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Resolution of Racemic Alcohols into Optical Isomers

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The review analyses two classes of methods for the resolution of racemic alcohols into optical isomers: resolution by the synthesis and separation of diastereoisomeric derivatives and resolution without the formation or isolation of diastereoisomers. The fundamental classical studies on the resolution of racemic alcohols are noted. Attention has been concentrated on modern trends and modifications based on the latest advances in organic chemistry. It has been shown that the application of physicochemical methods leads to fundamentally new possibilities for the resolution of racemic alcohols. The bibliography includes 128 references.

CONTENTS

I. Introduction 592
II. Resolution of racemic alcohols by the synthesis and separation of diastereoisomers 592
III. Resolution of racemic alcohols without the synthesis or isolation of diastereoisomers 598

I. INTRODUCTION

The problem of the resolution of racemic alcohols arose in the past century in connection with the development of stereochemical hypotheses and a series of fundamental studies by Pasteur[1]. Pasteur's work determined the trend in studies in this field of organic chemistry for many decades. The list of racemic alcohols resolved hitherto is extremely impressive. The advances achieved in this field have been described in detail in a series of reviews[2,3] and monographs[4,5]. Modern studies on the resolution of racemic compounds differ qualitatively from earlier investigations as regards the aims of the investigators and the methods employed.

In connection with the vigorous development of biochemistry, it has become evident that the optical activity of natural compounds has a deep significance. The stereochemical characteristics of structure have a great influence on the biological activity of organic compounds. It is not fortuitous that all substances entering into the composition of cells and involved in fundamental vital processes (proteins, nucleic acids, lipids, polysaccharides, etc.) are optically active. Therefore the aim of the resolution of a racemate is frequently to obtain the optical isomer with the natural configuration. The principal task of the chemist is the creation and the preservation in the substances which he synthesises of the structures and configurations of the natural compounds.

A second feature of modern investigations is the improvement and modification of classical methods for resolution and, what is most important, the introduction into this field of modern physicochemical methods: gas–liquid chromatography (GLC), paper chromatography (PC), adsorption and ion-exchange chromatography, etc., which would make it possible to develop fundamentally new procedures for the resolution of racemates. The attempts at theoretical generalisations concerning resolution processes are important, since the available data for these processes still have more empirical features than any others in organic chemistry. The creation of a theory of resolution will make it possible both to predict the possibility of the resolution of a racemate by a particular process and to select the optimum method.

Together with the fundamental classical studies, this review describes the modern trends in the field of resolution of racemic alcohols based on the latest advances in organic chemistry. The methods of resolution have been divided into two main groups: (1) resolution by the synthesis and separation of diastereoisomeric compounds and (2) resolution without the synthesis or isolation of diastereoisomers.

II. RESOLUTION OF RACEMIC ALCOHOLS BY THE SYNTHESIS AND SEPARATION OF DIASTEREOISOMERS

The entire resolution process may be reduced to three consecutive operations (the so called "Pasteur's second method"): (1) the formation of a pair of diastereoisomers; (2) the separation of this pair using the differences between the properties of the diastereoisomers; (3) decomposition of the individual diastereoisomers with isolation of the optically pure enantiomorphs. For the first operation, it is necessary that the reaction of the racemic alcohol with the asymmetric agent should have a fairly high yield. The possibility of the second operation has been greatly improved recently when effective physicochemical methods have become available together with the crystallisation procedure. The third stage should be quantitative and should occur under mild conditions excluding the possibility of racemisation.

The two principal versions of resolution via diastereoisomeric compounds are discussed below.

1. INTRODUCTION INTO THE RACEMIC ALCOHOL MOLECULE OF A FUNCTIONAL GROUP CAPABLE OF FORMING DIASTEREOISOMERIC SALTS WITH OPTICALLY ACTIVE BASES

Historically this is one of the first and widely used methods. Salt formation is convenient because the resulting diastereoisomeric crystalline salt can be separated by fractional crystallisation. The first mention of the theoretical possibility of a large-scale employment of this type of resolution occurs in an early communication by Erlenmeyer and Arnold[6]. The fundamental idea of this method consists in the introduction into the alcohol molecule of the so called "connecting link" containing a functional group (carboxy-group) capable of forming a salt with an optically active base, for example:

$$R{-}OH + HOOCR_1COOH \rightarrow ROOCR_1COOH \xrightarrow{R^*} ROOCR_1COOH \cdot R^*,$$

where R–OH is the racemic alcohol, $HOOCR_1COOH$ the "connecting link", and R* the optically active base.

Evidently in this case the "connecting link" is a dibasic acid. Phthalic acid has been most frequently employed. The work of Pickard and Kenyon [7] was one of the earliest. Subsequently this acid was employed in many cases for the resolution of various racemic alcohols [8-10]. There is no necessity to enumerate all the resolutions achieved via acid phthalates—only a few need be considered. The classical method of Pickard and Kenyon (acid phthalate → brucine salt) has been used to resolve a number of diols, for example 3-(2-methylphenoxy)propane-1,2-diol [11] and butane-2,3-diol [12], and acetylenic alcohols, for example 3-methylpent-1-yn-3-ol [13] and 3,5-dimethylhex-1-yn-3-ol [14], difficulties arising in the last case in the fractional crystallisation of the brucine salts owing to a possible adsorption of the more soluble salt on the crystals of the less soluble salt. Recently the same method was employed to resolve 2-octanols (crystallisation of the salts with phenylethylamine, employed for the first time instead of the usual brucine) [15] and 2-butanols (salts with brucine) [16]. It is also possible to achieve the optical resolution of steroids containing a hydroxy-group via cinchonine salts of acid phthalates [17].

An interesting modification of this method was proposed in 1969, [18] consisting in the simultaneous application of the processes of Pope and Peachey [19] and Kantor and Hauser [20]. Pope and Peachey [19] showed that the resolution, which depends on relatively small differences between the solubilities of diastereoisomeric salts, can be made more effective when it involves an optically inactive reactant (A) competing with an optically active resolving agent (B) in the reaction with the racemic substance (±C). In successful cases the inactive reactant interacts completely with one enantiomorph while the optically active reactant interacts with the other.

