A STUDY ON SYNTHESIS, NMR SPECTRA OF SOME AZOMETHINE COMPOUNDS CONTAINING QUINOLINE AND FUROXAN SYNTHESIZED FROM EUGENOL IN *OCIMUM SANCTUM* L. OIL

Le Thi Hoa[1], Dang Thi Huong[2], Le Thi Binh[3] , Trinh Thi Huan[1]

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Abstract: *5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-methylquinoline (**2**) has been synthesized from eugenol, the main constituent of Ocimum sanctum L. oil, following the Döebner – Miler method in toluene – HCl heterogeneous system. The key 5,6-Dimethoxy-8-(3-methylfuroxan-4-yl) quinoline-2-carbaldehyde (**3**) obtained by oxidation of compound **2** by SeO_2 in dioxane solvent at 70 ^oC. Compound **3** was used as a key compound for further synthesis to 2 azomethines contain quinoline and furoxan moiety. The structure of the synthesized compounds was characterized by spectroscopic methods.*

Keywords: *Azomethine, quinoline, furoxan, polysubstituted quinoline, 5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)quinoline.*

1. Introduction

Furoxan derivatives display a variety of biological activities, anti-parasitic properties, anticancer effects, anti-microbial are listed [1-4]. Their vasodilator activity and inhibition of platelet aggregation is well known [5,6]. Quinoline an important class of fused heterocyclic compounds has attracted high attention in organic chemistry due to their significance and wide range of biological activities. The quinoline skeleton has been used as the basis for the design of many synthetic antimalarial [7,8], antibacterial, antifungal [9,10], anticancer compounds [11-13].

Some time ago, we focused our attention on several natural arylolefins (eugenol, methyleugenol, safrole, anethole) from vegetable essential oils that, owing to their structure, could act as good substrate in order to prepare heterocyclic compounds. For example, some furoxans and metallacyclic complexes were prepared from safrole (in sassafras oil) [14,15] and from eugenol (in clove oil) [16,17], thiazolidinones and indoles were synthesized from anethole (in star anise oil) [18], many polysubstituted quinolines and quinazolines were also synthesized from eugenol [19-21].

In this study, we present the result of the synthesis some azomethine compounds of quinolines incorporating furoxan moiety from eugenol (1-hydroxy-2-methoxy-4-allylbenzene), the main constituent of *Ocimum sanctum L.* oil (a cheap natural source for commerical extraction of eugenol) and to investigate whether some compounds have useful biological activities.

[1] Faculty of Natural Science, Hong Duc University; Email: lethihoatn@hdu.edu.vn
[2] Sam Son Hight School, Thanh Hoa Province
[3] Dong Son 2 Hight School, Thanh Hoa Province

2. The Experimental

2.1. General information

IR spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr discs at 400-4000 cm^{-1}. ESI mass spectra were recorded using Agilent LC-MSD-Trap-SL series 1100 spectrometer. NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer, in DMSOd_6 with TMS as the internal standard, at 298–300 K. C, H, and N were analyzed on a LECO CHNS model 932 elemental analyser. The anticancer activities were tested at the Experimental Biological Laboratory - Institute of Chemistry of Natural Compounds (in Hanoi), according to the described method [14]; IC_{50} values were calculated based on OD values taken on an Elisa instrument at 515-540 nm.

2.2. Preparation

2.2.1. 5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-methylquinoline (2).

A solution of 4,5-dimethoxy-2-(3-methylfuroxan-4-yl)phenylamine (**1**, previously prepared in reference [16], 251 mg, 1 mmol) in hydrochloric acid 1:1 (6 mL) was heated at 80 ^oC, add 3 ml toluene and paraldehyde (1 mL) was slowly added during 20 minutes under stirring. The reaction mixture was stirred for 4 h at 80 ^oC. After cooling down to room temperature, the obtained mixture was neutralised with 5M NaOH solution. The precipitate was filtered out and recrystallized from EtOH to give white crystals (**1)** in 256 mg and 85% yield, mp 179-180 ^oC [22].

2.2.2. 5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)quinoline-2-carbaldehyde (3).

