Stereoelectronic Effects in the Iodine-Promoted Oxidation of Pentacyclic Tetrahydroisoquinolines

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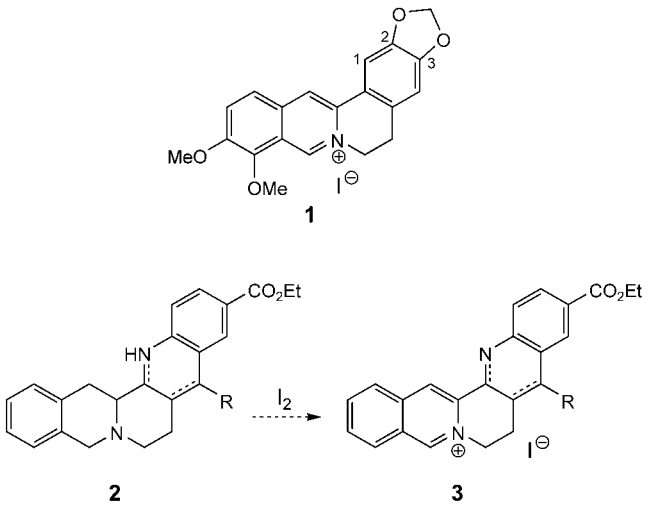
Iodine-promoted oxidations of the pentacyclic tetrahydroisoquinolines **4a**, **4b**, and **10** were investigated. Whereas the all-*cis* diastereoisomer **4a** containing an arylamino moiety gave the iminium ion **5** as the primary product, which subsequently underwent intramolecular aminal formation to **6**, the corresponding all-*trans* diastereoisomer **4b** epimerized to the all-*cis* diastereoisomer **4a** *via* iminium ion **7**. In contrast, tetrahydroisoquinoline **10** could be cleanly oxidized to the corresponding isoquinolizidinium ion **11**. Mechanistic considerations were supported by molecular-modeling calculations.

Introduction. – Berberine (**1**), the most-prominent member of the protoberberine alkaloids, displays a broad spectrum of biological activities [1]. The antitumor activity of **1**, which is mediated by inhibition of topoisomerases I and II [2], is of particular interest. Based on NMR studies of berberine–DNA complexes, it was suggested that the planar structure, the iminium ion, and the presence of polar functional groups at the periphery of the molecule are relevant for topoisomerase inhibition [3]. Thus, as part of our ongoing investigations of heterocyclic berberine analogues [4], we were interested to study the effects of these three structural features on DNA binding. For this purpose, we needed to convert pentacyclic 5*H*-benz[*b*]isoquino[2,3-*h*][1,7]naphthiridines **2** to the corresponding iminium ions **3** by iodine-mediated oxidation (*Scheme 1*). Although this oxidation has been successfully used in protoberberine chemistry [5][1]), we encountered unexpected reactivities of compounds of type **2**, which are presented below.

Results and Discussion. – Compound all-*cis*-**4a** (=ethyl (8a*R*,14a*S*,14b*S*)-7,8,8a,9,14,14a,14b,15-octahydro-9,9-dimethyl-5*H*-benz[*b*]isoquino[2,3-*h*][1,7]naphthyridine-11-carboxylate)[2]) was treated with I_2 in the presence of AcOK in MeOH at 60° (*Scheme 2*). After 3 h, the starting material had completely reacted (according to TLC), and aqueous workup yielded a solid whose ^{1}H-NMR spectrum showed the anticipated iminium H-atom at δ(H) 9.7. Signals for the benzylic position at δ(H) 3.40 and 3.89 (H–C(15)) and the signals of H–C(14b) at δ(H) 4.81 confirmed the presence of compound **5**. However, upon attempted purification of the iminium salt **5** by flash

[1]) For other chemical protoberberine oxidations, see [6]; for enzymatic oxidations, see [7].
[2]) Compounds **4a**, **4b**, and **10** (see below) were obtained *via Lewis* acid ($EtAlCl_2$ for **4a**, $SnCl_2$ for **4b**, and BF_3 for **10**) catalyzed hetero-*Diels–Alder* reaction of the corresponding tetrahydroisoquinoline carbaldehyde-*N*-arylimine by the method described in [4].

Scheme 1



chromatography (FC), the bridged aminal **6** was isolated as a yellow solid in 59% yield (*Scheme 2*).

