700. *Methods of Resolution. Part III. Variations of the Resolution of Alcohols through Acid Esters.*

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The optically active benzylamine derivative (—)-*p*-aminomethylbenzomenthylamide has been prepared and used in a successful resolution. It is representative of a class of compounds which may replace natural alkaloids as basic resolving agents.

The possibility of effecting resolution of acid esters of racemic alcohols by passing them through a column of active base has been examined, and positive results have been obtained in particular cases; but the method is not of general application in its present form.

In the further study of the resolution of alcohols attention has been directed to the possibility of finding bases more suitable than natural alkaloids for combination with acid esters. Simple synthetic bases such as 1-phenylethylamine may be resolved to both active forms and have been used to a limited extent, as have also a few of the simple active amines derived from terpene ketones (Gough, Hunter, and Kenyon, *J.*, 1926, 2052; Pickard and Littlebury, *J.*, 1907, **91**, 1973; Dickison and Ingersoll, *J. Amer. Chem. Soc.*, 1939, **61**, 2477) but in many cases their salts with acid esters are too soluble for convenient use. It seemed to us that useful compounds might be obtained by building up simple synthetic reagents into stable bases of higher molecular weight which would give salts of lower solubility and of a type from which the active component could readily be recovered by degradation. Active amino-amides of the structure $NH_2{\cdot}X{\cdot}CO{\cdot}NHR$, derived from an amino-acid and an active amine should have the desired properties, and the structure is capable of wide variation to provide a range of reagents.

For convenience, (—)-menthylamine was chosen as the active unit in the preparation of typical substances, and tests have been carried out with (−)-*p*-aminobenzomenthylamide, (−)-3 : 5-diaminobenzomenthylamide, (−)-N^4-menthylsulphanilamide, and (−)-*p*-aminomethylbenzomenthylamide (I), which are all readily available. The first three of these, being aromatic, proved to be too weakly basic to give stable salts with acid esters, but the benzylamine derivative (I) gave stable salts, and by its use (±)-2-octyl hydrogen phthalate was readily resolved to the (−)-form, but (±)-*trans*-2-methyl*cyclo*hexyl hydrogen phthalate could be only partly resolved, and (±)-2-butyl hydrogen phthalate completely resisted resolution. In view of the work of Sheehan and Frank (*J. Amer. Chem. Soc.*, **1949**, **71**, 1856), active amides, $NH_2 \cdot CH_2 \cdot CO \cdot NHR$, derived from glycine should also be readily available, but have not been tested as yet.

An investigation had been started of the possibility of resolving glycols through salts of acid esters, when a paper was published by Rigby (*J.*, 1949, 1588) describing a resolution of *trans*-resorcitol through its di(hydrogen phthalate). This result is of considerable interest, because it has been stated (Ingersoll, " Organic Reactions," Vol. II, 1944, p. 386) that resolution through salts of acid esters cannot be applied to glycols and phenols because they do not yield simple acid esters with phthalic anhydride. There is no foundation for this statement, because the formation of polymeric esters or phthaleins respectively requires treatments more severe than those used for the preparation of hydrogen phthalates. Phenyl hydrogen phthalate has long been known (Bischoff and von Hedenstrom, *Ber.*, 1902, **35**, 4084), and simple acid esters derived from glycols (Hirsjärvi, *Ann. Acad. Sci. Fennicae*, AII, 1946, No. 23; *Chem. Abstr.*, 1948, **42**, 2936; Rigby, *loc. cit.*) and some polysaccharides (McIntire, Roth, and Shaw, *J. Amer. Chem. Soc.*, 1948, **70**, 1193; Levey, *Ind. Eng. Chem.*, 1920, **12**, 743) have been described. Although it was not claimed as such, the publication by Rigby apparently is the first recorded resolution of a glycol through its di(hydrogen phthalate). In view of Rigby's work our own investigation was not pursued beyond noting that ethylene glycol and propylene glycol were easily converted into their di(hydrogen phthalates) by the method of Levene and Mikeska (*J. Biol. Chem.*, 1927, **75**, 587), and that the acid esters gave stable salts with (−)-menthylamine and alkaloids. Salts with menthylamine showed better crystallising power than those with strychnine or brucine, and this indicates that a wide range of reagents is now available for the resolution of glycols, which was formerly regarded as a difficult problem with a limited choice of methods.

