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Bishydrocotarnines – Stereochemical Aspects

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The bishydrocotarnines **2a** and **2b**[1]**) 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**[1]) 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 Cellulosecarbamat-Säule 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*[1]) 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.[1]) 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[1]). In this context "*cis*" and "*trans*" refer to H at C-1 (C-1′) and CH_3 at the adjoining N-atoms (see[1]), page 16).

According to *Dreiding* models, *Freund*'s meso forms[1]) 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_3-groups and a bi-axial linkage of C-1

+) Dedicated to Prof. Dr. *Maurice Shamma*, The Pennsylvania State University, on the occasion of his 60th anniversary.

) Index **a: racemates; index **b**: meso forms.

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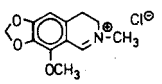
with C-1′. When *Freund* and *Kupfer*[1] heated the minor isomer of **2** to temp. exceeding the m. p., it was converted to the major isomer. This was explained as a thermal *cis-trans*-rearrangement. We became aware of *Freund*'s isomers when we tried to cleave α-narcotine **(3)** regioselectively by 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*[1], **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.



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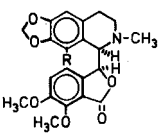
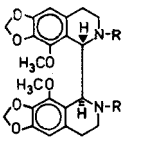
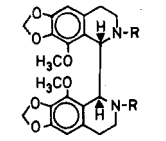


	R
3	OCH_3
4	OH



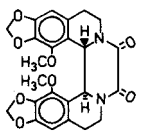
+ enantiomers

	R
2a	CH_3
9a	$CO\text{-}OC_2H_5$
10a	$CO\text{-}OCH_2\text{-}CCl_3$
11a	H

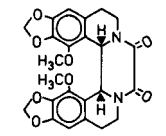


meso forms

	R
2b	CH_3
9b	$CO\text{-}OC_2H_5$
10b	$CO\text{-}OCH_2\text{-}CCl_3$
11b	H

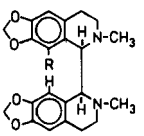


12a

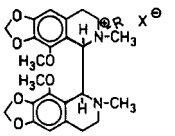


12b

Contrary to *Freund*[1] 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_5-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′-bishydrohydrastinines **5**[2]) 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**[1]. Moreover, this experiment points towards diastereoisomerism of **2a** and **2b**.



	R
5	H
6	OCH_3



	R	X
7	$(CH_2)_4Br$	Br
8	CH_3	I

2a and **2b** could not be resolved on microcrystalline cellulose triacetate[3], probably on account of insufficient solubility in suitable solvents (EtOH; $CHCl_3$: 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 compund **7**. In this context it is noteworthy that *Freund*[1] as well as ourselves obtained the monomethylated derivative **8** from **2a** even with an excess of CH_3I under vigorous conditions. So we adopted *Dreiding*'s approach[4] 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[5] 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 $LiAlH_4$[6]: no isomerisation had occurred.

Various racemic compounds have been resolved by HPLC on cellulose triphenylcarbamate coated on silica gel[7]. This chiral stationary phase resolved **9a** partially into enantiomers. Cellulose tris-(p-chlorophenylcarbamate)[8] 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[7]. This experiment clearly indicates that **9a** is the racemate, **9b** is the meso form.

The 250 MHz-^{1}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 $\underline{H_3C}$-CH_2-regions are shown in fig. 1.

Therefore, addition of (+)-Eu(facam)$_3$ 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[9], β,β,β-trichloroethyl carbamates are converted to sec. amines by mild reductive cleavage[9]. When we reacted **2a** and **2b** with Cl-CO-O-CH_2-CCl_3, the urethanes **10a** and **10b** arose, which were split to the amines **11a** and **11b** by Zn/acetic acid. Twofold amidation with diethyl oxalate[4] 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 $\delta = 5.16$ ppm of H-1 and