The structure of **6** was elucidated by means of 1D- and 2D-NMR experiments. In an attempt to circumvent the undesired aminal formation observed during oxidation of diastereoisomer **4a**, the corresponding all-*trans* diastereoisomer **4b** (=ethyl (8a*R*,14a*R*,14b*S*)-7,8,8a,9,14,14a,14b,15-octahydro-9,9-dimethyl-5*H*-benz[*b*]isoquino-[2,3-*h*][1,7]naphthyridine-11-carboxylate)[2]) was treated with I_2 and AcOK in MeOH under similar conditions (*Scheme 2*). After aqueous workup, the crude product was analyzed by ^{1}H-NMR spectroscopy. Unfortunately, NMR data did not provide useful information. Thus, the crude product was purified by FC to give a product (50%), which was identified by NMR and MS as the *cis* diastereoisomer **4a**, and, in addition, a minor by-product in 3% yield[3]). Thus, it seems likely that the oxidation proceeded *via* imine **7** as the primary intermediate.

At first glance, the outcome of the I_2-mediated oxidations were surprising. Until now, incomplete dehydrogenations have been observed only in the oxidation of 1,2-disubstituted tetrahydroberberines, in which the substituent at C(1) has a dominating influence on the conformation of the quinolizidine moiety [5a][4]). As a result of inversion about N(6), *cis* and *trans* conformations of the quinolizidine moiety are possible. While a *trans* conformation is favored for 2,3-disubstituted berberines in solution, the *cis* conformation is preferred in the case of 1,2-disubstituted berberines [8].

For each of the diastereoisomers **4a** and **4b**, two conformations of the B-ring[4]) are possible, while the conformation of the C-ring is more or less fixed as a result of the planar N(14) of the arylamino moiety (*Fig. 1*). Consequently, *trans*,*cis* (**4a-A**) and

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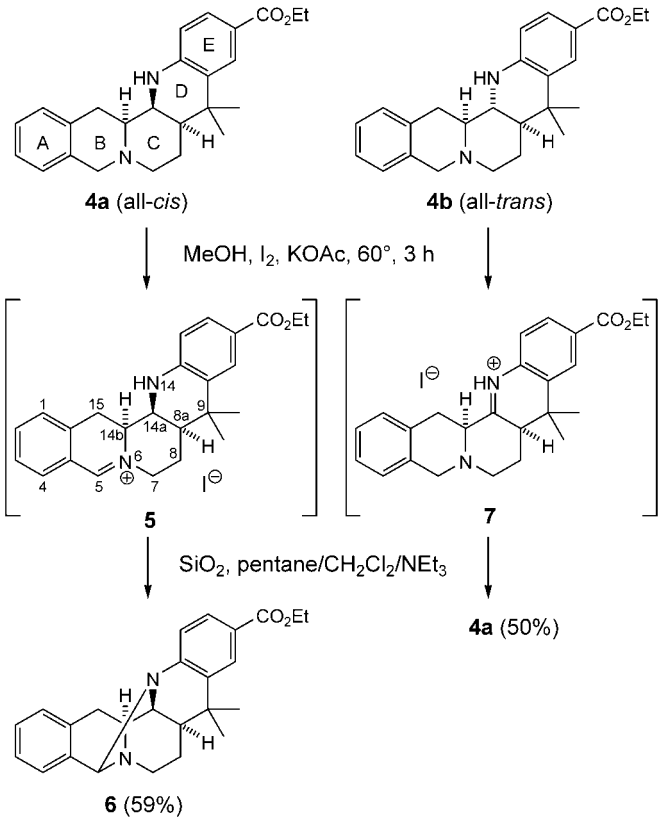
[3]) The by-product was identified as the diastereoisomer in which C(8a), C(14a), and C(14b) are epimerized.

[4]) For the ring designations and peripheral numbering, see **4a** and **5**, resp., in *Scheme 2*.

Scheme 2



cis,*cis* conformers (**4a-B**) are possible for the all-*cis* diastereoisomer **4a**. On the other hand, *trans*,*trans* (**4b-A**) and *cis*,*trans* conformers (**4b-B**) are possible for the all-*trans* diastereoisomer **4b**.

