GAS CHROMATOGRAPHIC BEHAVIOUR OF SUBSTITUTED 6,7-DIHYDROPYRAZOLO[1,5-*d*] [1,2,4]TRIAZIN-4(5H)-ONES AND PYRAZOLECARBOXYLIC ACID HYDRAZONES

FERENC SZEDERKÉNYI*, ENDRE TIHANYI, MELIDA GÁL and ÖDÖN FEHÉR

*Institute for Drug Research, P.O.B. 82, H-1325 Budapest (Hungary)*

(Received September 30th, 1983)

SUMMARY

The gas chromatographic behaviour of the title compounds was studied. On the basis of the Kováts retention indices (δI) the pyrazolotriazine and the isomeric pyrazolecarboxylic acid hydrazone structures could be distinguished. The δI values of the pyrazolotriazine isomers and homologues were also determined and correlated with their structures.

INTRODUCTION

The pyrazolo[1,5-*d*] [1,2,4]triazine ring system was first reported by Ainsworth[1] in 1955, and in recent years a number of substituted pyrazolo[1,5-*d*] [1,2,4]triazines have been synthesized for pharmacological purposes in our Institute[2,3]. These compounds were prepared by ring closure of pyrazolecarboxylic acid hydrazides (1) (Scheme 1) with orthoesters[2] or carbonyl compounds[3–6]. Using carbonyl compounds as reagents either the acid hydrazone (2) or the pyrazolotriazine ring (3) was formed, depending on the reagents.

R₁,R₂ = H₁Me
R₃,R₄ = H₁Me₁Ph
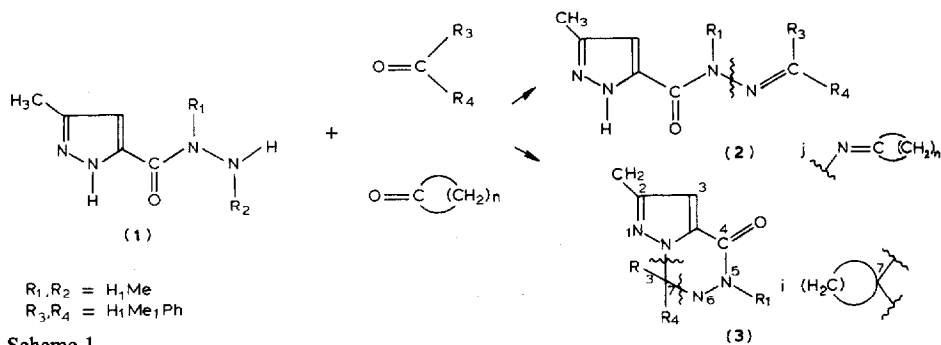
Scheme 1.

The direction of the reaction was studied by IR and NMR spectroscopy of the products[4,5]. Gas chromatography (GC) also proved to be useful for the differentiation between the cyclized (3) and the open-chain hydrazone (2) structures.

There have been few reports on the GC investigations of pyrazoles. Grandberg *et al.*[7] described the GC analysis of 33 alkylpyrazoles on a column packed with 3% PEG sebacate on acid-washed Celite 545. 4-Methyl- and 4-iodopyrazole were studied by Rydberg and Buijten[8] using a 5% Carbowax 20M column on acid-washed Chromosorb W. Ward and Grimmet[9] reported a systematic GC study of alkyl-, nitro- and bromopyrazoles. They used OV-17 and OV-225 stationary phases and found that, in contrast to imidazoles[10], N-unsubstituted pyrazoles were amenable to direct GC analysis and no prior acylation was required. They stated that inert supports, much as silanized Chromosorb W, were necessary.

No data are available on the GC of pyrazolecarboxylic acid hydrazones (2) and pyrazolo[1,5-*d*] [1,2,4]triazines (3). It was clear that structures 2 should have higher dipole moments than their cyclic isomers 3[11]. Thus, GC seemed to be an appropriate means for the differentiation of structures 2 and 3.

