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Determination of energy barriers and racemization mechanisms for thermally interconvertable barbituric and thiobarbituric acid enantiomers

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Abstract—The enantiomers of the 5,5-dimethyl-1-(*o*-aryl)barbituric and 2-thiobarbituric acid derivatives have been separated by micropreparative liquid chromatography on the Chiralcel OD-H column. The activation barriers for the conversion of one enantiomer to its counterpart (M ⇄ P) have been determined upon thermal racemization of the separated enantiomers by following the intensity changes in the HPLC chromatograms with time. The activation barrier of the 1-(*o*-tolyl)barbituric acid has been determined by temperature-dependent NMR. The racemization mechanisms are discussed with reference to the determined barriers.

1. Introduction

Barbituric acid derivatives are a well-known class of compounds with various pharmacological activities.[1] Chiral barbituric acid derivatives having asymmetric substitution on 5-position of the ring have been resolved by enantioselective liquid chromatography on triacetylcellulose.[2] The *N*-*o*-aryl substituted barbituric and thiobarbituric acid derivatives studied in this work (Fig. 1) are axially chiral due to nonplanar ground states of the molecules,[3] the C_{aryl}–N_{sp^2} bond being the chiral axis and all of them exist as a pair of thermally interconvertable M and P enantiomers (Fig. 1). The work covers the determination of the energy barriers of these compounds by either thermal racemization of the micropreperatively separated enantiomers or by temperature-dependent NMR and discussion of the mechanism of racemization based on the found values.

2. Results and discussion

^{1}H and ^{13}C NMR spectra of the synthesized barbituric and thiobarbituric acids showed that the methyl groups on C-5 of the heterocyclic ring had two distinct ^{1}H (Table 1) and ^{13}C (Table 2) NMR signals. The protons at C-5 on the other hand showed AB type splittings (Table 3). These results indicate that the R groups on C-5 (Fig. 1) are diastereotopic which in turn demonstrates the chirality of these compounds in their ground states. Enantioselective liquid chromatography has been used to resolve the enantiomers for which NMR anisochrony has been observed. The Chiralcel OD-H column proved to be the most efficient for this purpose, on which the enantiomers of **1**–**6** which are the 5,5-dimethyl derivatives, have been micropreparatively separated or highly enriched. Table 4 shows the chromatographic parameters of the separation.

The barriers to partial rotation about the C–N bond in **1-6** were determined by thermal racemization of preparatively enriched enantiomers. The rate constants for enantiomerization have been calculated using reversible first order kinetics with the equation $\ln([M]-[M]_{eq}/[M]_o-[M]_{eq}) = -2kt$,[4] $[M]$ being the molar concentration of the enantiomer at time t, $[M]_o$ the initial and $[M]_{eq}$ the equilibrium concentration. In place of $[M]$ and $[M]_o$ the percentage values of the enantiomers obtained from HPLC chromatograms have been used where $[M]_{eq}$ is fifty percent. The free energy of activation values, $\Delta G^{\neq}$ for the interconversion of the enantiomers have been calculated using the Eyring equation $\Delta G^{\neq} = RT \ln(k_b T/kh)$. The rate constants and barriers found are listed in Table 5.

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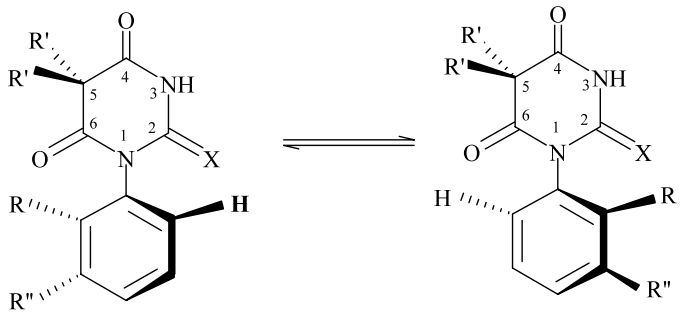


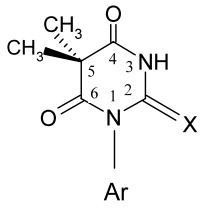
M **P**

Compound	X	R	R'	R"
(±)-**1**	O	CH_3	CH_3	H
(±)-**2**	S	CH_3	CH_3	H
(±)-**3**	S	F	CH_3	H
(±)-**4**	S	OCH_3	CH_3	H
(±)-**5**	S	Cl	CH_3	H
(±)-**6**	S	benzo	CH_3	benzo
(±)-**7**	O	CH_3	H	H
(±)-**8**	O	Cl	H	H
(±)-**9**	S	CH_3	H	H
(±)-**10**	S	Cl	H	H

Figure 1. The structure of the *N*-*o*-aryl substituted barbituric and -2-thiobarbituric acid derivatives studied.

