SYNTHESIS OF 2,6-DIAMINOPIMELIC ACID AND ITS 4-SUBSTITUTED DERIVATIVES

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Alkylation of diethyl acetamidomalonate with 5-bromo-N-phthaloyl-L-norvaline methyl ester (*V*) gives rise to a mixture of all three isomers of 2,6-diaminopimelic acid. Alkylation of diethyl acetamidomalonate with ethyl 2-acetamido-5-bromo-2-ethoxycarbonyllevulinate (*XI*) and subsequent hydrolysis of the resulting product gave 2,6-diamino-4-oxopimelic acid (*VIII*) which in turn was converted to 4-oximino- (*XIII*), 4-amino- (*XIV*), and 4-hydroxy-2,6-diaminopimelic acid (*XV*). 2,6-Diaminopimelic acid was chlorinated to the 4-chloro derivative (*XVI*) which treated with silver sulphate afforded also compound *XV*. From 1,7-diacetoxy-4-heptanol (*XIX*) were prepared 1,7-diacetoxy-4-fluoroheptane (*XX*) and 4-fluoro-1,7-heptanediol (*XXI*). The latter yielded on oxidation 4-fluoropimelic acid (*XVII*) from which 2,6-diamino-4-fluoropimelic acid was prepared by a modified method.

2,6-Diaminopimelic acid is a fundamental building component of the cell wall peptides of microorganisms. From natural material it was first isolated by Work[1], though its chemical synthesis was accomplished already earlier[2]. In studying the metabolism of the amino acids and their peptides it is a very helpful tool the application of radioisotope-labelled amino acids and their homologues. Previously we have already described[3-5] the synthesis of 2,6-diaminopimelic-acid-[2-^{14}C] and -[4-^{3}H] and also the preparation[4] of ^{14}C-labelled higher homologues. In the present work we attempted the preparation of the natural L,L- and *meso*-2,6-diaminopimelic-acid [2-^{14}C] respectively and of some of their 4-substituted derivatives.

The first synthesis of 2,6-diaminopimelic acid is based[2] on the alkylation of diethyl phthalimidomalonate with diethyl 2-(3'-bromopropyl)-2-phthalimidomalonate and on the acid hydrolysis of the resulting alkylation product. Thus, using diethyl acetamidomalonate-[2-^{14}C] we prepared in our previous work[3] the 2-^{14}C-labelled derivative. In both cases, however, results a mixture of all three isomers in the ratio L,L : D,D: *meso* = 1 : 1 : 2.

We prepared therefore first the 5-bromo-N-phthaloyl-L-norvaline methyl ester (*V*). The 1-methyl ester of N-phthaloyl-L-glutamic acid (*I*) afforded on hydroboration followed by cyclisation of the not isolated hydroxy ester *II* 3-phthalimido-L-δ-valerolactone (*III*). Treatment of lactone *III* with hydrogen bromide gave 5-bromo-N-

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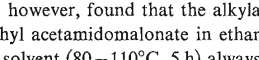
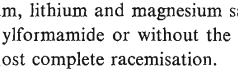
phthaloyl-L-norvaline (*IV*) which was esterified with diazomethane to the methyl ester *V*. We expected that the alkylation of diethyl acetamidomalonate with compound *V* and the subsequent hydrolysis of the formed triester *VI* would afford only the L,L- and *meso*-forms of 2,6-diaminopimelic acid whose chromatographic separation should be possible[6,7]. By use of diethyl acetamidomalonate-[2-^{14}C] in trace amounts we could easily quantitatively follow the presence of the individual stereoisomers. It was, however, found that the alkylation of sodium, lithium and magnesium salts of diethyl acetamidomalonate in ethanol or dimethylformamide or without the use of any solvent (80–110°C, 5 h) always leads to almost complete racemisation.

