UNSATURATED ACIDS AND MACROCYCLIC LACTONES

COMMUNICATION 10. SYNTHESIS OF THE LACTONE OF 3-HYDROXY-2,4,6-TRIMETHYLHEPTANEDIOIC ACID

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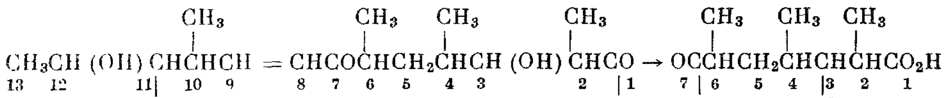
In the oxidative cleavage of macrolidic antibiotics (methymycin, neomethymycin, picromycin, and narbomycin) two groups of investigators have isolated the dextrorotatory lactone of 3-hydroxy-2,4,6-trimethyl-heptanedioic acid (d-II) [1-3]. The establishment of the structure of this lactone was one of the decisive links in the chain of proof of the macrocyclic skeleton of these antibiotics, but the stereochemistry of this important key compound has not yet been elucidated completely. As the lactone (d-II) was formed from the C_1-C_7 fragment of the molecule of neomethynolide (I), for which the configuration 4L, 6L has been proved [4], the same configuration must be possessed by the C_4 and C_6 atoms in the lactone (d-II). The configuration of the remaining asymmetric centers of the lactone (d-II) has not been determined; its establishment would enable us to obtain new valuable data on the absolute configuration of macrolidic antibiotics.

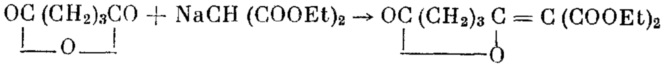


$$CH_3CH(OH)CH\overset{CH_3}{C}HCH{=}CHCO\overset{CH_3}{C}HCH_2\overset{CH_3}{C}HCH(OH)\overset{CH_3}{C}HCO \rightarrow OC\overset{CH_3}{C}HCH_2\overset{CH_3}{C}HCH\overset{CH_3}{C}HCO_2H$$

(I) (d-II)

In continuation of our study of ways of synthesizing macrolides [5], we synthesized the corresponding racemic lactone (II) and its stereoisomers (IIa), (IIb), and (IIc). In the course of preliminary investigations we tried the following possible methods of synthesizing 3-hydroxyheptanedioic and 3-hydroxy-2-methylheptanedioic acids.

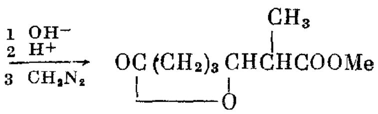
a) The condensation of glutaric anhydride with sodiomalonic ester. In this attempt we isolated the enol lactone of 6,6-bisethoxycarbonyl-5-oxohexanoic acid (III) as a crystalline substance, readily split when heated with water with formation of glutaric acid. Attempts to hydrogenate the enol lactone (III) over a platinum catalyst or Raney nickel were not successful.



$$OC(CH_2)_3CO + NaCH(COOEt)_2 \rightarrow OC(CH_2)_3C=C(COOEt)_2$$

(III)

b) Reformatskii reaction between ethyl glutaraldehydate and ethyl 2-bromopropionate:

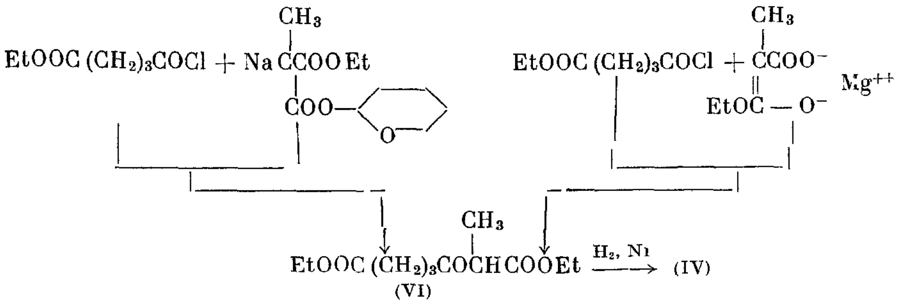


$$\xrightarrow[3\ CH_2N_2]{1\ OH^-\quad 2\ H^+} OC(CH_2)_3CH\overset{CH_3}{C}HCOOMe$$

