Synthesis of 5-Substituted 5-Hydroxy-2-pyrrolidones, Metabolites of the Antipsychotic Benzamide Remoxipride

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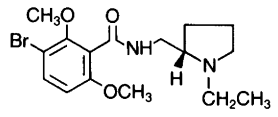
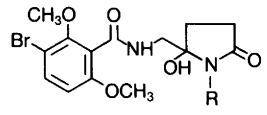
This paper describes the synthesis of 5-[(3-bromo-2,6-dimethoxybenzamido)-methyl]-5-hydroxy-2-pyrrolidone (**3**) and its 1-ethyl analogue **2**, two urinary metabolites of the dopamine D-2 antagonist remoxipride {**1**, (*S*)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide}. Two synthetic schemes leading to a common intermediate, 5-benzamido-4-oxopentanoic acid **4**, were developed. This key intermediate permits conversion into either metabolite. Reaction of **4** with isobutyl chloroformate furnished a mixed carbonic anhydride, which upon treatment with ethylamine or ammonia gave the 4-oxopentanamides **5** and **6**, respectively. Ring-closure afforded the corresponding 5-hydroxy-2-pyrrolidones **2** and **3**.

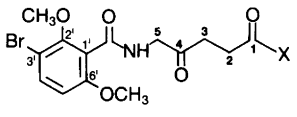
Remoxipride {**1**, (*S*)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)-methyl]-2,6-dimethoxybenzamide} is an atypical antipsychotic agent with pronounced antidopaminergic activity,[1,2] which is currently under investigation in clinical trials.[3] During the work on the biotransformation of **1**, the extensively oxidized compounds **2** and **3** were indicated as tentative metabolites. In order to confirm unambiguously their structures, syntheses of these compounds were undertaken. Two synthetic schemes leading to the same key intermediate, i.e. the open-chain acid **4**, were investigated. This common intermediate **4** permits conversion into either metabolite. In one scheme, the side-chain is built in a stepwise but short sequence from the corresponding benzoic acid. In the other method, the protected 5-amino-4-oxopentanoic acid is synthesized separately and coupled with the benzoic acid. The latter procedure allows for a facile variation of the benzamide part, which is of importance for future studies on other benzamides since this type of hydroxylated pyrrolidone is to be expected in structurally related benzamides such as sulpiride, 5-aminosulfonyl-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxybenzamide.[4]



remoxipride *1*



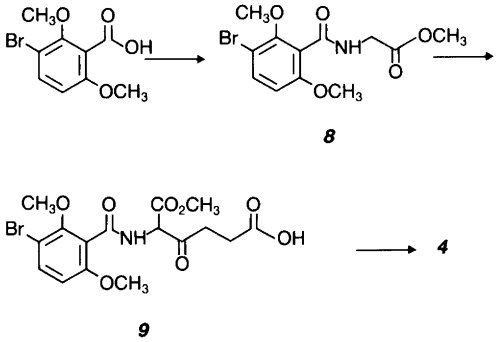
2: R = C_2H_5
3: R = H



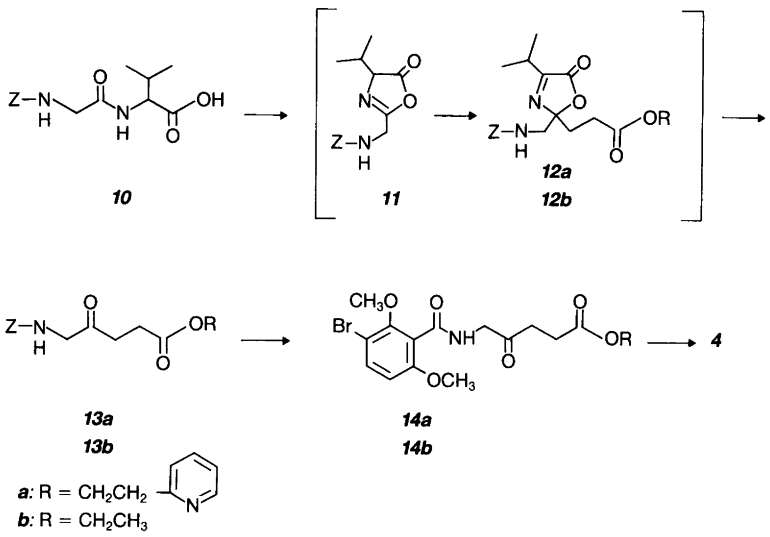
4: X = OH
5: X = $NHCH_2CH_3$
6: X = NH_2

Results and discussion

It has been demonstrated that 4-keto amides exist in open-chain or cyclic forms, which can be interconverted.[5] Since the proposed structures of the metabolites **2** and **3** correspond to the cyclic forms of the amides **5** and **6**, a synthesis of the parent open-chain acid **4** was undertaken. In the first synthetic method (A) we employed a reaction sequence (Scheme 1) described by Evans and Sidebottom in the



Scheme 1.



