Analysis of the kinetics of isomerization of spiro oxindole alkaloids

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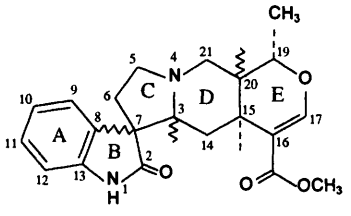
The isomerization of the spiro oxindole alkaloids mitraphylline, isomitraphylline, pteropodine, isopteropodine, speciophylline and uncarine F in water has been studied at several temperatures and the rate coefficients have been determined. The effect of pH on the rate of reaction and the equilibrium composition has been investigated. The rate coefficients in water and in organic solvents correlate satisfactorily with the Dimroth–Reichardt solvent polarity parameter. The present results support the existence of a zwitterionic intermediate stabilized by polar solvents and show that protonation of the alkaloids inhibits the isomerization. The crystal structure of pteropodine has been determined.

Introduction

Spiro oxindole alkaloids of the general formula shown below have been obtained from a number of *Uncaria*, *Mitragyna* and other species.[1] It was noticed as early as 1959 that related alkaloids isomerize readily and a concept of the underlying mechanism was put forward independently by two research groups.[2] They proposed a retro-Mannich type reaction involving an open-ring zwitterionic intermediate. In cases where the D/E ring junction has the conformationally rigid *trans* configuration, pairs of interconvertible alkaloids are found, but if this junction is *cis* then a ring interconversion is possible, giving rise to four isomers. The composition of the equilibrium mixture depends on whether an acidic or a basic solvent is employed. In fact, this isomerization behaviour has been utilized for the identification and assignment of stereochemistry in alkaloids isolated from natural sources,[3–5] but no detailed studies on the kinetics of this isomerization have been reported so far.



1 3*S*, 7*R*, 15*S*, 19*S*, 20*R*

2 3*S*, 7*S*, 15*S*, 19*S*, 20*R*

3 3*S*, 7*R*, 15*S*, 19*S*, 20*S*

4 3*S*, 7*S*, 15*S*, 19*S*, 20*S*

5 3*R*, 7*S*, 15*S*, 19*S*, 20*S*

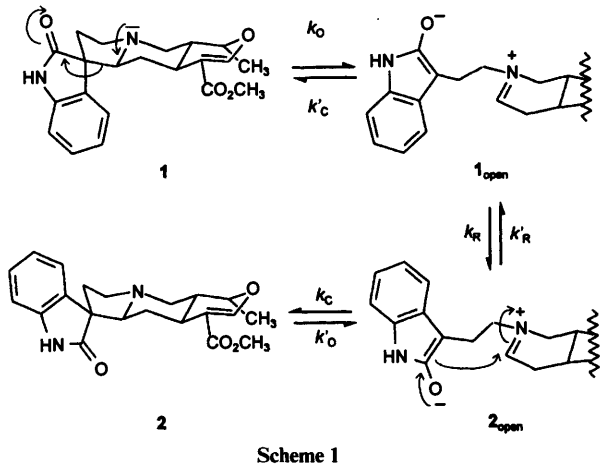
6 3*R*, 7*R*, 15*S*, 19*S*, 20*S*

Results and discussion

The isomerization of spiro oxindole alkaloids in water proceeds straightforwardly to give pH-dependent mixtures of isomers. The reactions were studied at pH 7 at three temperatures (25, 37 and 50 °C), while at pH values other than 7 only one temperature (50 °C) was used. In less polar solvents the isomerizations are inconveniently slow for kinetic measurements, therefore only initial rates were measured at 50 °C. No by-products were detected except in very acidic solutions (pH ≤2).

Alkaloids with *trans* D/E ring junction

Isomerization of oxindole alkaloids with a trans D/E ring junction gives pairs of 7-epimers;† examples are mitraphylline **1**–isomitraphylline **2**, formosanine–isoformosanine (19-epimers of the mitraphyllines) and rhynchophylline–isorhynchophylline (*E*-seco analogues of the mitraphyllines). The first pair will be treated in some detail here. The overall process of isomerization can be regarded as consisting of three reversible steps. These are described in Scheme 1 by the rate coefficients k_O and k'_O for ring



Scheme 1

opening, k_R and k'_R for rotation and k_C and k'_C for ring closure. It is assumed that the zwitterionic forms may be treated as steady-state intermediates.

