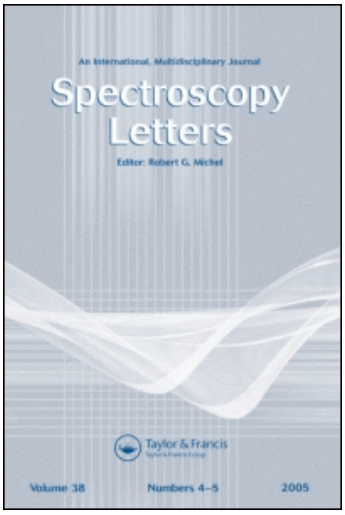

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REACTIONS OF BARBITURIC AND 2-THIOBARBITURIC ACID DERIVATIVES WITH ACETONE

Keywords: 1-Arylbarbituric acids, 1-(*o*-Aryl)-2-thiobarbituric acids, active methylene reactions

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ABSTRACT

Barbituric and 2-thiobarbituric acid derivatives carrying a 1-N-aryl substituent were found to react with acetone at the 5-position of the heteroring. Acetone adducts were identified by their ^{13}C NMR and mass spectra.

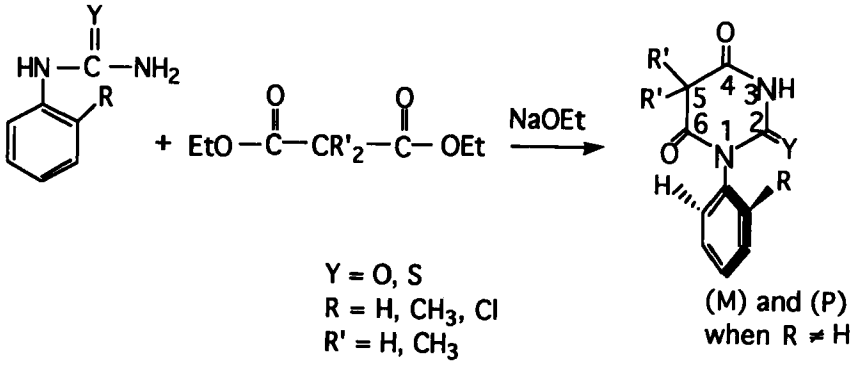
INTRODUCTION

Our interest in the heterocyclic analogues of sterically hindered chiral biaryls[1,2,3] encouraged us to synthesize 1-*o*-arylbarbituric and -2-thiobarbituric acid derivatives (scheme 1) in which resolution and racemization experiments together with NMR studies could be carried out[4]. During the NMR studies on these compounds we found out an active methylene reaction of the barbituric and 2-thiobarbituric acids with acetone-d_6 at the position 5 of the heteroring at room temperature. We identified the acetone adducts using ^{13}C NMR and mass spectroscopy. Here we report the adducts formed and propose a mechanism for their formation.

RESULTS AND DISCUSSION

Novel[5] barbituric and 2-thiobarbituric acid derivatives have been synthesized (table 1), their purities were checked and compounds have been fully characterised[6]. 1-Arylbarbituric acids and 1-aryl-2-thiobarbituric acids were synthesized by the condensation reaction of phenylureas or phenylthioureas and diethylmalonate as shown in scheme 1.

The 200 MHz ^1H NMR spectrum of N-(*o*-tolyl)barbituric acid (figure 1) taken in hexadeutoroacetone gave peaks at δ=2.15 ppm (3H, s) δ_A = 3.87 ppm δ_B = 3.78 ppm (2H, AB) δ=7.35 - 7.16 (4 H, m). The AB system was observed for the 5-CH_2 protons of the heterocyclic ring because they are diastereotopic due to the axial chirality[2] of the

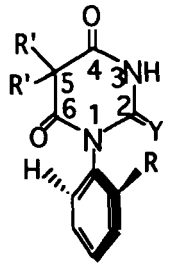


Scheme 1. Synthesis of the barbituric and thiobarbituric acids studied.

