Synthetic Reactions of 2-(2-Amino-3-cyano-4*H*-[1]benzopyran-4-yl)propane-1,3-dinitrile with Reactive Methylene Compounds

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Derivatives of dibenzo[*b*,*d*]pyran, [1]benzopyrano[2,3-*b*]pyridine, [1]benzopyrano[3,4-*c*]pyridine and [1]benzopyrano[4,3,2-*de*][1,6]naphthyridine are obtained from the reaction of 2-(2-amino-3-cyano-4*H*-[1]benzopyran-4-yl)propane-1,3-dinitrile with compounds containing a reactive methylene group. Consideration of these reactions suggests that the dicyanomethyl group is released from the 4-position of the starting material, and that it then reacts at the 2-position of the newly formed iminium ion. The 4-position is now available for Michael addition of a compound containing a reactive methylene group, but the nature of the final product depends on the substituents on the methylene group.

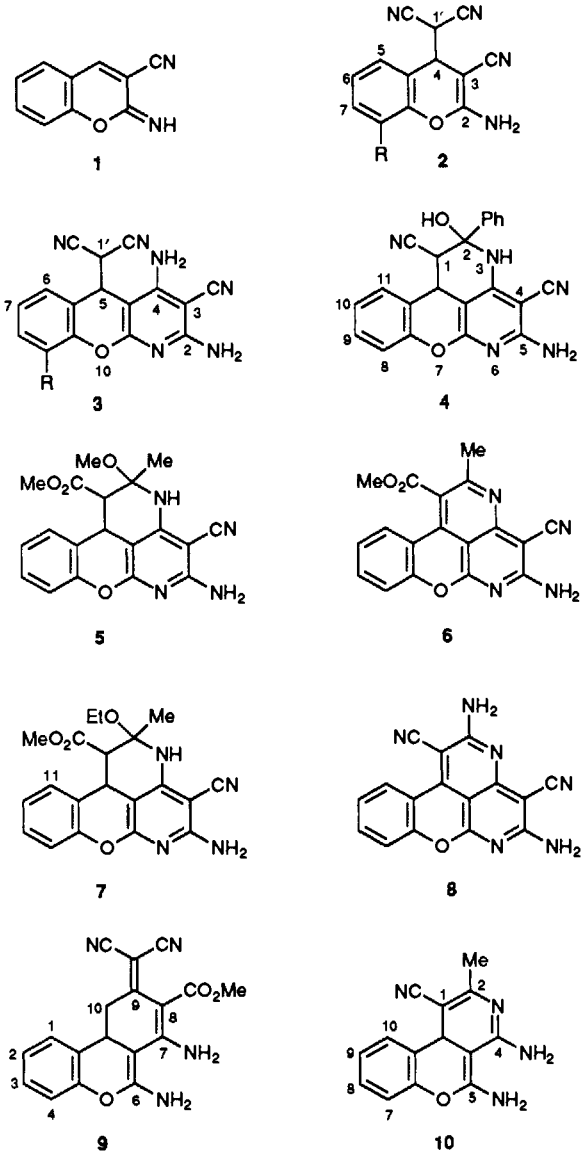
Heterocyclic β-enaminonitriles are useful synthetic intermediates for the preparation of heterocyclic systems having potential biological activity, (*cf.* reviews[1-3]), but relatively little work has in fact been published. The known reactions of these synthetic intermediates with γ-oxo alcohols, amines *etc.*, involve initial direct reaction of either the amino group (with the attacking oxo group) or the nitrile group (with the attacking amine group), and this is then followed by cyclisation through the alternative group. In contrast to these known reactions, the present work concerns β-aminonitrile derivatives of 4*H*-[1]benzopyrans, and the reactions are quite different, involving the addition of compounds containing a reactive methylene group.

