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# Acid catalyzed stability studies on atomoxetine, fluoxetine and nisoxetine

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**ABSTRACT**

*Under acidic stress conditions the anti depressant drugs undergoes rearrangement. The rearranged products are characterized thoroughly. All the rearrangements are triggered by carbocation formation.*

**Key words:** Anti Depressants, Perchloric acid, Rearrangement

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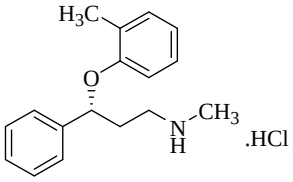
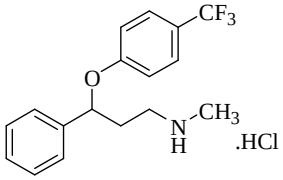
## INTRODUCTION

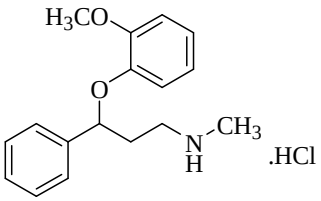
Atomoxetine, Fluoxetine and Nisoxetine are marketed as an antidepressant drugs. Duloxetine was introduced later for the same biological disorder (fig- I). During our studies on the acidic stress conditions of duloxetine [1] we observed that it undergoes rearrangement. To our knowledge similar studies were not studied in detail on the older marketed drugs.



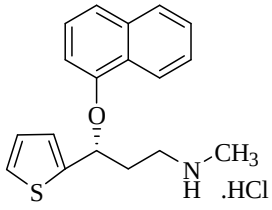

Atomoxetine. HCl




Fluoxetine. HCl




Nisoxetine. HCl




Duloxetine. HCl

Fig I: Antidepressant drugs

## MATERIALS AND METHODS

**General:** Most of the reagents used in this work were obtained from commercial suppliers and were of LR/AR grade. Solvents were purified before use by standard procedures. Melting points were determined using open capillary tubes on POLMON melting points apparatus (Model-96) and are uncorrected. $^{1}$H (400 MHz) and $^{13}$C (100 MHz) NMR spectra were recorded by using a Bruker 400 Spectrometer with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer Spectrum 100 FTIR Spectrophotometer as KBr pellets or with the neat products. Mass spectra were recorded on an API 2000 LCMS/MS Applied BioSystems MDS Sciex spectrometer. Microanalysis was performed on a Perkin-Elmer 240CHN elemental analyzer. Analytical TLC was conducted on E-Merck 60F254 aluminium-packed plates of silica gel (0.2 mm). Developed plates were visualized by using UV light or in an iodine chamber. HPLC was performed by using a Shimadzu 2010 instrument.

**Acid catalyzed rearrangement of Fluoxetine hydrochloride:** Free base of Fluoxetine (20 g, 0.064 mol) was dissolved in MDC (200 mL) and stirred for 10 min. Perchloricacid (7.8 g, 0.0775 mol) was added to the reaction mass over 15-20min. After complete addition, mass temperature was increased to reflux temperature (39°C) and maintained for 12 h. After completion of the reaction (monitored by TLC), RM was cooled to RT and 200 mL of water was added, stirred for 5 min and basified with aq.$NH_4OH$ solution ($P^H$~9.5-10) and stirred for 30 min, MDC (200 mL) was added and stirred for 15 min. Organic layer was separated and aq.layer was again extracted with MDC (200 mL). The Combined organic layers were washed with water (300 mL x 2), and was dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure (at below 35-40°C) to give crude 18 g. The crude material was separated on silica gel column to afford 2-(3-Methylamino-1-phenyl-propyl)-4-trifluoromethyl-phenol i.e. ortho isomer (**1**) (6.0 g), Methyl-(3-phenyl-allyl)-amine i.e. an olefin (**2**) (6.0 g) and 4-trifluoromethyl phenol (**3**) (8 g). Ortho isomer was purified by derivatisation of hydroxyl and amino group with *p*-nitro benzene sulfonyl chloride and the di nosyl salt was crystallized to get pure off white color nosylate (**4)** solid obtained (6.0g,)

