Some Derivatives of Benz[*f*]azepine. Part III

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We report the synthesis by two routes, of hitherto unknown 3,4-epoxy-2,3,4,5-tetrahydrobenz[*f*]azepine-2,5-dione and hence a new route to 2,3,4,5-tetrahydrobenz[*f*]azepine-2,4,5-triones which are precursors of 2-quinolonecarboxylic acids.

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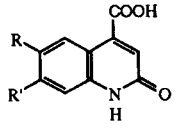
Various quinoline-4-carboxylic acids **1** have been obtained by ring contraction of suitable benzazepines **2**, in turn made by three routes a) from keto-lactams **3** [1,2],



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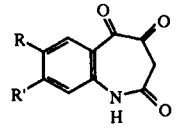

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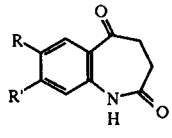
b) from azidoquinone **4** [3], and c) by hydrogen azide ring expansion of methoxyquinone **5** [4], giving **2** (R = H, R' = MeO).



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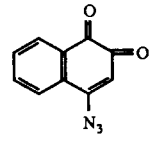

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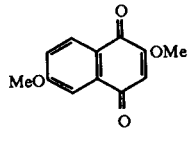
The reaction of quinisatins *e.g.* **6** with diazoalkanes [5,6] claimed to give benzazepinones type **2** was not supported by their ring-contraction to the quinolone acids and later workers [7] have refuted some of these findings, using ^{13}C nmr spectroscopy.



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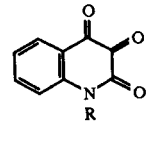

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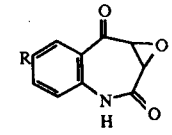
We now report a new route to some of the benzazepinones that can undergo ring contraction to quinolinecarboxylic acids.

On hydrogen azide ring expansion, 2,3-dihydro-2,3-epoxy-1,4-naphthoquinone gave 3,4-epoxy-2,3,4,5-tetrahydrobenzazepine-2,5-dione **7**, (R = H). This was identical with the product of epoxidation of the known [2,8] benzazepine **8**. Ring opening of this epoxide to give benzazepine **9** went in very poor yield. We therefore reduced the epoxide with sodium borohydride when it gave the epoxy-alcohol **10**. An anticipated neighbouring group effect by the 5-OBH_3^- group to open the epoxide ring giving also a 3-hydroxy group, providing an intermediate for oxidation to **9**, was not observed. Oxidation of the epoxy-alcohol by Jones reagent [9] regenerated the epoxide **7**, (R = H) which in turn, on reduction by chromous chloride [10], gave benzazepine **8**.



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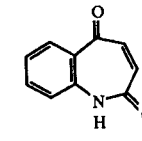

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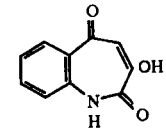

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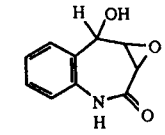

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From our epoxide/acid reactions we obtained another, rather insoluble product which on later investigation proved to be from the alternative and indeed major opening mode. Monitoring different conditions in uv cells, we found concentrated sulfuric acid to be the best reagent, yielding trioxo-compound **2**, (R = R' = H) in good yield, having the reported properties [2].

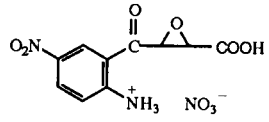
Base hydrolysis of epoxide **7**, (R = H) gave isatin though we were able to develop conditions for the direct synthesis of the acid **1**, (R = R' = H).

The epoxide **7**, (R = R) being generally fairly stable to acid, we were able to effect nitration to epoxide **7**, (R = NO_2). This product could also be rearranged to trioxo-compound **2** (R = NO_2, R' = H).

In one nitration, we obtained the amino-acid nitrate **11**. This multifunctional compound was not stable under neutral or mildly basic conditions and was not further studied but it demonstrated that the epoxide was more stable than the lactam ring.

The trioxo-compounds (lactam diones) **2**, (R = R' = H

and R = NO_2, R' = H) were converted by base to the corresponding acids, identical with samples synthesized from the appropriately substituted *N*-acetylisatins [11].



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EXPERIMENTAL

Unless otherwise stated, the ir spectra (cm^{-1}) were in nujol, uv spectra, nm (log E) in ethanol, ^1H nmr (60 Hz) in deuteriochloroform relative to TMS (internal) and ms m/e (%) on the probe of the AEI MS 12, or MS 30 at 70 eV. Melting points are uncorrected.

