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Manufacture of High-Purity Meloxicam via Its Novel Potassium Salt Monohydrate

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Abstract:

An improved procedure for the manufacture of 4-hydroxy-2-methyl-*N*-(5-methyl-1,3-thiazol-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (meloxicam) is described. The key intermediate of this protocol is the new potassium salt monohydrate of meloxicam, which makes possible the efficient removal of impurities, resulting in an environmentally friendly manufacturing process of the high-purity (>99.90%) drug substance.

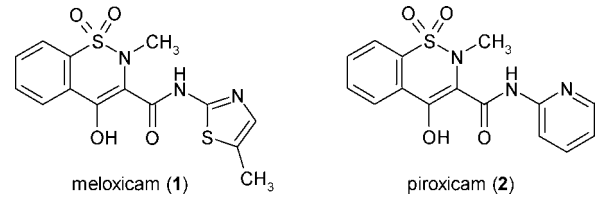

Figure 1. **Two representatives of the oxicam family of NSAIDs.**

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs)[1] are drugs with analgesic, antipyretic, and in higher doses, anti-inflammatory effects: they reduce pain, fever and inflammation. Part of the popularity of NSAIDs is that, unlike opioids, they do not produce sedation or respiratory depression and have a very low addiction rate. Certain NSAIDs, including ibuprofen and aspirin, have become accepted as relatively safe over-the-counter drugs.

Most NSAIDs act as nonselective inhibitors of the cyclooxygenase enzyme, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes,[2] thereby inhibiting the transformation of arachidonic acid into prostaglandins that act as messenger molecules in the process of inflammation. NSAIDs can be classified on the basis of their chemical structure, meloxicam (**1**, Figure 1) and the structurally related piroxicam (**2**) belong to the class of drugs called oxicams. **1** has been shown, especially at its low therapeutic dose, to selectively inhibit COX-2 over COX-1.[3] It significantly decreases symptoms of pain and stiffness in patients. In a comparative study, **1** exhibited a lower incidence of gastrointestinal side effects than **2**,[4] and it also proved to be a safe alternative to conventional NSAIDs.[5] Meloxicam (**1**) was launched in 1996 by Boehringer Ingelheim for the treatment of osteoarthritis and rheumatoid arthritis. The active ingredient of the drug product is polymorph Form I.[6,7] Further known crystalline forms are Form II,[7] Form III,[7] Form IV (zwitterionic form)[6] and Form V.[7]

As regards published synthetic procedures leading to **1**, two viable synthetic pathways are described in the literature for the synthesis of **1**.[8−10] The key intermediate of the first route (Scheme 1, route A) is a 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide ester **3**,[11] which is reacted with 5-methyl-1,3-thiazol-2-amine (**4**). The second literature procedure (Scheme 1, route B) for the synthesis of meloxicam (**1**) proceeds via 4-hydroxy-*N*-(5-methyl-1,3-thiazol-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (**5**), which is methylated in position 2 in the last step, with methyl iodide,[8] in the presence of a base.

A common drawback of the literature procedures is the formation of impurities **6**, alkylated at the nitrogen atom of the thiazole ring. Similar reactions of *N*-(5-methyl-1,3-thiazol-2-yl) carboxylic amides, i.e. alkylation of the thiazole nitrogen

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(6) Luger, P.; Daneck, K.; Engel, W.; Trummlitz, G.; Wagner, K. *Eur. J. Pharm. Sci.* **1996**, *4*, 175–187.

(7) Coppi, L.; Sanmarti, M. B.; Montserrat, C. C. Crystalline forms of meloxicam. U.S. Pat. Appl. 2003/109701, 2003. *Chem. Abstr.* **2003**, *139*, 26613.

(8) (a) The basic patent of meloxicam is: Trummlitz, G.; Engel, W.; Seeger, E.; Engelhardt, G. 4-Hydroxy-2*H*-1,2-benzothiazin-3-carboxamid-1,1-dioxides. Ger. Pat. DE 2756113, 1979. *Chem. Abstr.* **1979**, *91*, 91656. (b) The U.S. equivalent of the basic patent is: Trummlitz, G.; Engel, W.; Seeger, E.; Engelhardt, G. U.S. Patent 4,233,299, 1980.

(9) The following paper applies the same starting materials (**3**, **4**), but the amidation step is performed in the presence of BF_3 catalyst and molecular sieves: Zia-ur-Rehman, M.; Choudary, J. A.; Ahmad, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 1771–1775. *Chem. Abstr* **2006**, *145*, 83282.