The energy barriers for enantiomerization of **1**–**6** are comparable to each other in spite of somewhat different temperatures. As can be seen from the Table 5 the rotation barrier for the compound **1**, the oxo derivative, is 102.8 kJ/mol, which is lower than the one observed for the compound **2**, the thioxo derivative at 116.1 kJ/mol. Kashima et al. have reported the activation energies for the racemization for the structurally similar compounds, namely *ortho* substituted 1-aryl-4,6-dimethylpyrimidin-2(1*H*)-ones and the corresponding thiones.[5] They unexpectedly observed a lower activation energy for the racemization of the thione derivatives compared to the oxo derivatives, although the standard bond length of the C=O double bond (1.22 Å) is shorter than that of the C=S (1.71 Å), and the van der Waals radius of oxygen (1.4 Å) is smaller than that of the sulphur atom (1.85 Å). They explained this behaviour in terms of the greater single bond character of the carbon–sulphur bond. They proposed that the greater single bond character would promote bond bending, which will cause a decrease in the inter-atomic repulsion between the sulphur atom and the *ortho*-methyl group on the aryl ring. Roussel et al. however proposed a ring opening-ring closure mechanism for the racemization of those pyrimidine derivatives.[6] In compounds **1**–**6** which we synthesized, since two methyl groups are attached to C-5, the ring-opening–ring-reclosure mechanism is impossible, so there is no possibility for a 3,3-electrocyclic reaction that had been suggested by Roussel et al.[6] The result, which shows that the barrier for racemization is higher in the thioxo derivative, **2**, than in oxo derivative, **1**, is consistent with the racemization for these compounds via rotation about the C–N bond and does not agree with Kashima's suggestion,[5] that the greater single bond character of the thiocarbonyl group results in a lower energy barrier for the heterocycles with the thioamide group.

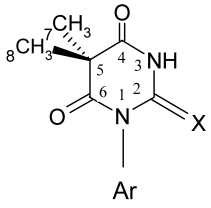
Table 1. 400 MHz ^{1}H NMR spectral data for the 5,5-dimethyl-1-(*o*-aryl)barbituric and -2-thiobarbituric acids in $CDCl_3$



Compd	X	Ar	δ (ppm) of 5-CH_3	δ (ppm) aromatic H	δ (ppm) 3-NH	δ (ppm) *o*-CH_3
(±)-**1**	O	*o*-Tolyl	1.68[a] and 1. 70[a]	7.07–7.38	8.04	2.16
(±)-**2**	S	*o*-Tolyl	1.69[a] and 1.70[a]	7.04–7.39	9.08	2.16
(±)-**3**	S	*o*-Fluorophenyl	1.59[a] and 1.62[a]	7.10–7.62	9.09	–
(±)-**4**	S	*o*-Methoxyphenyl	1.66[a] and 1.70[a]	7.00–7.45	9.14	3.81[b]
(±)-**5**	S	*o*-Chlorophenyl	1.68[a] and 1.75[a]	7.24–7.54	9.13	–
(±)-**6**	S	α-Naphtyl	1.75[a] and 1.81[a]	7.30–8.00	9.17	–

[a] Diastereotopic groups.
[b] δ (ppm) of *o*-OCH_3.

Table 2. ^{13}C NMR spectral data for the 5,5-dimethyl-1-(*o*-aryl)barbituric and -2-thiobarbituric acids in $CDCl_3$



Carbon no.	(±)-**1**	(±)-**2**	(±)-**3**	(±)-**4**	(±)-**5**	(±)-**6**
2	148.89	177.71	177.68	178.36	177.28	178.11
4, 6	171.98, 172.59	169.75, 171.13	169.53, 171.08	169.78, 171.20	169.60, 170.78	169.65, 171.53
5	48.10	48.67	48.83	48.76	48.75	48.86
7, 8	24.34, 25.67,	24.07, 25.38	23.40, 25.65	23.19, 25.86	23.18, 26.26	24.49, 25.27
Aromatic	127.40–135.90	127.47–136.93	116.47–131.57	112.41–154.50	128.10–135.38	121.16–134.58
o-(CH_3)	17.78	17.74	–	56.22	–	–

Table 3. 400 MHz ^{1}H NMR spectral data for the 1-(*o*-aryl)barbituric and -2-thiobarbituric acids in $CDCl_3$

Compd	X[a]	R[a], R″[a] = H, R′[a] = H	δ (ppm) of 5-CH_2	δ (ppm) aromatic H	δ (ppm) 3-NH	δ (ppm) *o*-CH_3
(±)-**7**	O	CH_3	3.84; 3.68 and 3.87[b,c]	7.09–7.38, 7.14–7.29[c]	8.11, 11.46[c]	2.18; 2.08[c]
(±)-**8**	O	Cl	3.84 and 3.88[b]	7.25–7.57	8.04	–
(±)-**9**	S	CH_3	3.87 and 3.89[b]	7.06–7.40	9.38	2.16
(±)-**10**	S	Cl	3.88 and 3.91[b]	7.62–7.98	9.31	–

[a] For the descriptions, see Figure 1.
[b] AB type splitting.
[c] ^{1}H NMR spectral data in DMSO-d_6.

