

CHROM. 9516

## CHROMATOGRAPHIC BEHAVIOUR OF DIASTEREOMERS

### III. THIN-LAYER CHROMATOGRAPHIC BEHAVIOUR OF DIASTEREOMERIC 4-SUBSTITUTED 6,7-DIALKOXY-3-ARYL-TETRAHYDROISOQUINOLINES AND -ISOCROMANS

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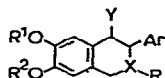
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(First received October 14th, 1975; revised manuscript received July 6th, 1976)

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#### SUMMARY

Twenty three pairs of diastereomeric tetrahydroisoquinolines (X = N) and isochromans (X = O) of the type



where Y = CO<sub>2</sub>Me or CH<sub>2</sub>OH have been separated by thin-layer chromatography on silica gel using solvent systems with and without secondary solvent effects. For the N-alkyltetrahydroisoquinolines and for isochromans having Y = CO<sub>2</sub>Me, the relation  $R_{F(trans)} > R_{F(cis)}$  has been established, whereas for the remaining compounds  $R_{F(cis)} > R_{F(trans)}$ . In terms of Snyder's theory, this difference in behaviour can be attributed to two-point adsorption in the first case and to one-point adsorption in the second case, via definite conformations.

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#### INTRODUCTION

Data are available on the thin-layer chromatographic (TLC) separation on silica gel or alumina of diastereomeric cyclic compounds possessing two<sup>1-13</sup> or more<sup>14-26</sup> asymmetric carbon atoms. On the basis of general considerations, the separation orders of the diastereomers is attributed to differences in the steric hindrances\* of the polar groups<sup>1,13,15,17,18,21-26</sup> or to the different possibilities for interaction with the solvent<sup>5,14,16</sup>. Feltkamp and Koch (see ref. 1 and p. 312 of ref. 30), as well as Pridgen<sup>11</sup>, consider that TLC can be useful in the assignment of the relative configurations of some diastereomeric cyclic compounds.

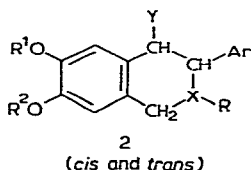
In our previous papers of this series<sup>31,32</sup>, a correlation of  $R_{F(erythro)} > R_{F(threo)}$

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\* Steric hindrance has often been assumed to be an important factor in the column chromatographic behaviour of axially and equatorially substituted compounds (see refs. 27-30).

was reported for 50 of the 52 diastereomeric pairs investigated of the type  $\text{Ar}-\text{CH}(\text{X})-\text{CH}(\text{Y})-\text{Ar}'$  (type 1), where X and Y are  $\text{NH}_2$ , OH,  $\text{CO}_2\text{H}$  or their derivatives. On the basis of semiempirical qualitative analysis by means of Snyder's theory, it was possible to predict the scope and limitation of the above correlation for diastereomers of the same type<sup>32</sup>. This is of importance in the assignment of the relative configurations of diastereomeric 1,2-disubstituted 1,2-diarylethanes determined by means of TLC on silica gel.

In the present paper we report TLC separations on silica gel of 23 pairs of diastereomeric cyclic compounds of the type 2 having known relative configurations. These compounds are related to the acyclic diastereomers of type 1. The relative retentions of the cyclic diastereomers are discussed in terms of Snyder's theory<sup>30,33-37</sup>, bearing in mind data on the conformations preferred in solution.