From this mechanism the following rate law is derived, where [**1**] and [**2**] are the concentrations of mitraphylline **1** and isomitraphylline **2**, respectively, and the concentrations of the open intermediate species $\mathbf{1}_{open}$ and $\mathbf{2}_{open}$ are cancelled.

† The numbering system is based on that customarily used for the hetero-yohimbinoid alkaloids.

Table 1 Common logarithms of the rate coefficients k_{ij} and Arrhenius activation parameters for the isomerization of the mitraphylline isomers **1** and **2** in aqueous buffer pH 7 and in MeOH at 25, 37 and 50 °C

Solvent	k_{ij}	log (k/s^{-1}) (298 K)	log (k/s^{-1}) (310 K)	log (k/s^{-1}) (323 K)	E_a/kJ mol^{-1}	log (A/s^{-1})
Water	k_{12}	−4.93	−4.19	−3.46	108	14.1
	k_{21}	−5.21	−4.51	−3.79	105	13.2
Methanol	k_{12}	−6.71	−6.10	−5.50	89	8.90
	k_{21}	−7.25	−6.58	−5.96	95	9.45

		Equilibrium data			
Solvent	Isomer	% (298 K)	% (310 K)	% (323 K)	ΔH_R (**1**→**2**)/ kJ mol^{-1}
Water	**1**	34.4	32.5	32.0	3.5
	2	65.6	67.5	68.0	
Methanol	**1**	22.5	25.0	26.3	−6.6
	2	77.5	75.0	73.7	

$$\frac{d[\mathbf{1}]}{dt} = \frac{k_0 k_R k_C}{k_C k'_C + k_C k_R + k'_C k'_R}[\mathbf{1}] + \frac{k'_0 k'_R k'_C}{k_C k'_C + k_C k_R + k'_C k'_R}[\mathbf{2}] \quad (1)$$

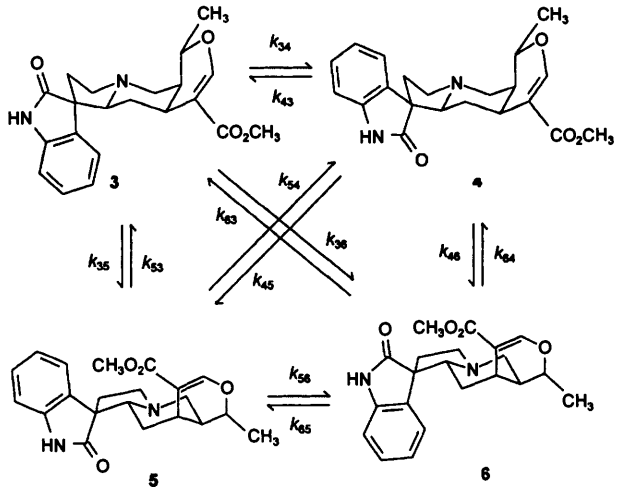
Eqn. (1) can then be simplified to the familiar rate law [eqn. (2)] for two compounds approaching equilibrium in a pseudo-first-order process.

$$\frac{d[\mathbf{1}]}{dt} = -k_{12}[\mathbf{1}] + k_{21}[\mathbf{2}] \quad (2)$$

The composition of the equilibrium mixture was determined accurately by multiple analyses, so only one rate coefficient had to be varied in order to fit the calculated curves to the experimental data by a least-squares method. It can be seen from the rate coefficients thus obtained (Table 1) that the isomerization in methanol is slower by approximately two orders of magnitude than in water. Since the activation energy of the reaction is lower in methanol, the decrease of the rate in methanol could be attributed to an overall negative entropy of activation due to charge separation, as indicated by the small Arrhenius factor A. The predominance of isomitraphylline **2** in the equilibrium in water increases further when the solvent is methanol. It can also be seen that the effect of temperature on the equilibrium is reversed by changing the solvent.

Alkaloids with *cis* D/E ring junction

Alkaloids of this rare kind have also been isolated as natural products from *Rauwolfia vomitoria* (substituted pteropodines) and prepared synthetically (oxindoles derived from raunitidine).[5] They have been recognized by their isomerization behaviour, which is more complex than in the case of the *trans* compounds in that the *cis*-ring system can undergo interconversion while the C ring is open. Therefore, not only two 7-epimers but four 3,7-isomers are formed (Scheme 2). Again, the rate of isomerization is apparently first-order with respect to each isomer, and thus can be described by the following set of linear differential eqns. (3–6), where [**3**], [**4**], [**5**] and [**6**] are the relative concentrations of pteropodine **3** isopteropodine **4**, speciophylline **5** and uncarine F **6**, respectively.



