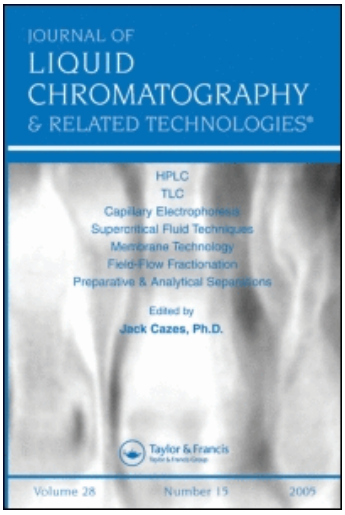

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HPLC Retention Index Scale for Nitrogen-Bridged Compounds

A. Shalaby[a]; Zs. Budvári-Brány[a]; Gy. Szász[a]
[a] Semmelweis Medical University, Pharmaceutical Chemical Institute, Budapest, Hungary

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HPLC RETENTION INDEX SCALE FOR NITROGEN-BRIDGED COMPOUNDS

A. Shalaby, Zs. Budvári-Brány, Gy. Szász

Semmelweis Medical University, Pharmaceutical Chemical Institute, Budapest, Hungary.

ABSTRACT

Retention indices of some nitrogen-bridged compounds having pharmacological activity have been determined. A retention index scale based on the relative retention of a homologous series of C_3-C_{23} 2-keto alkanes has been worked out. Linear relationships were found between RI and logP, allowing a prediction of retention indices.

The relationships between the structures and the retention indices of these compounds have been interpreted.

INTRODUCTION

Unlike gas chromatography, retention index RI for characterization of HPLC behaviour has been rarely used and only a few papers have been published [1,2]. In this work, we tried to determine HPLC retention indices to prove that RI can be used also in HPLC, i.e. may be useful in the field of SAR-research. In addition, are tried to predict the retention indices of these compounds using the linear correlation between logP and RI which was obtained. A series of nitrogen-bridged compounds, synthesized at our laboratory [3,4], seem to be good examples

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for our purpose (see Tables 1,2,3). The correlation if it exists between logP and RI may be useful to predict logP values i.e. biological activity for other compounds of the same structural type.

EXPERIMENTAL

Materials

All the model substances have been synthesized at our laboratory [3,4]. The identification and quality control of these compounds was made by melting point determination and chromatography.

All chemicals were analytical (Merck), and were used without further purification.

All solvents were HPLC grade (Merck), and were used without further purification.

Apparatus

The HPLC apparatus was from LABOR MIM LIQUOCHROM, MODEL 2010, Budapest, Hungary.

The reversed phase C_{18} column was 250 mm X 4.6 mm prepacked with 5 um particle size materials (Beckman).

10 ul of sample solutions (0.1 mg/ml in methanol) were injected.

Procedure

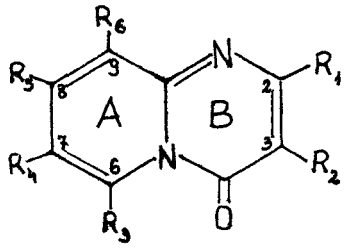
Three concentrations of methanol have been used: 70 %, 60 %, 50 %; each contained a 0.025 M NaH_2PO_4 buffer that had been adjusted to pH 7.0 before adding the methanol.

The flow rate was 0.7 ml/min.

Table 1

Structure of model substances

pyridopyrimidines with unsaturated "A"-ring

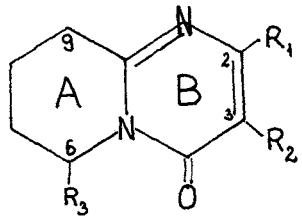


Nr	Substituents on C_2	C_3	C_6	C_7	C_8	C_9
1	H	H	H	H	H	H
2	CH_3	H	H	H	H	H
3	H	CH_3	H	H	H	H
4	H	H	CH_3	H	H	H
5	H	H	H	CH_3	H	H
6	H	H	H	H	CH_3	H
7	H	H	H	H	H	CH_3
8	CH_3	CH_3	H	H	H	H
9	CH_3	H	CH_3	H	H	H
10	CH_3	H	H	H	H	CH_3
11	H	CH_3	CH_3	H	H	H
12	CH_3	H	$_2H_5$	H	H	H
13	H	C_2H_5	CH_3	H	H	H
14	CH_3	C_2H_5	CH_3	H	H	H
15	CH_3	C_2H_5	CH_3	H	CH_3	H
16	C_2H_5	CH_3	CH_3	H	H	H
17	C_3H_7	C_2H_5	CH_3	H	H	H

