Article

Diastereoselective T-reaction of 1-alkyl-(5-nitro-2-N-morpholino-benzyliden)barbituric acids in the solid state: synthesis of 1-alkyl-2,4,6-trioxoperhydropyrimidino-5-spiro-5'-(8'-nitro-1',3',4',9',10',10#'-hexahydro-2-oxa)-4a-phenanthrenes and their thia analogues

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Diastereoselective T-reaction of 1-alkyl-(5-nitro-2-*N*-morpholino-benzyliden)barbituric acids in the solid state: synthesis of 1-alkyl-2,4,6-trioxoperhydropyrimidino-5-*spiro*-5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa)-4a-phenanthrenes and their thia analogues

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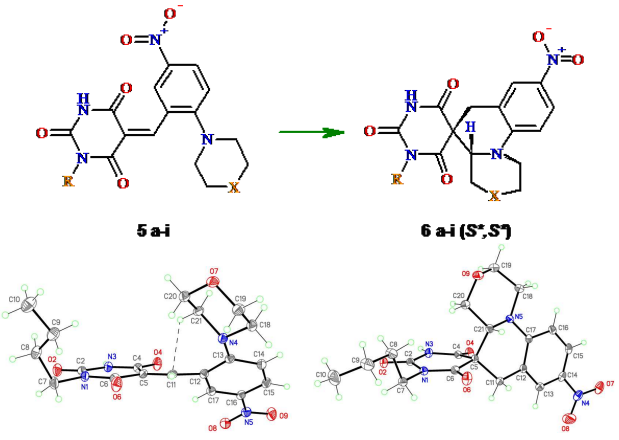
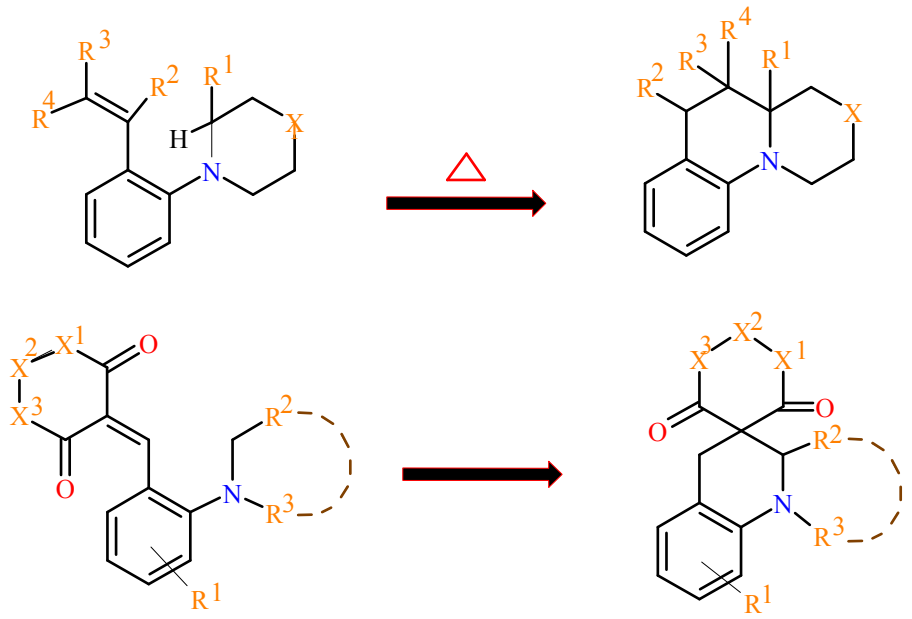
ABSTRACT: 1-Alkyl-(5-nitro-2-*N*-morpholinobenzylidene) barbituric acids undergo *tert*-amino effect reactions (T-reactions) yielding 1-alkyl-2,4,6-trioxoperhydropyrimidino-5-*spiro*-5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa)-4a-phenanthrene derivatives as a mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers. A novel heterophase modification of the T-reaction is proposed, which makes it possible to afford nearly pure (*S**,*S**)-diastereomers in high yields, whereas rearrangement reactions in solutions usually lack stereoselectivity. To our best knowledge, this is the first example of deliberate tuning stereodirection of a T-reaction by external conditions. Using X-ray diffraction analysis we demonstrate that this diastereoselectivity of the solid state T-reaction is due to peculiar crystal structure of starting 5-arylidene barbiturates, which accommodates only one specific conformation fixed by a strong intramolecular C-H…π interaction.



■ INTRODUCTION

The concept of the *tert*-amino effect as formulated by Meth-Cohn and Suschitsky[1] refers to a great number of cyclization reactions involving *o*-substituted tertiary aromatic amines. One of the most important manifestations of the *tert*-amino effect includes the thermal isomerization of 2-vinyl-*N*,*N*-dialkylanilines giving rise to annelated 1,2,3,4-tetrahydroquinoline systems[2-6] (Scheme 1).

Scheme 1. Isomerization (T-reaction) of 2-vinyl-*N*,*N*-dialkylanilines into 1,2-annelated 1,2,3,4-tetrahydroquinolines.



tert-Amino effect reactions (T-reactions) typically require harsh conditions and can be promoted by micro-wave irradiation.[7,8]

Recently, the synthetic potential of the *tert*-amino effect has been considerably extended due to the use of cyclic β-dicarbonyl reagents, which allow such isomerizations to proceed under surprisingly mild conditions.[9,10] A number of 1,2,3,4-tetrahydroquinoline derivatives bearing spirocyclic barbituric acid, Meldrum's acid, or cyclohexene-1,3-dione moieties have been prepared in this fashion.[4,11,12]

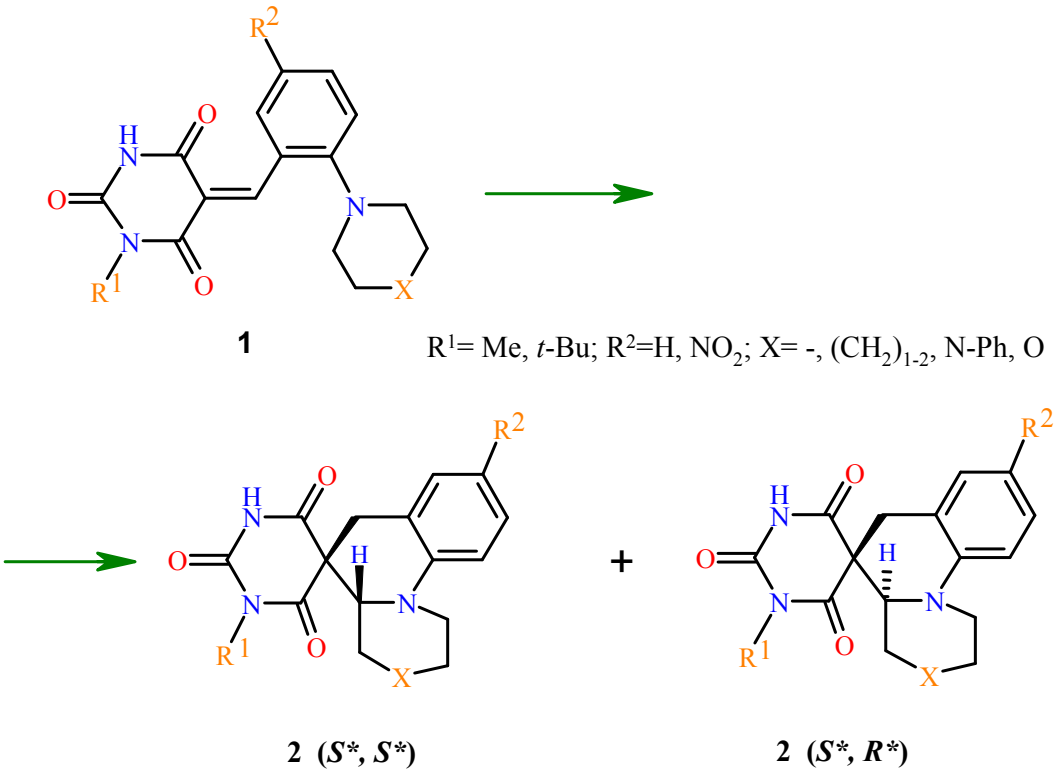
Stereoselective intramolecular cyclizations are of special interest. A few examples of diastereodirected and enantiodirected T-reactions have been described so far even for cyclization reactions proceeding under harsh conditions.[13,14]

If an asymmetric carbon atom is present in the *tert*-amino group, the isomerizations may proceed diastereoselectively.[4,12,15] In some cases, a new chiral center is formed and enantiomerically

pure 1,2,3,4-tetrahydroquinolinic systems can be afforded from chiral substrates.[16-18] In all the above examples, the stereoselectivity of the T-reactions was due to the presence of an asymmetric carbon atom in a starting reactant.

Recently, we have described a stereoselective T-reaction that gives rise to the formation of compounds with two new asymmetric centers. 1-Alkyl-5-arylidenebarbiturates (**1**) obtained by the Knoevenagel condensation of 1-alkylbarbituric acids with corresponding *o*-dialkylaminobenzaldehydes were further cyclized into spirocyclic derivatives (**2**) (Scheme 2)[19]. Compounds **1** for R^2=H were highly reactive so as we were unable to isolate them due to the spontaneous intramolecular cyclization that readily proceeded already at room temperature.

