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THREE COMPONENT CONDENSATION OF 6-QUINOLYLAMINE WITH AROMATIC ALDEHYDES AND CYCLOHEXYL 1,3-DIKETONES

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A three component condensation of 6-quinolylamine with 4-bromo-or 4-methoxybenzaldehyde, and 1,3-cyclohexanedione or dimedone gave 12-(4-bromophenyl)- and 12-(4-methoxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-7H-benzo[b][4,7]phenanthrolin-11-ones. The reaction intermediates obtained were N-arylmethylene-6-quinolylamines, 2-arylmethylenebis(1,3-cyclohexanediones), 3-(6-quinolylamino)-2-cyclohexenone, and 5,5-dimethyl-3-(6-quinolylamino)-2-cyclohexenone.

Keywords: arylaldehydes, arylmethylene-6-quinolylamines, 2-arylmethylenebis(1,3-cyclohexanediones), 12-aryl-8,9,10,12-tetrahydro-7H-benzo[*b*][4,7]phenanthrolin-11-ones, dimedone, 6-quinolylamine, 3-(6-quinolylamino)-2-cyclohexenone, 1,3-cyclohexanedione

Up to this time various multi component reactions have been widely used in synthetic organic chemistry, including the chemistry of heterocyclic compounds [1, 2]. Such reactions include the three component condensation of aromatic amines with aldehydes and CH-acids and were the basis of novel methodology developed by us for the synthesis of polycondensed nitrogen containing heterocycles of the aza- and diazaphenanthrene series [3-6], which are of promise as light sensitive materials, luminophores, and bioactive material with a broad range of action [7-9].

With the object of preparing novel 4,7-phenanthrolines we have studied in this work the condensation of 6-quinolylamine **1** with the substituted benzaldehydes **2a,b** and the cyclic β-diketones 1,3-cyclohexanedione **3a** and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) **3b**.

The reactions were carried out by heating an equimolar mixture of reagents in *n*-butanol. Thanks to the high reactivity of the β-dicarbonyl compound its reaction with the amine and aldehyde in alcoholic medium occurs in the absence of a catalyst, the role of which is fulfilled by the proton of the dissociated enol form of the β-diketone. On the basis of previous investigations [4, 5] we proposed that the final products of the cascade of heterocyclization are the 8-aryl-7,8,9,10,11,12-hexahydrobenzo[*a*][4,7]phenanthrolin-11-ones **A**, these being formed *via* reaction of the 6-quinolylamine **1** with arylaldehydes with separation of the Schiff bases **5a,b**, addition of a molecule of 1,3-diketone to the C=N bond of the azomethine, and the following cyclocondensation of the product **B**. However, on the basis of the ^{1}H NMR spectroscopic data (Table 1) we have shown that the reaction results selectively in the structures formed (which are isomeric with **A**) and these are the 12-aryl-8,9,10,12-tetrahydro-7H-benzo[*b*][4,7]phenanthrolin-11-ones **4a,b**.