Table 2

Structure of model substances

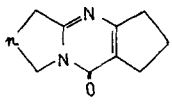
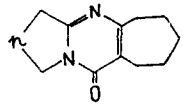
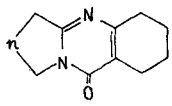
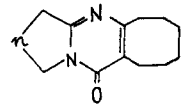
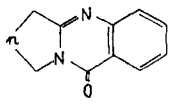
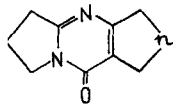
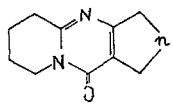
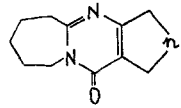
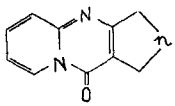
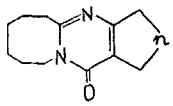
pyridopyrimidines with saturated "A"-ring



Nr	Substituents on			
	C_2	C_3	C_6	C_9
18	H	H	H	H
19	CH_3	H	H	H
20	H	H	CH_3	H
21	CH_3	CH_3	H	H
22	CH_3	H	CH_3	H
23	H	CH_3	CH_3	H
24	CH_3	C_2H_5	CH_3	H
25	CH_3	H	H	CH_3

Table 3. Structure of model substances

Three ring systems with different ring size

Number of compounds			Number of compounds		
26.	n = 1		38.	n = 1	
27.	n = 2		39.	n = 2	
28.	n = 3		40.	n = 3	
29.	n = 4		41.	n = 4	
30.	n = 1		42.	n = 1	
31.	n = 2		43.	n = 2	
32.	n = 3		44.	n = 3	
33.	n = 4		45.	n = 4	
34.	n = 1		46.=26.	n = 1	
35.	n = 2		47.	n = 2	
36.	n = 3		48.	n = 3	
37.	n = 4		49.	n = 4	
34.a	C_8 Me		47.a	C_8 Me	
34.b	C_3 Me				
36.a	C_3 Me				
50.	n = 1		58.	n = 1	
51.=31.	n = 2		59.	n = 2	
52.	n = 3		60.	n = 3	
53.	n = 4		61.	n = 4	
54.	n = 1		62.	n = 1	
55.	n = 2		63.	n = 2	
56.	n = 3		64.	n = 3	
57.	n = 4		65.	n = 4	

All the experiments were run at room temperature 25 °C.

Measurement of retention indices

The retention indices have been calculated using the following equation:

$$I = 100 \frac{\log K_D - \log K_N}{\log K_{N+1} - \log K_N} + 100\ N \qquad \text{equ.n. 1.}$$

where

K_D = the capacity factor of the drug

K_N + the capacity factor for 2-keto alkane eluting just before the test compound.

K_{N+1} = the capacity factor for 2-keto alkane eluting just after the test compound.

Results and discussion

Retention indices of about 40 compounds have been calculated using equation 1. LogP values for the same compounds have been published earlier [5,6]. The correlations between logP and RI values are shown in Fig. 1, 2 and in Table 5.

The best linear relationship was found between logP and measured RI for the 2-ring and 3-ring nitrogen-bridged compounds at a solvent composition of 70 % methanol and 30 % buffer (pH 7) using a C_{18} column (see Fig. 1 and Fig. 2). From this correlation, either retention index or the logP of the same compounds may be obtained. Table

