Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Studies in [3, 3] Sigmatropic Rearrangement: Regioselective Cyclization of 5-(Cyclohex-2-Enyl)-6-Hydroxy-1-Methylquinolin-2(1H)-One

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Published online: 04 Dec 2007.

To cite this article: K. C. Majumdar , P. Biswas & S. K. Ghosh (2000) Studies in [3, 3] Sigmatropic Rearrangement: Regioselective Cyclization of 5-(Cyclohex-2-Enyl)-6-Hydroxy-1-Methylquinolin-2(1H)-One, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:22, 4113-4128, DOI: 10.1080/00397910008087028

To link to this article: http://dx.doi.org/10.1080/00397910008087028

SYNTHETIC COMMUNICATIONS, 30(22), 4113–4128 (2000)

STUDIES IN [3, 3] SIGMATROPIC REARRANGEMENT : REGIOSELECTIVE CYCLIZATION OF 5-(CYCLOHEX-2-ENYL)-6-HYDROXY-1-METHYLQUINOLIN-2(1H)-ONE

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Abstract : Thermal [3,3] sigmatropic rearrangement of 6-cyclohex-2-enyloxy-1-methylquinolin-2(1*H*)-one (**3**) afforded 5-cyclohex-2-enyl-6-hydroxy-1-methylquinolin-2(1*H*)-one (**4**) in 86% yield. Compound **4** on treatment with pyridine hydrotribromide in CH_2Cl_2 gave exclusively non-bridged product **6** (85%) whereas compound **4** by a different route *viz*., acetylation followed by bromine addition and cyclization gave the bicyclic product **7** (80%). Compound **4** also furnished a bicyclic product **11** (80%) on treatment with conc. H_2SO_4.

Quinolone alkaloids are interesting owing to their antimicrobial activity and cytotoxicity against animal and plant tumours.[1] Recently a novel class of 4-hydroxyquinolin-2(1*H*)-one derivatives as selective glycine site NMDA antagonists possessing potent centrally mediated *in vivo* activity after oral administration has been reported.[2] However, quinolone derivatives exhibit different activities depending on their structural type.[3] Furo[2,3-*c*]quinolin-4(5*H*)-one and 2*H*-

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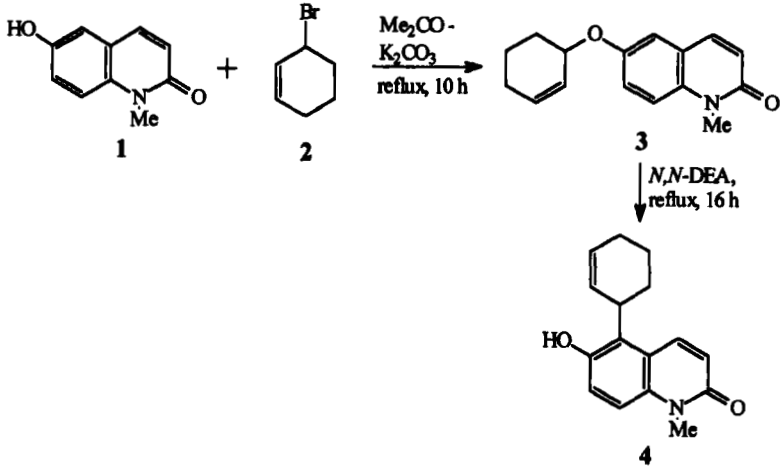
pyrano[3,2-*c*]quinolin-5(6*H*)-one derivatives are abundantly distributed in nature[4] and a number of syntheses for these heterocycles have been reported[5] which also includes our work.[6] Continuous interest in this area prompted us to undertake the present investigation on the cyclization of 5-(cyclohex-2-enyl)-6-hydroxy-1-methylquinolin-2(1*H*)-one (**4**).

