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Thermal behaviour of some spiro benzodiazepine derivatives

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Abstract

The thermal behaviour of some benzodiazepine derivatives have been studied by differential thermal analysis (DTA) and thermogravimetry (TG). It was founded that pyrolytic decomposition accompanied melting of the compounds, some of which were hydrates. Dehydration is followed by total pyrolytic decomposition in two stage. GC–MS was used to identify the products of the pyrolytic decomposition.

Keywords: Spiro benzodiazepine derivatives; Thermal behaviour; Pyrolysis; DTA/TG/DTG

1. Introduction

Benzodiazepines have been known to possess important medicinal properties for over 30 years. Some benzodiazepine derivatives have been found to be potent antagonists of the peptide hormones cholecystokinin (CCK) and gastrin [1–3]. The isolation from *Aspergillus alliaceus* of asperlicin (Scheme 1a) a potent non-peptide cholecystokinin (CCK) antagonist selective for peripheral tissues [4] initiated studies which led to the discovery of a benzodiazepine series of non-peptide CCK receptor antagonists such as the selective CCK_A antagonist MK-329 (Scheme 1b) [5] and dual histamine H_2-gastrin receptor antagonists [6,7].

In this study, a series of spiro benzodiazepines derivatives (Spiro[2,3′-(1′methyl-1′,3′-dihydro-2′-oxo-5′-phenyl-(2′H)-1′,4′-benzodiazepinyl]-4-(2′-naphthyl)-3, 7-diaza-6, 8-dioxobicyclo[3.3.0]octane) (SBIN), Spiro[2,3′-(1′ methyl-1′,3′-dihydro-2′-oxo-5′-phenyl-(2′H)-1′,4′-benzodiazepinyl]-4-(N′-phenylsulphonyl)-indolyl]-3,7-diaza-6,8-dioxobicyclo[3.3.0]octane (SBII) and cyclocompounds (SBFN, SBFI)) as shown in Scheme 2 have been prepared [8,9] and studied by differential thermal analysis (DTA) and thermogravimetry (TG) and the mechanism of thermal decomposition have been determined.

2. Experimental

The spiro benzodiazepine derivatives (SBIN, SBII, SBFN and SBFI) were synthesised using analytical pure reagents as described in [8,9].

2.1. Instrumentation

The thermal studies were carried out on a Shimadzu DT-40 Thermal Analyser with simultaneous DTA-TG module. The thermal analysis system was used over

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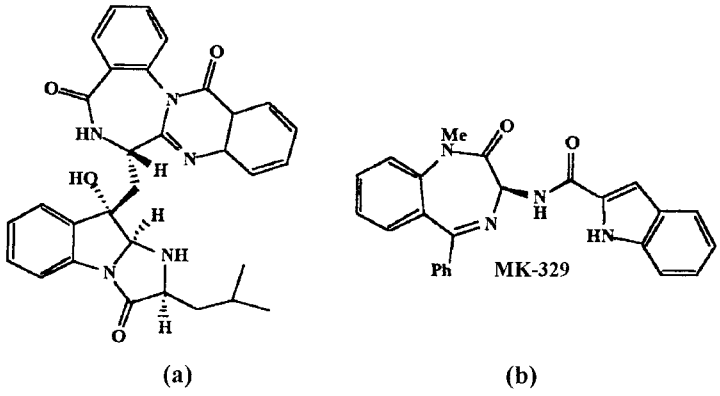


Scheme 1.

the temperature range 273–1823 K. The samples were placed in Pt crucibles and α-Al_2O_3 was used as the reference material. The measurement was performed using a dynamic nitrogen furnace atmosphere at a flow rate of 60 $cm^3\,min^{-1}$. The heating rate was 10 K min^{-1} and the sample sizes ranged in mass from 4 to 6 mg.

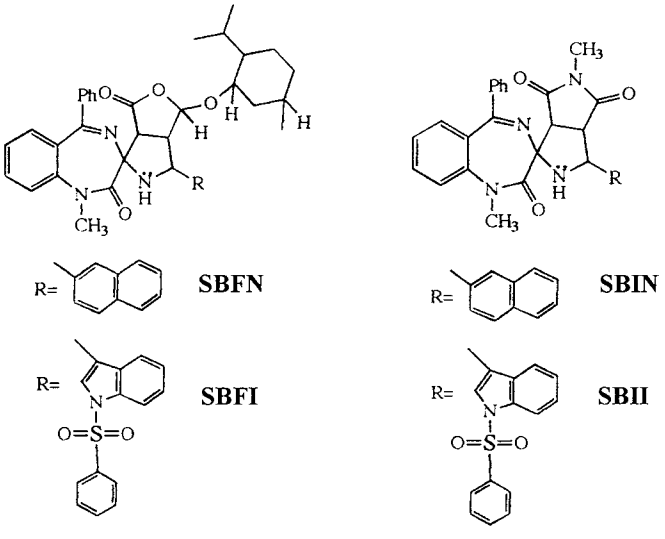
A GC–MS system VG-ZabSpect model DFMS, was used to identify pyrolysis products evolved during heating. Melting point determination was performed with a digital melting point instrument from Electrothermal model 9200. Microanalyses were obtained using a Carlo Erba MOD 11016 instrument.