2,5-Dihydro-2,5-dioxo-3,4-epoxybenz[*f*]azepine **7** (R = H).

a) 1,4-Naphthoquinone epoxide (Aldrich), 0.21 g (0.0012 mole) was added to 1.5 g of stirred sulfuric acid (98%) at 0°. Sodium azide, 0.07 g (1 equivalent) was added slowly. After nitrogen evolution had ceased, the mixture was poured into ice-water and the benzazepine **7** (R = H) was collected, 0.2 g yield 0.1 g, 83% from butanone, mp 233-235°; ir: 3250, 3100, 1680, 1605, 1585, 1490, 1460, 1340, 1300, 1240, 1220, 900, 790, 760; uv: 234 (4.23), 328 (3.45); OH^-: 215 (4.21) 242 (4.24), 284 (3.99), 370 (3.49); ^1H nmr (δ) 4.08 (s, 2H), 7.3 (m, 4H), 10.52 (s, 1H); ms: 189 (100, M^+), 145 (5), 132 (11), 119 (38), 104 (8), 91 (32), 77 (14).

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.5; H, 3.7; N, 7.4. Found: C, 63.5; H, 3.8; N, 7.4.

b) 2,5-Dihydro-2,5-dioxobenz[*f*]azepine [2,8], 0.173 g (0.001 mole) in 30 ml of chloroform was treated with 0.204 g (20% excess) of *m*-chloroperbenzoic acid at 20° for 120 hours. The solution was washed with sodium bicarbonate solution then with water, dried (magnesium sulfate) and concentrated. Thick layer chromatography (1 m x 20 cm x 1 mm silica HF_{254}) gave the product at Rf 0.5 developed with butanone/60-80 petrol (1:1). Extraction with and crystallization from butanone gave the pure epoxide, mp undepressed by a sample from method a) and having the identical ir spectrum, pure yield 15 mg.

2,5-Dihydrobenz[*f*]azepine-2,5-dion-3-ol **9**.

The epoxide **7** (R = H), 0.58 g (0.003 mole) was heated at 85° with 60 ml of acetic acid and 1 ml of aqueous hydrochloric acid (1:1). After 10 minutes the mixture was filtered and the residue neutralized with a few drops of sodium bicarbonate solution then washed with water and dried. The chloroform extract of the solid was run onto a tlc plate of alumina and developed with butanone. A poor yield, 7 mg of the 3-hydroxy compound **9** was obtained, Rf 0.4, mp 247-249°, undepressed by an authentic sample [4] and having the identical ir spectrum.

2,5-Dihydro-2-oxo-3,4-epoxybenz[*f*]azepin-5-ol **10**.

To the epoxide **7** (R = H), 0.567 g (0.003 mole) in 15 ml of methanol, sodium borohydride, 0.11 g (0.003 mole) in 10 ml of methanol/water (4:1) was added with stirring. After 2 hours, dilute sulfuric acid and excess of water were added until no further precipitate appeared. Filtration left a white solid, 0.4 g which gave 0.37 g of white needles (67%) from butanone, mp 184-185°; ir: 3250, 1690, 1645, 1590, 1500, 1450, 1240, 1230, 1120, 1090, 1060, 880, 810, 750; uv; 205 (3.94), 242 (3.70), H^+ 205 (3.96), 242 (3.70); OH^- 212 (4.28), 242 (3.88); pmr; 3.3 (s, 1H), 3.5 (m, 1H), 5.0 (d, 1H), 7.1 (m, 4H); ^{13}C nmr† (DMSO-d_6): C2 167.3, C3 57.8, C4 62.2, C5 198.0, C5a 126.3, C6 129.4, C7 123.9, C8 133.7, C9 119.7, C9a 136.1; ms; 191 (67 M^+), 146 (40), 130 (35), 117 (71), 93 (100), 77 (29).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.8; H, 4.75; N, 7.3. Found: C, 62.5; H, 4.69; N, 7.4.

Oxidation of Epoxy-alcohol **10**.

The epoxyalcohol **10**, 5 mg in 50 ml of acetone was titrated with Jones reagent and the decanted solvent evaporated. The residue, crystallized from hot butanone, was shown by mp, mixed mp and ir spectrum to be the epoxydione **7** (R = H).

