Synthesis of {3-(2-dimethylamino-ethy1)-2-[3-(2-dimethylaminoethyl)-1*H*-indol-5-ylmethyl]-1*H*-indol-5-yl}-*N*-methyl-methanesulfonamide, the main Sumatriptan impurity

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Abstract
An improved multistep synthesis of {3-(2-dimethylamino-ethy1)-2-[3-(2-dimethylaminoethyl)-1*H*-indol-5-ylmethyl]-1*H*-indol-5-yl}-*N*-methyl-methanesulfonamide, the main Sumatriptan impurity, is described, as a model for other related triptan derivatives.

Keywords: Indole derivatives, sumatriptan, drug impurities

Introduction

Among the many serotonin-like compounds studied, the discovery of the anti-migraine drug sumatriptan **1** stimulated the development of other 5-HT_{1D} receptor agonists.[1] From the chemical point of view, several of them (sumatriptan **1**,[2] avitriptan **2**,[3] and almotriptan **3**,[4] rizatriptan **4**[5]) have the common feature of a functionalized indole, with a XCH_2- group in the 5 position, in which X can act as a leaving group (Figure 1). As a result, most of the synthesis of those compounds, based on the conventional Fischer indole synthesis, using acid catalysis, generates compounds **5** as impurities, with yields depending both of the product and the method used. The product corresponding to Sumatriptan, **5a**, has long been identified as the main impurity.[6] In the synthesis of Avitriptan **2**, the corresponding **5b** has been identified and Remuzon[7] has studied the process, proposing a protecting group for the methylaminosulphonyl moiety, while Brodfuehrer[8] studied the conditions of the Fischer indolization, in order to reduce the formation of the impurity. Moreover, Rizatriptan **4**, bearing a triazole group, which can be converted in a good leaving group under acid catalysis, has similar problems in his preparation, and a recent patent has been published describing a synthesis adapted to reduce the presence of the corresponding impurity **5c** to a minimum.[9] No data have been found for Almotriptan **3**, although by its structure should have the same problem.

