Studies on Quinones. Part 25. Synthetic Approaches to 6,9-Dioxygenated-benzazepinones [1]

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The Schmidt and Beckmann rearrangement of 3,4-dihydro-4,4-dimethyl-1(2*H*)-naphthalenones bearing oxygenated groups at the 5,8-positions, and some of their oximes are reported. Depending upon the structure of the substrates and the reaction conditions 4,5-dihydro-3*H*-naphth[1,8-*cd*]isoxazol, benzazepin-2-one and 5,6-dihydro-7*H*-tetrazolo[1,5-*a*][2]benzazepine derivatives were generated.

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Introduction.

As part of a program directed towards the synthesis of heterocyclic quinones [2,3,4,5] we have reported a short synthetic sequence to prepare 1,2,3,4-tetrahydro-5*H*-benzazepine-2,6,9-trione **1** [6] starting from 3,4-dihydro-5-methoxy-1(2*H*)-naphthalenone **2** through the Schmidt rearrangement. Now we report synthetic attempts to prepare benzazepinones [7] as suitable precursors of the corresponding heterocyclic quinones. The Schmidt and Beckmann rearrangement are used to produce ring enlargement of 5,8-dioxygenated-3,4-dihydro-4,4-dimethyl-1(2*H*)-naphthalenones and their oximes.

3,4-Dihydro-5,8-dihydroxy-4,4-dimethyl-1(2*H*)-naphthalenone **9**, which contains a latent quinonic nucleus and two geminal methyl groups on C-4, was selected to start the study because its precursor **5** is obtained easily by acid-induced rearrangement of benzo[*b*]furan **3** [8]. Furthermore, the presence of geminal methyl groups at C-5 on benzazepinones, is pharmacologically relevant in the analgesic activity of 1-benzazepin-2-ones [9].

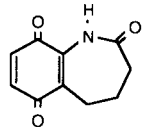
Results and Discussion.

The naphthalenone **9** required for this study was prepared in 96% yield from naphthalenone **5**, by catalytic hydrogenation over 10% palladium on charcoal. Terada *et al.* [10] have reported the preparation of **9**, in 38% yield, by reaction of the **13** and **14** isomers mixture with boron trifluoride etherate.

We attempted to induce the ring enlargement on naphthalenone **9** by reaction with sodium azide in trichloroacetic acid. However, no reaction was observed and the starting material was recovered. The monomethyl ether **10**, prepared in 79% overall yield by methylation of **5** followed by catalytic hydrogenation of **6** over 10% palladium on charcoal, was also unreactive toward the Schmidt rearrangement using sodium azide and trichloroacetic acid. On the other hand, the treatment of the monomethyl ether **10** with sodium azide in sulfuric acid afforded naphthisoxazol **15** in 45% yield, and no rearranged products were detected by ^{1}H nmr.

We decided to investigate the reactivity of oxime **17** toward the Beckmann rearrangement. Compound **17** was prepared in 90% yield by reaction of naphthalenone **9** with hydroxylamine hydrochloride. The treatment of **17** with polyphosphoric acid gave the naphthisoxazol **16** in 97% yield.

Quinone **19**, prepared quantitatively by oxidation of **17** with manganese dioxide in dichloromethane [11], was the subject of rearrangement with polyphosphoric acid as well. The treatment afforded a complex mixture of products in which naphthisoxazole **16** was detected by tlc and ^{1}H nmr. The formation of **16** probably is mediated by product **17**, which is generated from quinone **19** through a redox reaction in acid medium.



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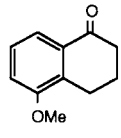

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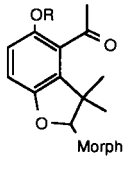
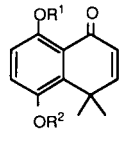


3. R = H
4. R = Me



5. $R^1 = R^2 = H$
6. $R^1 = H$, $R^2 = Me$
7. $R^1 = Me$, $R^2 = H$
8. $R^1 = R^2 = Me$

These results indicated that the hydroxy group at the 8-position in substrates **9**, **10** and **17** prevents the rearrangement to the corresponding benzazepinones. In the case of naphthalenone **9** and **10**, the hydrogen bonding probably decreases the reactivity of the carbonyl toward hydrazoic acid [12]. The formation of naphthisoxazole **16** from the oxime **17** can be explained considering that the hydroxy group prevents the ring enlargement by cyclization during the generation of the iminium cation intermediate.

