LXVI.—*The Action of Heat on α -Hydroxycarboxylic Acids. Part IV. Racemic $\alpha\alpha'$ -Dihydroxyadipic Acid and meso- $\alpha\alpha'$ -Dihydroxyadipic Acid.*

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THE results of the investigation of the action of heat on several α -monohydroxymonocarboxylic acids and on one $\alpha\alpha'$ -dihydroxy-derivative of a dicarboxylic acid (sebacic acid) have been already communicated to the Society (Trans., 1904, **85**, 827; 1905, **87**, 1888; 1907, **91**, 1365).

Sebacic acid was, until recent years, the only higher member of the oxalic acid series available in large quantities, but the fact that *cyclo*-hexanone can now be purchased at a reasonable price, and that it yields adipic acid on oxidation with potassium permanganate, has enabled the work to be extended to α -hydroxy-derivatives of this acid.

The dibromoadipic acid, obtained by the action of bromine on the acid chloride, was readily converted into the corresponding hydroxy-derivatives by boiling an aqueous solution of its sodium salt. On attempting to purify the resulting product, it was soon recognised that it was not a homogeneous substance, but consisted of two hydroxy-acids, which were eventually obtained in a pure state by fractional extraction with acetone and repeated crystallisation from a mixture of acetone and chloroform. One of these $\alpha\alpha'$ -dihydroxyadipic acids melts at 146° , and when heated readily loses water and gives a beautifully crystalline sublimate of its dilactone:

The other $\alpha\alpha'$ -dihydroxyadipic acid melts at 174° , and when heated loses water, but no trace of a sublimate is formed, and the resulting

$$\begin{array}{c} \text{H} \\ | \\ \text{CO}_2\text{H} \cdot \text{C} \cdot \text{OH} \\ | \\ [\text{CH}_2]_2 \\ | \\ \text{H} \cdot \text{C} \cdot \text{CO}_2\text{H} \\ | \\ \text{OH} \end{array}$$

this in no way affects the validity of the above deductions, in fact, the presence of these groups only renders the formation of a dilactone from the meso-acid all the more improbable.

If the above arguments be correct, then the acid melting at 146° and which easily forms a dilactone must be the racemic variety, and the acid which melts at 174° and yields a lactone-lactide but not a dilactone is the meso-acid. In order definitely to settle this point, both acids were submitted to the alkaloid method of resolving optically inactive compounds containing asymmetric carbon atoms, and the results obtained are in complete agreement with, and fully justify, the above conclusions. By fractional crystallisation of the cinchonidine salt of the acid melting at 146° , it was resolved into its *d*- and *l*-forms, whereas a similar treatment of the meso-acid failed to produce any trace of an optically active acid. In connexion with this resolution, it is interesting to note that the ammonium salt of the *d*-acid is strongly *l*ævrotatory.

That the hydroxyl groups in both acids are attached to *d*-carbon atoms and not to β - or γ -atoms is conclusively proved by the fact that both acids yield succinic acid when they are oxidised with potassium permanganate:

Rosenlew (*Ber.*, 1904, **37**, 2092) obtained two *aa'*-dihydroxyadipic acids, one melting at 173° and the other at 132 — 134° , and concluded from the melting points and the relative solubilities of these acids that the first was the racemic acid and the second the meso-variety. The results now described show that Rosenlew's deductions are not correct, and that his acid melting at 173° corresponds with the meso-acid (m. p. 174°) mentioned in this paper, and the acid which he describes as melting at 132 — 134° is undoubtedly the impure racemic acid.

EXPERIMENTAL.

Preparation of aa'-Dibromoadipic Acid.