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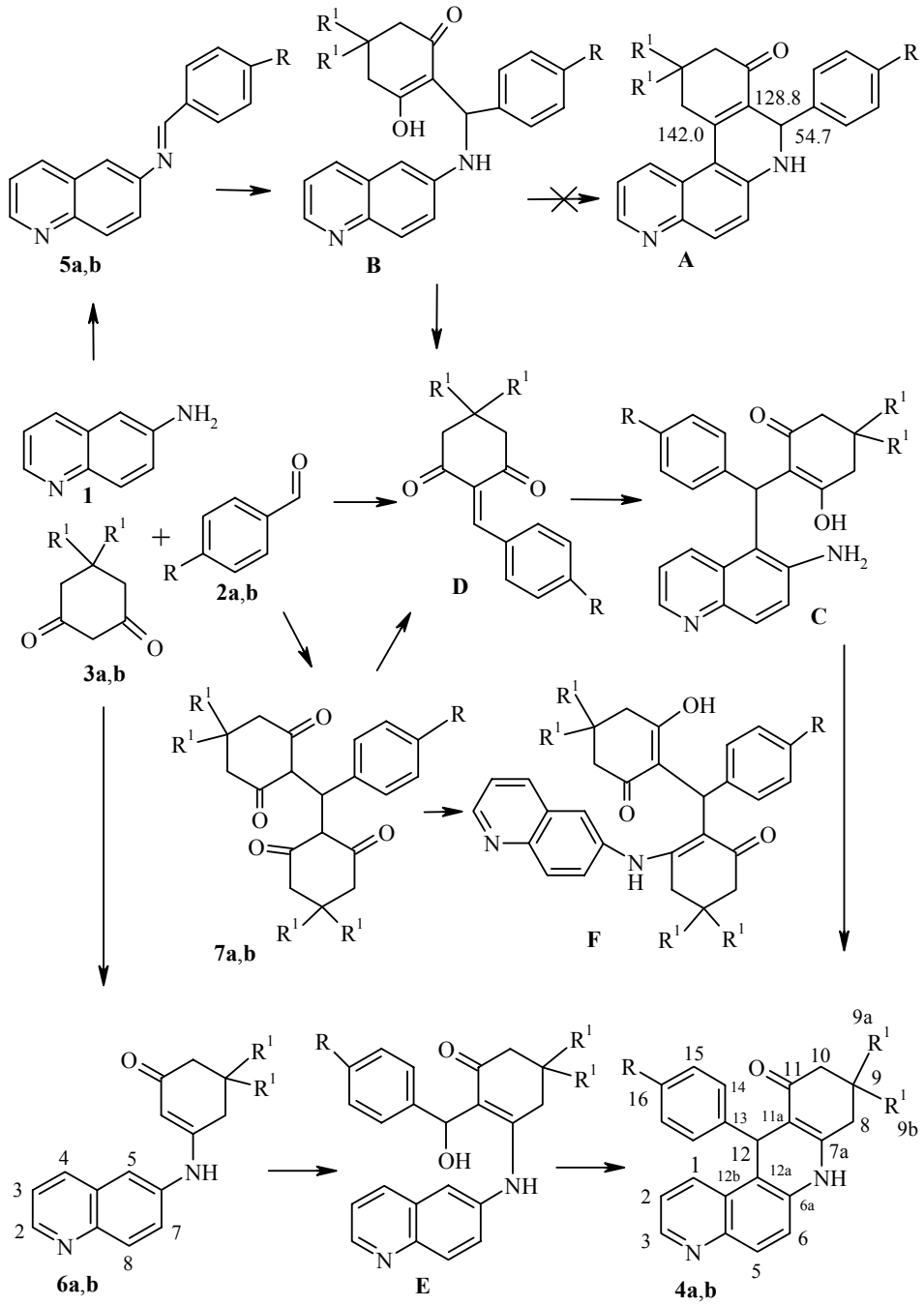


2, **4**, **5**, **7** **a** R = Br, **b** R = OMe; **3**, **4**, **6**, **7** **a** R^1 = H, **b** R^1 = Me

Detailed analysis of the NMR spectra of the reaction products **4a** and **4b** shows that they belong to one and the same structural type. Comparison of the experimental values of the chemical shifts of the carbon nuclei with those calculated by an additive scheme show that for the structure **A** it is impossible to explain the appearance of the signals at 107.8 (107.25) and 35.07 (34.71) ppm while in the structures **4a** and **4b** the $C_{(11a)}$ and $C_{(12)}$ atoms have such shifts. On the other hand, in the case of structure **A** other signals should appear (see reaction scheme) and these are, in fact not found. Analysis of the H–H and C–H spin-spin couplings allows