In order to avoid the isoxazol ring formation and induce

the ring enlargement of the 3,4-dihydro-1(2*H*)-naphthalenone system or its oximes, we investigated the rearrangement with 3,4-dihydro-5,8-dimethoxy-4,4-dimethyl-1(2*H*)-naphthalenone **12**, in which the methoxy group at C-8 should have no interference on the expansion. For this purpose we explored the synthesis of **12** through 5,8-dimethoxy-4,4-dimethyl-1(4*H*)-naphthalenone **8** which could be prepared by methylation of naphthalenone **5**. However, attempts to convert **5** to **8** with dimethyl sulfate in basic medium under a variety of conditions, was unsuccessful affording the monomethyl ether **6** as the sole product.

Taking into account that the reluctance to methylation of the hydroxy group at 8-position in **5** or **6** is due to the hydrogen bonding, we explored the synthesis of compound **8** through the synthetic sequence **3-4-7-8**. Benzo[*b*]-furan **3**, in which the hydroxy group is unchelated [8] was converted to the methyl ether **4**, in 91% yield, by treatment with dimethyl sulfate under standard conditions. Then, benzo[*b*]furan **4** was rearranged to 5-hydroxy-8-methoxy-4,4-dimethyl-1(4*H*)-naphthalenone **7** in 90% yield by treatment with hydrochloric acid in ethanol solution. Finally, methylation of naphthalenone **7** produced dimethyl ether **8** in nearly quantitative yield.

An attempt to convert **7** into naphthalenone **11** by catalytic hydrogenation over 10% palladium on charcoal generated a mixture of product **11** and naphthalenol **20** as revealed by the ^{1}H nmr spectrum of the crude substance. A better result was obtained when the hydrogenation was carried out under basic conditions, where naphthalenone **11** was achieved in 89% yield. This procedure was employed to convert compound **8** into **12** which was accomplished in 58% yield. Compound **12** was also obtained by methylation of **11** with dimethyl sulfate in 96% yield.

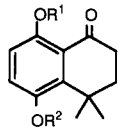
The investigation of the behaviour of the naphthalenone **11** toward the Schmidt rearrangement showed that its treatment with sodium azide in trichloroacetic acid yielded a mixture of 2-benzazepinone **21** (36%), tetrazole **23** (28%), naphthalenone **9** (15%) and starting material.

The structure of **21** was established by the ^{1}H nmr spectrum that shows the signals of two methylenic protons (δ 2.90 ppm) at C-3 coupled with the vicinal methylenic and amidic protons at δ 1.72 and 7.78 ppm, respectively. The structure of tetrazole **23** was deduced by the absence of infrared carbonylic absorption and the ^{1}H nmr spectrum which shows two methylenic protons (δ 4.44 ppm) deshielded by the influence of the tetrazole ring.

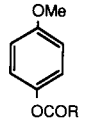
The Schmidt rearrangement was attempted with naphthalenone **12** under the same conditions employed in the rearrangement of ether **11**. This treatment afforded a mixture of 2-benzazepinone **22** (51%), tetrazole **24** (18%), naphthisoxazole **15** (8%), and starting material.

The above results indicating that alkyl migration is more favored than aryl transposition in naphthalenones **11** and **12** were unexpected considering that the aromatic ring of both substrates contains two strongly electron-releasing substituents, which should favor the aryl migration [7]. Furthermore, we have observed that aryl migration is the main process involved in the Schmidt rearrangement of 1-naphthalenones containing methoxy and hydroxy substituents at C-6. We assume that the alkyl migration observed in the rearrangement of compounds **11** and **12** might occur through intermediate **26** which could arise from an iminodiazonium intermediate **25** [12-14]. The existence of intermediate **26** could explain the generation of naphthisoxazole **15** from **12** by a competitive carbon-oxygen bond cleavage with the alkyl migration.

