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Activated nitriles in organic synthesis: synthesis of pyranoquinolinone, 6*H*-2-benzopyrano[4,3-*c*]quinolinone and thieno[2,3-*b*]pyridine

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Summary — Several new quinoline derivatives **6** were prepared from reaction of 4-hydroxy-2(1*H*)-quinolinones **1** and the ylidenenitriles **2**. Compounds **9** were prepared from reaction of 1-ethylidenemalononitrile **2e** with **1c,d** or **1f,g**. Reaction of pyrano[3,2-*c*]quinoline **10** with **2a** or **2c** afforded benzo[*b*]pyrano[4,3-*c*]quinolines **11** and **12** respectively. Treatment of **1b,c** with malononitrile and elemental sulfur yielded **17**.

quinolinone / pyranoquinolinone / 6*H*-2-benzopyrano[4,3-*c*]quinolinone / thieno[2,3-*b*]pyridine

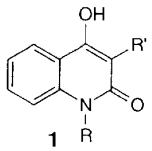
Résumé — Activation des nitriles en synthèse organique: synthèse de la pyranoquinoléinone, de la 6*H*-2-benzopyrano[4,3-c]quinoléinone et de la thiéno[2,3-*b*]pyridine. *Plusieurs nouvelles quinoléines* ***6*** *ont été préparées par réaction des 4-hydroxyquinoléin-2(1*H*)-ones* ***1*** *et des ylures de nitrile* ***2****. Les composés* ***9*** *sont obtenus par réaction du 1-éthylidènemalononitrile* ***2e*** *avec* ***1c, d*** *ou* ***1f, g****. La réaction de la pyrano[3,2-c]quinoléine* ***10*** *avec* ***2a*** *ou* ***2c*** *conduit respectivement aux benzopyrano[4,3-c]quinoléines* ***11*** *et* ***12****. Le traitement de* ***1b,c*** *avec le malononitrile et le soufre élémentaire conduit à* ***17****.*

quinoléin-2(1*H*)-one / pyranoquinoléinone / 6*H*-2-benzopyrano[4,3-*c*]quinoléinone / thiéno[2,3-*b*]pyridine

Introduction

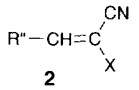
Our previous studies were concerned with the synthesis of 4*H*-pyrans and quinoline derivatives by the reaction of α-substituted cinnamonitriles [1, 2]. In view of the continued interest in the utility of α-substituted cinnamonitriles in the synthesis of aromatic and heteroaromatic systems [2–4] like benzo[*c*]coumarins, benzo[*c*]pyrano[3,2-*c*]quinolines, 4*H*-pyrans and 4*H*-naphthodipyrans, and because of the biological and medicinal activities [5, 6] of these ring systems, we report here the simple synthesis of quinoline derivatives from hydroxy pi-deficient heterocycles such as 4-hydroxyquinolinones **1** and pi-deficient olefines **2** as starting components.

It has been found that 3-acetyl-4-hydroxy-2(1*H*)-quinolinones **1a,c,d** react with the ylidenenitriles **2b,d** in ethanol and the presence of catalytic amounts of triethylamine, for which two products **3** and **6** seemed possible. Structure **3** was readily ruled out by analytical data and mass spectra of the reaction products. Thus, structure **6** was established for the reaction product based on ^{1}H NMR spectra which revealed the presence of a 4*H*-pyran proton at δ = 4.5–5 ppm. Compound **6** is assumed to be formed via addition of quinolinyl C-3 to the pi-deficient center in **2** to give the adduct **4**, which hydrolyzed and readily eliminated its acetyl group under the reaction conditions to give the intermediate **5**. This was cyclized to 4*H*-pyrano[3,2-*c*]quinolines **6**. Elimination of acetyl groups in this reaction parallels the reported deacetylation of similar systems under



