

## Synthesis of some cyclooctane-based pyrazines and quinoxalines. Part 2

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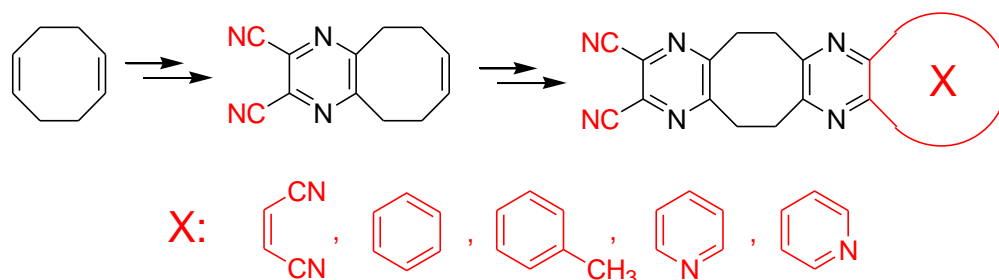
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### Abstract

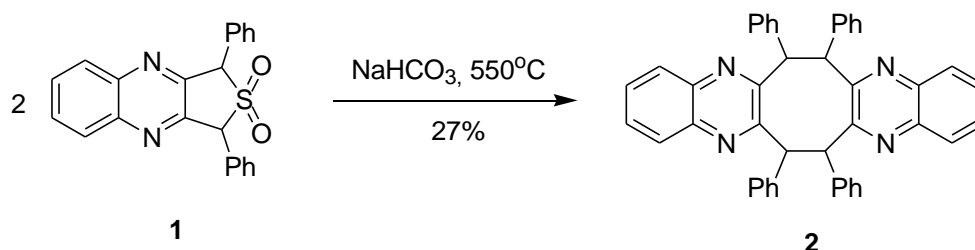
The reaction of 5-cyclooctene-1,2-dione with 1,2-diaminomaleonitrile, produces 5,6,9,10-tetrahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile which was easily oxidized cleanly, under heterogeneous conditions by a combination of  $\text{KMnO}_4$ ,  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ , *t*-BuOH in  $\text{CH}_2\text{Cl}_2$  and water, to give 7-hydroxy-8-oxo-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile. This 2-hydroxy-ketone undergoes cyclocondensation with 1,2-diamines in hot acid acetic to furnish cyclooctane products with quinoxaline or pyrazine rings in a linear array, in good yields, for example 5,6,11,12-tetrahydrocycloocta[1,2-*b*:5,6-*b'*]dipyrazine-2,3,8,9-tetracarbonitrile and 9-methyl-5,6,13,14-tetrahydropyrazino[2',3':5,6]cycloocta[1,2-*b*]quinoxaline-2,3-dicarbonitrile.



