

## Nitriles in Heterocyclic Synthesis. Synthesis and Reactions of Pyrano[3,2-*h*]quinoline Derivatives

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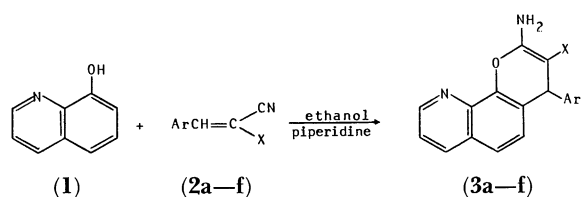
8-Quinololinol reacts with cinnamonnitrile derivatives in presence of a basic catalyst to afford pyrano[3,2-*h*]quinolines (**3a–f**). The reaction of **3a** with reagents such as acetic anhydride/pyridine, formamide, formic acid/formamide, and carbon disulfide gave the fused heterotetracyclic systems pyrimido[4',5':6,5]pyrano[3,2-*h*]quinolines.

A variety of pyrans and condensed pyrans were prepared recently by utilizing nitriles as starting materials.<sup>1–5</sup> The cinnamonnitrile derivatives react with different heterocyclic compounds containing hydroxyl group to produce condensed pyran derivatives.<sup>6–8</sup> Within this respect and also for continuation of our work for the synthesis of heterocycles containing the quinoline moiety,<sup>9,10</sup> the present work is aimed to synthesize different pyrano[3,2-*h*]quinolines.

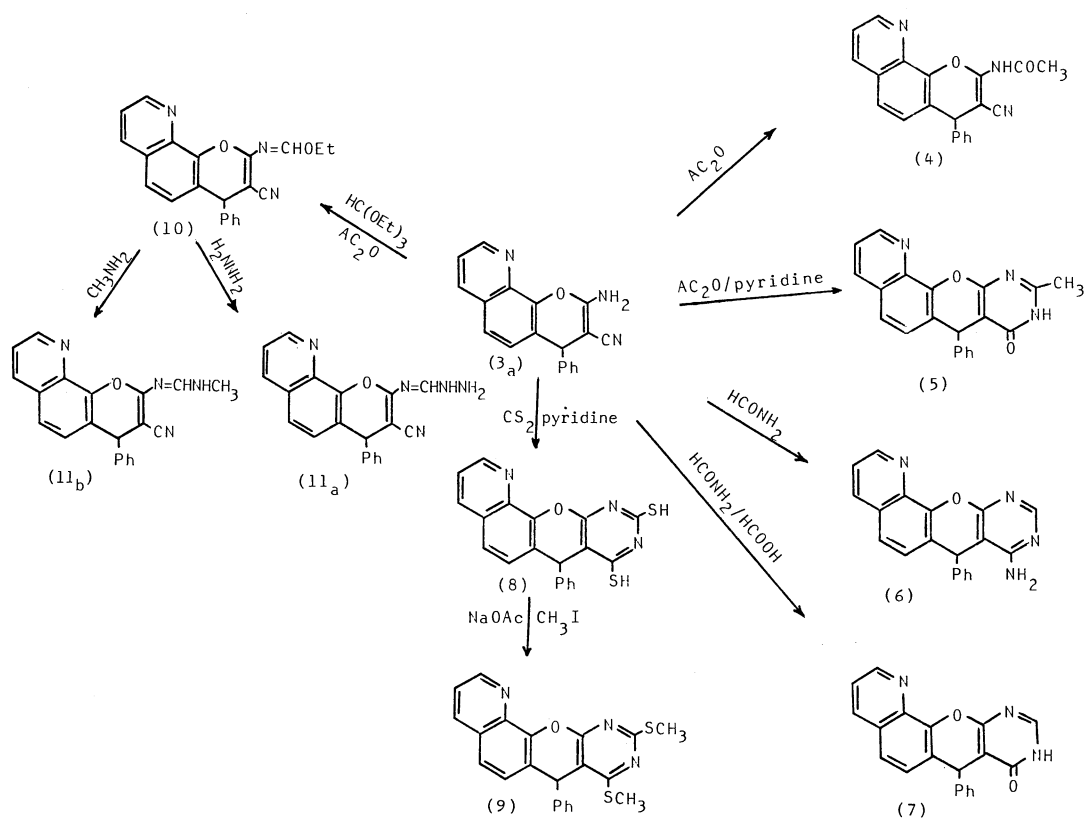
### Results and Discussion

8-Quinololinol (**1**) reacts with cinnamonnitrile derivatives (**2a–f**) in an ethanolic solution in the presence of piperidine to afford 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitriles (**3a–c**) or ethyl 2-

amino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carboxylates (**3d–f**) in moderate yield.



