

THE THIN LAYER CHROMATOGRAPHIC BEHAVIOUR OF SOME *E seco* OXINDOLE ALKALOIDS, AND THEIR RELATIONSHIP WITH INDOLIZIDINE AND SOME SIMPLE OXINDOLES

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INTRODUCTION

TLC has been used to identify oxindole alkaloids isolated from species of *Mitragyna*^{1,2} and also to distinguish between A and B series of oxindole alkaloids³. The behaviour of some heteroyohimbine alkaloids of known stereochemistry on thin layers has been explained in terms of hydrogen bond formation between adsorbent hydroxyl groups and the nitrogen lone pair of electrons of the alkaloids⁴. This communication discusses the behaviour of some *E seco* oxindole alkaloids on silica gel and alumina layers and relates it to the presence of hydroxy and methoxy substituents and to configurational differences. Their behaviour is also discussed in the light of the behaviour of oxindole, hydroxy and methoxy substituted oxindoles and indolizidine.

METHODS

The details of plate preparation and development of the chromatograms has previously been described³. Indolizidine and the alkaloids were detected by means of Dragendorff's reagent whilst the oxindoles were detected by ferric chloride-perchloric acid (0.2 M FeCl₃ in 35 % HClO₄) spray reagent. The following solvent systems were used for alumina and silica gel layers:

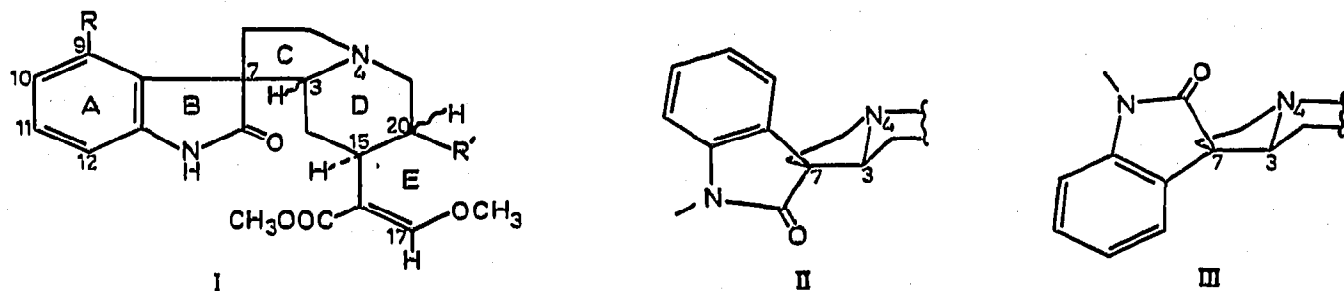
- (A)
1. Ether
 2. Benzene-ethyl acetate (7:2)
 3. Cyclohexane-chloroform (3:7)
 4. Chloroform
 5. Chloroform-acetone (5:4)
 6. Ether-ethanol (95:5)
 7. Chloroform-ethanol (95:5).
- (B)
1. Ether-diethylamine (9:1)
 2. Benzene-ethyl acetate-diethylamine (7:2:1)
 3. Cyclohexane-chloroform-diethylamine (3:7:1)
 4. Chloroform-diethylamine (9:1)
 5. Chloroform-acetone-diethylamine (5:4:1)
 6. Ether-ethanol-diethylamine (95:5:10)
 7. Chloroform-ethanol-diethylamine (95:5:10).

RESULTS

The results of the separations obtained are shown in Figs. 1-4. The hR_F values given are the average of six separate determinations.

DISCUSSION

The *E seco* oxindole alkaloids (I) have asymmetric centres at C(3), C(7) and C(20) [C(15)-H are all α] giving eight possible isomers^{5,6}.



The asymmetric centres at C(3) and C(20) give rise to four possible configurations classified as follows:

allo C(3)-H α ; C(20)-H α ; *epiallo* C(3)-H β ; C(20)-H α ;
normal C(3)-H α ; C(20)-H β ; *pseudo* C(3)-H β ; C(20)-H β

and these configurations may exist either as an A or a B series alkaloid by isomerisation about the spiro carbon C(7). A and B oxindole alkaloids are classified according to the position of the lactam carbonyl group relative to the plane of the C/D ring, the A series having the lactam carbonyl group below the plane of the C/D rings (II) and the B series having the lactam carbonyl group above the plane of the C/D rings (III)⁶.

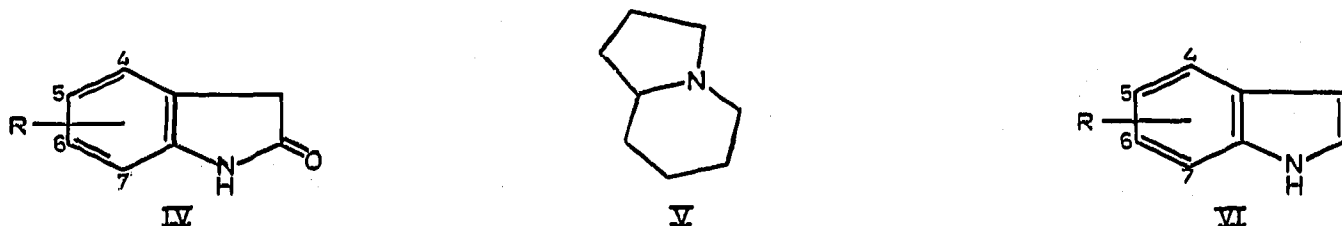
The configurations⁶ of the alkaloids examined are given in Table I.

