114)

Stereoselective Synthesis of the Quettamine Skeleton[1)]

Doris Dirnberger and Wolfgang Wiegrebe*, **)

Institute of Pharmacy, University, P.O Box 397, D-8400 Regensburg

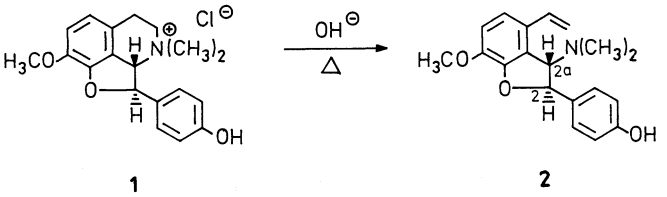
Received May 8, 1989

A synthesis of the quettamine skeleton **29** is described comprising ring closure of the diastereomeric phenolic 1-(α-bromobenzyl)-tetrahydroisoquinolines **27a** and **27b**. In both cases only one diastereomer was obtained. NOE-experiments confirm *Shamma's* [2,3)] assignments concerning the stereochemistry. - Various attemps to cleave the dithiane derivative **5** of an α-amino ketone in order to obtain the ketone **6** failed on account of the non-bonding electron pair at the N-atom.

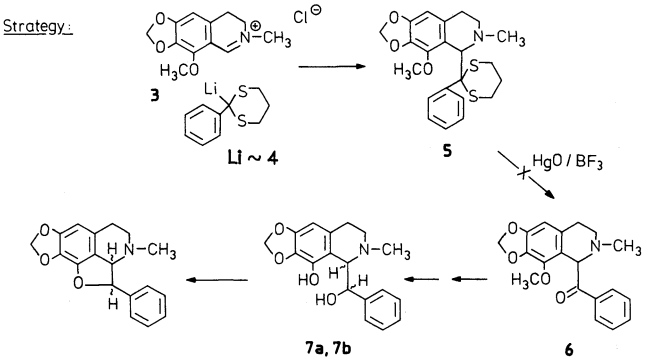
Stereoselektive Synthese des Quettamin-Gerüsts

Wir beschreiben die Synthese des Quettamin-Gerüstes **29** durch Ringschluß der diastereomeren 1-(α-Brombenzyl)-tetrahydroisochinoline **27a** und **27b**. In beiden Fällen resultierte nur ein Diastereomer. NOE-Messungen bestätigen *Shamma's* [2,3)] Aussagen zur Stereochemie. - Zahlreiche Versuche, das Dithian-Derivat **5** eines α-Aminoketons zum Keton **6** zu spalten, schlugen fehl wegen des nichtbindenden Elektronenpaars am Stickstoff.

In 1981 *Shamma* et al. [2)] reported upon the isolation of quettamine chloride (**1**) from *Berberis baluchistanica* (Quetta is the provincial capital of Baluchistan). This alkaloid represents a new type of isoquinoline alkaloids, characterized by its 2a,3,4,5-tetrahydro-2H-furo[2,3,4-i,k]isoquinoline moiety (scheme 1).



Scheme 1



Scheme 2

In spite of the two centers of chirality quettamine (**1**) exists as a racem. diastereomer in the plant. The trans-configuration at C-2 and C-2a was deduced from J = 1.5 Hz of the corresponding protons in the methine base **2**. - *Shamma* and *Chattopadhyay* [3)] synthesized quettamine (**1**) as just one diastereomer, identical with the natural product.

For spectroscopic reasons we intented to synthesize the unnatural diastereomer of the quettamine ring system. The cis-configurated quettamine analogue, however, was not obtained (vide infra).

1-Acylated-2-methyl-1,2,3,4-tetrahydroisoquinolines with a protected carbonyl group at C-α can be obtained by addition of a lithiated 1,3-dithiane to 3,4-dihydroisoquinolinium-ions according to *Seebach* [4)]. - We intended to get the diastereomeric amino alcohols **7a** and **7b** from cotarnine (**3**) and C-2-lithiated 2-phenyl-1,3-dithiane (**4**) [7)] via the dithioketal **5**, its deprotection to ketone **6** (scheme 2) and subsequent reduction.

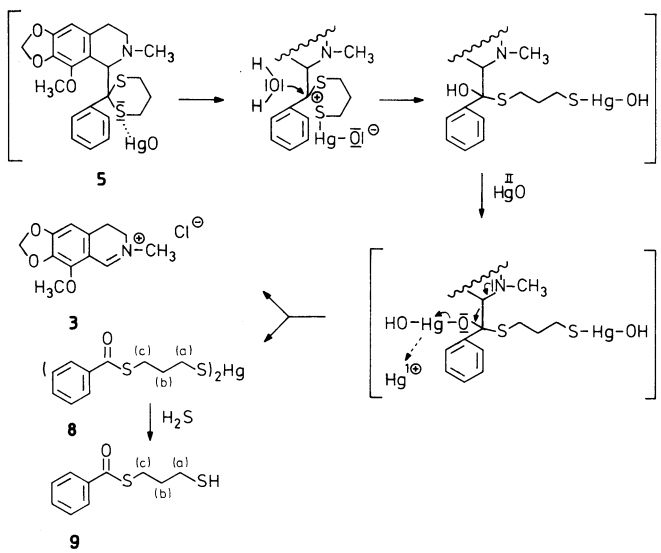
Ketal **5** was obtained in 78% yield. *Gröbel* and *Seebach* [6)] reported upon the hydroylsis of dithioketals. We executed a series of pertinent experiments but all of them failed on account of reasons discussed below. Red HgO/BF_3 is reported to be very mild [7)] and affording high yields. The consumption of the calculated amount of HgO misled us to the assumption that hydrolysis had proceeded as expected. Instead of ketone **6**, however, cotarnine (**3**) had been formed. Besides **3** a molecule free of N, containing S and Hg was obtained. Analytic data indicate the symmetric compound **8**: the IR-spectrum shows two intensive C=O-bands at 1660 and 1670 cm^{-1} characteristic for C_6H_5-CO-S[8)]. The ^{1}H-NMR spectrum reveals a "quintett" at δ = 2.05 ppm arising by coupling of the CH_2-increment (**b**) with the protons of CH_2 (**a**) and CH_2 (**c**) indicating $J_{ab} \approx J_{bc}$; the multiplett at δ = 3.21 comprises the tripletts of the CH_2-groups **a** and **c**. Decomposition of **8** with H_2S afforded the thioester **9**. Its ^{1}H-NMR-spetrum reveals a 1H-t at δ = 1.43 ppm (SH), disappearing by H/D exchange; fortunately, here the coupling of SH with the neighbouring CH_2-group is observed [9)]. The pseudo-q at 2.65 ppm is caused by CH_2 (**a**) (cf. **8**). - The MS of **9** shows $M^{+\cdot}$ at m/z = 212, base peak is m/z = 105 $(C_6H_5\text{-CO})^+$. - The inorganic material contains Hg (I)! Based on these observations we explain the formation of compounds **3** and **8** according to scheme 3.

**) Dedicated to Prof. *G. Märkl*, Regensburg, appreciating his merits to the development of the Institute of Pharmacy at the University of Regensburg

  0365-6233/90/0606-0323 $ 02.50/0

Table 1: Attempts for cleaving the dithioketal function in **5**

1. Acidic Hydrolysis
   F_3C-COOH 99%, room temp. (RT), 20 min, N_2, lit.[10]: decomp.
2. Transketalization
   $(HO)_2CH$-COOH (50 mmole), conc. HCl or conc. F_3C-COOH (50 mmole), lit.[11]: no reaction
3. Hydrolysis catalyzed by transition metals
   a) $AgNO_3$ (2 mmole) in 90% THF, 1 h, RT, N_2, lit.[12]: black precipitate and **3**
   b) $CuCl_2$ (2 mmole), CuO (4 mmole), acetone 99%, 1 h reflux, lit.[13]: starting material, some **3**
   c) HgO (2 mmole), $BF_3 \cdot Et_2O$ (2 mmole), 85% THF, 15% H_2O, 30 min, RT, N_2, lit.[7]: quantitative cleavage to **3**
   d) $Hg(ClO_4)_2$ (2 mmole), CH_2Cl_2/MeOH (1:1), 1 h, RT, N_2, lit.[14]: quantitative cleavage to **3**
   e) $HgCl_2$ (2 mmole) in THF/H_2O (1:1)
      I. 1 h, RT, N_2: partial cleavage to **3**
      II. + $CaCO_3$ (2 mmole), 1 h, RT, then 5 h reflux, N_2, lit.[15]: partial cleavage to **3**
      III. + $BF_3 \cdot Et_2O$, 1 h, RT, N_2: quantitative cleavage to **3**
      IV. + $CdCO_3$ (big excess) 24 h, RT, lit.[16]: partial cleavage to **3**
      V. + $CdCO_3$, $BF_3 \cdot Et_2O$, 24 h, RT: quantitative cleavage to **3**
   f) $CdCO_3$ in THF/H_2O (1:1), 24 h, RT: no reaction
   g) $TiCl_4$ (4 mmole) in glacial AcOH, 30 min, RT, lit.[17]: quantitative cleavage to **3**
4. Oxidation with subsequent hydrolysis
   a) N-Chloro-p-toluenesulfonamide, Na-salt (4 mmole), 80% MeOH, 15 min - 24 h, RT, lit.[18]: crude mixture, no C=O-absorption (IR)
   b) $Ce(NH_4)_2(NO_3)_6$ (4 mmole), CH_3-CN/H_2O (3:1), 3 min, RT, lit.[19]: mainly **5**, some new product, Dragendorff reaction +, but no C=O-absorption (IR)
   c) 30% H_2O_2, conc. HCl in MeOH, 5 min, RT, lit.[20]: quantitative cleavage to **3**
   d) CH_3I (excess), MeOH 96%, 5 - 24 h reflux, lit.[21]: quantitative cleavage to **3**, no quaternization

