

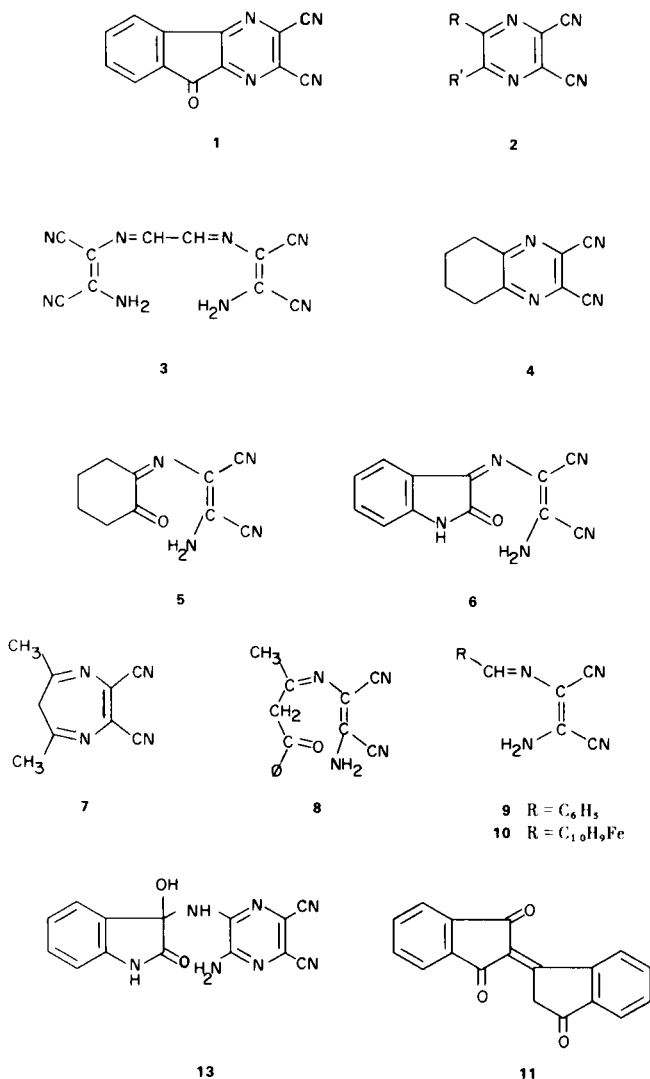
Synthesis of Potential Antineoplastic Agents. XXIV.
Reaction of Diaminomaleonitrile with 1,2-Diones (1)

Frank D. Popp

Department of Chemistry, Clarkson College of Technology,
Potsdam, New York 13676

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Some time ago (2) we reported the condensation of ninhydrin with diaminomaleonitrile to give the dicyanopyrazine derivative **1**. Although **1** was essentially inactive against animal tumors (T/C = 112 against L-1210) it exhibited reproducible activity in the KB cell culture screen (3). In view of this lead, it was decided to investigate compounds related to **1** further.

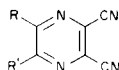


The condensation of diaminomaleonitrile with a number of 1,2-diones has been reported (4-7). We have carried out this type of condensation with a wide variety of 1,2-diones and the new dicyanopyrazines (**2**) prepared are shown in Table I. These reactions were generally carried out for thirty minutes in refluxing aqueous-ethanol containing a small amount of acetic acid. When diaminomaleonitrile was allowed to react with glyoxal in aqueous solution compound **3** (8) which could readily be converted to 2,3-dicyanopyrazine (**4**) was obtained. The reaction of 1,2-cyclohexanedione with diaminomaleonitrile gave a mixture of **4** and **5**. Shortening of the reaction time gave only **5** while a longer reaction time gave only **4**. Compound **5** could be converted to **4** upon recrystallization from dilute oxalic acid. Isatin has been reported (6) to react only at the 3-position to give **6** and this observation has been confirmed.

Reaction of 2,4-pentanedione with diaminomaleonitrile under the above conditions gave the diazepine **7** but under these conditions benzoylacetone gave **8** and dibenzoylmethane did not react (**9**). Reaction of 3-benzylidene-2,4-pentanedione with diaminomaleonitrile under these conditions gave only **9** which had previously (4) been prepared from benzaldehyde and diaminomaleonitrile. An analogue of **9** (**10**) was prepared from ferrocene-carboxaldehyde.

