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Correlation between structure and gas chromatographic behaviour of nitrogen-containing heterocyclic compounds

I. Methyl substitution of pyridopyrimidine derivatives

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ABSTRACT

The methyl isomers of 4-oxopyridopyrimidine and tetrahydro-4-oxopyridopyrimidine and their 2,3-polymethylene derivatives were investigated. The compounds were characterized by their gas chromatographic retention indices measured on apolar and medium-polarity stationary phases. On the basis of the retention index increments, numerical values are given to characterize the shielding effects exerted on the polar centres of the molecule by methyl groups substituted at different positions. The steric and electronic effects are also characterized by retention index values.

INTRODUCTION

Investigations on the relationships between chemical structure and physico-chemical data have already led to many valuable results [1,2]. Some investigations have revealed a correlation between the retention data and other physico-chemical parameters [3–6]. Retention data can be processed by mathemtical methods, *e.g.*, by factor analysis [7], graphical evaluation [8] or pattern recognition [9]. As surveyed by Ettre [10], the Kováts retention index and its derivatives can be used to characterize retention.

The behaviour of C_9–C_{14} alkylbenzene was described by Engewald and Wernrich [11] using H^S, dI_{CH_2} and ΔI values determined on four stationary phases with different polarities on the basis of the retention index additivity.

The structure–retention index relationship for aliphatic fatty acid esters was examined in detail by Haken and Srisukh [12]. For about 70 benzene and naphthalene derivatives, Macák *et al.* [13] found a correlation between the retention index and the type and position of the functional group [13]. The structure–retention index

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relationship for cyclic alcohols was described by Heintz *et al.* [14]. Nakazawa *et al.* [15] examined 37 methyl derivatives of carbazole and found a relationship between the sites and number of the substituents and their t'_R values. Morishita *et al.* [16] determined the shielding effect of certain carbon atoms of the alkyl chain with respect to the sulfhydryl group attached to it.

In previous investigations on the physico-chemical properties of nitrogen-containing pyrido[1,2-*a*]pyrimidines and condensed quinazolines, we reported the determination of some parameters that play important roles in the pharmacokinetic phase (solubility [17,18], log *P* [19,20], pK_a [21], molar refraction [22]), and also structural relationships. In this series of papers, we demonstrate how the site of alkyl substitution, the number of carbon atoms in the substituent and variations in the number of atoms in the ring system are manifested in the retention data. This paper presents gas chromatographic results that provide information about the manner and extent to which methyl groups substituted at different points on the skeleton influence the retention behaviour and associated physico-chemical properties. In the evaluation of the retention index increments, we accepted that $dI_{Me}^{apol} = 100$ index units (i.u.) (Me = methyl) only for those alkyl side-chains where the increment relates to a carbon atom following after a carbon chain with $Z > 5$. Accordingly, for methyl groups on heterocyclic rings a considerable difference from 100 i.u. is to be expected, and this can give information on the position-dependent interaction of the stationary phase and the chromatographed compound, and hence on the electronic and steric properties of the molecules in a systematically constructed series of positional isomers.

EXPERIMENTAL

Thirty-four nitrogen-containing heterocyclic compounds were synthesized by a method described elsewhere [23]. The purity of the compounds was controlled by spectroscopic and chromatographic methods. In three of the compounds (**1**, 4*H*-pyrido-[1,2-*a*]pyrimidin-4-one; **3**, 4*H*-cyclopenteno[2,3-*e*]pyrido[1,2-*a*]pyrimidin-4-one; **5**, 1,2,3,4-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one), ring A is aromatic; the other three (**2**, 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one; **4**, 6,7,8,9-tetrahydro-4*H*-cyclopenteno[2,3-*e*]pyrido[1,2-*a*]pyrimidin-4-one; **6**, 1,2,3,4,6,7,8,9-octahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one) are tetrahydro derivatives.

The positions of the substituents and the retention data are shown in Tables I and II.

For compounds **1** and **2** there are methyl substituents at all possible positions. Compounds **3** **6** were regarded as 2,3-polymethylene derivatives of **1** and **2**, and hence substituted only at positions 6–9.

