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Structure Assignment of a Pharmacopeial Impurity of Meloxicam

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Supporting Information

ABSTRACT: The most characteristic impurity of the meloxicam drug substance is an *N*-methylated derivative, equally formed in the various known manufacturing syntheses of the compound. An *N*-methylated impurity is listed in the European Pharmacopeia monograph of meloxicam as Impurity C, although no evidence has been published for its structure. An unambiguous structure proof of the *N*-methylated impurity formed in our manufacturing synthesis is disclosed in the present paper, demonstrating its identity with Impurity C.

INTRODUCTION

Recently, we have published 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, **1**, Scheme 1).[1] The significance of meloxicam in the therapy of inflammation and its advantages over the other NSAID's have also been summarized.[1]

The main point of our manufacturing procedure is the efficient removal of an impurity formed in the amidation reaction of ester **2** (Scheme 1), which exhibits an additional *N*-methyl group, according to MS and ^{1}H NMR measurements. Our purification methodology,[1,2] via the potassium salt monohydrate of meloxicam (**3**),[3] proved to be much more powerful than the various known recrystallization[4−7] or salification−reacidification[8,9] processes.

Formation of the *N*-methyl impurity was rationalized so that both ester **2** itself or the methanol formed in the condensation reaction can act as methylating agents; thus, they can methylate the primarily formed **1** under the harsh reaction conditions needed for the amidation (e.g., xylene, reflux, 24 h). The first sample of the *N*-methyl impurity was obtained by flash chromatography of the crude product. Then, authentic samples of the *N*-methyl impurity could be obtained also by methylation of meloxicam (**1**) with methyl iodide or dimethyl sulfate.[1] Identity of the prepared compound with the separated sample was demonstrated by MS, NMR, and HPLC measurements.

The structure of the *N*-methyl impurity has not been published in the literature. A wider literature search, extended also for *N*-thiazolylcarboxamide derivatives other than **1**, showed that during the alkylation of related compounds with alkyl halogenides, the carboxamido nitrogen could be alkylated.[10,11] Nevertheless, these papers[10,11] also shed light on the fact that alkylation can occur simultaneously at the nitrogen of the carboxamido group and the dihydrothiazole ring of **1**, leading to a mixture of two regioisomeric alkylated products. In the patent application of Hadida Ruah et al., the compound alkylated at the carboxamido nitrogen atom was prepared in 28%, while the one alkylated at the dihydrothiazole nitrogen in 20% yield.[10] Since the crude product prior to the preparation step was not analyzed, the site selectivity of the reaction remains unclear. Masuda et al. described a similar reaction, where the dominance of the thiazole *N*-alkylated product (81%) over the carboxamido *N*-alkylated derivative (19%) is obvious.[11] Furthermore, in alkylation reactions of other *N*-thiazolylcarboxamide derivatives, the compound *N*-alkylated at the dihydrothiazole ring was the only prepared product of the reaction,[12−14] although the formation of the other isomer can not be excluded because the yield was low[12,13] or not reported.[14] Despite the fact that isomers alkylated at the dihydrothiazole nitrogen atom can exist in (*E*) or (*Z*) form, only one paper discloses any analytical evidence for the configuration (*Z*) of the double bond.[14]

On the basis of the above literature analogues and our initial spectral data, three different structures could be assigned to the *N*-methyl impurity of **1** (Figure 1). Methylation may occur either at the amide nitrogen to give compound **4** or at the nitrogen atom of the thiazole ring, potentially giving rise to the formation of geometrical isomers **5** and **6**. Structural formula 5 was first published in the European Pharmacopeia (Ph. Eur.) monograph of meloxicam in 2009, designated as Impurity C.[15] To the best of our knowledge, no published data prove either the position of the newly introduced methyl group or the geometry of the newly formed double bond.

In our publication[1] on the improved manufacturing synthesis of **1** we have demonstrated by the help of detailed NOE and MS fragmentation measurements that the investigated impurity contained an *N*-methylated thiazole ring (Figure 2.). Nevertheless, the geometry of the double bond could not be determined from the available spectroscopic data.

RESULTS AND DISCUSSION

Since the structure determination of critical impurities of drug substances is an important regulatory requirement, the unambiguous assignment of the geometry of the double bond of the *N*-methylated derivative of meloxicam remained a problem for us to be solved by all means. Single-crystal X-ray diffraction seemed to be the ultimate solution of this problem, but our first experiments revealed that obtaining a single crystal was harder than expected. Finally, our continuous efforts to obtain suitable

