

## Bishydrocotarnines – Stereochemical Aspects

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The bishydrocotarnines **2a** and **2b**<sup>1),\*\*)</sup> were converted into the urethanes **9a** and **9b** and into the carbamates **10a** and **10b**, which in turn were split to yield the sec. amines **11a** and **11b**. Cyclisation with diethyl oxalate led to the diketopiperazines **12a** and **12b**. Contrary to **9b**, compound **9a** was resolved into enantiomers on a cellulose carbamate column. This indicates that **9a** is the D, L- and **9b** is the meso form. NMR spectra of **12a** and **12b** led to an analogous conclusion.

### Bishydrocotarnine – Stereochemische Gesichtspunkte

Die Bishydrocotarnine **2a** und **2b**<sup>1)</sup> werden in die Urethane **9a** und **9b** bzw. in die Carbamate **10a** und **10b** umgewandelt. Spaltung von **10a** bzw. **10b** in die sek. Amine **11a** und **11b** und deren Cyclisierung führen zu den Diketopiperazinen **12a** und **12b**. **9a** ließ sich im Gegensatz zu **9b** an einer Cellulosecarbamatsäule in Enantiomere spalten. Danach ist **9a** die D, L-, **9b** die meso-Form. NMR-Spektren von **12a** und **12b** führen zu derselben Schlußfolgerung.

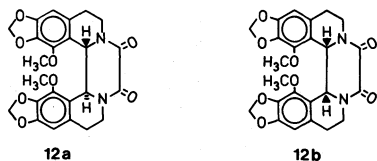
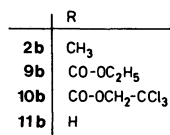
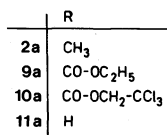
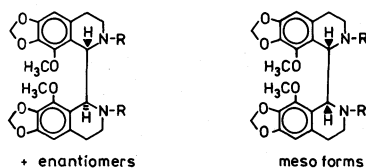
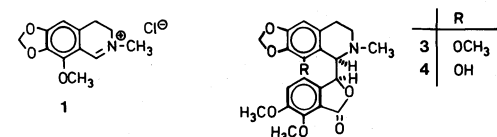
In 1911, *Freund* and *Kupfer*<sup>1)</sup> described the formation of two isomeric bishydrocotarnines **2** by reductive dimerisation of cotarnine (**1**). This reduction occurs when a bulky *Grignard* reagent obtained from 1,2-dibromoethane was used, whilst small monofunctional *Grignard* reagents added smoothly to the carbenium-iminium-ion in **1**. *Freund* et al.<sup>1)</sup> separated the isomers of **2** and elucidated their structures unequivocally. The authors recognized that these symmetric molecules should exist as two enantiomers and as one meso form and tried to resolve one of the **2**-isomers by formation of diastereomeric salts. When all their efforts failed they concluded that both isomers should be meso forms which arise by combination of two *cis*- and of two *trans*-forms of the tetrahydropyridine-moiety<sup>1)</sup>. In this context "*cis*" and "*trans*" refer to H at C-1 (C-1') and CH<sub>3</sub> at the adjoining N-atoms (see<sup>1)</sup>, page 16).

According to *Dreiding* models, *Freund's* meso forms<sup>1)</sup> nowadays might be regarded as two conformers, the one with a bi-equatorial bond between C-1 and C-1' and axial methyl-groups, the other one with equatorial CH<sub>3</sub>-groups and a bi-axial linkage of C-1

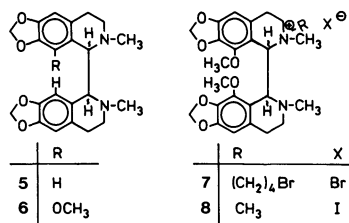
<sup>\*)</sup> Dedicated to Prof. Dr. *Maurice Shamma*, The Pennsylvania State University, on the occasion of his 60th anniversary.

<sup>\*\*)</sup> Index **a**: racemates; index **b**: meso forms.

with C-1'. When *Freund* and *Kupfer*<sup>1)</sup> heated the minor isomer of **2** to temp. exceeding the m. p., it was converted to the major isomer. This was explained as a thermal *cis-trans*-rearrangement. We became aware of *Freund*'s isomers when we tried to cleave *n*-narcotine (**3**) regioselectively by various bases to get narcotoline (**4**). **3** was recovered nearly quantitatively, **2a** and **2b** arose as minor products besides **1** and opianic acid (6-formyl-2,3-dimethoxybenzoic acid). As already stated by *Freund*<sup>1)</sup>, **2a** and **2b** have the same m. p. (163°), the mixed m. p. is depressed significantly. The isomers are easily differentiated by tlc on alumina (ethyl acetate): **2a** exhibits a low, **2b** a high *rf*-value.



