Transition Metal Free Reductive Dimerization of Nitrogen Containing Barbituric Acid Benzylidenes

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Through the NMR monitoring of the reactive intermediates in the condensation of barbituric acid with nitrogen containing heterocyclic 2-carboxaldehydes, a synthetic procedure was developed for the preparation of each of the intermediates. The simple high yield procedure for the preparation of the reductive dimer from corresponding barbituric acid benzylidenes was developed, although we were not able to elucidate the source of the reduction. The structure of the dimer was confirmed by X-ray analysis.

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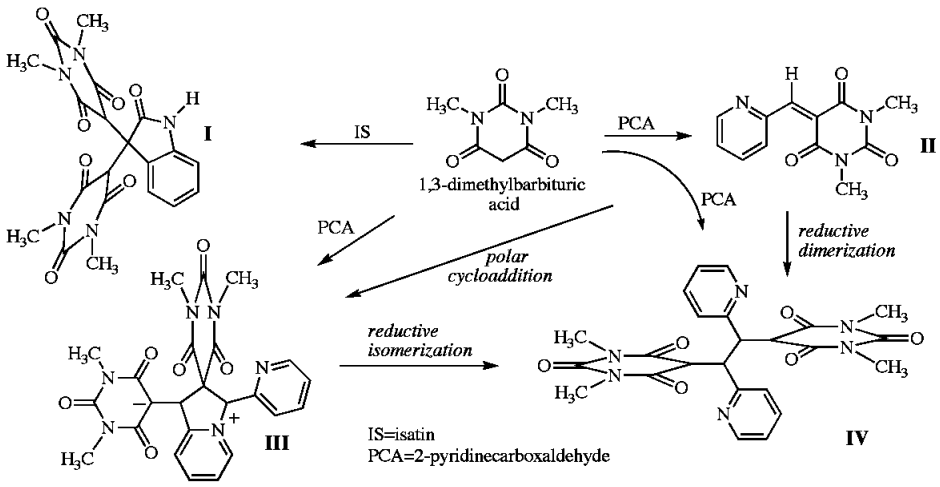
Heterocyclic derivatives of pyrimidinetriones (barbituric acids) are proven to have a wide variety of biological activity [1]. One of the their most exciting pharmacological properties comes from the fact that they can stimulate immune lymphocyte activity [2]. There are also indications that salts of aromatic dibarbiturates might have immune-modulating activity [3]. In some of our previous studies, we were able to add two barbituric acid moieties to heterocycles such as isatin, which resulted in the generation of the new flexible dibarbituric acid heterocycle **I** (Scheme 1) [4]. It was postulated that the reactive intermediate of this reaction is the Knoevenagel-type of condensation product **II** [5]. In many cases, this reactive intermediate is hard to isolate and a second barbituric acid is added by virtue of Michael-type reaction [6]. The condensation product **II**, synthesized from heterocyclic aldehydes such as 2-pyridinecarboxaldehyde, is a very reactive species that readily dimerize into the polar [2+3] cycloadduct **III** (Scheme 1) [7]. Unfortunately, our preliminary results suggest that this compound does not have either immune-modulating or strong sedative activity [8]. We believe this is due to the inflexibility of both the barbituric acids and heterocyclic moieties in the polar cycloadduct **III**. Therefore, we have focused our research towards the preparation of the new and more flexible dibarbituric acid heterocyclic derivatives **IV** that are reductive isomers of **III**. Through close examination of the structural similarity of **II**, **III**, and **IV**, it becomes evident that the latter can be prepared either by controlled reductive dimerization of **II** or by reductive isomerization of **III** (Scheme 1). Unfortunately, there is no literature evidence that suggests any of the transformations into **IV** outlined in Scheme 1. There are, however, several reports that target the reductive dimerization of aromatic α,β-unsaturated compounds [9].