The energy barriers for racemization of the *o*-methyl and the *o*-chloro derivatives, compounds **2** and **5**, were found to be similar (115.8 kJ/mol). When the steric effects of a methyl and a chlorine atom are compared in different types of *N-ortho*-aryl substituted heterocyclic systems, for arylhydantoins,[7] arylquinolones,[8] and arylrhodanines,[9] it had been observed, that a chlorine atom exerts a greater energy barrier than a methyl group in restricted internal rotation. These results were explained by the dipolar repulsion between the exocyclic oxygen of the heterocyclic ring and the chlorine atom. This repulsion might increase the free energy of the transition state of the compound with a chlorine atom as the *ortho* substituent relative to that of the methyl group as the *ortho* substituent. For arylrhodanines and for arylhydantoins the difference was found to amount to 6–7 kJ/mol, whereas for *N*-aryl-2(1*H*)quinolones and *N*-aryl-6(5*H*)-phenanthridinones,[8] it was only 0.2 kJ/mol. In 2,4-quinolinediones,[10] on the other hand, the *ortho*-methyl derivative caused a higher barrier by 0.8 kJ/mol

Table 4. Chromatographic data for the separation of enantiomers on Chiralcel OD-H

Compound	k'_1	k'_2	α
(±)-**1**[a]	0.66	1.00	1.52
(±)-**2**[b]	2.22	3.49	1.57
(±)-**3**[b]	1.23	1.83	1.49
(±)-**4**[b]	2.78	3.41	1.23
(±)-**5**[b]	3.22	5.27	1.64
(±)-**6**[b]	3.79	4.67	1.23

[a] Eluent: ethanol, flow rate 0.2 ml/min.
[b] Eluent: hexane:ethanol mixture = 80:20, flow rate: 0.5 ml/min.

than the *ortho*-chloro derivative. It can be argued that the difference in the steric effects of these two groups depends on the geometries of the transition states that the two rings assume in passing one another. The tetrahedral nature of the methyl substituent may allow, depending on the geometry, a lower barrier despite its larger reported van der Waals radius[11] than the spherical chlorine atom.

The energy barrier for the *o*-methoxy derivative, **4** has been found to be less than the *o*-methyl, **2** and *o*-chloro, **5** and α-naphthyl, **6** derivatives as had previously been observed in literature.[8,10] The *o*-fluoro derivative, **3** has the lowest energy barrier where fluorine is the *ortho* substituent with the smallest van der Waals radius.[11]

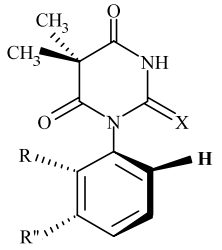
Attempts to resolve racemic 1-(*o*-aryl)barbituric and -2-thiobarbituric acids **7**–**10** (unsubstituted at C-5) on TAC and OD-H columns failed. The activation barrier to enantiomerization for compound **7**, 1-(*o*-tolyl)-barbituric acid, has been determined by temperature-dependent NMR as 70.7 kJ/mol observing the coalescence (at 350 K) of the diastereotopic 5-CH_2 AB signal (Fig. 3) in DMSO-d_6. This barrier is considerably low compared with that of **1**, which is 102.8 kJ/mol and cannot be explained by a solvent effect.

The only structural difference between the compounds **1** and **7** is at the 5 position of the heterocyclic ring. The reason for the higher barrier with the 5,5-dimethyl compound (±)-**1** compared to that of (±)-**7** may be partly due to the buttressing effect of the methyl groups. In addition to this **1** is unable to undergo a keto-enol tautomerization (Fig. 4), whereas **7**, in principle, can. Although ^{13}C NMR did not show any sign of tautomerization for **7**, a fast equilibrium with respect to NMR time scale cannot be excluded. The enol tautomer on the other hand may be expected to stabilize the planar transition state by resonance, thus lowering the $\Delta G^{\neq}$. Also over the enol form (Fig. 4, tautomer **D**) the ring opening–reclosure mechanism that had been suggested by Roussel may also be operating.[6] The fast tautomerization equilibrium may be shifted to the enol side as the heterocycle ring opens over the enol form.

For 1-(*o*-chlorophenyl)barbituric acid, **8**, the coalescence temperature could not be reached even at 423 K in dideuterated tetrachloroethane, $C_2D_2Cl_4$, which would correspond to a barrier >88 kJ/mol.

Excellent separation of the enantiomers (Fig. 2) gave rise to enantiopurities close to 100%. The high barriers of the thioxo derivatives would not allow rapid rotation at ordinary NMR probe temperatures. The structure of the 2-thiobarbituric acid derivative, **6** shows an N–H bond capable of H-bonding, a naphthyl group for π–π interaction and carbonyl groups for possible H-bonding. This may make the separated enantiomers of the (±)-**6** good candidates for chiral auxiliary, which is cheap and easily synthesizable to be used in enantiomeric purity determinations by NMR.

Table 5. Results of the thermal racemization experiments followed by the change in HPLC chromatograms at a constant temperature with time (column: Chiralcel OD-H; solvent: ethanol)



M and **P**

Compd	X	R	R″	T (K)	k (10^{-5} s^{-1})	$\Delta G^{\neq}$, energy barrier (kJ/mol)
(±)-**1**	O	CH_3	H	313	4.0	102.8±0.3
(±)-**2**	S	CH_3	H	343	1.7	115.8±0.3
(±)-**3**	S	F	H	297	22.9	93.1[a]
(±)-**4**	S	OCH_3	H	321	8.8	103.7±0.3
(±)-**5**	S	Cl	H	345	2.1	115.8±0.4
(±)-**6**	S	Benzo	Benzo	343	1.5	116.1±0.4

[a] Only two data were available because of fast racemization.