3. Result and discussion

3.1. SBFI ($C_{45}H_{46}N_4O_6S$)

TG studies on SBFI using Electrothermal type mode 9200 showed that the sample first melted and was immediately accompanied by decomposition. The sample decomposed in two stages over the temperature range 440–1060 K (Fig. 1). The first decomposition occurs between 440 and 760 K with a mass loss of 49.5% and the second decomposition occurs between 760–1060 K with a 50.4% mass loss.

From the corresponding DTA analysis, one endotherm and two exotherms were observed with



Scheme 2.

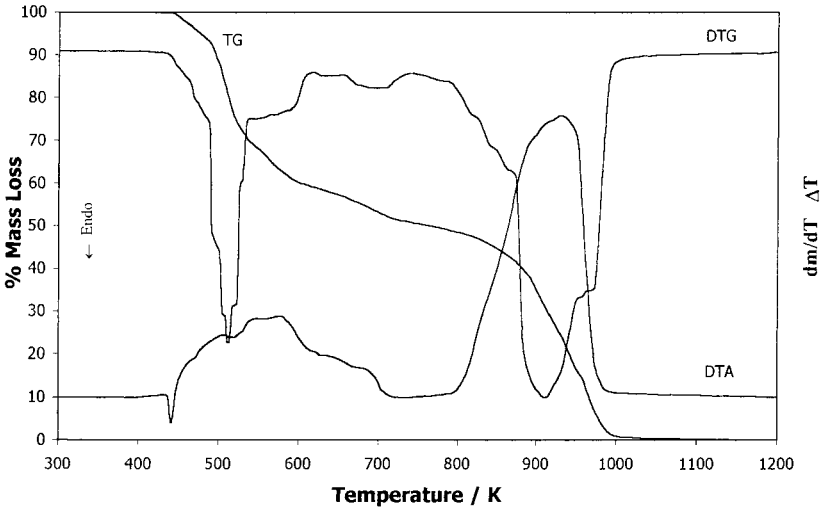
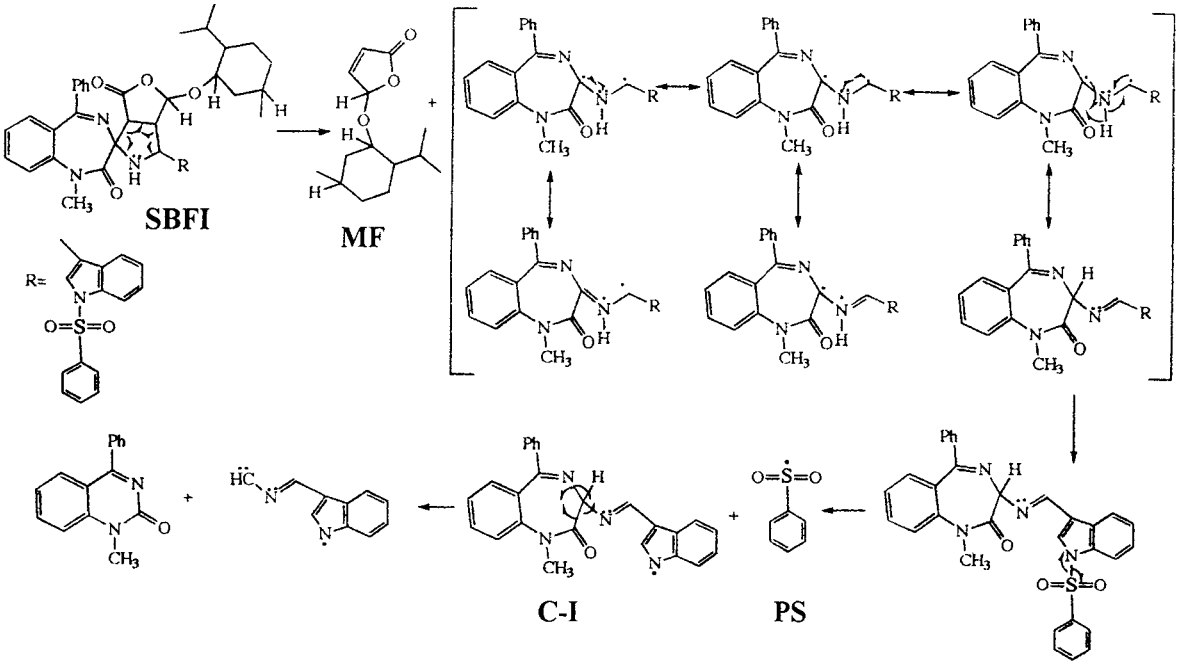


Fig. 1. DTA/TG/DTG diagram of SBFI.

the endotherm between 439 and 448 K and a maximum temperature difference at 445 K, the first exotherm peak between 450 and 750 K with a maximum peaks at 583 K and the second exotherm peak between 775 and 1006 K with a maximum at 935 K.

