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Thermal and ^{1}H NMR studies on some azo derivatives of barbituric acid

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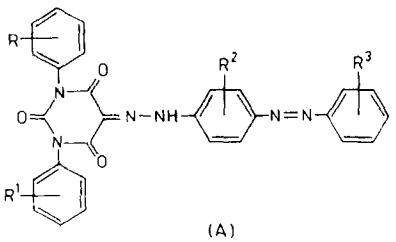
Abstract

Thermal and ^{1}H NMR spectral studies on some diazo-based pyrimidinetriones, namely 1,3-diaryl-1,3-dihydro-1H,3H,5H-5[4-(arylhydrazono)benzeneazo]pyrimidine-2,4,6-triones, have shown that these compounds display strong intramolecular hydrogen bonding between the hydrogen of the β nitrogen and the adjacent oxygen atom of the barbituric acid moiety.

INTRODUCTION

The barbiturates are a group of depressant drugs that act on the central nervous system [1,2]. Unsubstituted barbituric acid has no depressant activity on the central nervous system but depression results when both hydrogen atoms in position 5 are replaced by organic groups [3,4]. Because of the significant biological properties associated with barbituric acid and its azo derivatives, it was of interest to synthesise barbituric acid containing a diarylazo group. The present work describes studies on some 1,3-diaryl-1,3-dihydro-1H,3H,5H-5[4-(arylhydrazono)benzeneazo]pyrimidine-2, 4, 6-triones (**A**).



(A)

$R^2=R^3=H$; $2-CH_3$

EXPERIMENTAL

The compounds synthesised were studied with the following instruments: a JEOL JMS-D300 spectrometer was used to record the mass spectra; a

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Perkin–Elmer 783 IR spectrometer was used for recording IR spectra in KBr pellets; a Hitachi 60 MHz R-600 NMR spectrometer was used for measuring ^1H NMR spectra (solvent; $CDCl_3$; internal standard, tetramethylsilane); a Du pont 910 thermal analyser was used for recording DSC curves in air at a heating rate of 10 °C min^{-1} and a chart speed of 50 cm h^{-1}.

RESULTS

The DSC curves of 1,3-diaryl-1,3-dihydro-1H,3H,5H-5[4-(phenylhydrazono)benzeneazo]pyrimidine-2,4,6-triones (**1–7**) and 1,3-diaryl-1,3-dihydro-1H, 3H, 5H-5[2-methyl-4 (2-methylphenylhydrazono) benzeneazo]pyrimidine-2,4,6-triones (**8–14**) are shown in Figs. 1 and 2, respectively. The structures of some isoquinolenes having the sequence –S–C=N–CO–C–N=N– in their structures have been studied by polarographic and IR spectroscopic methods: it was found that these compounds exist predominantly in the azo form [5]. However, few papers have been reported on the tautomeric equilibria of the azo derivatives of barbituric acid. The methods of synthesis of azo derivatives of barbituric acid are well established [6,7]. In recent studies we have synthesised two series of new types of diazo compound of barbituric acids by the reaction of 1,3-diaryl barbituric acids with diazotised *p*-aminoazobenzene or *o*-aminoazotoluene respectively, as shown in Scheme 1 [8].

