

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

### III. Variation of ring size

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#### ABSTRACT

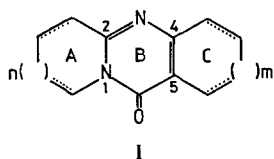
Ring homologues of the desoxyvasicinone type, which exert an antiasthmatic effect, were investigated. The retention indices and the solvent–solute interactions (expressed by the  $dI$  and  $\Delta I$  values) revealed that an increase in ring size led to a decrease in the polar character in the investigated heterocyclic rings, but not in the homocyclics. The  $dI_{Me}$  values of methyl groups introduced at the same position in the ring homologues demonstrated that an increase in the number of ring atoms ensures conformational freedom in ring A that can be expressed by numerical data. The structural and conformational differences influencing the retention data were confirmed by NMR investigations.

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#### INTRODUCTION

The tricyclic pyrrolo [2,1-*b*] quinazolone alkaloid desoxyvasicinone is a drug [1,2] with a theophylline-like antiasthmatic effect. Wide-ranging research work was started to develop a favourable effect profile, as a result of which effective derivatives were found among aromatic analogues with different ring sizes [3,4]. Following extensive synthetic investigations by Hermech *et al.* [5], homologues varying in ring size were available, on the basis of which the physico-chemical changes and characteristics could be analysed.

The methyl isomers of nitrogen-containing heterocyclic compounds and their alkyl homologues were earlier characterized by means of the Kováts retention index and derivative data. This paper describes gas chromatographic investigations of tricyclic ring-homologue derivatives condensed in the 1,2- and 4,5-positions containing a central pyrimidone ring (I).



$$n = 0, 1, 2, 3; \quad m = 0, 1, 2, 3$$

TABLE I  
CLASSIFICATION OF INVESTIGATED COMPOUNDS

Series	Group				
	1	2	3	4	5
(a) $m = 0, 1, 2, 3$	$n = 0$	$n = 1$	$n = 2$	$n = 3$	$n = 1$
(b) $n = 0, 1, 2, 3$	$m = 0$	$m = 1$	$m = 2$	$m = 3$	$m = 1$

TABLE II  
RETENTION INDICES OF COMPOUNDS OF TYPE I ON OV-1 AND OV-225 STATIONARY PHASES

Compound	Ring size		Aromatic ring	$I_{240^\circ\text{C}}^{\text{OV-1}}$	$I_{240^\circ\text{C}}^{\text{OV-225}}$	$I_{240^\circ\text{C}}^{\text{OV-225-OV-1}}$
	$n$	$m$				
1	0	0	—	1870	2875	1005
2	0	1	—	1973	2969	996
3	0	2	—	2050	3057	1007
4	0	3	—	2117	3091	974
5	1	0	—	1961	2917	965
6	1	1	—	2059	2995	936
7	1	2	—	2144	3064	920
8	1	3	—	2200	3110	910
9	2	0	—	2003	2891	888
10	2	1	—	2102	2984	882
11	2	2	—	2162	3045	883
12	2	3	—	2226	3100	874
13	3	0	—	2081	2969	888
14	3	1	—	2165	3049	884
15	3	2	—	2243	3110	867
16	3	3	—	2300	3166	866
17	1	0	A	1968	2890	922
18	1	1	A	2064	2972	908
19	1	2	A	2158	3059	901
20	1	3	A	2216	3104	888
21	0	1	C	1958	3005	1047
22	1	1	C	2058	3048	910
23	2	1	C	2101	3030	929
24	3	1	C	2181	3086	905

## EXPERIMENTAL

The apparatus and chromatographic conditions were as described in Part I [6].

*Materials*

Ten series were prepared from 24 tricyclic compounds with the general formula I. Two series contain aromatic rings A and C (**5a**, **5b**), and eight series contain saturated rings A and C. The ring size was changed between 5 and 8. The series investigated are listed in Table I.

