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PRACTICAL AND EFFICIENT PROCESSES FOR THE PREPARATION OF 4-(4-AMINOPHENYL)MORPHOLIN-3-ONES ON A LARGER SCALE: PRECURSOR OF FACTOR Xa INHIBITORS

Werner W. K. R. Mederski,* Peter Ludwig Wendel, and Markus Woissyk

Preclinical Pharmaceutical Research, Merck KGaA, 64271 Darmstadt, Germany

Abstract – Factor Xa inhibitors are interesting targets for the development of antithrombotic agents. Our personal efforts in the discovery of small molecule inhibitors led to the compounds **EMD 495235** and **EMD 503982**, which entered preclinical and clinical studies, respectively. Therefore, kilograms of both drugs in particular 4-(4-aminophenyl)morpholin-3-one moieties have to be provided. The scale-up results of these special P-4 ligands will be described herein.

INTRODUCTION

Factor Xa (fXa), a trypsin-like serine protease, is involved in the process of blood coagulation. At the convergence point of the extrinsic and intrinsic coagulation pathways fXa, as a component of the prothrombinase complex, converts prothrombin to thrombin *via* proteolysis. Due to the specific mechanism within these pathways it is assumed that inhibition of this penultimative enzymatic step will allow the effective control of thrombogenesis with a minimal effect upon bleeding.[1] Inhibition of this enzyme has been identified as an attractive target for the development of antithrombotic agents and has emerged as a particularly active area of research.[2]

Most of the known first and second generation factor Xa inhibitors have a benzamidine residue. These molecules displayed undesired poor pharmacokinetic properties. In an effort to develop inhibitors with more favorable oral profiles, we have discovered a series of potent non-benzamidines as exemplified by the compounds shown in Figure 1.[3]

*Corresponding author. E-mail: mederski@merck.de

This paper is dedicated to Prof. Dr. Dr.h.c. Ekkehard Winterfeldt on the occasion of his 75th birthday