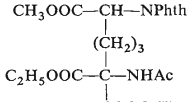


I



II, X = OH; R = H
IV, X = Br; R = H
V, X = Br; R = CH_3

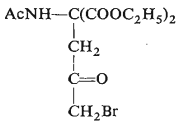
III



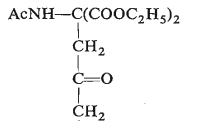
VI

Of the substituted derivatives the 2,6-diamino-3-hydroxypimelic[8] and 2,6-diamino-4-fluoropimelic acids[9] are known. For our purpose we considered it to be most suitable to prepare first 2,6-diamino-4-oxopimelic acid (*VIII*) since this substance might be also the starting compound for further 4-substituted derivatives. By treating the 1-benzyl ester of N-phthaloyl-L-aspartic acid[10] with thionyl chloride we prepared its 4-chloride *IX* which on reaction with diazomethane followed by treatment with hydrogen bromide afforded the benzyl ester of 5-bromo-4-oxo-N-phthaloyl-L-norvaline (*X*). On alkylation of diethyl acetamidomalonate with the bromide *X* in dimethylformamide or toluene or without any solvent, however, darkening of the reaction mixture always instantly occured, and we did not succeed in isolating any definite product from it. Therefore we used for the alkylation of diethyl acetamidomalonate ethyl 2-acetamido-5-bromo-2-ethoxycarbonyllevulinate[11] (*XI*) and obtained diethyl 2,6-diacetamido-2,6-diethoxycarbonyl-4-oxopimelate (*XII*) in 65% yield. Acid hydrolysis of the ester *XII* gave the oxo acid *VIII* which was transformed by means of hydroxylamine to the oxime XIII. Catalytic hydrogenation of the oxime *XIII* gave 2,4,6-triaminopimelic acid (*XIV*).

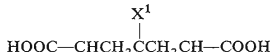
By hydrogenation of the oxo-acid *VIII* was prepared 2,6-diamino-4-hydroxypimelic acid (*XV*) in almost quantitative yield. This acid, when evaporated with



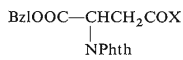
XI



XII



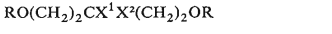
VIII, $X^1 + X^2 = 0$
XIII, $X^1 + X^2 = N—OH$
XIV, $X^1 = NH_2$; $X^2 = H$
XV, $X^1 = OH$; $X^2 = H$
XVI, $X^1 = Cl$; $X^2 = H$



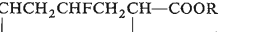
IX, X = Cl
X, X = CH_2Br

concentrated hydrochloric acid and also on reaction with thionyl chloride, afforded a substance which showed on electrophoresis basic properties and might therefore be the lactone of acid *XV*. However, we did not succed in opening the supposed lactone ring even by the action of hydrogen bromide in acetic acid at 80°C. For the preparation of 4-chloro-2,6-diaminopimelic acid (*XVI*) we applied the procedure[12] which consists in the radical chlorination of free amino acids in a medium of strong mineral acids. The position of chlorine in compound *XVI* was determined both by converting it into acid *XV* on treatment with silver sulphate and by its oxidation with potassium permanganate to 3-chloroglutaric acid[13].

The main problem in synthetising 2,6-diamino-4-fluoropimelic acid is the difficult preparation of 4-fluoropimelic acid (*XVII*), since the only hitherto known procedure[14] which consists in the simultaneous action of nitrous and hydrofluoric acids on 2-pyrrolidone-5-carbonic acid is unsatisfactory on account to the low yield (6%). In our work we started from 1,7-diacetoxy-4-heptanone (*XVIII*) which we transformed to 1,7-diacetoxy-4-heptanol (*XIX*) by catalytic hydrogenation. The reaction of *XIX* with N-(2-chloro-1,1,2-trifluoroethyl)-N,N-diethylamine led to 1,7-diacetoxy-4-fluoroheptane (*XX*), the methanolysis of which afforded 4-fluoro-1,7-heptanediol (*XXI*). The diol *XXI* was oxidised with nitrogen dioxide[15] to acid *XVII*. The prepara-



XVIII, $X^1 + X^2 = O$; R = CH_3CO
XIX, $X^1 = OH$; $X^2 = H$; R = CH_3CO
XX, $X^1 = F$; $X^2 = H$; R = CH_3CO
XXI, $X^1 = F$; $X^2 = H$; R = H



VII, X = NH_2; R = H
XVII, X = H; R = H
XXII, X = Br; R = CH_3
XXIII, X = NPhth; R = CH_3

tion of the amino acid *VII* from compound *XVII* was accomplished by an analogous reaction sequence as that described in the literature[9], but instead of using the ethyl esters we applied the methyl esters. The overall yield of substance *VII* is then ten times higher than that by the referred procedure[9].