TABLE 1. Correlation of ^{13}C and ^{1}H NMR Spectra for Compounds **4a,b**

Compound	δC*i* ppm	*	$^{n}J_{Ci—H}$, Hz	δH*i*, ppm ($J_{Hi—Hj}$, Hz)	δH*j*, ppm, for $^{2,3}J_{Ci—Hj}$ *[2]	Assignment
1	2	3	4	5	6	7
4a	193.63	s	—*[3]	—		11
	152.54	s	—*[3]	—		7a
	147.58	d	178.3, 7.4, 3.4	8.66 (1H, dd, *J* = 4.1, *J* = 1.5)	8.36	3
	146.38	s	3 × 6.7	—	5.83	13
	145.48	s	12.2, 9.8, 5.3	—		4
	134.48	s	9.8, 5.0	—		6a
	130.87	d	168.4, 5.7	7.32 (2H, d, *J* = 8.5)		15
	130.53	d	161.9, 6.0	8.30 (1Hddd, *J* = 8.6, *J* = 1.5, *J* = 0.9)		1
	129.79	d	162.7, 7.2, 4.6	7.17 (2H, d, *J* = 8.5)	5.83	16
	129.20	d	164.3	7.89 (1H, d, *J* = 9.0)	5.74	5
	126.34	s	—*[3]	—		12b
	121.75	d	164.6, 8.9	7.38 (1H, dd, *J* = 8.6, *J* = 4.1)		2
	120.40	d	162.7	7.55 (1H, d, *J* = 9.0)		6
	118.76	s	2×11.0, 2×3.1	—		16
	115.69	s	—*[3]	—	5.83	12a
	107.80	s	—*[3]	—	5.83	11a
	36.62	t	2×129.6*[3]	2.20-2.31 (2H, m)		10
	35.07	d	133.2, 2×3.6	5.83 (1H, s)	0.85, 1.02	12
	26.73	t	2×127.9*[3]	2.64 (2H, dd, *J* = 7.0, *J* = 4.3)		8
	20.79	t	2×128.6*[3]	1.77 (2H, m)		9
				9.74 (1H, s)		NH

TABLE 1. (continued)

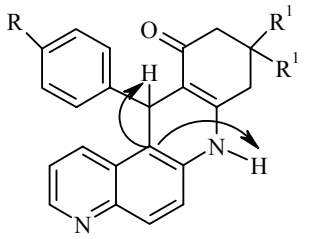
1	2	3	4	5	6	7
4b	193.35	s	2×5.5	—	2.03, 2.20	11
	157.12	s	—*[3]	—	3.60	16
	150.35	s	3×6.7*[3]	—	2.40, 2.55, 5.74	7a
	147.51	d	178.3, 7.7, 3.4	8.65 (1H, dd, *J* = 4.0, *J* = 1.4)	8.36	3
	145.52	s	12.2, 9.8, 6.0	—		4
	139.34	s	3×6.7	—	5.74	13
	134.42	s	9.4, 4.1	—	5.74, 7.87	6a
	130.76	d	162.2, 6.0	8.36 (1H, ddd, *J* = 8.5, *J* = 4.2, *J* = 1.4)		1
	128.87	d	163.6	7.87 (1H, d, *J* = 9.1)		5
	128.51	d	157.2, 7.4, 4.6	7.15 (2H, d, *J* = 8.5)	5.74	14
	126.50	s	—*[3]	—	5.74	12b
	121.65	d	164.3, 9.1	7.38 (1H, dd, *J* = 8.5, *J* = 4.2)		2
	120.46	d	160.5	7.54 (1H, d, *J* = 9.1)		6
	116.82	s	3×4.8*[3]	—	5.74, 9.79	12a
	113.29	d	158.8, 5.0	6.68 (2H, d, *J* = 8.5)		15
	107.25	s	—*[3]	—	5.74, 2.40, 2.55, 9.79	11a
	54.78	q	3×144.0	3.60 (3H, s)		CH_3O–
	50.32	t	2×127.9*[3]	2.22 (1H, d, *J* = 16.1); 2.03 (1H, d, *J* = 16.1)	0.85, 1.02	10
	40.09	t	2×131.0*[3]	2.55 (1H, d, *J* = 16.6); 2.40 (1H, d, *J* = 16.6)	0.85, 1.02	8
	34.71	d	132.7, 2×3.8	5.74 (1H, s)		12
	32.14	s	6×3.8*[3]	—	0.85, 1.02, 2.03, 2.22, 2.40, 2.55	9
	29.16	q	3×126.2*[3]	1.02 (3H, s)	0.85	9a
	26.37	q	3×125.5*[3]	0.85 (3H, s)	1.02, 2.22, 2.55	9b
				9.79 (3H, s)		NH

* Multiplicity of spectroscopic signals with off resonance irradiation of protons.

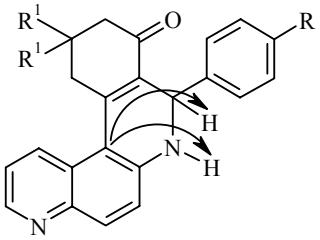
*[2] From long range spin spin coupling data in the heteronuclear ^{13}C-^{1}H correlations.