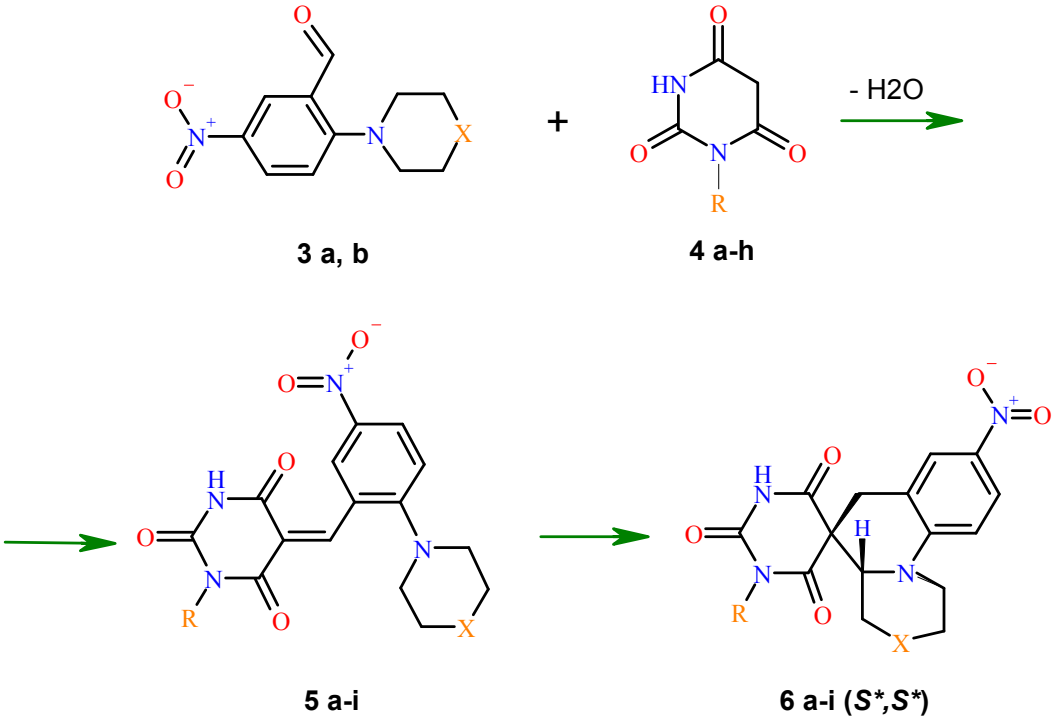
Scheme 2. Formation of 5-spiro barbiturates (**2**) from 5-arylidene-barbituric acids (**1**).



The «rapid» T-reactions typically proceed stereoselectively to afford predominantly (*S**,*S**)-diastereomers of 5-spiro barbituric acid derivatives **2**. In some cases, the diastereomeric purity was as high as 90-100%. To the contrary, 5-arylidenebarbiturates **1** with R^2=NO_2 and X=O were quite stable, their rearrangement required heating and proceeded non stereoselectively.

In this paper, we apply a new procedure to improve diastereoselectivity of the T-reactions by conducting them in the solid state. The study is performed for a series of 1-alkyl-5-(2-morpholin-4-yl-5-nitrobenzylidene)barbiturates (**5a-i**) synthesized from 2-morpholin-4-yl-5-nitrobenzaldehyde (**3**) and 1-alkylbarbituric acids (**4**) (Scheme 3).

Scheme 3. Synthesis of 1-alkyl-5-(2-morpholin-4-yl-5-nitrobenzylidene)barbiturates (5a-i) and their isomerization into 5-spiro barbituric acid derivatives (6a-i) (*S**,*S**).



■ EXPERIMENTAL SECTION

The ^{1}H and ^{13}C NMR spectra were recorded on a AM-500 Bruker spectrometer (500 and 200 MHz, respectively). The purity of synthesized compounds was determined by elemental analysis and ^{1}H NMR spectroscopy. The relative amounts of (*S**,*S**)- and (*S**,*R**)-diastereomers in products **6a-i** were derived from relative intensities of proton signals of NH groups (in ^{1}H NMR spectra) at the integration accuracy better than 2%. The relevant data are collected in Table 1.

Starting aldehyde **3a** was prepared from 2-chloro-5-nitrobenzaldehyde and morpholine by the standard method.[9] 4-Nitro-2-(1,4-thiazinan-4-yl)benzaldehyde **3b** was synthesized by a similar method from 2-chloro-5-nitrobenzaldehyde and thiomorpholine in a yield of 90%, M.p. 117 °C.

Starting 1-alkylbarbituric acids **4a-h** were synthesized from 2-chloro-5-nitrobenzaldehyde and morpholine by the general method.[20]

Single crystals of compound **5f** suitable for X-ray structural analysis were grown from the reaction mixture. Single crystals of compound **6a** were obtained by recrystallization from ethanol. Single crystals of compound **6f** were obtained by a slow evaporation of a solution of **6f** in a CH_2Cl_2-methanol 1:1 mixture.

Spirocyclic products **6** as mixtures of (*S**,*S**)- and (*S**,*R**)-diastereomers were synthesized by method C.

Table 1. Synthesis of spirocyclic derivatives 6a-i under different conditions: overall yields and diastereomeric purities.

Product	R	X	Procedure[a]	Overall yield, %	(*S**,*S**), %
			A	99	>99
6a	Me	O	C	95	50
			D	90	77
6b	Me	S	A	98	95
6c	Et	O	A	98	98
6d	*n*-Pr	O	A	98	93
6e	$CH_2CH{=}CH_2$	O	A	98	96
6f	*n*-Bu	O	B	99	99
6g	*i*-Pr	O	B	94	90
6h	CH_2Ph	O	B	96	94
6i	CH_2CH_2Ph	O	B	97	96

[a] See experimental section

X-ray Single Crystal Structure Analysis. Data were collected on a Bruker SMART APEX-II CCD diffractometer (λ(MoK$_\alpha$)-radiation, graphite monochromator, ω and φ scan mode) and corrected for absorption using the *SADABS* program[21]. For details, see Table 2. The structures were solved by direct methods and refined by a full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms of the NH-groups were localized in the difference-Fourier map and included in the refinement with fixed positional and isotropic displacement parameters. The other hydrogen atoms in both compounds were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters (U_{iso}(H) = 1.5U_{eq}(C) for the CH_3-groups and U_{iso}(H) = 1.2U_{eq}(C) for the other groups). All calculations were carried out using the *SHELXTL* program package[22]. Crystallographic data for **5f** and **6f** have been deposited with the Cambridge Crystallographic Data Center. CCDC 997090 and CCDC 997091 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

Table 2. Crystallographic data for 5f and 6f.

compound	**5f**	**6f**
empirical formula	$C_{19}H_{22}N_4O_6$	$C_{19}H_{22}N_4O_6$
fw	402.41	402.41
T, K	100(2)	100(2)
crystal size, mm	0.30 x 0.24 x 0.01	0.28 x 0.22 x 0.20
crystal system	monoclinic	triclinic
space group	$P2_1/n$	P-1
a, Å	12.065(5)	6.7833(3)
b, Å	11.414(5)	11.0656(5)
c, Å	13.752(5)	13.3501(6)
α, deg.	90	70.2880(10)
β, deg.	92.538(7)	87.0620(10)
γ, deg.	90	84.8850(10)
V, Å^3	1891.9(13)	939.36(7)
Z	4	2
d_c, g · cm^{-3}	1.413	1.423
F(000)	848	424
μ, mm^{-1}	0.107	0.108
$2\theta_{max}$, deg.	56.2	56.0
index range	-15 < = h < = 15	-8 < = h < = 8
	-14 < = k < = 15	-14 < = k < = 14
	-18 < = l < = 18	-17 < = l < = 17
no. of rflns collected	20614	10726
no. of unique rflns	4579	4535
no. of rflns with $I > 2\sigma(I)$	2758	3783
data/restraints/parameters	4579 / 0 / 266	4535 / 0 / 266
R_1; wR_2 ($I > 2\sigma(I)$)	0.0552; 0.1006	0.0397; 0.1019
R_1; wR_2 (all data)	0.1114; 0.1168	0.0479; 0.1071
GOF on F^2	1.000	1.001
T_{min}; T_{max}	0.969; 0.999	0.971; 0.979

General procedure for the synthesis of 5-arylidene barbiturates *5a-f*.

Synthesis of 1-methyl-5-[1-(2-morpholino-4-nitrophenyl)methylidene]hexahydro-2,4,6-pyrimidinetrione (5a). A solution of 5 mmol (0.71 g) 1-methylbarbituric acid **4a** in 50% ethanol (20 ml) was added to a hot solution of 5 mmol (1.18 g) aldehyde **2a** in 96% ethanol (30 ml). The reaction mixture was stirred at 50 °C for 10 min and allowed to stand at 20 °C for 12 h. A precipitate was filtered out, washed with 50% ethanol and dried in air to give 1.45 g (81%) compound **5a** as yellow-orange prismatic crystals, m.p. 197-198 °C; [Found: C 53.14, H 4.65, N 15.21. $C_{16}H_{16}N_4O_6$ required C 53.33, H 4.48, N 15.55%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.56 + 11.50 (1H, s+s, NH, *E* + *Z*), 8.75+8.71 (1H, d+d, *J* 2.6 Hz, $\underline{H}_{arom}$, *E* + *Z*), 8.25 (1H, dd, *J* 8.4, 2.6 Hz, $\underline{H}_{arom}$), 8.23+8.20 (1H, s+s, =C$\underline{H}$, *E* + *Z*), 7.18 (1H, d, *J* 8.4 Hz, $\underline{H}_{arom}$), 3.80 (4H, t, *J* 5.5 Hz, 2OC$\underline{H}_2$), 3.27+3.22 (3H, s+s, N$\underline{Me}$, *E* + *Z*), 3.18 (4H, t, *J* 5.0 Hz, 2NC$\underline{H}_2$).