(1) Classical resolution:

$$2(\pm C) + 2B_{act} \rightarrow (+)\text{-C.B.} + (-)\text{-C.B.}$$

(2) Pope and Peachey process:

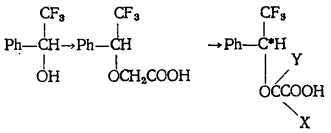
$$2(\pm C) + B_{act} + A_{inact} \rightarrow \begin{matrix}(+)\text{-C.B} + (-)\text{-C.A} \\ \text{or} \\ (-)\text{-C.B.} + (+)\text{-C.A}\end{matrix}.$$

Owing to the slight differences between the solubilities of the diastereoisomers, in process (1) their separation requires repeated recrystallisations. In process (2), where the products are not diastereoisomers, with a successful choice of A the separation could be achieved more readily and with a smaller number of recrystallisations. The process of Pope and Peachey was applied in the classical procedure [7] for the resolution of various secondary alcohols using triethylamine as A, brucine as B and acid phthalates derived from secondary alcohols as ±C. The optical purity of the alcohols isolated was high even without additional recrystallisation. The resolutions of 2-butanols, 2-octanols, and 1-phenylethanols were achieved. An additional advantage of this modification consists in a decrease of the consumption of the asymmetric reactants (B) which are usually expensive. In 1953 Kantor and Hauser [20] modified process (1) in the resolution of acid phthalates derived from 2-butanol by using a deficiency of the solvent for the reactants. After prolonged refluxing, the salts formed are effectively recrystallised before their isolation, which leads to higher optical yields in a single stage than in the usual procedure (82% optical purity in the case of 2-butanol). The simultaneous use of the process of Pope and Peachey and the modification of Kantor and Hauser leads to secondary alcohols with a higher optical purity than can be obtained by processes (1) and (2), [18] albeit at the expense of the yield.

In 1951 Zeiss showed [21] that tertiary alcohols, for example ethylmethylphenylmethanols, can be resolved by the method of Pickard and Kenyon (via the acid phthalate with subsequent formation of a brucine salt). Later Kenyon and coworkers carried out a similar resolution of 2-(1-naphthyl)butan-2-ol [22], 2-phenylbutan-2-ol [23], and 2-methyl-3-phenylpropane-1,2-diol [24]. Admittedly in the last case the resolution via the acid phthalate was unsuccessful since neither the phthalate nor its salts with various alkaloids were crystalline. The resolution was achieved by the reaction of 3-nitrophthalic acid followed by the formation of its strychnine salt. The diastereoisomeric salts were separated by crystallisation and decomposed with ammonia. Subsequent treatment of the 3-nitrophthalate with alkali yielded the optically active 2-methyl-3-phenylpropane-1,2-diol [24]. 3-Nitrophthalic acid was used in a number of other cases, for example by Holding et al. [25]

Succinic acid has also been used as a "connecting link" in the resolution of alcohols [26]. The optical isomers of cyclopent-2-en-1-ol were separated via the formation of salts of the acid esters of succinic acid and (+)-α-(1-naphthyl)ethylamine [27]. A number of resolutions have been carried out using phthalamic [28] and sulphuric [29] acids. Sulphates may be suitable for the resolution of certain glycols although as a rule acid alkyl sulphates are unstable and difficult to prepare.

It should be noted that the method under consideration does not always lead to the desired results. For example, the attempt to resolve the acid phthalates derived from 2,2,2-trifluoro-1-phenylethanols (I) via diastereoisomeric salts with optically active bases [30] was unsuccessful, since the ester of this alcohol proved to be readily hydrolysable even on treatment with brucine. This is because of the acidity of the alcoholic hydroxyl group. In 1968 the separation of the optical isomers of compound (I) was achieved [31] with a low yield by the fractional crystallisation of its esters with acetoxyandrost-5-ene-17β-carboxylic acid by a method which is discussed in detail in the next section. The high interest in 2,2,2-trifluoro-1-phenylethanol is due to the fact that in many cases the optically pure enantiomorph of this alcohol is a suitable solvent for NMR spectroscopic studies. Recently Pirkle et al. [32] achieved a new and novel resolution of compound (I) using a monobasic acid (substituted acetic acid) as the "connecting link":

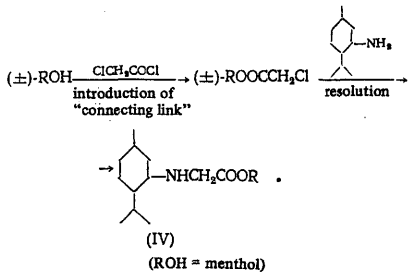


(I) (II) (IIIa-c)

(a, X=H, Y=Br; b, X=Br, Y=H; c, X=Y=Br)

The interaction of the alcohol (I) with ethyl bromoacetate led to 2-trifluoro(phenyl)ethoxyacetic acid (II), the optical isomers of which were then separated via salts with amphetamine [$PhCH_2CH(CH_3)NH_2$]. The α-bromoesters (III, a – c), readily hydrolysable to the optical isomers of the alcohol (I), were obtained by regenerating the optical isomers of the acid (II) from the diastereoisomeric salts and by treating them with bromosuccinimide. The introduction of bromine is necessary to facilitate the subsequent hydrolysis. 2,2,2-Trifluoro(1-naphthyl)ethanol optical isomers were separated similarly [32]. This method can be used for the resolution of other acids and similar alcohols when the classical process does not lead to the desired result.

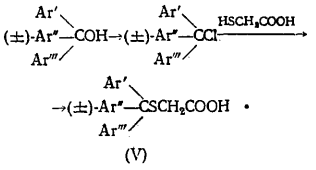
The formation of an ester with chloroacetic acid has been used to separate menthol isomers[33]. Here the asymmetric agent is (−)-menthylglycine formed by the reaction:



(IV)
(ROH = menthol)

The diastereoisomeric esters (IV) obtained were separated by crystallisation. The addition of acrylic acid has been used[34] to introduce a carboxy-group into the molecule. The reaction of (±)-1-trifluoromethylethanol with acrylic acid led to the adduct (±)-β-(1-trifluoromethylethoxy)-propionic acid the optical isomers of which were separated via diastereoisomeric salts with strychnine. The alcohol isolated from the separated adduct racemate was optically active.

