XII.—Some α -Alkyl Substitution Products of Glutaric, Adipic, and Pimelic Acids.

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THE α -alkyl substitution products of glutaric, adipic, and pimelic acids have been comparatively little studied, and, as it was thought that it would be interesting to prepare some of these derivatives and determine their dissociation constants, I undertook the following work at the suggestion of Professor W. H. Perkin, jun.

The α -methyl- and α -ethyl-glutaric acids have been prepared by Auwers and Titherly (*Annalen*, 1896, **292**, 209—213).

In preparing derivatives of adipic acid, I have employed a modification

* Reaction verified by the authors.

of the process described by Montemartini (*Ber.*, 1895, 28, 985). Montemartini first prepared ethyl butanetricarboxylate by the interaction of the sodium compound of ethyl malonate with ethyl γ -chlorobutyrate :

This ester, by hydrolysis and subsequent decomposition of the resulting tricarboxylic acid by heat, yields adipic acid. Montemartini also showed that α -substituted derivatives of adipic acid may be obtained by using homologues of ethyl malonate in this synthesis, and in this way he prepared α -methyl- and α -ethyl-adipic acids.

Since, however, the ethyl γ -chlorobutyrate required for these experiments had to be prepared by the hydrolysis of γ -chlorobutyronitrile, $\text{CH}_2\text{Cl}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CN}$, by a troublesome operation conducted in sealed tubes, I have simplified the process by carrying out the synthesis with the nitrile instead of with the ester. The preparation of adipic acid, for example, may be readily accomplished as follows :

The sodium compound of ethyl malonate is treated with γ -chlorobutyronitrile, when the following decomposition takes place :

It is now only necessary to boil the ethyl ω -cyanobutane- $\alpha\alpha$ -dicarboxylate thus formed with dilute sulphuric acid, when hydrolysis and elimination of carbon dioxide simultaneously occur, and adipic acid is formed.

If instead of ethyl malonate the substitution products of ethyl malonate are employed in the above synthesis, it is an easy matter to prepare any α -substitution product of adipic acid. However, in the examples given in the paper, the γ -chlorobutyronitrile was converted into ethyl γ -chlorobutyrate, $\text{CH}_2\text{Cl}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$, and this was digested with the sodium compound of the ethyl alkylmalonate. The ester thus obtained gave, on hydrolysis, the desired substituted acid, with elimination of carbon dioxide. The simplification in the process above-mentioned was suggested to me by Professor Perkin after the three alkyl-adipic acids had been prepared.

In the preparation of the substituted pimelic acids, the process employed was essentially that of Crossley and Perkin (*Trans.*, 1894, 65, 989). The sodium compound of a substitution product of ethyl malonate is first treated with trimethylene chlorobromide, when the following reaction takes place :

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The chloro-ester so prepared is then allowed to react with the sodium compound of ethyl malonate, thus :

The tetracarboxylic ester so produced is digested with hydrochloric acid, when hydrolysis and elimination of carbon dioxide takes place, and the α -substituted pimelic acid is prepared.

 α -ALKYL-GLUTARIC ACIDS.

α -Methylglutaric Acid, $\text{CO}_2\text{H}\cdot\text{CH}(\text{CH}_3)\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$.—In preparing this acid, sodium (1 at.) is dissolved in absolute alcohol and mixed with ethyl propanetricarboxylate, $(\text{CO}_2\text{Et})_2\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$ (1 mol.). A slight excess of methyl iodide (1 mol.) is then added, and after heating for 2 hours on the water-bath, the product is diluted with water and the oily ester extracted with ether in the usual way. After drying over calcium chloride and fractionation, the ethyl methylpropanetricarboxylate, $(\text{CO}_2\text{Et})_2\text{C}(\text{CH}_3)\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$, which distils at 165° under 20 mm. pressure, is digested with concentrated hydrochloric acid for about 6 hours. After evaporation to dryness, a viscid mass remains which soon solidifies. The product crystallises from water in a vacuum, melts at 77 – 78° , and consists of pure α -methylglutaric acid.

This acid has been prepared in a variety of ways, but the above appears to be the best method.

The dissociation constants were as follows :

<i>v.</i>	μ_m	<i>m.</i>	<i>K.</i>
85	22.66	0.0642	0.0052
170	32.23	0.0913	54
340	45.18	0.1280	55
680	61.42	0.1740	54

Temp. 24.4° ; $\mu_\infty = 352$; $K = 0.0054$.

Bethmann (*vide infra*) gives 0.0054; Walden (*vide infra*) 0.0052.