A possible mechanism for pyrolysis is shown in Scheme 3 [10–12]. The products of the decomposition were confirmed by GC–MS spectroscopy. The m/z peaks were observed at 771, 532, 392, 237 on the volatile products. The theoretical and the observed



Scheme 3.

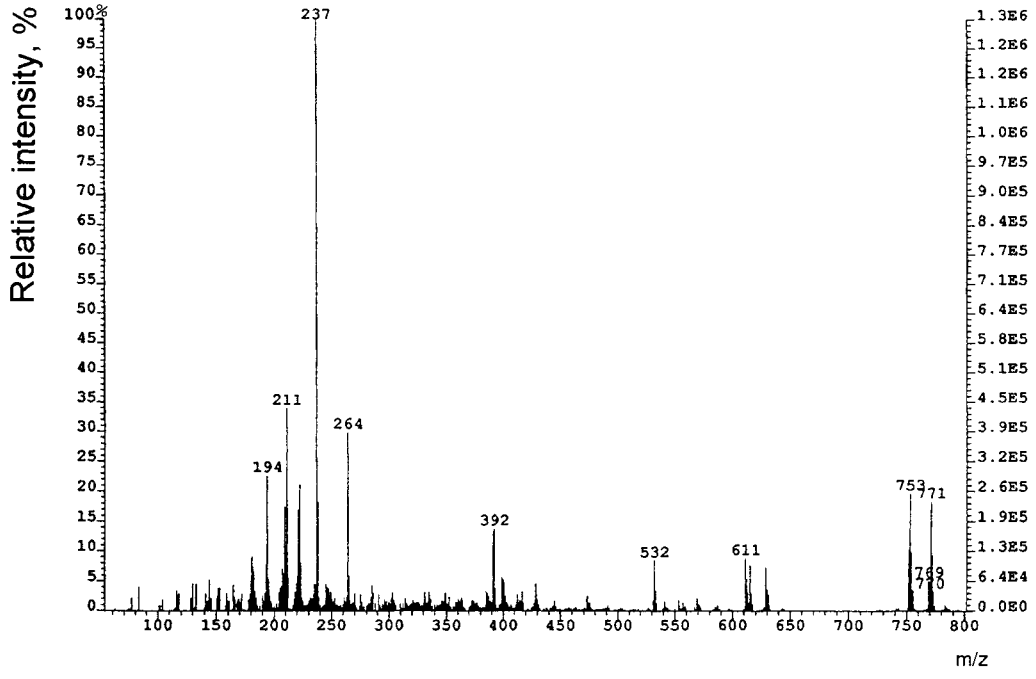
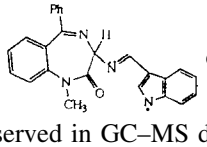


Fig. 2. GC–MS Spectrum of SBFI.

percent mass losses obtained from these decomposition stage are in good agreement.

The first stage of the decomposition corresponded with a theoretical mass loss of 49.2% compares with 49.5% from TG studies. The second stage correspond to a theoretical mass loss of 50.8% and the experimentally value was 50.4% from TG studies. The mass loss of the second stage corresponded to the evolution of the  compound I (C-I) (392 m/z) as observed in GC–MS data (Fig. 2).

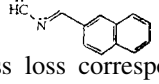
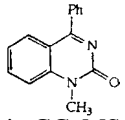
The mechanism of reaction Scheme 3 proceeded in two stages, the first of which is gave (R)-5(1R)-menthyloxy-2-(5H)-furanone (MF) and phenylsulphonyl group (PS) which form C-I. The end product of this stage underwent pyrolysis in the second stage.

3.2. SBFN ($C_{41}H_{46}N_3O_4$)

SBFN lost 99.98% of its mass between 480–1100 K in two stages. The first decomposition occurs between 480–750 K with a mass loss of 63.8%, the second decomposition started at 752 K and ended at 1098 K with a 36.2% mass loss. The DTA/TG/DTG profiles of SBFN is shown in Fig. 3.

One endothermic and two exothermic peaks were observed in the DTA analysis. The endothermic peak which observed over the range 490–504 K corresponded with the melting (decomp.). The first exothermic peak was observed between 505 and 760 K with a maximum at 663 K and the second between 789 and 962 K with a maximum at 914 K.

