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6,6-Heptamethylenetetrahydropyran-2,4-dione in the Synthesis of Benzo[*f*]pyrano[3,4-*b*]quinolines and Pyrano[4,3-*b*][4,7]phenanthrolines

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Abstract—Three-component condensation of 6,6-heptamethylenetetrahydropyran-2,4-dione with 2-aminonaphthalene or 6-aminoquinoline and aromatic aldehydes in an aliphatic alcohol afforded 12-aryl-9,9-heptamethylene-8,9,10,12-tetrahydro-7*H*-benzo[*f*]pyrano[3,4-*b*]quinolin-11-ones and 12-aryl-9,9-heptamethylene-8,9,10,12-tetrahydro-7*H*-pyrano[4,3-*b*][4,7]phenanthrolin-11-ones, new N,O-heterocycles which include aza- or diazaphenanthrene system fused to α-pyrone ring and aromatic and spiro substituents.

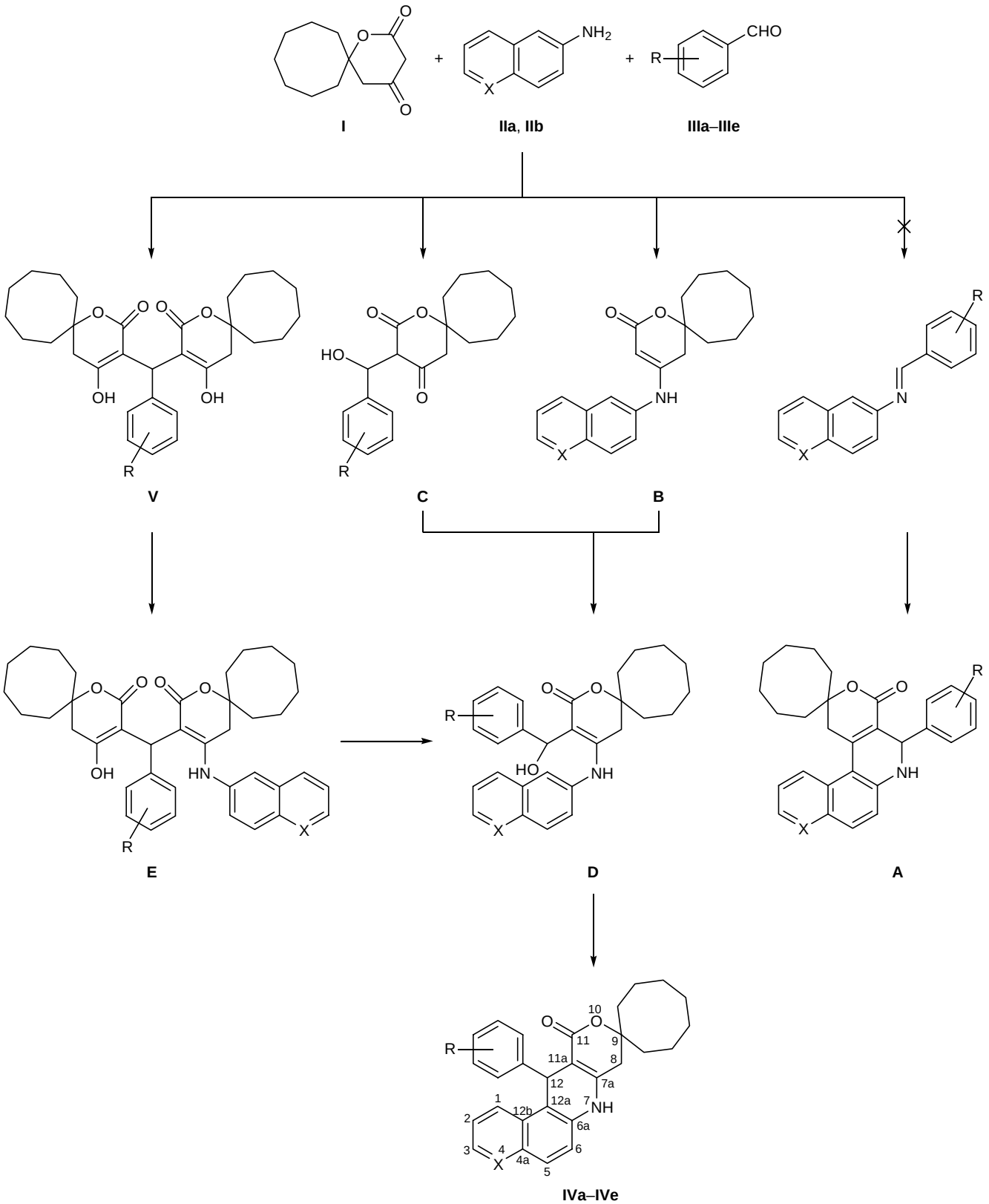
High and versatile biological activity of benzo[*f*]-quinoline and 4,7-phenanthroline derivatives [1–6] makes it promising to search for new synthons ensuring preparation of previously unknown derivatives of the above series. We showed in [7–9] that cyclic β-diketones are highly effective reagents in the synthesis of fused benzo[*f*]quinoline and 4,7-phenanthroline derivatives.