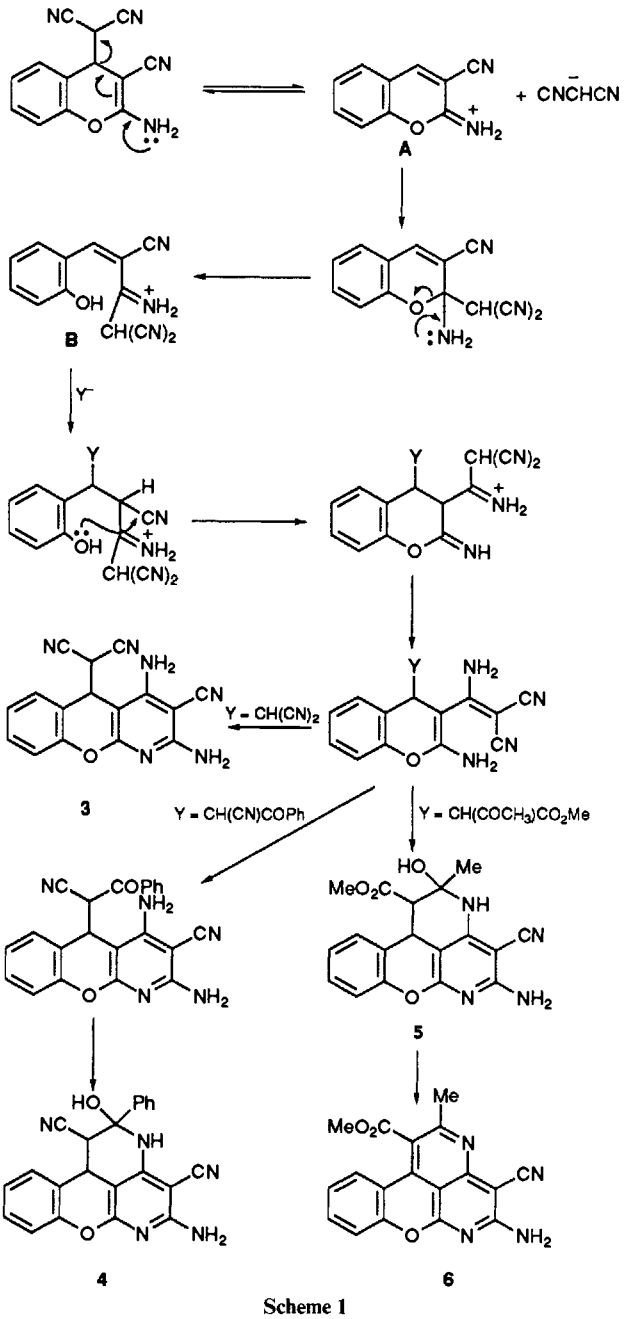
Reaction of salicylaldehyde with malononitrile in 1:1 ratio affords the relatively unstable 2-imino-2*H*-[1]benzopyran-3-carbonitrile **1** (analogues of which are currently attracting considerable interest as inhibitors of protein tyrosine kinase[4,5]). The formation of 2-(2-amino-3-cyano-4*H*-[1]benzopyran-4-yl)propane-1,3-dinitrile **2a** (from the reaction of salicylaldehyde with malononitrile in 1:2 ratio) was reported in 1984.[6] The reactions of this compound, which are now reported, differ substantially from those of other β-aminonitrile derivatives described in the literature.

Reaction of the trinitrile derivative **2a** with malononitrile readily affords the tricyclic product **3a**. (The reaction is not confined to the 5,6,7,8-unsubstituted compound **2a**; the 8-methoxy derivative **2b** reacts similarly to form the corresponding tricyclic product **3b**.) Some formation of the [1]benzopyrano[2,3-*b*]pyridines **3** also occurs during prolonged heating of the trinitriles **2** in alcoholic solution (but not under normal recrystallisation conditions); the yield of tricyclic products **3** from this disproportionation is naturally much less than that from the reaction with malononitrile.

A related reaction takes place when the trinitrile derivative **2a** is treated with benzoylacetonitrile. In this case, the product is the tetracyclic derivative 4. The reaction with methyl 3-oxobutanoate, in methanol containing acetic acid, affords the [1]benzopyrano[4,3,2-*de*][1,6]naphthyridine derivatives **5** and **6**.