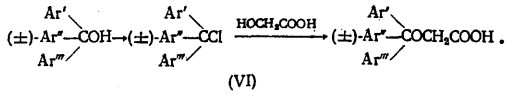
The separation of the isomers of trityl alcohols presents considerable difficulties. The separation of the isomers of biphenylyl-α-napthylphenylmethanol and 12-phenyl-12-benzoxanthenol, a trityl alcohol in which two aryl groups are linked together to form a heterocyclic ring, via the diastereoisomeric salts of substituted thioglycolic acid and alkaloids was reported by Wallis and Adams as late as 1933:[35]



(V)

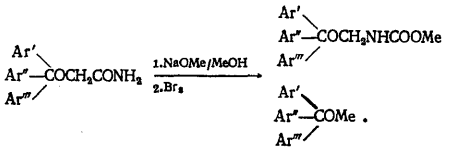
The isomers of the acid (V) were separated via their brucine salts. Treatment of the separated acids with silver nitrate in aqueous acetone yielded the optically active alcohols. Later this method was recognised as unsatisfactory[2] but Murr[36] showed that the optical yield amounts to 60% and may be increased.

The difficulty of separating the optical isomers of trityl alcohols is due to the lability of the trityl ester bond formed on introduction of a carboxy-group via the esters of dibasic acids. Although the separation of the isomers of α-naphthylphenyl-*p*-tolylmethanol by the classical method of Pickard and Kenyon[7] has been reported[37], it was not reproducible[38,39]. It was therefore suggested that the carboxy-group be introduced into the trityl alcohol molecule via an ether linkage[36,38]. The formation of an ether with glycolic acid was employed:

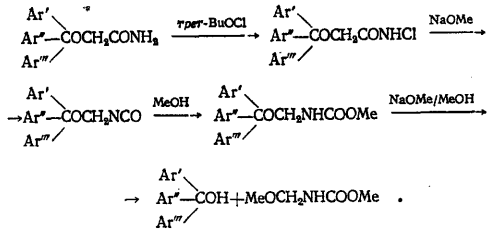


(VI)

The isomers of the acid (VI) were separated via salts with brucine [for the (−)-form] and cinchonidine [for the (+)-form]. The attempt to regenerate the optically active alcohol from the acid (VI) via the formation of an amide with subsequent Hofmann degradation did not yield the desired result owing to the dissociation of the ether linkage:

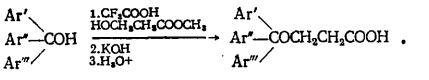


The yield of the ethyl ether of the tritylmethanol was 85%. The regeneration was achieved via the chloramide according to the following scheme:



The isomers of biphenylyl-α-naphthylphenylmethanol were separated in this way[38] but the attempt to separate those of biphenylyl-*p*-chlorophenylphenylmethanol were unsuccessful.

Derivatives of hydracrylic acids were used in 1969 to separate the isomers of α-naphthylphenyl-*p*-tolylmethanol[39]:



(±)-β-(α-Naphthylphenyl-*p*-tolylmethoxy)propionic acid was resolved via the diastereoisomeric salts with brucine. The alcohols were regenerated from the methyl esters of the separated acids by the reverse Michael reaction.

In conclusion mention should be made of a study[40] which proved to be useful in the isolation of the acid ester of an alcohol with a dibasic acid from the separated diastereoisomeric salts. The authors suggest that ion-exchange chromatography be used for this purpose, which makes it possible to isolate the acid ester in almost quantitative yield.

Summarising this method for the resolution of alcohols (using a "connecting link"), we should note that it made it possible to obtain a large number of optically active alcohols. The numerous dibasic acids and optically active bases (among which alkaloids are frequently employed) permit an extensive variation of their combinations in cases of failure. Nevertheless the investigator cannot be absolutely certain that the differences between the solubilities of the diastereoisomeric salts and their chemical stabilities will be sufficient for a successful resolution. A serious disadvantage of the method is associated with the isolation in a pure form and a sufficiently large amount of only one of the enantiomorphs (from the less soluble salt), while the other is isolated in only a small amount and with an inadequate optical yield. In view of the salt-like nature of the diastereoisomers, crystallisation is perhaps the only process suitable for their separation. The next modification of the resolution procedure via diastereoisomeric compounds does not suffer from this disadvantage.

2. DIRECT INTERACTION OF THE RACEMIC ALCOHOL WITH THE OPTICALLY ACTIVE RESOLVING AGENT AND THE FORMATION OF DIASTEREOISOMERIC DERIVATIVES

This method has the advantage that the stage involving the introduction of the "connecting link" is eliminated and the diastereoisomeric products are obtained by the direct interaction with a particular asymmetric agent. However, until recently this method had not been used quite so widely as the preceding one, since the diastereoisomeric compounds obtained (usually esters of an optically active acid) are normally difficult to crystallise. Nevertheless the use of modern physicochemical methods and of new asymmetric agents for the resolution (such as carbohydrate derivatives) has greatly extended the scope of this method.

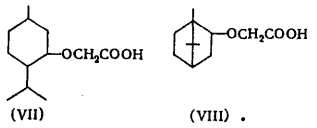
a. The Formation of Diastereoisomeric Esters of Optically Active Acids

Many optically active acids have been employed in classical resolution of this kind.

Mandelic acids [41]. This expensive reagent, which is used, in particular, for the resolution of (±)-menthol, is fully racemised in the alkaline hydrolysis of the diastereoisomers, which constitutes a serious disadvantage. The resolution of *erythro*-1-(4-hydroxyphenyl)-2-(1-methyl-2-phenoxyethylamino)propan-1-ol isomers [42] may serve as an example of resolutions with the aid of mandelic acid. The isomers of synthomycin were separated via esters with D-(−)-acetylmandelic acid, which yielded laevomycetin [43].

