Pergamon

*Tetrahedron* Vol. 50, No. 27, pp. 8003-8010, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $7.00+0.00

0040-4020(94)00417-X

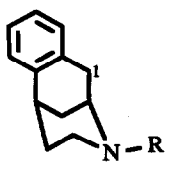
# Benzomorphan Analogous CNS Agents: Synthesis of Homochiral Epoxybenzocyclooctenamines

**Bernhard Wünsch*, Matthias Zott and Georg Höfner**

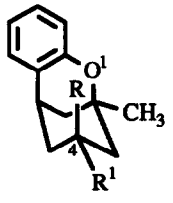
Institut für Pharmazie und Lebensmittelchemie der Universität München,
Sophienstr. 10, D-80333 Munich, Germany

**Abstract:** The crucial steps in the preparation of the enantiomerically pure amine **5** from the enol ester **3** are: 1. Stereoselective reduction of the enol ester **3** to give the β-hydroxy ester **6**; 2. elimination of the hydroxy group of **6** according to the method of Barton and McCombie; 3. Hofmann rearrangement of the amide **12** with [bis(trifluoroacetoxy)iodo]benzene to yield the ammonium chloride **14**·HCl. In contrast to the racemic amines (±)-**1a** and (±)-**2a** the homochiral amine **5** did not influence the behaviour of mice. Therefore, we conclude that **5** after intraperitoneal application has no effects on the central nervous system.

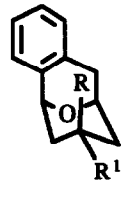
Benzomorphan analogues bearing the basic nitrogen atom *at* instead of *in* the tricyclic ring system can display remarkable effects on the central nervous system (CNS). Thus, anxiolytic and anticonvulsant activities were found for the methanobenzoxocinamine (±)-**1a**,[1] where the C-1 carbon atom of the benzomorphans is replaced by an oxygen atom. In this series the orientation of the amino group in position 4 is very important: The diastereomer (±)-**1b** with an axially oriented amino group led only to weak excitation of the mice.[2] Moving the oxygen atom to the methano bridge leads to the regioisomeric epoxybenzocyclooctenamines (±)-**2** (regioisomeric concerning the ring oxygen). Recently, we prepared the epoxybenzocyclooctenamines (±)-**2** via a [3+5] annulation reaction and found a similar relationship between the orientation of the amino group and the CNS effects: (±)-**2a**, the diastereomer with an equatorially oriented amino group was sedative and analgesic active, while (±)-**2b** (axial amino group) did not cause any central effects.[3]




Benzomorphan



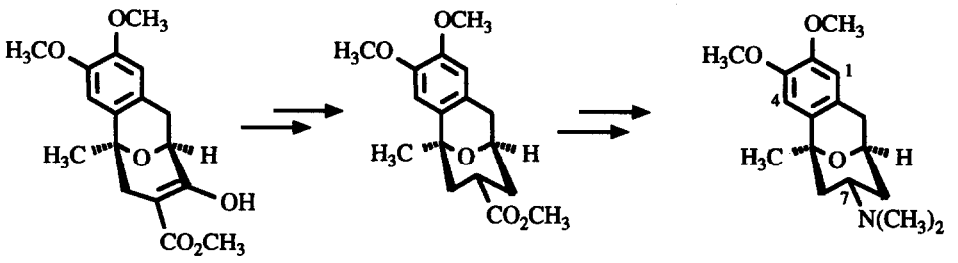

(±)-**1a,b**




(±)-**2a,b**

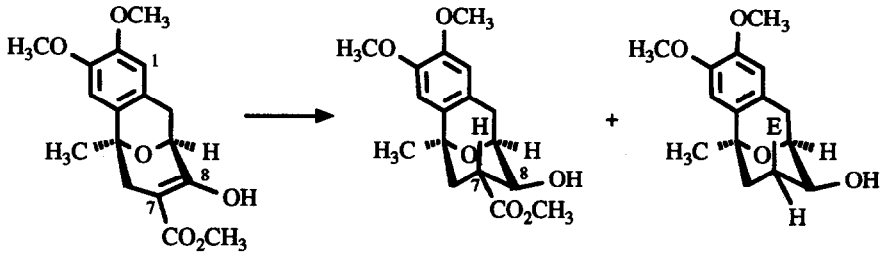
| 1,2 | R | $R^1$ |
|---|---|---|
| a | H | $N(CH_3)_2$ |
| b | $N(CH_3)_2$ | H |

