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Studies on novel polycyclic heterocycles: synthesis of new naphthaquinoxaline and naphthazaquinoxaline derivatives from naturally occurring quinones

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A facile synthesis of novel polycyclic heterocycles namely naphthaquinoxaline and naphthazaquinoxaline derivatives is carried out by the reaction of lapachol and β-lapachone, naturally occurring naphthoquinones with *o*-phenylene diamine and 2,3-diaminopyridine. Regioselectivity in the reaction of β-lapachone with 2,3-diaminopyridine is confirmed by single crystal X-ray diffraction of a representative compound 6,7-dihydro-8,8-dimethyl-8*H*-pyrano[3',2':4]-naphtha[2,1-*e*]pyrido[2,3-*b*]pyrazine; $C_{20}H_{17}N_3O$, crystallizes as orthorhombic in the space group Pbca with cell parameters a =9.793(3)Å, b=17.514(6)Å, c=18.334(6)Å, V=3144.5(17) Å^3, Z=8,1.332 mg/m^3, R_1=0.3076, WR_2=0.3595.

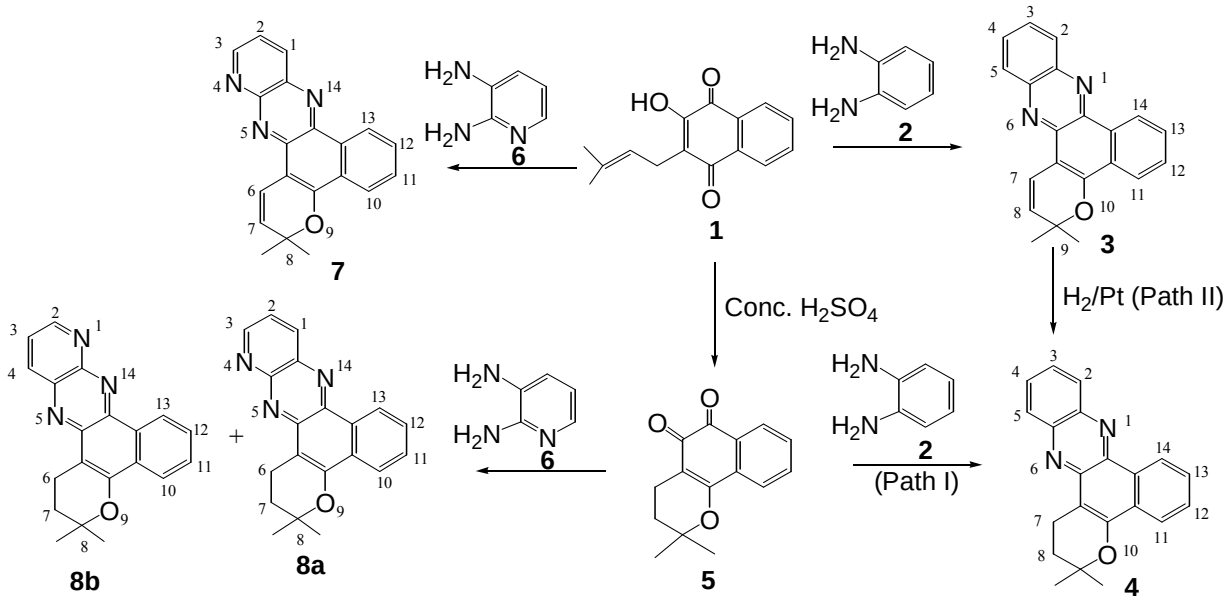
Keywords: Lapachol**,** β-lapachone, 1,2-diamines, regioisomers