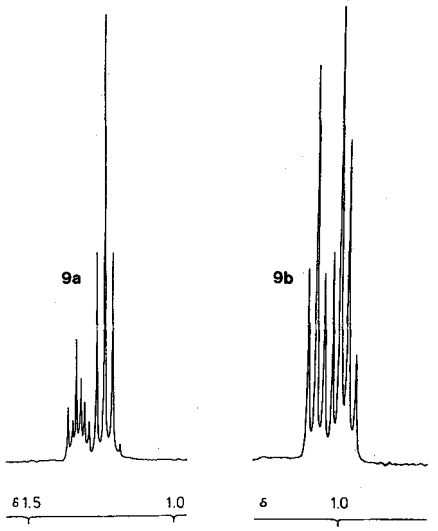


Fig. 1: $\underline{H_3C}$–CH_2-multiplets of **9a** and **9b**

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, whith 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}*H-NMR*: Varian EM 390 (90 MHz), Bruker (250 MHz), 35°, 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[10] as follows: 4.13 g (10 mmol) narcotine base **(3)** in 40.0 g HNO_3 (18 %) was stirred at 50° (+/–2°) until **3** had disappeared (tlc, 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° (0.1 torr): yield 2.10 g (88 %). From benzene: colourless needles, yield 1.87 g (79 %), mp. 132° (lit.[10]: 132°). – IR (KBr): 1620 cm^{-1} (C=C, arom.). – ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 2.25–3.25 (m; 4H, CH_2), 2.60 (s; 3H, NCH_3), 4.10 (s; 3H, OCH_3), 5.48 (s; 1H, C-1), 5.95 (s; 2H, O–CH_2-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° **1** was collected; yield 1.8 g (85 %), faint yellow crystals, m. p. 197° (decomp.), (lit.[11] 197°). – IR (KBr): 1670 (C=N), 1615 cm^{-1} (C=C, arom.). – ^{1}H-NMR (90 MHz, CD_3OD): δ (ppm) = 2.70 (t; 2H, CH_2 of C-4), 3.29 (s; 3H, NCH_3), 3.49 (t; 2H, CH_2 of C-3), 3.72 (s; 3H, OCH_3), 5.67 (s; 2H, O–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 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 CH_2Cl_2 each. After drying the organic phases over Na_2SO_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° (EtOH); $C_{24}H_{28}N_2O_6$ (440.5) Calc. C 65.4 H 6.40 N 6.4. Found C 65.3 H 6.29 N 6.4. – UV: λ max (log ε) = 213 (4.6), 260 (3.2), 285 nm (3.5). – IR (KBr): 1625 cm^{-1} (C=C, arom.). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.36–2.48 (m; 4H, CH_2), 2.44 (s; 6H, 2 × NCH_3), 2.56–2.67 (m; 2H, CH_2), 2.84–2.98 (m; 2H, CH_2), 3.69 (s; 6H, 2 × OCH_3), 4.15 (s; 2H, C-1 and C-1′), 5.81, 5.83 (AB-system; 4H, 2 × O–CH_2-O, J = 1.44 Hz), 6.28 (s; 2H, arom.). – MS (FI): 441 (M + H)$^+$, 440 M$^{+\cdot}$, 220 (M/2)$^+$.

2a: rf = 0.33; 1.2 g (27 %), rhombic crystals, mp. 163–164° (EtOH). $C_{24}H_{28}N_2O_6$ (440.5) Calc. C 65.4 H 6.40 N 6.4. Found C 65.4 H 6.38 N 6.4. – UV: λ max (log ε) = 212 (4.6), 260 (3.1), 285 nm (3.4). – IR (KBr): 1625 cm^{-1} (C=C, arom.). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.26 (s; 6H, 2 × NCH_3), 2.58–2.84 (m; 6H, CH_2), 3.49–3.65 (m; 2H, CH_2), 3.62 (s; 6H, 2 × OCH_3), 3.99 (s; 2H, C-1 and C-1′), 5.72, 5.76 (AB-system; 4H, 2 × O–CH_2-O, J = 1.43 Hz), 6.28 (s; 2H, arom.). – MS (FI): 441 (M + H)$^+$, 440 M$^{+\cdot}$, 220 (M/2)$^+$.

Bishydrohydrastines **(5)**

The mixture of the bishydrohydrastines **(5)** was prepared following *Freund*[2]. 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 $CHCl_3$, was resolved on a cellulose tris-(p-chlorophenylcarbamate) column (25 × 0.46 cm), prepared by the previous method[7], using a Jasco-TRIROTAR-II instrument equipped with detectors Jasco-UV-100-III (254 nm), 1 mm cell, and Jasco-DIP-180C (Hg), 50 × 2 mm cell. Eluent: hexane/2-propanol/chloroform (7:1:2-vol); flow rate: 0.5 ml/min; pressure: 22 kg/cm^2; temp.: 25°.

