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Note

N-Desmethyltriptans: One pot efficient synthesis of *N*-methyl-2-[5-[substituted-1*H*-indole-3-yl]ethanamines

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A straightforward and highly improved method to synthesize N-methyl-2-[5-[substituted-1H-indole-3-yl]ethanamines **4-6**, which are the metabolites of tryptans **1-3**, is reported**.** The significance of the process is its simplicity and efficiency in isolating the N-desmethyltriptans derivatives as a free base.

Keywords: *N*-Desmethyltriptans, ethanamines, migraine, metabolites

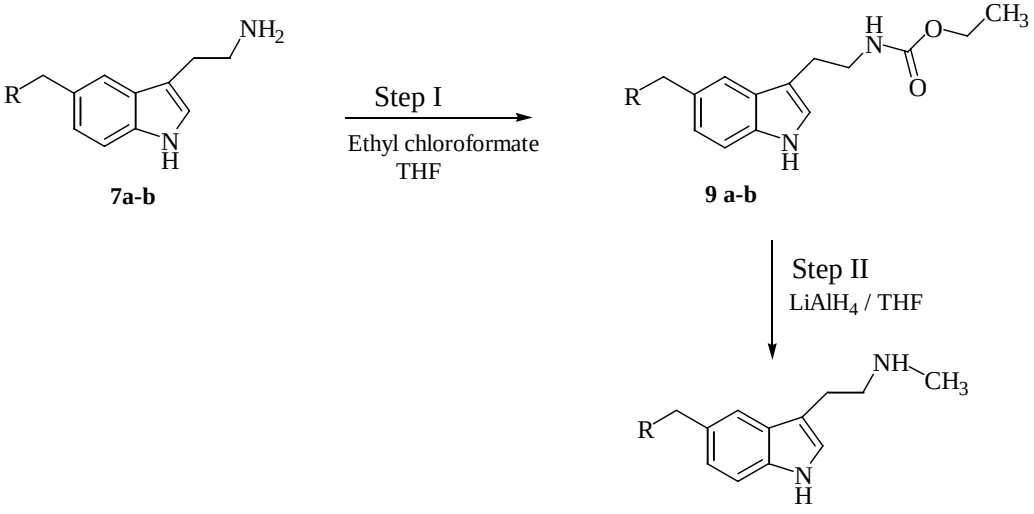
Rizatriptan **1**, sumatriptan **2** and zolmitriptan **3** are believed to be effect migraine relievers by binding to serotonin (5-hydroxy tryptamine) receptors in the brain, where they act to induce vasoconstriction of extracerebral blood vessels and also reduce neurogenic inflammation[1]. The clinical and pharmacolinetic intractions between triptans and the selective serotonin reuptake inhibitor is investigated. In this study, *N*-desmethylrizatriptan **4** (Ref. 2), *N*-desmethylsumatriptan **5** (Ref. 3), and *N*-desmethylzolmitriptan **6** (Ref. 4), were extracted as metabolites from plasma by a solid-phase extraction (SPE). The metabolite may be stable **5** or chemically reactive **4** and **6,** the resultant toxicity being either a direct extension of the pharmacology of the drug, or unrelated to the known pharmacology of the drug and dependent on the chemical properties of the compound. Thus, pure compounds are required not only to assess their biological effects but also for determination of compound specific properties.

All known methods for the preparation of title compounds **4** (Ref. 5), **5** (Ref. 6) and **6** (Ref. 7) have certain drawbacks such as lengthy routes (three to four steps from 4-substituted aniline **8)**, low overall yields etc. The only reported synthetic method of **6** is not reproducible at our end. Spectral data for all the compounds is not available. For these reasons, the development of new and efficient methods for the synthesis of *N*-desmethyltriptans remains an area of strong interest. The efforts are focused in the synthesis of these metabolites and in this paper, an efficient, simple and one pot procedure for the synthesis of *N*-desmethyltriptans **4-6** is reported.