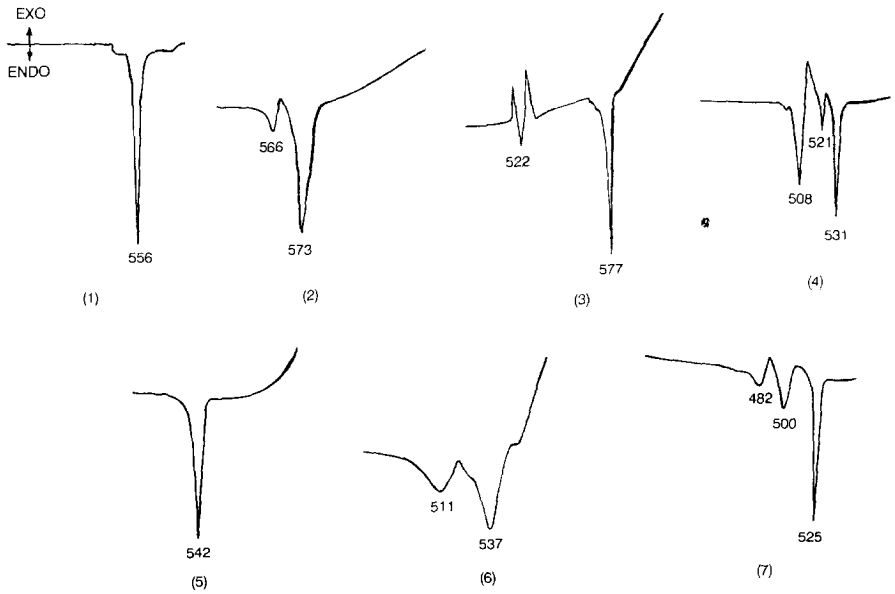


Fig. 1. DSC thermal curves of 1,3-diaryl-1,3-dihydro-1H,3H,5H-5[4-(phenylhydrazono)benzeneazo]pyrimidine-2,4,6-triones (**1–7**).

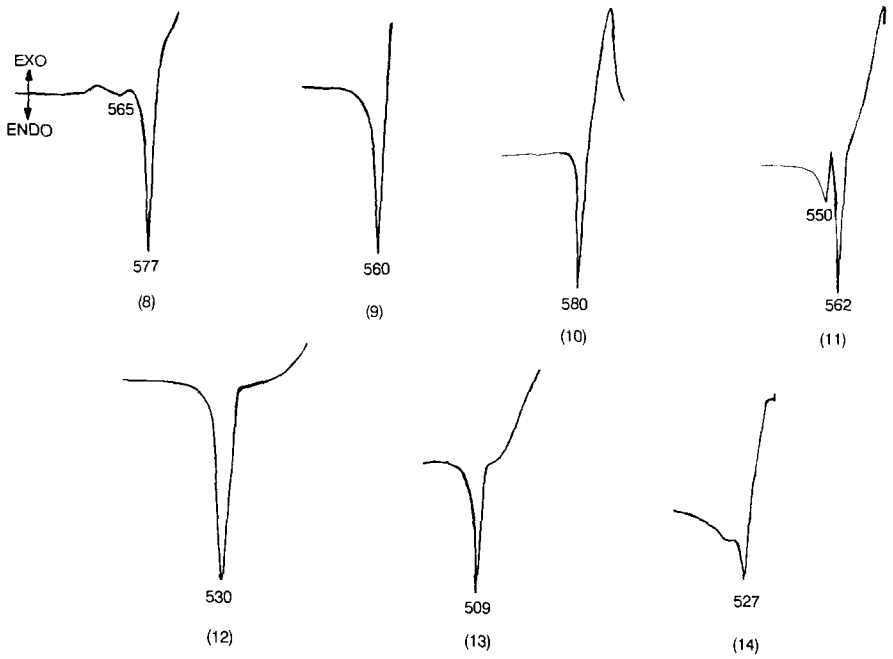
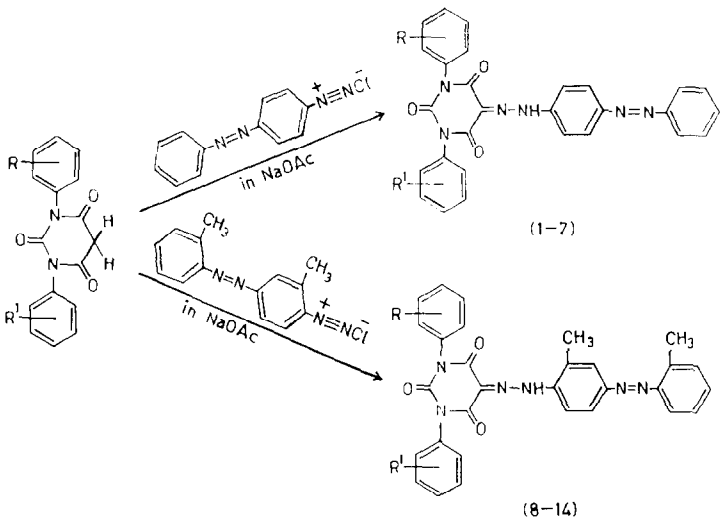


Fig. 2. DSC thermal curves of 1,3-diaryl-1,3-dihydro-1H,3H,5H-5[2-methyl-4-(2-methylphenylhydrazono)benzeneazo]pyrimidine-2,4,6-triones (**8**–**14**).