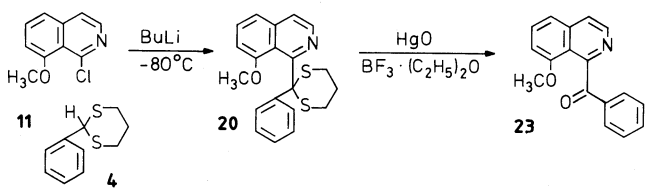


Scheme 3

Further experiments to hydrolize **5** to **6** are summarized in table 1.

The target molecule **6** was not obtained so that this strategy broke down at this stage. We tried to get ketone **6** via an α-cyanobenzylamine (masked ketone) by addition of α-morpholinobenzylcyanide to cotarnine (**3**), but this reaction did not work in our hands. - The synthesis of **6**-analogues starting from 2-bromo-5-methoxybenzaldehyd via the pertinent β-phenethylamine, its acylation with phenylacetic acid and *Bischler-Napieralski* ring closure was frustrating on account of far too low yields of the pertinent 1-benzyl-3,4-dihydroisoquinoline[5].

The failure of our strategy comprising the addition of a phenyldithiane to **3** (schemes 2 and 3) is based on the electron donating effect of the tetrahydroisoquinoline N. Therefore, we avoided this disadvantage by condensation of 2-phenyl-1,3-dithiane (**4**) with 1-chloro-8-methoxyisoquinoline (**11**) (scheme 4).



Scheme 4

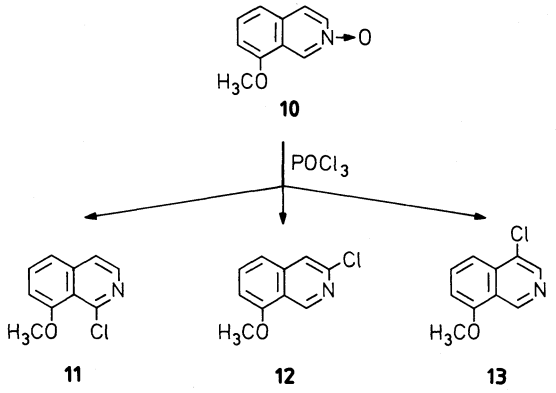
According to *Katritzky* [22] 1-chloroisoquinolines are prepared by chlorination of isoquinoline-N-oxides or of 1-(2H)isoquinolinones.

Schenker et al. [23] obtained 8-methoxyisoquinoline in high yield from 8-hydroxyisoquinoline which in turn had been synthesized according to *Robinson* [24].

Neither we nor *Okamoto* [25] were able to repeat *Robinson's* results (sulfonation of isoquinoline by 60% oleum at 300°C with subsequent alkali fusion). - *Hendrickson* et al. [26] got 8-methoxyisoquinoline by a modified *Pomeranz-Fritsch* reaction in 65% yield although there are no activating substituents. We have confirmed their results. - According to *Katritzky* [27] isoquinoline N-oxides afford 1-choroisoquinolines in good yield. - We converted 8-methoxyisoquinoline into its N-oxide **10** with 81% yield. Treatment of **10** with $POCl_3$ led to the 1-, 3-, and 4-monochloro-8-methoxyisoquinolines **11** - **13** (scheme 5).

There are some discussions concerning nucleophilic substitution in isoquinoline-N-oxide at C-4 [28], but S_N-reactions at C-3 do not seem to be reported.

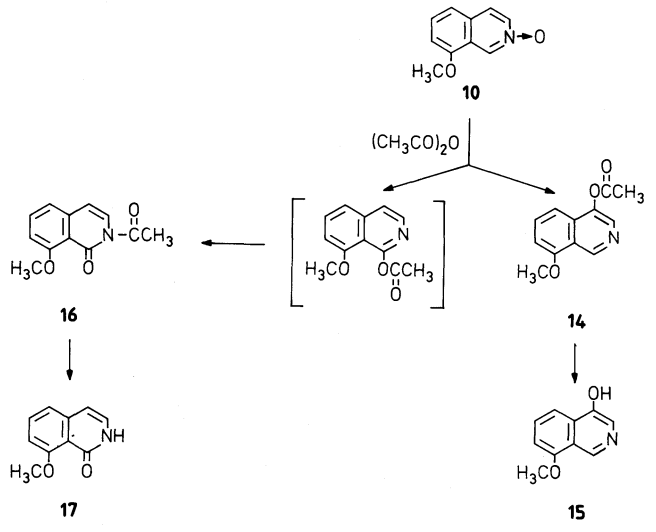
The structure of 3-chloro-8-methoxyisoquinoline (**12**) is characterized by a singulet for H-4 (7.60 ppm, overlap with the pseudo-t for H-6) and a



Scheme 5

singlet at 9.39 ppm for H-1. - The EI-MS of **11**, **12**, and **13** are nearly identical.

Because 1-choro-8-methoxyisoquinoline (**11**) was obtained in 20% yield only we tried the procedure of *Haimova* [31] but the reaction of the N-oxide **10** with acetic anhydride/KOH led to 4-acetoxy-8-methoxyisoquinoline (**14**), the 4-hydroxy-congener **15**, and to 2-acetyl-8-methoxyisoquinoline(2H)-1-one (**16**) besides the desired lactame **17** (scheme 6).

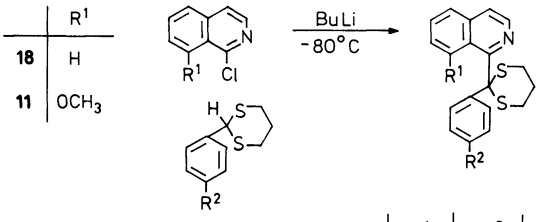


Scheme 6

Treatment of pyridine-N-oxide with acetic anhydride yields 2-acetoxypyridine as an intermediate[30]. Contrary to this analogy we could not identify 1-acetoxy-8-methoxyisoquinoline as a link between **10** and the N-acetylated lactame **16**. This is supported by *Robison's* fruitless experiments to synthesize 1-acetoxyisoquinoline by this route[28b]. - An explanation, deviating from those of *Robison*[28b] or *Oae*[28a], might be based on the increased electron density at C-4 due to the +I-effect of the C-8-OCH_3-group.

17 was smoothly converted to **11** in 80% yield, but on the whole this laborious strategy is not superior to that using the N-oxide **10** directly.

We elaborated suitable reaction conditions for the condensation of **11** with the lithiated dithane **4** using easily available [31] 1-choroisoquinoline (**18**) (cf. Experim. Part). For pertinent examples see scheme 7.



	R^1	R^2	% yield
19	H	H	90
20	OCH_3	H	78
21	H	OCH_3	82
22	OCH_3	OCH_3	68
–	H	NO_2	~0
–	OCH_3	NO_2	~0

Scheme 7

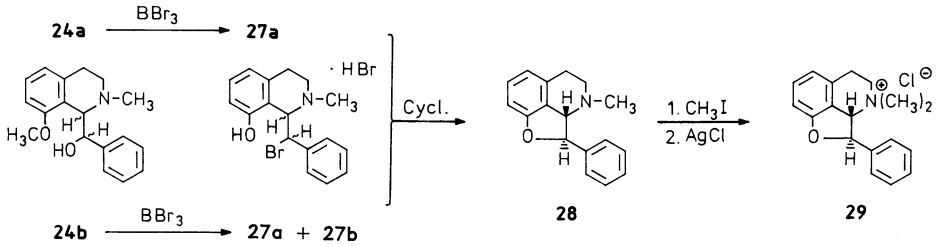
Because this reaction opens a suitable approach to 1-benzoylisoquinolines, 4'-OCH_3-**4** and 4'-NO_2-**4** were used in addition to **18** and **11**. The masked ketones **21** and **22** were obtained in high yield, whilst 4'-NO_2-**4** failed to react: even at -80°C the reaction mixture turned black, but quenching led to recovery of a high percentage of 4'-NO_2-**4**, **18**, or **11**, respectively.

