AN INVESTIGATION INTO THE ENANTIOMERIC RESOLUTION OF AMINO ALCOHOLS AND RELATED COMPOUNDS

by

CHRISTOPHER J. WELCH

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

Christopher J. Welch

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APPROVED: H. L. Haight

HEAD OF DEPARTMENT OF CHEMISTRY

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INTRODUCTION

The direct resolution of enantiomers by high pressure liquid chromatography upon a chiral stationary phase (CSP) has been the subject of recent intensive investigation. The resolution of amino alcohols by this method is of great importance for a variety of reasons. Among the amino alcohol family there are many drugs and biologically important compounds in which chirality is very important. For example, the enantiomers of chloramphenicol, a drug of the amino alcohol family whichinhibits prokaryotic protein synthesis, have quite different activities. An investigation into the liquid chromatographic resolution of the enantiomers of amino alcohols is of considerable importance because it can provide a quick and easy method of determining enantiomeric purity, assigning absolute configuration, or even of preperatively resolving large quantities of these interesting molecules.

HISTORICAL

The seperation of optical isomers has long been an important area of study in the field of Chemistry. Since optical isomers, or enantiomers, have identical physical properties (melting point, boiling point, solubility, etc.) the problem of their seperation is a substantial one. The first seperation of enantiomers was the seperation of R and S sodium ammonium tartrate, first done by Pasteur in 1848[1]. Pasteur's method consisted of seperating the different shaped drystals of this compound with the aid of a magnifying lens and a pair of tweezers. This method of differential crystallization of enantiomers works in very few cases, and is much too tedious ever to be used on a practical scale.

Soon it was discovered that diasteriomeric salts formed from an optically pure resolving agent (usually a natural product which is found enantiomerically pure) and a racemic counterion could be seperated by differential crystallization of the diasteriomeric salts. This method was estensively used throughout the nineteenth and early twentieth centuries, and is still widely used today.

Differential crystallization of diasteriomeric salts (method I) works very well as a method for seperating some enantiomers. Unfortunately, this method is by no means general. Most enantiomeric compounds cannot be seperated by this method. No rules exist for predicting which dia-

steriomeric salts will preferentially crystallize. It is largely a matter of trial and error.

An improvement upon the differential crystallization method has been made. In many cases the diasteriomeric salts can be directly resolved by liquid chromatography (method II). This is a tremendous improvement over the old methods. The delicate art of growing crystals and the generally poor yields afforded by the differential crystallization method are no longer problems in the direct chromatographic resolution of the diasteriomeric salts.

MethodII, although it is a vast improvement upon method I, still has some serious drawbacks which keep it from being a general method for resolving enantiomers. Most importantly, not all enantiomeric compounds can form salts. Many interesting enantiomeric compounds contain no ionizable groups, and therefore their seperation by method II is impossible. Another drawback of method II is that in order to do seperations on a practical scale only very inexpensive resolving agents can be used. This seriously limits the number and kind of compounds which can be resolved. As in method I, the choice of which resolving agent to use for a given set of enantiomer is largely a matter of trial and error.

A solution to these problems was to bind the optically pure resolving agent to the stationary phase, and rely uponthe formation of transient diasteriomeric compleses to afford resolution (method III). This method was first suggested by Dalgleish in 1952,[2] but was never employed systematically until 1971, when Baczuk designed a chiral stationary

which seperated the enantiomers of DOPA[3].

Method III is a vast improvement upon the chromatography of diasteriomeric salts. Since the resolving agent is used only once (when it is attached to the stationary phase), relatively exotic and expensive resolving agents can be used in a cost effective manner. The enantiomers are eluted from the column in a purified form. No seperation from the resolving agent counterion is necessary. Perhaps most important is the fact that an ionizable group on the resolving agent or the compounds chromatographed is no longer necessary.

As Dalgleigh pointed out in his 1952 paper, any three interactions, at leastone of which is chirally dependant, are sufficient for the seperation of enantiomers. These interactions can be hydrogen bonding, dipole-dipole forces, charge transfer complexes, steric repulsions, hydrophobic attractions, or a variety of other possible interactions. It is readily seen that with the advent of method III the number and types of resolvable enantiomeric compounds took a quantum leap.

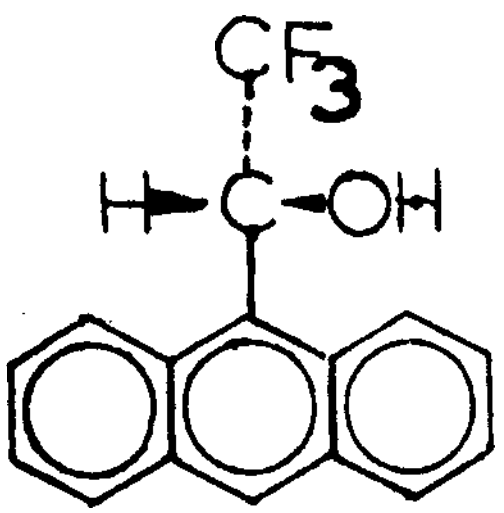
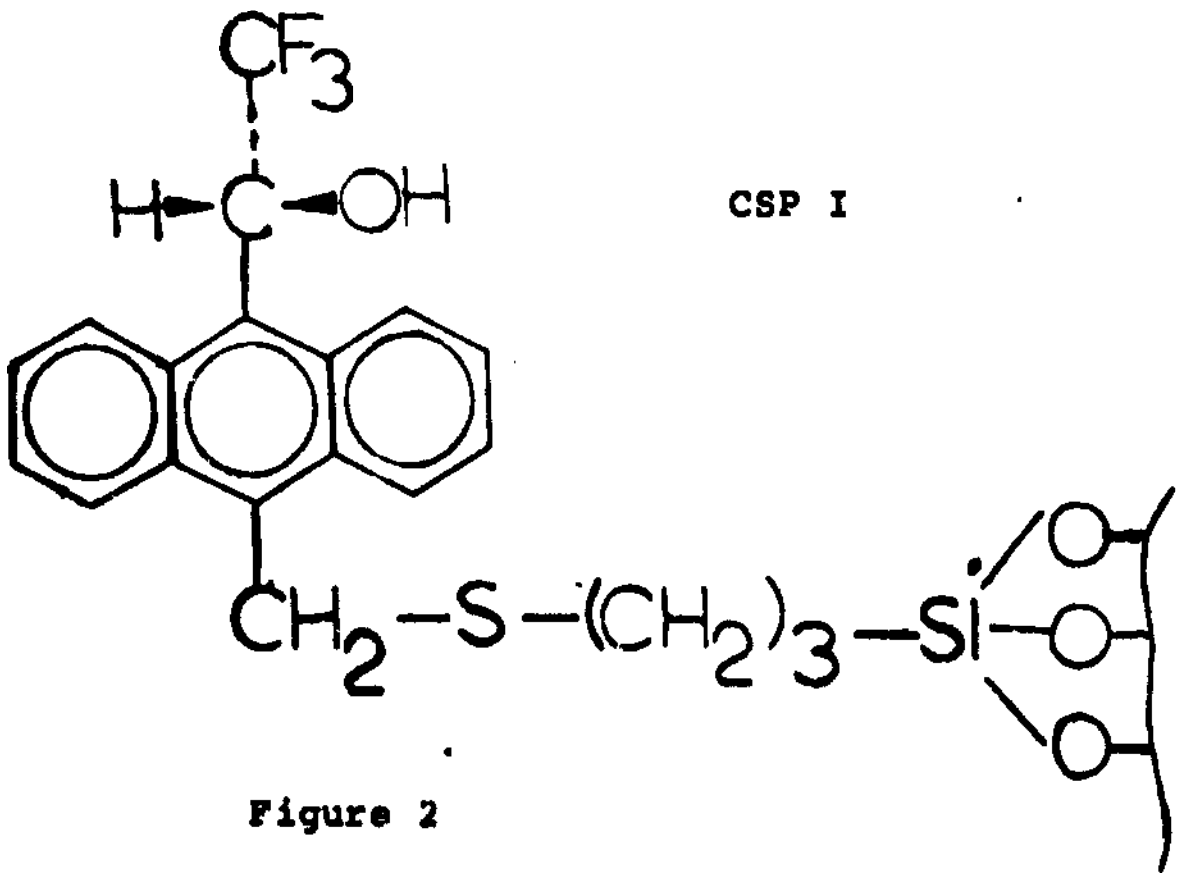


Figure 1

Pirkle's work with 9-anthryl trifluoromethyl carbinol (Figure 1) as a chiral NMR shift reagent showed that this compound fulfilled all of Dalgleigh's rules for a possible resolving agent. The compound was then covalently attached to silica gel to afford CSP I (Figure 2). The properties of enantiomeric resolution of this stationary phase were investigated and subsequently reported[4].



