

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* strategy⁵. 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.

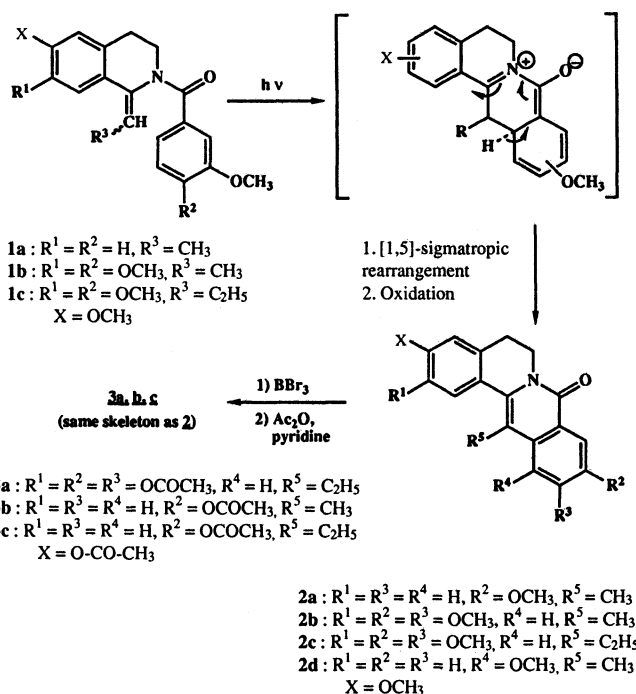
a) Photochemical synthesis of C-13-alkylated 8-oxoberbines

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 method⁶ 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 esters⁷.

Amides **4** are cyclized to the 1-alkyl substituted 3,4-dihydroisoquinolines **5** by *Bischler-Napieralski* reaction with POCl₃ in acetonitrile (Scheme 2). The nitrilium ion - formed



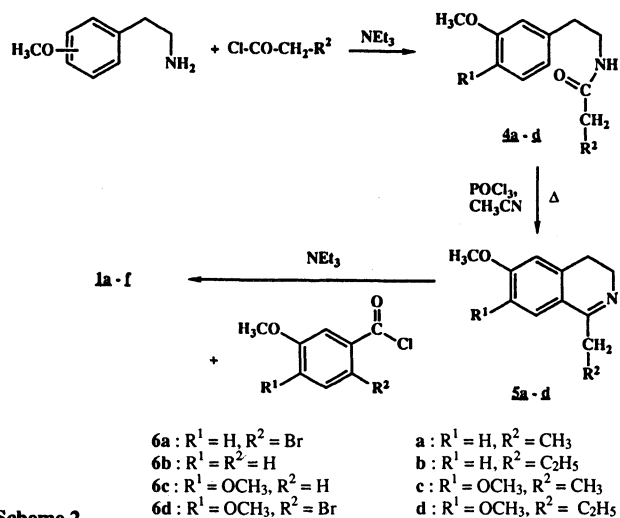
Scheme 1: Photocyclization of the not brominated enamides **1a-c**

as an intermediate in this reaction - effects the ring closure with the C-atom of the aromatic ring. Use of acetonitrile favours cationic intermediates⁸ and therefore affords higher yields and less side products; the 3,4-dihydroisoquinolines **5** were purified *via* their hydrochlorides, and are low melting solids.

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-

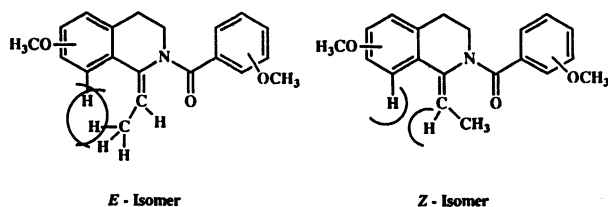
[†] Dedicated to Prof. Dr. Drs. h.c. H. Oelschläger, Frankfurt am Main, on the occasion of his 70th birthday appreciating his merits to the development of the Institute of Pharmacy at the University of Regensburg.