Camphoric acid. The majority of the diastereoisomeric esters of camphoric acid could not be separated by crystallisation, so that resolution with the aid of this agent is usually only partial [44]. Camphorsulphonic acids have also been used [45].

The employment of menthoxyacetic acid (VII) and bornylacetic acid (VIII) as asymmetric agents is promising for the resolution of phenols, glycols, and alcohols with a high molecular weight:



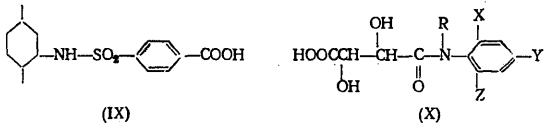
(VII) (VIII).

This version resembles the previous method, since an optically active alcohol is in fact employed for the resolution and the acetic acid residue constitutes a "connecting link". The acids (VII) and (VIII) are readily obtained from chloroacetic acid and the sodium derivatives of the corresponding alcohols. The resulting esters of the racemic alcohols have a fairly high specific optical rotation and are readily crystallised. Hydrolysis of the separated esters leads to an optically active alcohol, while the asymmetric agent is regenerated. The isomers of *trans*-cyclohexane-1,2-diol were separated in this way [46]. With the aid of the chloride of the acid (VII), Taub et al. [47] separated the isomers of the 4-*O*-methyl ester of the macrolide zearalenone and obtained the product with the natural configuration.

Recently the range of acids suitable for the resolution of alcohols via the diastereoisomeric esters have been greatly extended. Thus the reaction of (+)-*threo*-2-amino-1-(*p*-nitrophenyl)propane-1,3-diol hydrochloride or hydrogen sulphate with dibenzoyl-D-tartaric acid readily yields the crystalline neutral ester only with the D-isomer, which permitted a ready separation of the optical isomers [48]. (±)-2-Dimethylaminocyclohexanol was resolved with the aid of dibenzoyl-L-tartaric acid [49]. 3β-Acetoxyandrost-5-ene-17β-carboxylic acid was used in the resolution [31] of trifluoromethylphenylmethanol mentioned above. On the other hand, certain racemic steroids (the 3-methyl ether of oestradiol and 19-nortestosterone) were resolved via the formation of esters with the monomethyl ester of diacetyl-D-tartaric acid [50].

Aminoacids have been used in a number of cases for the resolution of alcohols. Halpern and Westley [51] proposed a method for the chemical resolution of racemic secondary alcohols into optical isomers, consisting in the esterification of the alcohol with an L-aminoacid in the presence of toluene-*p*-sulphonic acid with subsequent separation of the resulting ester sulphonates by fractional crystallisation and isolation of the optically pure (98 to 100%) (+)-isomer of the alcohol. Valine and alanine, with the aid of which it was possible to separate the isomers of 2-butanol, 2-methylcyclohexanol, menthol, and other alcohols, were employed as the L-aminoacids. In 1967 Germyn [52] extended the Halpern–Westley method to primary alcohols having obtained the enantiomorphs of 2-methylpentan-1-ol by the crystallisation of the tosyl derivatives of their esters with D- and L-valine; the use of alanine, tyrosine, leucine was unsuccessful. Probably a successful choice of aminoacid would make it possible to resolve also other racemic alcohols by the Halpern–Westley method, which can therefore be regarded as fairly general.

Campholic acid (1,2,2,3-tetramethylcyclopentanecarboxylic acid) has been proposed as a new convenient asymmetric agent for the resolution of menthol isomers [53], since only one of the diastereoisomeric esters [the (−)-menthyl ester of (+)-campholic acid] is crystalline, while the other is a liquid. This method is unsuitable for the resolution of the neo- and iso-forms of menthol, because neither diastereoisomeric ester is crystalline. Other agents which may serve for the resolution of alcohols are (−)-menthyl-*p*-sulphamoylbenzoic acid (IX), proposed by Everard and Mills [54], and also substituted tartranilic acids (X) suggested recently [55] for the resolution of racemic bases, since tartranilic acid itself has been used for the resolution of alcohols [56]:



(IX) (X)

(R=H, Me; X=NO₂, Cl, Br, Me, H; Y=H, Cl, Br; Z=H, Cl, Br.).

So far we have considered studies in which diastereoisomeric esters of racemic alcohols and an optically active acid were separated by crystallisation processes. As mentioned above, the development of physicochemical methods has made it possible to achieve the separation of many diastereoisomers, including those which are not crystalline. This has occurred mainly owing to advances in adsorption, ion-exchange, gas–liquid, and paper chromatography. Small differences between the physical properties of diastereoisomeric esters proved sufficient to separate small amounts of substances both for preparative and for analytical purposes. As a rule the use of physicochemical methods yields both enantiomorphs with a high optical purity.

Thus optically active secondary alcohols can be separated with about 100% optical purity via the chromatography of their esters with optically active acids on an optically inactive ion exchanger. The enantiomorphs of (±)-2-butanol were separated via the esters with

(−)-mandelic acid by chromatography on Dowex-50W-X2.[57] The resolution by analogous chromatography of 3-methylbut-2-yl lactate was even easier, 26 millimoles of a mixture of diastereoisomeric esters yielding 1.2 millimoles of the optically pure (+)-3-methylbutan-2-ol.[58] The separation of esters formed by (±)-2-methylbutan-1-ol with mandelic acid was not achieved by ion-exchange chromatography[58] but by gas–liquid chromatography (g.l.c.)[59]; the authors suggested that, for the successful chromatographic separation of the esters, it is necessary that the hydroxy-group should be linked to the asymmetric carbon atom.

