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Nitriles in Heterocyclic Synthesis. The Reaction of Polyhydric Naphthalenes, 4-Methylcoumarin-3-carbonitrile, and Alkylidenemalononitrile with Methylenemalononitrile

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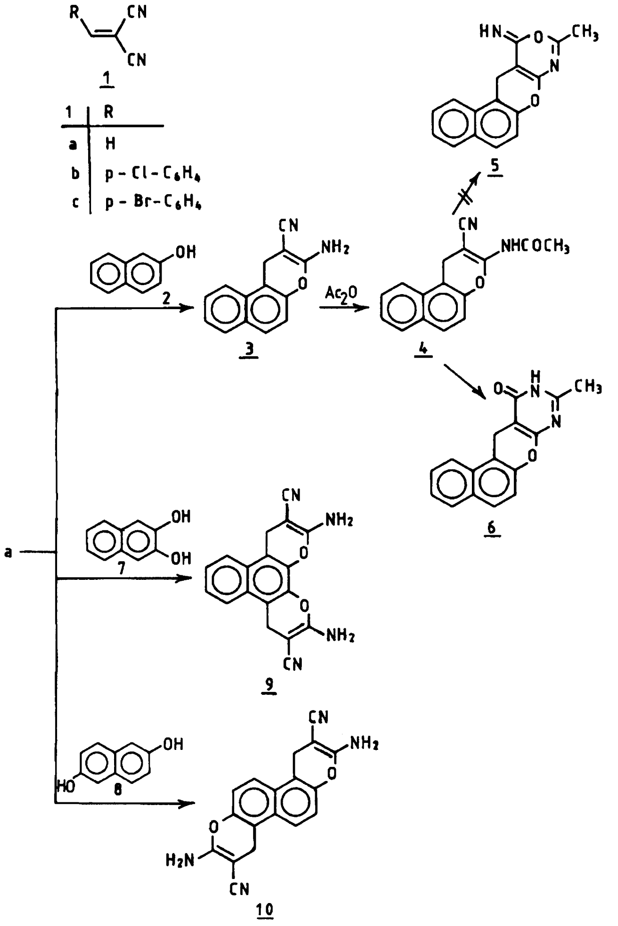
2-Naphthol and naphthalenediols react with methylenemalononitrile, generated in situ from reaction of formaldehyde and malononitrile, to yield naphthopyrans and naphthodipyrans. 5-Hydroxynaphtho[2,1-*b*]pyrans reacted further with methylenemalononitrile to yield naphthodipyrans. The reaction of methylenemalononitrile with 4-methylcoumarin-3-carbonitrile afforded benzopyrano[4,3-*h*]quinoline. 6-Cyanomethyl-3-pyridinecarbonitriles, prepared via reacting 1-arylethylidenemalononitriles with malononitrile, afforded 4*H*-quinolizines on treatment with methylenemalononitrile.

Arylmethylenemalononitriles are versatile reagents and their chemistry has received considerable attention.[1—6] Although substituted methylenemalononitrile has been extensively utilized as starting materials for synthesis of variety of polyfunctionally substituted heterocycles[7,8], methyenemalononitrile has found very little utility. The difficulty of preparing this reagent in pure form is surely behind lack of its utility. Recently, we have shown that a mixture of malononitrile and formaldehyde may be utilized as a synthetic equivalent of methylenemalononitrile[8]. By this way a variety of otherwise not readily obtainable heterocycles could be synthesized. In conjunction of this work, we report results of our investigations on reactivity of variety of active methylene reagents toward a formaldehyde/malononitrile mixture. Thus, it has been found that 2-naphthol reacts with the formaldehyde/malononitrile mixture to yield 3-amino-1*H*-naphtho[2,1-*b*]pyran-2-carbonitrile (**3**). This compound is assumed to be formed via addition of 2-naphthol to methylenemalononitrile (**1**) to yield an acyclic Michael adduct which spontaneously cyclized into the final isolable product **3**. The 4*H*-pyran structure of this reaction product was preferred over a possible 2*H*-pyran structure which might result from the addition of the naphthol oxygen atom to the double bond in **1** and subsequent cyclization, based on the ^{1}H NMR which revealed the methylene proton signal at $\delta=3.80$ comparable to these expected for 4*H*-pyran derivative and different than that expected for 2*H*-pyran.