EXPERIMENTAL

The temperature data are uncorrected. Melting points were determined on a Kofler block. Gas chromatographic analysis was carried out on a Packard apparatus, type 871.

1-Methyl N-phthaloyl-L-glutamate (*I*)

The reaction was performed by a modification of the described method[16]. A mixture of N-phthaloyl-L-glutamic acid (55.4 g; 0·2 mol), dimethylformamide (50 ml), triethylamine (28 ml), and methyl iodide (16 ml) was allowed to stand at room temperature for 16 hours, then it was poured into 400 ml of water and extracted with ethyl acetate. The ethyl acetate phase was re-extracted with aqueous sodium hydrogen carbonate, the combined carbonate fractions were acidified with hydrochloric acid and the deposited oil was taken into ethyl acetate. After evaporating, the residue was crystallised from ether–light petroleum and the crude product was recrystallised from ethyl acetate–light petroleum; yield 15 g (26%) of compound *I*, m.p. 130–136°C and after repeated recrystallisation 135–138°C, $[\alpha]_D^{25}$ −56·7° (0·5M, ethyl acetate). Literature[17] gives for compound *I* prepared by a different procedure m.p. 136–137°C, $[\alpha]_D^{20}$ −39·8 (*c* 2·8, dioxan), $[\alpha]_D^{26}$ −55·9° (*c* 3·2, ethyl acetate). The mother liquors from crystallisation of the crude methyl ester *I* were evaporated *in vacuo* and the residue, dissolved in ethyl acetate, was treated with an equivalent of dicyclohexylamine and put in the refrigerator where after addition of ether the dicyclohexyl-ammonium salt (15 g) crystallised. After recrystallisation from ethyl acetate–light petroleum it had m.p. 128–132°C; literature[16] gives for this salt m.p. 132–134°C. Acidifying the aqueous solution of this salt yielded further 7 g of ester *I*.

3-Phthalimido-L-δ-valerolactone (*III*)

Diborane (from 4 g of $NaBH_4$) was passed at −10°C into a solution of ester *I* (9·2 g; 31·6 mmol) in tetrahydrofuran (70 ml). After about half of the diborane volume had been liberated, the reaction temperature was raised to 0°C and the remaining diborane continued to pass into the solution. The reaction mixture was then acidified with dilute HCl, the solution adjusted to pH 7 by addition of sodium hydrogen carbonate, and the tetrahydrofuran was removed *in vacuo*. The residue was distributed between aqueous sodium hydrogen carbonate and ethyl acetate, the ethyl acetate layer was dried and the solvent evaporated. The oily ester *II* (8·7 g) was without further purification converted into the crystalline lactone *III* by dissolving it in benzene, adding a catalytic amount of *p*-toluene sulphonic acid and distilling off most of the benzene in the course of 2 h. After cooling, the benzene solution was shaken with aqueous sodium hydrogen carbonate and the separated benzene layer evaporated. The residue was crystallised from benzene–light petroleum to yield 4.5 g (58%) of product *III*; m.p. 148–150°C, $[\alpha]_D^{25}$ −53·1° (0·5M, dioxan). For $C_{13}H_{11}NO_4$ (245·2) calculated: 63·70% C, 4·48% H, 5·72% N; found: 63·55% C, 4·72% H, 5·63% N.