The same method was used to synthesize:

1-Methyl-5-(1-[4-nitro-2-(1,4-thiazinan-4-yl)phenyl]methylidene)hexahydro-2,4,6-pyrimidinetrione (**5b**). From 1-methylbarbituric acid **4a** and aldehyde **2b** (yield 86%) as yellow-orange prismatic crystals, m.p. 220 °C (Dec.); [Found: C 50.93, H 4.35, N 14.81. $C_{16}H_{16}N_4O_5S$ required C 51.06, H 4.28, N 14.89%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.52 + 11.64 (1H, s+s, NH, *E* + *Z*), 8.65 (1H, d, *J* 2.6 Hz, $\underline{H}_{arom}$,), 8.23 + 8.20 (1H, d+d, *J* 2.6 Hz, $\underline{H}_{arom}$, *E* + *Z*), 8.09+8.06 (1H, s+s, =C$\underline{H}$, *E* + *Z*), 7.22 (1H, d, *J* 8.3 Hz, $\underline{H}_{arom}$), 3.40 (4H, m, 2NC$\underline{H}_2$), 3.21+3.16 (3H, s+s, N$\underline{Me}$, *E* + *Z*), 2.45 (4H, m, 2SC$\underline{H}_2$).

1-Ethyl-5-[1-(2-morpholino-4-nitrophenyl)methylidene]hehahydro-2,4,6-pyrimidine-trione (5c). From 1-ethylbarbituric acid **4b** and aldehyde **2a** (yield 79%) as yellow-orange prismatic crystals, m.p. 189-191 °C; [Found: C 54.64, H 4.80, N 14.88. $C_{17}H_{18}N_4O_6$ required C 54.54, H 4.85, N 14.97%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.56 + 11.49 (1H, s+s, NH, *E* + *Z*), 8/74 + 8.69 (1H, d+d, *J* 2.6 Hz, $\underline{H}_{arom}$, *E* + *Z*), 8.23 (1H, dd, *J* 8.2, 2.6 Hz,, $\underline{H}_{arom}$,), 8.12+8.09 (1H, s+s, =C$\underline{H}$, *E* + *Z*), 7.20 (1H, d, *J* 8.2 Hz, $\underline{H}_{arom}$), 3.79 (4H, m, 2 OC$\underline{H}_2$), 3.75 (2H, m, NC$\underline{H}_2$CH$_3$), 3.17 (4H, m, 2NC$\underline{H}_2$), 1.14 (3H, t, *J* 5.9 Hz, C$\underline{H}_3$).

1-*n*-Propyl-5-[1-(2-morpholino-4-nitrophenyl)methylidene]hehahydro-2,4,6-pyrimidinetrione (5d). From 1-*n*-propylbarbituric acid **4c** and aldehyde **2a** (yield 87%) as yellow-orange prismatic crystals, m.p. 192-194 °C; [Found: C 55.75, H 5.22, N 14.32 $C_{18}H_{20}N_4O_6$ required C 55.67, H 5.19, N 14.43%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.56 + 11.48 (1H, s+s, NH, *E* + *Z*), 8/73 + 8.70 (1H, d+d, *J* 2.6 Hz, $\underline{H}_{arom}$, *E* + *Z*), 8.20 (1H, dd, *J* 8.4, 2.6 Hz,, $\underline{H}_{arom}$,), 8.11+8.08 (1H, s+s, =C$\underline{H}$, *E* + *Z*), 7.24 (1H, d, *J* 8.4 Hz, $\underline{H}_{arom}$), 3.80 (2H, m, NC$\underline{H}_2$), 3.77 (4H, m, 2 OC$\underline{H}_2$), 3.16 (4H, m,

2NC$\underline{H}_2$), 1.52 (2H, m, C$\underline{H}_2$CH$_3$), 1.11 (3H, t, *J* 6.7 Hz, C$\underline{H}_3$).

1-Allyl-5-[1-(2-morpholino-4-nitrophenyl)methylidene]hehahydro-2,4,6-pyrimidine-trione (5e). From 1-allylbarbituric acid **4d** and aldehyde **2a** (yield 89%) as yellow-orange prismatic crystals, m.p. 203-205 °C (Dec.); [Found: C 55.88, H 4.76, N 14.39. $C_{18}H_{18}N_4O_6$ required C 55.96, H 4.70, N 14.50%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.69 + 11.53 (1H, s+s, NH, *E* + *Z*), 8.72 + 8.69 (1H, d+d, *J* 2.7 Hz, $\underline{H}_{arom}$,), 8.24 (1H, m, $\underline{H}_{arom}$), 8.10+8.09 (1H, s+s, =C$\underline{H}$, *E* + *Z*), 7.23 (1H, d, *J* 8.4 Hz, $\underline{H}_{arom}$), 5.83 (2H, m, C$\underline{H}$=CH$_2$), 5.16 (2H, m, =C$\underline{H}_2$), 4.41+4.35 (2H, d+d, *J* 4.9 Hz, NC$\underline{H}_2$, *E* + *Z*), 3.73 (4H, m, 2 OC$\underline{H}_2$), 3.18 (4H, m, 2NC$\underline{H}_2$).

1-n-Butyl-5-[1-(2-morpholino-4-nitrophenyl)methylidene]hehahydro-2,4,6-pyrimidinetrione (5f). From 1-buthylbarbituric acid **4e** and aldehyde **2a** (yield 88%) as yellow-orange prismatic crystals, m.p. 196-198 °C; [Found: C 56.59, H 5.45, N 13.80. $C_{19}H_{22}N_4O_6$ required C 56.71, H 5.51, N 13.92%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.57 + 11.44 (1H, s+s, NH, *E* + *Z*), 8.72 + 8.68 (1H, d+d, *J* 2.6 Hz, $\underline{H}_{arom}$,), 8.25 (1H, m, $\underline{H}_{arom}$), 8.09 + 8.08 (1H, s+s, =C$\underline{H}$, *E* + *Z*), 7.23 (1H, d.d, *J* 8.2, 2.6 Hz, $\underline{H}_{arom}$), 3.80 (2H, t, *J* 6.2 Hz, OC$\underline{H}_2$), 3.74 (4H, m, 2NC$\underline{H}_2$), 3.17 (4H, m, 2NC$\underline{H}_2$), 1.53 (2H, m, C$\underline{H}_2$CH$_2$), 1.32 (2H, m, C$\underline{H}_2$CH$_3$), 0.90 (3H, t, *J* 6.9 Hz, C$\underline{H}_3$).

1-*i*-Propyl-5-[1-(2-morpholino-4-nitrophenyl)methylidene]hehahydro-2,4,6-pyrimidinetrione (5g). From 1-*i*-propylbarbituric acid **4f** and aldehyde **2a** (yield 73%) as yellow-orange prismatic crystals, m.p. 184-186 °C; [Found: 55.79, H 5.13, N 14.29 $C_{18}H_{20}N_4O_6$ required C 55.67, H 5.19, N 14.43%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.48 + 11.36 (1H, s+s, NH, *E* + *Z*), 8.56 (1H, d, *J* 2.8 Hz, $\underline{H}_{arom}$,), 8.25 (1H, m, $\underline{H}_{arom}$), 8.08+8.06 (1H, s+s, =C$\underline{H}$, *E* + *Z*), 7.23 (1H, d.d, *J* 8.8, 2.8 Hz, $\underline{H}_{arom}$, *E* + *Z*), 4.95 (H, m, NC$\underline{H}$), 3.75 (2H, t, *J* 6.2 Hz, OC$\underline{H}_2$), 3.18 (4H, m, 2NC$\underline{H}_2$), 1.40 + 1.38 (3H + 3H, d+d, *J* 7.0 Hz, 2C$\underline{H}_3$, *E* + *Z*).

1-Benzyl-5-[1-(2-morpholino-4-nitrophenyl)methylidene]hehahydro-2,4,6-pyrimidinetrione (5h). From 1-benzylbarbituric acid **4g** and aldehyde **2a** (yield 94%) as red-orange powder, m.p. 144-148 °C; [Found: 60.36, H 4.71, N 12.66 $C_{22}H_{20}N_4O_6$ required C 60.55, H 4.62, N 12.84%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.71 + 11.57 (1H, s+s, NH, *E* + *Z*), 8.76 + 8.71 (1H, d+d, *J* 2.9 Hz, $\underline{H}_{arom}$, *E* + *Z*), 8.25 (1H, d.d, *J* 8.9, 2.9 Hz, $\underline{H}_{arom}$), 8.13 + 8.10 (1H, s+s, =C$\underline{H}$, *E* + *Z*), 7.29 (6H, m, 6 $\underline{H}_{arom}$), 5.02 + 4.96 (2H, s+s, ArC$\underline{H}_2$N, *E* + *Z*), 3.74 (4H, m, 2OC$\underline{H}_2$), 3.18 (4H, m, 2NC$\underline{H}_2$).

