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

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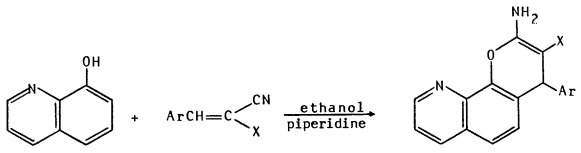
8-Quinolinol reacts with cinnamonitrile derivatives in presence of a basic catalyst to afford pyrano[3,2-*h*]quinolines (**3a—f**). The reaction of **3a** with reagents such as acetic anhydride/pyridine, formamide, formic acid/formamide, and carbon disulfide gave the fused heterotetracyclic systems pyrimido[4′,5′:6,5]pyrano[3,2-*h*]quinolines.

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

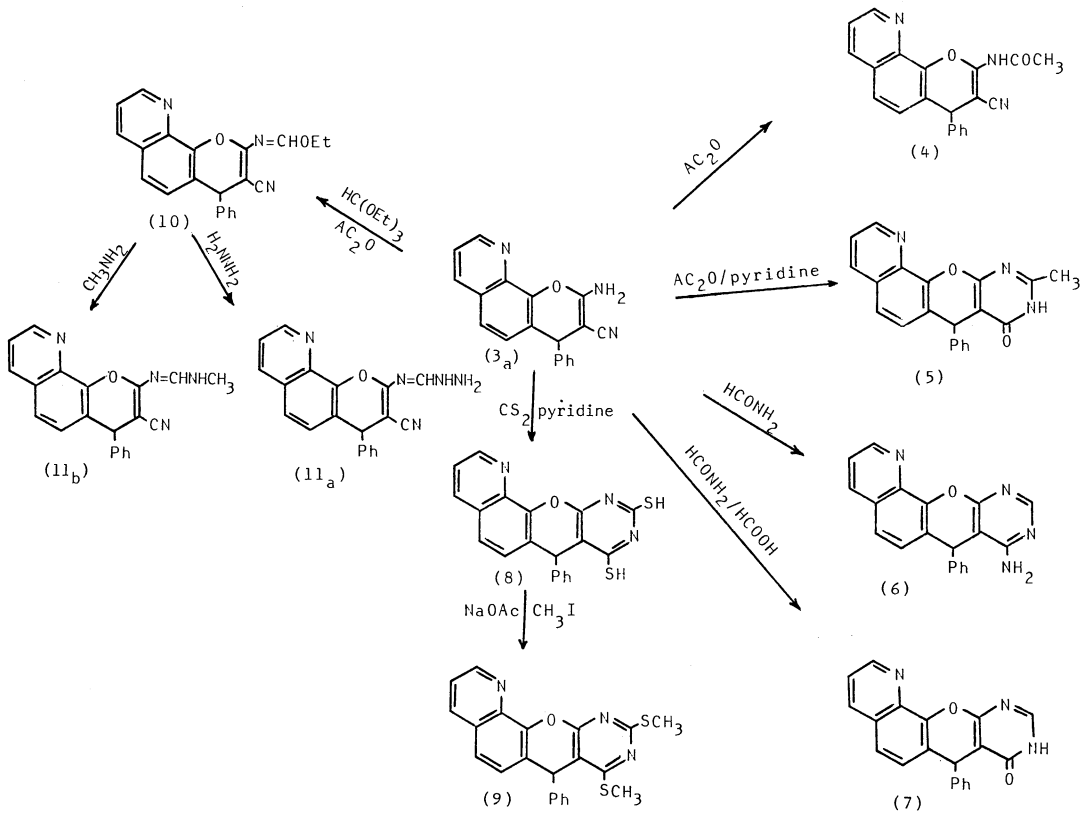
Results and Discussion

8-Quinolinol (**1**) reacts with cinnamonitrile 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.



(**1**) (**2a—f**) (**3a—f**)

	X	Ar
a;	CN	C_6H_5
b;	CN	*p*-$CH_3OC_6H_4$
c;	CN	*p*-ClC_6H_4
d;	COOEt	C_6H_5
e;	COOEt	*p*-$CH_3OC_6H_4$
f;	COOEt	*p*-ClC_6H_4



Scheme 1.