Therefore, we planed a stereoselective synthesis of the *enantiomerically pure* epoxybenzocyclooctenamine **5**, which bears an equatorial amino group in position 7. Starting with the enol ester **3** (the β-keto ester exists quantitatively in the enol form)[4] the enol group should be stereoselectively reduced and eliminated to give the ester **4**, which, subsequently, should be degraded without epimerization at C-7 to afford the homochiral amine **5**.




**3** **4** **5**

Reduction of the enol ester **3** with $NaBH_4$ in methanol provided a 40 : 60 mixture of the β-hydroxy esters **6** and **7** bearing the hydroxy group in the equatorial position, respectively. However, the methoxycarbonyl group of the main diastereomer **7** is axially arranged and, therefore, **7** is not suitable for the preparation of the epoxybenzocyclooctenamine **5**.

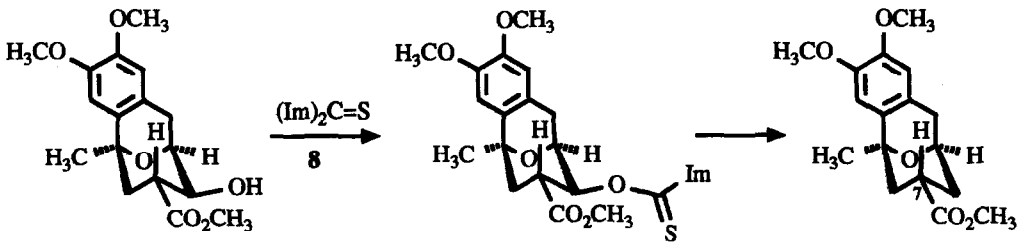



**3** **6** **7** (E = $CO_2CH_3$)

Table 1: Diastereoselectivity in the reduction of the enol ester **3** with $NaBH_4$

| Solvent $CH_3OH$ : $CH_3CN$ | Molequivalents of $NaBH_4$ | Transformation in % | Ratio **6** : **7** |
|---|---|---|---|
| 100 : 0 | 3 | 100 | 40 : 60 |
| 50 : 50 | 1 | 100 | 80 : 20 |
| 34 : 66 | 1 | 100 | 92 : 8 |
| 0 : 100 | 5 | 10 | 100 : 0 |

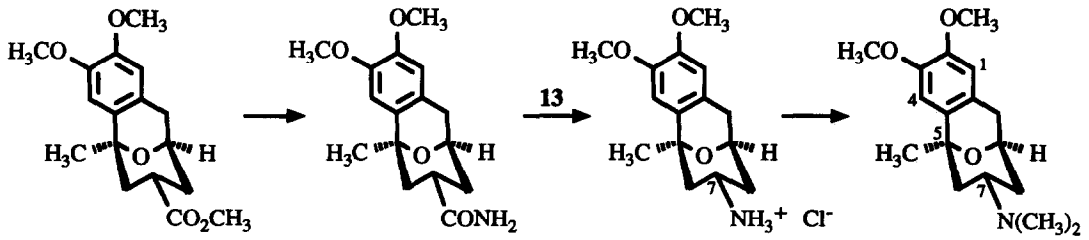
We supposed that predominant formation of **7** may be influenced by properties of the solvent and, therefore, investigated exchange of methanol by aprotic acetonitrile. In fact, after 12 hours the signals of only one reduction product - **6** - were observed in the $^1H$ NMR spectrum of the crude reaction product. This high diastereoselectivity in favour of the diequatorial β-hydroxy ester **6** was payed with a very low yield (transformation only 10%). But, quantitative transformation of **3** was achieved after adding methanol to the solvent acetonitrile. A ratio of 34 : 66 (methanol : acetonitrile) proved to be the optimum. In this solvent mixture the $NaBH_4$ reduction of the enol ester **3** provided the diastereomeric β-hydroxy esters **6** and **7** in a ratio of 92 : 8 (100% transformation, see table 1). The preferred formation of the diequatorial β-hydroxy ester **6** in acetonitrile or acetonitrile/methanol mixtures may be explained with an equilibration of the anion in position 7, which is created by hydride attack in position 8 of **3**. This equilibration is suppressed by a great amount of methanol, which immediately protonates the anion. A reduction of a tautomeric β-keto ester is not likely, because the $^1H$ NMR spectra of **3** in $CD_3OD$, $CD_3CN$ and $CDCl_3$ indicate the existence of **3** quantitatively in the enol ester tautomer.