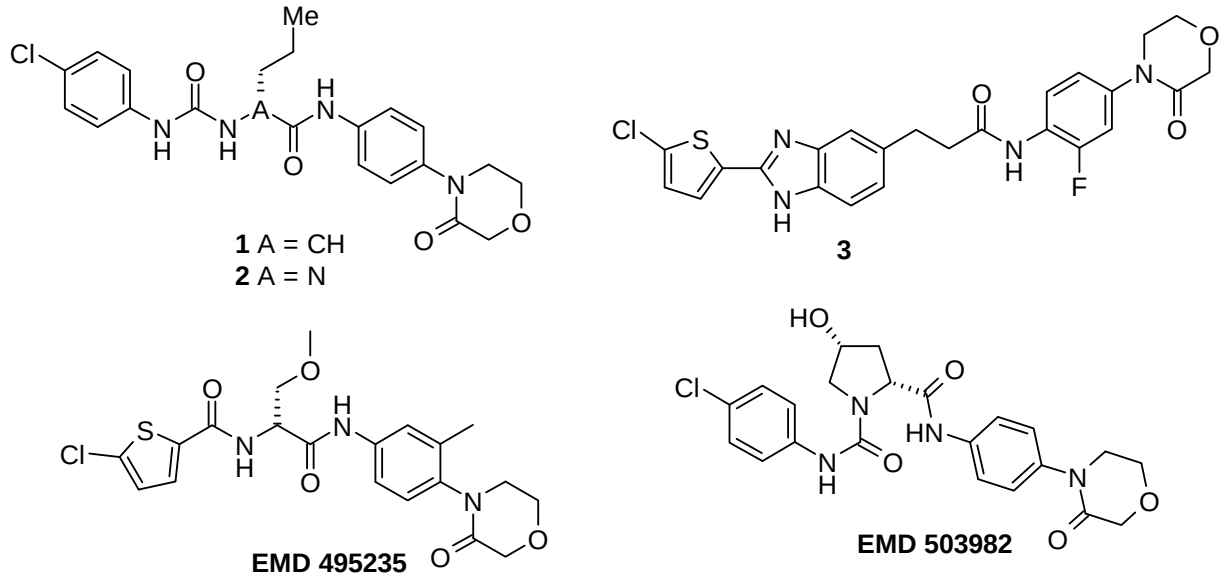


Figure 1

Key feature of these molecules is the 4-(4-aminophenyl)morpholin-3-one moiety, which serves as a P4-ligand within the respective enzyme pocket. A thorough investigation of the central part of the molecule and the S1 binding pocket led to the discovery of amino acid derivatives **EMD 495235** and **EMD 503982**. Both amino acid derivatives displayed excellent in vitro and in vivo efficacy and good pharmacokinetic profiles and were chosen as candidates for in-depth in vivo investigations as anti-coagulating drugs. From that hydroxyprolyl derivative **EMD 503982** was selected for clinical development for the prevention and treatment of thromboembolic diseases.

However, in both cases kilogram quantities of the respective aryl-morpholinones were needed to support toxicological and clinical evaluation studies.

In this paper the scale-up results of the two different 4-(4-aminophenyl)morpholin-3-ones of **EMD 495235** and **EMD 503982** will be described.

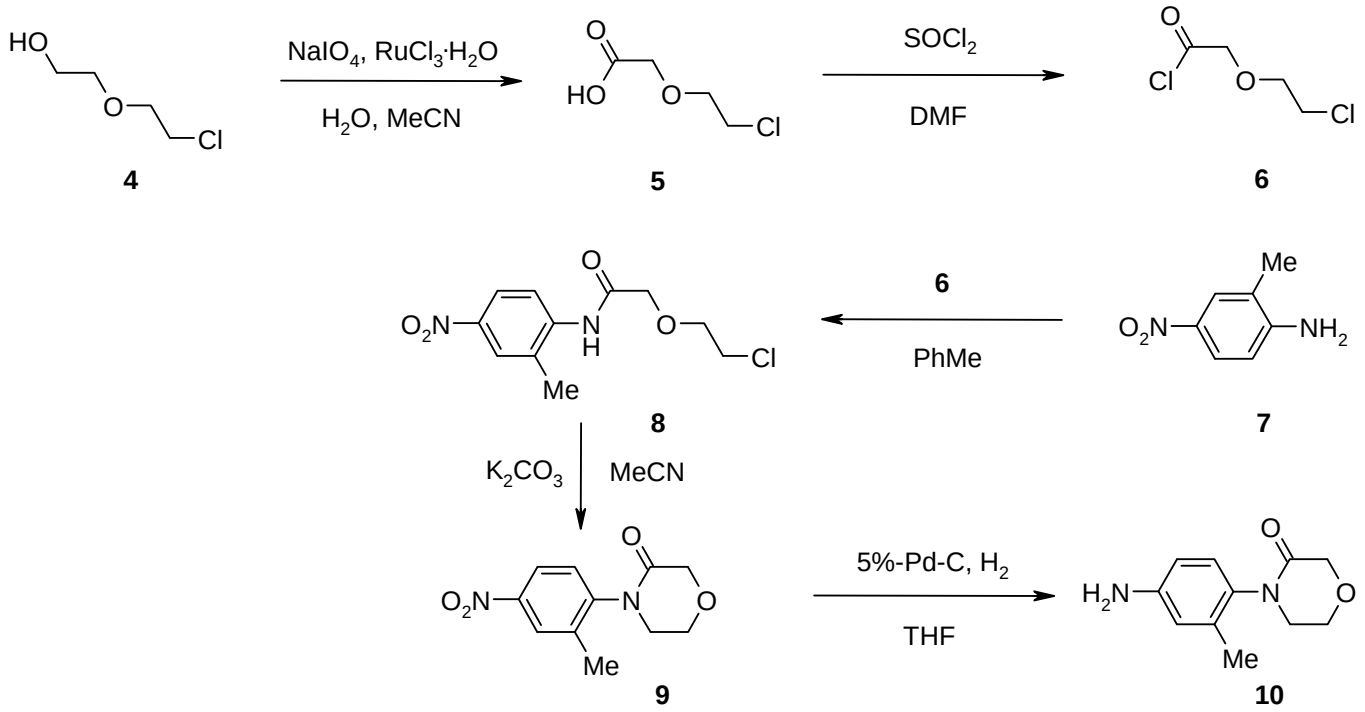
RESULTS AND DISCUSSION

For the syntheses of different 4-(4-aminophenyl)morpholin-3-ones it was envisaged to prepare 4-nitro derivatives with variable substituents at the phenyl ring following by a reduction of the nitro group resulting in the respective aniline.