With the goal of introducing a fused oxygen-containing ring and a spiro-fused cycloalkane ring into the nitrogen heterocycle molecule, in the present work we were the first to examine the reaction of 6,6-heptamethylenetetrahydropyran-2,4-dione (**I**) with 2-aminonaphthalene (**IIa**) or 6-aminoquinoline (**IIb**) and substituted benzaldehydes **IIIa**–**IIIe**. Spirocyclic pyrandione **I** was synthesized by the procedure developed by us previously [10]; it may be regarded as a heterocyclic analog of substituted 1,3-cyclohexanedione. However, unlike the latter, the ketone and lactone carbonyl groups in the enolizable β-dicarbonyl fragment of molecule **I** are chemically nonequivalent.

The condensation of pyrandione **I** with amines **IIa** and **IIb** and benzaldehydes **IIIa**–**IIIe** were carried out by heating equimolar amounts of the reactants in boiling ethanol or 1-butanol in the absence of a catalyst. As a result, we isolated pure benzo[*f*]-pyrano[3,4-*b*]quinoline (**IVa**, **IVb**) and pyrano[4,3-*b*]-[4,7]phenanthroline (**IVc**–**IVe**) derivatives in 67–87% yield (Scheme 1).

Theoretically, the three-component condensation of ketolactone **I**, amine **II**, and aldehyde **III** can take several pathways to give different isomeric products. Analogous reactions with cyclic ketones are known to involve intermediate formation of Schiff bases from the corresponding amine and aldehyde, and the subsequent condensation with cycloalkanone yields azaphenanthrene derivatives [11, 12] following the well-known mechanism for reactions of CH acids with Schiff bases [1]. In this case, the condensation of ketolactone **I** with 2-aminonaphthalene (**IIa**) or 6-aminoquinoline (**IIb**) and benzaldehyde **III** could lead to formation of benzo[*f*]pyrano[3,4-*c*]quinoline or pyrano[3,4-*a*][4,7]phenanthroline derivatives like **A**. However, the formation of benzo[*f*]pirano[3,4-*b*]quinolines and pyrano[4,3-*b*][4,7]phenanthrolines **IV** indicates that the condensation takes a different pathway. We believe that in the initial stage spirocyclic pyrandione **I** reacts with amine **II** or aldehyde **III** to give, respectively, enamine **B** or enol **C**. Reactions of

Scheme 1.



IIa, **IVa**, **IVb**, X = CH; **IIb**, **IVc**–**IVe**, X = N; **III**, **IV**, R = 4-OH (**a**), 4-Cl (**b**), 4-Br (**c**), 2,4-$(MeO)_2$ (**d**), 3,4-$(MeO)_2$ (**e**); **V**, R = 4-Br.

intermediates **B** and **C** with the third component (**III** or **II**) yields the same intermediate enaminoketone **D**, and dehydration of the latter results in formation of final products **IVa**–**IVe** (Scheme 1). Analogous products, benzo[*f*]quinoline derivatives, were obtained previously by reaction of 2-aminonaphthalene with dimedone (which is a carbocyclic analog of pyrandione **I**) and aromatic aldehydes [13].

In the reaction with *p*-bromobenzaldehyde (**IIIc**), apart from the major product, 4,7-phenanthroline **IVc**, we isolated a small amount of *p*-bromophenylmethylene-3,3'-bis(6,6-heptamethylene-4-hydroxy-5,6-dihydro-2*H*-pyran-2-one) (**V**). Compound **V** was also synthesized in a preparative yield by reaction of pyrandione **I** with aldehyde **IIIc** under the above condensation conditions; by heating with 6-aminoquinoline (**IIb**), bis-ketone **V** was converted into pyranophenanthroline **IVc**. Obviously, elimination of pyrandione molecule from intermediate **E** gives enaminoketone **D** whose dehydration leads to compound **IVc**. Taking into account that the lactone carbonyl group in **I** is less prone to enolization, as compared to the ketone carbonyl [14, 15], these reactions involve just the ketone carbonyl group. As a result, the lactone carbonyl group is retained in the structure of polycyclic compounds **IVa**–**IVe**.