We have also investigated the possibility of applying column techniques to the resolution of acid esters. Considerable attention has been directed in recent years to the behaviour of stereoisomers on columns of adsorbent with a view to effecting optical resolutions by chromatographic techniques, and a review by Zechmeister is available (*Ann. N.Y. Acad. Sci.*, **1948**, **49**, 220). Published procedures involve the preferential adsorption of one enantiomorph on an optically active surface, but our own work has been concerned with the behaviour of salts in columns containing excess of base, where exchange reactions might be more important than selective adsorption.

If a racemic acid is combined with an active base B, and the mixture of salts A_+,B and A_-,B is washed through a column of excess B, with a solvent which dissolves the salts and free base only sparingly, a series of exchange reactions is possible. Some dissociation of the salts in dilute solution is to be expected, and the free acids A_+ and A_- may then react with the surfaces of solid B in the column, re-forming A_+,B and A_-,B which in part may be held on the surface of solid B at the moment of formation but will later re-dissolve. This process may be repeated through the column and, if there are differences in solubility and stability of the salts and in the degree of their adsorption on solid B, one salt should be preferentially removed from the column by continued washing.

This hypothesis was tested by combining (±)-2-octyl hydrogen phthalate with brucine, and washing the salts through a column of brucine (mixed with filter aid) by means of light petroleum containing a little acetone. The first fractions contained the brucine salt of highly active (−)-2-octyl hydrogen phthalate, which was followed by a small, less active fraction, and then the salt of (+)-2-octyl hydrogen phthalate, which was much more difficult to remove. In one operation up to 80% of the theoretically possible amount of (−)-2-octyl hydrogen phthalate could be recovered, of 97% optical purity. Comparable results were obtained with the strychnine salt of (±)-*trans*-3-methyl*cyclo*hexyl hydrogen phthalate in a column of strychnine, the salt first eluted being that of the (+)-enantiomorph, of 98% purity. These results were interesting in that the separations in each case readily afforded the enantiomorph giving the more soluble salt, *i.e.*, the one which is more difficult to purify by the usual technique of fractional crystallisation (Pickard and Kenyon, *J.*, 1907, **91**, 2058; Macbeth and Mills, *J.*, 1947, 205).

However, further experiments have shown that such good results cannot be obtained with all systems and, when the method was applied to (±)-2-butyl hydrogen phthalate (on brucine),

(±)-*trans*-2-methyl*cyclo*hexyl hydrogen phthalate (on strychnine), and (±)-menthyl hydrogen phthalate (on cinchonine), it gave only partial or slight resolution in each case. This suggested that differences in solubility rather than exchange reactions occurring in the column of alkaloid might be the most important factor in achieving a resolution. This idea is supported by the fact that the efficiency of the resolutions in columns was not affected by altering the fineness of division of the alkaloid, or by using a column of alkaloid precipitated on active carbon. In the case of 2-octyl hydrogen phthalate the alkaloid could be omitted from the column altogether: a 97% resolution was still effected when the mixture of brucine salts was eluted through a column of pure filter aid. Arrangement into a column was necessary, however, as simple extraction by shaking of a mixture of (±)-2-octyl hydrogen phthalate, brucine, and filter aid gave only 95% resolution, and in the case of *trans*-3-methyl*cyclo*hexyl hydrogen phthalate the material collected contained only 66% of the (+)-, together with 34% of the (−)-isomer. Part of the separations observed in columns may be caused by selective adsorption of one diastereoisomer on the filter aid (" Hyflo Supercel ") which was mixed with the alkaloids to prevent caking and channelling.

