Ring opening and cycloadditions of novel fused 1,2,4-triazines

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Dedicated to Professor Gábor Bernáth on his 70th birthday

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Abstract

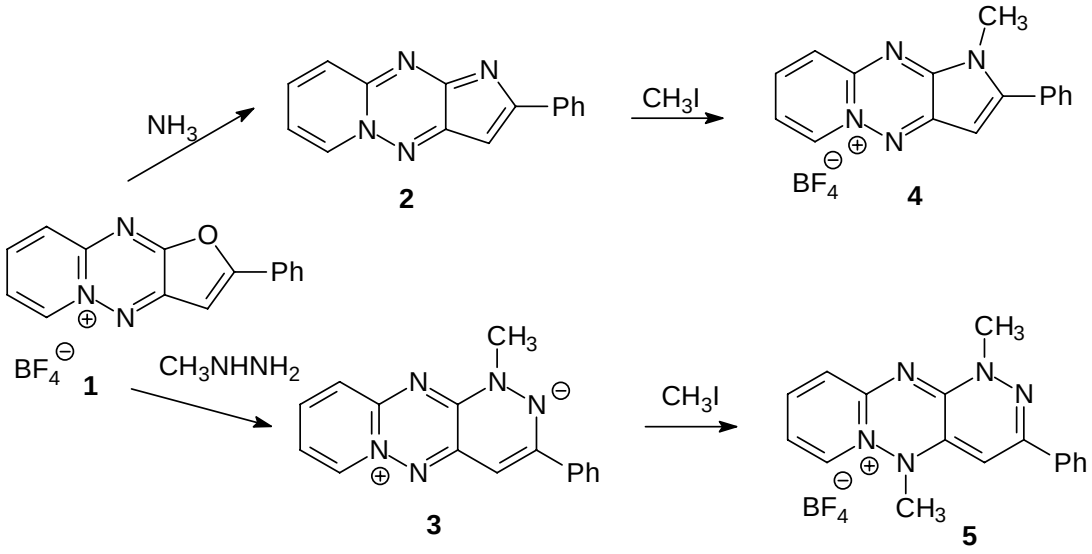
Ring opening of two ring transformation products of furo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazinium salt, *i.e.* a pyrrolo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazine derivative and a zwitterionic pyrido[1,2-*b*]-pyridazino[3,4-*e*][1,2,4]triazine compound has been investigated. The pyrrole-fused tricycle when reacted with some dienophiles resulted, unlike its zwitterionic pyridazine analogue, only in Michael addition and/or subsequent ring opening. Reaction of the methylated *N*-methylpyrrolo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazinium derivative and dimethyl pyrido[1,2-*b*]pyridazino[3,4-*e*][1,2,4]triazinium salt with secondary amines afforded new hetaryldienes which, in some cases, were successfully subjected to Diels-Alder reaction to give regular cycloadducts.

Keywords: Fused 1,2,4-triazines, zwitterion, hetaryldiene, cycloaddition, ring opening