X = N (tetrahydroisoquinolines) or O (isochromans)  
 Y =  $\text{CO}_2\text{Me}$  or  $\text{CH}_2\text{OH}$   
 R = H, Me, Et, Pr-n,  $\text{PhCH}_2$  or a lone electron pair (the latter case applies to the isochromans)

## EXPERIMENTAL

Silica gel DG (Riedel de Haen, Hannover, G.F.R.) was used for TLC as previously<sup>31,32</sup>. Coating of the plates, application of the samples and visualization of the zones was performed as indicated in ref. 32. The solvent systems used were: A = benzene-diethyl ether (1:1),  $\epsilon^0 \sim 0.34$ ; B = heptane-benzene-diethyl ether (2:5:5),  $\epsilon^0 < 0.34$ ; C = benzene-diethyl ether-acetone (2:2:1),  $\epsilon^0 > 0.34$ ; D = heptane-diethyl ether (1:1),  $\epsilon^0 \sim 0.34$ ; E = hexane-benzene-diethyl ether-acetic anhydride (20:5:5:1); F = diethyl ether-methanol (19:1),  $\epsilon^0 > 0.38$ ; G = diethyl ether,  $\epsilon^0 = 0.38$ ; H = diethyl ether-methanol (17:3),  $\epsilon^0 > 0.38$ ; I = hexane-acetone (4:1),  $\epsilon^0 \sim 0.39$ ; J = heptane-diethyl ether-methanol-ethanol-ammonia (25:25:1:1:1),  $\epsilon^0 > 0.34$ ; K = hexane-benzene-acetone (2:2:1),  $\epsilon^0 > 0.34$ ; L = hexane-diethyl ether (1:1),  $\epsilon^0 \sim 0.34$ ; M = benzene-methanol (10:1),  $\epsilon^0 > 0.39$ ; N = methylene chloride,  $\epsilon^0 = 0.32$ ; O = benzene,  $\epsilon^0 = 0.25$ . The relative solvent strength<sup>30</sup>,  $\epsilon^0$ , is a parameter characterizing the eluent strength of the solvent relative to that of *n*-pentane. The above approximate values of  $\epsilon^0$  were estimated using the data of Tables III-4 and 8-2 of ref. 30.

## THEORY

Some aspects of Snyder's theory of linear adsorption chromatography<sup>30,33-37</sup> will now be given.

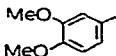
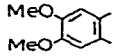

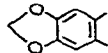
It is clear from the previous paper<sup>32</sup> (see Theory section) that the TLC separation order of non-ionic diastereomers (in the case of cyclic compounds,  $R'_{M(\text{trans})} - R'_{M(\text{cis})} = \Delta R'_M$ ) depends on the four terms of eqn. 3. These terms measure the differences within the diastereomeric pair of the electronic and steric effects, of the localization, of the solute area adsorbed and of the secondary solvent effects. The concept of localization concerns the maximum adsorption of a given solute group on an

(see Fig. 1 in ref. 32). The secondary solvent effects refer to specific interactions between the solvent and solute or adsorbent. The differences in the electronic and steric effects and in the localization determine the relative adsorptivity of the diastereomers.

A measure of the adsorption affinity of a given group *i* of the solute molecule is its free energy of adsorption ( $Q_i^0$ ) relative to that of *n*-pentane having a solvent strength  $\epsilon^0 = 0$ . The higher the  $Q_i^0$  value, the greater is the adsorption of the group *i*. With a solvent having  $\epsilon^0 > 0$  (i.e., all of the organic solvents except *n*-pentane), the adsorption of the group *i* is possible only if the energy gained on adsorption exceeds the energy lost on displacement of the adsorbed solvent molecules from the adsorbent surface, i.e., if  $Q_i^0 - \epsilon^0 a_i > 0$  (see Snyder in ref. 38;  $a_i$  is the effective area of the group *i* under adsorption). The left-hand term of this expression is denoted as "nett free energy of adsorption". It becomes zero for solvents having solvent strengths ( $\epsilon^0$ ) equal to  $Q_i^0/a_i$ , the so called critical solvent strength ( $\epsilon_c$ ). The group *i* does not participate in the adsorption of the molecule when the solvent system used has  $\epsilon^0 \geq \epsilon_c$ . The values of  $Q_i^0$ ,  $\epsilon_c$  and  $Q_i^0 - \epsilon^0 a_i$  for the groups of interest are given in Table I. They refer to the case when the group *i* is localized, electronic and steric interactions of the groups within the solute molecules being absent.

