O - AND C-METHYLATION OF SOME 2-ACETYL-1,3-CYCLOALKANEDIONES

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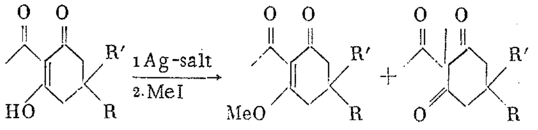
The silver salts of 2-acetyl-1,3-cyclohexanediones when treated with methyl iodide are easily converted to the corresponding 1(3)-O-methyl derivatives, which exhibit a high reactivity when compared with the starting β-triketones [1-3]. This makes it possible to predict the formation of highly diverse polyfunctional compounds from them. In the present paper is discussed the possibility of applying this method to other β-triketones, and also its extension to obtaining other O-derivatives.

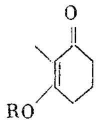
A careful analysis of the products of the studies by us of the reaction of the silver salt of 2-acetyldihydroresorcinol (Ia) with methyl iodide [3] disclosed that, together with ether (IIa), the triketone (IIIa) is formed as a by-product. The structure proposed for (IIIa) is unequivocally corroborated by the data of the IR and UV spectra, which indicate the absence of a conjugated carbonyl function in the molecule, the presence of the three-proton single signal of methyl with δ 1.45 ppm in the NMR spectrum, which testifies to the substantial deshielding effect of the neighboring C = O groups, and, finally, its rapid hydrolytic decomposition to 2-methyldihydroresorcinol (IVa).

The main reaction product of the silver salt of the phenyl analog (Ib) with methyl iodide is, the same as in the case of (Ia), the ether (IIb). The structure of this ether follows from a comparison of its IR, UV, and NMR spectra with the corresponding spectra of ether (IIa), and is corroborated by its hydrolysis under mild conditions to the starting triketone (Ic), and also by its conversion to the pyrrolidine enaminodiketone (V). In the presence of amines the methyl ethers (II) undergo nucleophilic displacement at the trigonal C-3 center, without involving the C = O function here [4]

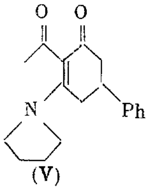


(Ia, b) (IIa, b) (IIIa, b)

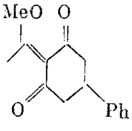
a R=R′=H; b R=H; R′=Ph



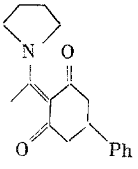
(IVa) R=H
(IVb) R=Ac



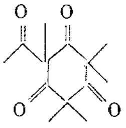
(V)



(VI)



(VII)



(VIII)

For this reason the discussed methyl ether has the structure of (IIb), and not the theoretically possible structure (VI), which, in turn, should correspond to the isomeric enaminodiketone (VII), obtained by the direct enamination of triketone (Ib) [5].

The same as in the above-discussed example, methyl ether (IIb) is accompanied by the methylated in the angular position triketone (IIIb), the structure of which follows from the method of preparation, and also

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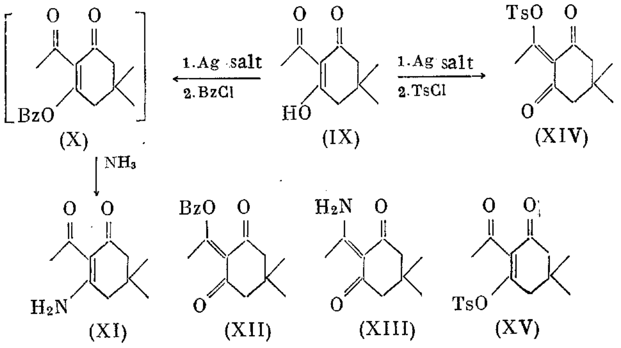
from a comparison of its IR, UV, and NMR spectra with the spectra of the analog (IIIa). Here it should be mentioned that the NMR spectra of the triketones (III) differ in the character of the signals of the protons of the two methyl groups. In triketone (IIIa) they have the shape of two narrow single lines, whereas in (IIIb) both signals are split by a value of approximately 1.5 Hz. It was shown by the binary resonance method that the splitting of the lines was apparently not caused by further spin – spin couplings, and the effect must obviously be explained by the noticeable decrease in the rate of converting molecule (IIIb), which contains a quite bulky substituent at C-5.

