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CHROMATOGRAPHY OF 1,3-BENZODIOXOLE DERIVATIVES

E. R. COLE, G. CRANK* and H. T. HAI MINH

Department of Applied Organic Chemistry, University of New South Wales, P.O. Box 1, Kensington, N.S.W. 2033 (Australia)

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SUMMARY

Study of the gas-liquid chromatography and high-performance liquid chromatography of 2-alkyl- and 2,2-dialkyl-benzodioxoles and their ring-substituted derivatives gave exponential relationships between retention values and carbon chain length of the substituents. The influence of the substituents on the benzene ring was evaluated for a variety of derivatives. An equation is presented relating the retention value of a derivative with that of its parent, and involves a constant due to the effect of the substituent.

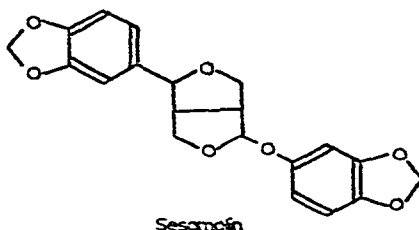
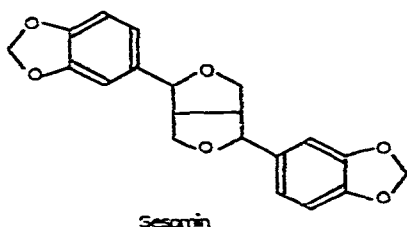
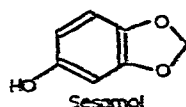
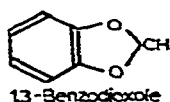
Separation by thin-layer chromatography does not display an exponential relationship of the above type.

INTRODUCTION

The 1,3-benzodioxole (or 3,4-methylenedioxyphenyl) system is part of the structure of many complex natural products including sesamol, sesamin and sesamolin present in sesame oil¹. Sesamol is an important natural anti-oxidant whilst the latter two compounds are synergists of pyrethrum insecticides. Many synthetic benzodioxoles based on sesamin and sesamolin have been prepared and several commercial synthetic synergists have thus been developed². However little data on the chromatography of benzodioxoles is available apart from information on the gas-liquid chromatography (GLC) of 5-substituted derivatives³.

In connection with studies of the synthesis⁴ and chemical reactivity of benzodioxoles⁵ a considerable number of novel compounds has now been prepared including new derivatives with either one or two substituents at the 2-position and in some cases with additional substitution at position 5 (6) or both positions 5 and 6. A full examination of the GLC and high-performance liquid chromatography (HPLC) of these new derivatives has been made and an analysis of structural effects on chromatographic behaviour is reported. Some thin-layer chromatographic (TLC) data are also included.

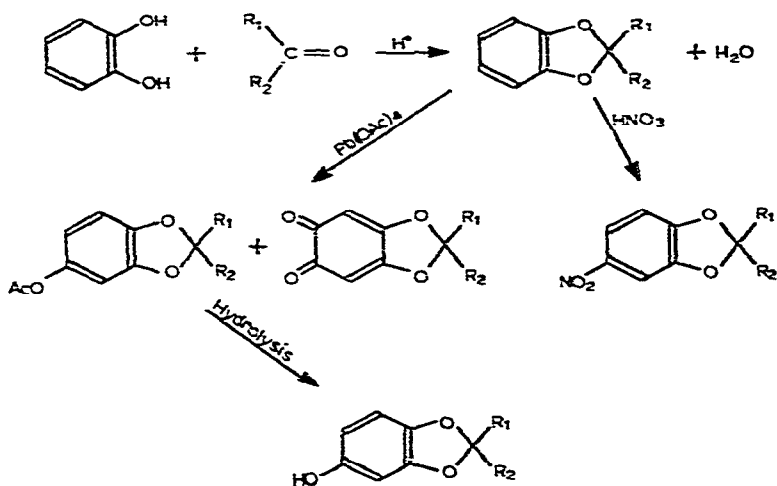
* To whom correspondence should be addressed.