Synthesis of 1-(2-phenylethyl)-5-[1-(2-morpholino-4-nitrophenyl)methylidene]heha-hydro-2,4,6-pyrimidinetrione (5i). 5 mmol (1.16 g) of 1-phenylethylbarbituric acid **4h** and 5 mmol (1.18 g) aldehyde **2a** were dissolved in dimethylsulfoxide (2 ml) at 50 °C and stirred at 50 °C for 10 min. The reaction mixture was cooled to 20 °C, diluted by water-ethanol 50% mixture (30 ml) and stirred for 10 min. Then water (20 ml) was added, the precipitate was filtered out and

washed with water. The crude product was worked-up by adding of water (70 ml) and stirring for 1 h at 20 °C. The precipitate was filtered out, washed with water and dried in air at room temperature to give 2.15 g (95%) of compound **5i** as red-orange powder, m.p. 187-189 °C; [Found: C 61.19, H 4.96, N 12.32. $C_{23}H_{22}N_4O_6$ required C 61.33, H 4.92, N 12.44%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.66 + 11.53 (1H, s+s, NH, *E* + *Z*), 8.72 + 8.66 (1H, d+d, *J* 3.0 Hz, $\underline{H}_{arom}$, *E* + *Z*), 8.26 (1H, m, $\underline{H}_{arom}$), 8.11 + 8.09 (1H, s+s, =C$\underline{H}$, *E* + *Z*), 7.26 (6H, m, 6 $\underline{H}_{arom}$), 3.99 (2H, m, C$\underline{H}_2$N), 3.75 (4H, m, 2OC$\underline{H}_2$), 3.17 (4H, m, 2NC$\underline{H}_2$), 2.85 (2H, m, C$\underline{H}_2$Ph).

General Method A – the procedure for the synthesis of 5-spiro barbiturates 6a-e.

Synthesis of (*S,*S**)-1-methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa-4a-phenanthrene)** (**4a**). 0.72 г (2 ммоль) of 1-methyl-5-[1-(2-morpholino-4-nitrophenyl)methylidene]hehahydro-2,4,6-pyrimidinetrione (**5a**) was dissolved in water (20 ml) and stirred at 90 ^{o}C 3 h. Then the reaction mixture was stirred under reflux for 4 h. Then the mixture was cooled for 20 °C, the precipitate was filtered out, washed with aqueous ethanol 25% and dried in air at a room temperature to give 0.70 g (97%) of compound **6a** as pale-yellow acicular crystals, m.p. 301 °C; [Found: C 53.29, H 4.50, N 15.52. $C_{16}H_{16}N_4O_6$ requires C 53.33, H 4.48, N 15.56%]; δ_H (500 MHz, DMSO-d_6) 11.55 (1H, s, N$\underline{H}$), 7.95 (1H, dd, *J* 8.5, 2.2 Hz, $\underline{H}_{arom}$), 7.82 (1H, d, *J* 2.2 Hz, $\underline{H}_{arom}$), 6.95 (1H, d, *J* 8.5 Hz, $\underline{H}_{arom}$), 4.07 + 3.80 + 3.77 + 3.56 (1H+1H+1H+1H, m + m + m + m, OC$\underline{H}_a\underline{H}_b$+NC$\underline{H}_a\underline{H}_b$), 3.93 (1H, dd, *J* 9.5, 4.6 Hz, NC$\underline{H}$), 3.35-3.23 (4H, m, C$\underline{H}_2$Ar+OC$\underline{H}_2$), 3.20 (3H, s, N$\underline{Me}$); δ_C (200 MHz, DMSO-d_6) 170.15, 167.44, 150,17, 149.99, 136.92, 124.20, 123.71, 120.78, 111.25, 66.68, 66.04, 58.14, 48.64, 46.38, 34.41, 28.10.

The same method was used to synthesize:

(*S,*S**)-1-methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-thia-4a-phenanthrene) (4b).** From 1-methyl-5-arylidene barbiturate (**5b**) as yellow prismatic crystals, m.p. 278-279 °C; [Found: C 51.09, H 4.26, N 14.85. $C_{16}H_{16}N_4O_5S$ requires C 51.06, H 4.28, N 14.89%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.51 (1H, s, N$\underline{H}$), 7.97 (1H, d, *J* 2.0 Hz, $\underline{H}_{arom}$), 7.94 (1H, dd, *J* 8.9, 2.0 Hz, $\underline{H}_{arom}$), 6.98 (1H, d, *J* 8.9 Hz, $\underline{H}_{arom}$), 4.50 + 3.60 (1H+1H, m + m, J^1 13.1 Hz, NC$\underline{H}_a\underline{H}_b$), 4.30 (1H, dd, *J* 10.4 Hz, NC$\underline{H}$), 3.44 + 2.98 (1H + 1H, d+d, *J* 17.2 Hz, C$\underline{H}_2$Ar), 3.03 (3H, s, N$\underline{Me}$), 2.77 + 2.36 (1H+1H, m + m, J^1 13.5 Hz, SC$\underline{H}_a\underline{H}_b$), 2.62 + 2.19 (1H+1H, d.d + d.d, J^1 13.3 Hz, SC$\underline{H}_a\underline{H}_b$); δ_C (200 MHz, DMSO-d_6) 169.82, 168.88, 151.06, 148.15, 137.65, 124.85, 123.73, 122.85, 112.59, 62.20, 52.91, 51.26, 28.34, 27.19, 26.34, 22.95.

(*S,*S**)-1-Ethyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-**

hexahydro-2-oxa-4a-phenanthrene) (4c). From 1-ethyl-5-arylidene barbiturate (**5c**) as yellow crystals, m.p. 287-288 °C; [Found: C 54.59, H 4.87, N 14.94. $C_{17}H_{18}N_4O_6$ requires C 54.54, H 4.85, N 14.97%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.74 (1H, s, NH), 7.99 (1H, dd, *J* 8.6, 2.2 Hz, H_{arom}), 7.84 (1H, d, *J* 2.2 Hz, H_{arom}), 7.03 (1H, d, *J* 8.6 Hz, H_{arom}), 4.09 + 3.82 + 3.74 + 3.43 (1H+1H+1H+1H, m + m + m + m, 2 OCH_aH_b), 3.90 (1H, dd, *J* 11.9, 3.3 Hz, NCH), 3.67 (2H, q, *J* 6.7 Hz, NCH_2), 3.38 + 3.20 (1H + 1H, d+d, *J* 16.2, $ArCH_aH_b$), 3.22 (2H, m, NCH_aH_b), 1.03 (3H, t, *J* 6.7 Hz, CH_3); δ_C (200 MHz, DMSO-d_6) 170.00, 167.67, 150,38, 150.16, 137.29, 124.53, 124.03, 121.27, 111.66, 66.22, 66.00, 58.49, 48.88, 46.67, 36.12, 34.35, 13.31.

***(S*,S*)*-1-*n*-Propyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa-4a-phenanthrene) (4d).** From 1- *n*-propyl-5-arylidene barbiturate (**5d**) as yellow crystals, m.p. 247-248 °C; [Found: C 55.62, H 5.20, N 14.38 $C_{18}H_{20}N_4O_6$ required C 55.67, H 5.19, N 14.43%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.73 (1H, s, NH), 7.96 (1H, dd, *J* 8.6, 2.4 Hz, H_{arom}), 7.81 (1H, d, *J* 2.4 Hz, H_{arom}), 7.02 (1H, d, *J* 8.6 Hz, H_{arom}), 4.07 (1H, m, *J* 13.0 Hz, OCHH), 3.90 (1H, dd, *J* 11.2, 2.5 Hz NCH), 3.84 (1H, dd, *J* 10.1, 2.8 Hz, OCHH), 3.70 (1H, m, OCHH), 3.59 (2H, t, *J* 6.7 Hz NCH_2), 3.37 + 3.20 (1H + 1H, d+d, *J* 16.1, $ArCH_aH_b$), 3.19 (2H, m, NCH_aH_b), 1.46 (2H, m, CH_3CH_2), 0.80 (3H, t, *J* 6.7 Hz, CH_3); δ_C (200 MHz, DMSO-d_6) 170.01, 167.79, 150,34, 150.25, 137.29, 124.53, 124.06, 121.13, 111.59, 66.24, 66.02, 58.34, 48.88, 46.62, 42.49, 34.66, 21.11, 11.55.

***(S*,S*)*-1-Allyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa-4a-phenanthrene) (4e).** From 1-allyl-5-arylidene barbiturate (**5e**) as yellow crystals, m.p. 240-241 °C; [Found: C 55.99, H 4.68, N 14.48. $C_{18}H_{18}N_4O_6$ required C 55.96, H 4.70, N 14.50%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.61 (1H, s, NH), 7.95 (1H, dd, *J* 8.6, 2.4 Hz, H_{arom}), 7.84 (1H, d, *J* 2.4 Hz, H_{arom}), 6.94 (1H, d, *J* 8.6 Hz, H_{arom}), 5.83 (1H, m, =CH), 5.18 (2H, m, $=CH_2$), 4.38 (2H, d, *J* 5.8 Hz, $NCH_2CH=$), 3.89 (1H, m, *J* 13.1 Hz, OCHH), 3.89 (1H, dd, *J* 12.1, 2.5 Hz NCH), 4.09 + 3.82 + 3.74 + 3.43 (1H+1H+1H+1H, m + m + m + m, 2 OCH_aH_b), 3.90 (1H, dd, *J* 11.9, 3.3 Hz, NCH), 3.73 (1H, m, *J* 11.1 Hz, OCHH), 3.40 + 3.24 (1H + 1H, d+d, *J* 16.1, $ArCH_aH_b$), 3.20 (2H, m, NCH_2); δ_C (200 MHz, DMSO-d_6) 170.01, 167.63, 150,31, 150.03, 137.33, 132.62, 124.62, 124.08, 123.00, 117.25, 111.62, 66.29, 66.00, 58.48, 49.08, 46.72, 43.49, 34.75.