Table 1. Physical and Spectral Data of Compounds **3—12**

Compd No.	Mp/°C (Solvent)	Yield/% (Color)	Molecular formula[a)]	IR cm^{-1}	^{1}H NMR δ
3a	225—226 (Ethanol)	72 (Buff)	$C_{19}H_{13}N_3O$	3460, 3340 (NH_2), 2200 (CN).	(DMSO-d_6) 4.9 (s, 1H, CH pyran), 7.1 (s, 2H, NH_2), 7.2—8.9 (m, 10H, arom.).
3b	219—220 (Ethanol)	70 (Pale brown)	$C_{20}H_{15}N_3O_2$	3420, 3300 (NH_2), 2200 (CN).	(DMSO-d_6) 3.9 (s, 3H, CH_3), 5.0 (s, 1H, CH), 6.8—9.0 (m, 11H, NH_2 and arom.).
3c	223—224 (Ethanol)	68 (Buff)	$C_{19}H_{12}ClN_3O$	3460, 3320 (NH_2), 2200 (CN).	(DMSO-d_6) 5.1 (s, 1H, CH pyran), 7.0 (s, 2H, NH_2), 7.1—9.0 (m, 9H, arom.).
3d	184—185 (Ethanol)	74 (Pale yellow)	$C_{21}H_{18}N_2O_3$	3400, 3300 (NH_2), 1680 (C=O).	($CDCl_3$) 1.3 (t, 3H, CH_3), 4.1 (q, 2H, CH_2), 5.1 (s, 1H, CH), 6.7 (s, 2H, NH_2) 7.1—8.9 (m, 10H, arom.).
3e	193—194 (Ethanol)	66 (Yellow)	$C_{22}H_{20}N_2O_4$	3420, 3300 (NH_2), 1690 (C=O).	($CDCl_3$) 1.3 (t, 3H, CH_3), 3.9 (s, 3H, CH_3), 4.1 (q, 2H, CH_2), 5.0 (s, 1H, CH), 6.6 (s, 2H, NH_2), 6.8—8.9 (m, 9H, arom.).
3f	197—198 (Ethanol)	62 (Pala yellow)	$C_{21}H_{17}ClN_2O_3$	3400, 3300 (NH_2), 1680 (C=O).	($CDCl_3$) 1.3 (t, 3H, CH_3), 4.1 (q, 2H, CH_2), 5.0 (s, 1H, CH), 6.7(s, 2H, NH_2), 6.7—8.9 (m, 9H, arom.).
4	257—258 (Acetic acid)	85 (Pale yellow)	$C_{21}H_{15}N_3O_2$	3200 (NH), 2220 (CN), 1700 (C=O).	(DMSO-d_6) 2.3 (s, 3H, CH_3), 4.9 (s, 1H, CH), 7.0—8.9 (m, 10H, arom.), 9.2 (s, 1H, NH).
5	356—357 (Acetic acid)	52 (Brown)	$C_{21}H_{15}N_3O_2$	3100 (NH), 1660 (C=O).	(CF_3COOH) 2.8 (s, 3H, CH_3), 5.1 (s, 1H, CH), 6.9—9.0 (m, 10H, arom.).
6	333—334 (Ethanol)	50 (Brown)	$C_{20}H_{14}N_4O$	3420, 3300 (NH_2).	(DMSO-d_6) 5.1 (s, 1H, CH), 6.8—9.1 (m, 13H, NH_2 and arom.).
7	281—282 (Ethanol)	66 (White)	$C_{20}H_{13}N_3O_2$	3100 (NH), 1650 (C=O).	(DMSO-d_6) 4.9 (s, 1H, CH), 6.2 (s, 1H, NH), 7.1—9.1 (m, 11H, CH and arom.).
8	284—285 (Dioxane)	68 (Yellow)	$C_{20}H_{13}N_3OS_2$	3120, 3100 (2NH), 1230 (C=S).	(CF_3COOH) 5.2 (s, 1H, CH), 6.9—9.1 (m, 10H, arom.).
9	194—195 (Ethanol)	84 (White)	$C_{22}H_{17}N_3OS_2$	2990 (CH, aliph.), 1630 (C=N).	($CDCl_3$) 2.6 (s, 6H, $2CH_3$), 5.0 (s, 1H, CH), 7.2—9.0 (m, 10H, arom.).
10	147—148 (Ethanol)	82 (Pale yellow)	$C_{22}H_{17}N_3O$	2220 (CN).	($CDCl_3$) 1.3 (t, 3H, CH_3),4.3 (q, 2H, CH_2), 4.9 (s, 1H, CH), 7.1—8.9 (m, 11H, CH and arom.).
11a	211—212 (Ethanol)	80 (White)	$C_{20}H_{15}N_5O$	3380, 3300 ($NHNH_2$), 2200 (CN).	(DMSO-d_6) 4.9 (s, 1H, CH), 5.3 (s, 1H, NH), 5.8 (s, 2H, NH_2), 7.1—9.0 (m, 11H, CH and arom.).
11b	177—178 (Ethanol)	74 (White)	$C_{21}H_{16}N_4O$	3320 (NH), 2200 (CN).	($CDCl_3$) 3.3 (s, 3H, CH_3), 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, ±0.36; H, ±0.22; N, ±0.23; S, ±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_2 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**.[11,12] 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. ^1H NMR spectra were obtained on 90 MHz Varian spectrometer in suitable deutrated solvent using TMS as internal standard. Analytical data were obtained by the microanalytical data Unit at Assiut University.

