Synthesis of C-13-Alkylated 8-Oxoberbines

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C-13-alkylated methoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-ones **2a-e** were synthesized by photocyclization of 1-alkylidene-*N*-benzoyl-1,2,3,4-tetrahydroisoquinolines **1**. Moreover, condensation of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-oxo-isoquinoline with homophthalic acid anhydrides **7a** and **b** leads to the C-13-alkylated 8-oxoberbines **2b** and **c** and improves the yields compared with those of the photocyclization method.

Synthese von C-13-alkylierten 8-Oxoberbinen

Die C-13-alkylierten Methoxy-8*H*-dibenzo[*a*,*g*]chinolizin-8-one **2a-e** wurden durch Photozyklisierung der 1-Alkyliden-*N*-benzoyl-1,2,3,4-tetrahydroisochinoline **1** synthetisiert, aber auch die Kondensation von 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-oxo-isochinolin mit den Homophthalsäureanhydriden **7a** und **b** führt zu den C-13-alkylierten 8-Oxoberbinen **2b** und **c** und verbessert die Ausbeuten, verglichen mit der Photozyklisierungsmethode.

In connection with our investigations of compounds with cytostatic activity and affinity to steroid receptors we synthesized a number of 8-oxoberbines[1,2]. These compounds were prepared either according to *Lenz*[3] or to *Ninomiya*[4] by photocyclization or using *Haimova's* strategy[5]. In this paper we describe the synthesis of *C-13-alkylated* 8-oxoberbines, because the C-13-substituent was regarded as a lipophilic anchor for the estrogen receptor.

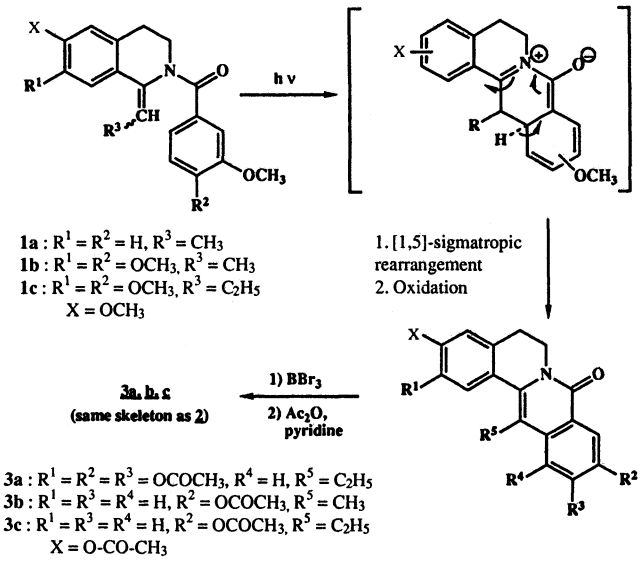
a) Photochemical synthesis of C-13-alkylated 8-oxoberbines

C-13-alkyl-8-oxoberbines with *one* methoxy group in each aromatic ring were obtained only by photocyclization, because alkylated mono-methoxy homophthalic acid anhydrides, necessary according to method *b)* (see below), are accessible with difficulties only. This photocyclization starts with enamides, often used for the preparation of protoberbines[3,4]. On account of the formation of a variety of products, quite often the reaction is not controllable because of the excess of energy used during photocyclization, resulting in poor yields and extensive purification. In spite of these handicaps C-13-alkylated 8-oxoberbines can be prepared rather easily by this method[6] and so we synthesized compounds **2a-e** according to this procedure.

1-Alkyl-3,4-dihydroisoquinolines **5** obtained *via* amides **4** (Scheme 2) are condensed with benzoic acid chlorides **6** affording 1-alkylidene-*N*-benzoyl-1,2,3,4-tetrahydroisoquinolines **1** which were cyclized to the 8-oxoberbines **2** which were subsequently converted to the acetoxy derivatives **3** (Scheme 1).

β-(3-Methoxyphenyl)-ethylamine or homoveratrylamine was condensed base catalyzed with the appropriate acid chlorides to get compounds **4**. The yields are nearly quantitative and are higher than those of the condensation of these β-phenylethylamines with the pertinent esters[7].

Amides **4** are cyclized to the 1-alkyl substituted 3,4-dihydroisoquinolines **5** by *Bischler-Napieralski* reaction with $POCl_3$ in acetonitrile (Scheme 2). The nitrilium ion - formed as an intermediate in this reaction - effects the ring closure with the C-atom of the aromatic ring. Use of acetonitrile favours cationic intermediates[8] and therefore affords higher yields and less side products; the 3,4-dihydroisoquinolines **5** were purified *via* their hydrochlorides, and are low melting *solids*.



Scheme 1: Photocyclization of the not brominated enamides **1a-c**

Besides the 8-oxoberbines **2a** and **2d** which were available only by this procedure, also compounds **2b**, **2c**, and **2e** have been synthesized by cyclization of the pertinent 1-alkylidene-*N*-benzoyl-3,4-dihydroisoquinolines **1**.

For the synthesis of enamides **1** *Lenz*[9] condensed the pertinent 1-alkyl-3,4-dihydroisoquinolines with benzoic acid anhydrides, whilst *Ninomiya*[10] used more easily available ben-

[+)] Dedicated to Prof.Dr.Drs.h.c. *H. Oelschläger*, Frankfurt am Main, on the occasion of his 70th birthday appreciating his merits to the development of the Institute of Pharmacy at the University of Regensburg.

