

The synthesis of potential DNA intercalators. Part 3. Triazanaphthalenes, tetraaza-anthracenes and - phenanthrenes from isoxazolones

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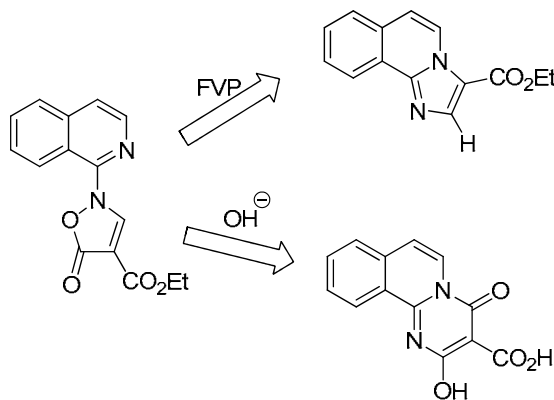
Abstract

The reaction of bis-isoxazolanyl pyrimidines and pyridazines with bases leads to a novel synthesis of tri- and tetra azaheterocycles, capable of intercalation with DNA.

Keywords: 2, 4-Dichloropyrimidine, 3,6-dichloropyridazine, 4-ethoxycarbonyl isoxazolone, bis-isoxazolanylpyrimidines, bis-isoxazolanylpyridazine

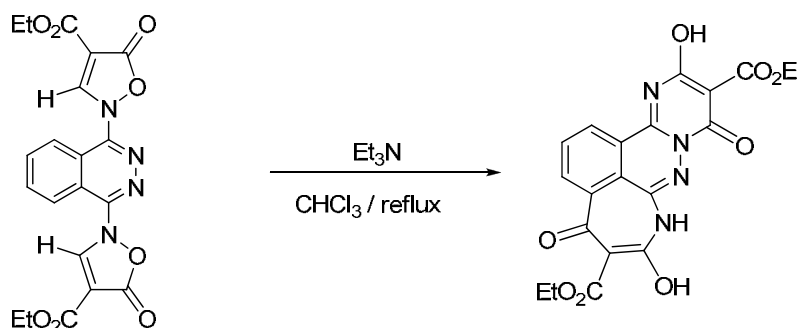
Introduction

We have previously shown^{1,2} that 2-isoxazolanyl azaheterocycles undergo rearrangement in the presence of bases, resulting in the annulation of a pyrimidine ring onto the azaheterocycle (Scheme 1). By contrast, the use of triethylamine,³ photolysis⁴ or pyrolysis⁵ led to annelation of an imidazole ring onto the azaheterocycle (Scheme 1).



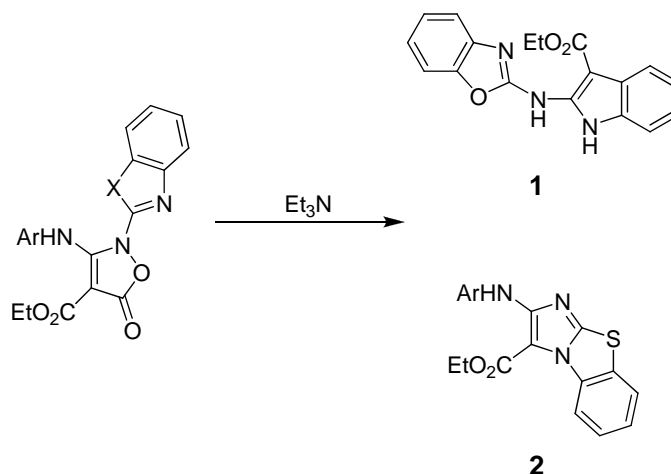
Scheme 1

This work was extended to the reaction of bis-isoxazolinyldiazaheterocyclic systems,² in which the rearrangements underwent more complex, but mechanistically consistent, pathways (Scheme 2).



Scheme 2

When the isoxazoline moiety contained an arylamino group at C-3,^{6,7} base induced rearrangements led to competitive cyclisation through the arylamino group or the azaheterocycle, depending on the nucleophilicity of the latter (Scheme 3).

