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Research Article

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Cyclisation of indoles by using orthophosphoric acid in sumatriptan and rizatriptan

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ABSTRACT

A simple and Novel improved process for the preparation of pure Sumatriptan and Rizatriptan, the cyclisation of indole ring by the using of ortho phosphoric acid. The present work describes the detection, origin, synthesis, characterization and providing a commercial method to synthesize Sumatriptan and Rizatriptan. The procedure developed has several advantages such as mild reaction conditions, convenient operations and easily obtained materials. The synthetic method is suitable for industrial manufacture.

Keywords: Cyclisation, Sumatriptan, Rizatriptan, ortho phosphoric acid,

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INTRODUCTION

Triptans are a family of tryptamine-based drugs used as abortive medication in the treatment of migraines and cluster headaches. They were first introduced in the 1990s. While effective at treating individual headaches, they do not provide preventative treatment and are not considered a cure. The first triptan (i.e., tryptamine derivative) to be marketed for the acute treatment of migraine, sumatriptan, has been so successful that a number of second generation triptans are now marketed or in the late stages of clinical development[1,2]. The triptans represent a breakthrough in acute migraine treatment, being far more selective for 5-HT1B-1D receptors than their relatively nonselective predecessor's ergotamine and dihydroergotamine (DHE)[3,4] . Three distinct pharmacological actions mediated by triptans have been identified as the most likely explanation for their antimigraine effectiveness: vasoconstriction of cranial blood vessels[5], inhibition of neurogenic inflammation in the dura mater[6], and inhibition of firing of trigeminal neurons[7]. Somewhat surprisingly, the second generation triptans which are already marketed (zolmitriptan, rizatriptan, and naratriptan) provide relatively little improvement, if any, over sumatriptan in terms of antimigraine effectiveness, despite improvements in pharmacokinetics, higher oral bioavailability, increased brain penetration, and longer plasma half-life. Less than half of the patients are pain free 2 h after treatment, and about a third of responders experience headache recurrence within 24 to 48 h. There appears to be room for substantial improvement over and above currently marketed triptans in terms of clinical antimigraine effectiveness and more so with respect to the "headache free at 2 h" criterion which is recommended by the International Headache Society Migraine Clinical Trials Committee as the primary end point in acute treatment evaluation[8].

The Fischer indole synthesis, which remains the most versatile method for preparing indoles, was reported in 1883 by Fischer. Today it is used in the synthesis of antimigraine drugs of the triptan class, which begins with the reaction of a (substituted) phenylhydrazine with an aldehyde or ketone, initially forming a phenylhydrazone which

isomerizes to the respective enamine. After protonation, a cyclic [3, 3]-sigma tropic rearrangement occurs producing an imine. The resulting imine forms a cyclic aminoacetal, which under acid catalysis that eliminates NH_3, resulting in the energetically favorable aromatic indole. The main paper describes synthesis of Sumatriptan and rizatriptan, are indole cyclisation by using of orthophosphoric acid.