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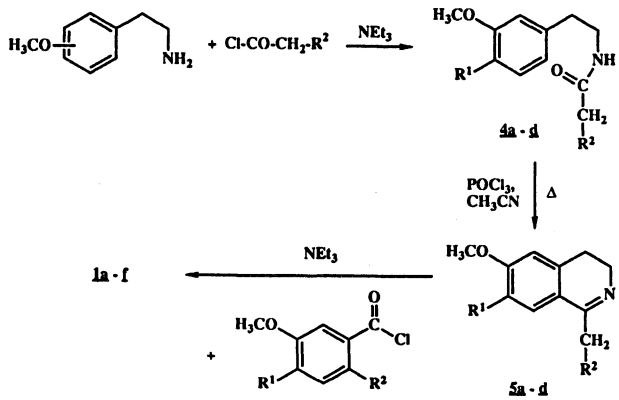


Scheme 2

zoic acid chlorides. Therefore, we also started from benzoic acid chlorides which were condensed base catalyzed in benzene with compounds **5** affording the 1-alkylidene-*N*-benzoyl-3,4-dihydroisoquinolines **1** (Scheme 2). The benzenic solution of the product can be used directly for photocyclization after separation from triethylamine hydrochloride.

The *E*- and *Z*-isomers of the enamides **1** arose in different ratios, but in some cases the *Z*-isomer came up only. *Ninomiya*[10] explained analogous findings by the different bulkiness of the *N*-aroyl groups, but also the aromatic protons of the isoquinoline ring system influence the ratio of the isomers[11]: C-8-H in ring A of the isoquinoline overlaps according to the *Van der Waals*-radii in *Dreiding*-models with the alkyl substituent, and so the formation of the *Z*-isomer is preferred on account of sterical hindrance (Fig. 1).

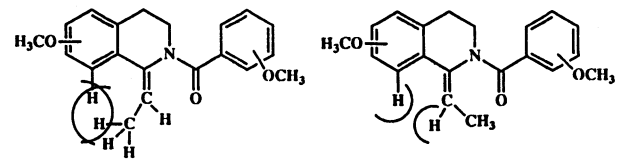


Fig. 1[12]

These considerations, however, can not fully explain our observations:

1) The C-3'-OCH_3-singlet is shifted upfield in the *Z*-isomer for 0.2-0.3 ppm, as compared with the *E*-isomer: when the aroyl rest is rotating around the N-CO-bond the methoxy group is influenced by the alkylidene moiety.
2) Rotation of the aroyl rest around this N-CO-bond leads to broad signals in the 250-MHz-spectra; at -50°C, however, the molecules are "frozen" and well resolved signals can be seen (Fig. 2).
3) In 1-ethylidene derivatives, not brominated in the aroyl ring system (**1a**, e.g. - Scheme 1), only the *Z*-isomer arises because of the interaction described above (Fig. 1). If, however, the aroyl ring system contains bromine (**1d**, e.g. - Scheme 3) also the *E*-isomer is formed on account of the rotation of the C-2'-brominated aroyl increment (*mono*-methoxy substitution: *E/Z* = 1:1; *di*-methoxy substitution: *E/Z* = 3:7).
4) In 1-propylidene substituted isoquinolines (**1c** or **1e**, e.g.), independent of the bromine substitution at the aroyl ring system, only the *Z*-isomer is formed; the sterical interaction of the propylidene group with the aromatic C-8-H is stronger than the sterical hindrance by the substituents of the benzoyl group so preventing the formation of the *E*-isomer.

Compound **1c**/*Z*-isomer (Fig. 2) exhibits the triplet of the propylidene group at δ = 0.72 ppm, the pertinent methylene group resonates as a multiplet at δ = 2.02 ppm. One C-3-H leads to a broad signal at δ = 2.82 ppm. The protons of the C-4-methylene group also show a multiplet in the 250-MHz-spectrum at -50°C at δ = 3.22 ppm. As described above the C-3'-methoxy group is shifted upfield, while the other methoxy groups form singlets near δ = 3.95 ppm. The second C-3-H, extremely shifted downfield, resonates as a multiplet at δ = 5.11 ppm. This effect can be explained by the anisotropic effect of the carbonyl group[6]. By this chemical shift the signals of the different isomers can be assigned (Fig. 1): In the *Z*-isomer of e.g. **1d** the methyl-doublet (δ = 1.53 ppm) is shifted upfield as compared to the *E*-isomer (δ = 1.92 ppm) because of this interaction, while the quartet of the vinylic proton is shifted downfield (*Z*-isomer: δ = 6.23 ppm, *E*-isomer: δ = 5.71 ppm).- The signals of the aromatic protons in *Z*-**1c** come up between δ = 6.6 ppm and 7.2 ppm (Fig. 2).

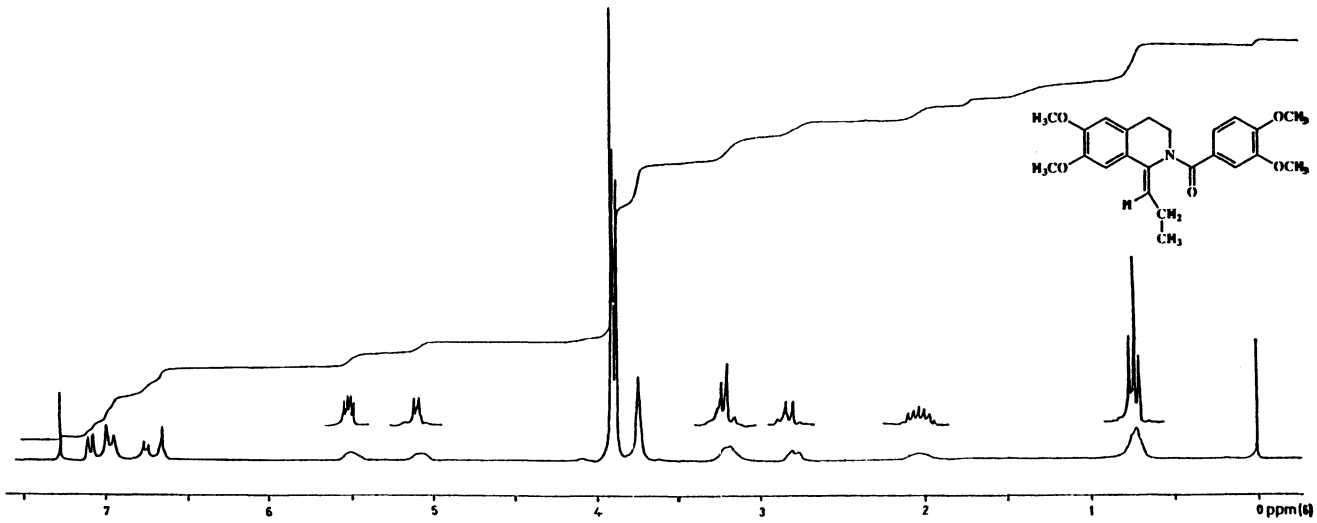
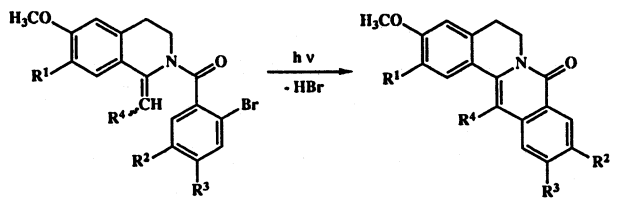