Results and Discussion

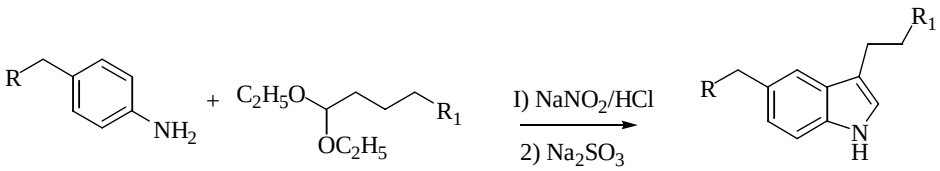
Initially, an alternative method was developed to synthesize **4** by reacting **7a** with ethyl chloroformate in THF to isolate carbamate derivative **9a,** followed by reduction with lithium aluminum hydride in THF. The structure was confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data**.** In continuation, **5** was similarly prepared (**Scheme I**). Encouraged by the results obtained from both **4** and **5**, an attempt to synthesize **6** was taken up. However, the oxazolidinone ring opened at the time of reduction with lithium aluminum hydride.

Finally, the target molecule **6** is constructed by diazotisation of (*S*)-4-(4-aminobenzyl)-1, 3-oxazolidin-2-one **8c** with nitrous acid, reduction with sodium sulfite followed by condensation with appropriate side chain -4-methylaminobutanal diethylacetal **10** in the acidic medium. The ESI mass data displayed the protonated molecular ion *m/z* 274. The IR spectrum of **6** showed bands at 3253 for N-H stretching and band at 1738 cm^{-1} due to carbonyl group. Its ^{1}H NMR spectrum in DMSO-d_6 showed a singlet at δ 2.50 for three protons due to methyl group. Besides, three multiplets at δ 2.87-3.10 (6H), 4.00-4.10 (2H) and 4.20-4.26 (1H) were attributed to three methylene groups, one methyleneoxy and methine protons, respectively. In the downfield region, a multiplet at δ 6.94-7.44 integrated for four aromatic protons. The spectrum also showed exchangeable protons at δ 8.41 (s, 1H) and 10.84 (s, 1H) for two N-H groups. Further, the peak at δ 33.33 in the ^{13}C NMR (75 MHz, DMSO-d_6) spectrum confirmed the presence of $NHCH_3$ group. Based on this preliminary spectral information, the molecular formula of the compound **6** was found to be $C_{15}H_{19}N_3O_2$. This formula matched well with the observed protonated molecular ion peak at *m/z* 274. Relied on these data, the structure of the compound 6 has been characterised as (*S*)-*N*-methyl-2-[5-(2-oxo-1, 3-oxazolidin-4-ylmethyl)-1*H*-indol-3-yl]ethanamine (**6**, **Scheme II**).

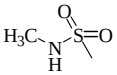
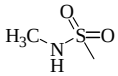
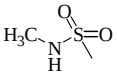
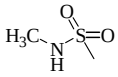
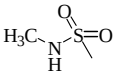


7a-b **9 a-b** **4,5**

Scheme I



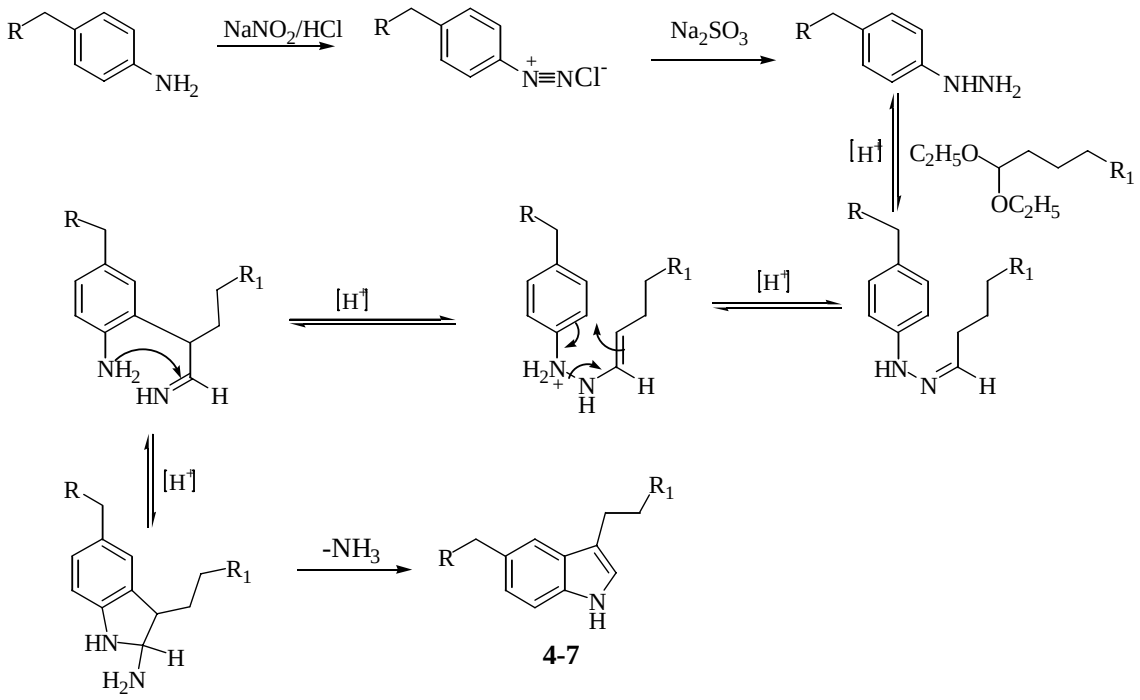
8a-c **10** R'= $NHCH_3$ **11** R'= NH_2 **4-7**