1

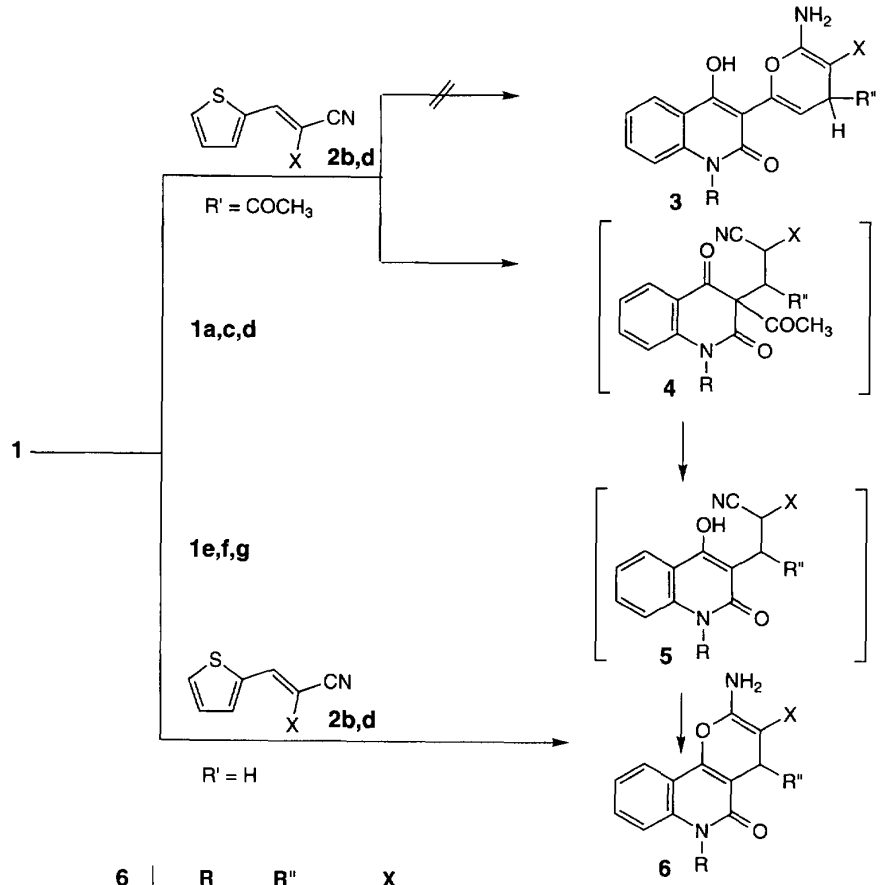
1a R = H R' = $COCH_3$ **1b** R = CH_3 R' = $COCH_3$
1c R = C_2H_5 R' = $COCH_3$ **1d** R = C_6H_5 R' = $COCH_3$
1e R = H R' = H **1f** R = C_2H_5 R' = H
1g R = C_6H_5 R' = H



2

2a R" = C_6H_5; X = CN **2b** R" =  ; X = CN
2c R" = C_6H_5; X = $CO_2C_2H_5$
2e R" = CH_3; X = CN **2d** R" =  ; X = $CO_2C_2H_5$