The structure of compounds **IVa**–**IVe** was proved by NMR, IR, and UV spectroscopy and mass spectrometry. The ^{1}H NMR spectra of **IVa**–**IVe** resemble those of the previously reported fused benzo[*f*]quinoline and 4,7-phenanthroline derivatives, as concerns the positions and multiplicities of signals belonging to the benzopyranoquinoline and pyranophenanthroline fragments [8, 9, 11, 12]. The spiro-fused cyclooctane ring gives rise to a 14-proton multiplet in the δ region from 1.30 to 2.05 ppm. The R substituent almost does not affect the chemical shifts of protons of the azaphenanthrene moiety; only in the spectrum of 2,4-dimethoxyphenyl-substituted 4,7-phenanthroline **IVd** we observed a downfield shift of the 1-H proton signal, in keeping with the assumed structure. Presumably, the presence of a bulky methoxy group in the *ortho* position of the phenyl ring changes spatial arrangement of the latter, so that its shielding effect on the 1-H proton of the phenanthroline fragment weakens. No such pattern would be observed for alternative struc-ture **A** where the 1-H proton is distant from the aryl substituent.

The IR spectra of compounds **IVa**–**IVe** contain strong absorption bands at 1665 and 1525 cm^{-1}, which should be assigned to the enaminoketone fragment (1580, 1520 cm^{-1}) [13]. A considerable shift of the first of these bands toward higher frequencies may be due to lactone nature of the carbonyl group. Strong bands at 3280 and 1640 cm^{-1} belong, respectively, to stretching and bending vibrations of the secondary amino group.

In the mass spectra of benzopyranoquinolines and pyrano-4,7-phenanthrolines **IVa**–**IVe** we observed the molecular ion peaks $[M]^+$ (I_{rel} 10–30%), while the most abundant ion was $[M - C_6H_4R]^+$ (100%) (or $[M - C_6H_3R]^+$ for dimethoxyphenyl-substituted compounds **IVd** and **IVe**), *m*/*z* 346 (**IVa**, **IVb**), 347 (**IVc**–**IVe**). The mass spectra of phenanthrolines **IVd** and **IVe** contained an ion peak with *m*/*z* 374, I_{rel} 55% (**IVd**) and 18% (**IVe**). The presence of that ion indicates concurrent elimination of the spirocyclooctane fragment C_8H_{14} from the molecular ion. Fairly abundant (I_{rel} 28–50%) ions with *m*/*z* 220 for benzoquinolines **IVa** and **IVb** and *m*/*z* 221 for phenanthrolines **IVc**–**IVe** result from successive elimination of the $C_6H_{4(3)}R$ and $C_8H_{14}O$ fragments from the molecular ion, and ions with *m*/*z* 192 (**IVa**, **IVb**) and 193 (**IVc**–**IVe**) (I_{rel} 34–53%) correspond to the subsequent elimination of carbonyl group from ion with *m*/*z* 220 (221). The fragment ion $[M - C_6H_{4(3)}R]^+$ derived from **IVa**, **IVd**, and **IVe** is stabilized by addition of hydrogen to give, respectively, phenol (*m*/*z* 94, I_{rel} 10%) and *m*- and *o*-dimethoxybenzene (*m*/*z* 138, I_{rel} 34–50%). The observed fragmentation pattern confirms the assumed structure of compounds **IVa**–**IVe**; specifically, the presence of an ion peak with *m*/*z* 192 (193) indicates that the polycyclic molecule contains a lactone carbonyl group. Just in this case the methylene group of the pyran ring, which is directly attached to the aza(diaza)phenanthrene skeleton, is included in the above ion.

The electron absorption spectra of spirocyclic benzopyranoquinoline and 4,7-phenanthroline derivatives **IVa**–**IVe** occupy the ultraviolet region and are characterized by clearly defined vibrational structure. Molecules **IVa**–**IVe** possess three independent chromophores: naphthalene (quinoline) fragment, aryl substituent, and carbonyl group. Insofar as the naphthalene (quinoline) core contributes most to π–π*-electron transitions, the first three bands in the spectra of **IVa**–**IVe** may be attributed to the 2-aminonaphthalene (6-aminoquinoline) system, λ_{max}, nm (log ε): 206–208 (4.08–4.11), 247–249 (4.35–4.39), 279–283 (3.59–3.64). An appreciable red shift and increase in the intensity of the first and third bands in the spectra of pyrano derivatives **IVa**–**IVe** are likely to result from

superposition of absorption bands belonging to the aromatic $C_6H_{4(3)}R$ substituent. Absorption bands in the short-wave region arise from the presence of a carbonyl group [16].