General Method B – the procedure for the synthesis of 5-spiro barbiturates 6f-i.

Synthesis of *(S*,S*)*-1-buthyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa-4a-phenanthrene) (6f). 20 ml of water was added to 0.99 g (2 mmol) 1-buthyl-5-[1-(2-morpholino-4-nitrophenyl)methylidene]hexahydro-2,4,6-

pyrimidinetrione (**5a**) and the mixture was stirred at 60 °C for 4 hrs. Then the temperature was increased to 70 °C and further to 100 °C at a heating rate of 5 °C/hr under constant stirring. The reaction mixture was boiled for 4 h. Then the mixture was cooled to 20 °C, the precipitate was filtered out, washed with aqueous ethanol 25% and dried in air at room temperature to give 0.70 g (97%) of compound **6f** as yellow crystals, m.p. 209-210 °C; [Found: C 56.66, H 5.49, N 13.88. $C_{19}H_{22}N_4O_6$ required C 56.71, H 5.51, N 13.92%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.63 (1H, s, NH), 7.95 (1H, dd, *J* 8.6, 2.4 Hz, H_{arom}), 7.80 (1H, d, *J* 2.4 Hz, H_{arom}), 7.02 (1H, d, *J* 8.6 Hz, H_{arom}), 4.09 (1H, m, *J* 12.6 Hz, OCHH), 3.90 (1H, m, *J* 12.5 Hz, OCHH), 3.85 (1H, dd, *J* 11.1, 2.5 Hz NCH), 3.71 (3H, m, NCH_2 + OCHH), 3.46 (1H, m, *J* 12.6 Hz, OCHH), 3.39 + 3.22 (1H + 1H, d+d, *J* 16.5, $ArCH_aH_b$), 1.46 (2H, m, $CH_3CH_2CH_2$), 1.28 (2H, m, CH_3CH_2), 0.88 (3H, t, *J* 6.7 Hz, CH_3); δ_C (200 MHz, DMSO-d_6) 170.30, 167.71, 150.28, 150.20, 137.33, 124.59, 124.08, 121.11, 111.66, 66.27, 65.96, 58.54, 49.08, 46.76, 41.25, 34.63, 29.81, 19.98, 14.07.

The same method was used to synthesize:

***(S*,S*)*-1-*i*-Propyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa-4a-phenanthrene) (6g).** From 1-*i*-propyl-5-arylidene barbiturate (**5f**) as yellow crystals, m.p. 218-219 °C; [Found: C 55.69, H 5.21, N 14.36 $C_{18}H_{20}N_4O_6$ required C 55.67, H 5.19, N 14.43%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.64 (1H, s, NH), 7.94 (1H, dd, *J* 8.1, 2.4 Hz, H_{arom}), 7.84 (1H, d, *J* 2.4 Hz, H_{arom}), 6.98 (1H, d, *J* 8.1 Hz, H_{arom}), 4.78 (1H, m, $CHMe_2$), 4.07 (1H, m, *J* 12.7 Hz, OCHH), 3.92 (1H, dd, *J* 11.3, 2.4 Hz NCH), 3.76 (2H, m, OCH_2), 3.51 (1H, m, NCHH), 3.28 (4H, m, $ArCH_2$ + NCHH + OCHH), 1.34 + 1.31 (3H + 3H, d+d, *J* 6.9 Hz, CH_3CHCH_3); δ_C (200 MHz, DMSO-d_6): 169.86, 168.17, 150.29, 150.17, 137.39, 124.52, 123.96, 121.54, 111.76, 66.25, 65.98, 58.47, 49.48, 46.83, 45.96, 34.26, 19.83, 19.60.

***(S*,S*)*-1-Benzyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa-4a-phenanthrene) (6h).** From 1-benzyl-5-arylidene barbiturate **(5h**) as yellow crystals, m.p. 216-217 °C; [Found: 60.43, H 4.66, N 12.81 $C_{22}H_{20}N_4O_6$ required C 60.55, H 4.62, N 12.84%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.95 (1H, s, NH), 7.96 (1H, dd, *J* 8.2, 2.4 Hz, H_{arom}), 7.83 (1H, d, *J* 2.4 Hz, H_{arom}), 7.26 (6H, m, 6 H_{arom}), 7.02 (1H, d, *J* 8.2 Hz, H_{arom}), 4.84 (2H, AB-system, *J* 14.6 Hz, ArH_aH_bN), 4.07 (1H, m, *J* 12.4 Hz, OCHH), 3.87 (2H, m, OCHH + NCH), 3.67 (1H, m, *J* 11.3 Hz, NCHH), 3.41 + 3.24 (1H + 1H, d+d, *J* 16.4, NCH_aH_bAr), 3.32 (1H, m, *J* 12.5, OCHH), 3.20 (1H, m, *J* 11.7, OCHH), 3.10 (1H, m, *J* 10.8, NCHH), δ_C (200 MHz, DMSO-d_6): 170.35, 167.82, 150.53, 150.29, 137.41, 136.96, 128.76, 128.10, 127.87, 124.62, 124.05, 121.19, 111.70, 66.19, 65.95, 58.64, 49.22, 46.82, 44.61, 34.77.

***(S*,S*)*-1-(2-Phenylethyl)-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-**

1',3',4',9',10',10a'-hexahydro-2-oxa-4a-phenanthrene) (6i). From 1-(2-phenylethyl)-5-arylidene barbiturate (**5i**) as yellow crystals, m.p. 255-256 °C; [Found: 60.43, H 4.66, N 12.81 $C_{22}H_{20}N_4O_6$ requires C 60.55, H 4.62, N 12.84%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.83 (1H, s, NH), 7.96 (1H, dd, *J* 8.2, 2.4 Hz, $\underline{H}_{arom}$), 7.77 (1H, d, *J* 2.4 Hz, $\underline{H}_{arom}$), 7.26 (6H, m, 6 $\underline{H}_{arom}$), 6.91 (1H, d, *J* 8.2 Hz, $\underline{H}_{arom}$), 4.90 + 4.83 (!H + 1H, d+d, *J* 13.7 Hz, Ar$\underline{H}_a\underline{H}_b$N), 3.98 (1H, m, *J* 12.4 Hz, OCH$\underline{H}$), 3.87 (1H, dd, *J* 11.2, 2.6 Hz NC$\underline{H}$), 3.75 (1H, m, *J* 12.0 Hz, OC$\underline{H}$H), 3.67 (1H, m, NC$\underline{H}$H), 3.28 (4H, m, ArC$\underline{H}\underline{H}$ + OC$\underline{H}\underline{H}$), 3.07 (1H, m, NCH$\underline{H}$), δ_C (200 MHz, DMSO-d_6): [Found: C 61.41, H 4.90, N 12.42. $C_{23}H_{22}N_4O_6$ requires C 61.33, H 4.92, N 12.44%]; δ_H ^{1}H NMR (500 MHz, DMSO-d_6): 11.90 (1H, s, NH), 7.95 (1H, dd, *J* 8.3, 2.3 Hz, $\underline{H}_{arom}$), 7.81 (1H, d, *J* 2.3 Hz, $\underline{H}_{arom}$), 7.24 (6H, m, 6 $\underline{H}_{arom}$), 7.03 (1H, d, *J* 8.3 Hz, $\underline{H}_{arom}$), 4.06 (1H, m, *J* 12.5 Hz, OCH$\underline{H}$), 3.88 (4H, m, NC$\underline{H}$ + NC$\underline{H}_2$CH$_2$ + OCH$\underline{H}$), 3.61 (1H, m, *J* 12.3 Hz, NC$\underline{H}$H), 3.39 (1H, m, *J* 11.1 Hz, NCH$\underline{H}$), 3.32 + 3.19 (1H + 1H, d+d, *J* 16.2, ArC$\underline{H}_a\underline{H}_b$), 3.16 (1H, m, OC$\underline{H}$H), 2.97 (1H, m, *J* 11.2, NCH$\underline{H}$), 2.79 (2H, t, *J* 6.8 Hz, NCH$_2$C$\underline{H}_2$); δ_C (200 MHz, DMSO-d_6): 170.22, 167.81, 150.15, 150.01, 138.84, 137.56, 129.01, 128.76, 126.76, 124.63, 123.92, 120.91, 111.49, 67.17, 66.99, 58.16, 48.83, 46.49, 42.22, 34.84, 33.76.

Method C – the procedure for the synthesis of a diastereomeric mixture ((*S,*S**)- and (*S**,*R**)-1-alkyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa-4*a*-phenanthrene)s (6).**

Synthesis of the mixture of (*S,*S**)- and (*S**,*R**)- diastereomers of 1-methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa-4a-phenanthrene) 6a (Table 1).** 2 mmol (0.72 g) of 1-methyl-5-arylidene barbiturate **5a** was dissolved in dimethylacetamide 7 ml and heated at 100 ^{o}C for 4 h. After cooling, the reaction mixture was diluted by 50 ml of water. A precipitate was filtered out, washed with 50% ethanol and dried in air to give compound **6a** as a mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers, pale-yellow acicular crystals, m.p. 299-300 °C; [Found: C 53.20, H 4.57, N 15.36. $C_{16}H_{16}N_4O_5$ requires C 53.33, H 4.48, N 15.56%]; δ_H (500 MHz, DMSO-d_6) 11.74 and 11.55 (0.5H+0.5H, s+s, N$\underline{H}$ (*S**,*S** and *S**,*R**)), 7.95 (1H, dd, *J* 9.5, 2.4 Hz, $\underline{H}_{arom}$), 7.82 (1H, d, *J* 2.4 Hz, $\underline{H}_{arom}$), 6.95 (1H, d, *J* 9.5 Hz, $\underline{H}_{arom}$), 4.07 + 3.75 + 3.56 (1H+2H+1H, m+m+m, OC$\underline{H}_a\underline{H}_b$+NC$\underline{H}_a\underline{H}_b$), 3.93 (1H, m, NC$\underline{H}$), 3.35-3.18 (4H, m, C$\underline{H}_2$Ar+OC$\underline{H}_2$), 3.20 and 3.10 (1.5H+1.5H, s+s, N$\underline{Me}$, *S**,*S** and *S**,*R**).