The mechanism of SBFN decomposition is shown in Scheme 4, and it is in agreement with that of Burakevich et al. [11]. The volatile products were confirmed by GC–MS data, with m/z peaks at 313 and 131.

Decomposition occurs in two stages. In the first stage, MF and  compound II (C-II) are lost. This mass loss corresponded with the loss of  compound III (C-III) (237 m/z) as observed in GC–MS data. The mass losses found experimentally was close to this theoretical value. In the second stage, C-III started to decomposition as shown in Scheme 4.

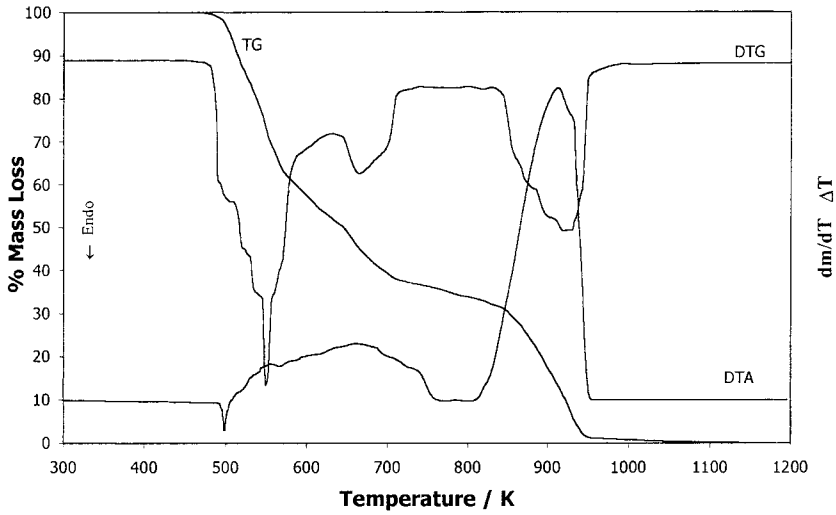
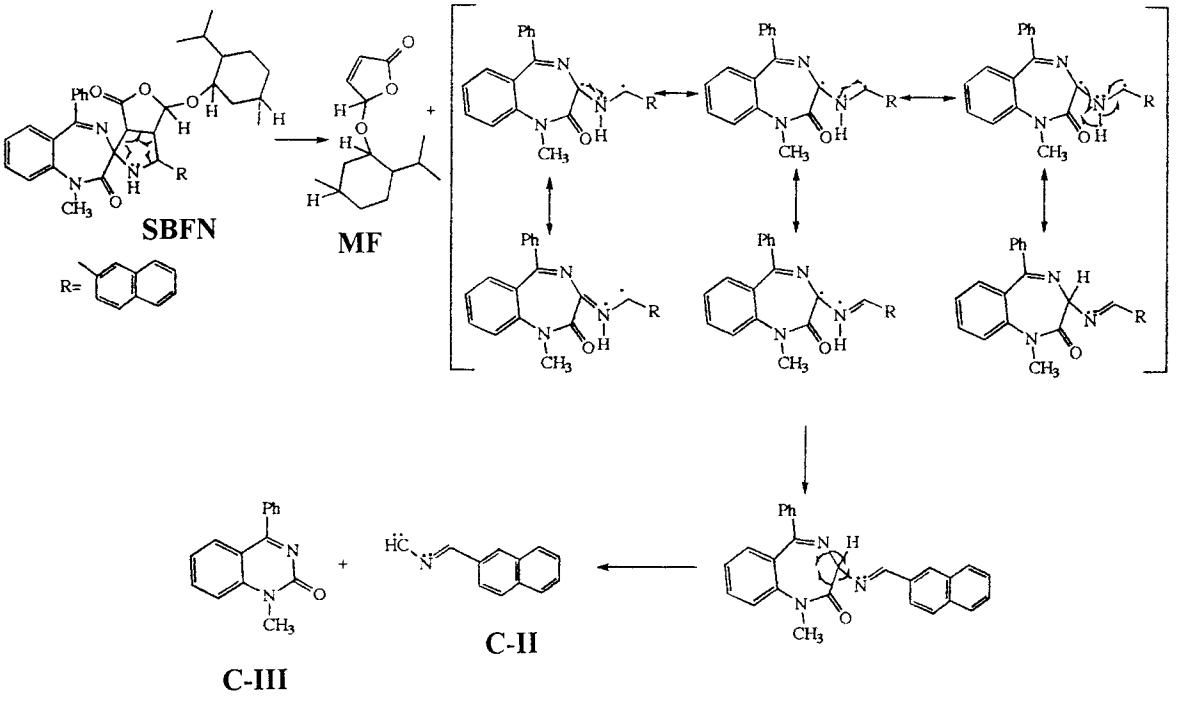


Fig. 3. DTA/TG/DTG diagram of SBFN.

