Studies on Quinones. Part 22.' Synthesis of 1-Benzazepine-6,9-Quinone Derivatives

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STUDIES ON QUINONES. PART 22. SYNTHESIS OF 1-BENZAZEPINE-

6,9-QUINONE DERIVATIVES

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ABSTRACT: A facile synthesis of 1,2,3,4-tetrahydro-5H-1-benzazepine-
quinone derivatives starting from 5-methoxy-1-tetralone is described.

Many examples are reported in the literature on the
preparation of heterocyclic quinones that have the quinone
moiety fused to a 5-, 6-, and 7-membered aza-heterocyclic
ring. The current interest in developing synthetic methods in
this field is important due to the biological activities
generally exhibed by these heterocyclic quinones, which are
related to the redox properties of the quinonic nucleus and
also to the heterocyclic system.[2]

In connection with our interest on the synthesis of
heterocyclic quinones[3-8] we decided to explore the preparation
of benzazepines having a p-quinonic nucleus. The synthesis of
benzazepinequinones has received little attention and only
recently Truscott,[9] have reported the formation of benzazepine-
p-quinone 1 in 10% yield, by autoxidation of 3-hydroxy-
anthranilic acid in the presence of proline, followed by
methylation.

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Our interest in these heterocyclic quinones comes from their potential application as key intermediates in the synthesis of benz- and naphthazepines. It is noteworthy that benzazepines have attracted considerable attention due to their numerous pharmacological activities.[10-13]

This communication describes the Schmidt rearrangement of the 5-methoxy- and 5-hydroxy-1-tetralone (2, 3), and the high-yield syntheses of benzazepinequinones prepared by oxidation from the corresponding 5-hydroxybenzazepines with the Fremy's salt or (diacetoxyiodo)benzene.

Taking into account that the Schmidt rearrangement is a well established method for synthesizing tetrahydrobenz-azepines from tetralones,[14] we investigate the possibility to prepare benzazepinequinones through the commercially available 5-methoxy-1-tetralone 2.

Treatment of 2 with sodium azide-trichloracetic acid for 6 h afforded a mixture of lactam 4, as the main product, along with a 4:1 mixture of the isomeric tetrazoles 6 and 8. The heterocycle 4 and the mixture of the isomers 6 and 8 were isolated in 55 and 6% yield respectively, by column chromatography on silica gel. Although our attempts to isolate the tetrazoles 6 and 8 by chromatographic methods were unsuccessful, the ratio of isomers could be determined by ¹H-NMR spectroscopy.

Since attempts to prepare hydroxybenzazepine 5 by dealkylation of heterocycle 4, with 48% aqueous hydrobromic acid induced the fission of the heterocyclic ring, we decided to prepare compound 5 by Schmidt rearrangement of hydroxytetralone 3. The precursor 3 was obtained in 85% yield by dealkylation of compound 2 with 48% aqueous hydrobromic
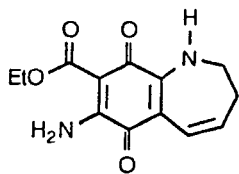
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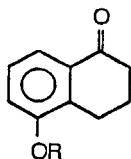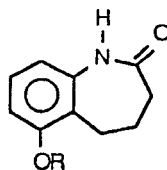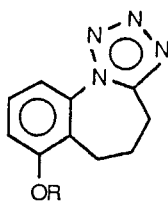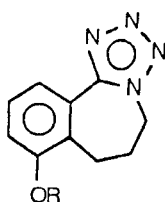
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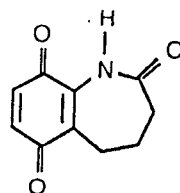
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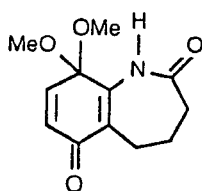
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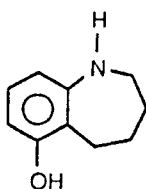
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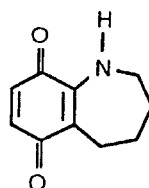
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acid. It is noteworthy that the synthesis of the tetralone 3 has been reported in the patent literature[13] from the 1,5-dihydroxynaphthalene and its application as precursor of compouds with pharmacological activities has been described.[16,17]

The rearrangement of 3 by warming with sodium azide-trichloracetic acid for 6 h afforded hydroxybenzazepine 5 along with the isomeric tetrazoles 7 and 9. Column chromathography of the crude afforded hydroxybenzazepine 5 and a 4:1 mixture of the isomers 7 and 9, in 59 and 11% yield, respectively.

