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Synthesis, X-ray analysis and spectroscopic characterization of the hemiaminal cyclization product from 2,4-dipyridine substituted 3,7-diazabicyclo[3.3.1]nonanone 1,5-diesters

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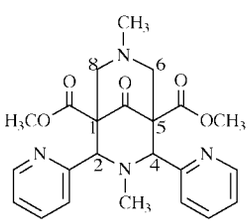
The 2,4-dipyridine substituted 3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one 1,5-diester, HZ2, is characterized by a high analgesic potency. The attempt to form ammonium salts of HZ2 or to *N*-demethylate position 7 resulted in an unexpected hemiaminal cyclization product **1**. The structure was elucidated by an X-ray analysis, the ^{1}H- and ^{13}C-NMR spectra could be fully assigned by means of H,H-COSY, Grad-HSQC-EA and ACCORD-HMBC experiments. The MS spectra of **1** exhibit a ring opening. Interestingly, ESI-MS/MS experiments of HZ2 in aqueous solution showed the formation of a hydrated product. The fragmentation pathways of HZ2 and the hydrated product are rather different indicating the formation of a carboxylate.

Introduction

The 2,4-dipyridine substituted 3,7-dimethyl-3,7-diazabicyclo-[3.3.1]nonan-9-one 1,5-diester, HZ2, was found to exhibit high affinity and selectivity to the κ-opioid receptor. Thus, the compound attracts interest as an opioid-like analgesic which can be used for the treatment of strong pain caused by tumours or operations.[1] In contrast to the classical morphine derived compounds used in clinical practice, animal experiments have revealed that HZ2 does not suffer from the typical side-effects such as constipation, respiratory depression, physical dependence and tolerance.[2] However, the compounds of this class were found to have a limited water solubility, which makes on the one hand the high-throughput-screening difficult and on the other hand will influence the bioavailability of the drug in human beings. As a part of a greater project, in which the structure–activity relationships of a series of structurally varied diazabicyclononanones are under investigation, it was the aim of this study to convert HZ2 (see Fig. 1) into more hydrophilic compounds. Therefore, the synthesis of various ammonium salts and an N7-demethylated compound was attempted.



HZ2

Fig. 1 Structural formula of HZ2.

Results and discussion

Synthesis

HZ2 was achieved by a double Mannich reaction, using, in the first step, oxoglutaric acid, methylamine and pyridine-2-carbaldehyde and, in the second step, the previously obtained piperidone, formaldehyde and methylamine.[3] The conversion of HZ2 into a hydrochloric, oxalic and perchloric salt was performed in EtOH by adding a more than tenfold surplus of the corresponding acid to the HZ2 solution. In the case of $HClO_4$ and oxalic acid, the salts could be isolated. From the reaction solutions with HCl and in some cases with $HClO_4$, crystals with properties different from the expected salts were isolated in yields ranging from 40 to 57%.

The demethylation was performed using α-chloroethyl chloroformate, which is reported to be a selective reagent for tertiary amines by Koreeda and Luengo.[4] The reaction pathway is characterized by the formation of an ammonium and a carbamate intermediate. From this reaction, 85% of a yellow–white, amorphous substance was isolated.

The NMR spectra of all obtained substances were found to be identical indicating that both reaction pathways have given the same product apart from the counter-anion. Interestingly, the NMR spectra clearly show that, in contrast to the starting product, a non-symmetrical molecule was formed under the reaction conditions applied. For example, in the aliphatic region, two singlets for the methoxy groups of the ester function at about 3.5 ppm and 3.7 ppm, as well as two singlets for the *N*-methyl groups at about 2.0 ppm and 3.1 ppm can be observed. Moreover, two singlets at about 4.0 and 5.1 ppm, each for one proton can be found. In the aromatic region a double set of signals was found with an unexpected downfield shift of a signal corresponding to a hydrogen next to the pyridine nitrogen at about 9.0 ppm (Table 1). The ^{13}C-NMR spectra gave similar results (Table 2). Most interestingly, for the expected C9-keto group no signal at about 200 ppm could be detected, indicating that the keto group has reacted with the reagents applied. Moreover, no other signal for the former C9 carbon atom could be found in the aromatic part of the