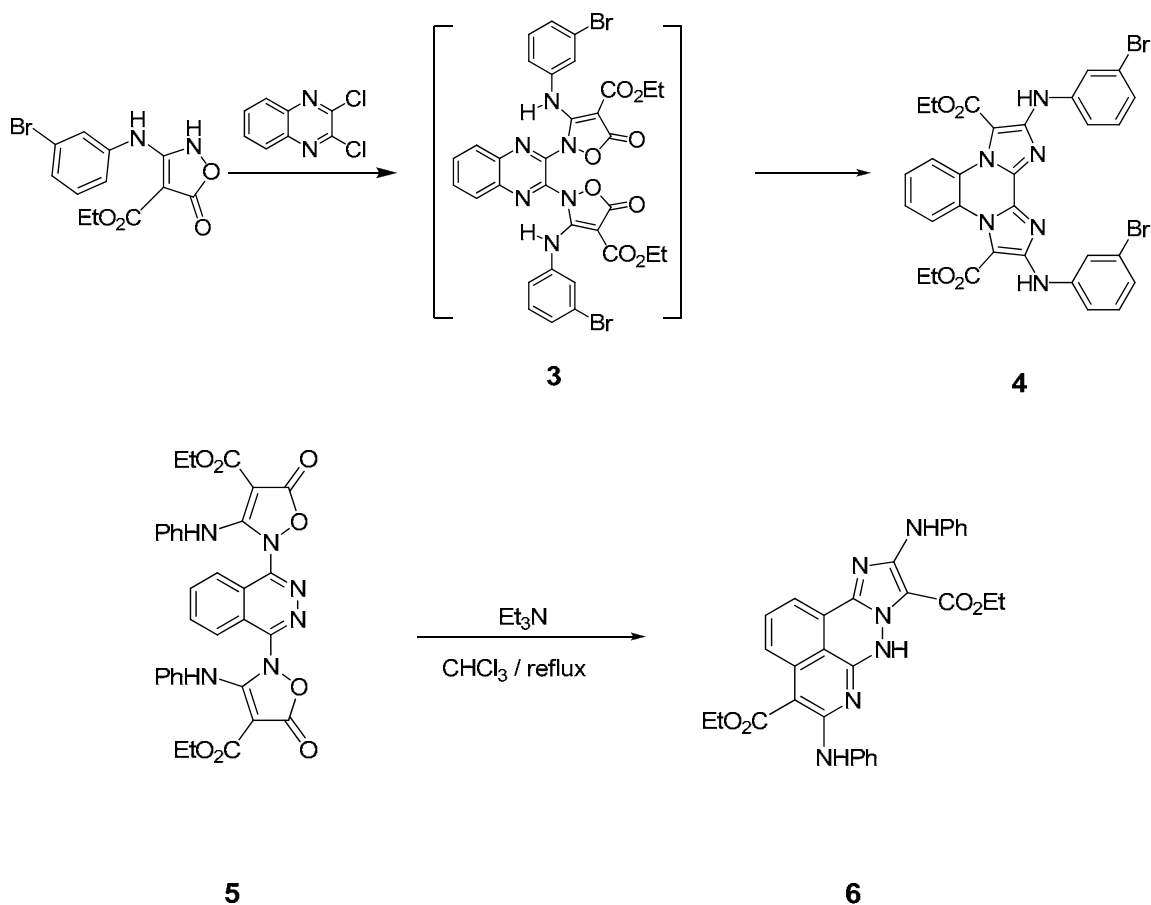


Scheme 3

Since imidazo[1,2-*a*]azaheterocycles such as those in Scheme 3 above may be converted to larger heterocycles that can be expected to intercalate with DNA because of their H-bonding donor and acceptor groups,⁸⁻¹⁰ this work was extended to bis-isoxazolinyldiazaheterocycles.²

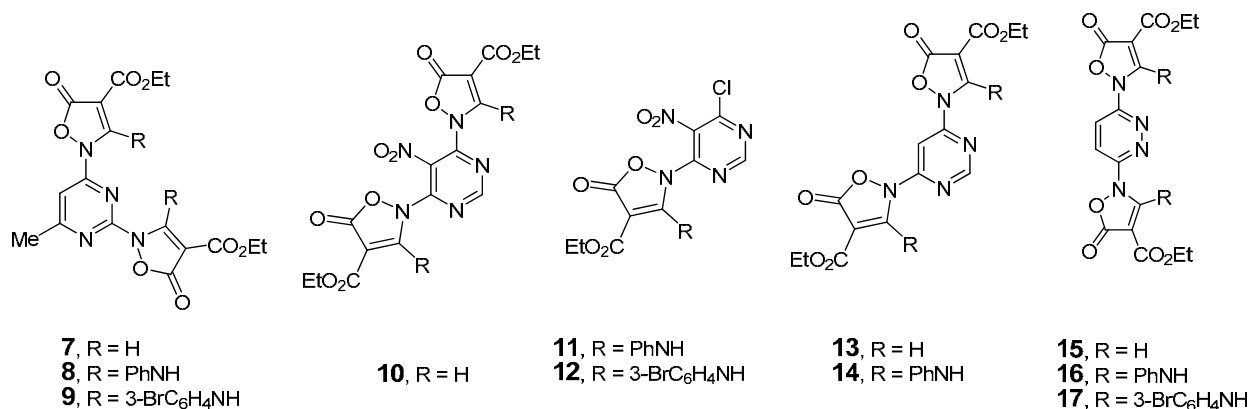
Structures **1**, **2**, and **4** are clearly well set up as precursors for polycyclic structures which are of considerable interest as pharmacophores for therapeutic drugs. Such compounds have been used to reduce neurotoxin injury associated with anoxia or ischemia,¹¹ or as antiviral agents.¹² Tricyclic aza-heterocycles also display platelet-derived growth factor inhibitory activity.¹³

Unfortunately, no definitive pattern emerged, that would allow prediction of the structure of the products from their reaction with bases. Thus, while the quinoxaline **3** gave the bis-imidazoquinoxaline **4**, the corresponding phthalazine **5** underwent partial annelation through the benzene ring to give **6** (Scheme 4).



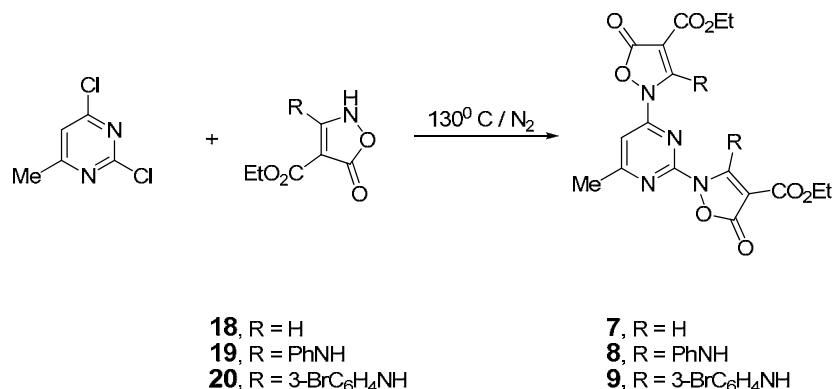
Scheme 4

In this paper we intended to extend the range of bis-isoxazolones investigated, in the hope of more clearly defining the synthetic utility of this mode of heterocyclic synthesis. Herein we report the synthesis of the bis-isoxazolinympyrimidines (**7-14**) and pyridazines (**15-17**), and the base catalysed reactions of **7-10**, **13** and **15**.



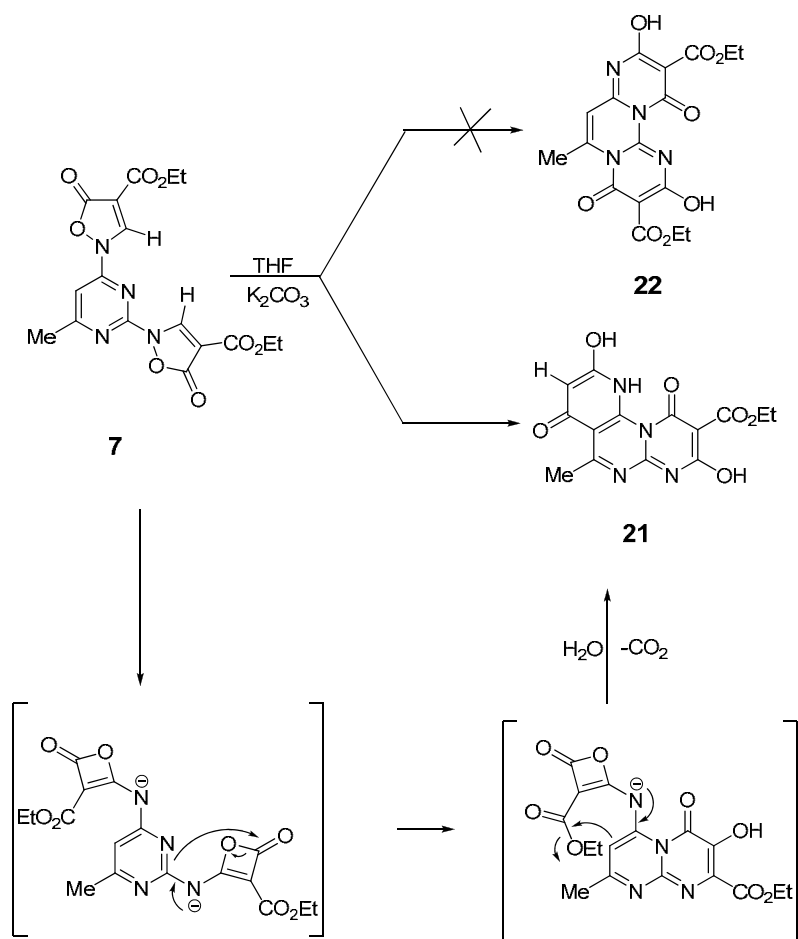
Results and Discussion

2,4-Dichloro-6-methylpyrimidine reacted with the 4-ethoxycarbonylisoxazolone **18** when heated briefly to 130 °C to give the bis substituted pyrimidine **7**. Similarly, heating the pyrimidine with the 3-phenylamino- **19** or 3-(3-bromophenyl)aminoisoxazolone **20** gave the bis substituted pyrimidines **8** and **9** respectively (Scheme 5).