CSP I

Figure 2

It was found that a variety of compounds coul resolve upon CSP I, among the the 3,5 dinitrobenzamides of amino acids. The "optimum" compound of this class was found to be the 3,5 dinitrobenzamide of phenylglycine. This compound was then ionically bonded to aminopropyl silica gel to afford CSP II [5] (Figure 3).

CSP II

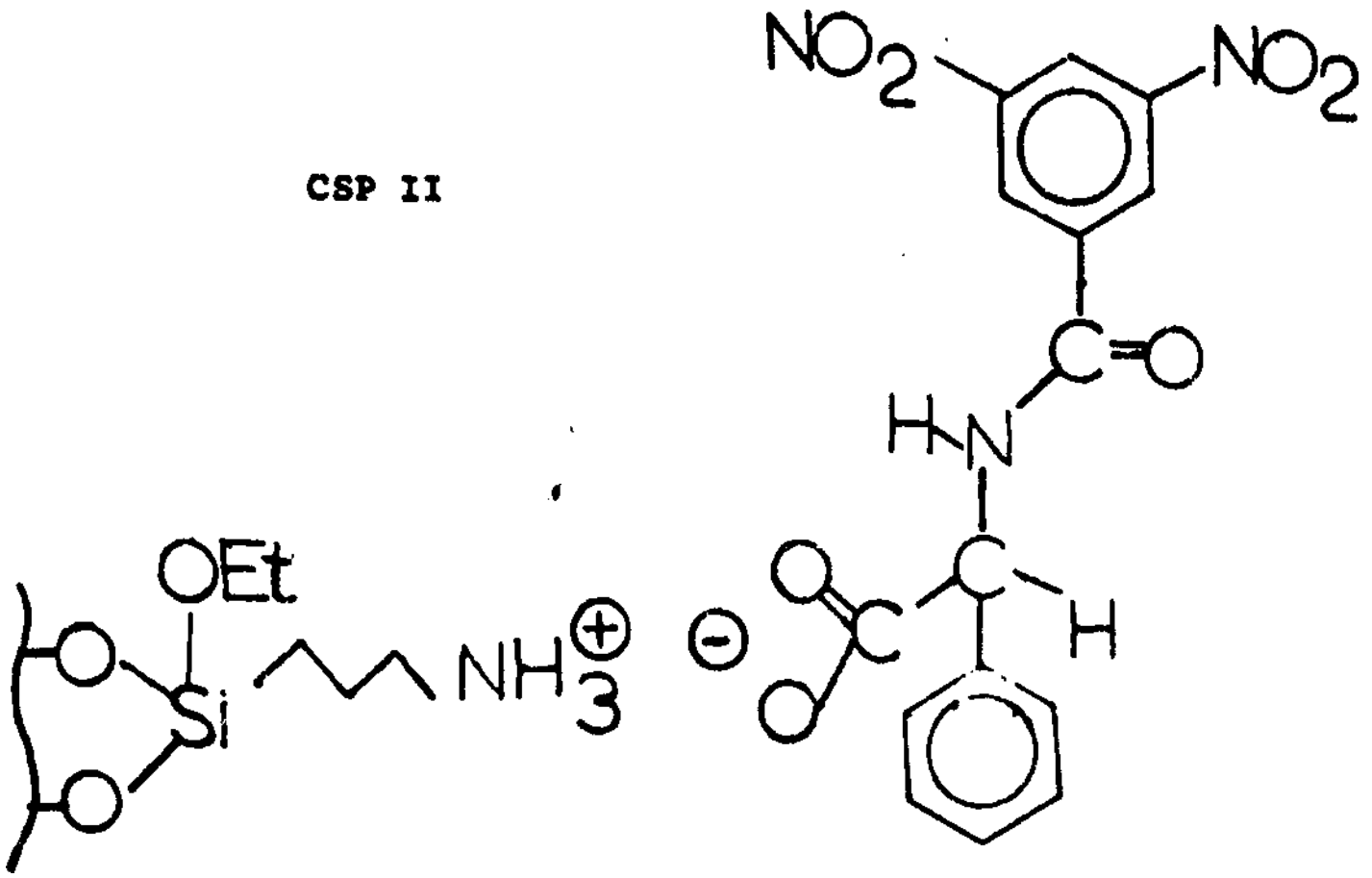


Figure 3

This new chiral stationary phase was shown to resolve a great variety of enantiomeric compounds[6]. One class of compounds which resolved quite well upon this new CSP was the Hydantoin family.

These compounds were investigated by Myung Ho Hyun, who developed a hydantoin with optimum resolution upon CSP II[7]. This optimized hydantoin was then covalently attached to silica gel to afford CSP III (Figure 4).

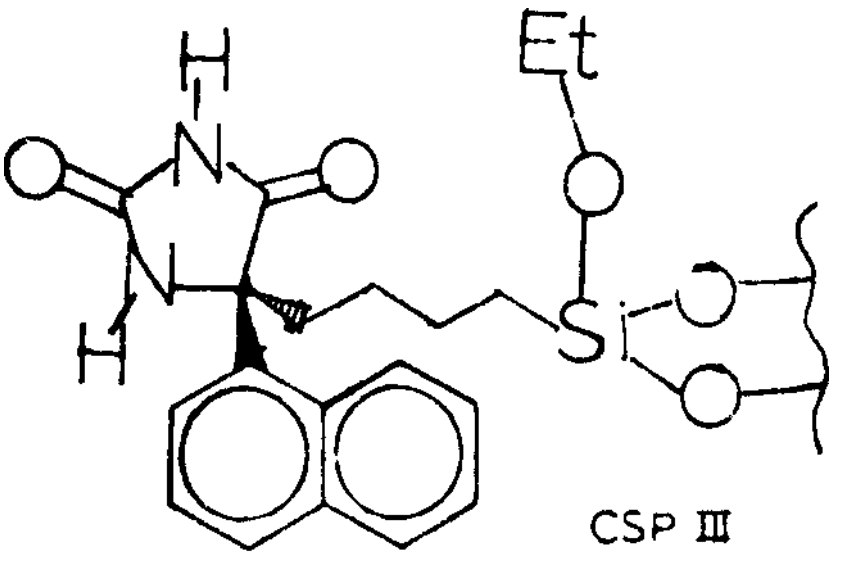


Figure 4

It was found, as was expected by the reciprocal nature of chiral resolutions, that 3,5 dinitrobenzamide derivatives of amino acids resolved quite well upon CSP III. It was also found that the 3,5 dinitrobenzamide derivatives of amino acid esters and amdides, as well as amino alcohols, resolved quite well upon the new CSP. In order to more fully understand the exact mechanism of resolution of enantiomers upon CSP III a study of resolution upon this column was undertaken.

