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Note

Gas chromatographic behaviour of dibenzo[*b,f*]thiepines

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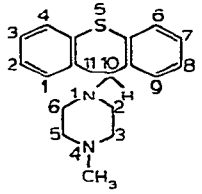
The research into new psychopharmaceuticals has been carries out in many biochemical and pharmaceutical institutions. In the Research Institute for Pharmacy and Biochemistry in Prague, a series of compounds involving the tricyclical system of dibenzo[*b*, *f*]thiepines has been synthesized (see, *e.g.*, refs. 1 and 2). Very effective neuroleptics have been found among these derivatives.



The initial substance is perathiepine {10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*, *f*]thiepine}. Its 8-chloro derivative, denoted as octoclothepine, is a prototype of sedatively and cataleptically highly effective neuroleptics in this series and has also been applied in practice[3]. Further modification of the structures of these substances by introduction of various substituents (*e.g.*, –F, –Br, $-CH_3$, $-SCH_3$, etc.) has led to even more powerful substances, that are less toxic and the efficiency of which is somewhat prolonged (see, *e.g.*, refs. 4 and 5).

The present paper reports the gas chromatographic (GC) behaviour of 19 derivatives of dibenzo[*b*, *f*]thiepines on two stationary phases of different polarities, Dexsil 400 and Dexsil 410. The relationships between the structure of the stationary phases and of the test substances are discussed in terms of the retention indices and the heats of solution, ΔH_s.

EXPERIMENTAL

The measurements were performed on a Carlo Erba Fractovap 2450 instrument with a flame-ionization detector. Glass columns (1 m × 3 mm I.D.) were used, packed with 3% Dexsil 400 (or Dexsil 410) on Supelcoport (100–120 mesh), pur-

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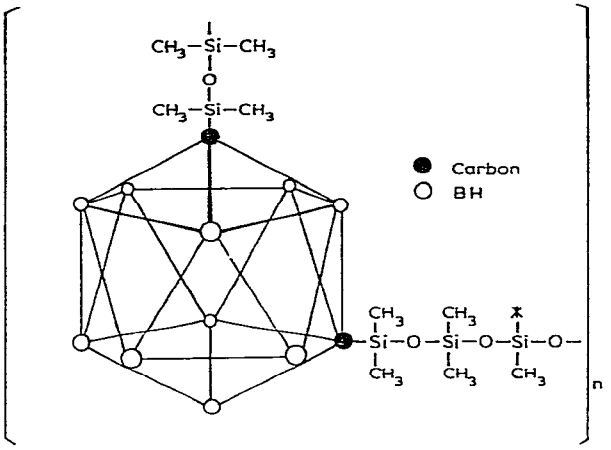
chased from Supelco, Lafayette, PA, U.S.A. The helium carrier gas had a flow-rate of 50 ml/min. The working temperatures were 245 or 250°C. The test substances were synthesized at the Research Institute for Pharmacy and Biochemistry, Prague, and kindly supplied by Drs. M. Protiva, J. O. Jílek and K. Šindelář.

RESULTS AND DISCUSSION

The Dexsil stationary phases are linear macromolecules containing carborane and siloxane units in their chains. Metacarborane, containing 10 boron and 2 carbon atoms, interconnected in a three-dimensional structure, considerably increases the thermal stability of the siloxane units. Dexsil 400 contains phenyl groups in the position denoted by the asterisk; Dexsil 410 contains cyanoethyl groups in this position:



Dexsil 400 resembles the OV-17 stationary phase and Dexsil 410 the OV-225 phase, but they are somewhat more polar, due to the presence of the metacarborane unit.

The retention indices and the heats of solution of the test substances on the two stationary phases are given in Table I. As can be seen from the table, the retention orders of the derivatives of perathiepine substituted in position 8 are identical for the two phases, namely: $CF_3 < F < H < CH_3 < Cl < OCH_3 < Br < SCH_3 < NO_2$ (*i.e.*, the principal type of interaction between dibenzo[*b*, *f*]thiepines and the two phases is the same). The retention indices of dibenzo[*b*, *f*]thiepines on the Dexsil 410 stationary phase are 50–150 units lower than those on Dexsil 400, although Dexsil 410 is much more polar. It is evident that the controlling mechanism does not involve dipolar interactions, but an electric overlap of the boundary orbitals. The $-(CH_2)_2CN$ and $-C_6H_5$ groups in the stationary phases must be considered in terms of hard-soft partners (the cyanoethyl group is harder than the phenyl group)[6,7]. Hard groups form strong complexes chiefly with hard partners and soft groups with soft partners. Dexsil 410 exhibits a smaller stability of hard-soft complexes, *i.e.*, smaller differences in the retention indices, resulting in somewhat poorer selectivity. This is also illustrated by the dependence of the retention indices of dibenzo[*b*, *f*]thiepines substituted in po-

sition 8 on two phases, $I_{Dexsil\,400}$ *vs.* $I_{Dexsil\,410}$, depicted in Fig. 1. The deviations from the slope $k = 1$ are proportional to the polarizability of the functional groups.

