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METHODS OF SYNTHESIS AND TECHNOLOGY OF DRUG PRODUCTION

CHLORINATION OF β-DICARBONYL COMPOUNDS

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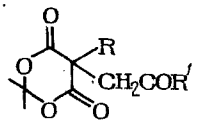
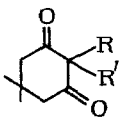
We propose a simple method of chlorination of cyclic β-dicarbonyl compounds by a $ClSiMe_3$ — KIO_3 system in DMFA at room temperature. For example, by the action of these reagents on 2,2-dimethyl-5-phenacyl-1,3-dioxane-4,6-dione (I), 5-p-bromophenacyl-2,2-dimethyl-1,3-dioxane-4,6-dione (II), 2,2-dimethyl-5-(2-oxoheptyl)-1,3-dioxane-4,6-dione (III), 5,5-dimethylcyclohexane-1,3-dione (IV), and 5,5-dimethyl-2-p-nitrobenzylcyclohexane-1,3-dione (V) the corresponding monochloro derivatives (VI-X) were obtained in yields of from 60 to 89% (see Table 1).



I-III, VI-VIII



IV, V, IX, X

R—H (I—V, IX), Cl (VI—VIII, X);
R^1=Ph (I, VI), p-Br C_6H_4 (II, VII), Am (III, VIII), H (IV),
p-$NO_2C_6H_4CH_2$ (V, X), Cl (IX)

Because of the high yields and simplicity of execution of the operations, the proposed method may compete with the previously described methods [1-5].

Chlorides VI-VIII are used as intermediates in the synthesis of compounds having cytoprotecting, antiulcer, and antirheumatic activity [1, 6-8].

EXPERIMENTAL

The PMR spectra were run on a "Geol FX-90 Q" spectrometer (Japan) in CF_3COOH with the addition of 5% $CDCl_3$. The course of the reaction and the purity of the synthesized compounds were monitored by thin layer chromatography on Silufol UV-254 in benzene (detection of the compounds by I_2 vapors and in UV light). The elemental analysis data of compounds V and X correspond to the calculated values.

Preparation of 5,5-Dimethyl-2-p-nitrobenzylcyclohexane-1,3-dione (V). A 2.8 g portion (20 mmoles) of dimedone and then 4.4 g (20 mmoles) of p-nitrobenzoyl bromide were added with stirring to a solution of 1.12 g (20 mmoles of KOH in 7 ml of 96% alcohol and 2 ml of water. The mixture was stirred for another 24 h at ~20°C, then boiled for 1 h, diluted with water, treated with excess of K_2CO_3, and filtered. The mother liquor was acidified with concentrated HCl, the precipitate was filtered off, washed with water, and dried in air. Yield, 2.5 g (45%) of diketone V, $C_{15}H_{17}NO_4$, mp 186-189°C (from alcohol). PMR spectrum, δ, ppm: 1.25 s (6H, $2CH_3$), 2.86 s (4H, $2CH_2$), 3.97 s (2H, CH_2), 7.50 d (2H of the aromatic ring, J = 8 Hz), 8.22 d (2H of the aromatic ring, J = 8 Hz).

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TABLE 1. Chloro Derivatives VI-X

Compound	Yield, %	mp, °C	Ref.
VI	80	92—4	[1]
VII	89	148—50	[1]
VIII	60	60—3	[1]
IX	82	160—2	[2]
X	78	123—6 (from ether)	—

General Method of Chlorination of β-Dicarbonyl Compounds (I-V). A 15 mmole portion (10 mmoles in the case of dimedone) of KIO_3 was gradually added, with stirring, to a mixture of 10 mmoles of I-V, 30 mmoles (15 mmoles in the case of dimedone) of $ClSiMe_3$, and 5 ml of DMFA. The mixture was stirred for 24 h (for IV — 6 h), diluted with water (IX), aqueous solution of K_2CO_3 (VI-VIII) or an aqueous solution of $NaHCO_3$ (X). The mixture was allowed to stand for 1-2 h at ~20°C, the precipitate was filtered off, washed with water and dried in air. Chloride X, $C_{15}H_{16}ClNO_4$. PMR spectrum, δ, ppm: 0.72 s (3H, CH_3), 1.25 s (3H, CH_3), 2.63 d (2H, J = 15 Hz), 3.25 d (2H, CH_2, J = 15 Hz), 3.70 s (2H, CH_2), 7.58 d (2H of the aromatic ring, J = 7 Hz), 8.20 d (2H of the aromatic ring, J = 7 Hz).

The physical constants of the synthesized compounds and their PMR spectra coincide with the literature data [1, 2, 9].

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