(10) A less common synthetic procedure, i.e. transamination of corresponding carboxamides with 5-methyl-1,3-thiazol-2-amine is also mentioned in the literature: see ref 8a example 10.

(11) For the synthesis of starting materials **3a** and **3b**, see: (a) Lombardino, J. G.; Wiseman, E. H.; McLamore, W. M. *J. Med. Chem.* **1971**, *14*, 1171–1175. (b) Lombardino, J. G. *J. Org. Chem.* **1971**, *36*, 1843–1845. (c) Lombardino, J. G.; Wiseman, E. H.; Chianini, J. *J. Med. Chem.* **1973**, *16*, 493–496. (d) Reference 9.

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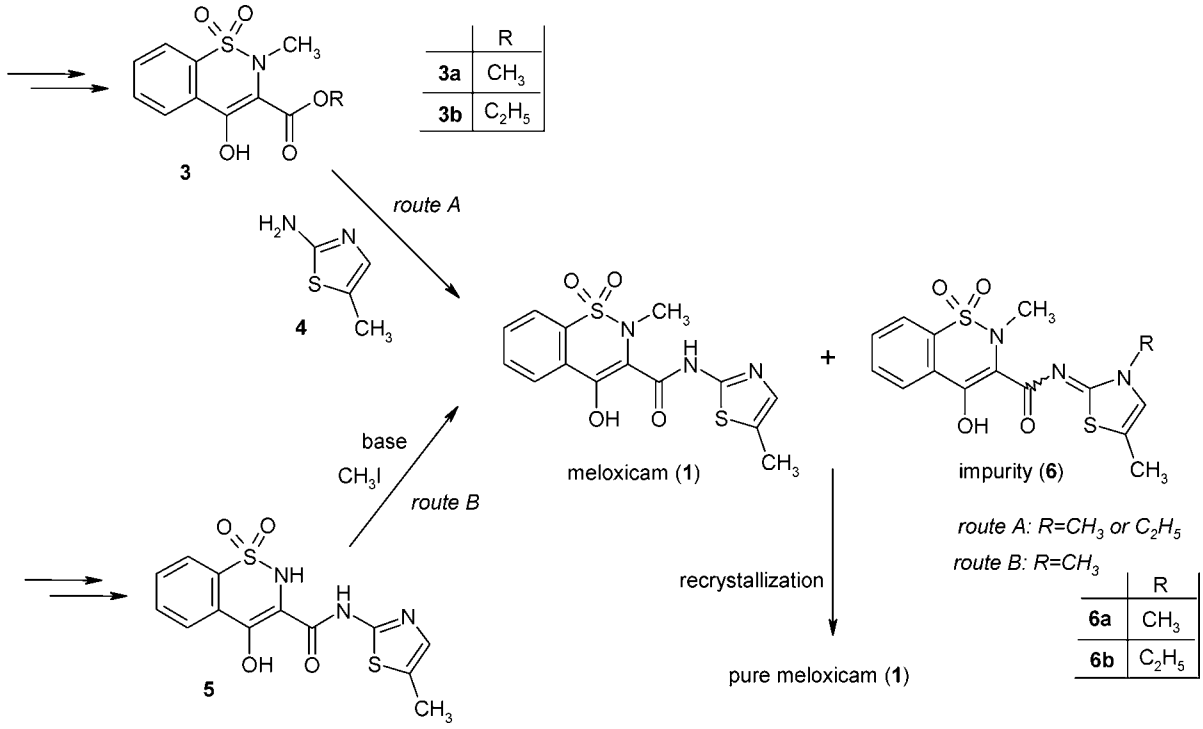
Scheme 1. **Literature procedures leading to meloxicam**



instead of the amide nitrogen, are precedented in the literature.[12,13] The quantity of impurities **6a**,**b** is limited to 0.05%, in the recently published European Pharmacopoeia monograph of meloxicam,[14] while the total allowed quantity of impurities is 0.3%.