* Correspondence and reprints



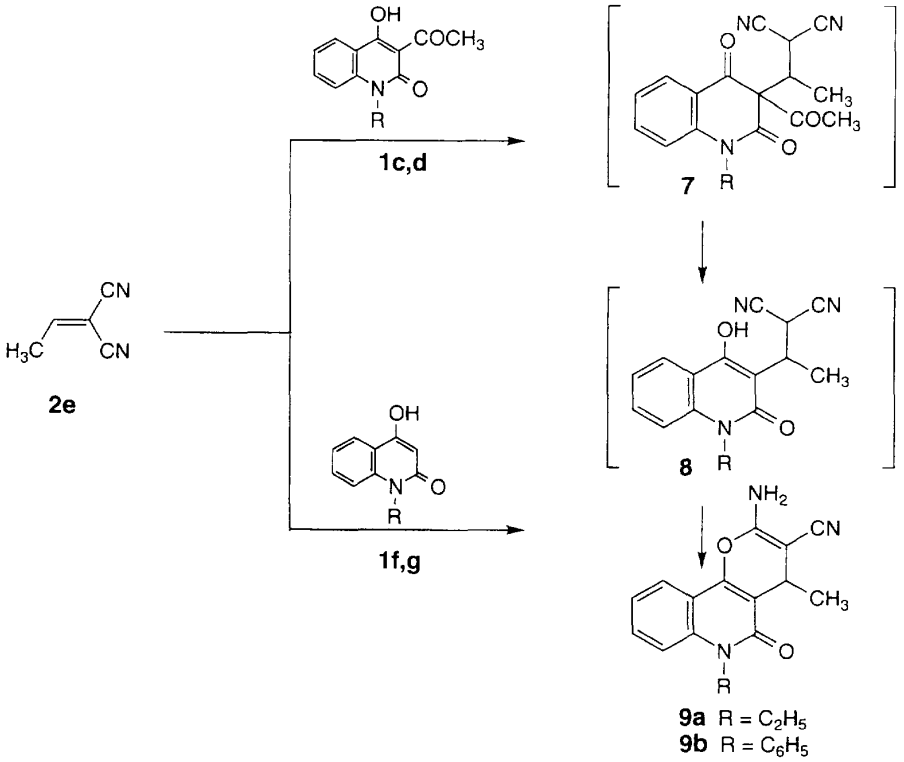
6	R	R"	X
a	H		CN
b	C_2H_5	"	"
c	C_6H_5	"	"
d	H	"	$CO_2C_2H_5$
e	C_2H_5	"	"
f	C_6H_5	"	"

Scheme 1

similar conditions [7–10]. The structures of compounds **6** were also confirmed by synthesizing them from **2b, d** and 4-hydroxy-2(1*H*)-quinolinones **1e–g** under the same reaction conditions (see scheme 1).

Compounds **9** have been prepared via reaction of acetaldehyde and malononitrile with 3-acetyl-4-hydroxy-2(1*H*)-quinolinones **1c,d**. Structures **9** were established for the reaction products based on their identification with the products of reaction of **1f** and **g** with an acetaldehyde/malononitrile mixture. It is suggested that they are formed via addition of the quinolinyl C-3 to the double bond in 1-ethylidenemalononitrile (formed in situ by treating acetaldehyde with malononitrile) to give **7** which deacetylated to give the intermediate **8** and then cyclized to **9** (see scheme 2).

Refluxing equivalent amounts of 3-acetyl-1-ethyl-4-hydroxy-2(1*H*)-quinolinone **1c** and malononitrile in glacial acetic acid containing catalytic amounts of ammonium acetate afforded pyrano[3,2-c]quinoline **10**. We investigated the reactivity of the methyl function in **10** towards a variety of electrophilic reagents. Thus, **10** reacted with α-cyanocinnamonitrile **2a** to give 6*H*-2-benzopyrano[4,3-*c*]quinoline **11**. This was assumed to form via addition of the methyl function in **10** to the activated double bond in **2a** to give the acyclic Michael adduct, which readily cyclizes and loses hydrogen cyanide to yield the final isolable, thermodynamically-stable compound **11**. Dehydrocyanation has been reported for the formation of similar systems [2, 3]. Unlike the behavior of **10** towards **2a**, compound **10** reacted with ethyl α-cyanocinnamate **2c** to give the corresponding ester derivative **12**, via hydrogen cyanide elimination [11]. Attempts to prepare **12** from **13** and ethyl



Scheme 2

cyanoacetate under the same experimental conditions were unsuccessful and finally the reaction was carried out in the presence of pyridine.