**4-Nitro-benzenesulfonic acid 2-{3-[methyl-(4-nitro-benzenesulfonyl)-amino]-propyl} -4-trifluoromethyl phenyl ester (4) :** Off white solid, (30% yield); M. R: 194.1-196.4°C; HPLC purity (210nm) 98.12%, IR (KBr, $cm^{-1}$): 3110, 1535, 1350, 1167, 1120, 1085, 859, 848, 762, 598, 463; $^{1}$H NMR (400MHz/ $CDCl_3$/ ppm): δ2.33 (m, 2H, $CH_2$), 2.79 (s, 3H, $CH_3$),2.89 (m, 2H, $CH_2$), 4.39 (m, 1H, CH), 7.0 (d, *J* = 6.81 Hz, 3H, ArH), 7.3 (m, 3H, ArH), 7.51 (m, 1H, ArH), 7.58 (s, 1H, ArH), 8.15 (d, *J* = 8.6 Hz, 2H, ArH),8.30 (d, *J* = 8.5 Hz, 23H, ArH), 8.35 (d, *J* = 8.6 Hz, 23H, ArH), 8.43 (d, *J* = 8.66 Hz, 23H, ArH); $^{13}$C NMR (100MHz/ $CDCl_3$): δ 33.1, 35.0, 40.7, 48.4, 122.0, 124.2, 12 4.6, 124.6, 125.1, 125.1, 125.8, 125.8, 127.2, 127.8, 128.3, 128.8, 129.7, 137.9, 140.2, 140.7, 143.0, 149.1, 149.9, 151.1; MW for $C_{29}H_{24}F_3N_3O_9S_2$ [M + H]: calcd: 679.64, observed [M – nosyl]: 495.4.

**Methyl-(3-phenyl-allyl)-amine (2)**: Colorless to light brown liquid, (30% yield); HPLC purity (210nm) 98.93%, IR (Neat, $cm^{-1}$): 3322, 2972, 1493, 1114, 967, 754, 693; $^{1}$H NMR (400 MHz, $CDCl_3$, δ/ ppm): 2.19 (s, 1H, NH), 2.50 (s, 3H, $CH_3$), 3.40 (d, *J*=6.0Hz, 2H, $CH_2$), 6.35 (m, 1H, CH), 6.58 (d, *J*=15.86Hz, 1H, ArH), 7.41 (m, 5H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$, δ/ppm): 35.79, 53.68, 126.1, 127.2, 128.1, 128 .4, 131.2; MW for $C_{10}H_{13}N$ [M + H]: calcd: 148.2, observed [M + H]: 148.1

**Acid catalyzed rearrangement of Atomoxetine:** Free base of racemic Atomoxetine (21 g, 0.082 mol) was dissolved in MDC (210 mL) and stirred for 10 min. Perchloricacid (9.9 g, 0.098 mol) was added to the reaction mass at RT in 15-20 min, after the addition was complete, mass temperature was increased to reflux temperature (41°C) and maintained at reflux for 12 h. After completion of the reaction (monitored by TLC), it was cooled to RT and 200 mL water was added and adjusted $p^H$ to 9.50-10.0 with aq.$NH_4OH$ solution and stirred for 30 min. MDC (200 mL) was added and stirred for 15 min, separated the organic layer, and aq.layer was again extracted with MDC (200 mL). Combined organic layers were washed with water (300 mL x 2), dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure (at below 35-40°C) to afford a crude material of 20 g. This material was separated on a silica gel column chromatography to afford 2-methyl-6-(3-(methyl amino)-1-phenyl propyl) phenol i.e. ortho isomer (**5**) (3.5 g), 2-methyl-4-(3-(methyl amino)-1-phenyl propyl) phenol i.e., para isomer (**6**) (3.8g) and *O*-cresol (**7**) (2.5g).