Next, we planed to eliminate the hydroxy groups of the β-hydroxy esters **6** and **7** according to the method of Barton and McCombie.[5] The thiocarbamates **9** and **10** were obtained by acylation of **6** and **7** with 1,1'-thiocarbonyldiimidazole (**8**). Interestingly, the transformation of the diequatorial β-hydroxy ester **6** with two equivalents of **8** was complete after two hours, while the analogous acylation of the β-hydroxy ester **7** required ten equivalents of **8** and a prolonged reaction time of five hours. In refluxing toluene the

thiocarbamate **9** was reduced with tributylstannane and 2,2'-azodi(2-methylpropanenitrile) (AIBN) to provide the desired ester **4** in 63 % yield. An epimerization at C-7 was not observed. Surprisingly, the reaction of the diastereomeric thiocarbamte **10** with tributylstannane resulted in elimination instead of reduction. We assume that an antiperiplanar orientation of the C-7 proton and the thiocarbamate residue in the *boat* conformation of the pyran ring of **10** favours the trans elimination to yield the α,β-unsaturated ester **11**.

Ammonolysis of the ester **4** led to the amide **12**, which was rearranged by the hypervalent iodo compound [bis(triflouroacetoxy)iodo]benzene (**13**)[6] to afford the primary ammonium chloride **14**·HCl in 84% yield. Urea derivatives resulting from addition of primary amines to the intermediate isocyanates, which are common side products in the Hofmann rearrangement of amides using bromine and NaOH as reagents,[6a] could not be detected in the rearrangement of the amide **12** with the iodo compound **13**, because the primary amine **14** was immediately protonated by the liberated trifluoroacetic acid. In agreement with Loudon et al.,[6b] the rearrangement of the amide **12** occurred without epimerization in position 7.




**4** **12** **14**·HCl **5**

Finally, the desired dimethylamine **5** was prepared by reductive methylation (formaldehyde, $NaBH_3CN$)[7] of the primary ammonium chloride **14**·HCl.

To investigate the CNS activity of the amine **5** we watched the behaviour of mice after intraperitoneal application of the test compound (Irwin screen).[8] However, doses of 50 mg/kg body weight and 100 mg/kg body weight did not cause any effects pointing to actions of **5** on the CNS of the mice. We suppose that the inefficacy of the dextrorotatory amine **5** in comparison with the racemic amines (±)-**1a** and (±)-**2a** is due to the methoxy substituents in position 2 and 3 of the ring system, which might influence the pharmacokinetic properties.

## Experimental

General: Unless otherwise noted reactions were conducted under dry nitrogen.- Flash chromatography:[9] Silica gel, 0.040 - 0.063 mm.- Melting points: Melting point apparatus Dr. Tottoli (Büchi), uncorrected.- Optical rotation: Polarimeter (Zeiss), 0.5 dm tube; polarimeter 241 (Perkin Elmer), 1.0 dm tube. The dimension of the specific optical rotation [α] is [grad·ml·dm$^{-1}$·g$^{-1}$]; concentration c in [g/100 ml]; temperature 20°C.- Elemental analyses: CHN elemental analyzer Rapid (Heraeus).- MS: Mass spectrometer CH 7 (Varian).- IR: IR spectrophotometer 710 B and 1600 FT-IR (Perkin Elmer).- NMR: GSX FT NMR spectrometer, 400 MHz (Jeol), tetramethylsilane as internal standard.- Experimental details concerning the pharmacological tests see ref[10].