Results and Discussion

The starting material for this investigation, compound **4** was obtained in 86% yield by the thermal [3, 3] sigmatropic rearrangement of 6-(cyclohex-2-enyloxy)-1-methylquinolin-2(1*H*)-one (**3**) in refluxing *N*,*N*-diethylaniline for 16 h. The compound **3** in turn was obtained in 60% yield by the reaction of 6-hydroxy-1-methylquinolin-2(1*H*)-one (**1**) with 3-bromocyclohexene (**2**) in refluxing dry acetone in the presence of anhydrous potassium carbonate for 10 h (**Scheme 1**).



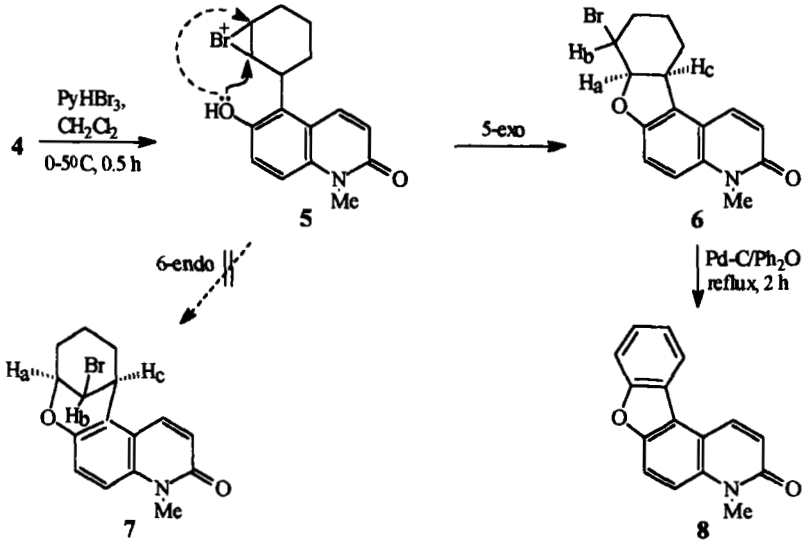
Scheme 1

The compounds **3** and **4** were characterized from their elemental analyses and spectral data. Mass spectra of these compounds showed molecular ion peak at m/z 255. The ^{1}H-NMR spectrum of compound **3** showed one proton broad singlet at δ 4.77 due to O-C**H**-C= proton, two one proton multiplets at δ 5.78-5.86 and 5.90-5.99 due to cyclohexenyl double bond protons, other six protons appeared as three multiplets at δ 1.56-1.69 (1H), 1.75-1.94 (3H) and 1.96-2.20 (2H). The ^{1}H-NMR spectrum of compound **4** showed two well-separated *ortho*-coupled aromatic one proton doublets (J = 9 Hz) centered at δ 7.16 and 7.27 as well as two one proton doublets (J = 9.5 Hz) centered at δ 6.52 and 8.20 due to quinolone π-bond protons. The presence of the two *ortho*-coupled aromatic protons at δ 7.16 and 7.27 conclusively shows that the [3, 3] sigmatropic rearrangement of compound **3** occurs at C-5 position.

In the present investigation four different approaches were made to generate the pyran or the furan ring in the resulting heterocycles derived from the substrate, 5-(cyclohex-2-enyl)-6-hydroxy-1-methylquinolin-2(1*H*)-one (**4**) *e.g.* i) reaction of the substrate with pyridine hydrotribromide, ii) conversion of the substrate to its acetate and then to dibromoacetate followed by cyclization with alcoholic alkali, iii) acid catalyzed cyclization of the substrate and iv) intramolecular epoxidative cyclization.

The brominating agent pyridine hydrotribromide has been found to be very efficient for the regio- and chemoselective cyclization of *o*-cyclohexenyl phenols.[7]

Therefore, the compound **4** was treated with pyridine hydrotribromide in dichloromethane at 0-5°C for 0.5 h to give a new product **6** in 85% yield (**Scheme 2**). This was characterized from its elemental analysis and spectral data. Mass spectrum of



