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Novel acid catalysed rearrangement of duloxetine

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A novel acid catalysed rearrangement of aryl methyl ethers (duloxetine) to diaryl methanes is described.

Keywords: Duloxetine base, Conc. HCl, aluminium chloride

Psychotic drugs[1] of SNRI class and selective seratonin reuptake inhibitors are useful in alievating psychotherapeutic problems. They have also been used as neuropathic pain relievers and stress urinary incontinence agents. The important successful drugs in this class are fluoxetine **1**, duloxetine[2] (Cymbalta®) **2** and atomoxetine **3** (**Scheme I**).

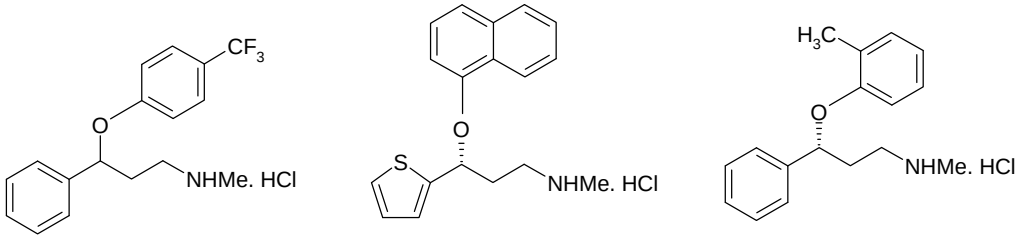
The duloxetine **2** is introduced as an optically active drug in 2004 (ref. 3). During the studies related to its synthesis and acidic stress conditions it was found that duloxetine **2** is not stable and undergoes degradation. In a typical reaction the duloxetine base is unstable in the presence of hydrochloric acid (36%, 1.2 *M*) to give ~ 5 products. Three major products that have been identified were formed in the ratio of 30, 17 and 12%. The other two unidentified were formed ~ 6% each. The three major products are **4**, **5** and **6** (**Scheme II**).

The α-naphthol **4** is confirmed by comparing with standard laboratory sample. The structure of the product **5** is confirmed by spectral analysis and also unequivocally by its X-ray crystal structure (**Figure 1**). The structure of compound **6** is deducted form its ^{1}H NMR, ^{13}C NMR and other analytical data. Both compounds **5** and **6** are novel and are racemic.

The observation of the racemic products and α-naphthol indicated that the ether bond is broken during rearrangement and the formed carbocation destroyed the optical activity probably assisted by neighbouring amino group. The naphthalene moiety reattacked with C-C bond formation leading to **5** or **6** (**Scheme III**).

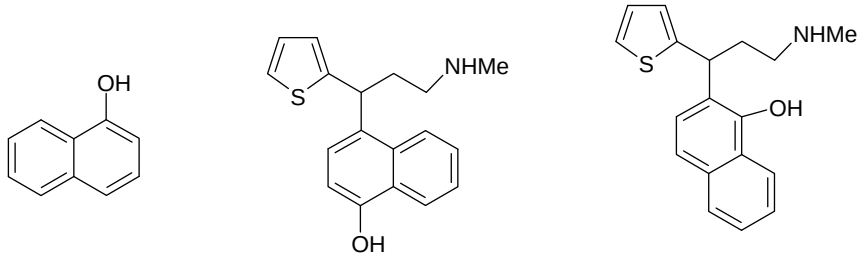
Ethers (aliphatic/benzylic) are reported to rearrange in poor yields except claisen rearrangement. For example Tarbell. D.S[4,5], reported the rearrangement of *o*-benzyl ethers of salicylic acid at ~ 200°C to give small amount (~ 5%) of benzyl-5-benzyl salicylate. In the next paper[5] they reported that heating of 9-phenanthryl methyl ether of 3,5-dichlorosalicylic acid **7** at 229°C to yield 41% of rearranged products **8** and **9**, but when heated the simple ether **10,** they obtained only 2,4-dichloro phenol.**11** (**Scheme IV**).

The rearrangement observed in duloxetine **2** case is similar to Hofmann-Martius rearrangement of *N*-aryl derivatives of **12** to give **13** and **14** as reported recently by Philip Magnus *et al.*[6]