In its present form this method of resolution is not of general application, but may be useful for recovering the more soluble component in cases where there is a considerable difference in solubility between the stereoisomerides; in particular, it might be applied to mother-liquors after the less soluble component has been removed by crystallisation. The necessity for handling large volumes of solvent is a disadvantage.

The possibilities of the method probably have not been exhausted, and one useful variation might be to use a polar type of solvent such as aqueous alcohol, which would promote the dissociation of the salts in solution and so facilitate exchange reactions in the column; the only solvents used have been light petroleums containing a little acetone, benzene, or chloroform. An allied problem of considerable interest is the possibility of resolving racemic bases by passage through a column of an optically active cation exchanger such as McIntire, Roth, and Shaw's " cotton acid succinate " (*loc. cit.*).

Consideration has also been given to the possibility of applying the technique of partition chromatography to the resolution of acid esters. Martin has given reasons for believing that this process is not well suited for the separation of stereoisomers (Biochem. Soc. Symposia, No. **3**, **1949**, p. 9), but in the present case the method seemed worthy of trial as it is known that in many cases the relative solubilities of a pair of diastereoisomeric salts may be reversed by changing from one solvent to another. Alkaloidal salts are unsuitable for partition experiments because of their instability and the difficulty of finding suitable pairs of solvents, and the stronger base (−)-menthyltrimethylammonium hydroxide was used. Its salts with the enantiomorphs of 2-octyl hydrogen phthalate could be partitioned between water and chloroform–light petroleum, and the two salts appeared to have significantly different partition coefficients. Attempts to use this difference in an actual resolution were uniformly unsuccessful, but the experiments failed in each case because of mechanical difficulties, and probably do not constitute a decisive test of the possibilities of the method.

EXPERIMENTAL.

(−)-p-*Aminobenzomenthylamide*.—Our preparation, obtained by hydrogenation of (−)-*p*-nitrobenzomenthylamide over Raney nickel in ethanol at 75°, had m. p. 188—189°. Day and Kelly (*J. Org. Chem.*, 1939, **4**, 101) reported m. p. 190·5—191°.

(−)-3 : 5-*Diaminobenzomenthylamide*.—(−)-3 : 5-Dinitrobenzomenthylamide (Read and Grubb, *J.*, 1934, 1779), hydrogenated in pure ethyl acetate over Raney nickel at 120° under pressure, yielded a crude red product, m. p. 136—140°, which, when dissolved in dilute hydrochloric acid, treated with active carbon, and reprecipitated with ammonia, yielded pure (−)-3 : 5-*diaminobenzomenthylamide* as a white, amorphous powder, m. p. 153°, rapidly darkening in air (Found: C, 69·9; H, 9·2. $C_{17}H_{27}ON_3$ requires C, 70·6; H, 9·3%). Attempts at recrystallisation from alcohol yielded oils, and from non-polar solvents it separated as a gelatinous mass.

(−)-N^4-*Menthylsulphanilamide*.—*p*-Nitrobenzenesulphonyl chloride (10·7 g.) was added in small lots during 15 minutes to a solution of (−)-menthylamine (7·5 g.) in dry pyridine (40 ml.), the temperature being kept below 40°. The mixture was set aside with occasional shaking for about 30 minutes and then heated on a water-bath for 10 minutes, cooled, and poured into dilute hydrochloric acid. The sulphonamide was precipitated as a dark red oil which soon solidified (15·5 g.) and when recrystallised from dilute alcohol had m. p. 115·5° (12 g.). The nitro-compound (11·5 g.) in alcohol (200 ml.) was reduced under pressure (1600 lbs./sq. in.) in the presence of Raney nickel (2 g.) at 75—85°. When the uptake of hydrogen ceased, the cooled contents of the bomb were filtered and steam-distilled. The yellow solid *amino-amide* remaining on removal of alcohol crystallised from alcohol and then had m. p. 165° (19 g.) (Found: C, 61·9; H, 8·25. $C_{16}H_{26}O_2N_2S$ requires C, 61·95; H, 8·4%).

