

# Methods of Optical Resolution

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## 1 Introduction

The practical problem of separating a racemic modification into its optically active components is one which has remained of paramount importance ever since the pioneering discoveries of Louis Pasteur in the nineteenth century. Indeed, many of the methods which he was the first to describe are still among the most important available to the chemist today. Nevertheless, as in all branches of chemistry, significant progress continues to be made, new reagents discovered and new techniques applied, and it is the intention of this review to give a concise account of those methods of resolution which are being found most useful by chemists at the present time, laying particular stress on the newer and more interesting reagents and techniques.

In principle, all methods of resolution depend on one or other of two facts. (i) Products formed by the interaction of two enantiomers with a chiral reagent will be diastereomerically related and will therefore be susceptible to separation by conventional physical methods such as fractional crystallisation, distillation, extraction, column chromatography, or gas-liquid chromatography.<sup>1</sup> Resolution is achieved if the desired enantiomers can be individually regenerated from the separated diastereomers. (ii) Enantiomers react at different rates with a chiral reagent. When a pair of enantiomers A and  $\bar{A}$  is allowed to interact with a chiral reagent B, the transition states of the interaction,  $A \dots B$  and  $\bar{A} \dots B$ , are no longer mirror images of each other. These transition states are diastereomeric rather than enantiomeric and they will differ in, amongst other properties, internal energy. It follows that the activation energy for the reaction of A with B will be different from that of  $\bar{A}$  with B and hence the difference in rates of reaction. Kinetic methods of resolution exploit this difference.

## 2 Resolution by Formation, Separation, and Decomposition of Diastereomers

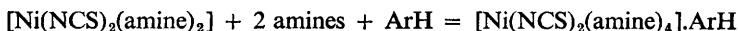
This general method of resolution is by far the most important. Since the type of reagent used depends on the functional groups present, it is convenient to consider separately the different classes of compound which may need to be resolved.

**A. Resolution of Acids.**—The naturally occurring alkaloids, which were first used as resolving agents by chemists in the nineteenth century, remain the most important reagents in use today for the resolution of acids. The only optically

<sup>1</sup> B. L. Karger, S. Herliczek, and R. L. Stern, *Chem. Comm.*, 1969, 625.

active base which rivals them in general usefulness is 1-phenylethylamine, both enantiomers of which have been widely employed since Theilacker and Winkler<sup>2</sup> described a simple resolution of the racemic base using tartaric acid. Ault has described a similar procedure<sup>3</sup> which has recently been modified,<sup>4</sup> and large quantities of (+)- and (-)-1-phenylethylamine are now easily obtainable in optically pure form. Related bases which have been used as resolving agents are 1-(1-naphthyl)ethylamine<sup>5</sup> and 1-(2-naphthyl)ethylamine.<sup>6</sup>

The enantiomers of most 1-arylalkylamines can be efficiently purified through clathrate formation between their co-ordination complex  $[\text{Ni}(\text{NCS})_2(\text{amine})_4]$  and an aromatic compound,  $\text{ArH}$ .<sup>7</sup> The clathrate is formed by reacting the diamine complex with additional amine, together with the aromatic compound.



It was found that if the additional amine used is already partially resolved and is added in excess, then racemic amine is preferentially co-ordinated into the clathrate, thus increasing the optical purity of the unreacted amine. In a single operation based on this procedure, the optical purity of a sample of 1-phenylethylamine was raised from 50—95%.

Only two other bases need be mentioned as reagents for resolution of acids. The first is dehydroabietylamine. Introduced by Sjöberg and Sjöberg<sup>8</sup> in 1964, it has since acquired considerable popularity, for it is inexpensive, relatively non-toxic, and forms highly crystalline salts with many organic acids.<sup>9</sup> It has proved successful on several occasions where conventional alkaloidal reagents failed.<sup>10</sup> The second is L(+)- and D(-)-*threo*-1-*p*-nitrophenyl-2-aminopropane-1,3-diol which was introduced some time ago as a very successful reagent for the resolution of *N*-derivatives of amino-acids and has also been used for resolving carboxylic acids.<sup>11</sup> The racemic base has been resolved by a wide variety of reagents<sup>12</sup> and recently a new method for its resolution was reported using (+)- and (-)-*N*-(1-phenylethyl)succinamic acid.<sup>13</sup> The D-enantiomer can be easily converted into the related D(-)-*threo*-2-dimethylamino-1-*p*-nitrophenylpropane-1,3-diol and this has also been used as a convenient resolving agent for carboxylic acids.<sup>14</sup>

<sup>2</sup> W. Theilacker and H.-G. Winkler, *Chem. Ber.*, 1954, **87**, 690.

<sup>3</sup> A. Ault, *J. Chem. Educ.*, 1965, **42**, 269; *Org. Synth.*, 1969, **49**, 93.

<sup>4</sup> A. C. Cope, W. R. Moore, R. D. Bach, and H. J. S. Winkler, *J. Amer. Chem. Soc.*, 1970, **92**, 1243.

<sup>5</sup> T. Y. Jen, G. A. Hughes, and H. Smith, *J. Amer. Chem. Soc.*, 1967, **89**, 4551.

<sup>6</sup> A. Fredga, B. Sjöberg, and R. Sandberg, *Acta Chem. Scand.*, 1957, **11**, 1609.

<sup>7</sup> M. Hanotier-Bridoux, J. Hanotier, and P. de Radzitzky, *Nature*, 1967, **215**, 502.

<sup>8</sup> B. Sjöberg and S. Sjöberg, *Arkiv Kemi*, 1964, **22**, 447.

<sup>9</sup> W. J. Gottstein and L. C. Cheney, *J. Org. Chem.*, 1965, **30**, 2072.

<sup>10</sup> A. Heymes, M. Dvolaitzky, and J. Jacques, *Bull. Soc. chim. France*, 1968, 2898; D. J. Cram, W. T. Ford, and L. Gosser, *J. Amer. Chem. Soc.*, 1968, **90**, 2598.

<sup>11</sup> L. D. Bergel'son, E. V. Dyatlovitskaya, M. Tichy, and V. V. Voronkova, *Izvest. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, 1962, 1612; *Egyesült Gyógyszer és Tápszergyár, B.P.* 851,789; (*Chem. Abs.*, 1961, **55**, P25864e).

<sup>12</sup> J. Kučera, *Coll. Czech. Chem. Comm.*, 1955, **20**, 968.

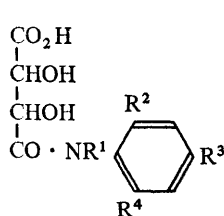
<sup>13</sup> E. Felder, D. Pitre, and S. Boveri, *Helv. Chim. Acta*, 1969, **52**, 329.

<sup>14</sup> G. Nominé, G. Amiard, and V. Torelli, *Bull. Soc. chim. France*, 1968, 3664.

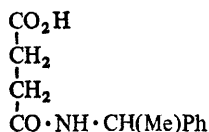
Reactions other than salt formation can be used for the resolution of acids. For instance, a racemic acid may be converted into diastereomeric amides using an optically active amine. Dehydroabietylamine has recently been used as the reagent in a resolution of this type.<sup>15</sup> Similarly, esterification of a racemic acid with an optically active alcohol will yield diastereomeric esters. The commonest optically active alcohol used as a reagent in this connection is menthol. Neither of these procedures has attained much importance, however.