Scheme 2.

preparation of 5-amino-4-oxopentanoic acid.[6] 3-Bromo-2,6-dimethoxybenzoic acid was allowed to react with thionyl chloride in the presence of *N,N*-dimethylformamide as a catalyst to give the acyl chloride **7**, which was transformed into **8** upon treatment with methyl glycinate. The benzamide **8** was treated at low temperature with two equivalents of lithium diisopropylamide in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA). The resulting dianion was then allowed to react with succinic anhydride to give the β-keto ester **9**. Ester hydrolysis and decarboxylation of **9** in 6 M HCl according to Evans and Sidebottom[6] or with 2M HCl resulted in complete or partial demethylation, respectively, of the methoxy group positioned between the amide group and the bromine. This sterically more encumbered methoxy group is forced out of planarity with respect to the aromatic ring,[7] which makes it more susceptible to nucleophilic attack. By choosing the less nucleophilic sulfuric acid, demethylation could be avoided. Thus, treatment of **9** with 2 M H_2SO_4 at 80 °C furnished the desired acid **4**. The use of the ethyl ester instead of the methyl ester resulted in a high degree of decomposition owing to the harsher conditions required for the hydrolysis.

Schultz and Steglich have described the synthesis of compound **13b** (Scheme 2) and its conversion into a variety of *N*-acyl-5-amino-4-oxopentanoic acid ethyl esters.[8] Following this method (B), the ester **14b** was prepared. Hydrolysis of the ethyl ester by heating it at 50 °C for 18 h in the presence of HCl in aqueous ethanol gave the desired acid **4**. Notably, at this temperature no demethylation was observed.

However, for future applications on more sensitive derivatives we required a more readily removable carboxy-protecting group. As an alternative, we chose the 2-(2-pyridyl)ethyl ester (Method C), which has been used successfully in peptide synthesis.[9] Thus, Z-Gly-Val-OH[10] (**10**) was cyclized to compound **11** by being heated in acetic anhydride. Base-catalyzed addition of **11** to 2-(2-pyridyl) ethyl acrylate furnished 3-oxazolin-5-one **12a**, which was hydrolyzed *in situ* to provide the ester **13a**. The benzyloxycarbonyl group was removed with HBr/HOAc and the free amine was acylated with benzoyl chloride **7** to give the amido ester **14a** in high yield. Methylation of the pyridine moiety of **14a** followed by cleavage of the ester by treatment with diethylamine furnished the acid **4**.

The materials obtained by methods A and C and by method B had different melting points. These materials are polymorphs as evidenced by the fact that recrystallization of the low-melting form from ethyl acetate gave the high-melting form with identical spectroscopic data. Analogous to the 4-keto amides the 4-keto acids can exist in open or cyclized forms.[11] In this case (**4**), only the open-chain form was isolated, i.e. in the ^{13}C NMR spectrum only the carbonyl resonance (204.2 ppm) could be detected. The ^1H NMR spectrum of **4** showed two mutually coupled triplets at 2.60 and 2.82 ppm for the methylene groups in the 2 and 3 positions. The methylene group adjacent to the amide nitrogen appeared as a doublet at 4.30 ppm. In the ring-closed isomer these methylene hydrogens should appear as an ABX pattern about 0.5 ppm further upfield (cf. the corresponding ^1H NMR signals in **3** and **6**).[11]

The keto acid **4** was converted into the amides **5** and **6** by reaction of ethylamine and ammonia, respectively, with the mixed carbonic anhydride formed *in situ* from isobutyl chloroformate and the acid **4**. In the preparation of the amide **5**, a low temperature was kept during the isolation procedure and the open-chain product was isolated as a white crystalline solid in 85% yield. Quantitative conversion into **2** was readily effected by dissolving **5** in methanol and adding a catalytic amount of ammonia. Evaporation of the solvent left a crystalline residue of the lactam **2**. Analogous amidation with ammonia provided a mixture of isomers **3** and **6** from which the two isomers could be isolated as crystalline solids by flash chromatography on silica gel.