Lapachol and its congener β-lapachone occur naturally in certain plant families and their molecular structures endow them with redox properties, being involved in different biological oxidative processes[1]. Lapachol, an isoprenylated hydroxy-1,4-naphthoquinone has been widely exploited for its antiviral, antimicrobial, analgesic, antiinflammatory, antimalarial, cercaricidal and schistosomicidal activities along with potential activity against *Trypnosoma cruzi*, the casual agent of chagas disease[2-8]. The main striking feature of the chemistry of lapachol is the ease with which the prenyl side chain cyclizes into an oxygen function to give an array of pyrano and furano naphthoquinone derivatives. β-Lapachone, an 1,2-naphthoquinone also exhibited a wide variety of activities including anticancer activity[9-16].This activity has been associated with a specific inhibition of topoisomerase enzymes involved in processes such as replication, transcription and mitosis[17-21]. Due to the synergistic effect of β-lapachone with taxol in a great variety of human tumour lines, the combination of these two drugs as a new approach in cancer therapy has been suggested[22]. It has been noticed that in neoplastic cells, this quinone was a potent inhibitor of the repair of DNA damage provoked by carcinogenic substances or deleterious radiations[23-24]. In addition to this, β-lapachone displayed a variety of pharmacological effects, including antibacterial, antifungal and trypnocidal activities[25].

Literature[26-29] has revealed that the structural modifications and the introduction of other heterocyclic moieties modified the pharmacological properties of the parent skeleton. Thus the modification in the quinonoid skeleton has recently been a subject of great interest, not only from the chemical but also from the pharmacological point of view.

Further, in recent years, there has been much interest in the use of microwave assisted techniques[30] in the synthesis of organic compounds including natural bioactive molecules due to its shorter reaction times, higher selectivity, improved yields and operational simplicity in comparison to conventional methods. There is an increasing interest in the use of environmentally benign reagents and conditions and particularly the coupling with dry media conditions which allow the reactions on a preparative scale in open vessels avoiding the risk of high pressures and explosions[31]. Thus more interest has been focused on dry media synthesis under microwave irradiation especially by carrying out experiments with supported reagents on mineral oxide.

In continuation of earlier studies on quinonoid chemistry[32] and microwaves enhanced synthesis[33] the reaction of lapachol and β-lapachone with *o*-phenylene diamine and 2,3-diaminopyridine under different reaction conditions has been investigated and naphthaquinoxaline and naphthazaquinoxaline



Scheme I

derivatives have been synthesized as novel polycyclic heterocycles.

In this report it is shown that the reaction of lapachol **1** with *o*-phenylene diamine **2** gives rise to quinoxaline derivative **3** (**Scheme I**), representing a new entry into the synthesis of heterocyclic compounds from hydroxylated naphthoquinones. The reaction of lapachol **1** with 2,3-diaminopyridine **6** under MW irradiation occurred regiospecifically giving only one product **7** (**Scheme I**)**,** while reaction was unsuccessful under conventional condition. The synthesis of product **4** has been carried out by the two process (i) by the hydrogenation of product **3** (ii) by the reaction of β-lapachone **5** with *o*-phenylene diamine **2** in ethanol at room temperature**.**

Reaction of β-lapachone **5** with 2,3-diamino-pyridine **6** in neutral, acidic and basic media by conventional heating and with solid support under microwaves irradiation avoiding the use of corrosive and polluting mineral acids led to the formation of a pair of regioisomers (azaquinoxaline derivatives, **8a** and **8b**) in 3:1 ratio indicating the regioselectivity in the process. Structure of product **8b** is unambiguously confirmed by single crystal X-ray diffraction study and it is identified as 6,7-dihydro-8,8-dimethyl-8*H*-pyrano[3',2':4]naphtha[2,1-*e*]pyrido[2,3-*b*]pyrazine.