S No	R	R_1	S No	R	R_1
1		$N(CH_3)_2$	**7b**		NH_2
2		$N(CH_3)_2$	**7c**		NH_2
3		$N(CH_3)_2$	**8a**		--
4		$NHCH_3$	**8b**		--
5		$NHCH_3$	**8c**		--
6		$NHCH_3$	**9a**		--
7a		NH_2	**9b**		--

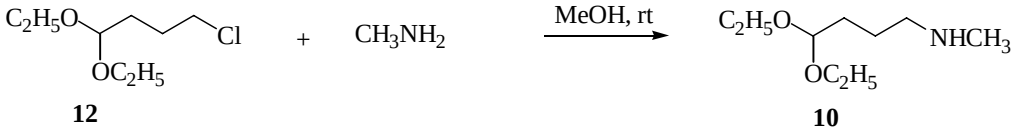
Scheme II

The mechanism of formation of **4-7** from **8a-c** is explained by diazotization, reduction followed by Fischer indole synthesis under acidic conditions (**Scheme III**).

The above method was also extended to two other aniline derivatives **7a-b**. In all these cases, the corresponding desmethyltriptans **4-5** were isolated**.** Aminobutanal diethylacetal **11** was used instead of **10** and the isolated corresponding **7a-c** had an improved yield. Surprisingly, **7c** was obtained as a solid with m.p. 250^{o}C (dec.). The spectral data of **7c** was found to be comparable with those reported in the literature[8].



Scheme III



Scheme IV

The reaction was also carried out with stannous chloride dihydrate instead of sidium sulfite for the reduction of diazonium chloride derivative.

The synthesis of appropriate side chain **10** is known in literature. It consists two steps and involves reduction reactions[9]. In this paper, a simple and one pot synthesis of **10** on condensation of **12** with methylamine (40%) in methanol is approached at ambient temperature (**Scheme IV**).

Thus, herein is reported a unique method by which 4-substituted aniline **8** can be converted directly to *N*-desmethyltriptans **4-6** in good yield**.** It may be mentioned here that all the reported methods for synthesis of **4-6** consists three to four steps from 4-substituted aniline **8.**

Experimental Section

Melting points were determined in capillaries using Polman digital melting point apparatus (Model No. Mp 96) and are uncorrected. TLC was carried out on silicagel 60 F_{254} precoated plates (0.25 mm, Merck, ART.5554) and spots were visualized by UV. All other reagents and solvents were purchased from Lancaster and S.D.fine chemicals. Infrared spectra were recorded on a Perkin-Elmer Spectrum FT-IR spectrometer by using 1% potassium bromide pellet. ^{1}H and ^{13}C NMR spectra were recorded on a 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 sample was introduced *via* the Direct Inlet Probe (DIP).

General procedure for the synthesis of *N*-desmethyltryptans 4-6

Method I

Step I: General procedure for the preparation of ethyl 5-substituted indolylethyl carbamate 9a-b. Ethyl chloroformate (0.028 mole) was added drop-by-

drop to a solution of **7a-b** (0.028 mole) in tetrahydrofuran (50 mL) and sodium carbonate solution (13.6 g in 125 mL of DM water) over a period of 20 min. The reaction-mixture was extracted with ethyl acetate (2 × 50 mL) after 2 hr. The extract was dried, evaporated under vacuum and the residue was eluted through a silica gel column (mesh 60-120) using hexane and ethyl acetate mixture to get a solid form of carbamate derivative **9a-b**.