One hundred and fifteen grams of adipic acid (m. p. 148.5 — 150°), obtained by the oxidation of *cyclohexanone* with potassium permanganate in alkaline solution, were converted into the acid chloride by the action of phosphorus pentachloride; 280 grams of dry bromine were gradually added to the resulting acid chloride, and the mixture heated on the water-bath until the whole of the bromine had disappeared. The resulting liquid bromo-acid chloride was gradually poured into 450 c.c. of formic acid (sp. gr. 1.20), and, when the somewhat violent reaction had subsided, the product was heated on the

water-bath for half an hour; on cooling, 234 grams (theory, 239 grams) of the dibromo-acid, melting at $180-182^{\circ}$, crystallised out. A small quantity was recrystallised from formic acid (sp. gr. 1.22) until its melting point was constant, when it was obtained in prismatic needles melting at $192-193^{\circ}$, a melting point which agrees with that of one of the dibromoadipic acids prepared by Rosenlew (*Ber.*, 1904, **37**, 2091):

0.1618 gave 0.2016 AgBr. Br = 53.0.

$C_6H_8O_4Br_2$ requires Br = 52.6 per cent.

Preparation of Racemic $\alpha\alpha'$ -Dihydroxyadipic Acid and meso- $\alpha\alpha'$ -Dihydroxyadipic Acid.

One hundred and nineteen grams of dibromoadipic acid (m. p. $180-182^{\circ}$) were added to 600 c.c. of water, neutralised with sodium hydroxide, and the resulting solution boiled under a reflux apparatus for three hours, at the end of which time the solution was strongly acid. It was again neutralised with sodium hydroxide and boiled for a further three hours. If at the end of this second period the solution is still neutral, this indicates that the reaction is completed, otherwise it must be neutralised again and boiled for three hours more. The hot solution of the sodium salt was added to an excess of a hot solution of copper sulphate, and the whole allowed to remain overnight, when the copper salt gradually separated in a crystalline form; it was filtered, washed free from sodium bromide, and decomposed with hydrogen sulphide. The filtrate obtained after removal of the copper sulphide was evaporated to dryness on the water-bath, powdered, and thoroughly dried over sulphuric acid in a vacuum.

The two isomeric $\alpha\alpha'$ -dihydroxyadipic acids which constitute the residue were separated as follows: 82 grams of the finely-powdered and dried residue were boiled with 250 c.c. of acetone and filtered, and this process repeated five times, using 250 c.c. of acetone for each extraction. The undissolved residue (A), which melted at $165-166^{\circ}$ and weighed 13 grams, consisted for the most part of the meso-acid (see p. 722).

The several filtrates were allowed to cool, and the six fractions which separated were filtered and their melting points determined. The filtrates obtained from these were concentrated to a small bulk, and another series of fractions obtained. These fractions, which melted at the same temperature, were mixed together and recrystallised from a mixture of acetone and chloroform until the melting point was constant, when the acid was obtained in aggregates of small plates melting at 146° (compare Rosenlew, *loc. cit.*):

0.1372 gave 0.2020 CO_2 and 0.0718 H_2O . $\text{C} = 40.15$; $\text{H} = 5.81$.

$\text{C}_6\text{H}_{10}\text{O}_6$ requires $\text{C} = 40.45$; $\text{H} = 5.62$ per cent.

r-aa'-Dihydroxyadipic acid is very soluble in water or alcohol, sparingly so in boiling acetone, and insoluble in ether, chloroform, light petroleum, or benzene. When heated, it loses water and the corresponding dilactone is formed. The molecular weight was determined by titration with *N*/10 sodium hydroxide, using phenolphthalein as indicator :

0.1812 required 20.16 c.c. *N*/10 NaOH. M.W. = 179.6.

A dibasic acid, $\text{C}_6\text{H}_{10}\text{O}_6$, requires M.W. = 178.

The *silver* salt was prepared by adding a hot solution of the ammonium salt to a hot solution of silver nitrate, when, on remaining for some time, a crystalline precipitate was obtained :

0.2084 gave 0.1142 Ag $\text{Ag} = 54.80$.