RESOLUTION OF 3,5 DNB DERIVATIVES OF β AMINO ALCOHOLS UPON CSP III

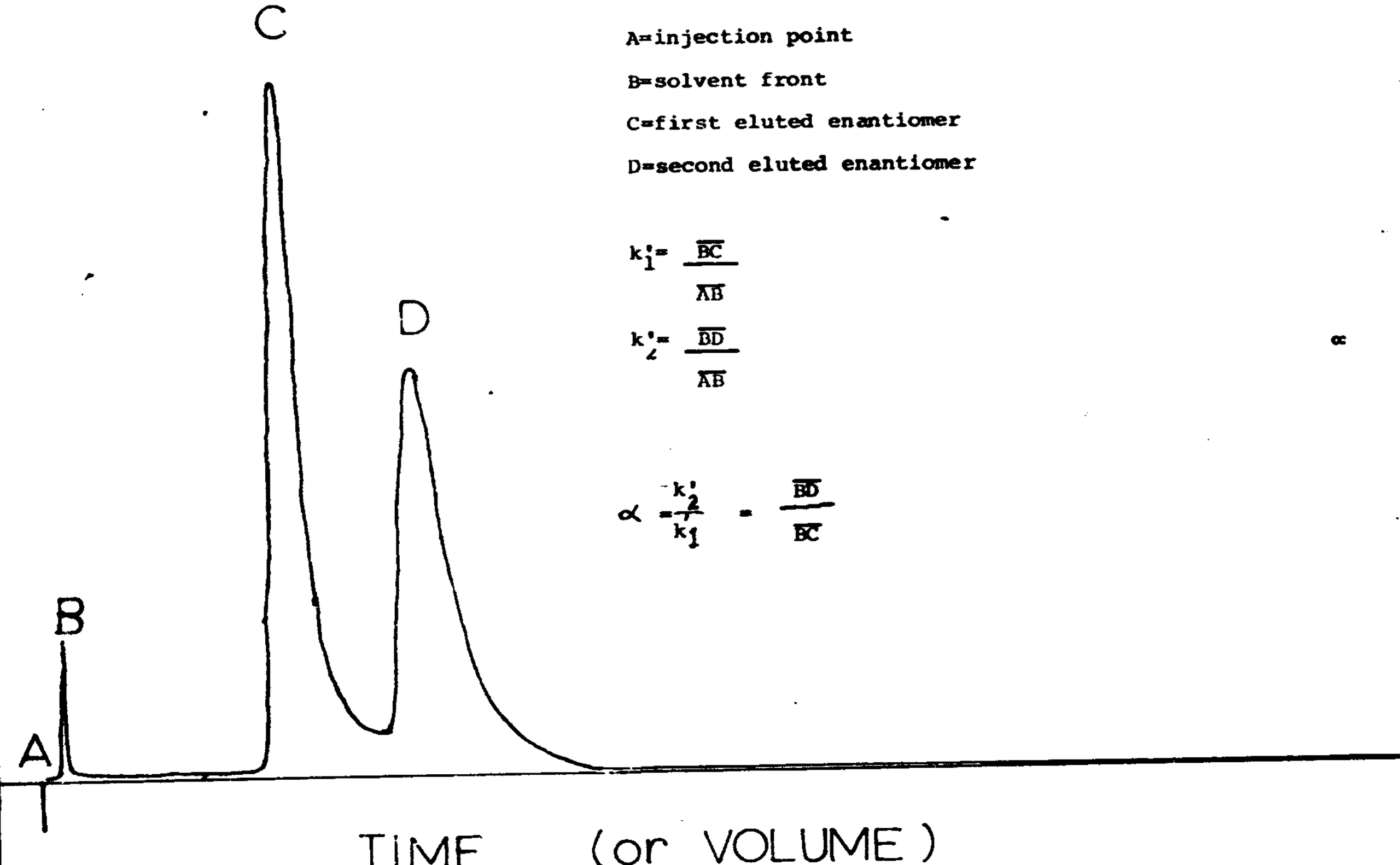
A number of compounds of the β amino alcohol family were synthesized, derivatized, and chromatographed upon CSP III. By studies of enantiomerically enriched mixtures it was determined that the S enantiomer is the first eluted. Using this fact, and the relative resolutions of a number of compounds, a mechanism for the resolution of 3,5 dinitrobenzamide (3,5 DNB) derivatives of amino alcohols was devised.

RESULTS

The compounds chromatographed are presented in tabular form. The term α is used as a convenient way of expressing the relative resolution of enantiomers. It is defined as the ratio of the capacity factor of the first eluted enantiomer to that of the second eluted enantiomer (Figure 5). The eluent used in these and all following resolutions was a mixture of 10% 2-propanol and hexane unless otherwise noted. The flow rate for all resolutions was 2 ml./minute.

Figure 5

SAMPLE CHROMATOGRAM



A=injection point

B=solvent front

C=first eluted enantiomer

D=second eluted enantiomer

$$k_1' = \frac{\overline{BC}}{\overline{AB}}$$

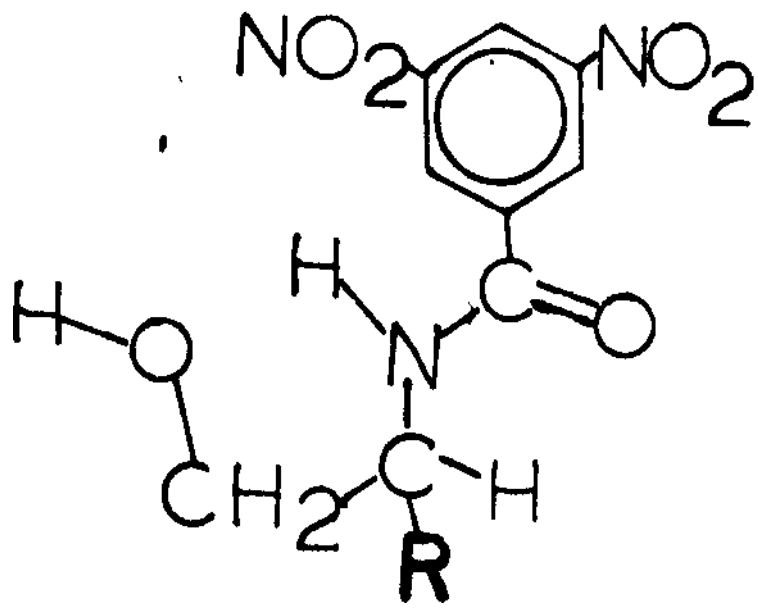
$$k_2' = \frac{\overline{BD}}{\overline{AB}}$$

$$\alpha = \frac{k_2'}{k_1'} = \frac{\overline{BD}}{\overline{BC}}$$

Figure 6

RESOLUTION OF 3,5 DNB DERIVATIVES OF β AMINO ALCOHOLS ON CSPIII

RESOLUTION TABLES

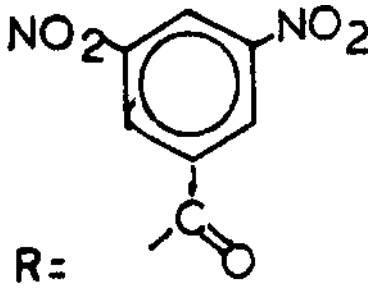


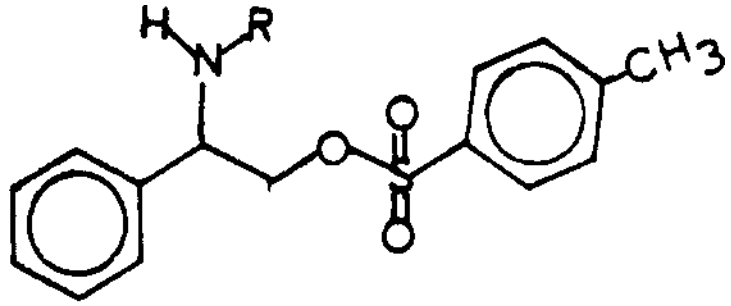
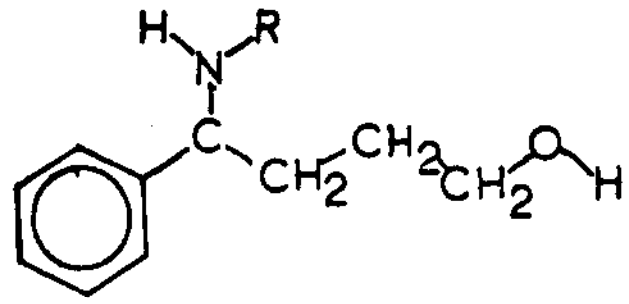
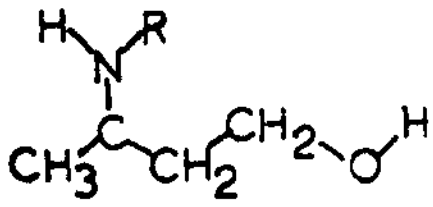
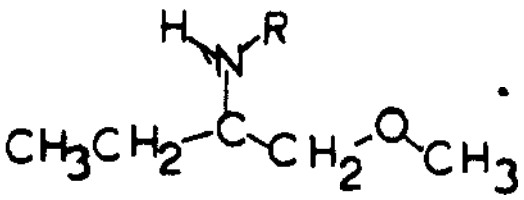
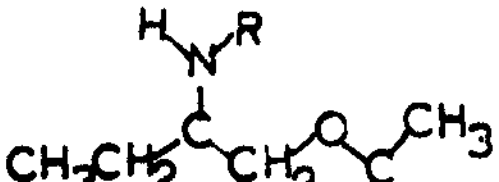
R=	α	k'_1
methyl	1.41	8.7
ethyl	1.64	8.3
n-propyl		
i-propyl	1.21	3.6
1-methyl propyl	1.16	4.0
1-methyl propyl	1.50	4.0
$CH_3SCH_2CH_2$-	1.34	6.1
phenyl	1.91	11.3
biphenyl	1.48	11.7
α-Naphthyl	1.90	12.6
β-Naphthyl	1.87	15.3
Benzyl	1.60	9.3
2-phenylethyl	1.25	9.3

