SYNTHESIS OF 1-BENZAZEPINES AS PRECURSORS OF 1-BENZAZEPINEDIONES

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Abstract.- The synthesis of 6-hydroxy-7-nitro-1-benzazepine-2-one **7** from 5-hydroxy-1-tetralone **1** and 6-hydroxy-1-benzazepine-2-one **2** is described. Bromination of 6-hydroxy-1-benzazepine-2-one **2** with NBS in ethyl acetate afforded 7-bromo-6-hydroxy-1-benzazepine-2-one **13** and 7,9-dibromo-6-hydroxy-1-benzazepine-2-one **14**. Oxidation of benzazepinone **13** with (diacetoxyiodo)benzene provided 7-bromo-1-benzazepine-2,6,9-trione **5**.

Much attention has been focused on 1-benzazepines a class of heterocycles with pharmaceutical potential featuring analgesic, antidepressant, antihypertensive and diuretic activities.[1] Although there are several methods to prepare 1-benzazepines,[2] the Schmidt rearrangement[3] offers a simple entry to these heterocycles mainly due to the readiness of the precursors.

In previous work[4] we have reported a facile synthesis of 1-benzazepine-2,6,9-trione **3** from 5-hydroxy-1-tetralone **1** by using the Schmidt rearrangement followed by oxidation of the 1-benzazepine intermediate **2** with the Fremy's salt[5] or (diacetoxyiodo)benzene.[6] Because evaluation of quinone **3** in the NCI displayed

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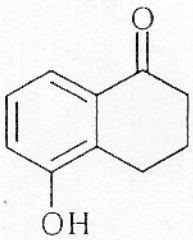
promissory *in vitro* antitumor activity against a variety of tumor cells we decided to extend the synthetic methodology used to prepare quinone 3 to the synthesis of new members of 1-benzazepinequinone family.

Here we wish to report the synthesis of new derivatives of the 6-hydroxy-1-benzazepine-2-one and attempts to construct the 1-benzazepinetriones 4 and 5.



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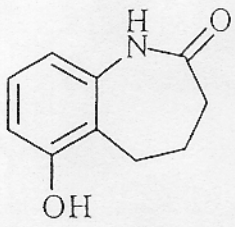

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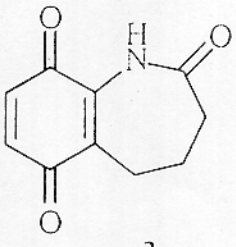

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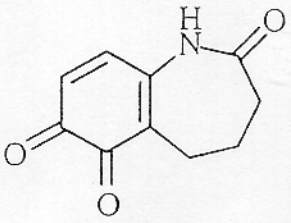

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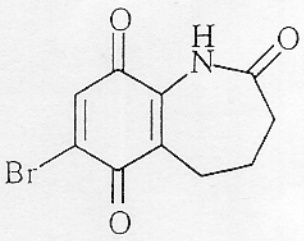