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Table 1 ^{1}H-NMR-spectroscopic data, δ (ppm)

	H2/4	H6/8	OCH_3	N^7–CH_3	N^3–CH_3	H6′/″	H3′/″	H4′/″	H5′/″
HZ2 300 MHz, DMSO-d_6	4.57 s	2.45 d/2.92 d J = 12 Hz	3.66 s	1.89 s	2.18 s	8.47 m		7.30–7.35/7.88–7.99 m/m	

	H10/12	H1/3	OCH_3	N^2–CH_3	N^{11}–CH_3	H3′	H4′	H5′	H6′	H6	H7	H8	H9
1 300 MHz, DMSO-d_6	5.21/+ s	4.23 d/4.56 d J = 13 Hz +/3.94 d J = 13 Hz	3.51 s/3.68 s	3.11 s	1.95 s	7.09 d	7.83 tr	7.46 tr	8.87 b	8.77 d	7.8–8.0 b	8.40 b	7.8–8.0 b
1 500 MHz, MeOH-d_4	5.07/3.96 s	4.12 d/4.31 d J = 13 Hz 3.59 d/3.82 d J = 12.5 Hz	3.54 s/3.68 s	3.11 s	2.10 s	7.03 d	7.80 dtr	7.46 dd	8.78 d	8.63 d	7.87 m	8.35 dtr	7.88 m

+ Signal hidden by HDO.

Table 2 ^{13}C-NMR-spectroscopic data, δ (ppm)

	C1/5	C2/4	C6/8	C9	CO–Ester	OCH_3	N^7–CH_3	N^3–CH_3	C2′/″	C3′/″	C4′/″	C5′/″	C6′/″
HZ2 300 MHz, DMSO-d_6	61.8	73.0	60.1	203.1	167.6	52.0	42.4	43.9	157.9		122.9, 123.2, 136.5, 148.6		

	C4/10a	C10/12	C1/3	C4a	CO–Ester	OCH_3	N^2–CH_3	N^{11}–CH_3	C2′	C3′	C4′	C5′	C6′	C6	C7	C8	C9	C9a
1 300 MHz, DMSO-d_6	+/+	69.5 66.5	58.5 +	+	165.0 165.7	53.0 53.1	42.8	39.4	153.0	124.6 *	138.1 *	124.3	150.7 *	150.2	124.6 *	138.1 *	124.1	150.7 *
1 500 MHz, MeOH-d_4	60.7 62.6	72.4 70.3	58.7 58.3	143.6	168.8 169.4	54.3 54.4	44.8	41.5	156.5	127.1	140.5	126.8	152.6	144.4	127.0	144.8	125.7	153.0

+ Signals could not be detected. * Since no two-dimensional NMR experiments were performed, a full assignment of the spectrum was impossible.

spectrum (>130 ppm). The ^{1}H and ^{13}C NMR data are given in Tables 1 and 2, respectively.

The EI mass spectrum showed a molecular ion peak at m/z = 438 which corresponds to the mass of HZ2 and indicates that the molecular formula has not changed upon the reaction. Positive FAB mass spectra also showing a molecular ion peak of m/z = 439 for all substances support the EI mass findings.

The IR spectra obtained from the crystals of the different reactions are characterized by a sharp peak at 3370 cm^{-1} and a broader one ranging from 3240 to 3350 cm^{-1} which might be caused by an OH group. Since the keto band (νC=O) at 1700 to 1710 cm^{-1} is missing, which is in line with the missing C=O signal in the ^{13}C NMR spectrum, it is likely that the keto group is converted into an alcohol function.

Taking these data together, they could not be reconciled for several reasons with the desired compounds. In the case of the demethylated HZ2, only one *N*-methyl signal should have been observed in the ^{1}H NMR spectrum, and the strong separation of signals of the former H2/4 and H6/8 (see Table 1) is neither in accordance with the structure of demethylated HZ2 nor with a salt of HZ2. In addition, the spectroscopic data can neither be explained by a previously observed *cis–trans* isomerization[3,5] nor by a rotational isomerization of the pyridine groups.[5,6] In order to elucidate the structure, crystals obtained from the perchlorate formation were subjected to an X-ray analysis.