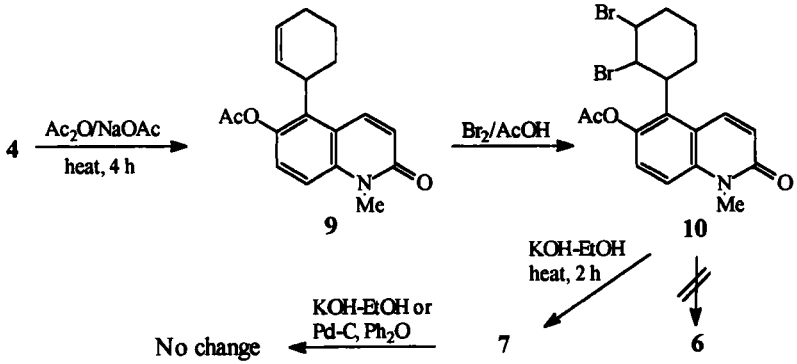
Scheme 2

this compound showed a molecular ion peak at m/z 333. The ^{1}H-NMR spectrum of compound **6** showed two well-separated *ortho*-coupled aromatic one proton doublets (J = 9 Hz) centered at δ 7.07 and 7.16 as well as two one proton doublets (J = 9.5 Hz) centered at δ 6.75 and 7.63 due to quinolone π-bond protons and three lone protons at δ 4.85 assignable to proton H_a, at δ 4.74 assignable to proton H_b and at δ 3.65-3.73 assignable to proton H_c. The signal at δ 4.85 due to H_a appeared as a multiplet, however, careful expansion of the region showed four lines (dd, J = 6.2, 3 Hz). The signal at δ 4.74 due to H_b appeared as a triplet which again on careful expansion appeared as a doublet of doublets with coupling

constants J = 7, 3.5 Hz. The signal at δ 3.65-3.73 due to H_c appeared as a multiplet merged with N-CH_3 protons.

The product **6** responded positively to dehydrogenation with palladised charcoal in refluxing diphenyl ether to furnish the fully aromatised 8-methyl-benzofuro[3,2-*f*]quinolin-9(8*H*)-one **8** (**Scheme 2**).

5-(Cyclohex-2-enyl)-6-hydroxy-1-methylquinolin-2(1*H*)-one (**4**) was converted to its acetate derivative **9** by heating with acetic anhydride and freshly fused sodium acetate[8] to deactivate the compound **4** towards electrophilic substitution. The acetate derivative **9** was brominated by addition of bromine to the cyclohexenyl double bond to afford dibromide **10**. Finally dibromide **10** was treated with alcoholic potassium hydroxide to furnish cyclic compound **7** in 80% yield (**Scheme 3**). This was characterized from its elemental analysis and spectral

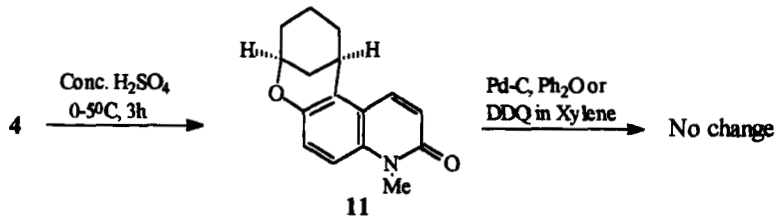


Scheme 3

data. The ^{1}H-NMR spectrum of compound **7** displayed one proton multiplet centered at δ 3.71 due to H_c, two proton multiplet at δ 4.36-4.61 due to H_a and H_b protons and other six protons of cyclohexane ring appeared as multiplet at δ 1.45-

2.21. Mass spectrum of compound **7** showed a molecular ion peak at m/z 333. The alternative structure **6** is discarded as the product **7** resisted dehydrohalogenation with base and dehydrogenation with palladised charcoal in boiling diphenyl ether, indicating its bicyclic nature.

