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REGIOSELECTIVE SYNTHESIS OF HETEROCYCLES FROM 3-CYCLOHEX-2-ENYL-4-HYDROXY- 1-METHYLQUINOLIN -2-(1*H*)-ONE.

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Abstract: 3-Cyclohex-2-enyl-4-hydroxy-1-methylquinolin-2(1*H*)-one (**5**) reacts with pyridine hydrotribromide in CH_2Cl_2 at 0-5°C for 0.75h to give a furo fused heterocycle **6** in 96% yield. Product **6** on treatment with KOH-EtOH eliminates HBr to give compound **8** which on treatement with Pd-C in refluxing diphenyl ether for 0.5h furnishes benzofuro[3,2-*c*]quinolone **9** in 90% yield. Substrate **5** on sequential treatment with Ac_2O-AcONa and Br_2/AcOH followed by KOH-EtOH, however produces bicyclic product **7** in excllent overall yield. Substrate **5** reacts with 1 equivalent of *m*-chloroperbenzoic acid in refluxing benzene to furnish bicyclic heterocycle **12** in 80% yield and with cold conc. H_2SO_4 at 0-5°C for 2h generates the bicyclic heterocycle **14** in 90% yield.

Some of the quinolinone alkaloids exhibit antimicrobial activity and marked cytotoxicity against animal and plant tumours[1]. Recent reports[2] describe a novel class of 4-hydroxyquinolin-2(1*H*)-one derivatives as selective glycine site NMDA antagonists which possess potent central mediated *in vivo* activity after oral administration. However, quinolinone derivatives exhibit different activities depending on their strutural type[3]. We have recently reported the regioselective synthesis[4] of furo[3,2-*c*]quinolin-4-(5*H*)-ones and pyrano[3,2-*c*]quinolin-5(6*H*)-

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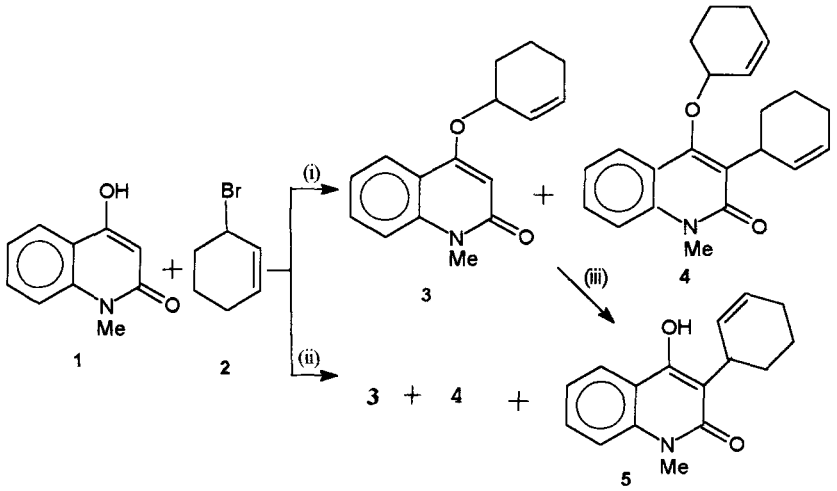
one by the application of sigmatropic rearrangement. In continuation of our work in this area we became interested to generate heterocycles containing quinolinone moeity from 3-cyclohex-2-enyl-4-hydroxy-1-methylquinolin-2-(1*H*)-one (**5**). Here we report the results of this investigation.