Reaction of 1,3-indandione with diaminomaleonitrile gave only the product of self-condensation (**11**) while 1,2-indanedione gave **12**.

TABLE I
2,3-Dicyanopyrazines



R	R'	M.p., °C	Formula	Yield	Calcd.	
					Anal. Found	H
CH ₃	H	94-96	C ₇ H ₄ N ₄	52	58.33	2.80
					58.17	2.84
C ₆ H ₅	H	167-168	C ₁₂ H ₆ N ₄	95	69.89	2.93
					69.78	3.05
C ₆ H ₅	CH ₃	133-135	C ₁₃ H ₈ N ₄	93	70.89	3.66
					70.84	3.57
<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -CH ₃ C ₆ H ₄	160-161	C ₂₀ H ₁₄ N ₄	50	77.40	4.55
					77.16	4.52
2-furyl	2-furyl	151-152	C ₁₄ H ₆ N ₄ O ₂	96	64.12	2.31
					64.13	2.43
— (CH ₂) ₄ —	—	138-139	C ₁₀ H ₈ N ₄ (a)	50	65.20	4.38 (b)
					64.96	4.55

(a) Reaction time of 1 hour, see Experimental. (b) Calcd.: N, 30.42. Found: N, 30.27.

In an attempt to prepare additional analogues of **1**, isatin was allowed to react in ethanol with 2,3-dicyano-5,6-diaminopyrazine (**10**) to give **13**. In view of results obtained from reactions of other diamines with isatin (**11**) the structure of this product is somewhat surprising. Under these conditions, ninhydrin failed to react with the 2,3-dicyano-5,6-diaminopyrazine.

Reaction of 5,6-dimethyl- and 5,6-diphenyl-2,3-dicyanopyrazine with hydrazine by the procedure of Patel and Castle (**12**) gave the diaminopyrazino[2,3-*d*]pyridazines **14**. Application of this reaction to **1** gave **15**. The mass spectrum of **15** did not exhibit a molecular ion but liberated large amounts of ammonia, nitrogen, and hydrazine and had a prominent peak at $m/e = 251$ (M-27).

Carbonyl derivatives of **1** were prepared by reaction with thiosemicarbazide and with aminonitroguanidine.

EXPERIMENTAL (13)

Preparation of 2,3-Dicyanopyrazines (**2**).

In a general procedure 0.0082 mole of the 1,2-dione and 0.86 g. (0.008 mole) of diaminomaleonitrile in a mixture of 10 ml. of water, 15 ml. of ethanol, and 0.7 ml. of acetic acid were heated on the steam bath for 30 minutes, cooled, filtered, and recrystallized from ethanol to give compounds with the reported (4-7) m.p. as well as those new compounds shown in Table I. All of the 2,3-dicyanopyrazines had ir that included peaks at 4.45 ± 0.02 , 6.38 ± 0.18 , $6.95 \pm 0.35 \mu$.

Condensation of Glyoxal with Diaminomaleonitrile.

Condensation of glyoxal with diaminomaleonitrile using the

above general procedure gave a 60% yield of **2** (R = R' = H), m.p. 130-132°, reported (4) m.p. 132°; ir (potassium bromide): 4.44, 6.45, and 7.20; Mass Spectrum: 130 (100%), 104 (4%), 103 (50%), 76 (20%).

Anal. Calcd. for C₆H₂N₄: N, 43.06. Found: N, 43.02.

When the condensation was carried out in warm water a 70% yield of **3**, m.p., turns black at 233° but does not melt up to 330°; ir (potassium bromide): 2.92, 3.02, 3.11, 4.40, 4.50, 6.18, 6.32, 6.40, 7.18; Mass spectrum: 238 (1%), 211 (12%), 185 (8%), 184 (35%), 157 (5%), 130 (77%), 119 (8%), 108 (38%), 104 (12%), 103 (100%), 81 (50%), 78 (26%), 77 (12%), 76 (62%), 27 (100%).

Anal. Calcd. for C₁₀H₆N₈: C, 50.42; H, 2.54; N, 47.04. Found: C, 50.39; H, 2.49; N, 46.92.

Recrystallization of **3** from boiling water containing a small amount of oxalic acid gave **2** (R = R' = H).

Condensation of 1,2-Cyclohexanedione with Diaminomaleonitrile.