**B. Resolution of Bases.**—Tartaric acid, camphor-10-sulphonic acid, and 3-bromocamphor-8-sulphonic acid\* remain the most useful reagents for the resolution of bases, although in recent years dibenzoyltartaric and di-*p*-toluoyl-tartaric acids have become almost as popular. Two other well-known reagents are malic and mandelic acids. A common problem in resolution is that the more soluble diastereomeric salt may be difficult to obtain pure and thus on regeneration will afford only partially resolved product. Leigh has recently described a promising new procedure for overcoming this difficulty.<sup>16</sup> The partially resolved mixture is stirred with petrol ether containing a simple primary or secondary amine or alcohol, *e.g.* *t*-butylamine. Leigh found that an optically active compound is more soluble in this solvent system than is its corresponding racemate so that material recovered from solution is almost optically pure while undissolved solid is largely racemic. Indications are that this procedure may be capable of general application.

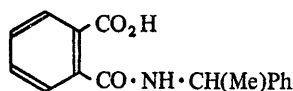
New resolving agents which may prove to be very useful<sup>17</sup> are the optically active tartranilic acids (1), prepared by reaction of a substituted aniline with (+)- or (–)-diacetoxy succinic anhydride [easily made from (+)- or (–)-tartaric acid] followed by hydrolysis. Several bases which had been previously resolved only with difficulty were readily resolved using reagents of this type. The optically active tartranilic acids are chiral monoamides of a dicarboxylic acid in which the centre of chirality lies in the acid moiety. One can also prepare a chiral dicarboxylic acid monoamide in which the centre of chirality lies in the amine residue and, recently, Felder, Pitre, and Boveri<sup>13</sup> reported that the monoamides



(1)



(2)



(3)

\* Older name is  $\alpha$ -bromocamphor- $\pi$ -sulphonic acid.

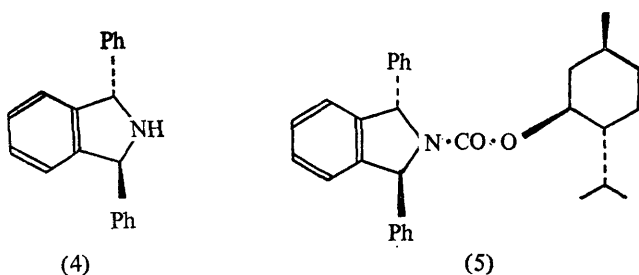
<sup>15</sup> G. Haas and V. Prelog, *Helv. Chim. Acta*, 1969, **52**, 1202.

<sup>16</sup> T. Leigh, *Chem. and Ind.*, 1970, 1016.

<sup>17</sup> T. A. Montzka, T. L. Pindell, and J. D. Matiskella, *J. Org. Chem.*, 1968, **33**, 3993.

formed from optically active 1-phenylethylamine and either succinic or phthalic acid, giving *N*-(1-phenylethyl)succinamic acid (2) and *N*-(1-phenylethyl)-phthalamic acid (3) respectively, can be used very effectively for the resolution of bases. Yields are good and the products are obtained in high optical purity. Another reagent which has been found useful in the resolution of a variety of bases is *N*-acetyl-leucine.<sup>18</sup>

Resolution of amines by conversion into diastereomeric amides is not a common procedure because the separated amides often prove difficult to hydrolyse. Carpino has suggested<sup>19</sup> the preparation of diastereomeric carbamates instead of amides and has shown how these can be successfully separated and cleaved to regenerate optically active amine. For instance, racemic amine (4) was



treated with (–)-menthyl chloroformate and after fractional crystallisation the carbamate (5) was obtained pure. This carbamate was cleaved with hydrogen bromide to yield dextrorotatory amine (4). The use of other carbamates was also investigated.

**C. Resolution of Amino-acids.**—Amino-acids, in the form of their *N*-acyl derivatives, may be resolved using any of the standard optically active basic resolving agents already described. Particular mention may be made of 1-*p*-nitrophenyl-2-aminopropane-1,3-diol, introduced by Velluz, Amiard, and Heymès,<sup>20</sup> and also of *D*- and *L*-tyrosinehydrazide, described more recently by Vogler and Lanz.<sup>21</sup> This latter reagent was used to resolve the *N*-carbobenzyloxy-derivatives of proline, alanine, and isoleucine. The procedure described is simple, gives high yields of each enantiomer (80%), even when using only half the molar amount of reagent, and should be capable of wider application. Furthermore, it is particularly useful in peptide synthesis because the optically active amino-acid is obtained with the amino-group already protected by the carbobenzyloxy-group.

An interesting method of resolution which obviated the necessity for preparing an *N*-acyl derivative of the amino-acid was described by Halpern, Sargeson, and

<sup>18</sup> L. Töke, K. Honty, and C. Szántay, *Chem. Ber.*, 1969, **102**, 3248.

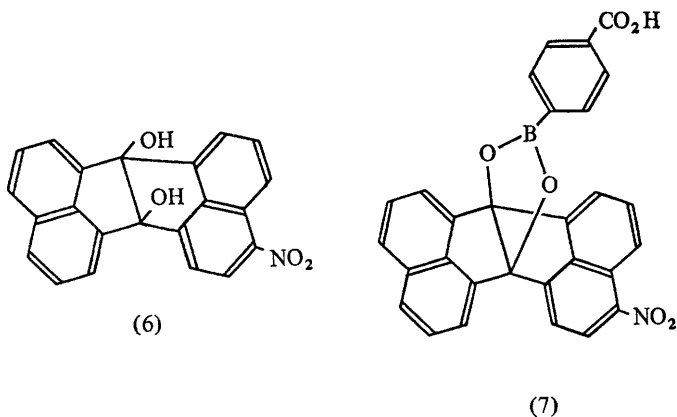
<sup>19</sup> L. A. Carpino, *Chem. Comm.*, 1966, 858.

<sup>20</sup> L. Velluz, G. Amiard, and R. Heymès, *Bull. Soc. chim. France*, 1955, 201.

<sup>21</sup> K. Vogler and P. Lanz, *Helv. Chim. Acta*, 1966, **49**, 1348.

Turnbull,<sup>22</sup> who treated racemic phenylalanine in alkaline solution with salicylaldehyde, thus forming a pair of enantiomeric Schiff bases in solution. One of these crystallised preferentially as its salt on addition of (+)-*cis*-dinitro $\beta$ is-(ethylenediamine)cobalt(III) acetate. After crystallisation, the salt was treated successively with sodium iodide which precipitated the cobalt(III) complex, cyclohexylamine which removed the salicylaldehyde, and ion exchange resin which regenerated optically active phenylalanine.

**D. Resolution of Alcohols.**—Most primary and secondary alcohols can be readily converted to their corresponding hydrogen phthalates or hydrogen succinates and these, since they contain a free carboxy-group, can be resolved as typical acids. This procedure, which was introduced many years ago,<sup>23</sup> remains the most important one used for the resolution of alcohols. For a long time the method was considered unsatisfactory for use with tertiary alcohols because of the difficulty of preparing their hydrogen phthalate derivatives,<sup>24</sup> but a number of tertiary alcohols have been successfully resolved,<sup>25</sup> and a convenient general procedure has been described for the preparation of hydrogen phthalate derivatives of tertiary alcohols in which the alcohol is treated with ethereal triphenylmethylsodium at room temperature, followed by phthalic anhydride.<sup>26</sup> It was also once thought that glycols could not be satisfactorily resolved by the hydrogen phthalate method<sup>24</sup> but several glycols have in fact been resolved via



<sup>22</sup> B. Halpern, A. M. Sargeson, and K. R. Turnbull, *Chem. and Ind.*, 1963, 1399.

<sup>23</sup> R. H. Pickard and W. O. Littlebury, *J. Chem. Soc.*, 1907, 91, 1973.

<sup>24</sup> A. W. Ingersoll, *Org. Reactions*, 2, 386.

