Synthesis of Several Polyfunctionally Substituted Fused Pyrimidines Incorporating Quinone Compounds

A. K. Khalafallah,* R. M. Abd El-Aal and N. A. A. El-Kanzi
Chemistry Department, Aswan-Faculty of Science, South Valley University, Aswan, Egypt

The synthesis of several new polyfunctionally substituted fused pyrimidines via reaction of 2-amino 1,4-naphthoquinone 2 with different reagents is described.

Keywords: Pyrimidine; Alkylidine malononitrile; Diazonium salts of aromatic amine.

INTRODUCTION

Polyfunctionally substituted heteroaromatics are biologically interesting molecules, and their synthesis has recently received considerable attention.[1-3] In previous work we have reported several synthese of azoles,[4] azines,[5] and benzoazines,[6] which are required as potential biodegradable agrochemicals. Among these are the considerable biological activities of pyridines and pipridinopyridines as antischistosomal agents[7] and antimetabolities.[8] As a part of a biological chemistry project in our laboratories, samples of certain polyfunctionally substituted fused pyrimidines were required.

RESULTS AND DISCUSSION

Our initial strategy of the synthesis of newly fused 4-amino-2-methyl-5,10-dioxo-1,5,10,11-tetrahydro-benz[g]-quinoline-3-carbonitrile **1** was synthesised by cycloaddition reaction of equimolecular ratios of an appropriate alkylidene malononitrile and 1,4-naphthoquinone in ethanol containing piperidine as catalyst. At first our theoretical conception of the obvious cycloaddition reaction led to the formation of compound **1′**. But the experimental evidence that depends on the different types of analysis to the reaction product proves that the cycloaddition reaction leads to the formation of compounds **1**[9] through the electronic cyclization according to the suggested mechanism (Scheme I illustrates the formation of compound **1**). By using the same pathway, we synthesised 4-amino-2-methyl-5,6,11-trioxo-1,4,4′a,5,6,11,12,12a-octahydro-1,12-diazanaphthacene-3-carbonitrile **2**[9] by cycloaddition reaction of benz[g]-1,2,3,4-tetrahydroquinoline 4,5,10-trione which was prepared in our laboratory as it has been reported in an earlier publication[10] with equimolar ratios of an appropriate alkylidene malononitrile in ethanol containing piperidine as catalyst.

The structures of the newly synthesised compounds **1,2** were confirmed by elemental analysis, IR, ^{1}H-NMR and mass spectral data [cf. Tables 1,2,3].

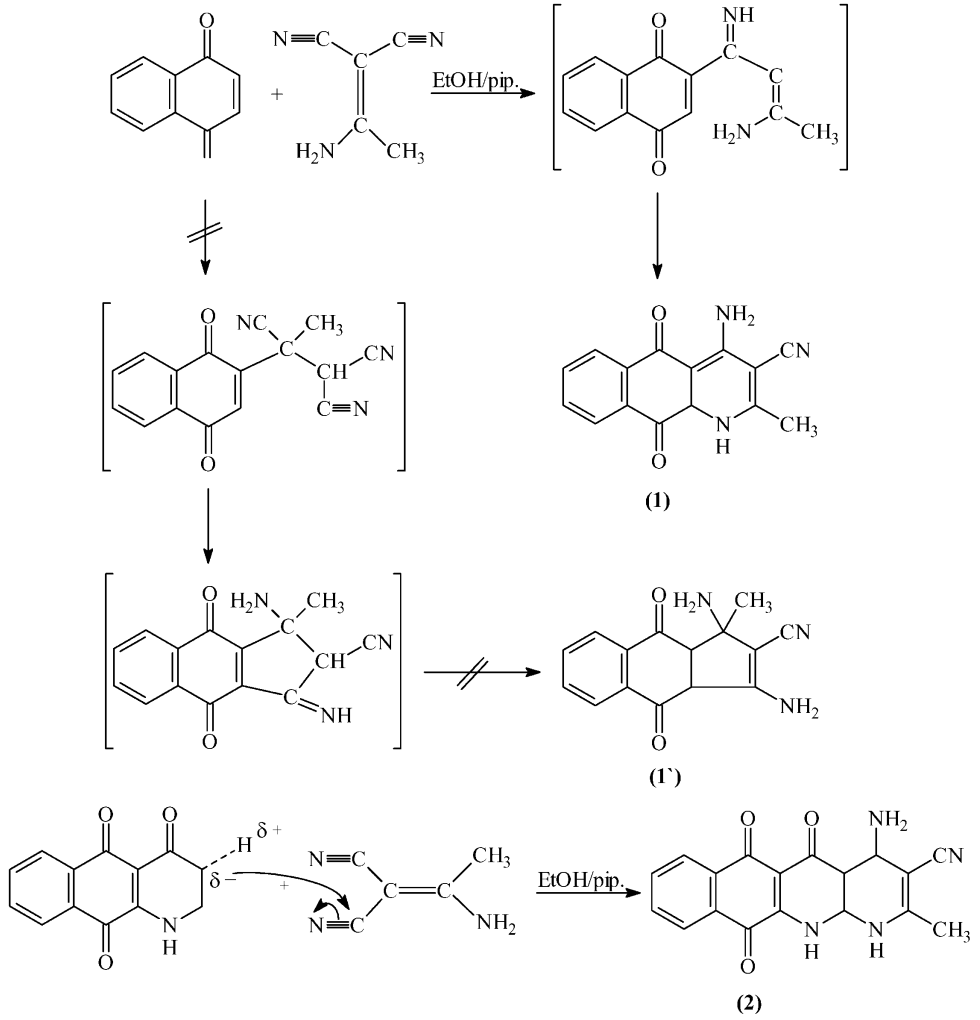
Also the activation exerted by the cyano group at C_3 on the exocyclic methyl group at C2 render it available for the reaction with different diazonium salts of aromatic amine, thus compound (**3a-c**) was synthesised by the reaction of different diazonium salts of aromatic amine with compound **1**. The structure of compound (**3a-c**) was confirmed by elemental analysis, IR, ^{1}H-NMR spectra and mass spectra (cf. Tables 1,2,3).

