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Synthesis of Bisarylmethyl-Substituted Pyrimidines and Quinolines

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Abstract—The condensation of 2-chloro-8-methylquinoline-3-carbaldehyde, 2-chloro- and 2-chloro-7,8,9,10-tetrahydrobenzo[*h*]quinoline-3-carbaldehydes, 2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde, 6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde, and 2-chloropyrido[1,2-*a*]pirimidine-3-carbaldehyde with N-substituted anilines gave the corresponding diaryl(hetaryl)methanes.

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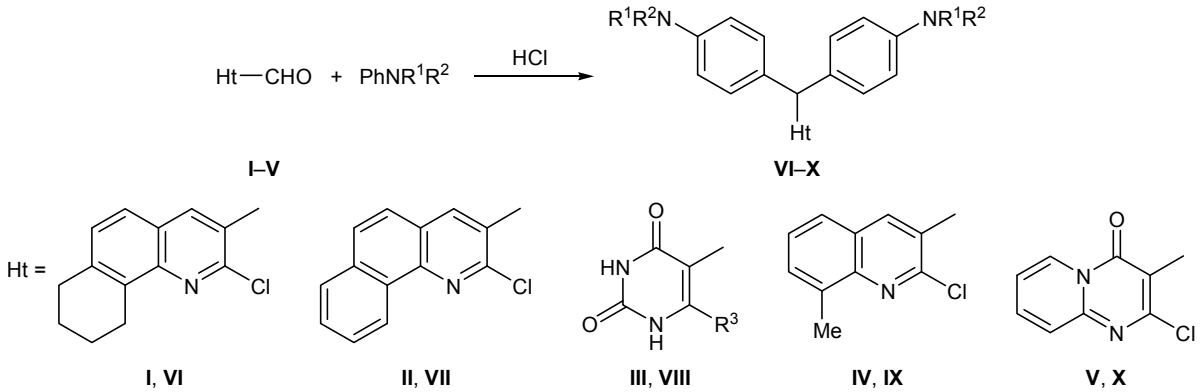
It is known that substituted triphenylmethanes (leuco bases of the corresponding triphenylmethane dyes) are potent chemotherapeutic and photodynamic agents [1]; they also exhibit nonlinear optical properties due to specific π-electron density distribution in their molecules [2].

Aryl and hetaryl triphenylmethane analogs containing five- and six-membered heterocycles and fused heterocyclic systems have recently been synthesized [3]. It should be noted that only a few examples of pyrimidine analogs of triphenylmethane and triphenylmethanol have been reported [4, 5]; some of them were tested as antiestrogens (aromatase inhibitors) [5].

In order to find new potential biologically active compounds in the series of diaryl(hetaryl)methanes, a number of heterocyclic aldehydes were brought into condensation with N-substituted anilines in the presence of various catalysts, in particular H_2SO_4, polyphosphoric acid, HCl, and $ZnCl_2$. The best results were obtained when a suspension of aldehyde **I**–**V** and the corresponding aniline in 30% aqueous HCl was heated under reflux for 12 h (Scheme 1). As a result, diaryl(hetaryl)methanes **VI**–**X** were isolated in good yields. However, 6-styryl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde [6] failed to react with *N*,*N*-dimethyl- and *N*,*N*-diethylanilines under the above conditions, and the initial aldehyde was recovered from the reaction mixture.

The structure of compounds **VI**–**X** was confirmed by elemental analyses and IR and ^{1}H NMR spectra.

Scheme 1.



I, **VI** **II**, **VII** **III**, **VIII** **IV**, **IX** **V**, **X**

III, R^3 = H (**a**), Me (**b**); **VI**, **VII**, **IX**, $R^1 = R^2$ = Me (**a**), Et (**b**); **VIII**, R^3 = H, $R^1 = R^2$ = Me (**a**), Et (**b**); $R^1 = R^3$ = H, R^2 = *i*-Bu (**c**); R^3 = H: $R^1 = R^2$ = Me (**d**), Et (**e**); **X**, $R^1 = R^2$ = Me.

Diaryl(hetaryl)methanes **VI**–**X** were tested for antibacterial activity against *S. aureus* 209, p 1, *Sh. dysenteriae Flexneri* 6858, and *E. coli* 0-55. Compound **VIIa** turned out to be weakly active against Gram-negative bacteria, compounds **VIIIb**, **VIIId**, and **VIIIe** were weakly active against Gram-positive bacteria, and compound **VIIIa** displayed activity against all the examined bacterial strains. Pyrimidines **VIIId** and **VIIIe** at a dose of 150 mg/kg inhibited by 30–40% the growth of sarcoma 37 in mice.

