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

Mostafa Honari Alamdari*

Department of Chemistry, Khoy Branch, Islamic Azad University, Khoy, Iran

E-Mail: mostafa_honari12@yahoo.com

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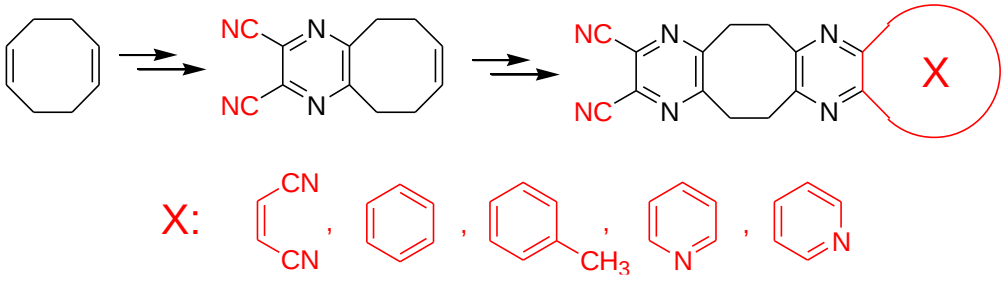
Abstract

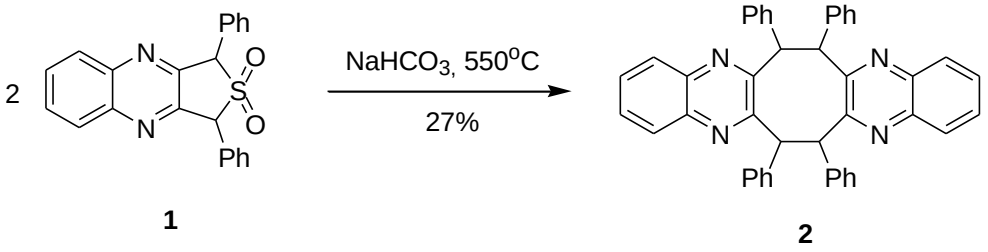
The reaction of 5-cyclooctene-1,2-dione with 1,2-diaminomaleonitrile, produces 5,6,9,10-tetrahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile which was easily oxidized cleanly, under heterogeneous conditions by a combination of $KMnO_4$, $CuSO_4{\cdot}5H_2O$, *t*-BuOH in CH_2Cl_2 and water, to give 7-hydroxy-8-oxo-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile. 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

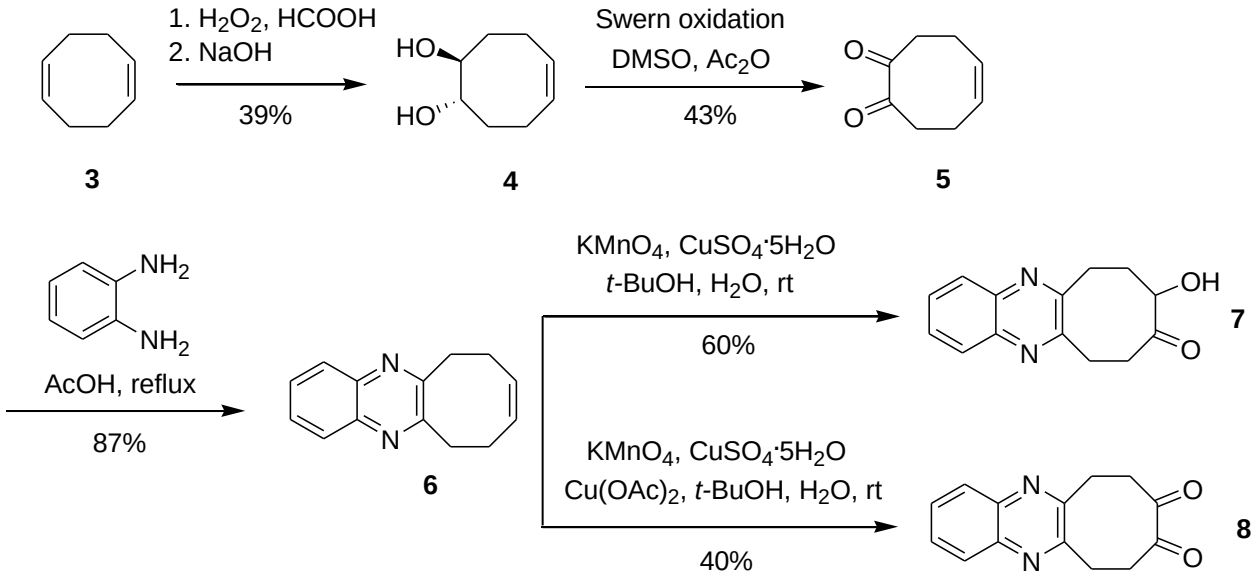
Molecules containing quinoxaline and pyrazine rings have attracted considerable attention because of their various biological activities, such as antiviral,[1] anticancer,[2] antibacterial,[3] anti-inflammatory,[4] and antidepressant activity.[5] However, the synthesis of heterocyclic compounds based on a cyclooctane scaffold is generally difficult to achieve.[6-10] 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).[11]



