UNSATURATED ACIDS AND MACROCYCLIC LACTONES

COMMUNICATION 11. TOTAL SYNTHESES OF cis-8-HEXADECENOIC, cis-11-HEXADECENOIC (PALMITOVACCENIC), cis-7-OCTADECENOIC, AND cis-9-HEXACOSENOIC ACIDS*

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We recently described a stereospecific modification of the Wittig reaction [2] which permitted the development of a new stereospecific method for the synthesis of natural cis-ethylenic fatty acids by the scheme:

$$CH_3(CH_2)_m CHO + \underset{(I)}{Ph_3P{=}CH(CH_2)_n COOR} \rightarrow \underset{(II)}{CH_3(CH_2)_m \overset{cis}{CH{=}CH}(CH_2)_n COOR} + Ph_3PO$$

By this method we synthesized cis-11-eicosenoic (II; $\underline{m}$ = 7, $\underline{n}$ = 9, R = H) and cetoleic (II; $\underline{m}$ = $\underline{n}$ = 9, R = H) acids for the first time [3].

In further development of these investigations on synthesis, we have now carried out the total syntheses of some difficultly accessible acids that we required as reference compounds in the analysis of the acid fractions of natural lipids. Starting with octanal and ethyl 8-(triphenylphosphoranylidene)octanoate (I; $\underline{n}$ = 6, R = Et), we prepared cis-8-hexadecenoic acid (II; $\underline{m}$ = $\underline{n}$ = 6, R = H) for the first time. This acid has not been isolated previously in the pure state, but it has been proved that it is present in herring fat [4]. By the condensation of valeraldehyde with ethyl 11-(triphenylphosphoranylidene)undecanoate (I; $\underline{n}$ = 9, R = Et) we carried out the first total synthesis of palmitovaccenic acid (II; $\underline{m}$ = 3, $\underline{n}$ = 9, R = H), which was isolated some years ago from the lipids of streptococci [5]. The condensation of undecanal with ethyl 7-(triphenylphosphoranylide)-heptanoate (I; $\underline{n}$ = 5, R = Et) led to cis-7-octadecenoic acid (II; $\underline{m}$ = 9, $\underline{n}$ = 5, R = H). It has been shown recently that this acid, or possibly its trans isomer, is one of the products of lipid exchange in man [6], but it has not yet been isolated in the individual state.

As starting compounds for the preparation of the phosphoranes (I) we used 9-chlorononanoic and 11-chloroundecanoic acids [7] and also 8-chlorooctanoic acid, which we synthesized from the readily available 7-chloroheptanoic acid [7] by the Arndt-Eistert method. In the course of the investigation we improved the previously described procedure in the preparation of phosphoranes, using sodium methoxide for this purpose instead of the ethoxide, because the methoxide reacts more rapidly with phosphonium salts and enables us to obtain solutions of phosphoranes that are neutral to phenolphthalein. We also changed the method of isolating the acids (II), for it was found that the latter are readily separated from triphenylphosphine impurity by chromatography on silica gel.

We also worked out a new variant of the method of synthesizing unsaturated acids of the type (II; R = H), in which the latter are obtained by the condensation of alkylidenetriphenylphosphoranes (III) with ethyl ω-formylalkanoates (IV; R = Et).

* Communication 5 in the series "Stereoregular Synthesis of Unsaturated Compounds"; for preceding communication see [1].

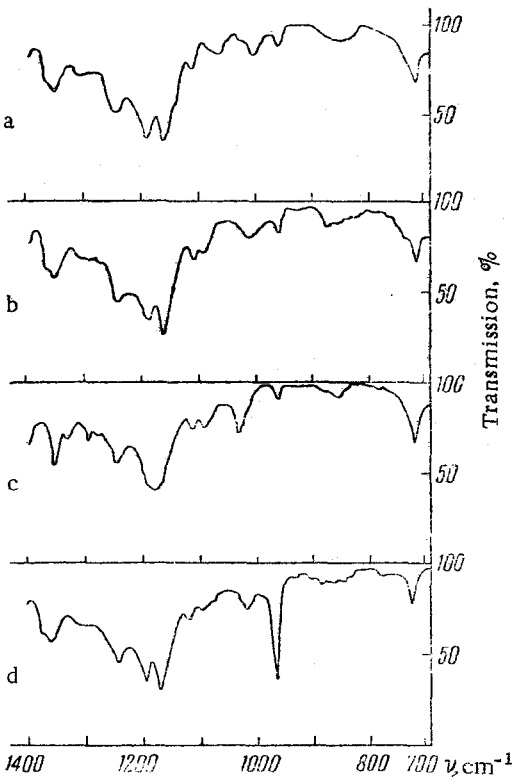
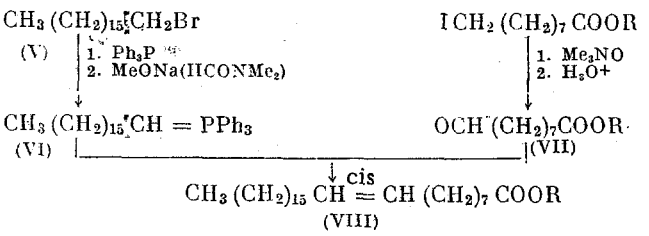


