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Synthesis of Some Dialkylated Pimelic Acids

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The synthesis of a number of new alkylated pimelic acids, namely, 4,4-tetramethylene-, 4,4-pentamethylene-, 3,3-tetramethylene-, *racemoid*-3-methyl-5-ethyl- and *threo*-3,4-dimethylpimelic acids, is reported. 3,4-Dialkylated pimelic acids have not been described previously in the literature.

A common feature of the syntheses is the use of appropriately substituted glutaric acids as intermediates. Three new dialkylated glutaric acids, namely 2-methyl-4-butylglutaric acid, probably the *mesoid*-form, and *racemoid*- and *mesoid*-2-methyl-4-isopropylglutaric acid, and also the imide of the latter, have been prepared. The 2-methyl-4-alkylglutaric acids were obtained by alkylation of diethyl 2-methyl-2-ethoxycarbonylglutarate followed by hydrolysis and decarboxylation.

The configurations of the *mesoid*-2,4-dialkylated and of the *threo*-2,3-dialkylated glutaric imides are sterically more favourable than those of their diastereomers. This fact was utilized in separating the diastereomeric forms of the glutaric acids. Extension of the carbon chains to produce pimelic acids was performed by Arndt-Eistert syntheses, in which the asymmetric centres are not affected.

2,6-Diaminopimelic acid (DAP) is known to be an essential metabolite of many bacteria, *e.g.* the tubercle bacillus. A systematic search for potential antimetabolites that are structurally related to DAP has been started in this school by Lund Jensen.[1] Among the compounds proposed in his research program are various alkylated DAPs; these may be obtained by amination of the corresponding alkylated pimelic acids. It was therefore desirable to develop generally applicable methods for synthesizing 3,3-, 4,4-, 3,5-, and 3,4-dialkylated pimelic acids. The present paper reports the main results of a systematic study of this problem. A detailed account of both successful and unsuccessful attempts to prepare dialkylated pimelic acids of the above-mentioned types has been presented in a thesis.[2] The study was confined to saturated, dialkylated pimelic acids containing 9—12 carbon atoms and included *gem*-polymethylene substituents.

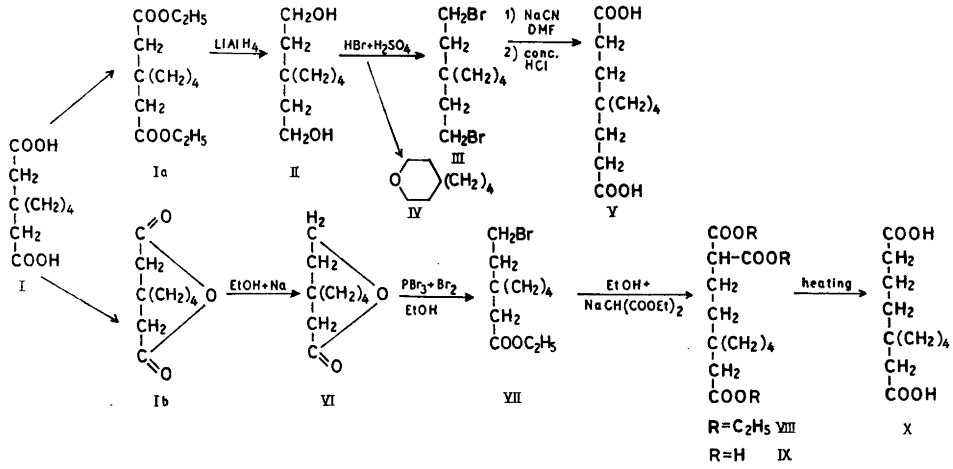
No 3,4-dialkylated and only a few 3,3-, 4,4-, and 3,5-dialkylated pimelic acids are known from the literature. The syntheses of these constituted in most cases relatively unimportant parts of the research described, and they are

consequently only briefly outlined. Diaper and Kuksis[3] have given a comprehensive, though not exhaustive, review of the synthetic routes to alkylated alkanedioic acids that have been described up to June 1958. Rakshit *et al.*[4] reported the preparation of 3-methyl-3-isohexylpimelic acid. Their method was found to be directly applicable to the syntheses of other 3,3-dialkylated pimelic acids. For the syntheses of the other types of dialkylpimelic acids major modifications of known procedures or new methods had to be developed. A common feature of all the syntheses performed is the use of appropriately substituted glutaric acids as intermediates.