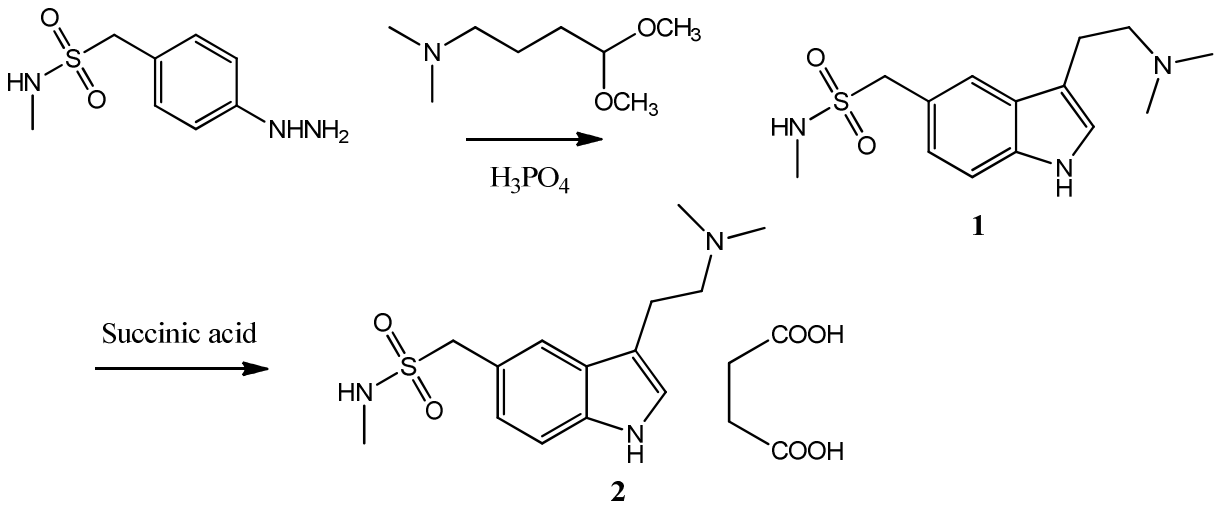
EXPERIMENTAL SECTION

Chemicals were procured from Sigma-Aldrich, Merck and Lancaster, and were used as such without further purification. Melting points (m.p.) were determined using a calibrated thermometer by Buchi Melting Point apparatus B-545. They expressed in degrees centigrade (°C) and are uncorrected. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence lamp. Silica gel (particle size 100-200 mesh) purchased from SRL India, was used for chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument. 1H NMR spectra were reported using Me4Si (δ 0.0 ppm) as internal standard or residual $CHCl_3$ peaks (δ 7.26 ppm) and DMSO-d_6 (δ 2.5 ppm). ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16 ppm) and DMSO- d_6 (δ 48.5 ppm). FTIR spectra were recorded on a Nicolet 6700 spectrometer and are reported in frequency of absorption (cm^{-1}). Optical rotations (in degrees, °) were recorded in ethanol, methanol, $CHCl_3$, DMF, acetonitrile on a Perkin-Elmer Model 241 polarimeter at the sodium D line. LC mass spectra were recorded on a Jeol SX 102 DA / 600 Mass spectrometer. Elemental analyses were performed by Central Drug Research Institute, Lucknow, INDIA.

1-[3-(2-Dimethylaminoethyl)-1H-indol-5-yl]-N-methyl-methanesulfonamide succinate (2).

A mixture of 20 gm of 4-hydrazino N-methylbenzene methane sulphonamide, 50 mL of purified water, 20 gm of N, N-Dimethyl-4-aminobutanal dimethyl acetal and 40 mL of 2N hydrochloric acid was taken and stirred for 4 hours at ambient temperature. The resulting mixture was basified with sodium carbonate and extracted with chloroform. The chloroform layer and 4 gm of orthophosphoric acid was stirred at ambient temperature for 4 hours and then 300 mL of water added. The organic layer was separated and aqueous layer was basified with potassium carbonate and the product was extracted with ethyl acetate. The organic layer was distilled off under reduced pressure and 20 mL of acetonitrile was added. After 2 hours of cooling at 5^0C, the crystals were filtered and dried results to gave 4 gm of crude 1-[3-(2-Dimethylaminoethyl)-1H-indol-5-yl]-N-methyl-methanesulfonamide and purified with acetone to give pure 1, and finally prepared succinate salts using of methanol obtained **2 (Scheme 1).**

Scheme 1



Melting range: 166.5-168 ^{0}C.