To demonstrate these structural differences, the Kováts retention indices (δI) were determined[12–14]. δI is defined by the equation

$$\delta I = I_1 - I_2$$

where I_1 and I_2 are the Kováts retention indices of homomorphic compounds measured on the same stationary phase under indentical conditions. The homomorph must be a homologue or an isomer of the compound being investigated[14].

EXPERIMENTAL AND RESULTS

Gas chromatography was carried out using a Hewlett-Packard 5720 A chromatograph with a single flame ionization detector. The glass (silanized) column (2 m × 2 mm I.D.) contained 3% OV-101, OV-17 or OV-225 stationary phases on Gas-Chrom Q (80–100 mesh). Nitrogen was used as the carrier gas at a flow-rate of 20 ml/min. The column temperatures were 220 and 250°C (isothermal) and the injector and detector temperatures were 270°C. The sample size was 1 μl (10-μl Hamilton syringe) of 10 or 20 mg/ml solutions in dry pyridine. The amplifier attenuations were 16 and 32 × 100. The recorder speed was 15 in./h.

The retention times were measured with a stop-watch to 0.1 sec accuracy. Kováts retention indices[12] were determined as averages of three measurements and the accuracy was calculated to be ±2 index units[15]. The retention indices of the compounds investigated are presented in Table I.

It was found that the Kováts retention indices measured for the cyclic pyrazolotriazines (3) on OV-101 and OV-17 increase with increasing size of the substituents at C-7. Thus, the retention index increments for the substituents at C-7 in the series A–D in good agreement with the number of methylene units inserted[13], as shown in Table II.

With hydrazones (2) however, there are only slight differences between the I values of the cyclopentyl and cyclohexyl compounds (see retention indices for 2b and 2c). This indicates that the retention is controlled mainly by the high polarity of the open-chain hydrazone structure. Table III shows the δI values for the acid hydrazone compounds (2a–2d) relative to the corresponding cyclic species (3c, f, i and k) for each series. As compounds 3c, f, i and k can be regarded as the higher cyclic hom-

TABLE I

RETENTION INDICES OF THE PRODUCTS OBTAINED BY REACTING OF PYRAZOLECAR-
BOXYLIC ACID HYDRAZIDES (I) WITH ACETONE (SERIES A), CYCLOPENTANONE (SERIES
B), CYCLOHEXANONE (SERIES C) AND BENZALDEHYDE (SERIES D)

Series*	Compound*	R_1	R_2	Kováts retention index			
				OV-101 (220°C)	OV-17 (220°C)	OV-225 (220°C)	OV-225 (250°C)
A	2a	H	—	1804	2288		3108
($R_3 = R_4 = CH_3$)	3a	CH_3	H	1554	1899	2364	2417
	3b	H	CH_3	1600	1956	2420	
	3c	CH_3	CH_3	1552	1858	2202	2270
B ($n = 4$)	2b	H	—	2122	2649		3537
	3d	CH_3	H	1842	2221	2721	2814
	3e	H	CH_3	1853	2254	2735	2817
	3f	CH_3	CH_3	1807	2121	2514	2570
C ($n = 5$)	2c	H	—	2137	2649		3537
	3g	CH_3	H	1955	2370	2872	2954
	3h	H	CH_3	1983	2406	2905	
	3i	CH_3	CH_3	1939	2302	2692	2752
D	2d	H	—	2400	3002		3488
($R_3 = H$, $R_4 = Ph$)	2e	CH_3	—	2291	2740		3488
	3j	H	CH_3	2047	2532	3130	3205
	3k	CH_3	CH_3	2000	2402	2878	2940

* For formulae, see Scheme 1.

TABLE II

RETENTION INDEX INCREMENTS OF THE SUBSTITUENTS AT C-7 IN CYCLIC COM-
POUNDS (3)

$R_1 = R_2 = CH_3$. $\delta I = I_x - I_{3c}$.

