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SYNTHESIS OF MUSCALURE - THE PHEROMONE OF Musca domestica

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A method for obtaining cis-tricos-9-ene (muscalure) — the pheromone of the housefly — from the readily available ethyl oleate has been developed.

The sex pheromone of the housefly *Musca domestica* L. was isolated by Carlson in 1971 and was identified as cis-tricos-9-ene (muscalure) [1]. Field trials have shown its high attractive capacity [2].



In 1979, Shani [3] reported a synthesis of muscalure from the oil of the seeds of *Simmondsia chinensis*, and also from technical oleyl alcohol.

Our aim was to develop a simple method of obtaining cis-tricos-9-ene. We have investigated a synthetic route to muscalure based on the readily available ethyl oleate, which was selected as the starting material. Ethyl oleate (I) was reduced to oleyl alcohol (cisoctadec-9-en-1-ol) (II) with lithium tetrahydroaluminate in absolute ether. The excess of lithium tetrahydroaluminate was decomposed with moist ether and then with a saturated solution of  $Na_2CO_3$ , and not with ethyl acetate, since in this case oleyl acetate may be formed as a by-product [3]. Oleyl p-toluenesulfonate (III) was obtained by the reaction of purified [4] p-toluenesulfonyl chloride in absolute ether with oleyl alcohol in the presence of triethylamine. Oleyl iodide (IV) was formed by treating oleyl p-toluenesulfonate (III) with anhydrous sodium iodide in boiling acetone. The condensation of oleyl iodide with amylmagnesium bromide using  $Li_2CuCl_4$  as catalyst [5] at 0°C gave the final product cis-tricos-9-ene (V), which was purified on a column of silica gel. The PMR spectrum of the purified cis-tricos-9-ene corresponded completely to that reported previously [6].

An attempt to obtain cis-tricos-9-ene by condensing oleyl p-toluenesulfonate with amylmagnesium bromide in the presence of Li<sub>2</sub>CuCl<sub>4</sub> at -5°C proved unsuccessful. Oleyl alcohol and p-tolyl amyl sulfone were isolated, which agrees completely with information [7] on the

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655

mechanism of the reaction of p-toluenesulfonates with Grignard reagents catalyzed by copper compounds.

## EXPERIMENTAL

IR spectra were obtained in a thin layer on a UR-20 instrument, and PMR spectra on a Varian XL-200 spectrometer. TMS was used as internal standard. Column chromatography was performed on silica gel L 100/160.

The ratio of substance to sorbent was 1:20. The eluent was hexane-ethyl acetate (17:3).

<u>cis-Octadec-9-en-1-ol (Oleyl Alcohol) (II)</u>. To a suspension of 6.84 g (0.18 mole) of lithium tetrahydroaluminate in 800 ml of absolute ether was added 56.5 g (0.178 mole) of ethyl oleate (I) in 80 ml of absolute ether dropwise at such a rate that the reaction mixture boiled gently. After the end of the addition of (I) the mixture was heated to boiling forr 30 min. The excess of lithium tetrahydroaluminate was decomposed by the careful addition of moist ether and then with saturated Na<sub>2</sub>SO<sub>4</sub> solution until the separation of the precipitate of lithium and aluminum hydroxides had ceased. The precipitate was separated off and was washed with 160 ml of ether. The filtrate was evaporated in vacuum. The residue after evaporation showed no carbonyl absorption in the UV spectrum. The yield was 44.4 g (92.62%);  $n_D^{20}$ 1.4610.

<u>Oleyl p-Toluenesulfonate (II)</u>. Freshly distilled triethylamine (25.25 g; 0.25 mole) and, with external cooling (maintaining the temperature of the reaction mixture at  $-5-0^{\circ}$ C) and effective stirring, 34.7 g (0.182 mole) of purified p-toluenesulfonyl chloride was added in portions to 44.4 g (0.165 mole) of oleyl alcohol in 350 ml of absolute ether. After the end of the addition, stirring was continued for another 30 min at the same temperature. Then the mixture was left in the refrigerator for 12 h. A white precipitate was deposited. The reaction mixture was poured into ice water. The ethereal layer was separated off and it was washed with cold water, with dilute H<sub>2</sub>SO<sub>4</sub> solution, with NaHCO<sub>3</sub> solution and with water again and was dried over Na<sub>2</sub>SO<sub>4</sub>. The ether was distilled off in vacuum, giving 59.0 g (82.5%) of unpurified product.