5-Bromo-N-phthaloyl-L-norvaline (*IV*)

4·5 g (18·4 mmol) of lactone *III* were added to 20 ml of a saturated solution of hydrobromic acid in acetic acid and allowed to stand for 15 h at room temperature. Then the solution was eva-

porated *in vacuo* and the residue distributed between water and ethyl acetate. The ethyl acetate layer was thoroughly extracted with aqueous sodium hydrogen carbonate. The combined carbonate fractions were acidified with hydrochloric acid and the separated oil taken up in ethyl acetate. Evaporation of the ethyl acetate gave 4 g (66%) of an oil which on standing crystallised. Treatment of the oil with ether–benzene yielded 0·5 g of product *IV*, m.p. 125—130°C; $[\alpha]_D^{25}$ —43·2° (0·5M, ethyl acetate). For $C_{13}H_{12}BrNO_4$ (326·1) calculated: 47·92% C, 3·71% H, 24·48% Br; found: 48·30% C, 3·96% H, 24·30% Br. The mother liquor from the crystallisation of the bromo acid *IV* was evaporated to dryness and the residue dried *in vacuo*. Its analysis showed it to be the pure compound *IV*.

A solution of 652 mg (2 mmol) of substance *IV* in 50% aqueous ethanol was hydrogenated under the catalysis of $Pd/BaSO_4$ in the presence of sodium hydroxide for 3 h. The crude product was hydrolyzed by boiling with 5M-HCl for 2 h. Work up of the reaction mixture gave L-norvaline in 80% yield; $[\alpha]_D^{25}$ 23·5° (0·4M, 5M-HCl) which corresponded to the pure L-form.

Methyl ester: The oily derivative *IV* was esterified with diazomethane in ether. After esterification, the ethereal solution was washed with aqueous sodium hydrogen carbonate and water and then dried. After evaporation the ether, the oily product *V* was obtained in quantitative yield. For $C_{14}H_{14}BrNO_4$ (340·2) calculated: 49·45% C, 4·12% H, 23·48% Br; found: 49·71% C, 4·40% H, 23·60% Br.

5-Bromo-4-oxo-N-phthaloyl-L-norvaline Benzyl Ester (*X*)

A mixture of 1-benzyl N-phthaloyl-L-aspartate[10] (1·3 g; 3·7 mmol) and ether (10 ml) was heated under reflux with thionyl chloride (0·45 ml) for 2 h. After cooling to 0°C chloride *IX* (1·05 g; 77%) with m.p. 88—90°C was obtained. 1 g of this chloride was added with stirring to an ethereal solution of 20 mmol of diazomethane at 0°C. The solution was evaporated *in vacuo* at a temperature not exceeding 20°C, and the residue was treated with glacial acetic acid (10 ml) and 48% hydrobromic acid (0·9 ml). After one hour at room temperature, the solution was concentrated at reduced pressure and the still remaining acids were removed by evaporation with water. The residue was dissolved in ether and after washing with aqueous sodium hydrogen carbonate and water and removing the ether, the residue was crystallised from ether–light petroleum to give 0·6 g (52%) of product *X*; m.p. 67—69°C, $[\alpha]_D^{25}$ —37·1° (0·5M, methanol). For $C_{20}H_{16}BrNO_5$ (430·2) calculated: 55·78% C, 3·72% H, 18·55% Br; found: 56·20% C, 3·81% H, 18·68% Br.

Diethyl 2,6-Diacetamido-2,6-diethoxycarbonyl-4-oxopimelate (*XII*)

To a solution of the sodium salt of diethyl acetamidomalonate (2·39 g; 10 mmol) in dimethylformamide (10 ml) ethyl 2-acetamido-5-bromo-2-ethoxycarbonyllevulinate[11] (3·35 g; 11 mmol) in dimethylformamide (10 ml) was added under cooling to —50°C and the mixture was stirred overnight at room temperature. From the neutral mixture dimethylformamide was evaporated under reduced pressure and the residue distributed between water and ethyl acetate. The ethyl acetate layer was washed with water, dried and evaporated to dryness. On addition of ether the product (3.3 g; 65%) crystallised; m.p. 140—142°C. For $C_{21}H_{32}N_2O_{11}$ (488·4) calculated: 51·62% C, 6·60% H; found: 51·40% C, 6·45% H.