Scheme 2

$$\frac{d[\mathbf{3}]}{dt} = -(k_{34} + k_{35} + k_{36})[\mathbf{3}] + k_{43}[\mathbf{4}] + k_{53}[\mathbf{5}] + k_{63}[\mathbf{6}] \quad (3)$$

$$\frac{d[\mathbf{4}]}{dt} = -(k_{43} + k_{45} + k_{46})[\mathbf{4}] + k_{34}[\mathbf{3}] + k_{54}[\mathbf{5}] + k_{64}[\mathbf{6}] \quad (4)$$

$$\frac{d[\mathbf{5}]}{dt} = -(k_{53} + k_{54} + k_{56})[\mathbf{5}] + k_{35}[\mathbf{3}] + k_{45}[\mathbf{4}] + k_{65}[\mathbf{6}] \quad (5)$$

$$\frac{d[\mathbf{6}]}{dt} = -(k_{63} + k_{64} + k_{65})[\mathbf{6}] + k_{36}[\mathbf{3}] + k_{46}[\mathbf{4}] + k_{56}[\mathbf{5}] \quad (6)$$

Integration gives eqn. (7),

$$A_t = e^{Kt} A_0 \quad (7)$$

where the vectors A_0 and A_t contain the concentrations at the beginning and at a given time t, respectively [eqn. (8)],

$$A_0 = \begin{pmatrix} [\mathbf{3}]_0 \\ [\mathbf{4}]_0 \\ [\mathbf{5}]_0 \\ [\mathbf{6}]_0 \end{pmatrix} \quad A_t = \begin{pmatrix} [\mathbf{3}]_t \\ [\mathbf{4}]_t \\ [\mathbf{5}]_t \\ [\mathbf{6}]_t \end{pmatrix} \quad (8)$$

and the matrix K [eqn. (9)] holds the rate coefficients.

The rate coefficients were obtained by fitting the calculated curves to the experimental data. The results and activation parameters are summarized in Table 2. In this case, the influence of temperature on the equilibrium is negligible, but again the solvent has a pronounced effect. The course of the reactions in water, starting with either **3**, **4**, **5** or **6**, is depicted in Fig. 1.

Effect of pH on rates and equilibria

It has been previously reported that different mixtures are obtained on equilibrating spiro oxindole alkaloids in either acidic or basic solutions[3,5] This is readily explained by the stabilizing effect of an intramolecular hydrogen bond between the protonated N-4 and the lactam carbonyl, when both groups are in a *syn* position to each other, as is the case for mitraphylline **1**, pteropodine **3** and speciophylline **5**. Consequently, these isomers predominate in acid. On the other hand, protonation at N-4 would be expected to inhibit the formation of the intermediate immonium ion and therefore slow down