2,3- and 2,4-dialkylglutaric acids occur in diastereomeric forms. Greater similarities between the diastereomers are to be expected as the alkyls become smaller. The methods used in the following, including separations of diastereomeric mixtures, are therefore probably of fairly general validity since dialkylglutaric acids with low molecular weights were chosen for the experimental work.

METHODS

4,4-Dialkylated pimelic acids



4,4-Tetramethylenepimelic acid (V). 3,3-Tetramethyleneglutaric acid (I) was prepared *via* the imide according to the method given by Vogel.[5] The ester (I a) was reduced by $LiAlH_4$ to the diol (II). Several attempts to isolate (II) failed, since dehydration to 4,4-tetramethylenetetrahydropyran (IV) occurred very easily. The crude product (II) was refluxed with a mixture of 48 % hydrogen bromide and concentrated sulfuric acid. After 6 h a 30 % yield of the dibromide (III) together with a 60 % yield of (IV) was obtained. The maximum yield of 50 % of (III) was produced after 20 h of refluxing. (IV) was removed from the reaction mixture by steam distillation, and (III) was isolated by extracting the residue with ether. Nitrilation of the dibromide (III) was performed with sodium cyanide in DMF-solution. The progress of

this reaction was followed with thin-layer chromatography (TLC); it was found that (III) was completely consumed after 2 h. The use of DMF resulted in a drastic enhancement of the reaction rate compared to that for the aqueous-alcoholic media usually employed for this type of reaction. The crude nitrile was hydrolyzed to give (V).

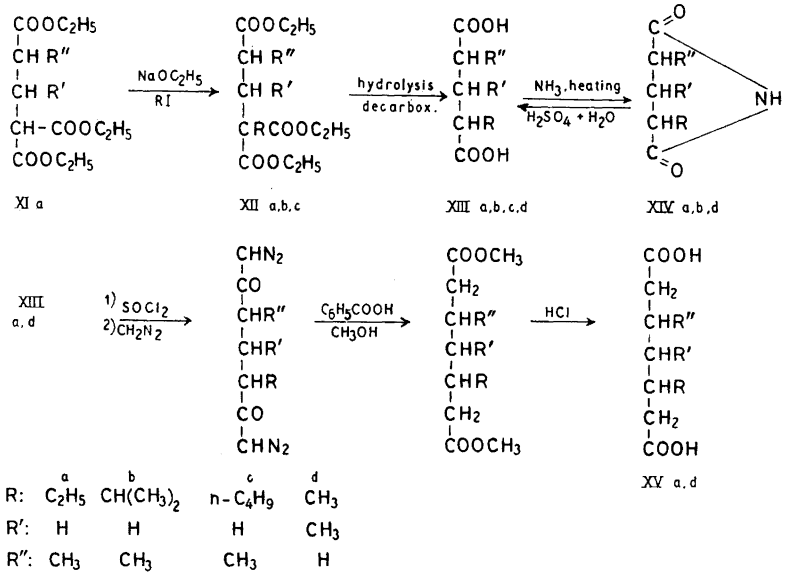
4,4-Pentamethylenepimelic acid was prepared in reactions similar to those above.

Reid and Gompf [6] described the synthesis of 4,4-dimethylpimelic acid starting from 3,3-dimethylglutaric acid. However, the technique described by these authors was found unsuitable for the preparation of other 4,4-dialkylated pimelic acids. The procedure described above is a modification of that of Reid and Gompf, the main difference being the technique used in the nitrilation step.

3,3-Dialkylated pimelic acids

3,3-Tetramethylenepimelic acid (X) was prepared by a series of reactions described by Rakshit *et al.*[4] The anhydride (I b) was reduced to the δ-lactone (VI), which was transformed to the δ-bromo-substituted ester (VII). This compound was used in a malonic ester synthesis to give (VIII), (IX), and (X).