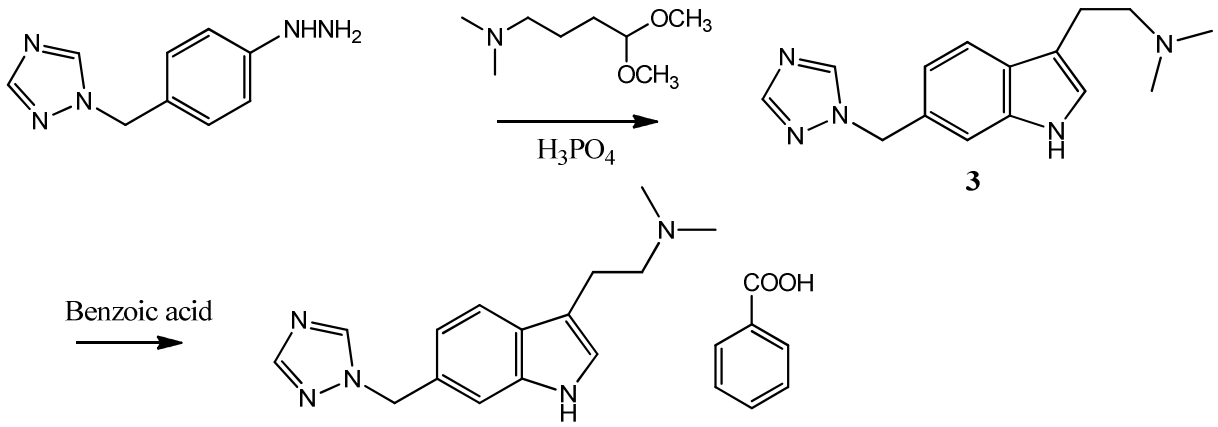
NMR (DMSO-d_6), 2.53(s, succinate CH_2), 2.74(s, $NHCH_3$), 2.89(s, $N(CH)_3$, 3.18(t, j=7.33 Hz, $CH_2N(CH_3)_2$), 3.41(t, $CH_2CH_2N(CH_3)_2$), 4.54(s, CH_2SO_2), 7.25(d,d j= 8.8/1.5 Hz, C_5H), 7.34(s, C_5H), 7.55(d j= 8, C_6H), 7.67(s, C_3H).

Mass spectra (m/z): 282 (M^+ + H)

N,N-Dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine benzoate (4)

A mixture of 10 gm 1-(4-hydrazinylbenzyl)-1H-1,2,4-triazole, 50 mL of purified water, 10 gm of N,N-Dimethyl-4-aminobutanal dimethyl acetal and 20 mL of 2N hydrochloric acid was taken and stirred for 4 hours at ambient temperature. The resulting mixture was basified with sodium carbonate and extracted with chloroform. The chloroform layer and 4.5 gm of orthophosphoric acid was stirred at ambient temperature for 4 hours and then 150 mL of water added. The organic layer was separated and aqueous layer was basified with potassium carbonate and the product was extracted with ethyl acetate. The organic layer was distilled off under reduced pressure results **3** obtained, used benzoic acid with ethanol **4** Rizatriptan benzoate obtained (**Scheme 2)**

Scheme 2



^{1}HNMR: 2.33 (s, 6H, $N(CH_3)_2$); 2.62 (t, J=8.2 Hz, 2H, $CH_{2CH.sub.2N}$); 2.88 (t, J=8.2 Hz, 2H, $CH_{2CH.sub.2N}$); 5.41 (s, 2H, $CH_{2\text{-benz.}}$); 7.06 (m, 2H, ar); 7.31 (d, J=8, 4 Hz, 1H, ar); 7.55 (s, 1H, ar); 7.96 (s, 1H, tz); 7.99 (s, 1H, tz); 8.59 (ba, 1H, NH-indole); ^{13}CNMR (200 MHz, $CDCl_3$): 23.5; 45.4; 54.5; 60.1; 111.8; 114.4; 119.2; 122.2; 122.6; 124.8; 127.7; 136.1; 142.7; 151.8. ; Mass spectra (m/z): 256 (M^+ + H)

CONCLUSION

In conclusion, we have developed a simple, efficient and successfully obtained by using of orthophosphoric acid for the cyclisation of indoles are sumatriptan and rizatriptan was prepared.

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