Under the above conditions, the retention indices of the 24 compounds in ten four-membered series, involving systematic changes in ring size, were determined on OV-1 and OV-225 stationary phases. The structures and the measured data are given in Table II.

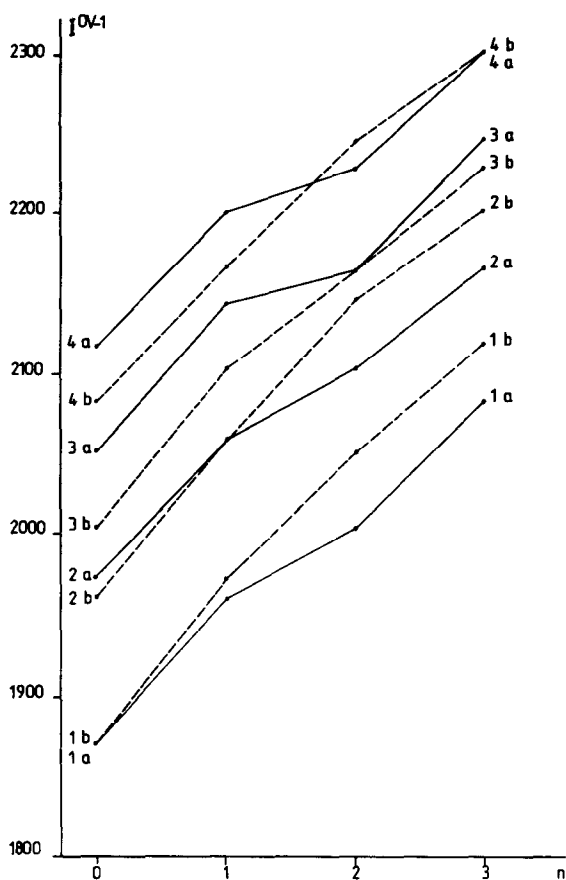


Fig. 1.  $I^{OV-1}$  values of tricyclic ring homologous series. Solid lines, heterocyclic homologues; dashed lines, carbocyclic homologues.

## RESULTS AND DISCUSSION

The series of curves depicting the retention index values of the ring homologues as a function of the ring size reveal that there is no appreciable difference in retention index in response to a change in the size of rings A and C on OV-1 apolar stationary phase (Fig. 1). However, it is striking that the retention index increases uniformly with an increase in the number of carbon atoms in the carbocycle, whereas in the heterocyclic series  $dI_{CH_2}$  varies as a function of the ring size.

The same correlation is manifested more strikingly on the more polar stationary phase OV-225 (Fig. 2). As a consequence, the retention index for compound **9**, which is longer than **5** by a  $CH_2$  group, is not larger, but smaller, by 26 index units (i.u.). At the same time the change in the size of ring C of the carbocycle leads to a change of nearly 100 i.u., which corresponds to the concept of Kováts [7] ( $dI_{CH_2} = 100$  i.u.).

The correlation  $dI_{CH_2} = 100$  i.u. demonstrates that the hydrophobic effect of the change in the size of ring C nearly corresponds to that for the *n*-alkane homologous series, but the behaviour of the heterocyclic system is essentially different. If the difference between the retention index values measured on the two stationary phases,  $\Delta I$ , is plotted as a function of the change in ring size (Fig. 3), there is little variation for ring C, whereas there is a steep decrease and then an approach to a limiting value for