Instruments and conditions

A Hewlett-Packard Model 5710A gas chromatograph provided with a flame

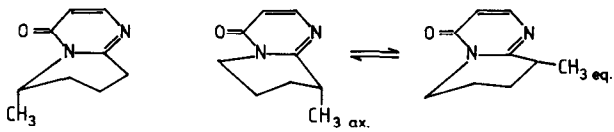

Fig. 1. 6-Methyl- (left) and 9-methyltetrahydropyridopyrimidine (right) conformers.

ionization detector was used. The retention times and the retention index values were determined from seven parallel measurements with a standard deviation of 2 i.u., using a Digint 80 integrator (Chinoin, Nagylétény, Hungary). The column temperature was 220 and 240°C and the injector port and detector temperatures were 250°C. The carrier gas was nitrogen at a flow-rate of 25 ml/min. The column (1.8 m × 2 mm I.D.) contained 5% OV-1, 5% OV-25 and 5% OV-225 (Macherey, Nagel & Co., Düren, F.R.G.) on Chromosorb W AW DMCS (80–100 mesh). The retention index values were calculated as means of seven measurements. The standard deviation was found to be less than 2 i.u.

RESULTS AND DISCUSSION

The chromatographic behaviour of the compounds was analysed by systematic comparison of the retention indices and their derivative values were calculated as follows: $dI_{Me}^{OV\text{-}1} = I_{toluene}^{OV\text{-}1} - I_{benzene}^{OV\text{-}1}$ and $\Delta dI_{Me} = dI_{Me}^{pol} - dI_{Me}^{apol}$, both at the same temperature. The numerical values for compounds **1**–**6** are given in Tables I and II.

The data for compound **1** reveal that, on the basis of the increments for the methyl groups, three regions can be characterized in the molecules: the environment of nitrogen N-1 (C-2 and C-9), the cyclic acid amide (C-3 and C-6) and the part of ring A distant from the polar groups (C-7 and C-8). The ability of N-1 to interact is decreased by the C-2 and C-9 substituents to almost the same extent as the C-3 and C-6 substituents decrease that of the carbonyl group. The C-7 and C-8 substituents not exerting a steric effect do not reduce the interaction ability of polar groups; indeed, they may even increase it slightly through a hyperconjugation effect. A comparison of the data on the aromatic system **1** with those on the tetrahydro derivative **2** demonstrates that the effects on ring B are almost the same, but those on ring A differ.

TABLE I

RETENTION INDEXES OF METHYL ISOMERS **1** AND **2** ON OV-1 AND OV-25 STATIONARY PHASES

Compound	Site of methyl substitution	Retention indices		Increments	
		$I_{220°C}^{OV\text{-}1}$	$I_{220°C}^{OV\text{-}25}$	$dI_{Me}^{OV\text{-}1}$	$d\Delta I_{Me}^{OV\text{-}25-OV\text{-}1}$
1	–	1580	2124	–	–
1a	2	1648	2189	68	−3
1b	3	1638	2168	58	−21
1c	6	1636	2150	56	−20
1d	7	1696	2234	116	−6
1e	8	1703	2239	123	−8
1f	9	1647	2159	67	−32
2	–	1581	2128	–	–
2a	2	1657	2203	76	−1
2b	3	1637	2170	56	−14
2c	6	1578	2081	−3	−50
2d	7	1654	–	73	–
2e	8	1638	–	102	–
2f	9	1615	2114	34	−48

TABLE II

RETENTION INDICES OF COMPOUNDS **3**, **4**, **5** AND **6** ON OV-1 AND OV-225 STATIONARY PHASES

Compound	Site of methyl substitution	Retention indices		Increments	
		$I^{OV\text{-}1}_{220°C}$	$I^{OV\text{-}25}_{220°C}$	$dI^{OV\text{-}1}_{Me}$	$d\Delta I^{OV\text{-}25-OV\text{-}1}_{Me}$
3	–	1968	2890	–	–
3a	6	2020	2865	52	−77
3b	7	2084	3017	116	11
3c	8	2089	3034	121	23
3d	9	2023	2880	55	−65
4	–	1961	2917	–	–
4a	6	1942	1820	−8	−59
4b	7	1998	2929	37	−25
4c	8	2000	2929	39	−27
4d	9	1978	2843	17	59
5	–	2064	2972	–	–
5a	6	2120	2947	56	−81
5b	7	2189	3098	125	−10
5c	8	2190	3125	126	−27
5d	9	2123	2951	59	−80
6	–	2059	2995	–	–
6a	6	2045	2902	−14	−79
6b	7	2095	3009	36	−22
6c	8	2097	3011	38	−22
6d	9	2071	2924	12	−83

The reason for this is presumably that the saturation of ring A eliminates the planar character of the sytem and the substituents may cause conformational changes in the multiplanar flexible ring.