EXPERIMENTAL

Materials

2-Substituted and 2,2-disubstituted 1,3-benzodioxoles were prepared by acid catalyzed condensation of catechol with aldehydes and ketones respectively. A new procedure was used⁴, in which catechol and the appropriate carbonyl compound in an aromatic hydrocarbon solvent were heated under reflux, in the presence of a trace of *p*-toluenesulphonic acid. Water, formed in the reactions, was removed azeotropically using a Dean and Stark apparatus. Yields of product were in the 60–95% range. 5-Acetoxy derivatives and 5,6-quinones were prepared by oxidation of parent hydrocarbons with lead tetraacetate⁵. 5-Hydroxy compounds were derived from acetoxy derivatives by hydrolysis⁵. 5-Nitro derivatives were formed by nitration under mild conditions⁴.



All derivatives showed satisfactory elemental analysis and spectroscopic properties.

Procedures

GLC on glass columns (90 × 0.5 cm I.D.) was carried out at various temperatures using SE-30 (10%), DEGA (10%) and Carbowax 20M (10%), applied by the filtration technique, to 100–120 mesh Celite, previously acid washed and treated with hexamethyldisilazane. Nitrogen (30 ml/min) was used as a carrier gas, with a flame-ionization detector. Retention times were corrected for column dead space.

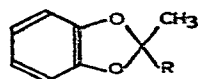
HPLC was performed on a Waters Assoc. instrument (M-6000A pump, 660 solvent programmer, 450 variable-wavelength detector) fitted with a μ Bondapak C₁₈ reversed-phase column operated at 1000 p.s.i. Solvents were redistilled analytical-reagent grade, degassed and filtered before use. Samples (10 μ l) in methanol (0.05% solutions) were chromatographed using various combinations of methanol–water or acetonitrile–water and were detected by absorption at 290 nm.

TLC was carried out on microscope slides coated with silica-gel 60 (Merck) using ethyl acetate–light petroleum mixtures. Spots were visualized by exposure to iodine vapour.

RESULTS AND DISCUSSION

Results of the GLC of 2,2-disubstituted-1,3-benzodioxoles for three columns are detailed in Table I. Retention times (t_R) at any particular temperature increase in the order t_R (Carbowax) \gg t_R (DEGA) $>$ t_R (SE-30), in accord with an electrostatic interaction between the oxygen atoms of the dioxole ring and the polar stationary phases. The best resolution of the lower members of the series was obtained by use of

TABLE I
GLC OF 2-METHYL-2-ALKYL-1,3-BENZODIOXOLES



R	Retention times (sec)													
	SE-30 column					DEGA column				Carbowax column				
	115°	135°	155°	175°	195°	135°	155°	175°	195°	135°	155°	175°	195°	
-H	66	30	18	12	9	—	—	—	—	258	138	78	56	
-CH ₃	72	36	18	12	9	102	54	30	20	216	120	66	48	
-C ₂ H ₅	126	60	30	18	12	138	72	36	28	330	168	96	69	
-C ₃ H ₇	228	108	54	30	18	204	102	54	37	510	252	144	90	
-CH(CH ₃) ₂	195	84	48	24	17	138	84	42	30	420	222	120	84	
-C ₄ H ₉	387	168	84	49	28	312	156	84	49	800	385	210	132	
-CH ₂ CH(CH ₃) ₂	277	126	66	37	24	180	108	54	42	570	290	156	96	
-C ₆ H ₁₁	678	276	132	72	40	468	222	108	66	1270	575	312	189	
-(CH ₂) ₂ CH(CH ₃) ₂	540	234	108	66	36	318	180	96	60	990	480	245	156	
-C ₈ H ₁₃	—	456	210	120	62	720	336	156	96	—	910	455	270	
-C ₇ H ₁₅	—	756	336	180	90	1120	492	222	132	—	1380	685	385	
-C ₈ H ₁₇	—	—	606	282	129	—	730	330	186	—	—	1015	550	
-C ₉ H ₁₉	—	—	888	420	198	—	1135	460	264	—	—	—	810	
-C ₁₀ H ₂₁	—	—	—	624	277	—	—	670	372	—	—	—	—	
-C ₁₁ H ₂₃	—	—	—	955	385	—	—	985	515	—	—	—	—	

the Carbowax column, which however was less useful for higher members due to prolonged retention times and broad peaks. Higher members were successfully separated on the SE-30 column, but here the lower members of the series were crowded together necessitating temperature programming (Fig. 1) in order to handle the full series. Best overall isothermal resolution was found for the DEGA column.