At the outset of our work three different approaches concerning the structure of 4-arylmorpholin-3-ones were described in the literature. One choice is the direct oxidation of an arylmorpholine by means of mercury (II) ethylendiaminetetraacetate[4] or potassium permanganate under phase transfer catalysis.[5] An alternative is the copper (I) promoted C-N coupling methodology of an arylhalide with morpholin-3-one.[6] As a third possibility anilines can serve as a starting point in two different ways. On the one hand they

react with 2-chloroethanol to the intermediate 2-hydroxyethylarylamines, which undergo ring closure with chloroacetic acid ethyl ester or chloroacetyl chloride, respectively.[7] On the other hand anilines are converted with halogenated alkanoic acid chlorides into arylanilides, which cyclized under appropriate conditions to the targeted 4-arylmorpolin-3-ones.[8] The availability of divers 4-nitroanilines and the access to the corresponding (2-chloroethoxy)acetyl chloride was the decisive factor for the selection as our medicinal chemistry route. Although the preparation of the acid chloride was described in the literature[9], the conditions were modified in order to guarantee a scalable synthesis. This method, depicted in Scheme 1, was applied for a large number of analogues and for kilogram quantities of **EMD 495235**.

The oxidation of the starting material 2-(2-chloroethoxy)ethanol (**4**) with sodium metaperiodate in the presence of catalytic amounts of ruthenium (III) chloride in a water acetonitrile suspension furnished the carboxylic acid (**5**).[10] The latter compound (**5**) was then treated with thionyl chloride in dimethylformamide to provide the corresponding acid chloride (**6**). This key intermediate (**6**) was condensed with the commercially available 2-methyl-4-nitroaniline (**7**) in toluene in the heat to afford the phenylacetamide (**8**). Ring closure to the morpholinone (**9**) occurred by treatment of **8** with potassium carbonate in acetonitrile at elevated temperature. Nitromorpholinone (**9**) was reduced to aminomorpholinone (**10**) in tetrahydrofuran in the presence of palladium on carbon under a hydrogen atmosphere. The choice of solvent is decisive under these conditions. Although an alcohol is usually applied for those transformations ring opened ester derivatives were observed as side products. Due to the ortho-positioning of the methyl group in **9** the morpholin-3-one is twisted, which gave rise to a nucleophilic attack of the corresponding alcohol at the amide position.

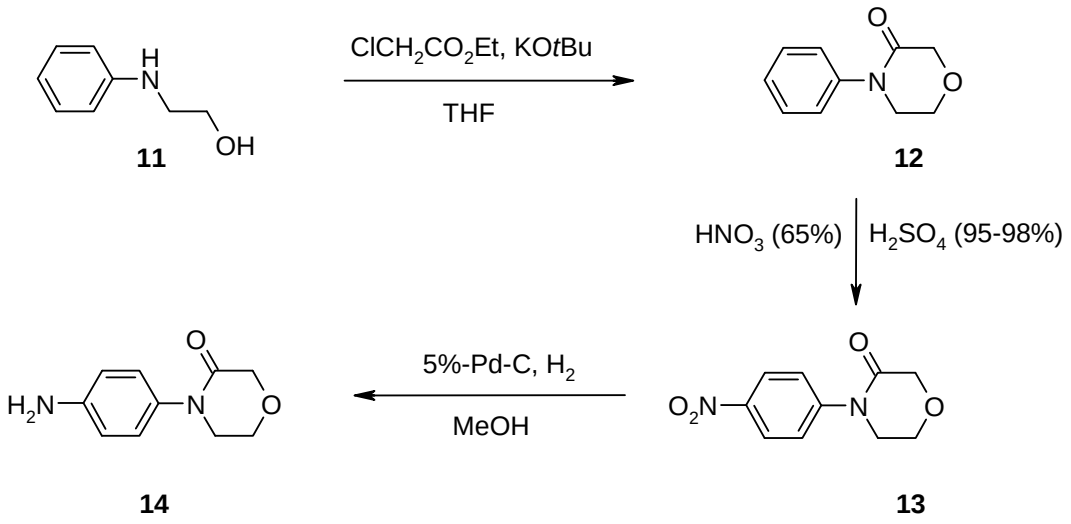


Scheme 1

Initially the parent 4-(4-aminophenyl)morpholin-3-one (**14**) in this series was successfully prepared following the 5-step sequence depicted in Scheme 1. However, reduction in cost of goods for the phase I clinical candidate **EMD 503982** focused our efforts to more convergent strategies.