molecule. When the spectrum of the same compound i.e. 1-(*o*-tolyl)barbituric acid was taken after being kept for 2 days at 23° C in hexadeutoroacetone, the intensity of the CH_2 signals[9] was found to decrease (figure 2), and the decrease was found to continue with time (figure 2). After an 8 days of reaction time at 23°C, the peak of the CH_2 protons almost disappeared (figure 2). However when the solvent was evaporated after this reaction time and ^1H NMR spectrum of the remaining compound was taken in trifluoroacetic acid, it was observed that the CH_2 peak reappeared with the original integral ratio. It was apparent that 1-(*o*-tolyl)barbituric acid reacted slowly with hexadeutoroacetone.

The other derivatives studied here (table1) reacted faster, within approximately 4 hours with

TABLE 1
The synthesized 1-(*o*-aryl)barbituric and 2-thiobarbituric acids



(M) and (P)
when R ≠ H

compound no	Aryl group	Y	R'	m.p.(°C)
1	phenyl[7]	O	H	259-261
2	o-tolyl	O	H	234-235
3	o-chlorophenyl[8]	O	H	224.5
4	o-tolyl	S	H	137
5	o-chlorophenyl	S	H	164
6	o-tolyl	O	CH_3	148-150

[7]see reference 7
[8]see reference 8

hexadeutoroacetone except for 5,5-dimethyl-1-(*o*-tolyl)barbituric acid which did not react at all.

To see the effect of water on the reaction, phenylbarbituric acid was refluxed with water and acetone mixture (approximately 3:1, just enough acetone was added to solubilize the compound in water). A slower reaction was observed in water-acetone mixture and any reaction with water itself was not seen.