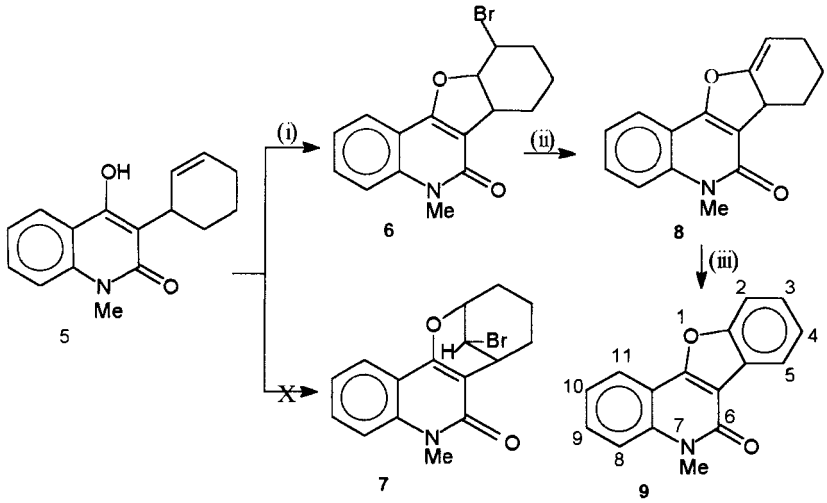
Scheme 1. Reagents and conditions: (i) Me_2CO_3/K_2CO_3, ↑↓, 8 h
(ii) TBAB, 20% aq. NaOH, CH_2Cl_2, 10 h
(iii) C_6H_5Cl, ↑↓.

The starting material 3-cyclohex-2-enyl-4-hydroxy-1-methylquinolin-2(1*H*)-one(**5**) for this study was obtained in almost quantitative yield from 4-cyclohex-2-enyloxy-4-methylquinolin-2(1*H*)-one (**3**) simply by refluxing **3** in chlorobenzene for 1h. The substrate **3** was in turn prepared from 4-hydroxy-1-methylquinolin-2(1*H*)-one (**1**) by reacting with 3-bromocyclohexene (**2**). The reaction may be conducted in refluxing acetone in the presence of anhydrous K_2CO_3. In this case product **3** is obtained in 70% yield along with dialkylated

product **4** (20%). However when the reaction is conducted under phase transfer catalysed conditions[5] in CH_2Cl_2 with 20% aqueous NaOH and tetrabutylammoniumbromide (TBAB) at room temperature for 10h a mixture of three products, **3** (20%), **4** (30%), and substrate **5** (40%) are obtained (Scheme1).

Altogether three different approaches were made to generate the pyran or the furan ring in the resulting heterocycles derived from the substrate, 3-cyclohex-2-enyl-4-hydroxy-1-methylquinolin-2(1*H*)-one (**5**) eg (i) 'Approach A_a' reaction of the substrate with pyridine hydrotribromide[6], (ii) 'approach A_b'- conversion of the substrate to acetate to dibromoacetate followed by cyclisation with alcoholic alkali[7], (iii) 'approach B'- treatment of the substrate with 1equiv. *m*-CPBA[8], (iv) 'approach C'- acid catalysed cyclisation of the substrate.

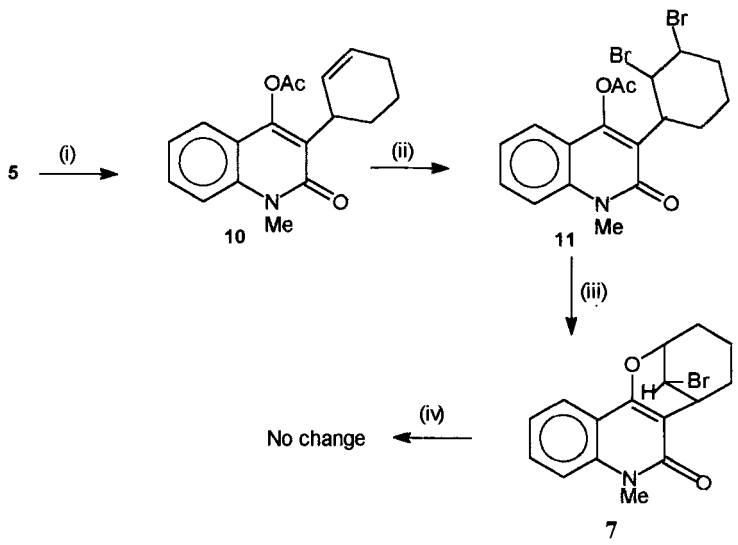
'Approach A_a' - The brominating agent pyridine hydrotribromide has recently been found to be very efficient for the regioselective cyclisation of *o*-cyclohex-2-enylphenols[6]. Therefore, 3-cyclohex-2-enyl-4-hydroxy-1-methyl quinolin-2(1*H*)-one (**5**) was treated with pyridine hydrotribromide in dichloromethane at 0-5 °C for 0.75 h to give exclusively one product in almost quantitative yield. This was characterised as the cyclic product **6** from its elemental analysis and spectral data. The alternative structure **7** is discarded as this product underwent an elimination of HBr when treated with alcoholic potassium hydroxide to give product **8**. Product **8** responded positively to dehydrogenation with palladised charcoal in refluxing diphenyl ether for 0.5 h to furnish the fully aromatised 7-methylbenzofuro[3,2-*c*]quinolin-6(7*H*)-one (scheme 2).