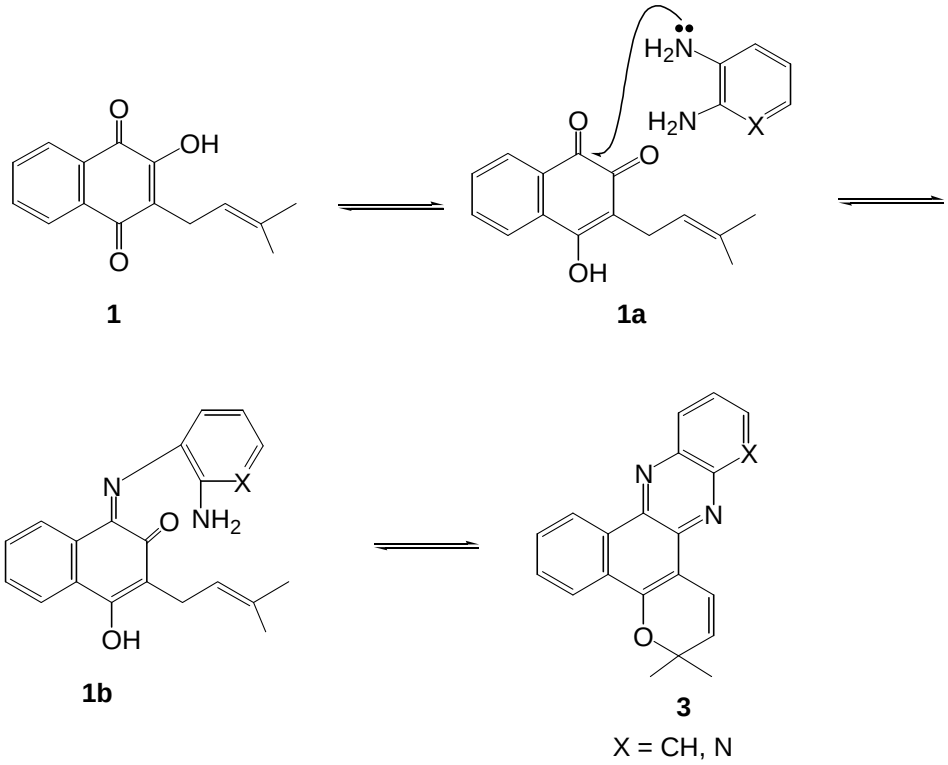
Results and Discussion

Initially the reaction of lapachol **1** with *o*-phenylene diamine **2** in ethanol was carried out at room temperature but it was very slow. To expedite the rate of reaction, it was refluxed and noticed that initially a dark pink coloured intermediate was formed which was found to be unstable and subsequently converted into yellow coloured product. It was identified as 9,9-dimethyl-9*H*-pyrano[3',2':4]naphtha-[1,2-*b*]quinoxaline **3.**

Further to study the role of microwaves, the reaction was studied under different conditions (**Table I**) and it can be concluded that the good yield of product **3** can be obtained under microwaves irradiation using basic alumina as solid support.

The synthesis of novel 8,8-dimethyl-8*H*-pyrano[3',2':4]naphtha[1,2-*e*]pyrido[2,3-b] pyrazine **7** (azaquinoxaline derivative) was carried out by reaction of lapachol **1** with 2,3-diaminopyridine **6**. Conventionally, **1** did not undergo reaction with **6**, however exclusive formation of product **7** in a satisfactory yield was achieved under microwaves irradiation using acidic alumina **Table II**. Theoretical there is possibility of two regioisomers but reaction occur regiospecifically giving only one product which was identified on the observation of earlier workers on the comparatively higher reactivity of C-1 carbonyl group of quinone and 3-amino group of 2,3-diaminopyridine[34-36].

The formation of quinoxaline and azaquinoxaline derivatives from lapachol can be rationalized by the reaction of tautomeric form **Ia** of lapachol with one amino group of *ortho* phenylene diamine leading to the formation of Schiff base **Ib**. The later undergoes cyclocondensation by the reaction of remaining keto



Scheme II

Table I — Comparative study for synthesis of **3**

Exp	Condition	Medium	Time	Yield (%)
1	Δ	Ethanol	18 hr	70
2	MW (300Watts)	Ethanol	6 min	74
3	MW (600Watts)	Neutral alumina	12 min	72
4	MW (600Watts)	Acidic alumina	9 min	68
5	MW (600Watts)	Basic alumina	9 min	80

group with second amino group of 1,2-diamine followed by cyclization of isoprenyl side chain into pyran ring **3** (**Scheme II**). Compound **3** has been converted into **4** by hydrogenation and same quinoxaline derivative **4** can also be obtained from β-lapachone **5** in good yield (**Scheme I**) thus favouring the proposed mechanism (**Scheme II**).

