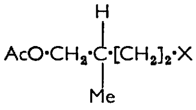
834. *The Synthesis of Some Methyl-substituted Dibasic Acids.*

By R. Brettle.

(−)-Ethyl 5-bromo-4-methylpentanoate (II; R = Et) and (+)-4-bromo-2-methylbutylacetate (I; X = Br) have been prepared from (+)-5-acetoxy-4-methylpentanoic acid.

The bromo-ester (II; R = Et) has been converted into 4-methylpimelic acid, from which (±)-4-methylsuberic acid (identical with a degradation product of alternaric acid) has been synthesised.

L(+)-5-Acetoxy-4-methylpentanoic acid * (I; X = CO_2H), an industrial by-product, is a useful intermediate in the synthesis of methyl-substituted compounds. It was initially used in anodic coupling reactions [1] and has recently been employed in the thiophen chain-extension procedure.[2] The preparation from it of the bromo-ester (II; R = Me), which was used in the synthesis of a pyrrolidine derivative, has also been briefly reported.[3] In seeking ways to exploit the synthetic potentialities of this acid we have investigated its conversion into the two bromo-esters (II; R = Et) and (I; X = Br) and have used the former to prepare several methyl-substituted dibasic acids, including two concerning whose melting points there are discrepant reports.



$$AcO{\cdot}CH_2{\cdot}\underset{\displaystyle Me}{\overset{\displaystyle H}{C}}{\cdot}[CH_2]_2{\cdot}X$$

(I)

$Br{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2R$

(II)

$Br{\cdot}[CH_2]_2{\cdot}CHMe{\cdot}[CH_2]_2{\cdot}CO_2Me$

(III)

The acetoxy-acid (I; X = CO_2H) with hydrogen bromide in acetic and sulphuric acid gave the crude bromo-acid (II; R = H), which was converted directly into the ester (II; R = Et). Degradation of the silver salt of the acetoxy-acid (I; X = CO_2H) with bromine gave the bromo-acetate (I; X = Br).

Replacement of the bromine atom in the ester (II; R = Et) by a cyano-group and subsequent hydrolysis gave optically pure (+)-3-methyladipic acid. Reaction of the ester (II; R = Et) with malonic ester, followed by hydrolysis and decarboxylation, gave 4-methylpimelic acid, in which the asymmetry at the branch point has been destroyed. Our product had m. p. 49°, in accord with a recent report by Ryhage and Stenhagen [4] that this acid, when prepared by bishomologation of 3-methylglutaric acid, had m. p. 48°. Earlier reports give the m. p. as 56—57° for a sample prepared by reduction of dibromo-*p*-cresotic acid [5] and as 56° for material prepared by the oxidation of a methylcycloheptene [6] in which the relative positions of the methyl group and the double bond were not established.

Methyl hydrogen 4-methylpimelate was prepared both by the partial esterification of the acid [7] and by partial hydrolysis of the corresponding diester.[8] Degradation of the silver salt of this half-ester with bromine then gave the optically inactive bromo-ester (III), which was converted by reaction with malonic ester, etc., into (±)-4-methylsuberic acid that was difficult to purify (cf. 2-ethylpimelic acid [9]). The pure acid had m. p. 65—66° and was identical with a specimen of (±)-4-methylsuberic acid, kindly supplied

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* For this use of *L*, see Linstead, Lunt, and Weedon, *J.*, 1950, **3333**.

[1] Bailey, Brice, Horne, and Polgar, *J.*, 1959, 661; Brettle, Polgar, and Smith, *J.*, 1960, 2802.

[2] Polgar and Smith, *Chem. and Ind.*, 1961, 1959.

[3] Burroughs, Dalby, Kenner, and Sheppard, *Nature*, 1961, **189**, 394.

[4] Ryhage and Stenhagen, *Arkiv Kemi*, 1959, **14**, 497.

[5] Einhorn and Ehret, *Ann.*, 1897, **295**, 175.

[6] Quadrat-i-Khuda and Ghosh, *J. Indian Chem. Soc.*, 1940, **17**, 19.

[7] Cf. Ahlquist, Asselineau, Asselineau, Serck-Hanssen, and Stallberg-Stenhagen, *Arkiv Kemi*, 1959, **14**, 171.

[8] Herout and Suchy, *Chem. Listy*, 1958, **52**, 1174.

[9] Ivanoff, *Bull. Soc. chim. France*, 1948, 660.

by Dr. J. R. Bartels-Keith, which had been prepared by the hydrogenation of 5-methylene-oct-2-enedioic acid, an oxidation product of alternaric acid.[10] A m. p. of 146° has been recorded[6] for the acid prepared by bishomologation of (±)-3-methyladipic acid. The cause of this discrepancy is not known.