TABLE I

VALUES OF  $Q_i^0$ ,  $\epsilon_c$  AND ( $Q_i^0 - \epsilon^0 a_i$ ) FOR THE GROUPS X, Y, Ar AND  ACCORDING TO DATA OF SNYDER<sup>30</sup> (TABLES 8-4 AND 10-2 UNLESS STATED OTHERWISE)

Group <i>i</i>	$Q_i^0$	$a_i$	$\epsilon_c \left( = \frac{Q_i^0}{a_i} \right)$	Netto relative free energy of adsorption of the group <i>i</i> when $\epsilon^0 = 0.32$ , i.e., ( $Q_i^0 - 0.32a_i$ )
R-NH <sub>2</sub>	8.00	8.7	0.92	5.22
R-NHMe	—	—	—	—*
R-NMe <sub>2</sub>	5.8	10.5	0.55	2.4
R-OH	5.60	8.5	0.66	2.88
R-CO <sub>2</sub> Me	5.27	10.5	0.50	1.91
R-OMe	3.63	9.0	0.40	0.75
 or 	5.16**	15.2***	0.34	0.30
 or 	<5.16 <sup>§</sup>	<15.2 <sup>§§</sup>	~0.34	<0.30
Ph	1.50	6.0	0.25	-0.42

\* The values for a secondary amine can be approximated to the arithmetical mean of the corresponding values of the primary and tertiary amines.

\*\* On the basis of eqn. 10-1 and the data in Table 10-2 for Ph (1.50) and Ar-OMe (1.83):  $1.50 + 2 \cdot 1.83 = 5.16$ .

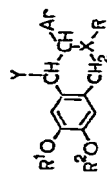
\*\*\* On the basis of eqn. 8-7 and the data in Table 8-4 for Ph (6.0) and Ar-OMe (4.60):  $6 + 2 \cdot 4.6 = 15.2$ .

§ Comparison of the  $R_F$  values of chromatograms 1 and 2, 10 and 11, 20 and 21, 22 and 23, 30 and 31 and 32 and 34 of Tables II and III, indicates lower adsorption of compounds of the type

2 having  compared to  groups, and hence  $Q_i^0$  for the former group is probably less than 5.16.

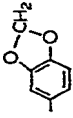
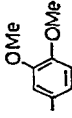
§§  $a_i$  is expected to be less than  $a_i$  of  $(\text{MeO})_2\text{C}_6\text{H}_3$ .

TABLE II

R<sub>F</sub> VALUES OF THE DIASTEREOMERIC PAIRS OF

Chromatogram No.	XR	Ar	Y	R <sup>1</sup>	R <sup>2</sup>	Configuration	Ref.	Compound No.	R <sub>F</sub>	Solvent system
<i>N</i> -Alkyltetrahydroisoquinolines										
1	NMe	Ph	CO <sub>2</sub> Me	CH <sub>2</sub>	CH <sub>2</sub>	<i>cis</i> <i>trans</i>	39	1 2	0.62 0.77	A
2	NMe	Ph	CO <sub>2</sub> Me	Me	Me	<i>cis</i> <i>trans</i>	39	3 4	0.26 0.36	A
3	NMe		CO <sub>2</sub> Me	CH <sub>2</sub>	CH <sub>2</sub>	<i>cis</i> <i>trans</i>	40	5 6	0.26 0.43	B
4								5 6	0.54 0.67	A
5	NMe		CO <sub>2</sub> Me	Me	Me	<i>cis</i> <i>trans</i>	41 39	7 8	0.59 0.68	C
6	NMe		CO <sub>2</sub> Me	Me	Me	<i>cis</i> <i>trans</i>	41 42	9 10	0.44 0.51	C
7	NEt	Ph	CO <sub>2</sub> Me	Me	Me	<i>cis</i> <i>trans</i>	43	11 12	0.47 0.58	A
8	NPr- <i>n</i>	Ph	CO <sub>2</sub> Me	CH <sub>2</sub>	CH <sub>2</sub>	<i>cis</i> <i>trans</i>	43	13 14	0.48 0.55	D
9	NPr- <i>n</i>	Ph	CO <sub>2</sub> Me	Me	Me	<i>cis</i> <i>trans</i>	43	15 16	0.64 0.71	A
10	NCH <sub>2</sub> Ph	Ph	CO <sub>2</sub> Me	CH <sub>2</sub>	CH <sub>2</sub>	<i>cis</i> <i>trans</i>	43	17 18	0.50 0.65	E*
11	NCH <sub>2</sub> Ph	Ph	CO <sub>2</sub> Me	Me	Me	<i>cis</i> <i>trans</i>	43	19 20	0.16 0.22	E*
12	NMe	Ph	CH <sub>2</sub> OH	Me	Me	<i>cis</i> <i>trans</i>	39	21** 22	0.31 0.44	F
13	NMe		CH <sub>2</sub> OH	CH <sub>2</sub>	CH <sub>2</sub>	<i>cis</i> <i>trans</i>		23** 24**	0.40 0.58	G
14	NMe		CH <sub>2</sub> OH	Me	Me	<i>cis</i> <i>trans</i>	39	25** 26	0.44 0.61	H