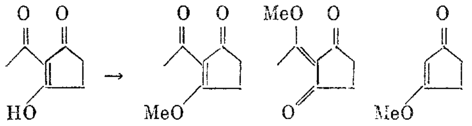
Nonenolizing methyltriketones of the (III) type represent independent interest, and only tetraketone (VIII) was described [6] in this series of compounds. Known is the unsuccessful attempt [7] to accomplish O → C-acyl migration and to synthesize in this way the triketone (IIIa) from the acetate (IVb) by the Dieckmann method [8], which is usually used to obtain enolizing β-triketones of the (I) type. Our attempt to accomplish a similar rearrangement of acetate (IVb) under various conditions also proved unsuccessful. At least, this result can be partially explained by the high sensitivity of triketone (IIIa) to hydrolytic cleavage, which is catalyzed by weak acids and bases.

As a result, the discussed data testifies that the methylation of the silver salts of β-triketones (I) in a nonpolar solvent proceeds predominantly at the oxygen atom of the ring. It is possible to assume that the given method will also prove suitable for obtaining other, for example, O-acyl derivatives of the β-triketones (I). For this we studied the reaction of their silver salts with acetyl chloride, chlorocarbonic ester, and benzyol chloride under various conditions. Only in the case of triketone (IX) and benzoyl chloride was a product obtained in low yield, which probably had the structure of benzoate (X). The latter could not be isolated in the pure state, and the conclusion as to its structure was made on the basis of its subsequent reaction with ammonia, as a result of which the known [4] enaminodiketone (XI) was isolated. Here, the same as in the discussion of the pair of ethers (IIb) and (VI), it is logical to assume that if the isomeric benzoate (XII) is formed, then the subsequent reaction with ammonia should lead to the structurally isomeric enaminodiketone (XIII), obtained directly from triketone (IX) [9]



Similar to acyl chlorides, the methane- and p-toluenesulfonyl chlorides react with the silver salt of 2-acetyldimedon (IX) under various conditions to give a complex mixture of products. In the case of p-toluenesulfonyl chloride the very unstable tosylate was isolated in low yield, which, in harmony with the data of the NMR spectrum, can be assigned the structure of (XIV). The alternate structure (XV) is rejected for the reason that the signal of the methylene protons, which is more in harmony with the symmetrical structure (XIV), has the shape of a broad single line, δ 2.42 ppm, which coincides with the signal of the protons of an aromatic methyl. An analogous position and shape of the signal of the methylene protons is also characteristic for enaminodiketones of the (XIII) type [10, 11].

As a result, the obtained data testify that it is possible to synthesize the 1(3)-O-methyl (and, apparently, other alkyl) derivatives of 2-acetyl-1,3-cyclohexanediones from their silver salts. As it proved, this reaction goes in a much more complicated manner with 2-acetyl-1,3-cyclopentanedione (XVI), although also in this case the main isolated product has an analogous structure. Thus, the reaction of the silver salt of β-triketone (XVI) with methyl iodide in tetrahydrofuran (THF) medium gives a product in approximately 15% yield, which is easily hydrolyzed to the starting triketone, and consequently is either the O-derivative (XVII) or (XVIII). The UV spectrum of the compound corroborates its α,β-unsaturated character, while the NMR spectrum has two single signals of the protons of the acetyl and methoxyl groups, δ 2.29 and 4.07 ppm respectively, and also a multiplet of the A_2B_2-spin system of the methylene protons with a center at δ 2.60 ppm. This character of the NMR spectrum of the discussed compound is more in agreement with structure (XVII) than with the symmetrical structure (XVIII). The final choice between the two possible structures in favor of (XVII) was made on the basis of the data of the IR spectra and the subsequent chemical transformations, which will be published later



(XVI) (XVII) (XVIII) (XIX)

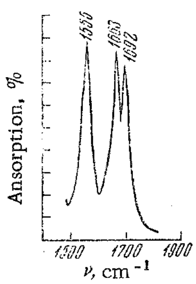


Fig. 1. Infrared spectrum of ether (XVII) (0.7 mg/200 mg of KBr).