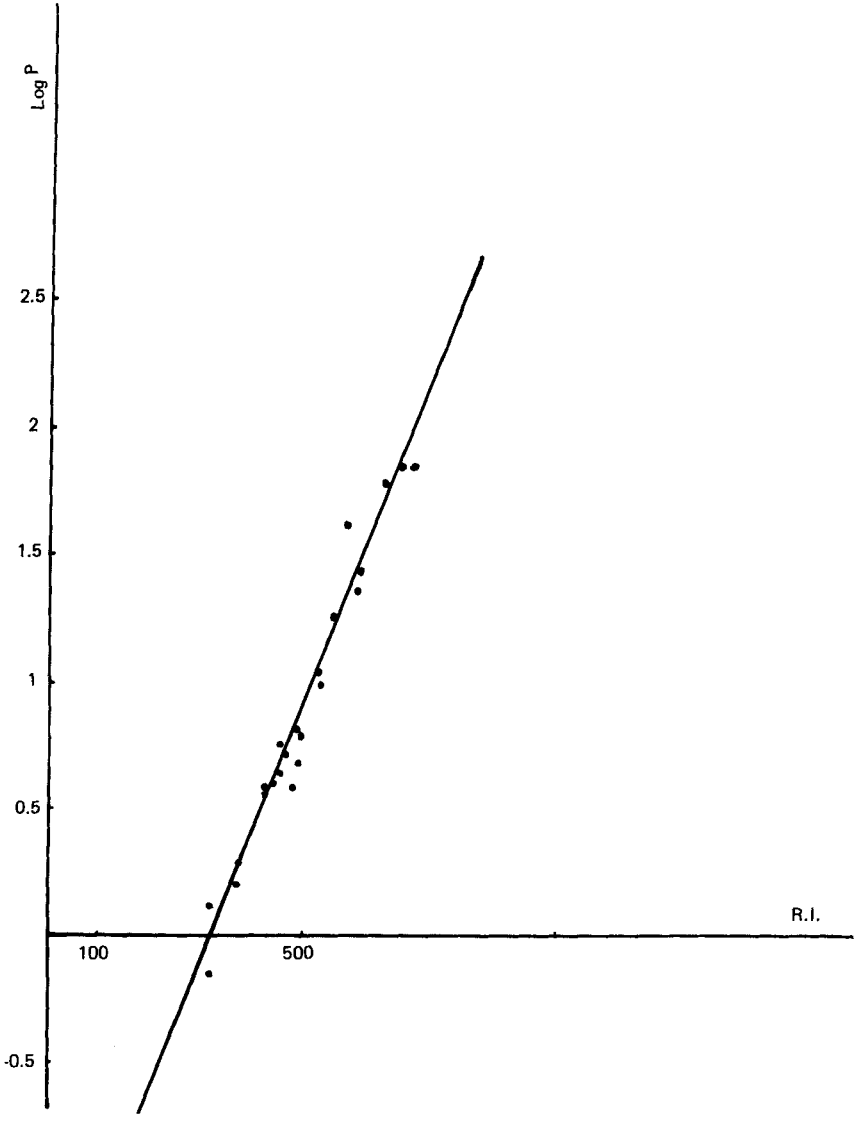


Fig. 1 Relationship between logP and RI of 2-ring compounds (saturated, unsaturated)