Compound **3** reacted with acetic anhydride to afford a pyrano[2,3-*d*]pyrimidine **6**[8] which was presumably derived by cyclization of **4**, the intermediately formed *N*-acetyl derivative of **3**. The structure of **6** was confirmed by the IR spectrum, which showed neither CN nor C=NH absorption and thus excluded the structure of a pyrano[2,3-*d*][1,3]oxazine **5**.

The reaction of two equivalents of methylenemalononitrile with 2,3-naphthalenediol (**7**) and 2,6-naphthalenediol (**8**) gave solid products which were assumed as 2,11-diamino-4,9-dihydronaphtho[2,1-*b*:3,4-*b′*]dipyran-3,10-dicarbonitrile (**9**) and 2,8-diamino-4,10-dihydronaphtho[2,1-*b*: 6,5-*b′*]dipyran-3,9-dicarbonitrile (**10**), respectively (Scheme 1). The ^{1}H NMR of **9** revealed the presence of four magnetically equivalent methylene protons appeared as one signal.

Similarly, the reactions of diols **11**—**14** with two equivalents of methylenemalononitrile formed by treat-



Scheme 1.

ing formaldehyde with malononitrile afforded **15**—**18**, respectively (Scheme 2). While the 4*H*-pyran protons of **15**, **16** and **18** gave two singlets as expected (cf. Experimental), the 4*H*-pyran protons of **17** appeared also as two different signals in spite of the fact that this molecule seems to have a plane of symmetry. These observations are accounted for by assuming that one of the two sp^3 carbons in **17** is pushed out from ring plane and pyran protons become thus magnetically different than the other sp^3 carbons.

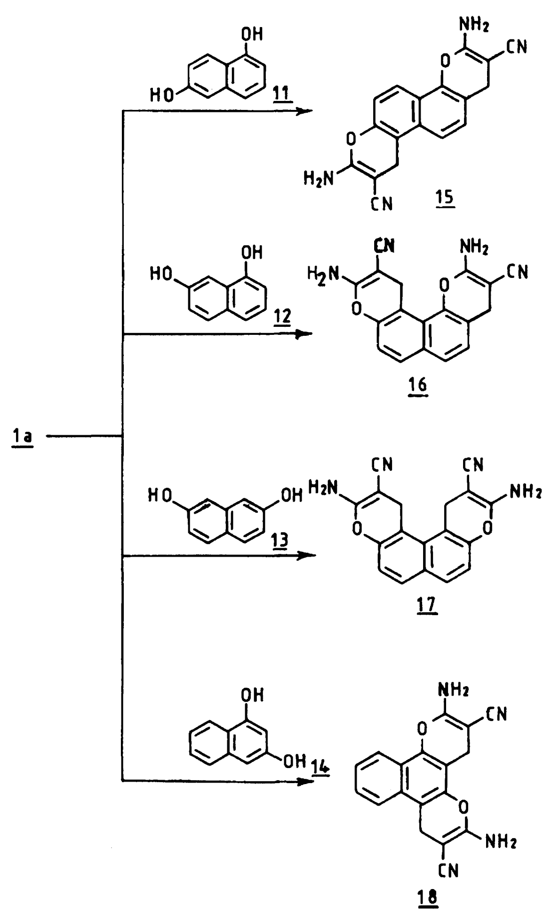
The ^{1}H NMR spectrum of **17** revealed all aromatic protons as doublets with $J \simeq 7$ Hz. If the α-carbons were not involved in the reaction one would expect one proton signal with a very low J value.

For all the above mentioned reactions, the possibility that the naphthol C-3 was involved in the reactions was ruled out as this position proved inert in our previous work.[2)] For example, 1,7- or 2,7-naphthalenediol did not react at all with cinnamonitriles. If these reactions attack at the α-carbon, it would produce a sterically crowded molecule. This position became now active when an aryl group in cinnamonitriles is replaced by H.