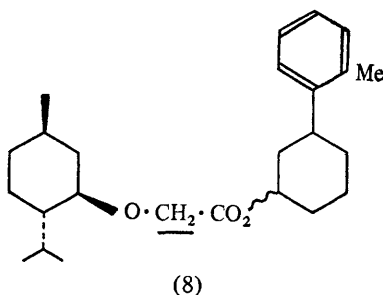
<sup>25</sup> B. Bielawski and A. Chrzaszczewska, *Lodz Tow. Nauk. Wydz. III Acta Chim.*, 1966, 11, 105; K. A. Thaker, N. S. Dave, S. H. Patel, and I. G. Vasi, *J. Sci. Ind. Res., India*, 1962, 21B, 209; K. A. Thaker and N. S. Dave, *ibid.*, 1962, 21B, 374; A. G. Davies, J. Kenyon, and K. Thaker, *J. Chem. Soc.*, 1957, 3151; A. G. Davies, J. Kenyon, and L. W. F. Salamé, *ibid.*, 1957, 3148.

<sup>26</sup> K. G. Rutherford, J. M. Prokipcak, and D. P. C. Fung, *J. Org. Chem.*, 1963, 28, 582.

their hydrogen phthalates.<sup>27</sup> A novel method of resolution for a glycol was devised by Agosta<sup>28</sup> who treated glycol (6) with *p*-boronobenzoic acid and converted it to the cyclic boronate (7). This was then successfully resolved with quinine and the optically active boronate hydrolysed to regenerate glycol (6).

The Pope and Peachey method of resolution for acids employs only one half an equivalent of optically active resolving agent together with one half an equivalent of optically inactive base. This procedure has been recommended recently as being particularly effective for the resolution of hydrogen phthalates.<sup>29</sup> It also works to great advantage when used in conjunction with the Kantor and Hauser method, in which the diastereomeric salts are refluxed in insufficient solvent to effect complete solution, thereby effecting a sort of continuous crystallisation process.

The only acid to have been widely used for the resolution of alcohols by converting them into diastereomeric esters is menthoxyacetic acid, which was first used many years ago and still proves very useful. Galpin and Huitric<sup>30</sup> reported an interesting resolution of *cis*- and *trans*-2-*o*-tolylcyclohexanol with this reagent. The diastereomeric menthoxyacetates (8) were separated by a



combination of crystallisation and chromatography and it was noted that the protons of the isolated methylene group (underlined) were non-equivalent in the n.m.r. Furthermore, the extent of non-equivalence was different in the diastereomeric esters and could be used to follow the progress of the resolution and to estimate the optical purity of the product. Resolutions of tertiary alcohols,<sup>31</sup> diols,<sup>32</sup> and phenols<sup>33</sup> have all been reported using menthoxyacetyl chloride as

<sup>27</sup> R. Neher, *Helv. Chim. Acta*, 1963, **46**, 1083; K. A. Thaker and N. S. Dave, *J. Sci. Ind. Res., India*, 1961, **20B**, 329; K. A. Thaker and S. H. Patel, *ibid.*, 1961, **20B**, 327; A. K. Macbeth, J. A. Mills, and R. Pettit, *J. Chem. Soc.*, 1950, 3538.

<sup>28</sup> W. C. Agosta, *J. Amer. Chem. Soc.*, 1967, **89**, 3926.

<sup>29</sup> S. H. Wilen, R. Davidson, R. Spector, and H. Steffanou, *Chem. Comm.*, 1969, 603.

<sup>30</sup> D. R. Galpin and A. C. Huitric, *J. Org. Chem.*, 1968, **33**, 921.

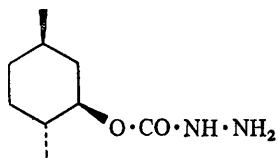
<sup>31</sup> F. M. Dean and B. Parton, *J. Chem. Soc. (C)*, 1969, 526.

<sup>32</sup> A. W. Allan, R. P. A. Sneeden, and J. Colvin, *J. Chem. Soc.*, 1958, 557; J. W. Cook, J. D. Loudon, and W. F. Williamson, *ibid.*, 1950, 911; J. Booth, E. Boyland, and E. E. Turner, *ibid.*, 1950, 2808; E. Romann, A. J. Frey, P. A. Stadler, and A. Eschenmoser, *Helv. Chim. Acta*, 1957, **40**, 1900.

<sup>33</sup> D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, 1968, **24**, 2443; S. Hishida, *Nippon Kagaku Zasshi*, 1955, **76**, 204; G. Anner and K. Miescher, *Helv. Chim. Acta*, 1948, **31**, 2173.

reagent. Diastereomeric esters have also been prepared from racemic alcohols by treatment with the acid chlorides derived from the steroidal compounds  $3\beta$ -acetoxyandrost-5-ene-17 $\beta$ -carboxylic† acid<sup>34</sup> and  $3\alpha$ -acetoxy-11-oxo-5 $\alpha$ -androstane-17 $\beta$ -carboxylic‡ acid,<sup>35</sup> reagents which may deserve more attention than they have received.

**E. Resolution of Aldehydes and Ketones.**—Many optically active hydrazines and semicarbazides have been investigated in the search for a reagent which could resolve aldehydes and ketones by formation of diastereomeric hydrazones or semicarbazones. Only two compounds have proved themselves generally useful for this purpose, however. One is menthyl-*N*-aminocarbamate (9), originally



(9)

described by Woodward, Kohman, and Harris,<sup>36</sup> and given by these authors the trivial name menthydrazide, by which it is now commonly known. It is a stable, beautifully crystalline compound and readily forms well-defined crystalline derivatives with most carbonyl compounds. These derivatives, called menthydrazones, are usually decomposed to the optically active carbonyl compound by acid hydrolysis with sulphuric acid, though they have also been decomposed by hydrolysis on a column of acid alumina<sup>37</sup> and by steam distillation in presence of phthalic anhydride.<sup>38</sup> Menthydrazide was used recently<sup>39</sup> to resolve 1,1,1-bromo-chlorofluoroacetone, which gave bromochlorofluoromethane on hydrolysis. This is structurally the simplest compound capable of optical activity.

The second important reagent is tartramidic acid hydrazide (10), sometimes called tartramazide, which was first described by Nerdel and Henkel.<sup>40</sup> Its derivatives with carbonyl compounds are referred to as tartramazonnes and these can be readily hydrolysed by acid to yield the desired optically active aldehyde

† Older names are  $3\beta$ -acetoxy- $\Delta^5$ -etienic or  $3\beta$ -acetoxy- $\Delta^5$ -etiocholenic acid.

‡ Older name is  $3\alpha$ -acetoxy-11-ketoetiocholenic acid.

<sup>34</sup> C. Djerassi, P. A. Hart, and E. J. Warawa, *J. Amer. Chem. Soc.*, 1964, **86**, 78; C. Djerassi and J. Staunton, *ibid.*, 1961, **83**, 736; R. B. Woodward and T. J. Katz, *Tetrahedron*, 1959, **5**, 70.

<sup>35</sup> R. B. Turner, K. H. Gänshirt, P. E. Shaw, and J. D. Tauber, *J. Amer. Chem. Soc.*, 1966, **88**, 1776.

<sup>36</sup> R. B. Woodward, T. P. Kohman, and G. C. Harris, *J. Amer. Chem. Soc.*, 1941, **63**, 120.

<sup>37</sup> W. Acklin, V. Prelog, F. Schenker, B. Serdarević, and P. Walter, *Helv. Chim. Acta*, 1965, **48**, 1725.

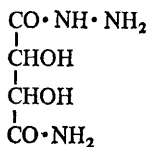
<sup>38</sup> H. Sobotka, E. Bloch, H. Cahnmann, E. Feldbau, and E. Rosen, *J. Amer. Chem. Soc.*, 1943, **65**, 2061.