Compound (**4a-c**) was prepared with the same pathway by reaction of compound **2** with different diazonium salts of aromatic amine which led to the formation of compound (**4a-c**). The structure of compound (**4a-c**) was confirmed by elemental analysis, IR, ^{1}H-NMR spectra and mass spectra (cf. Tables 1,2,3).

The activity of the methylene group render it avaliable for the reaction of compound (**3a-c**) with ethyl cyanoacetate; the reaction can lead to two different pathways giving compounds (**5a-c**) or (**5′a-c**). The ^{1}H-NMR spectrum of the product in DMSO sign to the absence of the singlet for the ester group thus the structure of compound (**5a-c**) was confirmed by elemental analysis, IR, ^{1}H-NMR and mass spectra (cf. Tables 1,2,3). Also compound (**6a-c**) was prepared by the same pathways; the ^{1}H-NMR spectrum of the product in DMSO showed the absence of the singlet for the ester group. Thus the reaction product (**6a-c**) was confirmed by elemental analysis, IR, ^{1}H-NMR spectra and mass spectra (cf. Tables 1,2,3). Thus the spectrum analysis does not support the structure (**6′a-c**).

Compounds **1** and **2** undergo acidic hydrolysis by acetic aid in the presence of a few drops of concentrated hydrochlo-

Scheme I



ric acid in to the carboxylic group. Thus the structures of both carboxylic compounds 4-amino-2-methyl-1H-benz[g]quinoline-5,10-dione-3-carboxylic acid **7** and 4-amino-2-methyl-1,2,3-trihydropiperidino[2,3-b]-benz[g]-1,2,3,4-trihydroquinoline-5,6,11-trion-3-carboxylic acid **8** were confirmed by elemental analysis, IR, ^{1}H-NMR and mass spectra (cf. Tables 1,2,3).

Compounds **7** and **8** react with different diazonium salts of aromatic amine to give compounds (**9a-c**) and (**10a-c**). The structures of compounds (**9a-c**) and (**10a-c**) was confirmed by elemental analysis, IR, ^{1}H-NMR and mass spectra (cf. Tables 1,2,3).

The activity of the methylene group in compounds (**9a-c**) and (**10a-c**) render it available for the reaction of compounds (**9a-c**) and (**10a-c**) with ethyl cyanoacetate; the reaction leads to the formation of compounds (**11a-c**) and (**12a-c**) but not (**11′a-c**) and (**12′a-c**) depending upon the ^{1}H-NMR spectra which showed the absence of signals signed to the ester group. The structures of compounds (**11a-c**) and (**12a-c**) were confirmed by elemental analysis, IR, ^{1}H-NMR and mass spectra (cf. Tables 1,2,3).