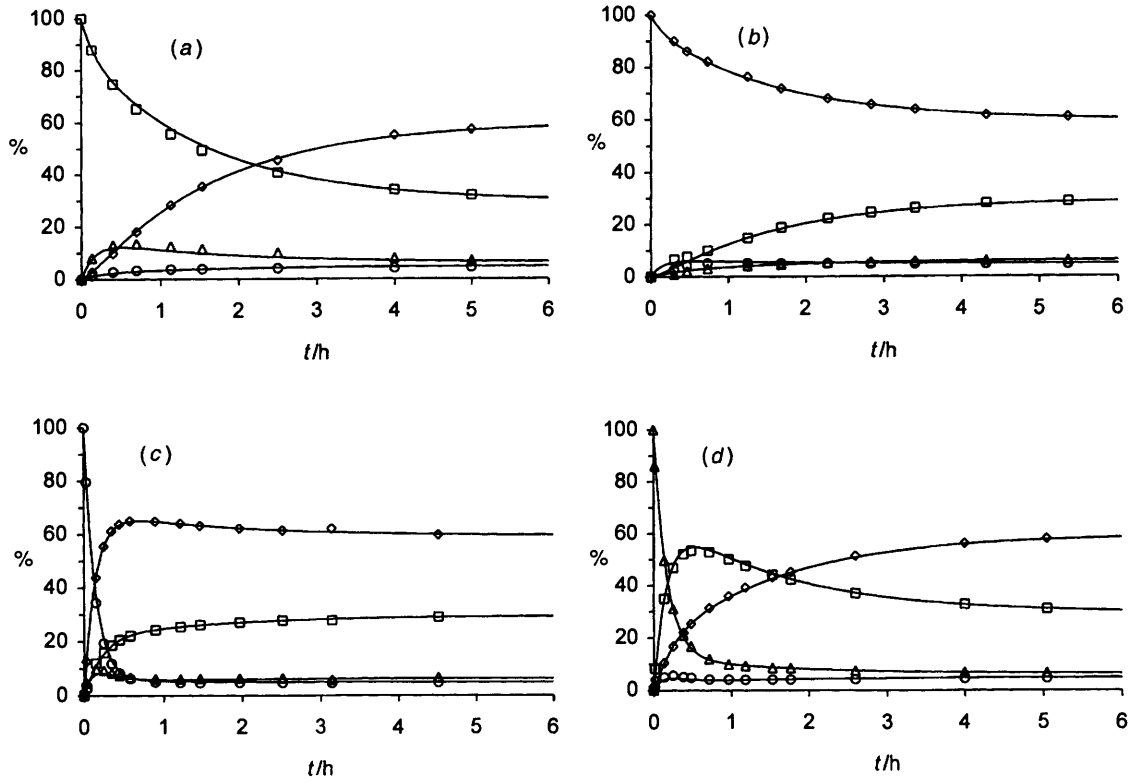


Fig. 1 Isomerization of spiro oxindole alkaloids in aqueous buffer pH 7 at 50 °C, as monitored by HPLC. Percent of **3** (□), **4** (◇), **5** (○) and **6** (△) as a function of time, starting with either (*a*) **3**, (*b*) **4**, (*c*) **5** or (*d*) **6**. The curves are calculated from eqn. (7) using the coefficients given in Table 2

$$K = \begin{pmatrix} -(k_{34}+k_{35}+k_{36}) & k_{43} & k_{53} & k_{63} \\ k_{34} & -(k_{43}+k_{45}+k_{46}) & k_{54} & k_{64} \\ k_{35} & k_{45} & -(k_{53}+k_{54}+k_{56}) & k_{65} \\ k_{36} & k_{46} & k_{56} & -(k_{63}+k_{64}+k_{65}) \end{pmatrix} \quad (9)$$

Table 2 Common logarithms of the rate coefficients k_{ij} and Arrhenius activation parameters for the isomerization of the pteropodine isomers **3**–**6** in aqueous buffer pH 7 at 25, 37 and 50 °C

k_{ij}	log (k/s^{-1}) (298 K)	log (k/s^{-1}) (310 K)	log (k/s^{-1}) (323 K)	E_a/kJ mol^{-1}	log (A/s^{-1})
k_{34}	−5.72	−5.02	−4.33	103	12.3
k_{35}	−6.02	−5.31	−4.60	104	12.3
k_{36}	−5.05	−4.34	−3.63	105	13.4
k_{43}	−6.00	−5.35	−4.71	95	10.7
k_{45}	−5.31	−4.60	−3.90	103	12.8
k_{46}	−6.28	−5.58	−4.88	103	11.8
k_{53}	−5.09	−4.35	−3.60	110	14.2
k_{54}	−4.21	−3.55	−2.88	98	13.0
k_{56}	−5.05	−4.26	−3.49	115	15.1
k_{63}	−4.35	−3.66	−2.97	102	13.5
k_{64}	−5.02	−4.32	−3.61	104	13.2
k_{65}	−5.21	−4.50	−3.78	106	13.3

	Equilibrium data at 323 K	
Isomer	% in H_2O	% in MeOH
3	29.6	23.5
4	59.4	73.5
5	4.6	1.0
6	6.4	3.0

the isomerization. The influence of the pH on the rate of isomerization was studied in the range pH 2–9 at 50 °C. Owing to the small rate of isomerization in acidic solutions we chose to monitor only the initial rate. Here, the concentrations of the products are negligible, so the rate laws may be simplified, *e.g.* eqn. (10) where k_{12} applies to unprotonated molecules only.