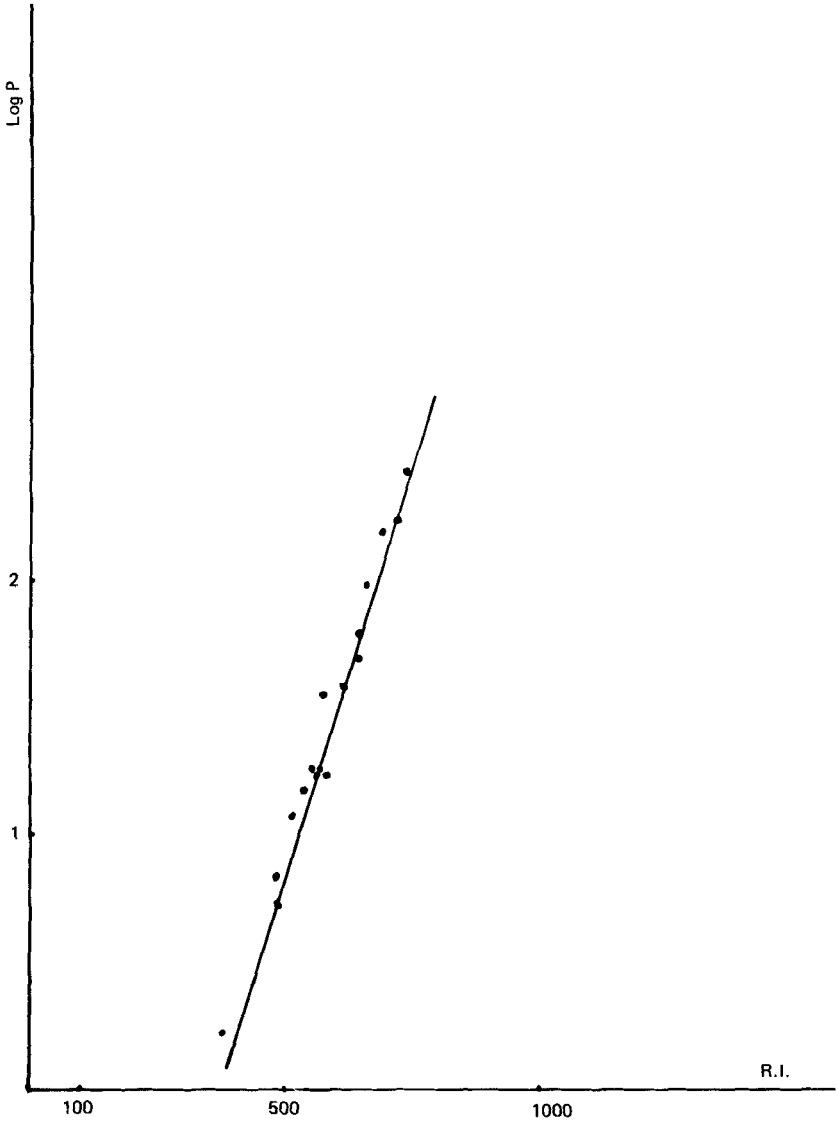


Fig. 2 Relationship between logP and RI of 3-ring compounds (saturated, unsaturated)

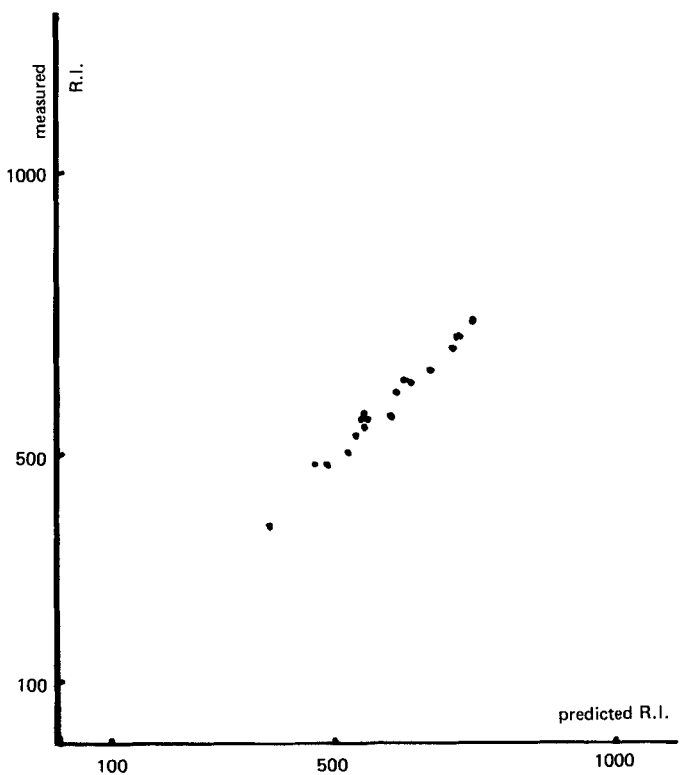
4, (a,b,c,d) and Fig. 3 also show that the measured and the predicted retention indices are very close.

As may be expected, a change in mobile phase concentration has almost no effect on the retention index values for the 2-ring and 3-ring compounds (Fig. 4).

As an alternative, the RI values of the model compounds can be determined by graphical interpolation of a plat of the capacity factor vs. retention index of a standard series of 2-ketoalkanes. Now, the measured logK of the test compound, as well as the assigned values of the ketoalkanes e.g. acetone 300, 2-butanone 400, etc. will be used see (Fig. 5).