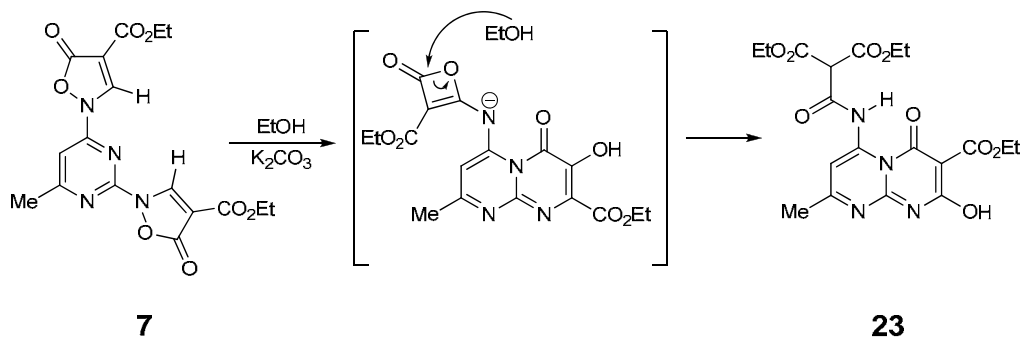


Scheme 5

Reaction of pyrimidine **7** with potassium carbonate in THF gave the bis-annulated tetraazaphenanthrene **21**, rather than the anticipated **22**: a suggested pathway for such a product is shown in Scheme 6. Some support for this pathway was found in the observation that reaction of **7** with potassium carbonate in ethanol gave the product **23** (Scheme 7).