We believe that, in contrast to the addition of **2c** to **10** in the reaction of **13** with ethyl cyanoacetate, the enamine **14** formed by another mechanistic pathway via addition of the methylene group of ethyl cyanoacetate to the cyano function in **13**. This then undergoes an internal 4 + 2 cycloaddition, followed by a 1,5-hydrogen shift and elimination of carbon monoxide and ethanol to give the final product **11**. The intermediate of this reaction product may form because its cyano group is highly conjugated with the enamine moiety; moreover, the hydrogen bonding in the cyclic intermediate facilitates the elimination of carbon monoxide and ethanol rather than HCN.

The reaction of **1b,c** with elemental sulfur and malononitrile (scheme 4), performed in boiling ethanolic solution in the presence of triethylamine, furnishes the thieno[2,3-*b*]pyridine derivatives **17**. IR spectra of **17** revealed the presence of amino and carbonyl functions, and the absence of cyano groups. This reaction is proposed to proceed as shown in scheme 4 and involves the condensation of **1** with the malononitrile dimer which exists in equilibrium with malononitrile [12] to give the intermediate **14**. The latter then reacted with elemental sulfur to give the mercapto derivative **15**, which cyclized by nucleophilic attack of the mercapto group at the cyano function to give the 3-substituted quinolines **16**. Hydrolysis then yielded **17** [13].

Experimental section

All melting points are uncorrected and measured on a Griffin & George MBF O10T (London) apparatus. Recorded yields correspond to the pure products. IR (KBr) spectra were recorded on a Perkin Elmer Sp-880 spectrophotometer at the Faculty of Science, New Damietta el Mansoura University, and ^{1}H NMR spectra were measured on a Varian 270 MHz spectrometer using TMS as an internal standard (chemical shifts are given as δ, ppm). The mass spectra were recorded and microanalysis performed at the Microanalytical Unit at Cairo University and the National Research Center, Giza, Egypt.

Preparation of 4H-pyrano[3,2-c]quinolines **6**

- *Method A*

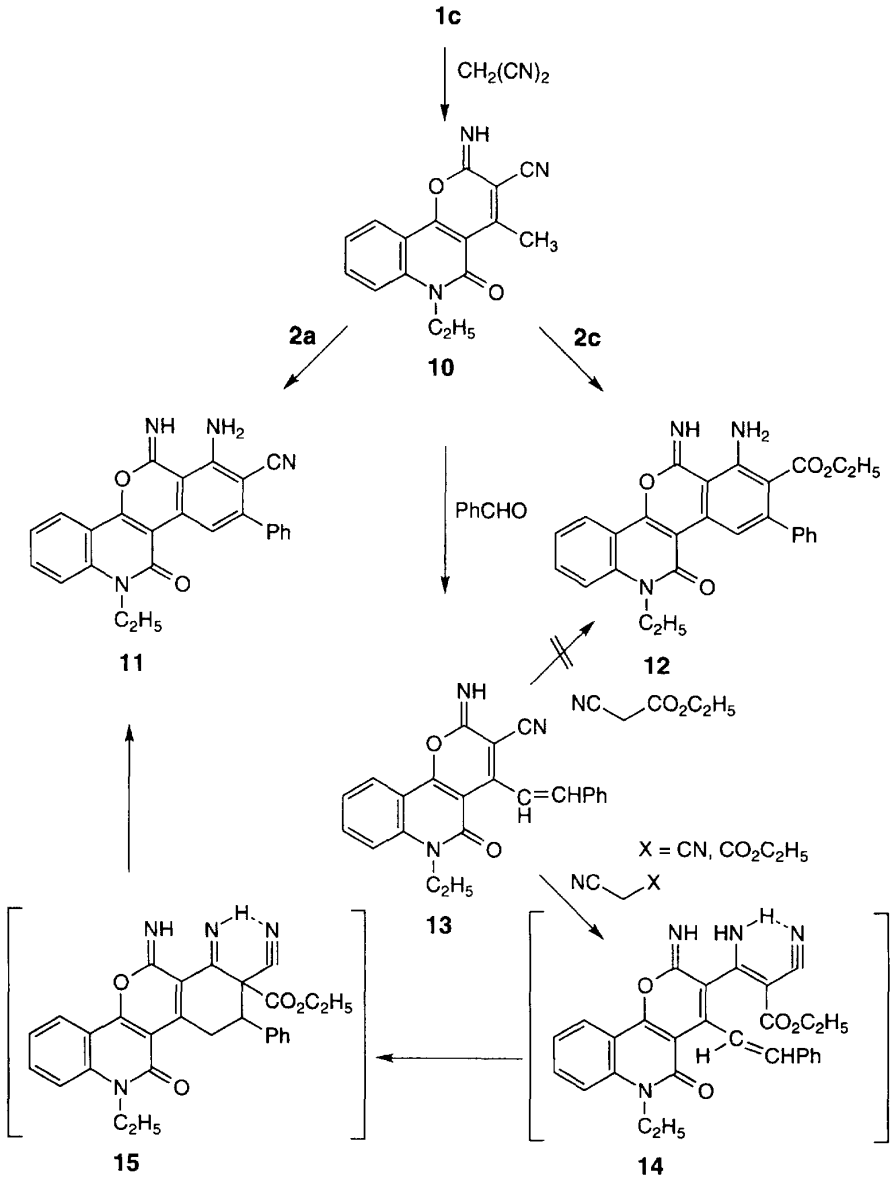
To a suspension of **1a,c,d** (0.01 mol) in ethanol (50 mL) containing two drops of triethylamine, 0.01 mol of the ylidenenitriles **2b,d** were added. The reaction mixture was refluxed for 1 h. The solid products formed were filtered and crystallized from methanol/DMF to give **6**.