Introduction

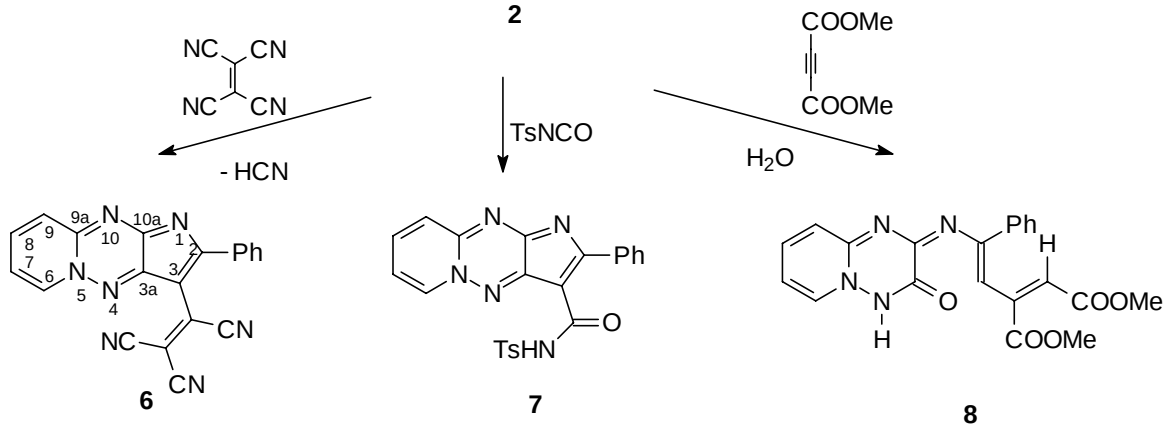
In the course of our activity in the area of ring transformation reactions of some polyfused triazines we have described that 2-arylfuro[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazinium salts (**1**) readily react with nucleophiles and undergo ring transformations to a pyrrole-fused tricyclic ring system (**2**) or differently substituted pyridazines, *e.g.* to the zwitterionic pyrido[1,2-*b*]pyridazino[3,4-*e*]-[1,2,4]triazine (**3**)[1]. We have also reported that these tricyclic derivatives (**2**, **3**) can be selectively alkylated to quaternary salts (**4**, and **5**, respectively)[2]. Furthermore, reactivity of the zwitterionic **3** has also been studied in detail: we found that this compound when reacted with acetylenedicarboxylic ester can undergo dipolar cyclization. Reaction with tetracyanoethylene resulted in oxydative dimerization to yield a stable radical cation, whereas reaction with tosyl isocyanate yielded Michael addition products[3]. All these results prompted us to explore the

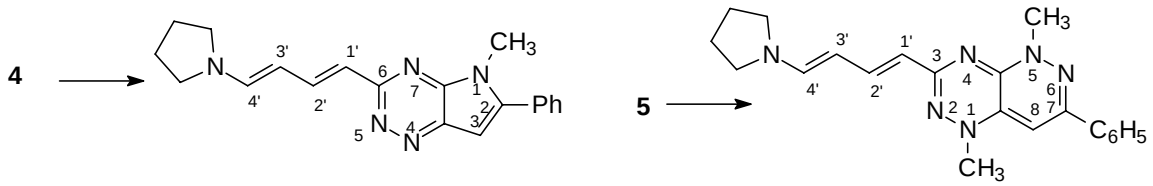
reactivity of the pyrrole-fused analogue **2** with particular respect to possible cycloaddition and ring opening transformations.