Acid-catalysis has been used to generate the pyran and the furan ring from 2-allylenols.[9] On treatment with cold conc. sulfuric acid compound **4** afforded the bicyclic compound **11** in 80% yield. This product was characterized from its elemental analysis and spectral data. The ^{1}H-NMR spectrum of compound **11** showed two broad singlets at δ 3.52 and 4.63 due to two ring juncture protons and other six protons of cyclohexane ring appeared as five multiplets at δ 1.20-1.38 (1H), 1.59-171 (2H), 1.76-1.92 (2H), 1.95-2.05 (2H) and 2.09-2.21 (1H). Mass spectrum of compound **11** showed a molecular ion peak at m/z 255. This product **11** resisted dehydrogenation when refluxed with palladised charcoal in diphenyl ether or with DDQ in xylene, indicating its bicyclic nature (**Scheme 4**).



Scheme 4

Recently there has been a lot of interest on the intramolecular epoxidative cyclization of suitably substituted alkenes for the synthesis of various furo[10] and pyrano[11] compounds as well as strategic molecules *e.g.*, lonomycin A,[12] lasalocids

and monensin.[13] The cyclization of substrate **4** was also attempted with *m*-chloroperoxybenzoic acid in dry thiophene free benzene but in this case no tractable product was obtained.

In conclusion, 5-(cyclohex-2-enyl)-6-hydroxy-1-methylquinolin-2(1*H*)-one (**4**) has been regioselectively cyclized under different conditions to give different polyheterocycles in good yields. Only in one case furo derivative is obtained by a 5-exo cyclization while in other two cases bicyclic pyran derivatives are obtained by 6-endo cyclization.

Experimental

Melting points are uncorrected. UV absorption spectra were recorded in EtOH on a Hitachi 200-20 spectrophotometer and IR spectra (KBr) on a Perkin-Elmer 1330 apparatus. ^{1}H-NMR spectra were recorded in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal standard on Bruker 200 MHz, and Bruker 300 MHz spectrometers. Chemical shifts and coupling constant are reported in standard fashion (δ) with reference to internal tetramethylsilane. Elemental analyses and mass spectra were recorded by RSIC (CDRI), Lucknow. Silicagel (60-120) was obtained from Spectrochem. Extracts were dried over anhydrous sodium sulphate.

Preparation of 6-(cyclohex-2-enyloxy)-1-methylquinolin-2(1*H*)-one (3).

A mixture of 6-hydroxy-1-methylquinolin-2(1*H*)-one (**1**, 23 mmol), 3-bromocyclohexene (**2**, 23 mmol) and anhydrous potassium carbonate (4 g) was

refluxed in dry acetone (150 ml) on a water-bath for 10 h. The reaction mixture was cooled and filtered. The solvent was removed and the residual mass was extracted with dichloromethane (3 x 50 ml). The combined extract was washed with water (3 x 50 ml) and dried (Na_2SO_4). After removal of solvent, the crude mass was chromatographed over silca gel using benzene-ethyl acetate (3 : 1) as eluent to give compound **3**.

Compound 3, m.p. 102°C (60%); UV : λ_{max} 214 (log ε 4.84), 234 (log ε 5.13) and 355 (log ε 4.26) nm; IR : ν_{max} 2910, 1635, 1550, 1430, 1320 and 1240 cm^{-1}, ^{1}H-NMR (300 MHz) . δ 1.56-1.69 (m, 1H), 1.75-1.94 (m, 3H), 1.96-2.20 (m, 2H), 3.66 (s, 3H), 4.77 (brs, 1H), 5.78-5.86 (m, 1H), 5.90-5.99 (m, 1H), 6.68 (d, J = 9.5 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 7.16 (dd, J = 9, 2.5 Hz, 1H), 7.25 (d, J = 9 Hz, 1H) and 7.55 (d, J = 9.5 Hz, 1H); m/z 255 (M^+). Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.66; N, 5.49%; found C, 75.20; H, 6.59; N, 5.41%.

Preparation of 5-(cyclohex-2-enyl)-6-hydroxy-1-methylquinolin-2(1*H*)-one (4).

Compound **3** (2.3 g, 9 mmol) was refluxed in *N,N*-diethylaniline for 16 h. The reaction mixture was then cooled and poured into ice-cold hydrochloric acid (1: 1). The solution was then extracted with dichloromethane (3 x 50 ml). The combined extract was washed with 6N HCl (3 x 50 ml), water (3 x 50 ml) and dried (Na_2SO_4). Solvent was removed and the crude mass was purified by column chromatography over silica gel using benzene-ethyl acetate (1 : 1) as eluent.