63.0% theoretical mass loss in the first decomposition corresponds with 63.8% from TG. The second stage in the mechanism corresponded to a mass loss of 37.0% for which the experimentally value was 36.2%.

3.3. SBIN ($C_{32}H_{26}N_4O_3 \cdot 1.0\ H_2O$)

The TG studies of SBIN showed that an initial mass loss occured at 423 K with a total mass loss at 1100 K.



Scheme 4.

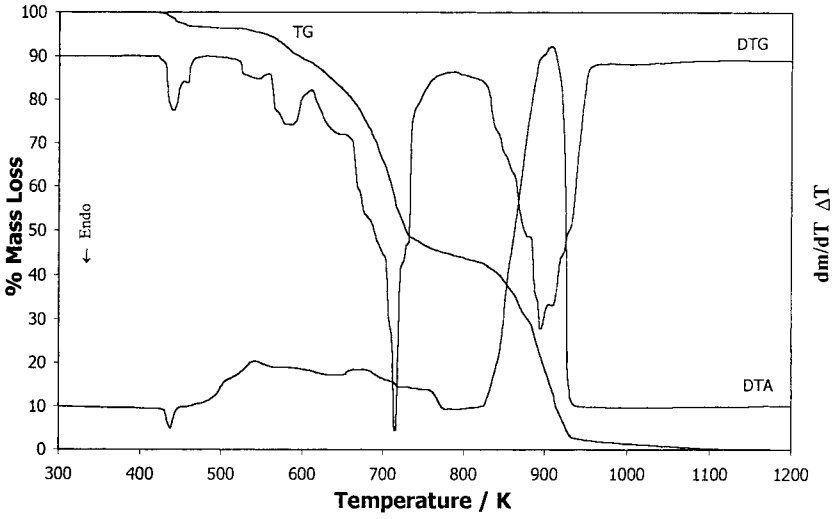
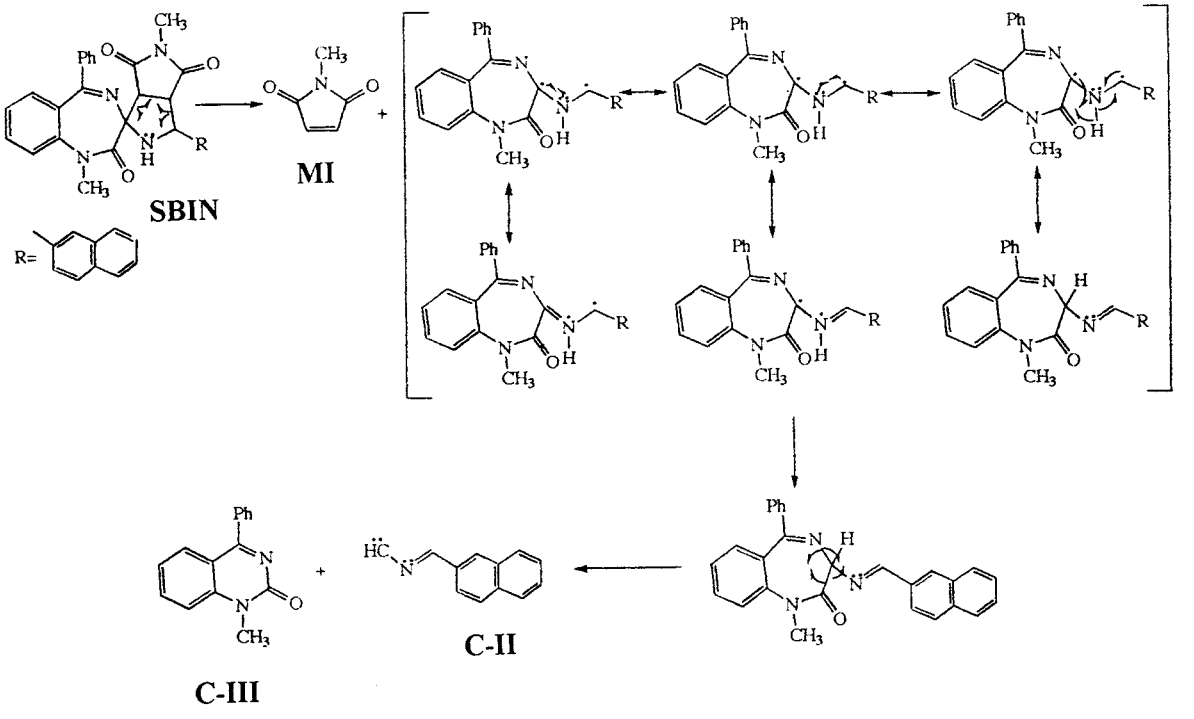


Fig. 4. DTA/TG/DTG diagram of SBIN.