X	Ar
a; CN	C <sub>6</sub> H <sub>5</sub>
b; CN	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
c; CN	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>
d; COOEt	C <sub>6</sub> H <sub>5</sub>
e; COOEt	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>
f; COOEt	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>



Scheme 1.

Table 1. Physical and Spectral Data of Compounds 3–12

Compd No.	Mp/°C (Solvent)	Yield/% (Color)	Molecular formula <sup>a)</sup>	IR		<sup>1</sup> H NMR	
				cm <sup>-1</sup>		$\delta$	
<b>3a</b>	225–226 (Ethanol)	72 (Buff)	C <sub>19</sub> H <sub>13</sub> N <sub>3</sub> O	3460, 3340 (NH <sub>2</sub> ), 2200 (CN).		(DMSO- <i>d</i> <sub>6</sub> ) 4.9 (s, 1H, CH pyran), 7.1 (s, 2H, NH <sub>2</sub> ), 7.2–8.9 (m, 10H, arom.).	
<b>3b</b>	219–220 (Ethanol)	70 (Pale brown)	C <sub>20</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	3420, 3300 (NH <sub>2</sub> ), 2200 (CN).		(DMSO- <i>d</i> <sub>6</sub> ) 3.9 (s, 3H, CH <sub>3</sub> ), 5.0 (s, 1H, CH), 6.8–9.0 (m, 11H, NH <sub>2</sub> and arom.).	
<b>3c</b>	223–224 (Ethanol)	68 (Buff)	C <sub>19</sub> H <sub>12</sub> ClN <sub>3</sub> O	3460, 3320 (NH <sub>2</sub> ), 2200 (CN).		(DMSO- <i>d</i> <sub>6</sub> ) 5.1 (s, 1H, CH pyran), 7.0 (s, 2H, NH <sub>2</sub> ), 7.1–9.0 (m, 9H, arom.).	
<b>3d</b>	184–185 (Ethanol)	74 (Pale yellow)	C <sub>21</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	3400, 3300 (NH <sub>2</sub> ), 1680 (C=O).		(CDCl <sub>3</sub> ) 1.3 (t, 3H, CH <sub>3</sub> ), 4.1 (q, 2H, CH <sub>2</sub> ), 5.1 (s, 1H, CH), 6.7 (s, 2H, NH <sub>2</sub> ), 7.1–8.9 (m, 10H, arom.).	
<b>3e</b>	193–194 (Ethanol)	66 (Yellow)	C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub>	3420, 3300 (NH <sub>2</sub> ), 1690 (C=O).		(CDCl <sub>3</sub> ) 1.3 (t, 3H, CH <sub>3</sub> ), 3.9 (s, 3H, CH <sub>3</sub> ), 4.1 (q, 2H, CH <sub>2</sub> ), 5.0 (s, 1H, CH), 6.6 (s, 2H, NH <sub>2</sub> ), 6.8–8.9 (m, 9H, arom.).	
<b>3f</b>	197–198 (Ethanol)	62 (Pale yellow)	C <sub>21</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>3</sub>	3400, 3300 (NH <sub>2</sub> ), 1680 (C=O).		(CDCl <sub>3</sub> ) 1.3 (t, 3H, CH <sub>3</sub> ), 4.1 (q, 2H, CH <sub>2</sub> ), 5.0 (s, 1H, CH), 6.7 (s, 2H, NH <sub>2</sub> ), 6.7–8.9 (m, 9H, arom.).	