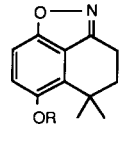
The reactivity of 3,4-dihydro-4,4-dimethyl-5-hydroxy-8-methoxy-1(2*H*)-naphthalenone oxime **18** toward the Beckmann rearrangement was examined under the conditions reported by Fujita [15]. Compound **18** prepared in 94% yield from **11** under standard conditions, was reacted with a diethylacetamide-phosphorus oxychloride mixture in acetonitrile solution to afford naphthoisoxazole **16** in 81%



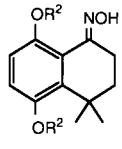
9. $R^1 = R^2 = H$
10. $R^1 = H$, $R^2 = Me$
11. $R^1 = Me$, $R^2 = H$
12. $R^1 = R^2 = Me$



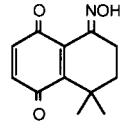
13. $R = CH_2CH{=}CMe_2$
14. $R = CH{=}CHCHMe_2$



15. R = Me
16. R = H



17. $R^1 = R^2 = H$
18. $R^1 = Me$, $R^2 = H$



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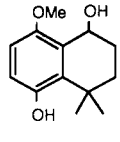

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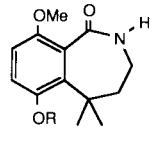
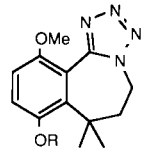
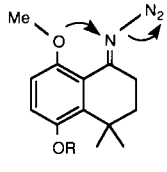


21. R = H
22. R = Me



23. R = H
24. R = Me



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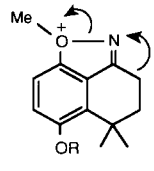

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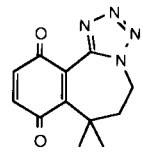

27

yield. The formation of heterocycle **16** probably occurs by cleavage of the C-O bond of the ether group in **18** followed by cyclization of **17**.

Finally, we examined the oxidative deprotection of compounds **21**, **22**, **23**, and **24** in order to prepare the corresponding heterocyclic quinones. Compounds **21** and **22** were unreactive to the oxidative demethylation with cerium ammonium nitrate [16] and with silver(II) oxide [17], and both substrates were recovered. However, the treatment of ether **23** and **24** with cerium ammonium nitrate produced the heterocyclic quinone **27** in 73 and 87% yields, respectively.

In conclusion, we have studied the reactivity of 3,4-dihydro-4,4-dimethyl-1(2*H*)-naphthalenones bearing oxygenated groups at the 5- and 8-position and the corresponding oximes toward the rearrangement to benzazepinones. The results reveal that the Schmidt rearrangement involves the alkyl migration to afford 2-benzazepinones and the ring enlargement requires the protection as the methyl ether of the hydroxy group at C-8. On the other hand, the naphthalenones oximes undergo a ready cyclization to the corresponding naphthisoxazole under Beckmann rearrangement conditions, providing a route to the synthesis of these heterocyclic compounds.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer model 1310 spectrophotometer as potassium bromide discs, and the wave numbers (ν) are expressed in cm^{-1}. The ^1H nmr spectra were run either on a Vairan XL-100 or Varian XL-300 spectrometers. The ^{13}C nmr spectra were determined on a Bruker AM-200. Chemical shifts are reported in ppm (δ) downfield from TMS. Mass spectra were determined on a VG-12-250 spectrometer at the Instituto de Química Orgánica General (C.S.I.C.), Madrid, Spain. Silica gel Merck 60 (70-230 mesh) and DC-Alufolien $60F_{254}$ were normally used for preparative column chromatography and analytical tlc, respectively.

3,4-Dihydro-5,8-dihydroxy-4,4-dimethyl-1(2*H*)-naphthalenone **9**.

A solution of the naphthalenone **5** [8] (740 mg, 4.86 mmoles), 10% palladium on charcoal (100 mg) in 2-propanol (200 ml) was stirred at room temperature in a Parr hydrogenation apparatus at 20 psi for 30 minutes. The solution was filtered and the filtrate was evaporated under reduced pressure to afford tetralone **9** (720 mg, 96%) as a yellow solid, mp 247-248° (benzene), lit [9] 238-240°; ir: 3280 (OH), 1622 (C=O); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.11 (s, 6H), 1.50 (t, 2H, J = 7 Hz), 2.25 (t, 2H, J = 7 Hz), 6.69 (d, 1H, J = 8 Hz), 6.63 (d, 1H, J = 8 Hz), 8.11 (s, 1H), 11.90 (s, 1H).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.24; H, 7.04.