Composite rate coefficients like $(k_{34} + k_{35} + k_{36})$ are designated as observed rate coefficients k_{obs} in the following. As we cannot distinguish between protonated and unprotonated molecules, we shall use k'_{obs} as the effective rate coefficient applying to the total concentration of alkaloid. For a weakly basic compound the nature of the pH $-\log k'_{obs}$ profile can then be predicted by eqn. (11), where K_A is the acidity constant of the protonated species.

$$\frac{d[1]}{dt} = -k_{12}[1]_{free} = -k'_{obs}[1]_{total} \quad (10)$$

$$\log k'_{obs} = \log k_{obs} + \log \frac{[1]_{free}}{[1]_{total}} = \log k_{obs} - \log\left(\frac{[H^+]}{K_A} + 1\right) \quad (11)$$

For sufficiently acidic solutions eqn. (11) simplifies to eqn. (12), giving a linear dependence of $\log k'_{obs}$ on pH.

$$\log k'_{obs} = \log k_{obs} - pK_A + pH \quad (12)$$

General acid catalysis was excluded by experiments with different buffer concentrations at constant pH. Rates were not affected by different ionic strengths. A typical plot of $\log k'_{obs}$ against pH is shown in Fig. 2, as obtained for the alkaloid mitraphylline **1**. Theoretically, the gradient of the graph below pH 6 should be unity, but it was found to be lower. This means that the rate of reaction is not as slowed by the protonation as would have been expected. Hence, there seems to be another effect involved. We suggest a pull effect at the lactam carbonyl by the protons, which causes an acceleration of the otherwise

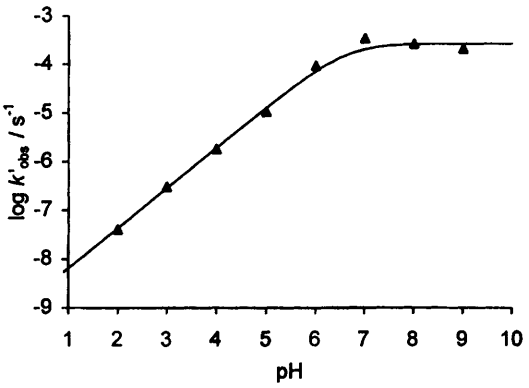


Fig. 2 pH–rate coefficient profile of the isomerization of the spiro oxindole alkaloid mitraphylline **1** in H_2O at 50 °C. The curve is calculated from eqn. (13)

Table 3 Distribution of alkaloids **1–6** in equilibrated aqueous solutions as a function of pH at 50 °C

	pH						
Isomer	2	3	4	5	6	7	8
1	75%	75%	74%	68%	51%	32%	31%
2	25%	25%	26%	32%	49%	68%	69%
3	41%	41%	41%	40%	36%	30%	30%
4	14%	15%	16%	22%	42%	59%	60%
5	37%	36%	35%	30%	15%	5%	4%
6	8%	8%	8%	8%	7%	6%	6%

slow reaction. Above pH 6 the reaction proceeds without hindrance, and k'_{obs} becomes equal to k_{obs}.

Eqns. (13)–(18) describe the observed pH–log k'_{obs} profiles of the isomerizations of **1–6**:

for **1**

$$\log(k'_{obs}/s^{-1}) = -3.57 - 0.82 \log(1 + 10^{(6.6 - pH)}) \quad (13)$$

for **2**

$$\log(k'_{obs}/s^{-1}) = -3.90 - 0.81 \log(1 + 10^{(5.7 - pH)}) \quad (14)$$

for **3**

$$\log(k'_{obs}/s^{-1}) = -3.73 - 0.63 \log(1 + 10^{(6.7 - pH)}) \quad (15)$$

for **4**

$$\log(k'_{obs}/s^{-1}) = -4.07 - 0.70 \log(1 + 10^{(5.2 - pH)}) \quad (16)$$

for **5**

$$\log(k'_{obs}/s^{-1}) = -2.73 - 0.87 \log(1 + 10^{(6.5 - pH)}) \quad (17)$$

for **6**

$$\log(k'_{obs}/s^{-1}) = -2.93 - 0.60 \log(1 + 10^{(6.1 - pH)}) \quad (18)$$

We hesitate to claim the numerical exponents in the above equations are pK_A constants, as expected from theory, but we have obtained approximately this value by pH measurement in aqueous solutions of pteropodine hydrochloride (pK_A 6.5; 6.7 in eqn. (15); lit.[6] 4.8 by titration). Also, the distribution of the alkaloids **1–6** in equilibrated aqueous solutions at different pH values was determined. The results are summarized in Table 3.