- *Method B*

A mixture of **1e–g** (0.01 mol) and **2b,d** (0.01 mol) in ethanol in the presence of a catalytic amount of triethylamine also yielded **6**.

- *2-Amino-5-oxo-4-(2-thienyl)-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile* **6a**

Colorless crystals (2.1 g, 65%), mp 293–295 °C.



Scheme 3

Anal calc for $C_{17}H_{11}N_3O_2S$ (321.36): C 63.54, H 3.45, N 13.08; found: C 63.31, H 3.56, N 13.22.

IR: 3 470, 3 310 (NH_2, NH), 2 210 (CN), 1 678 (CO), 1 630 (δ NH_2).

^{1}H NMR (DMSO-d_6): 4.87 (s, 1H, pyran 4-H); 6.92–7.92 (m, 9H, ArH + NH_2); 11.90 (s, 1H, NH).

MS: m/z 321 (M^+).

• *2-Amino-6-ethyl-5-oxo-4-(2-thienyl)-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile* **6b**

Pale yellow crystals (2.1 g, 60%), mp 257–259 °C.

Anal calc for $C_{19}H_{15}N_3O_2S$ (349.41): C 65.31, H 4.33, N 12.03; found: C 65.11, H 4.4, N 12.12.

IR: 3 480, 3 315 (NH_2), 2 210 (CN), 1 670 (CO), 1 635 (δ NH_2).

• *2-Amino-5-oxo-6-phenyl-4-(2-thienyl)-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile* **6c**

Colorless crystals (2.5 g, 66%), mp 282–285 °C.

Anal calc for $C_{23}H_{15}O_3N_2S$ (397.46): C 69.50, H 3.80, N 10.57; found: C 69.22, H 4.03, N 10.13.

IR: 3 300, 3 170 (NH_2), 2 200 (CN), 1 675 (CO), 1 630 (δ NH_2).