Compound 5 was oxidized to the benzazepinequinone 10 by either Fremy's salt or (diacetoxyiodo)benzene procedure[18,19,20] Fremy's salt provided quinone 10 in 96% and the hypervalent iodine oxidation gave 10 in 62% yield.

When compound 5 was reacted with (diacetoxyiodo)benzene in methanol solution at room temperature, the p-quinone monoketal 11 was obtained in high yield.

The heterocyclic quinone 10, which is quite stable, displays in the ^{1}H-NMR spectrum the signals of the methylenic protons at δ 1.98-2.09 and 2.70-2.80 ppm, the amidic proton at δ 8.15 ppm and the quinonic protons appeared as a singlet at δ 6.80 ppm. Moreover, the ^{13}C-NMR spectrum displays the carbonylic carbons of the quinone nucleus at δ 186.60 and 181.10 ppm. Probably, the carbonylic group at C-6 of 10 is magnetically shielding by the conjugative effect of the nitrogen atom. This magnetic difference of the carbonyl quinonic groups in the compound 10 probably, have influence upon the regioselectivity on the nucleophilic addition to the external quinonic double bond.

On   the basis of these remarkable results in the synthesis
of   the   quinone 10   and   its   monoketal 11   we explored   the
preparation of   1,2,3,4-tetrahydro-5H-1-benzazepine-6,9-quinone
13 from   benzazepinone 5. Heterocycle 5 was treated with LiAlH₄
in   THF to afford the   respective benzazepine   12 in 84% yield.

The reaction   of 12   with (diacetoxyiodo)benzene gave   the
heterocyclic quinone 13, as an unstable solid, in 63% yield.

In   conclusion,   we   have   developed   a   short   synthetic
sequence   to prepare benzazepines having a p-quinonic or latent
system, starting from   the commercially   available 5-methoxy-1-
tetralone   2. Further studies on the functionalisation of these
new benzazepine-p-quinones and investigation   of the   vasocon-
strictor properties detected in` preliminary screening[21] on   the
quinone 10, are in progress.

E X P E R I M E N T A L

M.p.s. were measured on   a Kofler hot-stage   apparatus and   are
uncorrected.   Unless otherwise stated, IR spectra were recorded
on   a Perkin-Elmer 1310 spectrophotometer   for KBr   disc,   max
are reported in   cm⁻¹. ¹H-NMR spectra were obtained   on a Varian
XL-100   or a   XL-300 spectrometer,   ¹³C-NMR   were recorded   on a
Bruker   WM 200   SY(200 MHz)   or a   Varian XL-300   spectrometer.
Samples   were   dissolved   in   CDCl₃   and   chemical   shifts   are
expressed in parts per   million (ppm)   downfield from SiMe₄ .
J-values are given   in Hz. Mass spectra were recorded on VB-12-
250   spectrometer. Silica   gel   Merck   60(70-230   mesh) and   DC-
alufolien   60F₂₅₄ ,   were normally   used   for preparative   column
chromatography and analytical TLC, respectively.

The Schmidt reaction   of   5-methoxy-1-tetralone 2.-   To   a
vigorously stirred solution   of compound 2 (0.35 g, 1.99   mmol)

in 3.0 g of trichloracetic acid heated to 60-65°C, was added

sodium azide (0.195 g, 3.00 mmol) in one portion. The mixture

was then heated to reflux for 6 h, allowed to cool to room

temperature, and poured into water (50 ml). The mixture was

neutralized with 10% aqueous NaHCO$_3$ and extracted with ethyl

acetate (2x50 ml). The extract was washed with water (25 ml),

dried (MgSO$_4$), and evaporated under reduced pressure. The

residue was chromatographied on silica gel with chloroform as

the eluent.