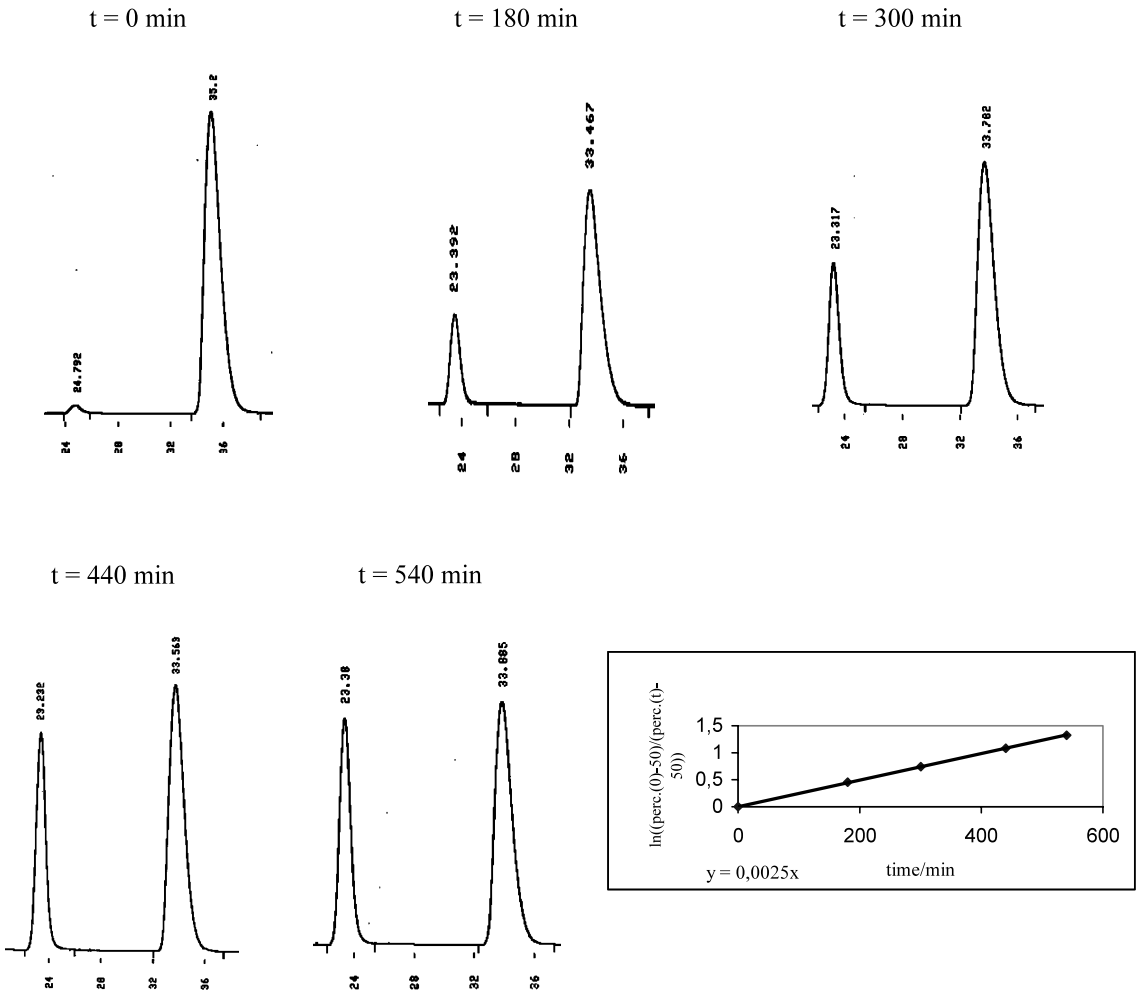


Figure 2. The liquid chromatograms of second eluted enantiomer of **5** during thermal racemization at 345 K. column: Chiralcel OD-H. solvent: hexane:ethanol = 80:20. flow: 0.5 ml/min. UV detection at $\lambda = 240$ nm. Inset: The plot of $\ln([M]-[M]_{eq}/[M]_0-[M]_{eq})$ versus time at 345 K for **5**.

3. Conclusion

The energy barriers for 5,5-dimethyl-1-(*o*-tolyl)-barbituric and 5,5-dimethyl-1-(*o*-tolyl)-2-thiobarbituric acids were found to be 102.8 and 114.5 kJ/mol, respectively. The racemization barrier for the thioxo derivative is found to be higher than the oxo derivative. This result is consistent with the racemization for the 5,5-dimethyl-1-(*o*-aryl)barbituric and 5,5-dimethyl-1-(*o*-aryl)-2-thiobarbituric acids occuring via rotation about the $C_{(aryl)}$–$N_{(sp2)}$ bond.