A solution of **2** (301 mg, 1 mmol) in dioxane (3 mL) was heated at 80 ^oC, add 111 mg (1 mmol) SeO_2. The reaction was heated at 80 ^oC for 6 h. After cooling down to room temperature, the precipitate was filtered out and recrystallized from EtOH by volume to give yellow needles (**3)** in 252 mg and 80% yield, mp 219-220 ^oC [22].

2.2.3. (E)-5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-((4methoxiphenyl)imido)methyliden quinoline (4)

The compound was prepared starting from **3** (315 mg, 1 mmol), 4-CH_3OPhNH_2 (136 mg, 1 mmol) and 1 ml acetic acid in 8 ml DMF under microwave irradiation. The yield was 75%, yellow needles (**4)** mp 202 ^oC. IR (cm^{-1}): 2963, 2941, 2844 (C-H); 1618 (C=N); 1593 (ring); ^{1}H NMR (DMSOd_6, 500 MHz) δ (ppm): 8.35 (d; J = 9 Hz, 1H, H3), 8.64 (d; J = 8.5 Hz, 1H, H4), 8.05 (s, 1H, H7), 2.12 (s, 3H, H12a), 4.06 (s, 3H, H5a), 4.05 (s, 3H, H6a), 8.73 (d; J = 16 Hz, 1H, H2a), 7.52 (m, 2H, H14 and H18), 7.01 (m, 2H, H15 and H17), 3.80 (s, 3H, H16a); ^{13}C NMR (DMSOd_6, 125 MHz) δ (ppm): 157.47(C2), 118.81(C3), 134.11(C4), 153.55(C5), 148.75(C6), 120.86(C7), 121.04(C8), 142.34(C9), 127.77(C10), 158.98(C11), 118.81(C12), 57.02(C5a), 55.35(C6a), 9.47 (C12a), 157.32(C2a), 140.31(C13), 123.37(C14 and C18), 115.14(C15), 114.45(C17), 144.20(C16), 61.21(C16a); MS, [M+H^+], m/z (au)/relative intensity (%): 421/100.

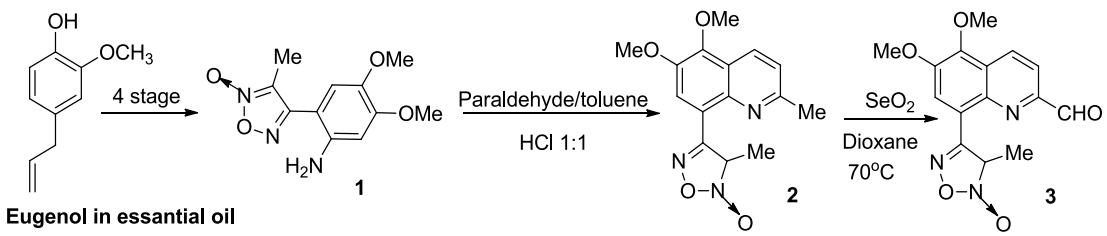
2.2.4. (E)-5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-((4-methylphenyl)imido)methyliden quinoline (5)

The compound was prepared starting from **3** (315 mg, 1 mmol) and 4-CH_3OPh-$COCH_3$ (150 mg, 1 mmol) according to the procedure for the preparation of **4**. The yield was 80%, yellow needles (**5)** mp 200 ^oC. IR (cm^{-1}): 3050, 2952, 2842 (C-H); 1614 (C=N); 1599 (ring); ^1H NMR (DMSOd_6, 500 MHz) δ (ppm): 8.36 (d; J = 9.0 Hz, 1H, H3), 8.65 (d; J = 9.0 Hz, 1H, H4), 8.07 (s, 1H, H7), 2.11 (s, 3H, H12a), 4.07 (s, 3H, H5a), 4.06 (s, 3H, H6a), 8.72 (d; J = 15.5 Hz, 1H, H2a), 7.39 (d; J = 8.5 Hz, 2H, H14 and H18), 7.27 (d, J = 7.0 Hz, 2H, H15 and H17), 2.35 (s, 3H, H16a); ^{13}C NMR (DMSOd_6, 125 MHz) δ (ppm): 153.30(C2), 118.87(C3), 131.21(C4), 144.15(C5), 148.84(C6), 120.91(C7), 121.11(C8), 140.26(C9), 121.60(C10), 157.43(C11), 115.10(C12), 61.25(C5a), 57.01(C6a), 9.44(C12a), 159.01(C2a), 147.21(C13), 121.60(C14 and C18), 129.74(C15 and C17), 140.26(C16), 20.61(C16a); MS, [M+H^+], *m/z* (au)/relative intensity (%): 405/100.