*[3] A number of small spin-spin couplings present.

ready identification of the signal for atom $C_{(12a)}$ (115.69 and 116.82 ppm in **4a** and **4b** respectively) for which long range spin spin coupling cross peaks with the methine hydrogen atoms at δ 5.83 and 5.74 and amino protons at 9.74 and 9.79 ppm are observed in the C-H correlation spectrum. Hence the cross peaks can be explained by geminal and vicinal interaction in the structures **4a,b**. In the case of the alternative structure **A** interaction with the methine proton would not be possible:



4a,b



A

The structure of compounds **4a,b** was also confirmed from IR and mass-spectrometric data. The IR spectra shown characteristic stretching bands for the NH and CO groups at 3290-3195 and 1625-1580 cm^{-1}. The stretching of the alkyl and cycloaliphatic CH bonds occurred at 2960-2870 and the aromatic CH bonds at 3060-3030 cm^{-1}. The IR spectrum of compound **4b** shows a band for the C–O–C fragment at 1230 cm^{-1}.

The mass spectra of the benzophenanthrolinones **4a,b** show molecular ion peaks $[M]^+$ (I_{rel} 14-18%). The strongest ion peak (100%) is seen for the $[M\text{-}C_6H_4R]^+$ peak (*m/z* 249 for compound **4a** and 277 for compound **4b**). Rather strong peaks are also seen in the spectra at *m/z* 193 (25-28%) which correspond to elimination from the $[M\text{-}C_6H_4R]^+$ ion of the fragment CH_2CH_2CO for compound **4a** and $(CH_3)_2CHCH_2CO$ for the dimethyl derivative **4b**.

The benzo[*b*]-annelated products **4a,b** can be considered as formed *via* the heterocyclization of the enaminohydroxy ketone **C**, formed through hydramine fission of amino diketone **B** to 6-quinolylamine and 2-arylmethylene-1,3-cyclohexanedione **D**, and then addition of the latter to 6-quinolylamine at the carbon atom of great electron density which occurs at position 5 of the quinoline ring [10].

In the three component mixture of reagents the 2-arylmethylene-1,3-cyclohexanedione **D** can be directly formed from aldehyde **2a,b** and cyclohexanedione **3a,b** and further reaction with the 6-quinolylamine **1** occurs as shown in the mechanism above.

In addition, it is possible for an initial reaction of 6-quinolylamine **1** with 1,3-cyclohexanedione **3a,b** to form 3-(6-quinolylamino)-2-cyclohexenone **6a,b**. The aldehyde **2a,b** then adds to the double bond of the cyclohexenone fragment of enamino ketone **6a,b**. The intermediate **E** formed is a substituted benzyl alcohol and can condense with a molecule of aromatic compound similarly to the occurrence in the case of the acid catalyzed reaction of arenes with aldehydes [11]. The condensation of amino alcohol **E** takes place *via* the aromatic part of the molecule itself and occurs at the electron rich 5 position of the quinoline ring to form the products **4a,b**.

In order to clear up the possible stages of formation of the benzophenanthroline ring we carried out consecutive reactions of each of the reagents of the three component mixture with the two others. Condensation of 6-quinolylamine with *para*-bromo- and *para*-methoxybenzaldehydes **2a,b** in an aliphatic alcohol gave the pure arylmethylene-6-quinolylamines **5a,b**. Heating the azomethines **5a,**b with 1,3-cyclohexanedione **3a** or dimedone **3b** in *n*-butanol readily gave the target compounds **4a,b**.

Refluxing the 6-quinolylamine **1** with 1,3-cyclohexanedione **3a** or dimedone **3b** in butanol gave the cyclohexenones **6a** and **6b**. However these compounds do not react in the free state with the third arylaldehyde component **2a,b**.