Isomerization in organic solvents

Investigating solvent effects usually has two main objectives: (*a*) the prediction of reaction rates in other solvents and (*b*) to gather some insight into the influences that affect them. Because solvent polarity cannot be described by a single physical parameter, empirical polarity scales have been introduced. The Dimroth–Reichardt scale using a solvatochromic dye, which is sensitive to the dipolarity and hydrogen-bonding properties of a solvent, has been successfully applied in many cases.[7] For the present investigation this polarity scale proved very useful.

The dependence of the rate of isomerization on the polarity of six organic solvents was studied at 50 °C. Owing to the small rate of isomerization in less polar solvents we again chose to measure only the initial rate.

By linear regression including the values in water the following eqns. (19)–(24) were derived:

for **1** $\log(k_{obs}/s^{-1}) = 5.2\,E_T^N - 9.2 \quad r^2 = 0.955 \quad (19)$

for **2** $\log(k_{obs}/s^{-1}) = 7.0\,E_T^N - 11.1 \quad r^2 = 0.971 \quad (20)$

for **3** $\log(k_{obs}/s^{-1}) = 9.1\,E_T^N - 12.8 \quad r^2 = 0.979 \quad (21)$

for **4** $\log(k_{obs}/s^{-1}) = 10.9\,E_T^N - 14.9 \quad r^2 = 0.982 \quad (22)$

for **5** $\log(k_{obs}/s^{-1}) = 5.5\,E_T^N - 8.4 \quad r^2 = 0.983 \quad (23)$

for **6** $\log(k_{obs}/s^{-1}) = 7.2\,E_T^N - 10.2 \quad r^2 = 0.998 \quad (24)$

Omission of the value in water for **1** leads to a significantly better correlation:

$$\log(k_{obs}/s^{-1}) = 4.1\,E_T^N - 8.7 \quad r^2 = 0.994 \quad (25)$$

Highly satisfactory correlations between the Dimroth–Reichardt solvent polarity parameter E_T^N and the logarithm of the rate coefficient k_{obs} were obtained, considering the variety of hydroxylic, dipolar and apolar solvents used. From these results (Table 4), reaction rates in other solvents or solvent mixtures should be predictable. In conclusion the higher solvent polarity reduces $\Delta G^{\ddagger}$ and hence increases log k_1 which is consistent with the existence of a zwitterionic intermediate stabilized by polar solvents.

Finally, it is interesting to note that there is evidence for catalytic action of hard electrophiles (HSAB concept) on the isomerization. Thus, pteropodine **3** and isopteropodine **4**, when treated with Meerwein's reagent in dichloromethane, gave rise to the same mixture of two imino ethers, regardless of the starting material.[8] We suggest as an explanation that the electrophile exerts a pull effect on the electrons of the oxindole oxygen atom, and thereby facilitates the retro-Mannich reaction even in a very apolar solvent.

Hydrogen bonding and crystal packing of pteropodine

The molecular structure of **3**·H_2O is shown in Fig. 3. Within the molecule there are five potential hydrogen-bond acceptors at O(1)–O(4) and N(2), and one potential hydrogen bond donor at N(1). This imbalance will be partly compensated by a water molecule, which acts once as an acceptor and twice as a donor. The water molecule, which is intramolecular between the acceptor atoms O(1) and N(2), exhibits O(5)···O(1) and O(5)···N(2) distances of 2.849(5) and 2.940(5) Å. At the oxygen atom O(5) bridge to another pteropodine molecule [at (0.5 + x, 1.5 − y, 0.75 − z)], the O(5)···N(1a) distance is 2.884(4) Å. In the crystal structure an infinite chain of hydrogen bonds along a twofold screw axis is formed as shown in Fig. 4. The structure can be regarded as being constructed from a stacking of two alternate sheets along the crystallographical *c*-axis. One sheet is built from parallel chains of hydrogen-bonded molecules along the *a*-axis, the second is formed by analogous

Table 4 Logarithmic correlation of the observed rate coefficients of the isomerization of the alkaloid isomers **1–6** at 50 °C with solvent polarity using the Dimroth–Reichardt polarity scale

Solvent	Polarity E_T^N (323 K)	log (k_{obs}/s^{-1}) 1	2	3	4	5	6
Water	1.00	−3.44	−3.76	−3.51	−3.80	−2.72	−2.83
Methanol	0.76	−5.52	−6.05	−6.27	−7.06	−4.24	−4.78
Ethanol	0.64	−6.12	−6.82	−6.91	−7.85	−5.22	−5.57
Propan-2-ol	0.54	−6.63	−7.52	−7.72	−8.86	−5.47	−6.27
Dimethyl sulfoxide	0.42	−6.97	−7.73	—[a]	—[a]	−5.88	−7.13
Pyridine	0.31	−7.48	−8.90	—[a]	—[a]	−6.87	−7.86
Dioxane	0.17	−7.98	—[a]	—[a]	—[a]	−7.30	—[a]

[a] Rate coefficients too small to be determined.