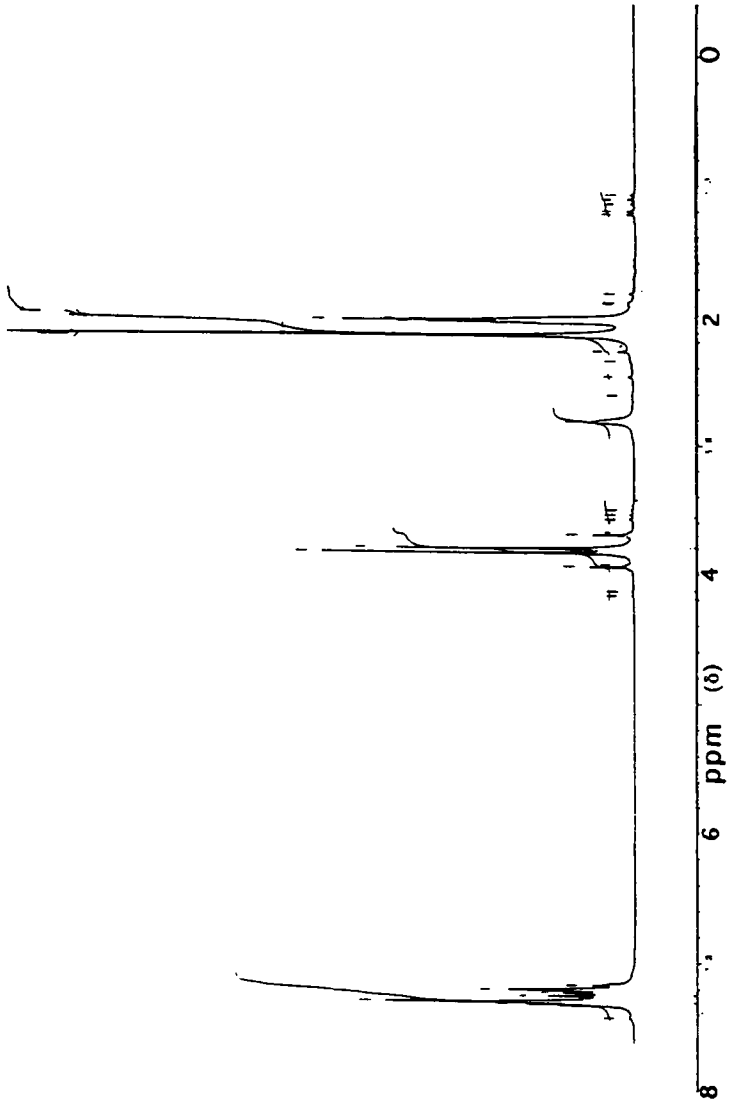


Fig.1. The 200 MHz ^{1}H NMR spectrum of 1-(*o*-tolyl)barbituric acid