Scheme 2. Reagents and conditions: (i) $PyHBr_3$, CH_2Cl_2, 0-5 ^0C, 1h.
or, $C_6H_{12}N_4HBr_3$, CH_2Cl_2, 0-5^0C, 20mins.
(ii) KOH/EtOH, 1h
(iii) Pd-C/Ph_2O, Δ

'Approach A_b'- The 3-cyclohex-2-enyl-4-hydroxy-1-methylquinolin-2-(1*H*)-one (**5**) was converted to its acetate on heating with acetic anhydride and freshly fused sodium acetate[7]. The acetate derivative was then treated with bromine in acetic acid to give the dibromide **11**. Finally the dibromide **11** was heated with alcoholic KOH to furnish the cyclic product **7**. The product resisted dehydrobromination in presence of a base. This also resisted dehydrogenation with palladised charcoal in boiling diphenyl ether to indicate its bicyclic nature (Scheme 3).

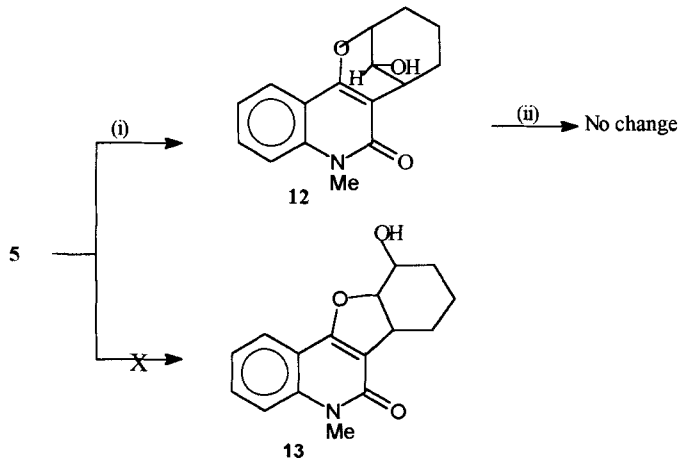
'Approach B'- Recently there is lot of activities on the intramolecular epoxidative cyclisation of suitably substituted alkenes for the synthesis of various



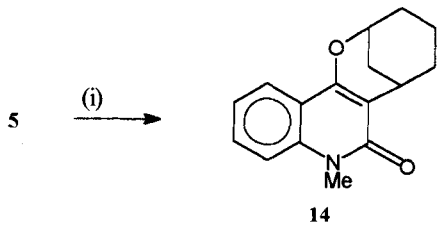
Scheme 3. Reagents and conditions: (i) Ac_2O, NaOAc, Δ, 3h
(ii) Br_2, AcOH, 2h
(iii) KOH, EtOH, Δ ,2h
(iv) Pd / C, Ph_2O, Δ

furo heterocycles[8a,8b] and pyrano heterocycles[8c] as well as strategic molecules eg. lonomycin A[8d], lasalocids and monensins[8c]. We also applied this methodology for the cyclisation of substrate **5**. Substrate **5** was treated with one equivalent of *m*-chloroperoxybenzoic acid in boiling benzene for 12 h to give a cyclic product **12**. This product also resisted dehydrogenation with DDQ in boiling xylene or with palladised charcoal in boiling diphenyl ether for 4 h (Scheme 4).

