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Extrusion Reactions - VIII[1]

A Facile Synthesis of 4-Alkyl Quinazolines and 1-Methyl-2-Aryl-4-Quinolones

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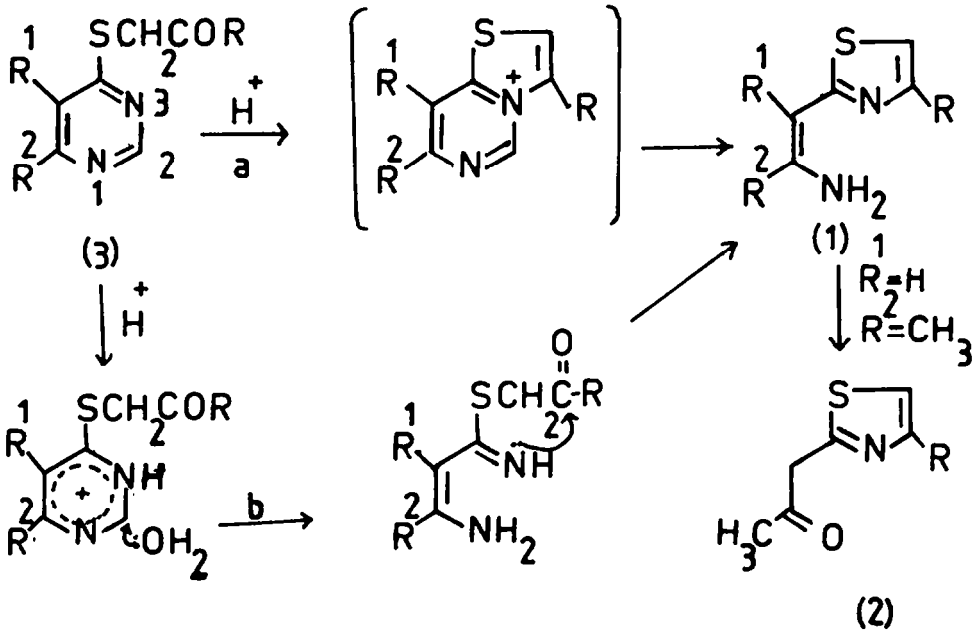
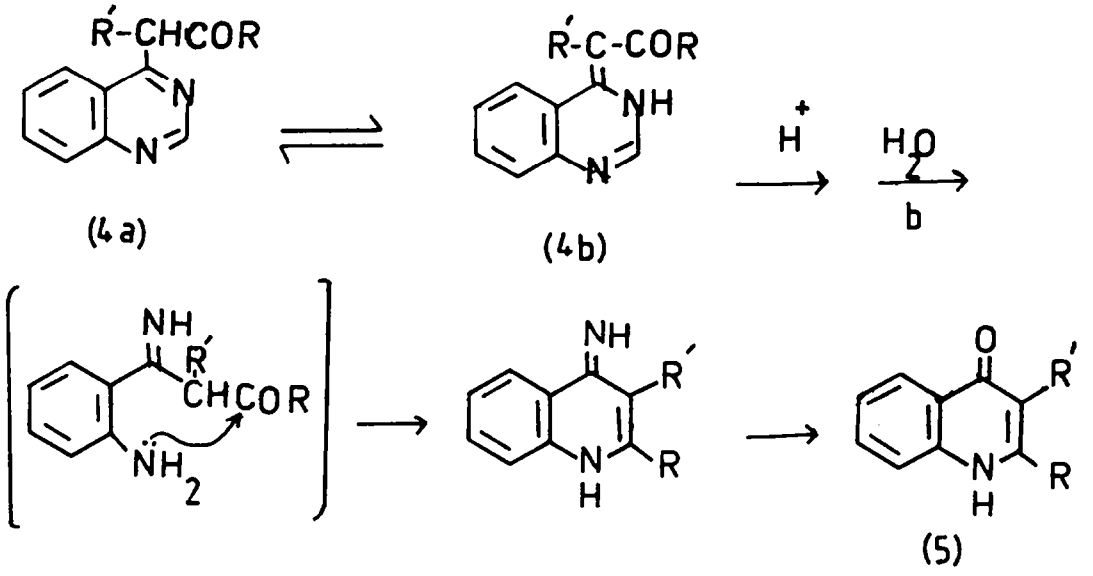
Abstract - With aq. sodium hydroxide, ω-(4(3H)-quinazolinylidene) acetophenones 4b (R'= H, R=Ar) or ω-(4-quinazolinyl) acetophenones 4a (R'= Me, Et; R = Ar) provide 4-alkylquinazolines 6 but 1-methyl-4-phenacyl or phenacylidene-3H-quinazolinium derivatives 10a or 10b give N-methyl-4-quinolone derivatives 11.