Ethyl[2-[5-[(1*H*-1.2.4-triazole-1-yl)methyl]-1*H*-indol-3-yl]ethyl]carbamate 9a. Yield: 94%; IR (KBr, cm^{-1}): 3319 (NH), 3227(NH), 1685 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.09 Hz, 3H, CH_3), 2.96 (t, *J* = 6.50 Hz, 2H, C*H*$_2$CH$_2$N), 3.49 (t, *J* = 6.50 Hz, 2H, CH$_2$C*H*$_2$N), 4.13 (q, *J* = 7.09 Hz, 2H, OCH_2), 4.81 (s, 1H, NH, D_2O exchangeable), 5.43 (s, 2H, triazole-CH_2-indole), 7.07-8.02 (m, 6H, Ar-H), 8.49 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.59, 25.67, 41.15, 54.44, 60.71, 111.92, 113.02, 119.09, 122.37, 123.17, 125.12, 127.57, 136.30, 142.77, 151.79, 156.69; DIP MS: *m/z* (%) 314 $[M+H]^+$(83).

Ethyl[2-[5-[(methylamino)sulphonyl)methyl]-1*H*-indol-3-l]ethyl]carbamate 9b. Yield: 90%; DIP MS: *m/z* (%) 340 $[M+H]^+$(100).

Step II

A solution of compound **9a-b** (0.03 mole) in dry THF (200 mL) was added drop-by-drop to a suspension of lithium aluminum hydride (500 mg) in dry THF (600 mL) under nitrogen atmosphere and heated to reflux for 2 hr. The resulting suspension was cooled to ambient temperature, treated with a saturated solution of potassium carbonate. The resultant solid was filtered. The filtrate containing both aqueous as well as organic phases were separated. The recovered organic phase was concentrated and the residue was eluted through a silica gel column (mesh 60-120) using chloroform/ methanol/triethyl amine (88:10:2 v/v) mixture as a mobile phase.

***N*-Methyl-2-[5-[(1*H*-1, 2, 4-triazole-1-yl)methyl]-1*H*-indole-3-yl]ethanamine 4**. Yield: 70%; IR (KBr, cm^{-1}): 3245 (NH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 2.77-2.81 (m, 4H, 2 × CH_2), 5.43 (s, 2H, triazole-CH_2-indole), 7.02-8.62 (m, 6H, Ar-H), 10.88 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.78, 35.64, 51.89, 53.15, 111.59, 112.52, 118.36, 121.29, 123.54, 125.89, 127.25, 135.91, 143.72, 151.41; DIP MS: *m/z* (%) 256 $[M+H]^+$(30).

***N*-Methyl-2-[5-[[(methylamino)sulphonyl]methyl]-1*H*-indol-3-yl]ethanamine 5**. Yield: 82%; m.p. 75-76°C; IR (KBr, cm^{-1}): 3327 (NH), 3119 ($NHSO_2$), 1385 and 1132 (SO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.56 (t, *J* = 5.00 Hz, 3H, CH_3), 2.62 (s, 3H, SO_2NHCH_3), 2.98-3.03 (m, 2H, C*H*$_2$CH$_2$N), 3.16-3.32 (m, 2H, CH$_2$C*H*$_2$N), 4.34 (s, 2H, SO_2CH_2-indole), 6.78-6.83 (q, *J*=4.67 Hz, 1H, NH, D_2O exchangeable), 7.10-7.54 (m, 4H, Ar-H), 8.31 (s, 1H, NH, D_2O exchangeable), 11.04 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.67, 29.01, 32.69, 48.72, 56.52, 109.26, 111.44, 120.13, 120.55, 124.05, 124.17, 126.82, 136.04; DIP MS: *m/z* (%) 282 $[M+H]^+$(85).

Method II

General procedure for the preparation of *N*-desmethyltriptans 4-6 and tryptamines 7a-c. 4-Substituted aniline (**8**, 0.052 mole) was suspended in a mixture of water (6.66 mole) and Conc. HCl (0.328 mole). The resulting mixture was cooled to –5°C and a solution of sodium nitrite (0.057 mole) in water (40 mL) was added dropwise to the stirred mixture over 15 min followed by 30 min stirring at –5 to 0°C. The solution then added to a stirred and pre-cooled solution of sodium sulfite (20 g in 76 mL water) at 0°C over 15 min and maintained for one hr. Then charged Conc. HCl (20 mL) at 50°C and maintained at 65°C for 16 hr. The reaction-mixture diluted with DM water (50 mL) at 60°C and raised the temperature to 90°C. The solution treated with 4-methylaminobutanal diethylacetal **10** and maintained at 90°C for 1 hr, concentrated to about 200 mL and adjusted the *p*H to 7 with 30% aq. NaOH. The aqueous layer washed with dichloromethane (20 mL) then adjusted the *p*H to 11 with 30% aq. NaOH. The aqueous layer was extracted with ethyl acetate, dried over anhyd. sodium sulphate. The solvent removed *in vacuo* and the residue was eluted through a silica gel column (mesh 60-120) using dichloromethane /methanol/triethylamine (90:10:0 to 88:10:2 v/v).