The 1-(*o*-aryl)barbituric and 1-(*o*-aryl)-2-thiobarbituric acids could not be resolved by liquid chromatography on an optically active sorbent. The energy barrier for the 1-(*o*-tolyl)barbituric acid was determined as 70.7 kJ/mol by temperature-dependent NMR. This barrier is rather low compared with that of 5,5-dimethyl-1-(*o*-tolyl)barbituric acid, being 102.8 kJ/mol. This low barrier could be explained either by the stabilization of the planar transition state by resonance due to enol tautomer formation (Fig. 4) or by the ring opening–reclosure mechanism that may take place over the enol form **D** (Fig. 4) as suggested by Roussel for 1-arylpyrimidine-2-thione and 3-arylthiazoline-2-thione derivatives.[6]

4. Experimental

^1H and ^{13}C NMR spectra were recorded on a Varian 400 NMR spectrometer. Melting points were recorded using an Electrothermal 9100 melting point apparatus or Fisher Jones melting point apparatus. The UV spectra were recorded on a Unicam UV2-100 spectrophotometer. Liquid chromatography analyses were performed on a Cecil 2100 instrument (pump and UV detector model) using the chiral sorbent, cellulose tris-(3,5-dimethyl)phenylcarbamate, Chiralcel OD-H, (Daicel Ltd, particle size: 5 μm, column size: 250×4.6 mm).

4.1. Thermal racemization

The thermal racemization is performed in the following way: First each fraction is collected separately. As soon as the fraction is collected, the solvent is evaporated by

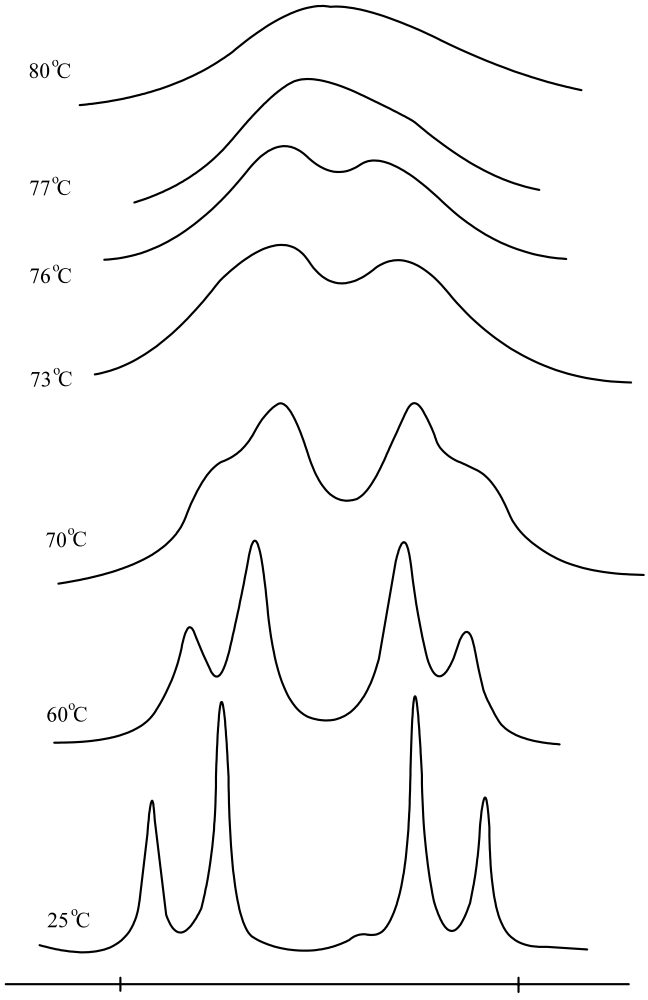


Figure 3. The temperature-dependent ^{1}H NMR spectrum of 5-CH_2 protons of compound **7** in DMSO-d_6 showing the coalescence of the AB type splittings.

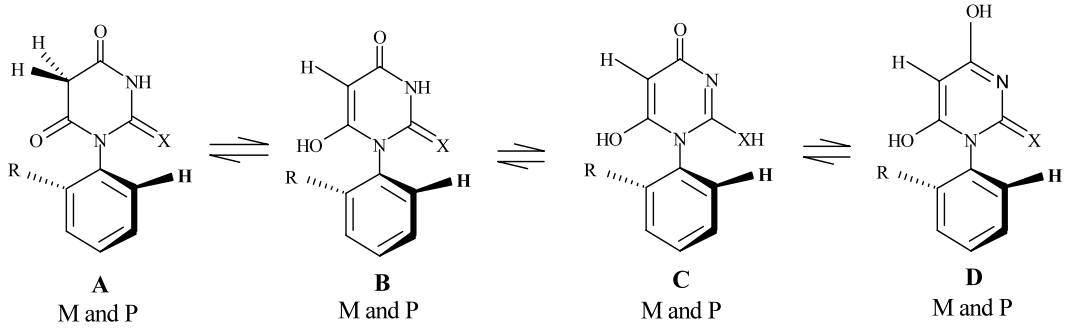
blowing nitrogen gas to the sample. This procedure is done successively, until about 0.2 mg of each enantiomer is collected. Then the solid is dissolved in 200 μl of absolute ethanol, and 30 μl of the solution is injected into the column to determine the initial concentration. The solution left is kept in a constant water or oil bath, and the racemization process is followed by taking 30 μl of the sample at regular time intervals and injecting to the column after quenching in an ice bath. This process is repeated until equilibrium is reached or for at least two half lives.