3,5-Dialkylated pimelic acids



Diethyl 2-methyl-4-ethoxycarbonylglutarate (XIa) was prepared by a Michael condensation of ethyl methacrylate and malonic ester. The experimental conditions were analogous to those used by Michael and Ross [7] for

preparing diethyl 3-methyl-4-ethoxycarbonylglutarate. Alkylation of (XI a) to give (XII a-c) proceeded smoothly. A TLC procedure was developed for following the progress of the alkylation reactions. NMR-spectroscopy was used to ensure that (XII a-c) were not contaminated with (XI a) since the methine proton at C-4 in (XI a) gives a signal at 200 cps which is well separated from those given by the protons in (XI) and (XII).

Acidic hydrolysis of (XII) was feasible only for (XII a), whereas prolonged heating with concentrated aqueous alkali was necessary to effect a complete hydrolysis of (XII b-c). An attempt to hydrolyse (XII b) by refluxing for 10 h with a 10 % solution of potassium hydroxide only led to partial saponification. From this reaction mixture a compound, for which the NMR-spectrum and the equivalent weight found by alkalimetric titration indicated the formula 2-methyl-4-isopropyl-4-ethoxycarbonylglutaric acid, was isolated. The formation of a compound of this constitution is to be expected from the steric hindrance to hydrolysis which the isopropyl group causes.

Separation of diastereomeric 2,4-dialkylglutaric acids. A partial separation of the mixtures of stereoisomers of (XIII a-c) formed from (XII a-c) has been achieved. Bendz [8] described a nearly quantitative separation of the diastereomers of (XIII a) based upon the different solubilities of the acidic calcium salts in water. Several attempts to reproduce this separation failed. Auwers and Thorpe [9] separated the diastereomeric 2,4-dimethylglutaric acids *via* the corresponding anhydrides. Attempts to utilize this procedure were also unsuccessful. The best results with (XIII a) were obtained from a combination of the acidic calcium salt method and imide formation. The least soluble acidic calcium salt was separated by filtering and, after acidification, following several crystallizations, yielded the highest-melting isomer. The filtrate of the acidic calcium salts contained an impure acid which, on reaction with concentrated ammonia, gave an imide. After two crystallizations from light petrol this compound had a sharp m.p. of 125°. This imide has been described previously, but was reported as having a lower m.p. of 116°. On hydrolysis of the imide the lowest-melting isomer of (XIII a) was obtained in a pure state after a single crystallization.

The diastereomers of (XIII b) were separated in a series of crystallizations of the acidic calcium salts. The yields were poor. Better results were obtained by converting the crude mixture of the diastereomeric acids to the ammonium salt. On heating, this substance was partly transformed to an imide. This imide was isolated and on hydrolysis yielded the lowest-melting isomer of (XIII b), which was obtained in a pure state from one crystallization. From the remaining ammonium salts the highest-melting isomer was obtained in a pure state after two crystallizations.

Only one crystalline compound was isolated from the mixture of the diastereomers (XIII c). This was obtained by conversion to the anhydride, hydrolysis, and precipitation of an acidic calcium salt. The acid liberated from this salt had to be purified by several crystallizations to obtain a sharp and constant melting point. All attempts to isolate the other isomer failed.

It is noteworthy that a single recrystallization was sufficient to purify the diastereomeric forms of the dialkylated glutaric acids, which were isolated *via* the imide, while several recrystallizations were needed to obtain pure products

via the anhydride or the acidic calcium salts. Apparently imide formation is the most selective of the reactions used to separate mixtures of diastereomeric glutaric acids.

Determination of the configurations of the diastereomeric forms of (XIII b-c). The configurations were deduced from comparisons of the IR-spectra of these and related compounds.

Table 1. Some data for diastereomeric 2,4- and 2,3-disubstituted glutaric acids.

