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The dimethyl ester of 4-ketododecanedioic acid (I) is used as an intermediate in the total synthesis of prostaglandins [1].

In a search for a rational method of obtaining (I), in the present paper we studied its synthesis by the bromination of the methyl ester of 9-ketodecanoic acid (IIb), the alkylation of Meldrum's acid (V) with the methyl ester of 9-keto-10-bromodecanoic acid (IIIb), the hydrolytic cleavage and decarboxylation of the intermediate 2,2-dimethyl-4,6-dioxo-5-(2-oxo-9-carbomethoxynonyl)-1,3-dioxane (VIIb), and the esterification of 4-ketododecanedioic acid (VIIId).



The development of the conditions for the monoalkylation of (V) was initially run on the model examples of p-bromophenacyl bromide (VI) and 1-bromo-2-octanone (IIIa). It proved that the monoalkylation of (V) by bromide (VI) can be realized in $\sim70\%$, provided the reaction is run in aqueous DMF in the presence of KOH and Et₄N⁺I⁻ (TAI) and excess (V) is used. The structure of the thus formed 2,2-dimethyl-4,6-dioxo-5-(p-bromophenacyl)-1,3-dioxane (VIIc) was confirmed by the PMR spectrum (see Experimental) and the hydrolytic cleavage of (VIIc) by aqueous AcOH to β -(p-bromobenzoyl)propionic acid (VIIIc) [2].

The starting bromoketone (IIIa), as a mixture with the isomeric bromoketone (IVa), was synthesized by us by the bromination of 2-octanone (IIa) with bromine in methanol as described in [3]. It was shown by special experiment that 3-bromo-2-octanone (IVa), obtained by the bromination of (IIa) in AcOH, practically does not react with (V) under the above indicated conditions. Consequently, it seemed possible to use the unseparated mixture of isomeric bromoketones (IIIa) and (IVa) in the alkylation reaction with excess (V) and obtain the desired monoalkylation product (VIIa), which without additional purification was subjected to hydrolytic cleavage with aqueous AcOH. 4-Ketodecanoic acid (VIIIa) was isolated as a result of these transformations, which was identified by comparing with an authentic sample [4].

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The bromination of methyl ester (IIb) with Br_2 in MeOH as described in [3] gave a mixture of the methyl esters of the bromoketo acids (IIIb) and (IVb), which was used as such in the reaction with excess (V). The alkylation, run in aqueous DMF in the presence of KOH and TAI, led to the 1,3-dioxane derivative (VIIb). The hydrolytic cleavage of the (VIIb) ring with aqueous AcOH and subsequent hydrolysis of the intermediate monoester (VIIIb) with hydrochloric acid permitted obtaining keto diacid (VIIId) in an overall yield of 18% when based on starting keto ester (IIb). In the final step of the synthesis the treatment of keto diacid (VIIId) with a mixture of MeOH and BF_3 etherate converted it to the sought diester (I), which was identified by comparing with an authentic sample [1].

EXPERIMENTAL

The IR spectra were taken as KBr pellets on a UR-20 instrument, and the PMR spectra were taken on a Varian DA-60-IL instrument.

2,2-Dimethyl-4,6-dioxo-5-(p-bromophenacyl)-1,3-dioxane (VIIc). To a solution of 0.6 g of KOH in 2 ml of water were successively added with stirring, 2 g of (V), 8 ml of DMF, 0.2 g of Et₄N⁺I⁻ (TAI), and 1.4 g of p-bromophenacyl bromide (VI), after which the mixture was stirred for another 48 h at 20°C, diluted with water, treated with excess K_2CO_3 , and filtered. The mother liquor was acidified with dilute HCl solution, and the precipitate was filtered and dried in the air to give 1.3 g (72%) of (VIIc), mp 148-149° (from alcohol). PMR spectrum (C_5D_5N , δ , ppm): 1.72 s (2CH₃), 4.15 s (CH₂), 7.50 d and 7.89 d (aromatic ring). Found: C 49.19; H 3.85; Br 23.49%. C₁₄H₁₂BrO₅. Calculated: C 49.43; H 3.56; Br 23.49%. When the reaction of bromide (VI) was run with an equivalent amount of (V) the yield of (VIIc) was 54%.

 β -(p-Bromobenzoyl)propionic acid (VIIIc). A mixture of 1.3 g of (VIIc), 3 ml of water, and 9 ml of AcOH was heated for 5 h at 90-100°, cooled to 20°, diluted with water, and the precipitate was filtered and dried in the air to give 0.8 g (82%) of (VIIIc), mp 148-148.5° [2]. PMR spectrum (C₅D₅N, δ , ppm): 2.84 t (CH₂COOH), 3.26 t, (CH₂CO), 7.44 d and 7.80 d (aromatic ring).

<u>3-Bromo-2-octanone (IVa).</u> To 14 g of 2-octanone (IIa) in 40 ml of AcOH was gradually added with stirring, 5.2 ml of Br₂, and the mixture was kept for 24 h at 20°, diluted with water, and extracted with CH_2Cl_2 . The extract was washed with NaHCO₃ solution and dried over Na₂SO₄. Then the solvent was removed and the residue was vacuum-distilled to give 12 g (53%) of (IVa), bp 155-160° (20 mm). PMR spectrum (CCl₄, δ , ppm): 0.85 m (CH₃), 1.28 m ((CH₂)₄), 2.22 s (CH₃CO), 4.10 m (CH). Found: C 46.02; H 7.10; Br 39.10%. C₈H₁₅BrO. Calculated: C 46.43; H 7.25; Br 38.65%.