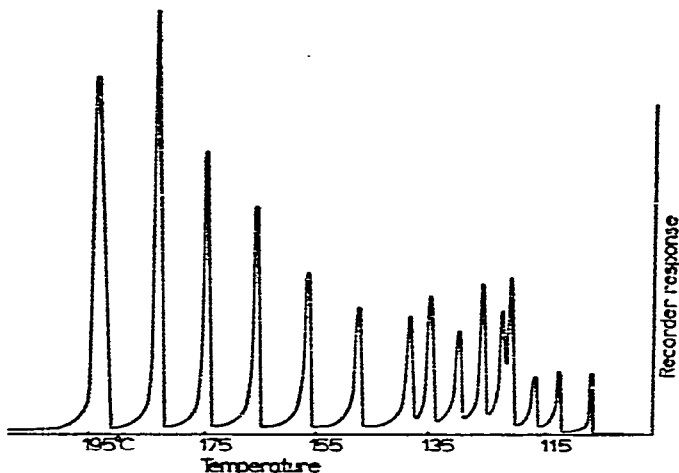


Fig. 1. Separation of 2-methyl-2-alkyl-benzodioxoles on an SE-30 column using temperature programming conditions. Initial temperature 115° (2 min), heating rate 6°/min, final temperature 195°. Peaks represent compounds listed in Table I in the order shown under column R.

Plots of $\log t_R$ vs. carbon number of the side chains gave straight line relationships (e.g., Fig. 2). Where the parent compound ($R = H$) was included its anomalous behaviour was clearly indicated, especially for the Carbowax column. The relationship between $\log t_R$ in the SE-30 and Carbowax columns at 175° is shown in Fig. 3. The expected straight line graph is observed for the homologous series and only slight deviation is found for the isopropyl, isobutyl and isoamyl compounds which also appear to give a straight line but with a slightly different slope.

Results of the GLC of 2-monosubstituted benzodioxoles on SE-30 and Carbowax are detailed in Table II, and the increased retention times in the latter column may be noted. $\log t_R$ vs. carbon number of side chains show the expected relationships (e.g., Fig. 4) with anomalous behaviour for the parent compound ($R = H$) especially on Carbowax. The plot of $\log t_R$ (SE-30) vs. $\log t_R$ (Carbowax) is a straight line (Fig. 3) parallel to that of the disubstituted series.

Data for the GLC of some 5-hydroxy, 5-acetoxy and 5,6-quinone derivatives of benzodioxoles are listed in Table III. For these types of compounds retention times on the SE-30 column increase in order of compound volatilities with the most polar hydroxy derivatives having least retention. It was not possible to obtain useful results for either DEGA or Carbowax columns as the very strong attachments of these compounds to the polar DEGA and Carbowax phases led to very long retention times. For each of the above homologous series an exponential relationship between $\log t_R$ and carbon number of side chains was found.

Fig. 5 shows plots of $\log t_R$ vs. the side chain carbon numbers for the 5-hydroxy,