Substituents	Configuration	M.p.	Splitting of IR carbonyl band	Formation *via* imide or anhydride	Possibility of both substituents equatorial in imide and anhydride
2,4-dimethyl	*racemic*	highest	+	−	−
	meso	lowest	−	+	+
2,4-diethyl	*racemic*	lowest	+	−	−
	meso	highest	−	+	+
2-methyl-4-ethyl (XIII a)	*racemoid*	107°	+	−	−
	mesoid	82.5–83.5°	−	+	+
2-methyl-4-isopropyl (XIII b)	*racemoid* proposed	129–30°	+	−	−
	mesoid	94–95°	−	+	+
2-methyl-4-butyl (XIII c)	*racemoid*			?	−
	mesoid proposed	85–86°	?	+	+
2,3-dimethyl (XV d)	*threo*	87°		+	+
	erythro	lowest		−	−

Using a grating spectrophotometer a splitting of the carbonyl band in the highest melting form of (XIII b) was detected, but an equivalent observation was not made for the lowest-melting form. Schotte [10] has described a similar splitting of the carbonyl band in the *racemic* forms of 2,4-dimethylglutaric acid and 2,4-diethylglutaric acid, and also in the highest-melting form of 2-methyl-4-ethylglutaric acid (XIII a). It was not observed in the lowest-melting form of this compound. These observations prompted Schotte to assign the *racemoid* configuration of (XIII a) to the highest-melting form. By analogy, the *racemoid* configuration is therefore proposed for the highest-melting isomer, and the *mesoid* form for the lowest-melting isomer, of the compound (XIII b) obtained in the present work.

The separation of the mixtures of stereoisomers of (XIII) *via* cyclic imides or anhydrides lends some support to the correctness of the above assignments.

Table 1 shows that, in all cases, the diastereomeric form isolated *via* the anhydride or imide is the *meso* or *mesoid* form. Molecular models of the imides and anhydrides indicate that in these 5-membered rings only the *mesoid* isomers can attain the sterically optimal conformation with both alkyl groups placed in equatorial positions. In the *racemoid* isomers only one alkyl group can be placed in an equatorial position, with the other axial. The molecular structures of the *mesoid* imides and anhydrides are thus energetically more favourable than those of the *racemoid* isomers. It might therefore be expected that in general the *mesoid* isomers are the main products when these cyclic derivatives are prepared from mixtures of the diastereomeric acids. On this basis it is suggested that the crystalline form of (XIII c) isolated *via* the anhydride is probably the *mesoid* form.

Synthesis of a 3-methyl-5-ethylpimelic acid (XV a). Extension of the carbon chains of the substituted glutaric acids (XIII) to give the corresponding pimelic acids (XV) may be performed by double Arndt-Eistert syntheses followed by Wolff-rearrangements of the bis-diazoketones formed. The choice of this method is based upon the fact that basic reagents, which may cause epimerizations at the α-carbon atoms of the starting material (XIII), are completely avoided in the Arndt-Eistert synthesis. Hydrolysis of the methyl esters obtained by the Wolff-rearrangements may be accomplished in both acidic and alkaline media with no risk of simultaneous epimerizations, since the α-carbon atoms in (XV) are not asymmetric.

This chain-extension method was used with the *racemoid* form of (XIII a) (m.p. 107 °), and with *threo*-2,3-dimethylglutaric acid. The final hydrolysis in each case gave a syrupy liquid which from TLC was found to contain only one dialkylpimelic acid contaminated by the starting material (XIII). After purification by column chromatography and subsequent evaporation of the eluent nearly pure crystals of (XV) were obtained.

3,4-Dialkylated pimelic acids

These compounds may be prepared from 2,3-dialkylated glutaric acids in an analogous manner to the preparations of the 3,5-disubstituted compounds; namely, by double Arndt-Eistert syntheses followed by Wolff-rearrangements.

2,3-Dimethylglutaric acid (XIII d) was prepared by the method of Michael and Ross.[7] The diastereomeric forms were separated *via* the imide, but only the *threo*-form of the acid was isolated. The configurations of the diastereomers are known from the work of Hughes.[11]

The *threo*-form of (XV d) obtained by chain-extension of *threo*-(XIII d) was purified as the well-crystallized *S*-benzylthiouronium salt, which was prepared in the manner reported by Berger.[12]

EXPERIMENTAL

The IR-spectra were recorded from potassium bromide discs on a Perkin Elmer spectrophotometer, Model 125. The NMR-spectra were made with a Varian A 60 NMR-spectrophotometer operating at a fixed frequency of 60 Mc/s, using tetramethylsilane as an internal standard.

