UNSATURATED ACIDS AND MACROCYCLIC LACTONES

COMMUNICATION 13. NEW METHOD FOR THE SYNTHESIS OF A 1,5-HEXADIENE SYSTEM*

(UDC 541.63)

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Substances containing the 1,5-hexadienylene group $-CH = CH(CH_2)_2CH = CH-have been discovered in nat$ ural products on several occasions. Thus, the leaves of the violet contain 2,6-nonadienal [1], and the correspondingalcohol is one of the aromatic principles of the flower of the violet [2]. The 1,5-hexadiene structure is found alsoin the isobutylamides of some polyenic acids isolated from <u>Anacyclus pyrethrum</u>, <u>Heliopsis logipes</u>, and other plants[3]. Finally, in the fats from a number of marine animals polyenic acids have been found which give succinic acidon oxidation with potassium permanganate or on oxidative ozonolysis. From this, it has been concluded that the hydrolyzates of these fats contain polyenic acids in which double bonds are separated by two methylene groups [4, 5].In particular, acids considered to be of the 1,5-hexadiene type are the hexadecatrienoic and eicosatetraenoic acidsfrom sardine fat, the docosapentaenoic and docosahexaenoic acids from mackerel fat, and some of the other fish-oilacids [6-8]. However, recent detailed studies of polyenic acids isolated from various natural sources have shownthat at least part of the so-called 1,5-hexadienic acids actually have a 1,4-pentadiene structure [9]. A substantialargument in the assignment of a natural unconjugated polyenic acid to the 1,4-pentadiene series is its behaviortoward hot caustic alkali solution, for it is known that 1,4-pentadienic acids are readily converted under these conditions into isomers having conjugated double bonds.

In the further investigation of the synthesis of unsaturated acids of different types [10-13] we have developed a new stereospecific way of building up a cis-cis-1,5-hexadiene system in accordance with the following scheme:

$$CH_{3}CH_{2}CHO + Ph_{3}P = CH (CH_{2})_{3}OAc^{\neg} \rightarrow CH_{3}CH_{2}CH \stackrel{Cis}{=} CH (CH_{2})_{3}OAc \stackrel{OH^{-}}{\longrightarrow} CH_{3}CH_{2}CH = PPh_{3} + OCH (CH_{2})_{3}OAc_{-} \rightarrow (I)$$

$$\rightarrow CH_{3}CH_{2}CH \stackrel{Cis}{=} CH (CH_{2})_{3}OH \stackrel{PBr_{3}}{\longrightarrow} CH_{3}CH_{2}CH \stackrel{Cis}{=} CH (CH_{2})_{3}Br \stackrel{Ph_{3}P}{\longrightarrow} (III) \qquad (III)$$

$$\rightarrow [CH_{3}CH_{2}CH \stackrel{Cis}{=} CH (CH_{2})_{3}PPh_{3}]^{+}Br^{-} \stackrel{MeONa}{\longrightarrow} CH_{3}CH_{2}CH \stackrel{Cis}{=} CH (CH_{2})_{2}CH = PPh_{3} \rightarrow (IV) \qquad (V)$$

$$\stackrel{OHC(CH_{2})_{7}COOEt}{\longrightarrow} CH_{3}CH_{2}CH \stackrel{Cis}{=} CH (CH_{2})_{2}CH \stackrel{Cis}{=} CH (CH_{2})_{7}COOEt (VI)$$

The main starting compound was the readily accessible 4-bromo-1-butanol acetic ester [14]. With tripehnylphosphine this acetoxy bromide gives a phosphonium salt, which, by treatment with sodium methoxide, is readily converted into (4-acetoxybutylidene)triphenylphosphorane. Condensation of the latter with propionaldehyde under conditions ensuring the maximum yield of the cis isomer [10] led to the unsaturated acetic ester (I), which, without purification, was subjected to alkaline hydrolysis. The infrared spectrum of the then formed 4-hepten-1-ol (II) contains a band of medium strength at about 720 cm⁻¹ characteristic for the cis -CH = CH -grouping [15] and only a very