When applying route B, formation of the *N*-methylated impurity (**6a**) can apparently be explained with dimethylation to a minor extent. On the other hand, when **1** is synthesised from esters **3** via route A, formation of impurity **6** (R = Me or Et, depending on **3**) is less evident. Nevertheless, both ester **3** itself or the alcohol (ROH) formed in the condensation reaction can act as alkylating agents; thus, they can alkylate the primarily formed **1** under the harsh reaction conditions needed for the amidation (e.g., xylene, reflux, 24 h). Vigano et al. used ethyl ester **3b** as starting material of the condensation reaction, and crude **1** obtained was contaminated with **6b** in a quantity of 0.23−0.78%.[15]

Removal of derivatives **6** and that of other eventual impurities is primarily described in the literature by recrystallization from 1,2-dichloroethane.[8] Nonetheless, use of 1,2-dichloroethane is not allowed in the pharmaceutical industry any more. Luger et al. found tetrahydrofuran to be an appropriate crystallization solvent for obtaining polymorph Form I,[6] however, the detailed methodology of purification is not disclosed. A recent patent application claims a laborious process for the recrystallization of crude **1** from acetone.[16] Acetic acid is also described as recrystallization solvent, but in this case acetic acid solvate is formed instead of Form I base.[17] Since no purity data can be found in the above processes, their purification potential can not be evaluated.

The preparation of sodium salt of **1** has been described in the basic patent of meloxicam.[8] Instead of recrystallization, formation of **1** and subsequent precipitation by acidification emerged as an alternative procedure for the purification of the crude product. The salification−reacidification process was first described in a patent application, using sodium hydroxide.[7] However, the authors did not use this step for the purification of **1**, they rather aimed at synthesizing new polymorphs of **1**. HPLC purity of the product is not disclosed in the patent application. Vigano et al.[15] used sodium alcoholates for the formation of the sodium salt from crude **1**, then the methanolic solution of the sodium salt obtained was reacidified to give **1**. Nevertheless, similarly to recrystallization of **1**, this method also proved to be inefficient for the reduction of the quantity of **6**

(12) For analogous thiazole *N*-alkylation leading to *N*-[3-alkyl-1,3-thiazol-2(3*H*)-ylidene]-carboxamide derivatives with *Z* configuration, see: (a) Ohta, H.; Ishizaka, T.; Tatsuzuki, M.; Yoshinaga, M.; Iida, I.; Tomishima, Y.; Toda, Y.; Saito, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6299–6304. (b) Manaka, A.; Ishii, T.; Takahashi, K.; Sato, M. *Tetrahedron Lett.* **2005**, *46*, 419–422.

(13) For papers discussing the simultaneous formation of products alkylated at the carboxamide nitrogen and the thiazole nitrogen atoms, see: (a) Hadida Ruah, S. S.; Grootenhuis, P. D. J.; Miller, M. T.; Hamilton, M. Preparation of mainly *N*-thiazolyl carboxamides as modulators of ATP-binding cassette transporters. PCT Pat. Appl. WO 2005/075435, 2005. *Chem. Abstr.* **2005**, *143*, 229835; example 28, (*E*)-(*Z*) isomerism not discussed. (b) Masuda, N.; Yamamoto, O.; Fujii, M.; Ohgami, T.; Moritomo, A.; Kontani, T.; Kageyama, S.; Ohta, M. *Synth. Commun.* **2005**, *35*, 2305–2316.

(14) *European Pharmacopoeia (Ph. Eur.)* Suppl. 6.3, **2009**; 2373.

(15) Vigano, E.; Landonio, E. Process for the purification of meloxicam. Eur. Pat. EP 1645559, 2006. *Chem. Abstr.* **2006**, *144*, 350700.

(16) Venkataraman, S.; Kumar, M. K.; Purandhar, K.; Reddy, B. K.; Reddy, L A.; Kondaiah, G. C.; Sreenath, K. Process for the preparation of crystalline form of meloxicam. U.S. Patent Appl. 2006/025408, 2006. *Chem. Abstr.* **2006**, *144*, 177433.

(17) (a) Trummlitz, G.; Sieger, P.; Werthmann, U.; Soyka, R.; Luger, P. Novel modification of 2*H*-1,2-benzothiazine-3-carboxamide-4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-1,1-dioxide (meloxicam) in form of a crystalline acetic acid solvate and use as drug. Ger. Pat. Appl. DE 10245882, 2004. *Chem. Abstr.* **2004**, *140*, 390403. (b) The PCT equivalent of this German patent application is: Trummlitz, G.; Sieger, P.; Werthmann, U.; Soyka, R.; Luger, P. PCT Pat. Appl. WO 2004/031183, 2004.

below the very strict level (0.05%) specified in the European Pharmacopoeia monograph.[14] Therefore, an additional refluxing of the suspension of **1** in acetone had to be applied. The yield of the salification−acidification step and that of the final purification is not disclosed.