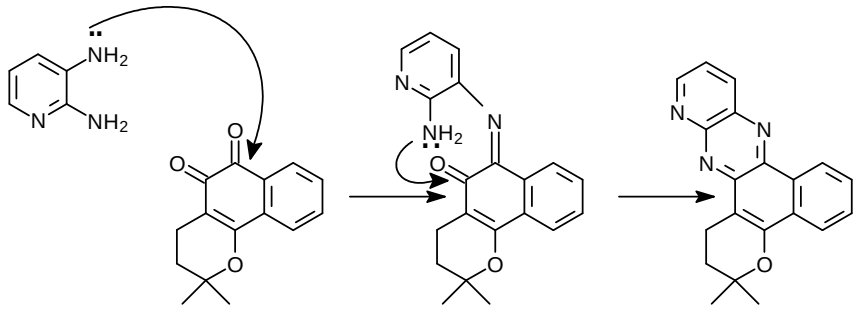
This is the first report for the cyclization of isoprenyl side chain into the pyran ring even in absence of basic catalyst[37].

The facile reaction of β-lapachone **5** with *o*-phenylene diamine **2** occurred efficiently in ethanol even at room temperature and afforded 7,8-dihydro-9,9-dimethyl-9*H*-pyrano[3',2':4]naphtha[1,2-*b*]quinoxaline **4 (Scheme I)**.

The reaction of β-lapachone **5** with and 2,3-diaminopyridine **6** led to the formation a pair of regioisomer azaquinoxaline derivatives (**8a** and **8b**, **Scheme I**). This reaction was carried out conventionally as well as under microwaves irradiation resulting in the formation of **8a** as major product and **8b** as minor product.

The major isomer **8a** is probably arised from the attack by more nucleophilic 3-amino group[34-36] of 2,3-diaminopyridine on the more electrophilic 1-carbonyl function of β-lapachone (**Scheme III**). There are several reports in the literature[28-29] indicating that the carbonyl nearest to the aromatic ring is more reactive than 2-carbonyl group in β-lapachone. Reaction was also tried in acidic and basic media both under conventional heating and microwaves irradiation (**Table III**). From the results obtained, it is obvious that acidic alumina is the most adaptable and simplest catalyst under microwaves for the synthesis of **8b**, since comparatively higher yield is achieved in shorter time. The structure of **8b** was unambiguously established by X-ray studies (**Table IV**).

The spectroscopic data IR, NMR (^{1}H and ^{13}C) and MS of the products are in agreement with the structures given. All the products showed absence of carbonyl group in ^{13}C and their IR spectra.



Scheme III

Table II — Comparative study for synthesis of **7**

Exp	Condition	Medium	Time	Yield (%)
1	Δ	Ethanol	3-4 days	no reaction
2	MW (600Watts)	Acidic alumina	10min	50
3	MW (600Watts)	Neutral alumina	12min	30
4	MW (600Watts)	Basic alumina	10min	46

Table III — Comparative study for synthesis of **8a** and **8b**

Exp	Condition	Medium	Time	Yield (%)	
				8a	**8b**
1	Δ	Ethanol	72hr	30	10
2	Δ	Ethanol + GAA	24hr	36	13
3	Δ	Ethanol + piperidine	24hr	29	8
4	MW(300Watts)	Ethanol	40 min	41	20
5	MW(450Watts)	Acidic alumina	4 min	47	30
6	MW(450Watts)	Basic alumina	5 min	42	22