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were measured as Kbr pellets on a Pye-Unicam sp 1000 spectrophotometer. ^{1}H-NMR spectra were recorded in [$^2H_6$] dimethylsulfoxide at 200 MHz on a Varian Gemini NMR spectrometer using Mesi as internal reference. Mass spectra were obtained on a Shimadzu GCMs-QP 1000 EX mass spectrometer at 70 eV. Elemental analysis were carried out at the Microanalytical

Table 1.

Comp. No.	Yield %	mp.	Crystal solvent	Mol. Formula	Mol. wt	MS
1	65	270	EtOH	$C_{15}H_{11}O_2N_3$	265.27	266 (M^{+1})
2	70	190	EtOH	$C_{18}H_{14}O_3N_4$	334.15	338 (M^{+4})
3a	69	> 300	DMF	$C_{21}H_{15}O_2N_5$	369.38	369
3b	75	> 300	DMF	$C_{21}H_{15}O_3N_5$	385.38	385
3c	73	> 300	DMF	$C_{21}H_{14}O_4N_6$	414.38	414
4a	69	> 300	DMF	$C_{24}H_{18}O_3N_6$	438.44	438
4b	80	> 300	DMF	$C_{24}H_{18}O_4N_6$	454.44	454
4c	84	> 300	DMF	$C_{24}H_{17}O_5N_7$	483.44	483
5a	70	> 300	DMF	$C_{24}H_{16}O_3N_6$	436.43	436
5b	76	> 300	DMF	$C_{24}H_{16}O_4N_6$	452.43	452
5c	80	> 300	DMF	$C_{24}H_{15}O_5N_7$	481.43	481
6a	85	> 300	DMF	$C_{27}H_{19}O_4N_7$	505.49	505
6b	80	> 300	DMF	$C_{27}H_{19}O_5N_7$	521.49	521
6c	83	> 300	DMF	$C_{27}H_{18}O_6N_8$	550.49	551 (M^{+1})
7	71	230	EtOH	$C_{15}H_{12}O_4N_2$	284.27	284
8	66	185	EtOH	$C_{18}H_{15}O_5N_3$	353.33	353
9a	70	> 300	DMF	$C_{21}H_{16}O_4N_4$	388.38	388
9b	68	> 300	DMF	$C_{21}H_{16}O_5N_4$	404.38	404
9c	75	> 300	DMF	$C_{21}H_{15}O_6N_5$	433.38	433
10a	69	> 300	DMF	$C_{24}H_{19}O_5N_5$	457.44	457
10b	76	> 300	DMF	$C_{24}H_{19}O_6N_5$	473.44	473
10c	70	> 300	DMF	$C_{24}H_{18}O_7N_6$	502.44	502
11a	80	> 300	DMF	$C_{24}H_{17}O_5N_5$	455.43	455
11b	83	> 300	DMF	$C_{24}H_{17}O_6N_5$	471.43	471
11c	85	> 300	DMF	$C_{24}H_{16}O_7N_6$	500.43	500
12a	84	> 300	DMF	$C_{27}H_{20}O_6N_6$	524.49	526 (M^{+2})
12b	80	> 300	DMF	$C_{27}H_{20}O_7N_6$	540.49	540
12c	83	> 300	DMF	$C_{27}H_{19}O_8N_7$	569.49	569

Center of Cairo University.

Synthesis of 4-amino-2-methyl-5,10-dioxo-1,5,10,11-tetrahydrobenzo[g]quinoline-3-carbonitrile 1

A solution of the appropriate acetamidine malononitrile was prepared in situ from the reaction of the acetamide and malononitrile (0.01 mole) in ethanol (20 mL) containing two drops of piperidine and treated with 1,4-naphthoquinone (0.01 mol); the reaction mixture was heated under reflux for 8-10 hr. The solvent was then evaporated under reduced pressure and poured onto ice/water acidified by HCl; the solid product so formed was collected by filtration and crystallized from ethanol.

Synthesis of 4-amino-2-methyl-5,6,11-trioxo-1,4,4a,5,6,11,12,12a-octahydro-1,12-diazanaphthacene-3-carbonitrile 2

A solution of the appropriate acetamidine malononitrile was prepared as above and treated with benz[g]1,2,3,4-tetrahydroquinoline (0.01) mole. The reaction mixture was heated under reflux for 8-10 hr. The solvent was then evaporated under reduced pressure. Poured onto ice/water acidified by HCl, the solid product so formed was collected by filtration and crystallized from ethanol.

