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ABSOLUTE CONFIGURATION OF α-METHYL-β-ALANINE

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Abstract—(−)-α-Methyl-β-alanine was correlated through the reaction stages (I–III) with (+)-2-methylbutanol. The resulting absolute configuration is represented by the projection formula (V).

(±)-α-METHYL-β-ALANINE was isolated from human urine in 1951.[1] The excretion of this amino acid by individual cancer patients is reported to vary noticeably and to be related to the neoplastic process.[2] The formation of this compound occurs in the metabolism of dihydrothymine.[3,4] α-Methyl-β-alanine has also been identified as an end-product of valine metabolism.[5,6] Considering the biological importance of this metabolite it is of interest to establish its absolute configuration.

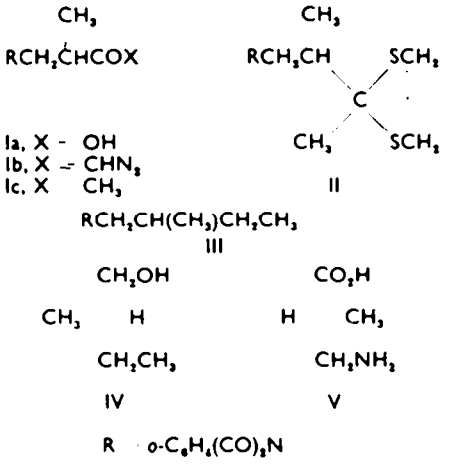
The correlation of the configuration of (±)-α-methyl-β-alanine and (−)-2-methylbutanol was outlined in a preliminary communication[7] and was effected by the conversion of the former compound into optically active 2-methyl-1-phthalimidobutane, earlier obtained from (−)-2-methylbutanol via (+)-1-bromo-2-methylbutane and its reaction with potassium phthalimide.[8]

(±)-α-Methyl-β-phthalimidopropionic acid (Ia) obtained from (±)-α-methyl-β-alanine has now been resolved by fractional crystallisation of the brucine salt into the (−) and (+)-α-methyl-β-phthalimido-propionic acids, showing $[\alpha]_D$ −23° and $[\alpha_D]$ −23° respectively. Hydrolysis of the (+)-antipode with hydriodic and glacial acetic acids gives (+)-α-methyl-β-alanine showing $[\alpha]_D$ +14° (in water) and the melting point 173–175°. The melting point of (±)-α-methyl-β-alanine is 181–182°;[9] the (+)-antipode isolated from urine has the melting point 183–184°, but the optical rotation values have not been reported.[1]

(+)-α-Methyl-β-phthalimidopropionic acid was converted into α-methyl-β-phthalimidopropionyl chloride and (+)-1-diazo-3-methyl-4-phthalimidobutan-2-one (Ib) showing $[\alpha]_D$ +72° (in ethyl acetate). This diazoketone racemises very readily: complete racemisation occurring after short heating in organic solvents or even after standing in the solid state at room temperature. Its conversion to the corresponding methyl ketone must, therefore, be effected immediately after preparation. The resulting (+)-2-methyl-1-phthalimidobutan-3-one (Ic), showing $[\alpha]_D$ +10° (in dichloromethane is also very sensitive with regard to racemisation, and considerable experimental work was performed before (II), required for the present correlation,

[1] H. R. Crumpler, C. E. Dent, H. Harris and R. G. Westall, *Nature, Lond.* **167**, 307 (1951).
[2] K. Fink, R. B. Henderson and R. M. Fink, *Proc. Soc. Exp. Biol. Med.* **78**, 135 (1951).
[3] R. M. Fink, K. Fink and R. B. Henderson, *J. Biol. Chem.* **201**, 349 (1953).
[4] K. Fink, R. E. Cline, R. B. Henderson and R. M. Fink, *J. Biol. Chem.* **221**, 425 (1956).
[5] M. J. Coon, *Fed. Proc.* **14**, 762 (1955).
[6] F. P. Kupiecki and M. J. Coon, *J. Biol. Chem.* **229**, 755 (1957).
[7] K. Balenović and N. Bregant, *Chem. & Ind.* 1273 (1957).
[8] W. Marckwald, *Ber. Dtsch. Chem. Ges.* **37**, 1038 (1904).
[9] M. A. Pollack, *J. Amer. Chem. Soc.* **65**, 1335 (1943).

could be prepared. This showing $[\alpha]_D$ + 14° (in benzene) was desulphurised by heating under reflux with Raney nickel catalyst in acetone solution. The resulting (+)-2-methyl-1-phthalimidobutane (III) showing $[\alpha]_D$ +24° has the identical sign of optical rotation as the same compound obtained earlier[8] from (−)-2-methylbutanol. It is known[10] that natural (−)-2-methylbutanol ("active amyl alcohol") has the configuration (IV). The same configuration (IV) can be assigned, therefore, to (+)-2-methyl-1-phthalimidobutane (III) and, consequently, (−)-α-methyl-β-alanine should have the configuration (V). In the earlier proposed terms[11] (−)-α-methyl-β-alanine would, therefore, be (*R*)-α-methyl-β-alanine.