4.2. Syntheses

The compounds, **2**–**6**, 5,5-dimethyl-1-(*o*-aryl)-2-thiobarbituric acids were prepared from the reaction of 2,2-dimethyl malonic acid and the appropriate arylthiourea by heating in a large excess of acetyl chloride for 24 h under reflux.[3] Ice water was added at the end of the reflux period and the solution was concentrated by vacuum evaporation. The precipitated crystals were collected by filtration and the crude product was purified by either successive recrystallisations from ethanol or by flash chromatography. Yields (unoptimized) were in the range 15–35%.

The compounds, **1** and **7**–**10**, 5,5-dimethyl-1-(*o*-tolyl)barbituric acid, 1-(*o*-aryl)-barbituric and 1-(*o*-aryl)-2-thiobarbituric acids were synthesized by the reaction of 2,2-dimethyldiethylmalonate or diethylmalonate with the appropriate arylurea or arylthiourea in sodium ethoxide solution.[3] The crude products were purified by recrystallization from ethanol.

4.2.1. 5,5-Dimethyl-1-(*o*-tolyl)barbituric acid, (±)-1. The compound has been synthesized using *o*-tolylthiourea and 2,2-dimethylmalonic acid. Yield: 6.5%. Mp 148–150°C (dec.). ^{1}H NMR ($CDCl_3$): $\delta = 2.16$ ppm (3H, s), 1.68 ppm (3H, s), 1.70 ppm (3H, s), 7.07–7.38 ppm (4H, m), 8.04 ppm (1H, b). ^{13}C NMR ($CDCl_3$): 148.89 ppm (C-2), 171.98 ppm (C-4 or C-6), 172.59 ppm (C-4 or C-6), 48.10 ppm (C-5), 24.34 ppm (C-7 or C-8), 25.67 ppm (C-7 or C-8), 127.40–135.90 ppm (aromatic C's), 17.78 ppm (*o*-CH_3). UV data (EtOH): λ_{max}, ($\log \varepsilon_{max}$) = 206 nm, (4.16). IR data: $\bar{\nu}$ N–H stretching: 3571, 3254 cm^{-1}, $\bar{\nu}$ N–C=O stretching: 1692 cm^{-1}, $\bar{\nu}$ C–N stretching: 1349 cm^{-1}.



compound **7:** X = O, R = CH_3 compound **9**: X = S, R= CH_3

compound **8**: X = O, R = Cl compound **10**: X = S, R = Cl

Figure 4. Possible tautomers of barbituric and 2-thiobarbituric acid derivatives in ethanol.

4.2.2. 5,5-Dimethyl-1-(*o*-tolyl)-2-thiobarbituric acid, (±)-2. The compound has been synthesized using *o*-tolylthiourea and 2,2-dimethylmalonic acid. Yield: 35%. Mp 146–147°C. ^{1}H NMR ($CDCl_3$): $\delta = 2.16$ ppm (3H, s), 1.69 ppm (3H, s), 1.70 ppm (3H, s), 7.04–7.39 ppm (4H, m), 9.08 ppm (1H, b). ^{13}C NMR ($CDCl_3$): 177.71 ppm (C-2), 169.75 ppm (C-4 or C-6), 171.13 ppm (C-4 or C-6), 48.67 ppm (C-5), 24.07 ppm (C-7 or C-8), 25.38 ppm (C-7 or C-8), 127.47–136.93 ppm (aromatic C's), 17.74 ppm (*o*-CH_3). UV data (EtOH): λ_{max}, ($\log \varepsilon_{max}$) = 238 nm, (6.7); 252 nm, (5.8); 288 nm, (6.38); 405 nm, (5.4). IR data: $\bar{\nu}$ of N–H stretching: 3247 cm^{-1}, $\bar{\nu}$ of N–C=O stretching: 1715, 1691 cm^{-1}, $\bar{\nu}$ of C–N stretching: 1335 cm^{-1}, $\bar{\nu}$ of C=S stretching: 1212 cm^{-1}. Mass (EI+): $C_{13}H_{14}N_2O_2S$ (M^+), found: m/z, 262, calculated for (M^+): m/z, 262.

4.2.3. 5,5-Dimethyl-1-(*o*-fluorophenyl)-2-thiobarbituric acid, (±)-3. The compound has been synthesized for the first time using *o*-fluorophenylthiourea and 2,2-dimethylmalonic acid. Yield: 34%. Mp 159°C. ^{1}H NMR ($CDCl_3$): $\delta = 1.59$ ppm (3H, s), 1.62 ppm (3H, s), $\delta = 7.10$–7.62 ppm (4H, m), $\delta = 9.09$ ppm (1H, b). ^{13}C NMR ($CDCl_3$): 177.68 ppm (C-2), 169.53 ppm (C-4 or C-6), 171.08 ppm (C-4 or C-6), 48.83 ppm (C-5), 23.40 ppm (C-7 or C-8), 25.65 ppm (C-7 or C-8), 116.47–131.57 ppm (aromatic C's). UV data (EtOH): λ_{max}, ($\log \varepsilon_{max}$) = 235 nm, (5.23); 252 nm, (5.29); 288 nm, (5.36); 392 nm, (2.83). IR data: $\bar{\nu}$ N–H stretching: 3292 cm^{-1}, $\bar{\nu}$ N–C=O stretching: 1747cm^{-1}, $\bar{\nu}$ C–N stretching: 1358 cm^{-1}, $\bar{\nu}$ C=S stretching: 1185 cm^{-1}. Mass (EI+): $C_{12}H_{11}FN_2O_2S$ (M^+), found: m/z, 266, calculated for (M^+): m/z, 267.