Synthesis of azodye (3a-c) and (4a-d)

A solution of compounds **1** and or **2** (0.01 mol) in ethanol was reacted with diazonium salt of **2** different aromatic amine (0.01 mol); the reaction product was cooled and collected by filtration and crystallized from the proper solvent to give the title compounds.

Synthesis of compounds (5a-d) and (6a-c)

A solution of compounds (**3a-c**) and or (**4a-c**) (0.01 mol) in ethanol (20 mL) was treated with ethylcyano acetate (0.01 mol) in the presence of a few drops of piperidine; the reaction mixture was heated under reflux for 10-12 h. The solvent was then evaporated under reduced pressure and poured onto ice/water acidified by HCl; the solid product so formed was collected by filtration and crystallized from the proper

Table 2.

Comp. No.	IR (υ_{max}/cm^{-1})	(Calcd.) Found		
		C	H	N
1	2216 (C≡N), 3400-3100 (NH, NH_2), 1640 (C=O).	(67.92) 67.90	(4.18) 4.15	(15.84) 15.80
2	2206 (C≡N), 3350-3200 (NH, NH_2), 1640 (C=O).	(64.70) 64.65	(4.22) 4.10	(16.77) 16.66
3a	2220 (C≡N), 3400-3100 (NH, NH_2), 1655 (C=O).	(68.29) 68.28	(4.09) 4.07	(18.96) 18.95
3b	2214 (C≡N), 3450-3100 (NH, NH_2), 1650 (C=O).	(65.45) 65.43	(3.92) 3.91	(18.17) 18.16
3c	2210 (C≡N), 3400-3150 (NH, NH_2), 1655 (C=O).	(60.87) 60.86	(3.41) 3.40	(20.28) 29.27
4a	2210 (C≡N), 3400-3100 (NH, NH_2), 1645 (C=O).	(65.75) 65.74	(4.14) 4.13	(19.17) 19.15
4b	2208 (C≡N), 3400-3100 (NH, NH_2), 1640 (C=O).	(63.43) 63.41	(3.99) 3.98)	(18.49) 18.47
4c	2215 (C≡N), 3400-3100 (NH, NH_2), 1655 (C=O).	(59.63) 59.62	(3.54) 3.52	(20.28) 20.27
5a	2218 (C≡N), 3400-3100 (NH_2, NH), 1645 (C=O).	(66.05) 66.04	(3.69) 3.68	(19.26) 19.25
5b	2217 (C≡N), 3450-3100 (NH_2, NH), 1655 (C=O).	(63.72) 63.71	(3.56) 3.55	(18.58) 18.57
5c	2220 (C≡N), 3400-3100 (NH_2, NH), 1650 (C=O).	(59.88) 59.87	(3.14) 3.12	(20.37) 20.35
6a	2213 (C≡N), 3450-3100 (NH_2, NH), 1645 (C=O).	(64.16) 64.15	(3.79) 3.78	(19.39) 19.38
6b	2215 (C≡N), 3400-3100 (NH_2, NH), 1644 (C=O).	(62.19) 62.18	(3.67) 3.65	(18.80) 18.79
6c	2219 (C≡N), 3400-3100 (NH_2, NH), 1650 (C=O).	(58.91) 58.90	(3.29) 3.27	(20.36) 20.35
7	3500-3150 (NH_2, NH, OH).	(63.44) 63.42	(4.25) 3.23	(9.85) 9.84
8	3350-3100 (NH_2, NH, OH), 1640 (C=O).	(61.19) 61.17	(4.28) 4.27	(11.89) 11.88
9a	3500-3100 (NH_2, NH, OH), 1645 (C=O), 2206 (C≡N).	(64.94) 64.93	(4.15) 4.13	(14.43) 14.42
9b	3500-3100 (NH, NH_2, OH), 1650 (C=O), 2210 (C≡N).	(62.38) 62.36	(3.99) 3.98	(13.86) 13.85
9c	3500-3100 (NH, NH_2, OH), 1655 (C=O), 2215 (C≡N).	(58.20) 58.19	(3.49) 3.47	(3.23) 3.22
10a	3500-3150 (NH, NH_2, OH), 1645 (C=O), 2216 (C≡N).	(63.02) 63.01	(4.19) 4.17	(15.31) 15.30
10b	3500-3100 (NH, NH_2, OH), 1644 (C=O), 2220 (C=N).	(60.89) 60.88	(4.05) 4.03	(14.79) 14.78
10c	3500-3150 (NH, NH_2, OH), 1645 (CO), 2217 (C≡N).	(57.37) 57.36	(3.61) 3.60	(16.73) 16.72
11a	3500-3100 (NH, NH_2, OH), 1640 (C=O), 2212 (C≡N).	(63.29) 63.28	(3.76) 3.75	(15.38) 15.36
11b	3500-3150 (NH, NH_2, OH), 1645 (C=O), 2213 (C≡N)	(61.15) 61.13	(3.64) 3.63	(14.86) 14.84
11c	3500-3100 (NH, NH_2, OH), 1640 (C=O), 2216 (C≡N).	(57.60) 57.59	(3.22) 3.21	(16.97) 16.95
12a	3500-3150 (NH, NH_2, OH), 1644 (C=O), 2218 (C≡N).	(61.83) 61.81	(3.84) 3.82	(16.02) 16.01
12b	3500-3100 (NH, NH_2, OH), 1645 (C=O), 2216 (C≡N).	(60.00) 60.00	(3.73) 3.72	(15.55) 15.54
12c	3500-3100 (NH, NH_2, OH), 1640 (C=C), 2214 (C≡N).	(56.95) 56.94	(3.36) 3.35	(17.22) 17.20