Synthesis of the diastereomeric mixtures of other 1-alkyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa-4*a*-phenanthrene) derivatives (**6**) were carried out similarly from respective 1-alkyl 5-arylidene barbiturates in dimethlyacetamide solution. Yields 95-97%. Ratio of diastereomers in mixtures *ca*. 1:1.

Method D – the procedure for the synthesis of (*S,*S**)-1-methyl-2,4,6-trioxospiro(perhydropyrimidino-5,5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa-4*a*-phenanthrene) (6a) (Table 1) in the solid phase.** 1 mmol (0.36 g) of 1-methyl-5-arylidene barbiturate **5a** were kept in a sealed ampoule at 100°C for 15 days. A substance was washed with ethanol, chloroform and dried in air to give a mixture of (*S**,*S**)- and (*S**,*R**)-diastereomers **6a** (see Table 1) as yellow powder, m.p. 293-293 °C.

■ RESULTS AND DISCUSSION

As it has been established, the isomerization of 5-nitrobenzylidene barbiturates (**5a-i**) under conditions typically applied (*viz*. heating of solutions in organic solvents, such as AcOH, EtOH, DMF) proceeds non stereoselectively giving rise to respective spirocyclic derivatives (**6a-i**) as a mixture of (*S**,*S**) and (*S**,*R**) diastereomers in a nearly 1:1 ratio.

Under alternative conditions, upon heating polycrystalline powder of **5a** in water (Procedure A, see Experimental section) we found that the spirocyclic product **6a** (Scheme 3) is afforded in an excellent yield as a nearly pure (*S**,*S**)-diastereomer (>99%, Table 1). This is indeed surprising since no successful example of tuning stereoselectivity of a T-reaction by external conditions has been reported so far.

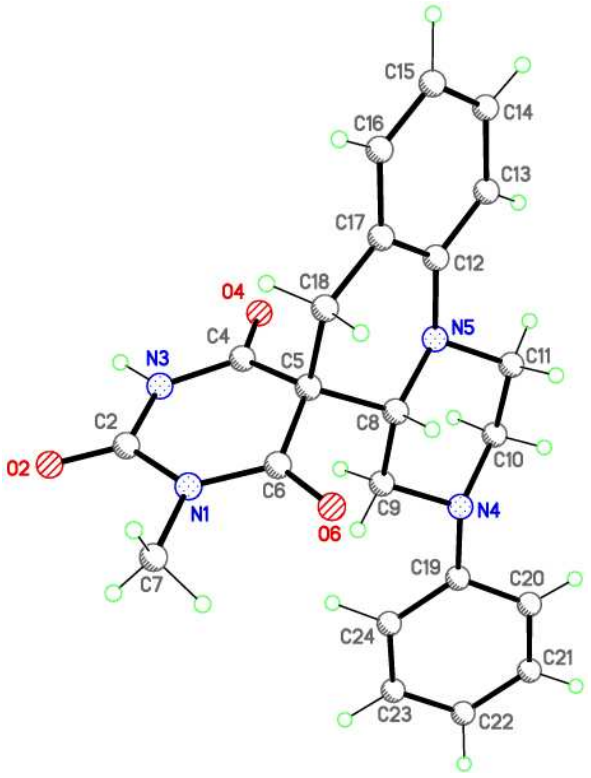


Figure 1. Molecular structure of **6a** (*S**,*S**).

The relative configuration of compound **6a** was reliably established by X-ray crystallographic analysis (its molecular structure is depicted in Figure 1), and its diastereomeric purity was determined by ^{1}H NMR using the intensity ratio of peaks attributed to NH protons.[19]

It is well known that (*S*,S**)- and (*S*,R**)-diasteromers of 5-spiro barbituric acid derivatives are characterized by distinctly different positions of signals of NH protons that makes ^{1}H NMR spectroscopy a very straightforward technique to assess diasteromeric purity of such compounds.[19]

The surprising diastereospecificity of our new approach to the isomerization of **5a** is explained by the fact that the reaction proceeds in the heterogeneous mode since both the reactant and product are virtually insoluble in water. To our best knowledge, such an approach to T-reactions has not been attempted so far although it is known that isomerizations can be accomplished in the solid state without any solvent.[7,19] In particular, we[19] synthesized the spirocyclic product **6a** by heating **5a** as a dry powder but the reaction was very slow (72 h at 120 °C, which is roughly 200 times more slowly than in solutions) and characterized by a low stereoselectivity giving rise to a mixture of (*S*,S**)- and (*S*,R**)-diastereomers in a 3:1 ratio. As a part of this work, we performed an analogous experiment on the isomerization of dry **5a** under less harsh conditions (100 °C, Procedure D, see Experimental section) but the reaction decelerated a lot (a 90% conversion was achieved within 15 days) and no significant improvement in the diastereomeric purity of **6a** was achieved (Table 1).

In the case of the new method, despite the heterogeneous character, the T-reaction proceeds nearly as fast as in solutions. Indeed, the heterophase isomerization of **5a** upon heating to 100 °C in water (Procedure A, see Experimental section) takes 3 hrs, whereas it requires 2 hrs at the same temperature in acetic solutions. But, as it has been mentioned before, the T-reaction with **5a** in solution proceeds non-stereospecifically, whereas the diastereoslectivity of the heterophase reaction is virtually 100%.

Therefore, the use of a two-phase system involving water and crystalline reactant **5a** has proven to be ultimately efficient in term of both reaction rate and stereospecificity. The implementation of this method is also very simple since only water is used as a solvent and the product afforded does not require any additional purification.

The heterophase rearrangement of (**5b**) that can be regarded as a thia analogue of 1-methyl-5-arylidenebarbiturates **5a** (Procedure A, see Experimental section) afforded the spirocyclic derivative (**6b**, (*S*,S**) with a diastereomeric purity of 93 % (Table 1).

A more detailed investigation into rearrangements of 1-alkylsubstituted 5-arylidenebarbiturates **5c-i** into respective spirocyclic derivatives (**6a-i**) demonstrated that the heterophase T-reactions always proceed stereoselectively giving rise to predominance of the (*S*,S**) diastereomers (Table 1). Especially high diastereomeric purities were achieved provided that both

reactant and product remained solid throughout the reaction process. The diastereoselectivity degraded a lot if the reaction mass underwent melting or coagulation of powder grains.

Compounds **5a-e** survived boiling in water and remained crystalline so as is was possible to accomplish the isomerization at 100 ^{o}C (Procedure A, see Experimental section) and afford the respective spirocyclic derivatives (**6a-e**) as highly pure (*S**,*S**)-diastereomers (Table 1).

In the case of 1-butyl 5-arylidenebarbiturate **5f**, temperature 100 ^{o}C appears to be too high for the initial stage of the reaction, since the precipitate starts to coagulate within approximately 0.5 h of stirring in boiling water. In order to avoid that we started the heterophase isomerization of **5f** at a lower temperature and gradually increased it to 100 ^{o}C in the course of the reaction (Procedure B, see Experimental section). As a result, the spirocyclic derivative **6f** was afforded with a diastereomeric purity of 99 %.

A similar stepwise temperature increase was used to isomerize 1-isopropyl- (**5g**), 1-benzyl- (**5h**), and 2-phenylethyl (**5i**) 5-arylidenebarbiturates to afford the respective spirocyclic derivatives (**6g**) and (**6h**) with diastereomeric purities above 90 % (Table 1).

Despite deliberate adjustment of the temperature regime we were unable to completely suppress coagulation of powder particles in the course of isomerization of 1-*i*-propyl-5-arylidenebarbiturate (**5g**). That is why the diastereomeric purity of spirocyclic product (**6g**) was lower than for other analogues.

Taking into account the results obtained it would be reasonable to suggest that the high stereoselectivity of the T-reactions under heterophase conditions is due to the fact that the primary reaction proceeds at the interface between the crystals of starting 5-arylidenebarbiturates **5** and water. Typically, several reactive conformations coexist in equilibrium in solutions but only one of them can be stabilized in the crystal structure. To get insight into this problem we grown single crystals of 1-*n*-butyl-[5-nitro-2-(*N*-morpholino)benzylidene]barbituric acid **5f** and of its rearrangement product, spirocyclic derivative **6f** and determined their structure by X-ray diffraction analysis (Table 2). The molecular structures of above compounds are depicted in Figures 2 and 3.