TABLE I
CONFIGURATIONS OF THE ALKALOIDS EXAMINED

Alkaloid (III)	Type	Series	R	R'
(a) Isorhynchophylline	<i>normal</i>	A	-H	-CH ₂ CH ₃
(b) Rhynchophylline	<i>normal</i>	B	-H	-CH ₂ CH ₃
(c) Rotundifoline	<i>normal</i>	A	-OH	-CH ₂ CH ₃
(d) Isorotundifoline	<i>normal</i>	B	-OH	-CH ₂ CH ₃
(e) Rhynchociline	<i>normal</i>	A	-OCH ₃	-CH ₂ CH ₃
(f) Ciliaphylline	<i>normal</i>	B	-OCH ₃	-CH ₂ CH ₃
(g) Isospecioxine	<i>normal</i>	A	-OCH ₃	-CH=CH ₂
(h) Specioxine	<i>normal</i>	B	-OCH ₃	-CH=CH ₂
(i) Corynoxine	<i>allo</i>	A	-H	-CH ₂ CH ₃
(j) Corynoxine B	<i>allo</i>	B	-H	-CH ₂ CH ₃
(k) Mitragynine oxindole B	<i>allo</i>	B	-OCH ₃	-CH ₂ CH ₃
(l) Speciofoline	—	—	-OH	-CH ₂ CH ₃

Compared with the heteroyohimbine alkaloids, the oxindole alkaloids have, in addition to the N(4) lone pairs of electrons, a carbonyl group in ring B also with free electrons. Thus, in order to investigate the behaviour of the *E seco* oxindole alkaloids on thin

layers it was decided to examine, at the same time, the behaviour of oxindole (IV, R = H) which corresponds to the A and B rings of the oxindole alkaloids for the effect of the carbonyl group and of indolizidine (V) which corresponds to the C and D rings of the oxindole alkaloids for the effect of the tertiary N with a lone pair of electrons. Since substitution in ring A also affects the behaviour of these alkaloids, the 4-, 5-, 6- and 7-hydroxy-oxindoles (IV, R = OH) and the 4-, 5-, 6- and 7-methoxy-oxindoles (IV, R = OCH₃) which correspond to 9-, 10-, 11- and 12-hydroxy or methoxy substituted alkaloids were also examined.



There is a further important difference between the heteroyohimbine alkaloids and the oxindole alkaloids which needs to be considered. In the heteroyohimbine alkaloids ring C is a six-membered ring attached to ring B at two carbons so that rings A, B and C together form the general curve of the molecule. In the oxindole alkaloids ring C is a five-membered ring attached to ring B at the spiro carbon C(7) only so that rings A and B together are at right angles to the remainder of the molecule giving rise to two isomers (II and III).

The behaviour of indolizidine (Fig. 1)

Indolizidine is very strongly adsorbed on silica gel with all systems, but in the presence of diethylamine the adsorption is not very strong. On alumina it is adsorbed fairly strongly with system 2 but is less strongly adsorbed with the other solvent systems and with systems 6 and 7 is very weakly adsorbed. When diethylamine is included in the solvent system the adsorption is very weak.

The behaviour of simple oxindoles (Fig. 1)

(a) *Oxindole*. Except on silica gel with solvent systems having no diethylamine, oxindole is more strongly adsorbed than indolizidine. On alumina the adsorption is very strong with the non polar solvents and decreases with increase in polarity of the solvent. It is more strongly adsorbed on alumina than on silica gel in four of the seven systems and slightly more strongly adsorbed in six of the seven systems when diethylamine is present.

(b) *Hydroxy-oxindoles*. These compounds are all very strongly adsorbed on alumina both with and without diethylamine in the solvent system, the sequence in order of increasing hR_F value being 7-, 6-, 4-, 5-hydroxy-oxindole. They are also strongly adsorbed on silica gel when diethylamine is present, the adsorption of the compounds being in the same order. In the absence of diethylamine, adsorption is fairly strong in the first four systems but is not so strong on systems 5, 6 and 7, and furthermore, the order of decrease of adsorption in these systems changes to 5-, 6-, 7- and 4-hydroxy-oxindoles.

