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Note

Relationships between the chromatographic behaviour and structure of some substituted dibenzo[*b,f*]thiepins and their analogues

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Recently considerable attention has been devoted to the relationships between chromatographic retention behaviour and structure. Such relationships can yield information on the polarity, hydrophobicity and steric properties of the compounds studied and may be useful in estimation of the retention indices of new compounds. The retention indices and steric and electronic interactions can be related by eqn. 1 proposed by Gassiot-Matas and Firpo-Pamies¹

$$I = \theta + B \quad (1)$$

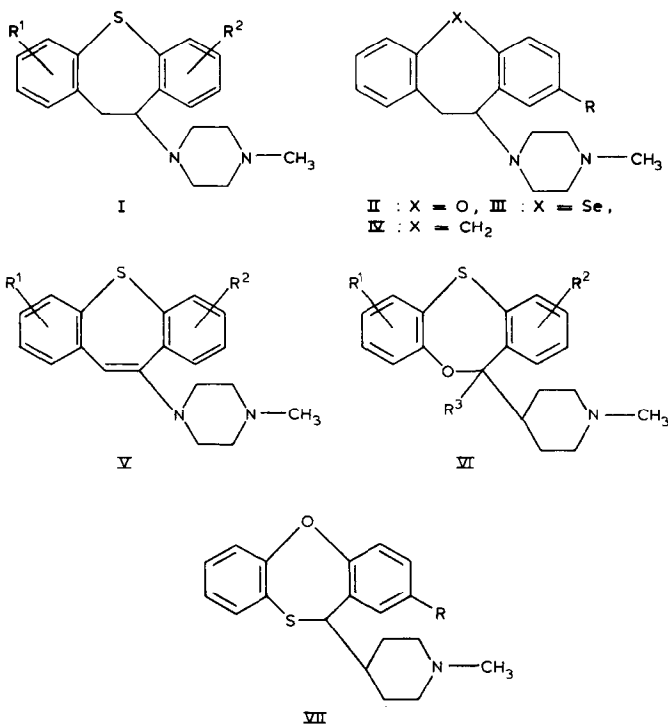
where θ is related to the molar volume of the compound and B characterizes the polar interactions with the stationary phase. If the polar interactions between the stationary phase and the solute are small, then B can be neglected and θ can be replaced by other suitable parameters describing the bulkiness of a molecule. Frequently, connectivity indices or the molar refraction have been used²⁻⁵, e.g.

$$I = k_1\chi + k_2 \quad (2)$$

where χ denotes the connectivity index developed by Randić⁶ and subsequently used by Kier *et al.*⁷⁻⁹, k_1 and k_2 are regression coefficients.

In the present paper the gas-liquid chromatographic behaviour of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepins (I) and their analogues II-VII is reported. These compounds were synthesized by Protiva and co-workers¹⁰⁻¹² and most of them show neuroleptic activity. The parent structure is that of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (Ia). This structure was modified by substitution of sulphur by oxygen (II), selenium (III), methylene (IV) or by introduction of a double bond in the seven-membered ring (V). The analogues containing two heteroatoms (VI, VII) in this ring were also prepared.

The retention increments, ΔI_x , were calculated as the differences in the Kováts indices, I , between the non-substituted and substituted compounds. They were used to characterize the interaction of the solute with the stationary phase. Since the additivity principle is valid only for the monosubstituted derivatives, the aforemen-



tioned method of computation of the retention indices is rather limited in scope. This limitation can, however, be overcome, at least on a non-polar phase, by means of relationships between the retention indices and a suitable physico-chemical property of the compounds under study, such as the molar refraction or valence connectivity indices. Such relationships can be used for tentative prediction of the retention behaviour of newly synthesized compounds.

EXPERIMENTAL

A Carlo Erba Fractovap 2450 gas chromatograph equipped with a flame ionization detector was used. The glass columns (1 m × 3.5 mm) were packed with 3% of Dexsil 300, 400 or 410 on Supelcoport (Supelco, Lafayette, PA, U.S.A.). Helium was used as a carrier gas, the flow-rate being 50 ml min⁻¹. The operating temperature was 250°C. The retention times were measured by a HP-3385 A integrator. The molar refractions, MR, were calculated from atom and bond increments¹³ or from the calculated values for corresponding substituents¹⁴. The connectivity indices were calculated as described in ref. 7. Regression coefficients were estimated by multiple regression analysis and were statistically evaluated by the multiple regression coefficient *r*, the standard deviation *s*, and the Fischer-Snedecor criterion *F*. The samples of compounds I–VII were kindly supplied by Dr. Provita from our Institute.

RESULTS AND DISCUSSION

The retention indices of 41 tricyclic compounds, measured on phases of different polarities, are summarized in Table I. As is evident from Table II, the order

TABLE I

KOVÁTS INDICES AND STRUCTURAL PARAMETERS OF COMPOUNDS I-VII

Indices I_{300} , I_{400} and I_{410} were measured on Dexsil 300, 400 and 410, respectively.

