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β-Methyl Aspartate Hydrochloride

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The reported ambiguity in the physical characteristics of β-methyl aspartate hydrochloride has been found to be due to the presence of aspartic acid formed from the former on storage.

SCHWARZ *et al.*[1] obtained β-methyl aspartate hydrochloride (I) by treating methanolic suspension of aspartic acid with thionyl chloride; m.p. 191-3° (decomp.), $[\alpha]_D^{25}$ +21·4° (*c* 1, 1: 3 EtOH-H_2O). Later, Goodman and Boardman[2] prepared (I) by the method of de Groot and Lichtenstein[3]; m.p. 204° (decomp.); and $[\alpha]_D^{25}$ +12·4° (*c* 1, 1: 3 EtOH-H_2O). Since the physical properties were at variance with those reported by Schwarz *et al.*, Goodman and Boardman purchased a sample of (I) from Cyclo Chemical Corp., and after recrystallization from methanol-ether mixture, confirmed its m.p. 204° and $[\alpha]_D^{25}$ +15·3° under the same conditions. On the basis of the above results, Goodman and Boardman concluded that the values reported by Schwarz *et al.* were in error. However, a survey of literature revealed that β-methyl aspartate hydrochloride prepared by different methods had varying physical characteristics, e.g. m.p. 180-1° (Puitti and Magli[4]), 190° (Coleman[5]) and 185-8° (Weygand *et al.*[6]). It appeared, therefore, of interest to resolve this ambiguity, particularly, because this compound is a frequently used intermediate in peptide synthesis.

On repetition of the experimental conditions reported by Schwarz *et al.*[1], we found that the melting point and optical rotation varied with each preparation. Descending paper chromatography on Whatman No. 1 filter paper (butanol-acetic acid-water, 4: 1: 5) revealed that different batches contained varying amounts of aspartic acid (ester, R_f 0·34; aspartic acid, R_f 0·21), and that crystallization from methanol-ether or acetic acid-ether solvent systems did not remove the contaminant completely. The hydrochloride salt was, therefore, purified as follows: crude ester hydrochloride (14 g.) was dissolved in methanol-water (3: 1) mixture and passed through a column (85×3 cm.) of Amberlite IR-45 ion exchange resin. The column was eluted with the same solvent and the eluate evaporated to dryness. The residue was crystallized from acetic acid-ether mixture, filtered and washed several times with ether to give β-methyl aspartate (II), m.p. 201-2° (lit.[7] m.p. 193-5°); $[\alpha]_D^{25}$ + 3° (*c* 1, 1: 3 EtOH-H_2O) (Found: C, 41·06; H, 6·36; N, 9·77. $C_5H_9NO_4$ (147·13) requires C, 40·83; H, 6·17; N, 9·52%). Paper chromatography (conditionsas above) revealed a single homogeneous spot, R_f 0·31. Compound (II) so obtained, was reconverted to its hydrochloride salt (by passing HCl through its acetic acid solution, followed by precipitation with ether), which when freshly crystallized from acetic acid-ether mixture melted at 199-200° and had $[\alpha]_D^{25}$ +14·4° (*c* 1, 1: 3 EtOH-H_2O). However, on keeping the solution for 1-2 hr at room temperature, the rotation changed to a higher value and this solution on chromatography revealed the presence of aspartic acid as an impurity. This was also found to be true when the hydrochloride salt was kept at room temperature for several days. This clearly indicates that (I) is labile and is easily hydrolysed to aspartic acid. In order to avoid this difficulty (I) may be purified and converted through Amerlite-IR 45 resin to the neutral ester, which is more stable.

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