Results and Discussion

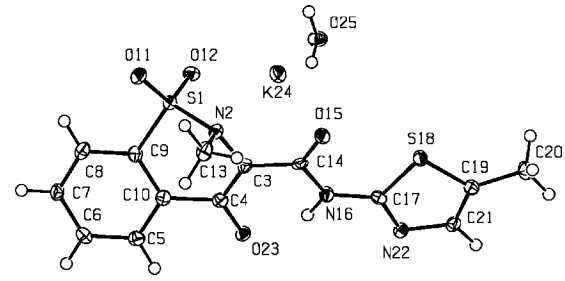
Since **3a** is a common intermediate of meloxicam (**1**) and piroxicam (**2**) and this latter had already been manufactured at our company, we aimed at optimizing the synthetic route starting from **3a**. Moreover, an efficient, robust, and green purification method of crude **1** was also sought.

The first step, i.e. amidation of ester **3a** with amine **4** was published in the basic patent of meloxicam[8] in good yield and under industrially applicable reaction conditions. Since the patent had already expired, we could apply practically the same method, without major modifications. We found in accordance with literature data[15] that, depending on the reaction time, 5−20% of impurity **6a** was formed in the amidation reaction.

Despite the numerous papers dealing with meloxicam, the synthesis and characterization of impurity **6a**, to the best of our knowledge, have not been published in the literature. Hereby, we have synthesised an authentic sample of **6a** *via N*-alkylation of **1**, at the thiazole nitrogen atom, and characterized it using spectroscopic methods. The fact that the newly introduced methyl group is attached to the thiazole N atom and not to the amide nitrogen was proved by NOE and MS fragmentation experiments. Irradiation of the thiazole *C*(4′)−H atom at 7.43 ppm resulted in interactions not only with the thiazole *C*(5′)−CH_3 moiety at 2.32 ppm, but also with another signal at 3.74 ppm, which later can be assigned to the *N*(3′)-CH_3 group. The $m/z = 113$ fragment (C_5H_7NS) in the MS spectrum, which corresponds to the *N*-methylated thiazole ring, also supports this statement. Determination of the geometry of the double bond in **6a** would necessitate structure determination by single-crystal X-ray diffraction; however, we did not succeed in obtaining appropriate crystals from **6a**. It is noteworthy that impurity **6a** has been published in the Ph. Eur. monograph[14] in the form of (*Z*) isomer, although no published data prove either the position of the newly introduced methyl group or the geometry of the newly formed double bond.

For the further purification of crude **1**, obtained in the amidation step, recrystallization from 1,2-dichloroethane has been first performed as a reference method.[8] However, it was found that the recrystallized product contained impurity **6a** in a quantity exceeding 0.2%.

When seeking an efficient purification method, we found surprisingly that potassium salt of **1** crystallized from aqueous KOH solution in its monohydrate form (**7**, Figure 2), in high purity. This observation led us to a very simple and robust process. Crude meloxicam obtained from **3a** was first treated with an equimolar amount of KOH in an aqueous solution. Since the solubility of **7** in water increased substantially between ambient temperature and 50 °C but there was no further significant increase up to 80 °C, 50 °C was found to be the optimal temperature. While **7** remained in the solution, impurity **6a** did not form a potassium salt and could be removed by filtration. For salting out **7** with an excess of potassium ion,



7

Figure 2. **Molecular diagram of 7 with the numbering of atoms. Atomic displacement ellipsoids are drawn at the 50% probability level.**