1,8; R=4-Cl, R^1=4-CH_3
2,9; R=4-Cl, R^1=4-Cl
3,10; R=4-Br, R^1=4-Cl
4,11; R=4-Cl, R^1=4-OCH_3
5,12; R=4-CH_3, R^1=H
6,13; R=2-OCH_3, R^1=H
7,14; R=4-OCH_3, R^1=H

Scheme 1

1,3-Bis(4-chlorophenyl)-1,3-dihydro-1H,3H,5H-5[4-(phenylhydrazono)benzeneazo]pyrimidine-2,4,6-trione (2)

This compound is an orange solid mass. Mass spectrum: m/z 556 (M^+). IR (KBr): 3431, 1730, 1688, 1633, 1585, 1506, 810 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 14.60$ (1H, s, NH), 7.10–7.90 (17H, m, Ar–H).

Two endothermic peaks are observed on the DSC curve: the first with $T_{max} = 566$ K is due to intramolecular hydrogen bonding (NH–OC); the second, with $T_{max} = 573$ K, corresponds to the melting of the compound (**2**).

1,3-Bis(4-chlorophenyl)-1,3-dihydro-1H,3H,5H-5[2-methyl-4(2-methylphenylhydrazono)benzeneazo]pyrimidine-2,4,6-trione (9)

This compound is an orange solid mass. Mass spectrum: m/z 584 (M^+). IR (KBr): 3430, 2916, 2890, 1730, 1687, 1630, 1590, 1511, 820 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 14.70$ (1H, s, NH), 7.15–7.75 (15H, m, Ar–H), 2.70 (3H, s, CH_3), 2.48 (3H, s, CH_3).

The endothermic peak at $T_{max} = 569$ K indicates the melting point of compound (**9**).

DISCUSSION

The results of DSC thermal studies on the compounds that are *p*-aminoazobenzene derivatives of barbituric acids normally show two to three endothermic changes. One of the higher temperature DSC peaks corresponds to the melting of the compound; the other smaller peaks are most probably due to intramolecular hydrogen bonding between the hydrogen atom of the β nitrogen and the carbonyl oxygen atom of the barbituric acid moiety, or are due to the existence of more than one polymorphic form at higher temperature, as some free rotations of the trans azo groups are possible. The rotation of the azo groups in the *o*-aminoazotoluene base moiety is restricted, mainly due to steric hindrance between the ortho-substituted methyl groups and the lone pairs of the nitrogen atoms of the trans hydrazo; the trans azo groups form a stable configuration in which the lone-pair orbitals of the β nitrogen atom and δ nitrogen atom are away from their respective ortho-substituted methyl protons. The thermal data are presented in Tables 1 and 2.

The X-ray crystallographic studies on the structures of some phenylhydrazones showed that the ring NH–N=C–CO fragment is essentially planar, implying that electron delocalisation persists throughout the molecule [9]. The broad NH stretching frequencies for these compounds appear in the range 3350–3440 cm^{-1}. Two strong bands at around 1650 and 1515 cm^{-1} can be assigned to the CO absorptions of amide I and amide II, respectively, due to δ(NH) vibrations. Throughout the series, the δ(NH) bands showed a

TABLE 1

1,3-Diaryl-1,3-dihydro-1H,3H,5H-5[4-(phenylhydrazono)benzeneazo]pyrimidine-2,4,6-triones