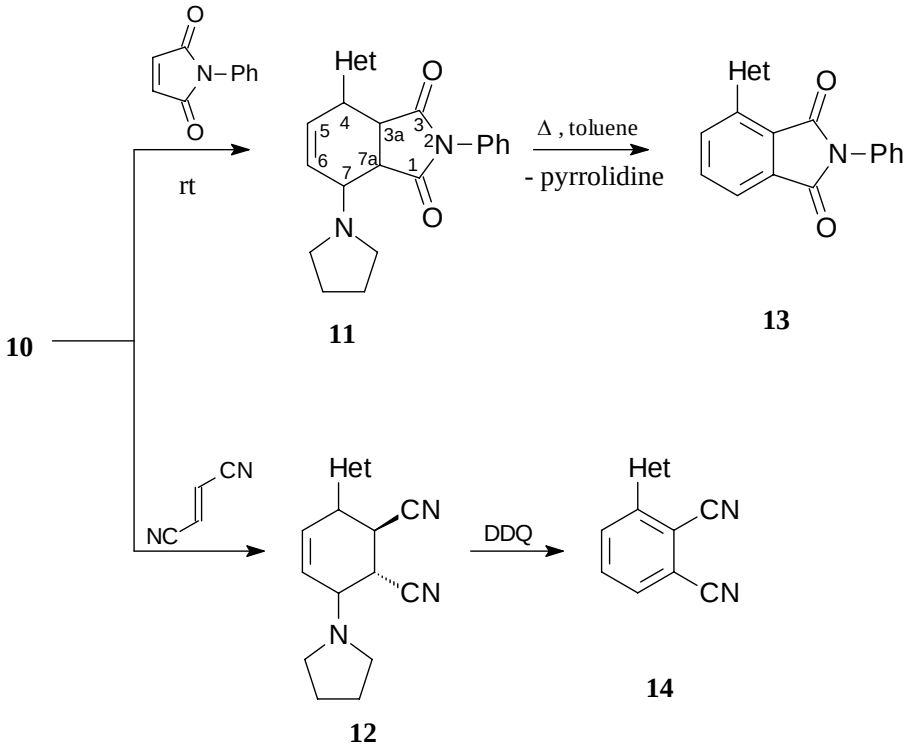
Results and Discussion

The pyrrole-fused tricyclic compound was reacted – for comparison with our earlier results with the analogous pyridazine derivative **3** – with dimethyl acetylenedicarboxylate, tosyl isocyanate and tetracyanoethylene. Interestingly enough, all these reagents resulted in Michael-additions and no cycloaddition or transformation of any other type was found. Thus, both with tetracyanoethylene and tosyl isocyanate the regular Michael adducts (**6** and **7**, respectively) were isolated in acceptable yields. A more interesting transformation was observed during the reaction of **2** and dimethyl acetylenedicarboxylate: although Michael addition also took place in this case, because of the presence of traces of water during the work up, the addition intermediate underwent hydrolytic ring opening to **8** which was obtained in good yield.





Both positively charged methylated salts (1-methyl-2-phenylfuro[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazinium tetrafluoroborate **4** and 1,5-trimethylpyrido[1,2-b]pyridazino[3,4-*e*][1,2,4]triazinium tetrafluoroborate **5**) reacted with secondary amines. In these transformations –like in several cases found by us earlier[4,5] – the pyridine moiety underwent ring opening to yield new hetaryldienes, **9** and **10**, respectively. The new dienes, in accordance with the general experience[6-8], had a *trans-trans* geometry as supported unambiguously by the coupling constants of the diene protons in the ^{1}H-NMR spectrum.



While our efforts to carry out cycloaddition reactions with **9** failed, diene **10** reacted relatively easily with *N*-phenylmaleinimide and fumaronitrile to yield regular cycloadducts containing a partially saturated benzene ring (**11** and **12**, respectively). Aromatization of the benzene moiety was carried out with both cycloadducts. In the case of cycloadduct **11** simple heating in toluene was enough to facilitate elimination of pyrrolidine and a subsequent spontaneous oxidation to give the corresponding isoindol-2,7-dione derivative **13**. The similar

transformation with the fumaronitrile adduct was carried out by oxidation with DDQ to yield the hetarylphtalonitrile **14**.

Conclusions

Transformations observed in these studies provided access to several new fused heterocyclic derivatives. These compounds seem to be promising candidates for biological (particularly DNA intercalation[9] – determined by measurement of the T_m point[10] - and multidrug resistance inhibitory[11]) tests which are now in progress in the frame of COST B16 action.

Experimental Section

General Procedures. Melting points were determined by a Büchi apparatus and are uncorrected. The IR spectra were recorded with a Nicolet Magna 750 FT-IR, spectrophotometers; the NMR spectra were recorded with a Varian UNITY INOVA spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) and Varian VXR200 spectrometer (200 MHz for ^{1}H).