EXPERIMENTAL

The IR spectra were recorded in mineral oil on a Nicolet Avatar 330 spectrometer. The ^{1}H NMR spectra were measured on a Varian Mercury-300 instrument at 300 MHz using tetramethylsilane as internal reference. Silufol UV-254 were used for thin-layer chromatography; spots were visualized by treatment with iodine vapor.

2-Chloro-7,8,9,10-tetrahydrobenzo[*h*]quinoline-3-carbaldehyde (I). Vilsmeier reagent prepared from 18.3 g (0.25 mol) of dimethylformamide and 107.5 g (0.7 mol) of phosphoryl chloride was cooled to –5 to 0°C, 18.9 g (0.1 mol) of *N*-(1,2,3,4-tetrahydronaphthalen-5-yl)acetamide [7] was added in portions, and the mixture was allowed to warm up to room temperature, heated for 2 h under reflux, and evaporated under reduced pressure. The residue was poured onto 0.5 kg of ice, the mixture was left to stand for 3 h in the cold, and the precipitate was filtered off and dried. Yield 15.6 g (64%), mp 160–162°C (from EtOH), R_f 0.70 (EtOH–dichloroethane, 1:10). IR spectrum, ν, cm^{-1}: 1682 (C=O), 1608 s (C=C$_{arom}$). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.85–2.00 m (4H, $CH_2C\mathbf{H}_2C\mathbf{H}_2CH_2$), 2.96 br.t and 3.24 br.t (2H each, $C\mathbf{H}_2CH_2CH_2C\mathbf{H}_2$, J = 5.4 Hz), 7.34 d and 7.79 d (1H each, 5-H, 6-H, J = 8.4 Hz), 8.69 s (1H, 4-H), 10.45 s (1H, CHO). Found, %: N 5.86. $C_{14}H_{12}ClNO$. Calculated, %: N 5.70.

Diaryl(hetaryl)methanes VI–X (*general procedure*). A mixture of 0.01 mol of aldehyde **I**–**V**, 2.4 g (0.02 mol) of 30% aqueous HCl, and 0.03 mol of the corresponding N-substituted aniline was stirred and heated for 12 h under reflux. The resulting suspension was made alkaline by treatment with aqueous ammonia, excess N-substituted aniline was removed by steam distillation, and the precipitate was filtered off, washed with water, and dried.

4,4′-[(2-Chloro-7,8,9,10-tetrahydrobenzo[*h*]quinolin-3-yl)methylene]bis(*N*,*N*-dimethylaniline) (VIa) was synthesized from aldehyde **I** and *N*,*N*-dimethylaniline. Yield 68%, mp 255–256°C (from 2-ethoxyethanol), R_f 0.80 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum: ν 1611 cm^{-1}, s (C=C$_{arom}$). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.84–1.96 m (4H, 8-H, 9-H), 2.90 m (2H, 7-H or 10-H), 2.93 s (12H, NCH_3), 3.21 m (2H, 10-H or 7-H), 5.71 s (1H, CH), 6.56–6.67 m and 6.83–6.89 m (4H each, C_6H_4), 7.17 d and 7.40 d (1H each, 5-H, 6-H, J = 8.4 Hz), 7.51 s (1H, 4-H). Found, %: N 8.74. $C_{30}H_{32}ClN_3$. Calculated, %: N 8.94.

4,4′-[(2-Chloro-7,8,9,10-tetrahydrobenzo[*h*]quinolin-3-yl)methylene]bis(*N*,*N*-diethylaniline) (VIb) was synthesized from aldehyde **I** and *N*,*N*-diethylaniline. Yield 72%, mp 201–202°C (from DMF–2-ethoxyethanol), R_f 0.73 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum: ν 1610 cm^{-1}, s (C=C$_{arom}$). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.15 t (12H, $CH_2C\mathbf{H}_3$, J = 7.0 Hz), 1.84–1.96 m (4H, 8-H, 9-H), 2.90 m and 3.21 m (2H each, 7-H, 10-H), 3.33 q (8H, $C\mathbf{H}_2CH_3$, J = 7.0 Hz), 5.66 s (1H, CH), 6.49–6.56 m and 6.78–6.85 m (4H each, C_6H_4), 7.16 d and 7.42 d (1H each, 5-H, 6-H, J = 8.4 Hz), 7.55 s (1H, 4-H). Found, %: N 7.82. $C_{34}H_{40}ClN_3$. Calculated, %: N 7.99.