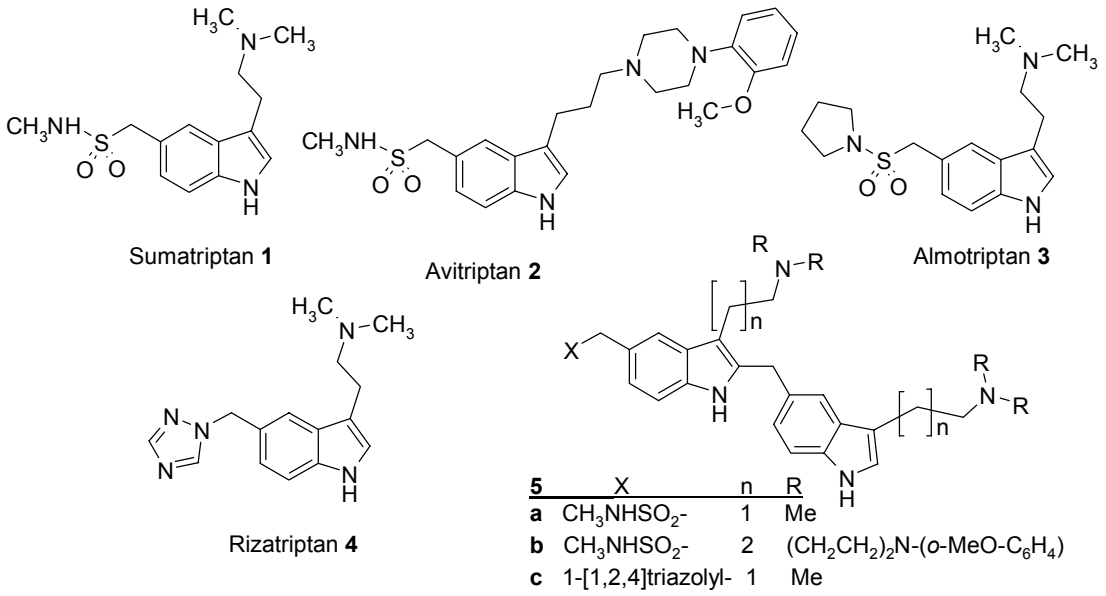


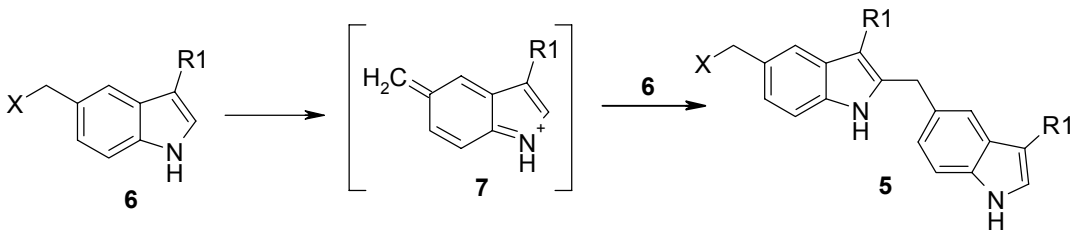
Figure 1

As it is usual in the pharmaceutical compounds, impurities produced in the corresponding preparation method should be extensively controlled, and they should be regularly prepared to be used in the quality controls of the main product. As a general consideration, being the impurities mostly produced by side reactions in one step of the production process, its synthesis is a good training method to study side reactions,[10] and either minimize them to improve the quality of the final product, or develop selective preparation methods in order to get samples for use in quality control methods.

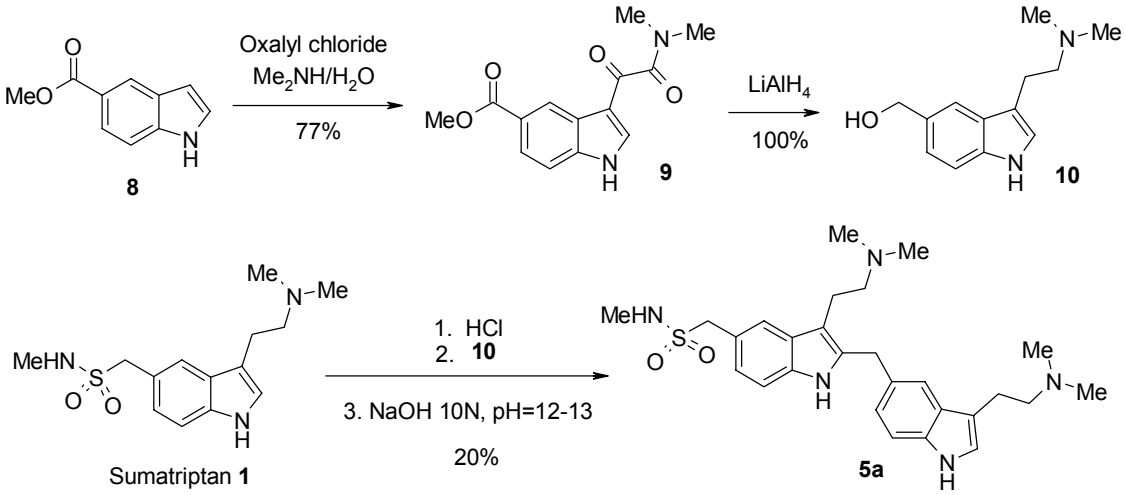
Results and Discussion

The compound **5a**, is the main impurity detected in Sumatriptan, whose classical Fischer synthesis has been studied in detail by Toke *et al.*[11] The formation of **5a** has been identified in the process as a consequence of the π-excedent character of indole and related with the temperature of the process. Thus, any indole with a sulfamoylmethyl group on the 5- position –or any other fragment bearing a different leaving group- would, in the presence of acid catalysis, or by thermal treatment, produce an intermediate like **7**, which would act as an electrophile, attacking the only available indole position in **6**. Intermediates related to **7** has been described as part of the chemistry of gramines, with the exocyclic vinyl fragment placed on the 3-position of the indole ring, which can be generated and substituted with the corresponding nucleophile.[12] The present example, however, is a case in which the intermediate **7** is produced on the benzene fragment. Sumatriptan analogs would easily produce impurities similar to **5** in the synthesis of

the main product, and the process has been studied for compounds like **2**,[7,8] **3.**[4b] Castro and Matassa had described a related process.[13]