The structural assignments of the isomeric pairs **2/5** and

3/6 were mainly based on NMR data. In the ^{1}H NMR spectra of compounds **5** and **6**, the protons α to the carbonyl functions gave rise to analogous patterns as found in the open-chain acid **4** (*vide supra*). The spectra of compounds **2** and **3** showed a more complex coupling pattern as expected from the ring structure. Further support was given by the ^{13}C NMR spectra. A ketone carbonyl resonance was shown only by compounds **5** and **6** (204.7 and 206.6 ppm, respectively), while compounds **2** and **3** showed signals at 91.9 and 88.7 ppm, respectively, indicating an amidal carbon.[12]

Compounds **2** and **3** were used as reference samples in the analysis of human urine from clinical trials with remoxipride. Isolation of the metabolites and purification by HPLC followed by mass spectroscopy and comparative HPLC showed that the main metabolites matched the structures of the synthetic products **2** and **3**.[13]

Experimental

Melting points were determined on a Mettler FP 61 apparatus and are uncorrected. NMR spectra (^{1}H at 200 MHz and ^{13}C at 50 MHz) were obtained on a JEOL FX200 instrument. ^{1}H NMR spectra were measured with $MeSi_4$ as an internal reference. For the ^{13}C NMR spectra the middle peak of the solvent signal was used as a reference and set to 77.16 ppm and 39.8 ppm in $CDCl_3$ and DMSO-d_6, respectively. Mass spectra were recorded on a LKB 9000 instrument at an electron energy of 70 eV. IR spectra were recorded on a Perkin-Elmer Spectrophotometer 157. Elemental analysis, performed by *Analytische Laboratorien*, Elbach, West Germany, were to within ±0.4 % of the theoretical values.

*Methyl 3-bromo-2,6-dimethoxybenzamidoacetate (**8**).* To a suspension of 3-bromo-2,6-dimethoxybenzoic acid[1a] (5.2 g, 20 mmol) in toluene (20 ml) were added a catalytic amount of *N,N*-dimethylformamide (3 drops) and $SOCl_2$ (2 ml, 27 mmol). The mixture was heated at 60 °C for 1 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (40 ml) and evaporated once again. The residual 3-bromo-2,6-dimethoxybenzoyl chloride (**7**) was dissolved in CH_2Cl_2 (100 ml) and cooled to 0 °C. Methyl glycinate hydrochloride (2.5 g, 20 mmol) was added, followed by the dropwise addition of a solution of triethylamine (5.5 ml, 40 mmol) in CH_2Cl_2 (40 ml). The reaction mixture was left at room temperature overnight and then washed successively with 2 M HCl, water, aqueous $NaHCO_3$ and brine (satd. aqueous NaCl). Drying ($MgSO_4$) and evaporation gave a crystalline residue (6 g), which was recrystallized from ethyl acetate/hexane (1:2, 90 ml) to give 5.3 g (80 %) of the title compound. M.p. 97.5–98 °C. ^{1}H NMR ($CDCl_3$): δ 7.50 (d, 1 H), 6.60 (d, 1 H), 6.49 (t, 1 H), 4.25 (d, 2 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 3.75 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 170.10, 164.68, 156.99, 155.05, 134.42, 122.06, 108.66, 108.32, 62.54, 56.39, 52.45, 41.72. Anal. ($C_{12}H_{14}BrNO_5$): C, H, N, O.