preliminary experiments were performed with various KOH amounts and concentrations. It was found that the amount of precipitated **7** increased strongly with increasing excess of KOH. On the other hand, a very high excess of KOH was considered to be disadvantageous because of the treatment of mother liquor and the sulfated ash test of the drug substance. For technological reasons, more concentrated solutions were preferred. As a result of these experiments, use of 5 equiv of KOH in a 23 w/w% KOH solution (30 g KOH in 100 mL water) proved to be optimal. Thus, to the clear yellow solution obtained after the filtration, a 23 w/w% KOH solution containing 5 equiv of KOH was added, and the precipitated yellow crystals of **7** were filtered off in high yield (81%, calculated for starting material **3a**) with an HPLC purity >99.90%, the amount of impurity **6a** being below 0.03%. Our experiments revealed that the solubility of **7** in aqueous KOH solutions showed a maximum at a concentration of 0.5 w/w%. Therefore, **7** was dissolved in a mixture of 0.5 w/w% aqueous KOH solution and ethanol, and then hydrochloric acid was subsequently added until pH = 6, resulting in high-purity **1**, as Form I polymorph. HPLC purity of the drug substance **1** thus obtained exceeded 99.95%, and the amount of impurity **6a** was below 0.03%. The efficiency of this purification procedure is best demonstrated by the fact that even a crude batch of **1** containing 12% of impurity **6a** led to a pure drug substance, which fulfilled the strict requirements of the European Pharmacopoeia.[14]

Meloxicam potassium salt monohydrate (**7**, Figure 2) is a novel salt. Its structure was confirmed by ^{1}H NMR, MS, and IR spectra, single-crystal X-ray diffraction, and elemental analysis; furthermore, it was characterized by DTG and DSC measurements. The water content was measured by the conventional Karl Fischer method, and DTG corresponds to the calculated value of the monohydrate form. The salt is thermally stable; loss of water does not occur below its melting point (170−171 °C).

Conclusion

The novel meloxicam potassium salt monohydrate is a valuable intermediate in the synthesis of high-purity meloxicam drug substance. The solubility of this salt form can be extensively altered with pH and K^+ concentration of the aqueous solution. On the contrary, the most crucial and common impurity of meloxicam, i.e. *N*-methylated derivative **6a**, being present in crude meloxicam in a relatively large quantity, does not form a water-soluble potassium salt under the same

conditions; thus, it can be efficiently removed. The new manufacturing process[18] is not only simple, efficient, and high-yielding, but it is also environmentally friendly, since it applies aqueous media for the purification of the drug substance, thereby circumventing recrystallization from chlorinated organic solvents.

Experimental Section

General Remarks. All melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker IFS-113v FT spectrometer in KBr pellets. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Varian Unity Inova 500 spectrometer (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively), using TMS as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. For the NOE measurements, the difference pulsed field gradient nuclear Overhauser enhancement (DPFGNOE) pulse sequence was applied. Mass spectrometry measurements were run on Thermo Finnigan LCQ Advantage ion trap MS/MS instrument, coupled with an HP1090 HPLC (column: Phenomenex MercuryMS Luna C18(2) 20 mm × 4.0 mm, 3 μm, acetonitrile/water gradient method: 5−95% acetonitrile/3 min, 0.1% formic acid), in positive electrospray ionization mode (4.5 kV spray voltage, 150−1000 mass range, 45% normalized collision energy). For purity determination, HPLC measurements were run on a Kromasil 100-5 C-18 column (150 mm × 4.6 mm, 5 μm) with linear gradient elution at a flow rate of 1 mL/min. Eluent A: 20 mM KH_2PO_4 buffer solution (pH = 6.8)/methanol = 70/30 (v/v); eluent B: 20 mM KH_2PO_4 buffer solution (pH = 6.8)/methanol = 30/70 (v/v); 0 min: 100% eluent A, 30 min: 100% eluent B. Column temperature was 30 °C, UV detection occurred at λ = 260 and 350 nm. TG measurements were run on a Perkin-Elmer Pyris 1 TG apparatus at a heating rate of 10 °C/min, with a 10 mg of sample, Al sample holder and N_2 as flushing gas. DSC was performed with a Perkin-Elmer DSC 7 calorimeter at a heating rate of 10 °C/min, with a 2 mg sample, Al sample holder, without flushing gas. Water content was measured using the traditional Karl Fischer method. Conditions of the single-crystal X-ray measurement are described in detail in the Supporting Information.

Crude Meloxicam (1). *Laboratory Method.* Under argon atmosphere, xylene (350 mL) was introduced into a flask, which was equipped with a condenser and a receiver. Methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**3a**, 35.0 g, 0.130 mol), 5-methyl-1,3-thiazol-2-amine (**4**, 15.0 g, 0.131 mol), and charcoal (6.0 g) were added under stirring. The suspension was heated to reflux temperature over a period of 30 min and was kept at this temperature for 24 h. Heating was maintained with an oil bath at such an intensity that only a minimal amount (2−3 mL/h) of distillate was formed and collected in the receiver during the reaction. The reaction mixture was cooled to ambient temperature. The crude product was filtered, the filter cake was washed with xylene (50 mL) and ethanol (80 mL) and dried at room temperature to give a mixture of the title product and charcoal (total mass: 43.0 g). The crude product contained ∼12% of **6a**.