2-Cyano-3-(2-phenylpyrrolo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazin-3-yl)but-2-enedinitrile (**6**)**.** Tetracyanoethylene (0.13 g, 1 mmol) was added to a suspension of 2-phenylpyrrolo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazine (**2**, 0.25 g, 1 mmol) in dichloromethane (5 mL), and the mixture was stirred at rt for 1 h. A solid separated which was filtered off and recrystallized from acetonitrile to give 0.15 g (43%) of red crystals, mp 250-252 ^{o}C. IR (KBr): 2216, 1581, 1519, 1502, 1481, 1455, 1409, 1242, 1184, 1153, 1138, 1127, 1102, 782 cm^{-1}; ^{1}H NMR δ ($CDCl_3$): 7.68 (m, 3H, H-phenyl), 7.71 (t, 1H, *J* = 7, 9 Hz, H-7), 8.01 (m, 2H, H- phenyl), 8.18 (t, 1H, *J* = 9, 9.3, Hz H-8), 8.31 (d, 1H, *J* = 9.3, Hz H-9), 9.11 (d, 1H, *J* = 7 Hz, H-6); ^{13}C NMR δ (DMSO-d_6): 82.9(C=C), 99.3(C=C), 112.9(CN), 113.2(CN), 113.6(CN), 120.8(C-7), 126.7(C-9), 128.5(C-phenyl), 130.5(C-3), 130.6, 132.2 and 133.1(C-phenyl), 137.3(C-8), 138.1(C-6), 144.6(C-9a), 145.3 (C-2), 154.9(C-3a), 179.4(C-10a). Anal. Calcd. for $C_{20}H_9N_7$ (347.35): C, 69.15; H, 2.61; N, 28.23. Found: C, 68.63; H, 2.68; N, 28.10.

4-Methyl-*N*-(2-phenylpyrrolo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazin-3-carbonyl)-benzenesulfonamide (**7**)**.** The reagent (*p*-toluenesulfonyl isocyanate, 1.0 mL, 6.6 mmol) was added to the compound of 2-phenylpyrrolo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazine (**2**, 0.25 g, 1 mmol) and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with diethylether (10 mL) and a yellow solid separated which was filtered off and recrystallized from DMF to give 0.32 g (72%) of product, mp 275-278 ^{o}C. IR (KBr): 3261, 3069, 1678, 1581, 1485, 1461, 1429, 1346, 1333, 1161, 1140, 1131, 1078, 1020, 750, 666 cm^{-1}; ^{1}H NMR δ (DMSO-d_6): 7.40 (d, 1H, H-9), 7.5 (m, 3H, H-phenyl), 7.55 (m, 1H, H-7), 7.76 (m, 1H, H-8), 7.92 (m, 4H, H-tolyl), 8.2 (m, 2H, H-phenyl), 9.26 (d, 1H, *J* = 7 Hz, H-6), 11.5 (NH); ^{13}C NMR δ (DMSO-d_6): 21.8, 119.6, 126.8,

128.0, 128.2, 129.6, 130.5, 131.4, 134.5, 135.8, 137.2, 137.9, 144.1, 144,6, 146.5, 160.9, 162.6. Anal. Calcd. for $C_{23}H_{17}N_5O_3S$ (443.50): C, 62.29; H, 3.86; N, 15.79. Found: C, 62.20; H, 3.95; N, 15.80.

Dimethyl 2-[2-(3-oxo-3,4-dihydropyrido[1,2-*b*][1,2,4]triazin-2-ylideneamino)-2-phenyl-vinyl]-but-2-enedioate (**8**)**.** Dimethyl acetylenedicarboxylate (0.3 mL, 2.4 mmol) was added to a suspension of 2-phenylpyrrolo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazine (**2**, 0.5 g, 2 mmol) in dichloromethane (10 mL), and the mixture was stirred at rt for 6 h. The reaction mixture was evaporated and the product was isolated by column chromatography (Alumuniumoxide, chloroform) and recrystallized from ethanol to give yellow crystals (0.15 g, 18%), mp 210-215 ^oC. IR (KBr): 3087, 3045, 2949, 1732, 1675, 1609, 1552, 1529, 1490, 1436, 1298, 1226, 1157, 1136, 770 cm^{-1}; ^1H NMR δ ($CDCl_3$): 3.19 (s, 3H, H-COMe), 3.82 (s, 3H, H-COMe), 5.60 (s, 1H, H-3'), 6.25 (s, 1H, H-5'), 6.95 (t, 1H, *J* = 7.2, 9 Hz, H-7), 7.40 (d, 1H, *J* = 9.3, Hz H-9), 7.60 (t, 1H, *J* = 9, 9.3, Hz H-8), 7.60-7.20 (m, 5H, H-phenyl), 8.32 (d, 1H, *J* = 7.2 Hz, H-6) 12.3 (NH); ^{13}C NMR δ ($CDCl_3$): 51.7, 52.3, 98.0, 98.5, 113.5, 123.7, 128.1, 130.0, 136.4, 136.6, 137.2, 145.6, 151.0, 151.5, 152.5, 159.9, 164.1, 168.2. Anal. Calcd. for $C_{21}H_{18}N_4O_5$ (406.41): C, 62.06; H, 4.46; N, 13.79. Found: C, 61.84; H, 4.62; N, 13.43.