**Keywords:** 5-Cyclooctene-1,2-dione, pyrazine-2,3-dicarbonitrile, quinoxaline, 2-hydroxy-ketone.

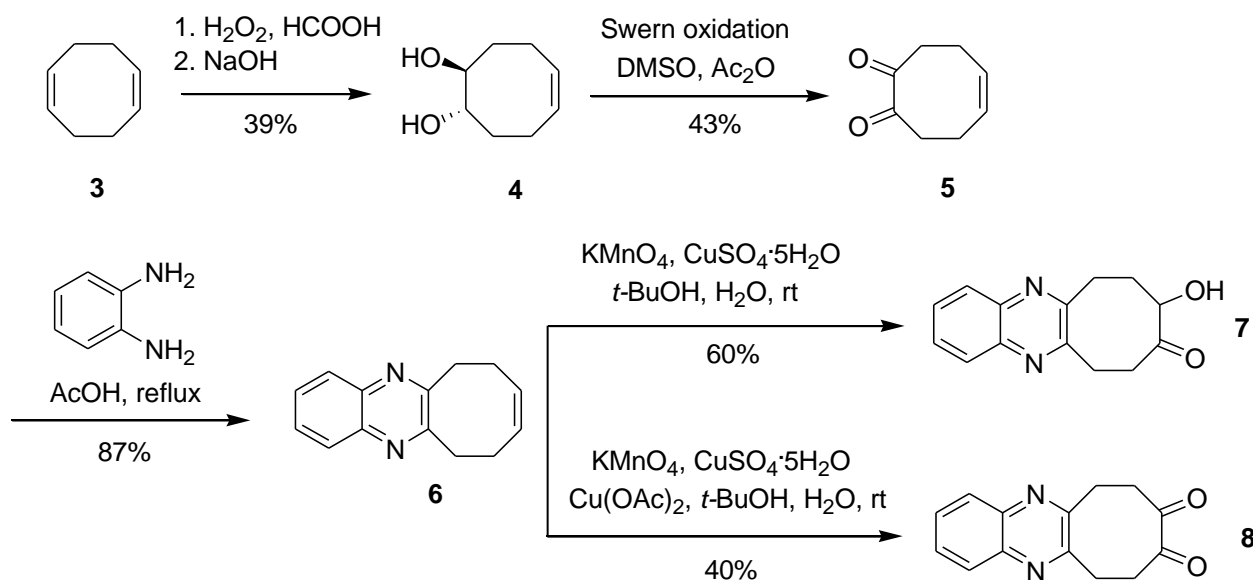
## Introduction

Molecules containing quinoxaline and pyrazine rings have attracted considerable attention because of their various biological activities, such as antiviral,<sup>1</sup> anticancer,<sup>2</sup> antibacterial,<sup>3</sup> anti-inflammatory,<sup>4</sup> and antidepressant activity.<sup>5</sup> However, the synthesis of heterocyclic compounds based on a cyclooctane scaffold is generally difficult to achieve.<sup>6-10</sup> In most cases the eight-membered ring has been constructed during the synthetic sequence. For instance, the cyclooctane ring in various quinoxaline/pyrazine compounds was produced via a dimerisation initiated by sulfur dioxide extrusion, for example **1** → **2** (Scheme 1).<sup>11</sup>



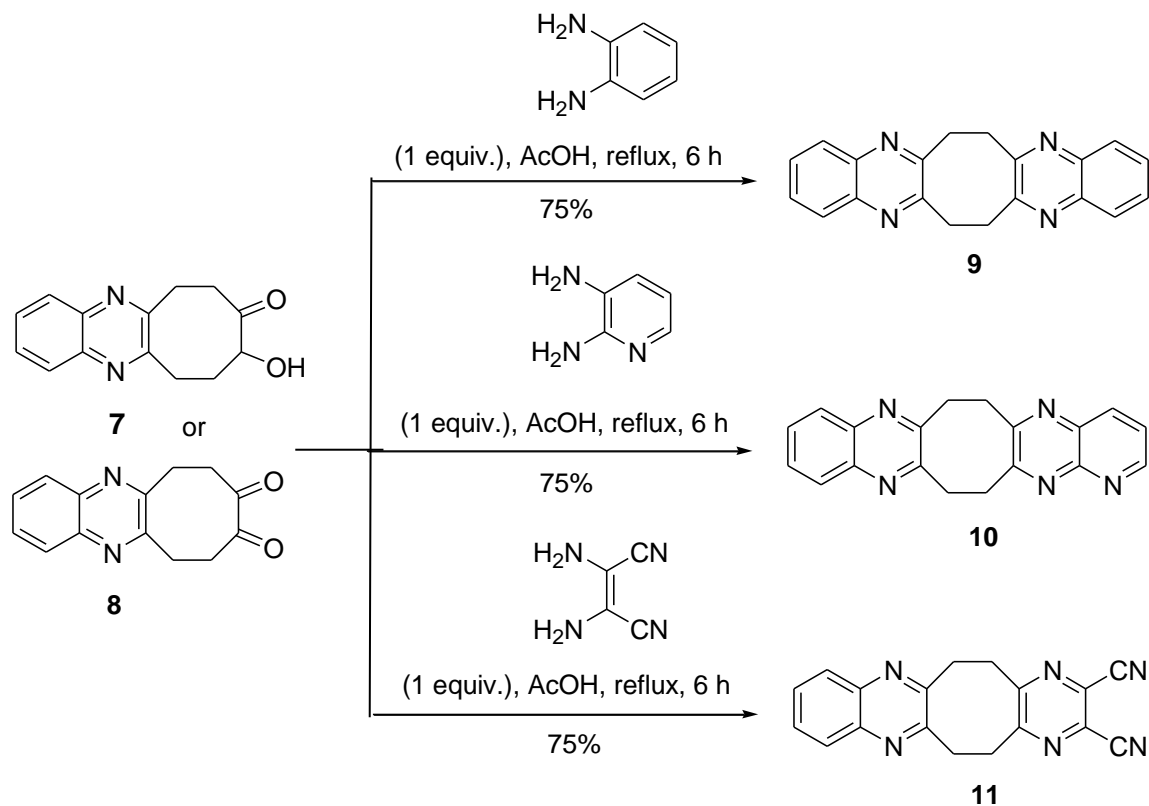
**Scheme 1.** Production of a quinoxaline-fused cyclooctadiene by pyrolysis of a sulfone.