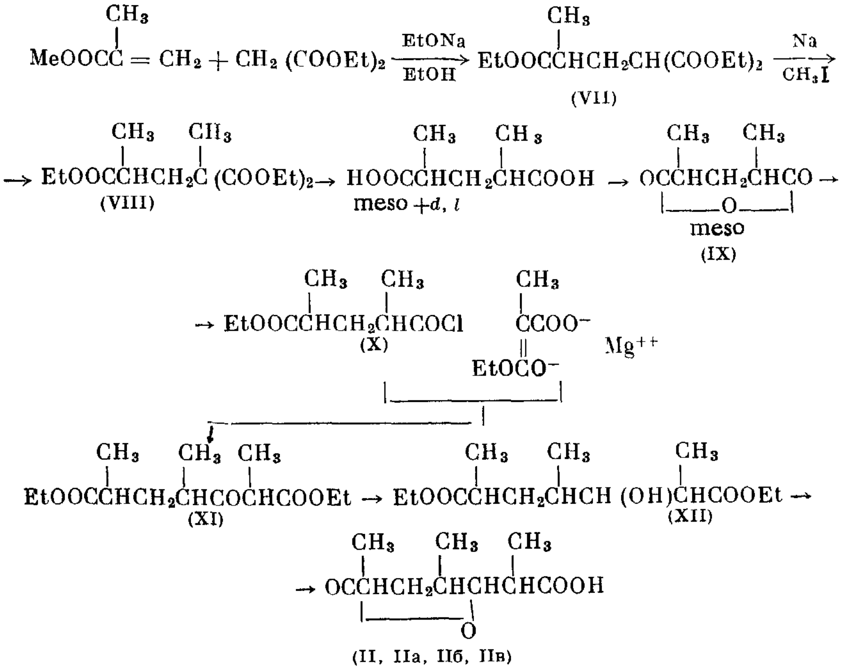
(V)

This reaction led in low yield to diethyl 3-hydroxy-2-methylheptanedioate (IV), which on hydrolysis and subsequent esterification gave the methoxycarbonyl lactone (V).

c) Condensation of ethyl 4-(chlorocarbonyl)butyrate with the tetrahydropyranyl derivative of methylmalonic monoester [6] or with the Mg salt of the same monoester [7]. As a result of these condensations (the latter method was found to be preferable) a satisfactory yield was obtained of diethyl 2-methyl-3-oxoheptanedioate (VI). Catalytic hydrogenation of this compound went stereoselectively and led to the hydroxy diester (IV), which was found to be identical to the compound obtained by method (b).



Since method (c) gave optimum results, we used it for the synthesis of the lactone of 3-hydroxy-2,4,6-trimethylheptanedioic acid by the scheme:



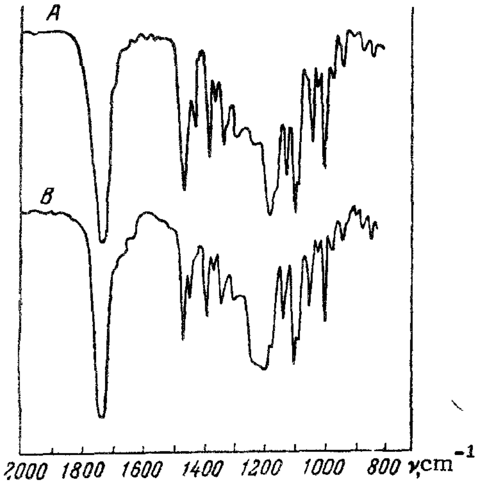
In accordance with this scheme we synthesized all the four possible stereoisomeric carboxy lactones with a cis disposition of methyl groups in the lactone ring (II, IIa, IIb, IIc).