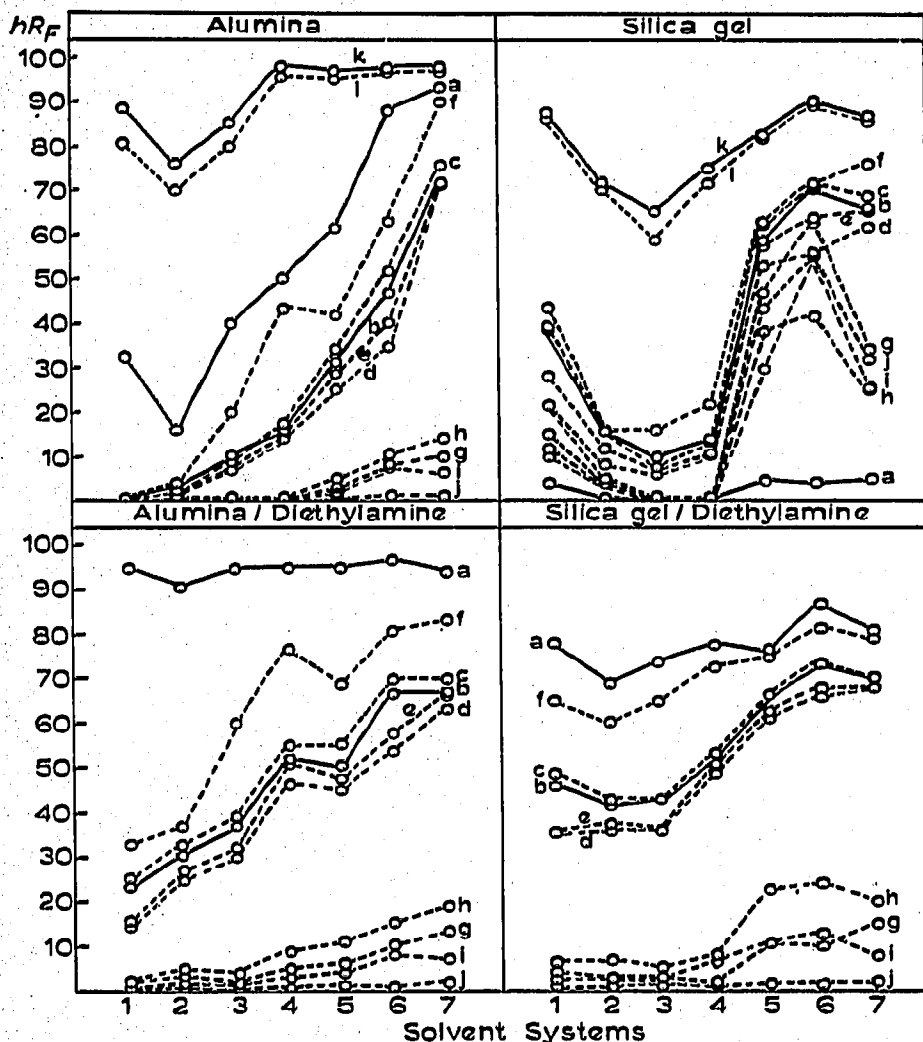


Fig. 1. hR_F values of Indolizidine (a), oxindole (b), 4-methoxy-oxindole (c), 5-methoxy-oxindole (d), 6-methoxy-oxindole (e), 7-methoxy-oxindole (f), 4-hydroxy-oxindole (g), 5-hydroxy-oxindole (h), 6-hydroxy-oxindole (i), 7-hydroxy-oxindole (j), indole (k), and 4-methoxy-indole (l).

(c) *Methoxy-oxindoles*. The behaviour of these compounds is similar to that of oxindole on both adsorbents and with all solvent systems. 7-Methoxy-oxindole is much less strongly adsorbed than oxindole, 4-methoxy-oxindole slightly less strongly adsorbed while 6- and 5-methoxy-oxindoles are slightly more strongly adsorbed than oxindole, in that order.

The behaviour of *E seco* oxindole alkaloids

(a) *Unsubstituted alkaloids*. The unsubstituted oxindole A alkaloids isorhynchophylline, (a, I, normal A, $R = H$, $R' = -CH_2CH_3$) and corynoxine (i, I, *allo* A, $R = H$, $R' = -CH_2CH_3$) have very similar hR_F values on alumina and silica gel layers with all solvent systems used (Fig. 2). The corresponding oxindole B alkaloids, rhynchophylline (b, I, normal B, $R = H$, $R' = -CH_2CH_3$) and corynoxine B (j, I, *allo* B, $R = H$, $R' = -CH_2CH_3$) are more strongly adsorbed but their hR_F values are different on some alumina and some silica gel systems in which rhynchophylline is

more strongly adsorbed than corynoxine B. The effect of diethylamine is to markedly increase the hR_F values of these four alkaloids on all systems used.

(b) *Hydroxy-substituted alkaloids*. The three alkaloids examined have hydroxy substituents at C(9). Rotundifoline (c, I, *normal* A, R = -OH, R' = -CH₂CH₃) has very similar hR_F values to isorhynchophylline, the corresponding unsubstituted alkaloid, and also to speciofoline (r, I, configuration unknown) (Fig. 3).

Isorotundifoline (d, I, *normal* B, R = -OH, R' = -CH₂CH₃) is less strongly adsorbed than the corresponding unsubstituted alkaloid rhynchophylline, the TLC behaviour of isorotundifoline resembling that of rhynchophylline rather than that of isorhynchophylline/rotundifoline. The hR_F values of these three alkaloids are increased by the addition of diethylamine to the solvent system.