Scheme 1



Scheme 2

There has been a synthesis of **5a** described by Skwierawska and Paluszkiewicz,[14] using Fischer indolization as a basis to build the indole fragment **10**. In the present paper, the synthesis has been simplified, starting from commercial **8**. As indicated in scheme 2, **8** was acylated in the 3-position with oxalyl chloride and dimethylamine. Then, **9** was treated with lithium aluminium hydride, to produce reduction of the amide, ketone and ester groups simultaneously. As a final step, sumatriptan **1** was suspended in HCl, and a solution of **10** was slowly added, which generates the reactive intermediate **7**, to produce the impurity **5a**. The method, simple and robust, can be easily adapted, using **10**, to produce analog impurities from Rizatriptan **3**, and Almotriptan **4**.

Experimental Section

General Procedures. All melting points were measured in capillary tubes and are uncorrected. IR spectra were determined on KBr disks using a Nicolet Impact 410 spectrometer. ^{1}H NMR spectra were obtained at 300 MHz (^{1}H) and 75 MHz (^{13}C). Chemical shifts (δ) were determined using TMS as internal standard, and multiplicity (s, singlet; d, doublet; dd, double-doublet; t, triplet; q, quartet; m, multiplet) and coupling constants are indicated for every signal. HPLC-MS analyses were performed on an Agilent 1100 apparatus. A chromatographic column Luna C18 (150 x 4.6 mm) 5 μm Phenomenex was used, with a mobile phase formed by a triple gradient of 4% aq. formic acid (A), water (B) and acetonitrile (C). The gradient started as A (2.5%), B (93%) and C (4.5%) and, in 30 min. reached A (2.5%), B (4.5%) and (93%). In the Mass detector, the fragmenter operated at 70eV. High Resolution Mass Spectra were performed on a Bruker Reflex IV (MALDI-TOF). All yields correspond to isolated pure compounds. 1H-Indole-5-carboxylic acid methyl ester has been obtained from Aldrich.

3-(Dimethylaminooxalyl)-1*H*-indole-5-carboxylic acid methyl ester (9). In a 3L reactor, under nitrogen atmosphere, the compound **9** (47.99g, 0.273 mol) was suspended in anh ethyl ether (700 mL). The mixture was cooled to 0º C and oxalyl chloride (47.63g, 0.546 mol) dissolved in anh. ethyl ether (70 mL) was added dropwise. Then, the mixture was stirred for 30 additional minutes, keeping the temperature of the process at 5º C, and then, stirring was maintained for one hour at room temperature. A yellow precipitate was formed, which was filtered and washed with ethyl ether (900 mL), yielding 63.60g of the product. Then, in a 3 L reactor, a solution of Me_2NH (283.1 mL) in H_2O (840 mL) was prepared, the yellow solid obtained was added, and the mixture was stirred for 12 h at room temp. Then, the solid was filtered, washed with water (1 L) and dried, yielding 56 g of **10**. The filtered waters can be extracted with dichloromethane (3x300 mL). Then, the organic extracts were washed with 1N HCl (1 L) and with sat NaCl solution (1 L). The organic phase, after drying with Na_2SO_4 was concentrated to dryness, yielded an additional crop of 2 g of **10.** (Overall yield 58.0g, 77%). Mp 194-195 ºC. IR (KBr, cm^{-1}): 3400, 3268, 3044, 2951, 1707, 1636, 1523, 1437, 1307, 1282, 1194, 1118, 1070, 791, 747.. ^{1}H-NMR ($CDCl_3$, 300MHz): 10.04 (bs, 1H); 8.97 (s, 1H); 7.95-7.89 (m, 2H); 7.37 (d, 1H, J=7.94Hz); 3.92 (s, 3H); 3.08 (s, 3H); 3.04 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 75MHz): 185.6, 167.6, 167.4, 138.1, 136.8, 125.6, 125.2, 124.9, 124.4, 115.1, 11.8, 52.0, 37.5, 34.6 ppm. HRMS (TOF MS): M^+: Found 275.1035, $C_{14}H_{15}N_2O_4$ requires 275.1032.