In each of these reported reductive dimerization reactions, the presence of transition metals or transition metal complexes are required. However, we would like to perform the reductive dimerization and prepare the target compounds without the use of a metal catalyst. Our target is to prepare nitrogen heterocycles with methylbarbiturate attached in the 2-position. Consequently, we decided to

Scheme 1



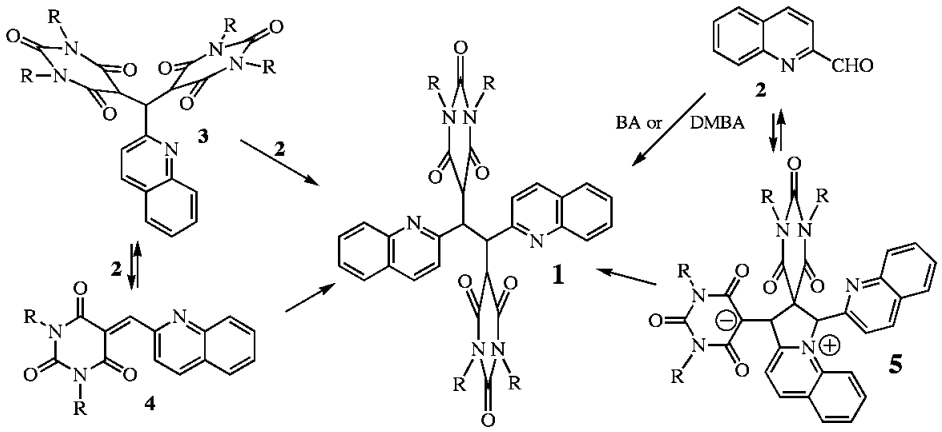
Some reaction routes for the preparation of the more flexible dibarbituric acid-dipyridine **IV**.

perform a thorough investigation of the condensation reaction between 2-quinolinecarboxaldehyde with barbituric acid derivatives. Possible reaction outcomes for this reaction are presented in Scheme 2.

cases, the preparation of **1** should be a "safe exit" from this reaction equilibrium.

An ideal solvent to explore the presence of the reaction intermediates by ^{1}H-NMR spectroscopy is dimethyl sul-

Scheme 2



All possible products of condensation between barbituric acid and 2-quinolinecarboxaldehyde.

From our previous spectroscopic studies, we know that many structural species are present in the reaction mixture when the condensation reactions between aromatic aldehydes and barbituric acid derivatives are performed. Many of these intermediates are in equilibrium and it is possible to select proper reaction conditions that enable the elimination (precipitation) of one of the reactive intermediates from the reaction mixture. In doing so, we would be able to develop synthetic procedures for the preparations of **3**, **4**, and **5**. On the other hand, if our target compound **1** can be prepared from **5** by reductive isomerization or from **4** by reductive dimerization, then these intermediates are eliminated from the reaction equilibrium. In any of these

foxide, simply because all of these intermediates are soluble in small quantities in this solvent. Part of our NMR reaction-following experiment is presented in Figure 1 [10]. The reaction is performed with low concentrations of 2-quinolinecarboxaldehyde (0.5 *M*) and 1,3-dimethylbarbituric acid (1 *M*). NMR signals for all but the reductive product **1b** can be observed in the NMR experiment. Formation of the Knoevenagel condensation product **4b** (distinctive doublet at 8.52 ppm) was the major intermediate in the reaction mixture for the first 15 minutes. To this intermediate, an additional molecule of barbituric acid was added and intermediate **3b** became predominant in the reaction mixture. If the reaction mixture was left at room

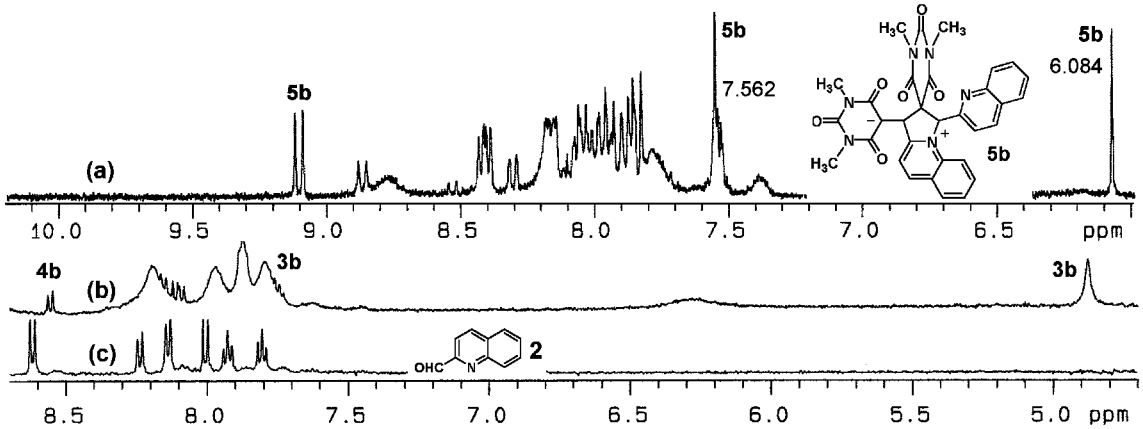


Figure 1. The NMR reaction-following experiment (DMSO-d_6) of the 2-quinolinecarboxaldehyde condensation with 1,3-dimethylbarbituric acid after one hour (b) and after 24 hours (a)

temperature for 24 hours, then the dominant reaction intermediate became the polar cycloadduct **5b** (Figure 1). This is not a surprising result because polar solvents such as dimethyl sulfoxide stabilize, by solvating, the intermediate with highest degree of charge separation, such as **5b**.

