CHEMICAL RESOLUTION OF SECONDARY (±)-ALCOHOLS*

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The preparative resolution of optically active alcohols might proceed most readily by direct esterification with optically active acids except that few esters crystallize satisfactorily.[1] We have now found that many secondary (±)-alcohols can be resolved by esterification with L-amino acids using *p*-toluenesulphonic acid (*p*-TsOH) and that sterically pure, crystalline *p*-toluenesulphonates of the L-amino acid (+)-alkyl esters can be obtained in good yields (60–80% of the available (+)-isomer).

TABLE 1

PHYSICAL CONSTANTS OF L-AMINO ACID-(+)-ALKYL ESTERS TOLUENE-*p*-SULPHONATES

Amino Acid	Alkyl Group	M.P.	α (*c*, 1% MeOH)	Gas Chromatography of *N*-Trifluoroacetyl Derivative*			
				Steric Purity (%)	Separation Temp.	Retention Times (min)	
						L-(−)	L-(+)
Valine	2-butyl	140–142°	+19·5°	98	100°	5·4	5·8
Valine	2-pentyl	134–136	+16·0	100	100	7·3	7·7
Valine	4-methyl-2-pentyl	171–173	+13·9	100	100	7·3	8·3
Valine	3-methyl-2-butyl	152–154	+11·0	99	110	5·0	5·5
Alanine	3,3-dimethyl-2-butyl	181–183	+ 9·6	98	110	5·9	6·6
Valine	2-methyl-cyclohexyl	188–190	+35·8	100	140	5·2	5·6
Alanine	menthyl	160–162	+45·7	100	140	8·3	9·3

* In a typical assay, the sample (5 mg) was dissolved in trifluoroacetic anhydride (0·5 ml) and after 1 hr at room temperature, the residue was dissolved in ethyl acetate (1 ml). After washing with aqueous sodium bicarbonate and water, and drying (Na_2SO_4) a part of the solution (1 μl) was injected into the gas chromatograph. Gas chromatographic analyses were carried out on a Wilkens Autoprep gas chromatograph using a 15 ft by ¼ in. column (0·75% DEGS/0·25% EGSS-X on chromosorb W). During the analysis the nitrogen flow was 60 ml/min.

In a typical preparation the L-amino acid (0·025 mole), the (±)-alcohol (0·058 mole), *p*-toluenesulphonic acid (6 g), benzene (35 ml), and toluene (15 ml) were refluxed (Dean and Stark apparatus) till a clear solution resulted (30–60 hr). The reaction mixture was then cooled and filtered to remove traces of unchanged

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[1] Ingersoll, A. W., *Org. React.*, 1944, **2**, 380.

amino acid. After evaporation of the solvents and the excess (±)-alcohol, the residual oil was set aside for several hours. The partially crystalline residue was diluted with anhydrous ether (10 ml), filtered, washed with ether, and dried. The *p*-toluenesulphonates (Table 1) after two recrystallizations from benzene (10–20% solution) are both chemically and sterically pure (gas chromatography).

The *p*-toluenesulphonates of the L-amino acid (+)-alkyl esters (0·01 moles) were hydrolysed with aqueous or aqueous methanolic caustic soda (0·02 mole) at 25°, and the reaction followed by thin-layer chromatography ($BuOH/HCOOH/H_2O$, 70 : 15 : 15). The active alcohols were isolated by solvent extraction (ether or chloroform), followed by fractional distillation and were shown to be optically pure. For example, the sterically pure salt of L-valine (+)-3-methyl-2-butyl ester yielded after hydrolysis and distillation (+)-3-methyl-2-butanol, α_D +3·87° (lit.[2] +3·89°).

Finally, it is believed that by a suitable choice of the amino acid resolving agent, this procedure could be readily adapted to the resolution of other (±)-alcohols.

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[2] Pickard, R. H., and Kenyon, J., *J. chem. Soc.*, 1911, **99**, 45.