Until recently the separation of diastereoisomeric esters by g.l.c. was used mainly for analytical purposes (for tests of the optical purity of the specimen, the determination of the absolute configuration, etc.)[60]. The optical purity of asymmetric alcohols was determined by g.l.c. in 1963.[61] Subsequently the formation of R-(−)-menthyloxycarbonyl derivatives of asymmetric alcohols (in particular α-phenylalkylmethanols) was used for this purpose[62]. Gil-Av et al. showed[60] that many gas–liquid chromatographic resolutions are possible also on a preparative scale. They separated[63] the esters formed by 2-alkanols containing between 4 and 19 carbon atoms with hydroxypropionic acids with the aid of g.l.c. on columns containing squalene, poly(propylene glycol), and other phases. The DL-(or LD-) derivatives have longer retention times than the LL-(or DD-) derivatives. Carbonic acid esters of the type ROCOOR' are particularly convenient for the preparative separation by g.l.c. of the enantiomorphs of racemic alcohols[64] in view of the ease of their synthesis and subsequent hydrolysis. The structural features of diastereoisomeric esters which favour their separation by g.l.c. have been investigated[65]. Such attempts at theoretical generalisation based on the accumulated factural data are particularly valuable, since they allow a well founded choice of a particular resolving agent for the racemic mixture, the prediction of the necessary chromatographic conditions (such as temperature, solvent, etc.), and an understanding of the reasons for the differences between the physicochemical properties of diastereoisomers. The authors deduced a number of relations: (1) the higher the conformational stability of the groups linked to both asymmetric centres, the better the separation; (2) in view of the small free energy differences, slight structural changes in diastereoisomeric esters can lead to a great improvement in separation; (3) in the study of the mechanism of the separation of esters by g.l.c., both steric and electronic factors can be taken into account.

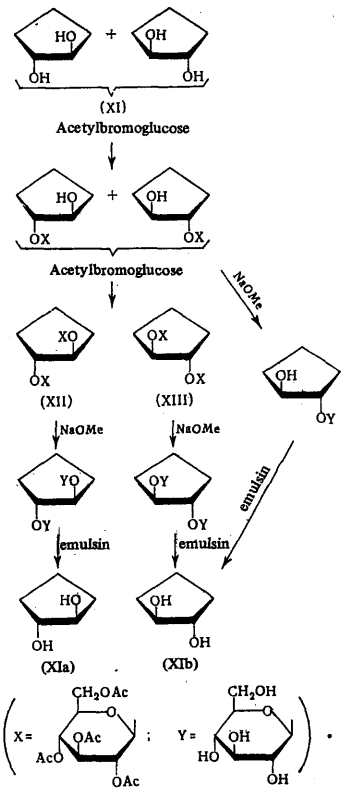
Among other modifications of this method, mention should be made of the possibility of separating the diastereoisomeric esters of lower alcohols and optically active acids by distillation through a sufficiently effective fractionating column using the slight differences between the vapour pressures of the diastereoisomers. This has been demonstrated in the separation of the optical isomers of 2-butanol via esters with L-lactic, L-2-acetoxypropionic, and D-2-propyloxypropionic acid by [fractional] distillation.

b. Formation of Diastereoisomeric Urethanes

The formation and separation of diastereoisomeric urethanes obtained by treating the racemic alcohol with L-menthyl isocyanate is one of the earliest methods of resolution[67]. However, the low availability of the asymmetric agent, the difficulty of hydrolysing the urethanes and also the conversion of L-menthyl isocyanate into an amine by hydrolysis greatly reduce its value[68]. The diastereoisomeric *N*-(1-phenylethyl)urethanes derived from certain secondary alcohols and obtained by the reaction of the aliphatic alcohol with a slight excess of (+)- or (−)-1-phenylethyl isocyanate, can be separated by thin-layer chromatography t.l.c. on silica gel G.[69] The following alcohols have been investigated: oct-1-en-3-ol, 2-octanol, 2-heptanol, 3-octanol, and 3-pentanol. It has been shown that the (++)-, and (−−)-diastereoisomers have a higher R_f than the (+−)- or (−+)-diastereoisomers, which makes it possible to establish the absolute configuration of the alcohol present in microamounts or to test its optical purity.

c. Resolution via Diastereoisomeric Carbohydrate Derivatives

Only a few cases of the use of carbohydrate derivatives as asymmetric agents for the resolution of racemic alcohols have been described in the literature. Probably this is because the glycosides employed are obtained in insufficient yields and the isolation of the optically active alcohols from the separated glycosides requires severe conditions or the use of enzymatic systems. Neuberg et al.[70] were the first to succeed in resolving pentyl alcohol, menthol, and borneol via the corresponding D-glucosides. Subsequently Helferich and Hiltmann[71] carried out a similar separation of the isomers of *trans*-cyclopentane-1,2-diol (XI):

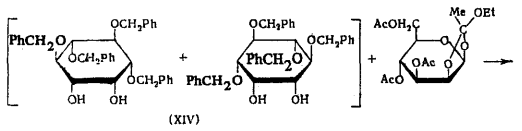


The diglucosides (XII) and (XIII) could be separated by crystallisation and enantiomorphs (XIa) $\{[\alpha]_D = -33.8°\}$ and (XIb) $\{[\alpha]_D = +33.8°\}$ were obtained after hydrolysing the

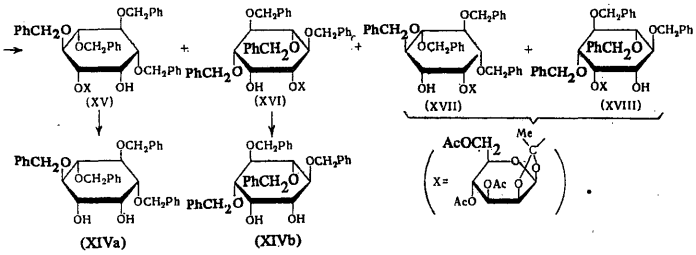
acetate groups and subsequent cleavage of the glycosidic linkage with the aid of emulsin. Hydrolysis of the monoglucoside led to a product the treatment of which with emulsin gave the dextrorotatory enantiomorph (XIb). The hydrolysis of a mixture of the diastereoisomeric menthol β-D-glucosides, as a result of which the menthol isolated after incomplete hydrolysis was optically active, shows an interesting optical selectivity [72].