(c) *Methoxy-substituted alkaloids*. The five alkaloids examined have methoxy substituents at C(9). Fig. 2 shows that mitragynine oxindole B (k, I, *allo* B, R = -OCH₃, R' = -CH₂CH₃) has similar hR_F values to the corresponding unsubstituted alkaloid, corynoxine B, being slightly more adsorbed than corynoxine B. Rhynchociline (e, I, *normal* A, R = -OCH₃, R' = -CH₂CH₃) and isospecionoxeine (g, I, *normal*

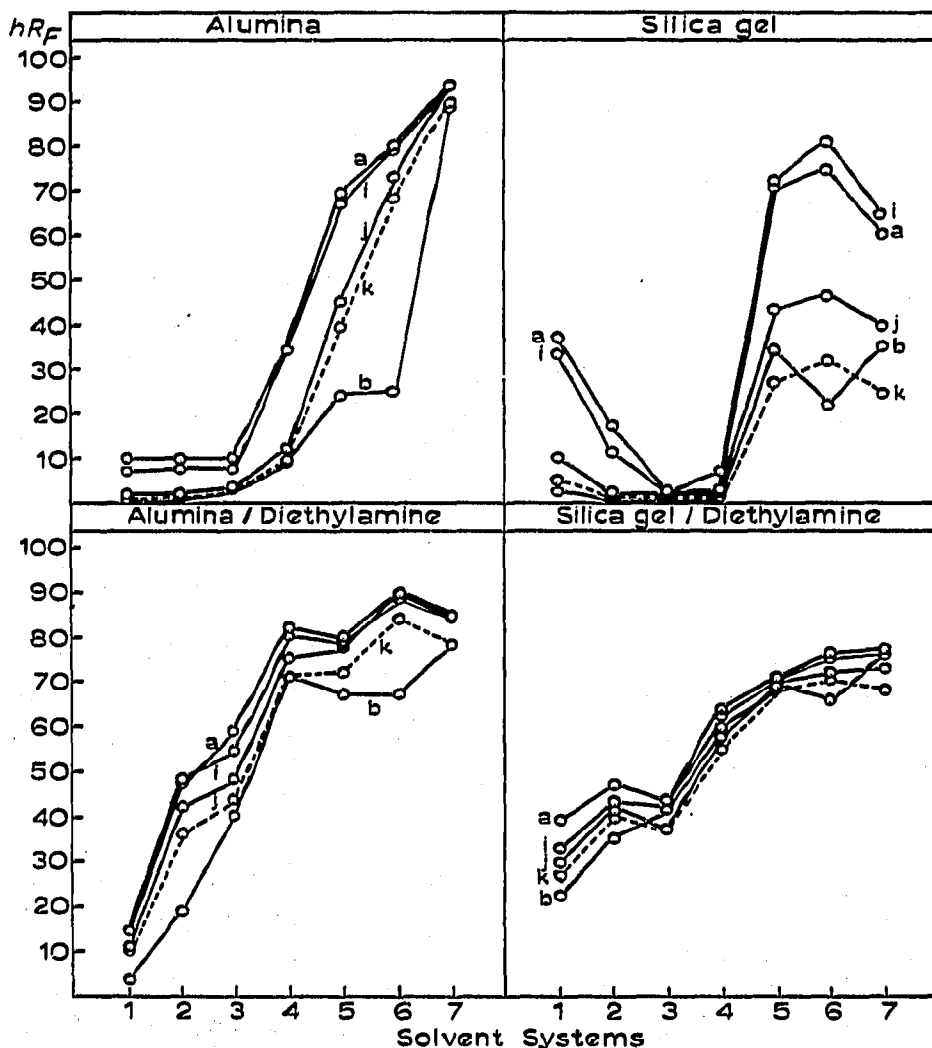


Fig. 2. hR_F values of isorhynchophylline (a), rhynchophylline (b), corynoxine (i), corynoxine B (j), and mitragynine oxindole B (k).