In general we can see that the RI values of unsaturated compounds are higher than those of the saturated compounds; this due to that the saturated compounds have been found more polar than the unsaturated. The difference in RI is lower for the unsubstituted pairs of compounds unsaturated-saturated Nr. 1, 18 than in case of methylsubstituted pairs (2, 19; 4, 20; etc.). This may be due to the increasing of the hyperconjugation and the electronic activity of the methyl group for the unsaturated compounds. This conclusion was found for the 2-ring compounds as well as the 3-ring compounds (see the RI values of compounds No. 2-8-9-10, and No. 19-21-22-25 resply Table 4/a, 4/b and Fig. 6).

As expected, RI values increase systematically on increasethe number of carbon atoms; the increment is nearly constant regardless of the position of the rings.



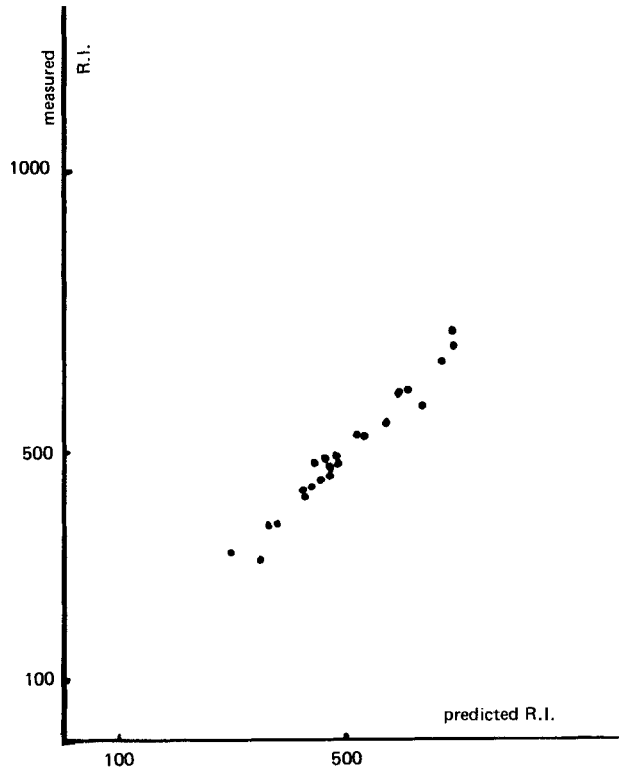


Fig. 3 Comparison of predicted and measured HPLC retention indexes for 2-ring compound A and 3-ring compound B