Salt Formation with the Foregoing Bases.—(−)-*trans*-3-Methyl*cyclo*hexyl hydrogen phthalate (0·48 g.) was dissolved in chloroform (10 ml.) containing the *p*-amino-amide (0·5 g.). Light petroleum was added until the solution was becoming cloudy. Crystals (0·3 g.) slowly separated which had m. p. 185—186° and proved to be the free base. (±)-*sec.*-Butyl hydrogen phthalate also fails to form a salt with this amide.

(—)-p-*Aminomethylbenzomenthylamide.*—*p*-Aminobenzoic acid (1 mol.) was diazotised in hydrochloric acid (3 mols.), and the diazonium salt solution was stirred into a solution containing nickel sulphate (1 mol.), potassium cyanide (5 mols.), and sodium hydroxide (3 mols.), the temperature being kept at 0—5°; the mixture was then acidified and heated to 55°. The precipitate collected after cooling of the solution was dried and extracted exhaustively with acetone, from which *p*-cyanobenzoic acid was recovered in 60% yield. This acid was refluxed for 1 hour with thionyl chloride (5 mols.) and a trace of pyridine, then the solution was concentrated by distillation, and the residue distilled under reduced pressure, to give a 93% yield of *p*-cyanobenzoyl chloride, b. p. 108°/1·6 mm.

The acid chloride (11·0 g.) was dissolved in benzene (120 ml.) and slowly stirred into a solution of (—)-menthylamine (10·6 g.) and pyridine (5·8 g.) in benzene (50 ml.). Next morning, the solution was worked up in the usual way and afforded a yellow solid, m. p. 116—123° (18·2 g.), which was recrystallised (charcoal) from 60% alcohol (75 ml.), to give pure (—)-*p*-cyanobenzomenthylamide as small white crystals having m. p. 123—124° (16·5 g.).

The cyano-derivative was rapidly hydrogenated when dissolved in saturated methanolic ammonia (5 mols.) and shaken at 100° with Raney nickel under 1000-lbs. pressure of hydrogen. Removal of ammonia and methanol and addition of concentrated sodium hydroxide solution precipitated a gum which soon solidified. Recrystallisation from dry benzene–light petroleum (most solvents tended to give gels) afforded (—)-p-*aminomethylbenzomenthylamide* as white granules, m. p. 164—165°, $[\alpha]_D$ —61·1° (*c*, 5 in chloroform) (Found : C, 74·8; H, 9·7. $C_{18}H_{28}ON_2$ requires C, 75·0; H, 9·7%).

Resolution Experiments.—(a) *Octan-2-ol.* (±)-2-Octyl hydrogen phthalate (3·4 g.) was dissolved in boiling light petroleum (b. p. 100—120°; 10 ml.) and added to a hot solution of the above base (3·5 g.) in the same solvent (15 ml.). On cooling, small white crystals (6·5 g.) separated, having m. p. 140—142°. Seven crystallisations from ethyl acetate yielded a head fraction (0·85 g.), m. p. 146°, $[\alpha]_D$ —23·6° (*c*, 4 in chloroform), not altered by a further crystallisation. Decomposition of this salt with aqueous sodium carbonate yielded (—)-2-octyl hydrogen phthalate, m. p. 75°, $[\alpha]_D$ —48·4° (*c*, 5 in ethanol) (cf. Pickard and Kenyon, *loc. cit.*).

(b) *Butan-2-ol.* The salt from the base and (±)-2-butyl hydrogen phthalate was obtained as white needles, m. p. 171—173°. Recrystallisations from benzene or from ethyl acetate caused no change in m. p., and decomposition of the salt after six such crystallisations gave an inactive hydrogen phthalate.

(c) trans-2-*Methyl*cyclo*hexanol.* The salt from the base and (±)-*trans*-2-methyl*cyclo*hexyl hydrogen phthalate had $[\alpha]_D$ —46° (*c*, 5 in ethanol). Six recrystallisations from benzene yielded a head fraction (35% of the original salt) with $[\alpha]_D$ —37°, which afforded a sample of free hydrogen phthalate with $[\alpha]_D$ —8° (in dilute alcohol) instead of ±63° (Gough, Hunter, and Kenyon, *loc. cit.*). The use of aqueous alcohol as solvent did not increase the rate of resolution.