2,6-Diamino-4-oxopimelic Acid (*VIII*)

Ester *XII* (18 g; 37 mmol) was refluxed with 15% HCl (100 ml) for 2 h. The hydrochloric acid was evaporated under reduced pressure and the residue three times more evaporated to dryness with excess of water. Then it was treated with 30 ml of 70% ethanol and the solution adjusted

with pyridine to pH 7. Upon standing in the refrigerator overnight 6·5 g (87%) of acid *VIII* crystallised which does not melt up to 360°C. For $C_7H_{12}N_2O_5$ (204·2) calculated: 41·18% C, 5·90% H, 13·73% N; found: 40·90% C, 6·02% H, 13·41% N.

2,6-Diamino-4-oximinopimelic Acid (*XIII*)

To a solution of acid VIII (2 g; 9·9 mmol) in 5 ml of water were added hydroxylamine hydrochloride (1 g; 14 mmol) and anhydrous sodium acetate (2 g; 25 mmol). The mixture was refluxed for 2 h and then put into the refrigerator. The product (1·2 g) was collected with suction. From the mother liquors crystallised on addition of ethanol another 0·6 g of the product; overall yield 1·8 g (84%) of acid *XIII* which does not melt up to 300°C. For $C_7H_{13}N_3O_5$ (219·2) calculated: 38·60% C, 6·98% H; found: 38·52% C, 6·27% H.

2,4,6-Triaminopimelic Acid (*XIV*)

1·65 g (7·5 mmol) of oxime *XIII* were hydrogenated in 15 ml of water and 1·7 ml of hydrochloric acid on Adams catalyst to the constant uptake of hydrogen (180 ml, 8 h). The catalyst was then filtered off, the filtrate evaporated to dryness, the residue dissolved in water and the still remaining chloride ions precipitated with silver oxide. The silver chloride was filtered off, the filtrate decolourised with active charcoal and concentrated to about 5 ml. This solution was applied to a column (2·5 × 30 cm) of Dowex 50. Elution with a buffer of pH 6·5 (2M pyridine brought to pH 6·5 with acetic acid) at a rate of 10 ml/1·5 min removed the neutral substances (which was controlled by electrophoresis). The column was then washed with water followed by 3% ammonia. The latter eluate afforded on evaporation 0·7 g of an oil containing a single ninhydrin positive basic substance. Acid *XIV* provides a definite tripicrate melting at 177—179°C (with decomposition). For $C_7H_{15}N_3O_4 \cdot C_{18}H_9N_9O_{21}$ (892·5) calculated: 33·65% C, 2·68% H, 18·82% N; found: 33·78% C, 3·00% H, 18·98% N.

2,6-Diamino-4-hydroxypimelic Acid (*XV*)

A) 3·06 g (15 mmol) of acid *VIII* were hydrogenated in 10 ml of 3% acetic acid on Adams catalyst (120 mg PtO_2) to the constant uptake of hydrogen (6 h). The catalyst was then filtered off, the filtrate neutralised with pyridine and the solvent removed under reduced pressure. The residue, dried in a desiccator, was triturated with ethanol and filtered with suction. The yield of acid *XV* which does not melt up to 360°C is almost quantitative. Paper electrophoresis carried out in water–pyridine–acetic acid (1 l of water, 2·5 ml of glacial acetic acid and 10 ml of pyridine; 600 V, 90 min) showed that the product contains as impurity traces of the corresponding lactone. For $C_7H_{14}N_2O_5$ (206·2) calculated: 40·77% C, 6·84% H, 13·59% N; found: 40·63% C, 6·70% H, 13·51% N.

B) To a solution of 448 mg (1·7 mmol) of the hydrochloride of acid *XVI* in 10 ml of water was added silver sulphate (600 mg; about 3 mmol) and the resulting mixture was stirred at 45°C for one hour. The precipitated silver chloride was filtered off, the filtrate was treated with barium carbonate (380 mg), and stirred for 8 h at room temperature until neutral. The precipitate was filtered off and the filtrate concentrated *in vacuo* to a volume of about 5 ml. On addition of methanol acid *XV* crystallises in form of the monohydrate; yield 153 mg (40%). The acid does not melt up to 360°C, only looses the water of crystallisation. For $C_7H_{14}N_2O_5.H_2O$ (224·2) calculated: 37·50% C, 7·19% H, 12·49% N; found: 37·80% C, 7·38% H, 12·80% N.