Despite the use of equimolar amounts of regents the reaction of aldehydes **2a,b** with 1,3-diketones **3a,b** in an aliphatic alcohol gave the 2-arylmethylenebis(1,3-cyclohexanediones) **7a,b** instead of the expected 2-arylmethylene-1,3-cyclohexanediones **D**. The formation of the bis-1,3-diketones **7a,b** is none the less unexpected since it is known [12, 13] that 1,3-cyclohexanedione and dimedone are used for the quantitative determination and qualitative identification of aldehydes as the bis-1,3-dicarbonyl derivatives. When heated with 6-quinolylamine **1** in *n*-butanol the bisdiketones **7a,b** form the target benzo[*b*][4.7]phenanthrolinones **4a,b**. It is likely that the intermediate **F** loses a molecule of 1,3-cyclohexanedione to form the amino ketoenol **E**, cyclocondensation of which then gives the phenanthroline **4a,b**. In the process of transforming the amino diketone **F** to the amino alcohol **E** it is suggested that the water involved in hydrating the starting molecule is that present in the alcohol solution. In aqueous alcoholic medium hydrolytic fission of bisdiketone **7a,b** is possible to give the 2-arylmethylene-1,3-cyclohexanedione **D** and this then reacts with the 6-quinolyl-amine **1** as described in the scheme above to form the benzo[*b*]phenanthrolines **4a,b**.

Since all three variants of the first stage of the three component condensation are feasible, the obtained intermediate N-arylmethylene-6-quinolylamines **5a,b** and 2-arylmethylenebis(1,3-cyclohexanediones) **7a,b** can form the final products **4a,b** in subsequent reactions, and the hetarylaminocyclohexenones **6a,b** can take part in the process of forming the phenanthrolines **4a,b** *in situ* it is impossible to make an unambiguous choice amongst the three reaction routes. However, independently of the order of reaction of the reagents in the three component mixture, the condensation of 6-quinolylamine with aromatic aldehydes and cyclic 1,3-diketones occurs in a single vessel to give a high yield of the target compounds selectively and thus forms the basis for considering this reaction as a high efficiency method for preparing inaccessible annelated 4,7-phenanthroline derivatives.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer (500 and 125 MHz respectively) using DMSO-d_6 [(*c* = 30 mg/ml) for compounds **4a,b** and **6a,b**, internal standard DMSO-d_6 solvent (δ_C 39.50, δ_H 2.50 ppm)] or chloroform-d (for compounds **7a,b** with TMS as internal standard.

Assignment of the signals was carried out using ^{13}C NMR Spectra recorded in the *J*- modulation regime (noise decoupling from protons, opposite phase for signals of atom with even and odd numbers of associated protons tuned to the constant *J* = 135 Hz) in single resonance mode and also for two dimensional spectra as: 1) homonuclear ^{1}H-^{1}H correlations; 2) heteronuclear ^{13}C-^{1}H correlations for direct spin spin coupling (*J* = 135 Hz), and 3) heteronuclear ^{13}C-^{1}H correlation for long range spin spin coupling (*J* = 10 Hz).

IR spectra were taken on a Nicolet Protégé-460 Fourier spectrometer. Mass spectra were recorded on a Finnigan MAT Incos 50 instrument with electron ionization energy 70 eV. Compound melting points were determined on a Koffler block.

N-Arylmethylene-6-quinolylamines 5a,b were prepared by method [4].

12-(*p*-Bromophenyl)- and 12-(*p*-Methoxyphenyl)-9,9-dimethyl-8,9,10,12-tetrahydro-7H-benzo[*b*]-[4,7]phenanthrolin-11-ones (4a,b). A solution of amine **1** (1.44 g, 10 mmol), the corresponding aldehyde **2a** or **2b** (10 mmol), and 1,3-cyclohexanedione **3a** (for compound **4a**) or dimedone **3b** (for compound **4b**) (10 mmol) in *n*-butanol (30 ml) was refluxed for 3 h. The precipitated product was filtered off and crystallized from a mixture of ethanol and benzene (3:1).

Compound **4a**. Yield 84%; mp 335-336ºC. Found, %: C 65.09; H 4.27; Br 19.52; N 6.59. $C_{22}H_{17}BrN_2O$. Calculated, %: C 65.19; H 4.20; Br 19.75; N 6.91.

Compound **4b**. Yield 79%; mp 312-313ºC. Found, %: C 77.94; H 6.07; N7 .18. $C_{25}H_{24}N_2O_2$. Calculated, %: C 78.13; H 6.25; N 7.29.