in hexadeutoroacetone at 23°C.

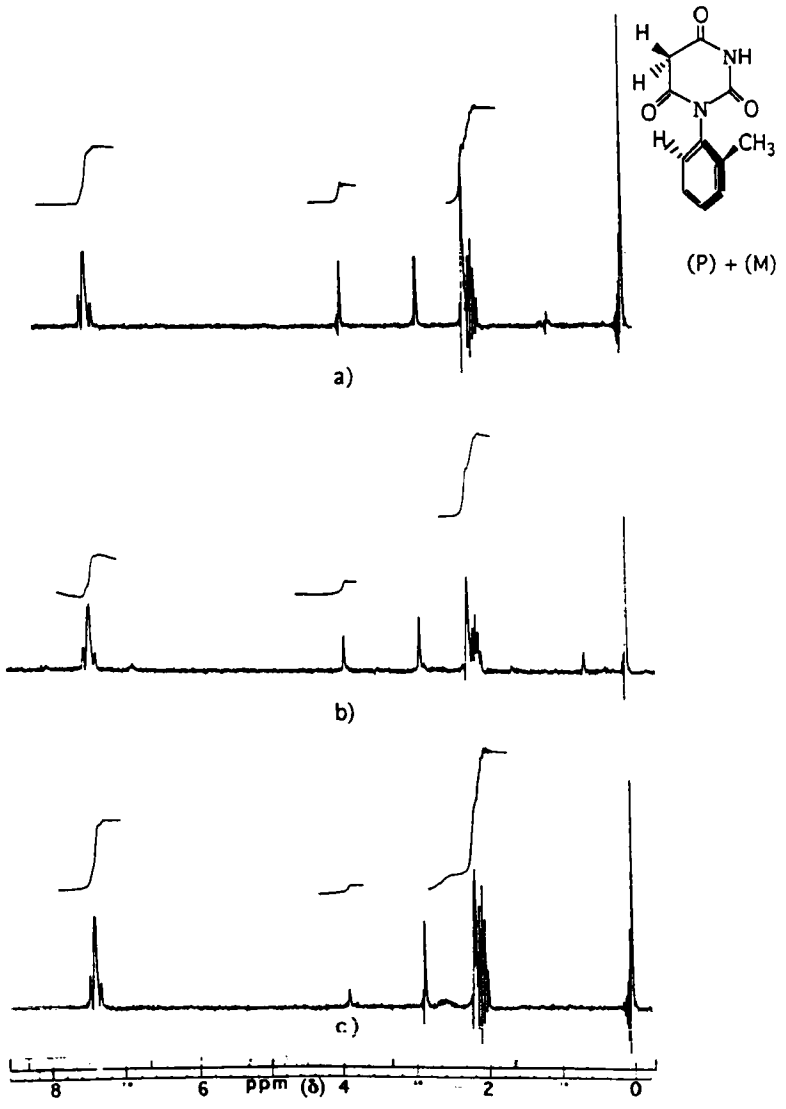
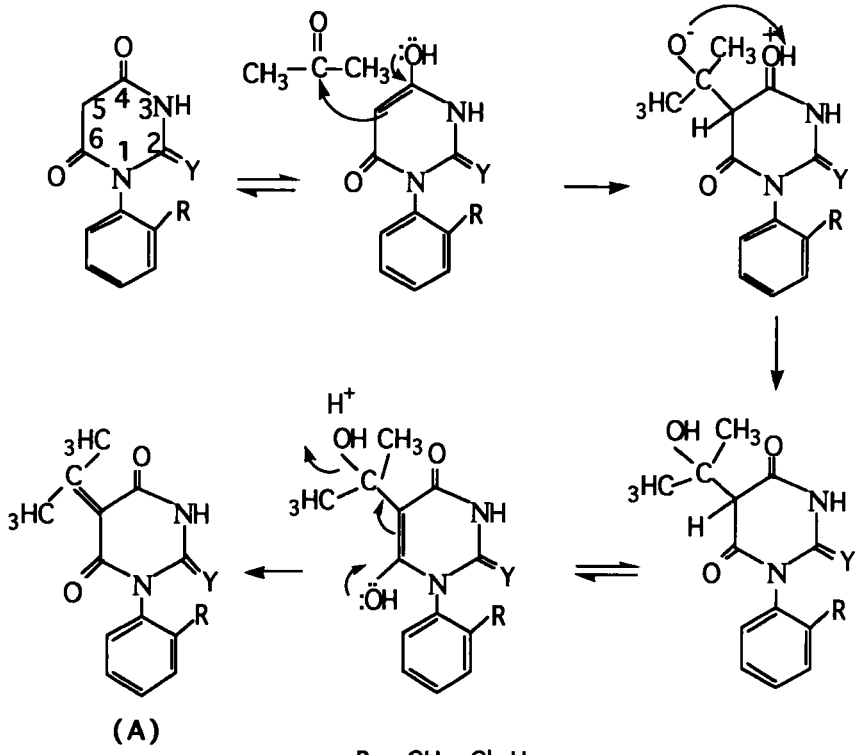