<sup>39</sup> M. K. Hargreaves and B. Modari, *Chem. Comm.*, 1969, 16.

<sup>40</sup> F. Nerdel and E. Henkel, *Chem. Ber.*, 1952, **85**, 1138.

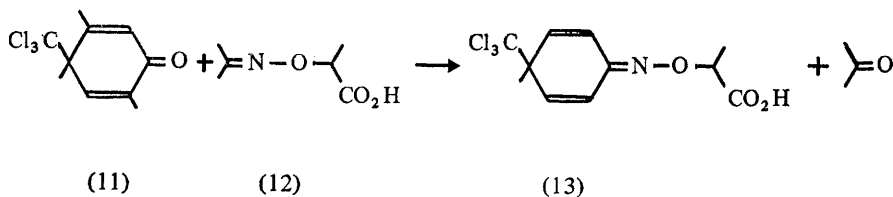
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or ketone. Mislow and Hamermesh used this reagent<sup>41</sup> to obtain optically active 2-phenylcyclopentanone which has the extraordinarily high specific rotation of +4190°.



(10)

An interesting resolution which may be capable of more general application was described by Newman and Layton<sup>42</sup> who reacted racemic ketone (11) with



(+)-2-(isopropylideneamino-oxy)propionic acid (12). An exchange reaction occurred to give a pair of diastereomeric derivatives of structure (13) together with acetone. Separation of sterically pure (13) by crystallisation and decomposition of it with levulinic acid and hydrogen chloride afforded optically active ketone (11).

Reaction of a racemic ketone with an optically active glycol or dithiol should give rise to two diastereomeric ketals or thioketals. This was first exploited by Corey and Casanova<sup>43</sup> who resolved camphor by treating it with D(-)-butane-2,3-diol and separating the diastereomeric ketals by gas-liquid chromatography, and the same reagent has been used to resolve a diketone as its bisketal.<sup>44</sup> Flavan-4-one has been resolved with L(+)-butane-2,3-dithiol. The diastereomeric thioketals were separated by crystallisation and reconverted to the optically active flavone by hydrolysis with mercuric chloride and mercuric oxide in aqueous methanol.<sup>45</sup> These methods, while of interest, have been little used, perhaps because the ketals and thioketals are not always susceptible to easy separation by crystallisation.

A general method for the resolution of ketones which appears to have con-

<sup>41</sup> K. Mislow and C. L. Hamermesh, *J. Amer. Chem. Soc.*, 1955, **77**, 1590.

<sup>42</sup> M. S. Newman and R. M. Layton, *J. Org. Chem.*, 1968, **33**, 2338.

<sup>43</sup> J. Casanova jun., and E. J. Corey, *Chem. and Ind.*, 1961, 1664.

<sup>44</sup> R. B. Turner, O. Buchardt, E. Herzog, R. B. Morin, A. Riebel, and J. M. Sanders, *J. Amer. Chem. Soc.*, 1966, **88**, 1766.

<sup>45</sup> E. J. Corey and R. B. Mitra, *J. Amer. Chem. Soc.*, 1962, **84**, 2938.





meric tertiary amines of structure (18) which could be resolved with (-)-malic acid. Resolved (18) was then converted back to optically active ketone (17) by oxidation with hydrogen peroxide and sodium tungstate catalyst in aqueous methanol.

**F. Resolution of Compounds containing Other Functional Groups.**—Compounds containing other functional groups may often be resolved by simple modifications of the methods already described. For instance, a number of phosphorus thioacids have been resolved using the common optically active bases.<sup>48</sup> Other compounds in which chirality was due to presence of an antimony,<sup>49</sup> arsenic,<sup>50</sup> phosphorus,<sup>51</sup> or silicon<sup>52</sup> atom or to a substituted ferrocene residue,<sup>53</sup> were readily resolved because in each case the molecule contained a free carboxy-group. If the racemate to be resolved is ionic, resolution may be effected by combining it with an optically active ion of opposite charge to give a pair of diastereomeric salts. The resolution of complex metal ions, which was first achieved many years ago, is usually carried out by this method and a great variety of optically active metal complex cations and anions has now been described. Those of cobalt are particularly well known. The commonest reagent used for resolving cationic metal complex ions is 3-bromocamphor-8-sulphonic acid, used in the form of its ammonium or silver salt. Other popular reagents are optically active sodium bis(oxalato)ethylenediaminecobaltate(III)<sup>54</sup> and potassium antimonyl tartrate.<sup>55</sup> Cations which are singly- or triply-charged usually give well-defined less soluble diastereomers with this latter reagent whereas doubly-charged cations give precipitates of an ill-defined nature.<sup>56</sup> Important optically active cationic complexes which have been used to resolve racemic anionic complexes include oxalatobis(ethylenediamine)cobalt(III) chloride<sup>57</sup> and *cis*-dinitrobis(ethylenediamine)cobalt(III) oxalate.<sup>58</sup> Many other kinds of ionic racemates have been resolved by the method of combination with an optically active ion of opposite sign. For instance, resolution of a long series of racemic phosphonium ions<sup>59</sup> was described by Kamai and Usacheva using mono-silver

<sup>48</sup> C. Donninger and D. H. Hutson, *Tetrahedron Letters*, 1968, 4871; H. P. Benschop and G. R. Van den Berg, *Rec. Trav. chim.*, 1968, **87**, 362; H. L. Boter and D. H. J. M. Platenburg, *ibid.*, 1967, **86**, 399; J. Michalski, A. Ratajczak, and Z. Tulimowski, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1963, **11**, 237.

<sup>49</sup> I. G. M. Campbell, *J. Chem. Soc.*, 1955, 3116.

<sup>50</sup> Yu. F. Gatilov and L. B. Ionov, *Zhur. obshchei Khim.*, 1969, **39**, 1064.

<sup>51</sup> J. Michalski and St. Musierowicz, *Angew. Chem. Internat. Edn.*, 1967, **6**, 1078.

<sup>52</sup> C. Eaborn and C. G. Pitt, *J. Chem. Soc. (C)*, 1966, 1524.

<sup>53</sup> G. Haller and K. Schloegl, *Monatsh.*, 1967, **98**, 603.

<sup>54</sup> D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *J. Amer. Chem. Soc.*, 1967, **89**, 825; B. Halpern, A. M. Sargeson, and K. R. Turnbull, *ibid.*, 1966, **88**, 4630; F. P. Dwyer, A. M. Sargeson, and I. K. Reid, *ibid.*, 1963, **85**, 1215; J. A. Broomhead and L. A. P. Kane-Maguire, *J. Chem. Soc. (A)*, 1967, 546.

<sup>55</sup> S. F. Mason and J. W. Wood, *Chem. Comm.*, 1968, 1512; C. F. Liu and J. Doyle, *ibid.*, 1967, 412.

<sup>56</sup> K. Garbett and R. D. Gillard, *J. Chem. Soc. (A)*, 1966, 802.

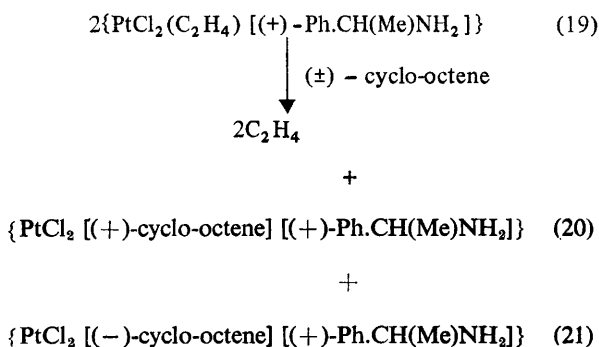
<sup>57</sup> F. P. Dwyer, T. E. MacDermott, and A. M. Sargeson, *J. Amer. Chem. Soc.*, 1963, **85**, 661.