While it is possible to visualise a simple mechanism for the formation of **3a** from the reaction of **2a** with malononitrile, a similar mechanism would not be applicable to the formation of the other products. It seems unlikely that two disparate mechanisms would be involved in reactions which are essentially very similar, and accordingly the results are rationalised according to the single mechanism shown in Scheme 1. We suggest that an equilibrium is established between the trinitrile derivative **2**, the dicyanomethyl anion and the iminium ion **A** (Scheme 1). The dicyanomethyl anion





Scheme 1

subsequently attacks the 2-position of the iminium ion **A**. It is only then that another anion (dicyanomethyl or the less nucleophilic anions derived from benzoylacetonitrile or methyl 3-oxobutanoate) attacks the ring-opened intermediate **B**. Ring-closure in the opposite sense leads to the products **3**, **4**, **5** and **6**.

A different product has been obtained from the reaction of the trinitrile **2a** with methyl 3-oxobutanoate when basic conditions were employed. In this case, the dibenzo[b,d]pyran derivative **9** was isolated. Not surprisingly, the reaction of the trinitrile **2a** with methyl 3-aminocrotonate affords the same products as methyl 3-oxobutanoate. Thus, in ethanol, the ethoxy derivative **7** is formed, together with small amounts of the related tetracyclic product **6** and the tricyclic product **9**. However, the main product formed from the bicyclic trinitrile **2a** in the presence of 3-aminocrotonate [(*E*)-3-aminobut-3-enoate] is not an ester derivative (resulting from addition of crotonate), but the insoluble tetracyclic derivative **8**. Clearly, this derives from the bicyclic starting material **2a** *via* the tricyclic compound **3a** (obtained as a result of disproportionation), which in turn affords the tetracyclic derivative **8** by cyclisation and loss of hydrogen. (The formation of **8** from **3** occurs to a limited extent when the latter is subjected to prolonged heating in acetone solution in the presence of base.)

When the bicyclic trinitrile **2a** is heated in ethanolic solution in the presence of 3-aminocrotononitrile, the tricyclic product **3a** is formed. As well as this, the [1]benzopyrano[3,4-*c*]pyridine **10** is obtained from the reaction of **2a** with 3-aminocrotononitrile.

The course of the reaction **2** ⟶ **3** ⟶ **8** needs little further explanation; the formation of the product **9**, however, involves modification of Scheme 1. As outlined in Scheme 2, the intermediate **A** is deprotonated by the base, and the dicyanomethyl anion reacts preferentially with methyl 3-oxobutanoate (*cf.* ref. 7). The anion from this reaction adds to **C** in the 2-position, leading to the product **9**. The reaction requires an inversion at the double bond **D** ⟶ **E**.

A similar modification of the general scheme operates in the presence of 3-aminocrotononitrile. This is more basic than the dicyanomethyl anion, and again addition takes place to the 2-position.

The formulation of the products **2**–**10** has been confirmed by spectral means, especially by ^1H and ^{13}C NMR. Assignment of ^{13}C NMR shifts necessitated the development of a method which combined gated decoupling with a study of the effects of selective deuteriation on neighbouring carbon atoms. This method is the subject of a separate communication.[8]