In the IR spectrum of ether (XVII), in the region of the frequencies of the vibrations of double bonds (2% solutions in CCl_4), are observed three bands: 1577, 1683, and 1706 cm^{-1}. In the crystalline state the corresponding frequencies are observed at 1555, 1663, and 1692 cm^{-1} (Fig. 1).

An assignment of the bands* can be made by comparing the spectrum of (XVII) with the spectrum of the keto form of the desacetyl analog (XIX), which was synthesized in our laboratory by V. A. Mironov and A. P. Ivanov, where the frequencies of the C = C and C = O bonds are respectively 1602 and 1712 cm^{-1} (in CCl_4). As a result, the introduction of the acetyl group into the molecule (XIX) leads to an important decrease in the frequency of the C = C vibrations in a five-membered ring (1577 cm^{-1}). It is obvious that the frequency of the vibrations of the cyclic C = O group, standing in conjugation with the C = C group, should also drop just as importantly, and consequently it is logical to assign to it the intense band at 1683 cm^{-1}. As regards the frequency of the vibrations of the acetyl C = O group (1706 cm^{-1}), then it is close to the value that is usually observed for an unconjugated keto function. Consequently, it is possible to assume, as was already done by us earlier [3] when discussing the IR spectra of ethers of the cyclohexane series, that the acetyl group in (XVII) is not found in the plane of the C = C bond of the ring. An examination of models discloses that such a coplanar state can hardly be realized due to the substantial steric interactions in molecule (XVII).

In view of this, a substantial change in the frequencies of the cyclic multiple bonds in ether (XVII) when compared with (XIX) must probably be attributed to the inductive influence of the acetyl group at C-2. The proposed assignment of the frequencies of the C = O group is also corroborated by the ratio in the intensities of the corresponding bands: the band of the conjugated cyclic carbonyl group (1683 cm^{-1}) in CCl_4 solution greatly exceeds in intensity the band at 1706 cm^{-1}.

A study of the IR spectra of ether (XVII) in various solvents (chloroform, acetonitrile, dioxane, dimethyl sulfoxide), and in the crystalline state, testifies to the fact that compound (XVII) exists predominantly in the keto form, and is less apt to undergo keto-enol tautomerism than its desacetyl analog (XIX). This conclusion is also corroborated by the data of the NMR spectrum of ether (XVII), a solution of which in deuterochloroform, containing trifluoroacetic acid, fails to exhibit the signals of olefinic protons.

EXPERIMENTAL

The melting points were determined on a Koffler block. The IR spectra were obtained on a UR-10 instrument, while the UV spectra were obtained on a Hitachi EPS-2 recording spectrophotometer. The NMR spectra of solutions in $CDCl_3$ were measured on a Varian DA-60 spectrometer, with an operating frequency of 60 MHz, at a temperature of 30°, using hexamethyldisiloxane as the internal standard.

2-Methyl-2-acetyl-1,3-cyclohexanedione (IIIa). Triketone (IIIa) is formed, together with the previously described methoxydiketone (IIa) [3], by the methylation of triketone (Ia). From the mother liquors, obtained from the crystallization of methoxydiketone (IIa), by further fractional crystallization of the products from an ether – hexane mixture was isolated the triketone (IIIa) in approximately 5% yield. The compound was obtained as colorless plates with mp 64-65°. Found: C 64.24; H 7.11%. $C_9H_{12}O_3$. Calculated: C 64.27; H 7.19%. Infrared spectrum (ν, cm^{-1}): 1700, 1715, 1745 (KBr). Ultraviolet spectrum (λ_{max}, nm): 294 (ε 250) (alcohol). NMR spectrum: δ 1.45 ppm (singlet; 3H); δ 2.08 ppm (singlet; 3H); δ 2.70 ppm (center of multiplet; 6H).