<sup>58</sup> F. P. Dwyer, I. K. Reid, and F. L. Garvan, *J. Amer. Chem. Soc.*, 1961, **83**, 1285.

<sup>59</sup> G. Kamai and G. M. Usacheva, *Zhur. obshchei Khim.*, 1964, **34**, 785.

dibenzoyl tartrate, and optically active quaternary ammonium<sup>60</sup> and arsonium<sup>61</sup> ions are also well known.

Cope and co-workers successfully resolved *trans*-cyclo-octene,<sup>62</sup> *cis-trans*-1,5-cyclo-octadiene,<sup>63</sup> and the very optically unstable *trans*-cyclononene<sup>64</sup> by a method involving the formation of diastereomeric platinum(II) complexes. The reagent, *trans*-dichloro(ethylene)(1-phenylethylamine)platinum(II) (19), is optically active since it is prepared from optically active 1-phenylethylamine. On treatment of it with racemic *trans*-cyclo-octene, ethylene was eliminated and the cyclo-octene became co-ordinated to the platinum, giving rise to two diastereomeric complexes, (20) and (21). These were separated by fractional crystallisation



and decomposed with aqueous sodium cyanide to regenerate the alkene, optically active. This method was more recently applied to the resolution of allenes,<sup>65</sup> with moderate success. Its great advantage is that it does not depend on the presence of other functional groups which can be used as a resolving 'handle'.

A useful new general method was recently described for the resolution of tertiary arsines.<sup>66</sup> Virtually the same procedure had earlier been described for phosphines.<sup>67</sup> The racemic arsine,  $\text{R}_3\text{As}, \S$  is treated with aqueous potassium

§ In which the three R groups are all different.

<sup>60</sup> A. C. Cope, W. R. Funke, and F. N. Jones, *J. Amer. Chem. Soc.*, 1966, **88**, 4693.

<sup>61</sup> G. Wittig and D. Hellwinkel, *Chem. Ber.*, 1964, **97**, 769; M. H. Forbes, F. G. Mann, I. T. Millar, and E. A. Moelwyn-Hughes, *J. Chem. Soc.*, 1963, 2833; G. Kamai and Yu. F. Gatilov, *Doklady Akad. Nauk S.S.S.R.*, 1961, **137**, 91.

<sup>62</sup> A. C. Cope, C. R. Ganellin, H. W. Johnson jun., T. V. Van Auken, and H. J. S. Winkler, *J. Amer. Chem. Soc.*, 1963, **85**, 3276.

<sup>63</sup> A. C. Cope, J. K. Hecht, H. W. Johnson jun., H. Keller, and H. J. S. Winkler, *J. Amer. Chem. Soc.*, 1966, **88**, 761.

<sup>64</sup> A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang, and H. J. S. Winkler, *J. Amer. Chem. Soc.*, 1965, **87**, 3644.

<sup>65</sup> A. C. Cope, W. R. Moore, R. D. Bach, and H. J. S. Winkler, *J. Amer. Chem. Soc.*, 1970, **92**, 1243.

<sup>66</sup> B. Bosnich and S. B. Wild, *J. Amer. Chem. Soc.*, 1970, **92**, 459.

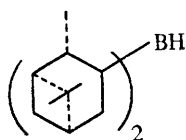
<sup>67</sup> T. H. Chan, *Chem. Comm.*, 1968, 895.

chloroplatinite(II) giving *cis*-[(R<sub>3</sub>As)<sub>2</sub>PtCl<sub>2</sub>], which with platinous chloride gives the dimeric species, *trans*-[(R<sub>3</sub>As)ClPtCl<sub>2</sub>PtCl(R<sub>3</sub>As)]. Treatment of this with an optically active amine converts it into a mixture of diastereomeric complexes, {PtCl[(+)-R<sub>3</sub>As] [(+)-amine]}Cl and {PtCl[(-)-R<sub>3</sub>As] [(+)-amine]}Cl, which are separated by fractional crystallisation. Each of these complexes can then be decomposed with aqueous potassium cyanide to regenerate the optically pure arsine.

Two methods have been described for the resolution of organomercurials of the type RHgBr. These can be converted to a mixture of diastereomeric mandelates,<sup>68</sup> RHgMand, either by treatment with potassium hydroxide followed by (-)-mandelic acid, or by direct treatment with silver (-)-mandelate. The second method was described by a group of Russian workers who symmetrised the RHgBr to R<sub>2</sub>Hg with sodium stannite and then effected resolution with ethyl mercuric (+)-tartrate.<sup>69</sup>

### 3 Kinetic Methods of Resolution

Kinetic methods of resolution depend on the different rates at which two enantiomers undergo reaction. They are of great interest theoretically but few of them are of importance practically. An exception is the asymmetric hydroboration of alkenes with di-isopinocampheylborane (22). This procedure was developed by Brown and co-workers<sup>70</sup> and offers one of the few methods available for the resolution of alkenes lacking functional groups other than the double bond. The reagent (22) is a dialkylboron and is prepared by the hydro-



(22)

boronation of optically active  $\alpha$ -pinene with diborane. When racemic 3-methylcyclopentene was hydroboronated using a deficiency of (+)-reagent (22), the (+)-alkene reacted faster and work-up of the reaction mixture afforded unreacted (-)-3-methylcyclopentene in good yield and with an optical purity of 65%. The method should be of general application for the resolution of disubstituted alkenes and has also been successfully used for the resolution of allenes.<sup>71</sup> Tri-

<sup>68</sup> E. D. Hughes, C. K. Ingold, and R. M. G. Roberts, *J. Chem. Soc.*, 1964, 3900; H. B. Charman, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1959, 2523; F. R. Jensen, L. D. Whipple, D. K. Wedegaertner, and J. A. Landgrebe, *J. Amer. Chem. Soc.*, 1960, **82**, 2466.

<sup>69</sup> O. A. Reutov and E. V. Uglova, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk.*, 1959, 757.

<sup>70</sup> H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, 1964, **86**, 397.

<sup>71</sup> W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Amer. Chem. Soc.*, 1968, **90**, 6741.

substituted alkenes undergo hydroboration stereoselectively but not asymmetrically.<sup>72</sup>

Other kinetic resolutions of alkenes which have been reported include their partial polymerisation<sup>73</sup> or copolymerisation<sup>74</sup> using an optically active organotitanium-zinc catalyst, and their bromination by bromine in the presence of dihydrocinchonine.<sup>75</sup> Products obtained by both of these procedures were of very low optical purity, however.

Asymmetric reduction of other functional groups besides double bonds may be applied to resolution. For example, ketones may be reduced using lithium aluminium hydride complexed with chiral amino-<sup>76</sup> or hydroxy-<sup>77</sup> compounds giving alcohols of predominantly one configuration. Asymmetric reduction may also be achieved with micro-organisms.<sup>78</sup> Although not strictly speaking a kinetic resolution, this offers a way of resolving suitable secondary alcohols by oxidation to the ketone followed by asymmetric reduction to the optically active alcohol. Ketones have been resolved by incomplete Meerwein-Ponndorf-Verley reduction using aluminium tertiary butoxide with an optically active alcohol.<sup>79</sup> A complex hydride reagent prepared from lithium aluminium hydride and (+)-quinidine was successfully employed to resolve a methoxy-silane.<sup>80</sup> Reduction using a deficiency of the reagent afforded unreacted (-)-methoxy-silane.