Contrary to *Freund*<sup>1)</sup> we found that both isomers are mutually converted to each other by melting them. Up to 150° we did not observe isomerisation in solution (*d*<sub>5</sub>-nitrobenzene, NMR-control); heating **2a** or **2b** to 190° (tetralin) led to mutual conversion. For differentiation between the possibilities of rotamers or products obtained from bond breaking and recombination, we synthesized the corresponding 8,8'-desmethoxybishydrocotarnines (1,1'-bishydrodrastinines **5**<sup>2)</sup>) as a mixture of stereoisomers with very similar *rf*-values. When we melted equal quantities of **5** and **2** (1:1 mixture of **2a** and **2b**), we obtained the "mixed" bistetrahydroisoquinoline **6** (scheme 2) besides the **5**-isomers, **2a** and **2b** (tlc). The FD-mass spectrum revealed molecular ions at *m/z* 440 (**2a**, **2b**), *m/z* 380 (**5**) and *m/z* 410 (**6**), indicating that at least in part bond breaking and recombination had occurred, so favouring *Freund*'s assumption of a pinacol type formation of **2a** and **2b**<sup>1)</sup>. Moreover, this experiment points towards diastereoisomerism of **2a** and **2b**.



**2a** and **2b** could not be resolved on microcrystalline cellulose triacetate<sup>3</sup>, probably on account of insufficient solubility in suitable solvents (EtOH; CHCl<sub>3</sub>; EtOH 1:9). Therefore, we decided to block the rotation around the C-1/C-1'-bond by construction of rigid cyclic derivatives of **2a** and **2b** in order to associate J (H-1/H-1') with **2a** and **2b**, respectively. Formation of bisquaternary cyclic derivatives failed: heating **2a** with 1,4-dibromobutane led to the mono-quaternized compound **7**. In this context it is noteworthy that *Freund*<sup>1</sup>) as well as ourselves obtained the monomethylated derivative **8** from **2a** even with an excess of CH<sub>3</sub>I under vigorous conditions. So we adopted *Dreiding's* approach<sup>4</sup>) which he had elaborated for a similar problem, i. e. formation of the pertinent 2,3-diketopiperazines **12a** and **12b**.

For twofold N-demethylation of **2a** and **2b** we slightly varied *Lee's* method<sup>5</sup>) for N-demethylation of tert. benzylamines with ethyl chloroformate (ECF) or β,β,β-trichloroethyl chloroformate. Heating **2a** and **2b** with a 5-fold molar excess ECF afforded the urethanes **9a** and **9b**. In order to rule out an isomerisation, **9a** and **9b** were reconverted to **2a** and **2b**, respectively, by LiAlH<sub>4</sub><sup>6</sup>): no isomerisation had occurred.

Various racemic compounds have been resolved by HPLC on cellulose triphenylcarbamate coated on silica gel<sup>7</sup>). This chiral stationary phase resolved **9a** partially into enantiomers. Cellulose tris-(p-chlorophenylcarbamate)<sup>8</sup>) was found to be a more effective chiral stationary phase for **9a** and base-line separation of the enantiomers was attained. The basic compound, **2a**, was not resolved to a detectable extent on the two cellulose phenylcarbamate columns showing a very broad peak with a long tailing. Similar results have been observed in the resolution of some amines on the columns<sup>7</sup>). This experiment clearly indicates that **9a** is the racemate, **9b** is the meso form.

The 250 MHz-<sup>1</sup>H-spectra of **9a** and **9b** indicate the presence of at least three different species – rotamers? – which leads to trebling of most of the signals; the H<sub>3</sub>C-CH<sub>2</sub>-regions are shown in fig. 1.

Therefore, addition of (+)-Eu(facam)<sub>3</sub> did not allow a clear-cut decision between the racemate and the meso form of **9**.

Whilst ethyl urethanes of type **9** can be hydrolyzed only under drastic conditions<sup>9</sup>), β,β,β-trichloroethyl carbamates are converted to sec. amines by mild reductive cleavage<sup>9</sup>). When we reacted **2a** and **2b** with Cl-CO-O-CH<sub>2</sub>-CCl<sub>3</sub>, the urethanes **10a** and **10b** arose, which were split to the amines **11a** and **11b** by Zn/acetic acid. Twofold amidation with diethyl oxalate<sup>4</sup>) afforded the diketopiperazines **12a** and **12b**, respectively. These molecules also provide an unequivocal differentiation between the precursors **2a** and **2b**: the racemate **12a** from **2a** shows a sharp singlet at δ = 5.16 ppm of H-1 and

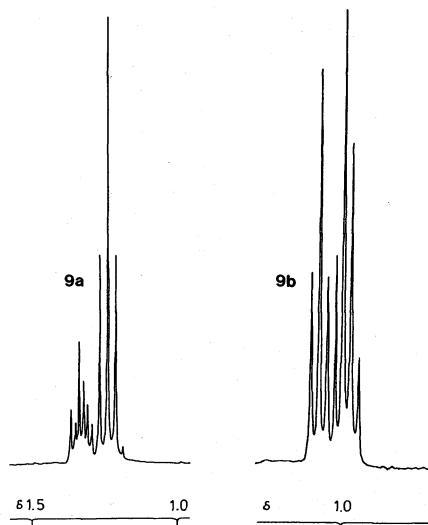


Fig. 1:  $\text{H}_3\text{C}-\text{CH}_2$ -multiplets of **9a** and **9b**

H-1', whilst H-1 and H-1' (or vice versa) in **12b** (meso form from **2b**) resonate at 5.49 and 5.66 ppm, respectively, with  $J = 3.72$  Hz.