*5-(3-Bromo-2,6-dimethoxybenzamido)-5-methoxycarbonyl-4-oxopentanoic acid (**9**).* To a solution of diisopropylamine (5.6 ml, 40 mmol) and TMEDA (6.04 ml, 40 mmol) in dry tetrahydrofuran (THF, 100 ml, distilled from sodium–benzophenone) was added a solution of butyllithium in hexane (26 ml, 40 mmol) via syringe under an N_2 atmosphere at −75 °C. Stirring was continued for 20 min at −75 °C. Compound **8** (6.6 g, 20 mmol) dissolved in dry THF (40 ml) was then added at such a rate that the temperature did not exceed −70 °C. An orange slurry was formed and stirring was continued for 1 h at −70 °C. A solution of succinic anhydride (2.0 g, 20 mmol) in dry THF (50 ml) was added dropwise such that the temperature remained below −60 °C. The reaction mixture that turned yellowish was stirred for a further 1 h at −60 °C. The temperature was allowed to rise to 0 °C and the reaction mixture poured into ice–water and the phases were separated. The aqueous phase was washed twice with Et_2O, adjusted to pH 2 by addition of 2 M HCl and extracted with $CHCl_3$. After drying ($MgSO_4$) and evaporation, a crystalline residue (9 g) was obtained. Purification of this by flash chromatography on SiO_2 ($CHCl_3$/MeOH/HOAc, 95:5:1), gave **9** (4 g, 46 %) as a white crystalline solid. M.p. 119–120 °C. ^{1}H NMR ($CDCl_3$): δ 7.55 (br s), 7.50 (d, 1 H), 7.25 (d, 1 H), 6.65 (d, 1H), 5.49 (d, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 3.25–2.85 (m, 2 H), 2.58 (t, 2 H). ^{13}C NMR ($CDCl_3$):δ 200.00, 176.82, 166.42, 164.56, 157.08, 155.18, 134.80, 120.96, 108.70, 108.29, 62.74, 62.56, 56.37, 53.45, 34.88, 27.81. Anal. ($C_{16}H_{18}BrNO_8$): C, H, N, O.

*2-(2-Pyridyl)ethyl 5-(N-benzyloxycarbonyl)-4-oxopentanoate (**13a**).* Z-Gly-Val-OH[10] (**10**, 3.88 g, 12.6 mmol) was heated with acetic anhydride (10 ml) at 75–95 °C for 1 h. The reaction mixture was concentrated under reduced pressure, dissolved in toluene (20 ml) and evaporated to dryness: a procedure which was repeated 6 times. To the residue was added 2-(2-pyridyl)ethyl acrylate[9] (2.23 g, 12.6 mmol) and the mixture was cooled in an ice–water bath. Triethylamine (2.55 ml) was added dropwise and the reaction mixture was left at room temperature. After 16 h the mixture was heated for 2 h at 50 °C and after being cooled it was concentrated under reduced pressure to leave compound **12a** as an oil. The residue was treated with a mixture of ethanol–aqueous $NaHCO_3$ (40+20 ml) for 16 h at 55 °C. The mixture was concentrated and partitioned between CH_2Cl_2 and water. The organic phase was separated, dried (Na_2SO_4) and concentrated to dryness to leave a brown oil which was purified by column chromatography on SiO_2 (ethyl acetate). From the main fraction was obtained the title compound **13a** (1.90 g, 41 %) as an oil which slowly crystallized. M.p. 58–59 °C. ^{1}H NMR ($CDCl_3$): δ 8.53 (d, 1 H), 7.65–7.57 (m, 1 H), 7.35 (s, 5 H), 7.19–7.10 (m, 2 H), 5.47 (m, 1 H), 5.12 (s, 2 H), 4.47 (t, 2 H), 4.10 (d, 2 H), 3.10 (t, 2 H), 2.75–2.50 (m, 4 H). Anal. ($C_{20}H_{22}N_2O_5$): C, H, O.

2-(2-Pyridyl)ethyl 5-(3-bromo-2,6-dimethoxybenzamido)-4-oxopentanoate (**14a**). The ester **13a** (1.83 g, 4.9 mmol) was stirred with 33 % HBr/HOAc (10 ml) for 2 h until the CO_2 evolution had ceased. Et_2O (100 ml) was added and the mixture cooled to −20 °C. An oil separated and the solvent was decanted. The remaining oil was washed with Et_2O (2×100 ml) and finally dissolved in CH_2Cl_2 (10 ml). The benzoyl chloride **7** (see the synthesis of **8**) (5.7 mmol) in CH_2Cl_2 (10 ml) was added and the mixture was cooled to −30 °C. A catalytic amount of 4-dimethylaminopyridine was added followed by the dropwise addition of triethylamine (2.25 ml) in CH_2Cl_2 (20 ml). After 2 days (weekend) at room temperature the reaction mixture was washed with water, dried (Na_2SO_4) and concentrated. Column chromatography on SiO_2 (ethyl acetate) gave 2.0 g (85 %) of the title compound. ^{1}H NMR ($CDCl_3$): δ 8.53 (d, 1 H), 7.70–7.55 (m, 1 H), 7.50 (d, 1 H), 7.21–7.10 (m, 2 H), 6.65 (br s, 1 H), 6.60 (d, 1 H), 4.47 (t, 2 H), 4.35 (d, 2 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.10 (t, 2 H), 2.78 (t, 2 H), 2.63 (t, 2 H).