Kinetic resolution based on different rates of esterification has been known for very many years.<sup>81</sup> Perhaps the most important development in this field has been the introduction of optically active  $\alpha$ -phenylbutyric anhydride as a new reagent by Horeau and co-workers<sup>82</sup> who showed that the (+)-form of this anhydride reacts faster with that enantiomer of an alcohol which has the *S* absolute configuration. This can be employed as a kinetic method of resolution for alcohols although its chief value lies in its use for the determination of their absolute configuration. Kinetic resolution of an alcohol by esterification may also be achieved by selective acetylation of one enantiomer with acetic anhydride in presence of brucine,<sup>83</sup> and an interesting partial resolution of chlorofluoroacetic acid was recently reported<sup>84</sup> in which the racemic acid was esterified by treatment with a half molar amount of an optically active epoxide, 5,6- $\alpha$ -epoxy-5 $\alpha$ -cholestan-3 $\beta$ -ol.

<sup>72</sup> D. K. Shumway and J. D. Barnhurst, *J. Org. Chem.*, 1964, **29**, 2320.

<sup>73</sup> P. Pino, F. Ciardelli, and G. P. Lorenzi, *Makromol. Chem.*, 1964, **70**, 182.

<sup>74</sup> F. Ciardelli, E. Benedetti, G. Montagnoli, L. Lucarini, and P. Pino, *Chem. Comm.*, 1965, 285.

<sup>75</sup> G. Bellucci, C. Giordano, A. Marsili, and G. Berti, *Tetrahedron*, 1969, **25**, 4515.

<sup>76</sup> W. H. Pirkle, *J. Amer. Chem. Soc.*, 1966, **88**, 1837.

<sup>77</sup> S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc. (C)*, 1967, 197; O. Cervinka, *Coll. Czech. Chem. Comm.*, 1965, **30**, 1684.

<sup>78</sup> W. Acklin, V. Prelog, F. Schenker, B. Serdarević, and P. Walter, *Helv. Chim. Acta*, 1965, **48**, 1725.

<sup>79</sup> P. Newman, P. Rutkin, and K. Mislow, *J. Amer. Chem. Soc.*, 1958, **80**, 465.

<sup>80</sup> A. Holt, A. W. P. Jarvie, and G. J. Jervis, *Tetrahedron Letters*, 1968, 4087.

<sup>81</sup> W. Marckwald and A. McKenzie, *Chem. Ber.*, 1899, **32**, 2130.

<sup>82</sup> R. Weidmann and A. Horeau, *Bull. Soc. chim. France*, 1967, 117.

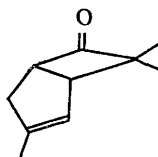
<sup>83</sup> S. Mitsui and Y. Kudo, *Tetrahedron*, 1967, **23**, 4271.

<sup>84</sup> G. Bellucci, G. Berti, A. Borraccini, and F. Macchia, *Tetrahedron*, 1969, **25**, 2979.

## Methods of Optical Resolution

A useful new general procedure for the resolution of secondary alcohols, yielding products of high optical purity, was described by Halpern and Westley<sup>85</sup> who refluxed the racemic alcohol in benzene and toluene with L-valine and *p*-toluenesulphonic acid. This gave a sterically pure *p*-toluenesulphonate of one of the diastereomeric L-valine alkyl esters, which could be hydrolysed by alkali to the optically pure alcohol. Essentially the same method can be used conveniently to resolve neutral amino-acids.<sup>86</sup> The DL-amino-acid is refluxed in benzene-toluene solution with (-)-menthol and *p*-toluenesulphonic acid. Work-up affords the *p*-toluenesulphonate of the D-amino-acid (-)-menthyl ester in 60–95% yield and 99–100% optical purity, and hydrolysis of this gives the D-amino-acid.

Huber and Dreiding recently described the kinetic resolution of ketone (23)



(23)

by a useful method which may be capable of more general application.<sup>87</sup> The racemic ketone was treated with one half of the molar amount of an optically active primary amine under conditions conducive to Schiff base formation. Excess unreacted ketone was distilled off and was found to be optically active, while hydrolysis of the distillation residue with acetic acid gave the enantiomeric ketone. The yields were about 30% although the optical purity of the products was not established. The first partial resolution of an ozonide<sup>88</sup> was achieved by a kinetic method in which the racemic ozonide was treated with less than the stoichiometric amount of brucine in methylene chloride at  $-70^{\circ}\text{C}$ . Unreacted ozonide was found to be optically active. A Grignard reagent has been partially resolved<sup>89</sup> by treatment with less than one equivalent of an optically active ketone. That one enantiomer of the Grignard reacted faster than the other was shown by carbonating the unreacted Grignard when an optically active carboxylic acid was obtained. The first resolution of a triarylphosphine<sup>90</sup> was achieved by a kinetic method in which the racemic phosphine  $\text{Ar}_3\text{P}^*$  was treated with paraformaldehyde in benzene, together with a half molar amount of (+)-camphor-10-sulphonic acid. The (+)-enantiomer of the phosphine reacted faster to give a salt of structure (24) which crystallised out of solution. Unreacted (-)-phos-

\* In which the three Ar groups are all different.

<sup>85</sup> B. Halpern and J. W. Westley, *Austral. J. Chem.*, 1966, **19**, 1533.

<sup>86</sup> B. Halpern and J. W. Westley, *Chem. Comm.*, 1965, 421.

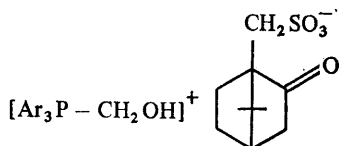
<sup>87</sup> U. A. Huber and A. S. Dreiding, *Helv. Chim. Acta*, 1970, **53**, 495.

<sup>88</sup> R. W. Murray, R. D. Youssefeyeh, and P. R. Story, *J. Amer. Chem. Soc.*, 1966, **88**, 3655.

<sup>89</sup> J. D. Morrison, A. Tomash, and R. W. Ridgway, *Tetrahedron Letters*, 1969, 565.

<sup>90</sup> G. Wittig, H. J. Cristau, and H. Braun, *Angew. Chem. Internat. Edn.*, 1967, **6**, 700.

phine was isolated from the mother liquor while decomposition of salt (24) with triethylamine gave (+)-phosphine. Both enantiomers were obtained in yields of 85%. Use of one molar amount of (+)-camphor-10-sulphonic acid gave rise to an inseparable mixture of diastereomeric salts of structure (24).



(24)

Kinetic resolutions effected by micro-organisms or enzyme preparations are among the most efficient of all resolutions because of the very high stereospecificity of enzymes. Many are of the utmost practical importance, *e.g.* the resolution of amino-acids by the selective hydrolysis of their *N*-acyl derivatives using hog kidney acylase, as developed by Greenstein and co-workers,<sup>91</sup> and also the papain-catalysed amino-acid anilide or hydrazide formation.<sup>91</sup> A complete survey of enzymatic methods of resolution cannot be undertaken here. Examples of interest from the more recent literature, however, include the first resolution of a chiral sulphite ester<sup>92</sup> which was achieved by selectively hydrolysing one enantiomer with pepsin, the partial oxidation of racemic sulphoxides by incubation with *Aspergillus niger* enabling unreacted optically active sulphoxide to be isolated,<sup>93</sup> the preferential oxidation of the (-)-form of a glycol<sup>94</sup> by incubation with *Acetobacter suboxydans*, and the selective dehydrogenation of steroidal 4-en-3-ones by species of *Corynebacterium*,<sup>95</sup> *Penicillium*,<sup>96</sup> and by the steroid dehydrogenase of *Arthrobacter simplex*.<sup>96a</sup>

#### 4 Other Methods of Resolution

The development of gas-liquid chromatography as a successful tool for the separation of enantiomers is largely due to Gil-Av and co-workers, although there are reports of earlier studies by other groups.<sup>97</sup> Gil-Av first used capillary columns of *N*-trifluoroacetyl-L-isoleucine lauryl ester<sup>98</sup> but has since developed

<sup>91</sup> See J. P. Greenstein and M. Winitz, 'Chemistry of the Amino-Acids', Wiley, New York, 1961, Vol. 1, p. 728 ff.