1 **2** **3**

Scheme I



4 **5** **6**

Scheme II

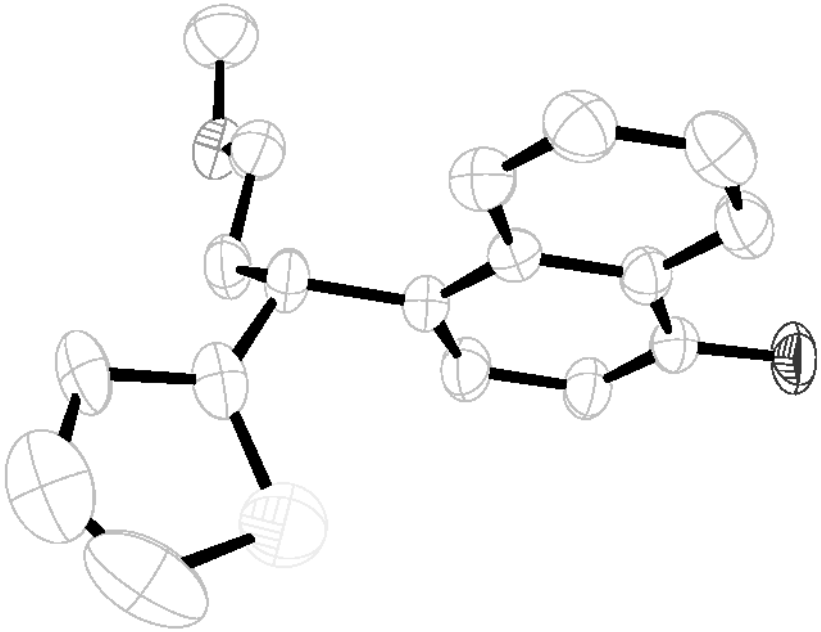
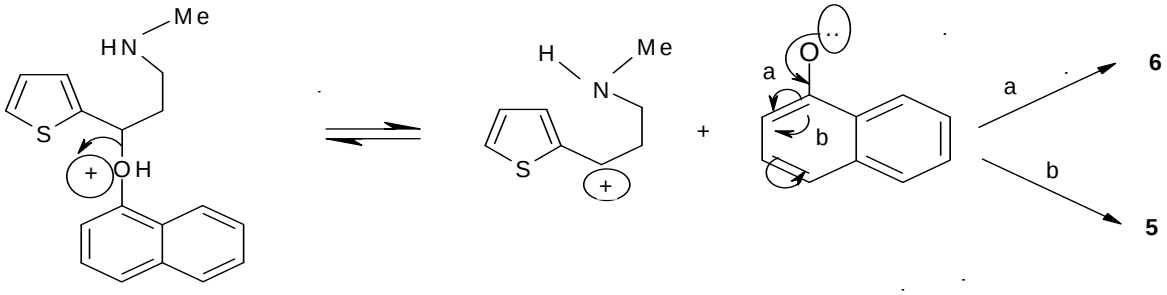


Figure 1 — ORTEP representation of **5,** X-ray structure[7]



Scheme III

The effect of lewis acids like $AlCl_3$ and BF_3. OEt_2 on **2** was studied and found that at room temp. (25-30°C) BF_3. OEt_2 has no effect but aluminium chloride rearranges **2** to give products of **6** (~ 45%), **4** (12%) and **5** (15%).

Experimental Section

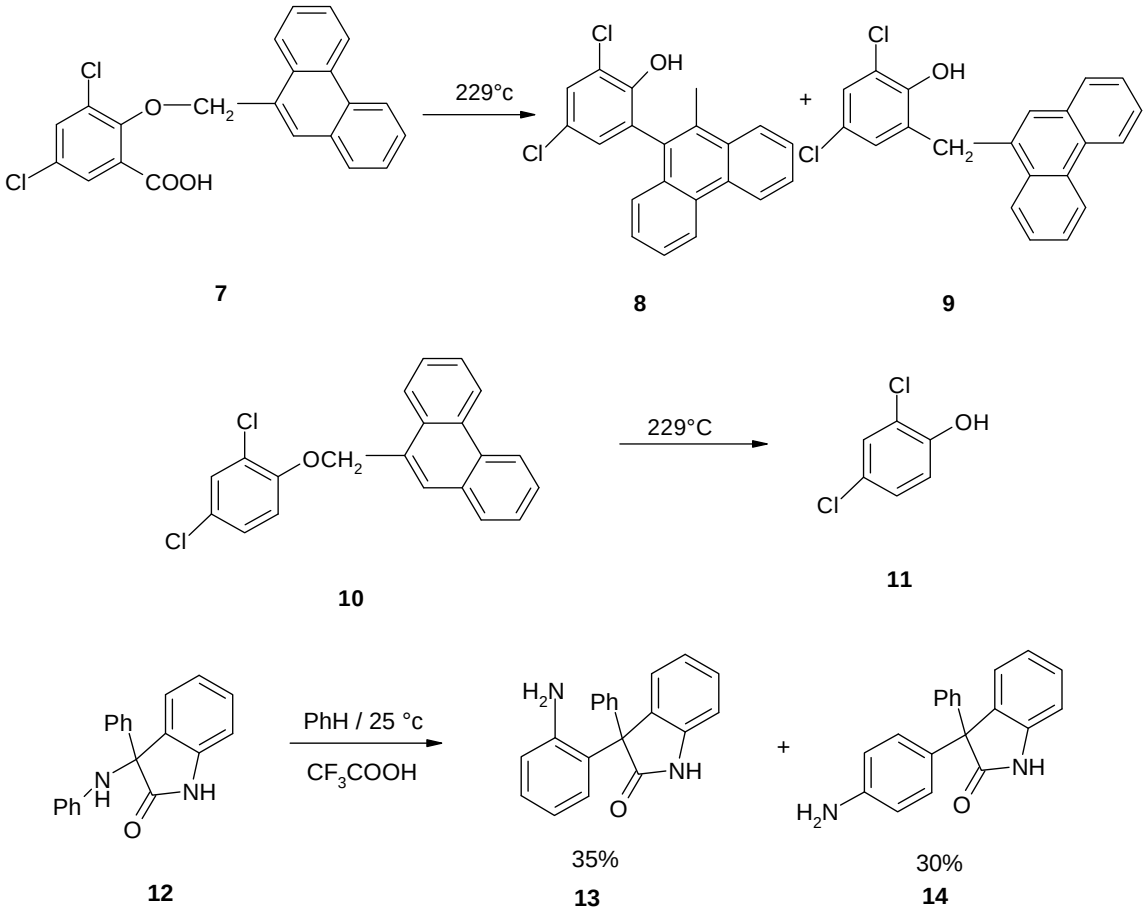
Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectra were recorded as KBr using Perkin-Elmer 2000 FT IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra on a Brucker 400 MHz instrument with TMS as internal standard (chemical shifts in δ ppm).