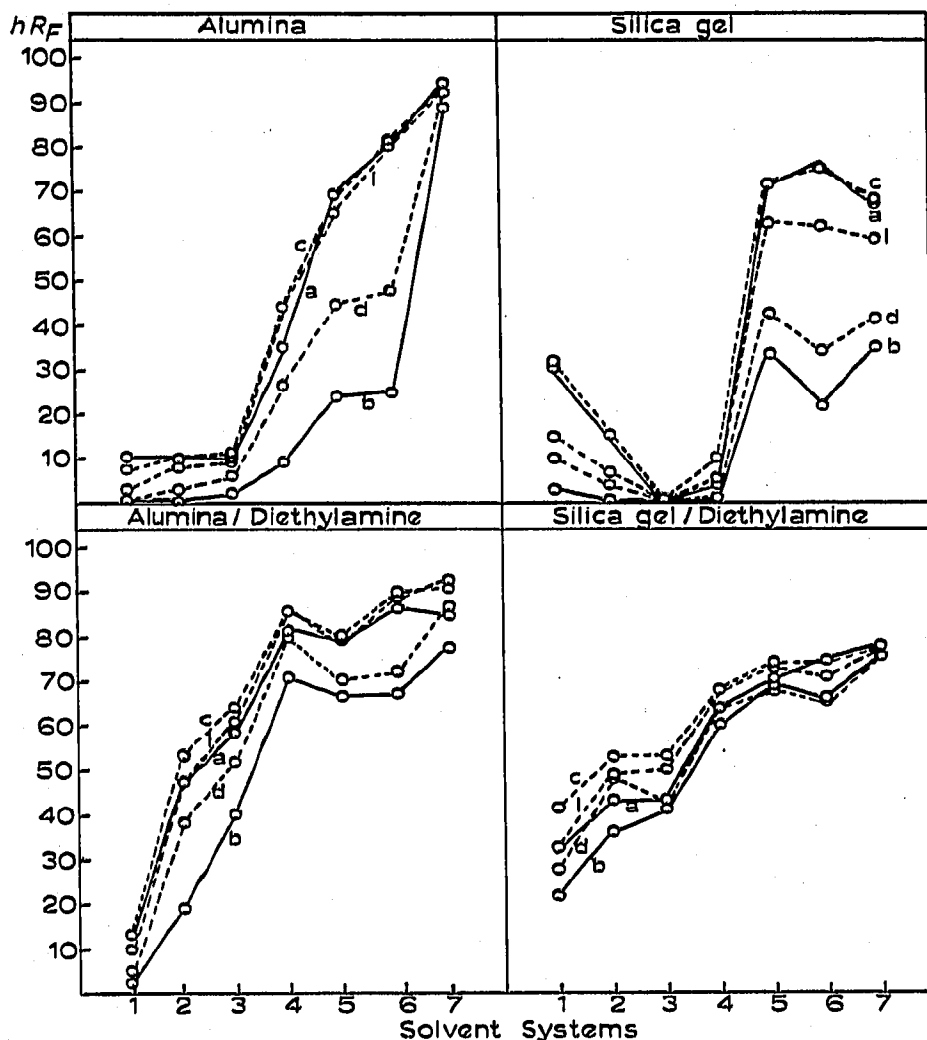


Fig. 3. hR_F values of isorhynchophylline (a), rhynchophylline (b), rotundifoline (c), isorotundifoline (d), and speciofoline (l).

A, $R = -OCH_3$, $R' = -CH=CH_2$) have similar behaviour patterns in all systems used (Fig. 4), the C(20) vinyl compound being slightly less adsorbed than the C(20) ethyl compound. Both these alkaloids have a similar behaviour to isorhynchophylline, the corresponding C(20) ethyl-unsubstituted alkaloid, on alumina with and without diethylamine present in the solvent and on silica gel systems with diethylamine in the solvent. However, on silica gel systems without diethylamine present in the solvent system, rhynchociline and isospecionoxeine are very strongly adsorbed, their behaviour patterns being similar to each other but quite different from that of isorhynchophylline. Ciliaphylline (f, I, *normal* B, $R = -OCH_3$, $R' = -CH_2CH_3$) and specionoxeine (h, I, *normal* B, $R = -OCH_3$, $R' = -CH=CH_2$) have similar behaviour patterns in all systems (Fig. 4), the C(20) vinyl compound being slightly less adsorbed than the corresponding C(20) ethyl compound. The behaviour pattern of both these alkaloids is very similar to that of the corresponding unsubstituted alkaloid, rhynchophylline, which is slightly less adsorbed.