Thus we have shown that three-component condensation of 6,6-heptamethylenetetrahydropyran-2,4-dione, 2-aminonaphthalene or 6-aminoquinoline, and aromatic aldehyde provides a convenient one-step procedure for the synthesis of difficultly accessible fused N,O-heterocycles containing aza(diaza)phenanthrene and pyran nuclei, spiro-fused cyclooctane ring, and aryl substituent.

EXPERIMENTAL

The mass spectra (70 eV) were recorded on a Finnigan MAT Incos-50 instrument. The IR spectra were measured on a Nicolet Protégé 460 Fourier spectrometer. The ^{1}H NMR spectra were obtained on a Tesla BS-567 instrument (100 MHz) in DMSO-d_6 (**IVa**–**IVe**) or $CDCl_3$ (**V**) using TMS as internal reference. The UV spectra were measured from solutions in ethanol ($c = 10^{-4}$ M) on a Specord UV-Vis spectrophotometer. The melting points were determined on a Koeffler device.

6,6-Heptamethylenetetrahydropyran-2,4-dione (**I**) was synthesized by the procedure described in [10].

12-Aryl-9,9-heptamethylene-8,9,10,12-tetrahydro-7*H*-benzo[*f*]pyrano[3,4-*b*]quinolin-11-ones IVa and IVb. A mixture of 5 mmol of pyrandione **I**, 5 mmol of 2-aminonaphthalene (**IIa**), and 5 mmol of aldehyde **IIIa** or **IIIb** in 20 ml of ethanol was heated for 1 h under reflux. The precipitate was filtered off, treated with boiling benzene to remove unreacted initial compounds, and dried.

9,9-Heptamethylene-12-(4-hydroxyphenyl)-8,9,10,12-tetrahydro-7*H*-benzo[*f*]pyrano[3,4-*b*]-quinolin-11-one (IVa). Yield 77%, mp 324–325°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20–2.03 m (14H, CH_2), 2.58 s (1H, 8-H), 5.57 s (1H, 12-H), 6.51 d and 6.98 d (4H, C_6H_4, ^3J = 7.5), 7.12–7.45 m and 7.58–7.80 m (6H, 1-H–6-H), 8.00 s (1H, OH), 9.38 s (1H, NH). UV spectrum, λ_{max}, nm (logε): 217 (4.63), 227 (4.73), 277 (4.21), 288 (4.31), 334 (3.98), 368 (3.94). Found, %: C 79.11; H 6.43; N 3.22. $C_{29}H_{29}NO_3$. Calculated, %: C 79.27; H 6.61; N 3.19.

12-(4-Chlorophenyl)-9,9-heptamethylene-8,9,-10,12-tetrahydro-7*H*-benzo[*f*]pyrano[3,4-*b*]quinolin-11-one (IVb). Yield 68%, mp 285–286°C. ^{1}H NMR spectrum, δ, ppm: 1.30–1.90 m (14H, C_8H_{14}), 2.59 s (1H, 8-H), 5.71 s (1H, 12-H), 7.20–7.50 m and 7.70–7.92 m (10H, 1-H–6-H, C_6H_4), 9.80 s (1H, NH). UV spectrum, λ_{max}, nm (logε): 213 (4.59), 223 (4.71), 274 (4.20), 289 (4.28), 336 (3.94), 371 (3.90). Found, %: C 75.89; H 5.94; Cl 7.53; N 3.18. $C_{29}H_{28}ClNO_2$. Calculated, %: C 76.07; H 6.12; Cl 7.76; N 3.06.

12-Aryl-9,9-heptamethylne-8,9,10,12-tetrahydro-7*H*-pyrano[4,3-*b*][4,7]phenanthrolin-11-ones IVc–IVe were synthesized in a similar way from pyrandione **I**, 6-aminoquinoline (**IIb**) and aldehyde **IIIc**–**IIIe** by heating in boiling 1-butanol for 2 h. Products **IVc**–**IVe** were recrystallized from ethanol–benzene (2 : 1) without preliminary treatment with boiling benzene.