EXPERIMENTAL

(±)-α-*Methyl-β-phthalimidopropionic acid* (Ia). A finely powdered mixture of (±)-α-methyl-β-alanine (prepared from glycine,[12] 7 g, 0·067 mole) and phthalic anhydride (11 g, 0·074 mole) was heated at 110° (temperature of the reaction mixture) in an oil bath for 1 hr. The cooled reaction mixture was recrystallised from ethanol–water (1 : 3). Lustrous leaflets of (±)-α-methyl-β-phthalimidopropionic acid were obtained (13 g, 83%). The analytical sample was recrystallised from the same solvent mixture and dried at 60°/0·01 mm, m.p. 161°. (Found: C, 61·83; H, 4·76. Calc. for $C_{12}H_{11}O_4N$: C, 61·80; H, 4·76%).

Resolution of α-methyl-β-phthalimidopropionic acid. A solution of (±)-α-methyl-β-phthalimidopropionic acid (Ia, 23·3 g, 0·1 mole) in 96% ethanol (400 cc) was added to a solution of brucine (46·6 g, 0·1 mole) in 96% ethanol (250 cc). The ethanol was removed under reduced pressure, and the yellow brucine salt of α-methyl-β-phthalimidopropionic acid was obtained, which crystallised on standing, yield 67 g, and showed $[\alpha]_D^{18}$ − 26·6° (*c*, 1·96 in chloroform).

The crude brucine salt (67 g) was dissolved in warm ethyl acetate (1600 cc), filtered, petroleum ether added (b.p. 40–60°, 260 cc) and the solution left at 0° overnight. Yellow crystals separated (51 g) showing $[\alpha]_D^{18}$ − 28·4° (*c*, 1·5 in chloroform). Repeated recrystallisation of this salt from ethyl acetate-petroleum ether afforded the

[10] J. A. Mills and W. Klyne, *Progress in Stereochemistry* (Edited by W. Klyne) p. 188. Butterworths, London (1954); L. Crombie and S. H. Harper, *J. Chem. Soc.* 2685 (1950).
[11] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).
[12] K. Balenović, I. Jambrešić and I. Ranogajec, *Croat. Chem. Acta* **29**, 87 (1957).

brucine salt of low solubility, $[\alpha]_D$ -44·2° (Found: C, 66·68; H, 6·03. Calc. for $C_{35}H_{37}O_8N_3$: C, 66·97; H, 5·94%).

A more soluble diastereomer could be isolated from the filtrates by fractional crystallisation.

(−)-α-*Methyl-β-phthalimidopropionic acid.* To a suspension of the brucine salt (11·4 g, $[\alpha]_D$ -44°) in water (500 cc) 4 N HCl (250 cc) was added and complete solution occurred; after standing for 1 hr at room temperature, crystals of (−)-α-methyl-β-phthalimidopropionic acid were filtered off, thoroughly washed with water, and dried, yield 3·5 g (83%), $[\alpha]_D^{16}$ −11·3° (*c*, 1·85 in chloroform). The filtrate was extracted with benzene (3 × 100 cc) and after removing the solvent under reduced pressure 0·46 g of (−)-α-methyl-β-phthalimidopropionic acid was obtained (total yield 92%), $[\alpha]_D^{18}$ -24°.

Fractional crystallisation of the acid (3·5 g, $[\alpha]_D$ - 11°) from aqueous ethanol (1 : 1) was carried out; 0·9 g of racemic acid was isolated. The optically pure (−)-α-methyl-β-phthalimidopropionic acid was obtained from the filtrates (0·9 g). A small sample showing $[\alpha]_D^{18}$ -20·1° was sublimed for analysis at 110–115°/0·001 mm and showed $[\alpha]_D^{17}$ −24·4° (*c*, 0·98 in chloroform) and the m.p. 145–146° (Found: C, 62·02; H, 4·99. Calc. for $C_{12}H_{11}O_4N$: C, 61·80; H, 4·76%.

(−)-α-*Methyl-β-alanine.* A solution of (−)-α-methyl-β-phthalimidopropionic acid (0·93 g, 0·004 mole) in glacial acetic acid (16 cc) and 47% HI (4 cc) was refluxed 8 hr; the glacial acetic and hydriodic acids were removed under reduced pressure. Water was added to the residue, the separated phthalic acid filtered off, washed with water, and the filtrate extracted with ether. The aqueous layer was evaporated to dryness. Addition of water and evaporation was repeated till no trace of free hydriodic acid remained.

The pale yellow (−)-α-methyl-β-alanine hydriodide was dissolved in water (400 cc) and passed through a column containing IR-4B Amberlite ion-exchange resin (10 g, 21 cc). The filtrate (1000 cc) was evaporated to dryness under reduced pressure, dissolved in water, and filtered (with a small quantity of charcoal). After evaporating the water, crystals of (−)-α-methyl-β-alanine were obtained (0·4 g, 99%), m.p. 169–174° the $[\alpha]_D^{16}$ - 9·4° (*c*, 1·37 in water). Sublimation at 110°/0·001 mm gave the pure acid with the m.p. 173–175° and $[\alpha]_D^{17}$ −14·2° (*c*, 0·42 in water) (Found: C, 46·63; H, 8·44. Calc. for $C_4H_9O_2N$: C, 46·59; H, 8·80%).