Hydrogen Phthalates of Glycols.—(a) *Ethylene glycol.* The freshly distilled glycol (6·2 g.) was dissolved in anhydrous pyridine (35 ml.), powdered phthalic anhydride (29·6 g.) was added, and the mixture was stirred. An exothermic reaction occurred, and after 7 minutes the solid had dissolved and the temperature was 47°. The clear viscous solution was left for 48 hours, then stirred slowly into ice-water (1 l.) containing concentrated hydrochloric acid (50 ml.). The voluminous precipitate was collected after 2 hours, washed well with water, and dried at 100° (yield, 34 g.; m. p. 160—162°). The crude *di*(*hydrogen phthalate*) was moderately soluble in benzene, ether, chloroform, or ethyl acetate, but was most satisfactorily crystallised from 50% methanol, from which it separated either as fine needles, m. p. 158—159°, or as large flat rods, m. p. 163—164°; the former changed slowly to the latter when left in contact with the mother-liquor (Found : C, 60·0; H, 4·1. $C_{18}H_{14}O_8$ requires C, 60·3; H, 3·9%).

(b) *Propylene glycol.* In a similar way, the *di*(*hydrogen phthalate*) was prepared from (±)-propylene glycol. This ester was rather more soluble than the ethylene derivative, crystallised less readily, tending to separate as an oil from aqueous methanol; from warm chlorobenzene it separated as very fine needles, m. p. 147—148° (Found : C, 61·5; H, 4·5. $C_{19}H_{16}O_8$ requires C, 61·3; H, 4·3%).

Resolutions by Means of a Column.—(a) (±)-2-*Octyl hydrogen phthalate.* After preliminary experiments it was found best to pass the solutions up the column and the following technique was generally used. A separating funnel was connected to the bottom of the column by a glass tube of a length to give a head of about 2·5 metres. The column was packed in a glass tube about a metre in length (diameter, 1·5 cm.) and consisted of a bottom layer containing an intimate mixture of (±)-2-octyl hydrogen phthalate (2 g.), brucine (5 g.), and filter-aid (" Hyflo Supercel "; 5 g.), and a second layer a mixture of brucine (25 g.) and the filter-aid (25 g.), the two sections being separated by a closely fitting porous pad. The solvent consisted of a mixture of acetone (25%) and light petroleum (b. p. 40—60°), and the tap of the separating funnel was adjusted to give a flow of some 40 ml./hr. The first eluate (470 ml.), after being well washed with dilute sulphuric acid and dried ($CaCl_2$), gave, on removal of the solvent, (—)-2-octyl hydrogen phthalate (0·78 g.), m. p. 73·5—74°, $[\alpha]_D$ —45·4° (c, 1 in alcohol) [97% of the (—)-ester]. Two crystallisations from 90% acetic acid gave the pure (—)-phthalate, m. p. 75°, $[\alpha]_D$ —48·2° (*c*, 5 in alcohol). The next eluate collected (500 ml.) gave a further yield of hydrogen phthalate (0·19 g.) which had a lower lævorotation.

The column was extruded, dried, and vigorously stirred (30 minutes) with sodium carbonate solution (5 g. in 600 c.c. of water) at about 50°. After filtration and acidification a dextrorotatory hydrogen phthalate (0·85 g.) was obtained having m. p. 73—74° and $[\alpha]_D$ +41·6°, which contained 93% of the (+)-isomer. Three crystallisations from acetic acid gave pure (+)-2-octyl hydrogen phthalate.

