INVESTIGATION OF UNSATURATED LACTONES

XXIV.* SYNTHESIS OF UNSATURATED δ-LACTONES BY CONDENSATION OF TERTIARY α-KETO ALCOHOLS WITH DIETHYL SUCCINATE

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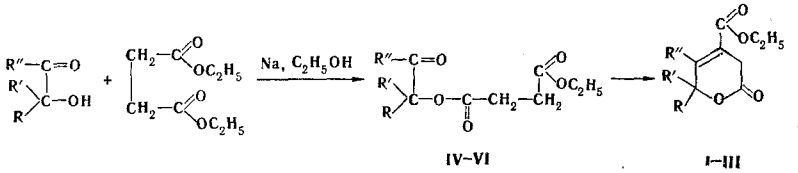
Transesterification with subsequent cyclization to 4-carbethoxy-5,6,6-trialkyl-3-hydro-2-pyrones occurs during condensation of α-keto alcohols with diethyl succinate. 4-Carbethoxy-5,6,6-trimethyl-3-hydro-2-pyrone was obtained by reaction of dimethylethynylcarbinol with the ethyl ester of succinic acid monochloride and subsequent hydration of the acetylenic ester and cyclization.

One of the inadequacies of the known methods for the synthesis of unsaturated δ-lactones [2, 3] is the synthetic difficulty involved in the introduction of various functional groups into the ring.

We have found that condensation of tertiary α-hydroxy ketones with diethyl succinate in the presence of catalysts of basic character leads to 4-carbethoxy-5,6,6-trialkyl-3-hydro-2-pyrones (I-III). Unsaturated δ-lactones with a carbethoxy group in the 4 position can be synthesized in this way.

Transesterification with subsequent intramolecular condensation of the resulting keto ester (IV-VI) and liberation of ethanol and water apparently occur in the reaction of α-keto alcohols with diethyl succinate.



IV-VI I-III

I $R = R' = R'' = CH_3$; II $R = C_2H_5$, $R' = R'' = CH_3$; III R, $R' = (CH_2)_5$, $R'' = CH_3$

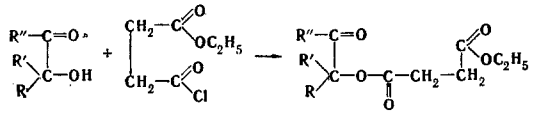
The assumption of the possibility of the occurrence of this reaction by means of crotonic condensation through the methylene groups of the ester component becomes superfluous, since the reaction does not proceed when the hydroxyl group of the keto alcohol is blocked by replacement by an acetoxy group, and the starting materials are recovered unchanged.

Thus, for example, condensation did not occur in the reaction of dimethylacetylcarbinol acetate (an α-acetoxy ketone) with diethyl succinate in the presence of sodium ethoxide or pyridine. Consequently, the reaction proceeds by means of prior transesterification of the α-keto alcohol to give keto esters (IV-VI). In fact, we were able also to isolate transesterification products – keto esters IV-VI – in a study of the condensation of α-keto alcohols with diethyl succinate.

These intermediate keto esters (IV-VI) were also synthesized by reaction of α-keto alcohols with the monoethyl ester of succinic acid monochloride in the presence of pyridine:

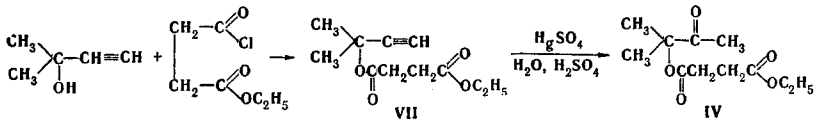
* See [1] for communication XXIII.

Erevan State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1604-1607, December, 1973. Original article submitted December 20, 1972.



IV–VI

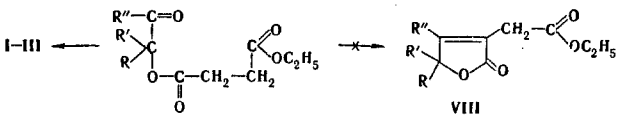
The structure of IV-VI was in turn proved by alternative synthesis in the case of dimethylethynylcarbinol by transesterification of it with the monoethyl ester of succinic acid monochloride and hydration of the resulting acetylenic ester (VII) in the presence of mercuric sulfate and sulfuric acid:



VII IV

Intermediate keto esters IV-VI undergo intramolecular cyclization in the presence of catalytic amounts of sodium ethoxide to give 4-carbethoxy-5,6,6-trialkyl-3-hydro-2-pyrones.

Two directions for the intramolecular cyclization of keto esters IV-VI, as a result of which six-membered or five-membered substituted unsaturated lactones could be obtained, are theoretically possible:

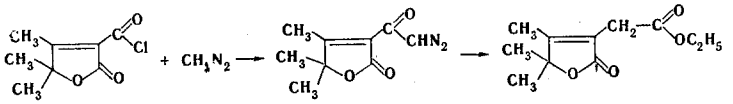


VIII

However, the experimental data show that the reaction proceeds via the first path.