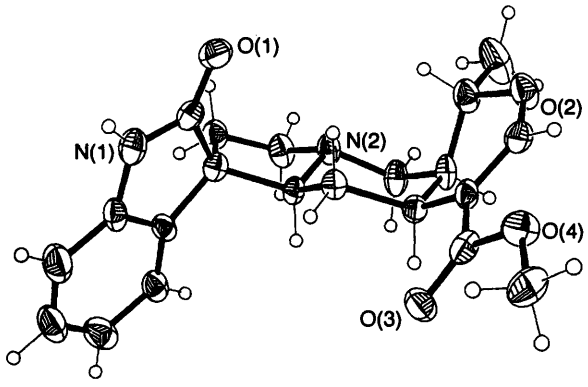


Fig. 3 Molecular structure of **3** showing 40% probability ellipsoids for heavy atoms

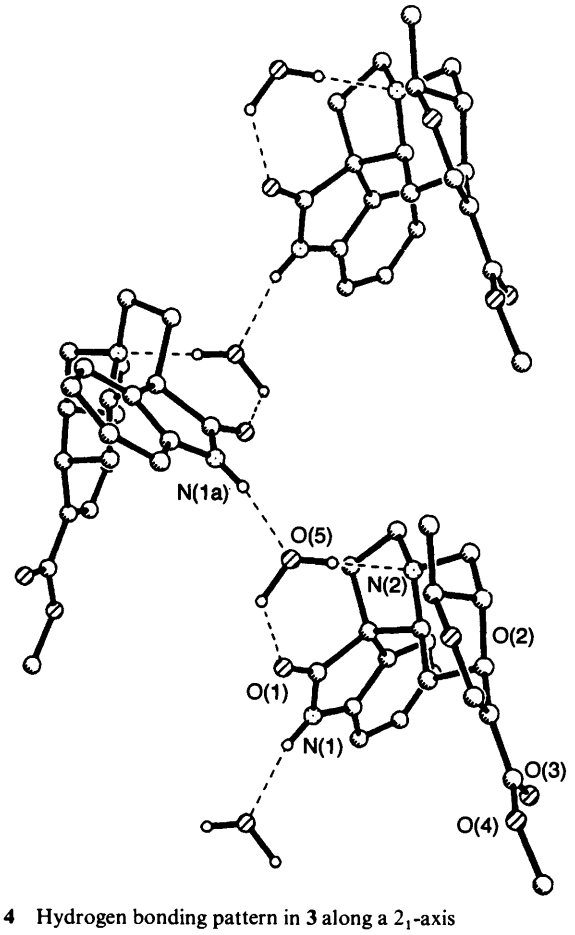


Fig. 4 Hydrogen bonding pattern in **3** along a 2_1-axis

chains, but in the direction of the crystallographically equivalent *b*-axis. Between the sheets the molecules are connected by strong van der Waals forces.

Experimental

Materials

The alkaloids **1–6** were obtained by extraction of *Uncaria tomentosa* root (Peru) with supercritical CO_2, followed by conventional acid–base work-up and separation by column chromatography. The structures of the oxindole alkaloids were corroborated by IR, UV, mass and particularly by NMR spectroscopy. ^1H and ^{13}C NMR spectra were acquired with a Bruker AC 200 F spectrometer using solutions of 30 mg alkaloid in 0.5 cm^3 $CDCl_3$. Standard pulse programs for CH–COSY and HH–DQF–COSY spectra were employed. All data were in complete accordance with the literature.[9] In addition, the structure of pteropodine **3** was proved by a single crystal X-ray analysis. Purity was also checked by elemental analyses (±0.3%). Optical rotation of anhydrous pteropodine **3** ($[\alpha]_D^{20} = -104$; *c* 1.0 in $CHCl_3$) was in good agreement with the reported values ($[\alpha]_D = -109$; *c* 1.1 in $CHCl_3$; $[\alpha]_D^{21} = -102.5$; *c* 1.0 in $CHCl_3$).[3,6] The absolute configuration is based on partial synthesis of **1** and **2** from ajmalicine and **3–6** from tetrahydroalstonine, respectively.[3,10] In turn, the complete stereochemistry of these indole alkaloids was established [11] and later proved by asymmetric total synthesis [12] and biomimetic synthesis.[13]