*N*-Unsubstituted tetrahydroisoquinolines

15	NH	Ph	CO <sub>2</sub> Me	CH <sub>2</sub>	<i>cis</i> <i>trans</i>	44	27	0.51 0.45	I*
16	NH	Ph	CO <sub>2</sub> Me	Me	<i>cis</i> <i>trans</i>	44	29 30	0.39 0.35	J***
17	NH		CO <sub>2</sub> Me	Me	<i>cis</i> <i>trans</i>	43 44	31 32	0.36 0.31	K*
18							31 32	0.33 0.29	J**
19	NH		CO <sub>2</sub> Me	Me	<i>cis</i> <i>trans</i>	43 44	33 34	0.31 0.27	K*
20	NH	Ph	CH <sub>2</sub> OH	CH <sub>2</sub>	<i>cis</i> <i>trans</i>	44	35 36	0.76 0.65	H
21	NH	Ph	CH <sub>2</sub> OH	Me	<i>cis</i> <i>trans</i>	44	37 38	0.52 0.34	H
<i>Isochromans</i>									
22	O	Ph	CO <sub>2</sub> Me	CH <sub>2</sub>	<i>cis</i> <i>trans</i>	45	39 40	0.60 0.67	L
23	O	Ph	CO <sub>2</sub> Me	Me	<i>cis</i> <i>trans</i>	46	41 42	0.26 0.34	L
24	O	Ph	CH <sub>2</sub> OH	CH <sub>2</sub>	<i>cis</i> <i>trans</i>	46	43 44	0.28 0.20	I
25							43 44	0.44 0.36	M
26	O	Ph	CH <sub>2</sub> OH	Me	<i>cis</i> <i>trans</i>	46	44 45 46	0.44 0.29 0.21	I*

\* Developed twice.

\*\* Compounds 21 and 23-25 were obtained by lithium aluminium hydride reduction of 3 and 5-7 respectively. The IR spectra of 21, 23 and 24 in 10<sup>-3</sup> M carbon tetrachloride solutions indicate the presence of intramolecularly bonded hydroxyl groups forming hydrogen bonds of the types OH...N (stronger) and OH...Ar (weaker). The bonds of the OH...N type in 21 are more populated than in 22 (ref. 39).

\*\*\* Developed three times

## RESULTS AND DISCUSSION

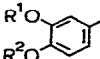
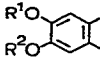
The main results of the TLC separations of the diastereomeric pairs of the type 2 are given in Table II. The relative configurations of the compounds are known (see the references). It is clear that the 23 diastereomeric pairs can be divided into two groups with respect to their relative TLC mobility, namely group a having  $R_{F(trans)} > R_{F(cis)}$  and which includes all of the N-alkyltetrahydroisoquinolines (1–26) and the isochroman esters (39–42), and group b having  $R_{F(cis)} > R_{F(trans)}$  and which comprises the N-unsubstituted tetrahydroisoquinolines (27–38) and the isochroman alcohols (43–46).