Fig. 1. Infrared spectra of the esters (II) in carbon disulfide at a concentration of 100 g/ml at a layer thickness of 0.104 mm: a) methyl cis-7-octadecenoate; b) methyl cis-11-hexadecenoate; c) ethyl cis-11-hexacosenoate; d) methyl elaidate.

$$\underset{\text{(III)}}{CH_3(CH_2)_m CH=PPh_3} + \underset{\text{(IV)}}{OCH(CH_2)_n COOR} \rightarrow \underset{\text{(II)}}{CH_3(CH_2)_m \overset{cis}{CH=CH}(CH_2)_n COOR} + Ph_3PO.$$

The modified method may be found useful for the preparation of higher acids of type (II) for which m > 11, for the higher alkyl bromides are usually more accessible than the corresponding aldehydes. We applied the new variant in the total synthesis of cis-9-hexacosenoic acid (VIII; R = H) in accordance with the scheme:



With the aid of the Borodin-Hunsdiecker reaction, from stearic acid we prepared heptadecyl bromide (V), which was then converted into the phosphorane (VI). Attempts to bring about the condensation of this with ethyl 8-formyloctanoate (VII) prepared by Rosenmund reduction of ethyl 8-(chlorocarbonyl)octanoate did not give satisfactory results because the product contained difficultly separable impurities which reacted with the phosphorane. Ethyl 8-formyloctanoate was therefore synthesized by the action of anhydrous trimethylamine oxide on ethyl 9-iodononanoate with subsequent acid hydrolysis [8]. This gave pure ethyl 8-formyloctanoate (VII), from which by condensation with the phosphorane (VI) and subsequent hydrolysis of the ester (VIII; R = Et) we obtained cis-9-hexacosenoic acid (VIII; R = H). This acid was earlier found in the acid fraction of the hydrolyzate of the lipids of the marine sponge Shpeciosponga vesparia, but was not isolated in the pure state [9].

The infrared spectra of the esters synthesized showed that they were almost pure cis isomers [3] (Fig. 1).

EXPERIMENTAL

8-Chlorooctanoic Acid. A mixture of 60 g of 7-chloroheptanoic acid and 72 ml of thionyl chloride in 70 ml of dry benzene was boiled for five hours. Solvent and excess of thionyl chloride were distilled off, and by vacuum distillation of the residue we isolated 60.7 g (89%) of 7-chloroheptanoyl chloride, b.p. 66-67° (0.4 mm). A solution of 35 g of this acid chloride in 100 ml of ether was added dropwise at 5° to a solution of diazomethane (from 75 g of methylnitrosourea) in 900 ml of ether; the mixture was stirred for one hour at 5° and then left overnight at room temperature. On the next day ether and excess of diazomethane were vacuum-distilled off, and the noncrystalline diazo ketone (38 g) that remained was dissolved in 500 ml of warm dioxane. This solution was added dropwise to a suspension of 23 g of freshly precipitated silver oxide and 37 g of sodium thiosulfate in 900 ml of water warmed to 80°. Stirring was continued for three hours at this temperature, after which the mixture was left overnight and the precipitate of silver was filtered off. The filtrate was acidified with concentrated nitric acid and extracted with four 100-ml portions of ether; the ether extract was washed with sodium carbonate solution, and the aqueous solution was acidified and again extracted with ether. The extract was dried with magnesium sulfate and solvent was distilled off. We obtained 11.2 g (33%) of 8-chlorooctanoic acid (b.p. 133-135° (1.5 mm); n_D^{20} 1.4581), which gradually solidified at 0°; m.p. 34.5-35° (from a 1 : 1 mixture of ether and heptane). Found: C 53.61; H 8.63%. $C_8H_{15}O_2Cl$. Calculated: C 53.78; H 8.46%.

Ethyl 8-Formyloctanoate. 200 ml of dry m-xylene was added to 12.0 g of trimethylamine oxide dihydrate, and the azeotropic mixture of xylene and water was quickly distilled off, after which the residue of solvent was removed in a vacuum. The anhydrous trimethylamine oxide was dissolved in 50 ml of dry chloroform, the solution was warmed slightly, and a chloroform solution of 0.05 mole of ethyl 9-iodononanoate, prepared from the corresponding ω-chloro ester [3], was added. The mixture was boiled for two hours, cooled, and treated successively with 2 N HCl, 5% sodium bicarbonate solution, and water. By distillation we isolated 4.83 g (48%) of ethyl 8-formyloctanoate; b.p. 100-105° (1.5 mm); n_D^{20} 1.4383; d_4^{24} 0.9604. 2,4-Dinitrophenylhydrazone: m.p. 62-63° (from alcohol). Found: N 14.65%. $C_{17}H_{24}O_6N_4$. Calculated: N 14.73%.