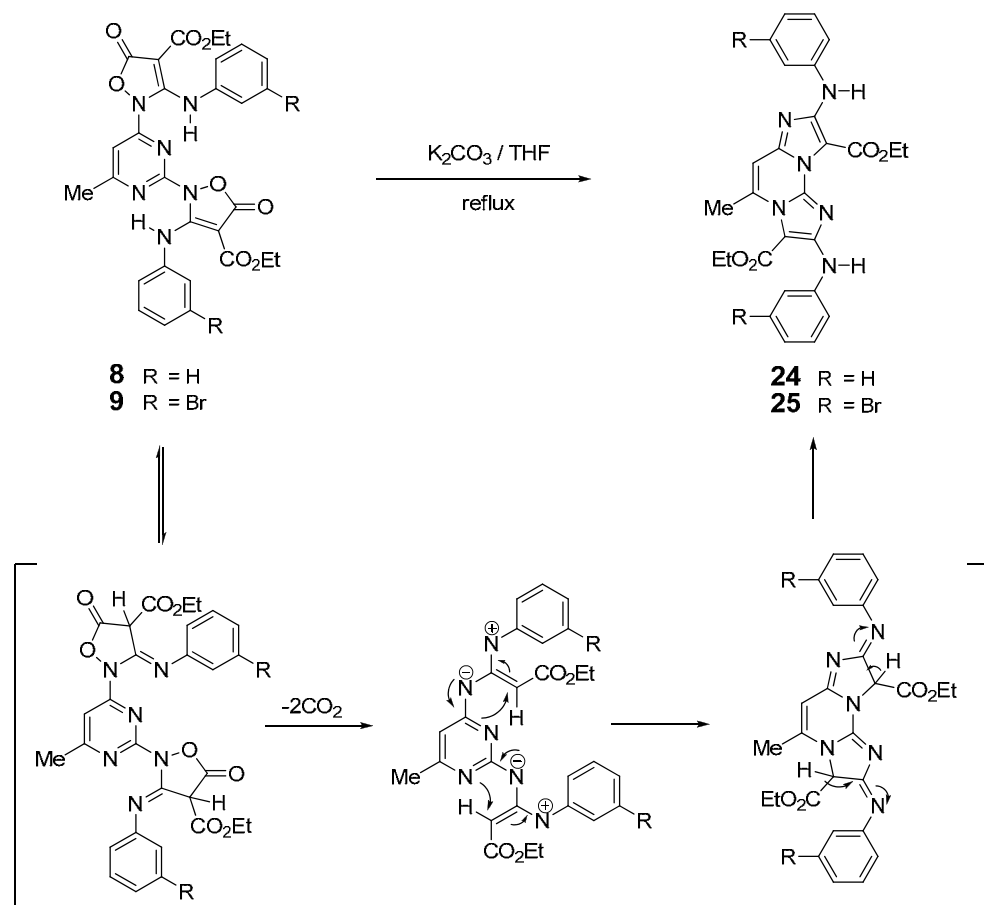


Scheme 6



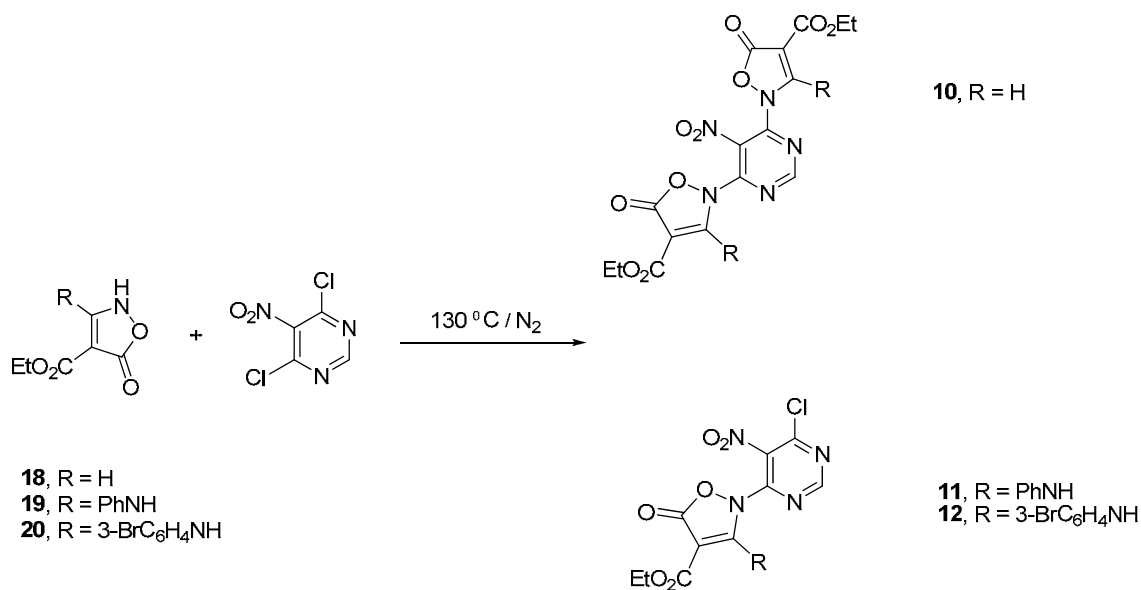
Scheme 7

The reaction of the aminoaryl derivatives **8** and **9** with potassium carbonate in THF followed the hoped pathway, with the annelation of two imidazole rings onto the pyrimidine to give **24** and **25** (Scheme 8).



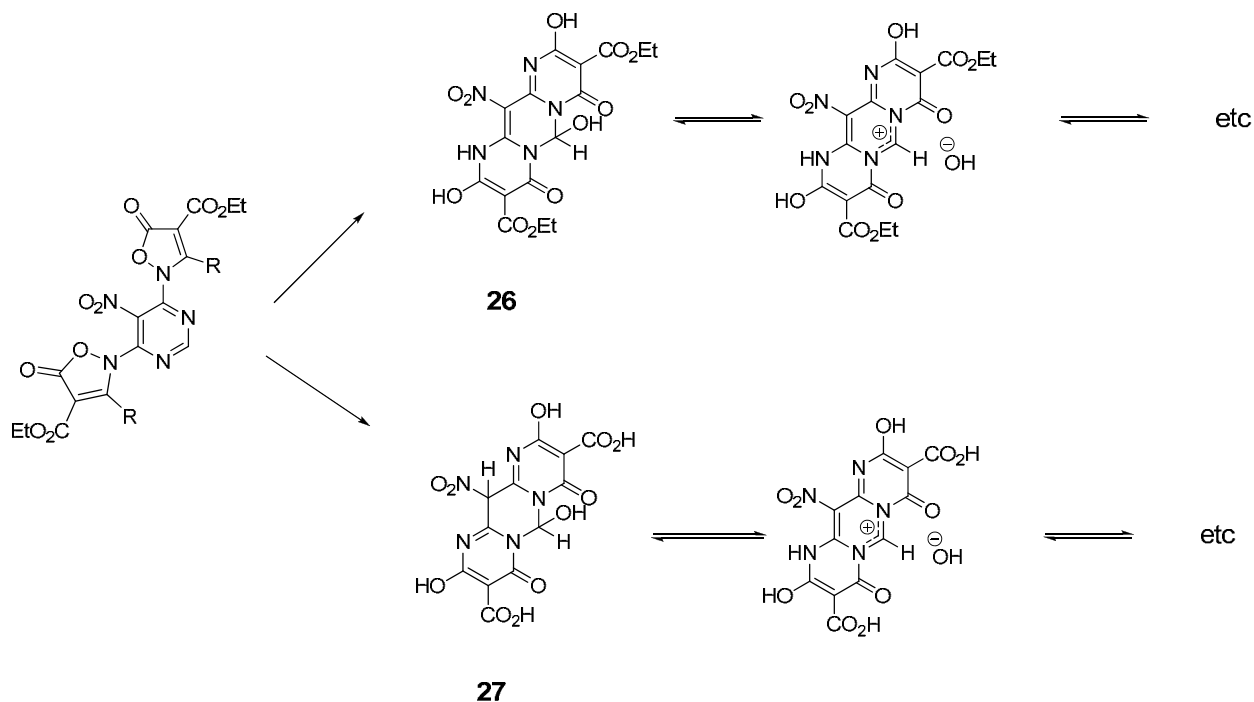
Scheme 8

Reaction of 4,6-dichloro-5-nitropyrimidine with the isoxazolones **18** by heating neat under nitrogen at 130 °C gave bis substituted pyrimidine **10**, but only mono substituted pyrimidines **11** and **12** were formed by heating the isoxazolones **19** and **20** with 4,6-dichloro-5-nitropyrimidine (Scheme 9).



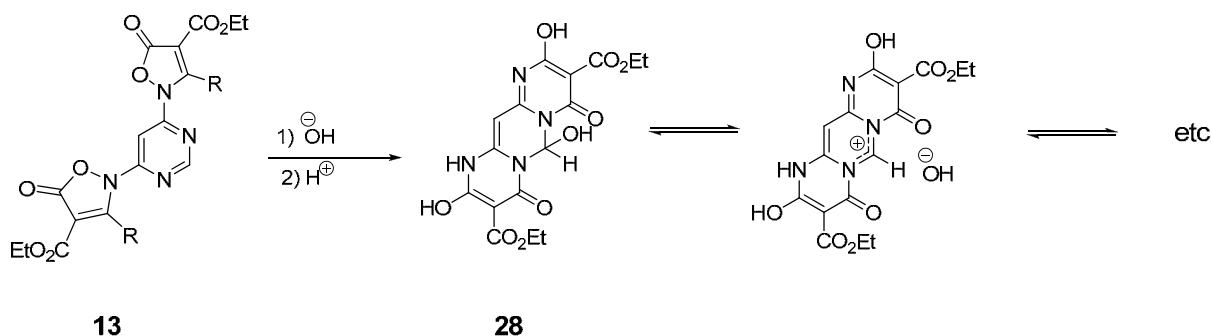
Scheme 9

The reaction of **10** with sodium hydroxide at room temperature gave **26** while under reflux conditions afforded **27** (Scheme 10). A number of alternative tautomeric structures for **26** and **27** can be written.