<u>Mixture of 1-bromo-2-octanone (IIIa) and 3-bromo-2-octanone (IVa)</u>. With stirring, to a solution of 4 g of 2-octanone (IIa) in 9 ml of MeOH was gradually added 1.5 ml of Br₂, and the mixture was kept for 2 h at $\sim 20^{\circ}$, diluted with water, stirred for 2 h at $\sim 20^{\circ}$, and extracted with CH₂Cl₂. The extract was washed with NaHCO₃ solution and dried over Na₂SO₄. Then the solvent was removed to give a mixture of bromoketones (IIIa) and (IVa) in an $\sim 1:1$ ratio. PMR spectrum (CCl₄, δ , ppm): 2.22 s (CH₃), 2.57 m (COCH₂), 3.76 s (BrCH₂CO), 4.15 m (COCHBr), and the ratio of the integral intensities was 3:2:2:1.

The obtained mixture of (IIIa) and (IVa) was used as such in the next step.

<u>4-Ketodecanoic acid (VIIIa)</u>. To a solution of 1.6 g of KOH in 4 ml of water were successively added with stirring, 3.6 g of (V), 20 ml of DMF, 0.3 g of TAI, and the above described mixture of bromoketones (IIIa) and (IVa), and the mixture was stirred for 48 h at 20° , diluted with water, treated with excess K_2CO_3 , and filtered. The filtrate was acidified with dilute HCl solution and extracted with benzene. The extract was dried over Na_2SO_4 and then evaporated to give 2.4 g of the oily alkylation product (VIIIa), which was used as such in the next step.

The obtained alkylation product (VIIa) was mixed with 10 ml of AcOH and 3 ml of water, and the mixture was refluxed for 4 h, diluted with water, and extracted with benzene. The extract was dried over Na₂SO₄ and then evaporated to give 1 g of (VIIIa) (17% when based on (IIa)), mp 67-68° (from ether at -50°) [4]. PMR spectrum (CD₃OD, δ , ppm): 0.82 t (CH₃), 1.02-1.70 m (CH₂CH₂CH₂CH₂), 2.22-2.78 m (CH₂CO, CH₂COOH).

Mixture of Methyl Esters of 8-Bromo- and 10-Bromo-9-ketodecanoic Acids (IIIb) and (IVb). To a solution of 3 g of the Me ester of 9-ketodecanoic acid (IIb) [5] in 15 ml of MeOH was gradually added with stirring 2.4 g of Br₂, and the mixture was kept for 1 h at $\sim 20^{\circ}$, diluted with water, stirred for another hour at $\sim 20^{\circ}$, and extracted with benzene. The extract was washed with NaHCO₃ solution, dried over Na₂SO₄, and evaporated to give an oily mixture of bromides (IIIb) and (IVb) in a 1:1 ratio. PMR spectrum (CCl₄, δ , ppm): 2.56 m (COCH₂), 3.76 s (BrCH₂CO), 4.08 m (COCHBr), and the ratio of the integral intensities was $\sim 2:2:1$. The obtained mixture was used as such in the next step.

<u>4-Ketododecanedioic acid (VIIId)</u>. To a solution of 2.4 g of KOH in 7 ml of water were successively added with stirring, 7.2 g of (V), 17 ml of DMF, 1 g of TAI, and the above described mixture of bromides (IIIb) and (IVb), and the mixture was stirred for 48 h at 20°. The reaction mixture was worked up as indicated above to give 3.5 g of oily alkylation product (VIIb), which was mixed with 20 ml of AcOH and 5 ml of water, and the mixture was refluxed for 4 h, 2 ml of concentrated HCl was added, and the mixture was refluxed for another 4 h, diluted with water, and extracted with EA. The extract was dried over Na₂SO₄ and evaporated. The residue was treated with ether, and the precipitate was filtered, washed with ether, and dried in the air to give 0.7 g (18%) of (VIIId), mp 109-111° (from EA) [6]. PMR spectrum (CD₃OD, δ , ppm): 1.20 m ((CH₂)₅), 1.98-2.68 m (2CH₂CO, 2CH₂COOH).

Dimethyl Ester of 4-Ketododecanedioic Acid (I). To a solution of 0.5 g of (VIIId) in 5 ml of MeOH was gradually added with stirring, 1 ml of BF₃ etherate, and the mixture was kept for 4 days at 20°, diluted with water, and the precipitate was filtered and dried in the air to give 0.35 g (62%) of (I), mp 35-36° (from ether at -50°) [1]. Infrared spectrum (ν , cm⁻¹): 1705 (CO), 1730 (COOCH₃). PMR spectrum (CCl₄, δ , ppm): 1.25 m and 1.52 m ((CH₂)₅), 1.98-2.68 m (2CH₂CO, 2CH₂COOCH₃), 3.53 s and 3.55 s (2CH₃O).

CONCLUSIONS

The dimethyl ester of 4-ketododecanedioic acid was synthesized by alkylating the K salt of Meldrum's acid with the methyl ester of 9-keto-10-bromodecanoic acid, hydrolytic cleavage of the alkylation product, and esterification of the intermediate 4-ketododecanedioic acid.

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