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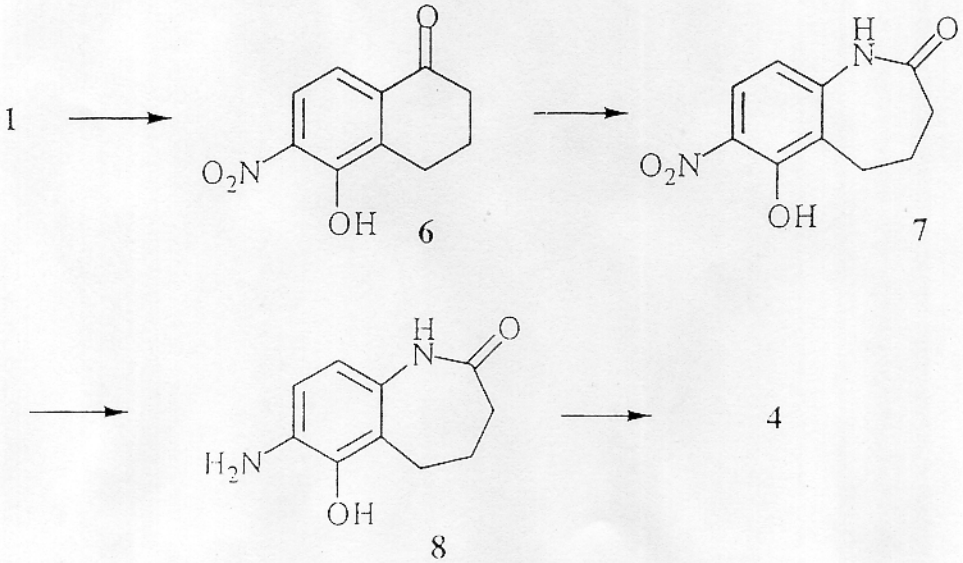
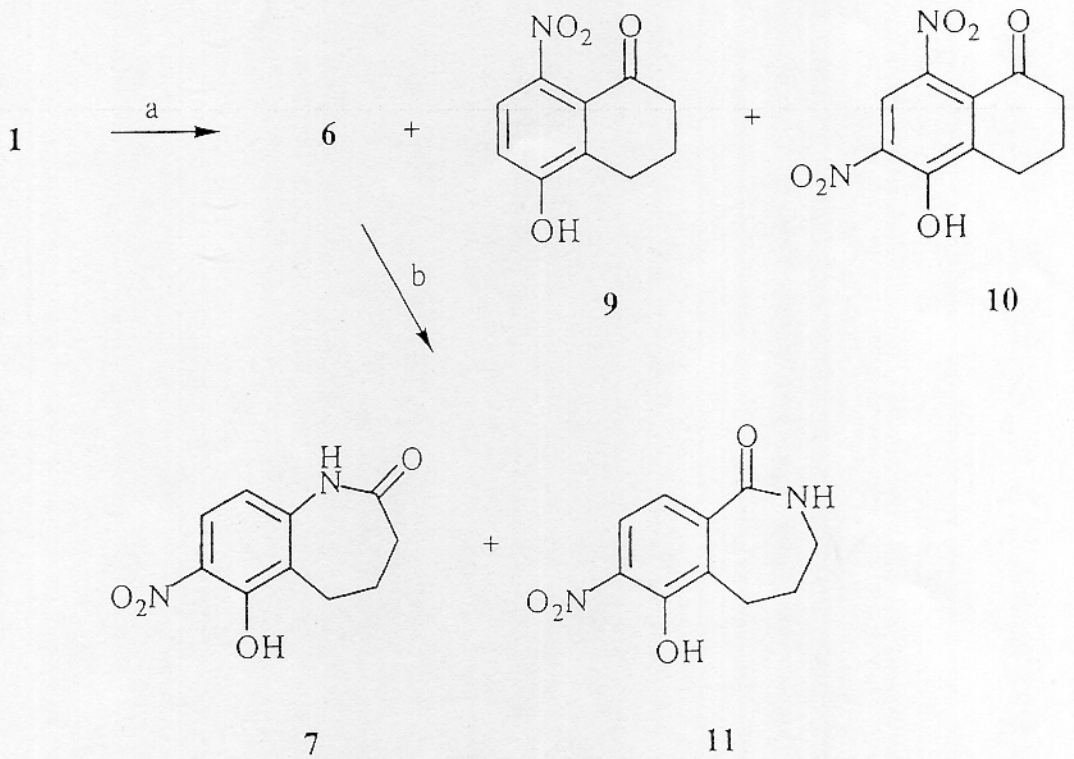
These quinones were selected as target compounds because of their relationship with the active quinone 3. Firstly we explored the access to *orto*-quinone 4 through the sequence outlined in Scheme 1.



Scheme 1

Nitration of **1** with nitric acid in acetic acid at room temperature was examined. The treatment afforded compound **6** in 47% yield along with the secondary product **10** (19%). When the nitration was carried out with the same reagents at reflux, heterocycles **6**, **9** and **10** were isolated in 21, 48 and 9% yield respectively. The structure of isomers **6** and **9** was mainly deduced by their ^1H NMR spectra which displayed the resonance frecuences for the OH protons at δ11.04 and 9.60 ppm. The low field signal was assigned to the chelated proton of the hydroxy group in **6**.[7]

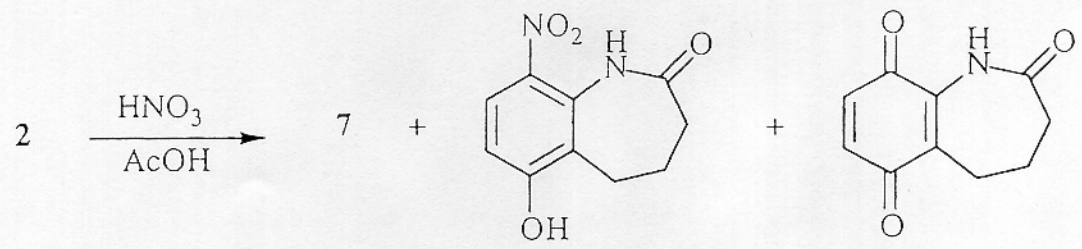


Reagents: a) HNO_3, AcOH, b) NaN_3, CCl_3-CO_2H

Scheme 2

Tetralone **6** was allowed to react with sodium azide in trichloracetic acid. The treatment afforded a mixture of two products which were isolated by column chromatography. These substances were characterized as the isomeric benzazepines **7** (26%) and **11** (61%). This result demonstrated that the Schmidt rearrangement of compound **6** proceeds mainly by alkyl migration than aryl migration.