We are grateful to Prof. Dr. A. Mannschreck, Regensburg, for helpful discussions and to Mr. Kawashima for skilful experimental help in chromatographic resolution. The financial support of Deutsche Forschungsgemeinschaft is gratefully acknowledged.

## Experimental Part

*Apparatus*: mp (uncorr.): apparatus according to Dr. Tottoli; *elementary analysis*: Microanalytical Laboratory (G. Wandinger) of the University of Regensburg. – *IR*: Beckman Acculab III. –  $^1\text{H-NMR}$ : Varian EM 390 (90 MHz), Bruker (250 MHz),  $35^\circ$ , TMS int. stand. – *UV*: Uvikon 810, MeOH Uvasol "Merck". – *MS*: Varian MAT CH5, excitation energy 70 eV, if not stated otherwise.

### Cotarnine base

It was produced by modifying Bruns' method<sup>10</sup> as follows: 4.13 g (10 mmol) narcotine base (**3**) in 40.0 g  $\text{HNO}_3$  (18 %) was stirred at  $50^\circ$  ( $\pm 2^\circ$ ) until **3** had disappeared (tlc,  $\text{SiO}_2$ , MeOH). After cooling the filtrate was chilled with ice and basified with 40 % KOH. The precipitate formed was filtered off immediately and dried at  $40^\circ$  (0.1 torr): yield 2.10 g (88 %). From benzene: colourless needles, yield 1.87 g (79 %), mp.  $132^\circ$  (lit.<sup>10</sup>:  $132^\circ$ ). – *IR* (KBr):  $1620\text{ cm}^{-1}$  (C=C, arom.). –  $^1\text{H-NMR}$  (90 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 2.25–3.25 (m; 4H,  $\text{CH}_2$ ), 2.60 (s; 3H,  $\text{NCH}_3$ ), 4.10 (s; 3H,  $\text{OCH}_3$ ), 5.48 (s; 1H, C-1), 5.95 (s; 2H,  $\text{O}-\text{CH}_2-\text{O}$ ), 6.40 (s; 1H, arom.).

### Cotarnine chloride (**1**) from cotarnine base

To an ice cold mixture of 2.0 g (8.5 mmol) crude cotarnine base and 5 ml absol. EtOH, 30 % HCl in EtOH was added drop by drop until the colour turned yellow (pH 5). Then 19 ml ice cold absol. acetone

was added. After 2 h at  $-10^{\circ}$  **1** was collected; yield 1.8 g (85 %), faint yellow crystals, m. p.  $197^{\circ}$  (decomp.), (lit.<sup>11</sup>  $197^{\circ}$ ). – IR (KBr): 1670 (C=N), 1615  $\text{cm}^{-1}$  (C=C, arom.). –  $^1\text{H-NMR}$  (90 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  (ppm) = 2.70 (t; 2H,  $\text{CH}_2$  of C-4), 3.29 (s; 3H,  $\text{NCH}_3$ ), 3.49 (t; 2H,  $\text{CH}_2$  of C-3), 3.72 (s; 3H,  $\text{OCH}_3$ ), 5.67 (s; 2H, O- $\text{CH}_2$ -O), 6.22 (s; 1H, arom.), 8.49 (s; 1H, C-1).

### Bishydrocotarnines **2a** and **2b**

0.4 g 1,2-Dibromoethane was added to 2.0 g (82 mmol) Mg in 60 ml absol. ether. After addition of a catalytic amount  $\text{I}_2$  the *Grignard* reaction was started by gentle heating. Then 7.6 g dibromoethane (altogether 42 mmol) were added drop by drop within 10 min so that the ether was boiling gently, the mixture was refluxed for 1 h and cooled to r.t. 5.1 g (20 mmol) well ground **1** was added in parts, then refluxing was continued for 1 h. After decomposing with water, the solvent was decanted and the residue extracted thrice with 50 ml  $\text{CH}_2\text{Cl}_2$  each. After drying the organic phases over  $\text{Na}_2\text{SO}_4$ , the solvents were evaporated i. vac. to yield 4.3 g (98 %) brownish powder, which was separated by column chromatography (cc) (Alumina Woelm N, act. II, ethyl acetate, later on methanol): **2b**: rf = 0.55; 1.8 g (41 %), rhombic crystals, mp.  $163$ – $164^{\circ}$  (EtOH);  $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_6$  (440.5) Calc. C 65.4 H 6.40 N 6.4. Found C 65.3 H 6.29 N 6.4. – UV:  $\lambda$  max (log  $\epsilon$ ) = 213 (4.6), 260 (3.2), 285 nm (3.5). – IR (KBr): 1625  $\text{cm}^{-1}$  (C=C, arom.). –  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 2.36–2.48 (m; 4H,  $\text{CH}_2$ ), 2.44 (s; 6H,  $2 \times \text{NCH}_3$ ), 2.56–2.67 (m; 2H,  $\text{CH}_2$ ), 2.84–2.98 (m; 2H,  $\text{CH}_2$ ), 3.69 (s; 6H,  $2 \times \text{OCH}_3$ ), 4.15 (s; 2H, C-1 and C-1'), 5.81, 5.83 (AB-system; 4H,  $2 \times \text{O-CH}_2\text{-O}$ ,  $J = 1.44$  Hz), 6.28 (s; 2H, arom.). – MS (FI): 441 (M + H)<sup>+</sup>, 440 M<sup>+</sup>, 220 (M/2)<sup>+</sup>.