Series	Compound	I_{OV-101}	δI	I_{OV-17}	δI	I_{OV-225}	δI
A	3c	1552	—	1858	—	2202	—
B	3f	1807	255	2121	263	2514	312
C	3i	1939	387	2302	454	2692	490
D	3k	2000	448	2402	544	2878	676

TABLE III

δI VALUES OF THE HYDRAZONE COMPOUNDS (2a–2d) RELATIVE TO THE CORRESPOND-
ING CYCLIC SPECIES (3c, f, i AND k)

$\delta I = I_2 - I_3$.

δI	Series	δI (OV-101) (220°C)	δI (OV-17) (220°C)	δI (OV-225) (250°C)
$I_{2a} - I_{3c}$	A	252	430	848
$I_{2b} - I_{3f}$	B	315	529	967
$I_{2c} - I_{3i}$	C	198	347	785
$I_{2d} - I_{3k}$	D	400	600	548

ologues of the corresponding hydrazones 2a, b, c and d, the $\delta I = I_2 - I_3$ values obtained indicate the significantly higher polarity of the acyclic hydrazone structure.

With increasing polarity of the stationary phase the δI values increased. The non-polar data (OV-101) were, however, sufficient to indicate the significant structural differences. Thus, on the basis of the retention indices of the known structures in a series of compounds, the direction of the reaction could be established simply by measuring the I values for a new reaction product. For example, with compound 2e prepared by using benzaldehyde as the carbonyl compound, the main peak in the reaction mixture had the following δI values compared with the corresponding $R_1 = R_2 = CH_3$ substituted cyclic compound 3k ($\delta I = I_{2c} - I_{3k}$): δI (OV-101) (220°C), 291; δI (OV-17) (220°C), 338; and δI (OV-225) (250°C), 610. These high positive values suggested the acyclic (hydrazone) structure 2c for the product, in contrast with the fact that the same starting N-methylhydrazide (1, $R_1 = CH_3$, $R_2 = H$), when reacted with aliphatic or cycloaliphatic carbonyl compounds, always afforded cyclic products (3), giving significantly lower δI values compared with the corresponding $R_1 = R_2 = CH_3$ substituted cyclic species (see Table IV).

In this instance, without any preparative effort or spectroscopic examination, simply by means of direct injections of the samples taken from the reaction mixture into the gas chromatograph, it was possible to ascertain the direction of the reaction. The structure 2e suggested by GC was confirmed by spectroscopic data of the isolated product.

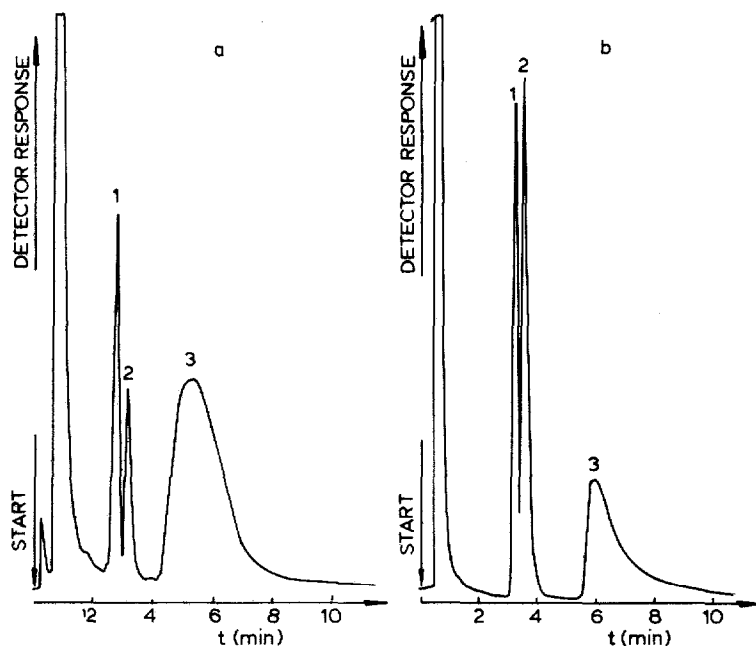An additional and a very simple indication has been used throughout this work

Fig. 1. Chromatograms of the cyclic isomeric pairs with the corresponding acid hydrazones 2 for series A and C on OV-101. Peaks: (a) 1 = 3a, 2 = 3b, 3 = 2a; (b) 1 = 3g, 2 = 3h, 3 = 2c. For chromatographic parameters see the beginning of Experimental and Results [$t = 190°C$ in (a)].

for the differentiation of the two types of structures, namely the peak widths. For the hydrazones 2 much wider peaks were usually observed (sometimes with tailing) than for the cyclic compounds 3. This phenomenon was attributed to both the higher polarity and the poorer solubility of the acyclic hydrazones (see Fig. 1).

