[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

New Methods for Resolution of Enantiomorphs. I. Rectification[1]

BY M. E. BAILEY[2] AND H. B. HASS

Despite the great theoretical and technological importance of the resolution of enantiomorphs, little success has heretofore attended efforts to develop new methods by the application of modern developments in laboratory technique. The procedures applied almost exclusively to resolution problems to date were invented by Pasteur more than 83 years ago.[3,4,5]

Of the various methods of counter-current separation, only the adsorption of liquid on solid has been used successfully on racemic mixtures. Nakamura[6] was able to resolve certain complex coördination compounds by preferential adsorption on *d*-quartz crystals. This work has been extended by Karagunis and Coumoulos[7] and by Henderson and Rule,[8] who found that *d*-β-naphthylazomandelic acid was adsorbed to a greater extent than the *l*-isomer by finely-divided *d*-lactose crystals.

As a result of the work herein described it is now possible to apply rectification, the most widely studied of all the multiplate separation processes, to the problem of resolving enantiomorphs which can be converted to volatile diastereoisomers. The extension of these general processes to other counter-current methods, such as liquid–liquid extraction and columnar adsorption of diastereoisomers from vapor phase and liquid phase, are being actively investigated in this Laboratory.

Experimental

Resolution of 2-Methylbutanoic Acid Using *d*-2-Methyl-1-butanol.—*dl*-2-Methylbutanoic acid, prepared by oxidizing *dl*-2-methyl-1-butanol according to the method of Marckwald,[9] was esterified with *d*-2-methyl-1-butanol in the following manner. A mixture of 60 ml. of acid, 65 ml. of the alcohol, 100 ml. of benzene, and 1 ml. of sulfuric acid was distilled in a Claisen flask until about 50 ml. of benzene and water had been collected. The water was retained and benzene returned to the flask. This process was repeated until the theoretical amount of water (about 11 ml.) had been collected. The residue was neutralized with sodium carbonate solution and rectified using a modified Podbielniak column. One hundred ten ml. of *d*-β-methylbutyl-*dl*-2-methylbutanoate (b. p. 184–187°) was recovered. This ester was rectified on a 60-plate Lecky column[10] at 45 mm. and the specific rotation of the distillate changed progressively from +2.0° to +3.3°. The 0–40% and 70–100% portions of the distillate were saponified with sodium hydroxide solution and samples of optically active 2-methylbutanoic acid were recovered: $[\alpha]^{25}\text{D}$ −0.25° and +0.29° for acid obtained from the first and last portions of the distillate.

Resolution of 2-Methylbutanoic Acid Using *l*-Menthol.—Following the same procedure, 130 ml. of *l*-menthyl *dl*-2-methylbutanoate (b. p. 117–120° at 7 mm.) was synthesized and rectified on the 60-plate column. The specific rotation of the distillate changed progressively from −53 to −57.5°. Alcoholic sodium hydroxide was used for the saponification of this ester. Active 2-methylbutanoic acid ($[\alpha]^{25}\text{D}$ −0.14°) was recovered from the 60–100% portion of the distillate.

Resolution of 2-Methoxypropanoic Acid Using *l*-Menthol.—*l*-Menthyl *dl*-2-methoxypropanoate (b. p. 120° at 7 mm.) was prepared from 2-chloropropanoic acid by treatment of the methyl ester of the latter with sodium methoxide followed by *trans*-esterification with *l*-menthol. The specific rotation of this ester changed progressively from −65.4 to −49.5° upon rectification in the 60-plate column. Samples of active 2-methoxypropanoic acid ($[\alpha]^{25}\text{D}$ −10.5° and +11.0°) were obtained from the 0–40 and 60–100% portions of the distillate.

Resolution of 2-Butanol Using Levorotatory Lactic Acid.—*dl*-2-Butanol was esterified by the technique described above with a commercial grade of lactic acid which had a configuration 60% levorotatory and 40% dextrorotatory. A 120-ml. sample was rectified in the 60-plate column at 51 mm. The specific rotation of the distillate changed from +2.2° to −0.8°. Samples of active 2-butanol ($[\alpha]^{25}\text{D}$ +0.57° and −0.59°) were obtained from the 0–36% and 56–100% portions of the distillate.

Resolution of 2-Butanol Using Levorotatory 2-Acetoxypropanoic Acid.—α-Methylpropyl 2-acetoxypropanoate was produced by treating with acetyl chloride a sample of *s*-butyl lactate (α-methylpropyl 2-hydroxypropanoate) prepared as in the previous experiment. A 120-ml. sample of this ester (b. p. 90–92° at 18 mm., d_{20} 0.9883 g./ml.) was rectified at 28 mm. The change in the specific rotation of the distillate was from +9.5° to +6.1°. Optically active 2-butanol ($[\alpha]^{25}\text{D}$ +1.08°) was obtained from the 0–36% portion of the distillate.

Resolution of 2-Butanol Using Levorotatory 2-Propionoxypropanoic Acid.—α-Methylpropyl 2-propionoxypropanoate (b. p. 122–124° at 45 mm., d_{20} 0.9850 g./ml.), pre-

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[1] This article contains material from the Ph.D. thesis of M. E. Bailey.

[2] Eli Lilly Research Fellow, 1940–1941.