Experimental

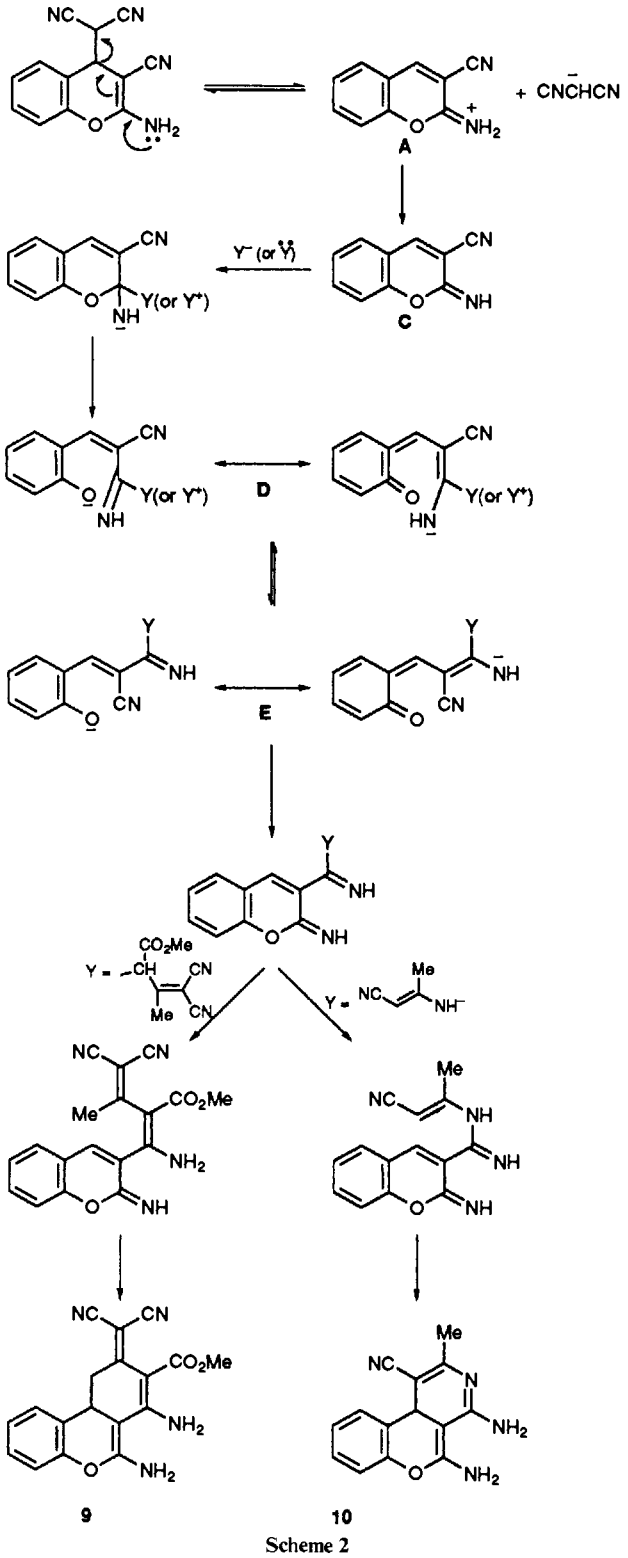
Melting points were determined in capillary tubes on a Gallenkamp apparatus and are uncorrected. IR spectra (Nujol) were recorded on a Perkin-Elmer 883 spectrometer. NMR spectra were recorded in ppm on a MSL 300 instrument, using [$^2H_6$]dimethyl sulfoxide as solvent unless otherwise stated; *J* values are given in Hz.

Improved Preparation of 2-(2-*Amino*-3-*cyano*-4H-[1]*benzopyran*-4-*yl*)*propane*-1,3-*dinitrile* **2a**.*—The literature preparation of the trinitrile **2a**[6] afforded a yield of 64%; the following preparation affords **2a** in 90% yield. Acetic acid (0.8 cm^3) and piperidine (0.03 cm^3) were added at 20 °C to a solution of salicylaldehyde (2.44 g, 20 mmol) and malononitrile (2.64 g, 40 mmol) in ethanol (20 cm^3). The mixture was set aside for 24 h, when the highly crystalline product separated. This was collected by filtration, dried and recrystallised from methanol (minimal heating, approximately 3 min, was used when dissolving the crude product for recrystallisation) to give pure title compound **2a** which was identical (m.p. and lit.,[6] m.p. 150–153 °C, ^1H NMR) with the literature product, δ_C 32.4 (C-1′), 37.1 (C-4), 48.8 (C-3), 112.9 (1′-C≡N), 113.1 (1′-C≡N), 116.4 (C-8), 118.0 (C-4a), 119.4 (3-C≡N), 125.1 (C-6), 128.9 (C-5), 130.2 (C-7), 149.7 (C-8a) and 163.4 (C-2).

2-(2-Amino-3-cyano-8-methoxy-4*H*-[1]benzopyran-4-yl)-propane-1,3-dinitrile **2b** (m.p. and lit.,[6] m.p. 173 °C) prepared by the improved method (above) in 89% yield, had δ_C 32.4 (C-1′), 37.3 (C-4), 48.8 (C-3), 55.8 (OCH_3), 112.7 (C-7), 112.9 (1′-C≡N), 113.1 (1′-C≡N), 118.8 (C-4a), 119.4 (3-C≡N), 119.7 (C-5), 124.9 (C-6), 139.1 (C-8), 147.1 (C-8a) and 163.4 (C-2).