Compound 4, m.p. 242°C (86%); UV : λ_{max} 214 (log ε 5.22), 235 (log ε 5.20), 285 (log ε 4.71) and 362 (log ε 4.51) nm; IR : ν_{max} 3200, 2930, 1630, 1540,

1400 and 1282 cm^{-1}; ^{1}H-NMR (300 MHz) : δ 1.72-1.79 (m, 2H), 1.82-1.91 (m, 2H), 2.08-2.20 (m, 2H), 3.56 (s, 3H), 4.29 (brs, 1H), 5.62-5.70 (m, 1H), 5.76-5.81 (m, 1H), 6.52 (d, J = 9.5 Hz, 1H), 7.16 (d, J = 9 Hz, 1H), 7.27 (d, J = 9 Hz, 1H), 8.20 (d, J = 9.5 Hz, 1H) and 9.47 (brs, 1H); m/z 255 (M^+). Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.66; N, 5.49%; found C, 75.32; H, 6.71; N, 5.54%.

Cyclization of 5-(cyclohex-2-enyl)-6-hydroxy-1-methylquinolin-2(1*H*)-one (4) with Pyridine Hydrotribromide.

Pyridine hydrotribromide (0.26 g, 1 mmol) was added to a solution of the compound **4** (0.25 g, 1 mmol) in dichloromethane (50 ml) at 0-5^{0}C. The reaction mixture was then stirred for 30 min on a magnetic stirrer at this temperature. The reaction mixture was washed with 5% sodium bicarbonate solution (2 x 25 ml), water (2 x 25 ml) and dried (Na_2SO_4). The solvent was removed and the residual mass was purified by column chromatography over solica gel using benzene-ethyl acetate (3 : 1) as eluent to give solid product **6**.

Compund 6, m.p. 165^{0}C (85%); UV : λ_{max} 215 (log ε 5.02), 237 (log ε 4.97), 283 (log ε 4.52) and 361 (log ε 4.01) nm; IR : ν_{max} 2930, 1645, 1550, 1410 and 1295 cm^{-1}; ^{1}H-NMR (300 MHz) : δ 1.18-1.31 (m, 1H), 1.56-1.64 (m, 1H), 1.82-1.97 (m, 1H), 2.05-2.17 (m, 3H), 3.65-3.73 (m, 1H, H_c), 3.70 (s, 3H, N-CH_3), 4.74 (dd, J = 7, 3.5 Hz, 1H, H_b), 4.85 (dd, J = 6.2, 3 Hz, 1H, H_a), 6.75 (d, J = 9.5 Hz, 1H), 7.07 (d, J = 9 Hz, 1H), 7.16 (d, J = 9 Hz, 1H) and 7.63 (d, J = 9.5 Hz, 1H); m/z 335, 333 (M^+). Anal. Calcd. for $C_{16}H_{16}BrNO_2$: C, 57.66; H, 4.80; N, 4.20%; found C, 57.75; H, 4.90; N, 4.16%.

Dehydrogenation of compound 6.

Compound **6** (0.1 g, 0.3 mmol) was refluxed with 10% palladised charcoal (0.02 g) in diphenyl ether (2 ml) for 2 h. The pure product, 8-methylbenzofuro[3,2-*f*]quinolin-9(8*H*)-one (**8**) was obtained when this was subjected to column chromatrography over silica gel using benzene as eluent.

8-Methylbenzofuro[3,2-*f*]quinolin-9(8*H*)-one (**8**), m.p. 159^{0}C (70%); UV : λ_{max} 214 (log ε 4.93), 280 (log ε 4.75) and 358 (log ε 4.31) nm; IR : ν_{max} 2930, 1630, 1545, 1400, 1280 cm^{-1}; ^{1}H-NMR (300 MHz) : δ 3.41 (s, 3H), 6.42 (d, J = 9.5 Hz, 1H), 6.90-7.07 (m, 3H), 7.24-7.30 (m, 3H) and 7.37 (d, J = 9.5 Hz, 1H); m/z 249 (M^+). Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.11; H, 4.42; N, 5.62%; found C, 77.21; H, 4.51; N, 5.53%.

