SYNTHESIS OF 2-ACYL-4-HYDROXYCYCLOHEXANE-1,3-DIONES — KAIROMONES AND PROTECTIVE SUBSTANCES OF SOME INSECTS

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The synthesis of some derivatives of \( \beta \)-triketones based on a new synthon — 4-hydroxycyclohexane-1,3-dione — is described. Using the proposed scheme, 4-hydroxy-2-(octadec-9Z,12Z-dienoyl)cyclohexane-1,3-dione, a kairomeone of some species of Lepidoptera, has been obtained.

Among the numerous natural and synthetic bioactive compounds containing a cyclic \( \beta,\beta' \)-tricarbonyl fragment in some form or other [1a], particular interest is aroused by the 2-acylcyclohexane-1,3-diones of general formula (1) and their 4-hydroxy derivatives (2) (where \( R \) is a \( C_{12}^- \), \( C_{14}^- \), \( C_{16}^- \), \( C_{18}^- \) or \( C_{20}^- \)-saturated, or mono- or diunsaturated carboxylic acid residue with different positions and configurations of the double bonds) that have recently been isolated from certain species of Lepidoptera and Hemiptera.

The compounds of this series that were first isolated from secretions of the mandibular glands of the caterpillar of *Ephestia kuehniella* [2a, b], which possess kairomone activity in relation to their parasite *Venturia canescens*, have also been detected in the secretions of other close species of Lepidoptera that are pests of stored products (*Plodia interpunctella, Ephestia cautella*, etc.) [2, 3]. 2-Dodecanoyl- and 2-tetradec-10E-enoyl-4-hydroxycyclohexane-1,3-diones (2), isolated as the main components of secretions of the larvae of *Corythucha ciliata* (Say) and *C. cydoniae* (Fitch.) fulfill protective functions [4, 5]. The biological function of the related hydroxytriketone (2) \( [R = (\text{CH}_2)_{10}\text{Ph}] \), detected [6] in the fruit of *Virola sebifera* and *V. elongata*, is as yet unknown.

A preparative synthesis of the deoxy derivatives (1) with both saturated and unsaturated acyl side chains does not present serious difficulties and has been described previously for a number of examples [7].

The task of forming the 2-acyl-4-hydroxycyclohexane-1,3-dione structure is considerably more complicated, since the introduction of the hydroxy group into the polyfunctional molecule of an enolized triketone requires multistage roundabout methods. Thus, in our laboratory, using 2-acetyldimedone and 2-butanoyldimedone as models, we have developed

\[
\begin{align*}
\text{Scheme 1.} & \quad \text{i: H}_2\text{O}, \text{HCl, NaOH; ii: LTA, AcOH; iii: Ni/Ra, AlCl}_3, \\
& \quad \text{MeOH}_2\text{H}_2; \text{iv: NaOH, a: R=C}_{11}\text{H}_{23}; \text{b: R=C}_{15}\text{H}_{31}; \text{c: R=C}_{17}\text{H}_{35}
\end{align*}
\]
variants of such modification of a $\beta$-triketone grouping via the oxidation of an isoxazole derivative in the first case and of enol esters in the second [7, 8c, 9].

In a development of the isoxazole approach, and using triketones (1a-c) as examples, we have achieved the synthesis of the corresponding hydroxytriketones (2a-c) (Scheme 1). However, the overall yield of the desired compounds proved to be small, amounting to 15-20%, because of the low yield (20-40%) of the 4-acetoxy derivatives (4) at the stage of oxidizing the isoxazoles (3-c). It must be mentioned that Oliver and Lusby [5] have reported the synthesis of compounds (2) (R = undecyl, tridec-9E-enyl, hexadec-8Z-enyl) using what is in essence the same approach.

It is obvious that common deficiencies of these syntheses of the hydroxytriketones (2) from the triketones (1) are the low yield of desired products and the multistage nature of the process connected with the necessity for protecting the cyclic $\beta$-dicarbonyl fragment, which is labile under the conditions described, and its subsequent regeneration. Furthermore, at the oxidation and reduction stages the additional problem of retaining the exocyclic multiple bonds arises, which makes the production of numerous derivatives of the hydroxytriketones (2) with unsaturated chains unpromising.

In connection with what has been said, we propose, with the use of compounds (2a–e) as examples, a common approach [1] to the synthesis of natural substances of the group under discussion on the basis of the 4-hydroxycyclohexane-1,3-dione (7), which were the first to describe [10].

\[
\text{C-}O_i + \text{OCO}_O \rightarrow \text{Olor ocoR ocoR}
\]

\[
\text{OH OCOR}
\]

\[
\text{OH OCOR OH}
\]

\[
\text{OCOR OH (21}
\]

Scheme 2. i: 2RCOCI, Py, DCE; ii: DMAP, DCE, 30°C, 2 h; iii: KOH (alc), then HCl; iv: RCOCl, Py, THF; v: acetone cyanohydrin.

MeCN, 20°C, 2 h. a: $R = C_{11}H_{23}$; b: $R = C_{13}H_{25}$; c: $R = C_{15}H_{31}$; d: $R = \text{heptadec-8Z-enyl}$; e: $R = \text{heptadec-8Z, 11Z-dienyl}$.

By decomposing the diketone (7), an improved method for preparing which in preparative amounts is given in the Experimental part, we have achieved a short and effective synthesis of the hydroxytriketones (2b–e) under mild conditions in accordance with Scheme 2. Thus, the interaction of the diketone (7) with the appropriate acyl chloride under standard conditions [7] led to the formation of a mixture (3:1) of the regioisomeric diacyl derivatives (8b–e), which, without additional purification, was subjected to O-C isomerization into the 4-acyloxytriketones (9b–c) under the action of 4-dimethylaminopyridine (DMAP) in benzene. Subsequent hydrolysis of the esters (9b–e) gave the hydroxytriketones (2b–e), which were isolated by chromatography. The overall yield of the hydroxytriketones (2) from the dione (7) amounted to 40-50%. Here, at the stage of the O-acylation of the diketone, the ester (10) was isolated as a by-product, and its subsequent acylation with the formation of the diacyl derivatives (8) took place with difficulty. When the dione (7) was acylated with a deficiency of the acid chloride in THF solution (method B), it was possible to obtain the enolic monoester (11a) as the sole reaction product. The isomerization of the enol ester (11a) in the presence of DMAP led to the formation a mixture of the 4-hydroxytriketone (2a), its ester (9a), and the ester of the diketone (10a) in a ratio of 2:2:1. Performing the isomerization in dilute acetonitrile solution in the presence of cyanide ions [11] enabled the yield of hydroxytriketone (2a) to be raised to 80%. At the same time, about 10% of the triketone ester (9a) was formed in the reaction mixture. The isomerization of the enol acylate (11a) under the action of DMAP apparently took place as an intermolecular process in which the reaction mechanism included both C- and O-acylation. Under the conditions of catalysis by cyanide ions, possibly, an intramolecular process was realized, since in this case the hydroxytriketone (2a) was formed as the main reaction product together with a very small amount of the by-product ester (9a).

The identification and the determination of the structures of the compounds synthesized were carried out with the use of chromatographic, elemental, and spectrometric methods of analysis, and also by comparing the physicochemical characteristics of the samples with literature information [1f (sic), 5] in the case of compounds that have been described.