Fig. 2: ^{1}H-NMR-spectra (250 MHz), compound **1c** (*Z*-isomer), at 24°C (below) and at -50°C (above)

The mechanisms of the photocyclizations of the enamides, either brominated or not brominated, have been discussed by *Lenz*[3,9] or *Ninomiya*[4,10], respectively. We used the oxidative photocyclization of enamides **1**, not substituted in the *ortho*-position, for the preparation of compounds **2a-d**. On account of the rotation around the N-CO-bond of the 3-methoxy-benzoyl-enamide **1a** we got 3,10- and 3,12-dimethoxy-8-oxoberbines **2a** and **2d** as regioisomers. The tetramethoxy derivatives **1b** or **1c** did not show this effect. Because the yields in the dimethoxy derivatives **2a** and **2d** were low on account of the regioisomers mentioned above we switched from this oxidative photocyclization to the "refined" methods of *Ninomiya*[10] or *Lenz*[9] making use of *ortho*-brominated benzoyl increments in the enamides **1d-f** (Scheme 3). Here elimination of the *ortho*-group by irradiation takes place.

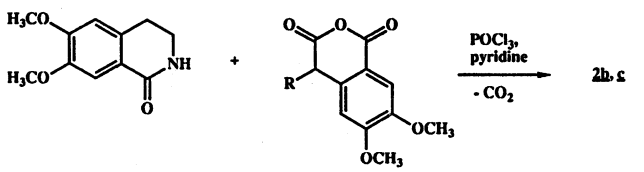


1d : $R^1 = R^3 = H$, $R^2 = OCH_3$, $R^4 = CH_3$ **2a** : $R^1 = R^3 = H$, $R^2 = OCH_3$, $R^4 = CH_3$
1e : $R^1 = R^3 = H$, $R^2 = OCH_3$, $R^4 = C_2H_5$ **2b** : $R^1 = R^2 = R^3 = OCH_3$, $R^4 = CH_3$
1f : $R^1 = R^2 = R^3 = OCH_3$, $R^4 = CH_3$ **2e** : $R^1 = R^3 = H$, $R^2 = OCH_3$, $R^4 = C_2H_5$

Scheme 3: Photocyclization of the brominated enamides **1d-f**

b) Synthesis of C-13-alkylated 8-oxoberbines by condensation of 1,2,3,4-tetrahydro-1-oxo-isoquinolines with C-4-alkylated homophthalic acid anhydrides

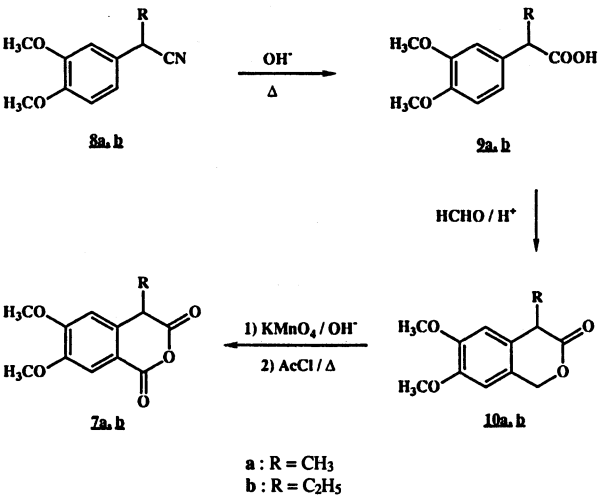
Haimova used this condensation for the synthesis of 2,3,10,11-tetramethoxy-8-oxoberbine [5]. It had to be shown whether C-4-alkylated homophthalic acid anhydrides **7** could also be used for this strategy (Scheme 4). We synthesized the tetramethoxy-8-oxoberbines **2b** and **2c** by this method. As C-4-alkylated *6-mono*-methoxy-substituted homophthalic acid anhydrides are not easily available, 8-oxoberbines with *C-11-mono*-methoxy substitution in ring D were not prepared by this route.



7a : R = CH_3
7b : R = C_2H_5

Scheme 4

Compounds **7** were synthesized *via* the dimethoxylactones **10a** and **10b**. First the alkylated dimethoxyphenylacetonitriles **8a**[12] and **8b** are hydrolysed to the phenylacetic acid derivatives **9a** and **9b** (Scheme 5). According to *Finkelstein* and *Brossi*[13] the methylene group *ortho* to the acetic acid increment was introduced into compounds **9** affording the lactones **10**, which are transformed by alkaline oxidation with $KMnO_4$ to the corresponding homophthalic acids. Under these conditions the alkyl groups are not oxidized. Ring closure to the homophthalic acid anhydrides **7** was effected by refluxing the acids with acetyl chloride (Scheme 5).



a : R = CH_3
b : R = C_2H_5

Scheme 5

This extension of *Haimova's* strategy[5] simplifies known methods, including photocyclization, for the preparation of C-13-alkylated 8-oxoberbines, improves the yields and, probably, the total synthesis of alkaloids with a berbine skeleton. Pharmacological tests are described in a forthcoming publication[2].