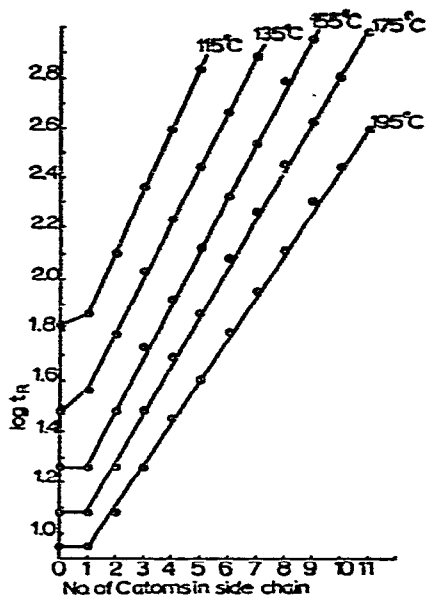
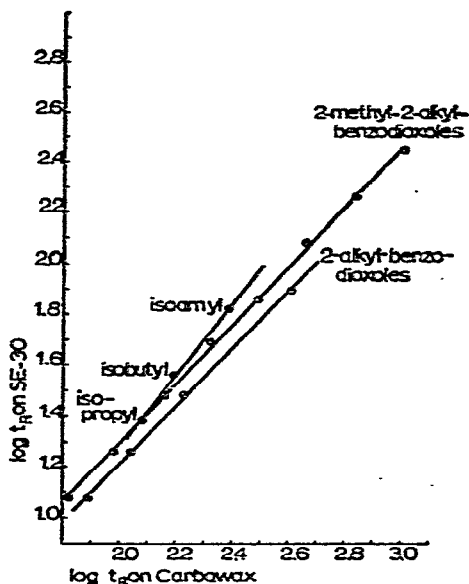
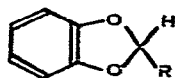

 Fig. 2. Log t_R of 2-methyl-2-alkyl-benzodioxoles vs. carbon number (SE-30).

 Fig. 3. Log t_R on SE-30 vs. log t_R on Carbowax for 2-methyl-2-alkyl-benzodioxoles and 2-alkyl-benzodioxoles.

TABLE II

GLC OF 2-ALKYL-1,3-BENZODIOXOLES



R	Retention times (sec)								
	SE-30 column					Carbowax column			
	115°	135°	155°	175°	195°	135°	155°	175°	190°
-H	60	27	18	12	9	305	162	91	66
-CH ₃	66	30	18	12	9	260	138	78	56
-C ₂ H ₅	114	54	32	18	12	385	205	110	78
-C ₃ H ₇	204	96	48	30	18	625	310	170	117
-C ₅ H ₁₁	670	295	143	78	48	1650	750	410	237

5-acetoxy and 5,6-quinone derivatives compared with the parent benzodioxoles at 175°. In this manner it is possible to see the effect of the substituents on the chromatographic behaviour of the system. A series of approximately parallel lines is obtained, thus the effect of the substituent on retention may be derived by measuring the distance between the intercepts of the lines on the y-axis. As anticipated an equation of the following type is indicated

$$\log t_R (\text{derivative}) = \log t_R (\text{parent}) + c$$

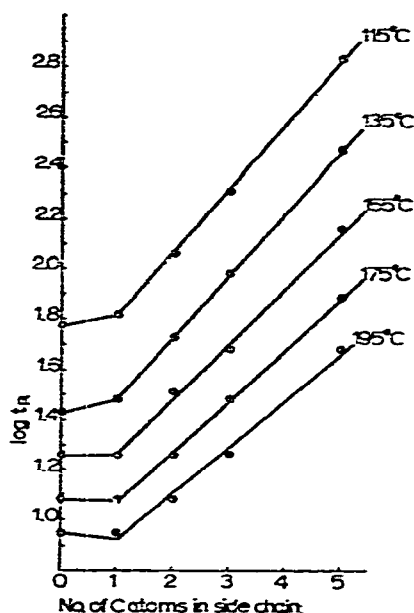


Fig. 4. Log t_R of 2-alkyl-benzodioxoles vs. carbon number (SE-30).

where c is a constant due to the influence of the substituent at a particular temperature. Values of c thus obtained are $+0.45$ for the hydroxyl group, $+0.60$ for the acetoxy group and $+0.98$ for the quinone function.

HPLC results for the 2,2-disubstituted benzodioxoles in several solvent combinations are shown in Table IV. Excellent separation was obtained with both the aqueous methanol and aqueous acetonitrile solvent systems, the latter allowing the resolution of the full series studied. On the μ Bondapak C_{18} column, separations should be by partition chromatography with a predicted linear relationship between log retention volumes (V_R) and side chain carbon numbers for the homologous series.