Synthesis of 2-(2,4-*Diamino*-3-*cyano*-5H-[1]*benzopyrano*-[2,3-b]*pyridin*-5-*yl*)*propane*-1,3-*dinitrile* **3a**.—A solution of the trinitrile **2a** (1.18 g, 5 mmol) and malononitrile (0.33 g, 5 mmol)

* Skin contact with the bicyclic compounds **2** can lead to dermatitis.



Scheme 2

in ethanol (50 cm^3) containing a catalytic amount of piperidine (0.03 cm^3) was heated under reflux for 15 min (when heating was stopped because of vigorous bumping). The mixture, set aside at room temperature for 24 h, afforded an essentially pure product. This was collected by filtration, dried and recrystallised from methanol to give pure *title compound* **3a** (1.26 g, 83%), slow decomposition 270–280 °C (Found: C, 63.8; H, 3.5; N, 27.8. $C_{16}H_{10}N_6O$ requires C, 63.6; H, 3.35; N, 27.8%), ν_{max}/cm^{-1} 3493, 3393, 3320, 3188 (NH_2), 2261, 2203 (C≡N) and 1645; δ_H 4.86 (1 H, d, *J* 4, 1′-H), 4.93 (1 H, d, *J* 4, 5-H), 6.71 (2 H, br s, NH_2), 7.10 (2 H, br s, NH_2) and 7.21–7.49 (m, 4 H, ArH); δ_C 30.5 (C-1′), 34.7 (C-5), 70.5 (C-3), 83.8 (C-4a), 112.9 (1′-C≡N), 113.5 (1′-C≡N), 116.3 (3-C≡N), 116.9 (C-9), 117.9 (C-5a), 124.2 (C-7), 129.1 (C-6), 130.2 (C-8), 151.6 (C-9a), 157.0 (C-4), 160.4 (C-10a) and 160.5 (C-2).

2-(2,4-*Diamino*-3-*cyano*-8-*methoxy*-5H-[1]*benzopyrano*-[2,3-b]*pyridin*-5-*yl*)*propane*-1,3-*dinitrile* **3b** was similarly prepared (in 55% yield), slow decomposition 270–280 °C (Found: C, 61.6; H, 3.55; N, 25.4. $C_{17}H_{12}N_6O_2$ requires C, 61.4; H, 3.6; N, 25.3%); ν_{max}/cm^{-1} 3465, 3373, 3339, 3247 (NH_2), 2256, 2201 (C≡N) and 1646; δ_H 3.86 (3 H, s, OCH_3), 4.86 (1 H, d, *J* 4, 1′-H), 4.93 (1 H, d, *J* 4, 5-H), 6.71 (2 H, br s, NH_2), 6.97 (1 H, d, *J* 7.5, ArH), 7.09 (2 H, br s, NH_2) and 7.08–7.23 (2 H, m, ArH); δ_C 30.3 (C-1′), 34.8 (C-5), 55.9 (OCH_3), 70.5 (C-3), 83.7 (C-4a), 112.7 (C-8), 113.0 (1′-C≡N), 113.5 (1′-C≡N), 116.3 (3-C≡N), 118.7 (C-5a), 120.0 (C-6), 124.0 (C-7), 141.0 (C-9), 147.7 (C-9a), 157.0 (C-4) and 160.4 × 2 (C-10a and C-2).

Synthesis of 5-*Amino*-2-*hydroxy*-2-*phenyl*-1,2,3,11b-*tetrahydro*[1]*benzopyrano*[4,3,2-de][1,6]*naphthyridine*-1,4-*dicarbonitrile* **4**.—A solution of the trinitrile **2a** (1.18 g, 5 mmol) and benzoylacetonitrile (0.71 g, 5 mmol) in ethanol (30 cm^3) was heated under reflux for 30 min, and then set aside at 20 °C for 48 h. The crystalline yellow product which separated was collected by filtration, dried and recrystallised from methanol to give the *title compound* **4** (0.89 g, 47%), m.p. 291–294 °C (decomp.) (Found: C, 69.0; H, 4.0; N, 18.2. $C_{22}H_{15}N_5O_2$ requires C, 69.3; H, 3.9; N, 18.4%); ν_{max}/cm^{-1} 3451 (OH), 3410, 3309, 3190 (NH_2, NH), 2252, 2215 (C≡N) and 1639; δ_H 4.37 (1 H, d, *J* 4, 11b-H), 4.64 (1 H, d, *J* 4, 1-H), 6.83 (2 H, br s, NH_2), 6.98 (1 H, s, NH or OH) and 7.13–7.74 (10 H, m, 9 ArH and OH or NH); δ_C 29.1 (C-11b), 40.8 (C-1), 70.6 (C-4), 81.4 (C-2), 83.8 (C-11c), 115.7 (4-C≡N), 116.8 (C-8), 117.5 (1-C≡N), 120.2 (C-11a), 124.4 (C-10), 126.7 × 2 (C-2′, C-6′), 126.8 (C-11), 128.1 × 2 (C-3′, C-5′), 128.8 × 2 (C-9, C-4′). 141.6 (C-1′), 151.0 (C-7a), 152.8 (C-3a), 158.8 (C-6a) and 160.2 (C-5).