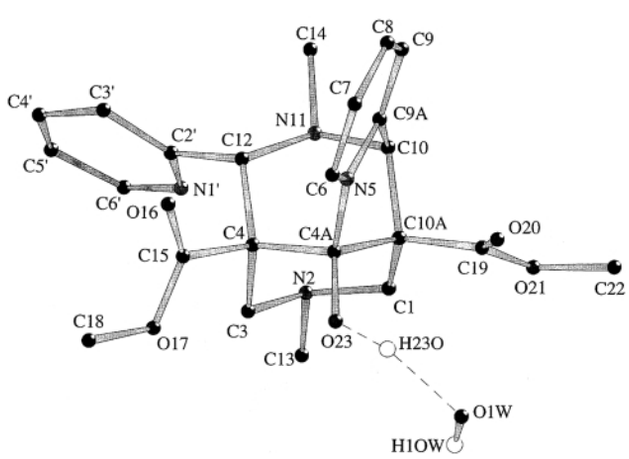

Fig. 2 Crystal structure of compound **1**.

Structure elucidation

The crystals investigated in the X-ray analysis were colourless prisms characterized by an orthorhombic unit cell. The structure analysis was performed by direct methods using SHELX-90[7] and SHELXL-93.[8] The experimental data and conditions are summarized in the Experimental section. The designation of the compound is: (±)-4a-hydroxy-4,10a-bis(methoxycarbonyl)-2,11-dimethyl-*syn*-12-(2-pyridyl)-2,3,4,*t*-4a,10,*t*-10a-hexahydro-*c*-10,*r*-4-(iminomethano)-1*H*-pyrido[3,4-*b*]indolizinium perchlorate monohydroperchlorate.

The pyridine ring at C10 is linked to the formerly C9 atom (see Fig. 2) and the pyridine rings have taken up a *trans*-position at the former bicyclononanone skeleton.

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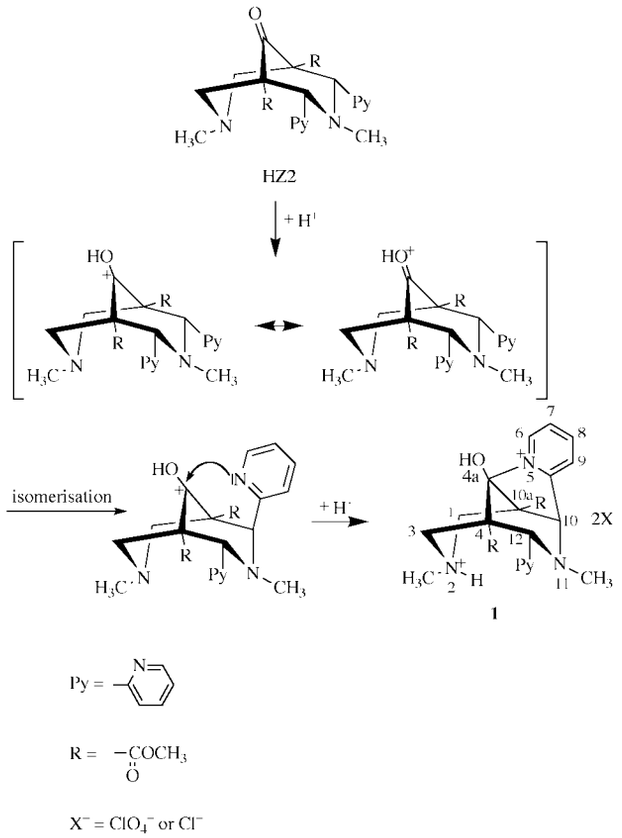

Fig. 3 Hypothesized mechanism of the cyclization reaction resulting in the hemiaminal compound **1**.

Reaction pathway

Interestingly, an intramolecular cyclization has occurred resulting in a 1*H*-pyrido[3,4-*b*]indolizinium skeleton. Since both reactions were carried out under acidic conditions, it is likely that, in the first step, the keto group was protonated leading to a tertiary carbocation. In an additional step, an isomerization of one of the two pyridine rings from the equatorial to the axial position must have taken place presumably using a retro-Mannich pathway;[5] in this configuration, the nitrogen of the pyridine ring is subsequently able to attack the carbocation at C9 leading to the hemiaminal compound **1** (see Fig. 3). In addition, a protonation of the former N7 has occurred.

