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NOTE

Synthesis and Antibacterial Activities of Some Quinoline Substituted Quinoxaline Derivatives

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p-Anisidine (**1**) on treatment with ethyl acetoacetate gave 1-(ethyl-3-[(4-methoxyphenyl)imino]butanoate) (**2**), which on cyclization in hot Dowtherm oil gave 4-hydroxy-6-methoxy-2-methylquinoline (**3**). The latter, on chlorination with SO_2Cl_2, gave 3-chloro-4-hydroxy-6-methoxy-2-methylquinoline (**4**) which with $POCl_3$ was transformed into 3,4-dichloro-6-methoxy-2-methylquinoline (**5**). Treatment of compound **5** with *o*-phenylenediamine gave the novel product 2-methoxy-6-methyl-7,7a,11a,12-tetrahydroquinolino[3,4-b]quinoxaline (**6**) whose structure was assigned based on spectral data.

Keywords: Quinoxilines, Quinolines, Diamines, Chlorination.

Quinoxaline derivatives are an important class of heterocycles that display a wide range of biological properties[1]. Quinoline ring system is present as a basic structure in a wide variety of heterocyclic synthetic and natural bioactive compounds[2]. Quinoline derivatives have been explored for the diverse types of pharmacological activities such as antimicrobial[3], antiinflamatory[4], antiamoebic[5], antiseptic/antiinfective[6], anticancer[7], antineurodegenarative[8] *etc*. Having many beneficial biological activities, quinoline derivatives have become the synthetic goals of many organic and medicinal chemists[1]. Quinoxalines are omnipresent in many heterocyclic structural units in pharmaceuticals and bioactive natural products[9]. They are the core constituents of various antibiotics such as echinomycin, levomycin and actinoleutin[10,11]. In view of these considerations, it was considered worthwhile to synthesize quinoline based quinoxaline type of compounds as new chemical entities and as potentially biologically active compounds.

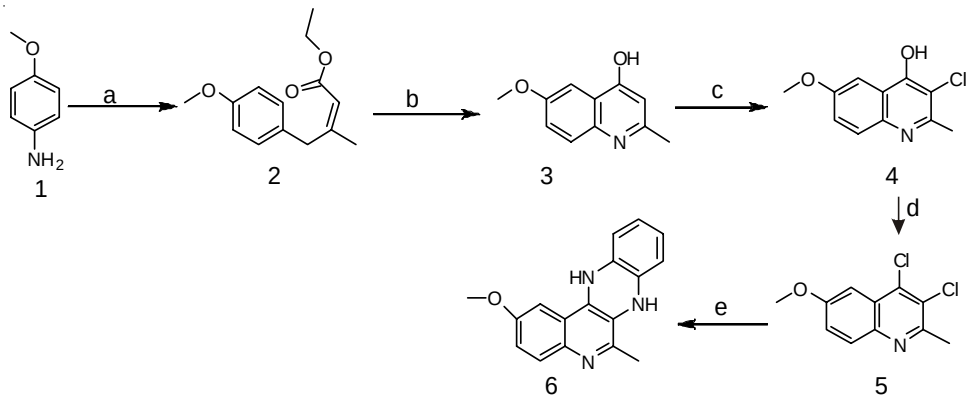
Melting points were determined in open capillary tubes using Buchi melting point apparatus and are uncorrected. IR spectra (in KBr pellets) were recorded on a Shimadzu FTIR 157 spectrometer. All ^1H and ^{13}C NMR spectra were recorded on a Bruker instrument, using TMS as an internal standard, operating at 400 MHz and 100 MHz, respectively. The mass spectra were recorded either on single quadrupole mass or XCT ion trap spectrometers. Completion of the reaction was monitored by TLC and plates which were visualized by UV light and/ or iodine vapours.

Preparation of ethyl-3-[(4-methoxyphenyl)imino] butanoate (2): A mixture of *p*-anisidine (1) (12.3 g, 100 mmol), ethyl acetoacetate (13 g, 100 mmol) and ethanol (150 mL) was refluxed for 4 h. At the end of this period, the reaction mixture was distilled to half its volume to remove ethanol and the residue cooled to room temperature. The separated solid was filtered, washed with cold ethanol (2 × 20 mL) and dried. Yield = 21 g (75 %), m.p.: 35 °C (Lit[13]. m.p. 38 °C).

Preparation of 4-hydroxy-6-methoxy-2-methylquinoline (3): Ethyl 3-[(4-methoxyphenyl)imino]butanoate (**2**) (17 g, 80 mmol) was added slowly to pre-heated Dowtherm oil (50 mL) at 250 °C in small lots. After the completion of addition, the reaction mixture was cooled to room temperature and diluted with hexane. The separated solid was filtered, washed with hexane (30 mL) and dried. The solid obtained was dissolved in 10 % NaOH (100 mL), filtered and neutralized with dil. HCl (20 %, 20 mL). The separated, off-white, solid was filtered, washed with water (2 × 20 mL) and dried. Yield = 10 g (68 %), m.p. 270 °C (Lit.[11] m.p.: 267-269 °C).