From the first eluat tetralone 2 (25 mg, 0.154 mmol) was

recovered. The second fraction afforded a 4:1 mixture of the

tetrazoles 6 and 8   (0.02 g, 6%)(Found: C, 60.85; H, 5.77; N,

25.42. Calcd. for C$_{11}$H$_{12}$N$_4$O: C, 61.09; H, 5.59; N, 25.91%); IR:

1590, 1470, and 1260; δ_H (300 MHz): 2.33 (q, 1.6 H, J 7, 4-H),

2.37 (q, 0.4 H, J 7, 4-H), 2.65 (t, 1.6 H, J 7, 3-H), 2.97 (t,

0.4 H, J 7, 5-H), 3.00 (t, 1.6 H, J 7, 5-H), 3.90 (s, 3H,

OMe), 3.92 (s, 3H, OMe), 4.55 (t, 0.4 H, J 7, 3-H), 6.98-7.08

(m, 1H, 7-H), and 7.27-7.46 (m, 2H, 8-H and 9-H); m/z (%): 216

(M$^+$, 18), 188 (34), 173 (20), and 160 (100).

From the third fraction 5-methoxy-1,2,3,4-tetrahydro-5H-

1-benzazepin-2-one 4 (0.195 g, 55%) was obtained; m.p. 155.5-

157°C (from benzene-petroleum ether 40-60°C); (Found: C,

68.92; H, 6.88; N, 7.62. Calcd. for C$_{11}$H$_{13}$NO$_2$: C, 69.09;

H, 6.85; N, 7.33%); IR: 3180, 1670, and 1580; δ_H (100 MHz):

2.05-2.40 (m, 4 H, 4-H and 5-H), 2.88 (t, 2 H, J 8, 3-H), 3.84

(s, 3 H, OMe), 6.67 (s, 2 H, 7-H and 8-H), 7.15 (t, 1 H, J 8,

8-H), 8.58 (s, 1H, NH); δ_C 21.68, 27.34, 33.15, 55.63, 107.48,

114.33, 122.44, 127.13, 139.31, 157.39, and 175.91; m/z (%):

191 (M , 51), 136 (100), and 106.1 (35).

5-hydroxy-1-tetralone 3.- A solution of 5-methoxy-1-tetralone 2 (1.0 g, 5.68 mmol), aqueous hydrobromic acid (48%, 100 ml) and glacial acetic acid (10 ml), was gently refluxed for 45 min. The mixture was allowed to cool at ambient temperature, neutralized with NaHCO$_3$ and extracted with ethyl acetate (2x25 ml). The extract was washed with water (10 ml), dried (MgSO$_4$), and evaporated under reduced pressure to afford the tetralone 3 which was chromatographed on silica gel (CHCl$_3$-AcOEt 1:1) to yield compound 3 (0.78 g, 85%); m.p. 210-211°C (Found: C, 74.02; H, 6.42. Calcd. for C$_1$H$_{10}$O$_2$: C, 74.05; H, 6.22%); IR: 3160, 1640, 1580, and 1230; δ$_H$ (DMSO-d$_4$, 100 MHz): 2.06 (m, 2 H, 3-H), 2.56 (t, 2 H, J 7, 2-H), 2.90 (t, 2 H, J 7, 4-H), 7.16-7.48 (m, 3 H, 6-H, 7-H, and 8-H).

The Schmidt reaction of 5-hydroxy-1-tetralone 3.- To a vigorously stirred suspension of compound 3 (0.39 g, 2.40 mmol) in 3.35 g of trichloracetic acid heated to 60-65°C, was added sodium azide (0.210 g, 3.35 mmol) in one portion. The mixture was neutralized with NaHCO$_3$ and extracted with ethyl acetate (2x50 ml). The extract was washed with water (25 ml), dried (MgSO$_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel, with a 1:1 mixture chloroform-ethyl acetate as eluent.