Experimental Part

Melting points: Büchi 510 apparatus, uncorrected.- Elemental analyses: Mikroanalytisches Laboratorium, University of Regensburg.- IR-spectra: Beckman Acculab III; KBr.- ^{1}H-NMR-spectra: Varian EM 390 (90 MHz), Bruker WM 250 (250 MHz); TMS as internal standard.- UV-spectra: Uvikon 810 (Kontron); solvent: acetonitrile.- Mass-spectra: Varian MAT CH 5.

N-Benzoyl-1,2,3,4-tetrahydroisoquinolines **1a-f**, *general procedure*

20 mmole of the acid chloride **6** in benzene (25 ml) are added to 2.2 g of triethylamine and 20 mmole of the 3,4-dihydroisoquinoline **5** in benzene (50 ml), then the solution is refluxed for 2 h. The precipitate is separated, the product in the remaining benzenic solution is used without purification.- Purified for identification by CC (SiO_2, $CHCl_3$/ether 1:1 or EtOAc).- Yields: 60-75% and small amounts of benzamide-derivatives.

1-Ethylidene-1,2,3,4-tetrahydro-6-methoxy-2-(3-methoxybenzoyl)isoquinoline (**1a**)

Prepared from **5a** and **6b**[6].

2-(3,4-Dimethoxybenzoyl)-1-ethylidene-1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinoline (**1b**)

From **5c** and **6c**; colorless crystals, m.p. 156-158°C (ether).- Z-isomer: $C_{22}H_{25}NO_5$ (383.4) Calc. C 68.5 H 6.47 N 3.6 Found C 68.9 H 6.57 N 3.7.- IR (KBr): 1625 (CO) cm^{-1}.- ^{1}H-NMR (250 MHz, -50°C, $CDCl_3$): δ (ppm) = 1.30 (d; J = 7 Hz; 3H; CH_3), 2.60-3.33 (m; 3H; CH_2; H-3/H-4), 3.76 (s; 3H, OCH_3); 3.91, 3.93, 3.94 (s; 9H, OCH_3), 5.11 (m; 1H; H-3), 5.68 (q; J = 7 Hz; 1H vinyl), 6.60-7.22 (m; 5H arom.).

N-[β-(3,4-Dimethoxy-6-[1-oxopropyl]phenyl)ethyl]-3,4-dimethoxybenzamide[*]

Isolation by CC (SiO_2, EtOAc).- m.p. 128-130°C (ether).- $C_{22}H_{27}NO_6$ (401.4).- IR (KBr): 3300 (NH), 1690 (CO), 1640 (CO-NH) cm^{-1}.- UV (MeOH): λ max (log ε) = 290 (4.02), 260 (4.25), 205 nm (4.64); no change by addition of HCl.- MS: m/z = 401 (5%, M^+), 383 (4, $(M - H_2O)^+$), 372 (1), 220 (24), 191 (16), 165 (23), 43 (100).

[*] This compound has probably come up by hydrolysis of the pertinent 3,4-dihydroisoquinoline derivative of **1b**.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-(3,4-dimethoxybenzoyl)-1-propylidene-isoquinoline (**1c**)

From **5d** and **6c**; colorless crystals; m.p. 134-136°C (ether).- Z-isomer: $C_{23}H_{27}NO_5$ (397.5) Calc. C 69.5 H 6.65 N 3.5 Found C 69.5 H 6.85 N 3.5.- IR (KBr): 1625 (CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.72 (t; J = 7 Hz; 3H, CH_3), 2.02 (m; 2H; $C\underline{H}_2$-CH_3), 2.82 (m; 1H; H-3), 3.22 (m; 2H; CH_2; H-4), 3.76, 3.91, 3.94, 3.95 (s; 12 H; -OCH_3), 5.11 (m; 1H; H-3), 5.52 (m; 1H vinyl), 6.60-7.20 (m; 5H arom.).

N-[β-(3,4-Dimethoxy-6-[1-oxobutyl]phenyl)ethyl]-3,4-dimethoxybenzamide[*]

Isolation by CC (SiO_2, EtOAc), m.p. 128-130°C (ether).- $C_{23}H_{29}NO_6$ (415.5) Calc. C 66.5 H 7.04 N 3.4 Found C 66.3 H 6.79 N 3.3.- IR (KBr): 3300 (NH), 1690 (CO), 1640 (CO-NH) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.00 (t; J = 7.5 Hz; 3H; CH_3), 1.57-1.90 (m; 2H; CH_2-$C\underline{H}_2$-CH_3), 2.77-3.10 (m; 4H; $C\underline{H}_2$-CH_2-CH_3 and $C\underline{H}_2$-CH_2-N), 3.57-3.85 (m; 2H; $C\underline{H}_2$-N), 3.90 (s; 12 H; OCH_3), 6.73-6.92 (m; 2H arom.), 7.10 (s; 1H arom.), 7.30-7.50 (m; 2H arom.), 7.83 (s [broad]; 1H; NH).- UV (MeOH): λ max (log ε) = 292 (4.03), 260 (4.25), 210 nm (4.58); no change by addition of HCl.- MS: m/z = 415 (3%, M^+), 397 (3, $(M - H_2O)^+$), 368 (1), 234 (96), 191 (52), 179 (30), 165 (100), 137 (12).