(b) (±)-trans-3-*Methyl*cyclo*hexyl hydrogen phthalate.* The bottom layer in this case consisted of the inactive hydrogen phthalate (1·5 g.) intimately mixed with strychnine (5 g.) and filter-aid (5 g.). The upper layer was a mixture of strychnine (25 g.) and filter-aid (20 g.). The solvent was chloroform (20%)–light petroleum (b. p. 40—60°), and the first eluate collected (400 ml.) after treatment in the usual way gave (+)-*trans*-3-methyl*cyclo*hexyl hydrogen phthalate (0·58 g.) having $[\alpha]_D$ +12·6° (*c*, 5 in chloroform) [98% of the (+)-isomer]. A further volume of eluate (350 ml.) contained only a small quantity (0·07 g.) of hydrogen phthalate with low dextrorotation. The extruded column yielded a hydrogen phthalate (0·75 g.) containing 91·5% of the (−)-isomer and having $[\alpha]_D$ −10·7° (*c*, 5 in chloroform).

(c) *Attempted further purification.* It was not possible to achieve any further concentration of the (−)-2-octyl or the (+)-*trans*-3-methyl*cyclo*hexyl hydrogen phthalates when the materials (97 and 98% respectively) obtained from the first resolutions were again treated in a similar way in freshly packed columns. This inability to get complete resolution is difficult to understand, but an explanation might possibly be found if the mixture of 97 or 98% purity represents a fairly stable diastereoisomeric compound which persists even in solution and has the highest solubility of any combination of salts in that particular system.

Modification of the Column.—Experiments with columns in which the upper layer consisted of alkaloid adsorbed on charcoal failed to give any hydrogen phthalate in the eluate and as the salts were apparently much too strongly adsorbed on the charcoal the method was abandoned.

Columns in which the upper layer consisted solely of filter-aid gave resolutions very similar to those described above in the case of (±)-2-octyl- and (±)-*trans*-3-methyl*cyclo*hexyl hydrogen phthalates. (−)-2-Octyl hydrogen phthalate of approx. 97% purity was in all cases obtained from the eluate, independent of the length of the column of filter-aid; and in the case of *trans*-3-methyl*cyclo*hexyl hydrogen phthalate no better separation from the eluate of the (+)-isomer than 98% purity was ever achieved.

Partition Chromatography.—(−)-*Menthyltrimethylammonium hydroxide.* Formic acid (11·2 ml.; 90%) was gradually added with cooling to (−)-menthylamine (7 g.) and, after addition was complete, the flask fitted with a reflux condensor was immersed in an oil-bath at 90° after the addition of formaldehyde (11 ml.; 36%). When the vigorous efferescence had subsided the mixture was allowed to cool and kept overnight, and thereafter it was refluxed for 3 hours. After cooling, acidification (10N-HCl; 6 ml.), and evaporation under reduced pressure, the residue was made alkaline with sodium hydroxide and steam-distilled. Chloroform extraction (four times) of the distillate, then drying ($CaCl_2$), and removal of solvent gave dimethylmenthylamine as a colourless oil, b. p. 100°/12·5 mm. (8 g.). The base (8 g.) was refluxed for 2 hours with methanol (10 ml.) and methyl iodide (6 ml.), and the solvent thereafter removed. Ice-cold concentrated potassium hydroxide solution (50 ml.) was added to the residue, and the methiodide (13·6 g.) was collected and washed with a little cold water. When dried (solid NaOH) it had m. p. 189°. The methohydroxide was obtained as a white amorphous solid (4·5 g.) when the methiodide (7 g.) in water (80 ml.) was shaken for 12 hours with freshly precipitated silver hydroxide (2·8 g.; 10% excess), and the filtered solution was evaporated to dryness. The base is very deliquescent and was not subjected to further purification.

The partition of the salt of the base and 2-octyl hydrogen phthalate was examined for aqueous solutions of the salt and various organic solvents, particularly chloroform–light petroleum mixtures. The mutual solubilities of the aqueous and the organic solvent were affected by the presence of the salt but the approximate distribution ratios determined [(+)- and (−)-hydrogen phthalate salts, 1 : 30 and 1 : 60 respectively, with chloroform (25%)–light petroleum] encouraged attempts at resolution with columns containing silica gel, potato starch, or paper as supports. In all cases only slight resolutions were achieved, and the work was discontinued on account of the technical difficulties encountered.

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