Fig. 1 illustrates the GC retention characteristics for series A and C when the cyclic isomeric pairs 3a and 3b (Fig. 1a) and 3g and 3h (Fig. 1b) were chromatographed together with the corresponding acyclic hydrazones 2a and 2c. For series B the elution trend was the same. These chromatograms show the good separation of the cyclic isomeric pairs.

TABLE IV

THE δI VALUES OF THE CYCLIC SPECIES (3) WITH METHYL SUBSTITUENTS AT N-5 AND/OR N-6

Series	$\delta I_1 = I_{(R_1 = CH_3)} - I_{(R_1 = H)}$			$\delta I_2 = I_{(R_1 = R_2 = CH_3)} - I_{(R_1 = H)}$		
	OV-101	OV-17	OV-225	OV-101	OV-17	OV-225
A	−46	−57	−56	−48	− 98	−218
B	−11	−33	−14	−46	−133	−221
C	−28	−36	−33	−44	−104	−213
D	−	−	−	−47	−130	−252

The δI values for the cyclic isomeric pairs 3a–b, 3d–e and 3g–h (δI_1) and for their homologues (δI_2) ($R_1 = R_2 = CH_3$) compared with the $R_1 = H$, $R_2 = CH_3$ compounds are summarized in Table IV.

The negative $\delta I1$ values indicate the stronger influence of the acidic hydrogen at N-5 on the retention compared with that of the electron pair on the nitrogen and the hydrogen at N-6. The higher negative δI_2 values show that substitution of both positions 5 and 6 with methyl groups (thus blocking the two important adhering zones of the molecules) resulted in a marked improvement in the GC retention characteristics.

REFERENCES

1 C. Ainsworth, *J. Amer. Chem. Soc.*, 77 (1955) 1148.
2 E. Tihanyi, P. Sohár, Ö. Fehér and M. Gál, *Heterocycles*, 14 (1980) 1291.
3 E. Tihanyi *et al.*, in preparation (partly included in refs. 4–6).
4 E. Tihanyi, Ö. Fehér, M. Gál and P. Sohár, *ESOC 11, STRESA, 1981 (poster)*.
5 E. Tihanyi, P. Dvortsák, Ö. Fehér, M. Gál and P. Sohár, *8th ICHC, Graz, 1981 (poster)*.
6 *Belg. Pat., 895 039*.
7 J. J. Grandberg, A. P. Krasnoschek and C. B. Dmitriev, *Izv. Timiryazevsk. Skh. Akad.*, 2 (1969) 224; *Anal. Abstr.*, 18 (1970) 3195.

8 U. Rydberg and J. C. Buijten, *J. Chromatogr.*, 64 (1972) 170.
9 D. D. Ward and M. R. Grimmett, *J. Chromatogr.*, 174 (1979) 221.
10 C. G. Begg and M. R. Grimmett, *J. Chromatogr.*, 73 (1972) 238.
11 V. J. Minkin, O. A. Osipov and Y. A. Zhdanov, in W. E. Vaughan (Editor of English translation), *Dipole Moments in Organic Chemistry*, Plenum Press, New York, London, 1970.
12 L. S. Ettre, *Annal. Chem.*, 6 (1964) 31A.
13 G. Schomburg and G. Dielmann, *J. Chromatogr. Sci.*, 11 (1973) 151.
14 E. Kováts, *Helv. Chim. Acta*, 41 (1958) 1915.
15 J. Takács and D. Králik, *J. Chromatogr.*, 50 (1970) 379.