Heptadecyltriphenylphosphonium Bromide. A mixture of 20.3 g of heptadecyl bromide [10], 21 g of triphenylphosphine, and 10 ml of benzene was heated for 15 hours at 150°. When cool, the reaction mixture was treated with dry ether, and the crystalline phosphonium salt was filtered off, washed with ether, and vacuum-dried. After crystallization from a mixture of acetone and dry ether we obtained 34.6 g (94%) of heptadecyltriphenylphosphonium bromide, m.p. 88-91°. Found: C 72.36; H 8.82; P 5.63%. $C_{35}H_{50}BrP$. Calculated: C 72.27; H 8.68; P 5.33%.

Preparation of Unsaturated Acids of Type (II). a) A solution of 0.025 mole of the phosphonium salt in 40 ml of dry N,N-dimethylformamide was added rapidly to 0.02 mole of dry sodium methoxide in an atmosphere of nitrogen, and the mixture was stirred for one hour at room temperature. A solution of 0.015 mole of the aldehyde in 10 ml of N,N-dimethylformamide was added to the orange-red solution of the phosphorane with cooling, stirring was continued for 2-3-hours, and the mixture was left overnight at room temperature. On the next day the mixture was diluted with water and extracted with hexane. The evaporated extract was subjected to alkaline hydrolysis under the previously described conditions [3], and the unsaturated acid (II) was chromatographed on KSK silica gel (40-70 mesh, column 500 × 15 mm); the triphenylphosphine impurity was eluted with hexane, and the unsaturated acid was eluted with a 1 : 1 mixture of hexane and ether. The yields of the acids (II), their constants, and the analytical results are shown in Table 1. By the esterification of these acids with excess of ethereal diazomethane we obtained the corresponding methyl esters (Table 2).

b) A solution of 12 mmoles of heptadecyltriphenylphosphonium bromide in 30 ml of N,N-dimethylformamide was added to 0.01 mole of dry sodium methoxide. After 30 minutes 7.5 mmoles of ethyl 8-formyloctanoate was added to the reddish-brown solution of the phosphorane, and the mixture was stirred for three hours and left at room temperature. On the next day N,N-dimethylformamide was distilled off, the residue was extracted with hexane, and the extract was evaporated and chromatographed in hexane on 250 g of neutral alumina (activity IV, column 400 × 30 mm). The course of the separation of the mixture was followed by means of thin-layer chromatography on plates carrying an unbound layer of alumina (development with a 1% solution of potassium permanganate in 2 N H_2SO_4). After the separation of triphenylphosphine we obtained 1.16 g (44%) of ethyl cis-9-hexacosenoate. By the hydrolysis of 0.2 g of this ester (for conditions see [3]) we obtained 0.17 g of cis-9-hexacosenoic acid, which was purified by recrystallization from petroleum ether (see Table 1); m.p. 43-45°.

TABLE 1. Unsaturated Acids $CH_3(CH_2)_m CH=CH(CH_2)_n COOH$

Acid	m	n	Yield, %*	B.p., °C (p, mm)	n_D^{20}	Found, %		Calc. %		Amide		
						C	H	C	H	m.p., °C	Found N, %	Calc. N, %
cis-11-Hexadecenoic	3	9	59	140(1,5·10⁻²)	1.4611	76.04	11.82	75.53	11.89	69—70	5.46	5.53
cis-7-Octadecenoic	9	5	53	164—165 (1)	1.4710	76.36	11.70	76.53	12.13	85—86	4.78	4.98
cis-8-Hexadecenoic	6	6	55	150 (1.5)**	1.4665	75.82	11.91	75.53	11.89			
cis-9-Hexacosenoic	15	7	44			79.10	12.63	79.12	12.77			

* Based on the amount of aldehyde taken.

† Temperature of bath.

TABLE 2. Unsaturated Esters $CH_3(CH_2)_mCH=CH(CH_2)_nCOOR$

Ester	m	n	R	B.p., °C (p, mm)	n_D^{20}	d_4^{20}	Found, %		Calc. %	
							C	H	C	H
Methyl cis-11 hexadecenoate	3	9	CH_3	90 ($2 \cdot 10^{-2}$)	1.4519	0.8826	76.17	12.10	76.06	12.02
Methyl cis-7-octadecenoate	9	5	CH_3	145 (1.5)*	1.4535	0.8724	77.32	12.02	76.97	12.22
Ethyl cis-9-hexacosenoate	15	7	C_2H_5	180 — 182 ($4 \cdot 10^{-2}$)	1.4584	—	79.31	12.74	79.55	12.88

* Temperature of bath.

SUMMARY

1. With the aid of a stereospecific modification of the Wittig reaction the total syntheses of the following were carried out: cis-8-hexadecenoic acid, cis-11-hexadecenoic acid, cis-7-octadecenoic acid, and cis-9-hexacosenoic acid.

2. A new variant of the stereospecific synthesis of unsaturated fatty acids having cis configuration at the double bond is proposed; it is based on the condensation of alkylidenetriphenylphosphoranes with ω-formylalkanoic esters.

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