Ethyl 5-(3-bromo-2,6-dimethoxybenzamido)-4-oxopentanoate (**14b**). A solution of ethyl 5-(*N*-benzyloxycarbonyl)-4-oxopentanoate[8] (**13b**, 2.36 g, 8 mmol) was deprotected and acylated for 15 h with the benzoyl chloride **7** (2.84 g, 10 mmol) according to the above procedure (**14a**). After successive washings with 1 M HCl, H_2O and aqueous $NaHCO_3$, the organic solution was dried (Na_2SO_4). Evaporation to dryness left 3.21 g (99 %) of an oil which slowly crystallized. An analytical sample was obtained upon recrystallization from ethyl acetate/petroleum ether. M.p. 78–79 °C. ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 1 H), 6.71 (d, 1 H), 6.80–6.60 (br, 1 H), 4.45 (d, 2 H), 4.20 (q, 2 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.00–2.60 (m, 4 H), 1.28 (t, 3 H). Anal. ($C_{16}H_{20}BrNO_6$): C, H, N, O.

5-(3-Bromo-2,6-dimethoxybenzamido)-4-oxopentanoic acid (**4**). *Method A* (Scheme 1). A solution of 2 M H_2SO_4 (100 ml) was added to the keto ester **9** (3 g, 6.9 mmol) and the mixture was stirred at 80 °C overnight. The solution was cooled to room temperature and a white precipitate was formed. Filtration and recrystallization from water gave pure **4** (1.3 g, 50 %). M.p. 95–96 °C. ^{1}H NMR ($CDCl_3$ + 2 drops DMSO-d_6): δ 7.92 (br s, 1 H), 7.49 (d, 1 H), 7.28 (t, 1 H), 6.63 (d, 1 H), 4.30 (d, 2 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 2.82 (t, 2 H), 2.60 (t, 2 H). ^{13}C NMR ($CDCl_3$ + 2 drops DMSO-d_6): δ 204.23, 174.19, 164.58, 156.52, 154.42, 133.84, 122.10, 108.32, 107.70, 62.10, 55.99, 49.25, 34.36, 27.58. IR (KBr): ν 3475, 3340, 2900, 1720, 1653, 1590, 1540 cm^{-1}. MS [*m/z* (% rel. int.)]: 375/373 (3/3), 275/273 (4/4), 274/272 (4/4), 246 (10), 245/243 (97/100), 244/242 (13/4), 230/228 (12/13), 187/185 (6/7), 165 (8), 132 (10), 44 (5). Anal. ($C_{14}H_{16}BrNO_6$): C, H, O, Br.

Method B (Scheme 2). The ester **14b** (200 mg, 0.5 mmol) was added to a mixture of 2 M HCl–EtOH (2+1 ml) and dioxane (0.5 ml). The resulting mixture was heated at 50 °C for 18 h. After cooling, the solvent was removed by means of a rotary evaporator and the residue was taken up in ethyl acetate. Washing with water, drying (Na_2SO_4) and evaporation *in vacuo* left an oil (136 mg, 73 %) which slowly crystallized. Two recrystallizations from ethyl acetate/hexane provided 84 mg of **4**. M.p. 115–117 °C. IR (KBr): ν 3475, 3340, 2900, 1720, 1653, 1590, 1540 cm^{-1}. Anal. ($C_{14}H_{16}BrNO_6$): C, H, N, O, Br.

Method C (Scheme 2). The ester **14a** (2.0 g, 4.2 mmol) in acetonitrile (15 ml) was mixed with methyl iodide (800 µl, 12.8 mmol) and left for 16 h at room temperature. The mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (2 ml). Diethylamine (2 ml) was added and the mixture was left for 16 h at room temperature. To the reaction mixture was added CH_2Cl_2 (4 ml) followed by an excess of 2 M HCl. The precipitate formed was isolated by filtration and washed with water. The yield of the acid **4** was 1.04 g (66 %). M.p. 91–93 °C.