Compound	Substituent	Kováts index			MR	$^1\chi^p$	σ
		I_{300}	I_{400}	I_{410}			
Ia	H	2687	2766	2675	96.92	8.702	0
Ib	8-Cl	2860	2949	2846	101.92	9.210	0.23
Ic	8-F	2666	2753	2621	96.81	8.500	0.06
Id	8-Br	2936	2996	2915	104.77	9.606	0.23
Ie	8-CF ₃	2578	2641	2569	100.91	8.528	0.54
If	8-SCH ₃	3073	3195	3112	109.71	10.150	0
Ig	8-OCH ₃	2902	2991	2871	103.76	9.314	-0.27
Ih	8-OC ₂ H ₅	3006	3108	2978	108.36	9.514	-0.27
Ii	8-CH ₃	2750	2824	2739	101.51	9.114	-0.17
Ij	8-NO ₂	3191	3289	3180	103.25	9.629	0.78
Ik	7-Cl, 8-F	2867	2941	2794	101.81	9.009	0.28
Il	3-F, 8-Cl	2853	2932	2771	101.81	9.020	0.28
Im	3,8-Cl ₂	3005	3139	2991	106.90	9.726	0.46
In	7,8-Cl ₂	3075	3141	2980	106.90	9.731	0.46
Io	7-F, 8-CH ₃ *	2737	—	2674	100.43	8.919	-0.11
Ip	2-F, 8-SCH ₃	2991	3132	2965	109.60	9.336	0.06
Ir	3,8-F ₂	2646	2702	2616	96.73	8.312	0.12
Is	3-F, 8-SCH ₃	3012	3154	2985	109.15	9.336	0.06
It	6,8-F ₂	2613	2668	2590	96.73	8.312	0.12
Iu	7-CF ₃ , 8-Cl	2812	2858	2834	105.91	9.046	0.72
IIa	H	2524	2559	2494	90.95	8.082	0
IIb	8-Cl	2606	2713	2620	95.95	8.595	0.23
IIc	8-CH ₃	2557	2586	2533	95.57	8.490	-0.17
IId	8-SCH ₃	2961	2998	2797	103.74	9.533	0
IIIa	H**	2768	2829	2697	100.11	—***	0
IIIb	8-Cl**	2920	3009	2853	105.14	—***	0.23
IVa	H	2550	2578	2530	93.38	8.382	0
IVb	8-Cl	2726	2778	2678	98.38	8.895	0.23
Va	7-F, 8-Cl	2884	2953	2803	102.50	8.762	0.29
Vb	2-Cl, 8-F	2910	2989	2843	102.50	8.790	0.29
Vc	7,8-Cl ₂	3095	3169	3007	107.61	9.473	0.46
Vd	7,8-F ₂	2756	2821	2646	97.39	8.049	0.12
Ve	7-CF ₃ , 8-Cl	2827	2890	2756	106.60	8.780	0.72
VIa	8-Cl	2821	2897	2744	99.30	9.190	0.23
VIb	8-CF ₃	2551	2579	2533	98.29	8.513	0.54
VIIa	8-CF ₃	2546	2602	2548	98.29	8.513	0.54
VIIb	8-OCH ₃	2912	2991	2840	101.14	9.160	-0.27
VIIc	8-Cl	2845	2922	2765	99.30	9.100	0.23
VIIId	8-Cl, 10-CH ₃	2897	2969	2848	102.92	9.470	0.06
VIIe	3-F, 8-OCH ₃ ^b	2882	—	—	101.03	8.932	-0.21
VIIIf	3-F, 8-Cl ^p	2806	—	—	99.19	8.921	0.29

* Compound not involved in eqns. 1 and 2.

** Compound not involved in eqns. 9-12.

*** The valence value¹⁵ δ^r for Se is not known.

TABLE II
KOVÁTS INDICES OF 8-CHLORO DERIVATIVES

Indices I_{300} , I_{400} and I_{410} were measured on Dexsil 300, 400 and 410, respectively.

Compound	I_{300}	I_{400}	I_{410}
IIIb	2920	3009	2853
Ib	2860	2949	2846
VIIc	2845	2922	2765
VIa	2821	2897	2744
IVb	2726	2778	2678
IIb	2606	2713	2620

of the Kováts indices for 8-chloro-substituted derivatives differing only in the structure of the middle ring is the same on all the phases studied. This indicates that the effect of the polar interactions upon retention is minimal. Evidence in support of this conclusion is provided by a similar behaviour for the compounds differing only in substitution at position 8. These derivatives are ordered in Table III according to the change in the Kováts index, ΔI_x , with respect to the non-substituted compound. The similarity in the interactions among the solutes and stationary phases studied is demonstrated by the relationships between the retention indices:

$$I_{300} = 1.003 I_{410} + 33.252 \quad n \quad r \quad s \quad F \quad (1)$$

$$I_{300} = 0.908 I_{410} + 194.598 \quad 38 \quad 0.974 \quad 41.66 \quad 635.3$$

$$I_{300} = 0.908 I_{410} + 194.598 \quad 38 \quad 0.990 \quad 25.52 \quad 1750.9 \quad (2)$$

The slopes of both equations are approximately equal to 1.

