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SHORT COMMUNICATIONS

Synthesis and Structure of Acetyl-Substituted Oxocyclohexanecarboxylates

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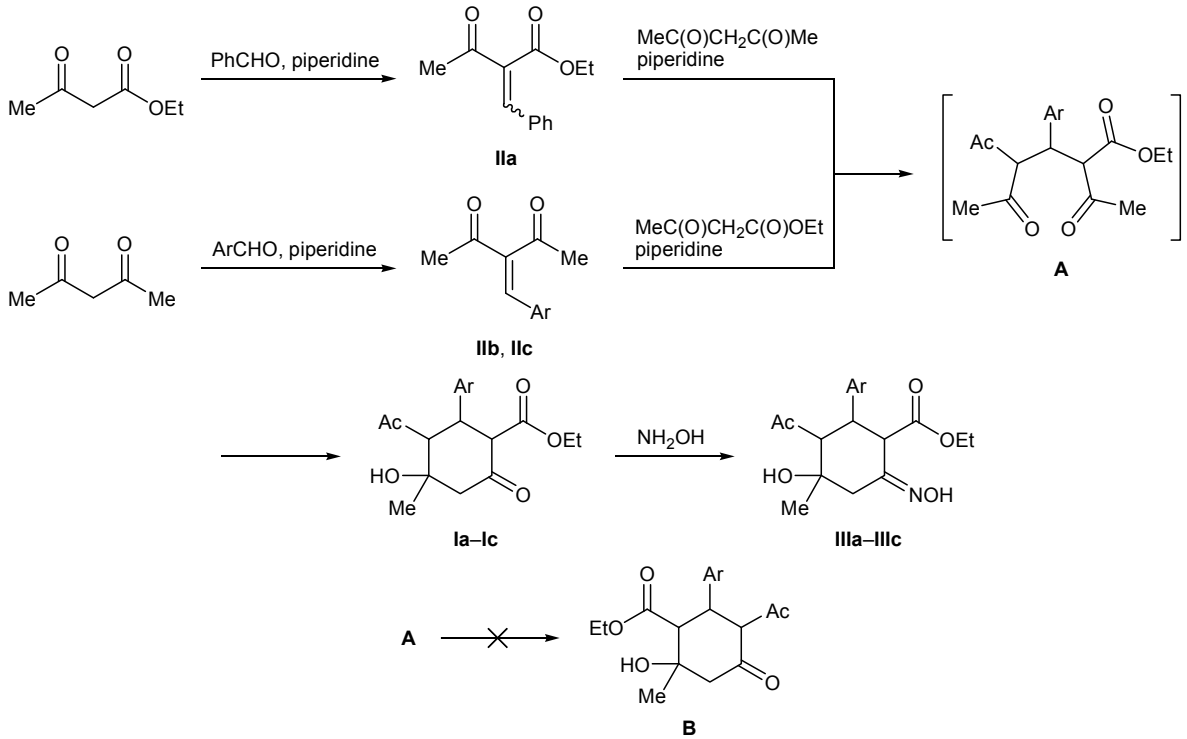
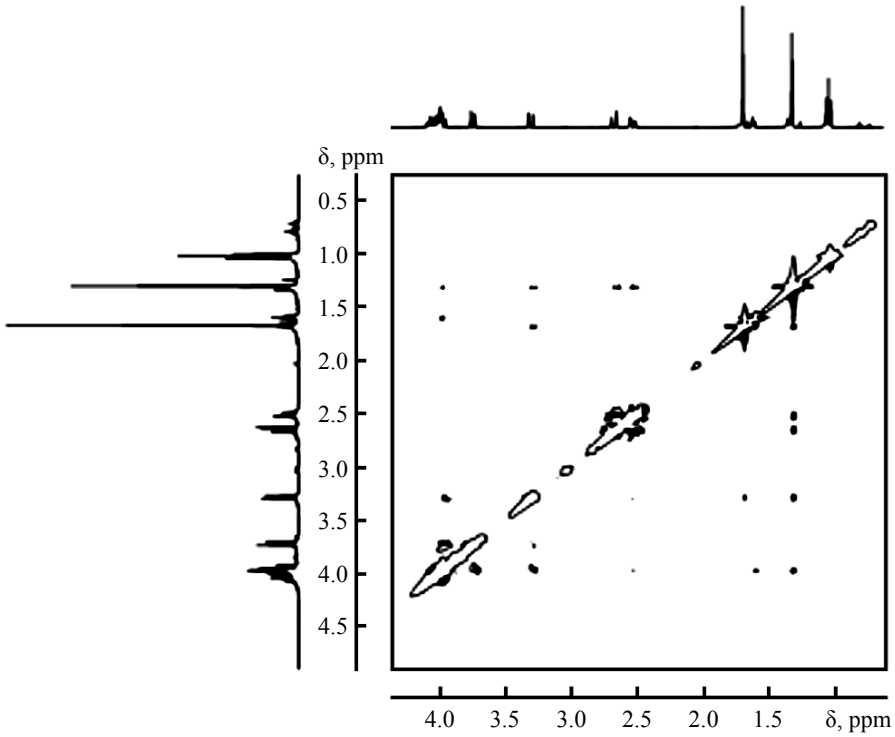
Dicarbonyl-substituted hydroxycyclohexanones with similar substituents (Ac or COOR) have been studied in sufficient detail [1]. Much less data are available on analogous compounds having different substituent groups (COR and COOR) [2]. However, such derivatives are promising from the viewpoint of their biological activity and design of carbo- and heterocyclic systems with specified functionalization pattern.