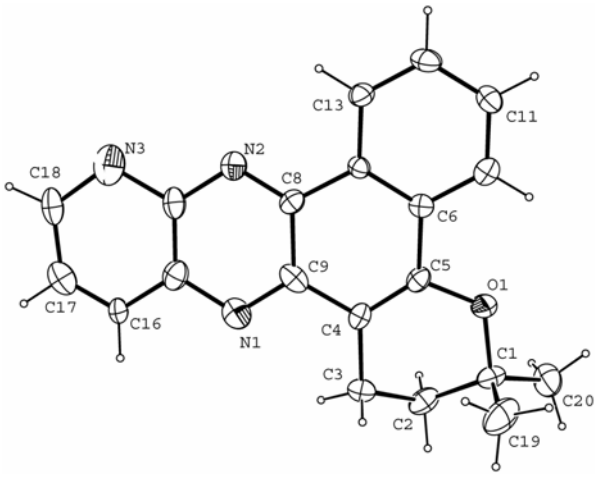


Figure 1 — ORTEP Plot of the asymmetric unit of $C_{20}H_{17}N_3O$

Molecular structure of 6,7-dihydro-8,8-dimethyl-8*H*-pyrano[3',2':4]naphtha(2,1-e)pyrido-[2,3-*b*]pyrazine: 8b

Compound **8b,** which crystallizes in the space group Pbca, is displayed in the ORTEP diagram (**Figure1**). The values of bond lengths 1.484 (8) Å for C(8)-C(9), 1.399 (9) Å for C(14)-C(15), 1.316 (7) Å for N(1)-C(9), 1.385 (8) Å for N(1)-C(15), 1.300 (7) Å for N(2)-C(8) and 1.368 (7) Å for N(2)-C(14) were consistent with the aromatization of the ring, confirming the formation of **8b**.

Experimental Section

Melting points were determined in soft glass capillaries in an electrothermal melting point apparatus and are uncorrected. Qualitative and quantitative thin layer chromatography were conducted on TLC aluminium sheets kieselgel $60F_{254}$ [E. Merck]. ^1H NMR and ^{13}C NMR spectra were recorded on JEOL AL 300 MHz FT NMR instrument using $CDCl_3$ as solvent. Mass spectra (FAB MS) were generated on a JEOL SX-102 spectrometer. Infrared spectra were recorded on FT IR 8400S spectrometer. All compounds were homogeneous on TLC in various solvent systems. Microwave assisted reactions were carried out in a multimode MW oven (Panasonic-NN-781JF) using ethanol as solvent or using different solid supports such as neutral alumina, acidic alumina or basic alumina.

(I) Investigation of the reaction of lapachol 1 with *o*-phenylene diamine 2: (Synthesis of 3)

The *o*-phenylene diamine (54 mg, 0.50 m mole) was added to the solution of lapachol (121 mg, 0.50 m mole) in ethanol (20 mL) and mixture was stirred thoroughly. The colour of reaction-mixture immediately changed from orange to red. Reaction-mixture was refluxed for 18 hr. The progress of reaction was monitored on TLC plate which showed the formation of dark pink coloured product which was found to be unstable and converted into yellow coloured product; R_f 0.50 (petroleum ether: benzene) with the passage of time. Resulting reaction-mixture was purified by preparative TLC using petroleum ether- benzene (3:1) to give **3** as yellow needles.

To check the role of solvent and mode of reaction activation the above reaction was also carried out under microwaves irradiation using either ethanol as solvent or on solid support (acidic or basic alumina). In all cases, similar product was obtained with high yield. The identity of products obtained under different conditions was checked by TLC, mixed m.p. and spectral studies.