N-Ethyl-5-(3-bromo-2,6-dimethoxybenzamido)-4-oxopentanamide (**5**). A mixture of the acid **4** (374 mg, 1.0 mmol) and *N*-methylmorpholine (125 µl, 1.1 mmol) in CH_2Cl_2 (6 ml) was cooled to −20 °C. Isobutyl chloroformate (150 µl, 1.0 mmol) in CH_2Cl_2 (1 ml) was added to the stirred solution and the reaction mixture was left at −20 °C. After 15 min at −20 °C to −15 °C, ethylamine (100 mg, 2.2 mmol) in CH_2Cl_2 (1.5 ml) was added and stirring was continued at −10 °C to +2 °C for 30 min. The reaction mixture was successively washed with ice-cooled solutions of 1 M citric acid, saturated aqueous $NaHCO_3$ and brine. After drying (Na_2SO_4), the solvent was evaporated under reduced pressure to leave **5** as a crystalline residue (340 mg, 85 % yield). M.p. 137–139 °C. ^{1}H NMR ($CDCl_3$): δ 7.48 (d, 1 H), 6.80 (br m, 1 H), 6.60 (d, 1 H), 5.90 (br s, 1 H), 4.35 (d, 2 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.35–3.15 (m, 2 H), 2.84 (t, 2 H), 2.50 (t, 2 H), 1.20–1.05 (m, 3 H). ^{13}C NMR ($CDCl_3$): δ 204.74, 171.16, 167.34, 164.65, 156.83, 134.23, 122.17, 108.53, 108.15, 62.40, 56.24, 49.58, 35.00, 34.48, 29.75, 14.75. MS [*m/z* (% rel. int.)]: 402/400 (0.6/0.6), 384/382 (14/14), 275/273 (8/8), 246/244 (10/13), 245/243 (98/100), 230/228 (13/14), 187/185 (5/6), 139 (6), 128 (42). Anal. ($C_{16}H_{21}BrN_2O_5$): C, H, N, O.

1-Ethyl-5-[(3-bromo-2,6-dimethoxybenzamido)methyl]-5-hydroxy-2-pyrrolidone (**2**). The amide **5** was dissolved in methanol (5 ml) and a catalytic amount of ammonia in methanol was added. After 10 min no starting material could be detected by TLC and the solution was evaporated to leave pure **2** (50 mg, 100 %) as a white crystalline solid. M.p. 85 °C (decomp.). ^{1}H NMR ($CDCl_3$): δ 7.48 (d, 1 H), 6.60 (d and t, 2 H), 5.35 (s, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.78–3.52 (m, 2 H), 3.42–3.12 (m, 2 H), 2.55–2.15 (m, 3 H), 2.15–1.88 (m, 1 H), 1.18 (t, 3 H). ^{13}C NMR ($CDCl_3$): δ 175.03, 166.19, 156.55, 154.71, 134.48, 122.36, 108.69, 108.23, 91.85, 62.62, 56.31, 46.56, 34.18, 31.46, 29.13, 14.91. MS [*m/z* (% rel. int.)]: 402/400 (0.2/0.2), 384/382 (14/14), 275/273 (3/3), 245/243 (97/100), 230/228 (13/13).

5-[(3-Bromo-2,6-dimethoxybenzamido)methyl]-5-hydroxy-2-pyrrolidone (**3**). A mixture of **4** (750 mg, 2 mmol) and triethylamine (202 mg, 2 mmol) in $CHCl_3$ (10 ml) was cooled to −20 °C and isobutyl chloroformate (273 mg, 2 mmol) was added. The reaction mixture was kept at −5 °C for 2 h. A slow stream of ammonia was then passed over the stirred solution at 0 °C for 1 h. Stirring was continued at room temperature overnight and the white precipitate formed was filtered off. The filtrate was evaporated to leave a residue (500 mg) that was purified by chromatography on SiO_2 ($CHCl_3/CH_3OH$; 95:5) to give the cyclized product **3** (281 mg, 38 %) as a white solid. M.p. 147–148 °C. ^{1}H NMR ($CDCl_3$): δ 7.43 and 7.39 (d and s, 2 H), 7.15 (t, 1 H), 6.58 (d, 1 H), 5.55 (s, 1 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 3.63 (d, 2 H), 2.87–2.66 (m, 1 H), 2.62–1.88 (m, 3 H). ^{13}C NMR ($CDCl_3$): δ 178.06, 165.90, 156.41, 154.32, 134.08, 122.82, 108.79, 107.93, 88.74, 62.52, 56.31, 47.68, 32.38, 29.85. MS [*m/z* (% rel. int.)]: 356/354 (10/10), 245/243 (97/100), 230/228 (16/17).