To assess the potential energies of the different conformers of the parent system, *i.e.*, without the ester group on the E-ring, molecular-modeling calculations [9] were carried out (*Fig. 2*). Within the all-*cis* series (**4a-A**, **4a-B**), the *cis* conformer **4a-B** appears to be slightly more stable than the *trans* conformer **4a-A**. One would assume that **4a-A** might be able to form an intramolecular H-bond. However, calculations indicate that the distance of 3.3 Å between the N(6) lone pair and H–C(14) is too large, and, moreover, the angle does not meet the requirements. Conformer **4a-A** is probably disfavored due to an additional 1,3-diaxial interaction between N(14) and H–C(15), steric interactions between H–C(14) and H–C(15), and lone-pair repulsion between N(6) and N(14). The attack of the bulky iodine at N(14) of the aryl amine should be disfavored in both conformers **4a-A** and **4a-B** of the all-*cis* series due to the axial Me group at C(9) and the resulting 1,3-diaxial interactions between the Me group and H–C(14a). Thus, the incoming I-atom is directed to the tertiary N(6). In conformer **4a-A**, the lone pair of N(6) points to the concave side of the folded

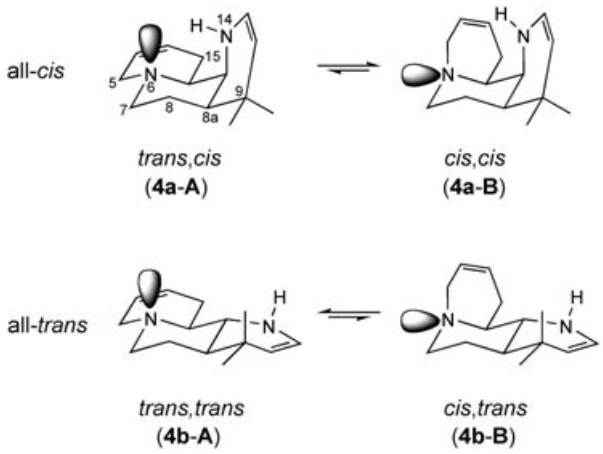


Fig. 1. *Possible conformations of diastereoisomers* **4a** and **4b**. Anellated aryl rings are omitted for clarity. Numbering of atoms corresponds to the peripheral numbering (see **5** in *Scheme 2*).

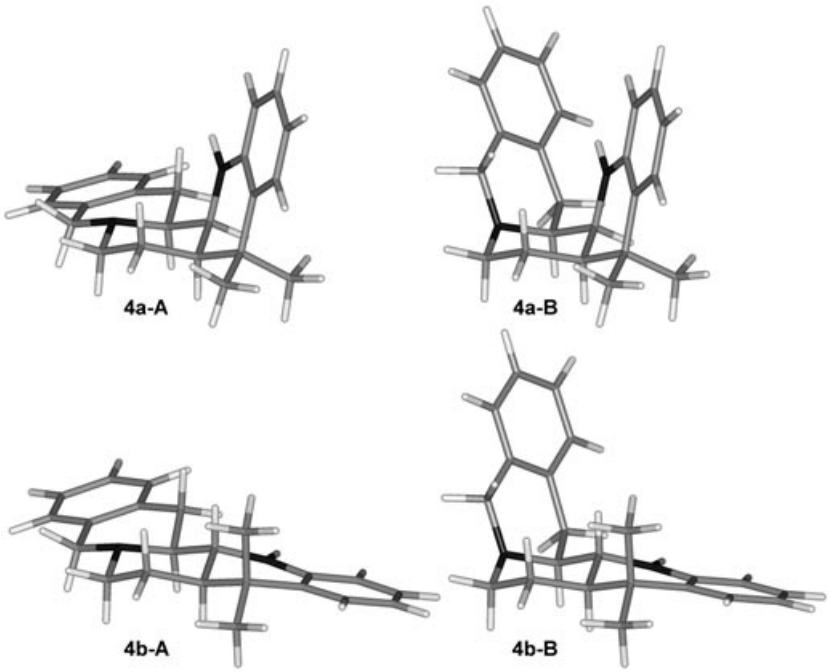
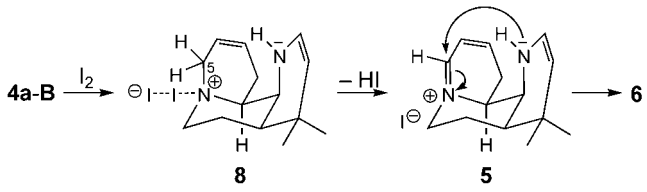


Fig. 2. *Molecular models of the* trans *and* cis *conformers of diastereoisomers* **4a** *and* **4b**. Potential energies calculated by the CVFF force field [9] are: 134.8 kcal mol^{-1} (**4a-A**), 134.0 kcal mol^{-1} (**4a-B**), 127.2 kcal mol^{-1} (**4b-A**), and 129.1 kcal mol^{-1} (**4b-B**).