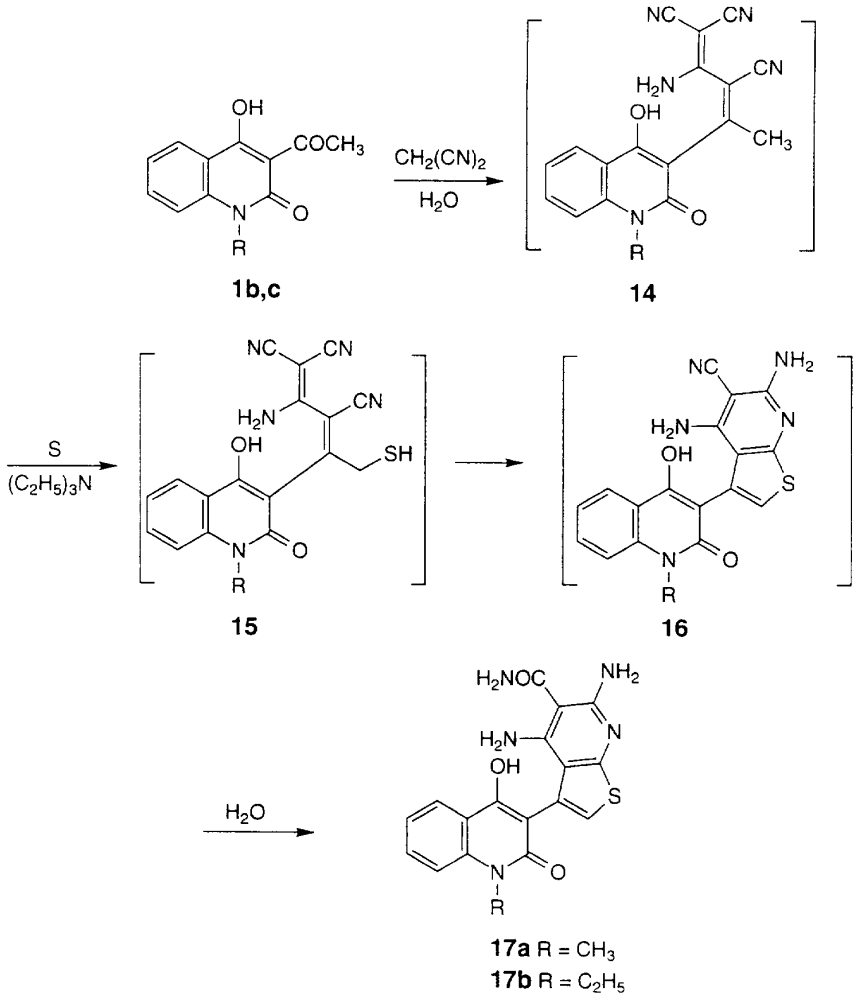
^{1}H NMR (DMSO-d_6): 4.92 (s, 1H, pyran 4-H); 6.58–8.09 (m, 14H, 12H, ArH + 2H, NH_2).

• *Ethyl 2-amino-5-oxo-4-(2-thienyl)-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carboxylate* **6d**

Colorless crystals (2.3 g, 62%), mp 280–283 °C.

Anal calc for $C_{19}H_{16}N_2O_4S$ (368.41): C 61.94, H 4.38, N 7.60; found: C 62.01, H 4.21, N 7.34.

IR: 3 400–3 300 (NH_2), 1 690 (CO), 1 660 (CO).



Scheme 4

MS: m/z 368 (M^+).

- *Ethyl 2-amino-6-ethyl-5-oxo-4-(2-thienyl)-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carboxylate* **6e**

Pale yellow crystals (2.4 g, 60%), mp 253–255 °C.

Anal calc for $C_{21}H_{20}N_2O_4S$ (396.47): C 63.62, H 5.46, N 7.58; found: C 63.51, H 5.64, N 7.60.

IR: 3 480, 3 315 (NH_2), 2 210 (CN), 1 670 (CO), 1 635 (δ NH_2).

^{1}H NMR (DMSO-d_6): 1.16–1.23 (t, J = 7 Hz, 6H, $2CH_3$); 4.29–4.32 (q, J = 7 Hz, 4H, $2CH_2$); 5.27 (s, 1H, pyran 4-H); 6.83–8.11 (m, 9H, 7H, ArH + 2H, NH_2).