2,6-Diamino-4-chloropimelic Acid (*XVI*)

A solution of 5 g (26 mmol) of 2,6-diaminopimelic acid in 25 ml of concentrated hydrochloric acid was irradiated with a high-pressure mercury lamp in an air-cooled quartz flask at 50—60°C for 6 h. When the reaction was over, the solution was left overnight in the refrigerator. The deposited crystals of the hydrochloride of acid *XVI* were collected with suction and thoroughly washed with ethanol and ether; yield 1 g (15%). On repeated chlorination of the mother liquor was obtained another 5% of the product. The hydrochloride of acid *XVI* does not melt up to 360°C. For $C_7H_{14}Cl_2N_2O_4$ (261·2) calculated: 32·16% C, 5·37% H, 27·20% Cl; found 31·89% C, 5·40% H, 27·50% Cl.

A solution of 0·5 g of the hydrochloride of acid *XVI* in water (5 ml) was neutralised with dilute ammonia. After adding 5 ml of methanol, acid *XVI* crystallises in almost quantitative yield. It does not melt to up 360°C. For $C_7H_{13}ClN_2O_4$ (224·6) calculated: 15·81% Cl; found: 16·18% Cl.

Acid *XVI* was degraded with aqueous potassium permanganate in dilute sulphuric acid by the procedure described for lysine[18]. The acid obtained was chromatographed on paper along with authentic samples of 2-chloroglutaric and 3-chloroglutaric acid and was identified as 3-chloroglutaric acid.

1,7-Diacetoxy-4-heptanol (*XIX*)

1,7-Diacetoxy-4-heptanone[19] (214 g) was dissolved in 90% ethanol (900 ml) and hydrogenated in the presence of Adams catalyst (8·4 g PtO_2) at 20°C and atmospheric pressure. After $2^1/_2$ h the hydrogenation was finished and the solution was evaporated *in vacuo*. The oily residue was taken up in 300 ml of ether, dried with a molecular sieve and distilled to give 204 g (95%) of compound *XIX* with b.p. 124—134°C/0·3 Torr which according to gas chromatography (20% Rheoplex on Chromosorb, 185°C) is the pure substance. The sample for analysis had b.p. 124 to 125°C/0·3 Torr, n_D^{20} 1·4487. For $C_{11}H_{20}O_5$ (232·3) calculate: 56·88% C, 8·68% H; found: 56·80% C, 8·45% H.

1,7-Diacetoxy-4-fluoroheptane (*XX*)

To a mixture of compound *XIX* (207·5 g) and dichloromethane (770 ml) N-(2-chloro-1,1,2-trifluoroethyl)-N,N-diethylamine (180 g) was added dropwise during one hour at a temperature kept below 33°C. Next day the solution was washed with water, sodium hydrogen carbonate and again with water, dried with a molecular sieve, carefully treated dropwise with 15 ml of bromine and stirred for 1 h. After repeated washing and drying, the solution was distilled yielding 145 g (91%) of chlorofluoroacetic acid diethyl amide, b.p. 40—60°C/0·3 Torr, and 110 g of a fraction with the boiling range 60—120°C/0·2—0·3 Torr. The second fraction afforded on rectification 80·2 g (38%) of the fluoro derivative *XX*, b.p. 80—93°C/0·15 Torr, in sufficient pure state to be used in the further synthesis (gas-chromatographic control: 15% diethyleneglycol adipate on Chromosorb W, 180°C). The sample for analysis had b.p. 88—91°C/0·2 Torr, n_D^{20} 1·4314. For $C_{11}H_{19}FO_4$ (234·3) calculated: 56·39% C, 8·17% H, 8·11% F; found: 56·72% C, 8·51% H, 7·56% F.