1-Methyl-2-phenyl-6-(4-pyrrolidin-1-yl-buta-1,3-dienyl)-1*H*-pyrrolo[2,3-*e*][1,2,4]triazine (**9**)**.** Pyrrolidine (0.7 mL, 8.4 mmol) was added to a solution of 1-methyl-3-phenylpyrrolo[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazinium tetrafluoroborate (**4**, 0.7 g, 2 mmol) in acetonitrile (10 mL), and the mixture was stirred at rt for 1 h. A solid separated which was filtered off and recrystallized from acetonitrile to give reddish crystals (0.34 g, 51%), mp 148-150 ^oC. IR (KBr): 2970, 1624, 1604, 1581, 1418, 1397, 1369, 1264, 1094, 980, 748 cm^{-1}; ^1H NMR δ ($CDCl_3$): 1.93 (m, 4H, H-pyrrolidine), 3.28 (m, 4H, H- pyrrolidine), 3.76 (s, 3H, H-1-Me), 5.28 (dd, 1H, *J*=12.8, 11.4 Hz, H-2'), 6.53 (d, 1H, *J* = 14.5 Hz, H-4'), 6.81 (s, 1H, H-3), 6.90 (d, 1H, *J* = 12.8 Hz, H-1'), 7.78 (dd, 1H, *J* = 14.5, 11.4 Hz, H-3'), 7.50-7.55 (m, 5H, H-phenyl); ^{13}C NMR δ ($CDCl_3$): 25.2, 29.0, 48.9, 98.7, 99.9, 115.8, 125.2, 128.9, 129.3, 130.7, 139.4, 143.6, 144.0, 146.6, 160.4. Anal. Calcd. for $C_{20}H_{21}N_5$ (331.41): C, 72.48; H, 6.39; N, 21.13. Found: C, 72.16; H, 6.21; N, 21.18.

1,5-Dimethyl-7-phenyl-3-(pyrrolidin-1-yl-buta-1,3-dienyl)-1,5-dihydropyridazino[3,4-*e*]-[1,2,4]triazine (**10**)**.** Pyrrolidine (2 mL, 24 mmol) was added to a solution of 1,5-dimethyl-3-phenylpyrido[1,2-b]pyridazino[3,4-e][1,2,4]triazinium tetrafluoroborate **5** (4 g, 10.6 mmol) in acetonitrile (20 mL), and the mixture was stirred at rt. A violet solid separated which was filtered off and recrystallized from acetonitrile to give 2.56 g (67%) of product, mp 188-90 ^oC. ^1H NMR δ ($CDCl_3$): 1.88 (m, 4H, H-pyrrolidine), 2.82 (s, 3H, H-1-Me), 3.19 (m, 4H, H- pyrrolidine), 3.31 (s, 3H, H-5-Me), 4.75 (s, 1H, H-8), 5.04 (dd, 1H, *J* = 12.6, 11.5 Hz, H-2'), 5.41 (d, 1H, *J* = 14.5 Hz, H-4'), 6.70 (d, 1H, *J* = 12.6 Hz, H-1'), 7.03 (dd, 1H, *J* = 14.5, 11.5 Hz, H-3'), 7.33-7.60 (m, 5H, H-phenyl); ^{13}C NMR δ ($CDCl_3$): 25.2, 39.1, 39.3, 48.8, 84.6, 98.3, 114.2, 125.2, 128.3, 129.1, 136.2, 136.8, 141.1, 142.4, 153.0, 158.3.