From the first eluat the ·substrate 3 (39 mg, 0.24 mmol) was recovered. Evaporation of the second fraction afforded a 4:1 mixture of the tetrazoles 7 and 9 (48 mg, 11%); (Found: C, 59.92; H, 4.88; N, 27.17. Calcd. for C$_{10}$H$_1$N$_4$O: C, 59.39; H, 4.98; N, 27.71%); IR: 3200, 1590, and 1470; δ$_H$ (DMSO-d; 100 MHz): 2.30 (q, 1.6 H, J 7, 4-H), 2.32 (q, 0.4 H, J 7, 4-H), 2.60 (t, 1.6 H, J 7, 3-H), 2.99 (t, 0.4 H, J 7, 5-H), 3.00 (t,

1.6 H, J 7, 5-H), 4.70 (t, 0.4 H, J 7, 3-H), 7.10-7.80 (m, 3H,

Ar-H), and 10.25 (br s, 1H, OH); m/z (%): 202 (M^{+}, 24), 174

(49), and 146 (100).

Evaporation of the third fraction gave 5-hydroxy-1,2,3,4-
tetrahydro-5H-1-benzazepin-2-one 5 (225 mg, 59%), m.p. 253-
254°C (Found: C, 67.86; H, 6.19; N, 8.12. Calcd. for $C_{10}H_1NO_2$:
C, 67.78; H, 6.26; N, 7.91%); IR: 3400, 3200, 1685, and 1580;
δ_H (DMSO-d$_6$; 300 MHz): 2.11 (q, 2 H, J 7, 4-H), 2.22 (t, 2 H,
J 7, 5-H), 2.76 (t, 2 H, J 7, 3-H), 6.53 (d, 1 H, J 8, 7-H or
9-H), 6.72 (d, 1 H, J 8, 9-H or 7-H), 7.06 (t, 1H, J 8, 8-H),
9.51 (s, 1H, NH or OH), and 9.56 (s, 1H, OH or NH); δ_c 21.9,
27.6, 33.3, 111.7, 112.98, 120.2, 127.0. 140.2, 155.1, and
174.1; m/z (%): 177 (M^{+}, 51), 148 (12), and 122 (100).

1,2,3,4-tetrahydro-5H-1-benzazepine-2,6,9-trione 10

Method A: To a solution of lactam 5 (96.55 mg, 0.5 mmol) in

methanol-water (1:2, 20 ml) was added Fremy's salt (1.17 g,

4.4 mmol) and KH$_2$PO$_4$ (111 mg, 0.82 mmol) and the mixture was

stirred at room temperature for 24 h. Then, the mixture was

filtered, the solution was neutralized with NaHCO$_3$, and

extracted with chloroform. The organic layer was dried (MgSO$_4$),

and evaporated under reduced pressure to give the quinone 10.

Further purification of the quinone by column chromatography

on silica gel (chloroform-ethyl acetate 1:1) afforded pure

quinone 10 (81 mg, 85%) as orange crystals, m.p. 116-117°C

(Found: C, 62.99; H, 4.72; N, 7.71. Calcd. for $C_{10}H_9NO_3$: C,

62.82; H, 4.75; N, 7.33%); IR: 3250, 1680, 1660, 1640, 1580,

and 1460; δ_H (300 MHz): 1.98-2.08 (m, 2 H, 4-H), 2.70-2.80 (m,

4 H, 3-H and 5-H), 6.80 (s, 2 H, 7-H and 8-H), and 8.15 (s,

1H, NH); δ_c 19.37, 26.67, 37.00, 124.12, 133.02, 134.87,

137.84, 173.67, 181.11, and 186.63; m/z (%): 191 (M⁺, 60), 162 (50), 146 (65), 55 (100), and 44 (82).

Method B: A solution of (diacetoxyiodo)benzene (37 mg, 1.46 mmol) in acetonitrile-water (4:1; 10 ml) was added with stirring to a solution of the benzazepine 5 (130 mg, 0.73 mmol) in acetonitrile-water (4:1; 10 ml), and the resulting solution was kept at ambient temperature for 30 min.