Preparation of acetate derivative of compound 4.

Compound **4** (0.51 g, 2 mmol) and freshly fused sodium acetate (0.2 g) was taken in acetic anhydride (4 ml) and was heated on a water-bath for 4 h. The reaction mixture was cooled and poured into excess ice-water, stirred well to decompose excess acetic anhydride. Then this was extracted with dichloromethane (3 x 25 ml). The extract was washed with water (3 x 25 ml) and dried (Na_2SO_4). The solvent was removed and the crude product **9** was purified by column chromatography over silica gel using benzene-ethyl acetate (3 : 1) as eluent.

Compound 9, viscous liquid (80%); UV : λ_{max} 214 (log ε 5.23), 233 (log ε 5.38), 280 (log ε 4.77) and 339 (log ε 4.59) nm; IR : ν_{max} 3020, 2935, 1750, 1645, 1585, 1445, 1370 and 1200 cm^{-1}; ^{1}H-NMR (300 MHz) : δ 1.52-1.95 (m, 6H), 2.31

(s, 3H), 3.72 (s, 3H), 3.99 (brs, 1H), 5.71-5.86 (m, 2H), 6.71 (d, J = 9.5 Hz, 1H), 7.21 (d, J = 9 Hz, 1H), 7.29 (d, J = 9 Hz, 1H) and 8.24 (d, J = 9.5 Hz, 1H); m/z 281 (M^+). Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.86; H, 6.76; N, 4.98%; found C, 76.81; H, 6.72; N, 4.95%.

Preparation of dibromo derivative 6 of 6-acetoxy-5-(cyclohex-2-enyl)-1-methylquinolin-2(1*H*)-one (9).

Bromine (0.16 g, 1 mmol) in glacial acetic acid (2 ml) was added dropwise to a well-stirred solution of compound **9** (0.281 g, 1 mmol) in glacial acetic acid (4 ml) at room temperature. After 2 h, the reaction mixture was diluted with water and the gummy mass was collected, which was chromatographed over silica gel. The product **10** was obtained when the column was eluted with benzene-ethyl acetate (3 : 1).

Compund 10, viscous liquid (90%); UV : λ_{max} 214 (log ε 5.33), 236 (log ε 5.49), 278 (log ε 4.87) and 340 (log ε 4.73) nm; IR : ν_{max} 2920, 1750, 1650, 1590 and 1200 cm^{-1}; ^{1}H-NMR (300 MHz) : δ 1.57-2.09 (m, 4H), 2.37 (s, 3H), 2.54-2.77 (m, 2H), 3.75 (s, 3H), 4.23-4.34 (m, 1H), 4.67 (s, 1H), 4.88 (s, 1H), 6.80 (d, J = 9.5 Hz, 1H), 7.25 (d, J = 9 Hz, 1H), 7.39 (d, J = 9 Hz, 1H) and 8.30 (d, J = 9.5 Hz, 1H); m/z 443, 441, 439 (M^+). Anal. Calcd. for $C_{18}H_{19}Br_2NO_2$: C, 49.20; H, 4.33; N, 3.19%; found C, 49.23; H, 4.28; N, 3.13%.

Cyclization of 6-acetoxy-5-(2′,3′-dibromocyclohex)-1-methylquinolin-2(1*H*)-one (10).

Compound **10** (0.22 g, 0.5 mmol) was refluxed with ethanolic potassium hydroxide solution (0.4 g KOH in 10 ml 95% ethanol). Ethanol was removed and

water (25 ml) was added to it. The aqueous solution was extracted with dichloromethane (3 x 25 ml) and the extract was washed with water (3 x 25 ml) and dried (Na_2SO_4). The solvent was removed and the crude mass was chromatographed over silica gel. The product **7** was obtained when the column was eluted with benzene-ethyl acetate (3 : 1).