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*Not excluded is the fact that interaction of equivalent groups during vibrations is possible in such a system; this can complicate an interpretation of the spectrum. This question requires additional study.

Hydrolytic cleavage of Methyltriketone (IIIa). To a solution of 150 mg of methyltriketone (IIIa) in 15 ml of aqueous dioxane (1 : 1) was added 1 ml of 10% HCl solution, and the mixture was allowed to stand at room temperature for 3 h, after which it was neutralized with $NaHCO_3$ and extracted with benzene. Conventional workup of the extract, followed by recrystallization of the product from alcohol, gave in quantitative yield 2-methyldihydroresorcinol (IVa) with mp 206-208°, which was identical with an authentic specimen.

Preparation of 3-Methoxy-2-acetyl-5-phenyl-2-cyclohexen-1-one (IIb) and 2-Methyl-2-acetyl-5-phenyl-1,3-cyclohexanedione (IIIb). To a suspension of 6.3 g of the silver salt of β-triketone (Ib) [8] (obtained in approximately 90% yield by the successive treatment of the β-triketone with equivalent amounts of aqueous NaOH and $AgNO_3$ solutions) in 150 ml of anhydrous ether was added 7 ml of CH_3I, and the stirred mixture was heated at reflux for 2.5 h. Then the AgI precipitate was filtered, washed with ether, the filtrate was evaporated, and the residue, weighing about 3 g, was recrystallized from ether. We obtained 1.1 g (20% when based on the starting β-triketone) of methyl ether (IIb) as colorless needles with mp 85-86°. Found: C 73.87; H 6.75%. $C_{15}H_{16}O_3$. Calculated: C 73.74; H 6.60%. Infrared spectrum (ν, cm^{-1}): 1090, 1600, 1640, 1703 (KBr). Ultraviolet spectrum (λ_{max}, nm): 263 (ε 21000) (alcohol). NMR spectrum: δ 2.33 ppm (singlet; 3H); δ 2.50-3.70 ppm (multiplet; 5H); δ 3.81 ppm (singlet; 3H); δ 7.28 ppm (center of multiplet; 5H).

From the mother liquors by fractional crystallization of the products from an ether – hexane mixture was isolated 0.6 g (11% when based on the starting β-triketone) of methyltriketone (IIIb) as colorless plates with mp 105-107° (sublimes). Found: C 73.61; H 6.69%. $C_{15}H_{16}O_3$. Calculated: C 73.74; H 6.60%. Infrared spectrum (ν, cm^{-1}): 1702, 1735 (KBr). Ultraviolet spectrum (λ_{max}, nm): 283 (ε 1585) (alcohol). NMR spectrum: δ 1.52 and 1.54 ppm (CH_3; singlet; 3H); δ 2.12 and 2.15 ppm (CH_3CO; singlet, 3H); δ 2.80-3.70 ppm (multiplet; 5H); δ 7.25 ppm (center of multiplet; 5H).

Preparation of 2-Acetyl-5-phenyl-3-N-pyrrolidinyl-2-cyclohexen-1-one (V). To a solution of 240 mg of methyl ether (IIb) in 20 ml of benzene was added 70 mg of pyrrolidine and the mixture was allowed to stand at room temperature for 30 min. The solvent was removed in vacuo, and the residue was recrystallized from a benzene – hexane mixture. We obtained 250 mg (90%) of enaminodiketone (V), which exists as three colorless polymorphous modifications: needles with mp 116-117°, and prisms with mp 135-137° and 152-153°. Found: C 76.58; H 7.58; N 4.83%. $C_{18}H_{21}O_2N$. Calculated: C 76.29; H 7.47; N 4.94%. Infrared spectrum (ν, cm^{-1}): 1520, 1609 (KBr). Ultraviolet spectrum (λ_{max}, nm): 273.5 (ε 24200); 313 (ε 27200) (alcohol).