Microanalyses were performed by Preben Hansen, Microanalytical Laboratory, University of Copenhagen. The melting points are uncorrected.

3,3-Tetramethylenepentanediol (II). 3,3-Tetramethyleneglutaric acid (I) was prepared according to the method given by Vogel,[5] and was transformed to the diester (I a) *via* the dichloride. Reduction of (I a) (Bergson [13]) yielded the crude diol (II) (86 %).

3,3-Tetramethylene-1,5-dibromopentane (III). 10 g (0.063 mole) of the crude diol (II) were refluxed for 20 h with a mixture of 26.4 g of 48 % hydrobromic acid and 11.2 g of concentrated sulfuric acid. The mixture was steam distilled to remove 4,4-tetramethylenetetrahydropyran [15] (IV). The yield of (IV) was 5.25 g, collected at 52°/4 mm. (Lit.[15] 63–64°/10 mm).

The residue was extracted with ether. The ethereal extract was washed with portions of cold 80 % sulfuric acid until these were no longer coloured, then with water, and finally with 10 % aqueous sodium carbonate. After drying and evaporation the residue was distilled to give 9 g (50 %) of (III), collected at 115°/1.5 mm. (Found: C 56.22; H 5.50; Br 37.95; Calc. for $C_9H_{16}Br_2$: C 56.36; H 5.51; Br 38.02).

4,4-Tetramethylenepimelic acid (V). A suspension of 0.49 g (0.01 mole) of dry sodium cyanide and 1.2 g (0.0045 mole) of (III) in 18 ml of dimethylformamide was heated to 100° for 2 h. 20 ml of water were added to the mixture which was then extracted with ether. The ether layer was dried and evaporated to give crude 4,4-tetramethylenepimelonitrile.

The nitrile was refluxed for 5 h with 2 ml of concentrated hydrochloric acid. After addition of 8 ml of water the mixture was extracted with ether. Drying and evaporation resulted in a crude product which, upon recrystallization from ether-petroleum ether, yielded 700 mg (77 %) of colourless crystals, m.p. 100°. (Found: C 61.32; H 8.09. Calc. for $C_{11}H_{12}O_4$: C 61.64; H 8.39).

4,4-Pentamethylenepimelic acid. The preparation was similar to that described for (V), and the yield was of the same order of magnitude. M.p. 89°. (Found: C 62.90; H 8.80. Calc. for $C_{12}H_{20}O_4$: C 63.15; H 8.77).

3,3-Tetramethylene-5-valerolactone (VI). A mixture of 15.5 g (0.68 g atom) of sodium and a solution of 15.0 g (0.089 mole) of 3,3-tetramethyleneglutaric anhydride [5] in 77 ml of dry ethanol was refluxed while 29 ml of dry ethanol were added in small portions. The mixture was refluxed for an additional 5 h and then allowed to stand overnight.

The reaction mixture was poured into water, acidified and extracted with ether. The ether extract was dried and evaporated. The residue on distillation gave 7.5 g (55 %) of product collected at 150°/10 mm. (Found: C 69.29; H 8.98. Calc. for $C_9H_{14}O_2$: C 70.08; H 9.14).

Ethyl 3,3-tetramethylene-5-bromovalerate (VII). 5 ml of phosphorus tribromide and 3 ml of bromine were successively added, with vigorous shaking and cooling to 0°, to 7.5 g (0.043 mole) of (VI). After standing at 0° overnight the mixture was heated to 60° and 35 ml of ethanol were added.

After cooling to room temperature and standing for 30 min, the mixture was evaporated *in vacuo*. The residue was dissolved in ether and washed with 2 N sodium hydrogen carbonate. After drying, the ether was evaporated and the residue was purified by distillation to give 9.8 g (76.5 %) of product collected at 86–90°/0.2–0.3 mm. (Found: C 49.50; H 7.25; Br 30.10. Calc. for $C_{11}H_{19}BrO_2$: C 50.20 H 7.22; Br 30.42).