3. Results and discussion

A compound containing both furoxan and quinoline heterocycle: 5,6- Dimethoxy-8-(3-methylfuroxan-4-yl)-2-methylquinoline was synthesized from 4,5-dimethoxy-2-(3-methylfuroxan-4-yl)phenylamine (**1**) following the Döebner - Miller was method as described in Scheme 1. (The numeration on presented structures is specifically used for NMR analysis) [23,24].

Scheme 1. *Synthesis of quinoline **1**.*



4,5-Dimethoxy-2-(3-methylfuroxan-4-yl)phenylamine (**1**) was prepared from methyleugenol through 4 stage according to our manner [16]. The compound **2** was synthesized from compound **1** following the Döebner - Miller method in toluene - HCl heterogeneous system in wich the crotonaldehyde was replaced with paraldehyde. In acidic medium, paraldehyde is gradually decomposed into acetaldehyde which underwent the aldol condensation to yield crotonaldehyde. We found that the Döebner - Miller reaction in a two-phase solvent system, along with paraldehyde replacement, decreases the polymerisation of the aldehyde, the yield of compound **2** was 85 %.

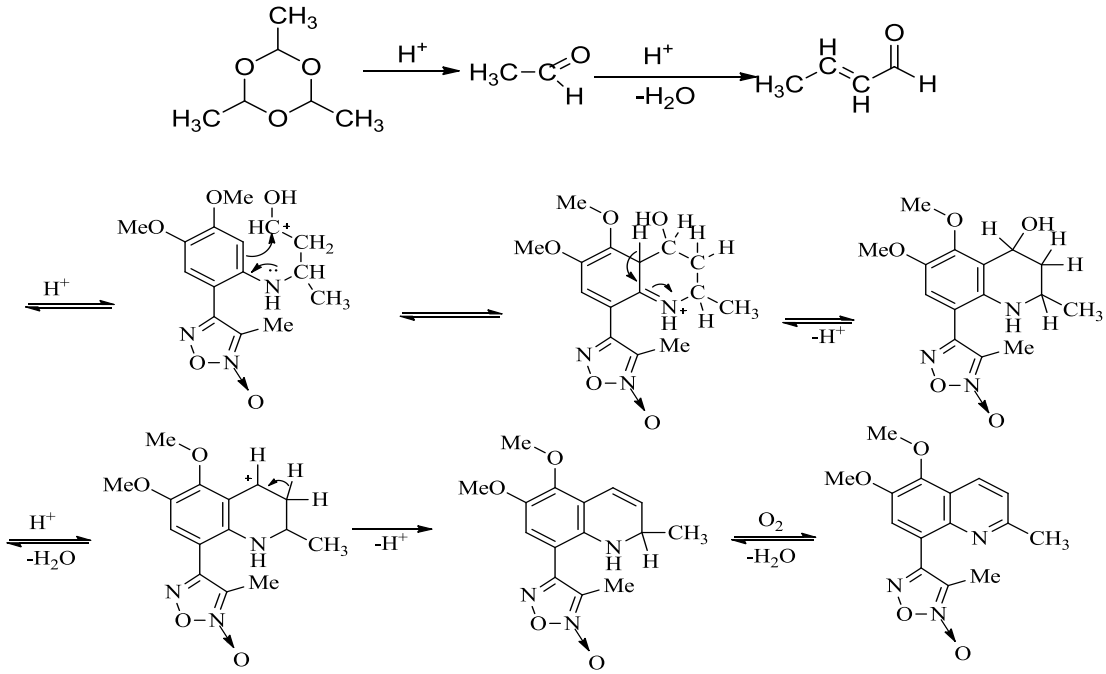
The ^1H NMR spectrum of compound **2** has three downfield protons with chemical shift greater than 7.0 ppm, while in amine **1** there are only two aromatic protons in the benzene ring with smaller chemical shifts. The upfield range in the spectrum of