Missing any additional substituent such as ortho-methyl at the phenyl ring alternative syntheses could be envisaged. One of them is the introduction of nitrogen functionality by electrophilic substitution. Literature precedents revealed, that nitration of phenyl-substituted *N*-heterocycles gave predominantly the para-product[11] with some exceptions leading to the meta-substitution as the main product.[12] Preliminary experiments with phenylmorpholinone (**12**) as the substrate showed, that the first and most prominent nitration took place in the para position of the phenyl ring. According to our literature survey[7] morpholinone (**12**) in turn could be prepared from the cheap 2-hydroxyethylphenylamine (**11**), which is available in bulk quantities. In this manner **EMD 503982** has been synthesized on a kilogram scale.

2-anilinoethanol (**11**) was condensed with ethyl chloroacetate in the presence of potassium *tert*-butoxide in tetrahydrofuran to afford the required phenylmorpholinone (**12**).[13] Nitration of the intermediate morpholinone (**12**) in a solution of concentrated sulphuric acid with nitric acid below room temperature provided after recrystallization the para-product (**13**) in > 99.5% HPLC purity. The mother liquor was enriched predominantly with unwanted ortho - and meta-isomers together with depleted para-product.[14] By subsequent hydrogenation of the nitro group in **13** with palladium on charcoal in methanol the target amine (**14**) was obtained.[15]



Scheme 2

For phase II developmental work batch-nitrations had to be kept below 500L due to increasing amounts of ring-opened by-products. To avoid these side-reactions a homemade pilot plant continuous micro-reaction system was installed.[16] Using this equipment over 200 kg of **12** can be nitrated within 50 hours.[16]

In conclusion two different scalable syntheses of arylmorpholin-3-ones have been elaborated, which led to variable anilines as intermediates of factor Xa inhibitors.

EXPERIMENTAL

Melting points were determined with a HWS Labortechnik SGV 500 Plus melting point apparatus and are uncorrected. IR, NMR and MS spectra are in agreement with the structures cited and were recorded on a Bruker 85 IFS 48 IR spectrophotometer, a Bruker Avance 250, AMX 300, Avance 400 or Avance DRX 500 (TMS as internal standard), and a Micromass (Manchester, England) VG 70-70E (electron-impact: EI) or 70-250SE (fast atom bombardement: FAB) at 70eV, respectively. HRMS spectra were recorded on an Autospec M from Micromass. Microanalyses were obtained with a Perkin-Elmer 240B CHN analyzer. HPLC was taken on a VWR-Hitachi LaChromElite apparatus. The column used was a monolithic silica column, Chromolith Performance RP-18e 100-4.6. The mobile phase used was acetonitrile/water (+ 0.2% trifluoroacetic acid) in a 15 min linear gradient 5-95% and a flow rate of 1 mL/min. Peak detection was achieved using a diode array detector at 220 and 254 nm, respectively. TLC was carried out on precoated silica gel 60 F_{254} plates with a layer thickness of 0.25 mm from Merck KGaA (Darmstadt, Germany). Visualization was performed with UV and I_2. Yields were not optimized. The preparative chromatography was performed on Merck KGaA silica gel 60 (230-400 mesh) and all solvents were of Merck extra-pure grade.