**2a**: rf = 0.33; 1.2 g (27 %), rhombic crystals, mp.  $163$ – $164^{\circ}$  (EtOH).  $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_6$  (440.5) Calc. C 65.4 H 6.40 N 6.4. Found C 65.4 H 6.38 N 6.4. – UV:  $\lambda$  max (log  $\epsilon$ ) = 212 (4.6), 260 (3.1), 285 nm (3.4). – IR (KBr): 1625  $\text{cm}^{-1}$  (C=C, arom.). –  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 2.26 (s; 6H,  $2 \times \text{NCH}_3$ ), 2.58–2.84 (m; 6H,  $\text{CH}_2$ ), 3.49–3.65 (m; 2H,  $\text{CH}_2$ ), 3.62 (s; 6H,  $2 \times \text{OCH}_3$ ), 3.99 (s; 2H, C-1 and C-1'), 5.72, 5.76 (AB-system; 4H,  $2 \times \text{O-CH}_2\text{-O}$ ,  $J = 1.43$  Hz), 6.28 (s; 2H, arom.). – MS (FI): 441 (M + H)<sup>+</sup>, 440 M<sup>+</sup>, 220 (M/2)<sup>+</sup>.

### Bishydrodrastines (**5**)

The mixture of the bishydrodrastines (**5**) was prepared following *Freund*<sup>2</sup>). The mixture was not separated (rf = 0.67 and 0.57) and was used for the cross-over experiment (see below) as such.

### Resolution of **9a** into enantiomers

**9a**, dissolved in  $\text{CHCl}_3$ , was resolved on a cellulose tris-(*p*-chlorophenylcarbamate) column ( $25 \times 0.46$  cm), prepared by the previous method<sup>7</sup>), using a Jasco-TRIROTAR-II instrument equipped with detectors Jasco-UV-100-III (254 nm), 1 mm cell, and Jasco-DIP-180C (Hg),  $50 \times 2$  mm cell. Eluent: hexane/2-propanol/chloroform (7:1:2-vol); flow rate: 0.5 ml/min; pressure: 22  $\text{kg/cm}^2$ ; temp.:  $25^{\circ}$ .

### Cross-over experiment

20 mg **2a**, 20 mg **2b** and 40 mg **5** were mixed thoroughly by grinding and heated for 180 sec under  $\text{N}_2$  in an oil bath of  $180^{\circ}$ . The mixture melted and turned brown. After cooling the cake was dissolved in  $\text{CHCl}_3$ , degradation products were separated by cc (Alumina Woelm N act. II, ethyl acetate). After evaporation i. vac. and drying ( $40^{\circ}$ , 0.1 torr): 55 mg of a yellowish powder, which was used for ms.

### *N*-Mono( $\delta$ -bromo-*n*-butyl)-bishydrocotarninium bromide (**7a**)

440 mg **2a** in 3 ml 1,4-dibromo-*n*-butane was heated to  $110^{\circ}$  for 10 min. Unreacted dibromobutane was removed i. vac., the residue was recrystallized from absol. acetone: 525 mg (80 %), mp.  $197^{\circ}$ .

$C_{28}H_{36}Br_2N_2O_6$  (656.4). Calc. C 51.2 H 5.53 N 4.3. Found C 51.4 H 5.60 N 4.3. – IR (KBr):  $1630\text{ cm}^{-1}$  (C=C arom.). –  $^1\text{H-NMR}$  (90 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 1.75–2.14 (m; 4H,  $\text{CH}_2$ ), 2.22–2.54 (m; 1H,  $\text{CH}_2$ ), 2.38 (s; 3H,  $\text{NCH}_3$ ), 2.79–3.54 (m; 8H,  $\text{CH}_2$ ), 3.64 (s; 3H,  $^+\text{NCH}_3$ ), 3.72, 3.74 ( $2 \times$  s; 6H,  $2 \times \text{OCH}_3$ ), 3.70–4.77 (m; 5H, C-1 and C-1', 3H of  $\text{CH}_2$ -groups), 5.60, 5.66 (AB-system; 2H,  $\text{O-CH}_2\text{-O}$ ,  $J = 0.74\text{ Hz}$ ), 5.72, 5.78 (AB-system; 2H,  $\text{O-CH}_2\text{-O}$ ,  $J = 0.74\text{ Hz}$ ), 6.21, 6.27 ( $2 \times$  s; 2H, arom.).