The values of ΔI_x for disubstituted derivatives I seem to indicate the existence of a mutual interaction between the substituents on the aromatic nuclei. Apparent differences were observed for the 7,8-disubstituted compounds I, where the sum of ΔI_x for both substituents was greater than that for the same substituents at position 8 (Table IV). The interactions with the stationary phase were stronger when the substituents were mutually *ortho* to each other. Such a synergism apparently depends on the nature of the substituents.

TABLE III
RETENTION INCREMENTS, ΔI_x , OF 8-SUBSTITUTED DIBENZO[*b,f*]THIEPINS

Compound	R^2	Retention increments, ΔI_x		
		D_{300}	D_{400}	D_{410}
Ie	CF ₃	-109	-125	-106
Ic	F	-21	-13	-54
Ii	CH ₃	63	58	64
Ib	Cl	173	183	171
Ig	OCH ₃	215	225	196
Ih	OC ₂ H ₅	319	342	307
Ij	NO ₂	504	523	505

TABLE IV

RETENTION INCREMENTS, ΔI_x , OF 7,8-DISUBSTITUTED DIBENZO[*b,f*]THIEPINS ON DEXSIL 300

Substituents	Retention increments, ΔI_x	
	Exptl.	Calc.
7-Cl, 8-F	180	152
7,8-Cl ₂	388	346
7-CF ₃ , 8-Cl	125	64
7-F, 8-CH ₃	50	42

The relationships between the retention indices and structural parameters were evaluated from the data obtained on Dexsil 300, the relationships found on the other phases being similar. Eqns. 3 and 4 describe the dependences of I_{300} on the molar refraction, MR, and the connectivity index, ${}^1\chi^v$, respectively, for the mono- and di-substituted thiepin derivatives I:

$$I_{300} = 31.851 \text{ MR} - 423.831 \quad n \quad r \quad s \quad F \quad (3)$$

$$I_{300} = 314.293 {}^1\chi^v - 12.809 \quad 20 \quad 0.806 \quad 105.72 \quad 33.4 \quad (4)$$

Trifluoromethyl and nitro derivatives deviate significantly from these equations. Although both of these substituents are strongly electronegative, they deviate in opposite senses. Use of the polar constants, σ , or their squares σ^2 did not improve the statistical significance of eqns. 3 and 4. Omission of the values for derivatives Ie, Ij and Iu yielded:

$$I_{300} = 30.503 \text{ MR} - 290.891 \quad n \quad r \quad s \quad F \quad (5)$$

$$I_{300} = 281.426 {}^1\chi^v + 283.296 \quad 17 \quad 0.935 \quad 54.96 \quad 111.7 \quad (6)$$

Eqns. 7 and 8 were calculated for the dehydro derivatives V:

$$I_{300} = 27.74 \text{ MR} + 54.45 \quad n \quad r \quad s \quad F \quad (7)$$

$$I_{300} = 199.28 {}^1\chi^v + 1149.97 \quad 5 \quad 0.946 \quad 46.94 \quad 25.5 \quad (8)$$

As is evident from the intercepts, the retention indices of the dehydro derivatives are higher than those of the respective dihydro analogues I.

Extension of the original series by addition of the compounds II, IV, VI and VII yielded eqns. 9 and 10:

$$I_{300} = 32.689 \text{ MR} - 501.462 \quad n \quad r \quad s \quad F \quad (9)$$

$$I_{300} = 339.449 {}^1\chi^v - 255.143 \quad 34 \quad 0.845 \quad 98.21 \quad 79.6 \quad (10)$$

$$I_{300} = 30.253 \text{ MR} - 246.920 \quad 34 \quad 0.930 \quad 67.40 \quad 205.0 \quad (11)$$

$$I_{300} = 307.109 {}^1\chi^v + 38.954 \quad 29 \quad 0.929 \quad 60.03 \quad 177.0 \quad (12)$$

$$I_{300} = 307.109 {}^1\chi^v + 38.954 \quad 29 \quad 0.937 \quad 56.90 \quad 200.2 \quad (12)$$

Here too, removal of trifluoromethyl and nitro derivatives improved the correlation (eqns. 11 and 12), especially between the retention indices and molar refraction. Values of $^1\chi^v$ and MR do not adequately describe the retention behaviour of the trifluoromethyl and nitro derivatives. This may be due to different influences of these groups upon the boiling points, determining to a great extent the retention on a non-polar phase.

It may be concluded that the relationships between the retention and structural parameters, which were originally verified in simple homologous series, can be used for prediction of the retention indices of more complex compounds. The interpretation of such relationships may also shed some light on the mechanism of separation.

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