The meso-2,4-dimethylglutaric anhydride (IX) required for these syntheses has been prepared previously by several methods, of which the best is the method in [8] based on the Michael condensation of methyl methacrylate with sodiomethylmalonic ester. To avoid the stage of preparing methylmalonic ester, we modified this method somewhat. By the condensation of methyl methacrylate with sodiomalonic ester we obtained the triester (VII), which after methylation, hydrolysis, and decarboxylation gave a mixture of d, *l*-and meso-2,4-dimethylglutaric acids. The meso-anhydride (IX) prepared from the latter was converted via the corresponding monoester into the acid chloride (X). To avoid epimerization we synthesized the acid chloride (X) by the action of oxalyl chloride at low temperature, the homogeneity of the acid chloride was confirmed by its conversion in almost quantitative yield into the crystalline anilide. Condensation of the acid chloride (X) with the Mg salt of methylmalonic monoester led to the keto diester (XI). Hydrogenation of this over Raney nickel gave the hydroxy diester (XII), which, according to thin-layer chromatography, consisted of a mixture of isomers; on hydrolysis it gave two crystalline carboxy lactones, m.p. 122-123° (IIa) and 157-158° (IIb), which differed from the "natural" product in their constants and in the infrared spectra of their methyl esters With the object of preparing other stereoisomers of the carboxy lactone we therefore studied the reduction of the keto diester (XI) with complex hydrides. An attempt at reduction with sodium borohydride led to a stable boron-containing compound, and, when the complex of lithium aluminum hydride with pyridine [9] was used, the main reduction product was the corresponding triol. We succeeded in effecting the selective reduction of the keto group of the keto diester (XI) with lithium aluminum hydrides at low temperature. This reaction is distinguished by considerable stereospecificity. When lithium triethoxyhydroaluminate is used it leads, after hydrolysis, mainly to the carboxy lactone (IIc), m.p.107-108°. When the reduction of the keto diester (XI) is carried out with lithium aluminum hydride, the product is the fourth stereoisomer (II), m.p. 125-126°, which forms a methyl ester of m.p. 74-75°. The carboxy lactone obtained and its methyl ester give melting point depression in admixture with the carboxy lactone (IIa) and its methyl ester, respectively. On the other hand, the infrared spectrum of the methyl ester of the racemic carboxy lactone (II) obtained as a result of lithium aluminum hydride reduction was found to be identical to the infrared spectrum of the methyl ester of the "natural" d-carboxy lactone (Fig 1), some difference in the region of 1200 cm^{-1} is due to difference in the concentrations of the solutions. Resolution of the racemic carboxy lactone (II) with the aid of D-threo-1-p-nitrophenyl-2-amino-1,3-propanediol led to the enantiomer of the "natural" d-lactone (l-II), it had m p. 125-126° and $[\alpha]_D^{22}$ −32° Hence, the carboxy lactone that we synthesized was the racemate of the carboxy lactone (d-II) formed in the oxidative cleavage of macrolidic antibiotics.

EXPERIMENTAL

The melting points of the preparations were determined in capillaries, Infrared spectra were determined with a UR-10 spectrograph (Zeiss, East Germany),* ultraviolet spectra were determined with an SF-4 spectrophotometer. Thin-layer chromatography on silica gel was carried out by the procedure described in [10]; here the detection of hydrazides was carried out with the aid of an aqueous-butanolic ammoniacal silver solution, and the remaining substances were detected with the aid of a solution of potassium permanganate in 2 N H_2SO_4, in thin-layer chromatography on unbound alumina (Grade III activity) on plates the substances were detected by treatment with iodine vapor.

Condensation of Glutaric Anhydride with Malonic Ester. With cooling 48.0 g of malonic ester was added to a suspension of 6.90 g of sodium in 500 ml of dry benzene. The mixture was heated for 3 hours with stirring at a gentle boil. It was cooled to room temperature, and a solution of 34.2 g of glutaric anhydride in 150 ml of benzene was added over a period of 1 hour; the mixture was then stirred for 3 hours at room temperature and for 2 hours at the boil. The mixture was cooled, neutralized with glacial acetic acid, and treated with 200 ml of water, the organic layer was separated, and the aqueous layer was extracted three times with ether. The combined extracts were washed with water and dried with sodium sulfate. Solvents and unchanged malonic ester were distilled off, and the residue crystallized out on cooling. Recrystallization of the crude product from a mixture of hexane and benzene gave 25.8 g (35%) of the enol lactone of 6,6-bisethoxycarbonyl-5-oxohexanoic acid (III), m.p. 72-73°, as a crystalline substance which rapidly deliquesced in air. Found· C 56 78, H 6.33%. $C_{12}H_{16}O_6$ Calculated: C 56.25; H 6.25%. Ultraviolet spectrum: λ_{max} 233 mμ, ε 16,600 (in alcohol). Infrared spectrum. ν_{max} 1795 cm^{-1} (enol ester), 1724 cm^{-1} (α,β-unsaturated ester), 1643 cm^{-1} (double bond) Treatment of an alcoholic solution of the enol lactone (III) with ammonia gave a triamide, which crystallized with one molecule of alcohol; m.p. 180-181° (from absolute alcohol). Found. C 45.77, H 7.62, N 16.21%. $C_{10}H_{19}O_5N_2$. Calculated: C 45.97; H 7 33; N 16.08%