1 **2**

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

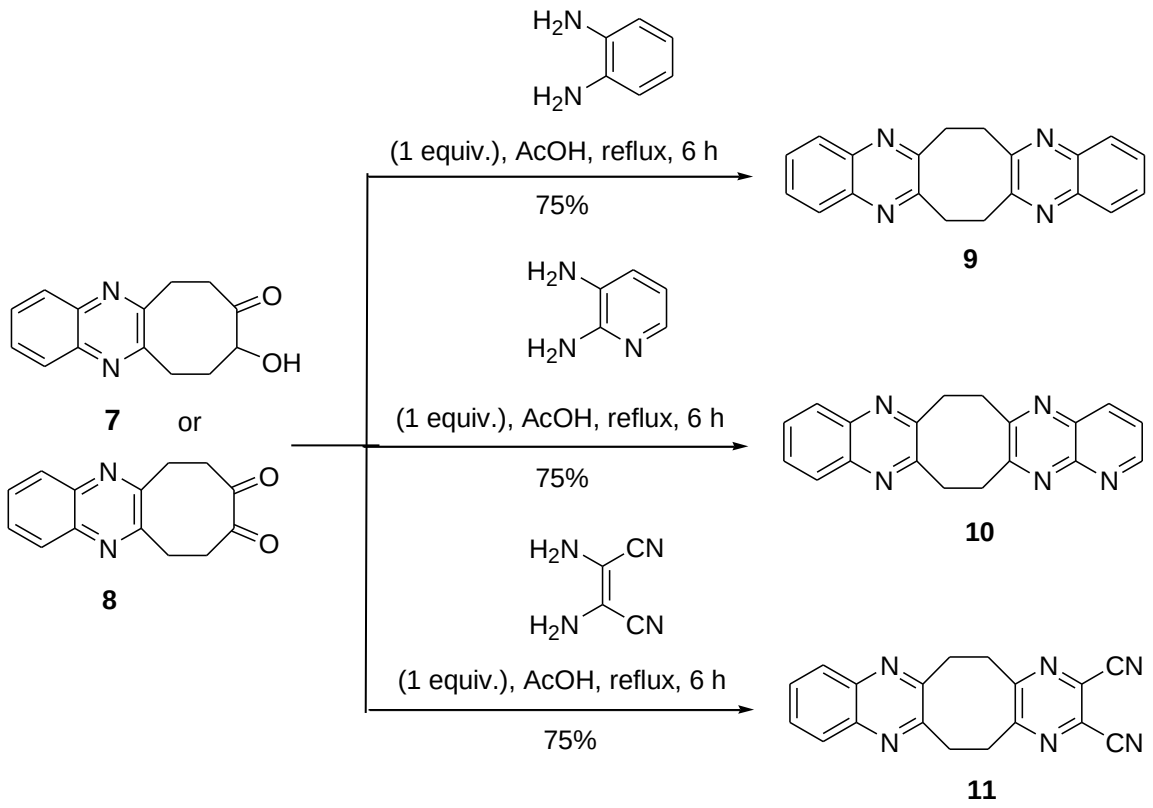
Previously, we reported the synthesis of some quinoxaline derivatives starting from cycloocta-1,5-diene **3**. Oxidation in two steps: (1) selective dihydroxylation of one of the carbon-carbon double bonds with hydrogen peroxide (33%) and formic acid, and then (2) Swern oxidation using dimethyl sulfoxide, 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). [12]



3 **4** **5** **6** **7** **8**

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**.