4-Fluoro-1,7-heptanediol (*XXI*)

A mixture of the diacetate *XX* (65·7 g), methanol (50 ml) saturated with hydrogen chloride and methanol (1 l) was distilled over a column at the reflux ratio of 10 : 1 until the boiling point reached 64°C (about 4 h). Then methanol was evaporated, the residue taken up in 50 ml of tetra-

hydrofuran and neutralised with solid sodium hydrogen carbonate under stirring. Distillation afforded 36·8 g (88%) of the hygroscopic diol *XXI* with the boiling range 100—115°C/0·2 Torr. The sample for analysis boiled at 109—112°C/0·4 Torr. For $C_7H_{15}FO_2$ (150·2) calculated: 55·98% C, 10·06% H, 12·65% F; found: 56·01% C, 10·15% H, 12·28% F.

The bis-phenylurethane of diol *XXI* had m.p. 132—134°C (ethanol). For $C_{21}H_{25}FN_2O_4$ (388·4) calculated: 64·93% C, 6·49% H, 4·90% F, 7·21% N; found: 64·75% C, 6·60% H, 4·83% F, 7·33% N.

4-Fluoropimelic Acid (*XVII*)

To the diol *XXI* (15·5 g) liquefied nitrogen dioxide (39·5 g) was added dropwise with stirring during 1 h and in the course of this operation the temperature was kept in the range of +10 to +20°C (at lower temperature exists the danger of undercooling and of an uncontrolled reaction course). The mixture was stirred for 2 h and afterwards kept in a closed vessel for 50 h. The nitrous fumes were then sucked off and the solid residue was triturated with 30 ml of ether, filtered with suction and washed with ether to give 9·2 g (50%) of the acid *XVII* with m.p. 117 to 127°C. Concentration of the mother liquors furnished a further, less pure portion of the product (2·8 g; 15%) with m.p. 107—114°C. The sample for analysis had after threefold recrystallisation from ether (cooled to −20°C) m.p. 133—136°C (sintering at 89°C); literature[14] gives m.p. 140—141°C. For $C_7H_{11}FO_4$ (178·2) calculated: 47·18% C, 6·22% H, 10·67% F; found: 47·46% C, 6·51% H, 10·44% F.

Dimethyl 2,6-Dibromo-4-fluoropimelate (*XXII*)

The ester *XXII* was prepared in 60% yield by a procedure described[9] for the preparation of the diethyl ester and boiled between 103—115°C/0·3—0·4 Torr. A sample for analysis had b.p. 111—112°C/0·3 Torr. For $C_9H_{13}Br_2FO_4$ (364·0) calculated: 29·69% C, 3·60% H, 43·91% Br, 5·21% F; found: 29·79% C, 3·56% H, 44·09% Br, 5·21% F.

Dimethyl 2,6-Diphthalimido-4-fluoropimelate (*XXIII*)

The bromo ester *XXII* (3·6 g), potassium phthalimide (3·66 g), and dimethylformamide (15 ml) were heated at 100°C for 45 min. The neutral mixture was then evaporated *in vacuo*, the residue distributed between 50 ml of ethyl acetate and 10 ml of water, the organic layer was washed with water, dried with molecular sieve and evaporated *in vacuo*. The oily residue was in the form of its ethereal solution applied to a column of 30 g of Florisil (100—200 mesh) and eluted with ether. The collected 25 ml fractions gave on evaporation sucessively 230 mg of phthalimide, 1·03 g of the oily ester *XXIII*, and 2·61 g of the solid ester *XXIII*, m.p. 65—70°C, which was analytically pure. Yield 3·64 g (74%). For $C_{25}H_{21}FN_2O_8$ (496·4) calculated: 60·48% C, 4·27% H, 3·82% F, 5·66% N; found: 60·18% C, 4·40% H, 3·69% F, 5·40% N.

From the diester *XXIII* was prepared by described procedure[9] 2,6-diamino-4-fluoropimelic acid (*VII*) in 45% yield. It does not melt up to 300°C. For $C_7H_{13}FN_2O_4$ (208·2) calculated: 9·12% F; found: 9·27% F.

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