<sup>92</sup> T. W. Reid, T. P. Stein, and D. Fahrney, *J. Amer. Chem. Soc.*, 1967, **89**, 7125.

<sup>93</sup> B. J. Auret, D. R. Boyd, and H. B. Henbest, *J. Chem. Soc. (C)*, 1968, 2374.

<sup>94</sup> P. Barbezat, D. Reymond, and Th. Posternak, *Helv. Chim. Acta*, 1967, **50**, 1811.

<sup>95</sup> G. Greenspan, L. L. Smith, R. Rees, T. Foell, and H. E. Alburn, *J. Org. Chem.*, 1966, **31**, 2512.

<sup>96</sup> G. Greenspan and D. Hartley, U.S.P. 3,395,080; (*Chem. Abs.*, 1969, **70**, 18910b).

<sup>96a</sup> J. Fried, M. J. Green, and G. V. Nair, *J. Amer. Chem. Soc.*, 1970, **92**, 4136.

<sup>97</sup> G. Karagounis and E. Lemperle, *Angew. Chem. Internat. Edn.*, 1962, **1**, 166; C. B. Coleman, G. D. Cooper, and J. F. O'Donnell, *J. Org. Chem.*, 1966, **31**, 975; A. Amariglio, *C.R. Acad. Sci., Paris, Ser. C*, 1969, **268**, 1981.

<sup>98</sup> E. Gil-Av, B. Feibush, and R. Charles-Sigler, *Tetrahedron Letters*, 1966, 1009.

both packed and capillary columns of *N*-trifluoroacetyl-L-valyl-L-valine cyclohexyl ester. This dipeptide derivative acts as a highly successful stationary phase for the resolution of *N*-trifluoroacetyl amino-acid esters<sup>99</sup> and Gil-Av has explained its resolving power in terms of hydrogen-bonded diastereomeric association complexes.<sup>100</sup> The use of paper chromatography for the resolution of amino-acids has become well established since its introduction by Dalgliesh and others,<sup>101</sup> and studies have been carried out in an effort to define the optimum experimental conditions.<sup>102</sup> It is no longer considered necessary for the amino-acid to contain an aromatic residue. There are a few instances of substances other than amino-acids being resolved on paper. These include the resolution of a pteridine derivative<sup>103</sup> and of a quaternary ammonium salt.<sup>104</sup>

Column chromatography using optically active adsorbents has been developed into a useful method of resolution. Early workers used columns packed with lactose, and many useful resolutions have been achieved with this adsorbent.<sup>105</sup> The most generally useful adsorbent, however, is potato starch. Requirements for effective resolution on starch have been discussed by Krebs and Schumacher<sup>106</sup> who noted that the greater the asymmetry of the molecule the greater the resolution. Useful experimental details are described by these workers and also by Steckelberg, Bloch, and Musso<sup>107</sup> who resolved a series of biphenyl derivatives in yields of up to 50% and optical purity 90–100%. Starch columns have also been effective for the resolution of metal complexes.<sup>108,109</sup> Another important optically active adsorbent is cellulose. Examples of its use include the resolution of metal complexes<sup>109,110</sup> and of pteridine derivatives.<sup>103</sup> Resolutions have also been achieved on dry cellulose powder columns<sup>111</sup> and by thin-layer chromatography on cellulose plates.<sup>112</sup> Other resolutions of interest though of little practical importance include those carried out on columns of optically active polymers.<sup>113</sup> Molecular asymmetry of the adsorbent is not a prerequisite for resolution to take place on a column. Resolution on columns of active quartz,

<sup>99</sup> E. Bayer, E. Gil-Av, W. A. König, S. Nakaparksin, J. Oró, and W. Parr, *J. Amer. Chem. Soc.*, 1970, **92**, 1738; E. Gil-Av and B. Feibush, *Tetrahedron Letters*, 1967, 3345.

<sup>100</sup> B. Feibush and E. Gil-Av, *Tetrahedron*, 1970, **26**, 1361.

<sup>101</sup> C. E. Dalgliesh, *J. Chem. Soc.*, 1952, 3940; M. Kotake, T. Sakan, N. Nakamura, and S. Senoh, *J. Amer. Chem. Soc.*, 1951, **73**, 2973.

<sup>102</sup> C. L. de Ligny, H. Nieboer, J. J. M. de Vijlder, and J. H. H. G. van Willigen, *Rec. Trav. chim.*, 1963, **82**, 213.

<sup>103</sup> A. Albert and E. P. Serjeant, *J. Chem. Soc.*, 1964, 3357.

<sup>104</sup> M. Tomita and M. Sugamoto, *Yakugaku Zasshi*, 1962, **82**, 1141.

<sup>105</sup> J. P. Collman, R. P. Blair, A. L. Slade, and R. L. Marshall, *Chem. and Ind.*, 1962, 141.

<sup>106</sup> H. Krebs and W. Schumacher, *Chem. Ber.*, 1966, **99**, 1341.

<sup>107</sup> W. Steckelberg, M. Bloch, and H. Musso, *Chem. Ber.*, 1968, **101**, 1519.

<sup>108</sup> R. D. Gillard, P. M. Harrison, and E. D. McKenzie, *J. Chem. Soc. (A)*, 1967, 618; L. G. Warner, N. J. Rose, and D. H. Busch, *J. Amer. Chem. Soc.*, 1967, **89**, 703.

<sup>109</sup> L. T. Taylor and D. H. Busch, *J. Amer. Chem. Soc.*, 1967, **89**, 5372.

<sup>110</sup> F. R. Keene, G. H. Searle, Y. Yoshikawa, A. Imai, and K. Yamasaki, *Chem. Comm.*, 1970, 784.

<sup>111</sup> L. V. Hanks, *Prepn. Biomed. Appl. Labeled Mol., Proc. Symp., Venice*, 1964, 77.

<sup>112</sup> S. F. Contractor and J. Wragg, *Nature*, 1965, **208**, 71.

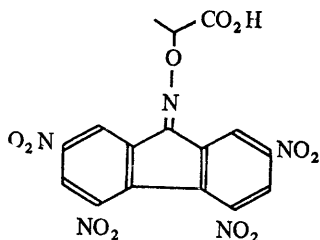
<sup>113</sup> G. Manecke and W. Lamer, *Naturwiss*, 1968, **55**, 491; P. Pino, F. Ciardelli, G. P. Lorenzi, and G. Natta, *J. Amer. Chem. Soc.*, 1962, **84**, 1487.



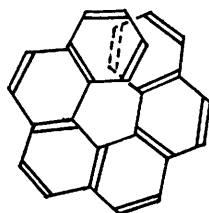
for instance, has been known for many years and a good example is the resolution of an arsonium bromide by a group of Russian workers.<sup>114</sup> A very interesting partial resolution of a beryllium complex was carried out by making use of preferential adsorption on optically active sodium chlorate crystals.<sup>115</sup> An unusual feature of the resolution, however, was that preferential adsorption was not equal for both antipodes. Optically active sodium chlorate crystals weighing several grams were obtained by slow crystallisation of sodium chlorate from a supersaturated solution, followed by mechanical separation of the enantiomers with the help of polarimetric examination.

