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SEQUENCE OF ALKYLATION OF CYCLOHEXANE-1,3-DIONE. ALTERNATIVE SYNTHESIS OF (±)-ANGUSTIONE

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UDC 547.443.3+547.594.3+547.914.4

A method is proposed for introducing one, two, or three alkyl substituents into positions 4 and 6 of the cyclohexane-1,3-dione molecule by successive alkylation under the action of strong bases. (±)-Angustione (a natural β-diketone) has been synthesized.

In the course of a study of the alkylation of enaminodiketones of the cyclohexane series under the action of strong bases, we developed a convenient method for the successive introduction of several alkyl groups into the cyclic part of the molecule and proposed a scheme for the synthesis of (±)-angustione [1]. We considered it desirable to employ an analogous approach for the alkylation of cyclohexane-1,3-dione with the aim of obtaining substituted β-diketones, which are intermediates in the synthesis of heteroanalogs of steroids [2], glutarimide antibiotics [3], and other natural compounds and their analogs.

A method is known for obtaining substituted β-diketones of the cyclohexane series by the alkylation of enol ethers of cyclohexane-1,3-dione under the action of strong bases with subsequent hydrolysis of the ether groups [4]. A more convenient, in our view, method of introducing an alkyl substituent by the direct alkylation of a cyclohexane β-diketone has also been described [5].

In the present communication we propose a method which permits monomethyl derivatives of cyclohexane-1,3-dione to be obtained with a higher yield, and also a method for obtaining derivatives of β-diketones with several alkyl groups by the successive alkylation of cyclohexane-1,3-dione under the action of strong bases.

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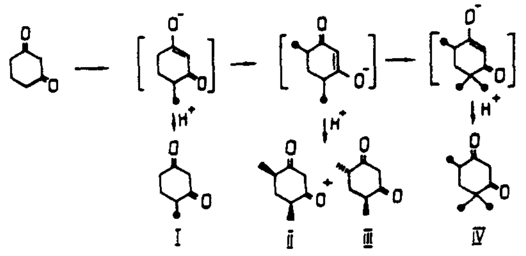
TABLE 1. Yields, Melting Points, and Elementary Analyses of the β-Diketones Obtained

Compound	Yield %	mp, °C (solvent)	M+	Found, % C	Found, % H	Formula	Calculated, % C	Calculated, % H	M, c.u.
II	18	111–113* (hexane–benzene)	140	68,33	8,78	$C_8H_{12}O_2$	68,54	8,63	140.18
III	69	72–73 (hexane–benzene)	140	68,47	8,86	$C_8H_{12}O_2$	68,54	8,63	140,18
IV	74	131–132** (hexane)	154	70,04	9.47	$C_9H_{14}O_2$	70,10	9,15	154.20

*According to the literature [6], mp 110-113°C.
**The melting point was determined in a sealed capillary. According to the literature [7], 131-132°C (petroleum ether).

The generation of the dianion and the treatment with the alkylating agent are carried out at a higher temperature than in [5], and triphenylmethane is used as the indicator of the formation of the β-diketone monoanion, which ensures a higher yield of monomethyl-substituted product with good reproducibility of the results. Compound (I) was obtained with a yield of 95%, its physicochemical characteristics corresponding to those given in [9] for 4-methylcyclohexane-1,3-dione.

To obtain disubsituted cyclohexane-1,3-diones we used the approach that we had employed previously for the synthesis of (±)-angustione [1]. After the performance of the successive double methylation of cyclohexane-1,3-dione we isolated two isomeric products: cis-4,6-dimethyl-cyclohexane-1,3-dione (II) and trans-4,6-dimethylcyclochexane-1,3-dione (III) in a ratio of 1:4 (Scheme 1).



Scheme 1.

The physicochemical characteristics of compound (II) corresponded to those for this compound given in the literature [6].