RESOLUTION OF 3,5 DNB DERIVATIVES OF α AMINO ALCOHOLS ON CSP III

RESOLUTION TABLES

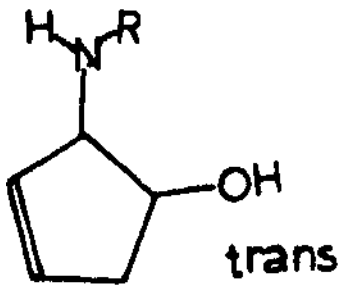
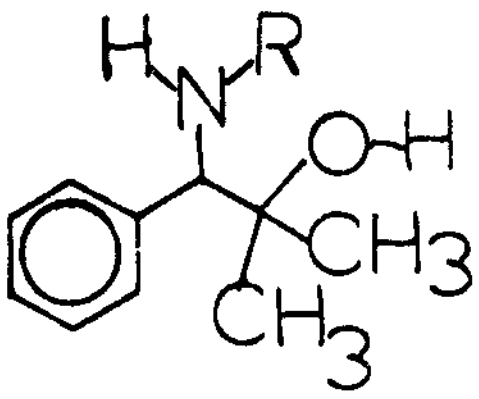
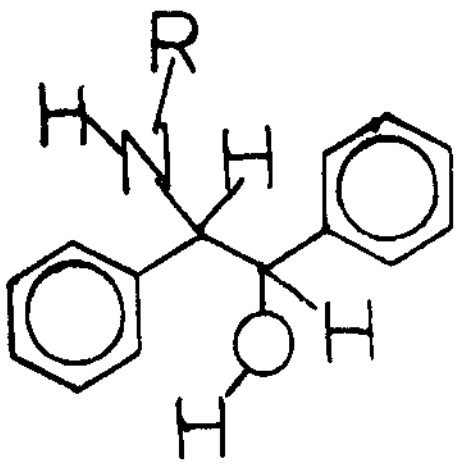
COMPLETE STRUCTURES



STRUCTURE	α	k'_1
	1.75	13.5
	1.37	19.0
	1.50	4.6
	1.31	2.6
	1.14	10.8

RESOLUTION TABLES

(continued)

STRUCTURE	α	k'_j
 trans	1.16	6.0
	1.50	9.3
 erythro		
threo	1.27	
cis		
trans	1.17	5.8

COMMENTS

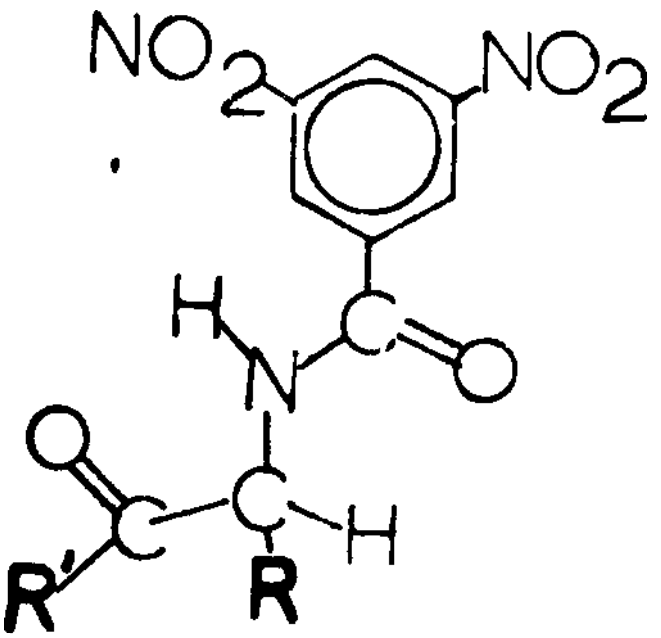
The general class of the β amino alcohol resolve quite well upon CSP III, as is evidenced by the preceeding tables. The mechanism of resolution, along with a detailed account of all interactions will be presented later. The results obtained for the resolution of members of the amino alcohol family were quite encouraging. The resolution of 3,5 dinitrobenzamide derivatives of α amino acids, amino acid esters, and amino acid amides was also known to be possible, and was also investigated.

RESOLUTION OF 3,5 DNB DERIVATIVES OF α AMINO ACIDS, AMINO ACID ESTERS, AND AMINO ACID AMIDES

A study of the resolution of 3,5 DNB derivatives of α amino acids, amino acid esters, and amino acid amides upon CSP III was undertaken. The resolution of these compounds is of interest for several reasons. There is a wide variety of enantiomeric compounds of this class whose resolution is of considerable interest. Also, because of their structural similarity to the amino alcohol family, the comparative resolutions of members of these two classes is of considerable interest for the elucidation of the mechanism of enantiomeric resolution. The results of this investication are summarized here in tabular form.

(Figure 7)

RESOLUTION OF 3,5 DNB DERIVATIVES OF α AMINO ACIDS,[8] AMINO ACID ESTERS, AND AMINO ACID AMIDES



R	R'	α	k'_1
methyl	H	1.19	2.65
i-propyl	H	1.35	5.75
1-methyl propyl	H	1.34	9.5
phenyl	H	1.34	10.7
α Naphthyl	H	1.50	35.0
m-Hydroxyphenyl	H	1.21	7.0
α Naphthyl	-O-Methyl	1.41	13.37
α Naphthyl	-O-Ethyl	1.35	10.3
α Naphthyl	-O-n-Propyl	1.27	8.33
α Naphthyl	-O-i-Propyl	1.30	7.7
α Naphthyl	-O-n-Butyl	1.26	7.6
α Naphthyl			

RESOLUTION OF 3,5 DNB DERIVATIVES OF α AMINO ACIDS, AMINO ACID ESTERS, AND AMINO ACID AMIDES

(continued)

R	R'	α	k'_1
αNaphthyl	$C_{12}N$-	1.30	
Methyl	MeO-	1.32	12.3
Methyl	n-Bu-N-	1.42	6.3
i-Propyl	MeO-	1.26	7.3
1-Methylpropyl	EtO-	1.50	4.0
Phenyl	MeΦ-	1.39	
Phenyl	EtO-	1.32	
Phenyl	n-Bu-N-	1.42	6.3
α-Phenylethyl	MeO	1.25	
$CH_3SCH_2CH_2$-	n-Bu-N-	1.43	
p-Chlorophenyl	EtO-	1.10	9.3
p-chlorophenyl	n-Bu-N-	1.15	9.0

(COMMENTS)

The 3,5 DNB derivatives of α amino acids, Amino acid esters, and amino acid amides resolve quite well upon CSP III. An in depth analysis of the properties which lead to increased resolution will be presented later. During a search to determine which interactions were necessary for resolution the 3,5 DNB of phenyl ethylamine was chromatographed. Sur-

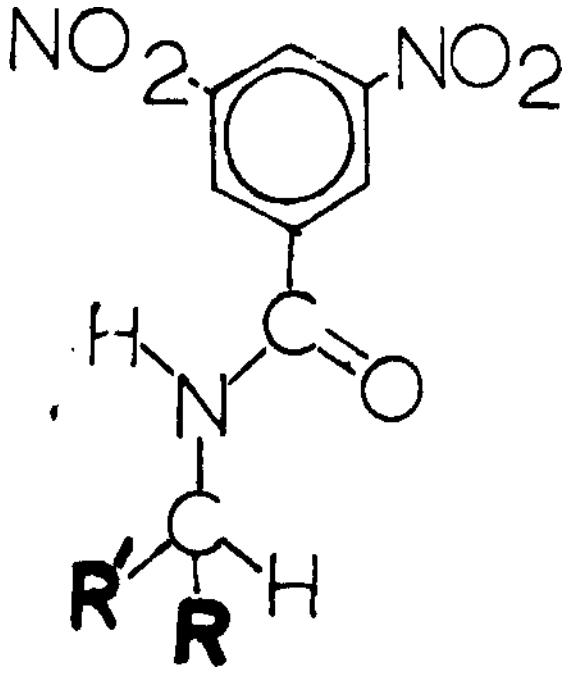
prisingly,the enantiomers seperated quite nicely. A varity of 3,5 DNB derivatives of amines were then prepared and Chromatographed.