In order to explore an alternative access to benzazepine 7 nitration of benzazepine 2 was studied. The reaction of 2 with nitric acid in acetic acid afforded benzazepine 7 (35%) along with its isomer 12 (18%) and quinone 3 (16%).



12 3

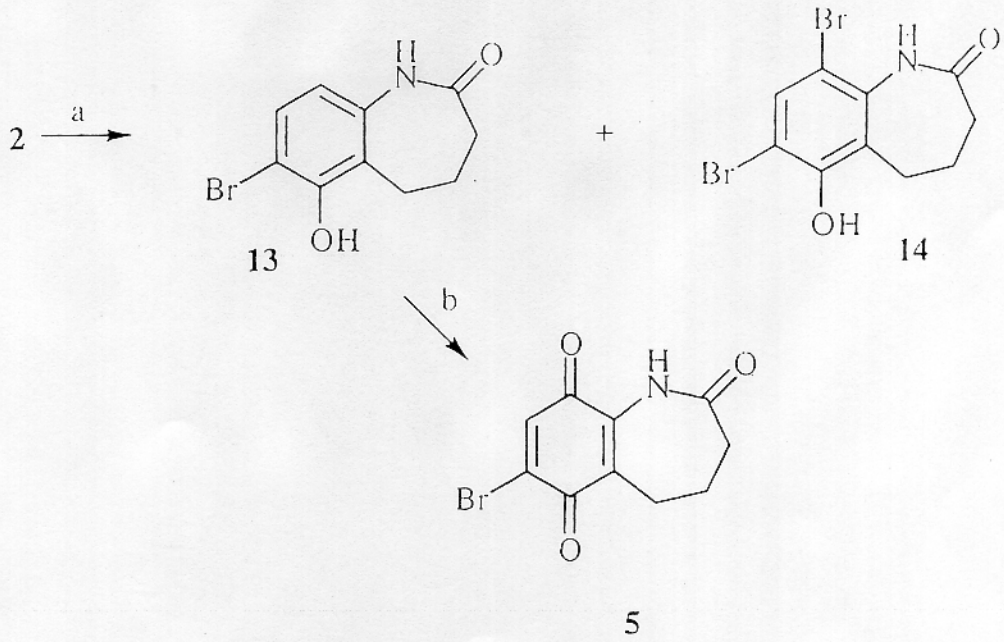
Benzazepine 7 was then subjected to hydrogenation over Pd-C to provide aminophenol 8 in 81% yield. Further attempts to obtain *orto*-quinone 4 by oxidation of 8 with chromium (VI) oxide were unsuccessful and the substrate was recovered in all the experiments.

On the basis of our result on the preparation of quinone 3 by oxidation of 6-hydroxy-1-benzazepine-2-one with (diacetoxyiodo)benzene[4] we studied the access to quinone 5 from bromophenol 13.

The preparation of 13 was attempted by bromination of 2 with NBS. The reaction performed in ethyl acetate afforded a mixture of compounds 13 and 14 in 21 and 33% yield respectively (Scheme 3). When 13 reacted with the hypervalent oxidant reagent, benzazepinetrione 5 was isolated in 72% yield. The structure of the *para*-quinone 5 was supported by the presence of a vinyl proton at δ 7.30 ppm, the infrared carbonyl absorption at 1680 cm^{-1}, and the presence of two carbonyl carbons at δ 179.2 and 179.7 ppm.

Compound 14 was also reacted with the hypervalent iodine reagent however the treatment did not lead to oxidation products and 14 was recovered in this assay.