'Approach C'- Acid catalysis has recently been used to generate furan and or the pyran ring from 2-allylenols[9]. 3-Cyclohex-2-enyl-4-hydroxy-1-methylquinolin-2(1*H*)-one (**5**) on treatment with concentrated sulphuric acid at 0-5 ^{0}C afforded the bicyclic pyran **14** in 90% yield. This product remains unchanged



Scheme 4. Reagents and conditions: (i) *m*-CPBA, C_6H_6, ↓↑, 12h
(ii) Pd-C, Ph_2O, △



Scheme 5. Reagents and conditions: (i) Conc. H_2SO_4, 0-5^{0}C, 2h

when refluxed in diphenyl ether with palladised charcoal or in xylene with DDQ (scheme 5).

In conclusion regioselctive heterocyclisation of 3-cyclohex-2-enyl-4-hydroxyquinolin-2(1*H*)-one gives polyhetrocycles in excellent yields. Only in one approach furo derivative is obtained by a 5-exo cyclisation while other approaches furnish bicyclic pyran derivatives by 6-endo cyclisation.

Experimental

Melting points are uncorrected. U.V absorption spectra were recorded on a Hitachi 200-20 spectrometer for solutions in absolute alcohol. I.R spectra were run in KBr discs on a Perkin-Elmer 1330 apparatus. P.M.R spectra were determined for solutions in deuteriochloroform with $SiMe_4$ as an internal standard on a Jeol Fx-100 (100 MHz) instrument at the Indian Institute of Chemical Biology, Calcutta. Elemental analyses and recording of mass spectra were carried out at RSIC (CDRI), Lucknow.

Preparation of 4-cyclohex-2-enyloxy-1-methylquinolin-2(1*H*)-one (3) by classical alkylation method.

A mixture of 4-hydroxy-1-methylquinolin-2(1*H*)-one (1.73 g, 0.01 mol), 3-bromocyclohexene (1.6 g, 0.01 mol) and anhydrous potassium carbonate (3 g) was refluxed in dry acetone (200 mL) on a water bath for 8 h. The reaction mixtuture was then cooled, filtered. The solvent was removed and the residue was extracted with $CHCl_3$ (3x25 mL). The chloroform extract was washed with water (twice) and dried (Na_2SO_4). Removal of the solvent gave a crude mass which was then chromatographed over silica gel (60-120 mesh) and elution of the column with benzene gave compound **4** and Ethylacetate- benzene (1:9) gave compound **3**. **Compound 3**, Viscous liquid (70%); UV (EtOH): λ_{max} 229 (log ε 3.35), 280 (log ε 2.51) and 318 (log ε 2.47) nm; IR (KBr): ν_{max} 2920, 1620, 1310 and 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.72-2.16 (m, 6H), 3.68 (s, 3H), 4.88-5.08 (m, 1H), 5.96-6.16 (m, 3H), 7.40-7.72 (m, 3H) and 8.00-8.14 (m, 1H); m/z 255 (M^+). Anal.

calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49%; found C, 75.38; H, 6.60; N, 5.32%.

Compound 4, Viscous liquid (15%); UV (EtOH): λ_{max} 227 (log ε 3.41), 277 (log ε 2.77) and 327 (log ε 2.65) nm; IR (KBr): ν_{max} 3020, 2940, 1640, 1310 and 1290 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ 1.70-2.42 (m, 12H), 3.70 (s, 3H), 3.86-4.04 (m,1H), 4.56-4.74 (m, 1H), 5.54-6.04 (m, 4H), 7.32-7.64 (m, 3H), and 7.88-7.98 (m, 1H); m/z 335 (M^+). Anal. calcd. for $C_{22}H_{25}NO_2$: C, 78.80; H, 7.46; N, 4.18%; found C, 78.92; H, 7.61; N, 4.32%.

Phase transfer catalysed alkylation of 4-hydroxy-1-methylquinolin-2(1*H*)-one (1)

To a mixture of 4-hydroxy-1-methylquinolin-2(1*H*)-one (0.9 g, 5 mmol) and 3-bromocyclohexene (0.8 g, 5 mmol) in dichloromethane (50 mL) was added a solution of TBAB (0.08 g) in 30% aqueous NaOH (50 mL) and the mixture was stirred at room temperture for 1 h. It was then diluted with water (100 mL) and extracted with $CHCl_3$ (3x20 mL). The combined extract was washed successively with 2M HCl (3x20 mL), brine (3x20 mL) and dried (Na_2SO_4). The solvent was distilled off to get the crude mass which was then column chromatogrphed. The dialkylated product **4** (30%) was obtained when the column was eluted with benzene. Elution of the column with Ethylacetate-benzene (1:9) gave compound **5** (40%) followed by compound **3** (20%).