If it is possible to protonate the nitrogen atom of intermediate **4**, then the formation of polar cycloadduct **5** should be eliminated. If the reaction was performed in aqueous hydrochloric acid as a reaction media, then 2-quinolinecarboxaldehyde **2** was fully protonated and the aldehyde group was hydrated (case (**a**) in Figure 2). This makes the aldehyde group quite more reactive and fully eliminates the formation of any other intermediate in the condensation reaction. In fact, this procedure was used for the high yield-high purity preparations of both hydrochlorides of **3a** and **3b**. When acetic acid was used as a reaction media then the non-protonated **3a** and **3b** derivatives were prepared.

Surprising results were obtained if the reaction was carried out in trifluoroacetic acid instead of acetic acid. A new product formed from the reactive intermediate **4b** (Figure 3). After the starting aldehyde was consumed (about 40 minutes) the reaction mixture contained almost equal amounts of **4b** and the new product, which we assumed to be our reductive dimer **1b**. We were able to separate both of the products. Compound **1b** has exceptionally low solubility and it is very hard to handle experimentally, nevertheless, we were able to purify and prepare an X-ray quality single crystal from CF_3SO_3H-CH_3CO_2H-H_2O solvent. The X-ray crystal structure fully agrees with our assumption that **1b** is the reductive dimer.

Compound **1b** exists as a trifluoromethanesulfonic acid salt and crystallized with two trifluoromethanesulfonates and two molecules of water. Both trifluromethanesulfonate and quinolinium moieties of the salt are involved in hydrogen bonding interactions with the two water molecules, and the molecule has C_i symmetry (Figure 4).

As seen in the NMR reaction-following experiment, trifluoroacetic acid is not a suitable reaction media for the preparation of our desired reductive dimer **1** because almost equal amounts of **1** and **4** are formed. It is not quite clear what molecular species in the reaction mixture is oxidized in the course of the reductive dimerization. Nevertheless, this experiment confirms the possibility to prepare flexible diheterocyclic dibarbiturates through reductive dimerization. Clearly, a better synthetic procedure was required for the synthesis of **1**. Realizing that one of the reasons it was possible to separate **4b** from **1b** in trifluoroacetic acid solution was due to the low solubility of **1b**, as well as the fact that this compound also has very low solubility in dimethyl sulfoxide, we concluded that dimethyl sulfoxide might be a suitable reaction media for the preparations of both **1** and **IV**. If the reaction is performed at high temperatures, then this solvent can be used to precipitate our target compound from the reaction mixture. As demonstrated earlier, if the reaction is performed at low concentrations of reactants, then polar cycloadduct **5b** is the dominant intermediate in the solution. To accomplish the synthesis of our desired product **1** in the same reaction media, the reaction was performed in highly concentrated dimethyl sulfoxide. This procedure was successful for the preparation of compound **1** in high isolated yield.

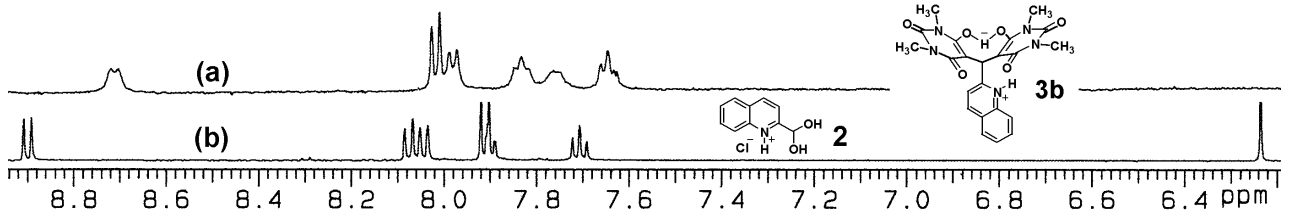


Figure 2. The ^{1}NMR reaction-following experiment in 5% HCl-D_2O 1 *M* aldehyde solution (a) after 20 minutes and (b) the pure aldehyde.