[3] L. Pasteur, *Ann. chim. phys.*, (3) **24**, 442 (1848).

[4] L. Pasteur, *Compt. rend.*, **36**, 197 (1853).

[5] L. Pasteur, *ibid.*, **46**, 615 (1858).

[6] A. Nakamura, R. Tsuchida and M. Kobayashi, *J. Chem. Soc. Japan*, **56**, 1339 (1935); *C. A.*, **30**, 926[8] (1936).

[7] G. Karagunis and G. Coumoulos, *Nature*, **142**, 162 (1938); *C. A.*, **32**, 7411[7] (1938).

[8] G. M. Henderson and H. G. Rule, *J. Chem. Soc.*, 1568 (1939).

[9] W. Marckwald, *Ber.*, **37**, 1045 (1904).

[10] H. S. Lecky and R. H. Ewell, *Ind. Eng. Chem., Anal. Ed.*, **12**, 544 (1940).

pared by treating *s*-butyl lactate (above) with propionyl chloride, was rectified at 28 mm. on the 60-plate column. The specific rotation of the distillate changed from +9.7° to +6.9°. The 0–20% and 80–100% portions of the distillate were saponified and active 2-butanol was recovered from each portion ($[\alpha]^{25}D$ +1.25° and −1.78°).

Resolution of 2-Pentanol Using Levorotatory Lactic Acid.—Esterification of *dl*-2-pentanol with the commercial grade of lactic acid yielded α-methylbutyl 2-hydroxypropanoate (b. p. 75–78° at 10 mm., d_{20} 0.9615 g./ml.). This ester was rectified at 20 mm. on the 60-plate column and the specific rotation of the distillate changed from +2.2° to +0.5°. Optically active 2-pentanol ($[\alpha]^{25}D$ +0.76°) was recovered from the 0–36% portion of the distillate.

Resolution of 2-Ethyl-1-hexanol Using *d*-2-Methylbutanoic Acid.—*l*-2-Methylbutanoic acid, prepared by the oxidation of *d*-2-methyl-1-butanol, was esterified with 2-ethyl-1-hexanol. The ester (b. p. 124–125° at 25 mm., d_{20} 0.8682 g./ml.) was rectified on the 60-plate column at 10 mm. The change in the specific rotation of the distillate was from +8.4° to +7.6°. The 0–36% and 60–100% portions of the distillate were saponified to produce samples of optically active 2-ethyl-1-hexanol ($[\alpha]^{25}D$ +0.03° and −0.05°).

Production of 85% *d*-2-Butanol by Rectification of α-Methylpropyl 2-Propionoxypropanoates.—*d*-Lactic acid, produced by fermenting whey using *Streptococcus lactus*, was esterified with *dl*-2-butanol and the product was treated with propionyl chloride. In this manner 140 ml. of α-methylpropyl 2-propionoxypropanoate (b. p. 110–111° at 25 mm.) was synthesized. The ester was rectified in the 60-plate column at 35 mm. and this caused the specific rotation of the distillate to change from −42.5° to −26.0°. 2-Butanol recovered from the 0–20% portion of the distillate had a specific rotation ($[\alpha]^{25}D$) of −6.26°, and that from the 85–100% portion gave $[\alpha]^{25}D$ +9.8°. The specific rotation of pure *d*-2-butanol is reported to be 13.84°.[11] The latter sample, therefore, contained 86% *d*-2-butanol.

In every case examined, at least a partial separation of the diastereoisomeric esters was obtained. The present method thus differs strikingly from all previous ones which fail completely in a large proportion of the cases attempted. This is attributable to the multiplate nature of rectification which is able to effect separations in spite of the small fugacity differences of diastereoisomers. In the case of *dl*-methylpropyl *d*-2-propionoxypropanoate it was possible to obtain 86% *d*-2-butanol at the first rectification. The best separations were obtained using lactic acid and its derivatives and with *l*-menthol.

The number of theoretical plates required for a complete separation of these particular diastereoisomers varies from about 60 to perhaps 300. Because of recent improvements in rectification equipment,[10] columns having such efficiencies are now fairly easily constructed.

This new technique for resolving enantiomorphs should find application in the synthesis of therapeutic agents since many medicinals are considerably more effective in their optically active forms than as racemates. Although in many cases the final product is involatile and cannot be resolved by this method, certain precursors, which contain the seat of asymmetry, may vaporize with sufficient ease to make the rectification method applicable. Attempts are under way in this Laboratory to construct apparatus suitable for effecting multiplate rectification at lower pressures than those at present usable in efficient columns.

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Summary

A new method is reported for the resolution of enantiomorphs by conversion to volatile diastereoisomers followed by rectification and reconversion to the original compounds.

Partial resolutions of 2-butanol, 2-pentanol, 2-ethyl-1-hexanol, 2-methylbutanoic acid, and 2-methoxypropanoic acid were accomplished using *l*-2-hydroxypropanoic acid, *l*-2-acetoxypropanoic acid, *l*-2-propionoxypropanoic acid, *d*-2-methylbutanoic acid, *d*-2-methyl-1-butanol, and *l*-menthol. Using a 60-plate column, it was possible to produce 86% *d*-2-butanol with a single distillation by this method using *d*-2-propionoxypropanoic acid.

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[11] "International Critical Tables," Vol. VII, 1930, p. 366.