RESOLUTION OF 3,5 DNB DERIVATIVES OF CHIRAL AMINES

A study of the resolution of 3,5 DNB derivatives of chiral amines upon the hydantoin CSP was undertaken. The resolution of these compounds was considered important for several reasons. Many chiral amines of chemical or biochemical interest were found to resolve upon CSP III. The resolution of some of these compounds had never before been effected using a CSP. From the relative resolutions of these chiral amines much can be learned about the general mechaniamof retention of CSP III, which has been postulated to be similar in the resolution of amino alcohol, amino acid and chiral amine derivatives. The results of the study of the resolution of 3,5 DNB derivatives of chiral amines are here presented in tabular form.

(Figure 8)

RESOLUTION OF 3,5 DNB DERIVATIVES OF CHIRAL AMINES



R	R'	α	k_1'
phenyl	methyl	1.30	14.8
p-methoxyphenyl	methyl	1.19	12.8
p-nitrophenyl	methyl	DNR	
benzyl	methyl	1.05	16.0*
αNaphthyl	methyl	1.19	10.9
biphenyl	methyl	DNR	15.0
phenyl	i-propyl	1.18	3.75**
n-butyl	methyl	1.07	19.0**
ethyl	methyl	DNR	

DNR= Does Not Resolve

*= 5% 2-propanol/hexane used

**= 20% 2-propanol/hexane used

COMMENTS

The resolution of 3,5 DNB derivatives of chiral amines upon CSP III is a topic which merits further research. The data obtained here are sufficient, however, to elucidate some details about the mechanism of resolution of these compounds.

PROPOSED MECHANISM OF RESOLUTION OF β AMINO ALCOHOLS AND RELATED COMPOUNDS UPON CSP III

A mechanism for the resolution of β amino alcohols and related compounds upon CSP III has been proposed on the basis of resolution studies and studies of elution orders of the enantiomers. Where possible, test compounds have been synthesized to test different facets of the proposed mechanism.

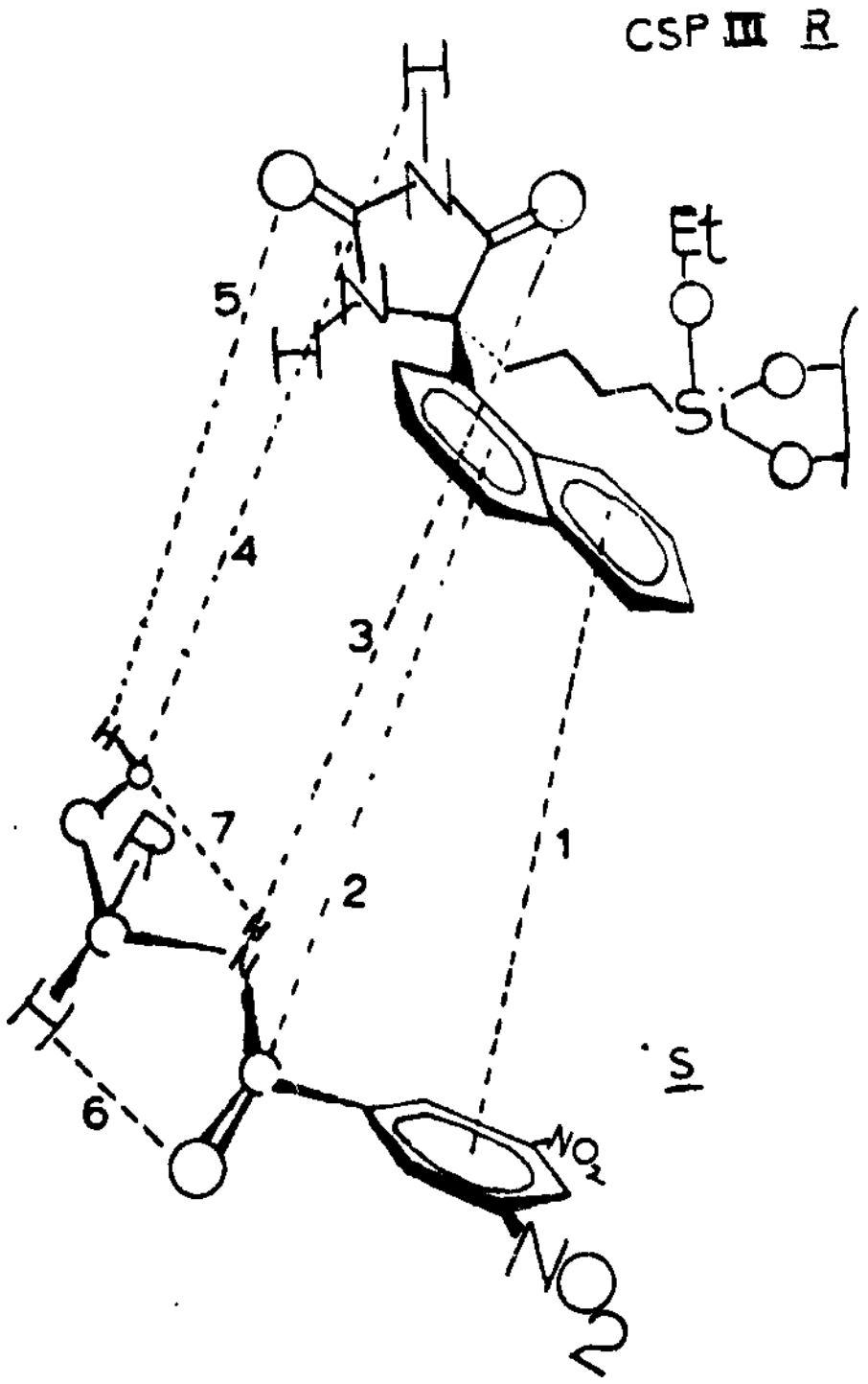
ANALYSIS OF DIASTEREOMERIC COMPLEX WHICH LEADS TO RETENTION

The basis of enantiomeric resolution is the formation of diastereomeric complexes of differing free energies between the CSP and the two enantiomers of the compound being resolved. A model of the diastereomeric complex which leads to longest retention (the complex of the lowest free energy) has been proposed (Fig. 9). This model is consistent with the elution of all known compounds upon CSP III.

From the proposed model of the diastereomeric comples of lowest free energy it can be seen that the retained inantiomer is in its most stable conformation with a relaxed distribution of steric bulk, and two favorable intramolecular hydrogen bonds. The hydantoin CSP is also in its mos favorable orientation. The plane of the Naphthyl ring is in its most favorable confirmation with respect to the hydantoin ring plane, an angle of approximately 60°. In the proposed model the retained enantiomer can make a total of five simultaneous in-

PROPOSED MODEL OF DIASTEREOMERIC COMPLEX WHICH LEADS TO RETENTION

(Figure 9)



S

teractions with the CSP, three of whic are quite strong. The Unretained enantiomer, in its most stable conformation can interact strongly with the CSP at only two sites. It is the difference in free energy between the two diastereomeric complexes which gives rise to α. In this case the energy difference appears to be equal to the energy of the π-π complex (interaction 1) averaged with the sum of the two hydrogen bonds of the hydroxyl group (interactions 4 and 5) since these seem to be the two possible ways in which thediastereomeric complex which does not give rise to retention can be arranged. Evidence for each proposed interaction will be given along with a detailed description of the interaction itself.

EVIDENCE FOR INTERACTION 1

One of the strongest of the proposed interactions is almost certainly the π-π complex formed between the Naphthyl ring of the CSP and the 3,5 DNB ring of the retained enantiomer. The observation that other amides of amino alcohols and related compounds resolve very poorly or not at all is strong evidence for this interaction. Benzoyl, acetyl, Napthoyl, and a variety of other amides were tried with almost no resolution seen in any cases.

Other evidence for this interaction concerns the analogous resolution of hydantoins upon CSP II. It has been found that there is a direct correlation between the π basicity of the hydantoin R group and its ability to be resolved upon CSP II.[1]

EVIDENCE FOR INTERACTION 2

The favorable perpendicular positioning of carbonyl dipoles over π basic ring systems has been shown to be important in the orientations of a number of molecules. In the diastereomeric complex proposed above the positioning of the carbonyl over the naphthyl ring is not at a very favorable angle, and therefore cannot be employed as an interaction per se. The important point is that the positioning of this carbonyl above the naphthyl ring does not have a deleterious effect upon the proposed structure, and may perhaps help in stabilizing it.