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 isomers¹¹: 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. 1¹²

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

- 1) The C-3'-OCH₃-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 $\delta = 0.72$ ppm, the pertinent methylene group resonates as a multiplet at $\delta = 2.02$ ppm. One C-3-H leads to a broad signal at $\delta = 2.82$ ppm. The protons of the C-4-methylene group also show a multiplet in the 250-MHz-spectrum at -50°C at $\delta = 3.22$ ppm. As described above the C-3'-methoxy group is shifted upfield, while the other methoxy groups form singlets near $\delta = 3.95$ ppm. The second C-3-H, extremely shifted downfield, resonates as a multiplet at $\delta = 5.11$ ppm. This effect can be explained by the anisotropic effect of the carbonyl group⁶. 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 ($\delta = 1.53$ ppm) is shifted upfield as compared to the *E*-isomer ($\delta = 1.92$ ppm) because of this interaction, while the quartet of the vinylic proton is shifted downfield (*Z*-isomer: $\delta = 6.23$ ppm, *E*-isomer: $\delta = 5.71$ ppm).- The signals of the aromatic protons in *Z*-1c come up between $\delta = 6.6$ ppm and 7.2 ppm (Fig. 2).

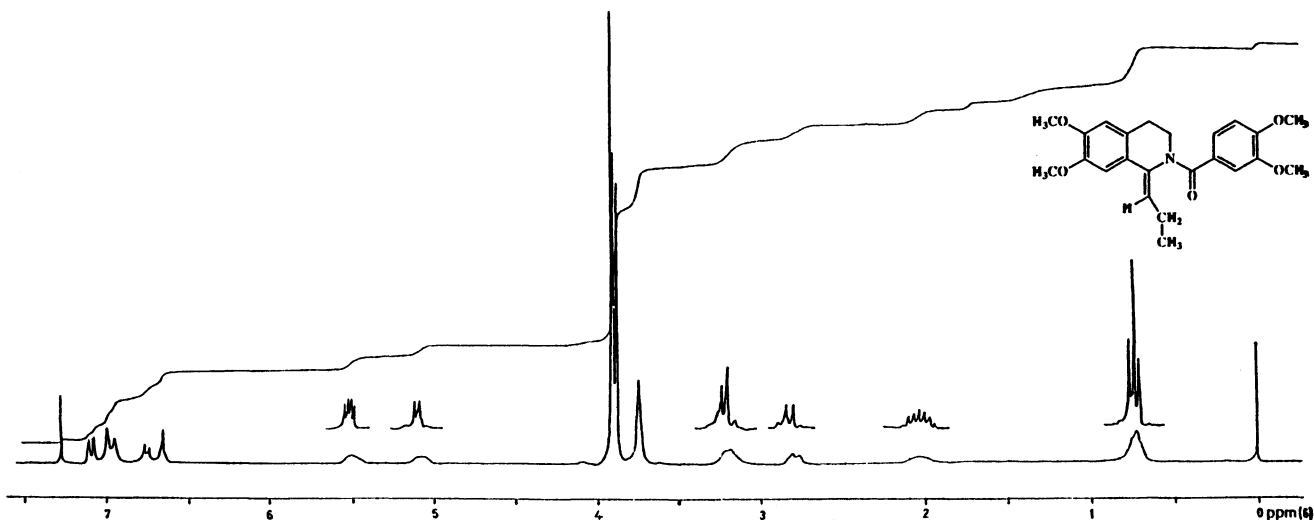
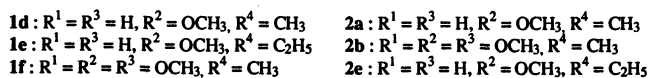
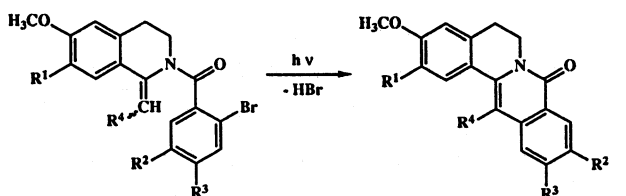


Fig. 2: ¹H-NMR-spectra (250 MHz), compound 1c (*Z*-isomer), at 24°C (below) and at -50°C (above)

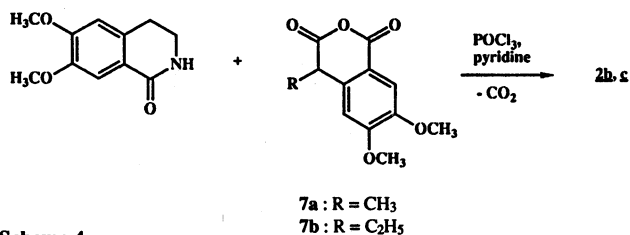
The mechanisms of the photocyclizations of the enamides, either brominated or not brominated, have been discussed by Lenz^{3,9)} or Ninomiya^{4,10)}, respectively. We used the oxidative photocyclization of enamides **1**, not substituted in the *ortho*-position, for the preparation of compounds **2a-d**. 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 Ninomiya¹⁰⁾ or Lenz⁹⁾ making use of *ortho*-brominated benzoyl increments in the enamides **1d-f** (Scheme 3). Here elimination of the *ortho*-group by irradiation takes place.



