948. *Correlation of the Configurations of α-Methyl-β-alanine and Methylsuccinic Acid*

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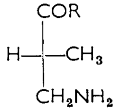
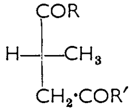
Correlation of the configurations of (—)-α-methyl-β-alanine (I) and (—)-2-methylbutanol by way of (+)-2-methyl-1-phthalimidobutane, described previously,[1] indicated the (*R*)-configuration for this amino-acid. However, our later experiments [2] showed that the optical purity of the 2-methyl-1-phthalimidobutane obtained by Raney nickel desulphurisation of (+)-2-methyl-1-phthalimidobutan-3-one ethylene mercaptol depended strongly on the nature of the catalyst, and another method for establishing the configuration of (I) was therefore desirable.



$$\begin{array}{c}\mathrm{COR}\\ \vert\\ \mathrm{H}\text{—}\vert\text{—}\mathrm{CH_3}\\ \vert\\ \mathrm{CH_2NH_2}\end{array}$$

(I; R = OH)
(Ia; R = NHPh)



$$\begin{array}{c}\mathrm{COR}\\ \vert\\ \mathrm{H}\text{—}\vert\text{—}\mathrm{CH_3}\\ \vert\\ \mathrm{CH_2{\cdot}COR'}\end{array}$$

(II; R = R′ = OH)
(IIa; R = OH, R′ = NHPh)
(IIb; R = NHPh, R′ = OH)

We now report the correlation of the configuration of (I) with that of (*R*)-(+)-methylsuccinic acid (II). From the latter compound, whose absolute configuration is known,[3] (+)-methyl-*N*-phenylsuccinimide (III) was prepared by a slight modification of the method described for the inactive compound.[4] Alkaline hydrolysis of the imide (III) afforded a mixture of (+)-α-methylsuccinanilic acid (IIa) and (+)-β-methylsuccinanilic acid (IIb). Both isomeric inactive methylsuccinanilic acids, with melting points 123 and 159°, respectively, were prepared by Morrel,[4] either by alkaline hydrolysis of (III) or by the reaction of methylsuccinic anhydride with aniline.

In their work with optically inactive compounds Cocker and Fateen [5] and later Hancock and Linstead [6] identified the higher-melting isomer as α-methylsuccinanilic acid (IIa) and the lower-melting one as β-methylsuccinanilic acid (IIb).

From the alkaline hydrolysate of the optically active imide (III) we isolated two methylsuccinanilic acids with m. p. 149—150°, $[\alpha]_D$ +16° (ethanol); and m. p. 140—141°, $[\alpha]_D$ +4° (ethanol), respectively. Using the Schmidt reaction [7] we degraded the lower-melting acid to (—)-β-aminoisobutyranilide (Ia), and then converted it into (—)-β-phthalimido-isobutyranilide, identified by m. p., mixed m. p., and infrared spectra with the same compound prepared from (—)-α-methyl-β-alanine. This affords, therefore, additional support for the (*R*)-configuration for (—)-α-methyl-β-alanine (I). Consequently, the methylsuccinanilic acid with m. p. 140—141° and $[\alpha]_D$ +4° should have the structure (IIb).

Experimental.—(+)-*Methyl-N-phenylsuccinimide* (III). A mixture of (+)-methylsuccinic acid (4·3 g.), $[\alpha]_D^{22}$ +8·8° (in H_2O) and aniline (2·9 ml.) was maintained at 170° for 2 hr., and then cooled to 20°; recrystallisation of the resulting solid from water afforded (+)-*methyl-*N-*phenylsuccinimide* (III) (5·2 g., 86%). After sublimation at 100°/0·01 mm., colourless prisms resulted, m. p. 132—134°, $[\alpha]_D^{22}$ +8° ±0·4° (*c*. 1·200 in $CHCl_3$); [lit.,[4] m. p. 109—110° for racemic (III)] (Found: C, 70·1; H, 6·05. $C_{11}H_{11}NO_2$ requires C, 69·8; H, 5·85%).