The composition and structure of compound (III) were deduced on the basis of elementary analysis and PMR, IR, and mass spectra (Tables 1 and 2). Elementary analysis confirmed its empirical formula. The mass spectrum showed the peak of the molecular ion. In the IR spectrum there was the absorption in the 1710-1745 cm^{-1} region that is characteristic for cyclohexane diketones. The PMR spectrum confirmed the trans arrangement of the methyl groups in compound (III). Thus, the spectrum contained a signal at 3.44 ppm in the form of a two-proton singlet corresponding to the CH_2-2 group. A signal at 2.74 ppm was observed in the form of a two-proton sextet with an SSCC of 6.8 Hz and corresponded to the H-4 and H-6 protons, and a six-proton doublet at 1.27 ppm with an SSCC of 6.8 Hz to the Me-4 and Me-6 methyl groups. A two-proton triplet at 1.85 ppm (SSCC 6.8 Hz) corresponded to the CH_2-5 methylene protons. This signal had the form of triplet, apparently because, in the trans-isomer (III) with the axial equatorial arrangement of the methyl groups and rapid inversion of the ring an averaging of the spin–spin coupling constant for CH_2-5 is observed.

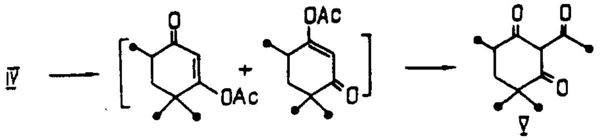
We have observed an analogous pattern in the PMR spectrum of 2-acetyl-trans-4,6-dimethylcyclohexane-1,3-dione [1]. It must also be pointed out that in this case, similarly to what we have described for trans-4,6-dimethyl-2-(1-pyrrolidinoethylidene)cyclohexane-1,3-dione [1], we observed a passage of the trans-isomer (III) into the corresponding cis-isomer (II). This spontaneous gradual transition of compound (III) into (II) indicates the greater thermodynamic stability of the cis-isomer (II) than of trans-isomer (III).

TABLE 2. IR and PMR Spectra of the β-Diketones Obtained

Compound	IR (C=O, C=C), cm^{-1}	PMR, δ, ppm; J, Hz
II	1605 br. 1715 1735	1,17(6H d Me-4 i Me-6, J=6.5), 1,21(1H, q, H_{ax}-5, J=14,0), 2,17(1H, dd, H_{eq}-5, J=5.5,14,0), 2,69(2H, q, H-4 and H-6), 3,39 (1H, d, H_a-2 of an AB system *AB*, J=16,2), 3,49 (1H, d, H_b-2 of an AB system *AB*, J=16.2)
III	1610 br. 1715 1735	1,27 (6H, d, Me-4 s Me-6, J=6,8), 1,85(2H, t, CH_2-5, J=6,8), 2,74 (2H, sextet, H-4 i H-6, J=6,8), 3,44 (2H, s, CH_2-2)
IV	1610 br. 1710 1730	1,16(3H d, Me-6, J=6,5), 1,18(3H s, Me-4), 1,32(3H, s Me-4) 1,49(1H t, H_{ax}-5, J=14,0), 1,88(1H, dd H_{eq}-5, J=14,0;5,5), 2,74(1H, m, H_{ax}-6), 3,35(1H, d, H_a-2 of an AB system *AB*, J=16,0) 3,59 (1H, d, H_b-2 of an AB system *AB*, J=16,0)

On the successive triple alkylation of cyclohexane-1,3-dione without isolating the intermediate compounds we obtained 4,4,6-trimethyl-cyclohexane-1,3-dione (IV) with a yield of 74%. The melting point of compound (IV) corresponded to that given in the literature [7]. The results of physicochemical analysis confirmed the correctness of the ascribed structure (see Tables 1 and 2). In the PMR spectrum of compound (IV), the value of the SSCC of H-6 on H_{ax}-5 was 14.0 Hz, and the value of the SSCC of H-6 on H_{eq}-5 was 5.5 Hz, which unambiguously showed the axial orientation of the H-6 proton and, correspondingly, the equatorial orientation of the Me-6 group.