**2-methyl-6-(3-(methyl amino)-1-phenyl propyl) phenol** (**5):** Off white solid, (17% yield); M. R: 169.5-171.5 °C; HPLC purity (210nm): 99.39%; IR (KBr, $cm^{-1}$): 3224, 3007, 1614, 1329, 1284, 1118, 840, 702.4; $^{1}$H NMR (400 MHz/ $CDCl_3$/ ppm) δ: 2.18 (m, 1H, $CH_2$ ), 2.35 (s, 3H, $CH_3$), 2.40 (m, 1H, $CH_2$), 2.43 (m, 1H, $CH_2$), 2.48 (s, 3H, $CH_3$), 2.79 (m, 1H, $CH_2$), 4.66 (dd, $J_1$ = 3.06 Hz, $J_2$ = 3.81 Hz, 1H, CH), 6.54 (d, *J* = 7.49 Hz, 1H, ArH), 6.64 (t, *J* = 7.4Hz, 1H, ArH), 6.95 (d, *J* = 7.05 Hz, 1H, ArH), 7.31 (m, 5H, ArH); $^{13}$C NMR (100 MHz/ $CDCl_3$/ ppm) δ: 16.9,

33.3, 35.1, 38.6, 47.7, 119.4, 125.9, 126.2, 126.4, 128.1, 128.22, 128.26, 130.7, 144.9, 154.6; MW for $C_{17}H_{21}NO$ [M + H] : calcd: 256.5, observed [M + H]: 256.5.

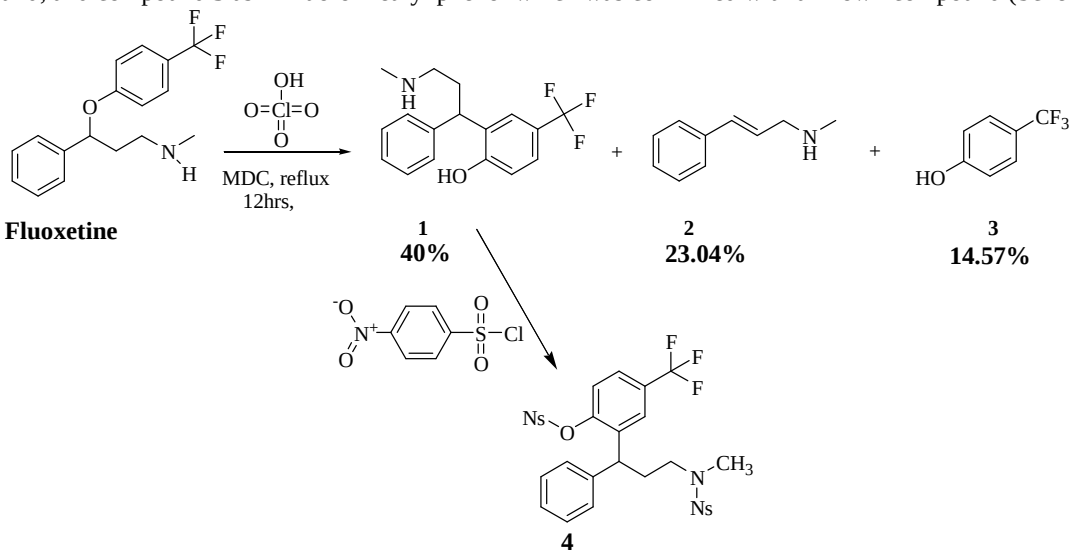
**methyl-4-(3-(methyl amino)-1-phenyl propyl) phenol (6):** Off White solid, (18% yield); M. R: 103-102 °C; HPLC purity (210nm): 97.05%; IR (KBr, $cm^{-1}$): 3299, 2911, 1424, 1263, 1201, 744, 708; $^1$H NMR (400 MHz/ DMSO-$d_6$, δ/ppm): 2.04 (s, 3H, $CH_3$ ), 2.19 (m, 2H, $CH_2$), 2.34 (s, 3H, $CH_3$), 2.53 (m, 2H, $CH_2$), 3.85 (t, *J* = 7.64 Hz, 1H, CH), 6.68 (d, *J* = 8.36 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 6.93 (s, 1H, ArH), 7.43 (m, 5H); $^{13}$C NMR (100 MHz/ DMSO-$d_6$, δ/ppm): 16.4, 31.0, 34.2, 47.5, 48.7, 114.8, 124.0, 125.7, 126.2, 127.6, 128.6, 130.0, 134.7, 145.6, 154.0; MW for $C_{17}H_{21}NO$ [M + H] : calcd: 256.5, observed [M + H]: 256.5.