*N-Mono( $\delta$ -bromo-*n*-butyl)-bishydrocotarninium bromide (7b)*

**7b** was prepared analogously in 85 % yield, m. p.  $196\text{--}197^\circ$ .  $C_{28}H_{36}Br_2N_2O_6$  (656.4). Calc. C 51.2 H 5.53 N 4.3. Found C 51.2 H 5.57 N 4.2. – IR (KBr):  $1630\text{ cm}^{-1}$  (C=C, arom.). –  $^1\text{H-NMR}$  (90 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 1.55–2.55 (m; 8H,  $\text{CH}_2$ ), 2.38 (s; 3H,  $\text{NCH}_3$ ), 2.95–3.55 (m; 6H,  $\text{CH}_2$ ), 3.32 (s; 3H,  $\text{OCH}_3$ ), 3.78 (s; 3H,  $^+\text{NCH}_3$ ), 4.05–4.78 (m; 3H,  $\text{CH}_2$  and 1H of C-1 or C-1'), 4.23 (s; 3H,  $\text{OCH}_3$ ), 5.13 (s; 1H, C-1 or C-1'), 5.80–6.01 (m; 4H,  $\text{O-CH}_2\text{-O}$ , 2 overlapping AB-systems), 6.29, 6.40 ( $2 \times$  s; 2H, arom.).

*N-Monomethyl-bishydrocotarninium iodide (8a)*

44Vmg (1 mmol) **2a** in 3 ml  $\text{CH}_3\text{I}$  were refluxed for 2 h. – The amorphous precipitate was crystallized from absol. EtOH; 460 mg **8a** (79 %), mp.  $232\text{--}233^\circ$  (lit.<sup>1)</sup>:  $233^\circ$ ). – IR (KBr):  $1630\text{ cm}^{-1}$  (C=C, arom.). –  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 2.31–2.48 (m; 1H,  $\text{CH}_2$ ), 2.38 (s; 3H,  $\text{NCH}_3$ ), 2.80–3.14 (m; 3H,  $\text{CH}_2$ ), 3.18–3.47 (m; 1H,  $\text{CH}_2$ ), 3.39 (s; 3H,  $^+\text{NCH}_3$ ), 3.60–3.88 (m; 1H,  $\text{CH}_2$ ), 3.70 (s; 3H,  $^+\text{NCH}_3$ ), 3.74, 3.76 ( $2 \times$  s, 6H,  $2 \times \text{OCH}_3$ ), 3.95–4.13 (m; 1H,  $\text{CH}_2$ ), 3.99 (d; 1H of C-1 or C-1',  $J = 6.25\text{ Hz}$ ), 4.50–4.64 (m; 1H,  $\text{CH}_2$ ), 4.52 (d; 1H of C-1 or C-1',  $J = 6.25\text{ Hz}$ ), 5.63, 5.67 (AB-system; 2H,  $\text{O-CH}_2\text{-O}$ ,  $J = 1.34\text{ Hz}$ ), 5.74, 5.79 (AB-system; 2H,  $\text{O-CH}_2\text{-O}$ ,  $J = 1.34\text{ Hz}$ ), 6.23, 6.29 ( $2 \times$  s; 2H, arom.).

*N-Monomethyl-bishydrocotarninium iodide (8b)*

**8b** was prepared analogously from 440 mg **2b**; 480 mg (82 %), mp.  $233^\circ$  (lit.<sup>1)</sup>:  $233^\circ$ ). – IR (KBr):  $1630\text{ cm}^{-1}$  (C=C, arom.). –  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 1.61–1.83 (m; 1H,  $\text{CH}_2$ ), 1.97–2.08 (m; 1H,  $\text{CH}_2$ ), 2.29–2.45 (m; 1H,  $\text{CH}_2$ ), 2.40 (s; 3H,  $\text{NCH}_3$ ), 2.55–2.73 (m; 1H,  $\text{CH}_2$ ), 3.11–3.21 (m; 2H,  $\text{CH}_2$ ), 3.28 (s; 3H,  $\text{OCH}_3$ ), 3.31 (s; 3H,  $^+\text{NCH}_3$ ), 3.71 (s; 3H,  $^+\text{NCH}_3$ ), 4.21 (s; 3H,  $\text{OCH}_3$ ), 4.32–4.47 (m; 1H,  $\text{CH}_2$ ), 4.44 (s; 1H, C-1 or C-1'), 4.48–4.64 (m; 1H,  $\text{CH}_2$ ), 4.87 (s; 1H, C-1 or C-1'), 5.86–5.96 (m; 4H,  $\text{O-CH}_2\text{-O}$ , 2 overlapping AB-systems), 6.29, 6.40 ( $2 \times$  s, 2H, arom.).

Of course, the index “b” does not indicate “meso” in **7b** and **8b** and is used only for systematic reasons.