Previously, we reported the synthesis of some quinoxaline derivatives starting from cycloocta-1,5-diene **3**. Oxidation in two steps: (1) selective dihydroxylation of one of the carbon-carbon double bonds with hydrogen peroxide (33%) and formic acid, and then (2) Swern oxidation using dimethyl sulfoxide, produced 5-cyclooctene-1,2-dione **5**. Reaction of this 1,2-dione with *ortho*-phenylenediamine gave 6,7,10,11-tetrahydrocycloocta[*b*]quinoxaline **6**, which also contains a cyclooctene double bond and which could be oxidized to 2-hydroxy-ketone **7** or alternatively to 1,2-dione **8** (Scheme 2).<sup>12</sup>



**Scheme 2.** Conversion of cycloocta-1,5-diene **3** into 6,9,10,11-tetrahydro-9-hydroxycycloocta[*b*]quinoxalin-8(7*H*)-one, **7** and 6,7,10,11-tetrahydrocycloocta[*b*]quinoxaline-8,9-dione, **8**.

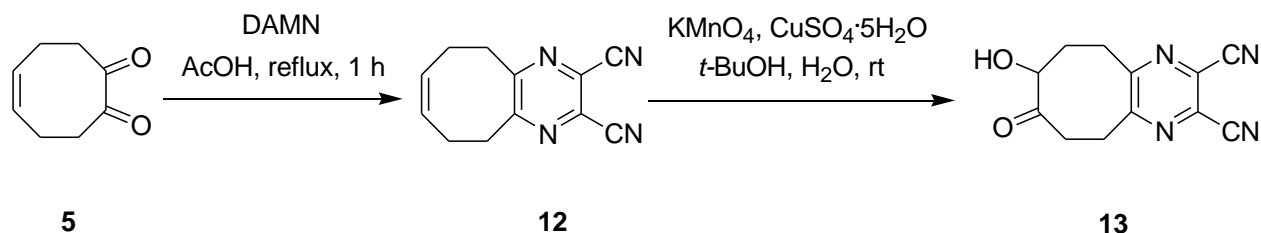
Condensation of 1,2-diamines to form pyrazine rings was possible with either the 2-hydroxy-ketone **7** or with the 1,2-dione **8**, and in this way pentacycles **9** and **10** and tetracycle **11** were produced.<sup>12</sup>