**(*5S,7R,8S,9S*)-(-) and (*5S,7S,8S,9S*)-(-)-Methyl 5,9-Epoxy-5,6,7,8,9,10-hexahydro-8-hydroxy-2,3-dimethoxy-5-methyl-benzocyclooctene-7-carboxylate (6) and (7)**

a) To a suspension of **3** (2.36 g, 7.37 mmol) in methanol (50 mL) $NaBH_4$ (0.84 g, 22.1 mmol) was added within 10 min at room temperature. After 1 h the solvent was evaporated and the residue was dissolved in $CH_2Cl_2$ (50 mL). The $CH_2Cl_2$ layer was washed with 0.5 N NaOH (40 mL), dried ($MgSO_4$), concentrated in vacuo and the residue (2.37 g, colourless oil) was purified by flash chromatography ($CH_2Cl_2$ : methanol = 96 : 4).

**6** ($R_f$ = 0.57): Yield 0.37 g (16%) colourless solid ($iPr_2O$), m.p. 162°C; $[\alpha]_{546}$ = -2.0; $[\alpha]_{578}$ = -1.8 (c = 0.500 in $CHCl_3$). $C_{17}H_{22}O_6$ (322.4) calcd. C 63.34 H 6.88 found 63.53 H 6.69.- Mol. mass 322 (ms).- IR (KBr): ν = 3444 (broad, OH), 1740 (C=O) cm$^{-1}$.- $^1$H NMR ($CDCl_3$): δ (ppm) = 1.60 (s, 3H, $CH_3$), 1.88 (t, J = 13.2 Hz, 1H, H-6 axial), 1.99 (dd, J = 13.2/4.4 Hz, 1H, H-6 equatorial), 2.34 (td, J = 13.2/4.4 Hz, 1H, H-7 axial), 2.99 (d, J = 17.6 Hz, 1H, H-10), 3.10 (dd, J = 17.6/7.3 Hz, 1H, H-10), 3.17 (d, J = 2.9 Hz, 1H, OH), 3.67 (s, 3H, $CO_2CH_3$), 3.86 (s, 6H, 2 x $OCH_3$), 4.20 (ddd, J = 13.2/7.3/2.9 Hz, 1H, H-8 axial), 4.38 (t, J = 7.3 Hz, 1H, H-9), 6.58 (s, 1H, aromat.), 6.62 (s, 1H, aromat.).

**7** ($R_f$ = 0.72): Yield 0.57 g (24%) colourless solid ($iPr_2O$), m.p. 122°C; $[\alpha]_{546}$ = -68.3, $[\alpha]_{578}$ = -59.2 (c = 0.265 in $CHCl_3$). $C_{17}H_{22}O_6$ (322.4) calcd. C 63.34 H 6.88 found C 63.41 H 6.63.- Mol. mass 322 (ms).- IR (KBr): ν = 3446 (sharp, OH), 1687 (C=O) cm$^{-1}$.- $^1$H NMR ($CDCl_3$): δ (ppm) = 1.56 (s, 3H, $CH_3$), 2.05 (dd, J = 13.9/5.9 Hz, 1H, H-6 axial), 2.47 (d, J = 13.9 Hz, 1H, H-6 equatorial), 2.88 (t, J = 5.9 Hz, 1H, H-7 equatorial), 2.93 (d, J = 16.9 Hz, 1H, H-10), 3.05 (s, 3H, $CO_2CH_3$), 3.14 (dd, J = 16.9/7.3 Hz, 1H, H-10), 3.85 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 4.14 (m, 1H, H-8 axial), 4.35 (dd, J = 7.3/5.9 Hz, 1H, H-9), 5.14 (d, J = 8.1 Hz, 1H, OH), 6.50 (s, 1H, aromat.), 6.57 (s, 1H, aromat.).

b) The reaction of **3** (1.00 g, 3.12 mmol) in acetonitrile (50 mL) and methanol (22 mL) with $NaBH_4$ (0.12 g, 3.12 mmol) provided **6** and **7** in a ratio of 92 : 8.