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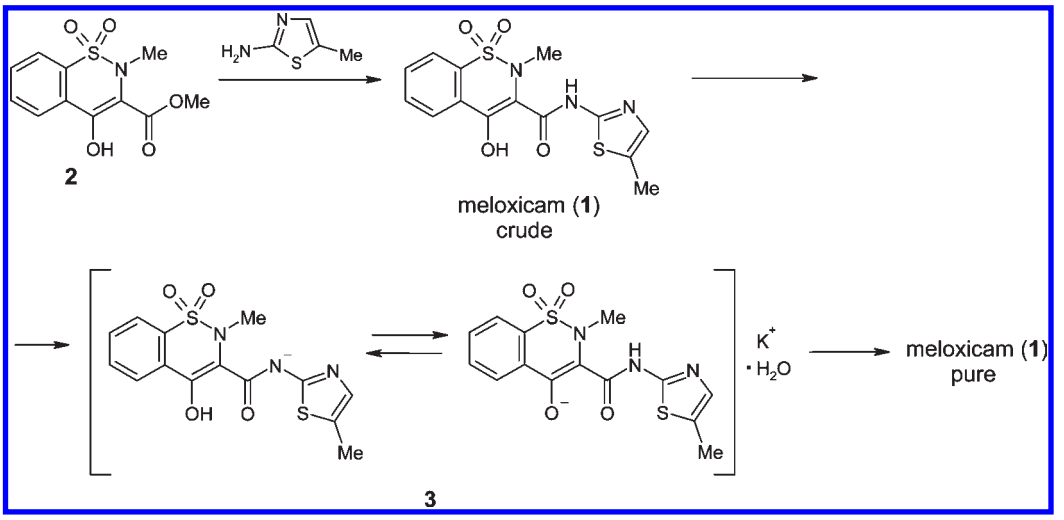
Scheme 1. Improved synthesis of meloxicam



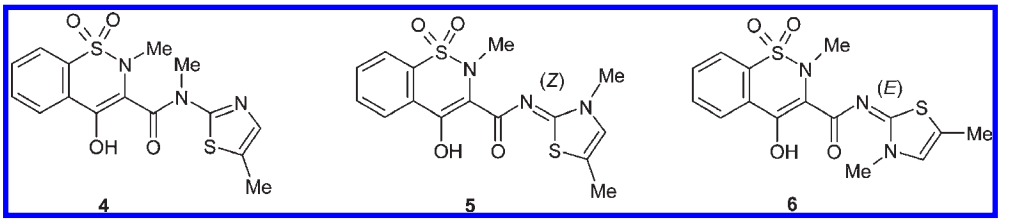


Figure 1. Possible structures of the *N*-methyl impurity.

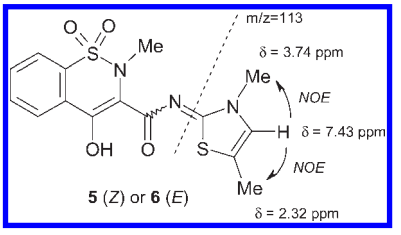


Figure 2. NOE effects and a characteristic MS fragment observed in the *N*-methylated impurity.

crystals from various solvents and solvent mixtures were crowned with success. *N*-Methyl derivative, obtained by the methylation of **1** with dimethyl sulfate in DMF, was dissolved in a mixture of methanol and DMSO (3:1). Upon standing in an open vial for several weeks, crystals developed that were appropriate for single-crystal X-ray diffraction measurements.

Single-crystal X-ray structure solution of the *N*-methyl derivative revealed that, in accord with structure **5** published in Ph. Eur.,[15] the compound exhibited a double bond with (*Z*) configuration (Figure 3.). On the other hand, it is noteworthy that the conformation of the molecule in solid state is different from that suggested by Ph. Eur. (see Figure 4, **5**, rotamer **A**) and corresponds to rotamer **B**. Since there was no sign of amide rotamers in the ^{1}H- and ^{13}C NMR spectra recorded in DMSO-d_6 and because of the extended conjugation, the rotation of the amide group is presumably hindered, rotamer **B** of Impurity C is supposed to be present also in solution. HPLC analysis, performed according to the Ph. Eur. method,[15] indicated the identity of the X-ray sample with the primary product **5** obtained by the methylation of **1**.

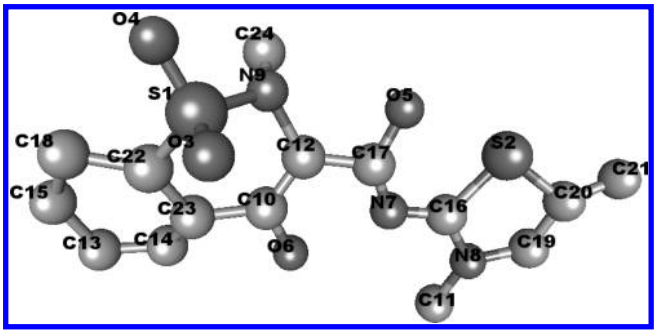


Figure 3. X-ray structure of the *N*-methylated impurity of meloxicam.

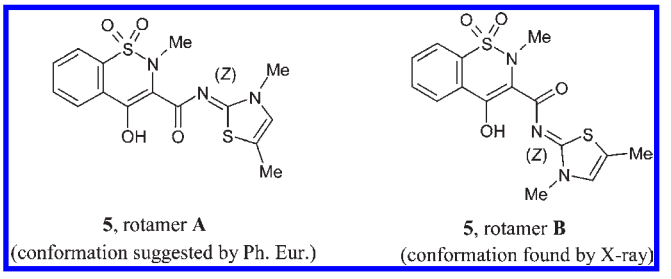


Figure 4. Conformation of meloxicam Impurity C.