**Acid catalyzed rearrangement of Nisoxetine oxalate:** Free base of Nisoxetine (6 g, 0.025mol) was dissolved into 1,2-dichloro ethane (60 mL) and stirred for 10 min. Perchloricacid (2.6 g, 0.0264 mol) was added to the reaction mass in 15-20 min, after complete addition, mass temperature was increased to reflux temperature (66 °C) and maintained at reflux for 12 h. After completion of the reaction (monitored by TLC), it was cooled to RT and 200 mL water was added and basified with aq.$NH_4OH$ solution and stirred for 30 min ($P^H$~9.50-10.0), MDC (200 mL) was added and stirred for 15 min. Organic layer was separated and the aq.layer was again extracted with MDC (200 mL). Combined organic layers were washed with water (300 mL x 2), and dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure at below 35-40°C to afford crude mixture. The crude product mixture was separated on a silica gel column (100-200 mesh). From the column the following compounds were isolated. Solid compounds are recrystalized to afford 2-Methoxy-6-(3-methylamino-1-phenyl-propyl)-phenol i.e. ortho isomer (**8**) (3.0 g), Methyl-(3-phenyl-allyl)-amine (**2**) (1.0 g), and guiacol (2.0g).

**2-Methoxy-6-(3-methylamino-1-phenyl-propyl)-phenol (8):** Off White color solid, (50 % yield); M. R: 192.9-193.8°C; HPLC purity (210nm): 98.01%; IR (KBr, $cm^{-1}$): 3401, 2952, 2786, 2433, 1511, 1269, 1131, 1030, 705; $^1$H NMR (400 MHz/ DMSO-$d_6$, δ/ppm): 2.37 (m, 2H, $CH_2$), 2.49 (s, 3H, $CH_3$), 2.70 (m , 2H, $CH_2$), 3.73 (s, 3H, $OCH_3$), 3.95 (t, *J* = 7.54 Hz, 1H, CH), 6.68 (d, *J* = 6.8 Hz, 2H, ArH), 6.84 (s, 1H, ArH), 7.27 (m, 1H, ArH), 7.28 (d, *J* = 4.2 Hz, 4H), 8.73 (s, 1H, NH), 8.83 (s, 1H, OH); $^{13}$C NMR (100 MHz/ DMSO-$d_6$, δ/ppm): 31.4, 32.5, 47.5, 56.0, 112.1, 115.8, 119.9, 126.5, 127.6, 128.7, 134.8, 145.3, 147.8; MW for $C_{17}H_{21}NO_2$ [M + H] : calcd: 272.3, observed [M + H]: 272.3.

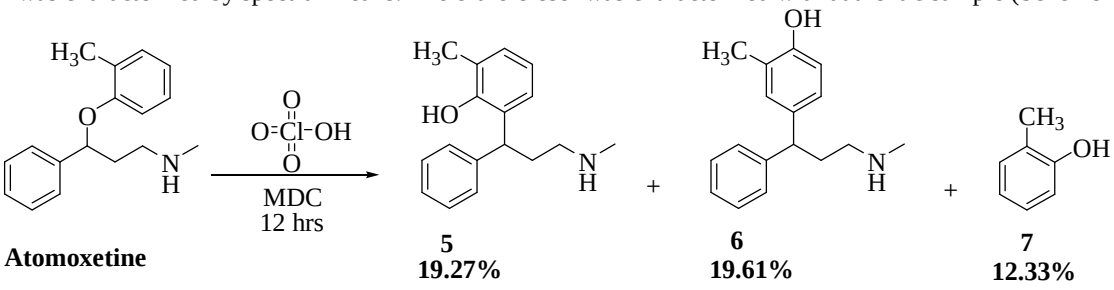
## RESULTS AND DISCUSSION

Thus when Fluoxetine [2-4] was treated with 70% $HClO_4$ in methylene chloride reflux decomposed to give three products in the ratio[9] of 40% of **1**, 23% of **2** and 15% of compound **3** . The compound **1** was identified as rearranged product and confirmed by derivitization as dinosyl compound **4.** Compound **2** was identified as olefinic compound, and compound **3** as 4- fluoro methyl phenol which was confirmed with a known compound (Scheme 1).