compound **2** differs from that in compound **2** which has an additional signal with an intensity of 3H at δ= 2.61 ppm, proving that the ring reaction according to Doebner - Miller method has occurred, affording 2-methylquinoline [22].

It is known that paraldehyde is the trimer of acetaldehyde, in acidic medium, paraldehyde is gradually decomposed into acetaldehyde which underwent the aldol condensation to yield crotonaldehyde. Crotonaldehyde then took part in the reaction with amine and was converted to the quinoline ring. The methyl group at posotion 2 of the quinoline heterocyclic is activated by the N atom, so **2** was subject for the crotonic condensation reaction to promote the side chain. The crotonic condensation reaction can be done in acid or alkaline solution, but with the structure of compound **1**, this reaction was performed in acid solution. There are two reasons: first, the furoxan ring is destroyed easily in boiling alkaline solution, secondly, activation's methylene by the OH^- agent is more difficult than activation's N atom by H^+ agent.

The formation of compound **1** from eugenol can be explained as in Scheme 2.

Scheme 2. *Explanation of the formation of compound **2**.*

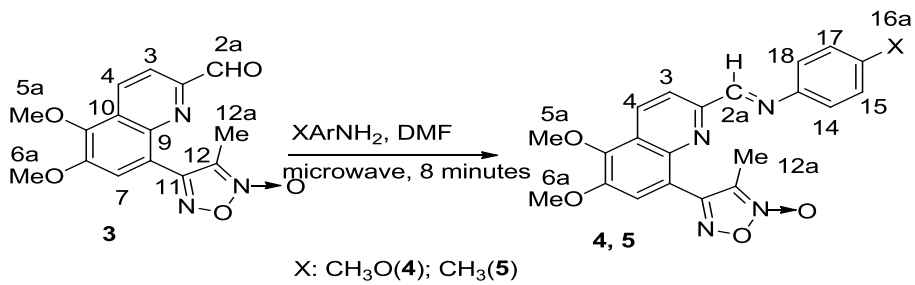


When compound **2** was reacted with SeO_2 in dioxane (Scheme 1), the reaction conditions were optimized by changing reaction temperature and time. The results show that the synthesis of quinoline-2-carbaldehyde **3** gave highest yield of 60% when performed at 70 °C for 4 h. The IR spectrum of **3** has the absorption band of the aldehyde carbonyl group at 1718 cm^{-1} The remarkable difference in ^1H NMR spectrum of **3** compound in comparision with spectrum of **2** compound is the appearance of a singlet at 10.01 ppm (-CHO group) and the disappearance of signal at 2.61 ppm (-CH_3 group) [22].

Azomethine derivatives synthesized from quinolinecarbaldehyde compounds often have high biological activity or complexing ability. A.Köppl et al. conducted a condensation reaction between 2-quinolinecarbaldehyde with aromatic amines and studied the ability to form complexes of the synthesized derivatives. The results show that the substances are capable of forming stable complexes with Ni^{2+}[25]. Therefore, we performed the condensation reaction of 8-(3-methylfuroxan-4-yl)-5,6-dimethylquinoline-2-carbaldehyde (**3**) with *p*-anisidine and *p*-totuidine as described in the actual section experience (Scheme 3). After 8 minutes of reaction in the microwave, the TLC test showed no trace of compound **3**. The obtained products (**4**, **5**) are dark yellow solids melting at about 200 - 202 ^oC (see Experimental).