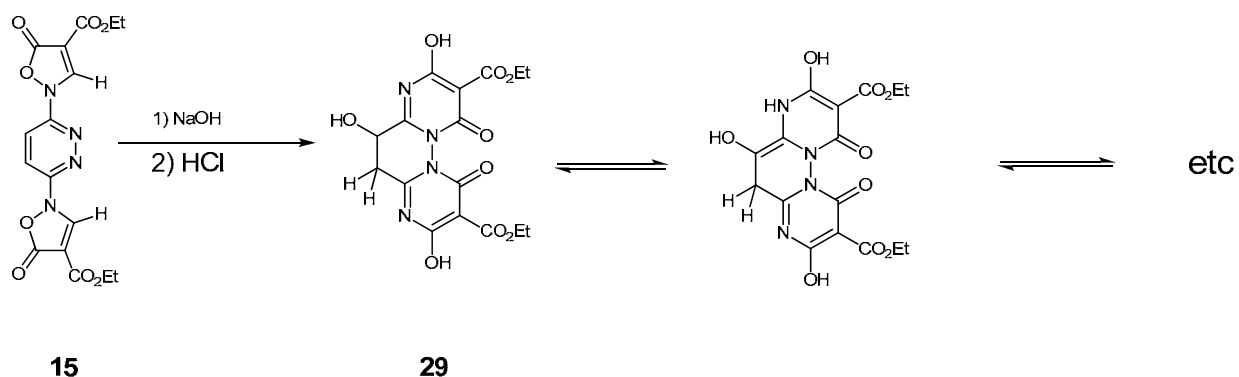
Scheme 10

Similarly, **13** and **14** were obtained from the isoxazolones **18** and **19** with 4,6-dichloropyrimidine. The 4,6-bis(isoxazolonyl)pyrimidines **13** reacted with sodium hydroxide at 40 °C to give the tetraazaanthracene **28** (Scheme 11).



Scheme 11

Similarly, the bis-isoxazolonyl derivative **15** reacted with sodium hydroxide to afford the tetraazaanthracene **29** (Scheme 12).



Scheme 12

Conclusions

The above base-catalyzed rearrangements again illustrate that the synthesis of several new tri- and tetra heterocycles appears possible, and because of their multiple H-bonding and H-acceptor sites, these compounds could be expected to intercalate with DNA.⁸⁻¹⁰ They could also serve as intermediates for new planar polycyclic heterocycles.

Experimental Section

General. Freshly distilled solvents were used throughout, and anhydrous solvents were dried according to Perrin and Armarego.¹⁴ Melting points were determined on a Philip Harris C4954718 apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet (Nexus 670) FT-infrared spectrometer, using sodium chloride cells and measured as film or KBr disks. ¹H (300 MHz) and ¹³C (75.5 MHz) NMR measurements were recorded on a Bruker 300 spectrometer in DMSO-d₆, CD₂Cl₂ or CDCl₃ using TMS as the internal reference. Mass spectra were recorded on a Varian Matt 311 spectrometer and relative abundances of fragments are quoted in parentheses after the m/z values.

General Procedure. 6-Methyl-2,4-bis(4-ethoxycarbonyl-5-oxo-2,5-dihydroisoxazolin-2-yl)pyrimidine (7)

Ethyl 5-oxo-2,5-dihydroisoxazole-4-carboxylate (**18**)¹⁵ (100 mg, 0.637 mmol) and 2,4-dichloro-6-methylpyrimidine (52 mg, 0.318 mmol) were heated neat under nitrogen at 130 °C for 15 min. The resulting product was recrystallised from ethanol to give the bis-isoxazolinyll derivative **7** (103 mg, 80%) as a white solid, mp 201-204 °C (lit¹⁶, 202-204 °C). ¹H NMR (DMSO-d₆) δ 1.29 (t, *J*=7.2 Hz, 6H), 2.49 (s, 3H), 4.27 (q, *J*=7.2 Hz, 2H), 4.28 (q, *J*=7.2 Hz, 2H), 7.35 (s, 1H), 10.25 (s, 1H), 10.33 (s, 1H); ¹³C NMR (DMSO-d₆) δ 14.68, 24.47, 60.89, 61.05, 96.33, 97.01, 103.34, 148.68, 149.38, 151.03, 153.38, 160.69, 160.9, 163.1, 163.66, 173.78; FT-IR (KBr) ν_{\max} / cm⁻¹: 1805, 1783, 1708, 1556, 1440, 1240, 1213, 1023, 765.

6-Methyl-2,4-bis(4-ethoxycarbonyl-3-phenylamino-5-oxo-2,5-dihydroisoxazolin-2-yl)pyrimidine (8). The same procedure as above with ethyl 5-oxo-3-phenylamino-2,5-dihydroisoxazole-4-carboxylate (**19**)⁶ (100 mg, 0.4 mmol) gave **8** (82 mg, 70%) as a cream solid, mp 174-175 °C. ¹H NMR (CDCl₃) δ 1.28 (t, *J*=7.2 Hz, 3H), 1.39 (t, *J*=7.2 Hz, 3H), 2.25 (s, 3H), 4.27 (q, *J*=7.2 Hz, 2H), 4.37 (q, *J*=7.2 Hz, 2H), 6.86 (s, 1H), 6.95 (d, *J*=7.8 Hz, 2H), 7.04-7.32 (m, 8H), 10.13 (s, 1H), 10.4 (s, 1H); ¹³C NMR (CDCl₃) δ 14.21, 14.38, 23.98, 60.98, 61.09, 78.73, 79.03, 106.36, 121.19, 121.39, 125.97, 126.27, 129.23, 129.4, 137.53, 137.64, 152.96, 157.16, 159.54, 160.32, 162.66, 162.92, 163.63, 164.9, 171.15; FT-IR (KBr) ν_{\max} / cm⁻¹: 3423, 1786, 1617, 1585, 1371, 1350, 1013, 764; MS m/z (%) 586(M⁺, 4), 538(22), 497(12), 404(24), 216(54), 214(28), 178(27), 144(76), 76(100).

6-Methyl-2,4-bis(4-ethoxycarbonyl-3-(3-bromophenylamino)-5-oxo-2,5-dihydroisoxazolin-2-yl)pyrimidine (9). The same procedure as above with ethyl 3-(3-bromophenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**20**)⁶ (100 mg, 0.3 mmol) gave **9** (85 mg, 75%) as a cream solid, mp 185-187 °C. ¹H NMR (CDCl₃) δ 1.27 (t, *J*=7.2 Hz, 3H), 1.36 (t, *J*=7.2 Hz, 3H), 2.18 (s, 3H), 4.26 (q, *J*=7.2 Hz, 2H), 4.35 (q, *J*=7.2 Hz, 2H), 6.92 (s, 2H), 7.06 (t, *J*=7.2 Hz, 1H), 7.16-7.35 (m, 6H), 10.21 (s, 1H), 10.5 (s, 1H); ¹³C NMR (CDCl₃) δ 14.21, 14.34, 24.11, 61.19, 61.29, 79.29, 79.74, 105.56, 119.88, 120.54, 122.71, 122.83, 124.51, 124.95, 129.06, 129.28, 130.48, 130.84, 138.93, 139.01, 152.77, 157.19, 158.97, 159.95, 162.34, 162.52, 163.04, 164.47, 171.23;

FT-IR (KBr) ν_{\max} / cm^{-1} : 3432, 1789, 1612, 1586, 1370, 1348, 1202, 1030; MS m/z (%) 744(M^+ , 4), 700(10), 656(21), 652(29), 563(12), 292(66), 180(100), 153(69), 88(92), 45(100).