Condensation of N-Arylmethylene-6-quinolylamines 5a,b with 1,3-Diketones 3a,b. A solution of the azomethine **5a** or **5b** (5 mmol), 1,3-cyclohexanedione **3a** (for compound **5a**) or dimedone **3b** (for compound **5b**)

(5 mmol) in *n*-butanol (20 ml) was refluxed for 2.5 h. The 4,7-phenanthroline reaction products **4a,b** were separated as described above. Yield of compound **4a** 83% and of compound **4b** 80%.

3-(6-Quinolylamino)- and 5,5-Dimethyl-3-(6-quinolylamino)-2-cyclohexenones (6a,b). A solution of 6-quinolylamine **1** (1.44 g, 10 mmol) and 1,3-cyclohexanedione **3a** or dimedone **3b** (10 mmol) in *n*-butanol or ethanol (20 ml) was refluxed for 2 h. After cooling, the reaction mixture the solvent was evaporated and the oily residue treated with ether, triturating with a glass rod. The precipitated compound **6b** was filtered off and crystallized from ethanol-benzene (1:1). In the case of the non crystallizing compound **6a** the ether was decanted and the residue was dried in air.

Compound 6a. Yield 70%, oily material. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.98 (2H, m, CH_2); 2.28 (2H, m, CH_2); 5.49 (1H, s, CH=); 7.42 (1H, dd, ^3J = 8.1, ^4J = 4.0, H-3); 7.56 (1H, d, ^3J = 8.1, H-4); 7.70 (1H, s, H-5); 7.97 (1H, d, ^3J = 8.8, H-7); 8.30 (1H, d, ^3J = 8.8, H-8); 8.76 (1H, d, ^3J = 4.0, H-2); 9.10 (1H, s, NH). Found, %: C 75.49; H 5.71; N 11.57. $C_{15}H_{14}N_2O$. Calculated, %: C 75.63; H 5.88; N 11.76.

Compound 6b. Yield 78%; mp 211-212ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (6H, s, 2 CH_3); 2.10 (2H, s, CH_2); 2.45 (2H, s, CH_2); 3.32 (3H, s, OCH_3); 5.58 (1H, s, CH=); 7.49 (1H, dd, ^3J = 8.5, ^4J = 4.1, H-3); 7.60 (1H, d, ^3J = 8.4, H-4); 7.73 (1H, s, H-5); 8.00 (d, ^3J = 8.9, H-7); 8.34 (1H, d, ^3J = 8.9, H-8); 8.80 (1H, d, ^3J = 4.6, H-2); 9.09 (1H, s, NH). Found, %: C 76.51; H 6.62; N 10.33. $C_{17}H_{18}N_2O$. Calculated, %: C 76.69; H 6.77; N 10.53.

2-(*p*-Bromophenyl)methylenebis(1,3-cyclohexanedione) (7a) and 2-(*p*-Methoxyphenyl)methylene-bis(5,5-dimethyl-1,3-cyclohexanedione (7b). A solution of aldehyde **2a** or **2b** (10 mmol) and 1,3-cyclohexanedione **3a** (for compound **7a**) or dimedone **3b** (for compound **7b**) (10 mmol) in 1-butanol (20 ml) was refluxed for 0.5 h. The solid produced after cooling was separated and recrystallized from ethanol.

Compound 7a. Yield 90%; mp 240-241ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.0 (4H, m, CH_2); 2.28 (4H, m, CH_2); 2.57 (4H, m, CH_2); 4.88 (1H, s, CH); 7.02 (2H, d, ^3J =7.4, $H_{arom.}$); 7.28 (2H, d, ^3J = 7.4, $H_{arom.}$), 11.90 (2H, br. s, OH).

Compound 7b. Yield 94%; mp 221-222ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (6H, s, CH_3); 1.26 (6H, s, CH_3); 2.40 (8H, m, CH_2); 3.78 (3H, s, OCH_3); 5.48 (1H, s, CH); 6.75 (2H, d, ^{3}J = 7.1, $H_{arom.}$); 6.97 (2H, d, ^3J = 7.1, $H_{arom.}$); 11.88 (2H, br. s, OH).

Condensation of 2-arylmethylenebis(1,3-cyclohexanediones) 7a,b with 6-Quinolylamine (1). A solution of bisketone **7a** or **7b** (5 mmol) and amine **1** (5 mmol) in butanol (20 ml) was refluxed for 2 h. The reaction products **4a,b** were separated as described above. Yield of compound **4a** 77% and phenanthroline **4b** 80%.

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