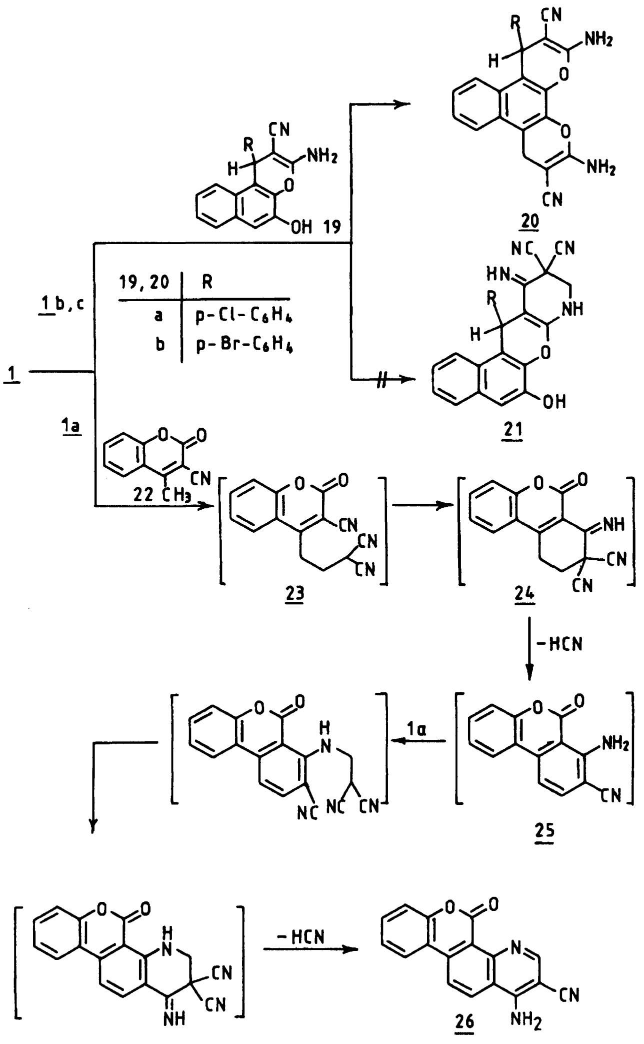
The naphthopyran derivative **19** reacted with formaldehyde/malononitrile to yield the naphthodipyran **20**. Another structure for the reaction product such as **21** was excluded since the enaminonitrile moiety was observed in the ^{1}H NMR spectrum.

Equimolar amounts of formaldehyde and malononitrile reacted with a coumarin derivative **22** to yield a product of molecular formula $C_{17}H_9N_3O_2$ ($M^+=287$). Structure **26** was assigned for the reaction product (Scheme 3). The same product was obtained by reacting formaldehyde, malononitrile, and **22** in a molar ratio of 2 : 2 : 1. Compound **26** is assumed to be formed by the addition of the methyl function in **22** to **1a** giving **23** which readily cyclized to **24**. Dehydrocyanation from **24** affords an intermediate **25** which similarly reacts again with methylenemalononitrile to afford **26**. A similar sequence has been previously suggested to account for the formation of benzenes and benzocoumarins on reacting methyl heterocyclic carbonitriles with arylmethylenemalononitriles.[3,9—11)]

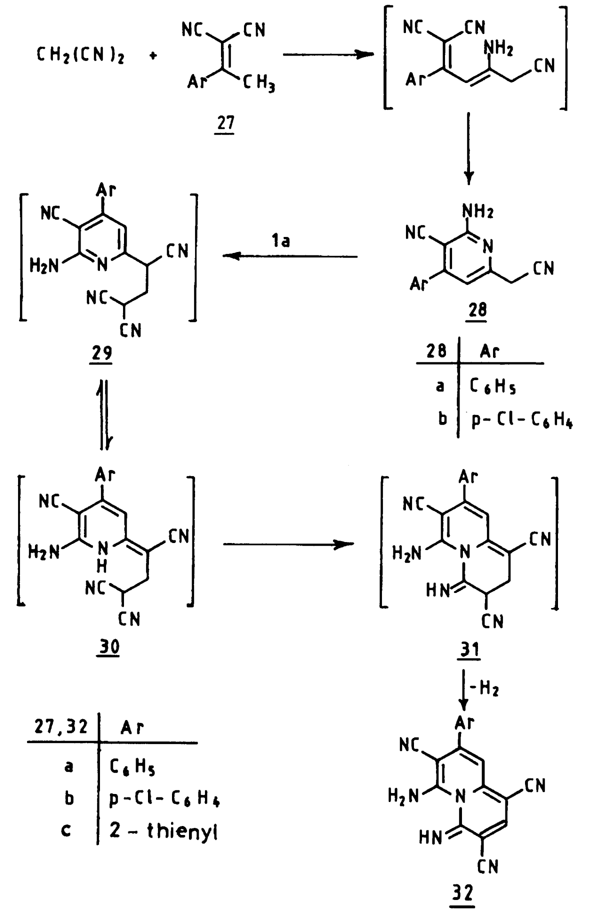
Compounds **27a**—**c** reacted with a formaldehyde/malononitrile mixture to yield **32a**—**c**, respectively (Scheme 4). Structure **32** could be established for the reaction products based on their identities with the products of reactions of formaldehyde/malononi-



Scheme 2.