Reaction of 2-(2-*Amino*-3-*cyano*-4H-[1]*benzopyran*-4-*yl*)-*propane*-1,3-*dinitrile* **2a** *with Methyl* 3-*Oxobutanoate*.—(a) *In acidic medium*. A solution of the trinitrile **2a** (472 mg, 2 mmol) and methyl 3-oxobutanoate (232 mg, 2 mmol) in methanol (25 cm^3) containing acetic acid (1.0 cm^3) was heated under reflux for 1 h. The solvent was then removed under reduced pressure to leave a solid residue that contained two yellow products, one of which was readily soluble in methanol, while the other was only slightly soluble. The more soluble compound, which was readily purified by extraction into methanol and recrystallisation, was *methyl* 5-*amino*-4-*cyano*-2-*methoxy*-2-*methyl*-1,2,3,11b-*tetrahydro*[1]*benzopyrano*[4,3,2-de][1,6]*naphthyridine*-1-*carboxylate* **5** (204 mg, 29%), slow melt and resolidification 160–190 °C (Found: C, 62.5; H, 4.7; N, 15.5. $C_{19}H_{18}N_4O_4$ requires C, 62.3; H, 4.9; N, 15.3%); ν_{max}/cm^{-1} 3342, 3315, 3188 (NH, NH_2), 2201 (C≡N), 1734 (C=O) and 1638; δ_H 1.55 (3 H, s, CH_3), 3.42 (3 H, s, OCH_3), 3.68 (1 H, d, *J* 5, 11b-H), 4.39 (1 H, d, *J* 5, 1-H), 6.5 (2 H, br s, NH_2), 7.06–7.37 (4 H, m, ArH) and 7.72 (1 H, br s, NH); δ_C 21.4 (CH_3), 27.9 (C-11b), 47.0 (C-1), 48.1 (OCH_3), 51.3 (OCH_3), 69.8 (C-4), 82.6 (C-2), 85.9 (C-11c), 116.1 (C≡N), 116.5 (C-8), 121.4 (C-11a), 123.8 (C-10), 125.7 (C-11), 128.2 (C-9), 151.0 (C-7a), 152.6 (C-4a), 158.1 (C-6a), 159.9 (C-5) and 169.3 (C=O).

The other, much less soluble product, was *methyl* 5-*amino*-4-*cyano*-2-*methyl*[1]*benzopyrano*[4,3,2-de][1,6]*naphthyridine*-1-*carboxylate* **6** (74 mg, 10%), m.p. > 320 °C (Found: C, 64.9; H, 3.6; N, 16.8. $C_{18}H_{12}N_4O_3$ requires C, 65.1; H, 3.6; N, 16.9%); ν_{max}/cm^{-1} 3373, 3328w, 3208 (NH_2), 2225 (C≡N), 1717 (C=O) and 1666; δ_H 2.50 (3 H, s, CH_3), 4.03 (3 H, s, OCH_3) and 7.47–7.73 (6 H, m, 4 ArH and NH_2); δ_C 23.6 (CH_3), 53.3 (OCH_3), 75.8 (C-4), 101.4 (C-11c), 115.3 (C-11a), 115.5 (C-1), 116.1 (4-C≡N), 118.7 (C-8), 125.1 (C-11), 125.6 (C-10), 133.6 (C-9), 134.0 (C-

11b), 152.0 (C-8a), 155.1 (C-4a), 158.7 (C-6a), 161.6 (C-5), 162.1 (C-2) and 169.4 (C=O).

