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Synthesis of [3-[2-(Dimethylamino)ethyl]-2-[[3-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide – the Main Sumatriptane Impurity

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Alkylation of sumatriptane in position 2 by 3-[2-(dimethylamino)ethyl]-5-indolemethanol has been described. Alternative multistep synthesis of 3-[2-(dimethylamino)ethyl]-5-indolemethanol has been presented.

Key words: indole derivatives, sumatriptane, drug impurities

The discovery of the anti-migraine drug sumatriptane [1] has stimulated development of 5-HT_{1D} receptor agonists. From the chemical point of view, many of these compounds (sumatriptane (**1**) [1], avitriptan (**2**) [2], almotriptan (**3**) [3]) have the common feature of possessing a sulfamoylmethyl group attached to the indole position 5 (Figure 1).

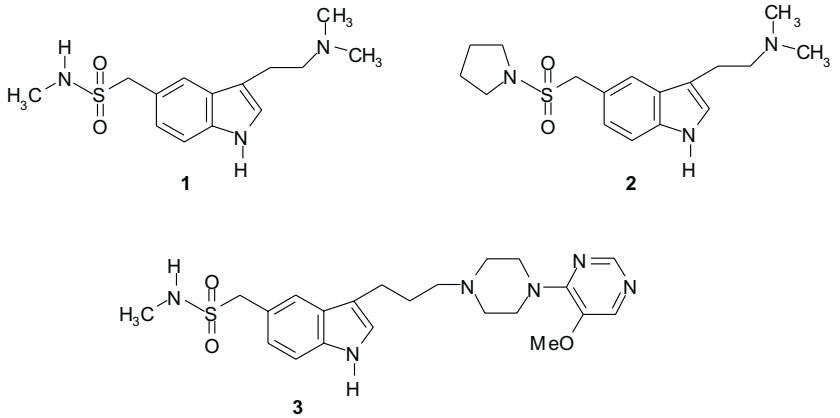
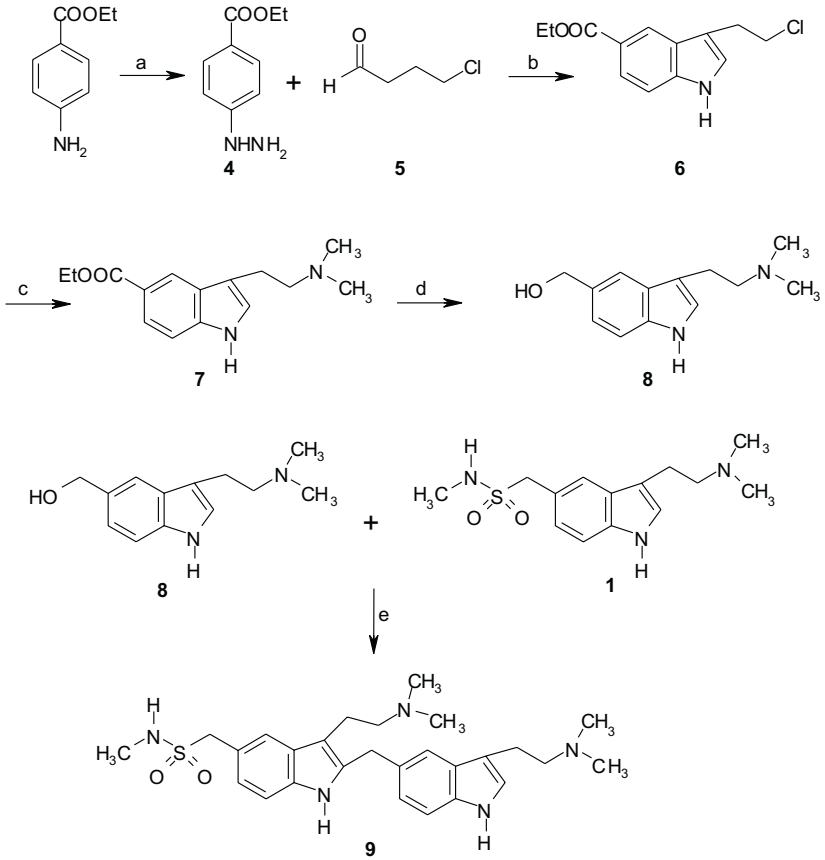


Figure 1.