Triethyl 2,2-tetramethylenepentane-1,5,5-tricarboxylate (VIII). 6.20 g (0.039 mole) of malonic ester were added to a solution of 0.89 g (0.039 g atom) of sodium in 18 ml of ethanol. The reaction was allowed to proceed for 15 min. 9.8 g (0.038 mole) of (VII) were then added and the mixture was refluxed for 12 h. After cooling, 40 ml of water were added and the mixture was extracted with ether. The ether layer was dried and evaporated *in vacuo*. The crude residue was distilled to give 8.5 g (67 %) of product collected at 138–140°/0.1–0.2 mm. (Found: C 63.00; H 8.72; Calc. for $C_{18}H_{30}O_6$: C 63.17; H 8.77).

2,2-Tetramethylenepentane-1,5,5-tricarboxylic acid (IX). A mixture of 8.5 g (0.025 mole) of (VIII) and 30 ml of 15 % aqueous sodium hydroxide was refluxed for 8 h. It was then acidified and extracted with three 50 ml-portions of ether.

The ethereal solution was dried and evaporated *in vacuo* and the crystals formed after drying over calcium oxide overnight were recrystallized from benzene-petroleum ether. Yield 4.0 g (67 %), m.p. 131–32°. (Found: C 55.75; H 7.11. Calc. for $C_{12}H_{18}O_6$: C 55.82; H 6.98). Equiv. weight by alkalimetric titration: 87.0 (Calc. 86.0).

3,3-Tetramethylenepimelic acid (X). 4.0 g (0.0155 mole) of (IX) were heated to 180° until evolution of carbon dioxide had ceased. After cooling the crystals produced were recrystallized from ether-petroleum ether. Yield 3.0 g (90 %), m.p. 96°. (Found: C 61.43; H 8.30. Calc. for $C_{11}H_{18}O_4$: C 61.66; H 8.41).

Diethyl 2-methyl-4-ethyl-4-ethoxycarbonylglutarate (XII a). 108 g (0.41 mole) of diethyl 2-methyl-4-ethoxycarbonylglutarate [7] (XI a) were added, with cooling to 0°, to a solution of 9.4 g (0.40 g atom) of sodium in 40 ml of ethanol. After addition of 10 ml of ethanol and 62.4 g (0.41 mole) of ethyl iodide the reaction mixture was cooled to 0° and left standing overnight. It was then acidified by addition of 36 ml of acetic acid and 400 ml of water.

The solution was extracted with two 150-ml portions of ether. The combined ether layers were washed with excess 2 N sodium carbonate, and dried. After evaporation *in vacuo* and subsequent distillation the yield of product was 108 g (90 %), b.p. 138°/2.5 mm. (Lit.[7] 144°/3 mm).

Diethyl 2-methyl-4-isopropyl-4-ethoxycarbonylglutarate (XII b). The preparation was similar to that described for (XII a), except that the reaction mixture was refluxed for 5 h. Yield 81 %, b.p. 127°/0.75 mm.

Diethyl 2-methyl-4-butyl-4-ethoxycarbonylglutarate (XII c). The preparation was similar to that described for (XII a), except that the reaction mixture was refluxed for 4 h. Yield 56.8 %, b.p. 149°/3 mm.

The preparations of (XII a-c) were followed by reversed-phase partition chromatography [14] on thin-layer plates of silica gel-G. The plates were soaked for 1 min each in a bath of 10 % liquid paraffin in petroleum ether. The mobile phase was acetonitrile-acetic acid-water 50:7:28. The spots were detected with iodine vapour.

Racemoid and mesoid 2-methyl-4-ethylglutaric acid (XIII a). A mixture of 100 g (0.365 mole) of (XII a), 200 ml of water and 400 ml of concentrated hydrochloric acid was refluxed for 24 h. It was concentrated to dryness *in vacuo*, the last traces of water being removed by azeotropic distillation with benzene.

The residue was heated to 180° until the evolution of carbon dioxide had ceased. After cooling to room temperature the crystals which had formed were triturated in the presence of petroleum ether and then dried to give 32 g (50 %) of product, m.p. 62—75°. Equiv. weight by alkalimetric titration: 86.5. (Calc. 87.0).