[*)] This compound has probably come up by hydrolysis of the pertinent 3,4-dihydroisquinoline derivative of **1c**.

2-(2-Bromo-5-methoxybenzoyl)-1-ethylidene-1,2,3,4-tetrahydro-6-methoxyisoquinoline (**1d**)

From **5a** and **6a**; colorless crystals, m.p. 150-152°C (ether).- 1:1-mixture of *E/Z*-isomers.- $C_{20}H_{20}BrNO_3$ (402.3) Calc. C 59.7 H 4.99 N 3.5 Found C 59.7 H 5.01 N 3.5.- IR (KBr): 1635, 1640 (CO) cm^{-1}.- Z-isomer: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.53 (d; J = 7 Hz; 3H; CH_3), 2.71-2.97 (m; 3H; CH_2; H-3/H-4), 3.54, 3.80 (s; 6H, OCH_3), 4.99-5.11 (m; 1H; H-3), 6.23 (q; J = 7 Hz; 1H vinyl), 6.25-6.88, 7.27-7.58 (m; 6H arom.).- *E*-isomer: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.92 (d; J = 7 Hz; 3H; CH_3), 3.14-3.40 (m; 2H; CH_2; H-4), 3.65 (s [broad]; 2H; CH_2; H-3), 3.80, 3.81 (s; 6H; OCH_3), 5.71 (q; J = 7 Hz; 1H vinyl), 6.25-6.88, 7.27-7.58 (m; 6H arom.).

2-(2-Bromo-5-methoxybenzoyl)-1,2,3,4-tetrahydro-6-methoxy-1-propylidene-isoquinoline (**1e**)

From **5b** and **6a**; colorless crystals, m.p. 54-56°C (ether).- $C_{21}H_{22}BrNO_3$ (416.3).- Z-isomer.- IR (KBr): 1640 (CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.97 (t; J = 7.5 Hz; 3H; CH_3), 1.73 (m; 2H; $C\underline{H}_2$-CH_3), 2.87 (t; J = 6 Hz; 2H; CH_2; H-4), 3.13 (t; J = 6 Hz; 2H; CH_2; H-3), 3.77 (s; 3H; OCH_3), 3.85 (s; 3H; OCH_3), 6.03 (s [broad]; 1H vinyl), 6.70-7.80 (m; 6H arom.).

2-(2-Bromo-4,5-dimethoxybenzoyl)-1-ethylidene-1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinoline (**1f**)

From **5c** and **6d**; colorless crystals, m.p. 190-192°C (ether).- $C_{22}H_{24}BrNO_5$ (462.3).- 3:7-mixture of *E/Z*-isomers.- IR (KBr): 1640 (CO) cm^{-1}.- Z-isomer: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.56 (d; J = 7.5 Hz; 3H; CH_3), 2.62-3.36 (m; 3H; CH_2; H-3/H-4), 3.56 (s; 3H; OCH_3), 3.88 (s; 9H; OCH_3), 5.09 (s [broad]; 1H, H-3), 6.38 (q; J = 7.5 Hz; 1H vinyl), 6.40-7.25 (m; 4H arom.).- *E*-isomer: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.96 (d; J = 7.5 Hz; 3H; CH_3), 2.62-3.36 (m; 2H; CH_2; H-4), 3.56 (s [broad]; 2H; CH_2; H-3), 3.88 (s; 3H; OCH_3), 3.91 (s; 9H; OCH_3), 5.75 (q; J = 7.5 Hz; 1H vinyl), 6.40-7.25 (m; 4H arom.).

General Procedure for the Photocyclization

The benzenic solution of the enamide **1** is degassed with N_2 in a preparative photoreactor for 15 min. Then the solution is irradiated with a 125 W Hg vapor lamp for 20-40 h and evaporated. The remaining oil is purified by CC (SiO_2, EtOAc or EtOAc/ether), yields 20-40%.

5,6-Dihydro-3,10-dimethoxy-13-methyl-8H-dibenzo[a,g]quinolizin-8-one (**2a**)

From **1a** or **1d**; colorless crystals, m.p. 178-180°C (EtOH).- $C_{20}H_{19}NO_3$ x 1/2 EtOH (344.4) Calc. C 73.2 H 6.44 N 4.1 Found C 73.2 H 6.31 N 4.1.- IR (KBr): 1640 (CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.52 (s; 3H; CH_3), 2.82 (t; J = 6 Hz; 2H; CH_2; H-5), 3.82 (s; 3H; OCH_3), 3.93 (s; 3H; OCH_3), 4.27 (t; J = 6 Hz; 2H; CH_2; H-6), 6.68-6.92 (m; 2H arom.), 7.20-7.73 (m; 3H arom.), 7.88 (d; J = 2.5 Hz; 1H arom; H-9).- UV: λ max (log ε) = 314 (4.22), 255 (4.13), 213 nm (4.22).

5,6-Dihydro-2,3,10,11-tetramethoxy-13-methyl-8H-dibenzo[a,g]quinolizin-8-one (**2b**)

a) From **1b** or **1f** by photocyclization.

b) By condensation of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-oxo-isoquinoline[14] with 6,7-dimethoxy-4-methyl-isochromane-1,3-dione (**7a**) (cf.[15,1]).- Light-brown crystals, m.p. 210-212°C (EtOH), lit. 213-215°C[9].- MS: m/z = 381 (100%, M^+), 366 (63, *351.59, $(M - CH_3)^+$), 220 (27), 190.5 (18, M^{2+}), 165 (42).