Pilot-Plant Process. A 630-L enamel-lined autoclave was equipped with a cambered paddle stirrer, a pressure gauge, a thermometer, an oil heating jacket, a valve for inert gas inlet, and a receiver with a flush-out valve. Into the autoclave, purged with argon gas, were introduced 5-methyl-1,3-thiazol-2-amine (**4**, 15.6 kg, 136.2 mol), charcoal (6.0 kg), 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**3a**, 36.0 kg, 133.7 mol), and finally xylene (450 L). The suspension was heated to reflux (138−142 °C) under argon atmosphere and stirred for 24 h. Meanwhile, the methanol formed in the condensation reaction was distilled off with xylene; the low intensity of distillation was maintained with the temperature-controlled oil heating. The total quantity of the distilled xylene/methanol mixture was 125−150 L. After 24 h reaction time, the suspension was cooled to 30−35 °C and centrifuged, and the filter cake was washed on the centrifuge with xylene (50 L). The obtained crude substance, containing charcoal, was suspended in the autoclave with ethanol (85 L) for 30 min at 30−35 °C, then it was centrifuged; finally the filter cake was washed on the centrifuge with ethanol (30 L) to give 50−60 kg charcoal-containing substance.

Meloxicam Potassium Salt Monohydrate (7). *Laboratory Method.* To the mixture (43.0 g) of crude **1** and charcoal, which was obtained in the above reaction, 0.5 w/w% aqueous KOH solution (1200 mL, 0.107 mol) was added, and the suspension was stirred at 50 °C for 1 h. The undissolved residues were filtered off with a G4 glass filter. To the clear yellow filtrate, a solution of KOH (30 g KOH in 100 mL of water, 23 w/w%, 0.536 mol) was added dropwise, over a period of 30 min. During the addition, a yellow product precipitated. The suspension was stirred at 10 °C for 2 h and filtered. The precipitate filtered off was washed with distilled water (150 mL) and dried at room temperature to give 42.9 g (81%, calculated for **3a**) of yellow crystals. Mp 170−171 °C. Water content by the Karl Fischer method: 4.6% (calcd 4.6%). Loss of mass by TG between 175 and 245 °C: 4.75%. HPLC purity: >99.90%. IR (KBr, cm^{-1}): ν 3462, 3364, 2919, 1603, 1560, 1517, 1392, 1325, 1168, 1151. ^{1}H NMR (DMSO-d_6, TMS, 500 MHz): δ 14.39 (s, 1H, NH), 8.04 (d, 1H, J = 7.7 Hz, H-5), 7.72 (t, 1H, J = 7.9 Hz, H-6), 7.64 (d, 1H, J = 7.9 Hz, H-8), 7.62 (t, 1H, J = 7.7 Hz, H-7), 7.00 (d, 1H, J = 1.3 Hz, H-4′), 2.77 (s, 3H, N-CH_3), 2.32 (d, 3H, J = 1.1 Hz, Ar-CH_3) ppm. ^{13}C NMR (DMSO-d_6, TMS, 125 MHz): δ 166.11 (C-4), 163.44 (C=O), 157.77 (C-2′), 136.08 (C-4a), 135.67 (C-8a), 134.47 (C-4′), 132.06 (C-6), 130.14 (C-7), 127.14 (C-5), 123.84 (C-5′), 122.62 (C-8), 107.82 (C-3), 39.26 (N-CH_3), 11.41 (Ar-CH_3) ppm. Elemental analysis for $C_{14}H_{12}KN_3O_4S_2 \cdot H_2O$ (407.52): calculated C 41.26, H 3.46, N 10.31, S 15.74%; found C 41.20, H 3.52, N 10.21, S 15.61%.