The key reaction of multistep synthesis of sumatriptane (**1**) is Fischer indole synthesis. During this reaction a lot of side products are formed and the typical yield of the desired product is 30–40%. The title compound **9** has been found as a significant impurity of sumatriptane [4]. In our studies on physicochemical properties of drug impurities we needed to synthesize a standard sample of the compound **9**.

RESULTS AND DISCUSSION

The synthesis of [3-[2-(dimethylamino)ethyl]-2-[[3-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide (**9**) is unknown. To obtain this compound, we alkylated sumatriptane (**1**) with 3-[2-(dimethylamino)ethyl]-5-indolemethanol (**8**) under acidic condition (Scheme 1). The choice of acid, that could provide protonation of the hydroxy group, was critical to the success of the reaction. Direct condensation of sumatriptane with alcohol **8** using 4% H_2SO_4 in toluene at 80°C afforded a complex mixture of products. Similar results were obtained with HCl or H_3PO_4 as catalysts. With weaker acids (acetic or propionic) the desired product **9** was obtained in 26% yield and unreacted sumatriptane (50%) was recovered. Alcohol **8** was obtained by $LiAlH_4$ reduction of ester **7**. Using of 3.4 equivalents of reducing agent for 1 equivalent of ester allowed to obtain the product **8** in 95% yield [5,6]. Ester **7** was synthesized by a two-step reaction: a Fischer reaction of hydrazine and 4-chlorobutanal **5** [7] to form indole **6**, followed by alkylation of dimethylamine by the resultant product **6**. The ease of cyclization and often the success



Scheme 1. Reagents and conditions: a) 1) $NaNO_2$, H_2O, concentrated HCl, –10°C; 2) $SnCl_2 \cdot 2H_2O$, concentrated HCl; 3) 10% Na_2CO_3; b) H_2SO_4, toluene; c) EtOH/H_2O, $HN(CH_3)_2$; d) $LiAlH_4$, THF; e) propionic acid, 100°C.

or failure of a Fischer indolization [8] depends on the catalyst, reaction condition, and type of carbonyl component in the hydrazone. Their combinations varied considerably. In [5] was described the synthesis of ester **6** in reaction of 4-chlorobutanal dimethyl or diethyl acetal with 4-ethoxycarbonylphenylhydrazine in the presence of concentrated HCl followed by reductive amination to produce **7** [5]. The same conditions for reaction of unprotected 4-chlorobutanal with 4-ethoxycarbonylphenylhydrazine led to a complex mixture of products. Using toluene as a solvent and concentrated sulfuric acid we obtained the desired product **6** in a yield similar to described in [5] without protection of aldehyde.

In summary, we have found an effective Fischer indole reaction of 4-ethoxycarbonylphenylhydrazine with 4-chlorobutanal. We overcame the reductive amination step of product **6** by a simple alkylation reaction with dimethylamine. Finally, we developed an efficient Friedel-Crafts reaction for direct alkylation of sumatriptane indole ring by alcohol **8**.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at 200 MHz or 500 MHz for ^{1}H, and 125 MHz for ^{13}C on Varian instruments. Mass spectra were recorded on AMD-604 apparatus. Thin layer chromatography (TLC) analyses were performed on silica gel 60-F-254. Preparative chromatography columns were packed with Kieselgel 60 (70–230 mesh). All reagents were commercially available. Solvents were HPLC grade and were used without further purification. 4-Ethoxycarbonylphenylhydrazine (**1**) [5] and 4-chlorobutanal (**2**) [7] were obtained according to literature data.