**Scheme 1. Fluoxetine degradation under acidic conditions**

In a similar way when Atomoxetine [5-8] was treated with 70% $HClO_4$ in methylene chloride reflux decomposed to give mainly three compounds. They were formed in the ratio [9] of 19.27% of **5,** 19.61% of **6,** and ortho cresol **7, 12.33%.** Both compounds **5** and **6** were rearranged products and were characterized by spectral means. The ortho cresol was characterized by spectral means. The ortho cresol was characterized with authentic sample (Scheme 2).




**Atomoxetine**

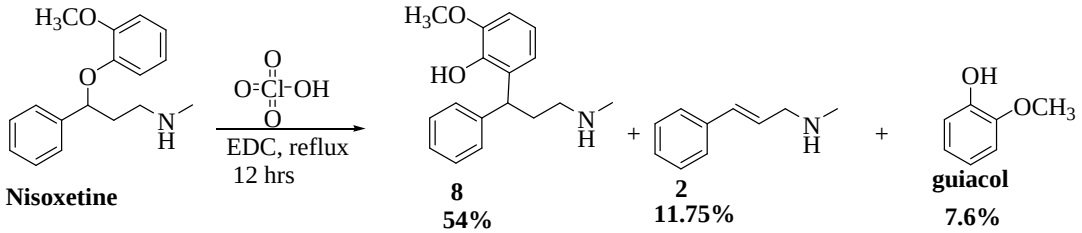
**5**
**19.27%**

**6**
**19.61%**

**7**
**12.33%**

**Scheme 2. Atomoxetine degradation under acidic conditions**

Similarly when Nisoxetine was treated with 70% $HClO_4$ in 1, 2- Dichloro ethane underwent decomposition to give four products. The rearranged product **8** was formed in the ratio [9] of 54%, olefin product **2** in the ratio of 12%, amino alcohol **9** in the ratio of 10.5% and Guiacol 7.6% (Scheme 3). All the compounds were characterized by spectral means.

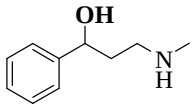



**Nisoxetine**

**8**
**54%**

**2**
**11.75%**

**guiacol**
**7.6%**




**9**
**10.41%**

**Scheme 3. Nisoxetine degradation under acidic conditions**

## CONCLUSION

In conclusion we observed that all three anti depressant drugs are unstable under acidic conditions and are rearranged to give diaryl methane compounds

**Acknowledgments**
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## REFERENCES

[1] A. Veera Reddy, S. Udaya Bhaskara Rao, B. Sreenivasula Reddy. *Indian J. Chem.* **2007,** 46B, 1695.
[2] J. K. Pekka; J. H. Petri; H. J. Anitta. (Orion-Yhtyma Oy), US Patent 5166437 (**1992**).
[3] I. Zinovi; K. Joseph; P. Gidon; E. Schwartz, (Teva Pharmaceutical Industries) Ltd. US patent 5225585 (**1993**)
[4] J. T. Kevin. **(**Albemarle Corporation), US patent 5917091 (**1999)**.
[5] B. M. Brayan; K. Klaus; Schmiegel. (Eli Lilly and Company); US Patent 4314081 **(1982).**
[6] C. B. Herbert. US Patent 4950791 A **(1990).**
[7] P. K. J. Douglas; T. L. Kurt . (Eli Lilly and company); US Patent 6541668 (**2003).**

[8] E. J. Corey; G. A. Reichard. *Tetrahedron Lett.* **1989,** 30, 5207-5210.
[9] HPLC Conditions for the separation of acid catalyzed reaction mixture. **Buffer:** 10ml Triethyl amine in 980ml Water $p^H$ 6.0 with ortho phosphoric Acid; filtered through 0.45 µm membrane and degassed; **Mobile phase:** Buffer 600ml+ 300ml THF+ 100ml Methanol mixed well and degassed; **Column:** YMC pack C8 250X4.6mm; 5µm. ; **Column temperature:** 25 °C; Run Time: 30 min; **System:** Waters Alliance 2695 with 2487 U. V detector or equivalent; **Detector wavelength (λ):** 215nm; **Diluent:** Mobile Phase

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