CONCLUSION

Structure determination of critical impurities of active pharmaceutical ingredients is an important regulatory requirement. Based on single-crystal X-ray diffraction analysis, an unambiguous structure

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assignment of the *N*-methylated impurity of meloxicam, formed in our manufacturing procedure was performed. It was demonstrated that *N*-methylation occurred at the nitrogen of the dihydrothiazole ring and the double bond formed in the course of the reaction exhibited a (*Z*) geometry, therefore it is identical with Impurity C listed in the European Pharmacopeia monograph of meloxicam. A structure for the preferred conformer of Impurity C is also suggested.

EXPERIMENTAL SECTION

General Remarks. 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 a Thermo Finnigan LCQ Advantage ion trap MS/MS instrument, coupled with an HP1090 HPLC (column: Phenomenex Mercury-MS 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).

***N*-[(2*Z*)-3,5-Dimethyl-1,3-thiazol-2(3*H*)-ylidene]-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (5), Meloxicam Impurity C.**[15] *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 ($SO_2N\underline{C}H_3$), 36.08 (N_{th}-$\underline{C}H_3$), 12.03 (C_{th}-$\underline{C}H_3$) ppm. MS (m/z): 366 (M + 1), 155 ($\overline{C_6H_7N_2OS}$), 113 ($\overline{C_5H_7NS}$, *N*-methylated dihydrothiazole), 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**, 2.00 g, 5.69 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 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 (42%) of the title product as pale-yellow crystals. Spectral data were identical to those of the product obtained by Method A.

Single-Crystal X-ray Measurement of 5. *Data Collection.* A colorless prism crystal of $C_{15}H_{15}N_3O_4S_2$ having approximate dimensions of 0.14 mm × 0.04 mm × 0.04 mm was mounted on a cactus needle. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Cu−Kα radiation. Indexing was performed from four oscillations that were exposed for 600 s. The crystal-to-detector distance was 127.40 mm. Cell constants and an orientation matrix for data collection corresponded to a primitive orthorhombic cell with dimensions: a = 14.4445(3) Å, b = 6.80950(10) Å, c = 32.7173(6) Å, V = 3218.07(10) Å^3. For Z = 7 and MW = 365.42, the calculated density is 1.320 g/cm^3. The systematic absences of h00: $h \pm 2n$; 0k0: $k \pm 2n$; 00l: $l \pm 2n$ uniquely determine the space group to be $P2_12_12_1$ (#19). The data were collected at a temperature of 20 ± 1 °C to a maximum 2Θ value of 144.7°. A total of 176 oscillation images were collected. A sweep of data was done using ω scans from 20.0 to 200.0° in 5.0° step, at χ = 54.0° and ϕ = 270.0°. The exposure rate was 120.0 [s/deg]. A second sweep was performed using ω scans from 20.0 to 200.0° in 5.0° step, at χ = 54.0° and ϕ = 90.0°. The exposure rate was 120.0 [s/deg]. Another sweep was performed using ω scans from 20.0 to 200.0° in 5.0° step, at χ = 0.0° and ϕ = 0.0°. The exposure rate was 120.0 [s/deg]. Another sweep was performed using ω scans from 20.0 to 190.0° in 5.0° step, at χ = 54.0° and ϕ = 180.0°. The exposure rate was 120.0 [s/deg]. Another sweep was performed using ω scans from 20.0 to 190.0° in 5.0° step, at χ = 54.0° and ϕ = 0.0°. The exposure rate was 120.0 [s/deg]. The crystal-to-detector distance was 127.40 mm. Readout was performed in the 0.100 mm pixel mode.

Data Reduction. Of the 36246 reflections that were collected, 6227 were unique (R_{int} = 0.179). The linear absorption coefficient, μ, for Cu−Kα radiation is 28.350 cm^{-1}. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement. The structure was solved by direct methods[16] and expanded using Fourier techniques. The nonhydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement[17] on F was based on 11172 observed reflections ($I > 2.00\sigma(I)$) and 201 variable parameters and converged (largest parameter shift was 6.67 times its estimated) with unweighted and weighted agreement factors of:

$$R = (|F_o| - |F_c|)/\sum |F_o| = 0.0945$$

$$R_w = \left[\sum w(|F_o| - F_c|)^2/\sum wF_o^2\right]^{1/2} = 0.1035$$

The standard deviation of an observation of unit weight[18] was 3.53. Unit weights were used. Plots of $\Sigma w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, sin Θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 7.09 and −8.89 e$^-$/Å^3, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[19] Anomalous dispersion effects were included in F_{calc};[20] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[21] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[22] All calculations were performed using the CrystalStructure[23] crystallographic software package.

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Further details of the single-crystal X-ray measurement are described in detail in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information. Conditions of the single-crystal X-ray measurement of **5**, further atomic coordinates, 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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(18) Standard deviation of an observation of unit weight: $[\Sigma w(|F_o| - |F_c|)^2/(N_o - N_v)]^{1/2}$, where: N_o = number of observations, N_v = number of variables.

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