$\text{C}_6\text{H}_8\text{O}_6\text{Ag}_2$ requires $\text{Ag} = 55.10$ per cent.

r-aa'-Dihydroxyadipamide,

was prepared by heating the dilactone with a saturated alcoholic solution of ammonia in a sealed tube at 120° for eight hours. The crystalline solid which separated out on cooling was crystallised from 92 per cent. alcohol, when it was obtained in small, glistening plates melting with effervescence at 177° . It readily dissolves in cold water, is sparingly soluble in boiling alcohol, and insoluble in ether, light petroleum, acetone, or chloroform :

0.1264 gave 17.2 c.c. moist nitrogen at 15° and 760 mm. $\text{N} = 15.93$.

$\text{C}_6\text{H}_{12}\text{O}_4\text{N}_2$ requires $\text{N} = 15.90$ per cent.

r-aa'-Dihydroxyadipic dianilide,

was prepared by boiling 2 grams of the acid with 6 grams of recently distilled aniline for seven hours. The resulting product was treated with dilute hydrochloric acid to remove excess of aniline, and the solid crystallised from alcohol, when it was obtained in glistening plates melting at 186° . It is insoluble in ether, benzene, chloroform, or light petroleum, and moderately soluble in boiling acetone or alcohol :

0.1394 gave 0.3342 CO_2 and 0.0768 H_2O . $\text{C} = 65.39$; $\text{H} = 6.12$.

0.1604 „ 12.35 c.c. moist nitrogen at 15° and 757 mm. $\text{N} = 8.97$.

$\text{C}_{18}\text{H}_{20}\text{O}_4\text{N}_2$ requires $\text{C} = 65.85$; $\text{H} = 6.10$; $\text{N} = 8.53$ per cent.

Action of Heat on Racemic aa'-Dihydroxyadipic Acid.

The acid was placed in a small retort connected to a receiver, and the latter connected to a water-pump. The pressure was reduced to 25—30 mm., and the retort and contents heated at 160 — 170° in an

air-bath, a slow current of dry air being passed through the apparatus. As soon as the substance had melted, water was evolved, and a crystalline sublimate collected in the neck of the retort; it was re-sublimed and analysed :

0.1246 gave 0.2300 CO₂ and 0.0530 H₂O. C = 50.34 ; H = 4.72.

C₆H₆O₄ requires C = 50.70 ; H = 4.23 per cent.

The dilactone of *r-aa'*-dihydroxyadipic acid,

melts at 134°, is insoluble in light petroleum, alcohol, or water in the cold, readily soluble in cold acetone and in boiling alcohol, from which it crystallises in well-defined plates on cooling. The dilactone is insoluble in water, but on remaining in contact with this liquid it is gradually hydrolysed to the parent acid, which dissolves in the water, giving a strongly acid solution. That this solution contains the parent acid was shown by analysis of the silver salt prepared from it :

0.1542 gave 0.0850 Ag. Ag = 55.12.

C₆H₅O₆Ag₂ requires Ag = 55.10 per cent.

Resolution of Racemic aa'-Dihydroxyadipic Acid.

Preliminary experiments with quinine, cinchonine, and cinchonidine showed that only the last of these alkaloids is suitable for this resolution. The following is the method adopted : 29 grams (1 mol.) of the *r*-acid were dissolved in 450 c.c. of water and 50 grams (1 mol.) of cinchonidine added ; these readily dissolved on warming. The resulting strongly acid solution was allowed to remain overnight, when 33 grams of a beautifully crystalline, neutral cinchonidine salt were deposited ; this was filtered and recrystallised from water until the optical activity was not increased by further recrystallisation. This was ascertained by dissolving 1 gram of the salt in water, precipitating the alkaloid by ammonia, filtering, and evaporating the filtrate to a few c.c. This solution had now a faintly acid reaction, so it was again made faintly alkaline with ammonia, allowed to remain for some time, and the small amount of alkaloid which had separated was filtered, washed with a little water, and the filtrate made up to the volume required to fill the 2.2-dcm. tube, in which it was examined. All these experiments were carried out under identical conditions, in order that the results might be truly comparable.

