

SYNTHESIS OF γ -MONOLACTONES OF 2,7-DIALKYL-2,7-DIAMINO-4-HYDROXYOCTANE-1,8-DIOIC ACIDS AND THEIR 4-METHYL-SUBSTITUTED DERIVATIVES

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γ -Monolactones of 2,7-dialkyl-2,7-diamino-4-hydroxyoctane-1,8-dioic acids and their 4-methyl-substituted derivatives were synthesized by the Gabriel reaction from the appropriate α, α' -dichlorolactone esters, which are formed by cyclization (catalytically with H_2SO_4 or thermally) of 2,7-dialkyl-2,7-dichloro-4-octene-1,8-dioic acids or their 4-methyl-substituted derivatives and subsequent esterification of the acid grouping.

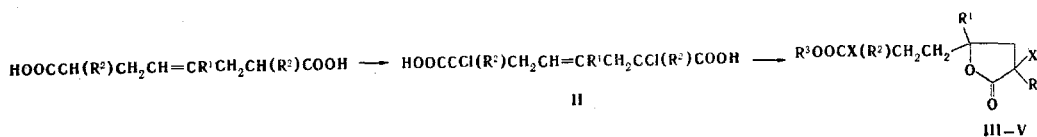
We have previously shown the possibility of the synthesis of unsaturated mono- and diamino dicarboxylic acids from 2,7-dialkyl-4-octene-1,8-dioic acids or their 4-methyl-substituted derivatives (I). In the present communication we describe the synthesis of α -amino acids containing, along with other substituents, a γ -lactone grouping, which is of physiological interest; the proposed method is very convenient from a preparative point of view and makes it possible to vary the substituents in both the lactone ring and the straight chain.

Starting acids I were converted to the dichlorides, which were chlorinated with PCl_5 in the α and α' positions and treated with water to give 2,7-dialkyl-2,7-dichloro-4-octene-1,8-dioic acids (II).

Spectroscopic kinetic studies of 20-70°C in carbon disulfide showed that the acid obtained is practically only the trans isomer. The intensity of the vibrations at 970 cm^{-1} decreases as the temperature is raised, and a peak at 720 cm^{-1} , which corresponds to the cis isomer, appears. Bands were also observed at 1710 cm^{-1} (C=O) and at $3100\text{--}3400$ (OH) cm^{-1} . The presence of a double bond was demonstrated by the iodine number by the Gorbach micromethod [1].

Acids II are readily converted thermally (by heating to 240-250°) or catalytically (by heating to 100° in the presence of catalytic amounts of sulfuric acid) to 4-hydroxyoctane-1,8-dioic acid lactones and their 4-methyl-substituted derivatives (III). The monocations of III obtained by both cyclization methods are identical with respect to their physicochemical constants and the results of thin-layer chromatography (TLC) on aluminum oxide. Vibrations of acid and γ -lactone carbonyl groups at 1710 and 1780 cm^{-1} , as well as at $1050\text{--}1200$ (C-O-C) and $3100\text{--}3400$ (OH) cm^{-1} , are observed in their IR spectra. Diacids II display basicities of 2, whereas lactone acids III have basicities of only 1 (in the cold); however, III display basicities of 2 when they are refluxed with an alkali solution, and it is known that the lactone ring opens up only when such compounds are refluxed in the presence of an alkali solution [2].

Lactone acids III readily form the corresponding ethyl esters IV in good yields; the individuality of IV was verified by gas-liquid chromatography (GLC). Vibrations at 1745 (ester) and 1780 (lactone) cm^{-1}



I-III a $R^1=H, R^2=C_2H_5$; b $R^1=H, R^2=C_4H_9$; c $R^1=CH_3, R^2=C_2H_5$; d $R^1=CH_3, R^2=C_2H_5$;
e $R^1=CH_3, R^2=C_4H_9$; IV-V a $R^1=H, R^2=C_2H_5$; b $R^1=CH_3, R^2=C_2H_5$; c $R^1=CH_3, R^2=C_2H_5$;
= C_4H_9 ; III X=Cl, $R^3=H$; IV X=Cl, $R^3=C_2H_5$; V X= $NH_2 \cdot HCl$, $R^3=H$

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TABLE 1. Physical Constants and Yields of the Products