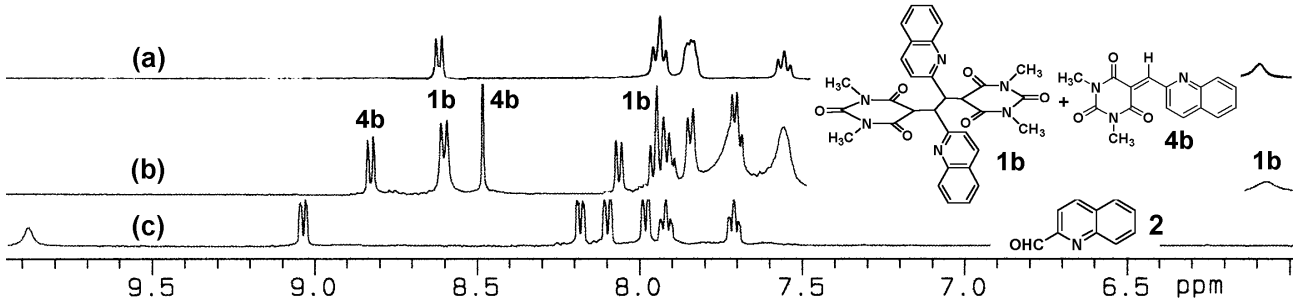


Figure 3. The ^{1}H-NMR (CF_3CO_2H-DMSO-d_6) reaction-following of the condensation reaction; (a) isolated pure product **1b**, (b) reaction mixture after 40 minutes, and (c) the pure aldehyde **2**.

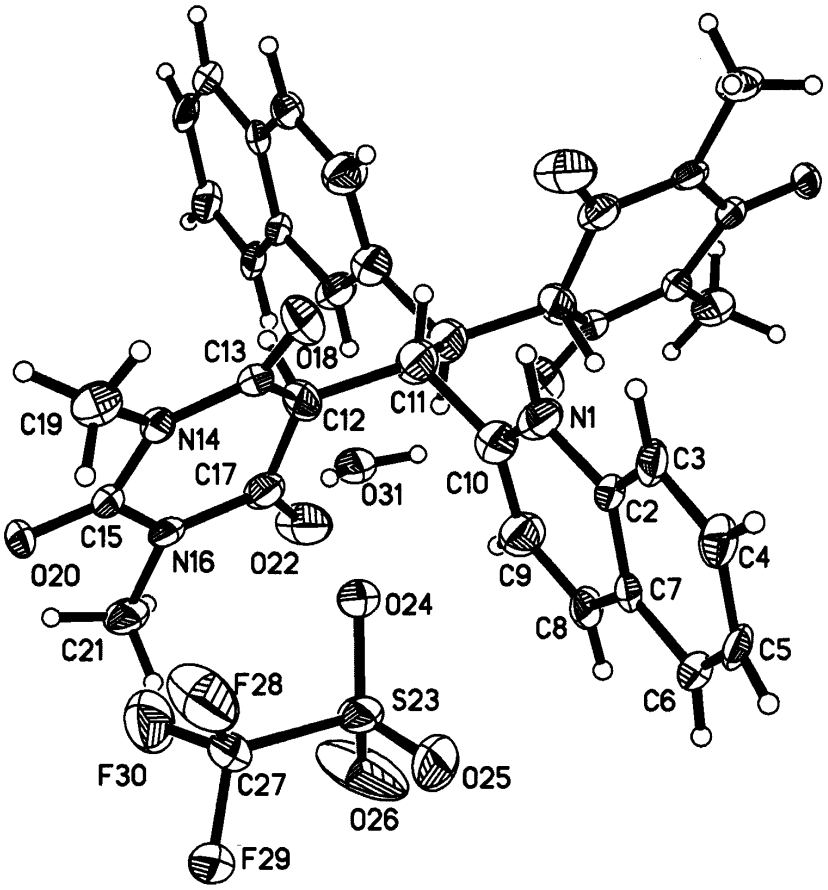


Figure 4. The ORTEP picture of the X-ray determined structure of trifluoromethanesulfonic acid salt of **1b**.

