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CHROMATOGRAPHIC BEHAVIOUR OF DIASTEREOMERS

V. EXTENSION OF THE RELATIONSHIP R_F(*erythro*) > R_F(*threo*) ON SILICA GEL TO DIASTEREOMERIC EPHEDRINE-LIKE 1,2-DISUBSTITUTED 1-ARYL-2-ALKYLETHANES

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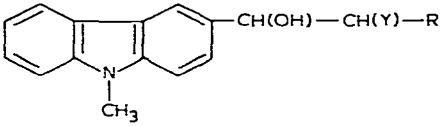
SUMMARY

Separation of 11 diastereomeric pairs of carbazole derivatives of the type



$Y = COOC_2H_5$, $CONHNH_2$, NH_2, $NHCH_3$ or COOH
$R = CH_3$ or C_2H_5

and related oxazolidones with known relative configurations is achieved by thin-layer chromatography on silica gel. For all the acyclic compounds studied the relationship R_F(*erythro*) > R_F(*threo*) is established. Having in mind the previous investigations, the scope of this relationship extends over diastereomers of the type Ar-CH(X)-CH(Y)-Z (X and Y = NH_2, OH, COOH and their derivatives, Z = R or Ar′). Further, diastereomeric hydroxyesters with Z = R or Ar′ show similar behaviour when Soczewiński's method of dilution is applied. Hence, the previously elaborated criteria for using R_F(*erythro*) > R_F(*threo*) should be valid also for the above type of diastereomers.

INTRODUCTION

In the previous papers of this series[1–3], the relationship R_F(*erythro*) > R_F(*threo*) was reported for 52 of the 54 diastereomeric pairs investigated of type 1. On the basis of Snyder's theory[4–10] it was attributed to one or two-point adsorption, via definite conformations. Semiempirical criteria concerning the scope and

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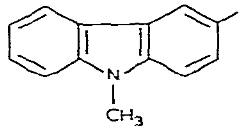
limitation of the above relationship were derived which enable thin-layer chromatography (TLC) to be used as a method for assignment of the relative configurations of diastereomers of type 1[2]. Further, experimental evidence was reported[3] for one-point adsorption of secondary aminoesters ($X{=}NHCH_3$, $Y{=}COOCH_3$) by the most strongly adsorbing group X, via conformations *erythro*-A′ and *threo*-B (see the formulae below) having X in the least sterically hindered position. In the case of tertiary aminoesters ($X{=}N(CH_3)_2$, $Y{=}COOCH_3$) and etheresters ($X{=}O$, $Y{=}COOCH_3$), the data supported two-point adsorption by X and Y, via conformations *erythro*-A′ and *threo*-B, where the two adsorbing groups are close.

Ar-CH(X)-CH(Y)-Ar′
type 1 (*erythro* and *threo*)
X and Y = NH_2, OH, COOH
or their derivatives
Ar and Ar′ = phenyl or
alkoxyphenyl

Ar-CH(OH)-CH(Y)-R
type 2 (*erythro* and *threo*)
Y = $COOC_2H_5$, $CONHNH_2$,
NH_2, $NHCH_3$ or COOH
R = CH_3 or C_2H_5

Ar =



Ar-CH(X)-CH(Y)-Z
type 3 (*erythro* and *threo*)
X and Y = NH_2, OH, COOH
or their derivatives
Z = Ar′ or R
Ar and Ar′ = phenyl,
alkoxyphenyl or carbazole
R = CH_3 or C_2H_5

In the present paper we report TLC separations on silica gel of eight diastereomeric pairs of ephedrine-like carbazole compounds of type 2, and of three diastereomeric pairs of oxazolidones (see the formulae in Table I) related to the acyclic compounds. The latter were similar to the diastereomers of type 1 on the basis of the same *erythreo–threo* retention order and of the similar behaviour when Soczewiński's method of dilution was applied.

THEORETICAL

The basic equation in the dilution method of Soczewiński and collaborators [11–24] is the following:

$$R_M \left[= \log\left(\frac{1}{\xi R_F} - 1\right)\right] = \text{const} - n \log X_S \qquad (1)$$

where ξ is a constant depending on the chromatographic conditions and X_s is the mole fraction of the more polar solvent in a binary solvent system. The parameter n is the number of solvent molecules displaced by a solute molecule from the adsorbent surface and thus corresponds to the number of the adsorbing groups; this is widely established in the aromatic series. According to Snyder's model[4–10]*, the parameter n is given by the ratio of the areas occupied at the surface of the absorbent by the solute molecule (A_s) and the polar solvent molecule (n_b)[13,23]:

$$n = \frac{A_s}{n_b} \qquad (2)$$

In the previous paper[3] linear R_M *versus* log X_s plots were established for diastereomeric aminoesters of type 1 and related cyclic compounds; the value of the slope, n, was related to the number of the adsorbing groups.