Fig.2. The 60 MHz ^{1}H NMR spectra of 1-(*o*-tolyl)barbituric acid in hexadeutoroacetone at 23°C taken after after a) 2 days, b) 4 days, c) 8 days.

From these results it was proposed that acetone reacts with the barbituric and thiobarbituric acids at C-5 over the enol form to form an adduct, in the same way as to be expected from an active methylene compound. This adduct is reversibly converted to the barbituric acid in acidic medium. The proposed mechanism for the formation of the adduct (A) and its conversion back to the barbituric acid are shown in schemes 2 and 3 respectively.

The 5,5-dimethyl-1-(*o*-tolyl)barbituric acid did not give any reaction under the same conditions because it does not have an enolizable proton at C-5 of the heteroring. Similar adducts were proposed to be formed[10] from the reaction of 2-thiobarbituric acid with aldehydes. In this study we show that not only 2-thiobarbituric acids but barbituric acid derivatives as well react with a carbonyl compound. In a study about the tautomerism of barbituric and thiobarbituric acid derivatives[11] a reaction of acetone with the compounds at the thiocarbonyl bond was proposed. Such a reaction was not observed in our case probably due to the steric hindrance brought by the *o*-aryl substituents.

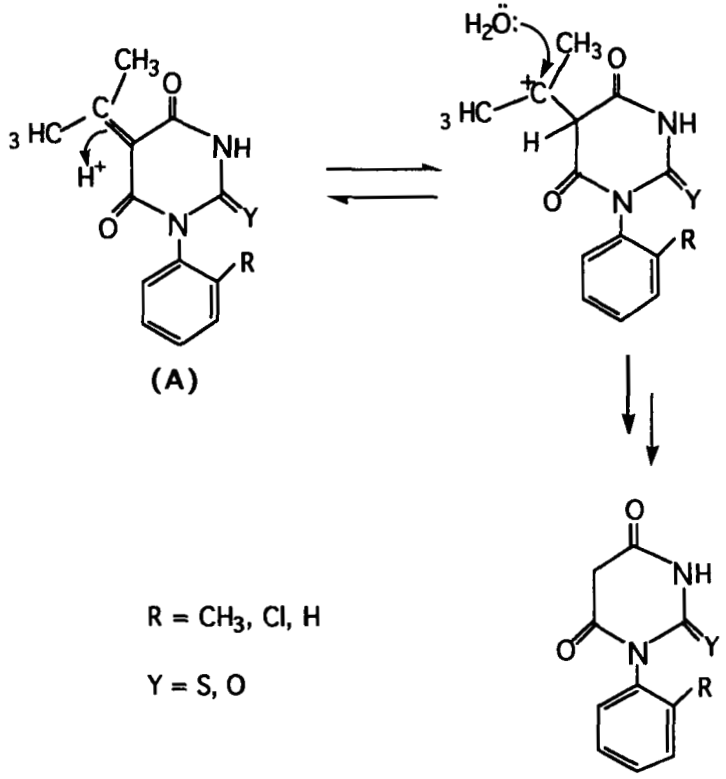
The ^{13}C NMR spectra of compounds 3,4 and 5 taken in hexadeutoroacetone were found to be different than the ^{13}C NMR spectrum of 5,5-dimethyl-1-(*o*-tolyl)barbituric acid which did not react with acetone. The C-5 carbon of



(A)

Scheme 2. Reaction of acetone with the barbituric and thiobarbituric acids studied to form the acetone adduct(A).

the heteroring which resonated at 48 ppm for example did not appear in the spectra of the former compounds. Instead additional peaks (small intensity) around 130 ppm were found. The ^{13}C NMR spectra ascribed to the acetone-d_6 adducts are given in table 2. The CD_3 carbon



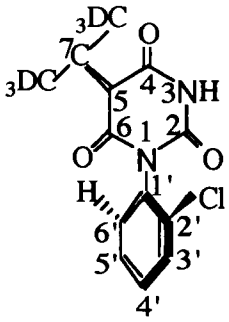
Scheme 3. Conversion of the acetone adduct (A) back to barbituric and thiobarbituric acids.

signals of the adducts overlaped with the acetone-d_6 signals, therefore they could not be observed.

The mass spectra of the acetone adducts of 1-phenylbarbituric and 1-(*o*-tolyl)barbituric acids (figures 3 and 4 respectively) showed molecular peaks of m/e 244 and 258 respectively. These peaks may be assigned to the structures 1' and 2' (Scheme4) which may be considered

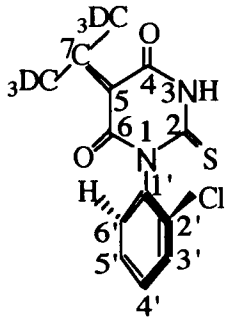
TABLE 2

^{13}C NMR chemical shifts of acetone adducts, 3, 4, and 5 in hexadeutoroacetone



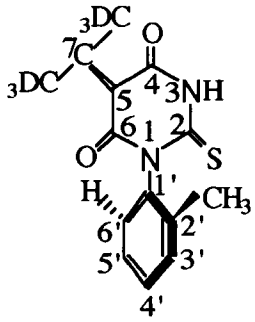
(M) + (P)

3



(M) + (P)

4



(M) + (P)

5

	Compound		
no of C atom	3	4	5
2	151.2	a	a
4, 6	164.3; 166.3	a	a
5[b], 7	131.10,	131.2; 132.0	129.50; 129.73
1'	133.74	a	a
2'	132.32	a	a
3'	132.05	132.28	131.29
4'	130.59	130.50	129.36
5'	131.32	130.95	129.95
6'	128.65	128.62	127.47
2'-CH_3	-	-	17.47

[a] It could not be observed due to longer relaxation time or overlaping.

[b] A small peak has been observed at 40.44 ppm, and has been ascribed to the C-5 carbon of the unreacted compound.