**(*5S,7R,8S,9S*)-Methyl 5,9-Epoxy-5,6,7,8,9,10-hexahydro-8-[1-imidazolyl-(thiocarbonyl)-oxy]-2,3-dimethoxy-5-methyl-benzocyclooctene-7-carboxylate (9)**

**6** (0.286 g, 0.887 mmol), 1,1'-thiocarbonyldiimidazole (**8**, 0.32 g, 1.77 mmol) and dry 1,2-dichloroethane (5 mL) were refluxed for 2 h. Then, $CH_2Cl_2$ (20 mL) was added, the organic layer was washed with 2 N HCl, dried ($MgSO_4$) and concentrated in vacuo. Yield 0.31 g (80%) colourless solid ($iPr_2O$), m.p. 136 - 137°C. $C_{21}H_{24}N_2O_6S$ (432.5) calcd. C 58.32 H 5.59 N 6.48 found C 58.38 H 5.98 N 6.01.- Mol. mass 432 (ms).- IR (KBr): ν = 1724 (C=O) $cm^{-1}$.-$^1$H NMR ($CDCl_3$): δ (ppm) = 1.51 (s, 3H, $CH_3$), 2.03 (m, 2H, H-6), 2.61 (d, J = 17.4 Hz, 1H, H-10), 2.77 (td, J = 11.7/5.9 Hz, 1H, H-7 axial), 3.16 (dd, J = 17.4/5.9 Hz, 1H, H-10), 3.53 (s, 3H, $CO_2CH_3$), 3.81 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 4.77 (t, J = 5.9 Hz, 1H, H-9), 5.98 (dd, J = 11.7/5.9 Hz, 1H, H-8 axial), 6.54 (s, 1H, aromat.), 6.55 (s, 1H, aromat.), 6.97 (s, broad, 1H, imidazole), 7.53 (s, broad, 1H, imidazole), 8.21 (s, broad, 1H, imidazole).

**(*5S,7S,8S,9S*)-Methyl 5,9-Epoxy-5,6,7,8,9,10-hexahydro-8-[1-imidazolyl-(thiocarbonyl)-oxy]-2,3-dimethoxy-5-methyl-benzocyclooctene-7-carboxylate (10)**

**7** (0.237 g, 0.735 mmol), 1,1'-thiocarbonyldiimidazole (**8**, 1.31 g, 7.35 mmol) and dry 1,2-dichloroethane (5 mL) were refluxed for 5 h. Work up as described for **9**. Yield 0.282 g (89%) colourless solid ($iPr_2O$), m.p. 134 - 136°C. $C_{21}H_{24}N_2O_6S$ (432.5) calcd. C 58.32 H 5.59 N 6.48 found C 58.20 H 5.76 N 6.42.- Mol. mass 432 (ms).- IR (KBr): ν = 1720 (C=O) $cm^{-1}$.- $^1$H NMR ($CDCl_3$): δ (ppm) = 1.63 (s, 3H, $CH_3$), 2.29 (dd, J = 13.9/5.9 Hz, 1H, H-6 axial), 2.54 (dd, J = 13.9/5.9 Hz, 1H, H-6 equatorial), 2.94 (d, J = 16.9 Hz, 1H, H-10), 3.19 (s, 3H, $CO_2CH_3$), 3.23 (dd, J = 16.9/5.9 Hz, 1H, H-10), 3.30 (q, J = 5.9 Hz, 1H, H-7 equatorial), 3.81 (s, 3H, $OCH_3$), 3.88 (s, 3H, $OCH_3$), 4.64 (t, J = 5.9 Hz, 1H, H-9), 6.11 (t, J = 5.9 Hz, 1H, H-8 axial), 6.48 (s, 1H, aromat.), 6.61 (s, 1H, aromat.), 7.02 (s, broad, 1H, imidazole), 7.49 (s, broad, 1H, imidazole), 8.31 (s, broad, 1H, imidazole).