The synthesis of VIII by another method was accomplished in order to prove the absence of the second direction of cyclization.

Ethyl 4,5,5-trimethyl-Δ^3-butenolidoacetate (VIII), the physicochemical properties of which differ completely from the properties of the I obtained by us, was obtained by reaction of diazomethane with 3-chlorocarbonyl-4,5,5-trimethyl-Δ^3-butenolide [4] via the Arndt–Eistert reaction.



IX VIII

Absorption bands at 1764, 1721, and 1650 cm^{-1}, which confirm the structure of ethyl 4,5,5-trimethyl-Δ^3-butenolidoacetate (VIII), are found in its IR spectrum. The characteristic absorption bands of a double bond (1677-1680 cm^{-1}) and of an ester carbonyl group (1703-1722 cm^{-1}) are found at 1734-1743 cm^{-1} in the IR spectra of I-III.

It is known that the substituted unsaturated five-membered lactone ring is not opened in the presence of a base even on prolonged heating [7]. In contrast to this, the unsaturated δ-lactones that we obtained undergo even cold titration with 0.1 N sodium hydroxide.

The presence of a double bond was proved by bromination.

EXPERIMENTAL

The purity of the products was monitored by thin-layer chromatography (TLC) on aluminum oxide (activity II) in diethyl ether.

4-Carbethoxy-5,6,6-trimethyl-3-hydro-2-pyrone (I). A 17.4-g (0.12 mole) sample of diethyl succinate and 10.2 g (0.1 mole) of diethylacetylcarbinol were added to 2 g of sodium metal in 50 ml of absolute alcohol, and the mixture was refluxed on a water bath for 15 h. The alcohol was removed by distillation, and the solid residue was acidified with dilute (1 : 1) hydrochloric acid and extracted with benzene. The extract was dried with anhydrous sodium sulfate, the solvent was removed, and the residue was vacuum-distilled to give 5.15 g (22.4%) of keto ester IV with bp 119-122° (2 mm) [n_D^{20} 1.4410, d_4^{20} 1.049. Found: C 57.8; H 7.8%; MR_D 55.4. $C_{11}H_{18}O_5$. Calculated: C 57.4; H 7.8%; MR_D 56.3. R_f 0.9] and 10.2 g (47.2%) of lactone I with bp 182-186° (2 mm) [n_D^{20} 1.4815, mp 114° (from xylene). Found: C 62.8; H 7.4%. $C_{11}H_{16}O_4$. Calculated: C 62.0; H 7.5%]. An alcohol solution of 0.028 g of the lactone was titrated with 1.3 ml of 0.1 N NaOH in the cold.

4-Carbethoxy-5,6-dimethyl-6-ethyl-3-hydro-2-pyrone (II). Similarly, refluxing 11.6 g (0.1 mole) of methylethylacetylcarbinol, 17.4 g (0.12 mole) of diethyl succinate, and 2 g of sodium in 50 ml of absolute alcohol for 10-15 h gave 5 g (20.1%) of keto ester V with bp 128-130° (3 mm) [n_D^{20} 1.4351. Found: C 58.8; H 7.9%. $C_{12}H_{20}O_5$. Calculated: C 59.1; H 8.2%] and 7.6 g (33.3%) of lactone II with bp 187-195° (2 mm) [n_D^{20} 1.4800, mp 129-131° (from xylene). Found: C 64.1; H 7.7%. $C_{12}H_{18}O_4$. Calculated: C 63.7; H 7.9%]. An alcohol solution of 0.05 g of the lactone was titrated with 2 ml of 0.1 N NaOH in the cold.

4-Carbethoxy-5-methyl-6-pentamethylene-3-hydro-2-pyrone (III). Similarly, a mixture of 12.6 g (0.1 mole) of 1-acetylcyclohexanol, 17.4 g (0.12 mole) of diethyl succinate, and 2 g of sodium in 50 ml of absolute alcohol gave 4.2 g (15.6%) of intermediate keto ester VI, with bp 167-170° (2 mm) and n_D^{20} 1.459, and 12 g (47.4%) of lactone III with mp 147-148° (from xylene). Found: C 66.2; H 7.6%. $C_{14}H_{20}O_4$. Calculated: C 66.4; H 7.9%. An alcohol solution of 0.0252 g of the lactone was titrated with 2.9 ml of 0.1 N NaOH in the cold.

Preparation of Acetylenic Ester VII. A solution of 16 ml of pyridine in 20 ml of anhydrous benzene was added in portions to a mixture of 32.8 g (0.2 mole) of the monoethyl ester of succinic acid monochloride, and the mixture was heated at 40° for 1 h. It was then neutralized with dilute (1 : 1) hydrochloric acid and extracted with ether. The extract was dried with sodium sulfate, and the ether was removed to give 26 g (61.34%) of VII with bp 104-105° (2 mm), n_D^{20} 1.4410, d_4^{20} 1.052, and R_f 0.89. Found: C 61.8; H 7.3%; MR_D 53.4 [in ether–alcohol (5 : 1)]. $C_{11}H_{16}O_4$. Calculated: C 62.2; H 7.5%; MR_D 54.3.