Scheme 3.



Scheme 4.

trile mixture with **28a**[7] and **28b**, prepared by reacting **27a,b** with malononitrile. Compound **32** is assumed to be formed by the reaction of malononitrile with **27** to yield the pyridine derivative **28** which then reacted with **1a** to yield **29**. Formation of **32** by the reaction of **28** with methylenemalononitrile finds parallelism to the reported reactions of pyridineacetonitriles with ethoxymethylenemalononitrile and ethyl ethoxymethylenecyanoacetate respectively[12—14].

Experimental

All mps are uncorrected. IR spectra (KBr) were recorded on a Pye-Unicam spectrophotometer. ^{1}H NMR spectra were measured on a Varian EM-390 spectrometer. Microanalysis were performed by the Microanalytical Data Unit at Cairo University. Mass Spectra were recorded with a mass spectrometer MS 9 (AEI) at 70 eV.

3-Amino-1*H*-naphtho[2,1-*b*]pyran-2-carbonitrile (3). To a suspension of 2-naphthol (0.01 mol) in ethanol (50 ml) was added a mixture of malononitrile (0.01 mol) and formaldehyde (0.01 mol), and then few drops of triethylamine. The reaction mixture was refluxed for 2 h and the solid formed on heating was collected by filtration, recrystallized from ethanol/DMF to give colorless crystals, yield 73%; mp 210°C. IR 3460, 3350, 3210 (NH_2), 2195 (CN), and 1680 cm^{-1} (δ-NH_2). ^{1}H NMR (DMSO-d_6) δ=3.80 (s, 2H, pyran 4-H), 6.8 (s, 2H, NH_2), and 7.0—7.82 (m, 6H, aromatic protons). MS m/z 222 (M^+). Found: C, 75.64; H, 4.45; N, 12.57%. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60%.

9-Methyl-12*H*-naphtho[1′, 2′:5, 6]pyrano[2, 3-*d*]pyrimidin-11(10*H*)-one (6). A solution of **3** (0.01 mol) in acetic anhydride (15 ml) was refluxed for 3 h, then evaporated in vacuo. The remaining solid product was triturated with water, and the resulting solid product was collected by filtration, crystallized from ethanol as colorless crystals, yield 80%; mp >300°C. IR 3485—3300 (NH), and 1665 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6) δ=2.38 (s, 3H, CH_3), 3.82 (s, 2H, pyran 4-H), and 7.0—7.88 (m, 7H, aromatic protons and NH). MS m/z 264 (M^+). Found: C, 72.70; H, 4.59; N, 10.63%. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.22; H, 4.58; N, 10.60%.

Reaction of Methylenemalononitrile with Naphthalenediols. To a solution of malononitrile (0.02 mol) and formaldehyde (0.02 mol) in ethanol (50 ml), 0.01 mol of naphthalenediol were added. The reaction mixture was refluxed for 1 h in the presence of piperidine (0.5 ml). The solid formed on heating was collected by filtration. Compounds **9** and **15**—**18** were crystallized from ethanol/dioxane mixture (1 : 1). As compound **10** was found highly insoluble in this mixture, it was crystallized from excess dioxane.

2,11-Diamino-4,9-dihydronaphtho[2,1-*b*:3,4-*b*′]dipyran-3,10-dicarbonitrile (9). Colorless crystals, yield 80%; mp >300°C. IR 3630, 3450, 3360 (NH_2), 2205 (CN), and 1668 cm^{-1} (δ-NH_2). ^{1}H NMR (DMSO-d_6) δ=3.8 (s, 4H, pyran 4-H), 7.25—8.0 (m, 8H, aromatic protons and NH_2 protons). MS m/z 316 (M^+). Found: C, 68.22; H, 4.02; N, 17.99%. Calcd for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71%.

