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Tungstate-catalyzed oxidation of triptans with hydrogen peroxide: A novel method for the synthesis of *N,N*- dimethyltryptamine *N*-oxides

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A straight forward oxidation method of triptans have been described for the synthesis of *N,N*-dimethyl-2-[5-[substituted-1*H*-indole-3-yl]ethanamine-*N*-oxides using sodium tungstate and 30% aqueous hydrogen peroxide solution in the presence of methanesulphonic acid. The significance of the process is its simplicity and efficiency in isolating the triptan *N*-oxide derivatives as free base and as malate salt.

Keywords: Sodium tungstate, sumatriptan *N*-oxide, rizatriptan *N*-oxide, Zolmitriptan *N*-oxide, Almotriptan-*N*-oxide

A new era in the treatment of migraine headache arrived with development of a revolutionary class of drugs known as the triptans[1], which are a family of tryptamine drugs, included sumatriptan **1**, rizatriptan **2**, zolmitriptan **3**, almotriptan **4**, naratriptan **5**, eletriptan **6** and frovatriptan **7** (**Scheme I**). Their action is attributed to their binding to serotonin 5-HT_{1D} (Ref. 2) and 5-HT_1 (Ref. 3) receptors in cranial blood vessels and subsequent inhibition of pro-inflammatory neuropeptide release.

From the chemical point of view, compounds **1-4** have the common feature of possessing a *N,N*-dimethylaminoethyl group attached to the indole position 3. During the process development of triptans **1-4** in the laboratory, several batches have been analysed for purity by HPLC. A potential related substance triptan *N*-oxide **8** was observed whose area percetage ranged from 0.10-0.11% area by HPLC. As per the stringent regulatory requirements for pharmaceutical products, the impurities $\geq$ 0.1% must be identified and characterised. Isolation of these related compounds is cumbersome and requires expensive techniques like preparative HPLC, flash chromatography and preparative TLC and synthetic methods for **8** are not available in the literature so far[4-9]. Hence, studies were initiated on the synthesis of triptan *N*-oxides **8**. The sodium tungstate-catalyzed oxidation of pyridine and halopyridines to produce the corresponding *N*-oxide is already known[10]. This methodology was now extended to synthesise the target molecules **8a-d.**

Results and Discussion

Sumatriptan **1** was oxidized with hydrogen peroxide (30%) in methanolic medium containing methanesulphonic acid and sodium tungstate at 50-55°C. The DIP mass spectrum of **8a** exhibited a molecular ion peak at *m/z* 312 (M+H), which has 16 units more than sumatriptan. In addition, in the ^{1}H NMR spectrum, peak at δ 3.14 for six protons and peak at δ 3.22-3.46 for four protons indicate deshielding of $CH_2CH_2N(CH_3)_2$ moiety. The corresponding values for sumatriptan are δ 2.40 (6H, 2 × CH_3) and 2.70-3.00 (4H,*N*-CH_2CH_2)[11]. Based on the spectral data, the structure of **8a** was confirmed as *N,N*-dimethyl-2-[5-[(methyl-sulphamoyl)methyl]-1*H*-indol-3-yl]ethanamine-*N*-oxide.

To examine the reproducibility of the synthetic method, **2, 3** and **4** have been oxidized with H_2O_2 and sodium tungstate to produce corresponding *N*-oxides **8b-d** (**Scheme II**). The spectral characterization data of compounds **8a-d** are given in **Table I**.

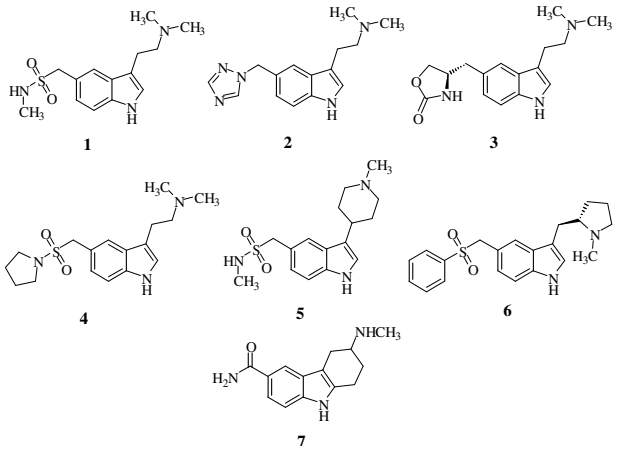
Experimental Section

Melting points were determined in capillaries using Polman digital melting point apparatus (Model No. Mp 96) and are uncorrected. Thin-layer chromatography (TLC) were run on silica gel 60 F_{254} precoated plates (0.25 mm, Merck, Art.5554) and spots were visualized inside an UV cabinet under short UV. All other reagents and solvents were purchased from Lancaster (Germany) and S. D. Fine Chemicals, Mumbai. Infrared spectra were recorded on Perkin Elmer Spectrum FT-IR Spectrometer by using 1% potassium bromide pellet. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz Advance NMR spectrometer at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR with TMS as an internal standard. Mass spectra were obtained using a Agilent 1100 Series LC-MSD-TRAP-SL system. The samples were introduced *via* the Direct Inlet Probe (DIP).