(*S*)-*N*-Methyl-2-[5-(2-oxo-1,3-oxazolidin-4-ylmethyl)-1*H*-indol-3-yl]ethan-amine 6. Yield: 60%; IR (KBr, cm^{-1}): 3253 (NH), 1738 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.50 (s, 3H, CH_3), 2.87-3.10 (m, 6H, 3 × CH_2); 4.00-4.10 (m, 2H, OCH_2); 4.20-4.26 (m, 1H, C*H*NHCO), 6.94-7.44 (m, 4H, Ar-H); 7.84 (s, 1H, N*H*CH$_3$, D_2O exchangeable); 8.41 (s, 1H, NHCO, D_2O exchangeable); 10.84 (s, 1H, indole NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6):

δ 22.67, 33.33, 40.60, 49.53, 53.09, 68.06, 110.14, 111.36, 118.68, 122.75, 123.33, 126.11, 127.17, 135.25, 158.68; DIP MS: *m/z* (%) 274 $[M+H]^+$(70).

2-[5-[[(Methylamino)sulphonyl]methyl]-1*H*-indol-3-yl]ethanamine 7b. Yield: 70%, m.p.134-36°C; IR (KBr, cm^{-1}): 3368, 3331 (NH and NH_2), 1278 & 1112 (SO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.53 (s, 3H, N-CH_3), 2.74-2.82 (m, 4H, CH_2-CH_2), 4.34 (s, 2H, SO_2-CH_2-indole), 7.06-7.52 (m, 4H, Ar-H), 10.85 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 29.10, 29.29, 42.52, 56.77, 111.39, 112.86, 119.79, 121.13, 123.38, 123.99, 127.55, 136.07; DIP MS: *m/z* (%) 334 $[M+Na]^+$(90), 312 $[M+H]^+$ (20).

(*S*)-2-[5-(2-Oxo-1, 3-oxazolidin-4-ylmethyl)-1*H*-indol-3-yl]ethanamine 7c. Yield: 60%; m.p.250°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.75-3.13 (m, 6H, 3 × CH_2); 4.01-4.08 (m, 2H, OCH_2); 4.10-4.27 (m, 1H, C*H*NHCO); 6.96-7.43 (m, 4H, Ar-H); 7.84-7.97 (brs, 3H, NH+NH_2, D_2O exchangeable); 10.95 (s, 1H, indole NH, D_2O exchangeable).^{13}C NMR (75 MHz, DMSO-d_6): δ 23.20, 39.32, 40.69, 53.16, 68.11, 109.34, 111.51, 118.62, 122.86, 123.67, 126.28, 127.08, 135.29, 158.71; DIP MS: *m/z* (%) 260 $[M+H]^+$(100).

Synthesis of 4-methylaminobutanal diethylacetal 10. To a solution of 4-chlorobutanal diethylacetal (**12,** 100 g) in methanol (450 mL), methylamine (40%, 450 mL) was added and kept aside for 48 hr. The reaction-mixture was distilled out completely under vacuum and extracted with ethyl acetate (50 mL), DM water (50 mL) followed by 5% NaOH (20 mL) under stirring to the obtained residue. The aqueous layer was extracted with ethyl acetate (2×250 mL) at *p*H 14. The combined organic layer (500 mL) was dried and distilled off completely under vacuum to obtain **10** as a light yellow colour liquid. Yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7.06 Hz, 6H, 2 × CH_3), 1.53-1.67 (m, 4H, 2 × CH_2), 2.43 (s, 3H, NHCH_3), 2.60 (t, *J* = 6.99 Hz, 2H, NHCH_2), 3.44-3.69 (m, 4H, 2×OCH_2), 4.49 (t, *J* = 5.41 Hz, 1H, 2×C*H*CH_2); DIP MS: *m/z* (%) 176 $[M+H]^+$ (100).

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