Cross-over experiment

20 mg **2a**, 20 mg **2b** and 40 mg **5** were mixed thoroughly by grinding and heated for 180 sec under N_2 in an oil bath of 180°. The mixture melted and turned brown. After cooling the cake was dissolved in $CHCl_3$, degradation products were separated by cc (Alumina Woelm N act. II, ethyl acetate). After evaporation i. vac. and drying (40°, 0.1 torr): 55 mg of a yellowish powder, which was used for ms.

N-Mono(δ-bromo-n-butyl)-bishydrocotarninium bromide **(7a)**

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

$C_{28}H_{36}Br_2N_2O_6$ (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 cm^{-1} (C=C arom.). – ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 1.75–2.14 (m; 4H, CH_2), 2.22–2.54 (m; 1H, CH_2), 2.38 (s; 3H, NCH_3), 2.79–3.54 (m; 8H, CH_2), 3.64 (s; 3H, $^+NCH_3$), 3.72, 3.74 (2 × s; 6H, 2 × OCH_3), 3.70–4.77 (m; 5H, C-1 and C-1′, 3H of CH_2-groups), 5.60, 5.66 (AB-system; 2H, O–CH_2-O, J = 0.74 Hz), 5.72, 5.78 (AB-system; 2H, O–CH_2-O, J = 0.74 Hz), 6.21, 6.27 (2 × s; 2H, arom.).

N-Mono(δ-bromo-n-butyl)-bishydrocotarninium bromide **(7b)**

7b was prepared analogously in 85 % yield, m. p. 196–197°. $C_{28}H_{36}Br_2N_2O_6$ (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 cm^{-1} (C=C, arom.). – ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 1.55–2.55 (m; 8H, CH_2), 2.38 (s; 3H, NCH_3), 2.95–3.55 (m; 6H, CH_2), 3.32 (s; 3H, OCH_3), 3.78 (s; 3H, $^+NCH_3$), 4.05–4.78 (m; 3H, CH_2 and 1H of C-1 or C-1′), 4.23 (s; 3H, OCH_3), 5.13 (s; 1H, C-1 or C-1′), 5.80–6.01 (m; 4H, O–CH_2-O, 2 overlapping AB-systems), 6.29, 6.40 (2 × s; 2H, arom.).

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

44Vmg (1 mmol) **2a** in 3 ml CH_3I were refluxed for 2 h. – The amorphous precipitate was crystallized from absol. EtOH; 460 mg **8a** (79 %), mp. 232–233° (lit.[1]: 233°). – IR (KBr): 1630 cm^{-1} (C=C, arom.). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.31–2.48 (m; 1H, CH_2), 2.38 (s; 3H, NCH_3), 2.80–3.14 (m; 3H, CH_2), 3.18–3.47 (m; 1H, CH_2), 3.39 (s; 3H, $^+NCH_3$), 3.60–3.88 (m; 1H, CH_2), 3.70 (s; 3H, $^+NCH_3$), 3.74, 3.76 (2 × s, 6H, 2 × OCH_3), 3.95–4.13 (m; 1H, CH_2), 3.99 (d; 1H of C-1 or C-1′, J = 6.25 Hz), 4.50–4.64 (m; 1H, CH_2), 4.52 (d; 1H of C-1 or C-1′, J = 6.25 Hz), 5.63, 5.67 (AB-system; 2H, O–CH_2-O, J = 1.34 Hz), 5.74, 5.79 (AB-system; 2H, O–CH_2-O, J = 1.34 Hz), 6.23, 6.29 (2 × s; 2H, arom.).