2-Amino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitriles (3a—c) and Ethyl 2-Amino-4-aryl-4*H*-pyrano[3,2-*h*]-quinoline-3-carboxylates (3d—f). General Procedure. A mixture of cinnamonitrile 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-4*H*-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-7*H*-pyrimido[4′,5′:6,5]pyrano[3,2-*h*]quinolin-8(9*H*)-one (5). A solution of **3a** (0.01 mol) in Ac_2O/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-7*H*-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-7*H*-pyrimido[4′,5′:6,5]pyrano[2,3-*h*]quinolin-8(9*H*)-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-7*H*-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-7*H*-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-4*H*-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 severl times with cold ethanol.

2-(Hydrazinomethyleneamino)-4-phenyl-4*H*-pyrano[3,2-*h*]quindine-3-carbonitrile (11a) and 2-(Methylaminomethyl-eneamino)-4-phenyl-4*H*-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.

References

1) L. Juergen and H. Horst, Ger. Offen. 106331 (1974); *Chem. Abstr.*, **82**, 97939 (1975).
2) P. Czerney and H. Hartmann, *J. Prakt. Chem.*, **324**, 21 (1982).
3) O. H. Hartwig and S. Herbert, *Monatsh. Chem.*, **110**, 279 (1979).
4) M. Quinteiro, C. Seoane, and J. L. Soto, *Tetrahedron Lett.*, **1977**, 1835.
5) M. Quinteiro, C. Seoane, and J. L. Soto, *J. Heterocycl. Chem.*, **15**, 57 (1978).
6) S. Abdou, S. M. Fahmy, K. U. Sadek, and M. H. Elnagdi, *Heterocycles*, **16**, 2177 (1981).
7) Z. E. Kandeel, K. M. H. Hilmy, F. M. Abdel-Razek, and M. H. Elnagdi, *Chem. Ind. (London)*, **1984**, 33.
8) H. A. Daboun, S. E. Abdou, M. M. Husein, and M. H. Elnagdi, *Synthesis*, **6**, 502 (1982).
9) Z. H. Khalil, A. S. Yanni, A. A. Khalaf, A. A. Abdel-Hafez, and R. F. Abdo, *Bull. Chem. Soc. Jpn.*, **61**, 1345 (1988).
10) Z. H. Khalil, A. A. Abdel-Hafez, A. S. Yanni, and A. M. Moharam, *Bull. Chem. Soc. Jpn.*, **61**, 4143 (1988).
11) E. C. Taylor, A. Mckckillop, and R. N. Warrener, *Tetrahedron*, **23**, 891 (1967).
12) A. Aviran and S. Vramer, *Chem. Ind. (London)*, **1967**, 1452.