(b) *In basic medium.* A solution of the trinitrile **2a** (472 mg, 2 mmol) and methyl 3-oxobutanoate (928 mg, 8 mmol) in methanol (25 cm^3) containing piperidine (0.06 cm^3) was heated on a water-bath for 5 min, then set aside in an open beaker at room temperature. Following gradual evaporation, the residual gum was triturated with methanol to afford a bright yellow crystalline material. This product was collected by filtration, dried and recrystallised from methanol to give *methyl* 6,7-*diamino*-9-(*dicyanomethylidene*)-10,10a-*dihydro*-9H-*dibenzo*-[b,d]*pyran*-8-*carboxylate* **9** (190 mg, 28%), m.p. 217–219 °C (Found: C, 64.6; H, 4.4; N, 16.8. $C_{18}H_{14}N_4O_3$ requires C, 64.7; H, 4.2; N, 16.8%); ν_{max}/cm^{-1} 3465, 3423, 3328, 3211 (NH_2), 2210, 2198 (C≡N), 1681w (C=O) and 1641; δ_H 2.51 (1 H, dd, *J* 13, 18, H_b of CH_2), 3.39 (1 H, dd, *J* 4.5, 18, 10a-H), 3.53 (1 H, dd, *J* 4.5, 13, H_a of CH_2), 3.74 (3 H, s, OCH_3), 7.01 (1 H, d, *J* 8, ArH), 7.09 (2 H, br s, NH_2), 7.16 (1 H, t, *J* 8, ArH), 7.29 (1 H, t, *J* 8, ArH), 7.45 (1 H, d, *J* 8, ArH) and 8.29 (2 H, br s, NH_2); δ_C 29.8 (C-10a), 43.1 (C-10), 50.5 (OCH_3), 60.1 (C-1′), 75.3 (C-6a), 97.6 (C-8), 115.6 (C-4), 116.9 (C≡N), 117.3 (C≡N), 121.5 (C-10b), 124.5 (C-2), 128.4 × 2 (C-1 and C-3), 148.0 (C-4a), 155.1 (C-7), 163.2 (C-6), 166.7 (C-9) and 168.2 (C=O).

Reaction of 2-(2-*Amino*-3-*cyano*-4H-[1]*benzopyran*-4-*yl*)*propane*-1,3-*dinitrile* **2a** *with Methyl* 3-*Aminocrotonate.*—A solution of the trinitrile **2a** (0.59 g, 2.5 mmol) and methyl 3-aminocrotonate (0.29 g, 2.5 mmol) in ethanol (40 cm^3) was heated under reflux for 30 min. An insoluble product separated, and when the mixture had been stored at room temperature overnight, this was collected by filtration and identified as 2,5-*diamino*[1]*benzopyrano*[4,3,2-de][1,6]*naphthyridine*-1,4-*dicarbonitrile* **8** (151 mg, 40%), m.p. > 320 °C (Found: C, 63.2; H, 2.9; N, 27.3. $C_{16}H_8N_6O{\cdot}1/4H_2O$ requires C, 63.05; H, 2.8; N, 27.6%); ν_{max}/cm^{-1} 3444, 3354, 3241, 3189 (NH_2), 2217, 2207 (C≡N), 1665w and 1640; δ_H([^{2}H]trifluoracetic acid) 7.85–7.89 (2 H, d, *J* 8, ArH and t, *J* 8, ArH), 8.17 (1 H, t, *J* 8, ArH) and 9.29 (1 H, d, *J* 8, ArH); δ_C([^{2}H]trifluoracetic acid) 73.8 (C-4), 79.2 (C-1), 97.5 (C-11c), 113.8 (C≡N),* 114.5 (C-11a),* 120.0 (C-8), 126.8 (C-10), 128.4 (C-11), 139.5 (C-9), 148.6 (C-7a), 153.4 (C-11b), 158.2 (C-3a), 160.0 (C-6a), 161.6 (C-5) and 162.6 (C-2).

