reflections unique	4669	1702
Completeness to θ	$\theta=29.86°$ 93.1%	$\theta=23.56°$ 99.0%
Data/parameters	4669/220	1702/276
Goodness-of-fit on F^2	1.135	1.203
Final R_1/wR_2 indices $[I>2\sigma(I)]$	0.0689/0.0647	0.0370/0.0859
R_1/wR_2 indices (all data)	0.1292/0.0700	0.0421/0.0863
Absolute structure parameter	−0.1(2)	0.0(2)

4.8. X-Ray diffraction crystallography

The crystals of **10a** were recrystallised from diethyl ether, those of **14** from acetone by slow evaporation. The crystal data (see Table 2) were measured using a KM4-CCD diffractometer equipped with a graphite monochromator. The structures were solved by straightforward direct methods[42] and refined (Table 2) by full-matrix least-squares.[43] In the **10a** structure a disorder of the 1-propenyl C(1″)=C(2″)–C(3″) in two nearly coplanar positions with clearly discriminated partly occupied sites of C(1″) and C(2″), but a common site of C(3″) has been observed, as illustrated in Fig. 1. The occupation of the sites denoted C(1″)=C(2″)–C(3″) and C(1″a)=C(2″a)–C(3″) was refined to 0.58(2) and 0.42(2), respectively. The positions of all hydrogen atoms, except those of the methyl groups, were determined from molecular geometry—their positions, including the protons of the methyl groups, were redetermined after each cycle of refinement; in the methyl C(3″) of **10a** a disordered model has been assumed with the hydrogen atoms disordered in two orientations, one at 60° to the other. Crystallographic data for **10a** and **14** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications numbered CCDC 175709 and CCDC 175710, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1233-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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