

Resolution of Neutral DL-Amino-acids *via* their (–)-Menthyl Ester Derivatives

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IN connection with another study, we have recently prepared the (–)-methyl esters of a number of neutral DL-amino-acids, by azeotropic distillation using toluene-*p*-sulphonic acid (*p*-Ts) as a catalyst.¹

A routine gas-liquid-chromatographic (g.l.c.) analysis of the crystalline reaction product derived from DL-norvaline however showed it to be a D-norvaline derivative. We have since shown that many

¹ K. Harada and T. Hayakawa, *Bull. Chem. Soc. Japan*, 1964, **37**, 191.

neutral DL-amino-acids can be readily resolved *via* their (–)-menthyl esters and that sterically pure *p*-Ts salts of the D-amino-acid (–)-menthyl ester are obtained in good yields (60–95% of the available D-isomer).

product was then diluted with anhydrous ether (20 ml.), filtered, washed with ether, and dried. The *p*-Ts salts (Table) as isolated and generally without further recrystallization are both chemically and sterically pure (g.l.c. analysis).

TABLE: *Physical constants of D-amino-acid (–)-menthyl esters toluene-p-sulphonates*

Amino-acid	m.p. (°C)	rotation [α] <i>c</i> = 1% (methanol)	G.l.c. Analyses of <i>N</i> -trifluoroacetyl derivative*		
			steric purity of sample (%)	retention times of diastereoisomers (min.)	
				L, (–)	D, (–)
alanine	155–156	–46.5	100	7.2	8.2
α -aminobutyric acid ..	160–162	–47.2	99	8.1	9.0
leucine	172–174	–44.2	99**	10.0	11.6
norleucine	153–154	–43.1	99	12.0	13.8
valine	209–210	–54.4	100	5.8	6.7
norvaline	159–160	–49.9	100	9.0	10.4
methionine	149–152	–30.7	100	10.9	11.8

* In a typical assays the sample (50 mg.) was dissolved in ethyl acetate (1 ml.) and triethylamine (0.15 ml.) and methyl trifluoroacetate (0.3 ml.) added. After 2 hours at 25° c, the solution was washed (H₂O), dried (Na₂SO₄) and injected into the gas chromatograph. G.l.c. analyses were carried out on a Wilkens 600C aerograph using a 5-foot \times $\frac{1}{8}$ -inch column (5% FFAP on Chromosorb W). During the analyses the separation temperature was 161° c (methionine 200° c) and the nitrogen flow 28 ml./min.

** Recrystallized from benzene–ether.

In a typical preparation the DL-amino-acid (0.025 moles), menthol (6 g.), *p*-Ts (6 g.), benzene (35 ml.) and toluene (15 ml.) were refluxed (Dean and Stark) till a clear solution resulted (30–60 hr.). The reaction mixture was then cooled and filtered to remove traces of unreacted amino-acid. After evaporation of the solvents, the residual oil was set aside for several hours. The partially crystalline

Finally, the *p*-Ts salts of the D-amino-acid (–)-menthyl esters (1 mM) were hydrolysed with methanolic caustic soda (3 mM) at 25°. The D-amino-acids were isolated by ion exchange chromatography (Dowex 50 W) and shown to be sterically pure by g.l.c. analysis.²

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² B. Halpern and J. W. Westley, *Chem. Comm.*, 1965, 247.