EXPERIMENTAL

Solutions in organic solvents were dried over anhydrous sodium sulphate.

Ethyl 5-Bromo-4-methylpentanoate (II; R = Et).—*L*-(+)-5-Acetoxy-4-methylpentanoic acid (200 g.) was dissolved in 48% hydrobromic acid (1 l.) and concentrated sulphuric acid (240 ml.) and after 2 hr. heated on a steam-bath for 4 hr. The solution was cooled, then diluted with water (2 l.), and the lower bromo-acid layer separated. The aqueous layer was saturated with ammonium chloride and extracted with ether. The crude bromo-acid was dissolved in the ethereal extract, which was then washed with saturated aqueous ammonium sulphate and dried. Distillation of the ether left crude 5-bromo-4-methylpentanoic acid which was esterified with ethanolic sulphuric acid. The ester was collected in ether, washed with dilute aqueous sodium hydroxide and water, and dried. Distillation gave *ethyl 5-bromo-4-methylpentanoate* (181 g., 71%), b. p. 110—111°/12 mm., n_D^{16} 1·4622, $[\alpha]_D^{23}$ − 1·04° (homogeneous; l = 2), with a penetrating fruity odour (Found: C, 43·4; H, 6·9; Br, 36·1. $C_8H_{15}BrO_2$ requires C, 43·05; H, 6·7; Br, 35·9%).

(+)-*4-Bromo-2-methylbutyl Acetate* (I; X = Br).—Silver nitrate (21·3 g.) in water (90 ml.) was added to the solution obtained by neutralising *L*-(+)-5-acetoxy-4-methylpentanoic acid (21·8 g.) with aqueous sodium hydroxide. The precipitated silver salt was collected, washed with water, ethanol, and ether, and dried *in vacuo* over phosphorus pentoxide. The anhydrous silver salt (29·6 g.) was suspended in dry carbon tetrachloride (100 ml.) to which bromine (6·0 ml.) was then added dropwise, with stirring, during 1 hr. The precipitate of silver bromide was collected and washed with ether. The solvents were distilled from the combined filtrate and washings, and the residue was taken up in ether, washed twice with 5% aqueous potassium hydroxide and then water, and dried. Distillation gave (+)-*4-bromo-2-methylbutyl acetate* (11·6 g., 44%), b. p. 117—118°/25 mm., n_D^{18} 1·4659, $[\alpha]_D^{22}$ +20·4° (homogenous; l = 2) (Found: C, 40·2; H, 6·25; Br, 37·9. $C_7H_{13}BrO_2$ requires C, 40·2; H, 6·2; Br, 38·3%).

(+)-*3-Methyladipic Acid*.—Ethyl 5-bromo-4-methylpentanoate (40 g.) and potassium cyanide (17 g.) in ethanol (250 ml.) were heated under reflux for 19·5 hr. The product, isolated with ether, was the crude cyano-ester (19 g.), b. p. 135—140°/20 mm. This was refluxed with concentrated hydrochloric acid (20 ml.) for 14 hr., the hydrolysate, when cold, was saturated with ammonium chloride, and the diacid was extracted into chloroform. Evaporation gave (+)-3-methyladipic acid (6 g.) which, after crystallisation from carbon tetrachloride and then benzene, had $[\alpha]_D^{22}$ +11·3° (c 10 in $CHCl_3$), m. p. 85—87°; the m. p. was undepressed on admixture with authentic 3-methyladipic acid,[11] $[\alpha]_D^{22}$ +11·4° (c 3 in $CHCl_3$), obtained by oxidation of pulegone.[12]

4-Methylpimelic Acid.—Ethyl 5-bromo-4-methylpentanoate (33·5 g.) was refluxed with ethyl sodiomalonate (from 3·5 g. of sodium, 26 g. of ethyl malonate, and 50 ml. of ethanol) for 7 hr. After acidification by dilute hydrochloric acid the product was isolated by means of ether and distilled, giving the triester (30 g.), b. p. 188—194°/12 mm. This was hydrolysed, and the resultant triacid decarboxylated in refluxing 5N-hydrochloric acid (50 ml.) (23 hr.), the ethanol formed being removed from time to time by distillation. Evaporation gave 4-methylpimelic acid, b. p. 187°/0·3 mm., m. p. 45—46°, which, after recrystallisation from water, carbon tetrachloride, ether–light petroleum (b. p. 60—80°), or cyclohexane–benzene, had m. p. 49°; the melt after resolidification had m. p. 43—45° [Found: C, 55·1; H, 8·1%; equiv., 87. Calc. for $C_9H_{14}O_4$: C, 55·2; H, 8·0%; equiv. (dibasic), 87]. Ryhage and Stenhagen[4] give m. p. 48°, the resolidified melt having m. p. 44°.