Some of the compounds studied possess intramolecular hydrogen bonds between the groups X and Y. The tetrahydroisoquinoline alcohols 21–26 and 35–38 have strong OH...N bonds, and the isochroman alcohols 43–46 have relatively weaker OH...O bonds and the extent of these two types of bonds is greater in the *cis*-isomers. It is expected that the distance between X and Y in the above bonds does not differ significantly from the intramolecular OH...N and OH...OH hydrogen bond lengths of the parent compounds of the type 1. Thus we may assume, as previously<sup>31,32</sup>, that the energy required to break the intramolecular hydrogen bonds in the cyclic compounds is compensated for by the energy gained under adsorption. This enables the TLC behaviours of the compounds with and without intramolecular hydrogen bonds to be interpreted together.

The data in Table II were obtained by use of solvent systems containing diethyl ether, acetone, methanol, ethanol, acetic anhydride or ammonia which exhibit secondary solvent effects. Several of the diastereomers were also studied in benzene and methylene chloride which are, to a first approximation, free from secondary solvent effects (*cf.* p. 220 of ref. 30) and these results are given in Table III.

The *cis-trans* retention sequence of compounds of the groups a and b was independent of the presence or absence of secondary solvent effects (*cf.* the chromatograms in Tables II and III). Hence, the secondary solvent effects may be neglected. Thus, as in the previous study<sup>32</sup>, the relative adsorptivity of the diastereomers determines their separation order. The question arises as to which groups are adsorbed. An approximate solution to this problem can be obtained on the basis of the solvent strengths ( $\epsilon^0$ ) of the systems used and on the data in Table I.

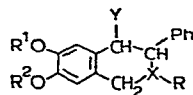
Almost all of the solvent systems in Tables II and III have a relative solvent strength ( $\epsilon^0$ ) near or greater than 0.34, which means that the critical solvent strength

( $\epsilon_c$ ) of the groups Ph,  and  may be attained or even exceeded

(see Experimental section and Table I). Hence, these groups are probably not adsorbed or their participation in the adsorption of the molecules is insignificant. Only groups X and Y which have higher values of  $\epsilon_c$  can be adsorbed. However, the extents of participation of X and Y are dependent on their nett free energies of adsorption and on their critical solvent strengths and will not be the same.

Two-point adsorption is expected for the isochroman esters 39–42. Here the difference in the nett free energy of adsorption of the groups X and Y is approximately one relative unit (1.91–0.75) when methylene chloride ( $\epsilon^0 = 0.32$ ) is used. In the case of the isochroman alcohols (43–44), this difference is approximately two

TABLE III

 $R_F$  VALUES OF SEVERAL OF THE DIASTEREOMERIC PAIRS OF

USING METHYLENE CHLORIDE (SOLVENT SYSTEM N) OR WITH BENZENE (SOLVENT SYSTEM O) WHICH ARE PROBABLY FREE FROM SECONDARY SOLVENT EFFECTS