As expected, hydrolysis of **20** with $HgO/BF_3 \cdot Et_2O$ in aqueous tetrahydrofuran [7] produced ketone **23** (Scheme 4); quanternization with CH_3I yielded the pertinent N-methoiodide (not shown) which in turn was reduced with $NaBH_4$ to the diastereomeric alcohols **24a** and **24b** besides some ketone **25**. We can only speculate why **25** shows two ketone bands (1680 and 1695 cm^{-1}) in its IR-spectrum. CI-MS (2-methylpropane) leads to $(M+1)^+$, which together with fragment ions at m/z = 176 (M - PhCO)$^+$ and m/z = 105 (Ph-CO)$^+$ prove structure **25**. - The diastereomeric alcohols **24a** and **24b** are formed at a ratio 9:1 (^{1}H-NMR). The formation of **25** and the ratio 2:1 of the pertinent diastereomeric alcohols **26a/26b** [32], obtained from **19** analogously to the sequence **20** → **24a/24b**, point towards reduction of the heterocycle prior to reduction of the ketone which in addition might be strongly influenced by the OCH_3-increment in its neighbourhood.

Scheme 8

Both **24a** and **24b** show an identical AB-system for H-1 and H-α (^3J = 5.7 Hz). Contrary to **24b**, **24a** exhibits a strong intramolecular H-Bond at 3440 cm^{-1}. The difference in the chemical shifts of H-α in **24a** and **24b** (5.21 ppm versus 4.50 ppm) supports this assumption. - (+)FAB spectra of **24a** and **24b** reveal $(M+H)^+$ at mz = 284, loss of water $(M+H^+ - 18)$ and loss of C_6H_5-$^{\cdot}$CH-OH from $M^{+\cdot}$.

Both **24**-diastereomers were cyclized separately. In order to support a S_N2-type transition state instead of a carbenium



Scheme 9

ion intermediate postulated by *Shamma* [3] we prepared the bromophenols **27a** and **27b** from **24a** and **24b**, respectively, by BBr_3. Whilst **24a** yielded only one isomer [**27a**], **27a** and **27b** (1:1) were obtained from stereochemical pure **24b** (Scheme 9).

The structures of **27a** and **27b** were checked by (+)FAB (glycerol): for $(M+H)^+$ two signals of equal intensity (^{81}Br, ^{79}Br) are found at m/z = 334 and m/z = 332, respectively; together with the fragment ions at m/z 252 $(MH-HBr)^+$ and m/z 162 $(M\text{-}Ph\text{-}\dot{C}HBr)^+$ they indicate the α-bromobenzyl moiety.

The ^{1}H-NMR spectrum of **27a** + **27b** in CF_3-COOH (!) is characterized by two dd at δ = 5.22 and 5.04 ppm (H-1 of **27a** and **27b**) and two doublets at δ = 5.63 and 5.45 ppm (H-α of **27a** and **27b**).

We could not spearate **27b** from **27a** on account of their labilities and of shortage of material. - **27a** and the mixture **27a/27b** were cyclized under solvolytic conditions in CF_3-COOH as reported by *Shamma* [3] for their ring closure: Both, the stereochemically homogenous bromo-phenol **27a** as well as the mixture **27a/27b** led to the same diastereomer **28**. Its ^{1}H-NMR data are comparable with those of the non-quaternised "quettamine" (not shown) [3]: the vicinal protons at C-2a and C-2 resonate as an AB-System at $\delta_{H\text{-}2a}$ = 3.82 and $\delta_{H\text{-}2}$ = 5.39 ppm with J = 10.14 Hz. The pertinent chemical shifts in the non-quaternised "quettamine" [3] are δ = 4.22 and δ = 5.37 ppm, respectively, with J = 10.7 Hz. - We used solvolytic conditions (vide supra) for the ring closure because preliminary experiments under basic conditions led to a complex mixture of products: ^{1}H-NMR-studies indicate the presence of olefinic protons.

28 was transformed into the methochloride **29** via the corresponding methoiodide (not shown). In **29** the AB-system of H-2a and H-2 resonates at δ = 5.63 (H-2a) and δ = 5.98 ppm (H-2) as expected from the values of quettamine-chloride (**1**): δ = 5.47 (H-2a) and δ = 5.94 ppm (H-2).

Shamma [2] has deduced the stereochemistry of quettamine (**1**) at C-2a and C-2 (named C-1 and C-α in his publication on account of biogenetic considerations) from the ^{1}H-NMR-spectrum of the methin base **2** (scheme 1). - We proved the

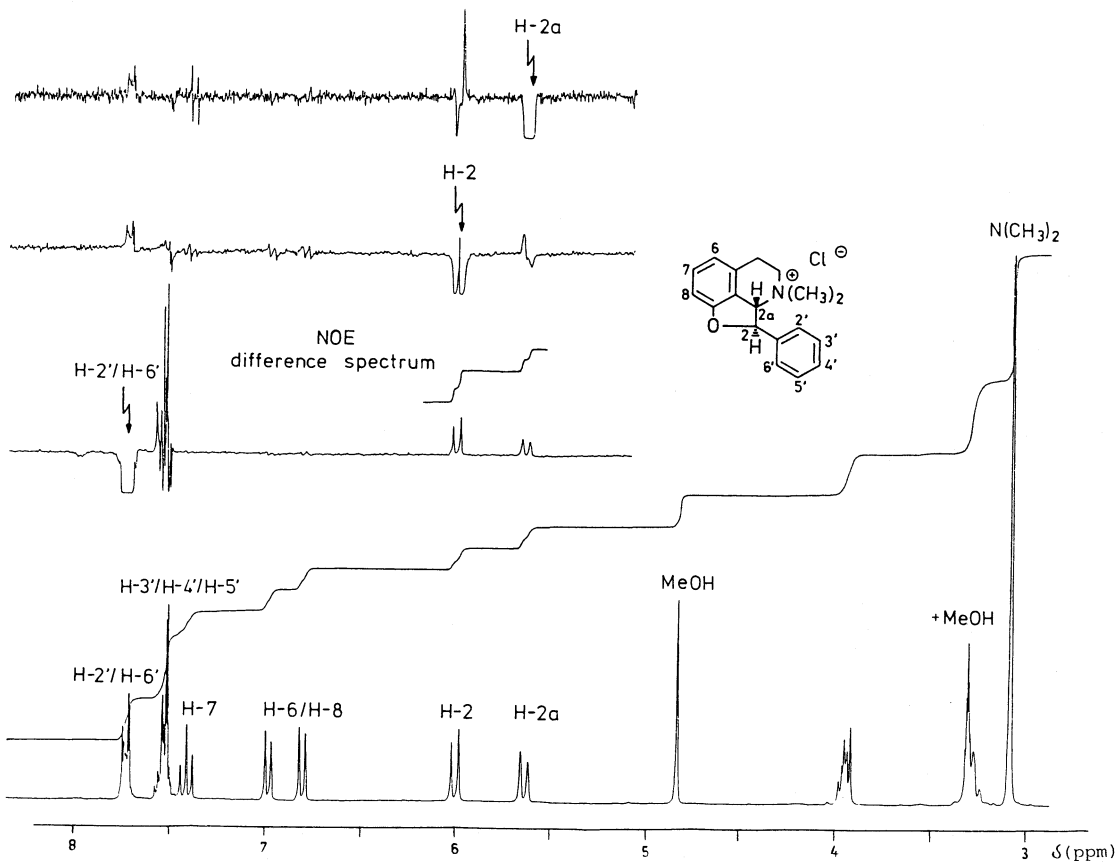


Fig.1: ^{1}H-NMR-Spectrum (250 MHz) of 29

stereochemistry of **29** by NOE-experiments (fig. 1): irradiation into the doublet at δ = 5.63 ppm (H-2a) did not increase the intensity of the doublet at δ = 5.98 ppm (H-2). Irradiation into this doublet revealed the same result. Irradiation into the absorption of the ortho H's of the phenyl ring (H-2'; H-6'; δ = 7.65-7.76 ppm) increases the intensity of H-2, together with the intensity of H-2a! This can only be due to the fact, that H-2a and the ortho-protons of the phenyl group are in close neighbourhood. This is only provided by a cis-configuration of C_6H_5 and H-2a, so proving trans configuration of H-2a and H-2.