EVIDENCE FOR INTERACTION 3

The primary evidence for this proposed interaction is the observation that of the several 3,5 DNB derivatives of secondary amines mes made, none resolved, wheras similar primary amines did resolve. This hydrogen bond is probably quite strong. The carbonyl and amide hydrogen are in a very favorable conformation, and are relatively free to adopt a favorable head-to-head linear conformation.

EVIDENCE FOR INTERACTION 4

The evidence for the basic interaction of the hydroxyl oxygen with the diamide hydrogen of CSP III is quite extensive. From previous research it was found that alkylation of hydantoins at this diamide position results in a substantial decrease, or even elimination,of resolution upon CSP II. It is also not-

ed that a substantial increase in resolution was seen between compounds which differ only in that one contains a methyl group, while the other contains a CH_2OH moeity (for example α-phenylethylamine α=1.3, and phenyl glycinol α=1.9). Compounds with a better basic group at this site, perhaps the sulfoxide moeity, will be synthesized in the future to further test the importance of this proposed interaction.

EVIDENCE FOR INTERACTION 5

The hydrogen bond between the hydroxyl hydrogen and the hydantoin carbonyl oxygen is rather long range, and probably is the weakest of the proposed intermolecular hydrogen bonds proposed. This interaction is, nevertheless, important for resolution as is evidenced by the comparative resolution of amino alcohols and amino ethers. Methylalanol (p.9 R=Ethyl) and the analogous amino methyl ether (p10) were prepared, derivatized, and chromatographed upon CSP II. The increased resolution of the amino alcohol, as compared to the amino ether (α=1.64 vs. α=1.31) can be taken as evidence for the importance of interaction 5. The decrease in resolution of the amino ether as compared to the amino alcohol could also be explained in terms of the steric bulk of the added methyl group, though this seems unlikely from model studies. Ethers other than methyl will be synthesized to determine the importance of steric bulk of the ether group. If, in the future an amino alcohol stationary phase is made, a study of the comparative resolution of lactams and succinimides can be undertaken. This Study would give a good idea of the extent to which

EVIDENCE FOR INTERACTION 6

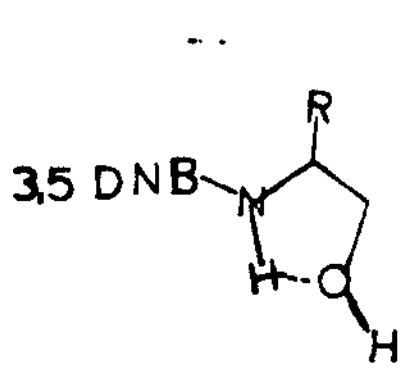
The conformation stabilizing intramolecular interaction between the acicic carbynyl hydrogen and the basic amide carbonyl oxygen is analogous to the interaction which is proposed as a conformation stabilizing interaction in the phenylglycine 3,5 DNB CSP[6]. The lack of resolution of quaternary amino alcohols (for example α methyl phenylglycinol) suggests that the conformation stabilizing efrect of the carbynyl hydrogen is important for resolution. Of course, this effect could also be explained by the conformation changing properties of the added steric bulk. Another indirect piece of evidence for this interaction is that when an aryl group is attached to a position α to the chiral center, resolution is increased much more than can be accounted for by arguments of simple steric bulk (for example p.9 R=phenyl α=1.91 R=benzyl α=1.60). A possible explanation of this phenomenon is that when the aryl group is in the position to the chiral center its inductive effect upon the carbynyl hydrogen serves to stabilize the preferred conformation by making the carbynyl hydrogen more acidic.

EVIDENCE FOR INTERACTION 7

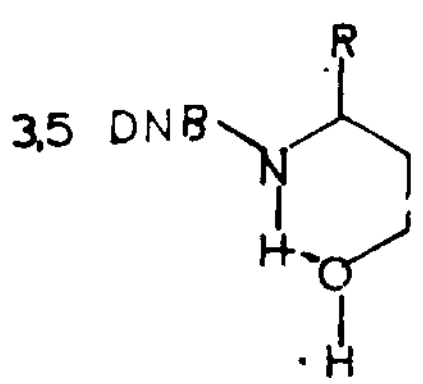
The intramolecular hydrogen bond between the amide hydrogen and the hydroxyl oxygen almost certainly does take place. The close proximity and great flexibility of these hydrogen bone donor and acceptor sites makes the interaction highly probable. Com-

parative resolution studies of beta, gamma, and delta amino alcohols (Fig. 10) also supports this hypothesized interaction. The comparative resolution of the few compounds of this type done fall into the same sequence as the inherent stability of the cyclic system formed: ie. six membered ring is better than five membered ring, is better than seven membered ring, or alternately stated gamma amino alcohols are better than beta amino alcohols, are better than delta amino alcohols. Only a few non beta amino alcohols have been investigated and it remains to be seen if this effect is general for all amino alcohols.

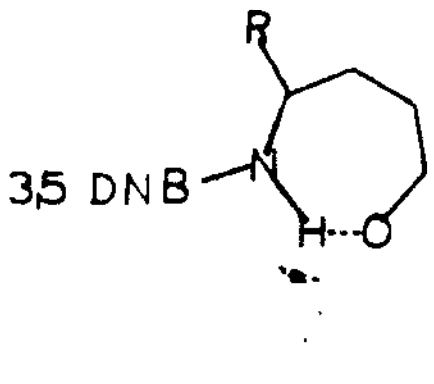
(FIGURE 10)



BETA
AMINO
ALCOHOL



GAMMA
AMINO
ALCOHOL



DELTA
AMINO
ALCOHOL

It is also possible that the enhanched resolution of the gamma amino alcohols is attributable to their increased ability to form interactions 4 and 5 simultaneously. As noted earlier, interaction 5 seems a little"long range" in the resolution model for beta amino alcohols. It is possible that with the extra methylene unit the gamma amino alcohols may be able to form this interaction easier. Future studies will hopefully

clarify this issue.

RETENTION MECHANISMS FOR AMINO ACID DERIVATIVES AND CHIRAL AMINES

Studies of enantiomerically enriched samples indicate that the same method of resolution is used for amino acid derivatives and chiral amines as that proposed for amino alcohols(p.21). Similar resolution trends among all three classes of compounds supports this hypothesis.

The resolution of amino acid derivatives upon CSP III relies upon the same resolution mechanism proposed for amino alcohols, except that interaction 5 can no longer take place since none of the amino acid derivatives contain good hydrogen bond donors in the appropriate position. The observed resolution of amino acid derivatives is in keeping with what would be expected from the proposed model. Amides generally work better than the corresponding ester, presumably because of the increase in the strength of interaction 4 due to the increased bascisity of the amide carbonyl oxygen.

The resolution of chiral amines follows the same mechanism as that proposed for amino alcohols and amino acid derivatives. In the resolution of chiral amines neither interaction 4 or 5 can take place. Instead, the chirally dependent reaction which allows for enantiomeric resolution is the steric repulsion of the unretained enantiomer. The difference between aryl and alkyl is easily distinguished by the CSP. The difference between butyl and methyl is also detectable. The difference between ethyl and methyl, however, is undetected.

EXPERIMENTAL

Various synthetic routes to the compounds desired for chromatographic study were undertaken. Many synthetic routes were tried, with the quick, easy, and reliable methods being used most and uncertain methods apandoned at an early stage. The synthetic routes are arranged according to functional group.

FORMATION OF 3,5 DINITROBENZAMIDE DERIVATIVES

The formation of 3,5 dinitrobenzamide derivatives of primary and secondary amines is straightforward. Equimolar amounts of acid chloride and pyridine in methylene chloride are added to a methylene chloride solution of the amin. The mixture is the agitated for several minutes, after which time the methylene chloride layer is washed several times with 1 M NaOH,then several times with 1 M HCl. The methylene chloride solution is then dried over sodium sulfate, the mixture filtered, and the solvent removed from the concentrated filtrate by rotary evaporation. The 3,5 dinitrobenzamide may then be recrystallized if desired.

The procedure is essentially the same for the derivization of amino acid esters, except sodium bicarbonate is substituted for sodium hydroxide. The reasons for this are twofold; first, it eliminates possible base catalyzed saponification of the ester which is a significant problem with some amino acid esters. Secondly, it eliminates the danger of base catalyzed racemization,if the amino acid ester is optically pure.