It can be concluded that we have developed a procedure for the reductive dimerization of barbituric acid benzylidenes with nitrogen in alpha position without the use of metal complexes. The recommended preparation should start from the desired barbituric acid and heterocyclic 2-carboxaldehyde in highly concentrated dimethyl sulfoxide [11]. Although the preparative yield of **1** is very high, we do not have an explanation as to which of the components in the reaction mixture causes the reductive dimerization.

EXPERIMENTAL

All solvents and starting materials in this synthesis were obtained from Aldrich and are used without further purification. Thin-layer chromatography was performed using plastic-based 0.25 mm thick silica gel 60 F-254 plates (E. Merc, Inc.) with CH_3COOH:CH_3OH=1:1 as solvent. All ^1H and ^{13}C NMR are recorded in DMSO-d_6 on Gemini 2000 Varian instrument with the chemical shift of the solvent at 2.49 and 36.0 ppm as referenced in hydrogen and carbon NMR spectra. The MS-ES$^+$ spectra of our product in CH_3OH-CH_3COOH solutions were acquired with a sector instrument with a mass of charge (*m/z*) range of 5000. A Micromass Autospec M mass spectrometer with an electro-spray source was used. The ES-MS parameters (*i.e*. pressure, temp, and voltage on the needle, *etc*.) were kept constant in each series of solutions. A flow rate of 10 μL/min was applied using 100 μL of sample solution. Elemental analyses were performed by Atlantic Microlab, Inc. X-ray structure determination was performed on Bruker SMART 1KCCD automated diffractometer. Crystals of compound 2 were obtained by crystallization from methanol by allowing slow solvent evaporation.

Preparation of Hydrochloride of 5,5'-(Quinolin-2-ylmethylene)-bispyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3aHCl**).

In an open beaker (100 mL) both 2-quinolinecarboxaldehyde (157 mg; 1 mmol) and barbituric acid (256 mg; 2 mmol) were dissolved in concentrated hydrochloric acid (20 mL). Both reactants instantly dissolved and clear brown reaction mixture resulted. The reaction mixture was left in an open beaker for 40 hours to eliminate the majority of gaseous hydrochloride from the reaction mixture. Yellow suspension was cooled in an ice-water bath for one hour and the solid was separated by filtration, washed with methanol and dried on open air resulting in 91% (395 mg) of the hydrochloride product. The compound is not soluble in acetic acid, dimethyl sulfoxide, and it is slightly soluble in D_2O. The NMR spectrum was recorded in D_2O with a few drops of DMSO-d_6 as internal standard (2.50 ppm). ^1H-NMR(D_2O-DMSO-d_6, 500 MHz): δ 8.78 (1H, d, *J* = 9 Hz), 8.17 (1H, d, *J* = 9 Hz), 8.07 (1H, d, *J* = 8.0 Hz), 7.912 (1H, t, *J* = 8.0 Hz), 7.80 (1H, d, *J* = 9 Hz), and 7.74 ppm (1H, t, *J* = 8.0 Hz).

Preparation of Hydrochloride of 5,5'-(Quinolin-2-ylmethylene)-bis(1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3bHCl**).

Concentrated hydrochloric acid (10 mL) solution of 2-quinolinecarboxaldehyde (157 mg; 1 mmol) was diluted with water (10 mL) and 1,3-dimethylbarbituric acid (320 mg; 2 mmol) was added. A clear red reaction mixture was left at room temperature overnight (~15 hours). The formed precipitate was separated by filtration, washed with ice water (3x5 mL) and stirred in methanol (50 mL) for 30 minutes. From the methanol suspension a solid material was separated by filtration, washed with methanol (3x10 mL) and dried at 110 ºC for one hour to afford 370 mg (76%) pure product. ^{1}H-NMR (D_2O-DMSO-d_6, 500 MHz): δ 8.68 (1H, d , *J* = 8.0 Hz), 8.08 (1H, d, *J* =8.5 Hz), 8.07 (1H, d, *J* =8.5 Hz), 7.91 (1H, t, *J* = 8.0 Hz), 7.77 (1H, d, *J* = 9.5 Hz), 7.73 (1H, t, *J* = 7.5 Hz), and 3.04 ppm (12H, s); ^{1}H-NMR (CD_3CO_2D, 500 MHz): δ 8.931 (1H, d, *J*=8.5 Hz), 8.25 (2H, d, *J*=8.0 Hz), 8.08 (1H, t, J=7.5 Hz), 8.06 (1H, d, *J*=8.5 Hz), 7.90 (1H, t, *J*=8.0 Hz), and 3.28 (12H, s, four CH_3 barbituric acid groups); ^{13}C-NMR (CD_3CO_2D, 500 MHz) δ 165.5, 162.5, 153.4, 147.3, 138.7, 135.5, 130.4, 129.9, 128.7, 123.7, 121.7. 86.4, and 29.2 ppm.