- *Ethyl 2-amino-5-oxo-6-phenyl-4-(2-thienyl)-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carboxylate* **6f**

Colorless crystals (2.7 g, 61%), mp 266–268 °C.

Anal calc for $C_{25}H_{20}N_2O_4S$ (444.51): C 67.55, H 4.53, N 6.30; found: C 67.26, H 4.82, N 6.27.

IR: 3 500–3 300 (NH_2); 1 690 (CO), 1 670 (CO).

Formation of **9**

A mixture of **1c,d** or **1f,g** (0.01 mol), acetaldehyde (0.01 mol) and malononitrile (0.01 mol) in ethanol (50 mL) was refluxed for 3 h in the presence of a few drops of piperidine. The reaction mixture was left to cool at room temperature. The precipitate was collected by filtration, crystallized from ethanol/dioxane and then identified as **9a,b**.

- *2-Amino-6-ethyl-4-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile* **9a**

Pale yellow crystals (1.7 g, 61%), mp 275–277 °C.

Anal calc for $C_{16}H_{15}N_3O_2$ (281.32): C 68.31, H 5.37, N 14.94; found: C 68.11, H 5.45, N 15.03.

IR: 3 400, 3 356 (NH_2), 2 195 (CN), 1 670 (CO).

- *2-Amino-4-methyl-5-oxo-6-phenyl-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile* **9b**

Yellowish crystals (2.1 g, 64%), mp 272–274 °C.

Anal calc for $C_{20}H_{15}N_3O_2$ (239): C 72.94, H 4.59, N 12.76; found: C 73.10, H 4.61, N 12.57.

IR: 3 416, 3 300, 3 165 (NH_2), 2 195 (CN), 1 675 (CO).

^1H NMR (DMSO-d_6): 1.17–1.20 (d, J = 8 Hz, 3H, CH_3); 3.56–3.63 (q, J = 8 Hz, 1H, CH); 6.5–8.18 (m, 11H, ArH + NH_2).

Formation of 6-ethyl-2-imino-4-methyl-5-oxo-5,6-dihydro-2H-pyrano[3,2-c]quinoline-3-carbonitrile **10**

To a mixture of **1c** (0.01 mol), ammonium acetate (2 g) and glacial acetic acid (2 mL) in dry benzene (100 mL) was added malononitrile (0.01 mol). The mixture was heated under reflux for 4 h in a Dean Stark apparatus. Evaporation of most of the benzene gave a residue which was crystallized from ethanol to give **10** as yellow crystals (1.8 g, 64%), mp 264–266 °C.

Anal calc for $C_{16}H_{13}N_3O_2$ (279.30): C 68.81, H 4.69, N 15.05; found: C 68.52, H 4.89, N 15.21.

IR: 3 450–3 400 (NH), 2 200 (CN), 1 665 (CO).

^1H NMR (DMSO-d_6): 1.09–1.21 (t, J = 7 Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.14–4.28 (q, J = 7 Hz, 2H, CH_2), 5.86 (s, 1H, NH), 7.16–7.78 (m, 4H, ArH).

Condensation of **10** *with benzaldehyde: preparation of 6-ethyl-2-imino-5-oxo-4-styryl-5,6-dihydro-2H-pyrano[3,2-c]quinoline-3-carbonitrile* **13**

A solution of **12** (0.01 mol) and benzaldehyde (0.01 mol) in ethanol (30 mL) with 0.1 mL piperidine was refluxed for 3 h. The solvent was removed in vacuo and the remaining products were triturated with a little water. The resulting solid, obtained on standing, was collected by filtration and crystallized from ethanol to give **13** as colorless crystals (2.3 g, 63%), mp 225–227 °C.

Anal calc for $C_{23}H_{17}N_3O_2$ (367.41): C 75.19, H 4.66, N 11.44; found: C 75.34, H 4.88, N 17.65.