4.2.4. 5,5-Dimethyl-1-(*o*-methoxyphenyl)-2-thiobarbituric acid, (±)-4. The compound has been synthesized for the first time using *o*-methoxyphenylthiourea and 2,2-dimethylmalonic acid. Yield: 15%. Mp 160°C. ^{1}H NMR ($CDCl_3$): $\delta = 1.66$ ppm (3H, s), 1.70 (3H, s), $\delta = 3.81$ ppm (3H, s), $\delta = 7.00$–7.45 ppm (4H, m), $\delta =$ 9.09 (1H, b). ^{13}C NMR ($CDCl_3$): 178.36 ppm (C-2), 169.78 ppm (C-4 or C-6), 171.20 ppm (C-4 or C-6), 48.76 ppm (C-5), 23.19 ppm (C-7 or C-8), 25.86 ppm (C-7 or C-8), 112.41–154.50 ppm (aromatic C's), 56.22 ppm (*o*-CH_3). UV data (EtOH): λ_{max}, ($\log \varepsilon_{max}$) = 226 nm, (5.62); 243 nm, (5.76); 294 nm, (5.14); 393 nm, (2.81), IR data: $\bar{\nu}$ N–H stretching: 3137 cm^{-1}, $\bar{\nu}$ N–C=O stretching: 1747, 1709 cm^{-1}, $\bar{\nu}$ C–N stretching: 1330 cm^{-1}, $\bar{\nu}$ C=S stretching: 1211 cm^{-1}. Mass (EI+): $C_{13}H_{14}N_2O_2S$ (M^+), found: m/z, 277, calculated for (M^+): m/z, 278.

4.2.5. 5,5-Dimethyl-1-(*o*-chlorophenyl)-2-thiobarbituric acid, (±)-5. The compound has been synthesized using *o*-chlorophenylthiourea and 2,2-dimethylmalonic acid. Yield: 29%. Mp 178°C. ^{1}H NMR ($CDCl_3$): $\delta = 1.68$ ppm (3H, s), 1.75 ppm (3H, s), $\delta = 7.24$–7.54 ppm (4H, m), 9.13 ppm (1H, b). ^{13}C NMR ($CDCl_3$): 177.28 ppm (C-2), 169.60 ppm (C-4 or C-6), 170.78 ppm (C-4 or C-6), 48.75 ppm (C-5), 23.18 ppm (C-7 or C-8), 26.26 ppm (C-7 or C-8), 128.10–135.38 ppm (aromatic C's). UV data (EtOH): λ_{max}, ($\log \varepsilon_{max}$) = 237 nm, (5.9); 253 nm, (5.08); 288 nm, (5.6); 407 nm, (4.6). IR data: $\bar{\nu}$ N–H stretching: 3248 cm^{-1}, $\bar{\nu}$ N–C=O stretching: 1721, 1695 cm^{-1}, $\bar{\nu}$ C–N stretching: 1334 cm^{-1}, $\bar{\nu}$ C=S stretching: 1211 cm^{-1}. Mass (EI+): $C_{12}H_{11}ClN_2O_2S$ (M^+), found (M^+–Cl): m/z, 247, calculated for (M^+–Cl): m/z, 247.

4.2.6. 5,5-Dimethyl-1-(α-naphthyl)-2-thiobarbituric acid, (±)-6. The compound has been synthesized using α-naphthylthiourea and 2,2-dimethylmalonic acid. Yield: 33%. Mp 209°C. ^{1}H NMR ($CDCl_3$): $\delta = 1.75$ ppm (3H, s), 1.81 (3H, s), $\delta = 7.30$–8.00 ppm (4H, m). 9.17 ppm (1H, b). ^{13}C NMR ($CDCl_3$): 178.36 ppm (C-2), 169.78 ppm (C-4 or C-6), 171.20 ppm (C-4 or C-6), 48.76 ppm (C-5), 23.19 ppm (C-7 or C-8), 25.86 ppm (C-7 or C-8), 112.41–154.50 ppm (aromatic C's), 56.22 ppm (*o*-CH_3). UV data (EtOH): λ_{max}, ($\log \varepsilon_{max}$) = 236 nm, (7.7); 253 nm, (7.05); 289 nm, (7.3); 406 nm, (6.6). IR data: $\bar{\nu}$ N–H stretching: 3274 cm^{-1}, $\bar{\nu}$ N–C=O stretching: 1716, 1692 cm^{-1}, $\bar{\nu}$ C–N stretching: 1334 cm^{-1}, $\bar{\nu}$ C=S stretching: 1211 cm^{-1}. Mass (EI+): $C_{16}H_{14}N_2O_2S$ (M^+), found: m/z, 298, calculated: m/z, 298.