α -Ethylglutaric Acid, $\text{CO}_2\text{H}\cdot\text{CH}(\text{C}_2\text{H}_5)\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$.—This acid has lately been prepared by Auwers and Titherly (*loc. cit.*) by the hydrolysis of ethyl α -ethylpropanetricarboxylate,

I used the same process, and found the boiling point of this ester to be 175 – 179° (30 mm.), and the melting point of the acid to be 60 – 61° (Auwers and Titherly give 60.5°).

The dissociation constants were as follows :

ν .	μ_{ν} .	m .	K .
44.6	16.86	0.0479	0.0054
89.2	23.99	0.0685	56
178.2	34.04	0.0967	58
356.8	47.03	0.1336	57
713.6	63.18	0.1795	55

Temp. 24.2° ; $\mu_{\infty} = 352$; $K = 0.0056$.

Pfaff (*Annalen*, 1896, **292**, 214) gives $K = 0.0058$.

α -Propylglutaric Acid, $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}(\text{CO}_2\text{H}) \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$.—This acid, which does not appear to have been previously described, was obtained in a similar way to the α -ethyl acid just mentioned.

Ethyl α -propylpropanetricarboxylate,

was first prepared by treating the sodium compound of ethyl propanetricarboxylate with propyl iodide, and the ester, which distils at 180 — 185° under 32 mm. pressure, was hydrolysed by boiling with hydrochloric acid. *α -Propylglutaric acid* crystallises by evaporation of the aqueous solution in a vacuum, and melts at 66 — 68° . On analysis:

0.1093 gave 0.2234 CO_2 and 0.0826 H_2O . $\text{C} = 55.7$; $\text{H} = 8.4$.

$\text{C}_8\text{H}_{14}\text{O}_4$ requires $\text{C} = 55.2$; $\text{H} = 8.1$ per cent.

The dissociation constants were as follows:

ν .	μ_{ν} .	m .	K .
62.54	20.20	0.0575	0.0058
125.08	28.67	0.0116	58
250.16	40.75	0.1161	61
500.32	55.36	0.1577	59
1000.64	76.07	0.2167	59

Temp. 24.4° ; $\mu_{\infty} = 35$; $K = 0.00586$.

α -Isopropylglutaric Acid, $(\text{CH}_3)_2\text{CH} \cdot \text{CH}(\text{CO}_2\text{H}) \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}$.—

The acid employed in the following determination was the specimen prepared by Perkin (*Trans.*, 1896, **69**, 1495). It melted at 94° .

The dissociation constants were as follows:

ν .	μ_{ν} .	m .	K .
36.5	15.30	0.0436	0.00548
73	21.85	0.0623	567
146	30.19	0.0860	555
292	41.59	0.1185	541
584	57.88	0.1649	559
1168	79.25	0.2258	563

Temp., 24.4° ; $\mu_{\infty} = 351$; $K = 0.00555$.

ADIPIC ACID AND THE α -ALKYL-ADIPIC ACIDS.

Adipic Acid, $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$.—According to Markownikoff (*Annalen*, 1898, 302, 34) and Aschan (*Ber.*, 1899, 32, 1771), adipic acid is readily prepared by the oxidation of Russian light petroleum, boiling at 80 – 82° , with nitric acid, but it is difficult to obtain Russian light petroleum in this country. The next best way of preparing adipic acid appears to be the following.

Trimethylene chlorobromide, $\text{CH}_2\text{Cl}\cdot\text{CH}_2\cdot\text{CH}_2\text{Br}$, is treated with potassium cyanide, and the product converted into γ -chlorobutyronitrile, $\text{CH}_2\text{Cl}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CN}$, as described by Gabriel (*Ber.*, 1890, 23, 1771; compare Henry, *Compt. rend.*, 1885, 101, 358). This nitrile is then digested with the calculated quantity of the sodium compound of ethyl malonate in the usual way, and the *ethyl cyanopropylmalonate*, $\text{CN}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}(\text{CO}_2\text{Et})_2$, boiling between 170° and 175° under 40 mm. pressure, thus obtained is boiled with dilute sulphuric acid (1 : 2) for 5 hours, and the adipic acid produced is extracted with ether, and purified by recrystallising once from water. This process not only gives a good yield, but the acid is at once obtained in a state of purity.

α -Methyladipic Acid, $\text{CO}_2\text{H}\cdot\text{CH}(\text{CH}_3)\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$.—This acid was first prepared by Bone and Perkin (*Trans.*, 1895, 65, 115), and subsequently by Montemartini (*Gazz.*, 1896, 26, ii, 278).