TABLE III

GLC OF RING-SUBSTITUTED BENZODIOXOLES ON SE-30

R	Type of compound												
Retention time (sec)													
	155°	175°	195°	215°	155°	175°	195°	215°	235°	175°	195°	215°	235°
-C ₂ H ₅	150	72	42	30	235	120	60	36	24	260	145	90	54
-C ₄ H ₉	335	155	78	48	480	220	115	66	42	540	280	150	78
-C ₇ H ₁₅	1350	530	250	132	1850	730	330	160	90	1660	780	335	175
-C ₉ H ₁₉	—	1330	500	252	—	1670	660	305	155	—	1670	660	315
-C ₁₁ H ₂₃	—	—	1040	490	—	—	1400	575	285	—	3500	1260	545

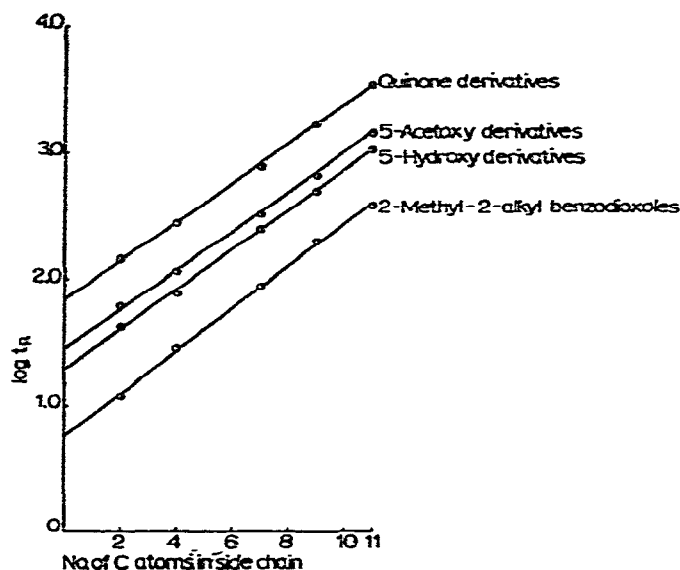


Fig. 5. Comparisons of $\log t_R$ vs. carbon number for various benzodioxole derivatives (SE-30).

When $\log V_R$ (uncorrected) was plotted vs. carbon numbers a series of curves was obtained diverging from theory, however when $\log V_R$ (corrected) was used instead, the expected straight line relationship was observed (Fig. 6). In contrast to GLC, where the dead space volume is usually insignificant compared to retention volumes of compounds, and can normally be ignored, the dead space volume is now

TABLE IV

HPLC RESULTS FOR 2,2-DISUBSTITUTED BENZODIOXOLES ON μ BONDAPAK C_{18}

See Table I for structural formula. Solvent systems: 1 = methanol-water (7:3); flow-rate, 1 ml/min; 2 = methanol-water (8.5:1.5); flow-rate, 1 ml/min; 3 = acetonitrile-water (5.5:4.5); flow-rate, 1.5 ml/min; 4 = acetonitrile-water (6.5:3.5); flow-rate, 1.5 ml/min; 5 = acetonitrile-water (7:3); flow-rate, 1 ml/min.

R	Retention volume (ml)									
	1		2		3		4		5	
	V_R	$V_R(\text{corr})$	V_R	$V_R(\text{corr})$	V_R	$V_R(\text{corr})$	V_R	$V_R(\text{corr})$	V_R	$V_R(\text{corr})$
-CH ₃	4.3	1.6	—	—	5.78	2.69	4.10	1.09	3.73	0.71
-C ₂ H ₅	5.2	2.5	—	—	7.03	3.94	4.56	1.54	4.03	1.01
-C ₃ H ₇	6.5	3.8	—	—	9.10	6.01	5.27	2.25	4.48	1.46
-C ₄ H ₉	8.5	5.8	—	—	11.96	8.87	6.14	3.12	5.04	2.02
-C ₅ H ₁₁	12.2	9.5	4.6	2.0	16.62	13.53	7.49	4.47	5.87	2.85
-C ₆ H ₁₃	18.2	15.5	5.5	2.9	—	—	9.50	6.48	7.09	4.07
-C ₇ H ₁₅	29.0	26.3	6.5	3.9	—	—	12.53	9.51	8.89	5.87
-C ₈ H ₁₇	47.0	44.3	8.3	5.7	—	—	17.0	13.98	11.50	8.48
-C ₉ H ₁₉	79.3	76.6	10.6	8.0	—	—	24.0	20.98	15.39	12.37
-C ₁₀ H ₂₁	—	—	14.3	11.7	—	—	34.55	31.53	21.20	18.18
-C ₁₁ H ₂₃	—	—	20.0	17.4	—	—	51.05	48.03	29.90	26.88