*5,5'-Bis-(*N*-ethoxycarbonyl-4-methoxy-5,6,7,8-tetrahydro)-1,3-dioxolo[4,5-*g*]isoquinolines (9a and 9b)*

440 mg (1 mmol) **2a**, 0.96 ml freshly distilled ethyl chloroformate and 30 mg  $\text{K}_2\text{CO}_3$  were refluxed in 10 ml absol. benzene for 48 h. After evaporation and drying i. vac. the oily residue was purified by cc ( $\text{SiO}_2$ , chloroform/ether 3:1-vol.): 445 mg (80 %) **9a**, m. p.  $207^\circ$  (EtOH), needles. –  $C_{28}H_{32}N_2O_{10}$  (556.6) Calc. C 60.4 H 5.80 N 5.0. Found C 60.4 H 5.88 N 5.0. – UV (MeOH):  $\lambda$  max (log  $\epsilon$ ) = 218 (4.5), 260 (3.2), 283 nm (3.5). – IR (KBr):  $1690\text{ (C=O)}$ ,  $1630\text{ cm}^{-1}$  (C=C, arom.). –  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 1.18–1.36 (m; 6H,  $2 \times \text{CH}_2\text{CH}_3$ ), 2.65–2.83 (m; 2H,  $\text{CH}_2$ ), 3.15–3.66 (m; 4H,  $\text{CH}_2$ ), 3.35, 3.38, 3.40 (3s; 6H,  $2 \times \text{OCH}_3$ ), 3.74–3.95 (m; 2H,  $\text{CH}_2$ ), 3.99–4.25 (m; 4H,  $\text{CH}_2$ ), 5.44–5.71 ( $6 \times$  s; 2H, C-1 and C-1'), 5.74–5.85 (m; 4H,  $2 \times \text{O-CH}_2\text{-O}$ ), 6.40, 6.42 ( $2 \times$  s; 2H, arom.). – MS (FD):  $556\text{ M}^+$ ,  $278\text{ (M/2)}^+$ .

**9b** was prepared analogously: 290 mg (52 %) **9b**, m. p.  $258^\circ$  (EtOH), lozenge-shaped crystals.  $C_{28}H_{32}N_2O_{10}$  (556.6) Calc. C 60.4 H 5.80 N 5.0. Found C 60.1 H 5.83 N 5.0. – UV:  $\lambda$  max (log  $\epsilon$ ) = 218 (4.5), 260 (3.2), 283 nm (3.5). – IR (KBr):  $1680\text{ (C=O)}$ ,  $1630\text{ cm}^{-1}$  (C=C, arom.). –  $^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) = 0.91–1.12 (overlapping t (fig. 1), 6H,  $2 \times \text{-CH}_2\text{CH}_3$ ), 2.67–2.85 (m; 2H,  $\text{CH}_2$ ), 3.14–3.62 (m; 6H,  $\text{CH}_2$ ), 3.73–3.92 (m; 4H,  $\text{CH}_2$ ), 4.01, 4.02, 4.03 and 4.04 (4s; 6H,  $2 \times \text{OCH}_3$ ),

5.49–5.75 (6 × s; 2H, C-1 and C-1'), 5.77–5.90 (m; 4H, 2 × O-CH<sub>2</sub>-O), 6.35–6.50 (m; 2H, arom.). – MS (FD): 556 M<sup>+</sup>, 278 (M/2)<sup>+</sup>.

*5,5'-Bis-(N-β,β,β-trichloroethoxycarbonyl-4-methoxy-5,6,7,8-tetrahydro)-1,3-dioxolo[4,5-g]-isoquinolines (10a and 10b)*

440 mg (1 mmol) **2a**, 0.3 ml (2.2 mmol) β,β,β-trichloroethyl chloroformate, 30 mg (0.21 mmol) K<sub>2</sub>CO<sub>3</sub> and 3 ml absol. toluene were heated in an oil bath at 110° for 48 h. After evaporation and drying (60°, 0.1 torr) crude **10a** was purified by cc (Alumina Woelm N act. II, chloroform/ether 1:1-vol.): 305 mg (40 %) white foam, which could not be crystallized. C<sub>28</sub>H<sub>26</sub>Cl<sub>6</sub>N<sub>2</sub>O<sub>10</sub> (763.2). Calc. C 44.1 H 3.43, N 3.7. Found C 44.8 H 3.74 N 3.6. – UV (CH<sub>3</sub>CN): λ max (log ε) = 220 (4.2), 260 (3.1), 284 nm (3.5). – IR (KBr): 1720 (C=O), 1630 cm<sup>-1</sup> (C=C, arom.). – <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ (ppm) = 2.52–3.00 (m; 2H, CH<sub>2</sub>), 3.05–3.64 (m; 4H, CH<sub>2</sub>), 3.28, 3.30, 3.35 (3 × s; 6H, 2 × OCH<sub>3</sub>), 3.65–4.23 (m; 2H, CH<sub>2</sub>), 4.47, 4.95 (AB-system, 2H, CH<sub>2</sub>, J<sub>AB</sub> = 12.0 Hz, the low field part shows additional doublet splitting, <sup>2</sup>J = 7.5 Hz), 4.63 (s; 2H, CH<sub>2</sub>), 5.52–5.84 (m; 6H, 2 × O-CH<sub>2</sub>-O and 2H of C-1 and C-1'), 6.32, 6.37 (2 × s; 2H, arom.). – MS (FAB(-), 18-crown-6/pyridine): calc. M (<sup>35</sup>Cl) = 760; found m/z 795; 797; 799; 801; 803; 805; (807), corresponding to (M + Cl)<sup>-</sup>.