We now report on the synthesis of new ethyl 3-acetyl-2-aryl-4-hydroxy-4-methyl-6-oxocyclohexanecarboxylates **Ia**–**Ic** whose structure was determined by spectral methods and chemical transformations. Compounds **Ia**–**Ic** were synthesized by condensation of aromatic aldehydes with ethyl acetoacetate or acetylacetone to give ethyl 2-benzylidene-3-oxobutanoate (**IIa**) or 3-arylmethylidenepentane-2,4-diones **IIb** and **IIc**, followed by Michael addition. Intramolecular aldolization of intermediate **A** gave cyclohexanecarboxylates **Ia**–**Ic** in up to 80% yield.

The spectral data (IR and ^{1}H NMR) for the synthesized compounds confirmed only the presence of carbonyl-containing fragments but not their position, so



Ar = Ph (**a**), 3-$O_2NC_6H_4$ (**b**), 4-$MeOC_6H_4$ (**c**).



Two-dimensional NOESY spectrum of ethyl 3-acetyl-4-hydroxy-4-methyl-6-oxo-2-phenylcyclohexanecarboxylate (**Ia**).

that alternative structure **B** cannot be ruled out. The structure of the products was unambiguously determined on the basis of the two-dimensional NOESY spectrum of compound **Ia**, which displayed coupling between methyl protons in the acetyl substituent and protons in the 4-methyl group. Such coupling is possible only if the above groups are attached to neighboring carbon atoms. In addition, cross peaks with 2-H_{ax}, 3-H_{ax}, 5-H_{ax}, and 5-H_{eq} were observed (see figure).

Mutual arrangement of the ester and acetyl groups was also proved by chemical transformation, specifically by reaction of cyclohexanecarboxylates **Ia**–**Ic** with hydroxylamine. It is known that reactions of diacetylhydroxycyclohexanones with hydroxylamine involve heterocyclization with participation of the 1,3-dioxo fragment and formation of isoxazoles and that bis(ethoxycarbonyl)-substituted analogs react via nucleophilic replacement at the endocyclic carbonyl group with formation of oximes [2]. The reactions of compounds **Ia**–**Ic** with hydroxylamine gave the corresponding oximes, ethyl 3-acetyl-2-aryl-4-hydroxy-6-hydroxyimino-4-methylcyclohexanecarboxylates **IIIa**–**IIIc**, whose IR and ^{1}H NMR spectra were consistent with the assumed structure.