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* For a comparison of the adsorption models elaborated by Snyder and by Soczewiński see ref. 8.

EXPERIMENTAL

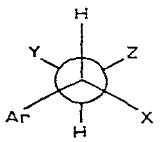
Silica gel DG (Riedel-de Haën, Hannover, G.F.R.) was used for TLC as previously[1–3]. Coating of the plates, application of the samples and visualization of the zones was performed as indicated in ref. 1. Layers 0.5 mm thick were used. No preliminary saturation of the tank with vapours of the solvent system was carried out. The solvent systems used were: A, hexane–ethyl acetate (2:1); B, benzene–diethyl ether–ethanol (5:5:1); C, benzene–methanol–methyl cellusolve (5:1:1); D, benzene–diethyl ether (1:1).

TLC investigations by Soczewiński's method were performed as previously[3].

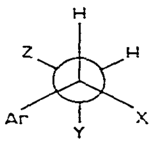
The preparations of the diastereomeric carbazole compounds studied and the assignment of their relative configurations are described in ref. 25.

RESULTS AND DISCUSSION

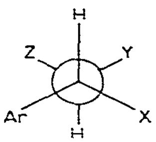
TLC separations of the diastereomeric pairs studied are indicated in Table I. Intramolecular hydrogen bonds $OH \cdots O{=}COC_2H_5$ are established in the hydroxyesters 1–4 (to a greater extent in the *threo*-isomers). $OH \cdots O{=}CNHNH_2$ bonds in the hydroxyhydrazides 5–8, and $OH \cdots NH_2$ bonds in the aminoalcohols 9–14 are assumed[25]. The conformations preferred are *erythro*-A′ and *threo*-B in $CDCl_3$ owing to the intramolecular hydrogen bonds between the synclinal OH and Y; in dimethyl sulphoxide, *erythro*-A is preferred because intermolecular hydrogen bonds with the solvent eliminate the role of the intramolecular ones[25]. Hence, the diastereomers of types 1 and 2 have one and the same preferred conformation. This means that for the two types of compound there is no significant difference in the conformational interactions and thus in the effective volumes of the corresponding groups.



erythro-A



erythro-A′



threo-B

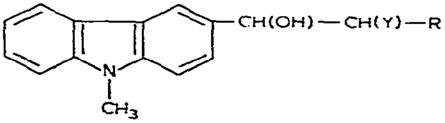
Z=Ar′ or R

The data of Table I show the relationship $R_F(erythro) > R_F(threo)$ for the acyclic compounds 1–16 of type 2, as in the case of the diastereomers of type 1. The same relationship has been reported recently for TLC separation on silica gel of the diastereomeric *l*-ephedrine and *d*-pseudoephedrine[26]. Within the non-ionic compounds 1–14 this relationship should be attributed as in ref. 2 to the greater adsorptivity and the smaller effective volumes of the groups OH and Y relative to those of Ar and R (see Table 10-2 of ref. 5 and the tabulated data of refs. 27 and 28). Consequently, the relationship $R_F(erythro) > R_F(threo)$ established in the diastereomers of types 1 and 2 is due to the same reason, and these two types of compound can be represented by the combined formula 3.

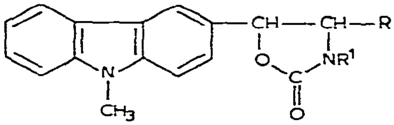
Soczewiński's method[11–24] was applied to the diastereomeric hydroxyesters 1–4 of type 2 and 23–26 of type 1 in order to check whether the adsorptions of the two types of compounds are similar. The substances are not bases but the use of the