Reduction of the Epoxydione **7** (R = H) by Chromous chloride.

The epoxydione **7** (R = H), 132 mg (0.007 mole) in 40 ml of acetone/acetic acid (1:1) was mixed with 10 ml of a 20% chromous chloride solution in a 50 ml flask which was firmly stoppered and left overnight. The mixture was poured into 200 ml of water and the whole extracted with 3 x 200 ml chloroform. The extract was neutralized with sodium carbonate solution, washed and dried (magnesium sulfate) then evaporated to dryness. The crude residue after thick layer chromatography as above, gave a band at Rf 0.5 yielding crystals mp 222-223° from ethanol, 50 mg, with the same ir as the dione **8** and undepressed in mixed mp.

2,3,4,5-Tetrahydrobenz[*f*]azepine-2,4,5-trione **2** (R = R' = H).

The epoxydione **7** (R = H), 0.5 g in 6 ml of concentrated sulfuric acid was heated 30 minutes on a steam-bath then cooled in ice. Water was added and the solid formed was filtered off and washed with water until neutral then dried. It had one spot on tlc (ethanol/ethyl acetate/benzene), 0.5 g, mp 250° dec; ir: as quoted, also strong peaks at 1230, 1190, 1165, 760, 725; ms: 189 M^+ (45), 161 (11), 133 (14), 120 (100), 104 (16), 92 (25), 91 (25), 77 (25), 69 (51), 65 (70), 40 (46), 39 (49).

2-Quinolone-4-carboxylic Acid **1** (R = R' = H).

The trione above, 200 mg in 0.45 ml of 2*M* sodium hydroxide solution, was heated 3 hours at 70°. The cold solution was acidified and the product washed with water, needles mp 346° dec, identical in all respects with a genuine sample of 2-quinolone-4-carboxylic acid [11], mixed mp undepressed.

Hydrolysis of Epoxydione **7** (R = H) by Base.

The epoxide, 0.378 g (0.002 mole) was dissolved in 50 ml of 2*M* sodium hydroxide solution and heated 1 hour on a steam-bath. The orange-red solution was neutralized with acid and filtered. The residue was extracted with chloroform and chromatographed with butanone to give one major component, Rf 0.9. After crystallization from aqueous ethanol 50 mg of pure isatin was obtained, ir identical with that of a commercial sample ir, mixed mp undepressed.

When the epoxide, 100 mg was warmed at 50° for ½ hour with 1 equivalent of base, acidification gave a bright yellow solid, recrystallized from acetic acid with mp 346° dec, ir identical with that of 2-quinolone-4-carboxylic acid, mixed mp undepressed.

2,5-Dihydro-2,5-dioxo-3,4-epoxy-7-nitrobenz[*f*]azepine **7** (R = NO_2).

Fuming nitric acid, 1 ml was added to 1.6 ml of acetic anhydride in 10 ml of glacial acetic acid. The epoxide, 0.4 g was added and the mixture was refluxed 4 hours then reduced to 4 ml and 25 ml of ice-water was added. The resulting nitro-compound was collected, washed with water to *p*H 7 and crystallized from water/acetic acid 1/15 giving 0.29 g of needles (59%) mp 206-207°; ir: 3199, 3062, 1681, 1612, 1583, 1535, 1500, 1485, 1341, 1275, 1240, 1215, 1145, 1130, 1075, 1031, 945, 885, 839, 820, 751, 725; uv: 220 (4.14), 315 (4.10); ms: 234 (M^+, 100), 189 (11), 177 (11), 166 (11), 165 (25), 132 (13), 131 (22), 104 (11), 91 (10), 90 (23), 76 (12), 75 (14), 74 (12), 71 (15), 63 (19); ^{1}H nmr (DMSO-d_6): 11.1 (NH, s), 8.15 (2H, d), 7.23 (1H, d), 4.16 (2H, s).

Anal. Calcd. for $C_{10}H_6N_2O_5$: C, 51.3; H, 2.58; N, 11.95; O, 34.2. Found: C, 51.7; H, 2.20; N, 11.8; O, 34.4.

7-Nitro-2,3,4,5-tetrahydrobenz[*f*]azepine-2,4,5-trione **2**, R = NO_2, R′ = H.