The sp^3 hybridised carbon atom placed between two heteroatoms of dihydro or perhydro derivatives of 1,3-heterocycles undergoes an easy extrusion[2] and the isolation of the extruded species as such or in a modified form provides a novel approach for the synthesis of a variety of organic compounds.[3-6] But the isolation of the residual skeleton of the precursor as such or in a modified form, which could also provide an entry into various categories of organic compounds,[7,8] has been much less exploited. Using the latter approach, we have reported a facile synthesis of 2-(o-aminophenyl) thiazoles 1 (R^1-R^2= $-C_4H_4-$)[9] and 2-acetonyl-thiazoles 2[1] by the acid catalysed hydrolytic C(2) extrusion cum cyclodehydration of ω-(4-quinazolinyl thio) acetophenones 3 (R^1-R^2= $-C_4H_4-$) and ω-(6-methyl-4-pyrimidinyl thio) acetophenones 3 (R^1=H, R^2=CH_3) respectively as depicted in scheme 1 through either mode a or b.

We envisaged that in the readily available ω-(4(3H)-quinazolinylidene) acetophenones 4b (R'=H, R=Ar) or ω-(4-quinazolinyl) acetophenones[10], 4a (R=Ar, R'=alkyl)



SCHEME-1



SCHEME-2

the appendage at position 4 possesses the electrophile at such a site that through the sequence depicted in scheme 1 only an unfavoured four membered ring could be formed and hence an alternate reaction involving N(1) and electrophilic site as depicted in scheme 2 could take place. Such a sequence of reactions would provide a facile synthesis of 4-quinolone derivatives 5.

4'-Methyl-ω-(4(3H)quinazolinylidene)acetophenone 4b (R'=H, R=$C_6H_4CH_3$(p)) on refluxing in methanol containing conc. HCl gave p-toluic acid and 4-methylquinazoline 6 (R'=H)[11]. The reaction of 4b (R'=H, R=$C_6H_4CH_3$(p)) with (i) freshly prepared PPA followed by treatment with water, (ii) aq. sodium hydroxide in ethanol (iii) 50% aq. sodium hydroxide under phase transfer conditions (PTC) using triethyl benzylammonium chloride (TEBA) as catalyst and benzene as solvent, also gave same products. Likewise, ω-(4(3H)-quinazolinylidene)acetophenone 4b (R'=H, R=Ph) also gave 4-methylquinazoline along with benzoic acid. Thus unlike ω-(4-quinazolinylthio)acetophenones 3 (R^1-R^2= $-C_4H_4-$, R=Ar), the C(2) extrusion of quinazoline ring of 4b with aq. acid has not been accomplished but hydrolytic cleavage at the carbonyl group in the side chain has taken place

Since 4a and 4b have been easily procured[10] by sulphur extrusion of ω-(4-quinazolinylthio)acetophenones 3 (R^1-R^2= $-C_4H_4-$, R=Ar), the hydrolytic cleavage, at the carbonyl group in appropriate derivatives of 4a or 4b could be used for procuring 4-alkylquinazoline derivatives 6. Thus it was found that α-(4-quinazolinyl)propiophenone 4a (R'=CH_3, R=Ph) and α-(4-quinazolinyl)cyclohexanone 7 - cyclic ketone, gave 4-ethylquinazoline 6 (R'=C_2H_5) and 6-(4'-quinazolinyl)hexanoic acid 8 respectively.

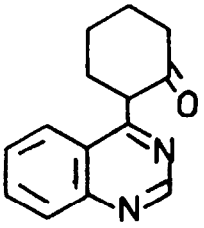
In order to procure α-(4-quinazolinyl)butyrophenone 4a (R'=Et, R=Ph), needed for the preparation of 4-propylquinazoline, α-(4-quinazolinylthio)butyrophenone 9 obtained from quinazoline-4-thiolate and α-bromobutyrophenone, was subjected to sulphur extrusion with DMF/NaOEt. The product (≈70%), m/z 172, δ_H 1.10 (3H, t, J=7Hz, CH_3), 1.95 (2H, sextet, J=7Hz, CH_2), 3.20 (2H, t, J=7Hz, CH_2), 7.40 - 8.30 (4H, m, ArH), 9.40 (1H, s, quinazoline C(2)H), was found to be 4-propylquinazoline 6 (R'=Et). Whereas α-(4-quinazolinylthio)butyrophenone 9 gave 6 (R'=Et) in one operation involving simultaneous sulphur extrusion and cleavage at carbonyl