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

8b was prepared analogously from 440 mg **2b**; 480 mg (82 %), mp. 233° (lit.[1]: 233°). – IR (KBr): 1630 cm^{-1} (C=C, arom.). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.61–1.83 (m; 1H, CH_2), 1.97–2.08 (m; 1H, CH_2), 2.29–2.45 (m; 1H, CH_2), 2.40 (s; 3H, NCH_3), 2.55–2.73 (m; 1H, CH_2), 3.11–3.21 (m; 2H, CH_2), 3.28 (s; 3H, OCH_3), 3.31 (s; 3H, $^+NCH_3$), 3.71 (s; 3H, $^+NCH_3$), 4.21 (s; 3H, OCH_3), 4.32–4.47 (m; 1H, CH_2), 4.44 (s; 1H, C-1 or C-1′), 4.48–4.64 (m; 1H, CH_2), 4.87 (s; 1H, C-1 or C-1′), 5.86–5.96 (m; 4H, O–CH_2-O, 2 overlapping AB-systems), 6.29, 6.40 (2 × 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 K_2CO_3 were refluxed in 10 ml absol. benzene for 48 h. After evaporation and drying i. vac. the oily residue was purified by cc (SiO_2, chloroform/ether 3:1-vol.): 445 mg (80 %) **9a**, m. p. 207° (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): λ max (log ε) = 218 (4.5), 260 (3.2), 283 nm (3.5). – IR (KBr): 1690 (C=O), 1630 cm^{-1} (C=C, arom.). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.18–1.36 (m; 6H, 2 × $CH_2\underline{CH_3}$), 2.65–2.83 (m; 2H, CH_2), 3.15–3.66 (m; 4H, CH_2), 3.35, 3.38, 3.40 (3s; 6H, 2 × OCH_3), 3.74–3.95 (m; 2H, CH_2), 3.99–4.25 (m; 4H, CH_2), 5.44–5.71 (6 × s; 2H, C-1 and C-1′), 5.74–5.85 (m; 4H, 2 × O–CH_2-O), 6.40, 6.42 (2 × s; 2H, arom.). – MS (FD): 556 $M^{+\cdot}$, 278 $(M/2)^+$.
9b was prepared analogously: 290 mg (52 %) **9b**, m. p. 258° (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: λ max (log ε) = 218 (4.5), 260 (3.2), 283 nm (3.5). – IR (KBr): 1680 (C=O), 1630 cm^{-1} (C=C, arom.). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 0.91–1.12 (overlapping t (fig. 1), 6H, 2 × $-CH_2\underline{CH_3}$), 2.67–2.85 (m; 2H, CH_2), 3.14–3.62 (m; 6H, CH_2), 3.73–3.92 (m; 4H, CH_2), 4.01, 4.02, 4.03 and 4.04 (4s; 6H, 2 × OCH_3),

5.49–5.75 (6 × s; 2H, C-1 and C-1'), 5.77–5.90 (m; 4H, 2 × O–CH_2-O), 6.35–6.50 (m; 2H, arom.). – MS (FD): 556 $M^{+\cdot}$, 278 $(M/2)^+$.

5,5'-Bis-(N-β,β,β-trichloroethoxycarbonyl-4-methoxy-5,6,7,8-tetrahydo)-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_2CO_3 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. $C_{28}H_{26}Cl_6N_2O_{10}$ (763.2). Calc. C 44.1 H 3.43, N 3.7. Found C 44.8 H 3.74 N 3.6. – UV (CH_3CN): λ max (log ε) = 220 (4.2), 260 (3.1),284 nm (3.5). – IR (KBr): 1720 (C=O), 1630 cm^{-1} (C=C, arom.). – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.52–3.00 (m; 2H, CH_2), 3.05–3.64 (m; 4H, CH_2), 3.28, 3.30, 3.35 (3 × s; 6H, 2 × OCH_3), 3.65–4.23 (m; 2H, CH_2), 4.47, 4.95 (AB-system, 2H, CH_2, J_{AB} = 12.0 Hz, the low field part shows additional doublet splitting, ^2J = 7.5 Hz), 4.63 (s; 2H, CH_2), 5.52–5.84 (m; 6H, 2 × O–CH_2-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 (^{35}Cl) = 760; found m/z 795; 797; 799; 801; 803; 805; (807), corresponding to $(M + Cl^-)^-$.

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_2CO_3 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°. $C_{28}H_{26}Cl_6N_2O_{10}$ (763.2). – Calc. C 44.1 H 3.43 N 3.7. Found C 44.0 H 3.58 N 3.6. – UV (CH_3CN): λ max: (log ε) = 220 (4.2), 260 (3.1), 284 nm (3.5). – IR (KBr): 1715 (C=O), 1630 cm^{-1} (C=C, arom.). – ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 2.51–3.05 (m; 2H, CH_2), 3.10–3.62 (m; 4H, CH_2), 3.70–4,35 (m; 2H, CH_2), 4.00, 4.03 (2 × s; 6H, 2 × OCH_3), 4.66–4.95 (m; 2H, CH_2), 5.71, 5.73 (2s; 2H, C-1 and C-1') 5.81–5.95 (m; 4H, 2 × O–CH_2-O), 6.36, 6.38, 6.40 (m; 2H, arom.). – MS (FD, acetone): calc. M (^{35}Cl) = 760; found 760 ($M^{+\cdot}$), 380 $(M/2)^+$.