(2-Chloroethoxy)acetic acid (5):

To a dry, nitrogen-purged 100-L reactor with a mechanically stirred solution of water (75 L) were successively added sodium metaperiodate (6.84 kg, 31.98 mol), ruthenium (III) chloride hydrate (40.0 g), and a solution of 2-(2-chloroethoxy)ethanol (2.0 Kg, 16.06 mol) in MeCN (10 L) at 25 °C. The resulting suspension was stirred at 20 °C for 16 h. The solid was filtered off. The pH of the remaining aqueous solution was adjusted to 13 with aqueous sodium hydroxide (32%, 1.9 L), and extracted three times with 2-methoxy-2-methylpropane (8 L each). The pH of the aqueous phase was then adjusted to 1 with hydrochloric acid (37%, 2.5 L). This solution was washed five times with EtOAc (15 L each). The organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo at 50 °C. The remaining crude oil was dissolved in 2-methoxy-2-methylpropane (15 L), and washed successively with an aqueuos solution of sodium disulfite (500 g in 1.0 L water) and brine. The organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo at 50 °C to afford 1.65 kg of the desired product **5** (74 % yield) as an oil, which was used for the next step without further purification. IR (KBr-capillary) 1730 cm^{-1}. ^1H NMR (DMSO-d_6) δ 11.00 (sbr, 1H), 4.03 (s, 2H), 3.75-3.64 (m, 2H), 3.51-3.35 (m, 2H). Anal. Calcd for $C_4H_7ClO_3$: C, 34.68; H, 5.09. Found: C, 35.5; H, 5.3.

(2-Chloroethoxy)acetyl chloride (6):

To a dry, nitrogen-purged 25-L reactor with a mechanically stirred solution of thionyl chloride (12.5 L) was added *N*,*N*-dimethylformamide (0.04 L) at 25 °C. The mixture was heated to 50 °C and (2-chloroethoxy)acetic acid **5** (1.6 kg, 11.55 mol) was added. After the addition, the reaction mixture was heated to 70 °C and stirred for 3 h. The mixture was cooled to 25 °C and stirred for additional 17 h. Excess thionyl chloride was distilled off under reduced pressure, and the residue was subjected to fractional distillation (bp 52 – 55 °C, 3-5 mbar), which afforded 1.53 kg of the desired product **6** (83 % yield) as an oil. IR (KBr-capillary) 1800 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.49 (s, 2H), 3.85 (t, *J* = 5.7 Hz, 2H), 3.64 (t, *J* = 5.6 Hz, 2H). Anal. Calcd for $C_4H_6Cl_2O_2$: C, 30.60; H, 3.85. Found: C, 31.1; H, 4.1.

(2-Chloroethoxy)-*N*-(2-methyl-4-nitrophenyl)acetamide (8):

To a dry, nitrogen-purged 65-L reactor with a mechanically stirred solution of toluene (16 L) was added 2-methyl-4-nitroaniline **7** (1.00 kg, 6.57 mol) at 25 °C. The mixture was heated to 60 °C and (2-chloroethoxy)acetyl chloride **6** (1.072 kg, 6.82 mol) was added. After the addition, the reaction mixture was heated to 100 °C and stirred for 17 h. The reaction was assayed by monitoring TLC and HPLC, indicating some of the starting material **7** remained. Additional (2-chloroethoxy)acetyl chloride **6** (0.207 kg, 1.41 mol) was added. The reaction mixture was stirred for 2 h, at which the disappearance of **7** was confirmed by monitoring TLC and HPLC. The mixture was cooled to 90 °C and let off into a PE-container, which cooled down to ambient temperature over night. The precipitates formed were collected by filtration and washed with toluene (2 L). The resulting solid was dried in a vacuum oven at 50 °C for 16 h to afford 1.73 kg of the desired product **8** (96 % yield) as a white solid, mp 115 – 116.5 °C. IR (KBr) 3376, 1710 cm^{-1}. ^1H NMR (DMSO-d_6) δ 9.30 (sbr, 1H), 8.16-8.14 (m, 1H), 8.10-8.06 (m, 2H), 4.25 (s, 2H), 3.90-3.80 (m, 4H), 2.36 (s, 3H). MS (EI): m/z 272 ([M^+], 36), 93 (57), 63 (100). HRMS calcd for (M^+) m/z 272.0563, found m/z 272.0563. Anal. Calcd for $C_{11}H_{13}ClN_2O_4$: C, 48.45; H, 4.81; N, 10.27. Found: C, 48.20; H, 4.80; N 10.20.