Pilot-Plant Process. A 1400-L enamel-lined autoclave was equipped with a turbine stirrer, a steam heating jacket (water−methanol cooling), a pressure gauge, and a thermometer. Potassium hydroxide (6.30 kg, 112.3 mol) was dissolved in water (1260 L) under stirring. To this 0.5 w/w % aqueous

(18) Mezei, T.; Simig, Gy.; Molnár, E.; Lukács, Gy.; Porcs-Makkay, M.; Volk, B.; Hoffmanné Fekete, V.; Nagy, K. Mesterházy, N.; Krasznai, Gy.; Vereczkeyné Donáth, Gy.; Körtvélyessy, Gy.; Pécsi, E. Process for preparation of high-purity meloxicam and meloxicam potassium salt. PCT Pat. Appl. WO 2006/064298, 2006. *Chem. Abstr.* **2006**, *145*, 83359.

potassium hydroxide solution was introduced the charcoal-containing substance obtained in the above reaction, and the mixture was stirred until complete dissolution (~1.5 h) at 50−55 °C. The charcoal and undissolved residues were filtered off with a pressure filter, into a 3000-L enamel-lined autoclave, which was equipped with a cambered paddle stirrer, a steam heating jacket (water−methanol cooling), a pressure gauge, and a thermometer. The filter cake was washed with warm (50−55 °C) water (150 L). To the yellow filtrate, a previously prepared aqueous KOH solution (30.9 kg KOH in 105 L water) was added over a period of 1 h, and meloxicam potassium salt monohydrate precipitated as a yellow solid. After the addition, the suspension was cooled to 10−15 °C at a cooling intensity of 15 °C/h and centrifuged, and the cake was washed on the centrifuge with cold (10−15 °C) water (150 L). The obtained wet meloxicam potassium salt monohydrate weighed 35−45 kg. The wet product was dried in a vacuum tray dryer at 80−85 °C for 20 h to give 36−38 kg (66−69%, calculated for **3a**) of yellow solid. The end-point of drying was determined by a loss on drying control (≤1.0%). The quality of the meloxicam potassium salt monohydrate was controlled by TLC (total impurity ≤1.0%) and HPLC (assay ≥99.5%).

Meloxicam (1), Polymorph Form I. *Laboratory Method.* Meloxicam potassium salt monohydrate (**7**, 34.1 g, 83.7 mmol) was dissolved in a mixture of 0.5 w/w% aqueous potassium hydroxide solution (1500 mL, 134 mmol) and ethanol (25 mL). The solution was stirred at 40−45 °C for 30 min. Charcoal (2.0 g) was added to the yellow solution, and it was filtered off with a G4 filter after an intense stirring of 10 min. To the filtrate, HCl solution (20 mL of cc. HCl + 80 mL of water) was added at 30 °C over 30 min. The suspension was stirred at 10 °C for 2 h and was filtered; the product was washed with distilled water (200 mL) and dried *in vacuo* (10 mmHg) at 80 °C for 6 h; 28.5 g (97%, calculated for **7**) title product was obtained. Mp 246−248 °C (lit. mp 254 °C,[8] 254−255 °C[19]). IR,[7,17,201]H NMR,[8,20] and XRPD[7] are in accordance with literature data. Elemental analysis for $C_{14}H_{13}N_3O_4S_2$ (351.41): calculated C 47.85, H 3.73, N 11.96, S 18.25%; found C 47.80, H 3.82, N 11.87, S 18.20%. HPLC purity: > 99.90%, Imp. C, D' 0.05%, any other impurity ≤0.1%. The purity of the product obtained meets the requirements of Ph. Eur. 6.3.[14]

Pilot-Plant Process. A 1250-L enamel-lined autoclave was equipped with an impeller stirrer, a pressure gauge, a steam-warm water heating jacket (water−methanol cooling)- and a thermometer. Meloxicam potassium salt monohydrate (**7**, 27.5 kg, 67.50 mol) was stirred at 50−55 °C in a mixture of water (550 L) and ethanol (139 L), until complete dissolution (~1 h). Then the solution was stirred with charcoal (8.25 kg) at this temperature. Charcoal and undissolved residues were filtered off with pressure filter into a 1000-L enamel-lined autoclave, equipped with a cambered paddle stirrer, a pressure gauge, a steam-warm water heating jacket (water−methanol cooling), and a thermometer. The filter cake was washed with warm (50−55 °C) water (2 × 55 L). A previously prepared aqueous hydrochloric acid solution (16 L of concentrated HCl in 64 L water) was added to this solution at 65−70 °C, over a period of 50−70 min. During the addition, a yellow solid precipitated. After the addition, the suspension was heated to reflux and kept at this temperature for 2−2.5 h, and then it was cooled to 25−30 °C and centrifuge; the filter cake was washed on the centrifuge with water (82 L). The obtained crude wet meloxicam was suspended in the autoclave in a mixture of ethanol (84 L) and purified water (82 L), for 1 h at 25−30 °C. Then it was centrifuged, and the filter cake was washed on the centrifuge with ethanol (56 L). The thus obtained wet meloxicam weighed 20−24 kg. The wet product was dried in a vacuum tray dryer at 78−80 °C for 24 h. The end-point of drying was determined by a loss on drying control (≤0.10%). The dried meloxicam was sieved to give the obtained meloxicam end-product 19−21 kg (83−91%, calculated for **7**) of the title product. Identification of the product was performed by IR and UV spectra; the quality was controlled by assay by titration (99.0−100.5%) and HPLC.