*Preparation of 10b:* 440 mg (1 mmol) **2b**, 0.3 ml (2.2 mmol) β,β,β-trichloroethyl chloroformate and 30 mg (0.21 mmol) K<sub>2</sub>CO<sub>3</sub> were refluxed in absol. benzene for 48 h. After evaporation and drying (see **10a**) **10b** was purified by cc on silica (chloroform/ether 3:1-vol): 504 mg (66 %) yellow oil, which was boiled with a little ether: 340 mg (44 %) colourless crystals, mp. 251°. Recrystallization from glacial acetic acid: 320 mg (42 %) double pyramids, mp. 256–257°. C<sub>28</sub>H<sub>26</sub>Cl<sub>6</sub>N<sub>2</sub>O<sub>10</sub> (763.2). – Calc. C 44.1 H 3.43 N 3.7. Found C 44.0 H 3.58 N 3.6. – UV (CH<sub>3</sub>CN): λ max: (log ε) = 220 (4.2), 260 (3.1), 284 nm (3.5). – IR (KBr): 1715 (C=O), 1630 cm<sup>-1</sup> (C=C, arom.). – <sup>1</sup>H-NMR (90 MHz, CDCl<sub>3</sub>): δ (ppm) = 2.51–3.05 (m; 2H, CH<sub>2</sub>), 3.10–3.62 (m; 4H, CH<sub>2</sub>), 3.70–4.35 (m; 2H, CH<sub>2</sub>), 4.00, 4.03 (2 × s; 6H, 2 × OCH<sub>3</sub>), 4.66–4.95 (m; 2H, CH<sub>2</sub>), 5.71, 5.73 (2s; 2H, C-1 and C-1') 5.81–5.95 (m; 4H, 2 × O-CH<sub>2</sub>-O), 6.36, 6.38, 6.40 (m; 2H, arom.). – MS (FD, acetone): calc. M (<sup>35</sup>Cl) = 760; found 760 (M<sup>+</sup>), 380 (M/2)<sup>+</sup>.

*5,5'-Bis-(4-methoxy-5,6,7,8-tetrahydro)-1,3-dioxolo[4,5-g]-isoquinolines (11a and 11b)*

200 mg (0.26 mmol) **10b** and 340 mg activated Zn-powder<sup>12)</sup>, were slightly heated in 5 ml glacial acetic acid, until strong evolution of H<sub>2</sub> occurred. Then the mixture was stirred at r. t. for 4 h, 3 ml H<sub>2</sub>O were added. The filtrate was basified by KOH and extracted with chloroform. Drying and evaporation i. vac. led to an oil which was dissolved in EtOH. Addition of a few drops conc. HCl (pH 5) and scratching led to white needles.

**11b**-di-HCl: 110 mg (87 %), m. p. 220–221° (decomp.). – <sup>1</sup>H-NMR (90 MHz, CF<sub>3</sub>COOH): δ (ppm) = 2.88–4.34 (m; 8H, CH<sub>2</sub>), 4.17 (s; 6H, 2 × OCH<sub>3</sub>), 5.34 (s; 2H, C-1 and C-1'), 6.00 (degenerated AB-system; 4H, 2 × O-CH<sub>2</sub>-O), 6.57 (s; 2H, arom.), 6.74–7.27 (broad s; 2H, 2 × HN), 8.27–8.83 (broad s; 2H, 2 × HN). The solution of this salt in a little water was basified (KOH) and extracted with chloroform. Drying (Na<sub>2</sub>SO<sub>4</sub>) and evaporation produced a colourless oil, which crystallized slowly: 85 mg (79 %) white material, mp. 192°–193° (EtOH). C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub> (412.4). Calc. C 64.1 H 5.87 N 6.8. Found C 64.2 H 6.01 N 6.7. – UV (CH<sub>3</sub>CN): λ max (log ε) = 223 (4.2), 260 (3.2), 285 nm (3.6). – IR (KBr): 1625 cm<sup>-1</sup> (C=C, arom.). – <sup>1</sup>H-NMR (90 MHz, CDCl<sub>3</sub>): δ (ppm) = 2.02 (s broad; 2H, 2 × HN, exchangeable with D<sub>2</sub>O), 2.33–3.22 (m; 8H, CH<sub>2</sub>), 3.67 (s; 6H, 2 × OCH<sub>3</sub>), 4.33 (s; 2H, C-1 and C-1'), 5.72 (degenerated AB-system; 4H, 2 × O-CH<sub>2</sub>-O), 6.20 (s; 2H, 2 × H, arom.). – MS (FAB(+), glycerol): 414 (M + 2H)<sup>+</sup>, 413 (MH<sup>+</sup>), 207 (M/2 + H)<sup>+</sup>, 206 (M/2)<sup>+</sup>.