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[12], were slightly heated in 5 ml glacial acetic acid, until strong evolution of H_2 occurred. Then the mixture was stirred at r. t. for 4 h, 3 ml H_2O 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.). – ^{1}H-NMR (90 MHz, CF_3COOH): δ (ppm) = 2.88–4.34 (m; 8 H, CH_2), 4.17 (s; 6H, 2 × OCH_3), 5.34 (s; 2H, C-1 and C-1'), 6.00 (degenerated AB-system; 4H, 2 × O–CH_2-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_2SO_4) and evaporation produced a colourless oil, which crystallized slowly: 85 mg (79 %) white material, mp. 192°–193° (EtOH). $C_{22}H_{24}N_2O_6$ (412.4). Calc. C 64.1 H 5.87 N 6.8. Found C 64.2 H 6.01 N 6.7. – UV (CH_3CN): λ max (log ε) = 223 (4.2), 260 (3.2), 285 nm (3.6). – IR (KBr): 1625 cm^{-1} (C=C, arom.). – ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 2.02 (s broad; 2 H, 2 × HN, exchangeable with D_2O), 2.33–3.22 (m; 8H, CH_2), 3.67 (s; 6H, 2 × OCH_3), 4.33 (s; 2H, C-1 and C-1'), 5.72 (degenerated AB-system; 4H, 2 × O–CH_2-O), 6.20 (s; 2H, 2 × H, arom.). – MS (FAB(+), glycerol): 414 $(M + 2H)^{+\cdot}$, 413 (MH^+), 207 $(M/2 + H)^+$, 206 $(M/2)^+$.

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

11a-di-HCl: 104 mg (82 %) white needles, mp. 220°–221° (decomp.) – ^{1}H-NMR (90 MHz, CF_3COOH): δ (ppm) = 2.80–4.28 (m; 8H, CH_2), 3.98 (s; 6H, 2 × OCH_3), 5.68 (s broad; 2H, C-1 and C-1′), 5.85 (s broad; 4H, 2 × O–CH_2–), 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 %). $C_{22}H_{24}N_2O_6$ (412.4) Calc. C 64.1 H 5.87 N 6.8. Found C 63.9 H 5.91 N 6.7. – UV (CH_3CN): λ max (log ε) = 229 (4.1), 260 (3.2), 285 nm (3.6). – IR (KBr): 1625 cm^{-1} (C=C, arom.). – ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 1.80 (s broad; 2H, 2 × HN, exchangeable with D_2O), 2.35 – (s; 6H, 2 × OCH_3), 4.86 (s; 2H, C-1 and C-1′), 5.77–5.90 (m; 4H, 2 × O–CH_2-O), 6.25 (s; 2H, 2 × H, arom.). – MS (FAB (+), glycerol): 413 (MH^+), 206 $(M/2)^+$.

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). $C_{24}H_{22}N_2O_8$ (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^{-1} (C=C, arom.). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.68–2.98 (m; 6H, CH_2), 3.39 (s; 6H, 2 × OCH_3), 4.85–4.97 (m; 2H, CH_2), 5.16 (s; 2H, C-1 and C-1′), 5.82 (s; 4H, 2 × O–CH_2-O), 6.38 (s; 2H, arom.). – MS (FD): = 466 $M^{+\cdot}$, 233 $(M/2)^+$.
12b was prepared analogously. Yield: 60 mg (63 %) small plates, mp. 273°–274° (EtOH). $C_{24}H_{22}N_2O_8$ (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^{-1} (C=C, arom.). – ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.64–3.14 (m; 4H, CH_2), 3.24 (s; 3H, OCH_3), 3.42–3.58 (m; 2H, CH_2), 3.85 (s; 3H, OCH_3), 4.10–4.28 (m; 2H, CH_2), 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_2-O, J = 1.41 Hz), 5.92, 5.93 (AB-system, 2H, O–CH_2-O, J = 1.35 Hz), 6.40, 6.48 (2 × s; 2H, 2 × H arom.). – MS (FAB(+), 18-crown-6): = 468 $(M + 2H)^{+\cdot}$, 467 $(MH)^+$, 466 $M^{+\cdot}$. – MS (FAB(–), 18-crown-6) = 466 $M^{-\cdot}$, 465 $(M–H)^-$.

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