13-Ethyl-5,6-dihydro-2,3,10,11-tetramethoxy-8H-dibenzo[a,g]-quinolizin-8-one (**2c**)

a) From **1c** by photocyclization.

b) By condensation of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-oxo-isoquinoline[14] with 6,7-dimethoxy-4-ethyl-isochromane-1,3-dione (**7b**) (cf.[15,1]).- Yellow needles, m.p. 197-198°C (EtOH).- $C_{23}H_{25}NO_5$ x 1/2 EtOH (418.5) Calc. C 68.9 H 6.74 N 3.4 Found C 69.2 H 6.74 N 3.2.- IR (KBr): 1635 (CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.55 (t; J = 7.5 Hz; 3H; CH_3), 2.82 (t; J = 6 Hz; 2H; CH_2; H-5), 3.08 (q; J = 7.5 Hz; 2H; $C\underline{H}_2$-CH_3), 3.97 (s; 6H; OCH_3), 4.08 (s; 6H; OCH_3), 4.28 (t; J = 6 Hz; 2H; CH_2; H-6), 6.83, 7.20, 7.27, 7.97 (s; 4H arom.).- UV: λ max (log ε) = 330 (4.39), 258 (4.45), 229 nm (4.58).- MS: m/z = 395 (100%, M^+), 380 (50, *365.57, $(M - CH_3)^+$), 349 (51, *320.53, $(380 - OCH_3)^+$), 334 (19, *319.64, $(349 - CH_3)^+$), 306 (5), 197.5 (7, M^{2+}).

5,6-Dihydro-3,12-dimethoxy-13-methyl-8H-dibenzo[a,g]quinolizin-8-one (**2d**)

From **1a**; colorless crystals, m.p. 177-179°C (EtOH).- $C_{20}H_{19}NO_3$ x 1/2 EtOH (344.4) Calc. C 73.2 H 6.44 N 4.1 Found C 73.5 H 6.48 N 4.0.- IR (KBr): 1640 (CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.70 (s; 3H; CH_3), 2.85 (t; J = 6 Hz; 2H; CH_2; H-5), 3.87 (s; 3H; OCH_3), 3.97 (s; 3H; OCH_3), 4.27 (t; J = 6 Hz; 2H; CH_2; H-6), 6.72-6.97 (m; 2H arom.), 7.02-7.70 (m; 3H arom.), 8.20 (dd; $J_{1/2}$ = 7.5 Hz/1.5 Hz; 1H arom; H-9).- UV: λ max (log ε) = 359 (4.26); 328 (4.20); 254 nm (4.20).- MS: m/z = 322 (24%, M^+), 321 (49, *320.00, $(M - H)^+$), 306 (41), 220 (27), 215 (76), 205 (93), 135 (100).

13-Ethyl-5,6-dihydro-3,10-dimethoxy-8H-dibenzo[a,g]quinolizin-8-one(**2e**)

From **1e**; yellow foam, m.p. 130-131°C (EtOH).- $C_{21}H_{21}NO_3$ (335.4) Calc. C 75.2 H 6.31 N 4.2 Found C 74.4 H 6.30 N 4.1.- IR (KBr): 1640 (CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.42 (t; J = 7.5 Hz; 3H; CH_3),

2.80 (t; J = 6 Hz; 2H; CH_2; H-5), 2.98 (q; J = 7.5 Hz; 2H; $C\underline{H}_2$-CH_3), 3.82 (s; 3H; OCH_3), 3.93 (s; 3H; OCH_3), 4.23 (t; J = 6 Hz; 2H; CH_2; H-6), 6.73-6.98 (m; 2H arom.), 7.20-7.83 (m; 3H arom.), 7.93 (d; J = 2.5 Hz; 1H arom; H-9).- UV: λ max (log ε) = 322 (4.23), 216 nm (4.54).

2,3,10,11-Tetraacetoxy-13-ethyl-5,6-dihydro-8H-dibenzo[a,g]quinolizin-8-one (**3a**)

From **2c** according to lit.[1]; m.p. 225-227°C (MeOH).- $C_{27}H_{25}NO_9$ x 1 H_2O (525.5) Calc. C 61.7 H 5.18 N 2.7 Found C 61.4 H 5.00 N 2.7.- IR (KBr): 1780, 1770 (CO-CH_3), 1650 (CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.43 (t; J = 7.5 Hz; 3H; CH_3), 2.33 (s; 12 H; H_3C-CO), 2.75-3.13 (m; 4H; $C\underline{H}_2$-CH_3 and CH_2/H-5), 4.28 (t; J = 6 Hz; 2H; CH_2; H-6), 7.20, 7.53, 7.70, 8.38 (s; 4H arom.).- UV: λ max (log ε) = 330 (4.30), 213 nm (4.52).

3,10-Diacetoxy-5,6-dihydro-13-methyl-8H-dibenzo[a,g]quinolizin-8-one (**3b**)

From **2a** according to lit.[1]; m.p. 232-234°C (EtOH).- $C_{22}H_{19}NO_5$ (378.4) Calc. C 70.0 H 5.07 N 3.7 Found C 69.9 H 5.07 N 3.1.- IR (KBr): 1760 (CO-CH_3), 1650 (CO) cm^{-1}.- ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.34 (s; 3H; H_3C-CO), 2.36 (s; 3H; H_3C-CO), 2.59 (s; 3H; CH_3), 2.93 (t; J = 6 Hz; 2H; CH_2; H-5), 4.28 (t; J = 6 Hz; 2H; CH_2; H-6), 7.07-7.11 (m; 2H arom.), 7.48 (dd; $J_{1/2}$ = 9/2.5 Hz; 1H arom.), 7.60 (d; J = 9 Hz; 1H arom.), 7.81 (d; J = 9 Hz; 1H arom.), 8.21 (d; J = 2.5 Hz; 1H arom.; H-9).- UV: λ max (log ε) = 328 (4.22), 211 nm (4.53).