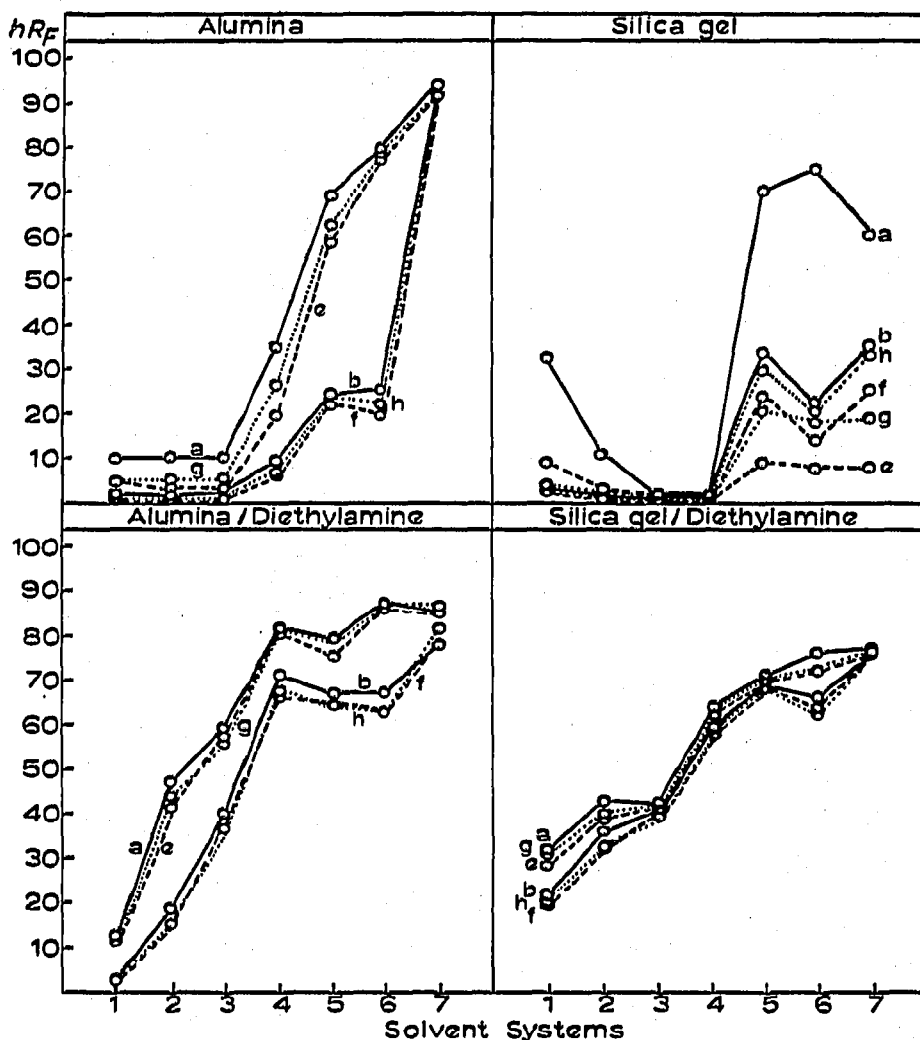


Fig. 4. hR_F values of isorhynchophylline (a), rhynchophylline (b), ciliaphylline (e), isospecionoxeine (g), and specionoxeine (h).

Adsorption of indolizidine

It is likely that indolizidine is adsorbed on silica gel by formation of hydrogen bonds between the nitrogen lone pair of electrons and the silanol hydroxyl groups. When diethylamine is present, this being a stronger base, it competes for the receptive sites on the silica gel thus partially reducing the formation of these bonds by indolizidine. On alumina the bonding is not so strong as on silica gel so that desorption by the more polar solvents results in higher hR_F values on this adsorbent with these solvent systems (Fig. 1).

Adsorption of simple oxindoles

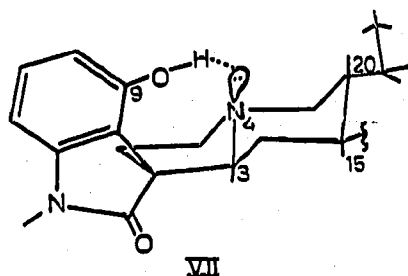
In the oxindole molecule the electrons associated with the imino group strengthen the carbonyl group which would tend to give fairly strong hydrogen bonding with the silanol hydroxy groups of alumina. The presence of hydroxy groups in the aromatic ring would considerably strengthen the binding power of the oxindole molecule since it would give two sites for hydrogen bonding. The 7-hydroxy-oxindole having its hydroxy group adjacent to the $-NH-C=O$ group would be most strongly

adsorbed, the relative adsorption of the others depending upon the distance of the $-OH$ group from the surface of the adsorbent. The presence of a methoxy group would add nothing to the strength of the carbonyl group, but depending upon its position in the aromatic ring might weaken or even prevent hydrogen bonding by keeping the carbonyl group away from the surface of the adsorbent. The importance of the carbonyl group is evidenced by the weak adsorption of indole (VI, $R = H$) and its substituted derivative (VI, $R = 4-OCH_3$) when compared with the corresponding oxindoles (Fig. 1).

Adsorption of the E seco oxindole alkaloid

If the nitrogen lone pair of electrons on $N(4)$ (I) in the *E seco* oxindole alkaloids are responsible for adsorption then it would be expected that these alkaloids would be more strongly adsorbed on silica gel than on alumina in the same way as indolizidine. The presence of diethylamine in the solvent system would be expected to show a dramatic increase in hR_F values of all alkaloids on both alumina and silica gel layers. If the carbonyl group of the oxindole nucleus is responsible for the adsorption of the oxindole alkaloids it would be anticipated that the presence of a hydroxy substituent would considerably decrease the hR_F values, the most dramatic effect being shown by 12-hydroxy alkaloids. The presence of methoxy substituents would not greatly affect the hR_F value unless substitution was at the $C(12)$ position when the hR_F value would be greatly increased. Since oxindole, 4-hydroxy and 4-methoxy-oxindole are more strongly adsorbed on alumina than on silica gel it might be expected that the alkaloids and their 9-hydroxy and methoxy substituted derivatives would also have lower hR_F values on alumina than on silica gel. However, the *E seco* oxindole alkaloids contain both the oxindole and indolizidine nuclei combined as either A or B type alkaloids, together with a further ring—the E ring. Thus the role played in adsorption by the lone pair of electrons at $N(4)$ and by the carbonyl group in the oxindole nucleus will depend upon the configuration and preferred conformation of the alkaloids (together with the effects of substituted hydroxy or methoxy groups in the aromatic nucleus).

Position of adsorption in E seco oxindole alkaloids



Rotundifoline (partial VII) possesses a strong internal hydrogen bond between $C(9)-OH$ and the lone pair of electrons of $N(4)$ ^{7a-d} and thus if this conformation remains unchanged during thin layer chromatography on alumina and silica gel the $N(4)$ lone pair electrons cannot be expected to take part in adsorption.