group, 3 (R^1-R^2= $-C_4H_4-$, R=Ph) even on keeping for a prolonged period in NaOEt/DMF provided only ω-(4-(3H)-quinazolinylidene)acetophenone 4b (R'=H, R=Ph). Thus, in general, derivatives of 4a or 4b and 7 obtained from α-(4-quinazolinylthio)ketones 3 underwent base catalysed cleavage at carbonyl group to provide 4-alkylquinazoline derivatives 6, which were earlier prepared through varied synthetic operations involving relatively difficultly available starting materials.[11-16] This methodology represents a general approach for procuring 4-alkylquinazoline derivatives 6 from easily available derivatives of 4a/4b and 7.

The above results of the reactions of ketones 4a/4b and 7 with aq. base/acid pointed to the fact that in case of reactions of ω-(4-quinazolinylthio)acetophenones 3 (R^1-R^2= $-C_4H_4-$) with aq. acids, a cation i.e. thiazolo [3,2-c] quinazolinium or 4-phenacylthioquinazolinium chloride or perchlorate was formed first and was then cleaved at C(2). In the case of latter cation, the driving force was probably provided by the ease of subsequent five membered thiazole ring formation. However, in an α-(4-quinazolinyl)ketone 4a/4b and 7, instead of cation formation and C(2) extrusion, an alternate hydrolytic cleavage at the carbonyl group in the side chain took place. Consequently, we argued that in case 4a or 4b were first converted to methiodides 10b or 10a stable cations, these might undergo hydrolytic C(2) extrusion cum alternate cyclisation (scheme-2) to provide N-methyl-4-quinolone derivatives 11 (scheme-3).

ω-(4-(3H)-Quinazolinylidene)acetophenone 4b (R'=H, R=Ph; ν_{max} 1600 (>C=O) cm^{-1}), 4'-methyl-ω-(4-(3H)-quinazolinylidene)acetophenone 4b (R'=H, R=$C_6H_4CH_3$(p); ν_{max} 1600 (>C=O) cm^{-1}), 4'-chloro-ω-(4-(3H)-quinazolinylidene)acetophenone 4b (R'=H, R=C_6H_4Cl (p); ν_{max} 1620 (>C=O)) and α-(4-quinazolinyl)propiophenone 4a (R'=CH_3, R=Ph); ν_{max} 1680 (>C=O) cm^{-1}) with methyl iodide gave 1-methyl-4-(phenacylidene)-3H-quinazolinium iodide 10b (R'=H, R=Ph; ν_{max} 1610 (>C=O) cm^{-1}), 1-methyl-4-(4'-methylphenacylidene)-3H-quinazolinium iodide 10b (R'=H, R=$C_6H_4CH_3$(p); ν_{max} 1600 (>C=O) cm^{-1}), 1-methyl-4-(4'-chlorophenacylidene)-3H-quinazolinium iodide 10b (R'=H, R=C_6H_4Cl (p); ν_{max} 1620 (>C=O) cm^{-1}) and 1-methyl-4-(α-methylphenacyl) quinazolinium iodide 10a (R'=CH_3, R=Ph; ν_{max} 1670 (>C=O) cm^{-1}) respectively.[10]

The compound 10b (R'=H, R=$C_6H_4CH_3$) on refluxing in methanol containing aq. HCl, however, underwent decomposition to form a multitude of products. Evidently, with HCl, 4-quinolone derivative 11 (R'=H, R=C_6H_4-CH_3(p)), if formed being an enaminone underwent decomposition. Therefore, the reaction of compound 10b (R'=H, R=C_6H_4-CH_3(p)) was performed with aq. sodium hydroxide in ethanol solution. The product (≈70%), m.p. 170-75°, on the basis of m/z 249, δ_H 2.40 (3H, s, CH_3), 3.63 (3H, s, NCH_3), 6.36 (1H, s, =C-H), 7.16-8.63 (8H, m, ArH), ν_{max} 1620 (conjugated >C=O) cm^{-1}, λ_{max} 250 (2.15×10^4) and 330 (1.36×10^4) nm, characteristic of quinolone derivatives,[17] was assigned the structure, 2-p-tolyl-1-methyl-4-quinolone 11 (R'=H, R=C_6H_4-CH_3(p)). Likewise 10b (R'=H, R=Ph, or R'H, R=C_6H_4-Cl (p)) and 10a (R'=CH_3, R=Ph) gave corresponding 11 in good yields.