**Scheme 3.** Reaction of **7** or **8** with vicinal diamines in refluxing acetic acid.

## Results and Discussion

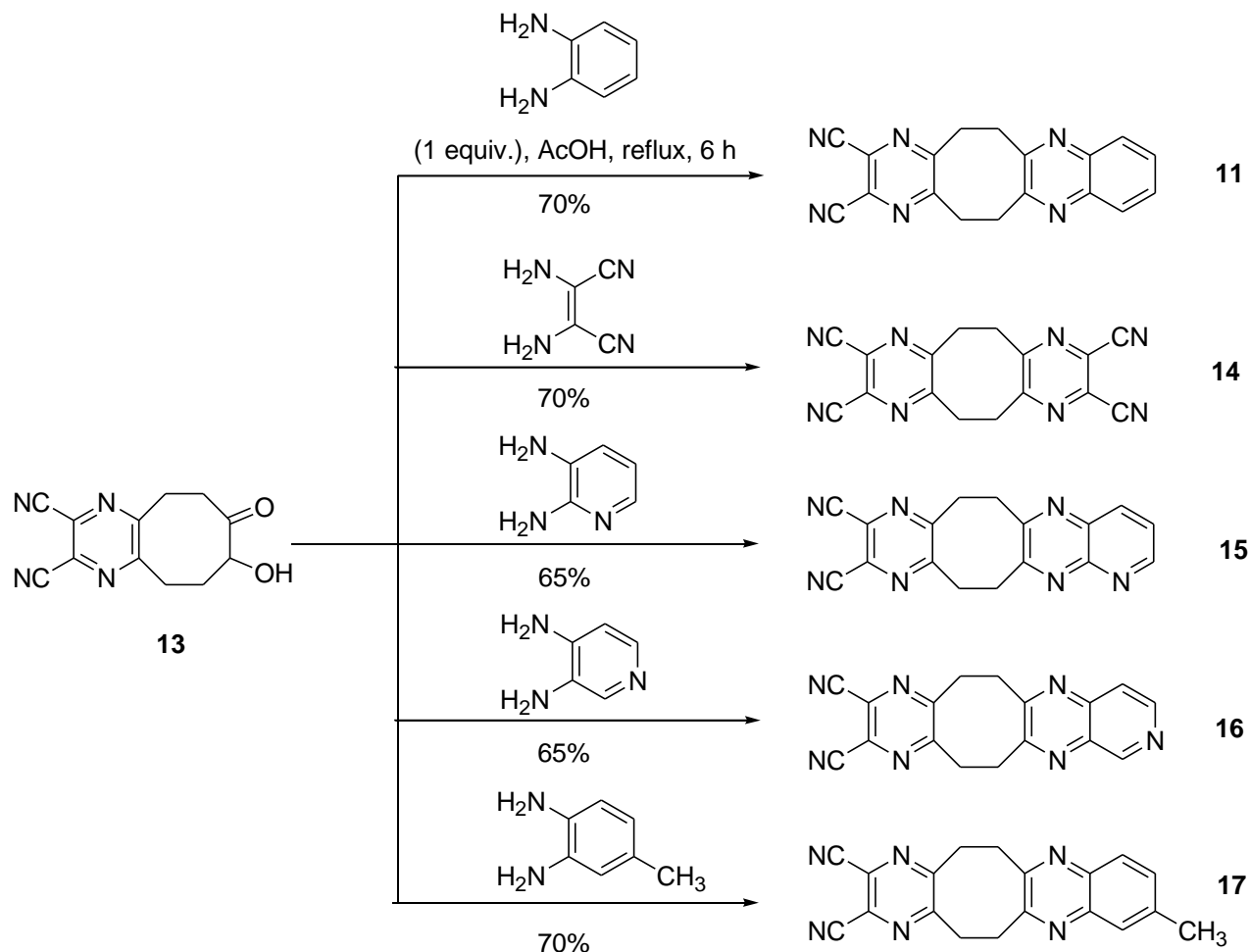
In continuation of our research in this area, we synthesized 7-hydroxy-8-oxocycloocta[*b*]pyrazine-2,3-dicarbonitrile **13** (Scheme 4). Thus, 5,6,9,10-tetrahydrocyclooctapyrazine-2,3-dicarbonitrile **12** was readily produced by the reaction of 5-cyclooctene-1,2-dione with 1,2-diaminomaleonitrile (NC(H<sub>2</sub>N)C=C(NH<sub>2</sub>)CN, DAMN) in hot acetic acid, in high yield. The oxidation of the double bond in compound **12** was accomplished under heterogeneous conditions by the mixture of reagents (KMnO<sub>4</sub>, CuSO<sub>4</sub>·5H<sub>2</sub>O, *t*-BuOH in CH<sub>2</sub>Cl<sub>2</sub>) which gave 7-hydroxy-8-oxo-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile **13**. The similarity of the <sup>1</sup>H NMR chemical shifts and splitting patterns for compounds **13** and **7** indicated their analogous structures.<sup>12</sup>



**Scheme 4.** Synthesis of 7-hydroxy-8-oxo-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile **13** from 5-cyclooctene-1,2-dione.