Infrared spectra of methyl esters of lactones of 3-hydroxy-2,4,6-trimethylheptanedioic acid: A) (d-II) and B) (II) (solution in chloroform; NaCl prism).

Hydrolysis of the Enol Lactone of 6,6-Bisethoxycarbonyl-5-oxohexanoic Acid (III). 1.28 g of the enol lactone of 6,6-bisethoxycarbonyl-5-oxohexanoic acid (III) was heated with 40 ml of water with vigorous stirring at 90° for 4 hours. The mixture was cooled and extracted with 5 20-ml portions of ether, and the combined ether extracts were dried with magnesium sulfate. Ether was driven off, and the oily residue crystallized out almost completely on standing. Recrystallization from benzene gave 0.57 g (87%) of glutaric acid, m.p. 97-98°, undepressed by admixture of a known sample.

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* The infrared spectra were determined by L. B. Senyavina

Diethyl 2-Methyl-3-oxoheptanedioate (VI). a) A solution of 17.52 g of ethyl hydrogen methylmalonate in 25 ml of dry benzene was added dropwise over a period of 30 minutes to a solution of 15.12 g of dihydropyran in 50 ml of benzene containing three drops of a 10% solution of p-toluenesulfonic acid in methanol. The mixture was then left at room temperature for 20 minutes, after which excess of dihydropyran and benzene were vacuum-distilled off. The ethyl tetrahydropyranyl methylmalonate obtained (27.0 g) was dissolved in 50 ml of dry benzene, and the solution was added dropwise over a period of 1 hour with cooling to a suspension of 2.76 g of sodium in 100 ml of benzene. The mixture was stirred for 30 minutes at room temperature, and then, at the same temperature, 21 42 g of ethyl 4-(chlorocarbonyl)butyrate was added over a period of 40 minutes, in the course of which the mixture thickened. The mixture was stirred for 5 hours at room temperature, 5 ml of glacial acetic acid was added, and stirring was continued further for 90 minutes at a gentle boil (until carbon dioxide ceased to be liberated). The mixture was cooled and treated with 100 ml of 2% hydrochloric acid, the benzene layer was separated, and the aqueous layer was extracted with three 150-ml portions of ether. The combined extract was washed with saturated sodium bicarbonate solution and with water; it was dried with magnesium sulfate. Solvents were distilled off, and the residue was vacuum-distilled. We obtained 14.68 g (51%) of diethyl 2-methyl-3-oxoheptanedioate, b.p. 99-100° (0 1 mm); n_D^{20} 1.4410; d_4^{20} 1.0642; found MR 60.62; calculated MR 60 79; ultraviolet spectrum: λ_{max} 255 mμ; ε 3610 (in heptane). Found: C 59.20; H 8.25%. $C_{12}H_{20}O_5$. Calculated: C 59.00; H 8.25%.

b) A solution of one mole of isopropylmagnesium bromide in 600 ml of dry tetrahydrofuran was added to a solution of 73.0 g of ethyl hydrogen methylmalonate in 150 ml of tetrahydrofuran over a period of 1 hour at 5-10°. The mixture was stirred for 30 minutes at room temperature and then for 30 minutes at 40-45°. The mixture was cooled to -5°, and with vigorous stirring 89 25 g of ethyl 4-(chlorocarbonyl)butyrate was added over a period of 90 minutes. The mixture was stirred further for two hours at room temperature and then for one hour at a gentle boil. Solvent was distilled off, and the residue was acidified with 1% hydrochloric acid and extracted with three 200-ml portions of ether, the combined ether extract was washed with sodium bicarbonate solution and with water, and was then dried with magnesium sulfate. Ether was driven off, and the liquid residue was vacuum-distilled. We obtained 86.0 g (71%) of diethyl 2-methyl-3-oxoheptanedioate; b.p. 100-101° (0.1 mm); n_D^{20} 1.4410; d_4^{20} 1.0645.