4,4-Dimethyl-8-hydroxy-5-methoxy-1(4*H*)-naphthalenone **6**.

A solution of naphthalenone **5** (310 mg, 1.52 mmoles), dimethyl sulfate (0.5 ml, 5.24 mmoles) and potassium carbonate (300 mg), in dry acetone (50 ml) was heated at reflux for 3 hours. The mixture was filtered and the filtrate was poured into a solution of 5% aqueous potassium hydroxide (20 ml) and methanol (20 ml) and left overnight at room temperature. The solution was neutralized with sodium bicarbonate and extracted with chloroform (2 x 30 ml). The extract was washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to afford ether **6** (298 mg, 90%) as a pure material, mp 70-72°; ir: 3200 br (O-H), 1650 (C=O), 1580 (C=C); ^1H nmr (deuteriochloroform): δ 1.58 (s, 6H), 3.90 (s, 3H), 6.30 (d, 1H, J = 10 Hz), 6.90 (d, 1H, J = 10 Hz), 6.92 (d, 1H, J = 9 Hz), 7.20 (d, 1H, J = 9 Hz), 12.80 (s, 1H).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.64; H, 6.22.

3,4-Dihydro-4,4-dimethyl-8-hydroxy-5-methoxy-1(2*H*)-naphthalenone **10**.

Method A.

To a solution of methoxynaphthalenone **6** (250 mg, 1.15 mmoles) in ethanol (40 ml) was added 10% palladium on charcoal (10 mg) and the mixture was stirred in a Parr hydrogenation apparatus at 30 psi for 2 hours at room temperature. The solution was filtered and evaporated under reduced pressure to afford **10** (222 mg, 88%). An analytical sample of **10** was obtained by column chromatography on silica gel using a dichloromethane-ethyl acetate 2:1 mixture as eluent, mp 38-40°; ir: 3200 br (O-H), 1640 (C=O); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.50 (s, 6H), 1.97 (t, 2H, J = 7 Hz), 2.70 (t, 2H, J = 7 Hz), 3.83 (s, 3H), 6.86 (d, 1H, J = 9 Hz), 7.20 (d, 1H, J = 9 Hz), 12.46 (s, 1H).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.42; H, 7.06.

Method B.

A solution of naphthalenone **9** (400 mg, 1.94 mmoles), dimethyl sulfate (0.75 ml, 7.76 mmoles) and potassium carbonate (400 mg) in benzene-acetone (1:1, 50 ml) was heated at reflux for 2 hours. The mixture was filtered and the filtrate was poured into a solution of 5% aqueous potassium hydroxide (20 ml) and methanol (20 ml) and then left overnight at room temperature. The solution was neutralized with sodium bicarbonate and extracted with chloroform (2 x 30 ml). The extract was washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to afford **10** (415 mg, 97%).

Reaction of Methoxynaphthalenone **10** with Sodium Azide in Sulfuric Acid.

To a stirred suspension of naphthalenone **10** (200 mg, 0.9 mmole) and sodium azide (120 mg, 1.82 mmoles) in chloroform (20 ml) cooled to 0° concentrated sulfuric acid (1.5 ml) was added and the resulting mixture was kept at 5-10° for 1 hour. The mixture was heated at reflux for 1.5 hours, cooled to room temperature and treated with potassium carbonate (2 g) followed by addition of 5% aqueous sodium hydroxide (5 ml). The mixture was filtered and the solids were washed with chloroform. The organic extract was washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to give crude 5,5-dimethyl-6-methoxy-4,5-dihydro-3*H*-naphth[1,8-*cd*]isoxazole **15**. Column chromatography on silica gel (chloroform) afforded pure **15** (88 mg, 45%), mp 54-56°; ir: 2940 (C-H), 1690 (C=N), 1235 (C-O-C); ^1H nmr (deuteriochloroform): δ 1.46 (s, 6H), 1.96 (t, 2H, J = 7 Hz), 3.04 (t, 2H, J = 7 Hz), 3.91 (s, 3H), 7.16 (d, 1H, J = 10 Hz),

7.30 (d, 1H, J = 10 Hz); ms: m/z (%), 217 (M^+, 69), 202 (100), 174 (22).