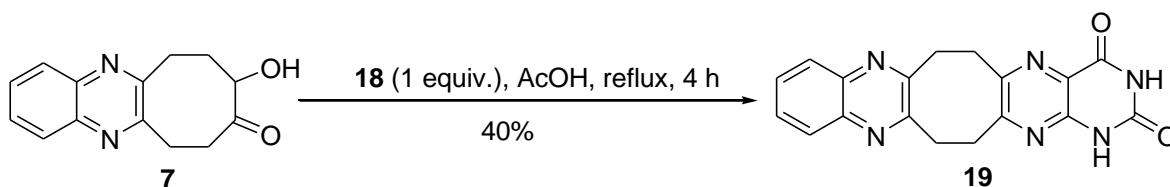
Next, the 2-hydroxy-ketone **13** was reacted with a range of 1,2-diamines in hot acid acetic acid (Scheme 5): *ortho*-phenylenediamine gave the previously prepared product **11** in 70% yield and 4-methylbenzene-1,2-

diamine led to the comparable tetracycle **17**. Reaction with DAMN produced the symmetrical tetranitrile **14**, and reaction with 2,3- and 3,4-diaminopyridines led to dinitriles **15** and **16**, both in 65% yield. (Scheme 5).



**Scheme 5.** Reaction of 2-hydroxy-ketone **13** with vicinal diamines in refluxing acetic acid.

As a further example of the use of 2-hydroxy-ketones for condensation reactions with 1,2-diamines, compound **7** was reacted with 5,6-diaminouracil sulfate **18** affording **19** in 40% yield (Scheme 6), however the attempted reaction between compound **13** and 5,6-diaminouracil sulfate under the same conditions was unsuccessful.



**Scheme 6**

## Conclusions

Cycloocta-1,5-diene was employed for the synthesis of the symmetrical and unsymmetrical three-, four-, and five-fused heterocycles containing quinoxaline/pyrazine and cyclooctane rings. It proved not to be necessary to use a 1,2-diketone for reaction with a 1,2-diamine to produce a pyrazine ring; the corresponding 2-hydroxy-ketone reacted well enough.

We suggest that the 2-hydroxy-ketone unit has emerged as a powerful synthon for condensation reactions, producing other novel heterocyclic compounds based on the eight-membered ring. We intend to convert the 1,2-dinitriles prepared in this work into dicarboxylates (or other functionalities), so that such products can act as pincer ligands for a wide variety of metal cations. Our further results will be described in due course.

## Experimental Section

**General.** All starting materials were purchased from Merck and used without further purification. Melting points were determined on a digital melting point apparatus (electrothermal) and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet (Nexus 670) FT-infrared spectrometer, using sodium chloride cells and measured as KBr discs.  $^1\text{H}$  (300 MHz) and  $^{13}\text{C}$  (75.5 MHz) NMR measurements were recorded on a Bruker 300 spectrometer in  $\text{CDCl}_3$  using TMS as the internal reference. High resolution mass spectra were recorded on an Agilent Technology (HP), MS Model: 5973 Network Mass, selective Detector Ion source: Electron Impact (EI) 70 eV, Ion source temperature: 230 °C, Analyzer: quadrupole, Analyzer temperature: 150 °C and relative abundances of fragments are quoted in parentheses after the  $m/z$  values.

**5,6,13,14-Tetrahydropyrazino[2',3':5,6]cycloocta[1,2-*b*]quinoxaline-2,3-dicarbonitrile (11).** A mixture of 2-hydroxy-ketone **13** (0.10 g, 0.41 mmol) and *ortho*-phenylenediamine (0.04 g, 0.41 mmol) was heated at reflux in AcOH (10 mL) for 6 h. The product precipitated from the reaction mixture. The reaction mixture was cooled, the precipitate was filtered off and washed with water, giving **11** (0.09 g, 70%). mp > 300 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$  +  $\text{CF}_3\text{CO}_2\text{H}$ )  $\delta$  3.79 (t,  $J$  6.9 Hz, 4H, 2 equivalent  $\text{CH}_2$ ), 3.96 (t,  $J$  6.9 Hz, 4H, 2 equivalent  $\text{CH}_2$ ), 8.08 (dd,  $J_1$  6.6,  $J_2$  3.3 Hz, 2H, aromatic), 8.24 (dd,  $J_1$  6.6,  $J_2$  3.3 Hz, 2H, aromatic).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$  +  $\text{CF}_3\text{CO}_2\text{H}$ )  $\delta$  32.3 (C aliphatic), 33.8 (C aliphatic), 112.4 (C nitrile), 125.6, 131.3, 134.2, 137.2, 153.1, 158.1. FT-IR (KBr)  $\nu_{\text{max}}$  / $\text{cm}^{-1}$ : 2937, 2238, 776. MS (EI, 70 eV):  $m/z$  (%) 312 ( $\text{M}^+$ , 100), 297 (89), 169 (46). Found:  $\text{M}^+$  312.1123,  $\text{C}_{18}\text{H}_{12}\text{N}_6$  requires  $\text{M}^+$  312.1123.