<u>Oleyl Iodide (IV)</u>. Anhydrous sodium iodide (15.66 g; 0.1045 mole) was added to 29.5 g (0.0695 mole) of unpurified oleyl p-toluenesulfonate in 250 ml of dry acetone, and the mixture was boiled under reflux for 3 h. The precipitate of sodium p-toluenesulfonate that deposited was separated off, and the filtrate was evaporated in vacuum. The residue was treated with 50 ml of water and the mixture was extracted with ether ( $2 \times 80$  ml). The ethereal extracts were combined and were washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and then with water. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The ether was evaporated off in vacuum. The residue consisted of a colorless liquid, the yield of unpurified product being 21.95 g (83.5%).

<u>cis-Tricos-9-ene</u>. With stirring and cooling (0°C), 18.9 g (0.05 mole) of oleyl iodide in 35 ml of absolute benzene was added to a solution of amylmagnesium bromide obtained from 2.43 g (0.1 mole) of magnesium and 15.1 g (0.1 mole) of amyl bromide in 10 ml of dry THF and 50 ml of absolute benzene in an atmosphere of nitrogen, and then 0.274 g (0.00125 mole) of Li<sub>2</sub>CuCl<sub>4</sub> in 15 ml of dry THF was added at such rate that the temperature of the reaction mixture did not rise above 0°C. After 2 hours' stirring at 0°C, the temperature was gradually raised to that of the room and the reaction mixture was carefully poured into an aqueous solution of NH<sub>4</sub>Cl, after which the organic layer was separated off and was dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was driven off to give 14.75 g (91.6%) of a colorless oil. The crude product (8.0 g) was purified on a column of silica gel with hexane—ethyl acetate (17:3) as eluent. This gave 6.0 g (75%) of chromatographically pure cis-tricos-9-ene,  $n_D^{20}$  1.4545. According to the literature [8]:  $n_D^{23}$  1.4532.

## SUMMARY

A method has been developed for obtaining the pheromone of the housefly, cis-tricos-9ene (muscalure), from ethyl oleate.

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ACYLATION OF STEROID ALCOHOLS WITH 3-CARBOXYPROPANAMIDO ACIDS

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Using N-(3-carboxypropanoy1)- $\beta$ -phenyl- $\alpha$ -alanine as a model it has been established that when steroid alcohols are esterified with 3-carboxypropanamido acids, the carboxy group of the succinic acid residue takes part in the esterification reaction. In order to obtain a steroid ester of a 3-carboxypropanamido acid in which the carboxyl of the amino acid is the esterifying group, the carboxy group of the succinic acid residue must first be esterified.

Androstane esters of 3-carboxypropanamido acids are biologically active substances. The esterification of a steroid hydroxy ketone with the chloride of a 3-carboxypropanamido acid leads to the formation of a monosteroid ester. It was of interest to determine which of the carboxy groups of the amino acid takes part in the esterification reaction.

Potentiometric titration showed that in their acidities the carboxy groups were close to one another and did not titrate separately. To demonstrate the structure of a dihydrotestosterone ester of a 3-carboxypropanamido acid we obtained the desired ester by three methods. The carboxy group participating in the acylation reaction was determined from the coincidence of the physicochemical properties of the desired product in two of the schemes. As the model acid we chose  $\beta$ -phenyl- $\alpha$ -alanine, with 17 $\beta$ -hydroxyandrostan-3-one (dihydrotestosterone).

The synthesis of the dihydrotestosterone ester of 3-carboxypropanoyl- $\beta$ -phenyl- $\alpha$ -alanine was carried out by the schemes given below.



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