Ethyl 2-benzylidene-3-oxobutanoate (**IIa**) and 3-arylmethylidenepentane-2,4-diones **IIb** and **IIc** were reported in [3, 4].

Ethyl 3-acetyl-2-aryl-4-hydroxy-4-methyl-6-oxocyclohexanecarboxylates Ia–Ic (*general procedure***).** A mixture of 18 mmol of compound **IIa**–**IIc** and 18 mmol of acetylacetone or ethyl acetoacetate was cooled to 10–15°C, a solution of 2 ml of piperidine in 10 ml of ethanol was added dropwise, and the mixture was kept for 78 h at room temperature. The precipitate was filtered off and recrystallized from ethanol.

Ethyl 3-acetyl-4-hydroxy-4-methyl-6-oxo-2-phenylcyclohexanecarboxylate (Ia). Yield 72%, mp 104–105°C. IR spectrum, ν, cm^{-1}: 3434 (OH), 1722 (C=O, ester), 1705 (C=O), 1602 (Ac). ^{1}H NMR spectrum, δ, ppm: 1.03 s (3H, CH_3CO), 1.31 s (3H, CH_3), 1.68 t (3H, $CH_2C\mathbf{H}_3$), 2.02 s (1H, OH), 2.49 d (1H, 5-H_{ax}), 2.63 d (2H, 5-H_{eq}), 3.27 d (1H, 3-H), 3.71 d (1H, 1-H), 3.93 t (1H, 2-H), 4.04 m (2H, OCH_2). Found, %: C 67.58; H 7.24. $C_{18}H_{22}O_5$. Calculated, %: C 67.91; H 6.97.

Ethyl 3-acetyl-4-hydroxy-4-methyl-2-(3-nitrophenyl)-6-oxocyclohexanecarboxylate (Ib). Yield 80%, mp 127–130°C. IR spectrum, ν, cm^{-1}: 3430 (OH), 1724 (C=O, ester), 1707 (C=O), 1696 (Ac), 1528 (NO_2). ^{1}H NMR spectrum, δ, ppm: 1.05 s (3H, CH_3CO), 1.32 s (3H, CH_3), 1.68 t (3H, $CH_2C\mathbf{H}_3$), 2.02 s (1H, OH), 2.60 d (1H, 5-H_{ax}), 2.68 d (1H, 5-H_{eq}), 3.23 d (1H, 3-H), 3.64 d (1H, 1-H), 3.86 t (1H, 2-H), 4.05 m (2H, OCH_2). Found, %: C 59.26; H 6.05;

N 4.05. $C_{18}H_{20}O_7N$. Calculated, %: C 59.50; H 5.83; N 3.85.

Ethyl 3-acetyl-4-hydroxy-2-(4-methoxyphenyl)-4-methyl-6-oxocyclohexanecarboxylate (Ic). Yield 78%, mp 137–140°C. IR spectrum, ν, cm^{-1}: 3416 (OH), 1726 (C=O, ester), 1696 (C=O), 1589 (Ac). ^1H NMR spectrum, δ, ppm: 1.09 s (3H, CH_3CO), 1.32 s (3H, CH_3), 1.69 t (3H, $CH_2C\mathbf{H}_3$), 2.02 s (1H, OH), 2.45 d (1H, 5-H_{ax}), 2.60 d (1H, 5-H_{eq}), 3.23 d (1H, 3-H), 3.64 d (1H, 1-H), 3.83 s (3H, OCH_3), 3.86 t (1H, 2-H), 4.05 m (2H, OCH_2). Found, %: C 65.32; H 6.94. $C_{19}H_{24}O_6$. Calculated, %: C 65.50; H 6.94.