**5,6,9,10-Tetrahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile (12).** 5-Cyclooctene-1,2-dione (1.00 g, 7.25 mmol), 1,2-diaminomaleonitrile (0.78 g, 7.24 mmol), and acetic acid (18 ml) were heated on the steam bath for 1 h. Water (*ca.* 60 mL) was added to the hot solution until it was slightly cloudy, and the mixture was allowed to cool, producing a deposit of almost colorless needles of compound **12** (1.33 g, 88%). mp 121-122 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) ppm  $\delta$ : 2.51-2.74 (m, 4H, 2 equivalent  $\text{CH}_2$ ), 3.35 (t,  $J$  7.2 Hz, 4H, 2 equivalent  $\text{CH}_2$ ), 5.51 (m, 2H,  $\text{CH}=\text{CH}$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) ppm  $\delta$ : 26.7, 35.1, 113.3 (C nitrile), 128.7 (C olefinic), 130.3 (C pyrazine), 161.4 (C pyrazine). FT-IR (KBr)  $\nu_{\text{max}}$  / $\text{cm}^{-1}$ : 2224 (CN), 1600, 3028. MS (EI, 70 eV):  $m/z$  (%) 210 ( $\text{M}^+$ , 100), 195 (83), Found:  $\text{M}^+$  210.0905  $\text{C}_{12}\text{H}_{10}\text{N}_4$  requires  $\text{M}^+$  210.0905.

**7-Hydroxy-8-oxo-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile (13).** To a mixture of  $\text{KMnO}_4$  (4.0 g),  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (2.0 g), and water (0.3 mL) in dichloromethane (15 mL) was added cyclooctapyrazine-2,3-dicarbonitrile **12** (0.276 g, 1.31 mmol) in dichloromethane (5 mL), and *tert*-butyl alcohol (1 mL). After 6 h, the reaction mixture was filtered, and the solvent was removed to yield 2-hydroxy-ketone **13** (0.143 g, 45%) as the

only product. mp 212-214 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) ppm  $\delta$  1.96-2.05 (m, 1H, CH), 2.12-2.25 (m, 1H, CH), 2.35-2.51 (m, 1H, CH), 2.94-3.13 (m, 1H, CH), 3.16-3.25 (m, 1H, CH), 3.42-3.57 (m, 2H, 2 CH), 3.82-3.97 (m, 1H, CH), 4.36 (m, 1H, CH-O), 5.13 (br s, 1H, OH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) ppm  $\delta$ : 30.1, 30.4, 33.1, 42.0, 75.8, 113.8 (2C nitrile), 131.0, 131.4, 160.4, 161.6, 212.1 (C carbonyl), FT-IR (KBr)  $\nu_{\text{max}}$  / $\text{cm}^{-1}$ : 3421 (OH), 2240 (CN), 1707 (C=O). MS (EI, 70 ev):  $m/z$  (%) 242 ( $\text{M}^+$ , 100), 214 (66), 185 (97), 169 (54). Found:  $\text{M}^+$  242.0804  $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_2$  requires  $\text{M}^+$  242.0803.