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

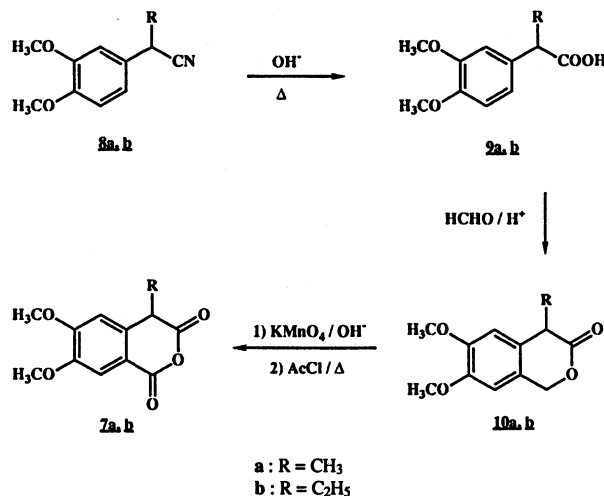
Haimova used this condensation for the synthesis of 2,3,10,11-tetramethoxy-8-oxoberbine⁵⁾. It had to be shown whether C-4-alkylated homophthalic acid anhydrides **7** could also be used for this strategy (Scheme 4). We synthesized the tetramethoxy-8-oxoberbines **2b** and **2c** by this method. As C-4-alkylated 6-methoxy-substituted homophthalic acid anhydrides are not easily available, 8-oxoberbines with C-11-methoxy substitution in ring D were not prepared by this route.



Scheme 4

Compounds **7** were synthesized *via* the dimethoxyacetone nitriles **8a** and **8b**. First the alkylated dimethoxyphenylacetone nitriles **8a** and **8b** are hydrolysed to the phenylacetic acid derivatives **9a** and **9b** (Scheme 5). According to Finkelstein and Bossi¹³⁾ 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

KMnO₄ 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).



Scheme 5

This extension of Haimova's strategy⁵⁾ 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 publication²⁾.

Experimental Part

Melting points: Büchi 510 apparatus, uncorrected.- Elemental analyses: Mikroanalytisches Laboratorium, University of Regensburg.- IR-spectra: Beckman Acculab III; KBr.- ¹H-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 (SiO₂, CHCl₃/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-dimethoxyisoquinoline (**1b**)

From **5c** and **6c**; colorless crystals, m.p. 156-158°C (ether).- *Z*-isomer: C₂₂H₂₅NO₅ (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.- ¹H-NMR (250 MHz, -50°C, CDCl₃): δ (ppm) = 1.30 (d; J = 7 Hz; 3H; CH₃), 2.60-3.33 (m; 3H; CH₂; H-3/H-4), 3.76 (s; 3H; OCH₃); 3.91, 3.93, 3.94 (s; 9H; OCH₃), 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 (SiO₂, EtOAc).- m.p. 128-130°C (ether).- C₂₂H₂₇NO₆ (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 - H₂O)⁺), 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: C₂₂H₂₇NO₅ (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.- ¹H-NMR (CDCl₃): δ (ppm) = 0.72 (t; J = 7 Hz; 3H, CH₃), 2.02 (m; 2H; CH₂-CH₃), 2.82 (m; 1H; H-3), 3.22 (m; 2H; CH₂; H-4), 3.76, 3.91, 3.94, 3.95 (s; 12 H; -OCH₃), 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 (SiO₂, EtOAc), m.p. 128-130°C (ether).- C₂₃H₂₉NO₆ (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.- ¹H-NMR (CDCl₃): δ (ppm) = 1.00 (t; J = 7.5 Hz; 3H; CH₃), 1.57-1.90 (m; 2H; CH₂-CH₂-CH₃), 2.77-3.10 (m; 4H; CH₂-CH₂-CH₃ and CH₂-CH₂-N), 3.57-3.85 (m; 2H; CH₂-N), 3.90 (s; 12 H; OCH₃), 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 - H₂O)⁺), 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-dihydroisoquinoline 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.- C₂₀H₂₀BrNO₃ (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: ¹H-NMR (CDCl₃): δ (ppm) = 1.53 (d; J = 7 Hz; 3H; CH₃), 2.71-2.97 (m; 3H; CH₂; H-3/H-4), 3.54, 3.80 (s; 6H; OCH₃), 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: ¹H-NMR (CDCl₃): δ (ppm) = 1.92 (d; J = 7 Hz; 3H; CH₃), 3.14-3.40 (m; 2H; CH₂; H-4), 3.65 (s [broad]; 2H; CH₂; H-3), 3.80, 3.81 (s; 6H; OCH₃), 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).- C₂₁H₂₂BrNO₃ (416.3).- Z-isomer.- IR (KBr): 1640 (CO) cm⁻¹.- ¹H-NMR (CDCl₃): δ (ppm) = 0.97 (t; J = 7.5 Hz; 3H; CH₃), 1.73 (m; 2H; CH₂-CH₃), 2.87 (t; J = 6 Hz; 2H; CH₂; H-4), 3.13 (t; J = 6 Hz; 2H; CH₂; H-3), 3.77 (s; 3H; OCH₃), 3.85 (s; 3H; OCH₃), 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-dimethoxyisoquinoline (1f)