Benzoylation of Silver Salt of 2-Acetyldimedon (IX). To a suspension of 2 g of the Ag salt (obtained in approximately 95% yield by the successive treatment of 2-acetyldimedon with equivalent amounts of aqueous NaOH and $AgNO_3$ solutions) in 100 ml of anhydrous ether was added 1.4 g of freshly distilled C_6H_5COCl, and the stirred mixture was heated at reflux for 4.5 h. After separating the precipitate and removal of the solvent we obtained approximately 1 g of an oily product, which was dissolved in 50 ml of benzene, and a stream of NH_3 was passed into the solution at room temperature for 30 min. After removal of the solvent in vacuo the residue was recrystallized from benzene. Here we obtained approximately 100 mg of enaminodiketone (XI), mp 160-162°, which did not depress the mixed melting point with an authentic specimen [4], and failed to differ from it chromatographically (on a loose layer of Al_2O_3).

Tosylation of Silver Salt of 2-Acetyldimedon (IX). To a suspension of 4 g of the Ag salt of triketone (IX) in 100 ml of anhydrous ether was added 3.5 g of p-toluenesulfonyl chloride, and the stirred mixture was heated at reflux for 3 h. After separating the precipitate and removal of the solvent we obtained approximately 6 g of a semicrystalline oily product, which was treated with hexane and then recrystallized from an ether – hexane mixture. We obtained 510 mg (7%) of 5,5-dimethyl-2-(α-tosyloxyethylidene)-1,3-cyclohexanedione (XIV) as colorless hygroscopic plates with mp 46-47°. Found: S 10.20%. $C_{17}H_{20}O_5S$. Calculated: S 9.53%. Infrared spectrum (ν, cm^{-1}): 1600, 1675 (film). Ultraviolet spectrum (λ_{max}, nm): 232 (ε 21000); 270 (ε 5200) ($CHCl_3$). NMR spectrum: δ 1.00 ppm ($>CMe_2$; singlet; 6H); δ 2.42 ppm (aromatic Me and two CH_2; broad singlet; 7H); δ 2.57 ppm (olefinic Me; singlet; 3H); δ 7.40 ppm (center of quadruplet; 4H).

Preapration of 3-Methoxy-2-acetyl-2-cyclopenten-1-one (XVII). Triketone (XVI) [12] (5.0 g) was successively treated with 21 ml of 1.9 N NaOH solution and 6.1 g of $AgNO_3$, and then the obtained precipitate of the Ag salt was dried to constant weight in vacuo. To a suspension of 9.5 g of the indicated salt was added 5 ml of CH_3I, and the stirred mixture was heated at reflux for 2 h. The precipitate was filtered, washed with THF, the filtrate evaporated, and the residue, weighing 780 mg, was recrystallized from an ether – hexane mixture. We obtained 700 mg (13% when based on the starting β-triketone) of methyl ether (XVII) as colorless needles with mp 74-75°. Found: C 62.28; H 6.57%. $C_8H_{10}O_3$. Calculated: C 62.32; H 6.54%. Ultraviolet spectrum (λ_{max}, nm): 230 (ε 8860); 258 (ε 14650) (methanol); 256.5 (ε 13400) ($CHCl_3$).

CONCLUSIONS

1. The reaction of the silver salts of 2-acetyl-1,3-cyclohexanediones with methyl iodide in a nonpolar solvent gives 3-methoxy-2-acetyl-2-cyclohexen-1-ones (main product) and 2-methyl-2-acetyl-1,3-cyclohexanediones.

2. 2-Acetyl-1,3-cyclopentanedione under the same conditions forms only the corresponding 1(3)-O-methyl ether in approximately 15% yield.

3. The data of the IR spectra for 3-methoxy-2-acetyl-2-cyclopenten-1-one testify that the side acetyl group is not coplanar with the cyclic multiple bonds.

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