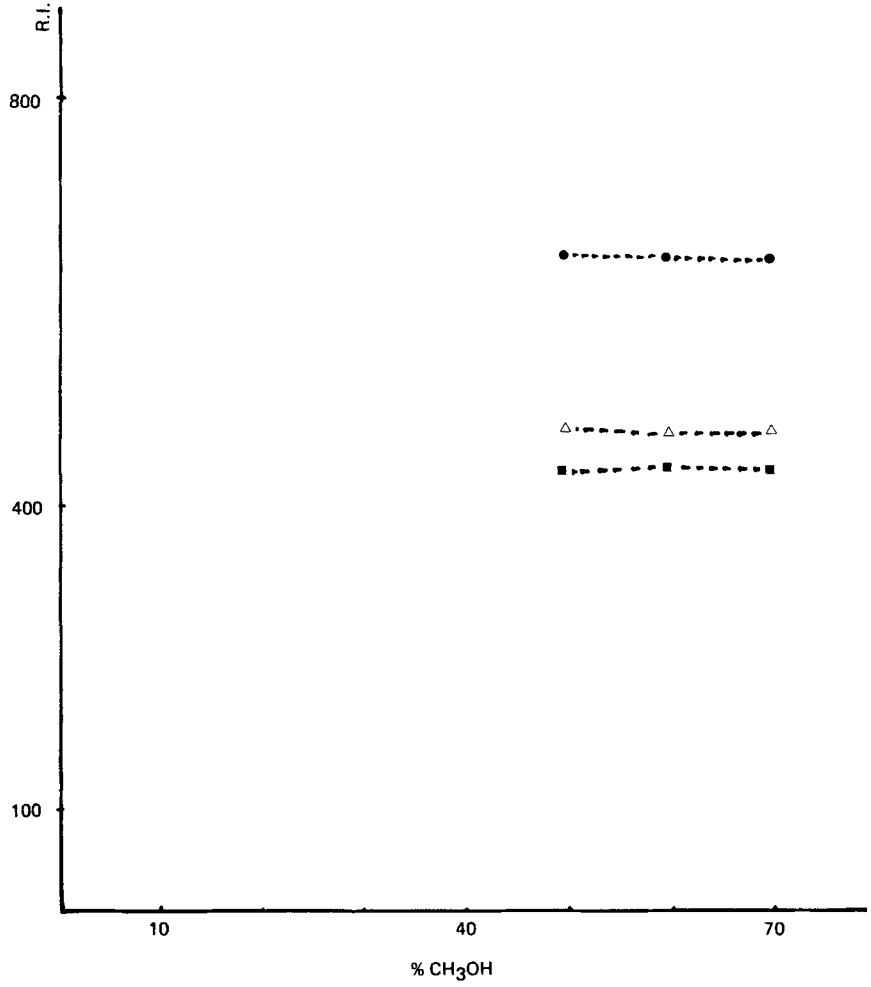


Fig. 4 Effect of methanol concentration of RI of some selected drugs: ● compound n. 32; △ compound n. 4; □ compound n. 2

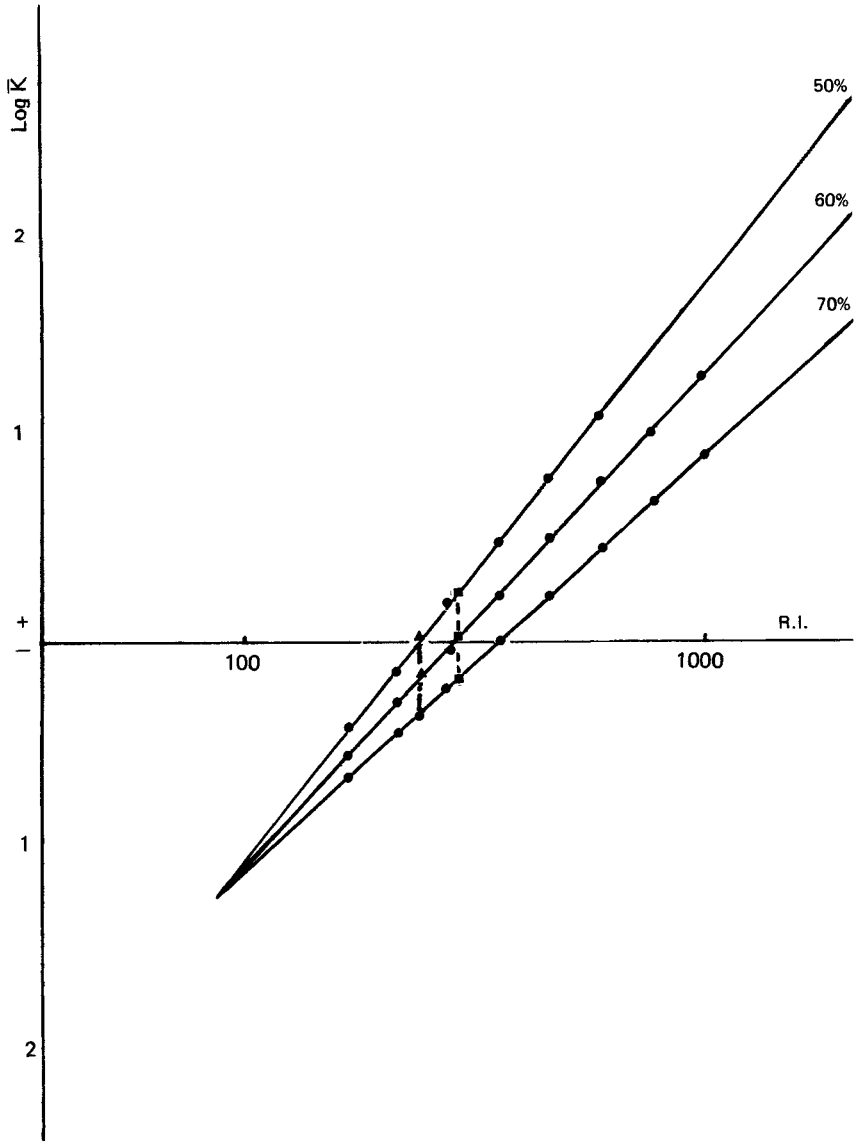


Fig. 5 Determination of RI of some selected drugs (Δ compound n. 5 and □ compound n.34) using series of 2-keto-alkanes at three different concentrations of methanol