The derivitization procedure for amino alcohols is identical to that used for amines except a 10% excess of the amino alcohol is used to insure no formation of doubly derivatized (ie. both amide and ester formation from the amino alcohol moeity) amino alcohol. The reactivity of the amine moety is substantially greater than that of the hydroxyl. If an excess of amino alcohol is used, no detection of the bis adduct is observed.

SYNTHESIS OF AMINO ACID ESTERS

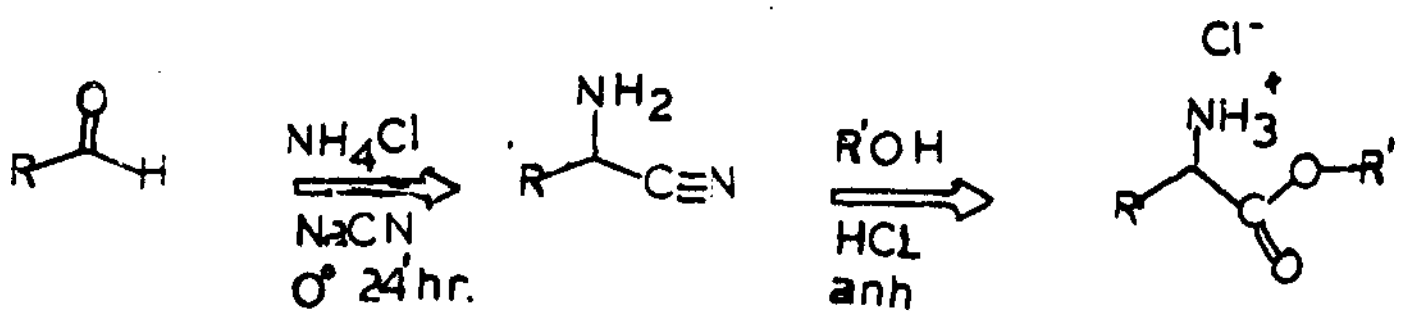
In cases where the corresponding amino acid was readilly available, the mino acid ester was formed by bubbling anhydrous HCl through a solution of the amino acid in the alcohol desired for esterification. Raotary evaporation of the solvent alcohos (when possible) yielded the amino acid ester hydrachloride. In cases where the alcohol used was high boiling, the amino acid ester was isolated by extraction techniques. Care must be taken not to use strong bases in the workup, as this could lead to saponification of the ester, or to racemization of the chiral center (if an optically pure amino acid ester has been made).

Trans esterification, the conversion of one ester to another, was done by repeating the above procedure with an amino acid ester substituted for the amino acid, and using the alcohol corresponding to the desired ester as a solvent.

In cases where the corresponding amino acids were not readilly available, the amino acid esters were synthesized from the corresponding aldehyde via the Strecker synthesis[9] (Fig 10). This synthetic route proved to be a quick and

easy method of preparing amino acid esters. Even such hindered aldehydes as 1-naphthaldehyde gave reasonable yields (about 30%).

Figure 10



SYNTHESIS OF AMINO ALCOHOLS

A variety od synthetic methods for the production of amino alcohols. For analogs of readilly available amino acid the easiest method was found to be reduction of the corresponding amino acid ester with sodium borohydride. Direct reduction of amino acids using lithium aluminum hydride was also tried. This method was abandoned after several attempts because of the slowness of reaction, large excess of LAH required, and difficult emulsion formation during workup.

The nucleophilic ring opening of epoxides with ammonia to give amino alcohols was also tried. Nucleophilic attack of amines upon epoxides is well known[10], but no literature reference was found on the use of ammonia to effect the ring opening. Nevertheless, this procedure (Fig. 11)

was tried and found to work reasonably well.

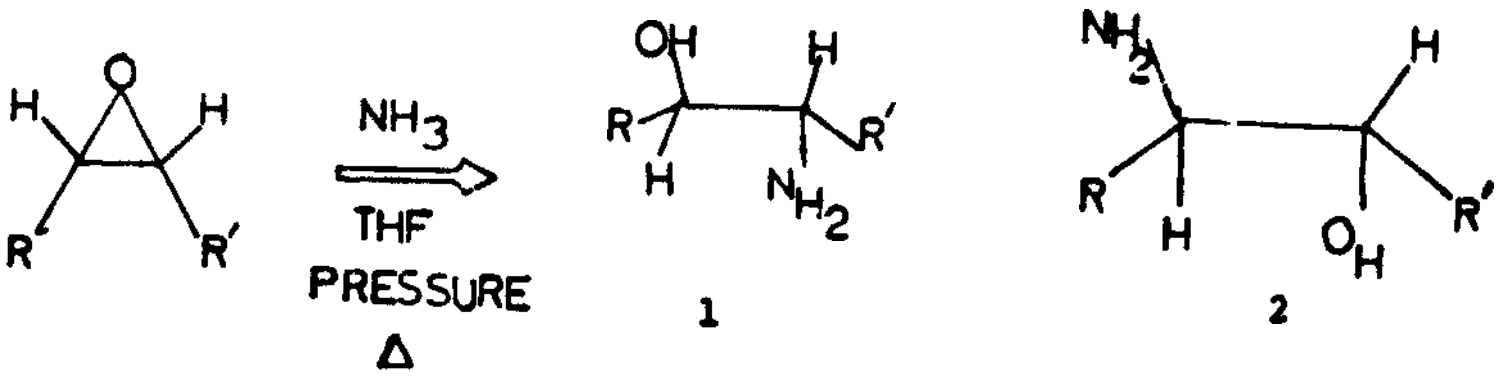
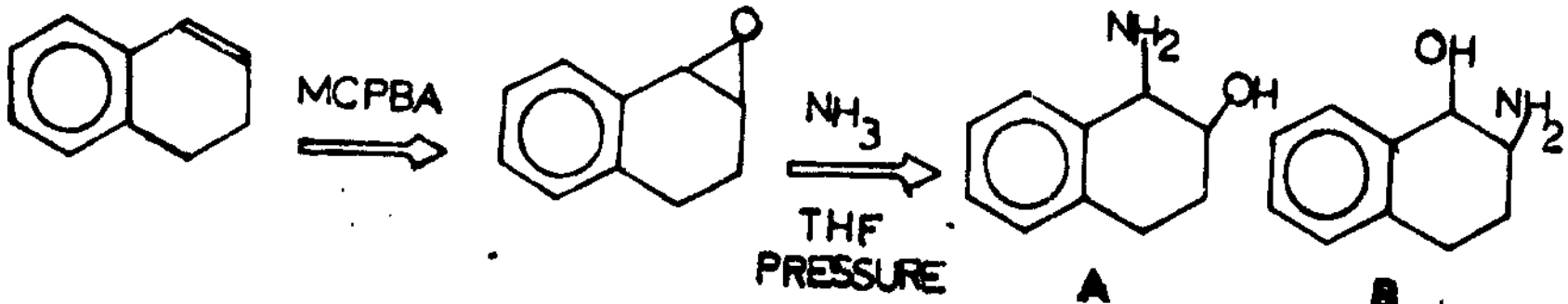


Figure 11

Ring opening of epoxides with ammonia proved to have some serious drawbacks. In non symmetric epoxides (ie. R≠R') a mixture of regioisomers is made. Compounds of type 1, the target molecule, were found to resolve quite well, whereas compounds of type 2 were not resolvable. When R=H. It is, of course, possible that changing reaction conditions, or using azide ion as the agent of nucleophilic attack could give primarilly the desired regioisomer, but even then this method has other serious drawbacks for most compounds. For example, the synthesis of compound A was undertaken by thepuoceure shown in Figure 12. More than one-half of the isolated product was the undesired isomer B. Furthermore only the trans amino alcohol is made. It was suspected that the cis amino alcohol would resolve better than the trans. In any event,a method which would give both cis and trans isomers was needed, because a

Figure 12



comparative study of the resolution of cis and trans isomers would be very informative about the mechanism of resolution. As a result of these problems the nucleophilic ring opening of αexpoxides was abandoned as a general synthetic route for amino alcohols.

The reductive amination of α hydroxy ketones using ammonium acetate and sodium cyanoborohydride[12] to give the amino alcohol was the preferred method when the corresponding amino acid ester was not readilly available or easilly synthesized by the strecker synthesis (Figure 13). The hydroxy ketones were prepared by the method of Simmons[9]. First the ketone was brominated in the α position using either bromine liquid or N-bromo succinimide[11]. The α bromo ketone was then converted to the α hydroxy ketone by refluxing in a sodium formate ethanol solution[9].