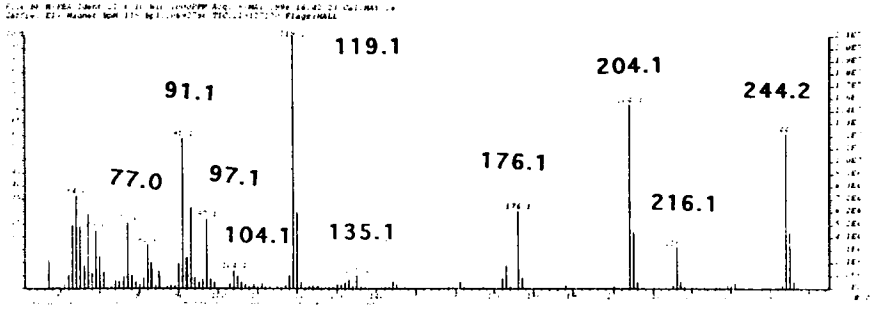


Fig.3. Mass spectrum of 1-phenylbarbituric acid.

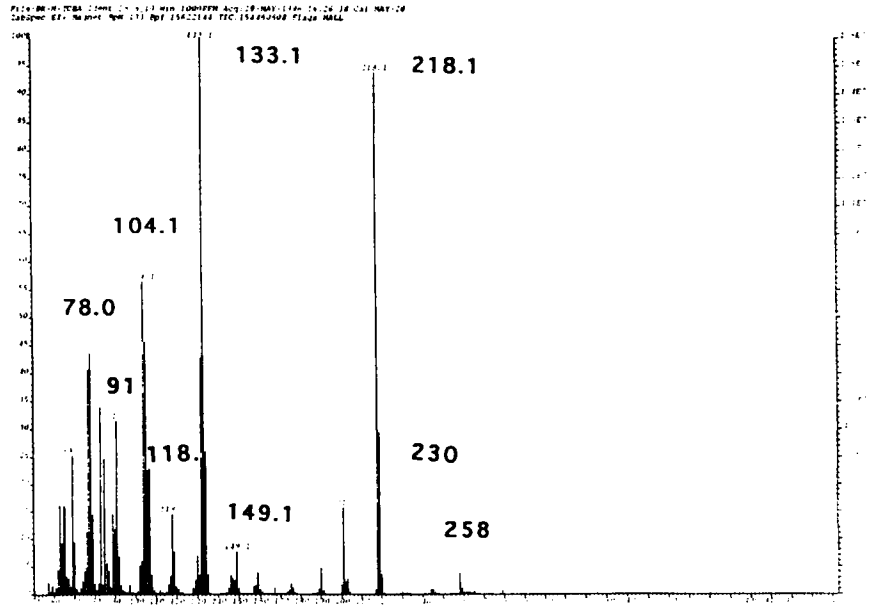
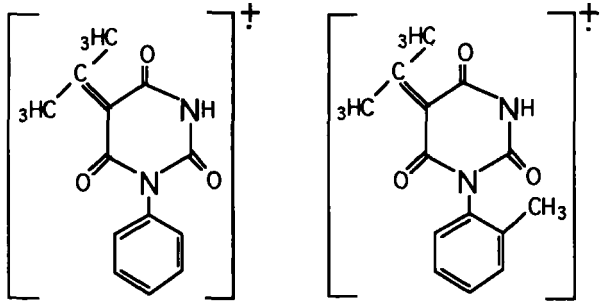


Fig.4. Mass spectrum of 1-(*o*-tolyl)barbituric acid.

m/e	Ion
244, 258	
	1' 2'

Scheme 4. The molecular ions of the acetone adducts from 1 and 2.

as a further proof for the formation of the acetone adducts.

APPARATUS

Proton NMR spectra were recorded on a Bruker AC-200 (200 MHz, T=23° C), or on a Varian T-60 A NMR (60 MHz, T=23° C) spectrometers. Carbon-13 NMR spectra were recorded on a Bruker AC (200 MHz, T=23° C). The mass spectra were recorded on a VG-ZABSPEC instrument (1000 resolution). Melting points were recorded using Electrothermal 9100 melting point apparatus.

ACKNOWLEDGMENTS

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9. The AB system observed at 200 MHz instrument was not observed at 60 MHz ^{1}H NMR instrument.

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