Then the mixture was diluted with water, extracted with chloroform (2x25 ml), and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was chromatographied on silica gel (chloroform-ethyl acetate 1:1) to afford pure trione 10 (91 mg, 65%).

9,9-dimethoxy-1,2,3,4-tetrahydro-5H-1-benzazepin-2,6-dione 11.- A solution of (diacetoxyiodo)benzene (363 mg, 1.13 mmol) in methanol (15 ml) was added with stirring to a solution of the hydroxybenzazepine 5 (100 mg, 0.565 mmol) in methanol (10 ml) and the mixture was kept at room temperature for 30 min. The mixture was diluted with water (25 ml), extracted with chloroform (2x25 ml), dried over MgSO₄, and evaporated under reduced pressure. The residue was chromatographed on silica gel (chloroform-ethyl acetate 1:1) to give monoketal 11 (91%) as an oily liquid; (Found: C, 60.50; H, 6.33; N, 6.08. Calcd. for $C_2H_{13}NO_4$: C, 60.75; H, 6.37; N, 5.90%); IR (neat): 3220, 1680, 1660, and 1610; δ_H (300 MHz): 2.08 (m, 2 H, 4-H), 2.69 (m, 4 H, 3-H and 5-H), 3.29 (s, 6H, 2 x OMe), 6.48 (d, 1H, J 10, 7-H), 6.70 (d, 1H, J 10, 8-H), and 7.46 (br s, 1H, NH); δ_c 22.55, 23.03, 36.70, 51.29, 94.49, 123.14, 132.50, 138.36, 144.30, 174.86, and 184.53; m/z (%): 237 (M⁺, 22), 206 (100), 177 (76), and 162 (42).

6-hydroxy-1,2,3,4-tetrahydro-5H-1-benzazepine 12.- To an ice-cooled solution of the heterocycle 5 (350 mg, 1.98 mmol) in anhydrous THF (100 ml) was added LiAlH$_4$ (300 mg, 7.9 mmol) and the resulting mixture was heated to reflux for 4 h. The mixture was reacted with ethyl acetate-water-acetic acid (1:1:1; 10 ml) and then neutralized with NaHCO$_3$. The solution was filtered and the solids were extracted with ethyl acetate (2 x 50 ml). The extract was dried (MgSO$_4$) and the solvent was removed to afford hydroxybenzazepine 12 (271 mg, 84%). An analytical sample of 12 was obtained by column chromatography on silica gel (benzene-ethyl acetate; 2:1); m.p. 145-146.5°C; (Found: C, 73.72; H, 7.66; N, 8.29. Calcd. for C$_{10}$H$_{13}$NO: C, 73.59; H, 8.03; N, 8.58%); IR: 3450, 1590, and 1450; δ_H (300 MHz): 1.60-1.90 (m, 4 H, 3-H and 4-H), 2.82 (t, 2 H, J 6, 5-H), 3.10 (t, 2H, J 6, 2-H), 3.60 (br s, 2H, NH and OH), 6.36 (d, 2H, J 8, 7-H and 9-H), and 6.88 (t, 1H, J 8, 8-H).

1,2,3,4-tetrahydro5-H-1-benzazepine-6,9-quinone 13.- To a solution of the benzazepine 12 (100 mg, 0.613 mmol) in acetonitrile-water (3:1 ; 20 ml) was added (diacetoxyiodo)-benzene in the same mixture (20 ml) and the resulting solution was kept at room temperature for 15 min. The reaction mixture was extracted with dichloromethane (2 x 15 ml) and the extract was washed with water, and dried over MgSO . Removal of the solvent afforded quinone 13 (68 mg, 63%) as an unstable violet solid, m.p. 77-79°C; IR: 3400, 1660, 1620, and 1560; δ_H (100 MHz): 1.82 (m, 4H, 3-H and 4-H), 2.66 (t, 2H, J 7, 5-H), 3.34 (t, 2H, J 7, 2-H), 5.76 (br s; 1H, NH), 6.52 (d, 1H, J 10, 8-H), and 6.68 (d, 1H, J 10, 7-H).

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