The structure of **4**, **5** was examined by IR, MS, ^1H NMR, ^{13}C NMR, HSQC and HMBC. The IR spectrum of **4**, **5** has no the absorption band of the aldehyde carbonyl group at 1718 cm^{-1}. The remarkable difference in ^1H NMR spectrum of azomethines **4**, **5** in comparision with spectrum of **3** is the disappearance of a singlet at 10.01 ppm (-CHO group). The number of aromatic protons is not three as in the key substance **3** but there are 5 protons appear, in which two signals of intensity 2H appear, corresponding to two groups of aromatic protons with amine components.

***Scheme 3**. Synthesis of azomethines*



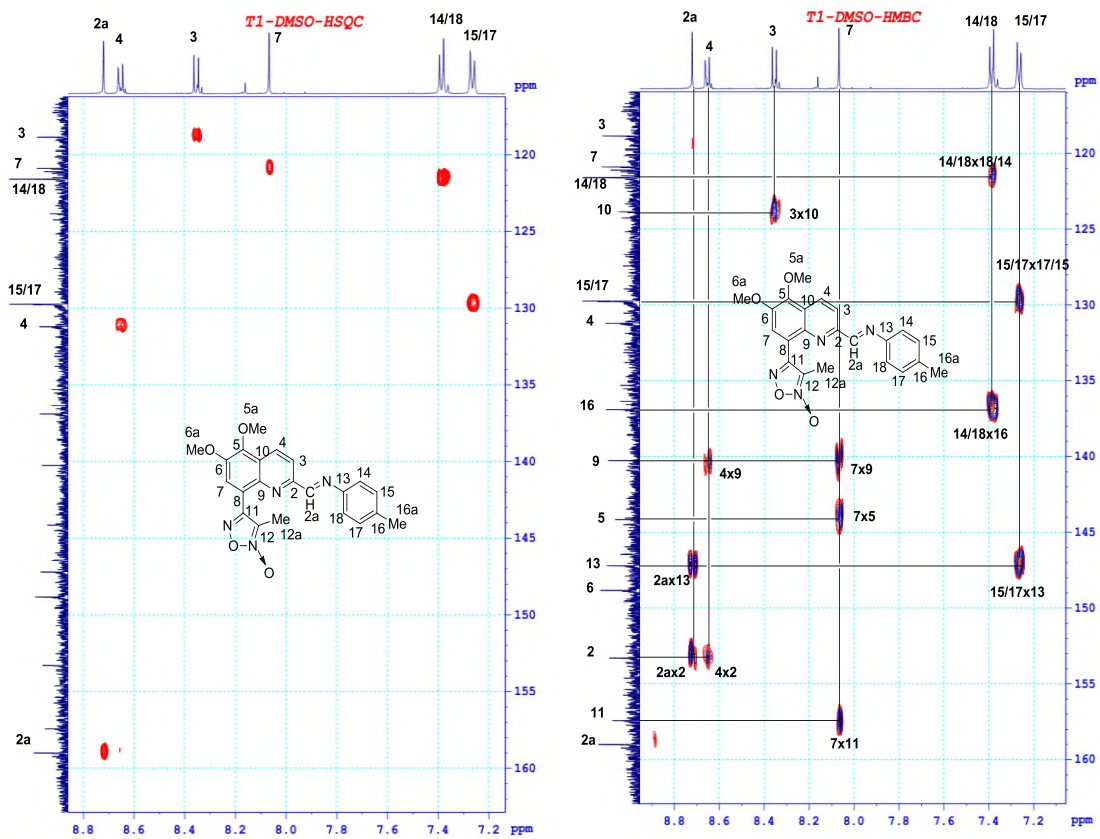
For example, The MS positive mode (+MS) of **5** showed pseudomolecular ion $(M+H)^+$ with relative intensity of 100% at m/z = 405, this is corresponding to formular $C_{22}H_{21}O_4N_4$ (M = 405 au) and consistent with molecular formular of 5 ($C_{22}H_{20}O_4N_4$, M = 404 au). In the ^1H NMR of **5**, two doublets at 8.65 (*J*=9.0 Hz) and 8.36 ppm (*J*=9.0 Hz) are assigned to H4 and H3, one singlet at 8.07 ppm is assigned to H7. In the ^{13}C NMR of **5**, there are 19 signals associated, 2 signals of OCH_3 groups (C5a, C6a at 61.25 and 57.01 ppm), and 2 signals of CH_3 groups (C12a, C16a at 9.44 and 20.61 ppm). At the same time, there is no signal of the C atom of the carbonyl group at δ = 193.3 ppm as in compound **3** [22].