4,6-Bis(4-ethoxycarbonyl-5-oxo-2,5-dihydroisoxazolin-2-yl)-5-nitropyrimidine (10). Ethyl 5-oxo-2,5-dihydroisoxazole-4-carboxylate (**18**) (100 mg, 0.637 mmol) and 2,4-dichloro-5-nitropyrimidine (61.7 mg, 0.318 mmol) were heated neat under nitrogen at 130 °C for 15 min. The resulting product was recrystallised from ethanol to give the isoxazolone (**10**) (111 mg, 80%) as white solid, mp 206-208 °C. ^1H NMR (DMSO- d_6) δ 1.27 (t, $J=7.2$ Hz, 6H), 4.25 (q, $J=7.2$ Hz, 4H), 9.04 (s, 1H), 9.77 (s, 2H); ^{13}C NMR (DMSO- d_6) δ 14.45, 61.48, 98.44, 145.04, 149.62, 157.77, 159.86, 162.35; FT-IR (KBr) ν_{\max} / cm^{-1} : 1816, 1708, 1538, 1447, 1373, 1196, 1021, 980, 770; MS m/z (%) 435(M^+ , 26), 389(5), 314(3), 268(3), 117(10), 68(39), 52(100).

4-Chloro-6-(4-ethoxycarbonyl-3-phenylamino-5-oxo-2,5-dihydroisoxazolin-2-yl)-5-nitropyrimidine (11). Using the same procedure as above with 5-oxo-3-phenylamino-2,5-dihydroisoxazole-4-carboxylate (**19**)⁶ (100 mg, 0.4 mmol) gave **11** (119 mg, 73%) as white crystals, mp 192-194 °C. ^1H NMR (CDCl_3) δ 1.4 (t, $J=7.2$ Hz, 3H), 4.42 (q, $J=7.2$ Hz, 2H), 7.12-7.32 (m, 5H), 8.45 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.37, 61.4, 79.07, 122.08, 127.13, 129.84, 136.38, 149.25, 154.03, 156.56, 161.96, 162.78, 164.85; FT-IR (KBr) ν_{\max} / cm^{-1} : 3293, 1804, 1649, 1625, 1562, 1487, 1444, 1199; MS m/z (%) 407[(M^+ +2), 2], 405(M^+ , 8), 358(24), 268(5), 215(22), 158(13), 143(45), 76(100).

4-Chloro-6-(3-bromophenylamino)-4-ethoxycarbonyl-5-oxo-2,5-dihydroisoxazolin-2-yl)-5-nitropyrimidine (12). Using the same procedure as above with ethyl 3-(3-bromophenyl)amino-5-oxo-2,5-dihydroisoxazole-4-carboxylate (**20**)⁶ (100 mg, 0.3 mmol) gave **12** (111 mg, 75%) as white crystals, mp 181-183 °C. ^1H NMR (CDCl_3) δ 1.41 (t, $J=7.2$ Hz, 3H), 4.42 (q, $J=7.2$ Hz, 2H), 7.14-7.3 (m, 3H), 7.4 (s, 1H), 8.52(s, 1H), 10.15(s, 1H); ^{13}C NMR (CDCl_3) δ 14.33, 61.57, 79.66, 120.33, 123.32, 125.27, 129.66, 130.07, 131.01, 137.62, 149.1, 154.34, 156.62, 161.6, 162.37, 164.67; FT-IR (KBr) ν_{\max} / cm^{-1} : 3282, 1799, 1650, 1626, 1560, 1490, 1122, 787; MS m/z (%) 488[(M^+ +4), 22], 486[(M^+ +2), 71], 484(M^+ , 55), 442(83), 439(100), 225(84), 221(100), 158(100), 154(87), 90(53), 75(76).

General procedure. 4,6-Bis-(4-ethoxycarbonyl-5-oxo-2,5-dihydroisoxazolin-2-yl)pyrimidine (13)

Ethyl 5-oxo-2,5-dihydroisoxazole-4-carboxylate (**18**) (100 mg, 0.637 mmol) and 2,4-dichloropyrimidine (47.4 mg, 0.318 mmol) were heated neat under nitrogen at 130 °C for 15 min. The resulting product was recrystallised from ethanol to give the isoxazolone **13** (111 mg, 80%) as a white solid, mp 206-208 °C. ^1H NMR (CDCl_3) δ 1.39 (t, $J=7.2$ Hz, 6H), 4.38 (q, $J=7.2$ Hz, 4H), 7.24 (s, 1H), 8.73 (s, 1H), 9.37 (s, 2H); ^{13}C NMR (CDCl_3) δ 14.24, 61.58, 90.91, 98.54, 145.36, 145.05, 158.26, 160.05, 162.08; FT-IR (KBr) ν_{\max} / cm^{-1} : 1808, 1716, 1599, 1518, 1473, 1192, 1023, 78; MS m/z (%) 390(M^+ , 13), 345(6), 301(23), 211(12), 118(12), 68(13).

4,6-Bis-(4-ethoxycarbonyl-3-phenylamino-5-oxo-2,5-dihydroisoxazolin-2-yl)pyrimidine (14). Using the same procedure as above with isoxazolone (**19**) (100 mg, 0.4 mmol) gave **14** (86.5 mg, 75%) as white crystals, mp 178 °C dec. ^1H NMR (CDCl_3) δ 1.2 (t, $J=7.2$ Hz, 6H), 4.15 (q, $J=7.2$ Hz,

4H), 7.12-7.34 (m, 11H), 8.16 (s, 1H), 10.41 (s, 2H); ^{13}C NMR (CDCl_3) δ 14.13, 60.95, 79.11, 97.17, 122.03, 126.43, 129.37, 137.75, 155.37, 157.56, 159.1, 162.47, 162.98; FT-IR (KBr) $\nu_{\text{max}} / \text{cm}^{-1}$: 3434, 1795, 1701, 1588, 1520, 1454, 1348, 1198, 1025, 777; MS m/z (%) 528[(M^+ - CO_2), 8], 485(18), 439(10), 393(15), 252(22), 216(73), 145(53), 105(100).

3,6-Bis(4-ethoxycarbonyl-5-oxo-2,5-dihydroisoxazolin-2-yl)pyridazine (15). The isoxazolone **18** (100 mg, 0.637 mmol) and 3,6-dichloropyridazine (47.4 mg, 0.318 mmol) were heated neat under nitrogen at 130 °C for 15 min. The resulting product was recrystallised from ethanol to give the isoxazolone **15** (105 mg, 85%) as pale yellow crystals, mp 209-211 °C dec (lit¹⁷, 210 °C dec).