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.10; H, 7.09; N, 5.98.

3,4-Dihydro-5,8-dihydroxy-4,4-dimethyl-1(2*H*)-naphthalenone Oxime **17**.

A solution of naphthalenone **9** (0.34 g, 1.65 mmoles), sodium acetate (0.195 g, 2.37 mmoles) and hydroxylamine hydrochloride (0.171 g, 2.48 mmoles) in ethanol (30 ml) was heated at reflux for 3 hours. The mixture was added into ice-water and extracted with chloroform (2 x 25 ml). The organic extract was washed with water (25 ml), dried over magnesium sulfate and evaporated under reduced pressure to give oxime **17** (0.33 g, 90%), mp 53-54°; ir: 3400 (O-H), 1620 (C=N) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.40 (s, 6H), 1.64 (t, 2H, J = 8 Hz), 2.75 (t, 2H, J = 8 Hz), 6.56 (d, 1H, J = 9 Hz), 8.76 (s, 1H), 11.33 (s, 1H), 11.66 (s, 1H).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.50; H, 7.20; N, 6.06.

Reaction of Oxime **17** with Polyphosphoric Acid.

A mixture of oxime **17** (180 mg, 0.8 mmole) and polyphosphoric acid (6 g) was heated at 110-120° for 35 minutes and then poured into water (50 ml). The resulting solution was neutralized with sodium bicarbonate, extracted with ethyl acetate (2 x 25 ml) and dried over magnesium sulfate. Removal of the solvent afforded 5,5-dimethyl-6-hydroxy-4,5-dihydro-3*H*-naphth[1,8-*cd*]isoxazole **16** (160 mg, 97%). An analytical sample was obtained by column chromatography on silica gel using chloroform as eluent, mp 166-168°; ir: 3200 (O-H), 1640 (C=N); ^1H nmr (deuteriochloroform): δ 1.45 (s, 6H), 1.98 (t, 2H, J = 7 Hz), 3.06 (t, 2H, J = 7 Hz), 5.8 (s, 1H), 7.00 (d, 1H, J = 8 Hz), 7.20 (d, 1H, J = 8 Hz); ^{13}C nmr (deuteriochloroform): δ 19.12, 27.01, 34.08, 39.98, 107.38, 121.65, 122.47, 126.02, 148.08, 155.88, 157.14; ms: m/z (%) 203 (M^+, 72), 188 (100), 160 (20).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.84; H, 6.70; N, 6.82.

7,8-Dihydro-8,8-dimethyl-5-hydroxyimino-(6*H*)-naphthalene-1,4-dione **19**.

A mixture of oxime **17** (200 mg, 0.91 mmole), manganese dioxide (1.0 g), magnesium sulfate (1.0 g) in dichloromethane (20 ml) was vigorously stirred for 15 minutes at room temperature. The mixture was filtered, washed thoroughly with dichloromethane and the filtrate was evaporated under reduced pressure to give quinone **19** (170 mg, 86%), mp 162-163° (benzene-ethanol-petroleum ether 3:1:2); ir: 3200 (O-H), 1640 br (C=O, C=N); ^1H nmr (deuteriochloroform): δ 1.42 (s, 6H), 1.70 (t, 2H, J = 8 Hz), 2.90 (t, 2H, J = 8 Hz), 6.72 (s, 2H), 11.40 (br s, 1H, exchangeable with deuterium oxide); ^{13}C nmr (deuteriochloroform): δ 19.54, 27.23, 34.61, 36.73, 132.82, 136.48, 137.06, 151.97, 152.12, 186.08, 187.23.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.00; H, 6.06; N, 6.63.

4-Acetyl-3,3-dimethyl-5-methoxy-2-morpholinobenzo[*b*]furan **4**.