Table 4. /a/

Number of compounds	RI		logP	
	measured	calculated	measured	calculated
1	377	366	0,2043	0,2562
2	427	439	0,5724	0,5082
3	458	479	0,7712	0,6643
4	473	472	0,7360	0,7399
5	443	446	0,6086	0,5888
6	443	437	0,5624	0,5888
7	499	483	0,7940	0,8709
9	535	535	1,0530	1,0523
11	558	577	1,2646	1,1683
8	535	524	1,0007	1,0523
10	608	596	1,3641	1,4202
12	585	648	1,6254	1,3043
13	661	681	1,7926	1,6873
15	696	694	1,8561	1,8636
16	719	696	1,8670	1,9795

Table 4. /b/

Number of compounds	RI		logP	
	measured	calculated	measured	calculated
18	331	297	-0,1436	0,0244
19	314	350	0,1212	-0,0612
20	377	385	0,2989	0,2562
21	487	444	0,5969	0,8105
22	452	456	0,668	0,6341
23	487	489	0,8220	0,8105
25	499	462	0,6894	0,8709
24	619	612	1,4416	1,4756

Table 4. /c/

Number of compounds	RI		logP	
	measured	calculated	measured	calculated
30	487	484	0,831	0,8465
31	578	549	1,231	1,4869
32	644	641	1,799	1,8164
33	696	705	2,196	2,1376
26	377	385	0,221	0,1670
27	487	465	0,716	0,8465
28	551	554	1,262	1,2419
40	716	712	2,238	2,2611
47/a	565	547	1,222	1,3283
48	565	552	1,249	1,3283
55	639	625	1,703	1,7855
54	535	543	1,194	1,1430

Table 4. /d/

Number of compounds	RI		logP	
	measured	calculated	measured	calculated
34	509	523	1,074	0,9824
35	-	595	1,515	-
36	649	672	1,995	1,8472
34/a	565	606	1,586	1,3283
34/b	617	607	1,591	1,6496
34/b	743	744	2,439	2,4279

Table 5

Relationship between RI and logP for 2- and 3-ring compounds

A: 2-ring compounds:	n = 23
m	= 0.005038
b	= -1.64308
r^2	= 0.95536
r	= 0.97742
$S_{RI\ measured} / S_{RI\ calculated}$	= 97.80 %
$S_{logP\ measured} / S_{logP\ calculated}$	= 97.73 %
B: 3-ring compounds	n = 17
m	= 0.0061774
b	= -2.161824
r^2	= 0.96657
r	= 0.983143
$S_{RI\ measured} / S_{RI\ calculated}$	= 98.75 %
$S_{logP\ measured} / S_{logP\ calculated}$	= 98.71 %