The precipitate that was filtered off was partitioned between water (10 ml) and CH_2Cl_2 (100 ml). The organic phase was dried and evaporated to give the open-chain derivative 5-(3-bromo-2,6-dimethoxybenzamido)-4-oxopentanamide **6** (170 mg, 22 %). M.p. 165–166 °C. ^{1}H NMR (DMSO-d_6): δ 7.92 (br s, 1 H), 7.49 (d, 1 H), 7.28 (t, 1 H), 6.63 (d, 1 H), 4.30 (d, 2 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 2.82 (t, 2 H), 2.60 (t, 3 H). ^{13}C NMR (DMSO-d_6):δ 206.61, 173.47, 164.25, 156.58, 153.97, 133.53, 123.51, 109.47, 107.16, 62.05, 56.36, 49.20, 34.54, 28.79. Anal. ($C_{14}H_{17}BrN_2O_5$): C, H, N, O.

References

1. (a) Florvall, L. and Ögren, S.-O. *J. Med. Chem. 25* (1982) 1280; (b) Ögren, S.-O., Hall, H., Köhler, C., Magnusson, O., Lindbom, L.-O., Ängeby, T. and Florvall, L. *Eur. J. Pharmacol. 102* (1984) 459.
2. Högberg, T., Rämsby, S., Ögren, S.-O. and Norinder, U. *Acta Pharm. Suec. 24* (1988) 289 and references therein.
3. (a) Lindström, L., Besev, G., Stening, G. and Widerlöv, E. *Psychopharmacology 86* (1985) 241; (b) McCreadie, R. G., Morrison, D., Gall, R. G., Loudon, J. and Mitchell, M. J. *Acta Psychiatr. Scand. 72* (1985) 139; (c) Laursen, A. L. and Gerlach, J. *Acta Psychiatr. Scand. 73* (1986) 17; (d) den Boer, J. A., Verhoeven, W. M. A. and Westenberg, H. G. M. *Acta Psychiatr. Scand. 74* (1986) 409; (e) Chouinard, G. and Turiner, L. *Psychopharmacol. Bull. 22* (1986) 267.
4. Brennan, J. J., Imondi, A. R., Westmoreland, D. G. and Williamson, M. J. *J. Pharm. Sci. 71* (1982) 1199.
5. (a) Keller, O. and Prelog, V. *Helv. Chim. Acta 54* (1971) 2572 and references therein; (b) Flitsch, W. *Chem. Ber. 103* (1970) 3205 and references therein.
6. Evans, D. A. and Sidebottom, P. J. *J. Chem. Soc., Chem. Commun.* 1978, 753.
7. Jardon, P. W., Vickery, E. H., Pahler, L. F., Pourahmady, N., Mains, G. J. and Eisenbraun, E. J. *J. Org. Chem. 49* (1984) 2130.
8. Schultz, G. and Steglich, W. *Chem. Ber. 113* (1980) 787.
9. (a) Kunz, H. and Barthels, R. *Angew. Chem., Int. Ed. Engl. 22* (1983) 783; (b) Kessler, H., Becher, G., Kogler, H. and Wolff, M. *Tetrahedron Lett. 25* (1984) 3971.
10. Weygand, F. and Steglich, W. *Chem. Ber. 93* (1960) 2983.
11. (a) Sterk, H. *Monatsch. Chem. 99* (1968) 1770; (b) Pascual, C., Wegmann, D., Graf, U., Scheffold, R., Sommar, P. F. and Simon, W. *Helv. Chim. Acta 47* (1964) 213.
12. (a) Nishida, T., Pilotti, Å. and Enzell, C. *Org. Magn. Reson. 13* (1980) 434; (b) Nguyen, T.-L., Dagne, E., Gruenke, L., Bhargava, H. and Castagnoli, N. *J. Org. Chem. 46* (1981) 758.
13. Widman, M. *To be published.*

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