IR: 2 200 (CN); 1 650 (CO); 1 620 (C=C).

Reaction of **10** *with* **2a,c**: *synthesis of 6H-2-benzopyrano[4,3-c]quinolines* **11** *and* **12**

- *Method A*

A solution of **10** (0.01 mol) in ethanol (30 mL) **2a** or **2c** (0.01 mol) and a few drops of piperidine was refluxed for 3 h. The resulting solids were collected by filtration, recrystallized from ethanol/DMF and then identified as **11** and **12** respectively.

- *Method B*

A suspension of **13** (0.01 mol) in ethanol (30 mL) was treated with malononitrile or ethyl cyanoacetate (0.01 mol) and dry pyridine (1 mL). The mixture was refluxed for 5 h and the solvent was concentrated in vacuo and crystallized (mp and mixed mps as **11**).

- *7-Amino-12-ethyl-6-imino-11-oxo-9-phenyl-11,12-dihydro-6H-2-benzopyrano[4,3-c]quinoline-8-carbonitrile* **11**

Colorless crystals (2.5 g, 62%), mp 245–247 °C.

Anal calc for $C_{25}H_{18}N_4O_2$ (406.45): C 73.88, H 4.46, N 13.78; found: C 73.71, H 4.18, N 13.55.

IR: 3 380, 3 320, 3 200 (NH_2, NH), 2 200 (CN), 1 680, 1 675 (CO), 1 630 (δ NH_2).

^1H NMR (DMSO-d_6): 1.06–1.19 (t, J = 7 Hz, 3H, CH_3), 4.05–4.31 (q, J = 7 Hz, 2H, CH_2), 4.53 (s, 1H, NH), 7.13–8.09 (m, 12H, ArH + NH_2).

- *Ethyl 7-amino-12-ethyl-6-imino-11-oxo-9-phenyl-11,12-dihydro-6H-2-benzopyrano[4,3-c]quinoline-8-carboxylate* **12**

Colorless crystals (2.8 g, 62%), mp 238–240 °C.

Anal calc for $C_{27}H_{23}N_3O_4$ (453.50): C 71.51, H 5.11, N 9.27; found: C 71.73, H 5.34, N 9.22.

IR: 3 390, 3 330 (NH_2, NH), 1 700, 1 645 (CO).

Synthesis of **17**

A solution of **1b** or **1c** (0.01 mol) in ethanol (30 mL) was treated with malononitrile (0.01 mol), elemental sulfur (0.01 mol) and triethylamine (0.01 mol). The reaction mixture was heated under reflux for 1 h. The solid deposited was filtered, crystallized from ethanol/DMF and then identified as **17**.

- *4,6-Diamino-3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)thieno[2,3-b]pyridine-5-carboxamide* **17a**

Pale yellow crystals (2.3 g, 60%), mp 287–289 °C.

Anal calc for $C_{18}H_{15}N_5O_3S$ (381.41): C 56.68, H 3.96, N 18.36; found: C 56.41, H 4.12, N 18.48.

IR: 3 450, 3 340 (NH_2, OH), 1 685, 1 650 (CO).

^1H NMR (DMSO-d_6): 2.98 (s, 2H, NH_2), 3.75 (s, 3H, NCH_3), 7.32–8.11 (m, 5H, ArH + OH + $2NH_2$).

MS: m/z 381 (M^+).

- *4,6-Diamino-3-(1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)thieno[2,3-b]pyridine-5-carboxamide* **17b**

Faint brown crystals (2.5 g, 63%), mp 250–252 °C.

Anal calc for $C_{19}H_{17}N_5O_3S$ (395.44): C 57.53, H 4.32, N 17.66; found: C 57.72, H 4.35, N 17.54.

IR: 3 435–3 340 (NH_2, OH), 1 670, 1 645 (CO).

MS: m/z 395 (M^+).

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