**(*5S,7S,9R*)-(+)-Methyl 5,9-Epoxy-5,6,7,8,9,10-hexahydro-2,3-dimethoxy-5-methyl-benzocyclooctene-7-carboxylate (4)**

To a solution of **9** (0.386 g, 0.89 mmol) in dry toluene (6 mL) 2,2'-azodi(2-methylpropanenitrile) (AIBN, 18 mg, 0.11 mmol) and a solution of tributylstannane (0.128 g, 0.44 mmol) in dry toluene (1.6 mL) were added. Then, the reaction mixture was heated under reflux and within 90 min a solution of tributylstannane (0.390 g, 1.34 mmol) and AIBN (18 mg, 0.11 mmol) in dry toluene (5 mL) was slowly added. After cooling down the solvent was evaporated, the residue was dissolved in n-hexane (10 mL) and extracted with acetonitrile (8 mL). The acetonitrile layer was concentrated in vacuo and the residue (0.41 g colourless oil) purified by flash chromatography (petroleum ether : ethyl acetate = 7.5 : 2.5; $R_f$ = 0.35). Yield 0.172 g (63%) colourless solid (n-hexane), m.p. 85 - 87°C; $[\alpha]_{546}$ = +34.4; $[\alpha]_{578}$ = +30.4 (c = 0.520 in $CHCl_3$). $C_{17}H_{22}O_5$ (306.4) calcd. C 66.65 H 7.24 found C 66.48 H 7.40.- Mol. mass 306 (ms).- IR (KBr): ν = 1733 (C=O) $cm^{-1}$.- $^1$H NMR ($CDCl_3$): δ (ppm) = 1.60 (s, 3H, $CH_3$), 1.80 (t, J = 13.2 Hz, 1H, H-6 axial), 1.87 (dd, J = 13.2/4.4 Hz, 2H, H-6 equatorial and H-8 equatorial), 2.05 (td, J = 13.2/7.3 Hz, 1H, H-8 axial), 2.41 (tt, J = 13.2/4.4 Hz, 1H, H-7 axial), 2.50 (d, J = 17.6 Hz, 1H, H-10), 3.37 (dd, J = 17.6/7.3 Hz, 1H, H-10), 3.61 (s, 3H, $CO_2CH_3$), 3.86 (s, 6H, 2 x $OCH_3$), 4.51 (t, J = 7.3 Hz, 1H, H-9), 6.57 (s, 2H, aromat.).

**(5*S*,9*S*)-(+)-Methyl 5,9-Epoxy-5,6,9,10-tetrahydro-2,3-dimethoxy-5-methyl-benzocyclooctene-7-carboxylate (11)**

A solution of **10** (0.282 g, 0.652 mmol) in dry toluene (5 mL) was treated and worked up as described for **4**. The residue (0.31 g colourless oil)) was purified by flash chromatography (petroleum ether : ethyl acetate = 7 : 3; $R_f$ = 0.40). Yield 46 mg (23%) colourless solid ($iPr_2O$), m.p. 121 - 122°C; $[\alpha]_{546}$ = +58.3; $[\alpha]_{578}$ = +53.2 (c = 0.235 in $CHCl_3$). $C_{17}H_{20}O_5$ (304.3) calcd. C 67.09 H 6.62 found C 66.81 H 6.89.- Mol. mass 304 (ms).- IR (KBr): ν = 2932 (C-H), 1702 (C=O) $cm^{-1}$.- $^1H$ NMR ($CDCl_3$): δ (ppm) = 1.64 (s, 3H, $CH_3$), 2.50 - 2.54 [m, 3H, H-10 (1H) and H-6 (2H)], 3.33 (dd, J = 15.4/6.6 Hz, 1H, H-10), 3.68 (s, 3H, $CO_2CH_3$), 3.83 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 4.86 (d, J = 6.6 Hz, 1H, H-9), 6.51 (s, 1H, aromat.), 6.59 (s, 1H, aromat.), 6.95 (d, J = 1.5 Hz, 1H, H-8).

**(5*S*,7*S*,9*R*)-(+)-5,9-Epoxy-5,6,7,8,9,10-hexahydro-2,3-dimethoxy-5-methyl-benzocyclooctene-7-carboxamide (12)**

At 0°C a solution of **4** (1.50 g, 4.90 mmol) and ammonium chloride (0.05 g) in dry methanol (30 mL) was saturated for 30 min with dry ammonia. Then, the reaction mixture was heated in a sealed tube (100°C) for 24 h. After cooling down the solvent was evaporated and the residue was purified by flash chromatography ($CH_2Cl_2$ : $CH_3OH$ = 95 : 5).