From 5c and 6d; colorless crystals, m.p. 190-192°C (ether).- C₂₂H₂₄BrNO₅ (462.3).- 3:7-mixture of *E/Z*-isomers.- IR (KBr): 1640 (CO) cm⁻¹.- Z-isomer: ¹H-NMR (CDCl₃): δ (ppm) = 1.56 (d; J = 7.5 Hz; 3H; CH₃), 2.62-3.36 (m; 3H; CH₂; H-3/H-4), 3.56 (s; 3H; OCH₃), 3.88 (s; 9H;

OCH₃), 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: ¹H-NMR (CDCl₃): δ (ppm) = 1.96 (d; J = 7.5 Hz; 3H; CH₃), 2.62-3.36 (m; 2H; CH₂; H-4), 3.56 (s [broad]; 2H; CH₂; H-3), 3.88 (s; 3H; OCH₃), 3.91 (s; 9H; OCH₃), 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 N₂ 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 (SiO₂, 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).- C₂₀H₁₉NO₃ 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.- ¹H-NMR (CDCl₃): δ (ppm) = 2.52 (s; 3H; CH₃), 2.82 (t; J = 6 Hz; 2H; CH₂; H-5), 3.82 (s; 3H; OCH₃), 3.93 (s; 3H; OCH₃), 4.27 (t; J = 6 Hz; 2H; CH₂; 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-isoquinoline¹⁴ with 6,7-dimethoxy-4-methyl-isochromane-1,3-dione (7a) (cf.^{15,11}).- Light-brown crystals, m.p. 210-212°C (EtOH), lit. 213-215°C⁹.- MS: m/z = 381 (100%, M⁺), 366 (63, *351.59, (M - CH₃)⁺), 220 (27), 190.5 (18, M²⁺), 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-isoquinoline¹⁴ with 6,7-dimethoxy-4-ethyl-isochromane-1,3-dione (7b) (cf.^{15,11}).- Yellow needles, m.p. 197-198°C (EtOH).- C₂₃H₂₅NO₃ 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.- ¹H-NMR (CDCl₃): δ (ppm) = 1.55 (t; J = 7.5 Hz; 3H; CH₃), 2.82 (t; J = 6 Hz; 2H; CH₂; H-5), 3.08 (q; J = 7.5 Hz; 2H; CH₂-CH₃), 3.97 (s; 6H; OCH₃), 4.08 (s; 6H; OCH₃), 4.28 (t; J = 6 Hz; 2H; CH₂; 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 - CH₃)⁺), 349 (51, *320.53, (380 - OCH₃)⁺), 334 (19, *319.64, (349 - CH₃)⁺), 306 (5), 197.5 (7, M²⁺).