3,6-Bis(4-ethoxycarbonyl-3-phenylamino-5-oxo-2,5-dihydroisoxazolin-2-yl)pyridazine (16). The isoxazolone **19** (100 mg, 0.4 mmol) and 3, 6-dichloropyridazine (30 mg, 0.2 mmol) were refluxed in ethanol for 48h. The solvent was removed under reduced pressure to give a yellow semi solid which was recrystallized from aqueous ethanol (30%) to afford **16** (59 mg, 51%) as pale yellow crystals, mp 143-145 °C. ^1H NMR (CDCl_3) δ 1.31 (t, $J=7.1$ Hz, 6H), 4.28 (q, $J=7.1$ Hz, 4H), 7.03 (d, $J=7.4$ Hz, 4H), 7.06 (t, $J=7.4$ Hz, 2H), 7.17 (t, $J=7.4$ Hz, 4H), 7.5 (s, 2H), 7.68 (s, 2H), 9.99 (s, 2H); ^{13}C NMR (CDCl_3) δ 13.28, 60.01, 78.05, 121.69, 123.85, 125.93, 128.41, 135.08, 152.9, 162.09, 162.65, 163.11; FT-IR (KBr) $\nu_{\text{max}} / \text{cm}^{-1}$: 3430, 1801, 1710, 1685, 1632, 1587, 1040; MS m/z (%) 590[(M^+ + H_2O), 13], 586(20), 546(5), 501(7), 324(23), 322(38), 217(48), 248(51), 202(100), 103(64), 44(63).

3,6-Bis(3-(3-bromophenylamino)-4-ethoxycarbonyl-5-oxo-2,5-dihydroisoxazolin-2-yl)pyridazine (17). Using the same procedure as above with the isoxazolone **20** (100 mg, 0.3 mmol) gave **17** (67 mg, 60%) as white crystals, mp 178 °C dec. ^1H NMR (CDCl_3) δ 1.32 (t, $J=7.2$ Hz, 6H), 4.3 (q, $J=7.2$ Hz, 4H), 6.99 (d, $J=8.3$ Hz, 2H), 7.06 (t, $J=8$ Hz, 2H), 7.21 (d, $J=8.3$ Hz, 2H), 7.24 (s, 2H), 7.68 (s, 2H), 10.13 (s, 2H); ^{13}C NMR (CDCl_3) δ 13.28, 60.23, 78.64, 119.68, 121.75, 123.46, 124.32, 128.65, 129.63, 136.6, 152.68, 161.08, 162.15, 162.83; FT-IR (KBr) $\nu_{\text{max}} / \text{cm}^{-1}$: 3433, 1790, 1701, 1676, 1578, 1478, 1031; MS m/z (%) 686[(M^+ - CO_2), 7], 642(6), 596(3), 497(3), 368(6), 276(12), 221(18), 197(23), 196(30), 90(30), 69(51), 46(100).

Ethyl 2,8-dihydroxy-5-methyl-4,10-dioxo-1,6,7,11-tetraaza-1,4,10,11-tetrahydrophenanthrene-9-carboxylate (21). The bis-isoxazolinyll derivative **7** (100 mg, 0.25 mmol) was refluxed in THF (8 mL) with potassium carbonate (34.5 mg, 0.25 mmol) for 24h. The solvent was removed under reduced pressure, water was added to the residue and the solution acidified to pH 2 with concentrated HCl. The pale yellow solid was filtered to give **21** (25 mg, 29%), mp 153-156 °C. ^1H NMR (DMSO-d_6) δ 1.2 (t, $J=7.2$ Hz, 3H), 2.68(s, 3H), 4.03 (q, $J=7.2$ Hz, 2H), 6.13 (s,1H), 8.38 (s, 1H), 8.39 (s, 1H), 11.41 (bs, 1H); FT-IR (KBr) $\nu_{\text{max}} / \text{cm}^{-1}$: 3421, 3255, 2918, 1736, 1703, 1618, 1438, 1318, 1283, 1181, 1078; MS m/z (%) 333[(M^+ +1),15], 332(M^+ , 10), 290(27), 264(56), 218(81), 175(65), 133(100), 108(85), 87(52), 69(32).

Ethyl 6-[2,2-bis-(ethoxycarbonyl)-acetamido]-2-hydroxy-8-methyl-4-oxo-4H-pyrimido[1,2-a]pyrimidine-3-carboxylate (23). The bis-isoxazolinyll derivative **7** (100 mg, 0.25 mmol) was refluxed in ethanol (8 mL) with potassium carbonate (34.5 mg, 0.25 mmol) for 24h. The solution was cooled, quenched with HCl (5 mL) and the resulting products filtered to afford compound

26 (62 mg, 56%), mp 175 °C dec. ¹H NMR (DMSO-d₆) δ 1.19 (t, *J*=7.2 Hz, 9H), 2.89 (s, 3H), 4.08 (q, *J*=7.2 Hz, 2H), 4.19 (q, *J*=7.2 Hz, 4H), 5.03 (s, 1H), 7.63 (s, 1H), 11.89 (s, 1H), 12.22 (bs, 1H); ¹³C NMR (DMSO-d₆) δ 14.42, 14.78, 24.19, 44.65, 60.98, 62.24, 104.22, 106.83, 157.05, 158.35, 159.51, 164.48, 164.91, 165, 168.03, 170.23; FT-IR (KBr) ν_{\max} / cm⁻¹: 3423, 3299, 1761, 1715, 1655, 1602, 1320, 1083; MS *m/z* (%) 450(M⁺, 4), 404(5), 345(20), 264(10), 205(21), 187(50), 177(80), 160(100), 114(44), 87(68).

Diethyl 5-methyl-2,8-bis(phenylamino)diimidazo[1,2-*a*:1',2'-*c*]pyrimidine-3,9-dicarboxylate (24). The bis-isoxazolinyll derivative **8** (100 mg, 0.171 mmol) was refluxed in THF (8 mL) with potassium carbonate (23.5 mg, 0.171 mmol) for 24h. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol to give **24** (59.5 mg, 70%), mp 182 °C dec. ¹H NMR (DMSO-d₆) δ 0.69 (t, *J*=7.2 Hz, 3H), 0.98 (t, *J*=7.2 Hz, 3H), 2.27(s, 3H), 3.45 (q, *J*=7.2 Hz, 2H), 3.89 (q, *J*=7.2 Hz, 2H), 6.66 (d, *J*=7.5Hz, 2H), 6.74(t, *J*=7.2Hz, 1H), 7.04-7.22 (m, 7H), 7.78 (s, 1H), ; ¹³C NMR (DMSO-d₆) δ 14.32, 14.34, 24.32, 58.16, 59.96, 77.82, 103.54, 120.35, 120.88, 122.87, 125.65, 128.43, 129.08, 138.76, 154.66, 155.71, 155.85, 159.42, 162.38, 163.32, 164.11, 166.3, 168.53; FT-IR (KBr) ν_{\max} / cm⁻¹: 3448, 1725, 1618, 1585, 1351, 1048, 695; MS *m/z* (%) 498(M⁺, 4), 339(6), 316(8), 213(24), 196(33), 169(24), 128(61), 93(100), 66(34).