2,8-Diamino-4,10-dihydronaphtho[2,1-*b*:6,5-*b*′]dipyran-3,9-dicarbonitrile (10). Colorless crystals, yield 76%; mp >300°C. IR 3460, 3380, 3210 (NH_2), 2200 (CN), and 1650 cm^{-1} (δ-NH_2). MS m/z 316 (M^+). Found: C, 68.33; H, 3.80; N, 17.69%. Calcd for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71%.

2,9-Diamino-4,7-dihydronaphtho[1,2-*b*:6,5-*b*′]dipyran-3,8-dicarbonitrile (15). Colorless crystals, yield 73%; mp >300°C. IR 3475, 3440, 3350, and 3200 (NH_2), 2200 (CN), and 1650 cm^{-1} (δ-NH_2). ^{1}H NMR (DMSO-d_6) δ=3.34 (s, 2H, pyran 4-H), 3.55 (s, 2H, pyran 4-H), and 6.75—7.90 (m, 9H, aromatic protons and NH_2 protons). MS m/z 316 (M^+). Found: C, 68.31; H, 3.79; N, 17.64%. Calcd for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71%.

2,10-Diamino-4,12-dihydronaphtho[1,2-*b*:7,8-*b*′]dipyran-3,11-dicarbonitrile (16). Colorless powder, yield 75%; mp >300°C. IR 3450, 3330, 3210 (NH_2), 2200 (CN), and 1665 cm^{-1} (δ-NH_2). ^{1}H NMR (trifluoroacetic acid) δ=3.25 (s, 2H, pyran 4-H), 3.45 (s, 2H, pyran 4-H), and 6.1—8.45 (m, 8H, aromatic protons and 2NH_2). MS m/z 316 (M^+). Found: C, 68.46; H, 3.86; N, 17.58%. Calcd for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71%.

3,10-Diamino-1,12-dihydronaphtho[2,1-*b*:7,8-*b*′]dipyran-2,11-dicarbonitrile (17). Colorless crystals, yield 82%; mp >300°C. IR 3420, 3330, 3210 (NH_2), 2195 (CN), and 1668 cm^{-1} (δ-NH_2). ^{1}H NMR (DMSO-d_6) δ=3.4 (s, 2H, pyran 4-H), 3.6 (s, 2H, pyran 4-H), 6.35—6.80 (d, 2H, J=7.2 Hz, aromatic H-5, H-8), 6.95—7.16 (d, 2H, J=7.2 Hz, aromatic H-6, H-7), and 7.60—7.82 (m, 4H, 2NH_2). MS *m/z* 316 (M^+). Found: 68.33; H, 3.78; N, 17.67%. Calcd for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71%.

2,6-Diamino-4,8-dihydronaphtho[1,2-*b*:3,4-*b*′]dipyran-3,7-dicarbonitrile (18). Colorless crystals, yield 83%; mp >300°C. IR 3435, 3335, 3205 (NH_2), 2195 (CN), and 1670 cm^{-1} (δ-NH_2). ^{1}H NMR (DMSO-d_6) δ=3.40 (s, 2H, pyran 4-H), 3.76 (s, 2H, pyran 4-H), 6.76—7.80 (m, 4H, aromatic protons), and 8.0—8.24 (m, 4H, 2NH_2). MS *m/z* 316 (M^+). Found: C, 68.39; H, 3.77; N, 17.69%. Calcd for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71%.

3-Amino-1-aryl-5-hydroxy-1*H*-naphtho[2,1-*b*]pyran-2-carbonitrile (19a,b). Equimolar amounts of **1b** (or **1c**) and 2,3-naphthalenediol (0.01 mol) in ethanol 50 ml were treated with a few drops of piperidine. The reaction mixture was refluxed for 6 h. The solid product, formed on standing, was collected by filtration and crystallized from ethanol, then identified as **19a** (or **19b**).