(−)-1-*Diazo-3-methyl-4-phthalimidobutan-2-one* (Ib). (−)-α-Methyl-β-phthalimidopropionic acid (Ia, 1·09 g, 0·0046 mole, $[\alpha]_D$ - 18°) and thionyl chloride (8·5 cc) were refluxed for 1·5 hr (oil bath, 70°). The excess of thionyl chloride was evaporated under reduced pressure, and last traces removed by dissolving the residue in benzene, and evaporating to dryness, leaving crystalline α-methyl-β-phthalimidopropionyl chloride (1·06 g, 96%).

A solution of the foregoing chloride (1·06 g, 0·0042 mole) in benzene (6 cc) was added to an ethereal solution of diazomethane (prepared from 17 g of nitrosomethylurea) at 0°. After standing for 6 hr at 0° the ethereal solution was filtered and evaporated to dryness under reduced pressure. The yield of crude (−)-1-diazo-3-methyl-4-phthalimidobutan-2-one was 1·1 g, (100%), crystallised in yellow needles m.p. 113–114° and $[\alpha]_D^{24}$ - 70° (*c*, 2·345 in ethyl acetate). The analytical sample was recrystallised from ethyl acetate–petroleum ether, m.p. 119° (decomp.) (Found: C, 60·96; H, 4·49. Calc. for $C_{13}H_{11}O_3N_3$: C, 60·69; H, 4·31%).

After heating this diazoketone in organic solvents or after prolonged standing at room temperature racemisation occurred.

(±)-2-*Methyl*-1-*phthalimidobutan*-3-*one* (Ic). To a solution of 1-diazo-3-methyl-4-phthalimidobutan-2-one (Ib, 0·32 g, 0·0012 mole) in chloroform (3·5 cc) at 0°, 47% HI (1·5 cc) was added with stirring. After standing for 15 min at −5° the reaction mixture was diluted with cold water (5 cc) and cold chloroform (3 cc). To the separated chloroform layer cold water (10 cc) and mercury (1 cc) were added, and the mixture shaken until the chloroform layer became colourless. The chloroform solution was treated with a small quantity of charcoal, filtered, and evaporated to dryness under reduced pressure. The crystalline residue of (±)-2-methyl-1-phthalimidobutan-3-one (0·28 g, 100%) showed $[\alpha]_D$ ± 7·6°; the analytical sample was recrystallised from dichloromethane and sublimed at 70°/0·001 mm. The pure compound crystallised in colourless needles, m.p. 82°, $[\alpha]_D^{24}$ ± 9·8°. (*c*, 0·61 in dichloromethane). (Found: C, 67·34; H, 5·49. Calc. for $C_{13}H_{13}O_3N$: C, 67·52; H, 5·67%).

(−)-2-*Methyl*-1-*phthalimidobutan*-3-*one ethylene mercaptol* (II). 2-Methyl-1-phthalimidobutan-3-one (Ic, 0·92 g, 0·004 mole) was dissolved at −20° in a mixture of ethanedithiol (14 cc) and ether (14 cc), and a solution of boron trifluoride ether complex (4 cc) in ether (20 cc) added, at −20°. The mixture was kept at −20° for 1 hr and then for 4 days at room temperature. Afterwards the ethereal solution was washed with water and evaporated to dryness. The traces of ethanedithiol were removed by drying at 0·01 mm at room temperature. The crystalline residue of (±)-2-methyl-1-phthalimidobutan-3-one ethylene mercaptol (1·25 g, 100%) showed $[\alpha]_D$ ± 7°. Recrystallisation from benzene–petroleum ether and sublimation at 120°/0·01 mm gave colourless needles, m.p. 126–128°, $[\alpha]_D^{20}$ +14° (*c*, 0·93 in benzene). (Found: C, 58·69; H, 5·58. Calc. for $C_{15}H_{17}O_2NS_2$: C, 58·60; H, 5·57%).

(−)-2-*Methyl*-1-*phthalimidobutane* (III). A solution of the foregoing mercaptol (II, 0·5 g) in acetone (80 cc) was heated under reflux with Raney nickel catalyst (7 g, W-1 activity) with stirring for 7 hr, and cooled. The catalyst was filtered off and washed with acetone, and the combined acetone filtrates evaporated under reduced pressure. A pale yellow oil remained (0·32 g, 93%, $[\alpha]_D$ −2·5°) which after two distillations at 60°/0·001 mm became colourless and consisted of pure (−)-2-methyl-1-phthalimidobutane, with $[\alpha]_D^{25}$ + 24° (*c*, 0·56 in benzene). The $[\alpha]_D$ + 7·5° was reported for the same compound obtained from natural, not quite pure (−)-2-methylbutanol.[8] (Found: C, 72·03; H, 6·80. Calc. for $C_{13}H_{15}O_2N$: C, 71·86; H, 6·96%.)