The pure *l*-base *d*-acid salt, which weighed 16 grams, was dissolved in water, the alkaloid precipitated with ammonia, and the resulting ammonium salt converted into the copper salt, which was filtered and decomposed with hydrogen sulphide. The filtrate from the copper

sulphide was evaporated on the water-bath, the residue dried in a vacuum, and then crystallised from a mixture of acetone and chloroform until its melting point was constant.

d-aa'-Dihydroxyadipic acid is insoluble in ether or light petroleum, readily soluble in water, moderately so in alcohol or acetone, and crystallises from a mixture of acetone and chloroform in long, slender needles melting at 157° with effervescence.

A determination of the specific rotation gave the following result :

0.9866, made up to 16 c.c. in a 2.2-dcm. tube, gave $\alpha^{16} + 0.52^{\circ}$,
whence $[\alpha]_D^{16} + 3.8^{\circ}$.

The above solution was carefully neutralised with ammonia and made up to 20 c.c., and on examination was found to have an opposite rotation to that of the free acid, and gave $\alpha^{11} - 2.77^{\circ}$, whence $[\alpha]_D^{11} - 21.4^{\circ}$.

Attempts were made to isolate the pure *l*-acid from the mother liquors from which the *d*-acid had been separated, but the amount of material was not sufficient to admit of the isolation of a pure specimen of the *l*-isomericide.

Oxidation of Racemic aa'-Dihydroxyadipic Acid.

One gram of the acid was dissolved in 20 c.c. of water, and to this a hot solution of 2.5 grams of potassium permanganate in 50 c.c. of water was gradually added. A vigorous oxidation took place, and, when all the potassium permanganate had been reduced, the manganese dioxide was filtered and the filtrate evaporated to dryness. The residue, when heated with resorcinol and a few drops of sulphuric acid and pouring into a solution of potassium hydroxide, gave a very marked fluorescein reaction. No attempt was made to isolate the succinic acid itself, and so the residue was boiled with excess of acetyl chloride for two hours, the excess of acetyl chloride evaporated, and the dried residue extracted with benzene. One gram of aniline was added to the benzene solution, and, after a short time, a crystalline solid separated out, which, after crystallisation from water, was obtained in aggregates of flat needles melting at 148° (succinanilic acid melts at 148.5°). The corresponding anil was obtained by boiling the anilic acid for a short time and crystallising the resulting product from alcohol, when it was obtained in long, slender needles melting at $153-154^{\circ}$.

meso-aa'-Dihydroxyadipic Acid.

The insoluble residue A (see p. 719), left after repeated extraction of the mixed acids with acetone, was crystallised from a mixture of alcohol and chloroform until its melting point was constant :

0.1524 gave 0.2254 $\cdot$ CO₂ and 0.0804 H₂O. C = 40.33; H = 5.86.

C₆H₁₀O₆ requires C = 40.45; H = 5.62 per cent.

meso- $\alpha\alpha'$ -Dihydroxyadipic acid is insoluble in ether or light petroleum, only slightly soluble in chloroform, acetone, or alcohol in the cold, and readily so in water or in boiling alcohol, from which it crystallises in small, glistening plates melting at 174°. This acid is considerably less soluble in alcohol than its racemic isomeride.

Attempts were made to resolve this acid by means of its cinchonidine salt, but no evidence whatever of the production of an optically active acid was obtained.

A mixture of equal parts of the above acid and the racemic isomeride contracts at 146° and melts at 161—165°.

The molecular weight was determined by titration with sodium hydroxide, using phenolphthalein as indicator:

0.1672 required 18.65 c.c. *N*/10 NaOH. M.W. = 179.2.

A dibasic acid, C₆H₁₀O₆, requires M.W. = 178.

The *silver* salt was prepared by adding a solution of the ammonium salt of the acid to a solution of silver nitrate. The crystalline salt was deposited more quickly than the corresponding salt of the racemic acid:

0.2076 gave 0.1142 Ag. Ag = 55.01.