**4** ($R_f$ = 0.90): Yield 0.54 g (36%) colourless solid.

**12** ($R_f$ = 0.20): Yield 0.92 g (64%) colourless solid ($iPr_2O$), m.p. 194°C; $[\alpha]_{546}$ = +30.2; $[\alpha]_{578}$ = +26.4 (c = 0.530 in $CHCl_3$). $C_{16}H_{21}NO_4$ (291.4) calcd. C 65.96 H 7.26 N 4.81 found C 65.71 H 7.23 N 5.08.- Mol. mass 291 (ms).- IR (KBr): ν = 3424 (NH, sharp), 1682 (C=O, amide I), 1508 (C=O, amide II) $cm^{-1}$.- $^1H$ NMR ($CDCl_3$): δ (ppm) = 1.53 (s, 3H, $CH_3$), 1.71 (dd, J = 13.2/4.4 Hz, 1H, H-6 equatorial), 1.79 (t, J = 13.2 Hz, 1H, H-6 axial), 1.78 - 1.80 (m, 1H, H-8 equatorial), 2.05 (td, J = 13.2/7.3 Hz, 1H, H-8 axial), 2.20 (tt, J = 13.2/4.4 Hz, 1H, H-7 axial), 2.42 (d, J = 17.6 Hz, 1H, H-10), 3.31 (dd, J = 17.6/7.3 Hz, 1H, H-10), 3.79 (s, 6H, 2 x $OCH_3$), 4.46 (t, J = 7.3 Hz, 1H, H-9), 5.23 (s broad, 2H, $CONH_2$), 6.50 (s, 1H, aromat.), 6.51 (s, 1H, aromat.).

**(5*S*,7*S*,9*S*)-(+)-5,9-Epoxy-5,6,7,8,9,10-hexahydro-2,3-dimethoxy-5-methyl-benzocycloocten-7-amine (14)**

Within 30 min a solution of [bis(trifluoroacetoxy)iodo]benzene (**13**, 1.36 g, 3.2 mmol) in acetonitrile (5.9 mL) and water (5.9 mL) was slowly added to **12** (0.92 g, 3.2 mmol) in acetonitrile (8 mL). The reaction mixture was stirred for 12 h at room temp. Then, 0.5 N HCl (180 mL) was added, the mixture was extracted with $CH_2Cl_2$ (3x) and the aqueous layer concentrated in vacuo. (Yield 0.80 g (84%) pale yellow solid [(+)-**14**·HCl], purity > 95%). To obtain the free base **14** solid NaOH was added to an ice cold solution of the residue (**14**·HCl) in water (pH = 14), the water phase was extracted with $Et_2O$, the $Et_2O$ layer was dried ($MgSO_4$) and evaporated in vacuo. Yield 0.202 g (24%) colourless solid, m.p. 127 - 130°C; $[\alpha]_{546}$ = +29.2; $[\alpha]_{578}$ = +26.7 (c = 2.155 **14**·HCl in $CH_3OH$). $C_{15}H_{21}NO_3$ (263.3) calcd. C 68.42 H 8.04 N 5.32 found C 68.27 H 8.14 N 5.36.- Mol. mass 263 (ms).- IR (KBr): ν = 3344 (NH, broad) $cm^{-1}$.- $^1H$ NMR ($CDCl_3$): δ (ppm) = 1.39 (t, J = 11.7 Hz, 1H, H-6 axial), 1.47 (s broad, 2H, $NH_2$), 1.58 (s, 3H, $CH_3$), 1.65 (td, J =

11.7/7.3 Hz, 1H, H-8 axial), 1.85 (dd, J = 11.7/4.4 Hz, 2H, H-6 equatorial and H-8 equatorial), 2.48 (d, J = 16.8 Hz, 1H, H-10), 2.67 (tt, J = 11.7/4.4 Hz, 1H, H-7 axial), 3.35 (dd, J = 16.8/7.3 Hz, 1H, H-10), 3.85 (s, 3H, $OCH_3$), 3.86 (s, 3H, $OCH_3$), 4.53 (t, J = 7.3 Hz, 1H, H-9), 6.55 (s, 1H, aromat.), 6.57 (s, 1H, aromat.).