Table 3.

Comp. No.	^{1}H-NMR (DMSO) δ ppm
1	3.43 (s, 3H, CH_3), 8.1-7.3 (m, 5H, aromatic protons and heterocyclic hydrogen), 6.7 (s, 2H, NH_2), 10.2 (s, 1H, NH).
2	3.44 (s, 3H, CH_3), 5.73 (s, 2H, NH_2), 8.01-7.48 (m, 7H, aromatic protons and heterocyclic hydrogen), 12, 41 (s, 2H, two NH).
7	3.42 (s, 3H, CH_3), 8.11-7.25 (m, 5H, aromatic protons and heterocyclic hydrogen), 6.65 (s, 2H, NH_2), 10.22 (s, 1H, NH), 10.5 (s, 1H, OH).
8	3.45 (s, 3H, CH_3), 8.2-7.47 (m, 7H, aromatic protons and heterocyclic hydrogen), 5.75 (s, 2H, NH_2), 10.55 (s, 1H, OH).
3a	5.7 (s, 2H, NH_2), 8.1-7.2 (m, 11H, aromatic protons and heterocyclic hydrogens), 12.25 (br. s., 2H, 2NH).
4a	5.76 (s, 2H, NH_2), 8.01-7.1 (m, 15H, aromatic protons and heterocyclic hydrogens), 12.24 (br. s., 1H, NH).
5a	5.75 (s, 2H, NH_2), 8.1-7.01 (m, 14H, aromatic protons and heterocyclic hydrogens).
6a	5.77 (s, 2H, NH_2), 8.01-7.1 (m, 16H, aromatic protons and heterocyclic hydrogens), 12.25 (brs. s., 1H, NH).

solvent to give the title compounds (**5a-c**) and (**6a-c**).

Synthesis of 4-amino-2-methyl-1H-benz[g]quinoline-5,10-dione-3-carboxylic acid (7) and 4-amino-2-methyl-1,2,3-trihydropiperidino[2,3-b] benz[g]-1,2,3,4-trihydroquinoline-5,6,11-trion-3-carboxilic acid (8)

A solution of **1** and or **2** (0.01 mole) in glacial acetic acid (20 mL) containing a few drops of concentrated hydrochloric acid respectively was heated under reflux for 6-7 h. The solvent was then evaporated under reduced pressure and the residue treated with alkali solution of sodium hydroxide; the solid product was collected by filtration and crystallized from ethanol to give the title compounds.