Diethyl 3-Hydroxy-2-methylheptanedioate (IV). a) A solution of 4.32 g of ethyl glutaraldehydate [11] and 13.58 g of ethyl 2-bromopropionate in 40 ml of dry benzene was added dropwise over a period of 45 minutes with vigorous stirring to 4.90 g of zinc turnings in 50 ml of benzene heated to the boil. The mixture was heated further at the boil for two hours, cooled, and treated with 5% sulfuric acid; the organic layer was separated, and the aqueous layer was extracted with three 75-ml portions of ether. The combined extract was washed with water and dried with magnesium sulfate. Solvents were distilled off, and vacuum distillation of the residue gave 2.29 g (31%) of diethyl 3-hydroxy-2-methylheptanedioate (IV); b.p. 112-114° (0.1 mm); n_D^{20} 1.4494; d_4^{20} 1.0638, found MR 62.20; calculated MR 62.45. By heating (IV) with hydrazine in methanol at 80° in a sealed tube for 16 hours we obtained a dihydrazide of m.p 148-149° (from absolute alcohol). Found: N 25.80%. $C_8H_{18}N_4O_3$. Calculated: N 25.69%.

b) 17.4 g of diethyl 2-methyl-3-oxoheptanedioate (VI) was hydrogenated in 150 ml of 95% alcohol over 1.0 g of W-2 Raney nickel in a rotating autoclave at 95°. The initial hydrogen pressure was 78 atm, and after 40 minutes it had fallen to 61 atm; no further absorption of hydrogen was observed. When the mixture was cool, catalyst was filtered off, alcohol was distilled off, and the liquid residue was vacuum-distilled. We obtained 16.85 g (95%) of diethyl 3-hydroxy-2-methylheptanedioate (IV), b.p. 110-111° (0.1 mm); n_D^{20} 1.4486, d_4^{20} 1.0630, found MR 62.16, calculated MR 62.45. Found: C 58.46; H 8.84%. $C_{12}H_{22}O_5$ Calculated: C 58.51; H 9.00%. Infrared spectrum: ν_{max} 1736, 3370, 3410, 3450 cm^{-1}.

The dihydrazide, prepared by the above-described method, had the same melting point as before, alone and in admixture with the sample obtained previously.

According to the results of thin-layer chromatography, the hydroxy diester and its dihydrazide were homogeneous substances On a plate carrying a bound layer of silica gel the hydroxy diester had Rƒ 0.35 in 1 : 4 ethyl acetate - hexane; on a plate carrying an unbound layer of alumina (development with ethyl acetate) it had Rƒ 0.76. The dihydrazide, on a plate carrying a bound layer of silica gel (development with methanol), had Rƒ 0.22.

Methyl Ester of the Lactone of 3-Hydroxy-2-methylheptanedioic Acid (V). 86.2 g of diethyl 3-hydroxy-2-methylheptanedioate (IV) was added with cooling to a solution of 46.2 g of potassium hydroxide in 350 ml of 80% alcohol. The mixture was heated for 6 hours at 45°, after which alcohol was vacuum-distilled off and the residue was dissolved in 300 ml of water. The aqueous solution was washed with ether, acidified with 5% hydrochloric acid, and extracted with four 200-ml portions of ether. The combined extract was washed with water and dried with magnesium sulfate. The viscous oily residue obtained after ether had been driven off (56.6 g) was treated with ethereal diazomethane. Ether was driven off, and the residue was vacuum-distilled. We obtained 46.2 g (72%) of the methyl ester of the lactone of 3-hydroxy-2-methylheptanedioic acid (V); b.p.94-95° (0.1 mm), n_D^{20} 1.4658, d_4^{20} 1.1153; found MR 44.70; calculated MR 44.87. Found: C 57.80; H 7.60%. $C_9H_{14}O_4$. Calculated: C 58.05; H 7.58% Heating of (V) with hydrazine in methanol at 80° in a sealed tube for 16 hours gave a dihydrazide of m.p. 149-150° (from absolute alcohol), undepressed by admixture of the dihydrazide prepared from (IV).