Experimental Part

General remarks: Y. Okamoto, D. Dirnberger, Th. Burgemeister, G. Dannhardt, and W. Wiegrebe, Arch. Pharm. (Weinheim) *319*, 1122 (1986).

8-Methoxy-2-methyl-6,7-methylendioxy-1-(2-phenyl-1,3-dithiane-2-yl)-1,2,3,4-tetrahydroisoquinoline (**5**)

0.86 g (4.4 mmole) 2-phenyl-1,3-dithiane (**4**) in 25 ml absol. tetrahydrofuran (THF) were cooled to -70°C under N_2 in a preheated three-necked flask closed with a septum. - To this solution 2.8 ml (4.4 mmole) of n-C_4H_9Li (15% in hexane) were added drop-by-drop (orange colour). After 30 min stirring at -70°C 1.0 g (4.0 mmole) finely ground cotarnine chloride (**3**) were added in portions during 10 min in a N_2-counter current. After 2 h stirring at -70°C the mixture was allowed to warm to room temp. and was hydrolized by saturated NH_4Cl solution. - THF was evaporated in vacuo and the residue was extracted several times with altogether 200 ml CH_2Cl_2. The crude material obtained after drying (Na_2SO_4) and evaporation of this extract was purified by column chromatography (cc) (SiO_2; 1. $CHCl_3$, 2. $CHCl_3$/MeOH 1:1): 1.30 g (78%) **5**. White crystals from EtOH, m.p. 138°C. - $C_{22}H_{25}NO_3S_2$ (415.6) Calcd. C 63.6 H 6.06 N 3.4 Found C 63.4 H 6.06 N 3.2. - UV (MeOH): λ max (log ε) = 212 (4.2), 266 (2.7), 279 nm (2.8). - ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.44-1.63 (m; 1H of CH_2), 1.77-2.19 (m; 4H, CH_2), 2.34-2.79 (m; 4H, CH_2), 2.53 (s; 3H, NCH_3), 3.16-3.30 (m; 1H of CH_2), 3.85 (s; 3H, OCH_3), 4.59 (s; 1H, C-1), 5.85, 5.87 (AB, J = 1.5 Hz; 2H, OCH_2O), 6.12 (s; 1H, C-5), 7.14-7.33 (m; 3H, arom.), 7.66-7.81 (m; 2H, arom.). - MS (70 eV, 130°C): m/z = 220 (100%), 205 (11), 195 (4).

Cleavage of Ketal **5** *to Cotarnine* (**3**) *and to the Mercuric Thiolate* **8**

The suspension of 0.22 g (1 mmole) red HgO in 10 ml of THF/H_2O 85:15 was stirred under N_2 first with 0.21 g (0.5 mmole) **5**, then with 0.25 ml (2.0 mmole) $BF_3 \cdot Et_2O$ for further 30 min. A clear solution resulted, addition of CH_2Cl_2 (50 ml) led to a white precipitate. This precipitate was discarded, the filtrate was washed with saturated Na_2CO_3- and NaCl-solution, dried (Na_2SO_4) and evaporated. The residue was worked-up by cc (SiO_2; CH_2Cl_2).

Fraction 1: rf = 0.5: 0.13 g (83%) **8** as an amorphous solid. $C_{20}H_{22}O_2S_4 \cdot Hg$ (623.2) Calcd. C 38.4 H 3.56 Found C 38.5 H 3.56. - IR (KBr): 1660; 1670 cm^{-1} (Ar-CO-S-R). - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 1.87-2.23 ("quint"; 4H, CH_2), 3.08-3.34 (m; 8H, CH_2), 7.30-7.69 (m; 6H, arom.), 7.94 (dd, J_1 = 8.1 Hz, J_2 = 2.1 Hz; 4H, arom.).

Fraction 2: rf = 0. After desorption with MeOH/H_2O (4:1) 0.05 g (39%) yellowish solid material, characterized as cotarnine chloride (**3**) by its IR- and ^{1}H-NMR-spectra.

S-Benzoyl-1,3-propanedithiol (**9**)

9 was obtained nearly quantitatively as an amorphous solid from 0.1 g **8** by treating its suspension in acetic acid/H_2O (3:1) with H_2S, extraction with CH_2Cl_2, evaporation and cc of the residue (SiO_2; CH_2Cl_2), rf = 1. - IR (Film): 1665; 1670 cm^{-1} (Ar-CO-S-R). - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 1.43 (t, J = 8.1 Hz; 1H, SH), 1.81-2.20 ("quint"; 2H; $CH_2CH_2CH_2$), 2.50-2.83 ("q"; 2H, CH_2CH_2SH), 3.18 (t, J = 6.6 Hz; 2H, SCH_2CH_2), 7.32-7.71 (m; 3H, arom.), 7.97 (dd, J_1 = 8.1 Hz, J_2 = 2.1 Hz; 2H, arom.). - MS (70 eV, RT): m/z = 212 (7%, $M^{+\cdot}$), 152 (2), 106 (18), 105 (100), 77 (35), 51 (9).

α-Morpholinobenzylcyanide

2.12 g (20.0 mmole) benzaldehyde and 4.10 g (22.0 mmole) morpholine perchlorate were stirred in 20 ml of morpholine at 80°C for 1 h. Stirring was continued for 1 h at 100°C after addition of 1.40 g (21.5 mmole) KCN in about 3 ml H_2O. - After cooling 50 ml of 10% K_2CO_3-solution were added, followed by extraction ($CHCl_3$), separation of unreacted aldehyde by $NaHSO_3$-solution, drying ($MgSO_4$), evaporation, and crystallisation of the residue from cyclohexane: 3.40 g (84%) of α-morpholinobenzylcyanide; white needles, m.p. 69-70°C. - $C_{12}H_{14}N_2O$ (202.3) Calcd. C 71.3 H 6.98 N 13.9 Found C 71.3 H 6.80 N 14.0. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 2.53 (t, J = 5 Hz; 4H, 2 x NCH_2), 3.70 (t, J = 5 Hz; 4H, 2 x OCH_2), 4.81 (s; 1H, CH), 7.32-7.63 (m; 5H, arom.).

8-Methoxyisoquinoline-N-oxide (**10**)

The mixture of 15.0 g (94.2 mmole) 8-methoxyisoquinoline, 10 ml 30% H_2O_2, and 30 ml of glacial acid was stirred for 3 h at 60-70°C. Then further 8 ml of 30% H_2O_2 were added and stirring was continued for 9 h. - Volatile components were evaporated in vacuo and the oily residue was suspended repeatedly in small quantities of water until a solid material remained after evaporation. The solution of this material in 100 ml of CH_2Cl_2 was washed with saturated Na_2CO_3-solution, the alkaline phase was reextracted with CH_2Cl_2 and the combined org. layers were dried (Na_2SO_4) and evaporated. After cc (SiO_2; 2-propanol) and Kugelrohr-distillation (0.01 Torr, 130°C) 13.85 g (84%) white crystals of **10**, m.p. 142°C, were obtained. - $C_{10}H_9NO_2$ (175.2) Calcd. C 68.6 H 5.18 N 8.0 Found C 67.9 H 5.36 N 7.9. - UV (MeOH): λ max (log ε) = 230 (3.8), 241 (3.8), 265 (3.9), 287 (3.4), 321 nm (3.8). - IR (KBr): 1575; 1280; 1255; 1230; 1215; 1100 cm^{-1}. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 4.00 (s; 3H, OCH_3), 6.92 (d, J = 7.5 Hz; 1H, C-7), 7.25-7.68 (2 x d und 1 x "t", overlap; 3H, C-4, C-5, and C-6), 8.12 (dd, J_1 = 7.1 Hz, J_2 = 2.0 Hz; 1H, C-3), 9.11 (d, J = 2.0 Hz; 1H, C-1). - MS (70 eV): m/z = 175 (100%, $M^{+\cdot}$), 160 (35), 159 (23), 148 (21), 133 (16), 132 (14), 116 (29), 105 (23), 104 (22), 89 (19), 77 (34), 63 (15).

1-,3-, and 4-Chloro-8-methoxyisoquinolines (**11, 12,** *and* **13**)

1.0 g (5.7 mmole) **10** were refluxed for 3 h in 15 ml $POCl_3$. The mixture got dark immediately. - Excess of $POCl_3$ was evaporated in vacuo and 15 ml of saturated Na_2CO_3-solution were added to the residue. Extraction with CH_2Cl_2, drying (Na_2SO_4), and evaporation led to 0.6 g (54%) of oily crude material which was separated by cc (SiO_2; CH_2Cl_2).