**(*5S,7S,9S*)-(+)-5,9-Epoxy-5,6,7,8,9,10-hexahydro-2,3-dimethoxy-5,N,N-trimethyl-benzocycloocten-7-amine (5)**

To an ice cold solution of **14**·HCl (0.80 g, 2.67 mmol) in methanol (10 mL) formaline (36%, 2.4 mL, 26.7 mmol), $NaBH_3CN$ (85%, 0.49 g, 6.68 mmol) and acetic acid (pH 5 - 6) were added successively. Then, the mixture was stirred at room temp. for 24 h. After the addition of conc. HCl (3.5 mL) the solvent was evaporated in vacuo at 50°C. The residue was dissolved in water (5 mL), the aqueous layer was brought to pH = 14 (solid KOH) and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), the solvent was evaporated in vacuo and the residue (0.69 g) was purified by flash chromatography ($CH_2Cl_2$ : $CH_3OH$ = 8 : 2; $R_f$ = 0.35). Yield 0.37 g (48%) colourless solid ($Et_2O$), m.p. 69 - 71°C; $[\alpha]_{546}$ = +15.0; $[\alpha]_{578}$ = +13.0 (c = 1.000 in $CHCl_3$). $C_{17}H_{25}NO_3$ (291.4) calcd. C 70.07 H 8.65 N 4.81 found C 69.84 H 8.81 N 4.73.- Mol. mass 291 (ms).- IR (KBr): ν = 2932 (C-H) $cm^{-1}$.- $^1H$ NMR ($CDCl_3$): δ (ppm) = 1.59 (s, 3H, $CH_3$), 1.80 - 1.84 (m, 4H, H-6 and H-8), 2.16 [s, 6H, $N(CH_3)_2$], 2.21 (tt, J = 11.0/4.4 Hz, 1H, H-7 axial), 2.47 (d, J = 16.9 Hz, 1H, H-10), 3.35 (dd, J = 16.9/8.1 Hz, 1H, H-10), 3.857 (s, 3H, $OCH_3$), 3.863 (s, 3H, $OCH_3$), 4.58 (t, J = 8.1 Hz, 1H, H-9), 6.56 (s, 2H, aromat.).

**Acknowledgements:** We wish to thank *Prof. F. Eiden* for generous support. Thanks are also due to the *Studienstiftung des Deutschen Volkes* for a stipend. This project is supported by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie.*

**References**

1. Glaxo Group Limited (Storer, R.), Eur. Pat. 24842 (11 March 1981); *Chem. Abstr.* **1981**, *95*, 62092f.
2. Eiden, F.; Gmeiner, P. *Arch. Pharm. (Weinheim, Ger.)* **1987**, *320*, 213 - 222.
3. Wünsch, B.; Zott, M.; Höfner, G. *Liebigs Ann. Chem.* **1992**, 1225 - 1230.
4. Wünsch, B.; Zott, M.; Höfner, G. *Arch. Pharm. (Weinheim, Ger.)* **1992**, *325*, 733 - 739.
5. a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. 1*, **1975**, 1574 - 1585.- b) Rasmussen, J. R. *J. Org. Chem.* **1980**, *45*, 2725 - 2727.
6. a) Waldmann, H. *Nachr. Chem. Tech. Lab.* **1991**, *39*, 828 - 832.- b) Loudon, G. M.; Rodhakrishna, A. S.; Almoud, M.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272 - 4276.
7. Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897 - 2904.
8. a) Irwin, S. *Psychopharmacologia* **1968**, *13*, 222 - 257.- b) Campbell, D. E. S.; Richter, W. *Acta Pharmacol. Toxicol.* **1967**, *25*, 345 - 363.
9. Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923 - 2925.
10. Wünsch, B.; Höfner, G.; Bauschke, G. *Arch. Pharm. (Weinheim, Ger.)* **1993**, *326*, 101 - 113.

(*Received in Germany* 25 *March* 1994; *accepted* 6 *May* 1994)