Chromatogram No.	XR	Y	R <sup>1</sup>	R <sup>2</sup>	Configuration	Compound No.	R <sub>F</sub>	Solvent system
<i>N-Alkyltetrahydroisoquinolines</i>								
27	NEt	CO <sub>2</sub> Me	Me	Me	<i>cis</i>	11	0.12	N*
					<i>trans</i>	12	0.18	
28	NPr- <i>n</i>	CO <sub>2</sub> Me		CH <sub>2</sub>	<i>cis</i>	13	0.08	N**
					<i>trans</i>	14	0.16	
29	NPr- <i>n</i>	CO <sub>2</sub> Me	Me	Me	<i>cis</i>	15	0.29	N*
					<i>trans</i>	16	0.38	
30	NCH <sub>2</sub> Ph	CO <sub>2</sub> Me		CH <sub>2</sub>	<i>cis</i>	17	0.25	N
					<i>trans</i>	18	0.25	
31	NCH <sub>2</sub> Ph	CO <sub>2</sub> Me	Me	Me	<i>cis</i>	19	0.14	N
					<i>trans</i>	20	0.14	
<i>Isochromans</i>								
32	O	CO <sub>2</sub> Me		CH <sub>2</sub>	<i>cis</i>	39	0.35	N
					<i>trans</i>	40	0.52	
33						39	0.11	O
						40	0.19	
34	O	CO <sub>2</sub> Me	Me	Me	<i>cis</i>	41	0.06	N
					<i>trans</i>	42	0.13	
35	O	CH <sub>2</sub> OH		CH <sub>2</sub>	<i>cis</i>	43	0.22	N
					<i>trans</i>	44	0.09	

\* Developed five times.

\*\* Developed twice.

relative units (2.88–0.75), and here only the group Y having the higher nett free energy of adsorption is expected to be adsorbed. This conclusion is supported by the fact that  $\epsilon^0 \approx 0.34$  for the solvent systems used in chromatograms 22 and 23 of Table II for the isochroman esters, and  $\epsilon^0 \approx 0.39$  in chromatograms 24–26 for the isochroman alcohols. With these solvents the critical solvent strength of the group Y (0.50 and 0.66, respectively) cannot be attained and this group is expected to be adsorbed in the two types of isochromans. However, the  $\epsilon_c$  value (0.40) of the group  $(-\text{CH})-\text{O}-\text{CH}_2-$  is approximately the same as the above  $\epsilon^0$  value in the case of the isochroman alcohols, and the group X in the latter compounds is not expected to be adsorbed.

Two-point adsorption is expected for all of the N-alkyltetrahydroisoquinolines having Y = CO<sub>2</sub>Me or Y = CH<sub>2</sub>OH. Here the difference in the nett free energy of adsorption of the groups X and Y is the same for the esters and alcohols and is less than one relative unit (2.4–1.91 for the esters, 2.88–2.4 for the alcohols). The expected significant increase in the nett free energy of adsorption of a secondary amine (see footnote\* of Table I) compared to a tertiary amine makes the one-point adsorption more probable with the tetrahydroisoquinolines which are not substituted at the nitrogen.

The above data suggest two-point adsorption with X and Y for the compounds

of group a, and one-point adsorption for the compounds of group b. The latter pattern of adsorption is expected to occur with X in the N-unsubstituted tetrahydroisoquinolines and with Y in the isochroman alcohols.

According to the Theory section, the relative adsorptivity of the diastereomers studied will depend on the steric effects and on the relative localization (the electronic effects can be ignored<sup>32</sup>). There is no difference in the relative localization of the diastereomers when adsorption occurs through the same number of groups. Thus only the steric effects need be considered, bearing in mind that, on the basis of NMR data<sup>39-46</sup>, *trans*-A and *cis*-C are the conformations preferred in solution for the compounds which do not possess intramolecular hydrogen bonds. The same conformations would be preferred for the compounds having intramolecular hydrogen bonds after cleavage of these bonds under adsorption. In the conformational scheme in Fig. 1 partial formulae are used. It can be assumed that for each pair of conformers the difference in their free energies is greater under TLC adsorption than in solution and that the equilibrium between the two forms is shifted towards the one conformer on the adsorbent.