^{*}Communication 6 of the Series "Stereoregular Synthesis of Unsaturated Compounds". For preceding communication see [13].

weak band at about 980 cm⁻¹, which enables us to conclude that the compound obtained contained less than 10% of trans isomer. A mixture of stereoisomers of about the same composition was obtained also as a result of the condensation of triphenylpropylidenephosphorane with 4-acetoxybutyraldehyde obtained by the treatment of 4-bromo-1-butanol acetate with trimethylamine oxide [16]. The bromination of 4-hepten-1-ol (II) with phosphorus tribromide led to 7-bromo-3-heptene (III), and when heated with triphenylphosphine this formed the crystalline phosphonium salt (IV), which was found to be practically pure cis isomer (absence of absorption at 980 cm⁻¹). By treatment with sodium methoxide the phosphonium salt (IV) was converted into the corresponding phosphorane (V), which, on condensation with ethyl 8-formyloctanoate in dimethylformamide in presence of Br⁻[10],formed ethyl 9,13-hexa-decadienoate (VI). Judging from the infrared spectrum and gas-liquid chromatography the product contained mainly the cis-cis isomer;only a small amount of 9-trans-13-cis-hexadecadienoic ester was present.

Having synthesized the dienic ester (VI), we could make use of it in a study of the ozonolysis of the 1,5-hexadiene system and also confirm data in the literature [17] on the stability of the 1,5-hexadiene system in presence of caustic alkali. The oxidative ozonolysis of the dienic ester (VI) (in ethyl acetate at -40° with subsequent treatment with hydrogen peroxide at 20°) showed that the cleavage of 9,13-hexadecadienoic acid is not accompanied by the formation of by-products and leads only to propionic, succinic, and azelaic acids, which were identified as their methyl esters with the aid of gas-liquid chromatography. On the other hand, it was shown that when the dienic ester (VI) was heated with a 23% solution of potassium hydroxide in ethylene glycol at 180° for 15 min, no substances with selective absorption in the ultraviolet were formed. Hence, unlike the 1,4-pentadiene system, the 1,5-hexadiene system is not isomerized under severe alkaline conditions. Since the above-mentioned polyenic acids isolated from fish fats are readily isomerized by alkali with formation of conjugated polyenes [9], they obviously cannot be built entirely from 1,5-hexadienylene groups.

EXPERIMENTAL

<u>4-Acetoxybutyraldehyde</u>. 6.83 g of 4-bromo-1-butanol acetate [14] was added to a solution of 5.28 g of dry trimethylamine oxide in 25 ml of dry chloroform at such a rate that the reaction mixture boiled gently. When the spontaneous evolution of heat stopped, the mixture was boiled for 2 h, cooled, and then washed successively with 2 N HCl, 5% sodium bicarbonate solution, and water. Chloroform was driven off, and the residue was vacuum-distilled. We obtained 2.15 g (47%) of a 4-acetoxybutyraldehyde; b.p. 90-91° (13 mm); nD²⁰ 1.4268; d₄²⁰ 1.0612. Found MR 31.47; calculated MR 31.57.

(4-Acetoxybutyl)triphenylphosphonium Bromide. A mixture of 19.51 g of 4-bromo-1-butanol acetate, 26.2 g of triphenylphosphine, and 15 ml of benzene was heated for 14 h at 130°. The reaction mixture was cooled and diluted with ether, and the sirupy phosphonium salt was washed with ether and vacuum-dried; yield 44.1 g (96.5%). Found: Br 17.29%. $C_{24}H_{26}BrO_2P$. Calculated: Br 17.47%.