Compound	DSC			^{1}H NMR ($CDCl_3$)	Mass spectrum
	Thermal effect	T_{max} (K)	ΔH_f (kJ mol^{-1})	δ (ppm) C=N–NHZ	(m/z) (M^+)
1	Endothermic	556	5.944	14.60	536
2	Endothermic	566	1.048	14.60	556
	Endothermic	573	5.042		
3	Endothermic	522	1.236	14.65	– [a]
	Endothermic	577	2.596		
4	Endothermic	508	7.212		
	Endothermic	521	2.086	14.60	552
	Endothermic	531	4.133		
5	Endothermic	542	10.507	14.70	502
6	Endothermic	511	8.148		
	Endothermic	537	14.996	14.80	518
7	Endothermic	482	1.782		
	Endothermic	500	4.124	14.80	518
	Endothermic	525	5.584		

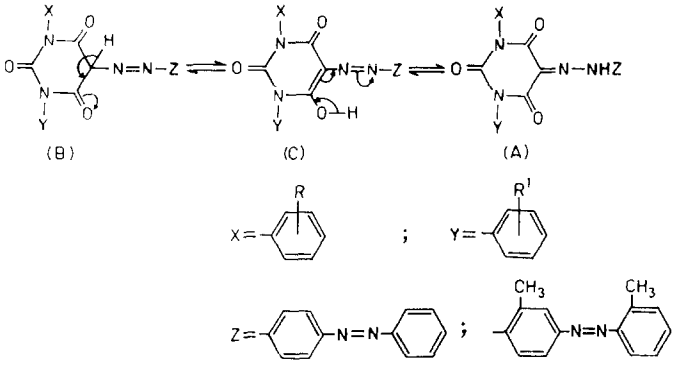
[a] The parent molecular radical ions could not be observed in the spectrum.

discernible low-field shift, which is due to the considerable intramolecular hydrogen bonding associated with the NH proton and the CO of the barbituric acid ring moiety. The compounds have a large δ(NH) value 14.60–14.80 ($CDCl_3$). In addition, it appears that the formation of intramolecular hydrogen bonding prevents the formation of $(CD_3)_2CO \cdots HN$ bonds, since the chemical shifts are essentially the same as in $CDCl_3$.

TABLE 2

1,3-Diaryl-1,3-dihydro-1H,3H,5H-5[2-methyl-4(2-methylphenylhydrazono)benzeneazo]pyrimidine-2,4,6-triones

Compound	DSC			^{1}H NMR ($CDCl_3$)	Mass spectrum
	Thermal effect	T_{max} (K)	ΔH_f (kJ mol^{-1})	δ (ppm) C=N–NHZ	(m/z) (M^+)
8	Endothermic	556	0.084	14.70	564
	Endothermic	577	1.430		
9	Endothermic	569	3.175	14.70	584
10	Endothermic	580	6.307	14.80	629
11	Endothermic	550	4.600	14.60	580
	Endothermic	562	7.157		
12	Endothermic	530	9.709	14.60	530
13	Endothermic	509	18.356	14.65	546
14	Endothermic	527	16.467	14.60	546



Scheme 2

The tautomeric structure (**B**), the alternative to the barbituric acid derivatives (**A**), was not considered as there was no signal due to the 5-methine proton in the ^{1}H NMR spectrum. The conversion of the sp^3 carbon into sp^2 carbon at the 5-position in the intermediate (**B**) allows an intramolecular proton transfer at the 6-position of tautomer (**C**), followed by tautomerisms into the much more stable product (**A**). The ^{1}H NMR spectra of the compounds throughout the series (**1**–**14**) in $CDCl_3$ or in $(CD_3)_2CO$ solution at room temperature show the presence of a singlet at around 14.60 ($CDCl_3$), due to the β-(NH) proton signal. Our attempts to separate the tautomers were unsuccessful. Assignment of the structures (**A**) and (**C**) in their ^{1}H NMR spectra was possible by considering the effect of hydrogen bonding and anisotropy on the methine proton induced by 4-carbonyl and 6-carbonyl groups, as shown in Tables 1 and 2 respectively (Scheme 2).

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