4-(2-Methyl-4-nitrophenyl)morpholin-3-one (9):

To a dry, nitrogen-purged 25-L reactor with a mechanically stirred solution of acetonitrile (18 L) were successively added (2-chloroethoxy)-*N*-(2-methyl-4-nitrophenyl)acetamide **8** (1.725 kg, 6.32 mol), and potassium carbonate (1.76 kg, 12.73 mol) [250 g portions every 0.5 h] at 25 °C. The reaction mixture was stirred at 50 °C for 40 h and monitored by TLC and HPLC, which indicated that no **8** remained. The mixture was filtered hot, washed immediately with acetonitrile (1 L), and concentrated in vacuo. The resulting solid was triturated with 2-methoxy-2-methyl-propane (4 L) for 2.5 h at ambient temperature, filtered, and dried in a vacuum oven at 50 °C for 48 h to afford 1.34 kg of the desired product **9** (90 % yield) as a yellow solid, mp 143.5 – 145.5 °C. IR (KBr) 1660 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.21 (d, *J* = 2.8 Hz, 1H), 8.12 (dd, *J* = 2.7 and 8.6 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 4.24 (s, 2H), 4.01 (t, *J* = 5.1 Hz,

2H), 3.80-3.50 (m, 2H), 2.27 (s, 3H). MS (EI): m/z 236 ([M^+], 100), 207 (84). HRMS calcd for (M^+) m/z 236.0797, found m/z 236.0797. Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.50; H, 5.00; N 11.80.

4-(4-Amino-2-methylphenyl)morpholin-3-one (10):

In a dry, nitrogen-purged 400-L autoclave was successively soaked up a solution of 4-(2-methyl-4-nitrophenyl)morpholin-3-one **9** (1.34 kg, 5.67 mol) and a suspension of palladium-on-charcoal (5%, 56% of water, 0.25 kg) in tetrahydrofuran (100 L and 10 L, respectively). The suspension was hydrogenated at 2 bar H_2 pressure at 40 °C until hydrogen consumption ceased (24 h, 381 L H_2). The catalyst was removed by filtration through a single-layer filter and washed with MeOH. The filtrate was concentrated in vacuo to give the crude product, which was re-crystallized from 2-methoxy-2-methylpropane to afford 1.112 kg of the desired product **10** (95 % yield) as a slight yellow solid, mp 163 – 164 °C. IR (KBr) 3436, 3356, 3428, 1650 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 6.80 (d, J = 8.3 Hz, 1H), 6.45-6.36 (m, 2H), 5.03 (sbr-NH_2, 2H), 4.14 (d, J = 3.5 Hz, 2H), 3.95-3.89 (m, 2H), 3.60-3.50 (m, 1H), 3.44-3.31 (m, 1H), 1.98 (s, 3H). MS (EI): m/z 206 ([M^+], 100), 133 (43). HRMS calcd for (M^+) m/z 206.1055, found m/z 206.1055. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.80; H, 6.90; N 13.50.

4-Phenylmorpholin-3-one (12):

To a dry, nitrogen-purged 100-L reactor with a mechanically stirred solution of THF (60 L) were successively added potassium 2-methylpropan-2-olate (6.54 kg, 58.3 mol), 2-phenylaminoethanol (8.0 kg, 57.15 mol) [within 0.25 h, rise in temperature to 30 °C], and chloroacetic acid ethyl ester (7.41 kg, 60.5 mol) [within 0.33 h, rise in temperature to 36 °C]. The resulting suspension was stirred at 25 °C for 16 h. The reaction was then carefully quenched with distilled water (30 L) and the pH was adjusted to 1-2 with hydrochloric acid (37%, 1.0 L). After separation of the two phases the organic layer was washed with brine (10 L), concentrated in vacuo to 15 L volume. Toluene was added five times (5 L each) and distilled in order to strip off the remaining water. The resulting solid was triturated with 2-methoxy-2-methylpropane (4 L) and dried in vacuo. The crude product (8.4 kg) was dissolved in toluene (35 L) at 65 °C, at which red oil collected at the bottom of the vessel.[13] The supernatant was cooled to ambient temperature over night. The obtained solid was slurried with 2-methoxy-2-methylpropane (25 L) for 0.25 h, filtered and dried in vacuo to afford 6.25 kg of the desired product **12** (62 % yield) as a white solid, mp 115 – 116 °C. (IR (KBr) 1660 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.45-7.23 (m, 5H), 4.20 (s, 2H), 3.98 (qd, J = 5.3 and 6.5 Hz, 2H), 3.72 (qd, J = 5.3 and 6.4 Hz, 2H). MS (EI): m/z 177 ([M^+], 100), 148 (68), 91 (74), 77 (66). HRMS calcd for (M^+) m/z 177.0789, found m/z 177.0787. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.40; H, 6.20; N 7.80.

