# UNSATURATED ACIDS AND MACROCYCLIC LACTONES

## COMMUNICATION 7. SYNTHESIS OF UNSATURATED ω-HYDROXY ACIDS

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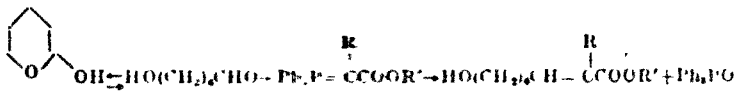
Some of the higher unsaturated fatty acids found in nature contain an ω-hydroxy group. These include ω-hydroxyeleostearic (kamlolenic) acid $HO(CH_2)_4(CH{=}CH)_2(CH_2)_7COOH$ [1, 2], ω-hydroxyoleic acid $HO(CH_2)_8CH{=}CH(CH_2)_7COOH$ [3], and ambrettolic acid $HO(CH_2)_8CH{=}CH(CH_2)_5COOH$ [4], which is present in plants as the macrocyclic lactone. From the royal jelly of the honey bee, yet another unsaturated ω-hydroxy acid, trans-10-hydroxy-2-decenoic acid, has been isolated [5]. This is of interest on account of its biological properties. It has been shown that this acid determines the development of a bee's egg into a queen [5] and that it also has antitumor activity [6].

With a view to the synthesis of various unsaturated ω-hydroxy acids and, in the first place, of analogs of trans-10-hydroxy-2-decenoic acid, we studied the possibility of using tetrahydropyran-2-ol (Ia) as a carbonyl component in the Wittig reaction. It is known that with malonic acid this compound reacts in the tautomeric form 5-hydroxyvaleraldehyde (Ib) [7]. It was found, however, that the condensation of tetrahydropyran-2-ol (Ia) with ethyl ω-(triphenylphosphoranylidene)alkanoates [8] does not lead to satisfactory results because it is much less reactive than aliphatic aldehydes and, on prolonged interaction with it, "ylides" of the given type are gradually decomposed. On the other hand, tetrahydropyran-2-ol (Ia) can condense with the more stable alkyl α-(triphenylphosphoranylidene)-alkanoates (II; R = H or $CH_3$, R' = $CH_3$ or $C_2H_5$) with formation of esters of α,β-unsaturated ω-hydroxy acids (III, R = H, $CH_3$, R' = $CH_3$), though this reaction proceeds less readily than the condensation of the same phosphoranes with aliphatic aldehydes.



(Ia) (Ib) (II) (III)

The reaction studied proceeds stereoselectively and leads to the trans isomers as in the case of the synthesis of trans-cinnamic ester, which we described earlier [9]. The trans configuration of methyl 7-hydroxy-2-heptenoate (III, R = H, R' = $CH_3$) is confirmed by its NMR spectrum*. The value found for the interaction constant for ol protons ($J_{AB}$~15.4 Hz) corresponds to the value characteristic for trans α,β-unsaturated esters ($J_{AB}$~15.7 Hz), as the cis isomers have $J_{AB}$~11.4 Hz [10]†. The trans configuration of the 7-hydroxy-2-methyl-2-heptenoic (III, R = R' = $CH_3$) was established by comparing its ultraviolet spectrum with the spectra of cis and trans α-methyl α,β-unsaturated esters of known configuration (table).

## EXPERIMENTAL

The NMR spectrum was determined with a RS-2 instrument (Trub and Teuber) in carbon tetrachloride (10% solution). The infrared spectrum was determined with a Zeiss UR-10 spectrophotometer.

*The infrared spectrum of this ester cannot be used for determining its configuration because ω-hydroxy acids absorb in the region of 820 $cm^{-1}$ [11], which is characteristic for cis α,β-unsaturated acids [12].

†The NMR spectrum was determined by É. I. Fedin and P. V. Petrovskii (Structural Analysis Laboratory, Institute of Heteroorganic Compounds, Academy of Sciences, USSR).

Ultraviolet Spectra of α-Methyl α,β-Unsaturated Esters in Alcohol

| Name of acid | $\lambda_{max}$, mμ(ε) | |
|---|---|---|
| | trans | cis |
| 2-methyl-2-pentenoic | 220 (12700) [13] | 216 (7500)* |
| 2-methyl-2-hexenoic | 214 (12380) [14] | 212 (7600) [14] |
| 7-hydroxy-2-methyl-2-heptenoic | 218 (12600)* | |

*Determined in the present work

Methyl (Triphenylphosphoranylidene)acetate [[(Methoxycarbonyl)methylene]triphenylphosphorane]. A mixture of 26.2 g of triphenylphosphine and 10.8 g of methyl chloroacetate in 50 ml of benzene was heated for eight hours. The precipitated crystals of (methoxycarbonylmethyl)triphenylphosphonium chloride were filtered off, carefully washed with ether, and dried. m.p. 149-150°, yield 34.2 g (92%). Found: C 68.10%, H 5.46%, Cl 9.57%, P 8.37%. $C_{21}H_{20}ClO_2P$. Calculated: C 68.02%; H 5.44%, Cl 9.56%, P 8.36%.