The separation of the optical isomers of alcohols via diastereoisomeric glycosides has not found a wide application owing to numerous difficulties encountered in this procedure. Angyal and Shelton [73] synthesised in this way diastereoisomeric mannosylmyoinositols in a yield of about 4%. Although the diastereoisomers were readily separated by fractional crystallisation, it is impossible to employ them as the starting materials for the preparation of optically active asymmetrically substituted myoinositols owing to their small amount.

Nevertheless the use of other derivatives of monosaccharides and alcohols and different methods for the separation of diastereoisomers may greatly extend the scope of this method. This has been demonstrated for the resolution of asymmetrically disubstituted myoinositols, which have attracted attention in connection with their role in biochemical processes. The attempts at the resolution of these compounds by classical methods were unsuccessful [74]. A recently proposed method for the resolution of racemic myoinositols [75] is based on the interaction of the racemate with the orthoacetates of D-mannose and lower alcohols under the conditions of the transesterification reaction with subsequent separation of the resulting diastereoisomeric D-mannose orthoesters and myoinositol derivatives by chromatography or crystallisation and the isolation of the enantiomorph from the separated orthoesters. For example, 1,4,5,6-tetra-*O*-benzylmyoinositol (XIV) was resolved in this way [76]:



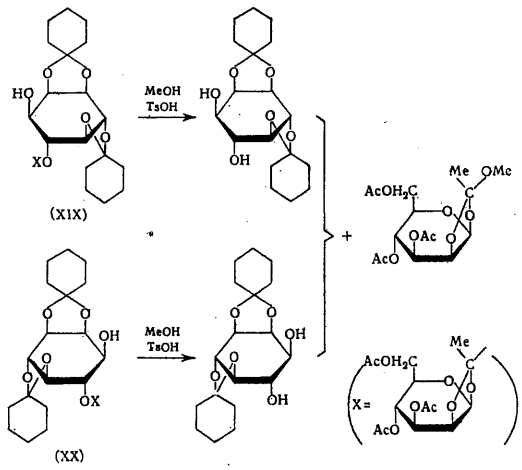
(XIV)



(XV) (XVI) (XVII) (XVIII)

(XIVa) (XIVb)

The diastereoisomeric orthoesters (XV), (XVI), and the mixture of (XVII) and (XVIII) were separated by crystallisation and preparative t.l.c. The enantiomorphs (XIVa) and (XIVb) were isolated by mild acid hydrolysis of the separated orthoesters (XV) and (XVI). The isomers of 1,2,4,5,6-penta-*O*-benzylmyoinositol [77] and 1,2:5,6-di-*O*-cyclohexylidenemyoinositol [78] were separated similarly, in the latter case the enantiomorphs being isolated from the separated diastereoisomeric orthoesters (XIX) and (XX) in high yields by "reverse" transesterification with methyl alcohol, since acid hydrolysis was inapplicable owing to the lability of the *trans*-cyclohexylidene group:



(XIX)

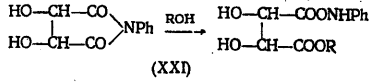
(XX)

We believe that this method may prove to be suitable for the resolution of other racemic compounds, in particular cyclic alcohols with a fixed steric configuration, with the aid of a suitably selected monosaccharide orthoester.

Mention should also be made of a study [79] where it was shown that the configuration of carbohydrates can be established by means of their diastereoisomeric derivatives with alcohols. This applies to the carbohydrates which can be readily and quantitatively oxidised to aldanic acids, the esterification of which with racemic alcohols (2-butanol, 3-methylbutan-2-ol, and 3,3-dimethylbutan-2-ol) leads to volatile diastereoisomers which can be separated by g. l. c. The peaks were identified by comparison with a specimen obtained as a result of esterification with an optically active alcohol. In all cases (lyxonic, ribonic, xylonic, arabonic, glyceric, and other acids), the separation was best with sterically hindered alcohols, in agreement with the findings of Karger and coworkers [64].

g. Other Asymmetric Agents

Of other agents proposed for the direct formation of diastereoisomeric derivatives of racemic alcohols, mention should be made of *N*-phenyl-D-tartrimide (XXI), which reacts with alcohols according to the following mechanism [56]:



(XXI)

If the alcohol molecule contains another functional group, it too can be used for the direct formation of diastereoisomeric products. Thus separation of the enantiomorphs of certain carbinols of the type RR'R"COH, where R = phenyl, R' = 2-pyridyl or 4-pyridyl, and R" = n-octyl, was achieved via salts with D-camphorsulphonic or tartaric acids [80]. Natural D-(+)-*erythro*-dihydrosphingosine was obtained by the separation of the racemic aminodiol via the salts with L-glutamic acid [81] and the enantiomorphs of 3-*O*-benzoylsphingosine were separated with the aid of D- and L-tartaric acids [82].

III. RESOLUTION OF RACEMIC ALCOHOLS WITHOUT THE SYNTHESIS OR ISOLATION OF DIASTEREOISOMERS

This large group of methods for the resolution of racemic alcohols, which includes, together with Pasteur's classical procedures, also modern methods which have been recently developed, involves a direct resolution of racemates without the formation or isolation of diastereoisomeric products. If the diastereoisomers are in fact formed, they are usually extremely unstable and cannot be isolated. An advantage of such methods is the absence of the necessity for the isolation of diastereoisomers which in many cases (for example in separation by adsorption) makes it possible to carry out the separation as a continuous process.

1. RESOLUTION OF RACEMIC ALCOHOLS BY THE CRYSTALLISATION OF ENANTIOMORPHS

The so called "Pasteur's first method" [83] is based on the mirror image differences between the enantiomorph crystals, which can therefore be separated mechanically. This method is laborious and slow and has not found a serious practical application. Very often attempts at resolution proved unsuccessful: for example, LeBel [84] could not separate the crystals of barium 2-butylsulphate; the attempt to separate mechanically the crystals of (±)-erythritol [85] was also unsuccessful. Although there is some evidence that (±)-*cis*-β-decalol can be separated by Pasteur's first method using the properties of its crystals [86], no actual resolution of this substance has been reported in the literature. The separation of the enantiomorphs of isohydrobenzoin has been quoted as a successful example [87].