Compound 5, m.p. 104 °C (40%); UV (EtOH): λ_{max} 220 (log ε 3.02), and 319 (log ε 2.44) nm; IR (KBr): ν_{max} 3380, 2920, 1640, 1570 and 1260 cm^{-1} ; ^{1}H-

NMR ($CDCl_3$): δ 1.68-2.32 (m, 6H), 3.72 (s, 3H), 4.00-4.32 (m, 1H), 5.96-6.36 (m, 2H), 7.32-7.68 (m, 4H) and 7.92-8.04 (m, D_2O exchangeable, 1H); m/z 255 (M^+). Anal. calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49%; found C, 75.38; H, 6.81; N, 5.58%.

Rearrangement of compound 3.

Compound **3** (1.25 g, 5 mmol) was refluxed in chlorobenzene (10 mL) for 40 minutes. T.L.C indicated quantitative conversion. Chlorobenzene was removed *in vacuo* and the residual mass was subjected to column chromatography over silica gel. The rearranged product **5** (90%) was eluted with ethylacetate-benzene (1:9).

Pyridine hydrobromide-Perbromide or Hexamethylene Tetramine Hydrotribromide mediated cyclisation of compound 5.

Solid pyridine hydrobromide-perbromide (0.16g, 0.5 mmol) was added slowly to a dichloromethane solution (20 mL) of the compound **5** (0.127 g, 0.5 mmol). The reaction mixture was then stirred for 1 h at 0-5 ^0C . When hexamethylenetetramine hydrotribromide was used in the same reaction, the reaction was completed within 20 minutes. The reaction mixture was washed with 5% Na_2CO_3 solution (2x20 mL), water (2x20 mL) and dried (Na_2SO_4). The residual mass after removal of the solvent was subjected to column chromatogrphy over silica gel. The product **6** was obtained when the column was eluted with ethylacetate-benzene (1:3).

Compound 6, m.p 154 ^{0}C (96%); UV (EtOH): λ_{max} 236 (log ε 3.10), and 310 (log ε 2.70) nm; IR (KBr): ν_{max} 2880, 1570, and 1260 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ 1.62-2.16 (m, 6H), 3.80 (s, 3H), 3.88-4.04 (m, 1H), 4.24-4.46 (m, 1H), 5.00-5.16 (dd, J=6 and 2 Hz, 1H), 7.40-7.76 (m, 3H) and 8.40-8.48 (d, J=8 Hz, 1H); m/z 335 and 333 (M^+). Anal. calcd. for $C_{16}H_{16}BrNO_2$ C, 57.49; H, 4.79; N, 4.19%; found C, 57.66; H, 4.51; N, 4.02%.

Dehydrobromination of compound 6.

A mixture of compound **6** (0.05 g, 0.15 mmol) and potassium hydroxide (0.08 g, 1.4 mmol) in rectified spirit (3 mL) was refluxed for 1 h. Ethanol was removed and the residual mass was extracted with chloroform, washed with salt water, water and dried (Na_2SO_4). After removal of the solvent it was subjected to column chromatography over silica gel. Elution of the column with ethylacetate-benzene (1:3) gave compound **8**.

Compound 8, Gummy liquid (92%); UV (EtOH): λ_{max} 228 (log ε 3.10), and 318 (log ε 2.57) nm; IR (KBr): ν_{max} 2920, 1620, 1600 and 1230 cm^{-1} ; ^{1}H-NMR($CDCl_3$): δ 1.64-2.18 (m, 6H), 3.68 (s, 3H), 4.00-4.12 (m, 1H), 5.92-6.12 (m, 1H), 7.36-7.72 (m, 3H) and 8.00-8.12 (d, J=8 Hz, 1H); m/z 253 (M^+). Anal. calcd. for $C_{16}H_{15}NO_2$: C, 75.89; H, 5.93; N, 5.53%; found C, 75.71; H, 5.65; N, 5.75%.