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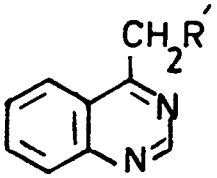

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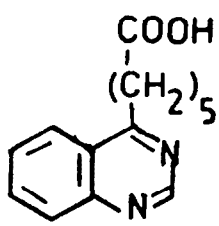

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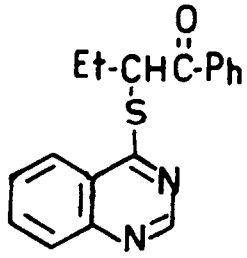

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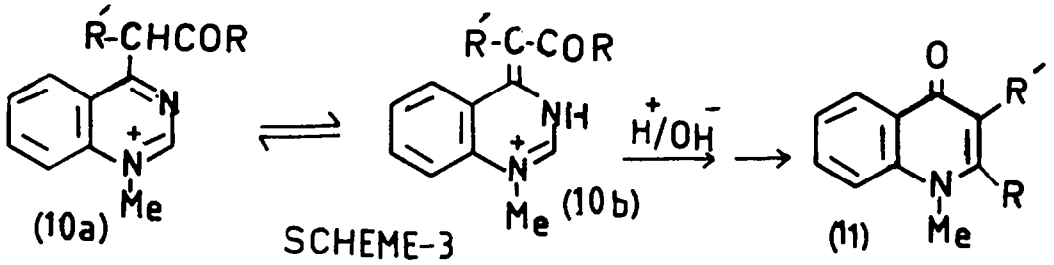

SCHEME-3

2-Phenyl-1-methyl-4-quinolone 11 (R'=H, R=Ph) isolated from various plant sources,[17-19] has been synthesised by different methods.[20,21] The above methodology for procuring N-methyl-2-aryl-4-quinolones 11 represents a general approach for the synthesis of such naturally occurring compounds and their analogs from easily available starting materials.

Experimental

For general experimental details see ref. 1

Reaction of ω-(4(3H)-quinazolinylidene)acetophenone 4b (R'=H, R=Ph) with :

A. 50% NaOH :

A solution of 4b (R'=H, R=Ph) (1.0g) in ethanol (20 ml) containing 50% aq. NaOH solution (15 ml) was refluxed on a water bath. After the completion of the reaction (tlc), ethanol was removed and the residue after neutralisation with acetic acid was diluted with water. It was extracted with chloroform (3x50 ml), extract was washed with water and dried (Na_2SO_4). The solvent was distilled off and the residue was chromatographed over silica gel using benzene or benzene: ethylacetate (8:2) as eluent to give 4-methyl quinazoline 6 (R'=H) (57%) as an oil,[11] δ_H ($CDCl_3$) 2.70 (3H, s, CH_3), 7.30-8.00 (4H, m, ArH) and 9.00 (1H, s, quinazoline C(2)H); m/z 144, 129 (144-CH_3), 102 (129-HCN) and 75 (102-HCN). The mother liquor after the removal of water followed by extraction with benzene gave benzoic acid (~30%).

B. Conc. HCl :

A solution of 4b (R'=H, R=Ph) (1.0g) in methanol (20 ml) containing conc. HCl (20 ml) was refluxed on a water bath till the completion of the reaction (tlc). After extractive work-up, 4-methylquinazoline 6 (R'=H)[11] (30%) and benzoic acid (25%), were isolated. 4'-Methyl-ω-(4(3H)-quinazolinylidene) acetophenone 4b (R'=H, R=$C_6H_4CH_3$(p)) with aq. NaOH or HCl gave 4-methylquinazoline 6(R'=H), 57% (30%)[22], and p-toluic acid which were identical with their authentic samples.

Following quinazoline derivatives were likewise obtained.

4-Ethylquinazoline 6 (R'=CH_3) α-(4-Quinazolinyl)propiophenone 4a (R'=CH_3, R=Ph) with aq. NaOH or HCl gave 6 (R'=CH_3)[15]; 70% (80%)[22], an oil; δ_H($CDCl_3$) 1.50 (3H, t, J=7Hz, CH_3), 3.35 (2H, q, J=7Hz, CH_2) 7.40-8.40 (4H, m, ArH) and 9.35 (1H, s, quinazoline C(2)H); m/z 158, 143 (158-CH_3), 129 (158-CH_2CH_3), 102 (129-HCN) and 75 (102-HCN) and was found to be identical with its authentic sample.