C₆H₈O₆Ag₂ requires Ag = 55.10 per cent.

Oxidation with Potassium Permanganate.—The oxidation was carried out exactly as described for the oxidation of the racemic isomeride. The product of oxidation gave the fluorescein reaction, and from it both succinanilic acid, melting at 148°, and succinil, melting at 153—154°, were prepared.

Methyl meso- $\alpha\alpha'$ -dihydroxyadipate,

was prepared by adding 12 grams of methyl iodide to 10 grams of the dry silver salt, suspended in dry benzene, and heating on the water-bath for three hours. The silver iodide was filtered and the filtrate evaporated, when the ester was obtained as a crystalline solid, which, after crystallisation from a mixture of benzene and light petroleum, was obtained in stout needles melting at 89°. It is somewhat readily soluble in cold acetone, alcohol, or water, and sparingly so in cold benzene or chloroform:

0.1520 gave 0.2568 CO₂ and 0.0956 H₂O. C = 46.10; H = 7.00.

C₈H₁₄O₆ requires C = 46.60; H = 6.80 per cent.

meso- $\alpha\alpha'$ -Dihydroxyadipamide,

was obtained by the following two methods: (1) the lactone-lactide, obtained by heating the *meso*-acid, was boiled with a concentrated

solution (sp. gr. 0·880) of ammonia, the solution filtered, and allowed to remain, when the diamide separated out; (2) the dimethyl ester was added to a concentrated solution (sp. gr. 0·880) of ammonia, in which it readily dissolved, and from this solution the diamide soon separated. It was crystallised from water, and obtained in glistening plates melting and decomposing at 242° . It dissolves somewhat readily in boiling water, and is insoluble in all the ordinary organic solvents:

0·1462 gave 19·7 c.c. moist nitrogen at 15° and 763 mm. $N = 15\cdot84$.

$C_6H_{12}O_4N_2$ requires $N = 15\cdot90$ per cent.

meso-aa'-Dihydroxyadipic dianilide,

was prepared in exactly the same way as the dianilide of the racemic acid. It is insoluble in water, ether, chloroform, benzene, or light petroleum, and moderately soluble in alcohol, from which it crystallises in glistening plates melting at 216° :

0·1526 gave 11·2 c.c. moist nitrogen at 15° and 775 mm. $N = 8\cdot76$.

$C_{18}H_{20}O_4N_2$ requires $N = 8\cdot53$ per cent.

Action of Heat on meso-aa'-Dihydroxyadipic Acid.

The acid was placed in a large test-tube fitted with a cork through which two tubes passed, the first of these was connected to a pump, and the second, which was drawn out to a fine point, served for the admission of a slow current of dry air. The test-tube and contents were gradually heated in an air-bath. At 174° , the substance melted and water-vapour was evolved, and the temperature was kept at 180 — 190° for about five minutes, the pressure being maintained at 35—40 mm. No sublimate was formed. The residue consisted of a hard, glassy substance, which gave the following results on analysis:

0·1552 gave 0·2710 CO_2 and 0·0670 H_2O . $C = 47\cdot62$; $H = 4\cdot80$.

$C_{12}H_{14}O_9$ requires $C = 47\cdot68$; $H = 4\cdot63$ per cent.

The *lactone-lactide* of *meso-aa'*-dihydroxyadipic acid,

is a hard, transparent, glassy substance, which does not melt at 250° , and when heated above this temperature it decomposes without previously melting. It is insoluble in water, alcohol, acetone, chloroform, ether, or benzene, and dissolves in a solution of potassium hydroxide. When boiled with a concentrated solution of ammonia, the diamide

(see p. 723) and the ammonium salt of the dihydroxy-acid are produced. The formation of the latter compound was proved by converting it into the corresponding silver salt, which was analysed :

0.1234 gave 0.0680 Ag. $\text{Ag} = 55.10$.

$\text{C}_6\text{H}_8\text{O}_6\text{Ag}_2$ requires $\text{Ag} = 55.10$ per cent.

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