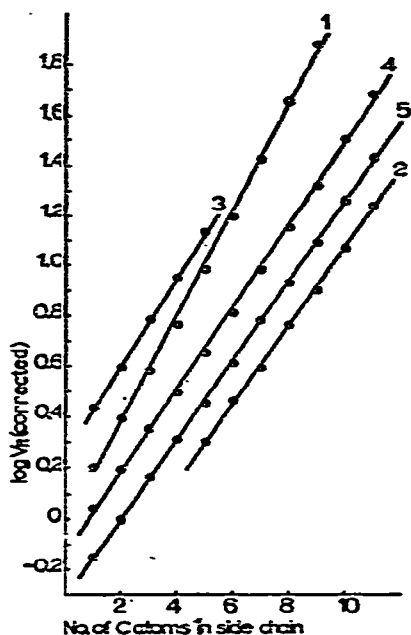


Fig. 6. $\log V_R(\text{corrected})$ of 2-methyl-2-alkyl-benzodioxoles vs. carbon number. Numbers of lines refer to solvent systems in Table IV.

very significant. In the small columns used in this technique failure to compensate for dead space results in serious error in interpretation of chromatographic behaviour.

The various ring-substituted benzodioxoles were also examined in the same column and their HPLC data are recorded in Table V. Good resolution of compounds was again obtained for the solvents used and analysis of data shows separation due to

TABLE V

HPLC RESULTS FOR RING-SUBSTITUTED BENZODIOXOLES ON μ BONDAPAK C_{18}

Solvent systems: 1 = methanol-water (4:1); flow-rate, 1 ml/min; 2 = acetonitrile-water (7:3); flow-rate, 1 ml/min.

R	Type of compound					
	Retention volume (ml) (corrected)					
	1	2	1	2	1	2
-CH ₃	—	—	—	—	1.17	—
-C ₂ H ₅	0.43	0.25	0.83	0.68	1.67	0.18
-C ₄ H ₉	0.87	0.60	1.83	1.35	2.80	0.41
-C ₇ H ₁₅	2.57	1.90	4.77	3.87	7.69	1.31
-C ₉ H ₁₉	5.57	3.94	10.67	7.89	15.67	2.71
-C ₁₁ H ₂₃	12.43	8.18	23.67	16.52	35.67	5.60

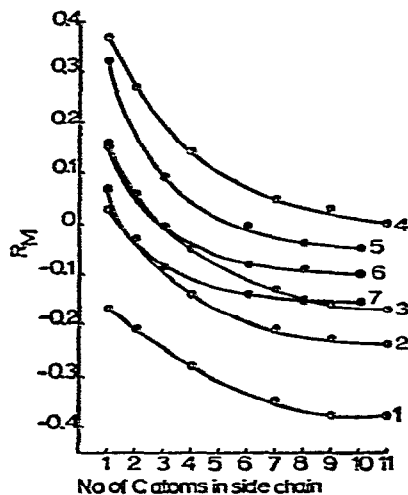
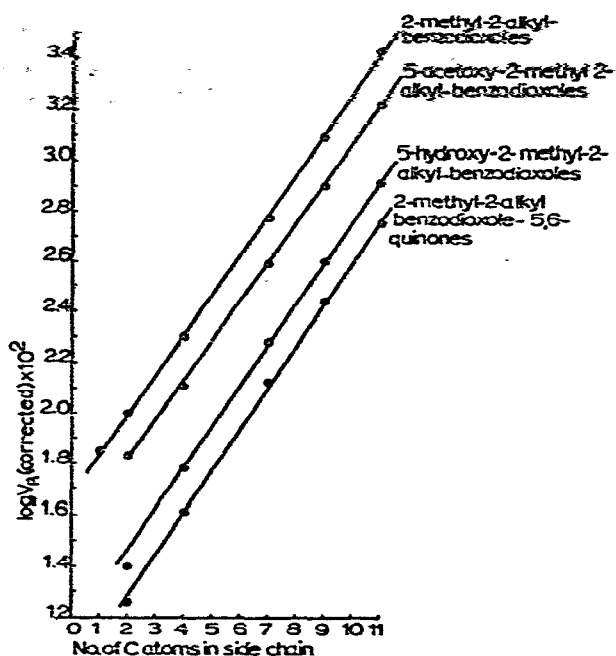
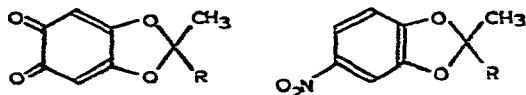