The acid used in the following determinations was prepared in the following way.

Ethyl γ -chlorobutyrate, obtained from γ -chlorobutyronitrile by the method described by Henry (*Bull. Soc. Chim.*, 1885, [ii], 45, 341), was digested with the calculated quantity of the sodium compound of ethyl methylmalonate for 2 hours. After adding water and extracting with ether, an oil was obtained which distilled constantly at 175 – 178° under 33 mm. pressure, and evidently consisted of ethyl α -methylbutanetricarboxylate. This, on hydrolysis with concentrated hydrochloric acid, yielded α -methyladipic acid melting at 63° (Perkin and Bone give the melting point as 64°).

The dissociation constants were as follows :

v .	μ_v .	m .	k .
54.31	15.84	0.0450	0.0039
108.62	22.46	0.0638	40
217.24	31.72	0.0901	41
434.48	44.86	0.1275	43
868.96	62.56	0.1780	44

Temp. 24.4° ; $\mu_\infty = 352$; $K = 0.0041$.

α -Ethyladipic Acid, $\text{CO}_2\text{H}\cdot\text{CH}(\text{C}_2\text{H}_5)\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$.—This

acid has already been obtained by Lean and Lees (Trans., 1897, 71, 1067), and by Montemartini (*Ber.*, 1896, 29, 1115).

The specimen used in the following experiments was prepared from ethyl α -ethylbutanetricarboxylate, $(\text{CO}_2\text{Et})_2\text{C}(\text{C}_2\text{H}_5)\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$, boiling at 180—183° under 28 mm. pressure, by hydrolysis with boiling hydrochloric acid and elimination of carbon dioxide. α -Ethyladipic acid melts at 48°.

The dissociation constants were as follows :

<i>v.</i>	μ_p	<i>m.</i>	<i>k.</i>
47.2	15.08	0.0429	0.0041
94.4	20.66	0.0589	39
188.8	30.20	0.0866	43
377.6	40.63	0.1158	40
755.2	57.57	0.1640	43

Temp. 24.2°; $\mu_\infty = 351$; $K = 0.00415$.

α -Propyladipic Acid, $\text{CO}_2\text{H}\cdot\text{CH}(\text{C}_3\text{H}_7)\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$.—This acid, which has not been previously described, was prepared in a similar way to the corresponding α -ethyl acid, namely, by the hydrolysis of *ethyl α -propylbutanetricarboxylate* and elimination of carbon dioxide. The last-named ester boils at 200—205° under 30 mm. pressure. The acid, which melted not quite sharply at 55—59°, was analysed with the following results :

0.1293 gave 0.2736 CO_2 and 0.1005 H_2O . C = 57.6; H = 8.6.

$\text{C}_9\text{H}_{16}\text{O}_4$ requires C = 57.4; H = 8.5 per cent.

The dissociation constants were as follows :

<i>v.</i>	μ_p	<i>m.</i>	<i>K.</i>
38.51	13.31	0.0380	0.0039
77.02	19.12	0.0546	41
154.04	27.35	0.0810	43
305.08	38.07	0.1088	43
601.16	52.53	0.1501	43

Temp. 24.4°; $\mu_\infty = 350$; $K = 0.0042$.

α -ALKYL-PIMELIC ACIDS.

α -Methylpimelic Acid, $\text{CO}_2\text{H}\cdot\text{CH}(\text{CH}_3)\cdot[\text{CH}_2]_3\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$.—This acid has already been prepared by Zelinsky and Generowsow (*Ber.*, 1896, 29, 729), and by Einhorn (*Annalen*, 1897, 295, 175). It melts at 57—58°. The determinations of the dissociation constant by Zelinsky and Generowsow gave the value $K = 0.00315$.

α -Ethylpimelic Acid, $\text{CO}_2\text{H}\cdot\text{CH}(\text{C}_2\text{H}_5)\cdot[\text{CH}_2]_3\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$.—This acid has already been obtained by Crossley and Perkin (*loc. cit.*), and is described by them as an oil. I have somewhat modified their

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method of preparation in the hope of obtaining the acid in a crystalline condition, but without success.