An aqueous solution of the salt was neutralized to phenolphthalein with 10% aqueous potassium hydroxide solution. We obtained 29.5 g (95%) of methyl (triphenylphosphoranylidene)acetate, m.p. 162-163° (from a mixture of ethyl acetate and hexane) [15].

Methyl trans-7-Hydroxy-2-heptenoate (III, R = H, R' = $CH_3$). A solution of 4.3 g of tetrahydropyran-2-ol [16] in 30 ml of N,N-dimethylformamide was added with stirring to a suspension of 17.7 g of methyl (triphenylphosphoranylidene)acetate in 50 ml of N,N-dimethylformamide. Stirring was continued at room temperature for 84 hours, after which 50 ml of water was added. To separate triphenylphosphine the mixture was extracted four times with petroleum ether (b.p. 40-60°) and then with ether. The extracts were dried, and solvent was vacuum distilled off. The residue crystallized out, and after treatment with ether we isolated 4.85 g of triphenylphosphine oxide and 4.25 g of oil containing, according to the results of thin-layer chromatography, still a certain amount of triphenylphosphine oxide. The oil obtained was stirred with 50 ml of 10% aqueous potassium hydroxide solution for four hours at room temperature. The triphenylphosphine oxide liberated (1.4 g) was filtered off, and after acidification with 4 N HCl the alkaline filtrate was extracted with ether. The ether extract was dried, solvent was distilled off, and we obtained 1.62 g of an oil, which we esterified with ethereal diazomethane. After chromatography on alumina (Grade II-III activity, pH 6) in a mixture of ethyl acetate and hexane we obtained 1.65 g (25%) of methyl trans-7-hydroxy-2-heptenoate; b.p. 94-96° (0.1 mm), $n_D^{20}$ 1.4670, $d_4^{20}$ 1.0270 (see [7]). Found: C 60.71%, H 9.05%, MR 42.35. $C_8H_{14}O_3$. Calculated: C 60.74%, H 8.92%, MR 41.86. Infrared spectrum (in a thin layer), $\nu_{max}$ ($cm^{-1}$) 3410 (OH), 1720 (C=O), 1650 (C=C), 980 (trans C=C), 818. Ultraviolet spectrum, $\lambda_{max}$ 211 mμ (ε 15950, in alcohol).

Methyl trans-7-Hydroxy-2-methyl-2-heptenoate (III, R = R' = $CH_3$). A solution of 2.55 g of tetrahydropyran-2-ol in 10 ml of N,N-dimethylformamide was added with stirring to a suspension of 11 g of methyl (triphenylphosphoranylidene)propionate [15] in 35 ml of N,N-dimethylformamide, and the mixture was stirred at room temperature for 72 hours. 30 ml of water was added to the reaction mixture, which was then extracted, first with petroleum ether and then with diethyl ether. The extract was evaporated, and the residue was washed with a little ether. We isolated 4.7 g of triphenylphosphine oxide and 0.92 g of oil. After the hydrolysis of the latter (see above) we obtained a further 2.5 g of triphenylphosphine oxide and 2.90 g of an oily acid fraction, which was methylated with diazomethane and chromatographed on alumina in a 1:1 mixture of ethyl acetate and hexane. We isolated 2.18 g (51%) of methyl trans-7-hydroxy-2-methyl-2-heptenoate, b.p. 100-101° (0.05 mm), $n_D^{20}$ 1.4702, $d_4^{20}$ 1.0268. Found: C 62.40%, H 9.23%, MR 46.82. $C_9H_{16}O_3$. Calculated: C 62.76%, H 9.37%, MR 46.47. 1-Naphthylurethan, m.p. 114-115° (from $C_6H_{12}$). Found: C 69.74%, H 6.02%. $C_{19}H_{21}NO_4$. Calculated: C 69.70%, H 6.47%. Infrared spectrum (in a thin layer), $\nu_{max}$ ($cm^{-1}$): 3450 (OH), 1720 (C=O), 1653 (C=C), 945, 818, 750.

## SUMMARY

A description is given of a stereoselective synthesis of trans α,β-unsaturated ω-hydroxy acids based on the condensation of 2-(triphenylphosphoranylidene)alkanoic esters with tetrahydropyran-2-ol.

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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-to-cover English translations appears at the back of this issue.

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