3-Amino-1-(4-chlorophenyl)-5-hydroxy-1*H*-naphtho[2,1-*b*]pyran-2-carbonitrile (19a). Colorless crystals, yield 60%, mp 278°C. IR 3460, 3400, 3325 (NH_2), 2200 (CN), and 1645 cm^{-1} (δ-NH_2). ^{1}H NMR (DMSO-d_6) δ=5.43 (s, 1H, pyran 4-H), 6.72 (brs, 2H, NH_2), 6.80—8.10 (m, 10 H, aromatic protons and OH). Found: C, 68.83; H, 3.68; N, 7.78; Cl, 10.12%. Calcd for $C_{20}H_{13}N_2O_2Cl$: C, 68.87; H 3.76; N, 8.03; Cl, 10.16%.

3-Amino-1-(4-bromophenyl)-5-hydroxy-1*H*-naphtho[2,1-*b*]pyran-2-carbonitrile (19b). Colorless crystals, yield 61%, mp 250°C. IR 3480, 3350, 3235 (NH_2), 2195 (CH), and 1650 cm^{-1} (δ-NH_2). ^{1}H NMR (DMSO-d_6): δ=5.45 (s, 1H, pyran 4-H), 6.79—8.21 (m, 12H, aromatic protons and NH_2), and 8.29 (s, 1H, OH). Found: C, 61.11; H, 3.24; N, 7.14; Br, 20.26%. Calcd for $C_{20}H_{13}N_2O_2Br$: C, 61.09; H, 3.33; H, 7.12; Br, 20.32%.

General Method for Reaction of 19 and 22 with 1a. To a suspension of naphthopyran **19** or 3-cyano-4-methylcoumarin **22** (0.01 mol) in ethanol (50 ml) was added a mixture of malononitrile (0.01 mol) and formaldehyde (0.01 mol), and then few drops of triethylamine. The reaction mixture was refluxed for 2 h and the solid product formed on heating was collected by filtration, crystallized from ethanol/DMF. The product was identified as **20** and **26**, respectively.

2,11-Diamino-4-(4-chlorophenyl)-4,9-dihydronaphtho[2,1-*b*:3,4-*b*′]dipyran-3,10-dicarbonitrile (20a). Colorless crystals, yield 70%, mp >300°C. IR 3500—3300 (NH_2), 2200 (CN), and 1680 cm^{-1} (δ-NH_2). ^{1}H NMR (DMSO-d_6) δ=2.85 (s, 2H, NH_2), 3.16 (s, 2H, pyran 4-H), 5.41 (s, 1H, pyran 4-H), 6.65 (brs, 2H, NH_2), and 7.0—7.95 (m, 8H, aromatic protons). MS *m/z* 426 (M^+). Found: C, 67.47; H, 3.65; N, 13.12; Cl, 8.19%. Calcd for $C_{24}H_{15}N_4O_2Cl$: C, 67.53; H, 3.54; N, 13.13; Cl, 8.30%.

2,11-Diamino-4-(4-bromophenyl)-4,9-dihydronaphtho[2,1-*b*:3,4-*b*′]dipyran-3,10-dicarbonitrile (20b). Colorless crystals, yield 68%; mp >300°C. IR 4200—3400 (NH_2), 2198 (CN), and 1660 cm^{-1} (δ-NH_2). ^{1}H NMR (DMR-d_6) δ=2.85 (s, 2H, NH_2), 3.10 (s, 2H, pyran 4-H), 5.44 (s, 1H, pyran 4-H), 6.51 (brs, 2H, NH_2), and 6.92—8.10 (m, 8H, aromatic protons). Found C, 61.08; H, 3.32; N, 11.84; Br, 16.92%. Calcd for $C_{24}H_{15}N_4O_2Br$: C, 61.16; H, 3.21; N, 11.89; Br, 16.95%.

1-Amino-5-oxo-5*H*-[1]benzopyrano[4,3-*h*]quinoline-2-carbonitrile (26). Pale yellow crystals, yield 62%; mp 265°C. IR 3450—3320 (NH_2), 2220 (CN), and 1745 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6) δ=6.74—7.95 (m, 8H, aromatic protons and NH_2), 8.2 (s, 1H, quinoline 2-H). MS *m/z* 287 (M^+). Found: C, 71.02; H, 3.14: N, 14.63%. Calcd for $C_{17}H_9N_3O_2$: C, 71.08; H, 3.16; N, 14.63%.

2-Amino-4-aryl-6-cyanomethyl-3-pyridinecarbonitriles (28). To a finely ground sodium metal (0.01 mol) in dry dioxane (30 ml) was added **27** (0.01 mol). The reaction mixture was refluxed for 30 min then left to cool, and malononitrile (0.01 mol) was added. The reaction mixture was left at room temperature overnight, then treated with dilute hydrochloric acid. The separated solid product was collected by filtration, washed with water and then crystallized and identified as **28**.