pentacyclic molecule. In contrast, attack of iodine at N(6) in conformer **4a-B** from the convex face is relatively unhindered (*Scheme 3*). Antiperiplanar abstraction of one H–C(5) from **8** results in the formation of the iminium ion **5**, where no further

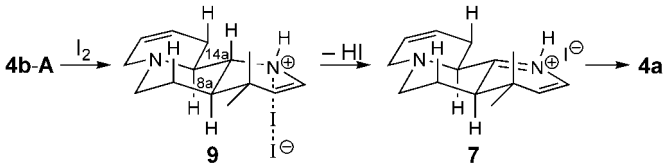
Scheme 3



oxidation is possible. The proximity of the nucleophilic N(14)- to the electrophilic C(5)-atom leads to intramolecular aminal formation to give the bridged derivative **6**. This reaction is in good agreement with other nucleophilic additions to the C=N bond of berberine derivatives [10].

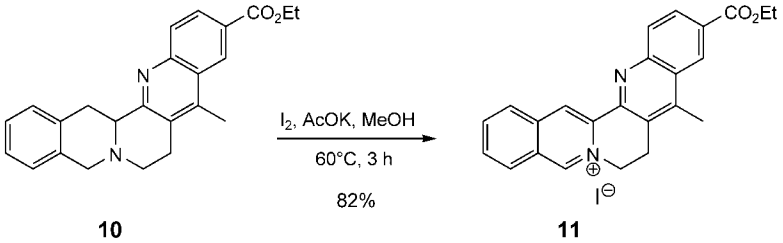
Opposite relative conformer stabilities were obtained for the all-*trans* series. Calculations revealed a somewhat lower stability of the *cis* conformer **4b-B** compared with the *trans* conformer **4b-A**. The *cis* conformer **4b-B** is probably disfavored due to steric interactions between H–C(5) and H–C(8) resulting from the folded B-ring. In the *trans* conformer **4b-A**, all substituents on the central C-ring are in equatorial positions. In contrast to the all-*cis* series, the N(14)-atom in the all-*trans* series is easily accessible from the convex face, and, thus, iodine attack at the more-reactive N(14) is preferred over N(6) (*Scheme 4*). Subsequent antiperiplanar elimination of H–C(14a) in the resulting intermediate **9** finally gives the unstable iminium ion **7**, which is further reduced to the *cis* diastereoisomer **4a**.

Scheme 4



Finally, derivative **10** (=ethyl (14b*S*)-7,8,14b,15-tetrahydro-9-methyl-5*H*-benz[*b*]-isoquino[2,3-*h*][1,7]naphthyridine-11-carboxylate)[2]) with an extended aromatic system was subjected to the I_2 oxidation (*Scheme 5*). After 3 h reaction time, followed by aqueous workup and FC, the desired oxidation product **11** was obtained in 82% yield.

Scheme 5



Thus, the oxidation state of N(14) did not have a major influence on the course of the oxidation.

Conclusions. – It has been demonstrated that an arylamino moiety in the vicinity of a tetrahydroisoquinoline strongly interferes with the oxidizing reagent. Depending on the relative configuration of the starting material **4**, oxidation with I_2 proceeded to give an unstable product with all-*cis* **4a** or, with all-*trans* **4b**, to give epimerized products. In contrast, tetrahydroisoquinoline **10** with a fully aromatized quinoline moiety can be oxidized to the corresponding quinolizidinium ion **11** without any difficulty. This should allow easy access to other berberine analogues containing heteroaryl building blocks. It remains an open question to what extent substituents on the aryl A- and E-rings influence the reactivity of these anellated heteroaryl systems. Further work along these lines is in progress.

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Experimental Part

General. IR Spectra: $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker AC 200*, *Bruker AM-400*, and *Bruker DRX-400*; δ in ppm and *J* in Hz. EI-MS: *m/z* (rel. %).

Oxidation of **4a** *and* **4b**. *General Procedure.* A soln. of I_2 (195 mg, 0.77 mmol) in abs. MeOH (5 ml) was added dropwise to a soln. of **4a** or **4b** (100 mg, 0.26 mmol) in abs. MeOH (10 ml), and the mixture was heated at 60° for 1 h. Then, AcOK (113 mg, 1.36 mmol) was added, and the mixture was heated at 60° for 1 h. After cooling to r.t., excess I_2 was removed with an aq. soln. of $Na_2S_2O_3$. The solvent was removed under vacuum, and the aq. layer was extracted with CH_2Cl_2/MeOH 10:1 (5×10 ml). The combined org. layers were dried ($MgSO_4$), concentrated, and the residue was analyzed by NMR spectroscopy.