*Preparation of 11a: analogous to that of 11b*

**11a**-di-HCl: 104 mg (82 %) white needles, mp. 220°–221° (decomp.) – <sup>1</sup>H-NMR (90 MHz, CF<sub>3</sub>COOH): δ (ppm) = 2.80–4.28 (m; 8H, CH<sub>2</sub>), 3.98 (s; 6H, 2 × OCH<sub>3</sub>), 5.68 (s broad; 2H, C-1 and C-1'), 5.85 (s broad; 4H, 2 × O–CH<sub>2</sub>–), 6.43 (s; 2H, 2 × H, arom.), 7.98–8.78 (broad s; 4H, 4 HN).

Corresponding base **11a**; mp. 193°–194° (EtOH), 79 mg (73 %). C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub> (412.4) Calc. C 64.1 H 5.87 N 6.8. Found C 63.9 H 5.91 N 6.7. – UV (CH<sub>3</sub>CN): λ max (log ε) = 229 (4.1), 260 (3.2), 285 nm (3.6). – IR (KBr): 1625 cm<sup>-1</sup> (C=C, arom.). – <sup>1</sup>H-NMR (90 MHz, CDCl<sub>3</sub>): δ (ppm) = 1.80 (s broad; 2H, 2 × HN, exchangeable with D<sub>2</sub>O), 2.35 – (s; 6H, 2 × OCH<sub>3</sub>), 4.86 (s; 2H, C-1 and C-1'), 5.77–5.90 (m; 4H, 2 × O–CH<sub>2</sub>–O), 6.25 (s; 2H, 2 × H, arom.). – MS (FAB (+), glycerol): 413 (MH<sup>+</sup>), 206 (M/2)<sup>+</sup>.

*1,2,7,8,12b,12c-Hexahydro-13,14-dimethoxy-pyrazino[2,1-a:3,4-a]di-(1,3-dioxolo[4,5-g]isoquinoline)-4,5-diones (12a and 12b)*

A suspension of 85 mg (0.2 mmol) **11a** and 150 mg (1.0 mmol) diethyl oxalate in 3.0 ml absol. EtOH was heated under reflux for 2.5 h. At first a clear solution is formed, later on **12a** precipitated partially. After 14 h at –20° the precipitation was complete. Washing with cold EtOH led to pure **12a** (white needles) mp. 360° (decomp., EtOH). C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>8</sub> (466.4) Calc. C 61.8 H 4.75 N 6.0. Found C 61.6; H 4.82 N 6.0. UV (MeOH): λ max (log ε) = 216 (4.6), 269 (3.5), 279 nm (3.5). – IR (KBr): 1695 (C=O), 1680 (CO), 1625 cm<sup>-1</sup> (C=C, arom.). – <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>): δ (ppm) = 2.68–2.98 (m; 6H, CH<sub>2</sub>), 3.39 (s; 6H, 2 × OCH<sub>3</sub>), 4.85–4.97 (m; 2H, CH<sub>2</sub>), 5.16 (s; 2H, C-1 and C-1'), 5.82 (s; 4H, 2 × O–CH<sub>2</sub>–O), 6.38 (s; 2H, arom.). – MS (FD): = 466 M<sup>+</sup>, 233 (M/2)<sup>+</sup>.

**12b** was prepared analogously. Yield: 60 mg (63 %) small plates, mp. 273°–274° (EtOH). C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>8</sub> (466.4) Calc. C 61.8 H 4.75 N 6.0. Found C 61.4 H 4.80 N 6.0. – UV (MeOH): λ max (log ε) = 218 (4.4), 265 (3.5), 279 nm (3.6). – IR (KBr): 1680 (CO), 1620 cm<sup>-1</sup> (C=C, arom.). – <sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>): δ (ppm) = 2.64–3.14 (m; 4H, CH<sub>2</sub>), 3.24 (s; 3H, OCH<sub>3</sub>), 3.42–3.58 (m; 2H, CH<sub>2</sub>), 3.85 (s; 3H, OCH<sub>3</sub>), 4.10–4.28 (m; 2H, CH<sub>2</sub>), 5.50, 5.66 (2 × d, 2H, C-1 and C-1', J = 3.7 Hz), 5.81, 5.85 (AB-system, 2H, O–CH<sub>2</sub>–O, J = 1.41 Hz), 5.92, 5.93 (AB-system, 2H, O–CH<sub>2</sub>–O, J = 1.35 Hz), 6.40, 6.48 (2 × s; 2H, 2 × H arom.). – MS (FAB(+), 18-crown-6): = 468 (M + 2H)<sup>+</sup>, 467 (MH)<sup>+</sup>, 466 M<sup>+</sup>. – MS (FAB(-), 18-crown-6) = 466 M<sup>-</sup>, 465 (M–H)<sup>-</sup>.

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