4-(1,5-Dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-*e*][1,2,4]triazin-3-yl)-7-pyrrolidin-1-yl-3a,4,7,7a-tetrahydroisoindol-1,3-dione (**11**)**.** A mixture of *N*-phenylmaleinimide (110 mg, 0.64 mmol), 1,5-dimethyl-7-phenyl-3-(pyrrolidin-1-yl-buta-1,3-dienyl)-1,5-dihydropyridazino[3,4-

e][1,2,4]triazine (**10**, 200 mg, 0.55 mmol), and toluene (10 mL) was stirred at rt. Orange-red crystals separated which were filtered off and washed with ether to give 226 mg (76%) of product, mp 166-8 ^{o}C. ^{1}H NMR δ($CDCl_3$): 1.85 (m, 4H, H-pyrrolidine), 2.72 (m, 4H, H-pyrrolidine), 2.79 (s, 3H, H-5'-Me), 2.90-2.96 (m, 2H, H-4, H-7), 3.20 (s, 3H, H-1'-Me), 3.54 (dd, 1H, *J* = 9.5, 7.0 Hz, H-3a or H-7a), 3.86 (dd, 1H, *J* = 9.0, 6.0 Hz, H-3a or H-7a), 4.63 (s, 1H, H-8'), 6.10 (dt, 1H *J* = 9.5, 3.5 Hz, H-6), 6.36 (dt, 1H, *J* = 9.5, 3.0 Hz, H-5), 7.23-7.26, 7.29-7.42 and 7.50-7.54 (m, 10H, H-phenyl); ^{13}C NMR δ ($CDCl_3$): 24.5, 40.3, 40.4, 41.7, 43.9, 44.3, 54.7, 64.8, 86.2, 126.4, 127.7, 129.3, 129.5, 129.8, 130.4, 131.8, 133.1, 137.0, 143.3, 155.5, 158.4, 158.6, 175.5, 176.6. Anal. Calcd. for $C_{31}H_{31}N_7O_2$ (533.62): C, 69.77; H, 5.86; N, 18.37. Found: C, 69.64; H, 5.86; N, 18.28.

3-(1,5-Dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-e][1,2,4]triazin-3-yl)-6-pyrrolidin-1-yl-cyclohexene-1,2-dicarbonitrile (12). A mixture of 1,5-dimethyl-7-phenyl-3-(pyrrolidin-1-yl-buta-1,3-dienyl)-1,5-dihydropyridazino[3,4-e][1,2,4]triazine (**10**, 400 mg, 1.1 mmol), fumaronitrile (100 mg, 1.28 mmol) and dichloromethane (10 mL) was stirred at rt for 4 d. The mixture was evaporated and the residue subjected to column chromatography on silica (with chloroform as an eluent). The main fraction gave 220 mg (45 %) of pale yellow product, mp 220–222 ^{o}C. ^{1}H NMR δ ($CDCl_3$): 2.69 (m, 4H, H-pyrrolidine), 2.71 (s, 3H, H-1'-Me), 2.73 (m, 4H, H-pyrrolidine), 3.11 (dd, 1H, *J* = 11.0, 6.0 Hz, H-1), 3.13 (s, 3H, H-5'-Me), 2.97 (ddd, 1H, *J* = 6.0, 4.5, 1.5 Hz, H-6), 3.63 (ddd, 1H, *J* = 10.2, 2.0, 1.5 Hz, H-3), 3.98 (dd, 1H, *J* = 11.0, 10.2 Hz, H-2), 4.70 (s, 1H, H-8'), 5.77 (ddd, 1H, *J* = 10.3, 4.5, 2.0 Hz, H-5), 5.84 (dt, 1H, *J* = 10.3, 1.5 Hz, H-4); ^{13}C NMR δ ($CDCl_3$): 24.4, 30.6, 32.1, 39.1, 40.1, 41.4, 48.4, 58.2, 86.3, 117.6, 119.7, 125.5, 127.6, 128.0, 128.7, 129.8, 135.7, 142.7, 155.4, 157.8, 158.5. Anal. Calcd. for $C_{25}H_{26}N_8$ (438.53): C, 68.47; H, 5.98; N, 25.55. Found: C, 68.23; H, 5.92; N, 25.54.