Ethyl 3-(2-chloroethyl)-5-indolecarboxylate (6): A solution of 4-ethoxycarbonylphenylhydrazine (**4**) 66.3 g (0.36 mol) and 4-chlorobutanal (**5**) 38.3 g (0.36 mol) in 200 mL of toluene was refluxed for 0.5 hour. To the vigorously stirred solution concentrated H_2SO_4 (6.25 mL) was added dropwise during 1 hour. The mixture was stirred under reflux for 6 hours. After cooling, the solvent was evaporated under reduced pressure. The resulting brown oil was dissolved in $CHCl_3$ and purified by column chromatography using hexane/ethyl acetate solvent system. The fractions containing the product were combined and concentrated by vacuum evaporation to give ethyl 3-(2-chloroethyl)-5-indolecarboxylate (**6**) as red oil. Yield 83.5 g (34%). ^{1}H NMR ($CDCl_3$): δ 1.45 (t, J = 7.1 Hz, 3H, CH_3), 3.28 (t, J = 7.4 Hz, 2H,$ArCH_2$), 3.81 (t J = 7.4 Hz, 2H, $ClCH_2$), 4.43 (q, J = 7.1 Hz, 2H, OCH_2), 7.18 (d, J = 1.4 Hz, 1H, Ar), 7.39 (d, J = 8.5 Hz, 1H, Ar), 7.94 (dd, J1 = 1.1 Hz, J_2 = 8.5 Hz, 1H, Ar), 8.35 (br s, 1H, NH), 8.38 (s, 1H, Ar). Mass spectrum (EI) $(M)^+$ 251; HRMS [EI, $(M)^+$] calculated for $C_{13}H_{14}ClNO_2$ 251.0713; found 251.0710.

Ethyl 3-[2-(dimethylamino)ethyl]-5-indolecarboxylate (7): Ethyl 3-(2-chloroethyl)-5-indolecarboxylate (**6**) (25 g, 0.1 mol) was dissolved in 100 mL of ethanol and aqueous solution of dimethylamine (50g in 100 mL of water) was added. The mixture was stirred for 6 hours at 50°C. After cooling, ethanol was evaporated under reduce pressure. The residue was extracted with chloroform (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was vacuum evaporated. The residue was dissolved in $CHCl_3$ and chromatographed on silica gel column with $CHCl_3$/MeOH. The orange fraction was collected and condensed under reduced pressure to give dark orange glassy solid. Yield 20 g (77%). ^{1}H NMR ($CDCl_3$): δ 1.42 (t, J = 6.8 Hz, 3H, CH_3), 2.36 (s, 6H, $N(CH_3)_2$), 2.64–2.72 (m, 2H, NCH_2), 2.94–3.02 (m, 2H, $ArCH_2$), 4.40 (q, J = 6.8 Hz, 2H, OCH_2), 7.01 (s, 1H, Ar), 7.26 (d, J = 8.43 Hz, 1H, Ar), 7.86 (dd, J_1 = 1.5 Hz, J_2 = 8.6 Hz, 1H, Ar), 8.38 (d, J = 1.0 Hz, 1H, Ar), 8.97 (br s, 1H, NH) and identical to literature data [5].

3-[2-(Dimethylamino)ethyl]-5-indolemethanol (8): A solution of ethyl 3-[2-(dimethylamino)ethyl]-5-indolecarboxylate (**7**) (20 g, 0.077 mol) in anhydrous THF (400 mL) was added dropwise under N_2 to a suspension of $LiAlH_4$ (10 g, 0.263 mol) in anhydrous THF (250 mL). The mixture was refluxed for 2 hours and cooled to 0–5°C. Then ethyl acetate (20 mL), H_2O (12 mL), 10% NaOH (12 mL) and H_2O (12 mL) were added successively. The resulting suspension was filtered through Celite (the cake was washed

with CH_2Cl_2 (2 × 100 mL) separately). The solvents were removed from filtrate under reduced pressure and the residue was diluted with water (80 mL). Aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic solutions were dried, filtered, and concentrated to give 3-[2-(dimethylamino)ethyl]-5-indolemethanol (**8**) as yellowish oil. Yield 16 g (95%). ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 6H, $N(CH_3)_2$), 2.51–2.60 (m, 2H, NCH_2), 2.81–2.89 (m, 2H, Ar CH_2CH_2N), 4.56 (br s, 1H, OH), 4.72 (s, 1H, Ar CH_2OH), 6.83 (d, J = 1.5 Hz, 1H, Ar), 7.16 (d, J = 8.1 Hz, 1H, Ar), 7.22 (d, J = 8.1 Hz, 1H, Ar), 7.51 (s, 1H, Ar), 9.19 (br s, 1H, NH) and identical to literature data [5].