All solvents were used as supplied (Merck–analytical grade or better). The water content, determined using Karl–Fischer titrations, was in all cases ≤0.02%. Reaction vials were kept under argon. Phosphate buffer concentration was 0.065 and 0.0325 mol dm^{-3}; acetate buffers were prepared from 0.01, 0.1 and 0.2 mol dm^{-3} acetic acid. 2,6-Diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenolate (Reichardt's Dye) was purchased from Aldrich. The polarity of the solvents was determined spectrophotometrically at 50 °C. Wavelengths were checked with a solution of holmium perchlorate according to the *European Pharmacopoeia*.

Kinetic procedures

The isomerization was followed by monitoring the composition of the thermostatted (±0.1 K) reaction mixture by HPLC analysis, using a RP-18 (5 μm) column (125 × 4 mm i.d., Merck) and a mixture of acetonitrile and 0.01 mol dm^{-3} aqueous phosphate buffer, pH 7.0 (45:55, 70 °C), as the eluent with a flow of 1.3 cm^3 min^{-1}. Detection was carried out at 247 nm. Retention times were as follows: speciophylline 2.4 min, mitraphylline 2.6 min, uncarine F 2.9 min, pteropodine 3.3 min, isomitraphylline 3.4 min and isopteropodine 4.8 min. Typically, solutions of 0.1 mg alkaloid in 10 cm^3 solvent were prepared. Solutions in organic solvents were diluted with buffer and acidic solutions were neutralized immediately prior to analysis. Relative standard deviation of the primary HPLC measurements was 0.8%.

X-Ray analysis

A colourless rectangular prism (0.8 × 0.7 × 0.3 mm) of **3**·H_2O·0.5 MeOH was obtained by slow evaporation of

a solution of **3** in a mixture of MeOH and H_2O (95:5).

Crystal data. $C_{21.5}H_{28}N_2O_{5.5}$, M = 402.4, tetragonal, space group $P4_12_12$ (No. 92) or the enantiomorphic space group $P4_32_12$ (No. 96), $a = b$ = 10.874(2) Å, c = 34.344(5) Å, V = 4061(1) Å^3 (from 32 reflections with 2θ = 11–25°), Z = 8, D_c = 1.317 g cm^{-3}, T = 223 K, μ = 0.095 mm^{-1}, $F(000)$ = 1720.

Data collection and processing. Diffractometer Siemens P4, graphite-monochromated Mo-Kα radiation, λ = 71.073 pm, ω-scans, 3233 data collected ($2\theta_{max}$ 42°, h − 1 to 11, l − 1 to 37), of which 2159 were independent (R_{int} = 0.027) and 1912 with $I \geqslant 2\sigma(I)$. Corrections for Lorentz and polarization effects were applied.

Structure analysis and refinement. The structure was solved by direct methods (SHELXS-86) for the space group $P4_12_12$ with atomic coordinates of the correct enantiomer and refined by a full-matrix least-squares procedure using F^2 (SHELXL-93).[14] The absolute structure and the accurate space group could not be determined from the data because the anomalous X-ray scattering effects were too small. All non-hydrogen atoms were refined with anisotropic displacement parameters. The atoms of the methanol molecule have a great thermal motion, the carbon atom lies on a twofold rotation axis and the oxygen atom is disordered (both atoms were refined with multiplicity of 0.5). The hydrogen atoms of **3** were included in the refinement at calculated positions using a riding model, hydrogen atoms of the water molecule were located and refined isotropically. Convergence was obtained for 276 parameters with the conventional R_1 value at 0.041 and a weighted wR_2 value at 0.097 for 1912 reflections; $w = 1/[\sigma^2(F_o^2) + (0.049P)^2 + 1.52P]$, with $P = (F_o^2 + 2F_c^2)/3$. Tables of bond lengths and angles, fractional coordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 188/14.

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