Compound	bp, °C (mm)	d_4^{20}	n_D^{20}	M_{R_D}		Found, %				Empirical formula	Calc., %				Yield, %
				found	calc.	C	H	Cl	N		C	H	Cl	N	
IIa	217—219 (1)	1.2605	1.5020	69.53	69.97	48.7	6.2	23.7	—	C ₁₂ H ₁₈ Cl ₂ O ₄	48.5	6.1	23.9	—	72
IIb	225—226 (2)	1.1507	1.4910	88.84	88.45	54.2	7.5	19.9	—	C ₁₆ H ₂₆ Cl ₂ O ₄	54.4	7.4	20.1	—	68
IIc	227—228 (3)	1.2319	1.5000	74.24	74.59	50.3	6.3	21.7	—	C ₁₃ H ₂₀ Cl ₂ O ₄	50.2	6.4	22.8	—	64
IId	230—232 (2)	1.1856	1.4958	83.49	83.83	52.8	7.2	21.1	—	C ₁₅ H ₂₄ Cl ₂ O ₄	53.1	7.1	21.0	—	68
IIe	235—237 (2)	1.1400	1.4900	93.06	93.06	55.8	7.9	19.2	—	C ₁₇ H ₂₈ Cl ₂ O ₄	55.6	7.6	19.3	—	71
IIIa	208—210 (2)	1.2680	1.4930	68.06	68.36	48.3	6.2	23.7	—	C ₁₂ H ₁₈ Cl ₂ O ₄	48.5	6.1	23.9	—	88
IIIb	214—215 (2)	1.1590	1.4810	86.68	86.86	54.4	7.2	20.3	—	C ₁₆ H ₂₆ Cl ₂ O ₄	54.4	7.4	20.1	—	90
IIIc	215—216 (2)	1.2356	1.4880	72.54	72.98	49.8	6.3	22.7	—	C ₁₃ H ₂₀ Cl ₂ O ₄	50.2	6.1	22.8	—	87
IIId	219—221 (2)	1.1895	1.4855	81.74	82.22	53.3	6.9	20.9	—	C ₁₅ H ₂₄ Cl ₂ O ₄	53.1	7.1	20.9	—	84
IIe	222—224 (2)	1.1470	1.4825	91.28	91.46	55.5	7.8	19.6	—	C ₁₇ H ₂₈ Cl ₂ O ₄	55.6	7.6	19.3	—	89
IVa	186—188 (2)	1.2018	1.4830	77.06	77.72	51.6	6.9	21.3	—	C ₁₄ H ₂₂ Cl ₂ O ₄	51.7	6.8	21.5	—	87
IVb	172—173 (2)	1.1756	1.4801	81.92	82.34	53.3	6.8	20.8	—	C ₁₅ H ₂₄ Cl ₂ O ₄	53.1	7.1	20.9	—	85
IVc	180—181 (2)	1.1384	1.4781	91.25	91.58	55.7	7.6	19.1	—	C ₁₇ H ₂₈ Cl ₂ O ₄	55.6	7.6	19.3	—	82
Va	122—124*	—	—	—	—	43.2	7.4	21.2	8.6	C ₁₂ H ₂₂ N ₂ O ₄ · · 2HCl	43.5	7.3	21.4	8.4	70
Vb	70—72*	—	—	—	—	45.5	7.7	20.4	8.3	C ₁₃ H ₂₄ N ₂ O ₄ · · 2HCl	45.2	7.5	20.6	8.1	61
Vc	98—100*	—	—	—	—	48.4	7.9	19.3	7.3	C ₁₅ H ₂₈ N ₂ O ₄ · · 2HCl	48.2	8.0	19.0	7.5	58

*These are the melting points.

are observed in their IR spectra. Esters IV give phthalimide derivatives, the acid hydrolysis of which without additional purification leads to the γ -monolactones of 2,7-dialkyl-2,7-diamino-4-hydroxyoctane-1,8-dioic acids or their 4-methyl-substituted derivatives V, in the IR spectra of which absorption bands are observed at 1600 (NH_3), 1706 (COOH), and 1760 (lactone) cm^{-1} , as well as a C—OH deformation vibration at 1250 cm^{-1} .