The epoxide **7**, (R = NO_2), 200 mg in 1 ml of concentrated sulfuric acid was heated overnight at 70°, cooled and diluted with water. The solid was collected and washed with water to give 145 mg, mp 240-250°. Vacuum sublimation gave large yellow-green prisms mp 247° recrystallized from ethanol, mp 254° which decomposed violently at a higher temperature; ir: 3295, 1690 (sh), 1675, 1645, 1625, 1610, 1340, 1235, 1190, 1030, 840, 745, 665; uv: 220, 292; (slightly soluble in DMSO-d_6) 11.7 (NH), 9.1 (H6, d), 8.4 (2H, m), 7.6 (2H, q); ms: 234 (M^+, 30), 206 (16), 176 (5), 166 (15), 165 (100), 160 (15), 149 (8), 138 (15), 119 (41), 108 (25), 91 (45), 69 (98), 63 (61), 52 (48).

Anal. Calcd. for $C_{10}H_6N_2O_5$: C, 51.3; H, 2.58; N, 11.95; O, 34.2. Found: C, 51.4; H, 2.67; N, 11.7; O, 34.4.

1-Amino-4-nitro-2-(2,3-epoxy-4-keto)phenylbutanoic Acid Nitrate.

The epoxide **7**, R = H, 0.8 g in 12 ml of acetic acid was treated with a mixture of 0.5 ml of fuming nitric acid and 1.2 ml of acetic acid. The mixture was refluxed until all was dissolved, about 15 minutes then cooled. After 20 minutes in an ice-bath, the solid was filtered off and crystallized from aqueous acetic acid, 0.58 g was obtained, mp 178-180°; ir: 3600, 3530, 3430, 3300, 3100, 2740 (w), 2670 (w), 2560 (w), 1740, 1670, 1625, 1595, 1570, 1530, 1330, 1300, 1235, 1220, 1140, 1120, 1085, 1065, 1050, 960, 940, 915, 895, 850, 825, 805, 780, 770, 750, 720, 710, 657; uv: 228, 328, 402; ^{1}H nmr: 4.2 (H4, d), 4.8 (H3, d, J = 5 Hz); ms: unstable, m/e max 234.

Anal. Calcd. for $C_{10}H_9N_3O_9$: C, 38.1; H, 2.88; N, 13.3. Found: C, 38.35; H, 3.1; N, 13.5.

6-Nitro-2-quinolone-4-carboxylic Acid **1** (R = NO_2, R′ = H).

The trioxo-compound **2** *(R = NO_2, R′ = H), 0.1 g was warmed* to 55° with 2 ml of 2*M* sodium hydroxide solution. On acidification, a tan product was obtained, mp 330° (acetic acid); ir: 3270, 2750 (w), 2720 (w), 2670 (w), 1660, 1620, 1580, 1335, 1230, 1190, 1120, 1100, 1030, 1010, 885, 840, 755, 740, 715; uv: 244, 277, 330; ms: 234 (M^+, 100), 204 (15), 190 (5), 189 (4), 188 (4), 187 (4), 176 (11), 160 (10), 142 (4), 132 (37), 126 (15), 125 (11), 124 (17), 104 (70), 103 (10), 102 (10), 89 (25), 88 (20), 87 (20), 86 (10), 79 (10), 78 (30), 77 (13), 76 (10), 75 (13), 63 (27), 62 (25), 51 (20); lit mp [11] over 300°.

5-Nitroisatin, 6 g was refluxed 4 hours with 12 ml of acetic anhydride. On cooling, a crystalline product was obtained which was collected and washed with ether giving 1-acetyl-5-nitroisatin mp 182-188°, lit [12] 193-194°; uv: 282, 318, ir: 1760, 1750, 1720, 1600, 1520, 1350, 1280, 1250, 1200, 1180, 1160, 1120, 1075, 1035, 985, 930, 910, 900, 865, 835, 745, 720; ms: 234 (M^+, 3), 191 (15), 175 (27), 43 (100).

Acetylnitroisatin, 1.3 g and 0.7 g of malonic acid were refluxed 2 hours with 0.05 g of anhydrous sodium acetate in 5 ml of acetic acid. On filtering, a yellow-green solid was obtained showing one spot on tlc, mp 330° (acetic acid) undepressed with the above sample and having identical spectra.

Acknowledgements.

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For Part **II**, see reference [4].

* To whom correspondance should be addressed.

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