***Table 1.** ^1H NMR signals of compounds 2–5, δ (ppm)*

Compd.	H3 H4	H7 H12a	H6a H5a	H2a	H14 H18	H15 H17	H16a
2	7.50 d; *J* 9 8.42 d; *J* 9	7.93 s 2.06 s	4.01 s 4.01 s	2.61 s	-	-	-

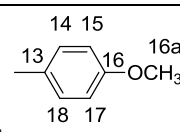
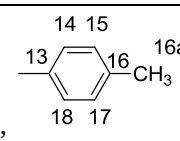
3	8.05 d; *J* 9 8.74 d; *J* 9	8.18 s 2.11 s	4.04 s 4.09 s	10.02 s	-	-	-
4	8.35 d; *J* 9 8.64 d; *J* 8.5	8.05 s 2.12 s	4.05 s 4.06 s	8.73 s	7.52 m 7.52 m	7.01 m 7.01 m	3.80 s
5	8.36 d; *J* 9 8.65 d; *J* 9	8.07 s 2.11 s	4.06 s 4.07 s	8.72 s	7.39 d; *J* 8.5 7.39 d; *J* 8.5	7.27 d; *J*7.0 7.27 d; *J*7.0	2.35 s

Fig.1. *Partial HMBC and HSQC spectrum of* ***5***



Partial HMBC and HSQC spectrum of **5** is shown on Figure 1. Based on the results of HSQC spectrum analysis, combined with HMBC spectrum analysis, combined with HMBC spectrum analysis, we attributed the following: In Fig.1, two cross peaks of methyl protons H12a indicates that signal at 115.10 ppm belongs to C2 and at 157.43 ppm belongs to C11. The cross peaks of two methoxy group (H5a, H6a) show signal of C5 and C6. Two cross peaks of methyl group (H12a) and the cross peak of H7 show signals of C12, C11. Similarly, proton and carbon signals of **5** were assigned. Spectra all ^{1}H NMR and ^{13}C NMR signals of **4**, **5** were assigned as listed in Table 1,2.

Table 2. *^{13}C NMR signals of compounds* ***4, 5*** *, δ (ppm)*

Compd., Ar	2, -	3, -	4, 	5, 
C2, C3	157.90, 122.98	150.88, 117.84	157.47, 118.81	153.30, 118.87
C4, C5	130.43, 144.42	132.20, 143.82	134.11, 153.55	131.21, 144.15
C6, C7	147.13, 120.26	149.82, 121.71	148.75, 120.86	148.84, 120.91
C8, C9	119.79, 140.28	121.90, 139.95	121.04, 142.34	121.11, 140.26
C10, C11	121.61, 157.76	125.23, 157.03	123.77, 158.98	123.25, 157.43
C12, C12a	114.95, 9.37	114.97, 9.32	118.81, 9.47	115.10, 9.44
C5a, C6a	61.15, 57.00	61.29, 57.07	57.02, 55.35	61.25, 57.01
C2a, C16a	24.68 , -	193.26, -	157.32, 61.21	159.0, 20.61
C13, C14	-	-	140.31, 123.37	147.21, 121.60
C15, C16	-	-	115.14, 144.20	129.74, 140.26
C17, C18	-	-	114.45, 123.37	129.74, 121.60

4. Conclusion

(*E*)-5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2 ((4methoxiphenyl)imido)methyliden quinoline (**4**) and (*E*)-5,6-Dimethoxy-8-(3-methylfuroxan-4-yl)-2-((4-methylphenyl)imido) methylidenquinoline (**5**) was synthesized from eugenol in basil essential oil. All proton and carbon signals of obtain compuonds were assigned based on analyzing the spin-spin splitting patterns and on the cross peaks in their HSQC and HMBC spectra.

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