Assignment of the NMR spectra

Knowing the structure of the hemiaminal **1** (for the numbering scheme see Fig. 2 and Fig. 3) the NMR-spectra can be assigned by means of a series of experiments: a 500 MHz ^{1}H NMR spectrum and the corresponding H,H-COSY, ^{13}C NMR spectra measured with a 90° pulse-length of $P1 = 4.6$ μs in the ^{1}H-decoupled mode using GARP-decoupling and in an additional experiment with a reduced transmitter pulse $P1 = 2$ μs and a relaxation delay of 10 s, which gave a further signal at $\delta = 143.6$ ppm. In order to determine the ^{1}H–^{13}C coupling constants a gated-decoupled spectrum was recorded. The Grad-HSQC-EA and ACCORD-HMBC experiments helped to assign both the ^{13}C and ^{1}H NMR chemical shifts (see Tables 1 and 2).

The aliphatic part of the ^{1}H NMR spectrum is characterized by two AB systems at $\delta = 3.59/3.82$ ppm and $\delta = 4.12/4.31$ ppm belonging to the two pairs of geminal hydrogens at C3 and C1, and two singlets at $\delta = 3.96$ and 5.07 ppm belonging to the hydrogens at C12 and C10. Using the HSQC experiments the corresponding ^{13}C NMR signals can be assigned. In order to find out which signal belongs to which side of the molecule (C3–C4–C12–C2′ *versus* C1–C10a–C10–C9a), the connecting pathways in the HMBC experiment were utilized. For example, cross peaks were found between the signals of H10 (5.07 ppm) and C10a (62.6 ppm), C1 (58.7 ppm) and C19 (168.8 ppm; C=O ester) as well as between H12 (3.96 ppm) and C4 (60.7), C3 (58.3 ppm) and C15 (169.4 ppm; C=O ester). The cross peaks between H10 (5.07 ppm), and C9 (125.7 ppm), and C9a (153.0 ppm) and, in turn, C10 (72.4 ppm) and H7/9 (7.88 ppm) on the one hand, and H12 (3.96 ppm) and C2′ (156.50 ppm) and, in turn, C12 (70.3 ppm) and H3′ (7.03 ppm) on the other hand exhibit the attachment of the positively charged pyridinium ring to the carbon atom C10 and the neighbourhood of the neutral pyridine ring and C12. The assignment is supported by the finding that the hydrogen attached to C10 and the positively charged pyridinium ring in an equatorial position is shifted downfield ($\Delta\delta = 1.1$ ppm) in comparison to the H12 in an axial position (*cf.* ref. 9). The remaining pyridine hydrogens and carbon signals can be assigned by using the cross peaks found in the H,H-COSY and the HSQC experiments. The ^1J (CH) coupling constants found in the positively charged pyridinium ring are always higher than corresponding coupling constants in the neutral aryl ring (see Table 2) which supports the above described assignment (*cf.* ref. 10).

The methyl group attached to the positively charged N2 can be assigned to $\delta_H = 3.11$ ppm and $\delta_C = 44.8$ ppm, respectively, and the CH_3 group attached to N11 to $\delta_H = 2.10$ ppm and $\delta_C = 41.5$ ppm. The assignment is ensured by the cross peaks between the hydrogens of the N11 methyl group and C10/C12 (72.4 and 70.3 ppm), and between the hydrogens of the N2 methyl group and C1/C3 (58.3 and 58.7 ppm). The hemiaminal carbon at 143.6 ppm showed three correlations to the equatorial protons H10, H1e and H3e. No cross peak was found to the axial standing hydrogens H12, H1a and H3a. In the H,H-COSY, the cross peaks of proton H1e at 4.31 ppm and H3e at 3.59 ppm are typical for a W-coupling of two equatorial protons. Interestingly, the hemiaminal carbon atom at 143.6 ppm showed a long relaxation time; even though the relaxation delay was increased to 10 s, only a very broad signal of intensity could be observed.