Preparation of 5,5'-(Quinolin-2-ylmethylene)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3a**).

2-Quinolinecarboxyaldehyde (157 mg; 1 mmol) and barbituric acid (260 mg; 2 mmol) were mixed with glacial acetic acid (50 mL) and stirred at room temperature. After approximately 10 minutes from the red reaction solution a white solid started to precipitate. The reaction suspension was stirred at room temperature for 16 hours. The white precipitate was separated by filtration, washed with methanol (3x25 mL) and dried at 110 ºC for three hours producing 310 mg (78%) of pure product. ^{1}H-NMR (D_2O-NaOH, DMSO-d_6, 500 MHz): δ 8.69 (1H, d, *J*=8.0 Hz), 8.49 (1H, d, *J*=8.5Hz), 8.47 (1H, d, *J*=8.0 Hz), 8.30 (1H, t, *J*=8.0 Hz), 8.12 (1H, t, *J*=8.0 Hz), 8.09 (1H, d, *J*=8.5 Hz), and 6.13 ppm (1H, s); ^{13}C-NMR (D_2O-NaOH-DMSO-d_6, 500 MHz): δ 172.7, 171.1 (two barbituric acid carbonyls), 161.1, 147.8, 137.1, 130.8, 139.3, 128.3, 128.0, 126.7, and 124.2 (nine quinoline carbons), 94.5 (benzyl carbon), and 42.1 ppm (barbituric C-5).

Anal. Calcd for $C_{18}H_{13}N_5O_6$: C, 54.69; H, 3.31; N, 17.72. Found: C, 54.75; H, 3.36; N, 17.84.

Preparation of 5,5'-(Quinolin-2-ylmethylene)bis(1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3b**).

Acetic acid (50 mL) solution of 2-quinolinecarboxyaldehyde (157 mg; 1 mmol) and 1,3-dimethylbarbituric acid (320 mg; 2 mmol) was stirred at room temperature for five hours. The solvent was evaporated at reduced pressure and jelly red residue was mixed with 100 mL methanol and stirred at room temperature for additional five hours. The solid product of the reaction was separated by filtration, washed with methanol (3x15 mL) and dried at 110 ºC for one hour. The yield of the reaction is 405 mg (90%). ^{1}H-NMR (CD_3CO_2D, 500 MHz): δ 8.93 (1H, d, *J*=8.5 Hz), 8.25 (1H, d, *J*=8.5 Hz), 8.24 (1H, d, *J*=8.0 Hz), 8.08 (1H, t, *J*=7.5 Hz), 8.06 (1H, d, *J*=8.5 Hz), 7.89 (1H, t, *J*=8.0 Hz), and 3.28 (12H, s, four CH_3 barbituric acid groups); %): ^{13}C-NMR (CD_3CO_2D, 500 MHz): δ 166.4, 162.8 (two different carbonyl carbons of the barbituric acid moieties), 153.4, 147.3, 138.7, 135.5, 130.3, 129.9, 128.6, 123.5, 121.5 (nine carbons of the quinoline ring), 41.0 (barbituric acid C-5 carbon), 86.7 (benzyl carbon) and 29.2 ppm (methyl carbon).

Anal. Calcd for $C_{22}H_{21}N_5O_6$: C, 58.53; H, 4.69; N, 15.51. Found C, 58.41; H, 4.77; N, 15.38.

Preparation of 1,3-Dimethyl-5-(quinolin-2-ylmethylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4b**).