First of all, it is clearly seen that molecules of 1-*n*-butyl 5-enzylidenebarbiturate **5f** are present in the crystal exclusively as (*E*)-isomers although two (*E*)- and (*Z*)-isomers relative to the double C=C bond are possible. Similarly, as it has been found before[19], only one (*E*)-isomer is present in the crystal structure of another related compound, 1-*tert*-butyl-[5-nitro-2-(*N*-morpholino)benzylidene]barbituric acid. Apparently, (*E*)-isomers of similar compounds are energetically favorable in crystals with respect to (*Z*)-isomers. Indeed, in the crystal, the (*E*)-isomers of **5f** are additionally stabilized by the extended system of intermolecular hydrogen bonds. As it can be seen from Figure 4, the molecules of **5f** form the *zigzag*-like chains towards [1 0 $\bar{1}$] by the strong intermolecular N-H...O hydrogen bonds (Table 3).

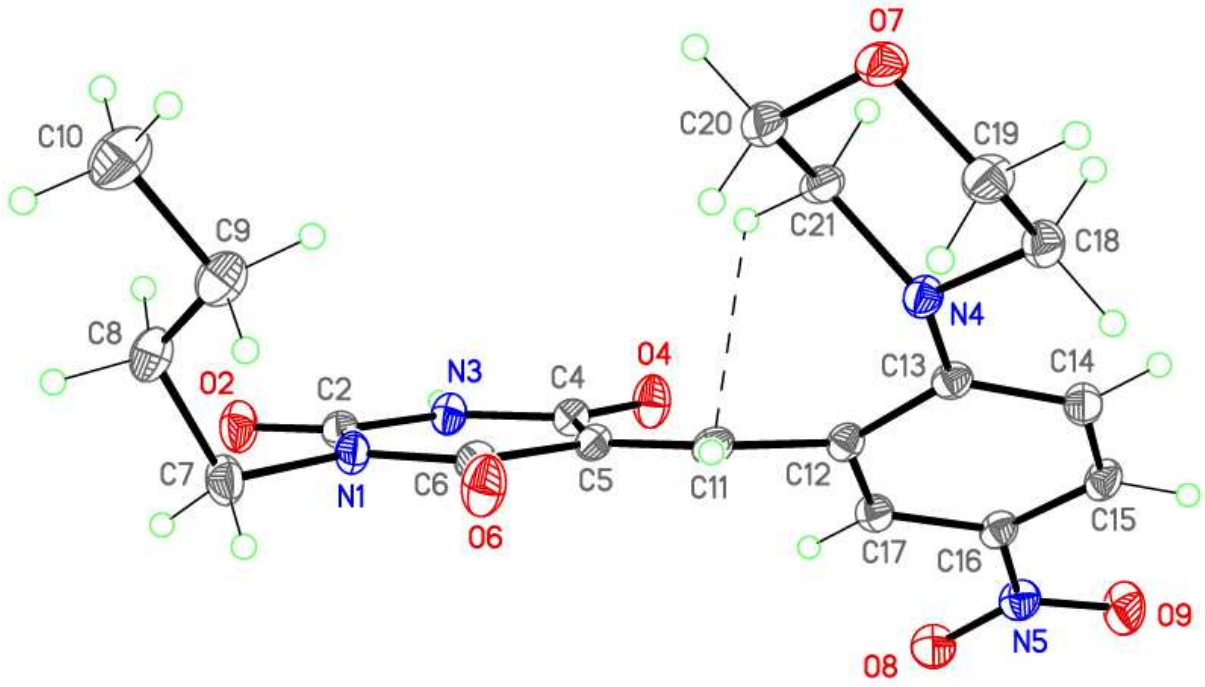


Figure 2. Molecular structure of **5f** (the structure- forming C-H…π contact is shown as dashed line)

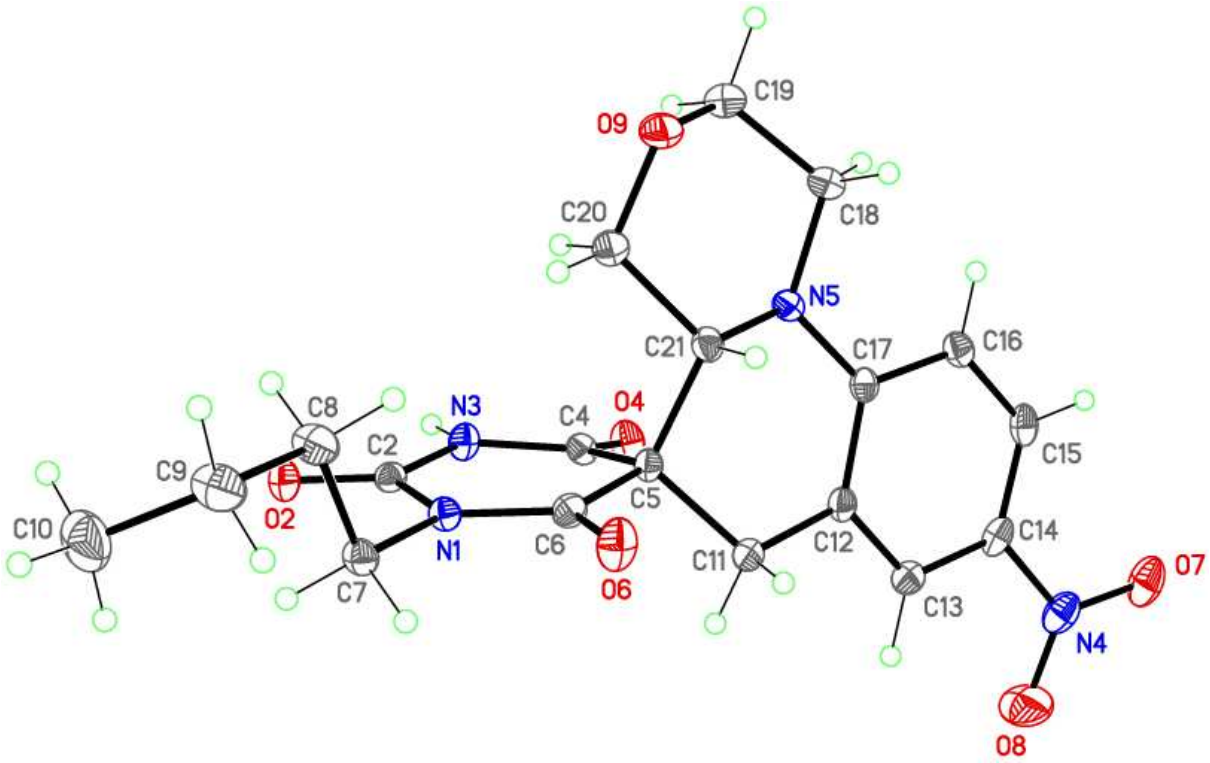


Figure 3. Molecular structure of **6f** (*S**,*S**)

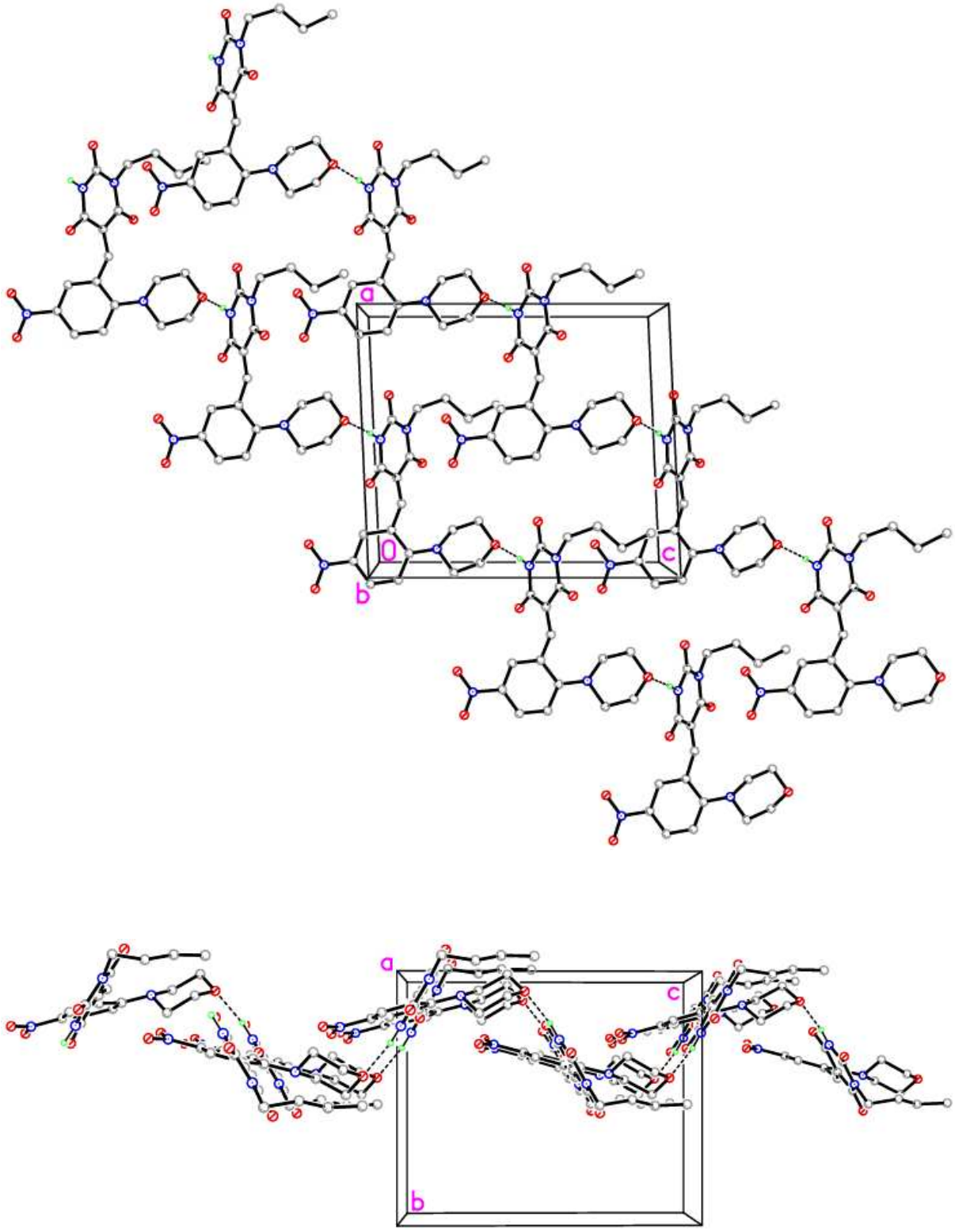


Figure 4. A portion of crystal packing of **5f** demonstrating the *zigzag*-like H-bonded chains along the direction [1 0 $\bar{1}$] (two projections are shown). The strong intermolecular N-H...O hydrogen bonds are drawn by dashed lines.