Mass spectra

Since the molecular weight of dipyridine substituted 3,7-diazabicyclo[3.3.1]nonanone does not change upon conversion to the hemiaminal cyclization product **1**, for comparison FAB and ESI-MS/MS spectra of the starting product were recorded. Surprisingly, both FAB spectra and ESI-MS/MS daughter scan of the starting material HZ2 and the cyclization product **1** were identical, indicating that the hemiaminal **1** seems to ring open again under the mass spectroscopic conditions to give the starting compound.

Furthermore, in aqueous solutions the diazabicyclo[3.3.1]-nonanone HZ2 spontaneously tends to form a hydrated product. The spectra of HZ2 and **1** showed the protonated pseudomolecular ions of 439 Da; HZ2 showed the additional molecular ion of 457 Da, which is equivalent to $M^+ + 18$ Da and corresponds to the hydrated product.[11] The addition of water could be proved by replacing the water with deuterated water. In this experiment, again two pseudomolecular ions could be detected: one of 440 Da, which is caused by the protonation of HZ2 by a deuterated hydrogen during the ion formation process, and one of 460 Da, corresponding to the reaction product of $m/z = 440$ with deuterated water (20 Da).

Although the starting compound of the mass spectroscopic measurement is HZ2, different fragmentation pathways were observed for $m/z = 439$ and $m/z = 457$ by means of the LC-MS/MS technique. These two different fragmentation pathways prove the estimation of the formation of an hydrated compound in aqueous solution. The daughter ion spectrum of

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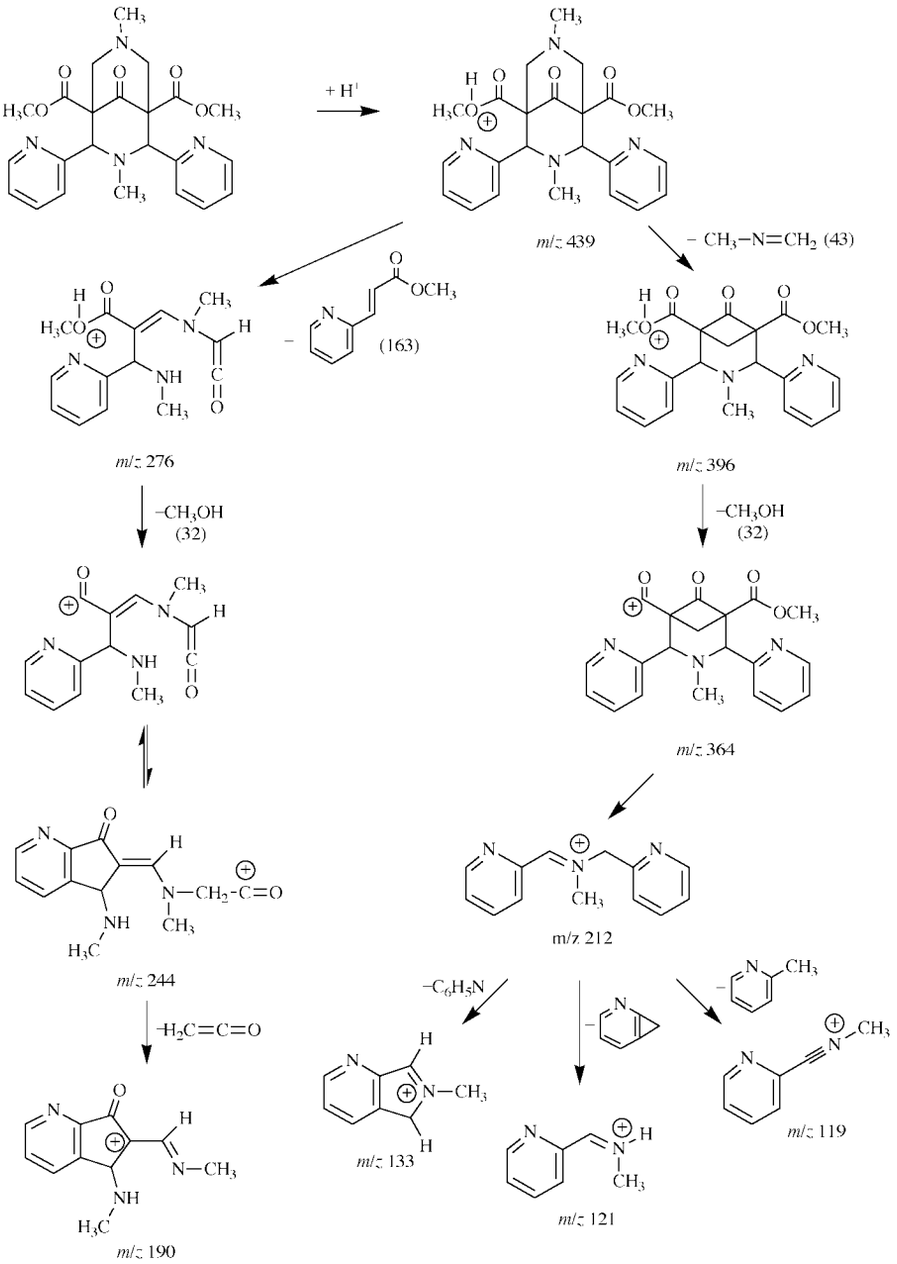