Figure 13

The synthesis of chiral amines was done either by formation of the oxime from the corresponding ketone, followed by LAH reduction, or by direct reductive amination using sodium cyanoborohydride.

SUGGESTED POSSIBLE IMPROVEMENTS OF CSP III

From the proposed mehanism of interaction of CSP III with amino alcohol 3,5 DNB derivatives (p. 21) it can be seen that the amide α to the chiral center serves no function other than the stabilization of the hydantoin ring. This amide hydrogen almost certainly leads to alternate mechanisms of retention which decrease resolution. If this amide hydrogen were removed, one would expect resolution to get better. This could be done by alkylation at this position, or by substitution of a methylene group at this position (Fig.14B R=H). Compounds of type B are known as succinimides. It is also possible that adding substituents to this methylene unit could increase resolution by adding conformational rigidity to the system and by blocking access to the back side of the naphthylene ring. These ideas will be tested by comparing resolution of hydantoins and succinimides upon CSP II.

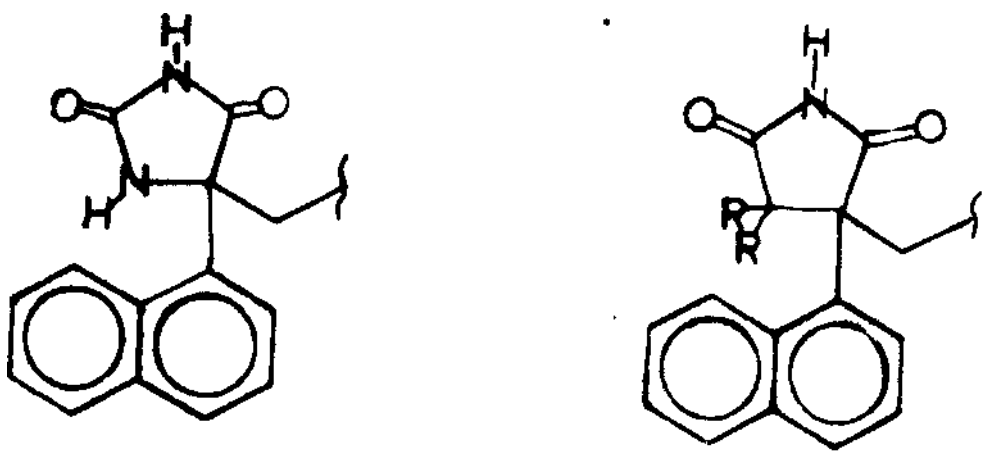
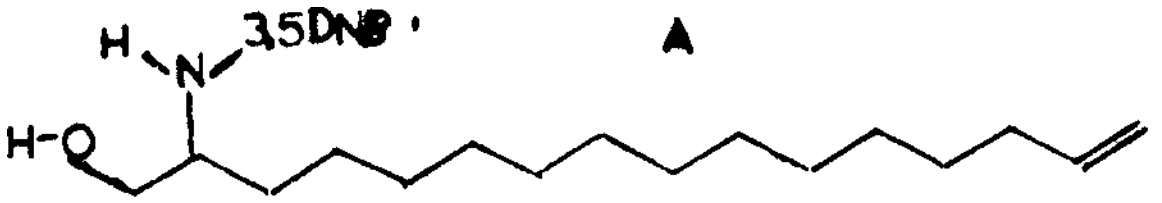


Figure 14

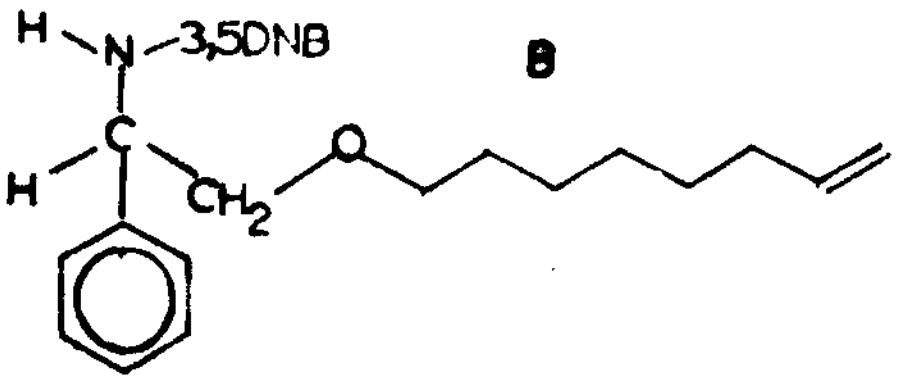
POSSIBLE AMINO ALCOHOL DERIVED CSPs

The possibility of an amino alcohol derived CSP has been investigated. Several possible CSP precursors are shown below in figure 15.

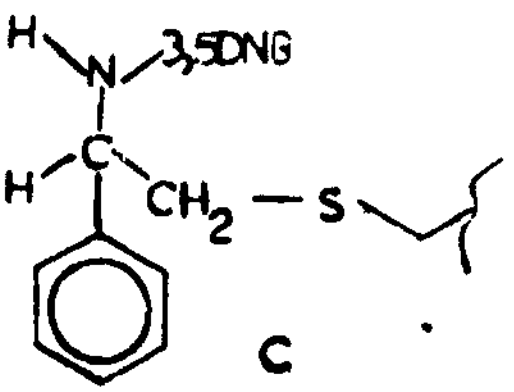
Figure 15



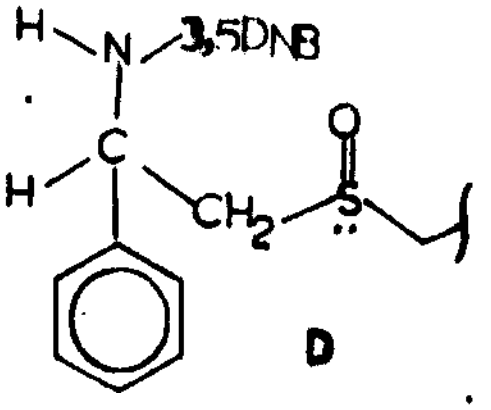
A



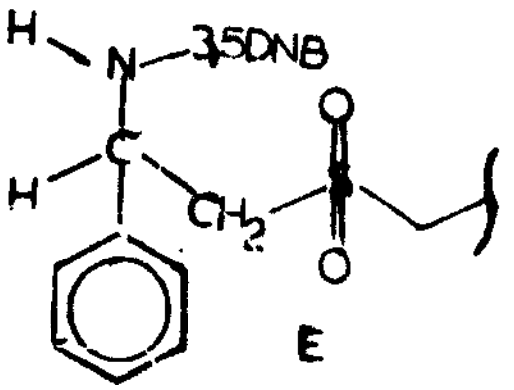
B



C



D



E

Compound A, which could be synthesized from the correspondin ω,ω olefin, could possibly be used as a precursor for an amino alcohol based CSP. This compound could probably be resolved preperatively upon CSP II to obtain resolved materiel for column production. This compound could be attached to silica gel using the method described by Myung Ho Hyun.[7] Alternately, the compound could be attached, with or without the terminal alkene, to an octadecyl silica gel column by hydrophobic interactions. This attachment procedure, while much simpler, allows only for reverse phase resolutions to be done on the CSP since organic solvents would wash compound A from the C_{18} support.

Compound B could be synthesized from the ketone derived from α bromo acetophenone and the anion of the alkyl alcohol. This compound could be attached covalently to silic using Hyun's method, or could be attached to C_{18} silica using hydrophobic attractions.

The corresponding thioether compound (Compound C) could be made using a similar route. This compound would probaly serve as a worse CSP than the amino ether compound (B) due to the lower basicity of the thioether sulfur, as compared to the ether oxygen. The thioether can easilly be converted into either the sulfoxide (compound D), or the sulfone (compound E). Both of these compounds would be expected to make excellent stationary phases. The introduction of another chiral center at the sulfoxide moeity may necessitateseperation of a single enantiomer for column formation. Besides lowering yields and being difficult the seperation of the sulfoxide enantiomers may prove futile since these compounds are known to be easilly racemized.

Model compounds of all the possible column precursors will be synthesized to determine the best cantidate for a new CSP.

CONCLUSION

A mechanism for the resolution of β amino alcohols and related compounds upon the hydantoin Chiral stationary phase has been proposed, and is well supported by the resolution data. Suggestions for improvements of the hydantoin CSP have been made on the basis of this mechanism. Several possible amino alcohol-type compounds have also been suggested as possible chiral stationary phases.

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