4,4′-[(2-Chlorobenzo[*h*]quinolin-3-yl)methylene]bis(*N*,*N*-dimethylaniline) (VIIa) was synthesized from aldehyde **II** [8] and *N*,*N*-dimethylaniline. Yield 60%, mp 221–222°C (from 2-ethoxyethanol), R_f 0.64 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum: ν 1610 cm^{-1}, s (C=C$_{arom}$). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 2.94 s (12H, CH_3), 5.79 s (1H, CH), 6.63 m and 6.90 m (4H each, C_6H_4), 7.62 d and 7.80 d (1H each, 5-H, 6-H, J = 8.8 Hz), 7.63–7.72 m (2H, 8-H, 9-H), 7.71 s (1H, 4-H), 7.90 m (1H, 7-H), 9.10 m (1H, 10-H). Found, %: N 8.86. $C_{30}H_{28}ClN_3$. Calculated, %: N 9.02.

4,4′-[(2-Chlorobenzo[*h*]quinolin-3-yl)methylene]bis(*N*,*N*-diethylaniline) (VIIb) was synthesized from aldehyde **II** and *N*,*N*-diethylaniline. Yield 66%, mp 224–225°C (from 2-ethoxyethanol), R_f 0.61 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum: ν 1610 cm^{-1}, s (C=C$_{arom}$). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.16 t (12H, $CH_2C\mathbf{H}_3$, J = 7.0 Hz), 3.34 q (8H, $C\mathbf{H}_2CH_3$, J = 7.0 Hz), 5.74 s (1H, CH), 6.54 m and 6.87 m (4H each, C_6H_4), 7.63 d and 7.80 d (1H each, 5-H, 6-H, J = 8.9 Hz), 7.64–7.72 m (2H, 8-H, 9-H), 7.75 s (1H, 4-H), 7.89 m (1H, 7-H), 9.11 m (1H, 10-H). Found, %: N 8.26. $C_{34}H_{36}ClN_3$. Calculated, %: N 8.05.

5-{Bis[4-(dimethylamino)phenyl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione (VIIIa) was synthesized from

aldehyde **IIIa** [9] and *N*,*N*-dimethylaniline. Yield 76%, mp 299–301°C (from EtOH), R_f 0.53 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum, ν, cm^{-1}: 3343 br (OH), 1707, 1672 (C=O), 1607 (C=C_{arom}). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.84 s (12H, CH_3), 5.05 s (1H, CH), 6.48 d (1H, 6-H, J = 5.8 Hz), 6.64 m and 6.89 m (4H each, C_6H_4), 10.52 d.d (1H, 1-H, J = 5.8, 1.5 Hz), 11.02 d (1H, 3-H, J = 1.5 Hz). Found, %: N 15.26. $C_{21}H_{24}N_4O_2$. Calculated, %: N 15.37.

5-{Bis[4-(diethylamino)phenyl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione (VIIIb) was synthesized from aldehyde **IIIa** and *N*,*N*-diethylaniline. Yield 85%, mp 280–281°C (from EtOH), R_f 0.43 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum, ν, cm^{-1}: 3232 br, 3155 br (NH), 1713, 1665 (C=O), 1607 (C=C_{arom}). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.13 t (12H, CH_2CH_3, J = 7.0 Hz), 3.31 q (8H, CH_2CH_3, J = 7.0 Hz), 5.04 s (1H, CH), 6.46–6.58 m (5H, 6-H, *m*-H), 6.85 m (4H, *o*-H), 10.11 br.d (1H, 1-H, J = 5.7 Hz), 10.74 br.s (1H, 3-H). Found, %: N 12.97. $C_{25}H_{32}N_4O_2$. Calculated, %: N 13.32.

5-{Bis[4-(isobutylamino)phenyl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione (VIIIc) was synthesized from aldehyde **IIIa** and *N*-isobutylaniline. Yield 65%, mp 237–238°C (from EtOH), R_f 0.58 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum, ν, cm^{-1}: 3287, 3170, 3140 (NH), 1709, 1653 (C=O), 1607 (C=C_{arom}). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.96 d (12H, CH_3, J = 6.6 Hz), 1.86 non (2H, $CHCH_2$, J = 6.6 Hz), 2.80 d (4H, CH_2, J = 6.6 Hz), 4.96 br.s (2H, $NHCH_2$), 4.99 s (1H, 5-CH), 6.43 m (4H, *m*-H), 6.44 d (1H, 6-H, J = 5.6 Hz), 6.76 m (4H, *o*-H), 10.38 d.d (1H, 1-H, J = 5.6, 1.8 Hz), 10.72 d (1H, 3-H, J = 1.8 Hz). Found, %: N 13.48. $C_{25}H_{32}N_4O_2$. Calculated, %: N 13.32.