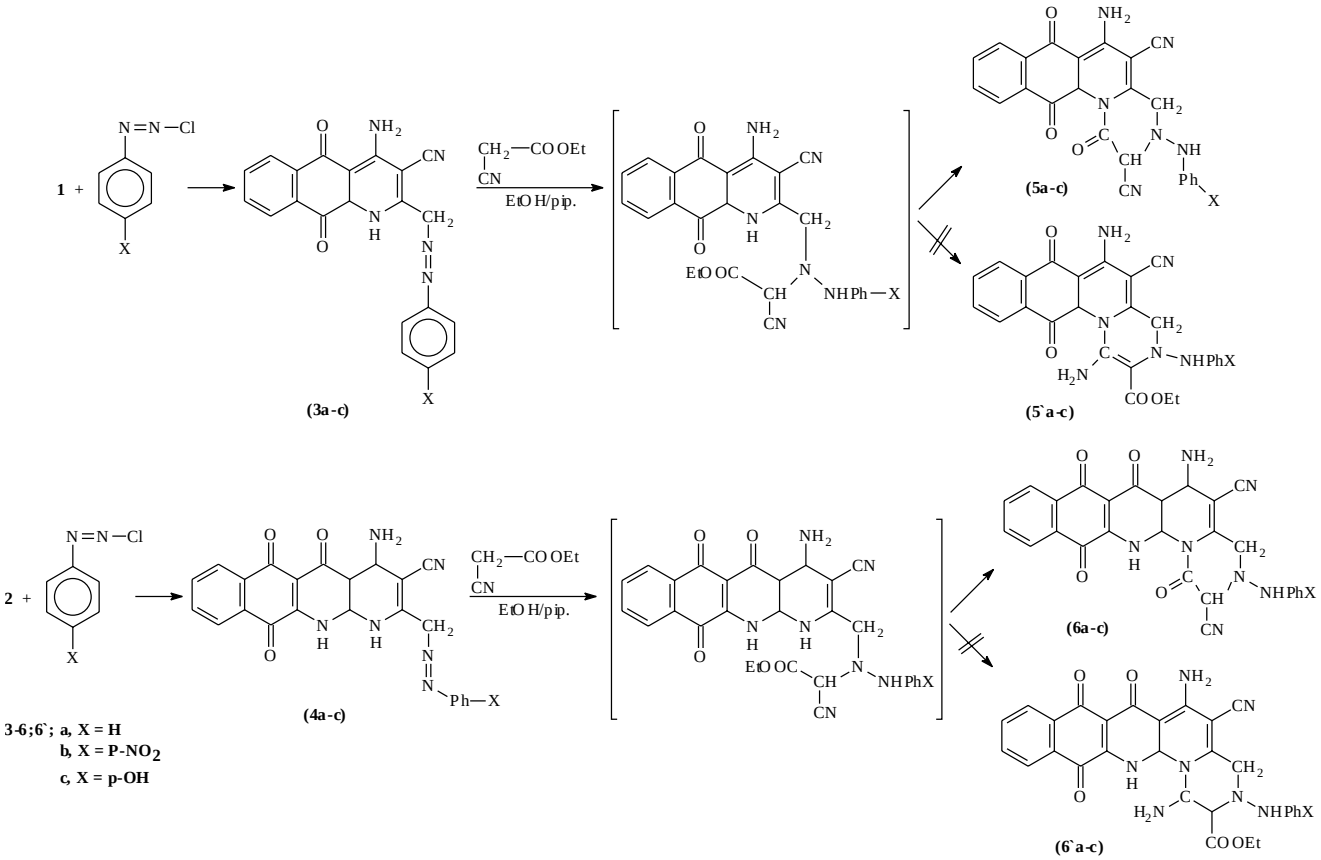
Synthesis of azodye (9a-c) and (10a-c)

A solution of compounds **7** and or **8** (0.01 mol) in ethanol was reacted with diazonium salt of a different aromatic amine (0.01 mol). The reaction product was cooled and collected by filtration and crystallized from the proper solvent to give the title compounds.