12-(4-Bromophenyl)-9,9-heptamethylene-8,9,-10,12-tetrahydro-7*H*-pyrano[4,3-*b*][4,7]phenanthrolin-11-one (IVc). Yield 67%, mp 299–300°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30–2.07 m (14H, CH_2), 2.60 s (1H, 8-H), 5.70 s (1H, 12-H), 7.16 d and 7.25 d (6H, C_6H_4, ^3J = 7.8), 7.28 d.d (1H, 2-H, ^3J = 8.2, ^4J = 2.8), 7.41 d and 7.83 d (2H, 5-H, 6-H, ^3J = 8.4), 8.16 d (1H, 1-H, ^3J = 4.2), 8.60 d (1H, 3-H, ^3J = 4.6), 9.51 s (1H, NH). UV spectrum, λ_{max}, nm (logε): 219 (4.60), 255 (4.20), 291 (4.18), 332 (4.00), 376 (3.89). Found, %: C 66.51; H 5.28; Br 15.94; N 5.33. $C_{28}H_{27}BrN_2O_2$. Calculated, %: C 66.80; H 5.37; Br 15.90; N 5.57.

9,9-Heptamethylene-12-(2,4-dimethoxyphenyl)-8,9,10,12-tetrahydro-7*H*-pyrano[4,3-*b*][4,7]phenanthrolin-11-one (IVd). Yield 87%, mp 258–260°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.42–2.05 m (14H, C_8H_{14}); 2.61 s (1H, 8-H); 3.70 s and 3.92 s (6H, 2OMe); 5.90 s (1H, 12-H); 6.37 s, 6.28 d, and 7.09 d (3H, C_6H_3, ^3J = 7.6); 7.27 d.d (1H, 2-H, ^3J = 8.2, ^4J = 2.8); 7.36 d and 7.74 d (2H, 5-H, 6-H, ^3J = 8.4), 8.51 d (1H, 1-H, ^3J = 4.2), 8.58 d (1H, 3-H, ^3J = 4.6), 9.37 s (1H, NH). UV spectrum, λ_{max}, nm (logε): 216 (4.62), 256 (4.22), 293 (4.19), 330 (3.99), 373 (3.91). Found, %: C 74.08; H 6.49; N 5.63. $C_{30}H_{32}N_2O_4$. Calculated, %: C 74.38; H 6.61; N 5.79.

9,9-Heptamethylene-12-(2,4-dimethoxyphenyl)-8,9,10,12-tetrahydro-7*H*-pyrano[4,3-*b*][4,7]phenanthrolin-11-one (IVe). Yield 79%, mp 252–253°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.35–2.00 m (14H, C_8H_{14}); 2.60 s (1H, 8-H); 3.68 s and 3.72 s (6H, 2OMe); 5.63 s (1H, 12-H); 6.53 d, 6.61 d, and 6.90 s (3H, C_6H_3, ^3J = 7.5); 7.29 d.d (^3J = 8.2, ^4J = 2.8); 7.42 d and 7.82 d (^3J = 8.4); 8.23 d (^3J = 4.2); 8.61 d (^3J = 4.6); 9.42 s (1H, NH). UV spectrum, λ_{max}, nm (logε): 213 (4.61), 252 (4.19), 290 (4.17), 333 (4.01), 374 (3.96). Found, %: C 74.24; H 6.52; N 5.39. $C_{30}H_{32}N_2O_4$. Calculated, %: C 74.38; H 6.61; N 5.79.

3,3'-*p*-Bromophenylmethylenebis(6,6-heptamethylene-4-hydroxy-5,6-dihydropyran-2-one) (V) was synthesized from dione **I**, amine **IIb**, and aldehyde **IIIc**, following the procedure described above for compounds **IVa**–**IVc**. After separation of the major product (phenanthroline **IVc**), the mother liquor was evaporated, and the residue was recrystallized from ethanol–benzene (4:1). Yield 8%, mp 205–206°C. IR spectrum, ν, cm^{-1}: 1655 (C=O), 2960–2880 (CH_2). ^1H NMR spectrum, δ, ppm: 1.40–2.35m (28H, CH_2), 2.60 s (4H, CH_2), 5.30 s (1H, CH), 6.88 d and 7.32 d (4H, H_{arom}), 11.3 br.s (2H, OH). Found, %: C 62.54; H 6.47; Br 13.73. $C_{30}H_{38}BrO_6$. Calculated, %: C 62.72; H 6.62; Br 13.94.

Bis-ketone **V** was also synthesized by heating a mixture of 10 mmol of pyrandione **I** and 5 mmol of aldehyde **IIIc** in 20 ml of ethanol for 1.5 h under reflux. Yield 86%.

Condensation of 3,3'-*p*-bromophenylmethylenebis(6,6-heptamethylene-4-hydroxy-5,6-dihydropyran-2-one) (V) with 6-aminoquinoline (IIb). A solution of 5 mmol of compound **V** and 5 mmol of amine **IIb** in 20 ml of 1-butanol was heated for 1 h. The product (compound **IVc**) was isolated as described above. Yield 76%.

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