EXPERIMENTAL

2,7-Dialkyl-2,7-dichloro-4-octene-1,8-dioic Acids and Their 4-Methyl Derivatives (IIa-e). A mixture of 0.01 mole of acid I, 30 ml of absolute benzene, and 0.03 mole of thionyl chloride was heated on a water bath for 1–2 h, after which the benzene and excess thionyl chloride were removed by distillation, and the residue was fractionated. A mixture of 0.01 mole of the dichloride and 0.02 mole of phosphorus pentachloride was heated at 140° for 4 h (until HCl evolution ceased), after which the PCl_3 was removed by distillation, and the residue was treated with water. The organic layer was separated, and the aqueous layer was extracted with ether. The ether extracts were added to the chief product, and the mixture was dried with anhydrous magnesium sulfate. The ether was removed by distillation, and the residue was fractionated. The physical constants of the dichloro acids are presented in Table 1.

The individuality of acids II was verified by TLC on aluminum oxide and silica gel in a benzene–carbon tetrachloride–methanol–acetic acid system (4:4:1.5:1) with development by iodine. Compounds IIa and IIc had R_f values of 0.45 and 0.43, respectively. Iodine numbers of 85.52 and 81.97 (calculated values 85.15 and 81.54), respectively, were found for IIa and IIc.

2,7-Dialkyl-2,7-dichloro-4-hydroxyoctane-1,8-dioic Acid γ -Monolactones and Their 4-Methyl-Substituted Derivatives (IIIa-e). A) A mixture of 0.01 mole of acid II, 30 ml of sulfuric acid (sp. gr. 1.61) was heated at 50–60° for ~ 6 h, after which it was cooled, partially neutralized with potassium carbonate solution until it was weakly acidic, and extracted with ether. The ether extracts were dried with anhydrous magnesium sulfate, the ether was removed by distillation, and the residue was vacuum fractionated. The physical constants of lactone acids III are presented in Table 1.

B) A mixture of 0.01 mole of acid II was heated in vacuo (water aspirator) at 220–230° for 2–3 h, after which the residue was vacuum fractionated. The physical constants of the lactone acids III obtained by methods

A and B were identical. The yields were also close to one another.

Thin-layer chromatography on aluminum oxide in benzene-methanol-acetic acid (3:1:0.5) gave one spot in each case with R_f 0.74 (IIIa) and 0.75 (IIIb).

Ethyl Esters of 2,7-Dialkyl-2,7-dichloro-4-hydroxyoctane-1,8-dioic Acid γ -Monolactones and Their 4-Methyl-Substituted Derivatives (IVa-c). A mixture of 0.02 mole of the lactone acid (IIIa,c,d), 30 ml of dry benzene, and 0.02 mole of thionyl chloride was heated on a water bath for 2-3 h, after which it was cooled, 20 ml of absolute alcohol was added to the crude acid chloride, and the mixture was heated for 4 h. The excess alcohol was removed by distillation, and the residue was fractionated. The physical constants of the esters of lactone acids IV are presented in Table 1. Gas-liquid chromatography was carried out with an LKhM-8MD chromatograph with a catharometer and a 2000 by 4 mm steel analytical column filled with 15% DMF on Chromosorb-6. The separation temperature was 290°, and the carrier-gas (helium) flow rate was 70 ml/min.

2,7-Dialkyl-2,7-diamino-4-hydroxyoctane-1,8-dioic Acid γ -Monolactone Hydrochlorides and Their 4-Methyl-Substituted Derivatives (Va-c). A mixture of 0.01 mole of ester IVa-c, 0.02 mole of potassium phthalimide, and 40-50 ml of dry dimethylformamide (DMF) was heated at 90-110° for 10 h, after which it was cooled and filtered, and the DMF was removed by distillation. The phthalimide derivative was dissolved in chloroform, the precipitate was removed by filtration, and the chloroform was removed from the filtrate by distillation. The residue was hydrolyzed with a mixture of hydrochloric and acetic acid by heating for 10 h. The aqueous layer was evaporated, and the residual hydrochloride was washed and dried. The physical constants and other data for Va-c are presented in Table 1.

The individuality of acids V was monitored by paper chromatography. The chromatograms were developed with a 0.1% solution of ninhydrin in a 95% solution of acetone; Va had R_f 0.44 in a butanol-acetic acid-water system (15:3:7).

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