4.2.7. 1-(*o*-Tolyl)barbituric acid, (±)-7. The compound has been synthesized using *o*-tolylurea and diethylmalonate. Yield: 12.8%. Mp 234–235°C. ^{1}H NMR ($CDCl_3$): $\delta = 2.18$ ppm (3H, s), 3.84 (2H, s), $\delta = 7.09$–7.38 ppm (4H, m), 8.11 ppm (1H, b); ^{1}H NMR (DMSO-d_6): $\delta = 2.08$ ppm (3H, s), 3.68, 3.87 (2H, AB), $\delta = 7.14$–7.29 (4H, m), 11.46 (1H, b). ^{13}C NMR ($CDCl_3$): 148.57 (C-2), 163.42 (C-4 or C-6), 164.60 (C-4 or C-6), 39.84 (C-5), 127.46–135.50, (aromatic C's), 17.05 (*o*-CH_3). UV data (EtOH): λ_{max}, ($\log \varepsilon_{max}$); 203.5 nm, (4.54); 259.5 nm, (4.33). IR data: $\bar{\nu}$ N–H stretching: 3224 cm^{-1}, $\bar{\nu}$ N–C=O stretching: 1720 cm^{-1}, $\bar{\nu}$ C–N stretching: 1342 cm^{-1}. Elemental analysis: found C, 60.31; H, 4.39; N, 12.57, calculated for $C_{11}H_{10}N_2O_3$: C, 60.31; H, 4.62; N, 12.89.

4.2.8. 1-(*o*-Chlorophenyl)barbituric acid, (±)-8. The compound has been synthesized using *o*-chlorophenylurea and diethylmalonate. Yield: 5.8%. Mp 224.5°C (dec.). ^{1}H NMR ($CDCl_3$): $\delta = 3.84$, 3.88 ppm (2H, AB), $\delta =$ 7.25–7.57 ppm (4H, m), 8.04 ppm (1H, b). ^{13}C NMR ($CDCl_3$): 163.58 ppm (C-4 or C-6), 164.17 ppm (C-4 or C-6), 39.82 ppm (C-5), 128.18–131.22 ppm (aromatic C's). UV data (EtOH): λ_{max}, ($\log \varepsilon_{max}$); 204.5 nm, (4.18); 259 nm, (3.86). IR data: $\bar{\nu}$ N–H stretching: 3218 cm^{-1}, $\bar{\nu}$ N–C=O stretching: 1724 cm^{-1}, $\bar{\nu}$ C–N stretching: 1346 cm^{-1}. Elemental analysis: found C, 50.41; H, 3.03; N, 11.48, calculated for $C_{10}H_7ClN_2O_3$: C, 50.31; H, 2.96; N, 11.78.

4.2.9. 1-(*o*-Tolyl)-2-thiobarbituric acid, (±)-9. The compound has been synthesized using *o*-tolylthiourea and diethylmalonate. Yield: 31.5%. Mp 137°C (dec.). ^{1}H NMR ($CDCl_3$): $\delta = 2.16$ ppm (3H, s), 3.87, 3.89 ppm (2H, AB), $\delta = 7.06$–7.40 ppm (4H, m), 9.38 ppm (1H, b). ^{13}C NMR ($CDCl_3$): 178.46 ppm (C-2), 162.19 ppm (C-4 or C-6), 163.37 ppm (C-4 or C-6), 40.29 ppm (C-5), 127.62–138.46 ppm (aromatic C's), 17.78 ppm (*o*-CH_3). UV data (EtOH): λ_{max}, ($\log \varepsilon_{max}$); 203 nm, (3.86); 267 nm, (3.28); 285 nm, (3.27); 450 nm, (3.30). IR data: $\bar{\nu}$ N–H stretching: 3228 cm^{-1}, $\bar{\nu}$ N–C=O

stretching: 1728 cm^{-1}, $\bar{\nu}$ C–N stretching: 1332 cm^{-1}, $\bar{\nu}$ C=S stretching: 1193 cm^{-1}. Elemental analysis: found C, 55.28; H, 4.25; N, 11.52, calculated for $C_{11}H_{10}N_2O_2S$: C, 56.37; H, 4.30; N, 12.0.

4.2.10. 1-(*o*-Chlorophenyl)-2-thiobarbituric acid, (±)-10. The compound has been synthesized using *o*-chlorophenylthiourea and diethylmalonate. Yield: 32%. Mp 164°C (dec.). ^1H NMR ($CDCl_3$): $\delta = 3.88$, 3.91 ppm (2H, AB), $\delta = 7.62$–7.98 ppm (4H, m), 9.31 ppm (1H, b). ^{13}C NMR ($CDCl_3$): 177.87 ppm (C-2), 161.26 ppm (C-4 or C-6), 163.01 ppm (C-4 or C-6), 40.34 ppm (C-5), 126.16–134.88 ppm (aromatic C's). UV data (EtOH): λ_{max}, (log ε_{max}); 206 nm, (4.09); 244 nm, (3.53); 268 nm, (3.66); 427 nm, (3.21). IR data: $\bar{\nu}$ N–H stretching: 3429 cm^{-1}, $\bar{\nu}$ N–C=O stretching: 1710 cm^{-1}, $\bar{\nu}$ C–N stretching: 1343 cm^{-1}, $\bar{\nu}$ C=S stretching: 1189 cm^{-1}. Elemental analysis: found C, 46.45; H, 2.59; N, 10.59, calculated for $C_{10}H_7ClN_2O_2S$: C, 47.14; H, 2.77; N, 11.04.

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