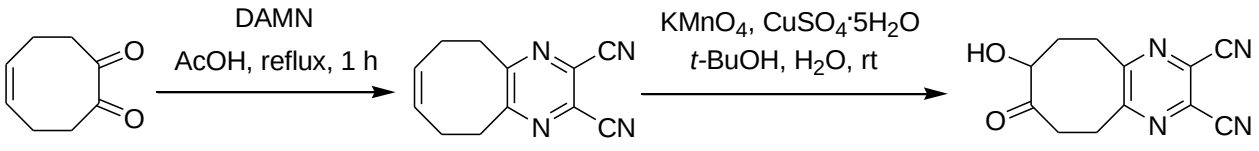
Condensation of 1,2-diamines to form pyrazine rings was possible with either the 2-hydroxy-ketone **7** or with the 1,2-dione **8**, and in this way pentacycles **9** and **10** and tetracycle **11** were produced.[12]



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

Results and Discussion

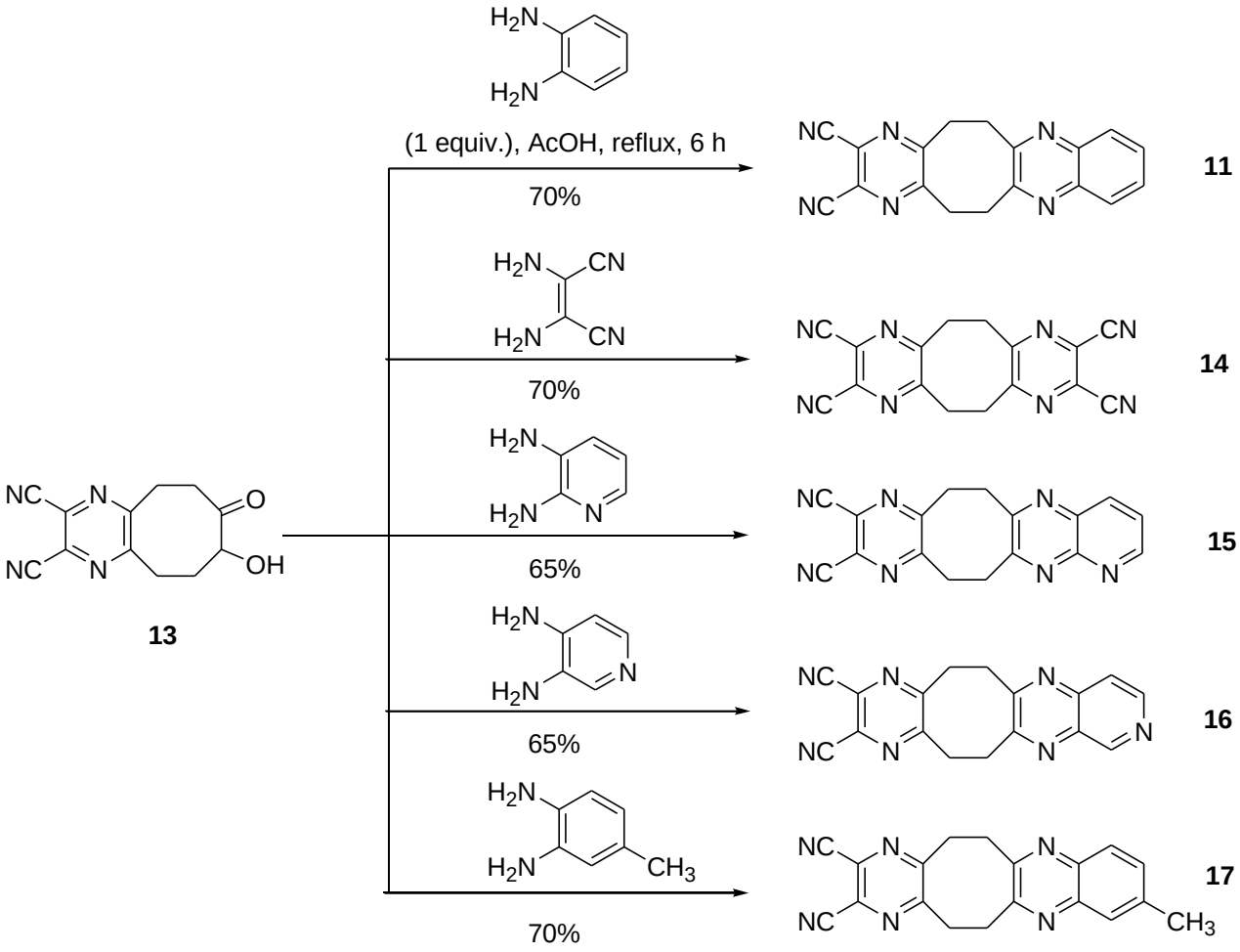
In continuation of our research in this area, we synthesized 7-hydroxy-8-oxocycloocta[*b*]pyrazine-2,3-dicarbonitrile **13** (Scheme 4). Thus, 5,6,9,10-tetrahydrocyclooctapyrazine-2,3-dicarbonitrile **12** was readily produced by the reaction of 5-cyclooctene-1,2-dione with 1,2-diaminomaleonitrile ($NC(H_2N)C=C(NH_2)CN$, 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 ($KMnO_4$, $CuSO_4{\cdot}5H_2O$, *t*-BuOH in CH_2Cl_2) which gave 7-hydroxy-8-oxo-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile **13**. The similarity of the ^{1}H NMR chemical shifts and splitting patterns for compounds **13** and **7** indicated their analogous structures.[12]