Racemoid *and* mesoid *2-methyl-4-isopropylglutaric acid (XIII b).* 140 g (0.44 mole) of (XII b) were added in portions to a solution of 92.5 g (1.65 mole) of potassium hydroxide in 100 ml of water. The mixture was refluxed for 10 h and, after cooling to room temperature, was extracted with two 50-ml portions of ether. 100 ml of water and 230 ml of concentrated hydrochloric acid were then added to the aqueous layer. The resulting solution was extracted with ether. The respective ether layers were combined and dried and evaporated *in vacuo*.

The residue was heated to 180° until the evolution of carbon dioxide had ceased. After cooling to room temperature and drying over calcium oxide overnight, 73 g (88 %) of crystals, m.p. 78—105°, were obtained. Equiv. weight by alkalimetric titration: 95.1 (Calc. 94.0).

Separation of the diastereomeric 2-methyl-4-ethylglutaric acids (XIII a). 1.45 g (0.0145 mole) of calcium carbonate were added to a hot (*ca.* 50°) solution of 6.7 g (0.0385 mole) of (XIII a) in 33.5 ml of water. The mixture was allowed to cool to room temperature. The precipitate was collected by filtration, acidified with 4 N hydrochloric acid, and extracted with ether. The ethereal extract was dried and evaporated *in vacuo* to give 2.6 g of crude acid. Recrystallization seven times from cyclohexane yielded 1.2 g (18 %) of the *racemoid* acid (XIII a, *racemoid*), m.p. 107°.

From the filtrate obtained in the above preparation were isolated 2 g of an acid, m.p. 62—79°. 10 ml of concentrated ammonia water were added to this, after which the solution was concentrated to dryness *in vacuo*. The residue was heated to 160° for 4 h. After cooling, 10 ml of water were added and the mixture was extracted with ether. The ethereal extract was dried and evaporated, yielding crystals which were recrystallized twice from ligroin to give 0.5 g of *mesoid* 2-methyl-4-ethylglutarimide, m.p. 125° (Lit.[16] 116°). The imide was refluxed with 30 % sulfuric acid for 3 h to give an acid which upon recrystallization from ether-petroleum ether yielded 0.5 g of (XIII a, *mesoid*), m.p. 82.5—83.5°) (Lit.[8] 83.5—84.5).

Separation of the diastereomeric 2-methyl-4-isopropylglutaric acids (XIII b). 6 g of (XIII b) were converted to the imide *via* the ammonium salt, in an analogous manner to the conversion of (XIII a). After recrystallization the yield was 0.8 g (15 %) of *mesoid* 2-methyl-4-isopropylglutarimide, m.p. 113–14°. (Found: C 63.80; H 8.83; N 8.34. Calc. for $C_9H_{15}NO_2$: C 63.90; H 8.88; N 8.29).

The imide was refluxed for 5 h with excess of 30 % sulfuric acid, and the acid obtained was recrystallized from ligroin to give 0.7 g (17 %) of (XIII b, *mesoid*), m.p. 94–95°. (Found: C 57.55; H 8.64. Calc. for $C_9H_{16}O_4$: C 57.45; H 8.54).

The aqueous solution from the preparation of the imide was acidified and gave 2.7 g of crude acid which upon recrystallization twice from tetrachloromethane-cyclohexane 3:1 yielded 1.8 g (30 %) of (XIII b, *racemoid*), m.p. 129–130°. (Found: C 57.05; H 8.42. Calc. for $C_9H_{16}O_4$: C 57.45; H 8.54).

2-Methyl-4-butylglutaric acid (XIII c). 45 g (0.136 mole) of (XII c) were treated in the manner described in the preparation of (XIII b). The yield of a viscous oil containing the mixed stereoisomeric acids (XIII c) was 15 g (54 %). Equiv. weight by alkalimetric titration 102.0. (Calc. 101.0). This product was transformed to the anhydride using the method given by Auwers and Thorpe.[9] Yield of anhydride, 11.4 g (83 %).