General Procedure. To a magnetically stirred solution of duloxetine base (10 g, 0.336 mole) in ethyl acetate (200 mL) was added Conc. HCl (36%) (4.0 g, 0.403 mole) at RT. The reaction mass was stirred for 1 hr at RT. Then, the solution was heated to 40-45°C for period of 45 minutes. The completion of reaction was checked by TLC and excess of ethyl acetate was distilled off under reduced pressure to obtain 10 g of crude product mixture. The pure products **4**, **5** and **6** were isolated using column chromatography.

Compound 4: Isolated yield 12%, identified as α-naphthol.

Preparation of 2-(1-(4-hydroxynaph-1-yl)-3-(methylamino)propyl)-thiophene hydrochloride 5: Yield 30%. m.p. 246-48°C; IR (KBr): 3211 (-NH, OH) 1595, 1586, 1379, 1260, 763, 711 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.48 - 2.53 (br s, 5H), 2.86 (br s, 2H, -NCH_2), 5.13 (t, 1H, benzylic H,), 6.91 – 8.19 (m, 9H, aromatic) , 9.14 - 9.20 (br s, 2H), 10.25 (s, 1H, -OH); ^{13}C NMR (DMSO-d_6): δ 36.4, 37.2, 38.2, 50.1, 107.9, 123, 123.6, 123.9, 124.3, 124.4, 124.7, 125.3, 126.4, 126.8, 130.8, 132.5, 150.5, 152.5; Anal. Calcd for $C_{18}H_{19}NSO.HCl$: C, 64.75; H, 6.03; N, 4.19; O, 4.79; S, 9.60, Cl, 10.6. Found: C, 64.77; H, 6.07; N, 4.18; O, 4.78; S, 9.59, Cl, 10.55%.

Preparation of 2-(1-(2-hydroxynaph-1-yl)-3-



Scheme IV

(methylamino)propyl)-thiophene hydrochloride 6: Isolated yield 17%. IR (KBr): 3443 (-NH, OH), 1596, 1570, 1394, 1260, 808, 701 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.04-2.43 (m, 2H, -CH2), 2.49 (s, 3H, -NCH_3), 2.53-2.78 (m, 2H, -NCH_2), 5.04 (dd, 1H, benzylic H, J_1=3.88 Hz, J_2 =12.0 Hz), 6.97–8.4 (m, 9H, aromatic), 9.21- 9.32 (br s, 2H), 10.24 (s, 1H, -OH). Anal. Calcd for $C_{18}H_{19}NSO.HCl$: C, 64.75; H, 6.03; N, 4.19; O, 4.79; S, 9.60, Cl, 10.6. Found: C, 64.77; H, 6.04; N, 4.18; O, 4.77; S, 9.59, Cl, 10.59%.

Conclusion

A novel acid catalysed rearrangement of aryl methyl ethers **2** to give diaryl methane derivatives **5** and **6** was developed.

Acknowledgement

The authors wish to thank Prof T N Gururow and Mr. Pratap of SSCU, IISc for X-ray crystal structure.

References and notes

1 *The Merck Index*, *XIII* edition, 3498, 4211.

2 Yoshito F, Masaya I, Inoue T & Matsumoto J, *Org Process Res Dev*, 10, **2006**, 905.

3 Cymbalta® is approved by FDA for the treatment of major depressive disorder as well as management of diabetic peripheral neuropathic pain (DPNP). It offers relief from both emotional and painful physical symptoms associated with depression. It is a balanced selective serotonin and norepinephrine reuptake inhibitor (SSNRI).

4 Tarbell D S & Wystrach V P, *J Am Chem Soc*, 65, **1943**, 2146.

5 Tarbell D S & Wystrach V P, *J Am Chem Soc*, 65, **1943**, 2149.

6 Philip M & Turnbull R, *Org Lett*, 8, **2006**, 3497.

7 The crystal structure has been deposited at Cambridge crystallographic data center and allocated the deposition number CCDC 621604.