Dehydrogenation of compound 8.

Compound **8** (0.05 g, 0.2mmol) was refluxed with 10% palladised charcoal (0.02 g) in diphenyl ether (2 mL) for 30 minutes. It was subjected to column

chromatography over silica gel. Diphenyl ether was eluted out with pet.ether and compound **9** was obtained when the column was eluted with ethylacetate-benzene (1:9).

Compound 9, m.p 134 ^{0}C (90%); UV (EtOH): λ_{max} 225 (log ε 3.06), 276 (log ε 2.54) and 323 (log ε 2.51) nm; IR (KBr): ν_{max} 3000, 1580, 1310 and 1230 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ 3.76 (s, 3H), 7.28-7.72 (m, 7H) and 8.00-8.12 (d, J=8 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, 77.33; H, 4.67; N, 5.35%.

Preparation of acetate derivative of compound 5.

The compound **5** (0.25 g, 1 mmol) and a few crystals of freshly fused sodium acetate (0.1 g) was taken in acetic anhydride (2 mL) and was heated on a water bath for 3h. The reaction mixture was cooled and poured into ice-water, stirred well to decompose the excess acetic anhydride and an insoluble solid was obtained. This was recrystallised from chloroform-pet.eher (60-80 ^{0}C) to give a white crystlline solid **10**.

Compound 10, m.p 120 ^{0}C (95%); UV (EtOH): λ_{max} 229 (log ε 3.39), 274 (log ε 2.71) and 330 (log ε 2.72) nm; IR (KBr): ν_{max} 2880, 1745, 1610, 1580 and 1190 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ 1.64-2.28 (m, 6H), 2.40 (s, 3H), 3.76 (s, 3H), 3.88-4.16 (br.s, 1H), 5.52-5.92 (m, 2H) and 7.16-7.68 (m, 4H); m/z 297 (M^+). Anal. calcd. for $C_{18}H_{19}NO_3$: C, 72.73; H, 6.39; N, 4.71%; found C, 72.84; H, 6.48; N, 4.85%.

Bromination of compound 10: Formation of dibromo derivative 11.

The solution of bromine (0.04 g, 0.5 mmol) in glacial acetic acid (1 mL) was added dropwise to a well stirred solution of compound **10** (0.15 g, 0.5 mmol) in glacial acetic acid (2 mL) at room temperature and left for 2h. The reaction mixture was diluted with water and the gummy mass was chromatographed over silica gel. The compound **7** was obtained when the column was eluted with ethylacetate-benzene (1:3).

Compound 11 Viscous liquid (90%); UV (EtOH): λ_{max} 235 (log ε 3.48), and 309 (log ε 3.07) nm; IR (KBr): ν_{max} 2900, 1570, 1500 and 1220 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ 1.36-2.20 (m, 6H), 2.32 (s, 3H), 3.70 (s, 3H) 4.12-4.26 (m, 2H), 4.90-5.06 (t, J=6 Hz, 1H), 7.32-7.60 (m, 3H) and 8.34-8.42 (d, J=8 Hz, 1H); m/z 459, 457 and 455 (M^+). Anal. calcd. for $C_{18}H_{19}Br_2NO_3$: C, 47.26; H, 4.16; N, 3.06%; found C, 47.36; H, 4.02; N, 3.27%.

Cyclisation of compound 11.

The compound **11** (0.1 g, 0.22 mmol) was refluxed with 4% ethanolic potassium hydroxide solution (5 mL) for 2h. Ethanol was reduced to one third by distillation and water was added to it. The aqueous solution was extrcted with chloroform (3x10 mL), washed with water (2x10 mL)and dried (Na_2SO_4). The solvent was removed and the crude mass was chromatographed over silicagel. Compound **7** was obtained when the column was eluted with ethylacetate-benzene (1:3).