Fig. 7. Comparisons of $\log V_R(\text{corrected})$ vs. carbon number for various benzodioxole derivatives (solvent acetonitrile-water, 7:3).

Fig. 8. R_m values vs. carbon numbers for 5-nitro-2-methyl-2-alkyl-benzodioxoles and 2-methyl-2-alkyl-benzodioxole-5,6-quinones. Identification numbers relate to solvent systems in Table IV.

TABLE VI
TLC OF BENZODIOXOLES



Solvents: ethyl acetate-light petroleum (b.p. 40–60°): 1 = (1:1); 2 = (3:2); 3 = (7:3); 4 = (1:19); 5 = (1:9); 6 = (1:4); 7 = (3:7).

	R_F values $\times 100$				R_m values			
	1	2	3		1	2	3	
Quinones								
R = $-\text{C}_2\text{H}_5$	32	41	46		+0.323	+0.163	+0.066	
$-\text{C}_4\text{H}_9$	45	50	55		+0.089	-0.005	-0.091	
$-\text{C}_7\text{H}_{15}$	50	55	58		-0.007	-0.084	-0.140	
$-\text{C}_9\text{H}_{19}$	52	55	59		-0.037	-0.089	-0.154	
$-\text{C}_{11}\text{H}_{23}$	53	56	60		-0.050	-0.103	-0.171	
Nitro derivatives								
R = $-\text{CH}_3$	30	41	48	60	+0.372	+0.150	+0.029	-0.170
$-\text{C}_2\text{H}_5$	35	47	52	62	+0.270	+0.056	-0.027	-0.210
$-\text{C}_4\text{H}_9$	42	53	58	66	+0.138	-0.050	-0.140	-0.280
$-\text{C}_7\text{H}_{15}$	47	58	62	69	+0.054	-0.133	-0.210	-0.350
$-\text{C}_9\text{H}_{19}$	48	59	63	71	+0.030	-0.158	-0.230	-0.380
$-\text{C}_{11}\text{H}_{23}$	50	60	64	71	0	-0.170	-0.240	-0.380

partition. Plots of $\log V_R$ (corrected), vs. carbon number are shown in Fig. 7, and consist of sets of virtually parallel lines. Accurate predictions may therefore be made concerning other homologues not included in the study. It is clear that once again the expected theoretical relationship described by the following equation is found:

$$\log V_R (\text{derivative}) = \log V_R (\text{parent}) + c$$

where c is a constant attributed to the substituent and can be evaluated from data such as it contained in Fig. 7. Values of c obtained are -0.19 for the acetoxy group, group, -0.53 for the hydroxyl group and -0.69 for the quinone function, based on the aqueous acetonitrile solvent system. This correlates well with the previously discussed GLC behaviour.

Satisfactory TLC methods were established for the various benzodioxoles and the technique was used extensively during chemical studies on the compounds. Compounds were readily located on chromatograms by either characteristic UV fluorescence or iodine staining. Many of the benzodioxoles gave intense colours with iodine vapour, and could be detected with considerable sensitivity. Two representative types of derivatives were subjected to chromatographic investigation and their results are listed in Table VI. Combinations of ethyl acetate and light petroleum enables adequate separation of compounds to be obtained with the usual fall-off of resolution with longer side chains. Plots of R_m values vs. side chain carbon numbers (Fig. 8) gave a series of smooth curves indicating that separation behaviour is not clearly defined. This is similar to the results obtained in previous studies of benzimidazoles⁶ and benzothiazoles⁷.

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