9,9-dimethyl-9*H*-pyrano[3',2':4]naphtha[1,2-*b*]-quinoxaline 3

Yellow needles, m.p.120-23°; (Found: C, 80.53; N, 8.80; $C_{21}H_{16}N_2O$, requires C, 80.77; N, 8.97%); IR (KBr, cm^{-1}); 2962, 1562-1500 (C=N), 1261 (C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si); 1.54 (6H, s, 2 Me), 5.74 (1H, d, *J* =10.08 Hz,=CH), 7.54 (1H, d, *J* =10.08 Hz, =CH), 7.75 (3H, m, 3 × Ar-H), 8.18 (2H, m, 2 × Ar-H), 8.27 (2H, m, 2 × Ar-H), 9.31 (1H, m, 1 × Ar-H); δ_C (75.45 MHz; $CDCl_3$; Me_4Si); 29.3 (C_9-CH_3), 29.3 (C_9-CH_3), 78.36 (C_9), 115-130 (aromatic C), 140.52 (C=N of C_{14b}), 141.52 (C=N of C_{6a}), 142.60 (C_{10a}). FAB MS (*m*/*z*): $[M+H]^+$ 313 (100) [$C_{21}H_{16}N_2O$], 297 $[M-Me]^+$(40).

(II) Investigation of the reaction of lapachol 1 with 2,3-diaminopyridine 6: (Synthesis of 7)

The reaction of lapachol **1** with 2,3-diaminopyridine **6** was studied under different conditions (conventional heating and microwaves irradiation). A equimolar (1 m mole) mixture of **1** and **6** was refluxed for 3-4 days in ethanol. TLC indicated the unchanged reactants and no product formation.

To make this reaction successful it was carried out under microwaves irradiation. An equimolar amount of lapachol (242 mg, 1 m mole) and 2,3-diaminopyridine (109 mg, 1m mole) was adsorbed on solid support (such as neutral, acidic or basic alumina) [20% by weight of the reactants] via a solution of ethanol. The dry free flowing powder was placed into a pyrex-glass opened vessel and irradiated in the microwave oven at 600 watt. for 10 min. Progress of reaction was monitored by TLC studies which revealed the formation of dark pink intermediate converted into purple coloured product, with some other minor products. Resulting reaction-mixture was chromatographed over neutral alumina using benzene. Further this fraction was purified by prep. TLC using benzene-ethylacetate (9:1, R_f 0.64) to give **7** as purple crystals.

Table IV — Crystal data and structure refinement for $C_{20}H_{17}N_3O$ (8b)

Empirical formula	$C_{20}H_{17}N_3O$
Formula weight	315.37
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P b c a
Unit cell dimensions	a = 9.793(3) Å alpha = 90 deg. b = 17.514(6) Å beta = 90 deg. c = 18.334(6) Å gamma = 90 deg.
Volume	3144.5(17) $Å^3$
Z, Calculated density	8,1.332 Mg/m^3
Absorption coefficient	0.084 mm^{-1}
F(000)	1328
Crystal size	0.22 × 0.17 × 0.11 mm
Theta range for data collection	2.22 to 28.31 deg.
Limiting indices	-12<=h<=13, -16<=k<=23, -21<=l<=24
Reflections collected / unique	19604 / 3900 [R(int) = 0.1871]
Completeness to theta = 28.31	99.7 %
Absorption correction	Empirical
Max. and min. transmission	0.9908 and 0.9817
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3900 / 0 / 249
Goodness-of-fit on F^2	1.059
Final R indices [I>2sigma(I)]	R1 = 0.1392, wR2 = 0.2752
R indices (all data)	R1 = 0.3076, wR2 = 0.3595
Extinction coefficient	n/a
Largest diff. peak and hole	0.493 and -0.291 e.$Å^{-3}$

8,8-Dimethyl-8*H*-pyrano[3',2':4]naphtha[1,2-e]pyrido[2,3-b]pyrazine 7

Purple crystals; m.p. 110-12°; (Found: C, 76.20; N, 13.1. $C_{20}H_{15}N_3O$ requires C, 76.67; N, 13.4%); δ_H(300 MHz, $CDCl_3$, Me_4Si);1.37 (6H, s, 2 × CH_3), 5.34 (1H, d, *J* = 10 Hz, =CH–), 6.87 (1H, d, *J* = 10 Hz, =CH–), 7.24 (1H, m, 1 × Ar-H), 7.75 (2H, m, 2 × Ar-H), 8.13 (1H, m, 1 × Ar-H), 8.37 (1H, m, 1 × Ar-H), 8.47 (1H, m, 1 × Ar-H) and 8.84 (1H, m, 1 × Ar–H); ESI MS (*m*/*z*) 314 $(M+H)^+$ 289, 272, 263.