NMR investigations by Tóth [24] indicated that the 6- and 9-methyl substituents are in pseudo-axial positions on the half-chair conformer (Fig. 1). In accordance with this, they hinder the solvent–solute interaction more effectively. On the other hand, the 7- and 8-methyl substituents are in equatorial positions [24] and hence they influence the molecule–stationary phase interaction only by modifying the ring conformation. For compounds **1**–**6**, the various polar and apolar solvent–solute interactions can be distinguished by comparing the dI_{Me} and $d\Delta I_{Me}$ values relating to the same positions. The difference of about 50 i.u. between the two series originates from the interaction of the aromatic system.

Subsequently, methyl-substituted tricyclics saturated or unsaturated in ring A were investigated. The dI_{Me} values for 6,7,8,9-methyl-substituted compounds **3** and **5** (planar because of aromatic ring A) correspond well with the data for **1**, but the dI_{Me} values for saturated **4** and **6** differ from those for **2** measured at the same position. In these instances, the polar groups are already shielded (2,3-polymethylenepyrido-pyrimidines) and the introduction of the second substituent probably causes a larger difference because of the resulting double shielding. However, the dI_{Me} values can be divided into two groups here too, according to the extent of the difference: positions 6 and 9 close to the polar centres, and positions 7 and 8 distant from them. In the latter

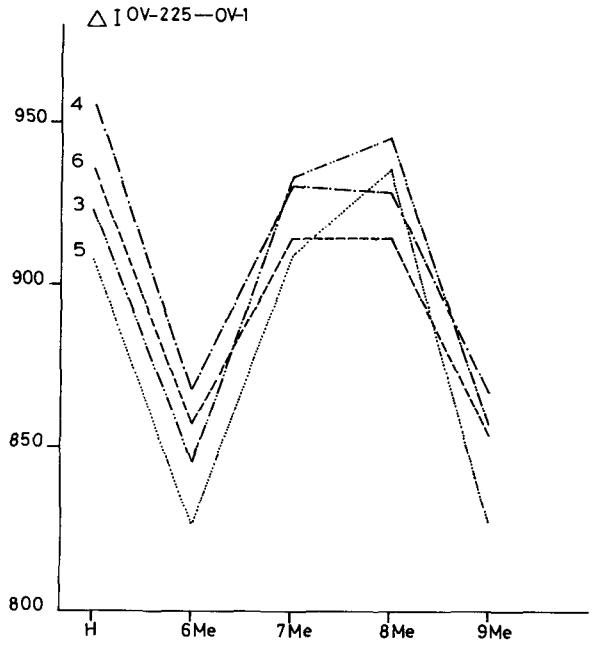

Fig. 2. ΔI values of methyl (Me) isomers **3**–**6** as a function of the substitution site.

instance the validity of the rule $dI_{Me}^{OV\text{-}1} = 100$ i.u. is presumed, and the surplus of 22 i.u. for the 7- and 8-methyl derivatives of **3** and **5** can be interpreted in terms of hyperconjugation, while the deficit of 62 i.u. for the similar derivatives of **4** and **6** can be explained by the increased steric influence. In contrast with the dI_{Me} values, which express several kinds of interactions, the steric effect does not participate in the $d\Delta I_{Me}$ values. This can also be seen on comparison of the dI and I values for **5** and **6**. The almost identical increment values in the same positions show that the planar or multiplanar character of the ring system can be characterized by different dI_{Me} values, but by similar ΔI_{Me} values.

The combined effect of the substituent and the skeleton is shown in Fig. 2, which presents the $\Delta I^{(OV\text{-}225)-(OV\text{-}1)}$ values for **3**–**6** and their methyl isomers as a function of the substitution site. The shapes of the curves indicate that the polarity sequence is influenced both by the saturated–unsaturated character of ring A and by the number of atoms in ring C. Thus, the polarity sequence for the ring size is **4** > **6** > **3** > **5** for both the non-substituted compounds and the majority of the methyl derivatives. The 7- and 8-methyl isomers of **3** and **5** differ from this sequence, because in these compounds the methyl substituent is involved in hyperconjugation interaction with the aromatic system, and this interaction causes a considerable retention index surplus on the polar stationary phase.

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