Fig. 4 Fragmentation pathway for the daughter ion spectrum of $m/z = 439$.

$m/z = 439$ is characterized by a cleavage of the higher substituted piperidone, which was previously found to be the unstable ring of HZ2,[12] caused by a loss of $H_3C–N^7=CH_2$. On the other hand, a pyridine analogue cinnamonium ester is split off to give the fragment $m/z = 276$. The further fragmentation is displayed in Fig. 4.

It was hypothesized that the addition of water ($m/z = 457$) resulted in a carboxylic function (at formerly C9), which is in the first step split off ($CO_2 = 44$) together with methylamine (31) to give the azepine fragment $m/z = 382$ (see Fig. 5). The subsequent ring fission resulted in azaindene systems. The FAB spectra of HZ2 showed the stepwise loss of the ester and the above mentioned ring fission of the higher substituted piperidone giving a 4-azaisoindole compound.

Conclusion

The aim of this study was to synthesize salts and demethylated HZ2 derivatives. Beside the expected oxalate and perchlorate salts the formation of the hemiaminal compound **1** was observed. The demethylation reaction resulted in the same product indicating the thermodynamic stability of this compound. However, preliminary pharmacological screening of **1** showed affinity neither to the μ nor to the κ opioid receptor. Thus, HZ2 has lost its high analgesic potency upon conversion to the pyrido[3,4-*b*]indolizinium.

Experimental

Chemicals and materials

Melting points were determined with a Dr Tottoli melting point apparatus (Büchi, Switzerland) and were not corrected. IR spectra, recorded as KBr discs, were obtained using a Perkin-Elmer 298 spectrometer. TLC was carried out using silica gel 60 F_{254} (Merck No. 5554). As eluent a mixture of cyclohexane–ethyl acetate–methanol (10/4/1) was used. Dry solvents were used throughout.

Synthesis

$HZ2{\cdot}C_2H_2O_4$: HZ2 was synthesized according to ref. 3. 0.00034 mol HZ2 were dissolved in warm EtOH and 197 mg oxalic acid were added. After 30 min the mixture was evaporated and the