TABLE I

R_F VALUES OF THE DIASTEREOMERIC COMPOUNDS STUDIED



Chromatogram no.	*Y*	*R*	*Configuration*	*Compound no.*	R_F	*Solvent system*
1	$COOC_2H_5$	CH_3	*threo*	1	0.42	A
			erythro	2	0.50	
2	$COOC_2H_5$	C_2H_5	*threo*	3	0.47	A
			erythro	4	0.55	
3	$CONHNH_2$	CH_3	*threo*	5	0.13	B
			erythro	6	0.26	
4	$CONHNH_2$	C_2H_5	*threo*	7	0.18	B
			erythro	8	0.44	
5	NH_2	CH_3	*threo*	9	0.10	C*
			erythro	10	0.18	
6	NH_2	C_2H_5	*threo*	11	0.13	C*
			erythro	12	0.25	
7	$NHCH_3$	CH_3	*threo*	13	0.11	C*
			erythro	14	0.23	
8	COOH	CH_3	*threo*	15	0.13	B
			erythro	16	0.30	



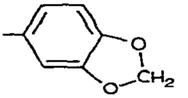
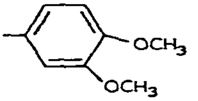
Chromatogram no.	*R*	*R*¹	*Configuration*	*Compound no.*	R_F	*Solvent system*
9	CH_3	H	*trans*	17	0.36	D**
			cis	18	0.32	
10	C_2H_5	H	*trans*	19	0.42	D**
			cis	20	0.38	
11	CH_3	CH_3	*trans*	21	0.44	D***
			cis	22	0.38	

* Second front with $R_F = 0.78$.

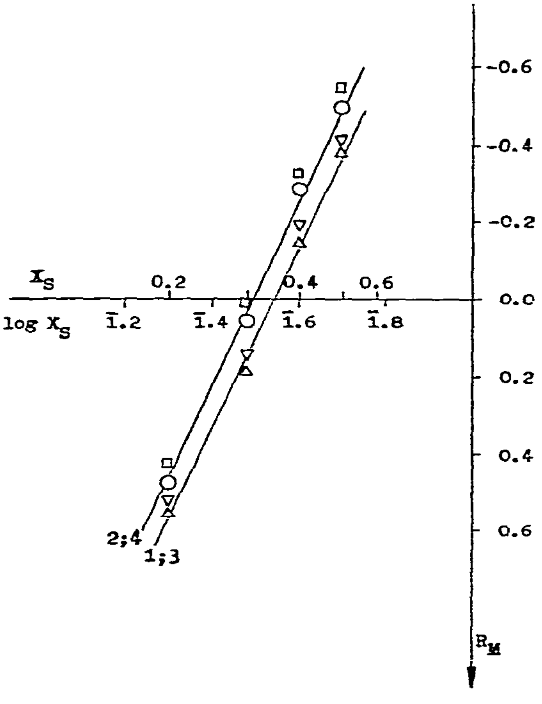
** Developing distance, 18 cm and developed twice.

*** Developing distance, 18 cm.

method is reasonable (see ref. 14). The value $\xi = 1.1$ was used in R_F–R_M conversions, as usually in the original method.

type 1	*Ar*	*Ar'*	*X*	*Y*	*Configuration*	*Compound No.*
	Phenyl		OH	$COOCH_3$	*threo* *erythro*	23 24
	Phenyl		OH	$COOCH_3$	*threo* *erythro*	25 26

(The preparations of compounds 23–26 are given in refs. 29 and 30.) For these compounds R_F(*erythro*) > R_F(*threo*) is established[1,2]. Plots of the R_M values of 1–4 and 23–26 *versus* log of the mole fraction of the polar solvent ethyl acetate (X_s) diluted by cyclohexane are shown in Figs. 1 and 2. The plots are linear as in ref. 3. The absolute values of the slopes, *n*, of about two units are consistent with two-point adsorption,



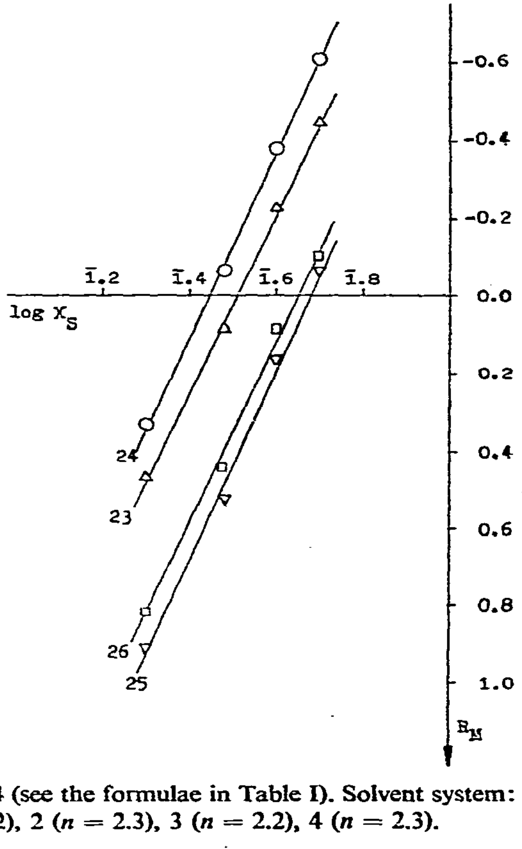
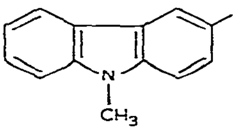