Condensation of 1,2-cyclohexanedione with diaminomaleonitrile using the above general procedure gave a mixture of **4** and **5**. Reduction of the reaction time to 15 minutes gave a 32% yield of **5**, m.p. 146-147° from ethanol; ir (potassium bromide): 2.93, 3.02, 3.12, 3.40, 4.42, 4.51, 6.19, 6.30, 6.40, 7.20; Mass spectrum: 202 (3%), 185 (14%), 184 (100%), 183 (49%), 169 (67%), 155 (20%), 76 (20%), 75 (20%).

Anal. Calcd. for C₁₀H₁₀N₄O: N, 27.72. Found: N, 27.42.

Increasing the reaction time to 1 hour gave the compound (**4**) described in Table I; ir (potassium bromide): 3.39, 3.46, 4.42, 6.55, 7.29; Mass spectrum: 184 (100%), 183 (51%), 169 (60%), 155 (19%).

Condensation of Isatin with Diaminomaleonitrile.

Use of the general procedure described above gave an 84% yield of **6**, m.p. 196-198°, reported (6) m.p. 200°; ir (potassium bromide): 3.0-3.2, 4.51, 4.46, 5.78, 6.17, 7.18.

Synthesis of Diazepine 7.

Use of the general procedure with diaminomaleonitrile and 2,4-pentanedione gave a 50% yield of diazepine **7**, m.p. 196-198°, reported (9) m.p. 200-201°; ir (potassium bromide): 4.45, 6.22, and 7.27.

Anal. Calcd. for C₉H₈N₄: C, 62.77; H, 4.68; N, 32.54. Found: C, 62.48; H, 4.79; N, 32.45.

Condensation of Benzoylacetone with Diaminomaleonitrile.

Use of the general procedure described above gave a 90% yield of **8**, m.p. 165-166° from ethanol; ir (potassium bromide): 2.93, 3.12, 4.42, 4.51, 6.03, 6.32, 7.19; Mass spectrum: 252 (33%), 251 (13%), 237 (9%), 219 (5%), 175 (8%), 132 (6%), 123 (4%), 120 (6%), 106 (9%), 105 (100%), 77 (50%).

Anal. Calcd. for C₁₄H₁₂N₄O: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.60; H, 4.70; N, 22.30.

Condensation of 3-Benzylidene-2,4-pentanedione with Diaminomaleonitrile.

Use of the general procedure described above gave an 80% yield of **9**, m.p. 192-193°, reported (4) m.p. 191°; ir (potassium bromide): 2.90, 3.00, 4.42, 4.50, 6.19, 7.26; Mass spectrum: 196 (44%), 195 (40%), 142 (6%), 120 (8%), 119 (100%), 116 (7%), 104 (11%), 90 (10%), 89 (15%), 78 (39%), 77 (16%).

Anal. Calcd. for C₁₁H₈N₄: C, 67.33; H, 4.11; N, 28.57. Found: C, 67.26; H, 4.16; N, 28.65.

The identical product was obtained from the condensation of diaminomaleonitrile with benzaldehyde.

Condensation of Ferrocenecarboxaldehyde with Diaminomaleonitrile.

Use of the general procedure described above gave a 70% yield of **10**, m.p. 191-193° from ethanol; ir (potassium bromide): 2.90, 3.00, 4.48, 4.52, 6.10, 7.10, 9.09, 10.0.

Anal. Calcd. for C₁₅H₁₂N₄Fe: C, 59.23; H, 3.98; N, 18.39; Fe, 18.36. Found: C, 59.07; H, 4.01; N, 18.33; Fe, 18.39.

Attempted Condensation of Diaminomaleonitrile with 1,3-Indanedione.

Use of the general procedure described above resulted in the self condensation of the 1,3-indanedione to give a 60% yield of **11**, m.p. 205-208°, reported (14) m.p. 208-210°; ir (potassium bromide): 5.80, 5.90, and 6.19; Mass spectrum: 274 (100%), 273 (32%), 257 (5%), 247 (16%), 246 (80%), 229 (2%), 218 (16%), 201 (2%), 190 (10%), 189 (41%), 146 (9%), 104 (9%), 76 (16%).

Anal. Calcd. for C₁₈H₁₀O₃: C, 78.82; H, 3.68. Found: C, 78.50; H, 3.85; N, 0.

Reaction of Diaminomaleonitrile with 1,2-Indanedione.