***N*-[3,5-Dimethyl-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (6a), Meloxicam Imp. C.**[14] *Method A.* Meloxicam (**1**, 24.0 g, 68.0 mmol) was suspended in DMSO (400 mL). To this suspension were added an aqueous solution of KOH (10.0 g, 122 mmol in 10 mL water) and methyl iodide (6.0 mL, 96 mmol), and stirring at 25 °C was continued for 24 h. The reaction mixture was acidified with glacial acetic acid (14 mL), then water (200 mL) was added. The resulting suspension was stirred for 1 h, and the precipitate was filtered and washed with hexane (100 mL). The yellow crude product (23.4 g, 94%) was recrystallized from DMF (100 mL). The product was filtered and washed with EtOH (50 mL) to give 7.0 g (28%) of pale-yellow crystals. Mp > 250 °C. IR (KBr, cm^{-1}): ν 3066, 1588 (C=O), 1561, 1515, 1418, 1337, 1179. ^{1}H NMR (DMSO-d_6, TMS, 500 MHz): δ 14.93 (bs, 1H, OH), 8.04 (dd, 1H, J = 7.5, 1.8 Hz, H-8), 7.87 (t, 1H, J = 7.2 Hz, H-7), 7.86 (dd, 1H, J = 7.5, 1.5 Hz, H-5), 7.82 (t, 1H, J = 7.2 Hz, H-6), 7.43 (d, 1H, J = 1.5 Hz, H-4′), 3.74 (s, 3H, $N_{th}-CH_3$), 2.91 (s, 3H, SO_2NCH_3), 2.32 (d, 3H, J = 1.4 Hz, $C_{th}-CH_3$) ppm. NOE (7.43 ppm): 3.74, 2.32 ppm. ^{13}C NMR (DMSO-d_6, TMS, 125 MHz) δ 169.67 (C-4), 164.14 (C-9), 155.45 (C-2′), 134.55 (C-8a), 133.03 (C-6), 132.25 (C-4′), 129.25 (C-4a), 126.13 (C-7), 125.88 (C-5), 123.28 (C-8), 122.39 (C-5′), 115.33 (C-3), 37.80 (SO_2NCH_3), 36.08 ($N_{th}-CH_3$), 12.03 ($C_{th}-CH_3$) ppm. MS (*m*/*z*): 366 (M + 1), 155 ($C_6H_7N_2OS$), 113 (C_5H_7NS), 100 (C_4H_6NS). Elemental analysis for $C_{15}H_{15}N_3O_4S_2$ (365.40): calculated C 49.29, H 4.14, N 11.50, S 17.55%; found C 49.18, H 4.09, N 11.46, S 17.43%.

Method B. Meloxicam (**1**, 2.0 g, 5.7 mmol) and dimethyl sulfate (0.47 mL, 4.97 mmol) were added to DMF (20 mL), and the suspension was stirred at 100 °C for 2 h. At this temperature, it became a clear solution. The reaction

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mixture was then cooled and stirred at ambient temperature for 12 h. The precipitate was filtered off and washed with EtOH (5 mL) to give 0.80 g (44%) of pale-yellow crystals. To the crude product thus obtained was added EtOH (20 mL). The suspension was refluxed for 10 min, cooled to room temperature, stirred for 2 h, and filtered to give 0.77 g (37%) of the title product. Spectral data were identical to those of the product obtained by Method A.

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Supporting Information Available

Conditions and interpretation of the single-crystal X-ray measurement of **7**, further bond lengths, bond angles, torsion angles and CIF structure file. This material is available free of charge via the Internet at http://pubs.acs.org.

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