Methyl Hydrogen 4-Methylpimelate.—(*a*) 4-Methylpimelic acid (50 g.), methanol (20 ml.), and concentrated hydrochloric acid (10 ml.) were heated under reflux for 7 hr. Two layers were formed on cooling; the lower, organic, layer was diluted with ether, washed five times with water, and dried. Distillation then gave the fractions: (i) b. p. 89—95°/0·1 mm. (8 g.);

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[10] Bartels-Keith, *J.*, 1960, 860.

[11] Eisenbraun and McElvain, *J. Amer. Chem. Soc.*, 1955, **77**, 3383 (footnote 13).

[12] Semmler, *Ber.*, 1892, **25**, 3513.

(ii) b. p. 95—130°/0·1 mm. (12 g.); and (iii) b. p. 130—132°/0·1 mm., n_D^{24} 1·4454 (12·3 g.). A colourless residue remained. Fraction (i), b. p. 130°/10 mm., n_D^{24} 1·4349, was dimethyl 4-methylpimelate (Ryhage and Stenhagen [4] give b. p. 122°/8 mm., n_D^{25} 1·4340). Fraction (iii) was the desired half-ester (Found: C, 57·7; H, 8·5. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·5%) (Herout and Suchy [8] give b. p. 166°/3 mm.).

(*b*) 4-Methylpimelic acid was esterified by azeotropic distillation, giving dimethyl 4-methylpimelate, b. p. 136—138°/12 mm., b. p. 98—101°/0·35 mm., n_D^{21} 1·4356 (Found: C, 59·4; H, 8·7. Calc. for $C_{10}H_{18}O_4$: C, 59·4; H, 8·9%). The methyl hydrogen ester, prepared by the method of Herout and Suchy,[8] had b. p. 136—139°/0·1 mm., n_D^{20} 1·4452.

Methyl 6-Bromo-4-methylhexanoate.—Silver methyl 4-methylpimelate (29·85 g.) was degraded with bromine by the method described above. Distillation of the product afforded *methyl 6-bromo-4-methylhexanoate* (18·12 g., 23%), b. p. 125°/15 mm., n_D^{22} 1·4654 (Found: C, 42·7; H, 6·7; Br, 36·1. $C_8H_{15}BrO_2$ requires C, 43·0; H, 6·7; Br, 35·9%).

Methyl 2-Methoxycarbonyl-5-methylsuberate.—Methyl 6-bromo-4-methylhexanoate (11·1 g.) was refluxed with methyl sodiomalonate (from 13·2 g. of methyl malonate, 1·15 g. of sodium, and 50 ml. of methanol) for 12 hr. Some of the methanol was distilled, the residue poured into dilute hydrochloric acid, and the product isolated with ether. Distillation gave the *triester* (10·0 g., 73%), b. p. 146—147°/0·25 mm., n_D^{20} 1·4479 (Found: C, 57·05; H, 7·9. $C_{13}H_{22}O_6$ requires C, 56·9; H, 8·0%).

(±)-4-*Methylsuberic Acid.*—The above triester (12·4 g.) was refluxed with 6N-hydrochloric acid (40 ml.) for 21·5 hr. From time to time methanolic solvent (20 ml.) was distilled, and replaced by 6N-hydrochloric acid (20 ml.). Finally the solution was evaporated to dryness, and the residue extracted with chloroform. Evaporation of the dried extract left (±)-4-methylsuberic acid (6·5 g.). After two recrystallisations from benzene–light petroleum (b. p. 60—80°) the acid had m. p. 58—65°. After four further recrystallisations from water, the acid, after drying at 35°/0·01 mm., had m. p. 65—66° [Found: C, 57·7; H, 8·3%; equiv., 95. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·6%; equiv. (dibasic), 94]. The acid did not depress the m. p. of (±)-4-methylsuberic acid of m. p. 64—66°, derived from alternaric acid,[10] and the two samples had identical infrared spectra (KBr disc).

We thank Glaxo Laboratories Ltd. for a gift of *L*-(+)-5-acetoxy-4-methylpentanoic acid.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, May 14th,* 1962.]