<b>4</b>	257–258 (Acetic acid)	85 (Pale yellow)	C <sub>21</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	3200 (NH), 2220 (CN), 1700 (C=O).		(DMSO- <i>d</i> <sub>6</sub> ) 2.3 (s, 3H, CH <sub>3</sub> ), 4.9 (s, 1H, CH), 7.0–8.9 (m, 10H, arom.).	
<b>5</b>	356–357 (Acetic acid)	52 (Brown)	C <sub>21</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	3100 (NH), 1660 (C=O).		(CF <sub>3</sub> COOH) 2.8 (s, 3H, CH <sub>3</sub> ), 5.1 (s, 1H, CH), 6.9–9.0 (m, 10H, arom.).	
<b>6</b>	333–334 (Ethanol)	50 (Brown)	C <sub>20</sub> H <sub>14</sub> N <sub>4</sub> O	3420, 3300 (NH <sub>2</sub> ).		(DMSO- <i>d</i> <sub>6</sub> ) 5.1 (s, 1H, CH), 6.8–9.1 (m, 13H, NH <sub>2</sub> and arom.).	
<b>7</b>	281–282 (Ethanol)	66 (White)	C <sub>20</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	3100 (NH), 1650 (C=O).		(DMSO- <i>d</i> <sub>6</sub> ) 4.9 (s, 1H, CH), 6.2 (s, 1H, NH), 7.1–9.1 (m, 11H, CH and arom.).	
<b>8</b>	284–285 (Dioxane)	68 (Yellow)	C <sub>20</sub> H <sub>13</sub> N <sub>3</sub> OS <sub>2</sub>	3120, 3100 (2NH), 1230 (C=S).		(CF <sub>3</sub> COOH) 5.2 (s, 1H, CH), 6.9–9.1 (m, 10H, arom.).	
<b>9</b>	194–195 (Ethanol)	84 (White)	C <sub>22</sub> H <sub>17</sub> N <sub>3</sub> OS <sub>2</sub>	2990 (CH, aliph.), 1630 (C=N).		(CDCl <sub>3</sub> ) 2.6 (s, 6H, 2CH <sub>3</sub> ), 5.0 (s, 1H, CH), 7.2–9.0 (m, 10H, arom.).	
<b>10</b>	147–148 (Ethanol)	82 (Pale yellow)	C <sub>22</sub> H <sub>17</sub> N <sub>3</sub> O	2220 (CN).		(CDCl <sub>3</sub> ) 1.3 (t, 3H, CH <sub>3</sub> ), 4.3 (q, 2H, CH <sub>2</sub> ), 4.9 (s, 1H, CH), 7.1–8.9 (m, 11H, CH and arom.).	
<b>11a</b>	211–212 (Ethanol)	80 (White)	C <sub>20</sub> H <sub>15</sub> N <sub>5</sub> O	3380, 3300 (NHNH <sub>2</sub> ), 2200 (CN).		(DMSO- <i>d</i> <sub>6</sub> ) 4.9 (s, 1H, CH), 5.3 (s, 1H, NH), 5.8 (s, 2H, NH <sub>2</sub> ), 7.1–9.0 (m, 11H, CH and arom.).	
<b>11b</b>	177–178 (Ethanol)	74 (White)	C <sub>21</sub> H <sub>16</sub> N <sub>4</sub> O	3320 (NH), 2200 (CN).		(CDCl <sub>3</sub> ) 3.3 (s, 3H, CH <sub>3</sub> ), 4.9 (s, 1H, CH pyran), 5.6 (s, 1H, NH), 7.1–9.2 (m, 11H, CH and arom.).	