Two-point adsorption of the compounds of type 2 will occur if the groups X and Y are localized simultaneously on a single strong adsorbent site. This so called site chelation (see p. 315 of ref. 30) requires the proximity of the two groups, which occurs in the preferred conformation C of the *cis*-isomers only when the lone electron pair of X and the group Y are in a *cis*-1,3-diaxial position. In the *trans*-series, site chelation can occur via conformation B. Due to the unfavourable axial position of

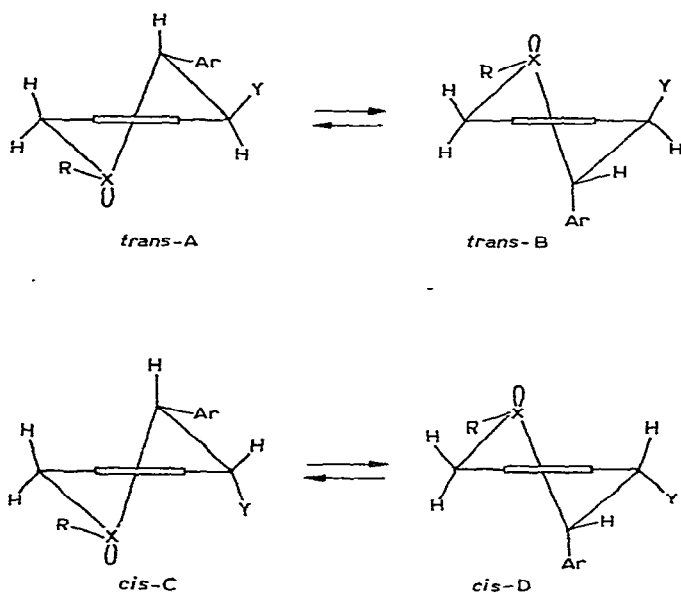


Fig. 1. Conformational equilibria in diastereomers of the type 2. Conformers A-D, having an equatorial lone electron pair and an axial group R, are also possible with the tetrahydroisoquinolines (where XR = NH) due to the flipping of the nitrogen. Such conformers are not expected with the N-alkyltetrahydroisoquinolines since they require the unfavourable axial position of the bulky group R.



the group Ar in conformation B, the *trans*-isomers are expected to have a lower adsorptivity and correspondingly higher  $R_F$  values than the *cis*-isomers. Hence, under two-point adsorption with the groups X and Y, the separation order of the diastereomers will be  $R_{F(trans)} > R_{F(cis)}$  as has been established for the compounds of group a.

One-point adsorption may occur through the lone electron pair of group X in an equatorial or axial position (the first possibility is more favourable) or through the group Y. The sequence of  $R_{F(cis)} > R_{F(trans)}$  is expected in all of the cases of one-point adsorption via the preferred conformations *trans*-A and *cis*-C, because in each case the adsorbed group in *trans*-A is less sterically hindered than in *cis*-C, bearing in mind that the effective volume of a lone electron pair and of a hydrogen atom is less than that of the group Y. One-point adsorption can also take place via the conformations *trans*-A and *cis*-D, where the adsorbed group is equally sterically hindered. For instance, the group Y is pseudo-equatorial in the latter conformations. However, the above separation sequence of the diastereomers will not alter since the conformation *cis*-D having an axial Ar group is less favourable than *cis*-C. Consequently the experimental correlation of  $R_{F(cis)} > R_{F(trans)}$  for the compounds of group b can be attributed to one-point adsorption of the group X or Y via the conformations indicated above.

## CONCLUSIONS

The use of TLC as a simple method for assigning the relative configurations of cyclic diastereomers of the type 2 is complicated compared to the case of the previously studied<sup>31,32</sup> parent acyclic compounds of the type 1. The *cis-trans* retention sequence depends on the number of the adsorbed groups and the conformational factors are more favourable in the *trans*-isomers under one-point adsorption and in the *cis*-isomers under two-point adsorption. The established correlations of  $R_{F(trans)} > R_{F(cis)}$  and  $R_{F(cis)} > R_{F(trans)}$  may be of practical importance if the adsorption of the groups X and Y can be reliably predicted for newly synthesized compounds of the type 2 without intramolecular hydrogen bonds or with bonds of the types OH...N or OH...O. In such cases, silica gel DG or an adsorbent with the same activity should be used, and the separation order must be established when the two isomers are above the start line as recommended in the previous paper<sup>32</sup>.

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