Trifluoroacetic acid solutions of 2-quinolinecarboxaldehyde (157 mg; 1 mmol in 10 mL of TFA) and 1,3-dimethylbarbituric acid (156 mg; 1 mmol in 5 mL of trifluoroacetic acid) were mixed together at room temperature and left at this temperature for one hour. ^{1}H-nmr data showed almost full transformation of the starting materials into products. Reaction mixture was ice cooled and poured into a suspension of ethyl acetate (400 mL) and anhydrous sodium carbonate. The resulting suspension was stirred at room temperature for one hour. The liquid was separated by filtration and evaporated to give an oily residue that contains substantial amount of sodium salts of both trifluoroacetic and acetic acid. The residue was dissolved in tetrahydrofuran and filtered through a short column of silica gel with THF as eluent to eliminate sodium salts. Tetrahydrofuran solution was evaporated to the solid residue that was crystallized from a small amount of tetrahydrofuran producing only 60 mg of the product (20% yield). ^{1}H-NMR (CF_3SO_3H-DMSO-d_6, 500 MHz): δ 8.56 (1H, d, *J*=8.5 Hz), 8.16 (1H, s, vinyl hydrogen), 7.74 (1H, d, *J*=8.5 Hz), 7.68 (3H, d+d+t), 7.45 (1H, t, *J*=8.0 Hz), 2.98 (3H, s, CH_3), and 2.91 ppm (3H, s, CH_3).

Typical Procedure for Preparation of Reductive Dimers. Preparation of 5,5'-(1,2-diquinolin-2-ylethane-1,2-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**1a**).

2-Quinolinecarboxaldehyde (157 mg, 1 mmol) was dissolved in dimethylsulfoxide (0.5 mL) and barbituric acid (128 mg; 1 mmol) was added. Clear reaction mixture was heated at 120 ºC for thirty minutes. Formed reaction suspension was diluted with methanol (20 mL). Insoluble product was separated by filtration, washed with methanol (3x20 mL) and dried at 110 ºC for one hour. The yield is 86% (230 mg). ^{1}H-NMR (CD_3CO_2D-CF_3SO_3H, 500 MHz): δ 9.18 (1H, d, *J*=8.5 Hz), 8.49 (1H, d, *J*=8.5 Hz), 8.35 (1H, d, *J*=9.0 Hz), 8.30 (1H, d, *J*=8.0 Hz), 8.17 (1H, t, *J*=8.5 Hz), 7.96 (1H, t, *J*=8.0 Hz), and 6.39 ppm (1H, s). ^{1}H-NMR (D_2O-NaOH-DMSO-d_6, 500 MHz): δ 8.24 (1H, d, *J*=8.5 Hz), 8.00 (1H, d, *J*=9.0Hz), 7.78 (1H, d, *J*=8.5 Hz), 7.74 (1H, d, *J*=8.0 Hz), 7.56 (1H, t, *J*=7.0 Hz), 7.39 (1H, t, *J*=8.0 Hz), and 5.95 ppm (1H, s).

Anal. Calcd for $C_{28}H_{20}N_6O_8$: C, 62.68; H, 3,76; N, 15.66. Found: C, 62.55; H, 3.85; N, 15.51.

1,3,1',3'-Tetramethyl-5,5'-(1,2-diquinolin-2-ylethane-1,2-diyl)-dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**1b**).

Reductive dimer **1b** was prepared in 88% yield (260 mg) by following the procedure for preparation **1a**. ^{1}H-NMR (CD_3COOD): δ 8.82 (1H, d, *J*=0.028, quinoline 3-H), 8.35 (1H, d, *J*=0.028, quinoline 4-H), 8.17 (1H, d, *J*=0.027, quinoline 8-H), 8.11 (1H, t, *J*=0.024, quinoline 7-H), 8.08 (1H, d, *J*=0.029, quinoline 5-H), 7.86 (1H, t, *J*=0.027, quinoline 6-H), 6.34 (1H, s, benzyl hydrogen), 3.13 (6H, s, methyl hydrogens), ^{13}C-NMR (CD_3COOD): δ 165.57, 162.01, and 161.96 (three different carbonyls from barbituric acid), 153.72, 146.33, 138.06, 135.11, 130.15, 129.69, 128.54, 124.30, and 121.91 (nine carbons for quinoline moiety), 87.66 (benzyl carbon, 43.15 (barbituric 5-C carbon), and 28.70 ppm (methyl carbon of barbituric acid moiety). In THF as a solvent compound has very low R_f value (0.04). ES-MS$^+$ in CH_3COOH; 593 (M+1).

Anal. Calcd for $C_{32}H_{28}N_6O_6$: C, 64.86; H, 4.76; N, 14.18. Found: C, 64.71; H 4.88, N 14.06.

1,3,1',3'-Tetramethyl-5,5'-(1,2-dipyridin-2-ylethane-1,2-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**IV**).