Triethyl 2,2,4-Pentanetricarboxylate (VIII). 210 g of triethyl 1,1,3-butanetricarboxylate (VII), prepared by the condensation of malonic ester with methyl methacrylate [12], was added to a solution of 17.9 g of sodium in 800 ml of absolute alcohol. The mixture was heated to 50-55°, and over a period of 90 minutes 142 g of methyl iodide was added with stirring; the mixture was then stirred at the boil for two hours, after which it became neutral Alcohol was distilled off, the residue was treated with 250 ml of water, and the reaction product was extracted with ether The combined ether extracts were washed with sodium thiosulfate solution and with water, and they were dried with magnesium sulfate. Ether was driven off, and the liquid residue was vacuum-distilled. We obtained 198 g (89%) of triethyl 2,2,4-pentanetricarboxylate (VIII); b.p. 112-114° (1.0 mm); n_D^{20} 1.4342 [8, 13, 14].

meso-2,4-Dimethylglutaric Anhydride (IX). By the hydrolysis and decarboxylation of triethyl 2,2,4-pentanetricarboxylate (VIII) with 70% sulfuric acid we obtained an 85% yield of a mixture of meso- and d, *l* -2,4-dimethylglutaric acids [13], and the mixture of meso- and d,*l*-2,4-dimethylglutaric anhydrides prepared from this was separated by crystallization from ethyl acetate [14]. The yield of meso-anhydride was 29%, calculated on the amount of (VIII) taken.

Ethyl Hydrogen meso-2,4-Dimethylglutarate. 71.0 g of meso-2,4-dimethylglutaric anhydride was heated with 32 ml of absolute alcohol at 100° for 5 hours Excess of alcohol was driven off, and the residue was vacuum-distilled We obtained 80.0 g (85%) of ethyl hydrogen meso-2,4-dimethylglutarate, b.p. 100-102° (0.4 mm), n_D^{20} 1.4350

Ethyl 4-(Chlorocarbonyl)-2-methylvalerate (X). 84.4 g of oxalyl chloride was added at 0° to 50.0 g of ethyl hydrogen meso-2,4-dimethylglutarate. The mixture was left at the same temperature for 3 hours and then overnight at room temperature. Excess of oxalyl chloride was then vacuum-distilled off, and by distillation of the residue we obtained 53.9 g (98%) of ethyl 4-(chlorocarbonyl)-2-methylvalerate (X), b.p. 56-57° (0.1 mm). Anilide, m.p. 73-74° (from a mixture of petroleum ether and diethyl ether). Found: C 68.31; H 7.92% $C_{15}H_{21}NO_3$. Calculated: C 68 41; H 8.04%

Diethyl 2,4,6-Trimethyl-3-oxoheptanedioate (XI). A solution of 0.98 mole of isopropylmagnesium bromide in 550 ml of dry tetrahydrofuran was added over a period of 1 hour with vigorous stirring at 5-10° to a solution of 71 5 g of ethyl hydrogen methylmalonate in 150 ml of dry tetrahydrofuran. The mixture was stirred for 30 minutes at room temperature and for 30 minutes at 40-45°. It was then cooled to 10-15°, and with vigorous stirring 100.7 g of ethyl 4-(chlorocarbonyl)-2-methylvalerate (X) was added over a period of 90 minutes; the mixture was then stirred for 2 hours at room temperature and for 1 hour at a gentle boil. Tetrahydrofuran was driven off, and the residue was acidified with 1% hydrochloric acid and extracted with three 200-ml portions of ether; the combined ether extracts were washed with saturated sodium bicarbonate solution and with water, and they were dried with magnesium sulfate. Ether was driven off, and the residue was vacuum-distilled. We obtained 90.8 g (68%) of diethyl 2,4,6-trimethyl-3-oxoheptanedioate (XI); b.p. 113-115° (0.2 mm); n_D^{20} 1.4408; d_4^{20} 1.0300; Found MR 69.81, calculated MR 70.17. Found: C 61.80; H 8.80%. $C_{14}H_{24}O_5$. Calculated: C 61.76; H 8.82%.