Table 3. Intermolecular hydrogen bonds (Å and deg.) for 5f.

D*-H...A*	d(D-H)	d(H...A)	d(D...A)	∠(D-H...A)
N3-H3...O7[a]	0.90(2)	1.93(2)	2.824(3)	171.8(14)
C14-H14...O2[b]	0.95	2.43	3.130(3)	130.0
C21-H21B...O6[c]	0.99	2.32	3.259(3)	158.5

*D – proton donor; A – proton acceptor.

Symmetry transformation used to generate equivalent atoms:

a: (*x*-0.5, -*y*+1.5, *z*+0.5); ***b***: (*x*+1, *y*, *z*); ***c***: (-*x*+1.5, *y*-0.5, -*z*+1.5).

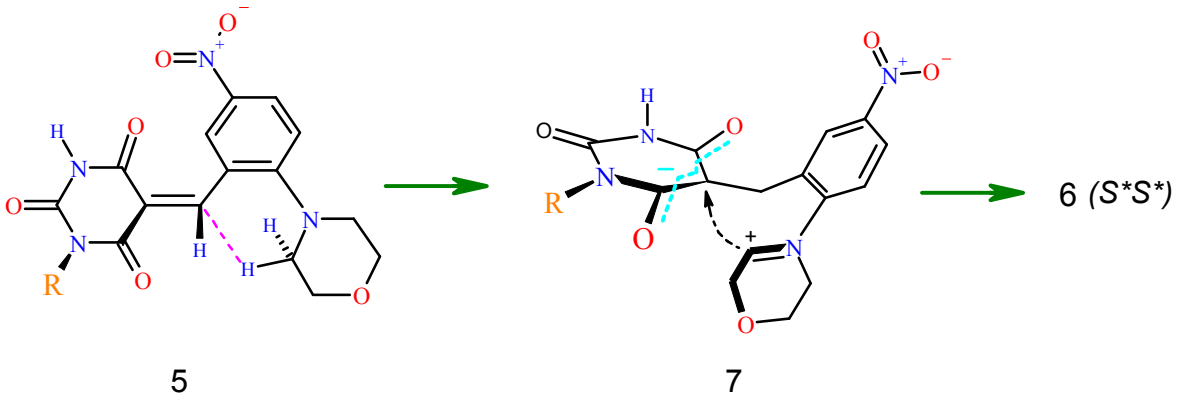
Further, the *zigzag*-like chains are linked by the intermolecular C-H...O hydrogen bonds (Figure 4, Table 3) into three-dimensional framework.

Meanwhile, according to ^{1}H NMR spectroscopy, both (*E*)- and (*Z*)-isomers of 1-alkyl 5-benzylidenebarbiturates **5** occur in solutions in nearly equal proportions due to the fast reversible isomerization around the C=C bond.

Secondly, a relatively short intramolecular C-H**…**π (C=C) contact between the hydrogen atom of -CH_2-N group and the exocyclic carbon atom of the vinyl fragment is of note in the crystal structure of 5-benzylidenebarbiturate **5f**. The respective H**…**C interatomic distance is only 2.31 Å. We reported on similar C-H**…**π contacts in crystal structures of related compounds earlier[10,19], but in the present case, this specific interaction plays a special role hindering the free rotation within the molecule and fixing a unique conformation of **5f** with the morpholine ring tilted towards the NH group and away from the *n*-butyl group. Importantly, exactly the same mutual arrangement of groups is observed in the actual reaction product, (*S*,S**)-diastereomer **6f**, whereas the opposite orientation is realized in the (*S*,R**)-diastereomer. Therefore, we may conlcude that the initial molecular conformation of **5f** in the crystal state is prone to rearrangement exactly into (*S*,S**)- rather than (*S*,R**)-diastereomer of **6f**.

This conclusion fully corresponds to currently adopted common mechanism of such reactions[1]. It is believed that the T-reaction in **5** started with the intramolecular transfer of hydride-ion from the α-alkylamino group to the vinyl carbon atom with the formation of a zwitter-ionic intermediate **7** (Scheme 4). The detachment of a hydride-ion is promoted by the non-typically strong C-H**…**π interaction observed in 5-(*o*-dialkylamino)arylidene derivatives of barbituric acid.[10]

Scheme 4. The currently adopted mechanism of the T-reaction.



Further, the intermediate **7** undergoes cyclization into the final spirocyclic derivative **6**. The cyclization is characterized by nearly zero energy barrier and apparently proceeds too fast for the molecule to change its initial conformation with a specific mutual orientation of moieties, which explains the reaction stereoselectivity. Probably, interface water present in the heterophase process also plays an important role stabilizing the zwitter-ion **7** by its specific hydration at the crystal surface.

In total contrast, different conformations of **5** coexist in equilibrium in solutions and thus its rearrangement affords (*S**,*S**)- and (*S**,*R**)-diastereomers of **6** with equal probabilities.

■ CONCLUSIONS

A new efficient approach to stereodirected T-reactions is proposed, which is based on the heterophase isomerization of 1-alkyl-5-(2-morpholin-4-yl-5-nitrobenzylidene)barbiturates **5a-i** conformationally confined in the crystal state. Spirocyclic derivatives of barbituric acid **6a-i** were successfully synthesized by this method in the diastereomerically pure (*S**,*S**)-form. We believe that the application of the method to other types of T-reactions will extend their synthetic potential as stereodirected rearrangements.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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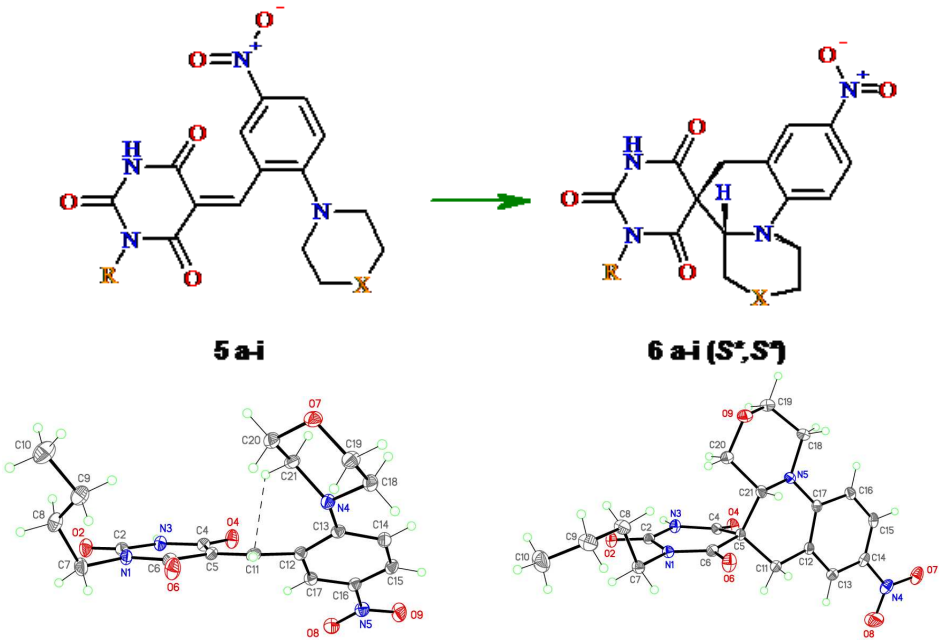
Entry for the Table of Contents

Diastereoselective T-reaction of 1-alkyl-(5-nitro-2-*N*-morpholino-benzyliden)barbituric acids in the solid state: synthesis of 1-alkyl-2,4,6-trioxoperhydropyrimidino-5-*spiro*-5'-(8'-nitro-1',3',4',9',10',10a'-hexahydro-2-oxa)-4a-phenanthrenes and their thia analogues

Konstantin A. Krasnov, Victor N. Khrustalev



A new efficient approach to stereodirected T-reactions is proposed, which is based on the heterophase isomerization of 1-alkyl-5-(2-morpholin-4-yl-5-nitrobenzylidene)barbiturates **5a-i** conformationally confined in the crystal state. Spirocyclic derivatives of barbituric acid **6a-i** were successfully synthesized by this method in the diastereomerically pure (*S**,*S**)-form. It has been demonstrated by X-ray diffraction study that this diastereoselectivity of the solid state T-reaction is due to peculiar crystal structure of starting 5-arylidene barbiturates, which accommodates only one specific conformation fixed by a strong intramolecular C-H…π interaction.