A mixture of heterocycle **3** [8] (243 mg, 0.84 mmole), dimethyl sulfate (0.3 ml, 3.15 mmoles) and potassium carbonate (300 mg) in benzene (30 ml) was heated for 3.5 hours with stirring. Work-up in the usual manner afforded crude methyl ether **5** which purified by column chromatography on silica gel (chloroform-ethyl acetate 1:1) to give pure **4** as a pale brown oil (230 mg, 91%); ir: 1690 (C=O), 1250 (O-Me); ^1H nmr (deuteriochloroform): δ 1.30 (s, 3H), 1.40 (s, 3H), 2.56 (s, 3H), 2.67 (t, 2H, J = 5 Hz), 3.66 (t, 2H, J = 5 Hz), 3.80 (s, 3H), 4.76 (s, 1H), 6.76 (s, 2H).

Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.58; H, 7.39; N, 4.33.

4,4-Dimethyl-5-hydroxy-8-methoxy-1(4*H*)-naphthalenone **7**.

Compound **4** (500 mg, 1.64 mmoles) in ethanol (30 ml) containing concentrated hydrochloric acid (0.5 ml) was heated at reflux for 4 hours and the hot solution was poured into ice-water mixture. The solution was extracted with chloroform (2 x 25 ml), dried (magnesium sulfate), evaporated under reduced pressure to give crude naphthalenone **7** (320 mg, 90%), mp 278-279° (benzene-ethanol-cyclohexane 2:1:1); ir: 3400 (O-H), 1650 (C=O), 1620 (C=C); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.56 (s, 6H), 3.74 (s, 3H), 6.06 (d, 1H, J = 10 Hz), 6.80 (d, 1H, J = 10 Hz), 6.92 (d, 1H, J = 9 Hz), 7.08 (d, 1H, J = 9 Hz), 9.52 (s, 1H).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.41. Found: C, 71.87; H, 6.53.

5,8-Dimethoxy-4,4-dimethyl-1(4*H*)-naphthalenone **8**.

A solution of compound **7** (300 mg, 1.37 mmoles), dimethyl sulfate (0.4 ml, 4.12 mmoles) and potassium carbonate (0.3 g) in benzene-acetone (3:1, 50 ml) was heated at reflux for 3.5 hours. The mixture was treated in the usual manner to afford pure dimethyl ether **8** as a yellow oil (307 mg, 99%). A pure sample of **8** was obtained by chromatography on silica gel (chloroform): ir: 1660 (C=O), 1630 (C=C); ^1H nmr (deuteriochloroform): δ 1.56 (s, 6H), 3.86 (s, 3H), 3.90 (s, 3H), 6.24 (d, 1H, J = 10 Hz), 6.70 (d, 1H, J = 10 Hz), 6.96 (d, 1H, J = 9 Hz), 7.14 (d, 1H, J = 9 Hz).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.70; H, 7.32.

3,4-Dihydro-4,4-dimethyl-5-hydroxy-8-methoxy-1(2*H*)-naphthalenone **11**.

A mixture of compound **7** (80 mg, 0.37 mmole), 10% palladium on charcoal and ethanolic potassium hydroxide solution (0.3*N*, 20 ml) was stirred in a Parr hydrogenation apparatus at 30 psi for 30 minutes at room temperature. The solution was filtered and the filtrate was neutralized with 8*N* hydrochloric acid. The mixture was extracted with chloroform (2 x 25 ml), dried (magnesium sulfate) and evaporated under reduced pressure to afford crude tetralone **11** (72 mg, 89%), mp 128-129° (benzene-ethanol 5:1); ir: 3300 (O-H), 1640 (C=O); ^1H nmr (deuteriochloroform): δ 1.56 (s, 6H), 2.00 (m, 2H), 2.68 (m, 2H), 3.82 (s, 3H), 4.68 (s, 1H), 6.74 (d, 1H, J = 9 Hz), 6.96 (d, 1H, J = 9 Hz).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.00; H, 7.00.

3,4-Dihydro-5,8-dimethoxy-4,4-dimethyl-1(2*H*)-naphthalenone **12**.

Method A.

Compound **8** (200 mg, 0.86 mmole) in ethanolic potassium hydroxide solution (0.3*N*, 20 ml) was hydrogenated on 10% palladium on charcoal at 30 psi for 1 hour at room temperature. Work-up as in the conversion of **7** to **11**, afforded dimethoxynaphthalenone **12** (118 mg, 58%) as a yellow liquid which solidified on standing at room temperature, mp 49-51° (118 mg, 58%); ir: 3030 (C-H), 1680 (C=O); ^1H nmr (deuteriochloroform): δ 1.48 (s, 6H), 1.96 (m, 2H), 2.64 (m, 2H), 3.86 (s, 6H), 6.82 (d, 1H, J = 9 Hz),

7.04 (d, 1H, J = 9 Hz).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.39; H, 7.37.