In conclusion, our attempts to prepare an *orto*-quinone analog of antitumor active quinone 3 were unsuccessful. However, we have found an access to the new



Reagents: a) *N*-bromosuccinimide, AcOEt, b) $(AcO)_2IC_6H_5$, MeCN, H_2O

Scheme 3

1-benzazepine-6,9-quinone **5**. The possibility to carry out nucleophilic substitutions of the bromine atom in **5** and the regioselective control induced by this atom in cycloaddition reactions[8] makes the use of quinone **5** as precursor of new bioactive benzazepines and policyclic analogs especially atractive.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were determined on a Perkin Elmer 1310 spectrophotometer for KBr disc and wave numbers are reported in cm^{-1}. The ^1H- and ^{13}C NMR spectra were performed on Varian XL-100 and on Bruker AM-200 spectrometers in deuteriochloroform. Samples were dissolved in DMSO-d_6 unless otherwise stated and chemical shifts are expressed in δ scale (ppm) downfield from tetramethylsilane. *J*-values are given in Hz. EIMS were recorded on VB-12-250 spectrometer. Silica gel Merck 60 (70-230 mesh) and DC-alufolien 60 F_{254} were normally used for column and TLC chromatography respectively.

Reaction of tetralone 1 with nitric acid

Assay A.- A solution of concentrated nitric acid (1.5 mL , 22.00 mmol) in glacial acetic acid (5mL) was added dropwise to a cooled (5-8 C°) magnetically stirred solution of **1** (500 mg, 3.09 mmol) in acetic acid -water (20 mL, 10:1). The resulting mixture was stirred for 45 min, neutralized with solid sodium hydrogencarbonate and extracted with ethyl acetate (2x 25 mL). The extract was washed with water, dried over magnesium sulphate and evaporated in vacuo. The residue was column cromatographed on silica gel ($CHCl_3$) to afford crude 3,4-dihydro-5-hydroxy-6-nitro-2*H*-1-naphthalenone **6**. Preparative TLC ($CHCl_3$: C_6H_6 = 1:1) provided pure compound **6** (300 mg, 47%); mp 127-128° C; *Anal* Calcd for $C_{10}H_9O_4N$: C, 57.97; H, 4.38; N, 6.76. Found : C, 58.00; H, 4.60; N 6.57; IR: 3400-3250, 1680 , 1520, 1360; ^{1}H NMR (100 MHz, $CDCl_3$): δ 2.20 (quint., 2H, *J* =7, 3-H), 2.70 (t, 2H, *J* =7, 2-H), 3.04 (t, 2H, *J* = 7, 3-H), 7.66 (d, 1H, *J* = 9. 7 or 8-H), 8.06 (d,1H, *J* = 9, 8 or 7-H), 11.04 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.0, 22.8, 38.4, 117.6, 122.2, 136.2, 138.2, 142.8, 153.3, 196.8. EIMS *m/z* (%): 207 (M^+, 99.5), 179 (100),151 (37).

Further elution of the column ($CHCl_3$: C_6H_6 = 1:1) afforded 3,4-dihydro-6,8-dinitro-5-hydroxy-2*H*-1-naphthalenone **10** (120 mg, 19%); mp 245-246°C (ethanol); *Anal.*Calcd for $C_{10}H_8O_6N_2$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.73; H, 3.30; N,10.85; IR: 3260, 1690,1540,1340; ^{1}H NMR : δ 2.1 (m, 2H. 3-H), 2,72 (t, 2H, *J* = 7, 2-H), 2.94 (t, 2H, *J* = 7, 4-H), 8.36 (s, 1H, 7-H); ^{13}C NMR: δ 21.3, 23.2, 37.8, 118.3, 129.0, 136.5, 139.7, 139.9, 152.2, 194.9; EIMS *m/z* (%): 252 (M^+,100), 224 (64),178 (66),150 (79).

Assay B.- A solution of concentrated nitric acid (1.5 mL, 22.00 mmol) in glacial acetic acid (5.5 mL) was added dropwise to a magnetically stirred solution of naphthalenone **1** (50 mg, 0.31 mmol) in glacial acetic acid (5 mL) and the resulting mixture was refluxed for 45 min. Work-up followed by column cromatography ($CHCl_3$:AcOEt = 1:1) afforded **6** (14 mg, 21%), **10** (7.6 mg, 9%) and 3,4-dihydro-5-hydroxy-8-nitro-2*H*-1-naphthalenone **9** (33 mg, 48%); mp 259-261; $C_{10}H_9O_4N$: C, 57.97; H, 4.38; N, 6.76. Found : C, 58.52; H, 4.95; N 6.74; IR: 3180, 1650. 1580, 1350; ^{1}H NMR (200 MHz, acetone-d_6) : δ 2.10 (m, 2 H, 3-H), 2.70 (t, 2H, *J* = 7, 2-H), 2.95 (t, 2H, *J* = 7, 4-H), 7.15 (d, 1H, *J* = 9, 6-H), 7.35 (d, 1H, *J* = 9, 7-H), 9.6 (br s, 1H, OH).