Fraction 1: 0.23 g (21%) **11**, white needles after Kugelrohr-distillation (0.01 Torr; 85°C), m.p. 52.5-53.5°C. - $C_{10}H_8ClNO$ (193.6) Calcd. C 62.0 H 4.16 N 7.2 Found C 62.0 H 4.43 N 7.1. - UV (MeOH): λ max (log ε) = 231 (4.0), 260 (3.0), 301 (3.6), 310 (3.5), 328 nm (3.7). - IR (KBr): 1615; 1565 cm^{-1} (C=C, arom.). - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 3.99 (s; 3H, OCH_3), 6.98 (d, J = 7.5 Hz; 1H, C-7), 7.30-7.72 (m; 3H, C-4, C-5, and C-6), 8.24 (d, J = 6.0 Hz; 1H, C-3). - MS (70 eV, 80°C): m/z = 195 (32%, $M^{+\cdot}$, ^{37}Cl), 193 (100, $M^{+\cdot}$, ^{35}Cl), 178 (3, *164.17), 163 (2, *137.66), 158 (4), 150 (46), 143 (16), 128 (17), 123 (10, *100.86), 115 (20).

Fraction 2: 80 mg (7%) **13**, sublimating during Kugelrohr-distillation (0.1 Torr; 120°C). Square and rectangular plates, m.p. 121°C. - $C_{10}H_8ClNO$ (193.6) Calcd. C 62.0 H 4.16 N 7.2 Found C 62.0 H 4.21 N 7.2. - IR (KBr): 1625; 1565 cm^{-1} (C=C, arom.). - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) =

4.00 (s; 3H, OCH_3), 6.84-7.02 (m, ABX; 1H, C-7), 7.54-7.82 (m, ABX; 2H, arom.), 8.57 (s; 1H, C-3), 9.53 (s; 1H, C-1). - MS (70 eV, 100°C): m/z = 195 (32%, $M^{+\cdot}$, ^{37}Cl), 193 (100, $M^{+\cdot}$, ^{35}Cl), 178 (11, *164.17), 163 (4), 158 (2), 150 (73, *126.40), 123 (10), 115 (9), 114 (7).

Fraction 3: 0.11 g (10%) **12**, fine white needles after Kugelrohr-distillation (0.1 Torr; 130°C), m.p. 81.5°C. - $C_{10}H_8ClNO$ (193.6) Calcd. C 62.0 H 4.16 N 7.2 Found C 62.0 H 4.24 N 7.2. - IR (KBr): 1630; 1565 cm^{-1} (C=C, arom.). - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 4.00 (s; 3H, OCH_3), 6.83 *7.24* (2 x d, J = 7.5 Hz; 2H, C-7, *C-5*), 7.47-7.71 ("t"; 1H, C-6), 7.60 (s; 1H, C-4), 9.39 (s; 1H, C-1). - MS (70 eV, 100°C): m/z = 195 (32%, $M^{+\cdot}$, ^{37}Cl), 193 (100, $M^{+\cdot}$, ^{35}Cl), 178 (4, *164.17), 163 (4), 158 (3), 150 (57), 128 (8), 123 (4), 115 (14), 114 (6).

1-Chloro-8-methoxyisoquinoline (**11**) *from 8-Methoxy-1(2H)-isoquinolinone* (**17**)

4.38 g (25 mmole) **17** (see below) were refluxed in 25 ml $POCl_3$ for 30 min. Work-up and purification as described for **11-13**: 3.8 g (78%) **11**.

8-Methoxy-1(2H)-isoquinolinone (**17**) *and 4-Hydroxy-8-methoxyisoquinoline* (**15**)

13.1 g (75.0 mmole) N-oxide **10** were heated in 130 ml of acetic anhydride under reflux for 5 h (the solution got dark red). Then the anhydride was distilled off in vacuo and the residue was Kugelrohr-distilled. The distillate was heated with 3.0 g (75 mmole) NaOH in 60 ml H_2O for 1 h at 80-90°C. After cooling to 4°C for 2 h the black crystalline precipitate was collected, dried and purified by cc (SiO_2; acetone) and recrystallization from EtOH/charcoal: 3.3-4.1 g (25-31%) **17**, white needles, m.p. 198°C. - Through the aqueous filtrate of **17** was bubbled CO_2 until a crystalline product separated. After 12 h in the refrigerator the black crystalls were filtered off. CC (SiO_2; acetone) and numerous crystallizations from absol. acetone/charcoal afforded 1.7-2.1 g (13-16%) white cotton-like needles of **15**, m.p. 238°C.

17: $C_{10}H_9NO_2$ (175.2) Calcd. C 68.6 H 5.18 N 8.0 Found C 68.6 H 5.27 N 8.0. - UV (MeOH): λ max (log ε) = 231 (3.9), 253 (3.7), 268 (3.6), 283 (3.8), 288 (3.8), 293 (3.8), 305 (3.4), 331 (3.9), 340 (3.8), 347 nm (3.8). - IR (KBr): 1690; 1670 (CO); 1650; 1615 cm^{-1}. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 4.02 (s; 3H, OCH_3), *6.48*, 7.23 (AB, J = 7.2 Hz; 2H, *C-4*, C-3), *6.91*, 7.10 (2 x d, J = 8.1 Hz; 2H, *C-7*, C-5), 7.34-7.67 ("t"; 1H, C-6), 12.18 (s, broad; 1H, NH, D_2O-exchange). - MS (70 eV): 175 (100%, $M^{+\cdot}$), 174 (36), 158 (12), 146 (73, *121.80), 145 (23), 129 (22), 128 (26, *112.20), 117 (14), 118 (28), 90 (18).

15: $C_{10}H_9NO_2$ (175.2) Calcd. C 68.6 H 5.18 N 8.0 Found C 68.3 H 5.20 N 8.0. - UV (CH_3CN): λmax (log ε) = 207 (3.2), 225 (4.1), 255 (3.3), 296 (3.8), 310 (3.6), 321 (3.8), 326 (3.8), 335 nm (3.9). - IR (KBr): 2600 (OH, very broad); 1635; 1595 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ (ppm) = 4.00 (s; 3H, OCH_3), 7.01-7.17 (m; 1H, arom.), 7.01-7.77 (m; 2H, arom.), 8.12 (s; 1H, C-3), 9.04 (s; 1H, C-1), 10.40 (s, broad; 1H, OH). - MS (70 eV): m/z = 175 (100%, $M^{+\cdot}$), 160 (21, *146.29), 146 (5), 132 (63, *108.90).

2-Acetyl-8-methoxy-1-isoquinolinone (**16**) *and 4-Acetoxy-8-methoxyisoquinoline* (**14**)

13.1 g (75 mmole) **10** in 130 ml of acetic anhydride were gently refluxed for 5 h. The anhydride was removed in vacuo and the residue was dried at room temp. and 0.01 Torr. After cc (SiO_2; CH_2Cl_2/Et_2O 9:1) were obtained:

A: 4.47 g (27.5%) **16**, rf = 0.8, m.p. 91-92°C (petrol ether 50-70°C). - $C_{12}H_{11}NO_3$ (217.2) Calcd. C 66.4 H 5.10 N 6.5 Found C 66.7 H 5.15 N 6.5. - UV (MeOH): λ max (log ε) = 240 (3.9), 252 (3.9), 260 (3.9), 273 (3.8), 277 (3.8), 283 (3.7), 289 (3.8), 299 (3.2), 331 (3.9), 340 (3.8), 346 nm (3.8). - IR (KBr): 1715; 1695 cm^{-1} (CO). - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 2.81 (s; 3H, $COCH_3$), 4.02 (s; 3H, OCH_3), *6.37*, 7.83 (AB, J = 8.1 Hz; 2H, *C-4*, C-3), 6.87-7.09 (2 x d, overlap, 2H, C-5 and C-7), 7.47-7.66 ("t"; 1H, C-6). - MS (70 eV, 95°C): m/z = 217 (35%, $M^{+\cdot}$), 175 (100, *141.13), 174 (38), 158 (11), 146 (86, *121.81), 128 (15), 118 (16), 117 (10),

B: 2.60 g (16%) **14**, rf = 0.4, m.p. 109-110°C (petrol ether 50-70°C). - $C_{12}H_{11}NO_3$ (217.2) Calcd. C 66.4 H 5.10 N 6.5 Found C 66.3 H 5.27 N 6.3. - UV (MeOH): λ max (log ε) = 234 (3.8), 258 (3.2), 298 (3.6), 306 (3.6), 327 nm (3.8). - IR (KBr): 1750 cm^{-1} (CO). - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 2.43 (s; 3H, $COCH_3$), 3.92 (s; 3H, OCH_3), *6.82*, 7.30 (2 x d, J = 8.1 Hz; 2H, *C-7*, C-5), 7.45-7.70 ("t"; 1H, C-6), 8.40 (s; 1H, C-3), 9.50 (s; 1H, C-1). - MS (70 eV, 95°C): m/z = 217 (13%, $M^{+\cdot}$), 175 (100, *141.13), 160 (12, *146.29), 146 (3), 132 (26, *108.9).