*(8a*R*,14a*S*,14b*S*)-11-(Ethoxycarbonyl)-7,8,8a,9,14,14a,14b,15-octahydro-9,9-dimethyl-benz[*b*]isoquino[2,3-*h*]naphthyridin-6-ium Iodide* (**5**). From **4a**. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.70 (*s*, H–C(5)); 7.85–7.75 (*m*, H–C(10)); 7.68–7.21 (*m*, H–C(1), H–C(2), H–C(3), H–C(4), H–C(12)); 6.09 (*d*, *J* = 8.3, H–C(13)); 4.93 (br. *s*, NH); 4.81 (br. *s*, H–C(14b)); 4.26–4.24 (*m*, H_a–C(7)); 4.19 (*q*, *J* = 6.8, CH_2Me); 4.16–4.04 (*m*, H_b–C(7), H–C(14a)); 3.89 (br. *s*, H_a–C(15)); 3.49–3.40 (*m*, H_b–C(15)); 2.08–1.92 (*m*, H–C(8a), H_a–C(8)); 1.50–1.39 (*m*, H_b–C(8)); 1.26 (*s*, Me(17)); 1.25 (*t*, *J* = 7.0, *Me*CH_2); 1.12 (*s*, Me(16)). ^{13}C-NMR (50 MHz, $CDCl_3$): 166.8 (C=O); 165.3 (C=N); 145.1 (C(13a)); 138.6 (C(4)); 134.4 (C(3)); 134.0 (C(4a)); 128.6 (C(12)); 128.0 (C(10)); 127.4 (C(9a)); 123.4 (C(15a)); 120.4 (C(11)); 114.7 (C(13)); 60.8 (C(14b)); 60.4 (Me*C*H_2); 58.3 (C(7)); 55.3 (C(14a)); 42.5 (C(8a)); 35.5 (C(9)); 33.2 (Me(16)); 28.4 (C(15)); 25.9 (Me(17)); 25.1 (C(8)); 14.4 (*Me*CH_2).

*Ethyl (6*R*,10*R*,17*S*)-5,8,9,10,11,16a-Hexahydro-11,11-dimethyl-6*H*-6,10,16-methenoisoquino[1,2-*b*]-[1,3]benzodiazonine-13-carboxylate* (**6**). Obtained during purification of **5** by FC (SiO_2; pentane/CH_2Cl_2/NEt_3 15:3:1 and MeOH/CH_2Cl_2 10:1; R_f (pentane/CH_2Cl_2/NEt_3 15:3:1) = 0.3): 60 mg (59%) of **6**. Yellow amorphous solid. $[\alpha]_D^{22} = +200.6$ ($c = 0.90$, CH_2Cl_2). IR (KBr): 2977, 2932, 2868 (*m*, C–H, aliphat.); 1702 (*s*, C=O); 1602, 1492 (*s*, C=C, arom.); 1291, 1268 (*s*, C–O); 763, 735 (*m*, 1,2-disubst. arom.). ^{1}H-NMR (400 MHz, $CDCl_3$)[5]): 7.85 (*d*, *J* = 2.0, H–C(10)); 7.69 (*dd*, *J* = 8.3, 2.0, H–C(12)); 7.06–7.18 (*m*, H–C(1), H–C(2), H–C(3), H–C(4)); 6.72 (*d*, *J* = 8.3, H–C(13)); 4.76 (*s*, H–C(5)); 4.24 (*dq*, *J* = 7.2, 1.5, CH_2Me); 3.47 (*d*, *J* = 1.3, H–C(14b)); 3.43 (*d*, *J* = 16.5, H_a–C(15)); 3.39–3.40 (*m*, H–C(14a)); 3.12–3.00 (*m*, H_2C(7)); 2.83 (*d*, *J* = 16.5, H_b–C(15)); 1.72 (*ddd*, *J* = 9.9, 6.7, 1.3, H–C(8a)); 1.36–1.42 (*m*, H_a–C(8)); 1.29 (*t*, *J* = 7.1, CH_2*Me*); 1.22 (*s*, Me(17)); 1.20 (*s*, Me(16)); 0.76–0.88 (*m*, H_b–C(8)). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.9 (C=O); 148.4 (C(13a)); 141.5 (C(11)); 132.6 (C(15a)); 130.7 (C(4a)); 129.1 (C(2)); 128.9 (C(10)); 128.4 (C(12)); 127.5 (C(3)); 125.6 (C(1)); 122.7 (C(4)); 120.8 (C(9a)); 116.3 (C(13)); 85.7 (C(5)); 64.4 (C(14b)); 60.3 (*C*H_2Me); 59.1 (C(14a)); 52.7 (C(7)); 42.1 (C(8a)); 37.8 (C(9)); 34.7 (C(15)); 30.8 (Me(16)); 25.8 (Me(17)); 21.2 (C(8)); 14.4

[5]) Numbering as for **5** in *Scheme 2*.