Schmidt rearrangement of naphthalenone 6

To a heated solution of nitrotetralone **6** (200 mg, 0.97 mmol) in trichloroacetic acid (2.0 gr) was added sodium azide (94.4 mg, 1.45 mmol) at 65-70 C° and the mixture was mantaining with stirring for 6 h. The mixture was diluted with water (10 mL), neutralized with solid sodium hydrogencarbonate, and extracted with ethyl acetate (2x25 mL). The organic layer was washed with water, dried over sodium sulphate and evaporated under vacum. The crude was filtered through silica gel to afford a mixture of isomer **7** and **11** which was separated by column cromatography on silica gel (CH_2Cl_2:AcOEt = 1:1). Evaporation of the first fraction afforded crude 1,2,3,4-tetrahydro-6-hydroxy-7-nitro-5*H*-1-benzazepin-2-one **7** which was purified by preparative TLC ($CHCl_3$:C_6H_6 = 1:1) to give pure **7** (55 mg, 26%); mp 226-227 °C; *Anal* Calcd for $C_{10}H_{10}O_4N_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.13; H, 4.70; N, 11.88; IR: 3400, 3180, 1670, 1600; ^{1}H NMR (100 MHz): δ 2.18 (m, 4H , 3- and 4-H), 2.82 (t, 2H, *J* = 7, 5-H), 6.68 (d, 1H, *J* = 9, 9-H), 7.96 (d,1H, *J* = 9, 8-H), 10.8 (s,1H, NH), 11.60 (s,1H, OH); ^{13}C NMR (50 MHz): δ 20.1, 28.8, 38.2, 116.9, 123.0, 128.6, 137.1, 142.9, 149.4 ,169.8; EIMS *m/z* (%): 222 (M^+, 97), 167 (100),150 (88).

Further elution of the column (CH_2Cl_2:AcOEt = 1:1) afforded 1,2,3,4-tetrahydro-6-hydroxy-7-nitro-5*H*-2-benzazepin-1-one **11** (130 mg, 61%); mp 247-248 C; *Anal* Calcd for $C_{10}H_{10}O_4N_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.22; H, 4.71; N 12.20; IR 3400, 3200, 1665, 1580, 1520 ; ^{1}H NMR: δ 1.86 (quint. , 2H, *J* = 7, 4-H) , 2.76-3.06 (m, 4H, 3- and 5-H) , 5.50 (br s, 1H, NH) , 7.13 (d, 1H, *J* = 9, 8- or 9-H) , 7.92 (d, 1H, *J* = 9, 9- or 8-H), 8.30 (br s, 1H, OH); ^{13}C NMR: δ 22.4, 26.9, 33.9, 113.2, 122.0,123.9, 130.9, 147.2, 152.4, 173.5 ; EIMS *m/z* (%): 222 (M^+, 100), 193 (10), 175 (71).

Nitration of benzazepinone 2

Concentrated nitric acid was added dropwise (0.4 mL, 6.40 mmol) to a stirred solution of benzazepinone **2** (180 mg, 1.01 mmol) in acetic acid (15 mL) at rt. The mixture was stirred for 10 min, neutralized with aqueous saturated sodium hydrogencarbonate, and extracted with ethyl acetate (3x30 mL). The extract was washed with water, dried over sodium sulphate and evaporated in vacuo. The residue

was cromatographed ($CHCl_3$: AcOEt = 1:1) and from the less polar fraction 1-benzazepinquinone **3** (30 mg, 16%) was isolated.

The second fraction afforded 6-hydroxy-7-nitro-1-benzazepin-2-one **7** (80 mg. 35%). The more polar fraction provided 1,2,3,4-tetrahydro-6-hydroxy-9-nitro-5*H*-1-benzazepin-2-one **12** (40 mg, 18%); mp 265-266°C; *Anal* Calcd for $C_{10}H_{10}O_4N_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.76; H, 4.56; N, 12.35; IR: 3400, 3200, 1650, 1580, 1520, 1300; ^{1}H NMR (100 MHz) : δ 2.0-2.4 (m, 4H, 3- and 4-H), 2.80 (t, 2H, J = 6, 5-H), 6.9 (d, 1H, J = 9, 7-H) , 8.00 (d,1H, J =9, 8-H), 7.0-8.0 (br s, 1H, NH), 9.40 (s, 1H, OH).