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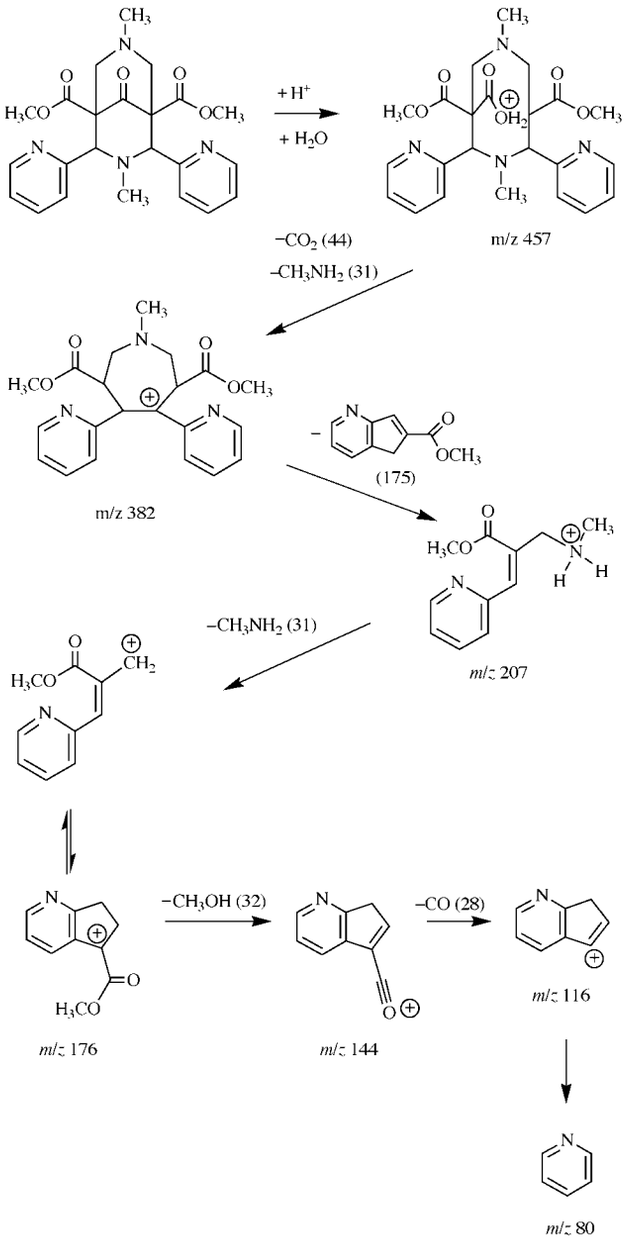

Fig. 5 Fragmentation pathway for the daughter ion spectrum of $m/z = 457$.

obtained oil dissolved in MeOH. Storage of this solution at 5 °C gave 150 mg (93%) of white crystals. Mp 140–145 °C (decomp.).

1·$HClO_4$: 0.002 mol HZ2 were dissolved in warm EtOH and 0.2 ml perchloric acid were added. After 30 min the reaction mixture became turbid. The mixture was evaporated *in vacuo* and the residual oil dissolved in a small amount of MeOH. 610 mg (57%) of colourless crystals were obtained. Mp 173–180 °C (decomp.).

1·HCl: 0.002 mol HZ2 were dissolved in warm EtOH and 0.2 ml 2 M hydrochloric acid were added. The deposited oil was dissolved by heating the reaction mixture. Storing the mixture at 5 °C the crystallization began after 1 h giving 380 mg (40%) of colourless crystals. Mp 144 °C (decomp.).

1 by demethylation: the synthesis was performed analogously to ref. 4, using CH_2Cl_2 as solvent. 0.001 mol of α-chloroethyl chloroformate were added to 0.001 mol HZ2 in 20 ml CH_2Cl_2 at 0 °C (15 min). The mixture was refluxed for 1 h, evaporated *in vacuo* and the residue heated in MeOH for 30–45 min at 50 °C. Storing the reaction mixture at 5 °C gave 360 mg (85%) of a yellow–white, amorphous substance, which was recrystallized from MeOH. Mp 132–140 °C (decomp.).

X-Ray analysis †

Crystal data. $C_{23}H_{26}N_4O_5 \cdot H_2O \cdot 2ClO_4$, $M = 655.39$. Orthorhombic, space group $P2_12_12_1$ (No. 19), $Z = 4$, $a = 15.127(9)$, $b = 17.123(5)$, $c = 11.304(4)$ Å, $V = 2928(2)$ Å^3, μ(Mo-Kα) = 3.0 cm^{-1}, $T = 21$ °C.

Data collection and processing. 3192 reflections measured ($1.5 \leq \theta \leq 20°$, hkl and $\bar{h}\bar{k}\bar{l}$), 2727 unique [merging $R = 0.131$], giving 1279 with $I > 2\sigma(I)$.