Method B.

Compound **11** (500 mg, 2.27 mmoles) was methylated with dimethyl sulfate (0.6 ml, 6.81 mmoles) in benzene-acetone (2:1, 50 ml). The mixture was worked-up in the usual way to give dimethyl ether **12** (511 mg, 96%).

Reaction of Naphthalenone **11** with Sodium Azide in Trichloroacetic Acid.

A solution of **11** (210 mg, 0.95 mmole), sodium azide (93 mg, 1.43 mmoles), and trichloroacetic acid (1.45 g, 8.78 mmoles) was heated at 65-70° for 8 hours. The solution was diluted with water (15 ml), neutralized with sodium bicarbonate and extracted with ethyl acetate (3 x 30 ml). The organic phase was washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to afford a residue which was chromatographed on silica gel. Elution with chloroform-ethyl acetate 1:1 gave dihydroxynaphthalenone **9** (30 mg, 15%), starting product **11** (90 mg), 5,6-dihydro-7,7-dimethyl-8-hydroxy-11-methoxy-7*H*-tetrazolo[1,5-*a*][2]benzazepine **23** (70 mg, 28%), mp 89-91°; ir: 3250 (O-H), 1580 (C=N); ^{1}H nmr (deuteriochloroform): δ 1.24 (s, 6H), 2.20 (t, 2H, J = 7 Hz), 3.76 (s, 3H), 4.44 (t, 2H, J = 7 Hz), 6.82 (d, 1H, J = 9 Hz), 7.24 (d, 1H, J = 9 Hz); ms: m/z (%) 260 (M^+, 100), 217 (16), 189 (48).

Further elution with ethyl acetate gave 3,4-dihydro-5,5-dimethyl-6-hydroxy-9-methoxy-(5*H*)-2-benzazepine-1-one **21** (68 mg, 36%), mp 263-264°; ir: 3250 (N-H), 1630 (C=O); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.48 (s, 6H), 1.72 (t, 2H, J = 6 Hz), 2.90 (m, 2H), 3.64 (s, 3H), 6.82 (s, 2H), 7.78 (t, 1H, J = 6 Hz), 8.72 (s, 1H).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.18; H, 7.21; N, 6.09.

Reaction of Naphthalenone **12** with Sodium Azide in Trichloroacetic Acid.

A solution of dimethyl ether **12** (460 mg, 1.96 mmoles), sodium azide (200 mg, 2.95 mmoles) and trichloroacetic acid (3.0 g, 18.0 mmoles) was heated at 65-70° for 8 hours. The solution was diluted with water (15 ml), neutralized with sodium bicarbonate and extracted with ethyl acetate (3 x 30 ml). The organic phase was washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to afford a residue which was chromatographed on silica gel. Elution with dichloromethane-ethyl acetate 2:1 gave naphthisoxazol **15** (29 mg, 8%), starting product **12** (70 mg), 5,6-dihydro-8,11-dimethoxy-7,7-dimethyl-7*H*-tetrazolo[1,5-*a*][2]benzazepine **24** (80 mg, 18%), mp 140-141°; ir: 1580 (C=N); ^{1}H nmr (deuteriochloroform): δ 1.15 (s, 6H), 2.20 (t, 2H, J = 7 Hz), 3.82 (s, 3H), 3.84 (s, 3H), 4.42 (t, 2H, J = 7 Hz), 6.98 (d, 1H, J = 9 Hz), 7.16 (d, 1H, J = 9 Hz); ms: m/z (%) 274 (M^+, 100), 231 (22), 203 (59).