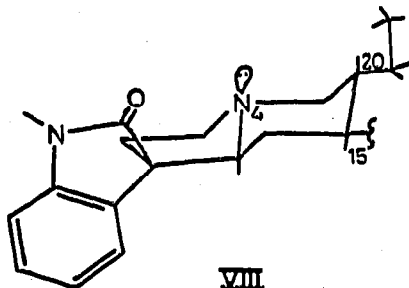
Similarly $C(9)-OH$ would not be expected to take part in adsorption and thus it is probable that the main portion involved during adsorption is the carbonyl group of the oxindole ring. This is partly substantiated by the behaviour pattern of rotundi-

foline being very similar to that of oxindole on silica gel layers and that rotundifoline is less strongly adsorbed than oxindole on alumina layers. Isorhynchophylline and corynoxine have very similar R_F values, in all systems used, to rotundifoline, thus indicating that in these alkaloids N(4) lone pair electrons do not play any appreciable role in adsorption. It is possible that in these alkaloids adsorption is mainly due to the oxindole carbonyl but if this is the only factor involved then it would be expected that rotundifoline, isorhynchophylline and corynoxine would be more strongly adsorbed on alumina than on silica gel layers. In fact this is not the case since these three alkaloids are adsorbed more strongly on alumina than on silica gel in only three out of seven solvent systems without diethylamine and in only one out of seven solvent systems containing diethylamine.

Thus it is apparent that adsorption of these alkaloids cannot be explained only in terms of oxindole carbonyl. It is possible that adsorption may also take place at the benzene ring of the oxindole portion or at ring E.

The fact that the corresponding B isomers of these three alkaloids, *i.e.*, isorotundifoline, rhynchophylline and corynoxine B are more strongly adsorbed on alumina and silica indicates that in addition to the oxindole carbonyl, adsorption also probably takes place at N(4).

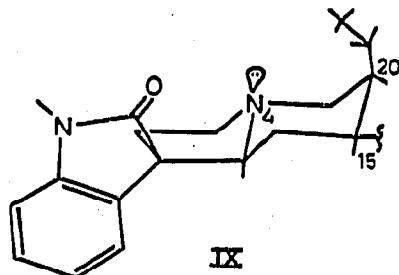
Differences in adsorption between A and B E seco oxindole alkaloids of allo or normal configuration



In the *allo* and *normal* alkaloids examined those with oxindole A configurations are less adsorbed than those with oxindole B configurations. By comparison of the TLC behaviour of rotundifoline with isorhynchophylline and corynoxine it is apparent that in these oxindole A alkaloids adsorption does not occur at N(4). The reason for this is that in these oxindole A alkaloids the benzene ring of the oxindole portion projects over the plane of the C/D rings (II) effectively hindering the N(4) lone pair electrons from taking part in any adsorptive processes. Hence adsorption can be considered to be mainly due to hydrogen bond formation between oxindole carbonyl and adsorbent hydroxyl groups. The oxindole B alkaloids rhynchophylline and corynoxine B are more strongly adsorbed than indolizidine on all alumina systems and as strongly adsorbed as indolizidine in three out of seven silica gel systems without diethylamine in the solvent. When diethylamine is present in the solvent systems the two alkaloids are more strongly adsorbed than indolizidine in all systems examined. These results would suggest that the N(4) lone pair of electrons takes part in adsorption but that some other factor(s) is involved. In rhynchophylline (partial VIII) and corynoxine B (partial IX) the N(4) lone pair electrons are in such a position as to enable hydrogen bond formation to take place with adsorbent hydroxyl groups;

moreover the oxindole carbonyl is on the same side of the molecule lying adjacent to N(4). Thus it is possible for N(4) and oxindole carbonyl to be available for hydrogen bonding with neighbouring adsorbent hydroxyl groups.

Differences in adsorption between allo and normal E seco oxindole alkaloids

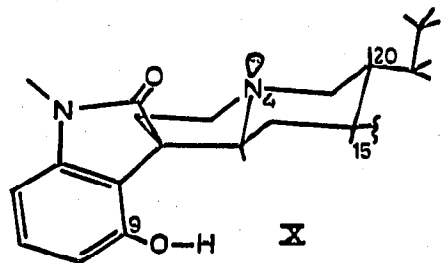


There is little difference in adsorption between the unsubstituted oxindole A *allo* (corynoxine) and *normal* alkaloids (isorhynchophylline) where N(4) plays no part in adsorption processes. However differences in adsorption are noticeable in the corresponding oxindole B *allo* (corynoxine B) and *normal* (rhynchophylline) alkaloids. On all alumina and silica gel systems examined corynoxine B is less strongly adsorbed than rhynchophylline. This can be explained by the fact that in corynoxine B (partial IX) the axial C(20) ethyl group will sterically hinder the availability of the N(4) lone pair of electrons and thus it is to be expected that corynoxine B would be less strongly adsorbed than rhynchophylline (partial VIII) with its equatorial C(20) ethyl group.