Preparation of benzazepine 8

A suspension of nitrobenzazepinone **7** (100 mg, 0.45 mmol), Pd-C (10%, 10 mg) in ethanol (20 mL), was shaken under hydrogen in a Parr apparatus at 30 psi for 2 h at rt. The solution was filtered and evaporated in vacuo to afford compound **8**. The residue was chromatographed on silica gel ($CHCl_3$:AcOEt = 1:1) to afford 1,2,3,4-tetrahydro-6-hydroxy-7-amino-5*H*-1-benzazepin-2-one **8** (70 mg., 81%); mp 215-216°C. *Anal* Calcd for $C_{10}H_{12}O_2N_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 61.81; H, 6.11; N, 14.17; IR: 3550-3200, 3380-3300, 3200, 1670, 1620; ^{1}H NMR (100 MHz): δ 2.34-2.52 (m, 6H, 3-, 4-H and NH_2), 3.20 (m, 2H, 5-H), 6.70-7.50 (m, 3H, 8-, 9-H, and NH); EIMS *m/z*(%):192 (M^+, 100),164 (12),137 (41), 136 (32).

Reaction of benzazepinone 2 and *N*-bromosuccinimide

A suspension of benzazepinone **2** (468 mg, 2.65 mmol), NBS (470 mg, 2.65 mmol) in ethyl acetate (50 mL) was stirred at rt for 1.5 h. The mixture was washed with water (2x20 mL), and the dry organic phase was evaporated. The residue was cromatographed ($CHCl_3$) to afford pure 7,9-dibromo-6-hydroxy-1-benzazepin-2-one **14** (224 mg, 33%); mp 245-246°C (ethanol-petroleum ether); *Anal* Calcd. for $C_{10}H_9O_2NBr_2$: C, 35.85; H, 2.71; N, 4.18. Found: C, 36.82; H, 2.91; N 4.21. IR: 3200-3100, 1660 , 1570; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.95-2.10 (m, 4H, 3- and 4-H) , 2.50 (t, 2H, J = 8.7 , 5-H), 7.69 (s, 1H, 8-H), 9.14 and 9.61 (2s, 2H, NH and OH); ^{13}C NMR (50 MHz): δ 24.7 , 27.5, 33.0, 107.9, 109.4, 126.3, 133.1, 138.2, 151.5, 173.3.

Further elution with $CHCl_3$ afforded 7-bromo- 6-hydroxy-1-benzazepin-2-one **13** (189 mg, 21%); mp 225-227°C (EtOH-petroleum ether); *Anal* Calcd. for $C_{10}H_{10}O_2NBr$: C, 47.06; H, 3.95; N, 5.49. Found : C, 46.61; H, 4.01; N, 5.57; IR: 3200-3100, 1650,1570 ; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.0-2.1 (m, 2H, 4-H) , 2.74 (m, 2H, 3- and 5-H), 6.46 (d, 1H, J = 7.6, 8- or 9-H), 7.32 (d, 1H, J = 7.6, 9- or 8-H) ; ^{13}C NMR (50 MHz): δ 23.5, 27.4, 33.3, 107.1, 115.0, 123.1, 130.3, 140.0, 151.5. 173.4.

Reaction of benzazepinone 13 and (diacetoxyiodo)benzene

To a stirred solution of **13** (113 mg, 0.64 mmol) in acetonitrile-water (3:1; 20 mL) was added a solution of (diacetoxyiodo)benzene (350 mg, 0.99 mmol) in 15 mL of the same mixture. The mixture was stirred at rt for 30 min, diluted with water (15 mL) and extracted with chloroform (2x20 mL). The solvent was removed and the red oil residue was mantained under vacum for 30 min at 90°C. The crude quinone **5** (117 mg, 98%) was cromatographed ($CHCl_3$) to afford pure compound **5** (86 mg, 72%) as orange solid mp 109-111°C; *Anal* Calcd for: $C_{10}H_8O_3NBr$: C, 44.47; H, 2.99; N, 5.19. Found: C, 44.38; H, 3.09; N 5.11. IR: 3100,1 680, 1660-1640; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.95-2.03 (quint., 2H, J = 6.6, 4-H), 2,74 (2H, m, 5-H), 2.81 (2H, t, J = 6.6, 3-H), 7.30 (s,1H, 8-H), 8.10 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.43, 28.1, 37.3, 123.7, 134.7, 135.2, 139,7, 173.6, 179.2, 179.7.

Acknowledgments

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