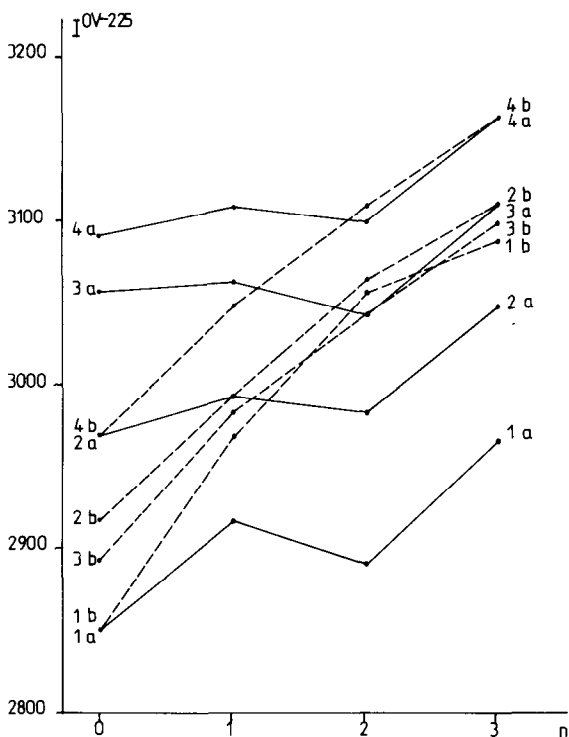


Fig. 2.  $I^{OV-225}$  values of tricyclic ring homologues series. Lines as in Fig. 1 and groups of compounds as in Table I.

ring A. The  $\Delta I$  values, which express the polar interaction of the compounds, indicate that the polarity changes to larger extent in response to a change in ring size for rings containing heteroatoms than for homocyclic rings.

In tricyclics containing a pyrimidine ring, the polarity of the system is determined by N-1 and the C-4 carbonyl group as structural elements. This effect is shown in Fig. 4 as a function of the variation in ring size.

Thus, the retention index values can be correlated with the difference originating from the positions of the rings and their freedom of conformational motion. Ring C, which is condensed to the unsaturated C-2-C-3 bond, contains four sterically rigidified cyclic carbon atoms, and the connected methylene groups cause changes with the same tendency. In the nitrogen-bridgehead condensed heterocycle, a more fundamental change occurs as a consequence of the freer conformational motion due to the change in the ring size.

This can be explained in part by the structural arrangement of the rings, and in part by the conjugational interaction of the isolated electron pair on N-5 with the C-4 carbonyl group and by the deformation of the ring system. The similar courses of the curves of the individual series express the general tendency of the correlation.

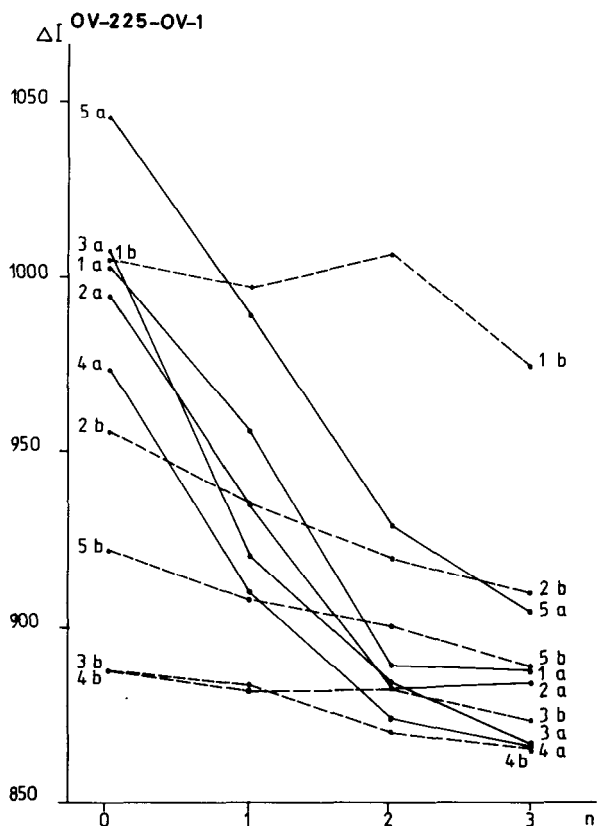


Fig. 3.  $\Delta I^{OV-225-OV-1}$  values of tricyclic ring homologues series. Lines as in Fig. 1 and groups of compounds as in Table I.