Ethyl 3-acetyl-2-aryl-4-hydroxy-6-hydroxyimino-4-methylcyclohexanecarboxylates IIIa–IIIc (*general procedure*). A solution of 2.5 mmol of hydroxylamine hydrochloride in 3 ml of water was added dropwise over a period of 5 min to a solution of 2.5 mmol of cyclohexanecarboxylate **Ia–Ic** in 15 ml of ethanol. The mixture was heated for 3 h under reflux and was kept for 78 h at room temperature. The precipitate was filtered off, washed with water and diethyl ether, and recrystallized from ethanol.

Ethyl 3-acetyl-4-hydroxy-6-hydroxyimino-4-methyl-2-phenylcyclohexanecarboxylate (IIIa). Yield 51%, mp 109–112°C. IR spectrum, ν, cm^{-1}: 3475 (OH), 3220 (NHOH), 1725 (C=O, ester), 1703 (Ac), 1656 (N=C). ^1H NMR spectrum, δ, ppm: 1.09 s (3H, CH_3CO), 1.31 s (3H, CH_3), 1.70 t (3H, $CH_2C\mathbf{H}_3$), 2.00 s (1H, OH), 2.44 d (1H, 5-H_{ax}), 2.60 d (1H, 5-H_{eq}), 3.23 d (1H, 3-H), 3.64 d (1H, 1-H), 3.81 s (1H, NHO**H**), 3.86 t (1H, 2-H), 4.05 m (2H, OCH_2). Found, %: C 64.68; H 7.01; N 4.20. $C_{18}H_{23}NO_5$. Calculated, %: C 64.85; H 6.95; N 4.20.

Ethyl 3-acetyl-4-hydroxy-6-hydroxyimino-4-methyl-2-(3-nitrophenyl)cyclohexanecarboxylate (IIIb). Yield 45%, mp 96–98°C. IR spectrum, ν, cm^{-1}: 3507 (OH), 3320 (NHOH), 1726 (C=O, estert), 1638 (Ac), 1527 (NO_2), 1652 (N=C). ^1H NMR spectrum, δ, ppm: 1.11 s (3H, CH_3CO), 1.32 s (3H, CH_3), 1.72 t (3H, $CH_2C\mathbf{H}_3$), 2.02 s (1H, OH), 2.46 d (1H, 5-H_{ax}), 2.64 d (1H, 5-H_{eq}), 3.24 d (1H, 3-H), 3.65 d (1H, 1-H), 3.82 s (1H, NHO**H**), 3.88 t (1H, 2-H), 4.08 m (2H, OCH_2). Found, %: C 57.12; H 5.81; N 7.01. $C_{18}H_{22}N_2O_7$. Calculated, %: C 57.14; H 5.86; N 7.40.

Ethyl 3-acetyl-4-hydroxy-6-hydroxyimino-2-(4-methoxyphenyl)-4-methylcyclohexanecarboxylate (IIIc). Yield 57%, mp 65–67°C. IR spectrum, ν, cm^{-1}: 3501 (OH), 3360 (NHOH), 1728 (C=O, ester), 1703 (Ac), 1644 (N=C). ^1H NMR spectrum, δ, ppm: 1.07 s (3H, CH_3CO), 1.30 s (3H, CH_3), 1.70 t (3H, $CH_2C\mathbf{H}_3$), 2.01 s (1H, OH), 2.65 d (1H, 5-H_{ax}), 2.67 d (1H, 5-H_{eq}), 3.12 d (1H, 3-H), 3.65 d (1H, 1-H), 3.81 s (1H, NHO**H**), 3.83 s (3H, OCH_3), 3.86 t (1H, 2-H), 4.02 m (2H, OCH_2). Found, %: C 62.88; H 6.93; N 4.05. $C_{19}H_{25}NO_6$. Calculated, %: C 62.80; H 6.93; N 3.85.

The IR spectra were measured in KBr on a Specord M-80 spectrometer. The ^1H NMR spectra were recorded on a Varian-400 instrument at 400 MHz using $CDCl_3$ as solvent and tetramethylsilane as internal reference. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates; spots were visualized under UV light or by treatment with iodine vapor. The melting points were determined using glass capillaries and were not corrected.

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