4-(1,5-Dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-e[1,2,4]triazin-3-yl)-2-phenylisoindol-1,3-dione (**13**)**.** A solution of 4-(1,5-Dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-*e*][1,2,4]triazin-3-yl)-7-pyrrolidin-1-yl-3a,4,7,7a-tetrahydroisoindol-1,3-dione (**11**, 300 mg, 0.56 mmol) in toluene (5 mL) was refluxed for 2 h. Evaporation of the mixture gave a residue which was crystallized from acetonitrile to give 182 mg (70 %) of dark gray crystals, mp 268–70 ^{o}C. ^{1}H NMR δ($CDCl_3$): 2.83 (s, 3H, H-1'-Me), 3.20 (s, 3H, H-5'-Me), 4.78 (s, 1H, H-8'), 7.35-7.58 (m, 10H, H-phenyl), 7.73 (t, 1H, *J* = 7.5 Hz, H-6), 7.88 (dd, 1H, *J* = 7.5, 1.0 Hz, H-5), 7.92 (dd, 1H, *J* = 7.5, 1.0 Hz, H-7); ^{13}C NMR δ ($CDCl_3$): 39.1, 39.6, 86.0, 123.9, 125.3, 126.7, 128.0, 128.5, 129.0, 129.6, 131.8, 132.8, 134.0, 134.2, 135.6, 135.7, 142.6, 154.9, 155.9, 157.8, 165.5, 166.7. Anal. Calcd. for $C_{27}H_{20}N_6O_2$ (460.49): C, 70.42; H, 4.38; N, 18.25. Found: C, 70.31; H, 4.28; N, 18.31.

3-(1,5-Dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-e][1,2,4]triazin-3-yl)phtalonitrile (14). A mixture of 3-(1,5-dimethyl-7-phenyl-1,5-dihydropyridazino[3,4-*e*][1,2,4]triazin-3-yl)-6-pyrrolidin-1-yl-cyclohexene-1,2-dicarbonitrile (**12,** 260 mg, 0.6 mmol), DDQ (297 mg, 1.3 mmol) and toluene (10 mL) was refluxed for 1 h. The mixture was evaporated, the residue treated with dichloromethane and the insoluble material was removed. The filtrate was evaporated and the residue was subjected to chromatography on silica (with a chloroform–

methanol 50:1 mixture as an eluent). The main fraction gave 110 mg (49 %) of green crystalline product, mp 239–41 ^{o}C. ^{1}H NMR δ ($CDCl_3$): 2.90 (s, 3H, H-5'-Me), 3.55 (s, 3H, H-1'-Me), 4.80 (s, 1H, H-8'), 7.39 (m, 3H, H-phenyl), 7.56 (m, 2H, H-phenyl), 7.60 (t, 1H, *J* = 8.0 Hz, H-5), 7.72 (dd, 1H, *J* = 8.0, 1.5 Hz, H-6), 8.14 (dd, 1H, *J* = 8.0, 1.5 Hz, H-4). Anal. Calcd. for $C_{21}H_{15}N_7$ (365.39): C, 69.03; H, 4.14; N, 26.83. Found: C, 68.90; H, 3.91; N, 26.78.

Acknowledgments

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