Use of the general procedure described above gave a 79% yield of **12**, m.p. > 330°; ir (potassium bromide): 4.44, 5.90, 6.20, 6.50, 6.80, and 6.90. Mass spectrum: 346 (100%), 318 (20%), 319 (8%), 317 (27%), 266 (6%), 265 (10%), 239 (6%), 219 (8%), 218 (45%), 214 (12%), 213 (9%), 131 (27%), 103 (7%), 90 (8%), 77 (12%).

Anal. Calcd. for C₂₂H₁₀N₄O: N, 16.18. Found: N, 16.37.

The same product was obtained in essentially the same yield when the condensation was carried out in refluxing ethanol.

Reaction of Isatin with 2,3-Dicyano-5,6-diaminopyrazine.

A solution of 0.40 g. (0.0025 mole) of 2,3-dicyano-5,6-

diaminopyrazine in 100 ml. of ethanol containing 3 ml. of acetic acid was filtered hot into 0.38 g. (0.00258 mole) of isatin and the mixture was refluxed for 30 minutes. Filtration gave 0.41 g. (53%) of **13**, m.p. 244-245°; ir (potassium bromide): 2.90, 3.01, 3.15, 4.79, 5.80, 5.98, 6.10, 6.19; Mass spectrum: 307 (1%), 160 (2%), 159 (15%), 147 (7%), 146 (56%), 132 (10%), 119 (10%), 118 (100%), 105 (3%), 92 (6%), 91 (61%), 90 (22%), 89 (9%), 76 (3%), 75 (11%).

Anal. Calcd. for C₁₄H₉N₇O₂: C, 54.72; H, 2.95; N, 31.91. Found: C, 54.61; H, 3.25; N, 31.83.

2,3-Dimethyl-5,8-diaminopyrazino[2,3-*d*]pyridazine (**14**, R = CH₃).

To a warm suspension of 0.79 g. (0.005 mole) of 2,3-dicyano-5,6-dimethylpyrazine (**2**, R = R' = CH₃) in 20 ml. of methanol was added with stirring 1.4 ml. of 95% hydrazine. The mixture was stirred at room temperature for 5 hours and filtered to give 0.88 g. (93%) of **14** (R = CH₃), m.p. > 300°; ir (potassium bromide): 2.90, 3.05, 3.20, 6.22, 6.82, 7.23.

Anal. Calcd. for C₈H₁₀N₆: C, 50.51; H, 5.30; N, 44.19. Found: C, 50.39; H, 5.41; N, 44.05.

2,3-Diphenyl-5,8-diaminopyrazino[2,3-*d*]pyridazine (**14**, R = C₆H₅).

In a similar manner 2,3-dicyano-5,6-diphenylpyrazine gave a 71% yield of **14** (R = C₆H₅), m.p. 253-255° from ethanol; ir (potassium bromide): 2.90, 2.98-3.08, 3.20, 6.21, 6.32, 7.39.

Anal. Calcd. for C₁₈H₁₄N₆: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.69; H, 4.51; N, 26.73.

Reaction of **1** with Hydrazine.

In a similar manner **1** gave a 70% yield of **15** as well as recovered starting material. Compound **15**, m.p. > 300°, was a difficult-to-purify black solid; Mass spectrum: 278 (0%), 251 (100%), 236 (16%), 223 (51%), 222 (18%), 208 (17%), 181 (22%), 180 (44%), 155 (18%), 154 (44%), 153 (29%), 140 (23%), 127 (27%), 42 (12%), 32 (56%), 29 (24%), 28 (100%), 27 (16%), 17 (99%), 15 (24%), 14 (28%).

Anal. Calcd. for C₁₃H₁₀N₈·0.5H₂O: C, 54.35; H, 3.86; N, 39.01. Found: C, 54.74; H, 4.05; N, 38.54. Calcd. for C₁₃H₁₀N₈: C, 56.11; H, 3.62. Found after prolonged drying at 100°: C, 55.98; H, 4.02.

Carbonyl Derivatives of **1**.

Compound **1** was allowed to react with aminonitroguanidine in the usual manner to give a solid, m.p. > 330°.

Anal. Calcd. for C₁₄H₇N₉O₂: N, 37.83. Found: N, 37.59.

Compound **1** was allowed to react in the usual manner with thiosemicarbazide to give a solid, m.p. > 300°.

Anal. Calcd. for C₁₄H₇N₇S·2H₂O: C, 49.26; H, 3.25. Found: C, 48.82; H, 2.78.

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