

AN EXTENSION OF THE HALPERN-WESTLEY PROCEDURE FOR RESOLVING ALCOHOLS*

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In the course of work in this laboratory on enzyme specificity it became desirable to prepare the (+) and (−) isomers from the readily available (±)-2-methylpentan-1-ol. Halpern and Westley¹ have described a procedure for resolving (±) secondary alcohols involving the crystallization of the toluene-*p*-sulphonates of their esters with L-amino acids and remark *inter alia* that the procedure should be readily applicable to all (±) alcohols. Valine proved to be the amino acid of choice for the resolution of 2-methylpentan-1-ol; the (+) alcohol was prepared simply and expeditiously using L-valine and the (−) alcohol using D-valine. The use of alanine, tyrosine, and leucine for this resolution was also tried, but with unsatisfactory results. There was wide variation in the crystallization behaviour of the mixed (±)-ester toluene-*p*-sulphonates for different amino acids, and it is unwarranted to suppose that valine would be the resolving agent of choice for other primary alcohols. This agrees with the conclusion of Halpern and Westley¹ for secondary alcohols.

It should in theory be simple to use the same mechanism to resolve a DL-amino acid with the aid of an optically active alcohol. The simplest optically active primary alcohol that is readily obtainable is (−)-2-methylbutan-1-ol. Attempts to use this alcohol to resolve both DL-alanine and DL-valine were unsuccessful and suggest that the solubilities of the D- and L-amino acid (−)-2-methylbut-1-yl toluene-*p*-sulphonates were nearly identical in the solvents tried.

Experimental

To facilitate comparisons, the experimental conditions of Halpern and Westley¹ were retained unchanged. Amino acid (0.025 mole), alcohol (0.058 mole), toluene-*p*-sulphonic acid (6 g), benzene (35 ml), and toluene (15 ml) were refluxed in a Dean and Stark apparatus. Microanalyses were by the Australian Microanalytical Service and all melting points were uncorrected.

(i) Resolution of 2-Methylpentan-1-ol

D-(or L-)Valine and (±)-2-methylpentan-1-ol.—The reaction was complete in 1–2 hr to give 3.5 g (38% on the total ester salt that could be formed) of product, $[\alpha]_D^{20} \mp 7.1$ (c, 10 in CH₃OH). Three recrystallizations from acetone gave white needles of valine 2-methylpent-1-yl toluene-*p*-sulphonate, D-(−) or L-(+) isomer, $[\alpha]_D^{20} \mp 8.0^\circ$ (c, 10 in CH₃OH), m.p. 129–130° (Found (from L-valine): C, 57.7; H, 8.4; N, 3.6; S, 8.6; (from D-valine): C, 57.8; H, 8.4; N, 3.9; S, 8.4. C₁₈H₃₁NO₅S requires C, 57.9; H, 8.4; N, 3.7; S, 8.6%).

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¹ Halpern, B., and Westley, J. W., *Aust. J. Chem.*, 1966, **19**, 1533.

The ester was rapidly hydrolysed by a slight excess of methanolic alkali, and 2-methylpentan-1-ol was recovered in about 90% yield by fractionating off the methanol, steam-distilling the residue, and redistilling the non-aqueous layer: b.p. 146–149°, $[\alpha]_D^{20} \pm 10.8^\circ$ (c, 8 in heptane). These last values may be compared with the reported $[\alpha]_D^{25}$ for the (–)-alcohol of -4.5° (c, 20 in heptane: calculated from the reported data²). The values of the density, refractive index, and boiling point of the initial (\pm)-2-methylpentan-1-ol used in this study (Fluka, purum) agreed with the literature values. It appears that the material studied by Levene and Rothen² was only partly resolved.

On starting with 10 g of valine and 24 ml (19.6 g) of (\pm)-2-methylpentan-1-ol, 4.1 ml (3.35 g) of resolved 2-methylpentan-1-ol of the indicated optical purity (about 34% of the total (+) or (–) isomer present) was recovered in 2 working days.

L-Alanine and (\pm)-2-methylpentan-1-ol.—Very low yields (<8%) of white needles of unknown configuration, m.p. 98°, $[\alpha]_D^{20} -2.8$ (c, 5 in CH₃OH) from acetone/ether.*

L-Leucine and (\pm)-2-methylpentan-1-ol.—White needles of obviously mixed composition from yield, optical rotation, and melting point data. The mixture appeared to be principally the L-(+) isomer, but this compound could not be obtained pure by recrystallization.*

L-Tyrosine and (\pm)-2-methylpentan-1-ol.—The product crystallized from the refluxing mixture, giving nearly the theoretical yield of tyrosine hexyl ester toluene-*p*-sulphonate in the cold. Multiple recrystallization from acetone failed to resolve the apparently nearly equimolar mixture of L-(+) and L-(–) isomers.*

(ii) Attempted Resolution of DL-Valine

It took much longer for the reaction mixture to become homogeneous with the DL-amino acid (about 3 hr) than with the D or L forms where homogeneity was almost immediate. This observation is apparently to be explained by the different solubility of the toluene-*p*-sulphonates of D- (or L-) and DL-valine. A similar phenomenon has been noticed with other amino acids.

L-Valine and (–)-2-methylbutan-1-ol.—If the reaction was stopped after 1 hr when the mixture was homogeneous and the crystal water of the toluene-*p*-sulphonic acid had been entrained, the product was *L-valine toluene-p-sulphonate*, white needles from ether, m.p. 150°, $[\alpha]_D^{20} +15.0$ (c, 9 in CH₃OH) (Found: C, 49.5; H, 6.6; N, 4.7; S, 11.3. C₁₂H₁₉NO₅S requires C, 49.8; H, 6.6; N, 4.8; S, 11.1%). Longer refluxing (8 hr) gave 4.65 g (52% on L-valine) of the much less soluble *L-valine (–)-2-methylbut-1-yl ester toluene-p-sulphonate*, white needles, m.p. 119–20°, $[\alpha]_D^{20} +9.4^\circ$ (c, 11 in CH₃OH) (Found: C, 56.8; H, 8.1; N, 3.7; S, 8.8. C₁₇H₂₉NO₅S requires C, 56.8; H, 8.1; N, 3.9; S, 8.9%).

D-Valine and (–)-2-methylbutan-1-ol.—The reaction as above gave *D-valine (–)-2-methylbut-1-yl ester toluene-p-sulphonate*, m.p. 136°, $[\alpha]_D^{20} -6.8^\circ$ (c, 10 in CH₃OH) (Found: C, 56.5; H, 7.9; N, 4.1; S, 8.9%).

DL-Valine and (–)-2-methylbutan-1-ol.—Successive crops of product up to nearly the theoretical yield on the DL-valine present could be recovered with $[\alpha]_D^{20}$ (c, 10 in CH₃OH) between $+0.8^\circ$ and $+1.2^\circ$, only slightly altered by recrystallization from acetone/ether mixtures.*

* These substances gave satisfactory elementary analyses (C, H, N, S). However, this is no index of purity since mixtures of isomers are involved.

² Levene, S. A., and Rothen, A., *J. biol. Chem.*, 1934, **116**, 215.