4-(4-Nitrophenyl)morpholin-3-one (13):

To a dry, nitrogen-purged 65-L reactor with a mechanically stirred solution of sulphuric acid (95-98%, 40 L) was added 4-phenylmorpholin-3-one **12** (5.83 kg, 32.9 mol) at 10 °C. While the temperature was maintained at 10 – 17 °C, nitric acid (65%, 2.72 L) was added drop by drop for 80 min to the reaction mixture, and then the resulting mixture was stirred for further 2.0 h at 25 °C. The crude reaction mixture was added to crushed ice (40 kg) in a 400 L reactor. The precipitates formed were collected by filtration, washed twice with distilled water (10 L each), and dried in a vacuum oven at 70 °C for 24 h. Recrystallization of the crude product from propan-2-one (60 L) afforded 5.83 kg (80 % yield) of the desired product **13** as a light yellow solid, mp 154 – 155 °C. IR (KBr) 1670 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.27 (d, J = 9.3 Hz, 2H), 7.77 (d, J = 9.3 Hz, 2H), 4.27 (s, 2H), 4.01 (qd, J = 5.8 and 6.8 Hz, 2H), 3.86 (qd, J = 5.8 and 6.8 Hz, 2H). MS (EI): m/z 222 ([M^+], 100), 193 (86). HRMS calcd for (M^+) m/z 222.0642, found m/z 222.0641. Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.80; H, 4.50; N 12.50.

4-(4-Aminophenyl)morpholin-3-one (14):

In a dry, nitrogen-purged 400-L autoclave was successively soaked up a suspension of 4-(4-nitrophenyl)morpholin-3-one **13** (5.8 kg, 26.09 mol) and palladium-on-charcoal (5%, 56% of water, 0.64 kg) in methanol (200 L and 20 L, respectively). The suspension was hydrogenated at 2 bar H_2 pressure at 40 °C until hydrogen consumption ceased (17 h, 1752 L H_2). The catalyst was removed by filtration through a single-layer filter and washed with methanol. The filtrate was concentrated in vacuo to give the crude product, which was re-crystallized from 2-methoxy-2-methylpropane to afford 4.79 kg of the desired product **14** (95 % yield) as a solid, mp 173 – 175 °C. IR (KBr) 3460, 3340, 1640 cm^{-1}. ^1H NMR (DMSO-d_6) δ 6.97 (d, J = 9.0 Hz, 2H), 6.57 (d, J = 9.0 Hz, 2H), 5.10 (s, 2H), 4.14 (s, 2H), 3.93 (qd, J = 5.2 and 5.2 Hz, 2H), 3.59 (qd, J = 5.2 and 5.2 Hz, 2H). MS (EI): m/z 192 ([M^+], 100), 163 (34), 119 (47). HRMS calcd for (M^+) m/z 192.0899, found m/z 192.0896. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.20; H, 6.30; N 14.50.

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13. According to HPLC investigations the red oil contained a mixture of starting material (7%), morpholinone (**12**) (70%) and the dimerized product of the open chain adduct (23%, MW = 354 g/mol). Ageing of the oil within a few days led to a crude solid, which could be crystallised to give a second crop of **12**. However, this was not taken into account concerning the yield.
14. HPLC investigations of the crude reaction mixture revealed a turnover of 99.8%. In the order of elution from the HPLC column the following compounds were detected: 0.2% of starting material, 5% of *m*-product, 12% of *o*-product, 82% of *p*-product, and 0.8% of the open-chain product.
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