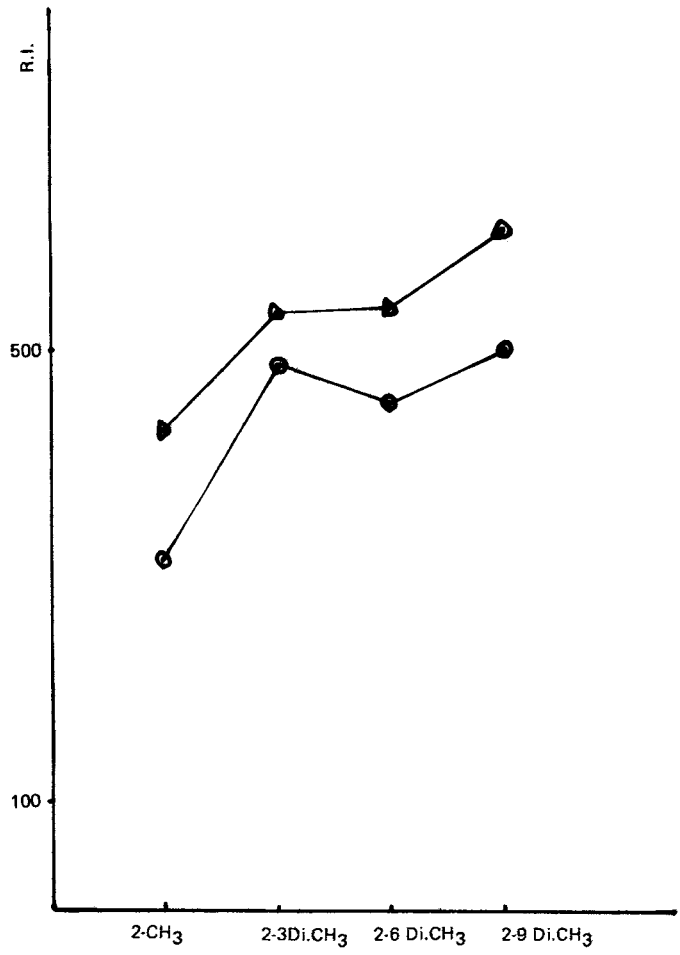


Fig. 6 Relationship between RI and the structure of some tested compounds (Δunsaturated 2-ring compounds and O saturated 2-ring compounds)

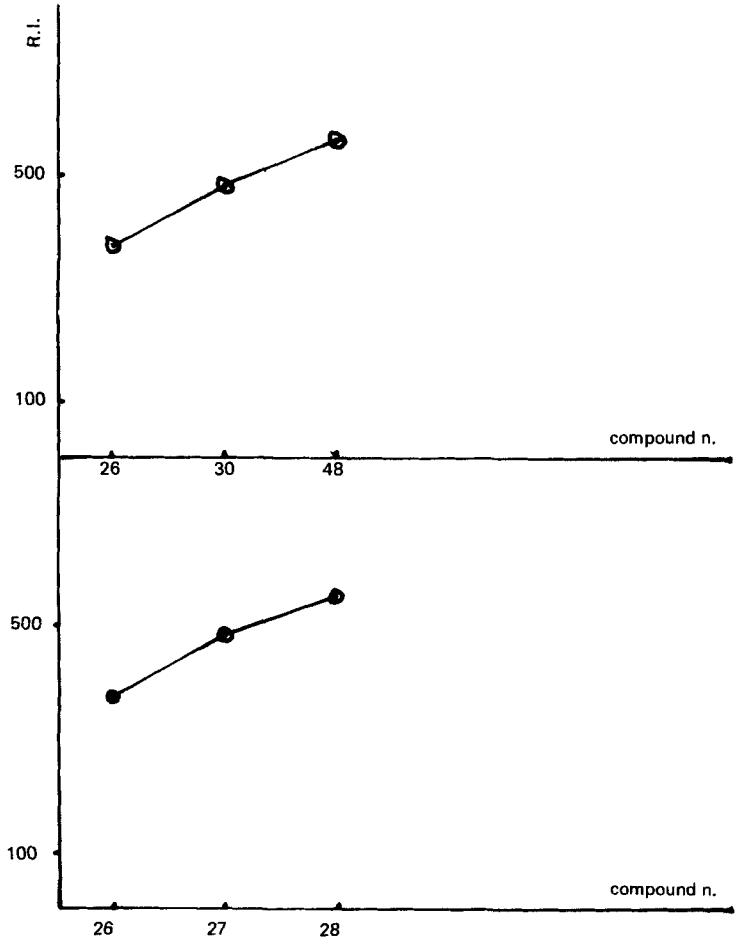


Fig. 7 Relationship between RI and some tested 3-ring compounds

This is illustrated in Fig. 7 compounds No. 26, 30, 48 where the increment in RI values are 110, 78 and also in compounds number 26, 27, 28 where the increments in RI are 110, 74 respectively . We can see, in the same figure, the similarity in RI between compounds number 27 and 30, and compounds No. 48 and 28 which differ from each other only in the positions of the rings. A similar observation was mode for the unsaturated compounds see Table 3, compound No. 34 and 54 .

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