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).- C₂₀H₁₉NO₃ 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.- ¹H-NMR (CDCl₃): δ (ppm) = 2.70 (s; 3H; CH₃), 2.85 (t; J = 6 Hz; 2H; CH₂; H-5), 3.87 (s; 3H; OCH₃), 3.97 (s; 3H; OCH₃), 4.27 (t; J = 6 Hz; 2H; CH₂; 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).- C₂₁H₂₁NO₃ (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.- ¹H-NMR (CDCl₃): δ (ppm) = 1.42 (t; J = 7.5 Hz; 3H; CH₃);

2.80 (t; J = 6 Hz; 2H; CH₂; H-5), 2.98 (q; J = 7.5 Hz; 2H; CH₂-CH₃), 3.82 (s; 3H; OCH₃), 3.93 (s; 3H; OCH₃), 4.23 (t; J = 6 Hz; 2H; CH₂; 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.¹¹; m.p. 225-227°C (MeOH).- C₂₇H₂₅NO₉ x 1 H₂O (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-CH₃), 1650 (CO) cm⁻¹.- ¹H-NMR (CDCl₃): δ (ppm) = 1.43 (t; J = 7.5 Hz; 3H; CH₃), 2.33 (s; 12 H; H₃C-CO), 2.75-3.13 (m; 4H; CH₂-CH₃ and CH₂/H-5), 4.28 (t; J = 6 Hz; 2H; CH₂; 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.¹¹; m.p. 232-234°C (EtOH).- C₂₂H₁₉NO₅ (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-CH₃), 1650 (CO) cm⁻¹.- ¹H-NMR (250 MHz, CDCl₃): δ (ppm) = 2.34 (s; 3H; H₃C-CO), 2.36 (s; 3H; H₃C-CO), 2.59 (s; 3H; CH₃), 2.93 (t; J = 6 Hz; 2H; CH₂; H-5), 4.28 (t; J = 6 Hz; 2H; CH₂; 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.¹¹; m.p. 195-197°C (MeOH).- C₂₃H₂₁NO₅ x 1 H₂O (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-CH₃), 1640 (CO) cm⁻¹.- ¹H-NMR (250 MHz, CDCl₃): δ (ppm) = 1.47 (t; J = 7.5 Hz; 3H; -CH₃), 2.35 (s; 3H; H₃C-CO), 2.36 (s; 3H; H₃C-CO), 2.88 (t; J = 7.5 Hz; 2H; CH₂; H-5), 3.03 (q; J = 7.5 Hz; 2H; CH₂-CH₃), 4.28 (s [broad]; 2H; CH₂; 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. CH₂Cl₂. The mixture is stirred for 1 h, the precipitate is dissolved with 2N HCl and stirred again. The org. layer is separated, dried (Na₂SO₄) 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 T⁶.

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.- ¹H-NMR (CDCl₃): δ (ppm) = 0.90 (t; J = 7.5 Hz; 3H; CH₃), 1.37-1.82 (m; 2H; CH₂-CH₂-CH₃), 2.10 (t; J = 7.5 Hz; 2H; CH₂-CH₂-CH₃), 2.77 (t; J = 7.5 Hz; 2H; CH₂-CH₂-NH-), 3.62 (q; J = 7.5 Hz; 2H; CH₂-CH₂-N; t after D-exchange), 3.73 (s; 3H; OCH₃), 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°C¹⁶.

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°C¹⁶.

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 POCl₃ for 3 h. Then excess of POCl₃ 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 (Na₂SO₄) 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 T⁶.

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

From **4b**; colorless oil, b.p. 160-162°C, 0.1 T.- C₁₃H₁₇NO (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.- ¹H-NMR (CDCl₃): δ (ppm) = 0.95 (t; J = 7.5 Hz; 3H; CH₃), 1.47-1.85 (m; 2H; CH₂-CH₂-CH₃), 2.60 (t [broad]; J = 7.5 Hz; 4H; CH₂-CH₂-CH₃ and CH₂-CH₂-N), 3.62 (t; J = 7.5 Hz; 2H; CH₂-CH₂-N), 3.80 (s; 3H; OCH₃), 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 mm¹⁶.- C₁₃H₁₇NO₂ (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 mm¹⁶.- C₁₄H₁₉NO₂ (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. CH₂Cl₂ and 5 drops of DMF. 22 ml of SOCl₂ 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 acid¹, 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 mm¹⁷.

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

From 3,4-dimethoxy benzoic acid (Merck); light-red precipitate, m.p. 65-66°C; lit. 70°C¹⁸.

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

From 2-bromo-4,5-dimethoxy benzoic acid¹, light-brown precipitate, m.p. 73-75°C.