The 11.4 g of anhydride were hydrolyzed with 60 ml of water, 9 ml of ethanol were added and the solution was heated to 80°. 2.14 g of calcium carbonate were then added and the mixture was allowed to cool to room temperature. The resulting precipitate was filtered by suction and, after drying, a yield of 6.5 g of product was obtained. The calcium salt was treated as described above to give 4.5 g of an acid, m.p. 78–85.°

1.5 g of this acid was recrystallized three times from ligroin-cyclohexane 5:2 to give 0.9 g of an acid with m.p. 85–86°. (Found: C 58.65; H 8.88. Calc. for $C_{10}H_{18}O_4$: C 59.40; H 8.91). Attempts to prepare other diastereomers of (XIII c) were unsuccessful.

Racemoid *3-methyl-5-ethylpimelic acid (XV a).* A mixture of 1.0 g (0.0058 mole) of (XIII a, *racemoid*), 3 ml of thionyl chloride, 4 ml of benzene, and 1 drop of triethylamine was heated to 50° for 2 h. Following evaporation *in vacuo* the resulting crude dichloride was dissolved in 8 ml of dry benzene. This solution was then added dropwise, and with stirring, to excess of ethereal diazomethane. After standing overnight the ether and the benzene were removed in an air stream. The residue was dissolved in 40 ml of dry methanol and cooled to 0°. A solution of 0.6 g (0.0026 mole) of silver benzoate in 5 ml of triethylamine was added, with stirring, and when nitrogen evolution had ceased the solution was left to stand at 0° overnight. It was then filtered with suction through Hyflo Super Cel and evaporated *in vacuo*. The residue was dissolved in 25 ml of ether and washed with successive portions of saturated aqueous sodium hydrogen carbonate. After drying and evaporation *in vacuo* a yield of 1 g of a viscous oil was obtained.

The oil was mixed with 3 ml of dioxane and 10 ml of 3 N hydrochloric acid and refluxed for 12 h. The mixture was extracted with ether, and after drying and evaporation of the ethereal extract the resultant oily residue was chromatographed on 50 g of silica gel (0.05–0.20 mm Merck) activated at 120° and mixed with 10 % of water. As eluent 250 ml of chloroform-formic acid 99:0.1, 250 ml of chloroform-methanol-formic acid 97.5:2.5:0.1 and 300 ml of chloroform-methanol-formic acid 96:4:0.1 were used. The fractions were investigated by TLC on silica gel G using chloroform-methanol-formic acid 90:10:0.2 as eluent. After heating at 120° for 10 min, the spots were detected by spraying with bromocresol green.

The yield of (XV a) after recrystallization from cyclohexane-tetrachloromethane 4:1 was 400 mg (37 %), m.p. 72.5–73.5°. (Found: C 59.20; H 8.78. Calc. for $C_{10}H_{18}O_4$: C 59.39; H 8.96).

threo-*3,4-Dimethylpimelic acid (XV d).* A Michael condensation [7] of diethyl methylmalonate and ethyl crotonate led to (XII d), which upon hydrolysis and decarboxylation gave (XIII d). A partial separation of the stereoisomeric acids was effected *via* the imide. 1.8 g of the imide were hydrolyzed and treated as described above to give 1.7 g of crude acid, which on recrystallization ten times from tetrachloromethane yielded 1.25 g of the pure *threo*-form (XIII d, *threo*), m.p. 86–87°.

(XV d) was prepared from (XIII d, *threo*) in a similar manner to that described for (XV a) from (XIII a). Column chromatography of 1 g of crude (XV d, *threo*), performed as described in the (XV a) preparation, yielded a viscous oil which was converted to the S-benzylthiouronium salt.[12] A yield of 0.5 g was obtained by crystallization from acetone.

M.p. 152–153°. (Found: C 56.40; H 7.05; N 10.74. Calc. for $C_{25}H_{36}N_4S_2O_4$: C 57.92; H 6.95; N 10.81).

The *S*-benzylthiouronium salt was acidified and treated in the conventional way, and after drying over phosphorus pentoxide, the acid was obtained as a hygroscopic crystalline product. M.p. 57–58°. (Found: C 57.65; H 8.59. Calc. for $C_9H_{16}O_4$: C 57.45; H 8.51).

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