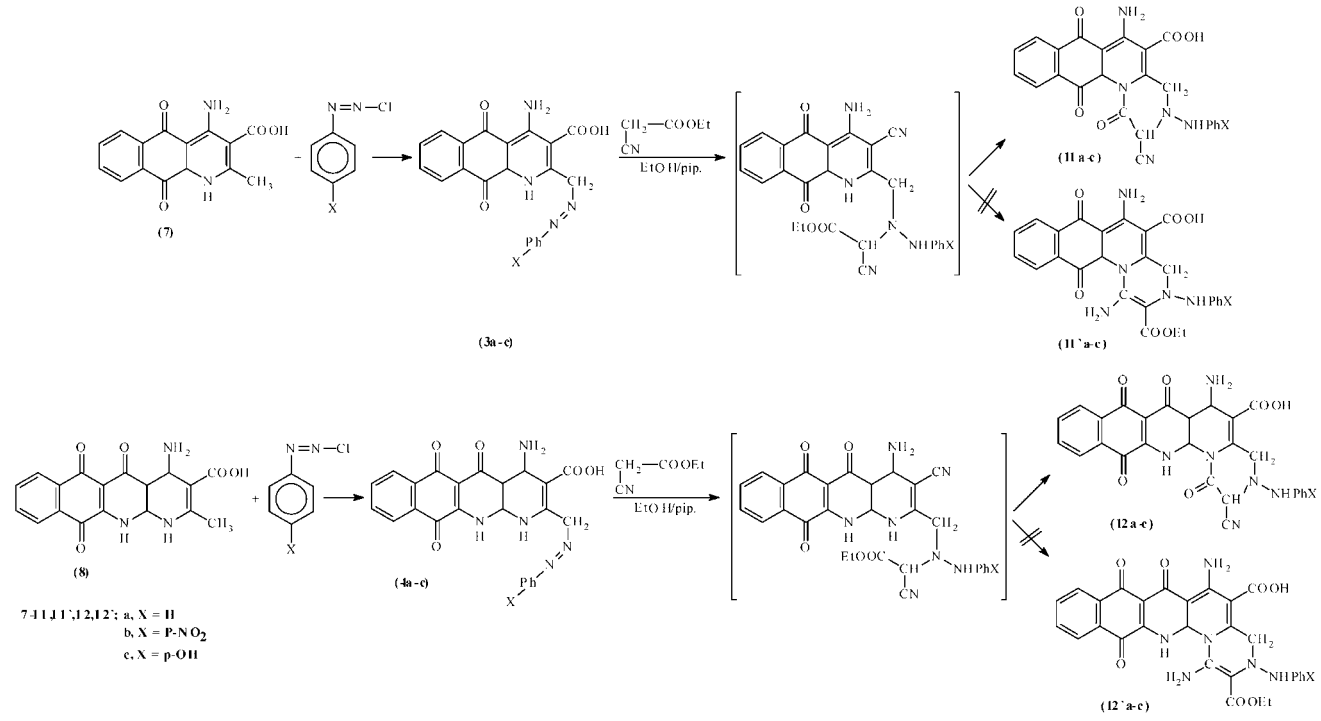
Synthesis of compounds (11a-c) and (12a-c)

A solution of compounds (**9a-c**) and or (**10a-c**) (0.01 mol) in ethanol (20 mL) was treated with ethylcyano acetate (0.01 mol) in the presence of a few drops of piperidine; the reaction mixture was heated under reflux for 10-12 h. The sol-

Scheme II



Scheme III



vent was then evaporated under reduced pressure and poured onto ice/water acidified by HCl; the solid product so formed was collected by filtration and crystallized from the proper solvent to give the title compounds (**11a-c**) and (**12a-c**).

Received July 16, 2003.

REFERENCES

1. Freeman, F. *Synthesis* **1981**, 925.
2. Tominaga, Y.; Honkawa, Y.; Hara, M.; Hosomi, A. *J. Heterocyclic Chem*. **1990**, *27*, 775.
3. Hanefeld, M.; Ress, C. W.; White, A. J. P.; Williams, D. J. *J. Chem. Soc. Perkin Trans*. **1996**, *1*, 1545.
4. Sadek, K. U.; Abohadid, K.; elghandour, A. H. H. *Liebigs Am. Chem*. **1989**, 501.
5. Sadek, K. U.; Elnagdi, M. H. *Synthesis* **1988**, 483.
6. Elnagdi, M. H.; Ibraheim, N. S.; Sadek, K. U.; Mohamed, M. H. *Liebigs Am. Chem*. **1988**, 1995.
7. Sadek, K. U.; Mourad, A. F. E.; Abdelhafeez, A. E.; Elnagdi, M. H. *Synthesis* **1983**, 739.
8. Robins, R. K. *J. Am. chem. Soc*. **1956**, *78*, 784.
9. Khalafallah, A. K.; Abd El-Aal, R. M.; El-Kanzi, N. A. A. *J. Chin. Chem. Soc*. **2002**, *49(3)*, 387.
10. Loven, L.; Brawn; Summer Fard, W. T. J. *Chem. Eng. Data* **1966**, *11*, 264.