5-{Bis[4-(dimethylamino)phenyl]methyl}-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (VIIId) was synthesized from aldehyde **IIIb** [10] and *N*,*N*-dimethylaniline. Yield 74%, mp 184–186°C (from EtOH), R_f 0.30 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum, ν, cm^{-1}: 1718 s (C=O), 1615 s (C=C_{arom}). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.79 s (3H, 6-CH_3), 2.85 s (12H, NCH_3), 5.42 s (1H, CH), 6.64 m (4H, *m*-H), 6.91 m (4H, *o*-H), 10.55 br.s (1H, 1-H), 10.90 br.s (1H, 3-H). Found, %: N 14.58. $C_{22}H_{26}N_4O_2$. Calculated, %: N 14.80.

5-{Bis[4-(diethylamino)phenyl]methyl}-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (VIIIe) was synthesized from aldehyde **IIIb** and *N*,*N*-diethylaniline. Yield 79%, mp 286–287°C (from EtOH), R_f 0.57 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum, ν, cm^{-1}: 1715 s (C=O), 1612 s (C=C_{arom}). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.06 t (12H, CH_2CH_3, J = 7.0 Hz), 1.79 s (3H, CH_3), 3.28 q (8H, CH_2CH_3, J = 7.0 Hz), 5.37 s (1H, CH), 6.56 m and 6.88 m (4H each, C_6H_4), 10.54 d (1H, 1-H, J = 1.5 Hz), 10.90 d (1H, 3-H, J = 1.5 Hz). Found, %: N 12.68. $C_{26}H_{34}N_4O_2$. Calculated, %: N 12.89.

4,4′-[(2-Chloro-8-methylquinolin-3-yl)methylene]bis(*N*,*N*-dimethylaniline) (IXa) was synthesized from aldehyde **IV** [11] and *N*,*N*-dimethylaniline. Yield 65%, mp 205–206°C (from EtOH), R_f 0.44 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum: ν 1612 cm^{-1}, s (C=C_{arom}). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 2.75 s (3H, 8-CH_3), 2.93 s (12H, NCH_3), 5.72 s (1H, CH), 6.60 m and 6.87 m (4H each, C_6H_4), 7.36 d.d (1H, J = 7.9, 7.3 Hz) and 7.48–7.55 m (2H) (5-H, 6-H, 7-H), 7.59 s (1H, 4-H). Found, %: N 9.50. $C_{27}H_{28}ClN_3$. Calculated, %: N 9.77.

4,4′-[(2-Chloro-8-methylquinolin-3-yl)methylene]bis(*N*,*N*-diethylaniline) (IXb) was synthesized from aldehyde **IV** and *N*,*N*-diethylaniline. Yield 73%, mp 177–178°C (from EtOH), R_f 0.48 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum: ν 1612 cm^{-1}, s (C=C_{arom}). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.15 t (12H, CH_3CH_2, J = 7.0 Hz), 2.71 s (3H, 8-CH_3), 3.33 q (8H, CH_2CH_3, J = 7.0 Hz), 5.68 s (1H, CH), 6.53 m and 6.83 m (4H each, C_6H_4); 7.36 d.d (1H, J = 8.0, 7.1 Hz), 7.49 m (1H), and 7.55 m (1H) (5-H, 6-H, 7-H), 7.63 s (1H, 4-H). Found, %: N 8.50. $C_{31}H_{36}ClN_3$. Calculated, %: N 8.64.

2-Chloro-3-{bis[4-(dimethylamino)phenyl]-methyl}-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (X) was synthesized from aldehyde **V** [12] and *N*,*N*-dimethylaniline. Yield 68%, mp 199–200°C (from EtOH), R_f 0.47 (*i*-BuOH–H_2O–AcOH, 2:2:1). IR spectrum, ν, cm^{-1}: 1782 (C=O), 1608 s (C=C_{arom}). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 2.90 s (12H, CH_3), 5.74 s (1H, CH), 6.57 m and 7.09 m (4H each, C_6H_4), 7.27 d.d.d (1H, 7-H, J = 7.3, 6.7, 1.3 Hz), 7.57 d.d.d (1H, 9-H, J = 8.8, 1.3, 0.8 Hz), 7.88 d.d.d (1H, 8-H, J = 8.8, 6.7, 1.6 Hz), 8.89 d.d.d (1H, 6-H, J = 7.3, 1.6, 0.8 Hz). Found, %: N 12.65. $C_{25}H_{25}ClN_4O$. Calculated, %: N 12.94.

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