Evaporation of the filtrate and extraction of the residues with methanol left undissolved methyl 5-amino-4-cyano-2-methyl-[1]benzopyrano[4,3,2-*de*][1,6]naphthyridine-1-carboxylate **6** (37 mg, 5%). From the methanol extracts there crystallised, successively, *methyl* 5-*amino*-4-*cyano*-2-*ethoxy*-2-*methyl*-1,2,3,11b-*tetrahydro*-[1]*benzopyrano*[4,3,2-de][1,6]-*naphthyridine*-1-*carboxylate* **7** (60 mg, 6%), m.p. 278–280 °C (Found: C, 63.4; H, 5.05; N, 15.0. $C_{20}H_{20}N_4O_4$ requires C, 63.2; H, 5.25; N, 14.7%); ν_{max}/cm^{-1} 3465, 3377, 3232 (NH_2, NH), 2204 (C≡N), 1730 (C=O) and 1634; δ_H 1.05 (3 H, t, *J* 7, OCH_2CH_3), 1.54 (3 H, s, CH_3), 3.38 (3 H, s, OCH_3), 3.56 (2 H, q, *J* 7, OCH_2), 3.64 (1 H, d, *J* 5, 1-H), 4.36 (1 H, d, *J* 5, 11b-H), 6.43 (2 H, br s, NH_2), 7.03 (1 H, d, *J* 8, ArH), 7.12 (1 H, t, *J* 8, ArH), 7.27 (1 H, t, *J* 8, ArH), 7.35 (1 H, d, *J* 8, ArH) and 7.63 (2 H, br s, NH_2); δ_C 15.5 (OCH_2CH_3), 22.2 (CH_3), 27.9 (C-11b), 47.0 (C-1), 51.2 (OCH_3), 55.7 (OCH_2), 69.7 (C-4), 82.3 (C-2), 85.8 (C-11c), 116.0 (C≡N), 116.4 (C-8), 121.3 (C-11a), 123.8 (C-10), 125.7 (C-11), 128.1 (C-9), 151.0 (C-7a), 152.6 (C-3a), 158.0 (C-6a), 159.8 (C-5) and 169.2 (C=O) and methyl 6,7-diamino-9-(dicyanomethylidene)-10,10a-dihydro-9H-dibenzo[*b*,*d*]pyran-8-carboxylate **9** (36 mg, 4%).

Reaction of 2-(2-*Amino*-3-*cyano*-4H-[1]*benzopyran*-4-*yl*)-*propane*-1,3-*dinitrile* **2a** *with* 3-*Aminocrotononitrile.*—A solution of the trinitrile **2a** (1.18 g, 5 mmol) and 3-aminocrotononitrile (0.41 g, 5 mmol) in ethanol (40 cm^3) was heated for 20 min under reflux. The mixture was set aside at room temperature for 4 h, when a colourless product separated. This was collected by filtration and identified as 2-(2,4-diamino-3-cyano-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-yl)propane-1,3-dinitrile **3a** (0.39 g, 52%). The filtrate was stored for a further 7 days, when a second product separated. This was collected by filtration, dried and recrystallised from methanol to give 4,5-*diamino*-2-*methyl*-10bH-[1]*benzopyrano*[3,4-c]*pyridine*-3-*carbonitrile* **10** (0.53 g, 42%), m.p. 157–160 ° (Found: C, 65.1; H, 5.2; N, 21.45. $C_{14}H_{12}N_4O{\cdot}1/3H_2O$ requires C, 65.1; H, 4.9; N, 21.7%); ν_{max}/cm^{-1} 3366, 3263, 3184 (NH_2), 2186 (C≡N) and 1645; δ_H 1.97 (3 H, s, CH_3), 4.75 (1 H, s, H-10b), 6.74 (2 H, br s, NH_2), 6.85 (2 H, s, NH_2) and 6.96–7.27 (4 H, m, ArH); δ_C 20.5 (CH_3), 31.6 (C-10b), 53.7 (C-1), 82.3 (C-4a), 115.8 (C-7), 120.4 (C≡N), 122.3 (C-10a), 122.5 (C-2), 124.6 (C-9), 128.2 (C-8), 128.5 (C-10), 148.6 (C-6a), 154.9 (C-4) and 160.6 (C-5).

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* Assignments are tentative. One signal (attributable to C-11a or C≡N) is not visible, presumably being concealed by the solvent signals in the 113–117 region.

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