(III) Synthesis of 7,8-dihydro-9,9-dimethyl-9*H*-pyrano[3',2':4]naphtha[1,2-*b*] quinoxaline 4: It was synthesized by two routes:

(i) By the reaction of β-lapachone 5 with *o*-phenylene diamine 2: (Path I). The reaction of β-lapachone **5** (242 mg, 1 m mole) with *o*-phenylene

diamine **2** (108 mg, 1 m mole) in ethanol at room temperature led to the formation of a single product with minor impurities. This product was subjected to preparative TLC using benzene (R_f 0.76) to give bright yellow needles, (Yield 90%).

(ii) By hydrogenation of 9,9-dimethyl-9*H*-pyrano[3',2':4]naphtha[1,2-*b*]-quinoxaline 3: (Path II) The conversion of **3** into **4** was carried out over palladium on charcoal (10%) using ethyl acetate as solvent. The reaction was run at room temperature and 50 psi under hydrogen pressure. The product was purified by silica gel column chromatography, eluting with petroleum ether-benzene (3:1). The product of this reaction had physical and spectral data identical to **4**.

7,8-Dihydro-9,9-dimethyl-9*H*-pyrano[3',2':4]naphtha[1,2-b]quinoxaline 4 Bright yellow needles, m.p. 113-15°; (Found: C, 80.51; N, 9.01. $C_{21}H_{18}N_2O$ requires C, 80.25; N, 8.93%); δ_H(300 MHz, $CDCl_3$, Me_4Si); 1.53 (6H, s, 2 × CH_3), 2.07 (2H, t, J = 7.0 Hz, –CH_2–), 3.35 (2H, t, J = 7.0 Hz, –CH_2–), 7.80 (4H, m, 4 × Ar-H), 8.30 (3H, m, 3 × Ar-H), 9.33 (1H, m, 1 × Ar-H); δ_C (75.45 MHz, $CDCl_3$, Me_4Si); 18.33 (CH_2), 26.86 (C_9–CH_3), 32.52 (CH_2), 76.03 (C_9), 109-130 (aromatic C), 140.79(–C=N of C_{14b}), 142.59 (–C=N of (C_{6a}), 144.55 (C_{10a}). MS (*m*/*z*, rel. int.%) 314 $[M]^+$ ($C_{21}H_{18}N_2O$) (75), 299 $[M–Me]^+$ (15), 285 $[299–CH_2]^+$ (10), 271 $(285–CH_2]^+$, 229 (20) etc.

(IV) Investigation of the reaction of β-lapachone 5 with 2,3-diaminopyridine 6: Synthesis of 8a & 8b.

A solution of β-lapachone (242 mg, 1 m mole), 2,3-diaminopyridine (109 mg, 1m mole) in ethanol (30 mL) containing few drops of gl. acetic acid was refluxed for 24 hr. The progress of reaction was monitored on TLC plate which indicated the formation of two products (**8a** and **8b**) (R_f 0.29 and 0.20 in benzene-ethyl acetate 9:1). These products were separated by preparative TLC [benzene: ethyl acetate (9:1)] in the ratio of 3:1 respectively.

The reaction has also been performed under microwaves using ethanol or on solid support (acidic or basic alumina). Adsorption of the reactants on solid support was carried out as explained above. In all cases, similar products were obtained. However in ethanol it took 40 minutes where as by the use of acidic alumina reaction occurred in 4 minutes at 450W. Under MW irradiation the reaction showed the formation of the isomers in the ratio of 3:2 indicating enhance yield of isomer **8b**.