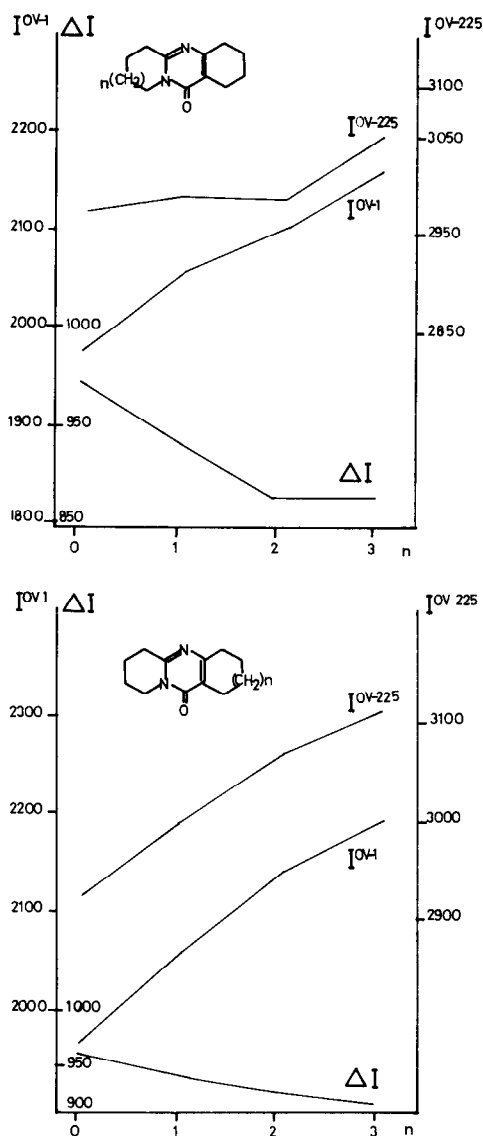
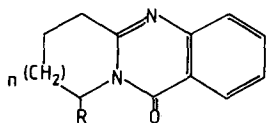


Fig. 4. Influence of changes in the size of rings A and C on retention indices.

To confirm that the change in polarity is influenced by the differences originating from the conformational motion of ring A, a gas chromatographic investigation was performed on a series in which there was a methyl substituent on the methylene group near the nitrogen bridgehead. The retention index values relating to the methyl group were determined by taking the difference between the retention indices for the two series (on OV-1 stationary phase).

The values obtained as a function of the change in ring size are given in Table III. The variation in the  $dI$  value of the 6-methyl substituents of the ring homologue

TABLE III

 $dI_{\text{Me}}^{\text{OV-1}}$  VALUES AND CHEMICAL SHIFTS AS A FUNCTION OF RING SIZE

Ring A size	$I_{240^\circ\text{C}}^{\text{OV-1}}$		$dI_{\text{Me}}$	Chemical shift, CH-CH <sub>3</sub> (ppm)	Coupling constant (Hz)
	R = CH <sub>3</sub>	R = H			
$n = 0$	1942	1973	-31	4.84 m	3.4
$n = 1$	2045	2059	-14	5.06 m	3.1
$n = 2$	2123	2101	22	5.84 m	3.0

derivatives can be explained predominantly by steric reasons. The  $^1\text{H}$  NMR data indicate that the investigated methyl groups are all quasi-axial, which can be explained by the 1,3-allyl strain between the methyl groups and the neighbouring carbonyl groups. The chemical shift of the quasi-equatorial methylene proton connected to the methyl group changes significantly with variation in the ring size and reveals the difference in the ring strain and configuration. The steric positions of the methyl groups also differ on the rings of different size, as a consequence of the change in conformation. This difference, originating from the changes in conformational and steric structure, is expressed by the difference in the  $\Delta I$  values obtained in the course of the gas chromatographic investigations.

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