<u>cis-4-Hepten-1-ol (II).</u> From (4-acetoxybutyl)triphenylphosphonium bromide and propionaldehyde: A solution of 44.1 g of (4-acetoxybutyl)triphenylphosphonium bromide in 50 ml of dimethylformamide was added to 0.072 mole of dry sodium methoxide, and the reaction mixture was stirred for 2 h at room temperature; it was then cooled to 0°, 2.81 g of freshly distilled propionaldehyde was added, and the mixture was left overnight. On the next day the mixture was diluted with 150 ml of water, and it was then extracted for 12 h with low-boiling petroleum ether in a continuous-extraction apparatus. The extract was evaporated, and the residue was shaken with 30 ml of a 5% solution of sodium hydroxide in 80% methanol; the aqueous solution was again subjected to continuous extraction with low-boiling petroleum ether for 6 h. The extract was dried with anhydrous magnesium sulfate, evaporated, and vacuum-fractionated. We obtained 1.54 g (28%) of 4-hepten-1-ol; b.p. 78-79° (15 mm); n_D20 1.4467; d₄20 0.8445. Found: C 73.54; H 12.39%. MR 36.11. C₇H₁₄O. Calculated: C 73.63; H 12.36%; MR 35.58.

From triphenylpropylphosphonium bromide and 4-acetoxybutyraldehyde: A solution of 1.44 g of 4-acetoxybutyraldehyde in 10 ml of dimethylformamide was added in the course of 30 min with cooling to a dimethylformamide solution of triphenylpropylidenephosphorane prepared from 0.017 mole of dry sodium methoxide, 8.47 g of triphenylpropylphosphonium bromide, and 30 ml of dimethylformamide. The reaction mixture was left for 12 h at room temperature, diluted with water, and treated as in the preceding experiment. The yield of 4-hepten-1-ol was 0.35 g (30%); nD²⁰ 1.4465; d₄²⁰ 0.8443.

<u>cis-4-Heptenyltriphenylphosphonium Bromide (IV)</u>. 0.3 ml of pyridine was added to a solution of 1.03 g of 4-hepten-1-ol in 15 ml of dry ether, and then, at $0-2^\circ$, 0.92 g of phosphorus tribromide was added. The reaction mixture waskept at room temperature for 24 h, diluted with water, and extracted with ether. The extract was washed

with 5% sodium bicarbonate solution and water and was dried with anhydrous magnesium sulfate; solvent was cautiously distilled off through a small column. The residue was mixed with 3 g of triphenylphosphine, and the mixture was heated for 15 h at 130° with an efficient reflux condenser. The phosphonium salt, which crystallized on cooling, was rubbed out with dry ether, filtered off, washed with the same solvent, and vacuum-dried. Yield 1.59 g (40%); m.p. 173-174°. Found: C 68.44; H 6.42; Br 18.21; P 7.05%. C₂₅H₂₈BrP. Calculated: C 68.33; H 6.43; Br 18.19; P 7.05%.

Ethyl 9,13-Hexadecadienoate (VI). 2.78 g of 4-heptenyltriphenylphosphonium bromide and 15 ml of dimethylformamide were added to 5 ml of dry sodium methoxide. The dark-red solution of the phosphorane was stirred for 2 h and then cooled to 0°; 0.8 g of ethyl 8-formyloctanoate in 5 ml of dimethylformamide was added, and the mixture was left for 24 h at room temperature. The mixture was then diluted with water and extracted with petroleum ether; the extract was washed with water, dried with magnesium sulfate, evaporated, and chromatographed on 130 g of neutral alumina (activity III) in petroleum ether. The yield of ethyl 9,13-hexadecadienoate was 0.66 g (59%); b.p. 140° (1 mm)*; $n_D^{21.5}$ 1.4600; $d_4^{21.5}$ 0.8949. The substance did not absorb in the range 210-300 m μ . Found: C 77.11 H 11.40%, MR 85.83. C₁₈H₃₂O₂. Calculated: C 77.09; H 11.50%; MR 86.04.

SUMMARY

With the aid of a stereospecific modification of the Wittig reaction a new way of building up cis-cis 1,5-hexadiene systems was developed.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-tocover English translations appears at the back of this issue.

^{*} Temperature of bath.