5 **12** **13**

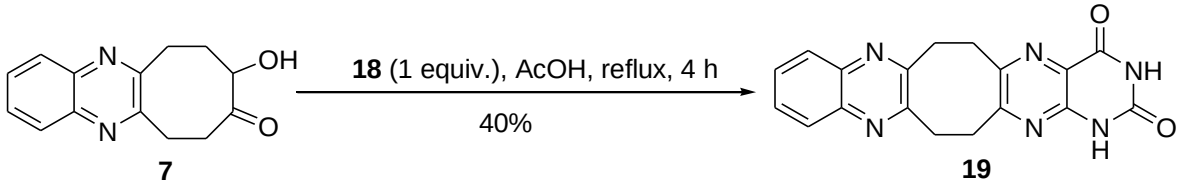
Scheme 4. Synthesis of 7-hydroxy-8-oxo-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile **13** from 5-cyclooctene-1,2-dione

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 Thermonicolet (Nexus 670) FT-infrared spectrometer, using sodium chloride cells and measured as KBr discs. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR measurements were recorded on a Bruker 300 spectrometer in $CDCl_3$ 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 ^{o}C, Analyzer: quadrupole, Analyzer temperature: 150 ^{o}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 ^{o}C. ^{1}H NMR ($CDCl_3$ + CF_3CO_2H) δ 3.79 (t, *J* 6.9 Hz, 4H, 2 equivalent CH_2), 3.96 (t, *J* 6.9 Hz, 4H, 2 equivalent 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}C NMR ($CDCl_3$ + CF_3CO_2H) δ 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) ν_{max} /cm^{-1}: 2937, 2238, 776. MS (EI, 70 ev): *m/z* (%) 312 (M^+, 100), 297 (89), 169 (46). Found: M^+ 312.1123, $C_{18}H_{12}N_6$ requires 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 ^{o}C. ^{1}H NMR ($CDCl_3$) ppm δ: 2.51-2.74 (m, 4H, 2 equivalent CH_2), 3.35 (t, *J* 7.2 Hz, 4H, 2 equivalent CH_2), 5.51 (m, 2H, CH=CH). ^{13}C NMR ($CDCl_3$) ppm δ: 26.7, 35.1, 113.3 (C nitrile), 128.7 (C olefinic), 130.3 (C pyrazine), 161.4 (C pyrazine). FT-IR (KBr) ν_{max} /cm^{-1}: 2224 (CN), 1600, 3028. MS (EI, 70 ev): *m/z* (%) 210 (M^+, 100), 195 (83), Found: M^+ 210.0905 $C_{12}H_{10}N_4$ requires M^+ 210.0905.