3-[2-(Dimethylamino)ethyl]-2-[[3-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-1*H*-indol-5-yl]-*N*-methylmethanesulphonamide (9): A solution of 3-[2-(dimethylamino)ethyl]-5-indolemethanol (**8**) (6.5 g, 0.03 mol) in propionic acid (100 mL) was added dropwise under N_2 to vigorously stirred solution of [3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]-*N*-methylmethanesulphonamide (**1**) (8.2 g, 0.03 mol) in propionic acid (400 mL) at 100°C. The mixture was refluxed for 3 hours. After cooling the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ and purified on silica gel column using $CHCl_3$:MeOH (5:1) solvent system as an eluent. The fractions containing the product were collected and condensed under reduced pressure to give colorless oil. Yield 3.9 g (26%). ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 6H, $N(CH_3)_2$), 2.37 (s, 6H, $N(CH_3)_2$), 2.58 (t, J = 7.8 Hz, 2H, NCH_2), 2.63 (t, J = 7.8 Hz, 2H, NCH_2), 2.73 (d, J = 3.4 Hz, 3H, CH_3NH), 2.92 (t, J = 7.8 Hz, 2H, $ArCH_2CH_2N$), 3.0 (t, J = 7.81 Hz, 2H, $ArCH_2CH_2N$), 4.23 (s, 2H, $ArCH_2$), 4.36 (s, 2H, $ArCH_2$), 7.03 (d, J = 9.3 Hz, 1H, Ar), 7.06 (s, 1H, Ar), 7.11 (d, J = 8.3 Hz, 1H, Ar), 7.18 (d, J = 8.3 Hz, 1H, Ar), 7.31 (d, J = 8.3 Hz, 1H, Ar), 7.47 (s, 1H, Ar), 7.54 (s, 1H, Ar), 7.9 (br s, 1H, NH), 8.1 (br s, 1H, NH). ^{1}H NMR ($CDCl_3$ + D_2O): δ 2.30 (s, 6H, $N(CH_3)_2$), 2.4 (s, 6H, $N(CH_3)_2$), 2.56–2.62 (m, 4H, NCH_2), 2.72 (d, J = 3.4 Hz, 3H, CH_3NH), 2.90 (t, J = 7.3 Hz, 2H, $ArCH_2CH_2N$), 3.00, (t, J = 7.8 Hz, 2H, $ArCH_2CH_2N$), 4.23 (s, 2H, $ArCH_2$), 4.36 (s, 2H, $ArCH_2$), 7.03 (d, J = 8.3 Hz, 1H, Ar), 7.05 (s, 1H, Ar), 7.11 (d, J = 8.3 Hz, 1H, Ar), 7.18 (d, J = 8.3 Hz, 1H, Ar), 7.31 (d, J = 8.3 Hz, 1H, Ar), 7.44 (s, 1H, Ar), 7.55 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ 23.06, 23.82 (NCH_2CH_2), 30.13, 33.00 ($ArCH_2CH_2N$), 45.48, 45.62 ($N(CH_3)_2$), 58.09 (CH_3NH), 60.42, 60.84 ($ArCH_2$), 109.96, 111.50, 112.16, 113.83, 119,01, 120.27, 120.84, 123.04, 123.26, 123.88, 128.28, 129.30, 129.63, 135.83, 136.12, 136.72 (Ar). Mass spectrum (ESI) $(M+H)^+$ 496; HRMS [ESI, $(M+H)^+$] calculated for $C_{27}H_{38}N_5O_2S$ 496.2741; found 496.2755.

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