6-(4'-Quinazolinyl)hexanoic acid 8 α-(4-Quinazolinyl)cyclohexanone 7 with conc. HCl gave 8 (40%); m.p. 93° (lit. m.p. 101-102°)[16]; ν_{max} ($CHCl_3$) 1695 (>C=O) cm^{-1}; δ_H ($CDCl_3$) 1.60 - 2.10 (6H, m, 3xCH_2), 2.45 (2H, t, J=6Hz, CH_2), 3.35 (2H, t, J=6Hz, CH_2), 7.25-8.30 (4H, m, ArH) and 9.30 (1H, s, quinazoline C(2)H); m/z 244.

α-(4-Quinazolinylthio)butyrophenone 9 α-Bromobutyrophenone (4.5g, 0.02 mol) was added to a solution of quinazoline-4(3H)-thione (3.24g, 0.02 mol) in

anhydrous DMF (40 ml) containing sodium ethoxide (1.36g, 0.02 mol). The reaction mixture was stirred for 8 hrs. It was treated with water and was extracted with chloroform (3x50 ml). The extract was washed with 2% aq. NaOH solution, water and dried (Na_2SO_4). The solvent was distilled off and the residue consisting of one major component was chromatographed over silica gel using benzene as eluent to give 9; 70% an oil; ν_{max} ($CHCl_3$) 1670 (>C=O) cm^{-1}; δ_H ($CDCl_3$) 1.20 (3H,t,J=7Hz,CH_3), 1.80 (2H,m,CH_2), 6.16 (1H,t, J=7Hz, CH), 7.30-8.36 (9H,m,ArH) and 9.10 (1H,s, quinazoline C(2) H); m/z 308.

4-Propylquinazoline 6 (R'=Et) A solution of 9 (3.08g, 0.01 mol) in anhydrous DMF (40 ml) containing sodium ethoxide (2.72g, 0.04 mol) was stirred for about 15 hrs. It was diluted with water. After extractive work-up, the residue consisting of one major component was purified by chromatography using a mixture of benzene: ethyl acetate (8:2) as eluent to give 6 (R'=Et)[11]; 70%, an oil; δ_H($CDCl_3$) 1.10 (3H,t, J=7Hz, CH_3), 1.95 (2H,sextet, J=7Hz, CH_2), 3.20 (2H,t, J=7Hz, CH_2), 7.40-8.30 (4H,m,ArH) and 9.40 (1H,s, quinazoline C(2)H); m/z 172, 157 (172-CH_3), 143 (172-CH_2CH_3).

1-Methyl-4-(4'-methylphenacylidene)-3H-quinazolinium iodide 10b(R'=H, R=C_6H_4-CH_3(p)

A mixture of 4b (R'=H, R=$C_6H_4CH_3$(p) and methyl iodide, which formed a clear solution, was kept in a stoppered flask at ambient temperature for two days. The product, 10b (R'=H, R=C_6H_4-CH_3(p), separated was washed with anhydrous ether, dried, and was pure enough for further use. Yield 85%; m.p. 240-43°; ν_{max} (KBr, 1600 (>C=O) cm^{-1}; δ_H (TFA) 2.31 (3H,s,CH_3), 3.98 (3H,s, NCH_3), 7.14-8.56 (9H,m,ArH & =C-H) and 9.30 (1H,s, quinazoline C(2)H). (Found : C, 53.46; H, 4.21; N, 6.93 $C_{18}H_{17}N_2OI$ required C, 53.87; H, 4.41; N, 7.01%).

The following compounds were obtained similarly by using appropriate derivatives of 4a or 4b.

1-Methyl-4-(phenacylidene)-3H-quinazolinium iodide 10b (R'=H, R=Ph) Yield 70%; m.p. 215-17°; ν_{max} (KBr) 1610 (>C=O) cm^{-1} δ_H (TFA) 4.00 (3H,s, NCH_3), 7.36-8.50 (10H,m, ArH & =C-H), 9.10 (1H,s, quinazoline C(2)H) (Found: C, 52.10; H, 3.61; N, 6.99, $C_{17}H_{15}N_2OI$ requires C, 52.30; H, 3.85; N, 7.18%).