a) All products gave satisfactory microanalysis (C,  $\pm 0.36$ ; H,  $\pm 0.22$ ; N,  $\pm 0.23$ ; S,  $\pm 0.28\%$ ).

Compound **3** was subjected for further reactions to produce fused heterotetracyclic systems incorporating pyrimidine nucleus in addition to pyranoquinoline moiety. Thus the reaction of **3a**, with acetic anhydride/pyridine mixture gave pyrimidopyranoquinoline **5**, while reaction of **3a** with acetic anhydride alone gave the acetamido derivative **4**. Interaction of **3a** with formamide afforded aminopyrimidine derivative **6**, while the reaction with formamide/formic acid mixture gave pyrimidinone derivative **7**.

The reaction of **3a** with carbon disulfide in pyridine proceeded through the addition of CS<sub>2</sub> on the amino group followed by cyclization by nucleophilic attack of the sulfur atom on the cyano group which underwent rearrangement to give pyrimidinedithiol derivative **8**.<sup>11,12</sup> Compound **8** reacted smoothly with methyl iodide in ethanol containing anhydrous sodium acetate to give bis(methylthio) derivative **9**.

Also, refluxing of **3a** with ethyl orthoformate in acetic anhydride gave the corresponding ethoxymethyleneamino derivative **10**. The latter compound further reacted with hydrazine hydrate or methylamine to give the corresponding derivatives **11a,b**, respectively. Attempts to cyclize compound **11a** by refluxing in ethanol containing piperidine and/or pyridine were unsuccessful.

### Experimental

Melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam spectrophotometer. <sup>1</sup>H NMR spectra were obtained on 90 MHz Varian spectrometer in suitable deuterated solvent using TMS as internal standard. Analytical data were obtained by the microanalytical data Unit at Assiut University.

**2-Amino-4-aryl-4H-pyrano[3,2-*h*]quinoline-3-carbonitriles (3a—c) and Ethyl 2-Amino-4-aryl-4H-pyrano[3,2-*h*]quinoline-3-carboxylates (3d—f).** **General Procedure.** A mixture of cinnamionitrile derivative (**2a—f**) (0.01 mol) and 8-quinolinol (0.01 mol) was refluxed in absolute ethanol (50 ml) containing a catalytic amount of piperidine for 5 h. The reaction mixture was concentrated, cooled and the precipitated product was collected by filtration. The physical and spectral data are summarized in Table 1.

**2-Acetamido-4-phenyl-4H-pyrano[3,2-*h*]quinoline-3-carbonitrile (4).** A mixture of **3a** (0.01 mol) was refluxed in acetic anhydride for 3 h, then cooled and poured onto ice/water mixture. The solid product thus formed was filtered off and washed several times with water.

**10-Methyl-7-phenyl-7H-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinolin-8(9H)-one (5).** A solution of **3a** (0.01 mol) in Ac<sub>2</sub>O/pyridine mixture (30 ml, 2:1 v/v) was heated on a water bath for 8 h, then cooled, and poured into ice/water mixture. The precipitate thus formed was collected by filtration and washed several times with water.

**8-Amino-7-phenyl-7H-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinoline (6).** A mixture of **3a** (0.01 mol) and formamide (20 ml) was refluxed for 1 h. After cooling the precipitated

brown crystalline product was filtered off and washed several times with cold ethanol.

**7-Phenyl-7H-pyrimido[4',5':6,5]pyrano[2,3-*h*]quinolin-8(9H)-one (7).** A mixture of **3a** (0.01 mol) and formic acid (5 ml) in formamide (20 ml) was refluxed for 2 h. After cooling the reaction mixture was poured onto ice/water mixture and the solid product thus formed was filtered off.

**7-Phenyl-7H-pyrimido[4',5':6,5]pyrano[3,2-*h*]quinolin-8,10-dithiol (8).** A mixture of **3a** (0.01 mol) and carbon disulfide (5 ml) in pyridine (30 ml) was heated on water bath for 8 h. The solid product thus formed was filtered off while hot and washed several times with ethanol.

**8,10-Bis(methylthio)-7-phenyl-7H-pyrimido[4',5':2,3]-pyrano[3,2-*h*]quinoline (9).** A mixture of **8** (0.001 mol) and methyl iodide (2 ml) in ethanol (30 ml) in the presence of anhydrous sodium acetate (2 g) was refluxed for 2 h. The reaction mixture was concentrated, poured into cold water and the solid product was collected by filtration.

**2-(Ethoxymethyleneamino)-4-phenyl-4H-pyrano[3,2-*h*]quinoline-3-carbonitrile (10).** A mixture of **3a** (0.01 mol) and ethyl orthoformate (2 ml) in acetic anhydride (10 ml) was refluxed for 1 h. After cooling the precipitated pale yellow crystalline product was filtered off and washed several times with cold ethanol.

**2-(Hydrazinomethyleneamino)-4-phenyl-4H-pyrano[3,2-*h*]quindine-3-carbonitrile (11a) and 2-(Methylaminomethyleneamino)-4-phenyl-4H-pyrano[3,2-*h*]quinoline-3-carbonitrile (11b).** **General Procedure:** A mixture of **10** (0.01 mol) and hydrazine hydrate or methylamine (0.01 mol) in absolute ethanol (50 ml) was stirred at room temperature for 15 min. The precipitated products (**11a** or **11b**) were collected by filtration.

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