(+)-α-*Methylsuccinanilic acid* (IIa). (+)-Methyl-*N*-phenylsuccinimide (III) (9·4 g.) was boiled under reflux for 30 min. with 6% aqueous sodium hydroxide (32 ml.), cooled, acidified with 2N-hydrochloric acid to pH 5, and the precipitate filtered off (5·8 g., 56%); m. p. 135—139°, $[\alpha]_D^{22}$ +12° (in EtOH). Several crystallisations from acetone–light petroleum (b. p. 40—60°) (1 : 3) gave homogeneous (+)-α-*methylsuccinanilic acid* (IIa) (2·5 g.), m. p. 149·5—150°, $[\alpha]_D^{22}$ +16·0° ±0·3° (*c* 1·240 in EtOH) (Found: C, 64·0; H, 6·4. $C_{11}H_{13}NO_3$ requires C, 63·7; H, 6·3%).

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[1] K. Balenović and N. Bregant, *Chem. and Ind.*, 1957, 1273; *Tetrahedron*, 1959, **5**, 44.

[2] K. Balenović and N. Bregant, unpublished experiments.

[3] A. Fredga, *Arkiv Kemi Min., Geol.*, 15*B*, 1942, no. 23; *Tetrahedron*, 1960, **8**, 126.

[4] G. F. Morrel, *J.*, 1914, 2698.

[5] W. Cocker and A. K. Fateen, *J.*, 1951, 2630.

[6] J. E. H. Hancock and R. P. Linstead, *J.*, 1953, 3490.

[7] K. F. Schmidt, *Z. angew. Chem.*, 1923, **36**, 511; H. Wolf, *Org. Reactions*, 1946, **3**, 307.

(+)-β-*Methylsuccinanilic acid* (IIb). The mother-liquor remaining after the isolation of compound (IIa) was acidified with 2N-hydrochloric acid to pH 1, and the precipitate (3·2 g.) repeatedly recrystallised from benzene to give (+)-β-*methylsuccinanilic acid* (IIb) (1·4 g.), which after sublimation at 150°/0·01 mm. had m. p. 140—141°, $[\alpha]_D^{22}$ +4·2° (*c* 1·415 in EtOH) (Found: C, 63·8; H, 6·55. $C_{11}H_{13}NO_3$ requires C, 63·7; H, 6·3%).

(−)-β-*Aminoisobutyranilide* (Ia). To a stirred solution of (+)-β-methylsuccinanilic acid (IIb) (2·25 g.) in chloroform (5 ml.) and concentrated sulphuric acid (8 ml.), sodium azide (0·9 g.) was added in small portions during 30 min. at 50—55°. The mixture was then heated at 50° for 3 hr. with stirring, diluted with ice, made alkaline, and extracted with chloroform (3 × 25 ml.). The product obtained by concentrating the chloroform extracts was purified by distillation at 100°/0·01 mm. to give oily (−)-β-aminoisobutyranilide (Ia) (0·624 g., 32%); $[\alpha]_D^{22}$ −20° (*c* 1·55 in $CHCl_3$).

(−)-β-*Phthalimidoisobutyranilide*. A solution of (−)-β-aminoisobutyranilide (0·4 g.), $[\alpha]_D$ −20°, from the above preparation, and phthalic anhydride (0·15 g.) in chloroform was evaporated to dryness, and the residue heated in an oil-bath (130°) for 30 min. Crystallisation of the cooled mixture from aqueous ethanol afforded crude (−)-β-*phthalimidoisobutyranilide* (0·35 g., 51%), which after repeated crystallisation from ethanol and sublimation at 120°/0·01 mm. gave colourless needles (0·18 g.), m. p. 202—204°, $[\alpha]_D^{22}$ −86·3° ±0·3° (*c* 0·365 in EtOH) (Found: C, 70·6; H, 5·4. $C_{18}H_{16}N_2O_3$ requires, C, 70·1; H, 5·25%). The same anilide, m. p. 208—211°, $[\alpha]_D^{23}$ −85·4° ±0·2° (*c* 0·550 in EtOH) was prepared from an ethereal solution of aniline and (−)-α-methyl-β-phthalimidopropionyl chloride, obtained as described previously [1] from (−)-α-methyl-β-alanine. The two specimens of the anilide had mixed m. p. 205—207°, and identical elemental analyses and i.r. spectra.

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