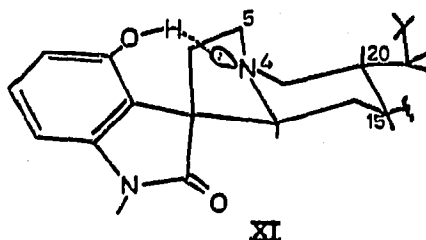
The behaviour of 9-hydroxy E seco oxindole alkaloids

The thin layer chromatographic behaviour of hydroxy oxindoles indicates that the presence of a 9-hydroxy substituent in an oxindole alkaloid would tend to reduce R_F values when compared with the corresponding unsubstituted alkaloid. The behaviour of rotundifoline has already been explained and the same arguments can be applied to speciofoline where, although the relative configurations at C(3) and C(20) are unknown, it is considered to possess a strong internal hydrogen bond between C(9)-OH and N(4)^{7c}. It is not possible to make predictions of relative configurations at C(20) because the N(4) lone pair electrons do not take part in the adsorption processes.

Isorotundifoline (partial X) would be expected to be adsorbed more strongly than the corresponding unsubstituted alkaloid rhynchophylline. In fact the results show that isorotundifoline is less strongly adsorbed on all TLC systems used than rhynchophylline; this is surprising because the oxindole carbonyl group and N(4) lone pair electrons are aligned in an identical way to rhynchophylline and the phenolic hydroxyl group would be expected to be a strong factor in adsorption processes, by analogy, to 4-hydroxy-oxindole.



These results suggest that either N(4) or C(9)-OH is not available for adsorption processes to take place. One possible explanation is that during chromatography on alumina and silica gel a conformational change takes place in which N(4) inverts to form an internal hydrogen bond with C(9)-OH (partial XI).

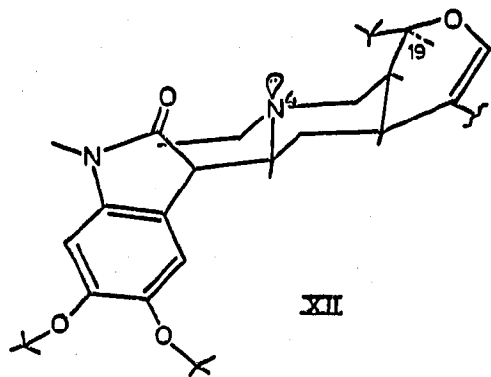


However this conformation would bring C(5) β and C(20) β protons adjacent and would not be as stable as conformation X so that it is difficult to envisage such a conformational change taking place. A further possibility may be in the structure of isorotundifoline; it is known that this alkaloid readily crystallises with a molecule of acetone which is very difficult to remove and it is possible that isorotundifoline associates with solvent molecules which effectively block C(9)-OH and N(4) lone pair electrons so that they are unable to take part in adsorption processes. A third possibility is that during thin layer chromatography isorotundifoline forms intermolecular hydrogen bonds in preference to bonding with adsorbent.

The behavior of 9-methoxy E seco oxindole alkaloids

The thin layer behaviour of the *allo*, 9-methoxysubstituted mitragynine oxindole B alkaloid is very similar in all systems used to that of the corresponding unsubstituted alkaloid, corynoxine B. The *normal*, 9-methoxy substituted oxindole B alkaloids ciliaphylline and specionoxeine also behave similarly to the corresponding unsubstituted alkaloid, rhynchophylline. These results are as expected when comparing the behaviour of 4-methoxy-oxindole and oxindole; the results can be explained in terms of oxindole carbonyl and N(4) bonding to adsorbent as for rhynchophylline.

The *normal* A alkaloid rhynchociline and its C(20) vinyl analogue isospecionoxeine behave similarly to the corresponding unsubstituted alkaloid, isorhynchophylline, on alumina systems without diethylamine and on alumina and silica gel systems with diethylamine present. However, an anomaly exists with rhynchociline and isospecionoxeine on silica gel layers when diethylamine is absent from the solvent system because both these alkaloids are very strongly adsorbed, more strongly in fact than the corresponding oxindole B alkaloids. If it is assumed that no conformational changes take place during chromatography on alumina and silica gel layers then it is reasonable to suppose that the methoxy group must also be taking part in adsorption as well as the lone pair of electrons at N(4). Rhynchociline and isospecionoxeine (partial XII) may therefore on silica gel bond with silanol hydroxyl groups at C(9)-OCH₃ and N(4) but it is difficult to understand why the same process does not take place on alumina. It is unlikely that these two alkaloids undergo a conformational change by nitrogen inversion because the resulting conformers would be too unstable with C(9)-O adjacent to C(14) β hydrogen.



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SUMMARY

Oxindole, hydroxy and methoxy oxindoles and indolizidine have been examined on alumina and silica gel thin layers using the same solvent systems in which diethylamine is first absent and then present. Twelve *E seco* oxindole alkaloids have been examined on the same systems and their behaviour related to the simple oxindoles (corresponding to alkaloid A and B rings) and to indolizidine (corresponding to alkaloid C and D rings). It has been proposed that N(4) does not take part in the adsorption of the *allo* and *normal* oxindole A alkaloids but that the oxindole carbonyl does. However the behaviour of these alkaloids cannot be completely explained in these terms. The *allo* and *normal* oxindole B alkaloids are generally more strongly adsorbed than the corresponding oxindole A alkaloids. This has been explained in terms of hydrogen bonding with N(4) and oxindole carbonyl bonding to adsorbent hydroxyl groups. The anomalous behaviour of three of these alkaloids is discussed.

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