**5,6,11,12-Tetrahydrocycloocta[1,2-*b*:5,6-*b'*]dipyrazine-2,3,8,9-tetracarbonitrile (14).** A mixture of 2-hydroxy-ketone **13** (0.100 g, 0.41 mmol) and 1,2-diaminomaleonitrile (0.045 g, 0.41 mmol) was heated at reflux in AcOH (1.5 ml) for 6 h. The reaction product precipitated. The reaction mixture was filtered and the precipitate was washed with water, giving **14** (0.090 g, 70%). mp > 300 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$  +  $\text{CF}_3\text{COOH}$ ) 3.70 (s, 8 H, 4 equivalent  $\text{CH}_2$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$  +  $\text{CF}_3\text{COOH}$ ) ppm  $\delta$ : 33.3 (4 equivalent C aliphatic), 114.5 (C nitrile), 131.3 (C pyrazine), 159.4 (C pyrazine). FT-IR (KBr)  $\nu_{\text{max}}$  / $\text{cm}^{-1}$ : 2978, 2242 (CN) MS (EI, 70 ev):  $m/z$  (%) 312 ( $\text{M}^+$ , 80), 297 (100), 272 (50), 169 (77). Found:  $\text{M}^+$  312.0827  $\text{C}_{16}\text{H}_8\text{N}_8$  requires  $\text{M}^+$  312.0827.

**5,6,13,14-Tetrahydropyrido[2'',3''':5',6']pyrazino[2',3':5,6]cycloocta[1,2-*b*]pyrazine-2,3-dicarbonitrile (15).** A mixture of 2-hydroxy-ketone **13** (0.100 g, 0.41 mmol) and pyridine-2,3-diamine (0.045 g, 0.41 mmol) was refluxed in AcOH (1.5 ml) for 6 h. The reaction product precipitated. The reaction mixture was filtered and the precipitate was washed with water, giving **15** (0.084 g, 65%). mp > 300 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$  +  $\text{CF}_3\text{COOH}$ ) ppm  $\delta$ : 3.78 (t,  $J$  6 Hz, 4H, 2 equivalent  $\text{CH}_2$ ), 3.84-3.92 (m, 4H, 2  $\text{CH}_2$ ), 8.3 (dd,  $J_1$  8.4,  $J_2$  5.4 Hz, 1H, aromatic), 9.22 (dd,  $J_1$  8.7,  $J_2$  1.5 Hz, 1H, aromatic), 9.32 (dd,  $J_1$  8.7,  $J_2$  1.5 Hz, 1H, aromatic).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$  +  $\text{CF}_3\text{COOH}$ ) ppm  $\delta$ : 33.6, 33.8, 34.1, 34.5, 111.8 (C nitrile), 111.9 (C nitrile), 126.1, 131.0, 131.1, 136.3, 141.9, 146.8, 148.7, 154.1, 158.7, 163.8, 164.4. FT-IR (KBr)  $\nu_{\text{max}}$  / $\text{cm}^{-1}$ : 2927, 2239 (CN), 1460, 1386, 792. MS (EI, 70 ev):  $m/z$  (%) 313 ( $\text{M}^+$ , 100), 298 (87), 170 (39). Found:  $\text{M}^+$  313.1076 requires  $\text{M}^+$  313.1077.

**5,6,13,14-Tetrahydropyrido[3'',4''':5',6']pyrazino[2',3':5,6]cycloocta[1,2-*b*]pyrazine-2,3-dicarbonitrile (16).** A mixture of 2-hydroxy-ketone **13** (0.100 g, 0.41 mmol) and pyridine-3,4-diamine (0.045 g, 0.41 mmol) was refluxed in AcOH (5ml) for 6 h. Water (ca. 10 ml) was added and the mixture was extracted with dichloromethane (3×20 ml) and the solvent was removed from the combined extracts. The crude product was crystallized ethanol/water to give **16** (0.084 g, 65%). mp > 300 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$  +  $\text{CF}_3\text{COOH}$ ) ppm  $\delta$ : 3.71-3.82 (m, 4H, 2 $\text{CH}_2$ ), 3.90-4.12 (m, 4H, 2 $\text{CH}_2$ ), 8.52 (d,  $J$  8.1 Hz, 1H, aromatic), 8.79 (d,  $J$  8.1 Hz, 1H, aromatic), 9.75 (s, 1H, aromatic).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$  +  $\text{CF}_3\text{COOH}$ ) ppm  $\delta$ : 33.7, 33.7, 34.4, 35.0, 111.0 (C nitrile), 112.0 (C nitrile), 126.9, 131.1, 131.2, 136.3, 136.9, 147.5, 148.0, 158.4, 158.6, 166.2, 166.8. FT-IR (KBr)  $\nu_{\text{max}}$  / $\text{cm}^{-1}$ : 2237 (CN), 1382, 1365, 1119. MS (EI, 70 ev):  $m/z$  (%) 313 ( $\text{M}^+$ , 100), 298 (80), Found:  $\text{M}^+$  313.1076  $\text{C}_{17}\text{H}_{11}\text{N}_7$  requires  $\text{M}^+$  313.1076.