C: A mixture containing inter alia **10** was obtained when the column was desactivated by EtOH. This mixture was separated on SiO_2 with acetone: 1.62 g (12%) **17**, 1.40 g (11%) **15**, and 1.23 g N-oxide **10**.

8-Methoxy-1-(2-phenyl-1,3-dithiane-2-yl)-isoquinoline (**20**)

2.55 g (13.0 mmole) 2-phenyl-1,3-dithiane (**4**) in 50 ml of absol. THF in a 3-necked flask with a septum were cooled to -80°C under dried N_2. 9.0 ml (14.7 mmole) n-C_4H_9Li (15% in n-hexane) were added slowly keeping the temp. of the mixture below -60°C. After 1 h stirring at -80°C, 2.52 g (13 mmole) of **11** in 10 ml of absol. THF were added drop by drop, the solution turned violet. After 6 h stirring at -70°C - -80°C the mixture was allowed to warm to room temp. over night (decolouring). - 25 ml of saturated NH_4Cl-solution were added slowly, THF was evaporated in vacuo, the aqueous phase was extracted 3 times with altogether 250 ml CH_2Cl_2. Drying (Na_2SO_4) and evaporation in vacuo yielded 4.55 g (99%) crude **20**, which was purified by cc (SiO_2; CH_2Cl_2) and crystallization from EtOH: 3.30 g (72%) **20**, white plates, m.p. 140°C. - $C_{20}H_{19}NOS_2$ (353.5) Calcd. C 68.0 H 5.42 N 4.0 Found C 67.7 H 5.42 N 3.9. - UV (MeOH): λ max (log ε) = 219 (4.5), 276 (3.6), 304 (3.7), 313 (3.7), 324 nm (3.7). - IR (KBr): 1620; 1560 cm^{-1}. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 1.80-2.16 (m; 2H, CH_2), 2.47-2.82 (m; 2H, CH_2), 3.05 (mc; 2H, CH_2), 3.21 (s; 3H, OCH_3), 6.65 (dd, J_1 = 7.5 Hz, J_2 = 2.4 Hz; 1H, arom.), 7.07-7.64 (m; 8H, arom.), 8.56 (d, J = 6.0 Hz; 1H, C-3). - MS (70 eV): m/z = 353 (37%, $M^{+\cdot}$), 322 (16, *293.72), 292 (18), 280 (35), 279 (30), 248 (100, *220.44), 232 (35), 195 (10), 192 (33), 176.5 (2, M^{2+}), 158 (2), 121 (26), 77 (10).

1-(2-Phenyl-1,3-dithiane-2-yl)-isoquinoline (**19**)

0.79 g (4.0 mmole) 2-phenyl-1,3-dithiane (**4**) and 0.65 g (4.0 mmole) **18** were processed as described for **20**. - After cc (SiO_2; $CHCl_3$/petrol ether (50-70°C) 9:1) and crystallization from absol. EtOH 1.16 g (90%) **19**, white plates, m.p. 145°C. - $C_{19}H_{17}NS_2$ (323.5) Calcd. C 70.5 H 5.30 N 4.3 Found C 70.4 H 5.29 N 4.1. - UV (MeOH): λ max (log ε) = 220 (4.2), 252 (3.8), 271 (3.8), 299 (3.4), 311 (3.6), 318 (3.6), 323 nm (3.6). - IR (KBr): 1595; 1560 cm^{-1}. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ(ppm) = 1.79-2.18 (m; 2H, CH_2), 2.57-3.28 (m; 4H, CH_2), 6.99-8.04 (m; 10 H, arom.), 8.61 (d, J = 6.0 Hz; 1H, C-3). - MS (70 eV, 150°C): m/z = 323 (8%, $M^{+\cdot}$), 290 (3), 262 (10), 249 (42), 217 (59), 195 (11), 162 (100), 128 (13), 121 (29).

1-[2-(4'-Methoxyphenyl)-1,3-dithiane-2-yl]-isoquinoline (**21**)

0.68 g (3.0 mmole) 2-(4'-methoxyphenyl)-1,3-dithiane and 0.49 g (3.0 mmole) **18** are reacted analogously to the preparation of **20**. - The oily curde material was purified by cc and crystallization (see **19**): 0.87 g (82%) **21**, white crystals, m.p. 158°C. - $C_{20}H_{19}NOS_2$ (353.5) Calcd. C 68.0 H 5.42 N 4.0 Found C 67.9 H 5.58 N 3.9. - UV (CH_3CN): λ max (log ε) = 221 (4.3), 253 (3.9), 265 (3.9), 300 (3.5), 311 (3.6), 318 (3.6), 323 nm (3.6). - IR (KBr): 1610; 1580 cm^{-1}.- ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 1.89-2.23 (m; 2H, CH_2), 2.63-3.39 (m; 4H, CH_2), 3.74 (s; 3H, OCH_3), 6.68-8.11 (m; 9H, arom.), 8.64 (d, J = 6.0 Hz; 1H, C-3). - MS (70 eV, 155°C): m/z =

353 (72%, $M^{+\cdot}$), 320 (7), 292 (30), 279 (100), 264 (41, *249.51), 247 (33), 232 (50), 225 (16), 204 (32), 192 (52), 162 (30), 151 (28), 128 (12).

8-Methoxy-1-[2-(4'-methoxyphenyl)-1,3-dithiane-2-yl]-isoquinoline (**22**)

2.94 g (13.0 mmole) 2-(4'-methoxyphenyl)-1,3-dithiane and 2.52 g (13.0 mmole) **11** were reacted as described above: 4.9 g (98%) crude **22**; purification by cc (SiO_2; CH_2Cl_2) and crystallization (EtOH): 3.4 g (68%), white crystals, m.p. 155°C. - $C_{21}H_{21}NO_2S_2$ (383.5) Calcd. C 65.8 H 5.52 N 3.6 Found C 65.8 H 5.52 N 3.5. - UV (MeOH): λ max (log ε) = 207 (4.6), 220 (4.5), 223 (4.5), 285 (3.7), 288 (3.7), 295 (3.7), 308 (3.7), 315 (3.7), 327 nm (3.8). - IR (KBr): 1620; 1560 cm^{-1}. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 1.80-2.15 (m; 2H, CH_2), 2.45-2.78 (m; 2H, CH_2), 2.79-3.28 (m; 2H, CH_2), 3.30 (s; 3H, OCH_3), 3.74 (s; 3H, OCH_3), 6.63-6.91 (m; 3H, arom.), 7.25-7.65 (m; 5H, arom.), 8.56 (d, J = 6.0 Hz; 1H, C-3). - MS (70 eV, 170°C): m/z = 383 (47%, $M^{+\cdot}$), 352 (3), 322 (17), 309 (10), 278 (100), 263 (14), 262 (40), 175 (40), 151 (13), 121 (15).

1-Benzoyl-8-methoxyisoquinoline (**23**)

3.20 g (14.8 mmole) red HgO were suspended in 50 ml THF/H_2O (85:15) and treated with 2.60 g (7.36 mmole) **20** and 3.7 ml (29.5 mmole) $BF_3 \cdot Et_2O$ as described for the cleavage of the dithiane derivative **5**. - After cc (SiO_2; Et_2O/petrol ether (50-70°C) 1:1) and crystallization from petrol ether 80-100°C: 1.8 g (93%) **23**, white crystals, m.p. 109-110°C. - $C_{17}H_{13}NO_2$ (263.3) Calcd. C 77.6 H 4.98 N 5.3 Found C 77.3 H 5.28 N 5.3. - UV (CH_3CN): λ max (log ε) = 235 (4.2), 268 (3.6), 285 (3.7), 305 (3.6), 325 nm (3.7). - IR (KBr): 1680 (CO); 1625; 1565 cm^{-1}. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 3.60 (s; 3H, OCH_3), 6.84 (dd, J_1 = 7.5 Hz, J_2 = 1.8 Hz; 1H, arom.), 7.27-7.90 (m; 8H, arom.), 8.57 (d, J = 6.0 Hz; 1H, C-3). - MS (70 eV): m/z = 263 (41%, $M^{+\cdot}$), 262 (23), 248 (7), 247 (13), 235 (44, *209.98), 234 (100), 232 (14), 220 (6), 206 (63, *181.35), 158 (4), 105 (76), 77 (88).