The β-diketone (IV) was then used for the synthesis of (±)-angustione a natural; β-diketone (V). Thus, the diketone (IV) was treated with sodium methanolate, acetyl chloride was added to the resulting salt, and the mixture of products of O-acetylation was isomerized in the presence of 4-dimethylaminopyridine, giving 2-acetyl-4,4,6-trimethylcyclohexane-1,3-dione — (±)-angustione (V) — with a yield of 50%.



The physicochemical characteristics of compound (V) coincided with those given in [1].

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument. PMR spectra were taken on a Bruker AC-200 instrument with a working frequency of 200 MHz, TMS as internal standard, and $CDCl_3$ as solvent. Chemical shifts are given in ppm on the δ scale. Mass spectra were obtained on a Varian MAT-311 spectrometer. The melting points of the compounds obtained were determined on a Boëtius stage. Reactions were conducted in THF, which was redistilled over lithium tetrahydroaluminate and stored over fused KOH. Hexamethylphosphorotriamide was redistilled over CaO and was stored over 4 Å molecular sieves and drops of mercury. Diisorpopylamine was redistilled and was stored over KOH. Butyllithium was used in the form of a 2.65 N solution in hexane. The monitoring of the course of the reaction and of the individuality of the compounds was carried out by the TLC method on DC-Plastikfolien UV-254 plates (Merck). Column chromatography was conducted on silica gel L 40/100 (Lachema-Chemapol) under pressure on 30 × 800 mm column (the eluent being petroleum ether—ethyl acetate (4:1)).

General Procedure for Successive Alkylation. a) Introduction of the First Methyl Group. A solution of 1.12 g of cyclohexane-1,3-dione, 3.0 g of diisopropylamine, 11 g of hexamethylphosphorotriamide and 0.005 g of triphenylmethylmethane in 80 ml of THF was cooled in an atmosphere of argon to —(5-0)°C, and then butyllithium was added gradually until a red coloration had appeared. Then another 3.8 ml of butyllithium was added and stirring was continued at the same temperature for 45 min. After this, 1.4 g of methyl iodide was added and the mixture was stirred for another 45 min.

b) Introduction of the Second Methyl Group. After the introduction of the first methyl group (as described in paragraph a), another 3.8 ml of butyllithium was added to the reaction mixture, and after 45 min it was treated with 1.4 g of methyl iodide, and stirring was continued for 45 min.

c) The introduction of the third methyl group was performed by the method described in paragraph b.

Working up of the Reaction Mixture. After the performance of alkylation (a, b, or c), the reaction mixture was poured into 200 ml of water. The solvent and low-boiling compounds were evaporated off under vacuum, the aqueous solution was washed with chloroform (3 × 50 ml) and was acidified with concentrated HCl, and the reaction products were extracted with chloroform (4 × 50 ml). The extract was dried over Na_2SO_4, the solvent was evaporated off under vacuum, and the residue was chromatographed.

2-Acetyl-4,4,6-trimethylcyclohexane-1,3-dione. (±)-Angustione (V). A solution of 3.1 g of 4,4,6-trimethylcyclohexane-1,3-dione (IV) in 50 ml of absolute methanol was treated with an equimolar amount of a solution of sodium methanolate in methanol. After 15 min, the solvent was evaporated off under reduced pressure, and then 50 ml of toluene was added and part of it was distilled off with the last traces of methanol, after which toluene was added to make the total volume of the reaction mixture 70 ml and then, with stirring, 1.6 g of acetyl chloride; after 30 min, the reaction mixture was heated to 50°C and was stirred at this temperature for another 3 h. The last traces of acetyl chloride were distilled off, the reaction mixture was cooled to 100-105°C, and 0.2 g of 4-dimethylaminopyridine was added. After 6 h, the mixture was cooled and it was washed with 1 N HCl solution (2 × 50 ml) and with 1 N NaOH (3 × 40 ml). The alkaline solution was washed with ether (1 × 50 ml) and was acidified with concentrated HCl. The products were extracted with ether (4 × 40 ml). The combined extract was dried over Na_2SO_4, and the solvent was evaporated off. After chromatographic separation (eluent: hexane—ether (95:5), 2.0 g (50%) of (±)-angustione (V) and 0.9 g (29%) of the β-diketone (IV) were obtained.

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