To check the possibility of conversion of **8a** to **8b** the reaction-mixture was further irradiated for a longer time of 10 min but it is converted into complex mixture of products, However which could not be separated.

6,7-Dihydro-8,8-dimethyl-8*H*-pyrano[3',2':4]naphtha[1,2-*e*]pyrido[2,3-b]pyrazine 8a. Bright yellow needles, m.p. 210-12°; (Found: C, 75.95; N, 12.99. $C_{20}H_{17}N_3O$ requires C, 76.19; N, 13.33%); IR (KBr cm^{-1}): 2900-2960, 1625, 1600, 1540 (C=N); δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.54 (6H, s, 2Me), 2.06 (2H, t, J=6.57 Hz,-CH_2-), 3.31 (2H, t, J=6.57 Hz, -CH_2-), 7.73 (1H, dd, J=8.43, 4.02 Hz, 1 × Ar-H), 7.80 (2H, m, 2 × Ar-H), 8.32 (1H, m, 1 × Ar-H), 8.57 (1H, dd, J=8.43, 1.83 Hz, 1 × Ar-H), 9.21 (1H, dd, J=1.83, 4.02 Hz, 1 × Ar-H) and 9.49 (1H, m, 1 ×Ar-H); δ_C (75.45 MHz; $CDCl_3$; DEPT, Me_4Si): 26.7 (C-CH_3), 26.7 (C-CH_3), 18.2 (CH_2), 32.30 (CH_2), 76.6 (C_8), 109.23 (C_{5b}), 124.59-128.09 (aromatic C), 129.71 (C_{9b}), 130.47 (aromatic C), 137.72 (aromatic C), 147.5 (C_{9a}), 142.25 (C_{14a}), 145.59 (C_{5a}),152.65 (aromatic C). FAB MS (*m*/*z*): $[M+H]^+$ 316 (100), 300 $[M-Me]^+$, 260, 120, 107.

6,7-Dihydro-8,8-dimethyl-8*H*-pyrano[3',2':4]naphtha[2,1-*e*]pyrido[2,3-*b*]pyrazine 8b. Bright orange needles, m.p. 202-05°; (Found: C, 76.01; N, 13.03. $C_{20}H_{17}N_3O$ requires C, 76.19; N, 13.33%); IR (KBr cm^{-1}): 2940-2975, 1600, 1625, 1550 (C=N), 1400; δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.54 (6H, s, 2 Me), 2.09 (2H, t, J=6.60 Hz,-CH_2-), 3.41 (2H, t, J=6.60 Hz, -CH_2-), 7.69 (1H, dd, J=8.40, 4.20 Hz, 1 × Ar-H), 7.79 (2H, m, 2 × Ar-H), 8.33 (1H, m, 1 × Ar-H), 8.64 (1H, dd, J=8.43, 1.83 Hz, 1 × Ar-H), 9.22 (1H, dd, J=4.20, 2.01 Hz, 1 × Ar-H) and 9.29 (1H, m, 1 × Ar-H); δ_C (75.45 MHz; $CDCl_3$; DEPT, Me_4Si): 26.8 (C-CH_3), 26.7 (C-CH_3), 18.2 (CH_2), 32.32 (CH_2), 76.6 (C_8), 109.23 (C_{5b}), 122.47-148 (aromatic C), 153 (C_2), 153.98 (C_{14a}); FAB MS (*m*/*z*): $[M+H]^+$ 316 (100), 300 $[M-Me]^+$, 260, 120, 107.

Conclusion

A facile method has been developed for quantitative synthesis of novel polycyclic ring system with in a few minutes involving the formation of pyrido-pyrazine ring by the reaction of lapachol and β-lapachone with 2,3-diaminopyridine separately.

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