{3-[2-(Hydroxymethylamino)ethyl]-1*H*-indol-5-yl}methanol (10). In a 10L reactor, Under nitrogen atmosphere, $LiAlH_4$ in THF 1N (1.89L) was added. The solution was cooled at –5 ºC and compound **4** (57.65g, 0.210 mol) suspended in THF (1.5L) was added dropwise, keeping the temperature under 10 ºC. The reaction was heated to reflux for 4.5h. After, the reaction was cooled to room temperature again and THF anhydrous was added (2.5L). The reaction was cooled at 0 ºC and H_2O (86mL), NaOH 5N (86mL) and H_2O (266mL) were added dropwise. The mixture was stirred overnight. The solid formed was filtered and washed with CH_2Cl_2 and this

solvent was concentrated to dryness. Over the residue CH_2Cl_2 (800mL) was added and washed with brine (360mL). The aqueous layer was extracted with CH_2Cl_2 (2x800mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. Compound **5** was obtained as a yellowish oil as described in ref 7 (45g, 100%).

{3-(2-dimethylamino-ethy1)-2-[3-(2- dimethylaminoethyl)-1*H*-indol-5-ylmethyl]-1*H*-indol-5-yl}-*N*-methyl-methanesulfonamide (5a). In a 1L reactor Sumatriptan **1** (12.2g, 41.2 mmol) was dissolved in HCl 1N (500 mL). Over this solution, compound **11 (**6g, 27.5 mmol) in CH_2Cl_2 (100mL) was added slowly. The mixture was stirred at room temperature for 20h. The reaction was cooled at 5 ºC and NaOH 10 N (50 mL) was added dropwise, keeping the temperature under 20 ºC until pH 13 was reached. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2x0.4L). The combined organic layers were washed with brine (400mL), dried over anh. Na_2SO_4, filtered and concentrated to dryness. The residue obtained was purified by flash chromatography using CH_2Cl_2/MeOH/NH_3 (90:9:1) as eluent, yielding **5a** as a solid (2.7g, 20 %)(described as an oil in ref 14). Mp 116-117 ºC. IR (KBr, cm^{-1}): 3397, 2942, 2823, 2779, 1623, 1462, 1312, 1155, 1117, 1097, 802. ^{1}H-NMR ($CDCl_3$, 500MHz): 8.18 (bs, 1H); 7.90 (bs, 1H); 7.48 (s, 1H); 7.42 (s, 1H); 7.26 (d, 1H, J=8.25Hz); 7.13 (d, 1H, J=8.25Hz); 7.06 (d, 1H, J=8.25Hz); 7.01-6.96 (m, 2H); 4.28 (s, 2H); 4.18 (s, 2H); 2.98-2.80 (m, 4H); 2.66 (s, 3H); 2.60-2.48 (m, 4H); 2.31 (s, 6H); 2.26 (s, 6H) ppm. ^{13}C-NMR ($CDCl_3$, 75MHz): 135.9, 135.4, 135.2, 129.0, 128.9, 127.8, 123.3, 123.0, 122.1, 120.3, 119.8, 118.7, 114.2, 111.5, 110.8, 109.9, 60.5, 60.1, 57.7, 45.4, 45.3, 32.5, 29.7, 23.6, 22.8 ppm. HRMS (TOF MS): M^+: Found 496.2748, $C_{27}H_{38}N_5O_2S$ requires 496.2746.

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