Asymmetric Transformation as a Means for Determination of Absolute Configuration of Acids with an Asymmetric Carbon Atom in the α-Position

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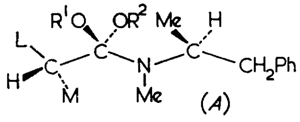
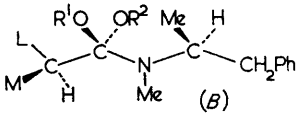
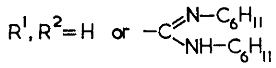
WE have previously developed a general method using asymmetric transformation for determining the absolute configuration of amines, amino-alcohols, amino-acids and amino-sugars.[1] This procedure can be modified according to requirements. Optically active hydratropic acid can be used, and the reaction carried out with racemic amino-compounds.[2] Using experience gained in these reactions we were able to determine the absolute configuration of carboxylic acids containing an asymmetric carbon atom in the α-position by reaction with optically active amines. In order to avoid some complications, which occurred by using optically active primary amines, we have used a secondary amine, *S*-(+)-2-methylamino-1-phenylpropane.[3] As racemic acids we used some substituted α-phenylacetic acids, prepared *via* alkylation of phenylmalonic acid.[4]



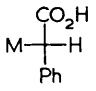
(*A*)



(*B*)



$R^1, R^2 = H$ or $-C(=N-C_6H_{11})NH-C_6H_{11}$



(I)

Reactions were carried out as follows. To the solution of 6—7·5 mmole of alkylphenylacetic acid in tetrahydrofuran, was added 5 mmole of dicyclohexylcarbodi-imide. After cooling, the nearly solid mixture was treated with a solution of *S*-(+)-2-methylamino-1-phenylpropane (5 mmole). The reaction mixture was kept for a least 24 hr. at room temperature, and unreacted acid was isolated. The acids isolated (I; L = Ph, M = Me, Et, Pr^n, Bu^n, n-C_5H_{11}, Pr^i, Bu^i, CH_2=CH–CH_2) have *S*-configuration and are, with exception of isopropyl- and isobutyl-phenylacetic acids, dextrorotatory.

We explain the steric course of these asymmetric reactions as follows. The acylating agent from the acid and dicyclohexylcarbodi-imide reacts with *S*-(+)-2-methylamino-1-phenylpropane in such a way that one of the two possible diastereoisomeric amides is formed preferentially. The ratio depends on the energy difference between the transition states (or intermediates) leading to these amides. The scheme below shows only such conformations of intermediates of reactions *A* and *B* as are, probably, energetically preferred. Because of lower steric interactions between the substituents of the acid and the amine, the activation energy of the reaction leading *via A* is lower, and therefore intermediate *A* is preferred to *B* ("L" means large, "M" medium-sized, substituents). The configuration of the acid isolated (I) is opposite to that of the one which forms the energetically preferred amide.

The application of this method to the determination of absolute configuration of some natural acids will be the subject of some future paper.

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[3] S. Senoh, *J. Pharm. Soc. Japan*, 1952, **72**, 1098.

[4] W. Wislicenus and K. Goldstein, *Ber*, 1896, **29**, 2599.