7-Hydroxy-8-oxo-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyrazine-2,3-dicarbonitrile (13). To a mixture of $KMnO_4$ (4.0 g), $CuSO_4{\cdot}5H_2O$ (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 ^{o}C. ^{1}H NMR ($CDCl_3$) ppm δ 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}C NMR ($CDCl_3$) ppm δ: 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) ν_{max} /cm^{-1}: 3421 (OH), 2240 (CN), 1707 (C=O). MS (EI, 70 ev): *m/z* (%) 242 (M^+, 100), 214 (66), 185 (97), 169 (54). Found: M^+ 242.0804 $C_{12}H_{10}N_4O_2$ requires 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}H NMR ($CDCl_3$ + CF_3COOH) 3.70 (s, 8 H, 4 equivalent CH_2). ^{13}C NMR ($CDCl_3$ + CF_3COOH) ppm δ: 33.3 (4 equivalent C aliphatic), 114.5 (C nitrile), 131.3 (C pyrazine), 159.4 (C pyrazine). FT-IR (KBr) vmax /cm^{-1}: 2978, 2242 (CN) MS (EI, 70 ev): *m/z* (%) 312 (M^+, 80), 297 (100), 272 (50), 169 (77). Found: M^+ 312.0827 $C_{16}H_8N_8$ requires 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}H NMR ($CDCl_3$ + CF_3COOH) ppm δ: 3.78 (t, *J* 6 Hz, 4H, 2 equivalent CH_2), 3.84-3.92 (m, 4H, 2 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}C NMR ($CDCl_3$ + CF_3COOH) ppm δ: 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) ν_{max} /cm^{-1}: 2927, 2239 (CN), 1460, 1386, 792. MS (EI, 70 ev): *m/z* (%) 313 (M^+, 100), 298 (87), 170 (39). Found: M^+ 313.1076 requires 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}H NMR ($CDCl_3$ + CF_3COOH) ppm δ: 3.71-3.82 (m, 4H, $2CH_2$), 3.90-4.12 (m, 4H, $2CH_2$), 8.52 (d, *J* 8.1 Hz, 1H, aromatic), 8.79 (d, *J* 8.1 Hz, 1H, aromatic), 9.75 (s, 1H, aromatic). ^{13}C NMR ($CDCl_3$ + CF_3COOH) ppm δ: 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) vmax /cm^{-1}: 2237 (CN), 1382, 1365, 1119. MS (EI, 70 ev): *m/z* (%) 313 (M^+, 100), 298 (80), Found: M^+ 313.1076 $C_{17}H_{11}N_7$ requires 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}H NMR ($CDCl_3$ + CF_3COOH) ppm δ: 2.70 (s, 3H, Me), 3.77-3.81 (m, 4H, $2CH_2$), 3.92-3.94 (m, 4H, $2CH_2$), 7.92-7.97 (m, 2H, aromatic), 8.149 (d, *J* 8.7 Hz, 1H, aromatc).^{13}C NMR ($CDCl_3$ + CF_3COOH) ppm δ: 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) vmax /cm^{-1}: 2960, 2933, 2242 (CN), 1384, 1360. MS (EI, 70 ev): *m/z* (%) 326 (M^+,100), 311 (76), Found: M^+ 326.1280 $C_{19}H_{14}N_6$ requires M^+ 326.1279.

6,7,14,15-Tetrahydroquinoxalino[2',3':5,6]cycloocta[1,2-*g*]pteridine-2,4(1*H*,3*H*)-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. ^{1}H NMR ($CDCl_3$ + CF_3COOH) ppm

δ: 3.70-3.83 (m, 4H, $2CH_2$), 3.92-4.10 (m, 4H, $2CH_2$), 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). ^{13}C NMR ($CDCl_3$ + CF_3COOH) 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_{max} /cm^{-1}: 3198 (NH), 3065, 2847, 1719 (NHC=O), 1700 (NHC=O), 1565, 1355, 780. MS (EI, 70 ev): *m/z* (%) 346 (M^+, 84), 331 (100), 169 (69)**.** Found: M^+ 346.1178 $C_{18}H_{14}N_6O_2$ requires M^+ 346.1178.

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