Diethyl 3-Hydroxy-2,4,6-trimethylheptanedioate (XII). a) 10.9 g of the keto diester (XI) was hydrogenated over Raney nickel under the above-described conditions. We obtained 7.2 g (66%) of diethyl 3-hydroxy-2,4,6-trimethylheptanedioate (XII); b.p. 99-100° (0.07 mm), n_D^{20} 1.4488; d_4^{20} 1.0304; found MR 71.38; calculated MR 71.68. Found: C 61.32; H 9.43%. $C_{14}H_{26}O_5$. Calculated: C 61.31; H 9.49%.

On hydrogenation of the keto diester (XI) over a chromium-nickel catalyst in 95% alcohol at 120° under an initial pressure of 140 atm, the yield of the hydroxy diester (XII) was 86%. According to the results of thin-layer chromatography the hydroxy diester (XII) consisted of a mixture of two substances: on a plate carrying a bound layer of silica gel (development with a 1 : 2 mixture of ethyl acetate and hexane) these had R_f 0.20 and 0.59; on a plate carrying an unbound layer of alumina (development with ethyl acetate) they had R_f 0.54 and 0.81.

By heating the hydroxy diester (XII) in methanol at 80° in a sealed tube for 16 hours we obtained a mixture of two dihydrazides (R_f 0.43 and 0.68 in chromatography on a plate carrying a bound layer of silica gel (development with methanol)).

b) In an atmosphere of nitrogen a solution of 45 mmoles of lithium triethoxyhydroaluminate in 100 ml of ether was added over a period of 90 minutes at -65° to a vigorously stirred solution of 10.90 g of the keto diester (XI) in 50 ml of dry ether. The mixture was stirred further at this temperature for 40 minutes, and the excess of lithium triethoxyhydroaluminate was then decomposed with acetone; at 0° the mixture was acidified with 1% hydrochloric acid and extracted with three 50-ml portions of ether. The combined ether extracts were washed with water and dried with magnesium sulfate. Ether was driven off, and the liquid residue was vacuum-distilled. We obtained 7.66 g (71%) of the hydroxy diester (XII); b.p. 102-104° (0.09 mm); n_D^{20} 1.4480; d_4^{20} 1.0308, found MR 71.25; calculated MR 71.68. Found: C 60.70; H 9.15%. $C_{14}H_{26}O_5$. Calculated: C 61.31; H 9.49%.

c) In an atmosphere of nitrogen a solution of 11 mmoles of lithium aluminum hydride in 25 ml of dry ether was added over a period of two hours at -65° to a vigorously stirred solution of 10.90 g of the keto diester (XI) in 50 ml of dry ether. The mixture was stirred at this temperature for 45 minutes, after which the excess of lithium aluminum hydride was decomposed with acetone. Then, at 0°, the mixture was acidifed with 1% hydrochloric acid and extracted with three 50-ml portions of ether. The combined ether extracts were washed with water and dried with magnesium sulfate. We obtained 5.23 g (48%) of the hydroxy diester (XII), b.p. 105-107° (0.1 mm); n_D^{20} 1.4480; d_4^{20} 1.0300; found MR 71.31; calculated MR 71.68.

Lactone of 3-Hydroxy-2,4,6-trimethylheptanedioic Acid (IIa, IIb, IIc, and II). a) 5.0 g of the hydroxy diester (XII) prepared by catalytic hydrogenation and 2.24 g of potassium hydroxide were dissolved in 20 ml of 80% alcohol The solution was left overnight at room temperature and then heated for three hours at 45°, after which alcohol was distilled off The residue was dissolved in 40 ml of water, and the solution was washed with ether to remove neutral products. The solution was acidified to pH 1 with 5% sulfuric acid, saturated with ammonium sulfate, and extracted with four 50-ml portions of ether. The combined ether extracts were washed with water and dried with magnesium sulfate. Ether was driven off, and we obtained 2.95 g of viscous residue, which, according to the results of chromatography on plates carrying bound layers of silica gel (solvent system – 1 : 1 ether-benzene), consisted of a mixture of two substances, R_f 0.09 and 0.62. The mixture was chromatographed on a column containing 300 g of ASM silica gel (development with a 4 · 5 mixture of ether and benzene), and 20-ml fractions were collected. Fractions IV-VIII contained a crystalline product, by the recrystallization of which from dipropyl ether we obtained 0.33 g [9 3% on the hydroxy diester (XII)] of the lactone of 3-hydroxy-2,4,6-trimethylheptanedioic acid (IIa), m.p. 122-123°. Found: C 60.07, H 7.84%. $C_{10}H_{16}O_4$. Calculated: C 59.99; H 8.05%. The methyl ester of the carboxy lactone (IIa) prepared by the action of ethereal diazomethane, had m.p. 72-73° (from hexane). Found: C 61.58, H 8.44% $C_{11}H_{18}O_4$ Calculated: C 61.68, H 8.41%.