The DTG/TG/DTG analyses of SBIN are shown in Fig. 4.

It was observed from the weight loss curve that the sample decomposed in three stages corresponding to 3.2, 51.7 and 45.1% mass loss, respectively. The temperature ranges of these decompositions was found to be 425–470, 470–760 and 760–1100 K, respectively.



Scheme 5.

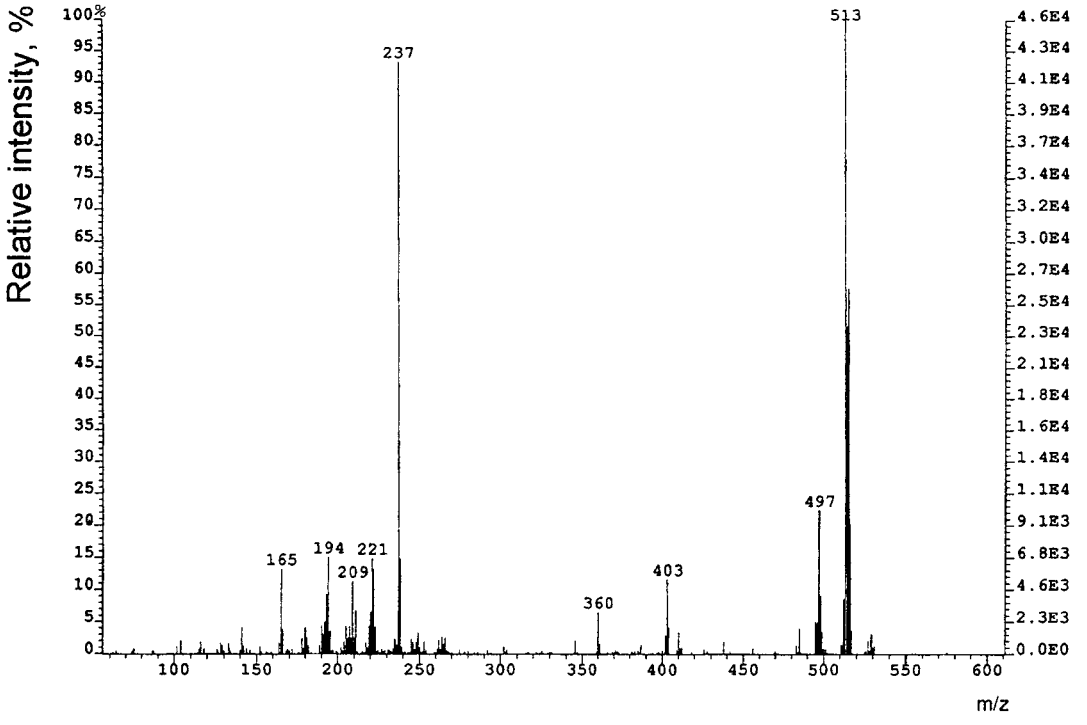


Fig. 5. GC–MS Spectrum of SBIN.

The DTA curve shows one endotherm and two exotherms. The endotherm between 421 and 445 K corresponded with the loss of one mole of water. The first exotherm occurs between 466 and 773 K. The second occurs between 800 and 940 K.

The mechanism of the decomposition is shown in Scheme 5. It proceeded in three stages. The theoretical and observed mass losses of each stage were as follows; first stage 3.4–3.2%, second stage 52.3–51.7% and third stage 44.4–45.1% in good agreement. The thermal decomposition mechanism is similar to that of SBFN. Micro analysis of SBIN showed that it contained one mole of water (found: C, 72.0%, H, 5.1%, N, 10.4%; $C_{32}H_{26}N_4O_3{\cdot}1.0\ H_2O$ required C, 72.15%; H, 5.25%; N, 10.5%). The mass loss in the first stage of SBIN corresponded to the loss of one mole water. The theoretical and observed percent mass losses obtained from these decomposition stages are in good agreement. In the second stage, *N*-methylmaleimide (MI) was lost and C-II and compound III are formed. In the third stage C-III decomposed in a similar way to that of SBFN as shown in Fig. 5 and confirmed by GC–MS data.

3.4. SBII ($C_{36}H_{29}N_5O_5S{\cdot}1.0\ H_2O$)

TG studies on SBII showed that an initial mass loss occured at 415 K. Decomposition ends with a total of 99.98% of the mass lost at 1064 K. DTA/TG/DTG analyses of SBII are shown in Fig. 6.

SBII decomposed in three stages. The sample loses 3.0% of its mass between 415 and 483 K, 37.6% between 483 and 771 K and 59.4% between 771 and 1064 K.

The DTA study of SBII showed one endotherm and two exotherms peaks. The endotherm appeared between 422 and 451 K. This corresponded to the loss of one mole of water. The first exotherm appeared between 480 and 771 K and the second between 790 and 981 K.