Table I — Spectral characterization data of compounds **8a-d**

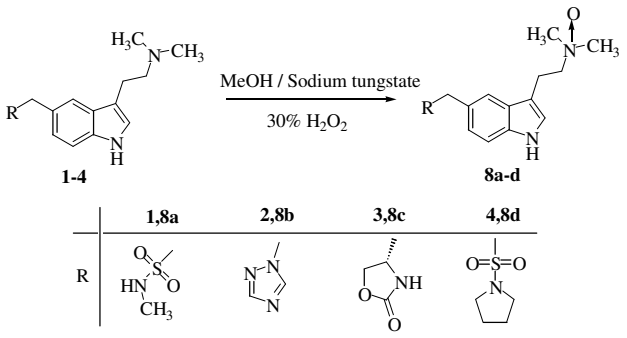
Compd	Mol. formula $[M+H]^+$	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
8a	$C_{14}H_{21}N_3O_3S$ (312)	2.54 (s, 3H, CH_3), 3.14 (s, 6H, 2 × CH_3), 3.22 (m, 2H, CH_2CH_2N), 3.46 (m, 2H, CH_2CH_2N), 4.32 (s, 2H, SO_2-CH_2-indole), 7.04 (s, 1H, NH, D_2O exchangeable), 7.08-7.56 (m, 4H, Ar-H), 11.15 (s, 1H, NH, D_2O exchangeable).	--
8b	$C_{15}H_{19}N_5O$ (286)	3.10 (s, 6H, 2 × CH_3), 3.21 (m, 2H, CH_2CH_2N), 3.43 (m, 2H, CH_2CH_2N), 5.42 (s, 2H, triazole-CH_2-indole), 7.03 - 8.61 (m, 6H, Ar-H), 11.15 (s, 1H, NH, D_2O exchangeable).	18.98, 53.14, 58.29, 69.96, 110.44, 111.75, 118.48, 121.47, 123.87, 125.98, 127.01, 135.94, 143.69, 151.39.
8c	$C_{16}H_{21}N_3O_3$ (304)	2.81 (m, 2H, CH_2), 3.11 (m, 8H, 2 × CH_3 and NCH_2), 3.39 (m, 2H, oxazolidinone-CH_2-indole), 4.09 (m, 2H, OCH_2), 4.27 (s, 1H, CHNHCO), 6.93-7.42 (m, 4H, Ar-H).).	20.26, 54.15, 58.56, 58.64, 70.04, 71.14, 110.63, 112.93, 120.33, 124.84, 124.96, 127.39, 128.31, 136.40, 161.85.
8d	$C_{17}H_{25}N_3O_3S$.$C_4H_6O_5$ (485)	1.73-1.77 (m, 4H, 2 × CH_2 of pyrrolidine), 2.27-2.54 (m, 2H, CH_2 of malate), 3.09-3.13 (m, 4H,-CH_2-N-CH_2-of pyrrolidine), 3.22-3.28 (m, 2H, N-CH_2-CH_2-), 3.40 (s, 6H, 2 × N-CH_3), 3.71-3.76 (m, 2H, N-CH_2-CH_2-), 3.85-3.89 (dd, *J* = 3.9 and 9.9 Hz, 1H, CH of malate), 4.41(s, 2H, SO_2CH_2), 7.14-7.17 (d, *J* = 8.4 Hz, 1H, Ar), 7.28 (d, *J* = 2.1 Hz, 1H, Ar), 7.37 (d, *J* = 8.4 Hz, 1H, Ar), 7.64 (s, 1H, Ar), 11.07 (s(br), 1H, OH, D_2O exchangeable).	18.68, 25.32, 41.79, 47.64, 54.11, 56.17, 66.92, 68.56, 108.94, 111.39, 119.64, 120.72, 124.04, 124.16, 126.79, 135.94, 172.98, 177.04

^{1}H and ^{13}C NMR of **8a**, **8b** and **8d** were recorded in DMSO-d_6 and those of **8c** were recorded in DMSO-d_6 + D_2O.



Scheme I

General procedure for preparation of *N,N*-dimethyl-2-[5-substituted-1*H*-indole-3-yl] ethanamine-*N*-oxides, 8. In a typical procedure a 250 mL round-bottomed flask was fitted with a reflux condenser and provided with an over head mechanical stirrer and water bath. *N,N*-Dimethyltryptamine derivative (**1**, **2, 3** or **4**, 15 mmole) followed by methanesulphonic acid (100 mg, 1 mmole), sodium tungstate dihydrate (100 mg, 0.3 mmole) in water (2 mL) were successively added to methanol



Scheme II

(90 mL) at ambient temperature. The reaction mass was heated to 50-55°C. Hydrogen peroxide (30%, ~1.9 mL, 16.5 mmole) was then added drop wise in 15 min and the reaction mass was maintained at that temperature for 3-5 hr. The progress of the reaction was monitored by TLC (chloroform: methanol-9:1). The product **8** that formed was isolated as follows.

Isolation of the *N*-oxides. The reaction mass was concentrated to about 50% volume *in vacuo*. Water (50 mL) and ethyl acetate (50 mL) were added under stirring. The separated solid was filtered to isolate **8c** (yield: 90%; m.p. 205-06°C). Ethyl acetate layer was concentrated to get the crude product, which was

purified by recrystallization from acetone (25 mL) to get pure **8a** as a white solid (yield: 80%; m.p. 190-93°C). The reaction mass was extracted with dichloromethane (100 mL) and the aqueous layer concentrated *in vacuo*. The pure **8b** was isolated from acetonitrile (25 mL) as a white solid (yield: 85%). The **8d** residue was dissolved in ethanol (15 mL) and malate solution (2.2 g in 8 mL ethanol) was added. After stirring at RT for 1 hr and refluxing for another 1 hr, the reaction mass was cooled to 25°C and stirred for 2 hr. The separated solid was filtered and washed with ethanol (10 mL) and dried at 60°C under vacuum for 5 hr to yield **8d** as a malate salt (yield: 88%).

Conclusion

An efficient and one pot synthesis of important metabolites, *N*-oxides of triptans has been developed using sodium tungstate as a catalyst

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