If 1 gram-molecule of trimethylene chlorobromide is treated with 1 gram-molecule of the sodium compound of ethyl malonate in the usual way, a 22 per cent. yield of ethyl ω -chloropropylethylmalonate is produced (Crossley and Perkin, *loc. cit.*, 991), distilling at 145° under 18 mm. pressure. When this chloro-ester is heated with a large excess of concentrated hydrochloric acid (sp. gr. 1.16) for 6 hours on a sand-bath, and the product extracted with ether in the usual way, δ -chlorovaleric acid, $\text{CH}_2\text{Cl}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, is obtained as an oil. This, on esterification with alcohol and hydrogen chloride, yields *ethyl δ -chlorovalerate*, $\text{CH}_2\text{Cl}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$, as a colourless oil, boiling at 120 — 125° under 40 mm. pressure. This ester was analysed with the following result:

0.1846 gave 0.1627 AgCl. $\text{Cl} = 21.8$.

$\text{C}_7\text{H}_{13}\text{O}_2\text{Cl}$ requires $\text{Cl} = 21.5$ per cent.

The chloro-ester was digested in alcoholic solution with the calculated quantity of the sodium compound of ethyl ethylmalonate, water was then added, and the oily product extracted with ether, the ethereal solution washed with water, dried over calcium chloride, and evaporated. The residual oil was purified by fractional distillation under reduced pressure. In this way, *ethyl ethylpentanetricarboxylate*, $(\text{CO}_2\text{Et})_2\text{C}(\text{C}_2\text{H}_5)\cdot[\text{CH}_2]_3\cdot\text{CH}_2\cdot\text{CO}_2\text{Et}$, was obtained as a colourless oil boiling at 189 — 191° under 20 mm. pressure. On analysis:

0.2055 gave 0.4528 CO_2 and 0.1658 H_2O . $\text{C} = 60.1$; $\text{H} = 8.9$.

$\text{C}_{16}\text{H}_{28}\text{O}_6$ requires $\text{C} = 60.8$; $\text{H} = 8.8$ per cent.

On hydrolysing this ester with hydrochloric acid in the usual way, α -ethylpimelic acid was obtained as a thick oil which even on standing for 3 months in a vacuum over sulphuric acid showed no signs of crystallisation.

No determinations of the dissociation constants were made, since the acid was not considered pure enough for the purpose.

THE DISSOCIATION CONSTANTS.

I have collected, in the table on p. 133, the known dissociation constants for the α -alkyl-succinic, -glutaric, -adipic, and -pimelic acids.

The numbers for the succinic acids are from Bethmann's (*Zeit. physikal. Chem.*, 1890, 5, 413), and Walden's (*ibid.*, 1892, 8, 433) papers, those for glutaric acid and adipic acid from Ostwald's paper (*ibid.*, 1889, 3, 170, 241, 369). The value for pimelic acid is the mean of those prepared by different methods given in Walden's paper, and is

α -Alkyl radicle.	Succinic acid.	Glutaric acid.	Adipic acid.	Pimelic acid.
Parent acid.....	0.0068	0.0047	0.0037	0.0035
Methyl	0.0085	0.0054	0.0041	0.0031
Ethyl	0.0086	0.0056	0.00415	—
Propyl.....	0.0089	0.0059	0.00423	—
isoPropyl.....	0.0075	0.0055	—	—
isoButyl	0.0088	—	—	—
Allyl	0.0109	—	—	—
(Benzoyl)	0.0091	—	—	—

identical for that of synthetical pimelic acid prepared by Perkin's process (Trans., 1887, 51, 241).

The chief point of interest lies in the fact that, although the avidity of succinic, glutaric, and adipic acids increases when hydrogen is replaced by an α -alkyl group, yet the effect with pimelic acid appears to be the converse of this. For example, the differences between the values of this constant for these acids and their respective α -methyl derivatives are as follows :—

Methylsuccinic acid – succinic acid	+0.0017
Methylglutaric acid – glutaric acid	+0.0007
Methyladipic acid – adipic acid.....	+0.0004
Methylpimelic acid – pimelic acid.....	–0.0004

The effect of the substitution thus appears to become less marked as the distance between the carboxyl groups increases. These facts may be shown graphically by plotting the number of carbon atoms

in the introduced methyl, ethyl, or propyl group, against the value of $K \times 10^4$.

The curves on page 133 indicate :

(1) The effect of the substitution is greater the heavier the alkyl group introduced.

(2) With succinic, adipic, and pimelic acids the effect of the substitution is less marked the further the carboxyl groups are apart, as is evident from the gradual flattening of the curves from succinic to adipic acid.

(3) The reversal in the direction of the slope of the curve in the case of pimelic acid and its methyl derivative seems to indicate that in the suberic, azelaic, and sebacic series a still greater reversal will be observed when the dissociation constants of the α -alkyl substitution products of these acids have been determined.