(CH_2Me). EI-MS: 388 (11, [$M^{+\cdot}$]), 373 (6, [$M-15$]$^+$), 343 (3, [$M-EtO$]$^+$), 244 (10), 216 (9), 170 (12), 157 (100, $C_{11}H_{11}N^+$), 144 (38), 129 (94, $C_9H_7N^+$).

I_2-Promoted Oxidation of **4b**. Purification by FC (SiO_2; pentane/CH_2Cl_2/NEt_3 15:3:1 and MeOH/CH_2Cl_2 10:1): 50 mg (50%) of **4a**. $[\alpha]_D^{22} = +216.1$ ($c = 1.00$, $CHCl_3$). Also obtained was 3 mg (3%) of a by-product identified as *ethyl 7,8,8a,9,14,14a,14b,15-octahydro-9,9-dimethyl-5*H*-benz[*b*]isoquino[2,3-*h*]naphthyridine-11-carboxylate*[3]). R_f (pentane/CH_2Cl_2/NEt_3 15:3:1) 0.38. EI-MS: 390 (3, [$M^{+\cdot}$]), 345 (2, [$M-EtO$]$^+$), 188 (3), 146 (100, $C_{10}H_{12}N^+$), 130 (4, $C_9H_8N^+$), 104 (8, $C_8H_8^+$).

*11-(Ethoxycarbonyl)-7,8-dihydro-9-methylbenz[*b*]isoquino[2,3-*h*][1,7]-naphthyridinium Iodide* (**11**). A soln. of I_2 (206 mg, 0.81 mmol) in abs. MeOH (5 ml) was added dropwise to a soln. of *ethyl (14b*S*)-7,8,14b,15-tetrahydro-9-methyl-5*H*-benz[*b*]isoquino[2,3-*h*][1,7]naphthyridine-11-carboxylate* (**10**; 100 mg, 0.27 mmol) in abs. MeOH (10 ml). The mixture was heated at 60° for 1 h, AcOK (113 mg, 1.36 mmol) was added, and the mixture was heated at 60° for a further 1 h. After cooling to r.t., excess I_2 was removed with an aq. soln. of $Na_2S_2O_3$. The solvent was removed under vacuum, and the aq. layer was extracted with CH_2Cl_2/MeOH 10:1 (5×10 ml). The combined org. layers were dried ($MgSO_4$), concentrated, and the residue was purified by FC (SiO_2; CH_2Cl_2/MeOH 10:1): 110 mg (82%) of **11**. Red amorphous solid. IR (ATR): 3074, 3021 (*m*, C–H, arom.); 2969, 2932 (*m*, C–H, aliphat.); 1709 (*s*, C=O); 1635 (*m*, C=N$^+$); 1616, 1517, 1460 (*s*, C=C, arom.); 1155, 1105 (*s*, C–O); 755, 747 (*m*, 1,2-disubst. arom.). ^{1}H-NMR (400 MHz, $CDCl_3$/TFA): 9.88 (*s*, H–C(5)); 9.50 (*s*, H–C(15)); 9.15 (*d*, $J = 1.1$, 1 H); 8.73 (*d*, $J = 8.4$, H–C(10)); 8.53–8.51 (*m*, 2 H); 8.41–8.40 (*m*, 2 H); 8.27–8.23 (*m*, 1 H); 5.23 (br. *s*, $H_2C(7)$); 4.60 (*q*, $J = 7.1$, CH_2Me); 3.80 (br. *s*, $H_2C(8)$); 3.14 (*s*, Me(16)); 1.53 (*t*, $J = 7.1$, CH_2Me). EI-MS: 368 (100, [$M-H$]$^+$), 339 (82, [$M-EtOH$]$^+$), 293 (19, $C_{21}H_{13}N_2^+$), 156 (24, $C_{11}H_{10}N^+$), 128 (41, $C_9H_6N^+$).

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