Further elution with ethyl acetate gave 3,4-dihydro-5,5-dimethyl-6,9-dimethoxy-5*H*-2-benzazepin-1-one **22** (211 mg, 51%), mp 53-55°; ir: 3240 (N-H), 1630 (C=O); ^{1}H nmr (deuteriochloroform): δ 1.55 (s, 6H), 1.86 (t, 2H, J = 6 Hz), 3.20 (m, 2H), 3.73 (s, 6H), 6.84 (d, 1H, J = 9 Hz), 7.00 (d, 1H, J = 9 Hz), 8.06 (t, 1H, J = 6 Hz); ^{13}C nmr (deuteriochloroform): δ 33.9, 39.0, 39.9, 47.1, 56.8, 57.5, 111.5, 117.6, 125.7, 132.9, 152.1, 152.2, 172.4; ms: m/z (%) 249 (M^+, 61), 232 (100), 205 (35).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.81; H, 8.01; N, 5.50.

3,4-Dihydro-4,4-dimethyl-5-hydroxy-8-methoxy-1(2*H*)-naphthalenoxe Oxime **18**.

A solution of methoxynaphthalenone **11** (530 mg, 2.40 mmoles), sodium acetate (283 mg, 3.46 mmoles) and hydroxylamine hydrochloride (250 mg, 3.6 mmoles) in ethanol (30 ml) was heated at reflux for 3 hours. The mixture was poured into ice-water and then extracted with chloroform (2 x 25 ml). The organic extract was washed with water (25 ml), dried over magnesium sulfate and evaporated under reduced pressure to give oxime **18** (530 mg, 94%), mp 191-193° (benzene); ir: 3400 (O-H), 3200 (O-H), 1590 (C=N) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.36 (s, 6H), 1.60 (t, 2H, J = 7 Hz), 2.65 (t, 2H, J = 7 Hz), 3.64 (s, 3H), 6.76 (s, 2H), 7.74 (s, 1H), 8.96 (s, 1H); ms: m/z (%) 235 (M^+, 14), 218 (9), 78 (100).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 69.47; H, 7.68; N, 5.94.

Reaction of Naphthalenone Oxime **18** with a Dimethylacetamide-phosphorus Oxychloride Mixture.

Phosphorus oxychloride (0.1 ml, 1.38 mmoles) was added to a solution of compound **18** (200 mg, 0.85 mmole) in dimethylacetamide-acetonitrile (1:2, 15 ml) at room temperature and the mixture was heated at 40-45° for 30 minutes. The reaction mixture was poured into ice-water, neutralized with sodium acetate and extracted with chloroform. The dry organic extract (magnesium sulfate) was evaporated to give crude naphtisoxazole **16** (140 mg, 81%).

Oxidative Demethylation of Benzazepine **23** with Cerium Ammonium Nitrate.

A solution of cerium ammonium nitrate (840 mg, 1.54 mmoles) in acetonitrile-water (3:1, 10 ml) was added in one portion to a solution of tetrazole **23** (200 mg, 0.8 mmole) in acetonitrile (30 ml) and the mixture was stirred at room temperature for 20 minutes. The reaction mixture was extracted with chloroform and the organic extract was washed with water, dried (magnesium sulfate), and evaporated under reduced pressure to give 5,6-dihydro-7,7-dimethyl-7*H*-tetrazolo[1,5-*a*][2]benzazepine-8,11-dione **27** (136 mg, 73%). A pure sample of quinone **27** was obtained by column chromatography on silica gel (chloroform-ethyl acetate 1:1), mp 215-217°; ir: 1670 and 1660 (C=O), 1580 (C=N); ^{1}H nmr (deuteriochloroform): δ 1.46 (s, 6H), 1.97 (m, 2H), 4.58 (m, 2H), 6.78 (d, 1H, J = 10 Hz), 6.89 (d, 1H, J = 10 Hz); ms: m/z (%) 246 (M^+, 100), 188 (44); ^{13}C nmr: 29.12, 41.20, 44.00, 44.08, 128.00, 135.77, 138.07, 148.33, 152.95, 183.42, 185.88.

Anal. Calcd. for $C_{12}H_{12}N_4O_2$: C, 59.00; H, 4.95; N, 22.94. Found: C, 57.90; H, 5.50; N, 22.33.

Oxidative Demethylation of Benzazepine **24** with Cerium Ammonium Nitrate.

Compound **24** (110 mg, 0.4 mmole) in acetonitrile (20 ml) was reacted with cerium ammonium nitrate (500 mg, 0.91 mmole) in acetonitrile-water (3:1, 10 ml) for 20 minutes. Work-up afforded quinone **27** (85 mg, 87%).

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