3,10-Diacetoxy-13-ethyl-5,6-dihydro-8H-dibenzo[a,g]quinolizin-8-one (**3c**)

From **2e** according to lit.[1]; m.p. 195-197°C (MeOH).- $C_{23}H_{21}NO_5$ x 1 H_2O (409.5) Calc. C 67.5 H 5.66 N 3.4 Found C 67.9 H 5.88 N 3.5.- IR (KBr): 1760 (CO-CH_3), 1640 (CO) cm^{-1}.- ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.47 (t; J = 7.5 Hz; 3H; -CH_3), 2.35 (s; 3H; H_3C-CO), 2.36 (s; 3H; H_3C-CO), 2.88 (t; J = 7.5 Hz; 2H; CH_2; H-5), 3.03 (q; J = 7.5 Hz; 2H; $C\underline{H}_2$-CH_3), 4.28 (s [broad]; 2H; CH_2; H-6), 7.12-7.17 (m; 2H arom.), 7.47 (dd; $J_{1/2}$ = 9/2.5 Hz; 1H arom.), 7.66 (d; J = 9 Hz; 1H arom.), 7.85 (d; J = 9 Hz; 1H arom.), 8.22 (d; J = 2.5 Hz; 1H arom.; H-9).- UV: λ max (log ε) = 327 (4.25), 210 nm (4.57).

Methoxyphenylethylamides **4a-d**, *general procedure*

100 mmole of propionic or butyric acid chloride are added under reflux to 100 mmole β-(3-methoxyphenyl)ethylamine or homoveratrylamine and 10.0 g triethylamine in 60 ml absol. CH_2Cl_2. The mixture is stirred for 1 h, the precipitate is dissolved with 2N HCl and stirred again. The org. layer is separated, dried (Na_2SO_4) and evaporated. The resulting pure methoxyphenylethylamides **4** are cyclized without purification.- Yields quantitative.

N-[β-(3-Methoxyphenyl)ethyl]propanamide (**4a**)

From 1-amino-2-(3-methoxyphenyl)ethane (Aldrich) and propionic acid chloride; colorless oil, b.p. 96-97°C, 0.05 T., lit. 97°C, 0.05 T[6].

N-[β-(3-Methoxyphenyl)ethyl]butanamide (**4b**)

From 1-amino-2-(3-methoxyphenyl)ethane (Aldrich) und butyric acid chloride; colorless oil, b.p. 185-187°C, 0.1 T.- IR (KBr): 3290 (NH), 1650 (CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.90 (t; J = 7.5 Hz; 3H; CH_3), 1.37-1.82 (m; 2H; CH_2-$C\underline{H}_2$-CH_3), 2.10 (t; J = 7.5 Hz; 2H; $C\underline{H}_2$-CH_2-CH_3), 2.77 (t; J = 7.5 Hz; 2H; $C\underline{H}_2$-CH_2-NH-), 3.62 (q; J = 7.5 Hz; 2H; CH_2-$C\underline{H}_2$-N; t after D-exchange), 3.73 (s; 3H; OCH_3), 6.22 (s [broad]; 1H; NH), 6.57-6.87 (m; 3H arom.), 7.07-7.33 (m; 1H arom.).

N-[β-(3,4-Dimethoxyphenyl)ethyl]propanamide (**4c**)

From homoveratrylamine and propionic acid chloride; colorless crystals, m.p. 54-55°C (ether), lit.: 57.5-59°C[16].

N-[β-(3,4-Dimethoxyphenyl)ethyl]butanamide (**4d**)

From homoveratrylamine and butyric acid chloride; colorless crystals, m.p. 49-50°C (ether), lit.: 51-53°C[16].

1-Alkyl-3,4-dihydroisoquinolines **5a-d**, *general procedure*

100 mmole of amide **4** are dissolved in 120 ml acetonitrile p.a. and refluxed with 35 ml of $POCl_3$ for 3 h. Then excess of $POCl_3$ and acetonitrile is distilled off and the remaining 3,4-dihydroisoquinoline hydrochloride is filtrated and dissolved in water. The solution is basified with 2N NaOH and extracted with 3 x 100 ml ether. The org. layers are dried (Na_2SO_4) and evaporated: low melting solids or colorless to light-yellow oils.- Purification by Kugelrohr distillation.- Yields 55-70%.

1-Ethyl-3,4-dihydro-6-methoxy-isoquinoline (**5a**)

From **4a**; yellow crystals, m.p. 32°C, b.p. 133-135°C, 0.01 T, lit. b.p. 135°C, 0.01 T[6].

3,4-Dihydro-6-methoxy-1-propyl-isoquinoline (**5b**)

From **4b**; colorless oil, b.p.. 160-162°C, 0.1 T.- $C_{13}H_{17}NO$ (203.3) Calc. C 76.8 H 8.43 N 6.9 Found C 76.5 H 8.22 N 6.8.- IR (KBr): 1625; 1610; 1570; 1505 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.95 (t; J = 7.5 Hz; 3H; CH_3), 1.47-1.85 (m; 2H; CH_2-$C\underline{H}_2$-CH_3), 2.60 (t [broad]; J = 7.5 Hz; 4H; $C\underline{H}_2$-CH_2-CH_3 and $C\underline{H}_2$-CH_2-N), 3.62 (t; J = 7.5 Hz; 2H; CH_2-$C\underline{H}_2$-N), 3.80 (s; 3H; OCH_3), 6.60-6.83 (m; 2H arom.), 7.42 (d; J = 7.5 Hz; 1H arom.).- UV: λ max (log ε) = 274 (3.73), 249 (3.70), 229 nm (3.58).- UV (plus HCl): λ max (log ε) = 316 (3.81), 307 (3.81), 236 nm (3.70).

1-Ethyl-3,4-dihydro-6,7-dimethoxy-isoquinoline (**5c**)

From **4c**; yellow crystals, m.p. 45°C, lit. b.p. 127-130°C, 0.3 mm[16].- $C_{13}H_{17}NO_2$ (219.3) Calc. C 71.2 H 7.81 N 6.4 Found C 70.9 H 7.87 N 6.2.