Structure analysis and refinement. Least-squares refinement[8] with all non-carbon atoms anisotropic, all other atoms isotropic. Hydrogen atoms with fixed U_{iso} in calculated positions. Final R_1 and R_w values are 0.096 and 0.157, GOF = 1.03. C4A–O23 = 1.359 Å and H23O–O23 = 1.18 Å indicate hydrolysation. According to U_{ij} of perchlorate oxygen atoms the second ClO_4 is considerably disordered.

NMR measurements

^{1}H and ^{13}C NMR experiments were performed on a Varian XL 300 FT NMR spectrometer operating at 299.956 MHz (^{1}H) and 75 MHz (^{13}C) with a sample temperature of 30 °C. In the case of the ^{1}H NMR spectra, a varying number of scans (depending on the experiment) with a frequency range of 2200 Hz were collected into 65 000 data points, giving a digital resolution of 0.33 Hz point^{-1}. An appropriate Gaussian function was applied before Fourier transformation to enhance the spectra resolution. Abbreviations for data quoted are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

1D and 2D NMR spectra of hemiaminal **1** were measured on a BRUKER AMX 500 spectrometer equipped with a SGI O^2 workstation. 1D experiments were done with a 5 mm ^{1}H/^{13}C dual probe with 12.0 μs for ^{1}H, and 4.6 μs for ^{13}C, 90° pulse length. 2D experiments were done with a 5 mm TXI probe with 6.5 μs for transmitter ^{1}H, and 8.0 μs for decoupler ^{13}C, 90° pulse length. The gradient HH-COSY experiment using the BRUKER standard pulsprogram was acquired with a size of 2k × 512 data points. After 8 dummy scans 2 scans were used for each increment. For processing zero filling in F1 to 2k × 2k data matrices and a nonshifted sinesquared window function was applied in both dimensions to gain real data matrices before Fourier transformation. The gradient HSQC-echo-antiecho experiment[13] was acquired with a size of 2k × 256 data points using 128 echo and 128 antiecho increments. After 8 dummy scans 2 scans were used for each increment. Zero filling in F1 (^{13}C) domain to 2k × 1k matrix and a $\pi/2$ phase shifted sine-bell function was employed in both dimensions before Fourier transformation was done in echo antiecho mode. The ACCORD-HMBC experiment[14] was acquired with a size of 2k × 512 data points and 32 scans for each increment after 8 dummy scans. The ACCORD-HMBC experiment was performed with a variable delay from 100 ms to 50 ms to record ^{1}H/^{13}C long-range couplings from 5–10 Hz. Zero filling in F1 (^{13}C) domain to 2k × 1k matrices and a nonshifted sine-bell function was employed in both dimensions before Fourier transformation.

A frequency range of 4166 Hz for ^{1}H dimensions in all experiments and 17250 Hz for ^{13}C dimensions in heteronuclear experiments was used. The gradient-pulses used by the 2D-experiments were all sine-pulses and the ratio of the gradient strength was for HH-COSY 50:50, HSQC-EA 80:20.15 for echo and −80:19.85 for antiecho. The ratio for the 8 gradient-pulses in the ACCORD-HMBC experiment was 15:−10:−5:50:30:40:−5:5.

† CCDC reference number 188/181. See http://www.rsc.org/suppdata/p2/1999/2083 for crystallographic files in .cif format.

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Mass spectroscopic experiments

ESI-MS/MS experiments were performed on a Micromass Quattro LC (Micromass, Altrincham, Cheshire, UK) triple quadrupole mass spectrometer with an ElectroSpray Interface. Ultrapure nitrogen served both as nebulizing and desolvation gas. Polypropylene glycol (PPG) was used for tuning and mass-axis calibration for each mass-resolving quadrupole (Q1 and Q3). Ultrapure argon was used as the collision gas in the collision cell (Q2). For MS/MS experiments, the first quadrupole (Q1) was programmed to focus the protonated molecule ions $[M + H]^+$, collision-induced fragmentation took place in Q2, and Q3 monitored the product ions in full scan mode. The pressure in the collision cell was held at 1.0×10^{-3} mbar. The collision energy for the recording of product ion spectra was varied between 15 and 50 V. The cone voltage was held at 50 V. Data were collected with MassLynx software (Version 3.0, Micromass, Altrincham, Cheshire, UK).

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