The resolution of racemates by selective crystallisation is of more interest. It is usually achieved by introducing a seed of one of the enantiomorphs into a supersaturated solution of the racemate. Studies on such resolution were begun with the publication in 1866 of the report by Gernez[88], but so far few attempts have been made at a theoretical generalisation of the numerous factural data available. It is now known only that the resolution is possible if the solubility of each pure enantiomorph is higher than that of the racemic modification [89] and if the racemate consists of a mechanical mixture of the enantiomorph crystals and not a solid solution. Many substances resolved by crystallisation are known. Thus Shelomova et al. [90], who employed the method of Velluz et al. [91], elaborated the conditions for the resolution of (±)-*threo*-2-amino-1-*p*-nitrophenylpropane-1,3-diol, which involve rapid cooling of a system consisting of 86% of the racemate in the form of the hydrochloride, 14% of the free racemic aminodiol, and 10% (relative to the weight of the racemate) of the L-(+)-form. The study of the solubility curves of the racemate and the enantiomorphs of the diol showed that, if the system contains an excess of one of the enantiomorphs, its crystallisation begins. In his large review, Secor [92] quotes numerous cases of selective crystallisation, discusses the theoretical possibilities and limitations of the method, and examines the phase diagrams for systems containing optical isomers.

Powell [93] noted that the racemic substance can form crystalline molecular compounds with an optically inactive compound. This results in overcoming the van der Waals forces maintaining the enantiomorphs in the crystalline racemate and, instead of the racemate (*dl*), the *Md* and *Ml* compounds crystallise from solution, *M* being the optically inactive substance. The majority of these molecular compounds are resolved spontaneously. The advantages of such resolutions are evident: no chemical reactions are involved, there is no need to introduce additional functional groups into the racemic alcohol molecule, it is possible to resolve small amounts of substances into their enantiomorphs, etc. Powell [93] suggests that similar processes may have resulted in the appearance of the initial asymmetry in nature. A study [36] of the resolution of biphenylyl-1-(8-methylnaphthyl)phenylmethanol may be quoted as an example of the "spontaneous" resolution of racemic alcohols: the (+)-enantiomorph was isolated by crystallisation from ether and the (−)-enantiomorph was crystallised from cyclohexane.

2. CHROMATOGRAPHIC RESOLUTION

This group of methods includes the chromatographic resolutions on natural asymmetric agents (wool, polysaccharides, crystals of optically active quartz, and others [94]) and also on synthetic asymmetric agents. Examples of resolution by adsorption are discussed in detail in Klabunovskii's review [95]. The relations governing the resolution of racemic substances on starch columns have been formulated [96]. The use of brucine as an adsorbent made it possible to resolve (±)-2-octyl hydrogen phthalate [97]. Recently many resolutions have been carried out on synthetic optically active ion-exchange resins. Many such ion exchangers have been synthesised. Suda and Oda [98] prepared resins from the chloromethylated copolymer of styrene with divinylbenzene and brucine or quinone. In a recent review, Suda [99] discusses the synthesis of optically active ion-exchange resins by the polycondensation of various optically active acids or bases and the separation of racemic substances on these exchangers. Poly{[L-(1-carboxy methyl)sulphamoyl]styrene} and the D-isomer of the polymer were employed for the partial resolution of atrolactic acid [$C_6H_5(OH)C(CH_3)COOH$], mandelic acid, and other substances [100]. There is no doubt that synthetic optically active ion-exchange resins can also be employed for the resolution of various derivatives of racemic alcohols. Mixtures of racemic terpene alcohols were resolved by being brought into contact with optically active polymers under the conditions of the transesterification reaction with subsequent elution [101]. Racemic menthol in tetrahydrofuran in the presence of catalytic amounts of toluene-*p*-sulphonic acid was introduced into a column containing a granular resin obtained by the copolymerisation of a 1 : 1 mixture of (+)-s-butyl methacrylate and maleic anhydride with 2–20 wt. % of divinylbenzene and then slowly eluted with tetrahydrofuran containing alcohol and toluene-*p*-sulphonic acid, which led to the isolation of the enantiomorphs of menthol.

In 1969 resolutions with the aid of liquid ion exchangers were achieved [102]. The authors synthesised two liquid ion-exchangers: (−)-*N*-methyl-α-methylbenzyl-(1-naphthyl)amine and (−)-*N*-α-methylbenzyl(n-octadecyl)amine and determined the separation factors for the enantiomorphs of the sodium salts of (±)-mandelic acid and (±)-*N*-acetylalaline in periodic partition between aqueous solutions of the salts and the solutions of the ion exchangers in chloroform. The optical isomers of the first salt were separated by countercurrent partition; the optically pure product can be isolated even if the liquid ion exchanger is not optically pure. Although this study concerns directly only the resolution of salts of racemic

acids, the equations and principles quoted are also applicable to the resolution of other racemic substances, including alcohol derivatives, by chromatography or countercurrent partition, which yields in a single operation both enantiomorphs in equal amounts.

The development of the gas–liquid chromatographic method has led to the possibility of direct resolution of racemic alcohols and other substances by g.l.c. on an optically active stationary phase. The studies in this field were stimulated by the fact that the influence of solvents (employed in adsorption chromatography), which might have a levelling effect on the difference between the absorption properties of the enantiomorphs, is eliminated in g.l.c. Experimental conditions for the resolution of α-pipecoline, acetylmethylmethanol and other compounds have been described [103] but subsequently this study could not be reproduced [104]. Later Gil-Av et al. reported the resolution of racemates by g.l.c. on an optically active stationary phase using capillary columns equivalent to a large number of theoretical plates. Apart from its use for analytical purposes, the resolution of racemates by g.l.c. can also be of preparative value [60]. The resolution of 2-butanol, 2-pentanol, and phenylethanol by g.l.c. on an optically active quartz column has been investigated [105] and has been shown to be unsatisfactory.