The mechanism of the decomposition is shown in Scheme 6 is confirmed by the GC–MS and TG data. The mass losses at each stage were 3.0, 37.6 and

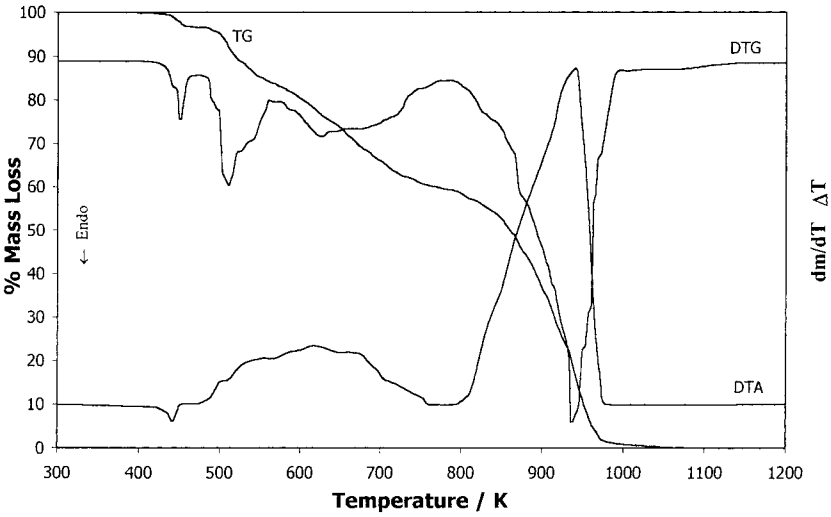
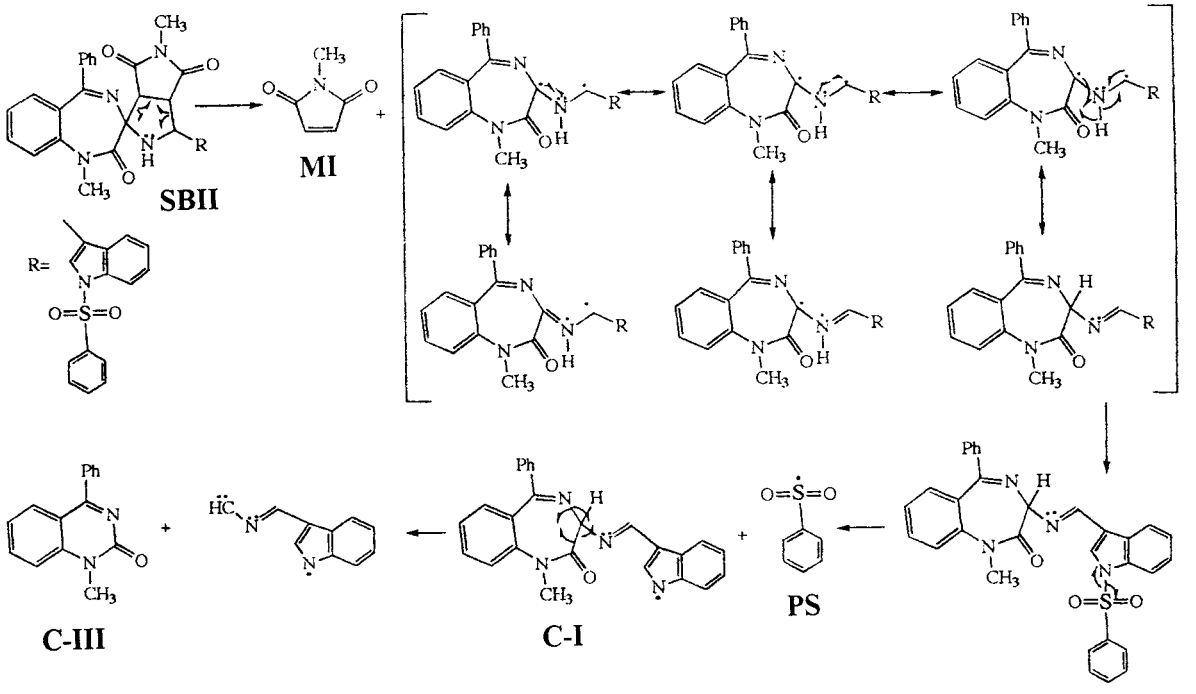


Fig. 6. DTA/TG/DTG diagram of SBII.

59.4%. The loss of water from SBII was confirmed by CHN analysis (found: C, 65.28%, H, 4.25%, N, 10.5%; $C_{36}H_{29}N_5O_3S{\cdot}1.0\ H_2O$ requires: C, 65.35%, H, 4.7%, N, 10.6%), and this was similar in behaviour to SBIN.

4. Conclusions

Each of the spiro benzodiazepine derivatives show similar decomposition mechanisms. The decomposition mechanisms of the compounds are shown in



Scheme 6.