1-Benzoyl-8-methoxy-2-methylisoquinolinium iodide

1.84 g (7.0 mmole) **23** were refluxed in 20 ml CH_3I and 40 ml of absol. acetone for 4 h. - After about 2 h a voluminous precipitate started to separate. - Volatile components were distilled off, the residue was resuspended in acetone and evaporated again in order to remove CH_3I completely: 2.60 g (92%) yellow crystalls, m.p. 175°C (absol. EtOH). - $C_{18}H_{16}NO_2I$ (405.2) Calcd. C 53.3 H 3.98 N 3.5. Found C 52.9 H 4.01 N 3.3. - UV (CH_3CN): λ max (log ε) = 217 (4.4), 228 (4.2), 244 (4.6), 326 (3.0), 381 nm (3.7). - IR (KBr): 1690 (CO); 1635; 1575 cm^{-1}. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 3.66 (s; 3H, OCH_3), 4.49 (s; 3H, $^+NCH_3$), 7.25-8.32 (m; 8H, arom.), 8.60, 9.41 (AB, J = 6.0 Hz; 2H, C-3, C-4). - MS (FAB, glycerol): 278 $(M\text{-}I)^+$.

1-Benzoyl-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**25**) *and 1-(α-hydroxybenzyl)-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (diastereomers)* (**24a, 24b**)

2.00 g (52.9 mmole) $NaBH_4$ were added in portions to the stirred and cooled suspension of 2.03 g (5.0 mmole) 1-benzoyl-8-methoxy-2-methylisoquinolinium iodide in 70% MeOH. After 1 h refluxing and cooling the mixture was acidified by 2N HCl and evaporated to dryness in vacuo. The residue was suspended in 20 ml H_2O and made slightly alkaline with 10% NH_3. Extraction with CH_2Cl_2, drying (Na_2SO_4) and evaporation in vacuo yielded 1.33 g crude materials. CC (SiO_2; 1. ethyl acetate, 2. MeOH) afforded 0.15 g (11 %) **25** and 1.02 g of the diasteromers **24a/24b**, which were separated by flash-chromatography (SiO_2; ethyl acetate/petrol ether (50-70°C) 1:1): 0.78 (55%) **24a**, 50 mg (4%) **24b** and 30 mg mixture **24a/24b**.

25: yellowish powder, m.p. 66°C after Kugelrohr-distillation at 130°C/0.01 Torr. - $C_{18}H_{19}NO_2$ (281.4) Calcd. C 76.8 H 6.81 N 5.0 Found C 76.4 H 6.64 N 5.0. - UV (CH_3CN): λ max (log ε) = 230 (4.1), 264 (3.5), 271 nm (3.5). - IR (KBr): 3060; 2940; 2860; 2820; 1695 (CO); 1680 (CO); 1600; 1480 cm^{-1}. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 2.54 (s; 3H, NCH_3), 2.63-3.33 (m; 4H, CH_2), 3.57 (s; 3H, OCH_3), 5.05 (s; 1H, C-1), 6.61, 6.81 (2 x d, J = 8.1 Hz; 2H, C-5, C-7), 7.07-7.29 ("t"; 1H, C-6), 7.30-7.65 (m; 3H, arom.), 7.94-8.19 (m; 2H, arom.). - MS (CI, 2-methylpropane): 282 (MH^+), 265, 176, 105.

24a: reddish powder, m.p. 56°C after Kugelrohr-distillation at 150°C/0.01 Torr. - $C_{18}H_{21}NO_2$ (283.4) Calcd. C 76.3 H 7.47 N 4.9 Found C 76.1 H 7.51 N 4.9. - UV (MeOH): λ max (log ε) = 225 (3.9), 257 (3.1), 271 (3.2), 276 (3.2), 279 nm (3.2). - IR (KBr): 3040 (OH); 2980; 2960; 2940; 2860; 1600; 1480 cm^{-1}. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 1.88-2.86 (m; 4H, CH_2), 2.48 (s; 3H, NCH_3), 3.70 (s; 3H, OCH_3), 4.25, 5.21 (AB, J = 5.7 Hz, 2H, C-1 and C-α), 6.54-6.80 (2 x d, overlap; 2H, arom.), 6.87-7.28 (m; 6H, arom.). - MS (FAB, glycerol): 284 (MH^+), 266, 176.

24b: yellowish oil, Kugelrohr-distillation 140-150°C/0.01 Torr. - IR (KBr): 3340 (OH); 2940; 2810; 1600; 1475 cm^{-1}. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 2.25 (s; 3H, NCH_3), 2.41-3.47 (m; 4H, CH_2), 3.37 (s; 3H, OCH_3), 4.02, 4.50 (AB, J = 5.7 Hz; 2H, C-1 and C-α), 6.57, 6.74 (2 x d, J = 8.1 Hz; 2H, C-5 and C-7), 7.03-7.46 (m; 6H, arom.). - MS (FAB, glycerol): 284 (MH^+), 266, 176.

1-(α-Bromobenzyl)-8-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrobromide (**27a**)

2.85 ml (30.0 mmole) BBr_3 in 5 ml of absol. CH_2Cl_2 were added drop by drop with stirring at -10°C to 0.85 g (3.0 mmole) **24a** in 15 ml of absol. CH_2Cl_2. Stirring was continued at room temp. for 15 h. After 1 - 2 h a white precipitate began to separate. - The cooled suspension was hydrolyzed carefully with 20 ml of absol. MeOH, then it was brought to dryness in vacuo. When adding 10 ml of absol. MeOH to the oily residue, a crystalline precipitate was formed. After filtration the mother liquors were concentrated and again crystals were precipitated by a little MeOH. This procedure was repeated until no more crystals arose. All the material was recrystallized from absol. MeOH: 0.87 g (70%) **27a**, white crystals, m.p. 195°C. - $C_{17}H_{19}BrNO \cdot Br$ (413.2) Calcd. C 49.4 H 4.64 N 3.4 Found C 49.4 H 4.77 N 3.3. - UV (CH_3CN): λ max (log ε) = 225 (4.0), 259 (3.2), 281 nm (3.4). - IR (KBr): 3170; 2970; 2850; 1620; 1600; 1480 cm^{-1}. - ^{1}H-NMR (90 MHz, D_6-DMSO): δ (ppm) = 2.51 (s; 3H, NCH_3), 2.75-3.90 (m; 4H, CH_2), 4.73, 5.11 (AB, J = 4.5 Hz; 2H, C-1 and C-α), 6.72 (d, J = 8.1 Hz; 2H, arom.), 7.03-7.61 (m; 6H, arom.), 10.16 (s; 1H, OH, H/D-exchange with D_2O). - MS (FAB, glycerol): 334, 332 ($C_{17}H_{19}BrNO^+$), 252, 162.

Mixture of diastereomers **27a/27b** *hydrobromides and ring closure to* **28**

0.05 g (0.18 mmole) **24b** were treated with 0.2 ml (2.1 mmole) BBr_3 in 1 ml CH_2Cl_2 as described for **24a**. The crude product (**27a** + **27b**) was stirred in 1 ml CF_3COOH for 3 h at 70-75°C. Work-up as depicted for the conversion of **27a** to **28** (see below). - Prep. tlc (SiO_2-plate 20 x 20 cm^2, 0.5 mm; ethyl acetate) and Kugelrohr-distillation (130°C/0.01 Torr) led to 8 mg **28**. Data see below.

27a/27b (hydrobromides): ^{1}H-NMR (90 MHz, CF_3COOH): δ (ppm) = 2.88, 2.94 (2 x s; 6H, 2 x NCH_3), 3.00-4.42 (m; 8H, CH_2), 5.04 (dd, J_1 = 6.9 Hz, J_2 = 3.0 Hz; 1H, C-1, **27b**), 5.22 (dd, J_1 = 6.9 Hz, J_2 = 3.0 Hz; 1H, C-1, **27a**), 5.45 (d, J = 6.9 Hz; 1H, C-α, **27b**), 5.63 (d, J = 6.9 Hz; 1H, C-α, **27a**), 6.64-7.55 (m; 16H, arom.).