**9-Methyl-5,6,13,14-tetrahydropyrazino[2',3':5,6]cycloocta[1,2-*b*]quinoxaline-2,3-dicarbonitrile (17).** A mixture of 2-hydroxy-ketone **13** (0.10 g, 0.41 mmol) and 4-methylbenzene-1,2-diamine (0.05 g, 0.41 mmol) was refluxed in AcOH (5ml) for 6 h. The reaction product was precipitated. The reaction mixture was filtered and the precipitate was washed with water, giving **17** (0.09 g, 70%). mp > 300 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$  +  $\text{CF}_3\text{COOH}$ ) ppm  $\delta$ : 2.70 (s, 3H, Me), 3.77-3.81 (m, 4H, 2 $\text{CH}_2$ ), 3.92-3.94 (m, 4H, 2 $\text{CH}_2$ ), 7.92-7.97 (m, 2H, aromatic), 8.149 (d,  $J$  8.7 Hz, 1H, aromatic).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$  +  $\text{CF}_3\text{COOH}$ ) ppm  $\delta$ : 22.2, 31.7, 32.4, 33.6, 33.8, 112.07 (C nitrile), 112.5 (C nitrile), 122.7, 125.5, 131.3, 136.7, 137.3, 147.9, 151.5, 152.1, 157.8, 158.1, 161.0, 161.6. FT-IR (KBr)  $\nu_{\text{max}}$  / $\text{cm}^{-1}$ : 2960, 2933, 2242 (CN), 1384, 1360. MS (EI, 70 ev):  $m/z$  (%) 326 ( $\text{M}^+$ , 100), 311 (76), Found:  $\text{M}^+$  326.1280  $\text{C}_{19}\text{H}_{14}\text{N}_6$  requires  $\text{M}^+$  326.1279.

**6,7,14,15-Tetrahydroquinoxalino[2',3':5,6]cycloocta[1,2-*g*]pteridine-2,4(1H,3H)-dione (19).** A mixture of 2-hydroxy-ketone **7** (0.100 g, 0.41 mmol) and 5,6-diaminouracil sulfate (0.156 g, 0.41 mmol) dissolved in DMSO with some AcOH was heated for 4 h. The reaction product precipitated. The reaction mixture was filtered and

the precipitate was washed with water, giving **19** (0.057 g, 40%). mp > 300 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub> + CF<sub>3</sub>COOH) ppm δ: 3.70-3.83 (m, 4H, 2CH<sub>2</sub>), 3.92-4.10 (m, 4H, 2CH<sub>2</sub>), 8.09-8.27 (m, 2H, aromatic), 8.33-8.45 (m, 2H, aromatic), 8.2 (br s, 1H NH), 9.4 (br s, 1H, NH). <sup>13</sup>C NMR (CDCl<sub>3</sub> + CF<sub>3</sub>COOH) ppm δ: 32.1, 32.2, 32.4, 33.2, 124.1, 124.7, 135.1, 136.2, 136.4, 146.5, 146.8, 150.9, 151.5, 153.0, 153.5, 156.3, 158.6, 162.2. FT-IR (KBr) ν<sub>max</sub> /cm<sup>-1</sup>: 3198 (NH), 3065, 2847, 1719 (NHC=O), 1700 (NHC=O), 1565, 1355, 780. MS (EI, 70 ev): m/z (%) 346 (M<sup>+</sup>, 84), 331 (100), 169 (69). Found: M<sup>+</sup> 346.1178 C<sub>18</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub> requires M<sup>+</sup> 346.1178.

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