Fig. 1. R_M versus log X_S plots of the compounds 1–4 (see the formulae in Table I). Solvent system: cyclohexane–ethyl acetate (polar solvent), 1 ($n = 2.2$), 2 ($n = 2.3$), 3 ($n = 2.2$), 4 ($n = 2.3$).

Fig. 2. R_M versus log X_S plots of the compounds 23–26 (see the formulae in the text). Solvent system: cyclohexane–ethyl acetate (polar solvent), 23 ($n = 2.2$), 24 ($n = 2.3$), 25 ($n = 2.4$), 26 ($n = 2.3$).

via the OH and $COOC_2H_5$ or $COOCH_3$ groups respectively, possessing the greatest free energy of adsorption. For the carbazole group  a lower free energy of adsorption is expected than that of $COOC_2H_5$ (*cf.* $Q^0_{Ar-CH=N-CH_3} = 4.46$ on alumina and $Q^0_{COOC_2H_5} = Q^0_{COOCH_3} + Q^0_{CH_2} = 5.22$ on silica gel, data of Table 10-2 in ref. 5). Thus, the carbazole group does not participate directly in the adsorption of 1–4.

Referring to eqn. 2, the areas under adsorption, A_s, of compounds 1–4 and 23–26 are approximately equal because n_b has a definite value (see Table 8-1 in ref. 5). Then, the position of OH and of the ester group under adsorption should be nearly the same since A_s is given by the sum of the areas of the adsorbing groups (ref. 5, p. 199). Thus, *erythro*-A′ and *threo*-B are the adsorbing conformations having OH and $COOC_2H_5$ or $COOCH_3$ in close proximity (*cf.* refs. 2 and 3).

The compounds 1–4 possess intramolecular hydrogen bonds between OH and $COOC_2H_5$, whereas in 23–26 such bonding is negligible[2]. The fact that all these compounds show $n \approx 2$ is the first experimental support for cleavage of intramolecular hydrogen bonds under the action of the adsorbent as assumed for $OH\cdots OH$ bonds and $OH\cdots NH_2$ bonds[1,2,31]. Cleavage of $OH\cdots O{=}CNHNH_2$ bonds in the hydroxyhydrazides 5–8 should be also assumed, otherwise R_F(*threo*) > R_F(*erythro*) is to be expected.

The relationship R_F(*trans*) > R_F(*cis*) within the oxazolidones 17–22 (see Table I) is probably due to adsorption of the O-CO-N fragment of the oxazolidone ring with Ar and R apart from the adsorbent surface within the *cis*-isomers. One of these two groups (probably R) should be directed towards the adsorbent surface, thus hindering such an adsorption of the *trans*-isomers. For this pattern of adsorption there is no difference within the diastereomeric pair in the localization and in the solute area under adsorption (*cf.* refs. 2 and 31). The electronic and the secondary solvent effects can be neglected[2,31].

CONCLUSIONS

The present and previous investigations indicate that the relationship R_F (*erythro*) > R_F(*threo*) on silica gel can be used for the assignment of the relative configurations of other non-ionic diastereomers of type 3 which do not possess intramolecular hydrogen bonds or which have such bonds of the types $OH\cdots OH$, $OH\cdots NH_2$, $OH\cdots O{=}COC_2H_5$ or $OH\cdots O{=}CNHNH_2$. The criteria given in ref. 2 should be borne in mind. Namely, on the basis of Tables of refs. 5, 27 and 28 and of the types of the group already investigated, it should be ascertained that the groups X and Y are adsorbed more strongly, and have smaller effective volumes, than the groups Ar and Z. The *erythro–threo* retention sequence must be established on silica gel DG or on an adsorbent with the same activity when the spots of the two isomers are above the starting line, as in all the cases studied.

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