3,4-Dihydro-6,7-dimethoxy-1-propyl-isoquinoline (**5d**)

From **4d**; yellow crystals, m.p. 37°C, lit. b.p. 150-170°C, 2-3 mm[16].- $C_{14}H_{19}NO_2$ (233.3) Calc. C 72.1 H 8.21 N 6.0 Found C 71.9 H 8.29 N 5.9.

Acid chlorides **6a-d**, *general procedure*

200 mmole (brominated) methoxybenzoic acid are suspended in 50 ml of absol. CH_2Cl_2 and 5 drops of DMF. 22 ml of $SOCl_2$ are added under stirring, then the mixture is refluxed for 2 h. Solvent and excess of reagent are distilled off. The resulting acid chlorides are purified by distillation or used without purification.- Yields 80-90%.

2-Bromo-5-methoxy-benzoic acid chloride (**6a**)

From 2-bromo-5-methoxy benzoic acid[1], yellow liquid, b.p. 105-107°C, 0.1 T.

m-Anisic acid chloride (**6b**)

From m-anisic acid, yellow liquid, b.p. 94-95°C, 0.1 T.; lit. b.p. 242-243°C, 733 mm[17].

3,4-Dimethoxy-benzoic acid chloride (**6c**)

From 3,4-dimethoxy benzoic acid (Merck); light-red precipitate, m.p. 65-66°C; lit. 70°C[18].

2-Bromo-4,5-dimethoxy-benzoic acid chloride (**6d**)

From 2-bromo-4,5-dimethoxy benzoic acid[1], light-brown precipitate, m.p. 73-75°C.

6,7-Dimethoxy-4-methyl-isochroman-1,3-dione (**7a**)

From **10a** *via* 4,5-dimethoxy-α-methyl-homophthalic acid[15], which was heated with CH_3COCl[1].

4-Ethyl-6,7-dimethoxy-isochroman-1,3-dione (**7b**)

From **10b** *via* 4,5-dimethoxy-α-ethyl-homophthalic acid[15], which was heated with CH_3COCl[1].

6,7-Dimethoxy-4-methyl-isochroman-3-one (**10a**)

From **9a**; colorless crystals, m.p. 122-124°C (EtOH).- $C_{12}H_{14}O_4$ (222.2) Calc. C 64.8 H 6.35 Found C 64.6 H 6.43.- IR (KBr): 1740 (CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.67 (d; J = 7.5 Hz; 3H; CH_3), 3.63 (q; J = 7.5 Hz; 1H; CH; H-4), 3.97 (s; 6H; OCH_3), 5.33 (s; CH_2; H-1), 6.83 (s; 2H arom.).

6,7-Dimethoxy-4-ethyl-isochroman-3-one (**10b**)

From **9b**; light-brown crystals, m.p. 84-85°C (EtOH).- $C_{13}H_{16}O_4$ (236.3) Calc. C 66.1 H 6.83 Found C 65.7 H 6.84.- IR (KBr): 1740 (CO) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.07 (t; J = 7 Hz; 3H; CH_3), 1.77-2.17 (m; 2H; $C\underline{H}_2$-CH_3), 3.50 (t; J = 7 Hz; 1H; $C\underline{H}$-CH_2; H-4), 3.93 (s; 6H; OCH_3), 5.30 (d; J = 5 Hz; 2H; CH_2; H-1), 6.68, 6.73 (s; 2H arom.).

2-(3,4-Dimethoxyphenyl)propionic acid (**9a**)

From **8a** according to *Jeffreys*[19]; yellow oil; lit. m.p. 50°C[19].

2-(3,4-Dimethoxyphenyl)butyric acid (**9b**)

From **8b** according to *Jeffreys*[19]; colorless crystals, m.p. 90-92°C (H_2O); lit. 103°C[20].

2-(3,4-Dimethoxyphenyl)propionitrile (**8a**)

Prepared from 3,4-dimethoxyphenylacetonitrile (Merck) according to *Chavdarian*[12] by the carboxylation procedure.- Colorless crystals; yield 87%; m.p. 67-69°C (toluene), lit. 67-69°C[12].

2-(3,4-Dimethoxyphenyl)butyronitrile (**8b**)

2.52 ml (18 mmole) of diisopropylamine are dissolved in 25 ml of absol. THF and cooled to -20°C. 7.74 ml of 2.3-molar n-BuLi (17.8 mmole) are added, the temp. should not exceed -10°C. Then the mixture is stirred for 15 min at -20°C and cooled to -50°C. 16.9 mmole of 3,4-dimethoxyphenylacetonitrile (Fa. Aldrich) in 10 ml of absol. THF are added below -40°C. After stirring for 5 min at -50°C, 1.45 ml (17.8 mmole) of C_2H_5I in 20 ml of absol. THF are added and the mixture is stirred again for 1 h at -60°C, then overnight at room temp. and poured on 50 ml of 2N HCl. The solution is extracted for a few times with ether, the org. layers are washed with H_2O, dried and evaporated.- Purification: CC (SiO_2, EtOAc), yield 80-90%.- Colorless oil, b.p. 93-94°C, 0.1 T.-Lit.[20]: m.p. 56-57°C.- $C_{12}H_{15}NO_2$ (205.3) Calc. C 70.2 H 7.37 N 6.8 Found C 70.1 H 7.30 N 6.7.- IR (film): 2260 (CN) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.03 (t; J = 7.5 Hz; 3H; CH_3), 1.93 (quin; J = 7.5 Hz; 2H; $C\underline{H}_2$-CH_3), 3.63 (t; J = 7.5 Hz; 1H; $C\underline{H}$-CH_2), 3.87 (s; 6H; OCH_3), 6.67-6.90 (m; 3H arom.).

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