Compound **IV** was prepared in 69% yield (170 mg) by following the procedure for preparation of **1a**. ^{1}H-NMR (CD_3CO_2D-F_3CSO_3H-D_2O): δ 8.58 (1H, d, *J*=6 Hz), 8.42 (1H, t, J=8.0 Hz), 8.15 (1H, d, *J*=8.0 Hz), 7.88 (1H, d, *J*=6.0 Hz), and 3.15 ppm (6H, s, CH_3); ^{13}C-NMR (CD_3CO_2D-F_3CSO_3H-D_2O): δ 164.28, 155.64, 153.16 (three carbonyls), 146.96, 141.24, 132.48, 128.70, 126.28 (five carbons of pyridine ring), 91.88 (benzyl carbon), 39.05 (barbituric C-5), and 29.04 ppm (methyl carbon).

Anal. Calcd for $C_{24}H_{24}N_6O_6$: C, 58.53; H, 4.91; N, 17.06; O, 19.49. Found: C, 58.41; H 5.02, N 16.86.

X-ray structure determination of structure **1b** at 155(2) K.

Crystal Data.

Crystals of compound **1b** were obtained by crystallization from CH_3CO_2H-CF_3SO_3H-H_2O. All reagents and solvents were purchased from Aldrich and used without prior purification. X-Ray Single Crystal Structure Determination of Compound **1b** at 150(2) K *Crystal Data*: $C_{17}H_{17}F_3N_3O_7S$; M_r=464.40, Triclinic, space group *P-1*, *a*=8.788(4) Å, *b*=9.548(5) Å, *c*=11.644(6) Å, α=92.651(9)°, β=106.162(9)°, γ=93.811(10)°, V=934.3(8) Å^3, Z=2, ρ_{calcd} 1.651 Mgm^{-3}, F_{000}=478, Wavelength (λ) = 0.71073 Å, Absorption coefficient (μ)=0.252 mm^{-1}. Data Collection and Reduction: Crystal size: 0.10x0.15x0.5 mm, Theta range: 1.82 to 23.37°, Index ranges: -9≤h≤9, -8≤k≤10, -12≤l≤11, Reflections collected: 4328, Independent reflections: 2426 [R_{int}=0.0295], Refinement method: Full-matrix least-squares on F^2, Data/restraints/parameters: 5388/253/293. Final *R* indices [I>2σ(I)]: R_1=0.0507, wR_2=0.0803, Goodness-of-fit on F^2: 1.112. *R* indices (all data) R_1=0.0758, wR_2=0.0758, Largest diff. peak and hole: 0.667 and -0.384 eÅ^{-3}. Compound **1b** belongs to C_i symmetry point group. This symmetry was used to generate its final structure. Measurement, Computing and Graphics: *SMART 1K CDD* (Bruker, 2000); cell refinement: *SMART*; data reduction *SAINT-Plus* (Bruker, 2000); programs(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELX97* (Sheldrick, 1997); molecular graphics: *SHELXTL97* (Sheldrick, 1997); software used to prepare material for publication: *SHELXTL97* [12].

Acknowledgement.

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[9] For instance see: [a] J. Shey, C. M. McGinley, K. M. McCauley, A. S. Dearth, B. T. Young and W. A. van der Donk, *J. Org. Chem.*, **67**, 837 (2002): [b] C. H. Oh, H. S. Yoo and S. H. Jung, *Chem. Lett.*, , 1288 (2001); [c] M. Yamashita,; K. Okuyama,; I. Kawasaki S. Nakamura, R. Nagamine, T. Tsujita and S. Ohta, *Chem. Pharm. Bull.*, **48**, 1799 (2000) and references therein.

[10] All NMR reaction monitoring was performed on VARIAN UNITY 500 operating 500 MHz with solvent signal as an internal standard starting with heterocyclic carboxaldehyde concentration to be 1 *M*.

[11] Although preparation of the reductive dimer of barbituric acid benzylidenes with both 2-pyridine and 2-quinoline moieties are synthetically excellent procedures the reductive dimerization product was not detected if nitrogen was in any other position of the aromatic ring or if benzene, naphthalene and antracene were used instead of pyridine and quinoline rings. At the present moment we do not have an explanation for these differences in the reactivity.

[12] Bruker(2000). *SMART*(Version 5.060) and *SMART-Plus*(Version 6.02). Bruker AXS Inc., Madison, Wisconsin, USA; [b] Sheldick, G. M. (1997). *SHELXTL* DOS/Windows/NT. Version 5.1. Bruker AXS Inc., Madison, Wisconsin, USA; [c] Sheldrick, G. M.(1997) *SHELXL-97*, University of Göttingen, Göttingen, Germany.