3-Methyl-2a,3,4,5-tetrahydro-2H-furo[2,3,4-i,k]isoquinoline (**28**)

0.62 g (1.5 mmole) **27a** in 5 ml CF_3COOH were stirred for 3 h at 70-75°C. The reaction was followed by ^{1}H-NMR. - After completion CF_3-COOH was carefully evaporated in vacuo and the residue was made

alkaline with saturated Na_2CO_3-solution. Extraction with CH_2Cl_2, drying (Na_2SO_4), and evaporation afforded 0.36 g (96%) of crude oil, which was purified by cc (SiO_2; ethyl acetate): 0.29 g (77%) **28**, white needles, m.p. 91°C. - $C_{17}H_{17}NO$ (251.3) Calcd. C 81.2 H 6.82 N 5.6 Found C 81.0 H 6.66 N 5.6. - UV (MeOH): λ max (log ε) = 213 (4.2), 250 (2.9), 276 (3.3), 279 (3.3), 282 nm (3.3). - IR (KBr): 3050; 2950; 2800; 2790; 1635; 1630; 1610; 1460 cm^{-1} . - ^{1}H-NMR (90 MHz, $CDCl_3$). δ (ppm) = 2.12 (s; 3H, NCH_3), 2.26-3.20 (m; 4H, CH_2), 3.82, 5.39 (AB, J = 10.1 Hz; 2H, C-2a and C-2), 6.65, 6.76 (2 x d, J = 7.8 Hz; 2H, arom.), 7.06-7.27 ("t"; 1H, arom.), 7.34-7.58 (m; 5H, arom.). - ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.16 (s; 3H, NCH_3), 2.42-2.57 (m; 1H, CH_2), 2.78-3.15 (m; 3H, CH_2), 3.82, 5.39 (AB, J = 10.14 Hz; 2H, C-2a and C-2), 6.62 (d, J = 7.98 Hz; 1H, arom.), 6.74 (d, J = 7.66 Hz; 1H, arom.), 7.09-7.17 ("t"; 1H, arom.), 7.29-7.47 (m; 3H, arom.), 7.48-7.63 (m; 2H, arom.). - MS (70 eV, 90°C): m/z = 251 (62%, $M^{+\cdot}$), 250 (16), 208 (3), 207 (5), 174 (45), 145 (100), 144 (10).

Cyclization of the mixture **27a** + **27b** afforded also only compound **28** (same stereochemistry).

3,3-Dimethyl-2a,3,4,5-tetrahydro-2H-furo[2,3,4-i,k]isoquinolinium-ion (**29**), *Iodide and Chloride*

0.10 g (0.4 mmole) **28** were refluxed for 2 h in 4 ml CH_3I and 8 ml CH_3CN. Evaporation of the volatile components in vacuo afforded an oil, which was dried in vacuo and dissolved in CH_2Cl_2. After about 5 min white crystals were formed, which were collected after 12 h at 4°C. Washing with CH_2Cl_2 and drying led to 0.15 g (95%) **29**-iodide, m.p. 187-188°C. - $C_{18}H_{20}NOI$ (393.3) Calcd. C 55.0 H 5.13 N 3.5 Found C 54.7 H 5.13 N 3.3. - ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 2.95-3.51 (m; 8H, $N(CH_3)_2$ and CH_2), 4.23-4.57 (m; 2H, CH_2), 5.87, 6.04 (AB, J = 9.9 Hz; 2H, C-2a and C-2), 6.70, 6.87 (2 x d, J = 7.5 Hz; 2H, arom.), 7.17-7.60 (m; 4H, arom.), 7.70-8.03 (m; 2H, arom.). - MS (FAB, glycerol): 266 ($C_{18}H_{20}NO^+$).

29-chloride: 0.12 g (0.30 mmole) **29**-iodide and 0.10 g (0.70 mmole) freshly precipitated AgCl were stirred in 10 ml MeOH/H_2O (1:1) for 24 h in the dark. After filtration and washing with MeOH/H_2O the filtrate was evaporated to dryness. The residue was dissolved in as little as possible MeOH, ethyl acetate (20 ml) was added and the hot solution was concentrated until a turbidity arose. After 12 h in the refrigerator **29**-chloride (white crystals) was collected: 75 mg, 82%, m.p. 198°C (decomp.). - $C_{18}H_{20}NOCl$ (301.8) Calcd. C 71.6 H 6.68 N 4.6 Found C 71.3 H 6.61 N 4.5. - IR (KBr): 1645; 1615 cm^{-1} (C=C; arom.). - ^{1}H-NMR (250 MHz, CD_3OD): δ (ppm) = 3.07, 3.08 (2 x s; 6H, $N(CH_3)_2$), 3.19-3.39 (m; 2H, CH_2), 3.89-4.01 (m; 2H, CH_2), 5.63, *5.98* (AB, J = 9.73 Hz; 2H, C-2a and *C-2*), 6.79 (d, J = 8.08 Hz; 1H, C-5 or C-7), 6.97 (d, J = 7.81 Hz; 1H, C-5 or C-7), 7.35-7.45 ("t"; 1H, C-6), 7.46-7.58 (m; 3H, C-3', C-4', C-5'), 7.65-7.76 (m; 2H, C-2', C-6').

Literature

1 Preliminary commun.: W. Wiegrebe and D. Dirnberger, Arch. Pharm. (Weinheim) *320*, 948 (1987).
2 M.H.A. Zarga, G.A. Miana, and M. Shamma, Tetrahedron Lett. *1981*, 541.
3 S. Chattopadhyay and M. Shamma, Heterocycles *19*, 697 (1982).
4 D. Seebach, V. Ehrig, H.F. Leitz, and R. Henning, Chem. Ber. *108*, 1946 (1975).
5 For 2-lithio-2-phenyldithiane see lit. [6], p. 368.
6 B.-Th. Gröbel and D. Seebach, Synthesis *1977*, 357.
7 E. Vedejs and P.L. Fuchs, J. Org. Chem. *36*, 366 (1971); F. Eloy and A. Deryckere, Helv. Chim. Acta. *52*, 1755 (1969).
8 M. Hesse, H. Meier and B. Zeeh, Spektroskopische Methoden in der Organischen Chemie, 2. ed., p. 69, G. Thieme Verlag, Stuttgart/New York 1984.
9 D.H. Williams and I. Flemming, Strukturaufklärung in der Organischen Chemie, 5. ed., p. 104/105 and p. 230, G. Thieme Verlag, Stuttgart/New York 1985.
10 D. Seebach and R. Bürstinghaus, Synthesis *1975*, 461.
11 H. Muxfeldt, W.-D. Unterweger, and G. Helmchen, Synthesis *1976*, 694.
12 C.A. Reece, J.O. Rodin, R.G. Brownlee, W.G. Duncan, and R.M. Silverstein, Tetrahedron *24*, 4249 (1968).
13 K. Narasaka, T. Sakashita, and T. Mukaiyama, Bull. Chem. Soc. Jpn. *45*, 3724 (1972).
14 E. Fujita, Chem. Pharm. Bull. *1978*, 3743.
15 E.J. Corey and B. Erickson, J. Org. Chem. *36*, 3553 (1971).
16 M.L. Wolfrom, J. Am. Chem. Soc. *51*, 2188 (1929); E.J. Corey and D. Crouse, J. Org. Chem. *33*, 298 (1968).
17 T. Mukaiyama, K. Kamio, S. Kobayashi, and H. Takei, Bull. Chem. Soc. Jpn. *45*, 3725 (1972).
18 W.F.J. Huurdeman, H. Wynberg, and D.W. Emerson, Synth. Commun. *2*, 7 (1972); same authors, Tetrahedron Lett. *37*, 3449 (1971).
19 T.L. Ho, Synthesis *1973*, 352.
20 G.A. Olah, S.C. Narang, and G.F. Salem, Synthesis *1980*, 657.
21 H.L. Wang-Chang, Tetrahedron Lett. *1972*, 1989.
22 A.R. Katritzky and J.M. Lagowski, Chemistry of the Heterocyclic N-Oxides, in: Organic Chemistry, vol. 19, p. 21, Academic Press Inc., London and New York 1971.
23 F. Schenker, R.A. Schmidt, T. Williams, and A. Brossi, J. Heterocycl. Chem. *8*, 665 (1971).
24 R.A. Robinson, J. Am. Chem. Soc. *62*, 1944 (1947).
25 M. Okamoto, Chem. Pharm. Bull *15*, 168 (1967).
26 J.B. Hendrickson and C. Rodriguez, J. Org. Chem. *48*, 3345 (1983).
27 Lit. 22, p. 265
28 a) S. Oae, T. Kitao, and Y. Kitaoka, Tetrahedron *19*, 827 (1963). - b) M.M. Robison and B.L. Robison, J. Org. Chem. *21*, 1337 (1957).
29 V.I. Ognyanov, M.A. Haimova, and M.M. Mollov, Heterocycles *19*, 1069 (1982).
30 Lit. 22, p. 281.
31 M. Ikehara, Pharm. Bull. (Japan) 2, 111 (1954); C.A. *50*, 1014 (1956).
32 W. Wiegrebe and W. Awe, Arch. Pharm. (Weinheim) *296*, 807 (1963).

[Ph673]