Diethyl 2,8-bis(3-bromophenylamino)-5-methyldiimidazo[1,2-*a*:1',2'-*c*]pyrimidine-3,9-dicarboxylate (25). Using the same procedure as above with the bis-isoxazolone **9** (100 mg, 0.134 mmol) gave **25** (60 mg, 68%) as white crystals, mp 190 °C dec. ¹H NMR (DMSO-d₆) δ 0.78 (t, *J*=7.2 Hz, 3H), 1.01 (t, *J*=7.2 Hz, 3H), 2.32 (s, 3H), 3.5 (q, *J*=7.2 Hz, 2H), 3.89 (q, *J*=7.2 Hz, 2H), 6.63 (d, *J*=7.8Hz, 1H), 6.77 (s, 1H), 6.87 (d, *J*=7.8Hz, 1H), 6.99 (t, *J*=7.8Hz, 1H), 7.1-7.19 (m, 3H), 7.28 (s, 1H) 7.71 (s, 1H); ¹³C NMR (DMSO-d₆) δ 14.38, 14.45, 24.39, 58.27, 59.78, 72.25, 103.33, 120.04, 121.62, 121.99, 122.57, 123.5, 125.81, 130.11, 130.68, 153.39, 155.82, 156.64, 158.95, 162.18, 162.99, 165.96, 168.77; FT-IR (KBr) ν_{\max} / cm⁻¹: 3443, 1725, 1611, 1580, 1378, 1040, 684.

Diethyl 2,5,8-trihydroxy-10-nitro-4,6-dioxo-1,4*a*,5*a*,9-tetraaza-1,4,5,5*a*,6,9-hexahydroanthracene-3,7-dicarboxylate (26). To bis-isoxazolinyll derivative **10** (100 mg, 0.23 mmol) was added 2.5M sodium hydroxide solution (10 mL) and the mixture was stirred at 40 °C for 10 min, after which time a homogenous solution formed. This solution was acidified to pH 2 with 2M HCl and the resulting precipitate was filtered to give **26** (60 mg, 68%) as a brown solid, mp > 300 °C. ¹H NMR (DMSO-d₆) δ 1.24 (t, *J*=7.2 Hz, 3H), 1.27 (t, *J*=7.2 Hz, 3H), 4.21 (q, *J*=7.2 Hz, 2H), 4.3 (q, *J*=7.2 Hz, 2H), 12.76 (bs, 1H), 13.62 (s, 1H); ¹³C NMR (DMSO-d₆) δ 14.32, 14.6, 31.14, 60.97, 62.24; FT-IR (KBr) ν_{\max} / cm⁻¹: 3413, 1697, 1637, 1569, 1473, 1375, 1233, 1127, 1081; MS *m/z* (%) 435[(M⁺-H₂O), 4], 407(20), 354(9), 310(19), 250(8), 205(26), 137(24), 105(40), 91(100), 90(90).

Diethyl 2,5,8-trihydroxy-10-nitro-4,6-dioxo-1,4*a*,5*a*,9-tetraaza-1,4,5,5*a*,6,9-hexahydroanthracene-3,7-dicarboxylic acid (27). The bis-isoxazolinyll derivative **10** (100 mg, 0.23 mmol) was refluxed in 2.5M sodium hydroxide solution (10 mL) for 15 min. The cooled solution was acidified to pH 2 and the resulting precipitate was filtered to give **27** (55.5 mg, 61%) as a black solid, mp > 300

$^{\circ}\text{C}$. ^1H NMR (DMSO- d_6) δ 5.05 (bs, 2H), 5.14 (s, 1H), 7.21 (s, 1H), 13.6 (bs, 1H); ^{13}C NMR (DMSO- d_6) δ 31.13, 34.75, 117.13, 120.74, 122.31, 124.92, 131.46, 141.4, 159.63, 174.84; FT-IR (KBr) $\nu_{\text{max}} / \text{cm}^{-1}$: 3413, 1630, 1508, 1430, 1092, 812; MS m/z (%) 396 [(M^+ -1), 4], 319(4), 304(5), 255(10), 236(13), 110(23), 96(49), 82(68), 68(81), 54(100).

Diethyl 2,5,8-trihydroxy-4,6-dioxo-1,4a,5a,9-tetraaza-1,4,5,5a,6,9-hexahydroanthracene-3,7-dicarboxylate (28). This compound was prepared as described for **22** using bis-isoxazolinyll derivative **13** (100 mg, 0.256 mmol) to afford the compound **28** (73 mg, 70%) as a black solid, mp > 300 $^{\circ}\text{C}$. ^1H NMR (DMSO- d_6 +CF₃CO₂H) δ 1.24 (t, $J=7.2$ Hz, 6H), 3.9 (s, 1H), 4.25 (q, $J=7.2$ Hz, 4H), 4.66 (s, 1H), 5.14 (s, 1H); FT-IR (KBr) $\nu_{\text{max}} / \text{cm}^{-1}$: 3500, 1654, 1570, 1419, 1333, 1209, 803; MS m/z (%) 408(M^+ , 13), 353(15), 345(20), 312(36), 283(51), 273(24), 223(39), 155(40), 119(100), 93(42).

Ethyl 10-ethoxycarbonyl-3,6,11-trihydroxy-8,9-dioxo-1,5,8a-tetraaza-3,4,8,8a-tetrahydropyrimido[1,2-a]naphthalene-7-carboxylate (29). The same procedure as above with the bis-isoxazolinyll derivative **15** (100 mg, 0.256 mmol) gave **29** (73 mg, 70%) as a brown solid, mp 257 $^{\circ}\text{C}$ dec. ^1H NMR (DMSO- d_6) δ 1.22 (t, $J=7.2$ Hz, 6H), 3.03 (d, $J=6.6$ Hz, 1H), 3.66 (d, $J=6.6$ Hz, 1H), 3.71 (s, 2H), 4.17 (q, $J=7.2$ Hz, 4H), 11.91 (s, 2H); ^{13}C NMR (DMSO- d_6) δ 14.59, 32.36, 53.01, 60.83, 155.33, 156.17, 162.36, 163.18, 166.4, 168.39, 168.83, 172.63, 173.33; FT-IR (KBr) $\nu_{\text{max}} / \text{cm}^{-1}$: 3492, 1763, 1675, 1581, 1556, 1425, 1264, 1192, 682; MS m/z (%) 408(M^+ , 6), 407(8), 367(8), 303(4), 235(12), 110(13), 96(27), 82(33), 68(40), 54(100).

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