Compound 7, Viscous liquid (92%); UV (EtOH): λ_{max} 226 (log ε 2.74), and 320 (log ε 2.10) nm; IR (KBr): ν_{max} 2910, 1600, 1580 and 1250 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ 1.52-2.32 (m, 6H), 3.44-3.52 (m, 1H), 3.60 (s, 3H), 4.00-4.08 (m, 1H), 4.68-4.80 (br.s, 1H), 7.36-7.72 (m, 3H) and 8.00-8.08 (m, 1H); m/z 335and 333 (M^+). Anal. calcd. for $C_{16}H_{16}BrNO_2$: C, 57.49; H, 4.79; N, 4.19%; found C, 57.65; H, 4.53; N, 4.35%.

Attempted dehydogenation of compound 7.

Compound **7** (0.05 g, 0.15 mmol) was refluxed with 10% palladised charcoal (0.02 g) in diphenyl ether (2 mL) for 2h. No change was observed and the starting material was recovered.

***m*-Chloroperbenzoic acid mediated cyclisation of compound 5.**

m-Chloroperbenzoic acid (50%, 0.275 g, 0.79 mmol) was added to compound **5** (0.2 g, 0.79 mmol) in thiophene free benzene (5 mL) and the mixture was refluxed for 12h. The reaction was worked up with benzene (2x25 mL), washed with sodium bi carbonate solution (2x25 mL), water (2x25 mL) and dried (Na_2SO_4). The solvent was removed and the residual mass was subjected to column chromatography over silica gel. A white solid **12** was obtained when the column was eluted with ethylacetate-benzene (1:9).

Compound 12 m.p 166 ^{0}C (80%); UV (EtOH): λ_{max} 235 (log ε 2.75) nm; IR (KBr): ν_{max} 3440, 2920, 1700,1650, 1360,and 1260 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ 1.20-1.80 (m, 6H), 2.22-2.42 (m, 1H), 3.04 (s, 2H), 3.50 (s, 3H), 4.04 (s, D_2O exchangeable, 1H), 7.08-7.72 (m, 3H), and 7.96-8.08 (m, 1H); m/z 271 (M^+).

Anal. calcd. for $C_{16}H_{17}NO_3$: C, 70.85; H, 6.27; N, 5.17%; found C, 70.64; H, 6.46; N, 4.95%.

Attempted dehydrogenation of compound 12.

Compound **12** (0.05 g, 0.17 mmol) was refluxed with 10% palladised charcoal (0.02 g) in diphenyl ether (2 mL) for 1h. No change was observed and the starting material was recovered.

Attempted oxidation of compound 12 .

Compound **12** (0.05 g, 0.17 mmol) was refluxed with DDQ (0.38 g, 0.17 mmol)in dry xylene for 5h. No change was obsereved and the starting material was recovered.

Cyclisation of compound 5 in concentrated sulphuric acid.

Compound **5** (0.1 g, 0.4 mmol) was added to a well stirred cold concentrated sulphuric acid (1.5 mL) at 0-5 ^{0}C and the stirring was continued for 2h at this temperture. The reaction mixture was poured into crushed ice and extracted with chloroform (3x10 mL). The chloroform extract was washed with 5% sodium bicarbonate solution (2x25 mL), water (2x20 mL) and dried (Na_2SO_4). Removal of the solvent gave a viscous oil which was subjected to column chromtography over silica gel using ethylacetate-benzene (1:9) as eluent to give a white solid **14**.

Compound 14, m.p 128 ^{0}C, (90%) UV (EtOH): λ_{max} 230 (log ε 3.20), 287 (log ε 2.46) and 317 (log ε 2.47) nm; IR (KBr): ν_{max} 2920, 1610, 1390 and

1290 cm^{-1} ; ^{1}H-NMR ($CDCl_3$): δ 1.26-2.00 (m, 8H), 3.40(br.s, 1H), 3.72 (s, 3H), 4.12 (br.s 1H), 7.16-7.66 (m, 3H) and 7.96-8.08 (m, 1H); m/z 255 (M^+). Anal. calcd. for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49%; found C, 75.51; H, 6.48; N, 5.27%.

Attempted dehydrogenation of compound 14.

Compound **14** (0.05 g, 0.2mmol) was refluxed with 10% palladised charcoal (0.01 g) in diphenyl ether (2 mL) for 2h. No change was observed and the starting material was recovered.

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