Many resolutions have now been reported which employ ion-exchange resins. A common approach is to prepare the resin by treating a chloromethylated polystyrene cross-linked polymer with an optically active amine. For instance, Lott and Rieman<sup>116</sup> prepared an optically active strong base anion exchange resin from chloromethylated cross-linked polystyrene and L(-)-*NN*-dimethyl-1-phenylethylamine and resolved sodium mandelate on a column of it by both frontal and displacement chromatography. An earlier approach was to prepare the optically active resin by treating an acidic ion-exchange resin with thionyl chloride followed by an optically active base such as quinine. Mandelic acid has been resolved on a resin of this type.<sup>117</sup> Ion-exchange resins are particularly useful for the resolution of metal complex ions.<sup>118</sup>

The most important reagent for effecting resolution by molecular complex formation has proved to be optically active 2-(2,4,5,7-tetranitro-9-fluorenylidene-amino-oxy)-propionic acid (TAPA) (25). This is particularly useful for the resolution of polycyclic aromatic compounds which do not possess functional groups that would permit resolution by other methods, and it can be easily pre-



(25)



(26)

<sup>114</sup> G. Kamai, E. I. Klabunovskii, Yu F. Gatilov, and G. S. Khodakov, *Doklady Akad. Nauk S.S.S.R.*, 1961, **139**, 1112.

<sup>115</sup> E. Ferroni and R. Cini, *J. Amer. Chem. Soc.*, 1960, **82**, 2427.

<sup>116</sup> J. A. Lott and W. Rieman, *J. Org. Chem.*, 1966, **31**, 561.

<sup>117</sup> N. Grubhofer and L. Schleith, *Naturwiss.*, 1953, **40**, 508.

<sup>118</sup> Y. Yoshikawa and K. Yamasaki, *Inorg. Nuclear Chem. Letters*, 1968, **4**, 697; G. R. Brubaker, J. I. Legg, and B. E. Douglas, *J. Amer. Chem. Soc.*, 1966, **88**, 3446; Y. Yoshino, H. Sugiyama, S. Nogaïto, and H. Kinoshita, *Sci. Papers Coll. Gen. Educ., Univ. Tokyo*, 1966, **16**, 57.

pared from ethyl 2-bromopropionate and acetone oxime.<sup>119</sup> When TAPA (25) is added to a solution of a racemate, the molecular complex which precipitates usually contains an excess of one of the enantiomers and this enantiomer can be obtained by decomposition of the complex with sodium bicarbonate or by chromatography. Sometimes the other enantiomer can be isolated from the mother liquor. Both hexahelicene<sup>120</sup> (26) and pentahelicene<sup>121</sup> have been resolved by this method. The former was the first example of the resolution of a purely aromatic hydrocarbon which owes its chirality to intramolecular crowding. Addition of TAPA (25) to a racemate may sometimes result in precipitation of both enantiomers as a mixture of diastereomeric complexes. Separation and individual decomposition of these will also lead to resolution.<sup>122</sup>

Resolution by the seeding of supersaturated solutions of a racemate continues to be a very important process, especially on the industrial scale, and the patent literature particularly abounds with descriptions of ingenious processes involving this principle. For instance, Dowling<sup>123</sup> simultaneously seeded an aqueous solution of DL-glutamic acid with large particles of L- and small particles of D-glutamic acid. The L- and D-forms therefore crystallised correspondingly in large and small crystals which could be subsequently separated by simple screening. Harada<sup>124</sup> described a useful inoculation procedure for the total resolution of amino-acids by seeding solutions of the racemate in aqueous ammonium formate. He found that no resolution could be achieved by seeding pure aqueous DL-aspartic solutions, but in presence of ammonium formate D- and L-aspartic acids were obtained in 95% and 99% optical purity respectively. He also resolved other amino-acids by this method. He suggested that the ammonium formate may act as an agent: (i) to stabilise the supersaturated solution; (ii) to slow down the crystallisation rate; or (iii) to weaken the attraction between the D and L molecules. Barton and Kirby<sup>125</sup> described an unusual resolution of the alkaloid narwedine in which crystallisation of racemic narwedine in presence of (-)-galanthamine (a reduction product of narwedine) yielded (+)-narwedine. This resolution was not one induced by seeding, neither was it due to preferential complex formation. The authors suggest that (-)-galanthamine is adsorbed on the surface of growing narwedine crystals and that the adsorbed (-)-galanthamine layer on (+)-narwedine crystals might either favour deposition of (+)-narwedine (behaving like a biological membrane) or, more probably, inhibit deposition of (-)-narwedine.

The old procedure of crystal picking by which Pasteur achieved the first ever optical resolution of a racemate in 1848, still finds occasional use where other methods have failed and a recent example of it is the resolution of hepta-

<sup>119</sup> P. Block jun. and M. S. Newman, *Org. Synth.*, 1968, **48**, 120.

<sup>120</sup> M. S. Newman and D. Lednicer, *J. Amer. Chem. Soc.*, 1956, **78**, 4765.

<sup>121</sup> Ch. Goedicke and H. Stegemeyer, *Tetrahedron Letters*, 1970, 937.

<sup>122</sup> D. T. Longone and M. T. Reetz, *Chem. Comm.*, 1967, 46.

<sup>123</sup> B. B. Dowling, U.S.P. 2,898,358 (*Chem. Abs.*, 1960, **54**, P 17284g).

<sup>124</sup> K. Harada, *Nature*, 1965, **206**, 1354.

<sup>125</sup> D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 1962, 806.

helicene,<sup>128</sup>  $[\alpha]_D^{20} + 6200^\circ$ . The highest specific rotation yet reported is that of nonahelicene,  $[\alpha]_D \pm 15\,000^\circ$ , which undergoes spontaneous resolution.<sup>127</sup>

Many other very interesting ideas have been applied to the problem of optical resolution and a few of them are worthy of mention, although of no practical importance. Photoresolution has been reported by two groups of workers<sup>128</sup> who investigated the effect of irradiating solutions of the trioxalatochromate(III) ion with circularly polarised light. The only photochemical reaction involved here is the conversion of one enantiomer into its optical antipode, *i.e.* a photoracemisation. Because of the different circular dichroisms, one enantiomer becomes racemised to a greater extent than the other and a small but real optical activity of the solution could be observed after irradiation. A series of organic racemates was resolved to a slight extent by partitioning them between an aqueous phase and an organic phase consisting of an optically active ester of tartaric acid,<sup>129</sup> and the same group of workers partially resolved some metal complexes by a countercurrent extraction procedure using (+)-di-isoamyltartrate.<sup>130</sup> A cobalt complex has been slightly resolved by making use of the fact that its enantiomers diffuse at different rates in an aqueous solution of sucrose,<sup>131</sup> and a novel method of resolution was suggested by Lendrum<sup>132</sup> who discussed a model based on a system of electrophoresis in presence of a magnetic or centrifugal field.

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<sup>128</sup> R. H. Martin, M. Flammang-Barbieux, J. P. Cosyn, and M. Gelbcke, *Tetrahedron Letters*, 1968, 3507.

<sup>127</sup> See A. P. Downing, *Chem. and Ind.*, 1969, 43.

<sup>128</sup> B. Norden, *Acta Chem. Scand.*, 1970, **24**, 349; K. L. Stevenson and J. F. Verdick, *J. Amer. Chem. Soc.*, 1968, **90**, 2974.

<sup>129</sup> N. S. Bowman, G. T. McCloud, and G. K. Schweitzer, *J. Amer. Chem. Soc.*, 1968, **90**, 3848.

<sup>130</sup> N. S. Bowman, V. G'ceva, G. K. Schweitzer, and I. R. Supernaw, *Inorg. Nuclear Chem. Letters*, 1966, **2**, 351.

<sup>131</sup> V. Carassiti, *Ann. Chim. (Italy)*, 1958, **48**, 167.

<sup>132</sup> F. C. Lendrum, *Nature*, 1953, **172**, 499.