Introduction of fluorine into the perathiepine molecule led to a decrease in the retention index on Dexsil 410 by 54 units. On introduction of three fluorine atoms into the meperathiepine molecule, the retention index decreases by 170 units, *i.e.*, approximately three times more. By substitution –H → –F and $-CH_3 \rightarrow -CF_3$ the hardness of the group increases and the retention indices simultaneously decrease.

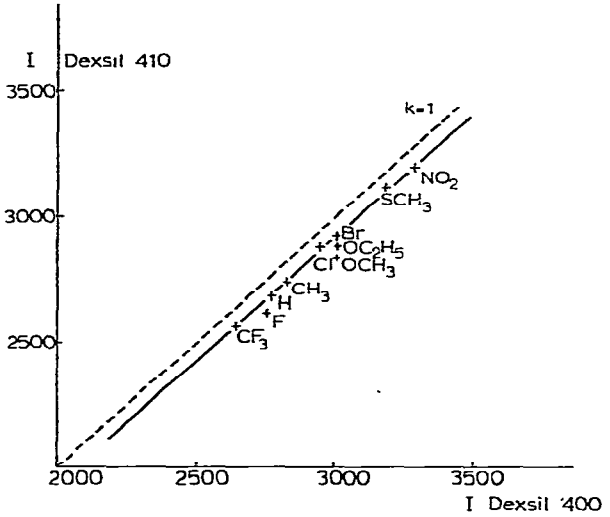


Fig. 1. The dependence of $I_{Dexsil\,410}$ *vs.* $I_{Dexsil\,400}$ for 8-substituted dibenzo[*b*, *f*]thiepines.

Substitution of hydrogen by methyl on the aromatic ring leads to an increase in I by 58 units on the Dexsil 400 and by 64 units on Dexsil 410. Substitution of hydrogen on the piperazine ring by methyl (substitution of –NH by $-NCH_3$) leads, on the other hand, to a decrease in the retention index by 59 units on Dexsil 400 and 32 units on Dexsil 410. The –NH group can form hydrogen bonds whose energy is proportional to the polarizibility of the π-bonds in the $-C \equiv N$ or $-C_6H_5$ groups of the stationary phase. The hydrogen bonding is more important with the phenyl group, as reflected in a greater ΔI difference for Dexsil 400.

The heats of solution, ΔH_s (in kcal mol^{-1}), given also in Table I, were calculated from the specific retention volumes measured at 245 and 250°C. Except for perathiepine, octoclothepine and methiothepine, the ΔH_s values are higher for Dexsil 410 stationary phase.

The retention data summarized in Table I show that monochloro derivatives are separated on both phases, while dichloro derivatives could not be separated on either phase. Substance 17, injected as the sodium salt, dissociated under the GC conditions and was eluted as the free acid. Compound 18 was not eluted on Dexsil 400 phase at 250°C.

We hope that the data obtained could be of some help in the GC examination of the metabolites of future drugs.

TABLE I
RETENTION INDICES AND HEATS OF SOLUTION OF DIBENZO[*b*,*f*]THIEPINES ON DEXSIL 400 AND DEXSIL 410

No.	*Trivial name*	*Substituent*	*Dexsil 400*		*Dexsil 410*	
			$I^{250°C}$	ΔH_s	$I^{250°C}$	ΔH_s
1	Perathiepine	8-H	2766	17.8	2675	14.4
2	Octoclothepine	8-Cl	2949	19.2	2876	16.6
3	Heptoclothepine	7-Cl	2998	17.9	2856	29.8
4	Hexoclothepine	6-Cl	3004	17.9	2860	29.5
5	Triaclothepine	3-Cl	2976	16.2	2840	28.1
6	Duoclothepine	2-Cl	2940	20.4	2803	27.8
7		6-Cl, 8-Cl	3139	16.5	2991	32.5
8		2-Cl, 8-Cl	3139	16.5	2991	32.5
9	Fluothepine	8-F	2753	18.7	2621	22.5
10	Trifluothepine	8-CF_3	2641	18.0	2569	19.3
11	Bromothepine	8-Br	2996	–	2915	30.1
12	Meperathiepine	8-CH_3	2824	16.8	2739	18.1
13	Octomethothepine	8-OCH_3	2991	21.2	2871	25.4
14		8-OCH_2CH_3	3008	23.7	2878	30.0
15	Methiothepine	8-SCH_3	3195	21.2	3112	20.5
16	Nitrothepine	8-NO_2	3289	17.8	3180	29.0
17		8-COOH	2970	23.6	2944	–
18		8-SO_3CH_3	–	–	3480	33.1
19		8-SCH_3	3254	21.7	3144	29.5

ACKNOWLEDGEMENT

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