Hydration of the Acetylenic Ester. A solution of 2 ml of concentrated H_2SO_4 in 10 ml of water was added carefully with stirring to a mixture of 10 ml of water and 0.6 g of red mercuric oxide, and the mixture was cooled to 20° and treated with 13 g (0.061 mole) of VII in 15 ml of ether. The ether layer was separated after 4-6 h, and the aqueous layer was extracted six to eight times with ether. The extracts were combined with the ether layer, and the ether solution was washed with concentrated sodium carbonate solution and dried with magnesium sulfate. The solvent was removed, and the residue was vacuum-distilled to give 8 g (56.7%) of IV with bp 112-114° (2 mm) and n_D^{20} 1.4361.

Condensation of α-Keto Alcohols with the Monoethyl Ester of Succinic Acid Monochloride. A solution of 7 g of anhydrous pyridine in 10 ml of benzene was added in portions to a mixture of 16.4 g (0.1 mole) of the monoethyl ester of succinic acid monochloride, 10.2 g (0.1 mole) of dimethylacetylcarbinol, and 15 ml of anhydrous benzene, and the mixture was heated at 40° for 1 h. It was then neutralized with dilute (1 : 1) hydrochloric acid and extracted with benzene. The extract was dried with magnesium sulfate, and the solvent was removed by distillation to give 8.4 g (64.6%) of keto ester IV. Cyclization of this keto ester in the presence of sodium ethoxide gave 4-carbethoxy-5,6,6-trimethyl-3-hydro-2-pyrone in 65% yield.

Similarly, 16.4 g (0.0 mole) of the monoethyl ester of succinic acid monochloride and 11.6 g (0.1 mole) of methylethylacetylcarbinol gave 11.3 g (46.9%) of keto ester V.

Similarly, 12.6 g (0.1 mole) of cyclohexylacetylcarbinol and 16.4 g (0.1 mole) of the monoethyl ester of succinic acid monochloride gave 18.3 g (68%) of VI.

Reaction of Dimethylacetylcarbinol Acetate with Diethyl Succinate. A 14.4-g (0.1 mole) sample of α-acetoxy ketone and 17.4 g (0.12 mole) of diethyl succinate were added to 2 g of sodium metal in 50 ml of absolute alcohol, and the mixture was refluxed on a water bath for 15 h. The alcohol was removed by distillation, and the solid residue was acidified with dilute (1 : 1) hydrochloric acid and extracted with benzene. The extract was dried with anhydrous sodium sulfate, the solvent was removed, and the residue was vacuum-distilled. No reaction had occurred, and the starting materials were recovered unchanged.

Preparation of Diazoketone IX. A solution of 18.9 g (0.1 mole) of 3-chlorocarbonyl-4,5,5-trimethyl-Δ^3-butenolide in 30 ml of absolute diethyl ether was added by drops to 550 ml of a cooled (to below 0°) ether solution of diazomethane (from 52 g of nitrosomethylurea and 175 ml of 40% KOH solution); the mixture became warm during the addition. It was stirred at below 5° for 4 h and at room temperature for 7 h. The ether was removed by distillation, and the precipitated diazoketone [17.2 g (88.3%)] was used without isolation in the next step.

Preparation of Ethyl 4,5,5-Trimethyl-Δ^3-butenolidoacetate (VIII). A small portion of a suspension of silver oxide, prepared from 10 ml of 10% aqueous solution of silver nitrate and 30 ml of ethanol, was added at 55-60° to a solution of 10 g of the diazoketone in 150 ml of ethanol. When nitrogen evolution had ceased, the next portion of silver oxide was added, and this procedure was continued until all of the oxide had been added. The mixture was then refluxed for 4 h, treated with activated charcoal, and filtered. The

filtrate was evaporated, and the residue was distilled to give 6.1 g (56.1%) of VIII with bp 142° (2 mm), n_D^{20} 1.4797, and d_4^{20} 1.1453. Found: C 62.1; H 7.2%; MR_D 52.6. $C_{11}H_{16}O_4$. Calculated: C 62.3; H 7.6%; MR_D 53.6. R_f 0.75.

LITERATURE CITED

1. A. A. Avetisyan, K. G. Akopyan, and M. T. Dangyan, Arm. Khim. Zh. (in press).
2. N. P. Shusherina and R. Ya. Levina, Usp. Khim., 3, 37 (1968).
3. N. P. Shusherina, N. D. Dmitrieva, E. A. Luk'yanets, and R. Ya. Levina, Usp. Khim., 3, 36 (1967).
4. A. A. Avetisyan, G. E. Tatevosyan, and M. T. Dangyan, Arm. Khim. Zh., 24, 688 (1971).