Fractions XIII-XXI contained 1.28 g (35%) of the stereoisomeric carboxy lactone (IIb), m.p. 157-158° (from dipropyl ether). Found: C 59.88; H 8.06%. $C_{10}H_{16}O_4$. Calculated: C 59.99, H 8.06%. The methyl ester, prepared by the action of ethereal diazomethane, had m.p. 55-56° (from a mixture of hexane and ether). Found: C 61.61; H 8.41%. $C_{11}H_{18}O_4$. Calculated: C 61.68; H 8.41%.

Judging from the results of thin-layer chromatography, Fractions IX-XII contained a mixture of the carboxy lactones (IIa) and (IIb).

b) By the hydrolysis of 5.48 g of the hydroxy diester (XII) prepared by method (b), with 2.65 g of potassium hydroxide in 30 ml of 80% alcohol under conditions analogous to those described above we obtained 1.0 g (25%) of the crystalline carboxy lactone (IIc), m.p. 107-108° (from dipropyl ether). Found: C 60.08; H 8.13%. $C_{10}H_{16}O_4$. Calculated: C 59.99; H 8.05%.

c) By the hydrolysis of 4.8 g of the hydroxy diester (XII) prepared by reduction with lithium aluminum hydride with 2.15 g of potassium hydroxide in 20 ml of 80% alcohol under conditions analogous to those described above we obtained 3.18 g of an oily product, by the chromatography of which on a column containing 300 g of ASM silica gel (development with a 4 : 5 mixture of ether and benzene) we isolated 2.03 g (58%) of the carboxy lactone (II), m.p. 125-126° (from dipropyl ether). A mixture with the carboxy lactone (IIa) melted at 84-105° Found: C 60.28; H 8 16% $C_{10}H_{16}O_4$. Calculated: C 59 99; H 8.05%. Methyl ester, m.p. 73-74° (from a mixture of petroleum ether and diethyl ether). A mixture with the methyl ester of the carboxy lactone (IIa) had m.p. 54-62° Found: C 61.84; H 8 56%. $C_{11}H_{18}O_4$. Calculated: C 61.68; H 8.41%.

Resolution of the Lactone of 3-Hydroxy-2,4,6-trimethylheptanedioic Acid (II). 0.38 g of the carboxy lactone (II) was added to a suspension of 0.36 g of D-threo-1-p-nitrophenyl-2-amino-1,3-propanediol in 20 ml of boiling ethyl acetate The homogeneous mixture was left overnight at room temperature. The crystals that were precipitated

(0.52 g) were filtered off and crystallized three times from a mixture of ethyl acetate and butanone. The salt obtained (0.25 g), which had m.p. 128-129° and $[\alpha]^{21}_{D}$-50° (c 1.674; alcohol), was dissolved in 5 ml of water, the solution was acidified to pH 1 with 1% hydrochloric acid and extracted with five 10-ml portions of ether. The combined extract was dried with magnesium sulfate. Ether was driven off, and two crystallizations of the residue from dipropyl ether gave the levorotatory carboxy lactone (*l*-II), m.p. 125-126°, $[\alpha]^{22}_{D}$ - 32° (c 5.26; chloroform).

We thank Prof. Djerassi, who kindly agreed to make a comparison of preparations and provided us with the infrared spectral curve of the methyl ester of the carboxy lactone (d-II).

SUMMARY

1. The synthesis was carried out of all four possible stereoisomeric lactones of 3-hydroxy-2,4,6-trimethylheptanedioic acid having cis-disposition of the methyl groups in the lactone ring.

2. One of the lactones obtained is the racemate of the product of the oxidative cleavage of methymycin, neomethymycin, picromycin, and narbomycin.

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