Preparation of 3-chloro-4-hydroxy-6-methoxy-2-methylquinoline (4): A mixture of compound **3** (14.15 g, 7.5 mmol), SO_2Cl_2 (8 mL, 8 mmol) and chloroform (50 mL) was stirred at room temperature. The reaction was monitored by TLC. After the completion of the reaction, the solvent was evaporated under reduced pressure. The residual solid obtained was washed with water (2 × 20 mL) and dried. The crude product was purified by recrystallisation from methanol to obtain compound **4** as off-white solid. Yield = 10 g (70 %), m.p. 269-271 °C.

Preparation of 3, 4-dichloro-4-hydroxy-6-methoxy-2-methylquinoline (5): A mixture of 4 (4.15 g, 1.5 mmol) and



Scheme-1: (a) Ethyl acetoacetate, ethanol, heat, 90 °C, 4 h (b) dowtherm oil, 250 °C, 0.5 h (c) SO_2Cl_2, $CHCl_3$, 6 h, r.t., (d) $POCl_3$, 100 °C, 1h, (e) OPDA, DMF, 90 °C, $Pd(PPh_3)_4$, 4 h

phosphorus oxychloride (4.5 mmol, 10 mL) was heated on a hot water bath at 100 °C for 1 h. The reaction was monitored by TLC. After the completion of reaction, the mixture was cooled to room temperature and diluted with ice-cold water (20 mL). It was then neutralised with sodium bicarbonate (5 %, 50 mL). The separated solid was filtered, washed with water (2 × 20 mL) and dried to obtain compound **5**. Yield = 3 g (70 %), m.p. 91-93 °C. For spectral data.

Preparation of 2-methoxy-6-methyl-7,7a,11a,12-tetrahydroquinolino[3,4-]quinoxaline (6a): A mixture of compound **5** (0.61 g, 0.25 mmol), *o*-phenylenediamine (0.27 g, 0.25 mmol), triphenylphosphine palladium (0.1 g) and DMF (25 mL) was heated for 4 h on a hot water bath at 100 °C. The reaction mixture was cooled to room temperature, diluted with water (15 mL) and filtered to remove triphenylphosphine palladium. The filtrate was washed with distilled water (2 × 20 mL), organic layer was extracted with ethyl acetate (3 × 30 mL) and the organic layer evaporated under reduced pressure to obtain a crude residue. The latter was recrystallised from ethanol to obtain compound **6**. Yield = 0.3 g (49 %), m.p.: 142-143 °C. For spectral data.

Condensation of *p*-anisidine (**1**) with ethyl acetoacetate in refluxing ethanol gave the previously reported[12] ethyl-3-[(4-methoxyphenyl)imino]butanoate (**2**) as shown in **Scheme-I**. The latter was thermally cyclized by heating at 250 °C using Dowtherm oil for 0.5 h to obtain 4-hydroxy-6-methoxy-2-methylquinoline (**3**), which is also known in literature[13]. Compound **3** on treatment with sulphuryl chloride in chloroform at room temperature gave 3-chloro-4-hydroxy-6-methoxy-2-methylquinoline (**4**), which was characterized based on its spectral data. Thus, its IR showed a diagnostic absorption at a 3275 cm^{-1} as a medium and broad peak assignable to a -OH stretching vibration and 1635 cm^{-1} assignable to -C=O functional group. Its ^1H NMR (400 MHz, DMSO-d_6) spectrum showed signals at δ 2.62 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 5.99-8.01 (m, 3H, aromatic). Its LC/MS (ESI-MS) showed *m/z* at 224 and 226 as twin peaks corresponding to molecular masses of 223 and 225. Compound **4** was then treated with $POCl_3$ in 1:3 ratio (w/v) under reflux at 105 °C to obtain 3, 4-dichloro-6-methoxy-2-methylquinoline (**5**) on processing the reaction mixture. The structure of compound **5** was confirmed by its spectral data. Thus, its IR in KBr phase showed the absence of any absorption in the 3500-3000 cm^{-1} region and also in 1800-1600 cm^{-1} region. Its ^1H NMR (400 MHz, $CDCl_3$) spectrum showed signals at δ 2.62 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.56-8.01 (m, 3H, aromatic). Its LC/MS (ESI- MS) showed *m/z* = 243 ($M^+ + 2$) and 245 ($M^+ + 4$) as twin peaks corresponding to a molecular mass of 241. Compound **5** on treatment with *o*-phenylenediamine in the presence of $Pd(PPh_3)_4$ catalyst in DMF on a hot water bath at 100 °C for 4 h gave 2-methoxy-6-methyl-7,7a,11a,12-tetrahydroquinolino[3,4b]quinoxaline (**6**) whose structure was assigned based on its spectral data. Thus, it's IR (KBr, ν_{max}, cm^{-1}) showed an absorption at ≈3000 (N-H, broad). Its ^1H NMR (400 MHz, $CDCl_3$) spectrum showed signals at δ 2.62 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 5.56-8.01 (m, 7H aromatic), 3.34 (s, two-NH protons). Its LC/MS showed the molecular ion peak ($M^+ + 1$) at (ESI-MS) *m/z* = 271 corresponding to a molecular mass of 270 when recorded in the Q + 1 mode.

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