Table 1
DTA and TG data for the some spiro benzodiazepine derivatives

Sample	Stage	Temperature of DTA peak maximum (K)	TG temperature range (K)	Evolved moiety	Mass loss (%)	
					TG	Theoretical
SBFI ($C_{45}H_{46}N_4O_6S$)	I	583	440–760	$C_{14}H_{22}O_3$ (MF), $C_6H_5O_2S$ (PS)	49.53	49.22
	II	935	760–1060	$C_{25}H_{19}N_4O$ (C-I)	50.44	50.78
SBFN ($C_{41}H_{43}N_3O_4$)	I	663	481–752	$C_{14}H_{22}O_3$ (MF), $C_{12}H_9N$ (C-II)	63.78	63.03
	II	914	752–1098	$C_{15}H_{12}N_2O$ (C-III)	36.20	36.97
SBIN ($C_{32}H_{26}N_4O_3 \cdot 1.0\ H_2O$)	I	437	423–468	H_2O	3.24	3.38
	II	542	468–761	$C_5H_5NO_2$ (MI), $C_{12}H_9N$ (C-II)	51.67	52.26
	III	910	761–1100	$C_{15}H_{12}ON_2$ (C-III)	45.08	44.36
SBII ($C_{36}H_{29}N_5O_5S \cdot 1.0\ H_2O$)	I	441	415–483	H_2O	3.04	2.72
	II	615	483–771	$C_5H_{12}N_2O$ (MI), $C_6H_5O_2S$ (PS)	37.55	38.12
	III	941	771–1064	$C_{25}H_{19}N_4O$ (C-I)	59.39	59.16

Schemes 1–4 and were derived from Arslan [10], Burakevich et al. [11] and Arslan et al. [12]. In spite of the fact that SBFI and SBII have the same indole moiety, they have different spiro groups and the last stage in the decomposition for each is the same (see Schemes 3 and 6). Similarly, SBFN and SBIN have the same napthyl moiety and a different spiro group. They also showed the same last decomposition stage (see Schemes 4 and 5). Compounds which are hydrates anhealing first dehydrate and then decomposed. It can be seen from the decomposition mechanism for each compound, that they first lose their spiro group to form an imine which then decomposes by lose of napthyl and indole moieties.

This is all summarised in Table 1.

References

[1] M.G. Bock, R.M. DiPardo, B.E. Evans, K.E. Rittle, W.L. Whittler, D.F. Vebber, P.S. Anderson, R.M. Freidinger, J. Med. Chem. 32 (1989) 13–16.
[2] V.J. Lotti, R.S.L. Chang, Eur. J. Pharmacol. 162 (1989) 273–280.
[3] A. Nishida, K. Miyata, R. Tsutsumi, H. Yuki, S. Akuzava, A. Kobayashi, T. Kamato, H. Ito, M. Yamano, Y. Katuyama, M. Satoh, M. Ohta, K. Honda, J. Pharmacol. Exp. Ther. 269 (1994) 631–725.
[4] R.S.L. Chang, V.J. Lotti, R.L. Monaghan, J. Birnbaum, E.O. Stapley, M.A. Goetz, G. Albers-Schönberg, A.A. Patchett, J.M. Liesch, O.D. Hensens, J.P. Springer, Science 230 (1985) 177–179.
[5] B.E. Evans, M.G. Bock, K.E. Rittle, R.M. DiPardo, W.L. Whittler, D.F. Vebber, P.S. Anderson, R.M. Freidinger, Proc. Natl. Acad. Sci. USA 83 (1986) 4918–4922.
[6] Y. Kawanishi, S. Ishihara, T. Tsushima, K. Seno, M. Miyagoshi, S. Hagishita, M. Shikawa, N. Shima, M. Shimamura, Y. Ishihara, Bioorg. Med. Chem. Letts. 6 (1996) 1421–1426.
[7] Y. Kawanishi, S. Ishihara, T. Tsushima, K. Seno, M. Miyagoshi, S. Hagishita, M. Shikawa, N. Shima, M. Shimamura, Y. Ishihara, Bioorg. Med. Chem. Letts. 6 (1996) 1427–1430.
[8] H.A. Döndaş, Ph.D. thesis, Leeds University, Leeds-UK, 1997.
[9] H.A. Döndaş, R. Grigg, M. Thornton-Pett, Tetrahedron 52 (1996) 13455–13466.
[10] H. Arslan, Ph.D. Thesis, Niğde University, Niğde-TR, 1998.
[11] J.V. Burakevich, A.M. Lore, G.P. Volpp, J. Org. Chem. 36 (1) (1971) 1.
[12] H. Arslan, N. Özpozan, T. Özpozan, Thermochim. Acta 329 (1999) 57–65.