Compound 7, m.p. 180^{0}C (80%); UV : λ_{max} 215 (log ε 4.87), 238 (log ε 4.92), 282 (log ε 4.36) and 362 (log ε 4.09) nm; IR : ν_{max} 2940, 1640, 1590, 1450 and 1240 cm^{-1}; ^{1}H-NMR (200 MHz/DMSO-d_6) : δ 1.45-2.21 (m, 6H), 3.56 (s, 3H), 3.71 (brs, 1H), 4.36-4.61 (m, 2H), 6.56 (d, J = 9 Hz, 1H), 7.06 (d, J = 9 Hz, 1H), 7.12 (d, J = 9 Hz, 1H) and 7.55 (d, J = 9 Hz, 1H); m/z 335, 333 (M^+). Anal. Calcd. for $C_{16}H_{16}BrNO_2$: C, 57.66; H, 4.80; N, 4.20%; found C, 57.59; H, 4.83; N, 4.25%.

Attempted Dehydrohalogenation of compound 7.

A mixture of compound **7** (65 mg, 0.2 mmol) and potassium hydroxide (0.1 g) in rectified spirit (3 ml) was refluxed on a water-bath for 4 h. No change was observed as evidenced from the tlc of the reaction mixture and also from co-tlc with the starting material **7**, mixed melting point etc.

Attempted Dehydrogenation of compound 7.

Compound **7** (65 mg, 0.2 mmol) was refluxed with 10% palladised charcoal (0.02 g) in diphenyl ether (2 ml) or DDQ in xylene for 2 h. No change was observed when examined by co-tlc, mixed melting point etc. with the starting material **7**.

Cyclization of 5-(cyclohex-2-enyl)-6-hydroxy-1-methylquinolin-2(1*H*)-one (4) with sulfuric acid.

The compound **4** (0.25 g, 1 mmol) was added to well-stirred concentrated sulfuric acid (3 ml) at 0-5^{0}C and the stirring was continued for 3 h at this temperature. The reaction mixture was poured into crushed ice and extracted with dichloromethane (3 x 20 ml). The dichloromethane extract was then washed with 10% sodium bicarbonate solution (2 x 20 ml), water (2 x 20 ml) and dried (Na_2SO_4). Removal of solvent gave a viscous liquid which was subjected to column chromatography over silica gel using benzene as eluent to give product **11**.

Compund 11, viscous liquid (80%); UV : λ_{max} 215 (log ε 5.21), 236 (log ε 5.23), 284 (log ε 4.74) and 360 (log ε 4.59) nm; IR : ν_{max} 2930, 1640, 1605, 1575, 1450, 1345 and 1240 cm^{-1}; ^{1}H-NMR (300 MHz) : δ 1.20-1.38 (m, 1H), 1.59-1.71 (m, 2H), 1.76-1.92 (m, 2H), 1.95-2.05 (m, 2H), 2.09-2.21 (m, 1H), 3.52 (brs, 1H), 3.72 (s, 3H), 4.63 (brs, 1H), 6.74 (d, J = 9.5 Hz, 1H), 7.11 (d, J = 9 Hz, 1H), 7.20 (d, J = 9 Hz, 1H) and 7.83 (d, J = 9.5 Hz, 1H); m/z 255 (M^+). Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.66; N, 5.49%; found C, 75.21; H, 6.59; N, 5.41%.

Attempted Dehydrogenation of compound 11.

Compound **11** (0.125 g, 0.5 mmol) was refluxed with 10% palladised charcoal (0.025 g) in diphenyl ether (4 ml) for 2 h. No change was observed as evidenced from tlc of the reaction mixture, co-tlc and superimposable IR spectrum with the starting material **11**.

Acknowledgment

We thank the CSIR (New Delhi) for financial assistance. Two of us (PB & SKG) are grateful to CSIR (New Delhi) for fellowship. We also thank Mr. S. Karmakar and Mr. S. Samanta for some help.

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Received in the UK 15 December 1999