2-Amino-6-cyanomethyl-4-phenyl-3-pyridinecarbonitrile (28a). Yellow crystals, yield 65%; mp 125°C. (Ref.[7] mp 125°C).

2-Amino-6-cyanomethyl-4-(4-chlorophenyl)-3-pyridinecarbonitrile (28b). Yellow crystals, yield 64%; mp 155°C. IR 3325, 3250 (NH_2), 2215, and 2195 cm^{-1} (CN). ^{1}H NMR (DMSO-d_6) δ=3.38 (s, 2H, CH_2), 6.78—8.00 (m, 6H, aromatic protons and NH_2), and 8.34 (s, 1H, pyridine H). Found: C, 62.61; H, 4.01; N, 20.76; Cl, 13.22%. Calcd for $C_{14}H_9N_4Cl$: C, 62.58; H, 3.98; N, 20.85; Cl, 13.19%.

6-Amino-8-aryl-4-imino-4*H*-quinolizine-1,3,7-tricarbonitrle (32a—c). Equimolar amounts of **27a—c** (0.01 mol), formaldehyde (0.01 mol), and malononitrile (0.02 mol) in ethanol (50 ml) was treated with 1 ml of piperidine. The reaction mixture was refluxed for 2 h, and the solid product formed was collected by filtration and crystallized from ethanol/dioxane.

6-Amino-4-imino-8-phenyl-4*H*-quinolizine-1,3,7-tricarbonitrile (32a). Yellow crystals, yield 70%; mp >300°C. IR 3475, 3360, 3240 (NH_2, NH), 2215, 2205, 2198 (CN), 1680 (C=N), and 1650 cm^{-1} (δ-NH_2). ^{1}H NMR (DMSO-d_6) δ=7.16—7.74 (m, 8H, aromatic protons and NH) and 7.95—8.12 (brs, 2H, NH_2). MS *m/z* 310 (M^+). Found: C, 69.57; H, 3.34; N, 26.89%. Calcd for $C_{18}H_{10}H_6$: C, 69.67; H, 3.25; N, 27.08%.

6-Amino-8-(4-chlorophenyl)-4-imino-4*H*-quinolizine-1,3,7-tricarbonitrile (32b). Orange crystals, yield 68%; mp >300°C. IR 3470, 3410, 3330, 3215 (NH_2, NH), 2220, 2215, 2205 (CN), and 1660 cm^{-1} (δ NH_2). ^{1}H NMR (DMSO-d_6) δ=7.13—7.60 (m, 7H, aromatic protons and NH) and 8.0—8.16 (brs, 2H, NH_2). MS *m/z* 344 (M^+). Found: C, 62.59; H, 2.82; N, 24.33; Cl, 10.24%. Calcd for $C_{18}H_9N_6Cl$: C, 62.71; H, 2.63; N, 24.38; Cl, 10.28%.

6-Amino-4-imino-8-(2-thienyl)-4*H*-quinolizine-1,3,7-tricarbonitrile (32c). Yellow crystals, yield 60%; mp >300°C. IR 3480, 3375, 3245 (NH_2, NH), 2220, 2210, 2195 (CN), 1665 (C=N), and 1650 cm^{-1} (δ-NH_2). ^{1}H NMR (DMSO-d_6) δ=6.64 (br, 2H, NH_2), 7.0—7.52 (m, 2H, thiophene H-3 and H-4), 7.6—7.9 (m, 3H, NH, and quinolizine protons), 8.35 (d, 1H, *J*=4 Hz, thiophene H-5). MS *m/z* 316 (M^+). Found: C, 60.61; H, 2.80; N, 26.51; S, 10.16%. Calcd for $C_{16}H_8N_6S$: C, 60.75; H, 2.55; N, 26.57; S, 10.14%.

Compound **32a** (or **32b**) was also obtained by refluxing **28a** or **28b** (0.01 mol) with formaldehyde (0.01 mol) and malononitrile (0.01 mol) in ethanol (50 ml) in the presence of few drops of piperidine, for 3 h. The products obtained was collected by filtration, crystallized and identified (mp and mixed mp).

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