1-Methyl-4-(α-methylphenacyl)quinazolinium iodide 10a (R'=CH_3, R=Ph) Yield 65%; m.p. 71-73° (highly hygroscopic); ν_{max} (KBr) 1670 (>C=O) cm^{-1} δ_H (TFA) 2.21 (3H,s, CH_3) 4.02 (3H,s, NCH_3), 4.90 (1H,q, CH), 7.28-8.90 (9H,m,ArH) and 9.20 (1H,s, quinazoline C(2)H). As the compound is hygroscopic analytical data could not be taken.

1-Methyl-4-(4'-chlorophenacylidene)-3H-quinazolinium iodide 10b(R'=H, R=C_6H_4-Cl(p)

Yield 70%, m.p. 228-30°; ν_{max} (KBr) 1620 (>C=O) cm^{-1}; δ_H (TFA) 4.00 (3H,s,NCH_3), 7.36-8.42 (9H,m,ArH & =C-H) and 9.29 (1H,s, quinazoline C(2)H). (Found: C, 47.94; H, 3.14; N, 6.33, $C_{17}H_{14}N_2OCl$ I requires C, 48.11; H, 3.30; N, 6.60%).

1-Methyl-2-p-tolyl-4-quinolone 11 (R'=H, R=C_6H_4-CH_3(p) A solution of 10b (R'=H, R=C_6H_4-CH_3(p)) (1.0g) in ethanol (25 ml) containing 1N aq. sodium hydroxide solution (15 ml) was refluxed on a water bath for about four hours. Ethanol was distilled off. The residue was diluted with water and was extracted with $CHCl_3$ (3x50 ml). It was dried (Na_2SO_4) and the solvent was distilled off. The residue, a brownish solid was washed with ether and was crystallised from ethyl acetate; ether to give 11 (R'=H, R=C_6H_4-CH_3(p)) in 70% yield; m.p. 170-74°; ν_{max}($CHCl_3$) 1620 (>C=O) cm^{-1}, δ_H ($CDCl_3$) 2.40 (3H, s, CH_3), 3.63 (3H,s, NCH_3), 6.36 (1H,s, =C-H), 7.16-8.63 (8H, m, ArH); λ_{max} (EtOH) 250 (2.15×10^4) and 330 (1.36×10^4)nm; m/z 249, 221 (249-CO), 206 (221-CH_3) and 191 (206-CH_3) (Found: C, 81.22; H, 5.93 N, 5.47, $C_{17}H_{15}NO$ requires C, 81.63; H, 6.02; N, 5.62%)

The following compounds were obtained similarly by using appropriate methodide derivatives of 10a or 10b.

1-Methyl-2-phenyl-4-quinolone 11 (R'=H, R=Ph) Yield 65%, m.p. 150-52° (lit. m.p. 142-45°)[20]; ν_{max} ($CHCl_3$) 1610 (>C=O) cm^{-1}; δ_H ($CDCl_3$) 3.58 (3H, s, NCH_3), 6.40 (1H, s, =C-H), and 7.26-8.73 (9H, m, ArH) λ_{max} (EtOH) 250 (2.54×10^4) and 340 (1.32×10^4) nm; m/z 235, 207 (235-CO), 192 (207-CH_3) and 77 (C_6H_5) (Found C, 81.86; H, 5.41; N, 5.72, $C_{16}H_{13}NO$ requires C, 81.70; H, 5.53; N, 5.96%).

1,3-Dimethyl-2-phenyl-4-quinolone 11 (R'=Me, R=Ph) Yield 60%; m.p. 63-65°, ν_{max} ($CHCl_3$) 1615 (>C=O) cm^{-1}, δ_H ($CDCl_3$) 1.90 (3H, s, CH_3), 3.53 (3H, s, NCH_3) and 7.23-8.00 (9H, m, ArH); λ_{max} (EtOH) 250 (2.08×10^4) and 330 (0.91×10^4) nm; m/z 249, 234 (249-CH_3), 219 (234-CH_3) and 77 (C_6H_5).

1-Methyl-2-p-chlorophenyl-4-quinolone 11 (R'=H, R=C_6H_4-Cl(p)) Yield 60%, semisolid; ν_{max} ($CHCl_3$) 1620 (>C=O) cm^{-1}, δ_H ($CDCl_3$) 3.62 (3H, s, NCH_3), 6.35 (1H, s, =C-H) and 7.16-8.60 (8H, m, ArH); λ_{max} (EtOH) 250 (1.85×10^4) and 330 (0.78×10^4) nm; m/z 269, 241 (269-CO), 226 (241-Me), 130 (241-C_6H_4-Cl).

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22 Figures in parenthesis refer to yields obtained by using method B.