The resolution of racemates by paper chromatography has been discussed by Yanovskaya [106]. The most detailed reviews of the chromatographic resolution of racemates have been published by Rogozhin and Davankov [107] and Buss and Vermeulen [108].

3. RESOLUTION WITH THE AID OF OPTICALLY ACTIVE LIQUID SUBSTANCES

A study of the resolution of racemates with liquid ion-exchangers has already been mentioned [104]. The different interfacial tensions between the enantiomorphs and an optically active liquid can also be used for the resolution of a racemic mixture [109]. If the liquid racemate is emulsified in an optically active liquid or in a solution of an optically active substance, the enantiomorphs will be deposited at different rates.

Nevertheless the most promising processes for resolution with the aid of optically active liquids are crystallisation and extraction. Although van't Hoff [110] suggested as early as the end of the last century that the solubilities of enantiomorphs in optically active substances will be different, for a long time resolution by crystallisation from optically active solvents could not be achieved. Recently examples of such resolutions have been published. 2,3-Dibromobutane-1,4-diol and di-(4-pyridyl)glycol were resolved into optical isomers by crystallisation from di-isopropyl-D-tartrate [111]; after the third recrystallisation 167 mg (!) of the optically active substance was obtained from 20 g of the racemate. The same substances were partly resolved by partitioning their racemic modifications between an aqueous medium and D-tartaric acid esters [112]. It has been suggested that there is a type of bonding between the racemate and the solvent medium and that, owing to the differences between the configurations, one enantiomorph is geometrically more suitable for the formation of such bonding than the other. If hydrogen bonds are possible, these are the most likely to be formed [113].

If each of the two enantiomorphs forms an azeotrope with a third optically active substance, the diastereoazeotropes can have boiling points differing so much that they can be separated by fractional distillation [114]. This hypothesis has not been confirmed in attempts to resolve 2-octanol with (+)-limonene as the third component under different experimental conditions. Nevertheless the study of the boiling point diagrams for systems gives rise to the hope that certain resolutions can be achieved by the distillation of diastereoazeotropes.

4. OTHER METHODS OF RESOLUTION

Sometimes the racemate is resolved by its interaction with an optically active substance which results in the formation of readily decomposed molecular complexes instead of diastereoisomers. By employing digitonin as the complex-forming agent, it proved possible to resolve the racemates of α-terpineol, tetrahydro-β-naphthol, and *i*-carvomenthol [115]. 2-Phenylbutan-1-ol was partly resolved into its optical isomers with the aid of deoxycholic acid [116]. The authors suggested that the optically selective action of lipolytic enzymes may be due to bile acids.

Numerous examples of the kinetic resolution of alcohols by selective interaction with an optically active agent have been described in the literature. Marckwald and McKenzie [117] carried out a partial esterification of (±)-2-octanol with D-tartaric acid, the unreacted part of the alcohol proving to be optically active. Here mention should also be made of stereoselective biochemical processes which consist in the selective action of various micro-organisms on one of the enantiomorphs (the so called "Pasteur's third method" [118]).

The methods enumerated in this section have been analysed in detail in special reviews and monographs [2–5].

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A good example of classical resolution carried out recently is the separation of the enantiomorphs of 2-chloro-9-fluorenol [119]. The attempts to resolve 2-chloro-9-fluorenyl phthalate with the aid of brucine, strychnine, quinidine, and cinchonidine in various solvents were unsuccessful; also unsuccessful were the attempts at resolution with the aid of ephedrine in benzene, chloroform, and acetone. A partial resolution was achieved via the diastereoisomeric salts with ephedrine in alcohol. The acid phthalate obtained was crystallised from chloroform; the racemate was less soluble (cubic crystals) and the optically active form was subsequently isolated in the form of long needles. The isolation of the enantiomorphs of 2-chloro-9-fluorenol from the acid phthalates was achieved by treatment with methylmagnesium iodide in ether, since hydrolysis leads to racemisation. Anders and Cooper [121] isolated by g.l.c. the diastereoisomeric esters formed by racemic alcohols with 3β-acetoxy-Δ^5-etienic acid, which were separated previously [120] by fractional crystallisation. Methylphenylmethanol, ethylphenylmethanol, cyclohexylphenylmethanol, n-hexylmethylmethanol, and other alcohols were resolved in this way. Preparative separation of diastereoisomeric alcohol derivatives by g.l.c. was achieved by a number of other investigators [122,123]. For example the racemic mixture of 3,3-dimethylbutan-2-ols was resolved [123] by synthesising their esters with *N*-trifluoroacetyl-L-alanine, which were then separated by g.l.c. In a continuation of studies [79] on the resolution of racemic carbohydrates, Pollock and Jermany [124] separated by g.l.c. the diastereoisomeric esters formed by galactonic and gluconic acids with 2-butanol, 3-methylbutan-2-ol, and

3,3-dimethylbutan-2-ol. A further development of the theoretical aspects of the resolution of diastereoisomers by g.l.c. is described by Feibush [125].

Recently the present authors reported [126] the separation of the optical isomers of 1,2,4,5,6-penta-*O*-acetylmyoinositol via the diastereoisomeric D-mannose orthoacetates and of 1,4,5,6-tetra-*O*-acetylmyoinositol with subsequent deacetylation of the separated orthoacetates and the isolation of the enantiomorphs of myoinositol penta-acetate by mild acid hydrolysis. Molotkovsky and Bergelson [127] carried out a new resolution of myoinositol penta-acetates by the crystallisation of the diastereoisomeric salts of the acid oxalates of myoinositol penta-acetate with quinidine or α -phenylethylamine. The physicochemical constants of the enantiomorphs, which they isolated by treating the separated acid oxalates with lead tetra-acetate in a pyridine–dioxan mixture in an atmosphere of argon, were close to those of the optically active myoinositol penta-acetates which we obtained previously [126].

Modern methods for the resolution of alcohols are described in a recent review by Boyle [128].

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