METHYLATION OF BIS(1,3-DIKETO-2-CYCLOHEXYL)METHANES

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The methylation of bis(1,3-diketo-2-cyclohexyl)methanes with diazomethane gives cyclic monomethyl esters.

It is known that bis(1,3-diketo-2-cyclohexyl)methanes exist in two forms — in a chelate form (open from I) and a cyclic hemiketal form (ring form II) [1, 2]. The conversion of one form to the other, which apparently proceeds through momoanions III and IV, has been established.

In order to study the reactivities of bis(1,3-diketo-2-cyclohexyl)methanes we methylated them with diazomethane in a solution of absolute ether at room temperature. We were able to isolate cyclic monomethyl ethers — 4a-methoxy-1,2,3,4,4a,5,6,7,8,9a-decahydroxanthene-1,8-diones (Va-j) — from the reaction mixture.

Compounds Va-j are colorless or light-yellow crystalline substances (Table 1) and their structures were confirmed by their IR, UV, and PMR spectra (Table 2).

Absorption bands of a cyclohexane carbonyl group at 1710-1728 cm^{-1}, of a conjugated carbonyl group at 1648-1670 cm^{-1}, and a double bond at 1621-1641 cm^{-1} are observed in the IR spectra of Va-j, but the stretching vibrations of a hydroxyl group at 2500-3500 cm^{-1} are absent. The pattern of the IR spectrum is retained in the case of a dioxane solution (Table 2).

The possibility of the presence of the open β-diketone structure [3] for Va-j is excluded by the absence of splitting of the carbonyl absorption at 1710-1728 cm^{-1}.

A maximum that attests to the presence of one chromophore system appears in the UV spectrum of a 50% ethanol solution of the product at λ_{max} 258-260 nm. Signals for the

TABLE 1. 4a-Methoxy-1,2,3,4,4a,5,6,7,8,9a-decahydroxanthene-1,8-diones (Va-j)

Compound	R	R_1	R_2	mp (dec.), °C	Empirical formula	Found, %		Calc., %		Yield, %
						C	H	C	H	
Va	H	H	H	156—158	$C_{14}H_{18}O_4$	67,5	7,5	67,2	7,3	49
Vb	H	H	CH_3	180—181	$C_{16}H_{22}O_4$	69,0	8,1	69,0	8,0	40
Vc	H	CH_3	CH_3	202	$C_{18}H_{26}O_4$	70,9	8,8	70,6	8,6	56
Vd	C_6H_5	CH_3	CH_3	199—201	$C_{24}H_{30}O_4$	75,8	8.0	75.4	7,9	79
Ve	C_6H_5	H	CH_3	176—178	$C_{22}H_{26}O_4$	74,5	7,3	74,6	7,4	32
Vf	C_6H_5	H	H	255—257	$C_{20}H_{22}O_4$	74,3	7,0	73,6	6,8	41
Vh	CH_3	H	CH_3	173—174	$C_{17}H_{24}O_4$	70,3	8,4	69,8	8.3	28
Vg	p-$CH_3OC_6H_4$	H	CH_3	151	$C_{23}H_{28}O_5$	71,9	7.5	71,9	7,3	37
Vi	p-ClC_6H_4	H	CH_3	165—166	$C_{22}H_{25}O_4Cl$*	68,4	6.3	68,0	6,5	31
Vj	p-$(NCCH_2CH_2)_2NC_6H_4$	CH_3	CH_3	142—144	$C_{30}H_{37}O_4N_3$**	72,0	7,7	71,5	7,4	73

*Found: Cl 9.30%. Calculated: Cl 9.12%.

†Found: N 8.35%. Calculated: N 8.34%.

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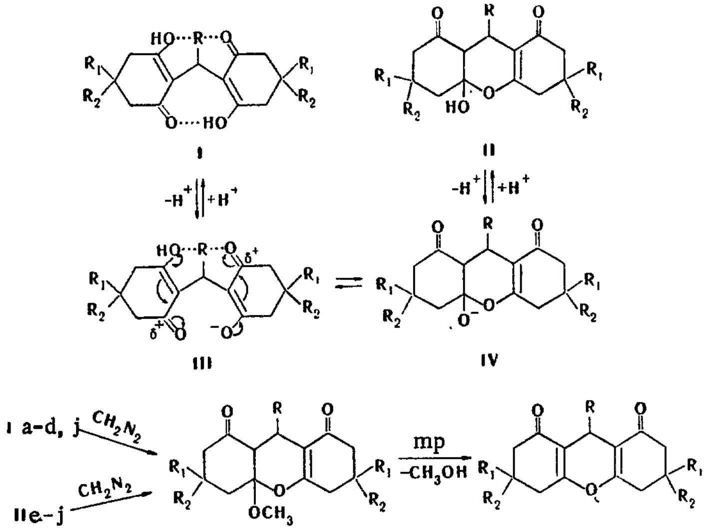
protons of only one methoxy group appear in the PMR spectrum, and the signal of a proton of an enol hydroxyl group is not observed.

The rate of the reaction of aliphatic diazo compounds with protic acids is proportional to the pH of the reaction medium. The open form (I) of bis(1,3-diketo-2-cyclohexyl)methanes is methylated more rapidly by diazomethane than ring-form II. This is associated with the different acidities of forms I and II. Ring-form II is ionized to a lesser extent. The ionization and tautomeric transformation can be depicted by the following scheme:



I

II

III

IV

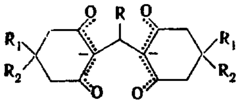
I a-d, j

IIe-j

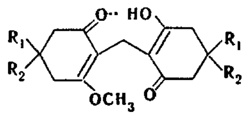
V a-j

VI

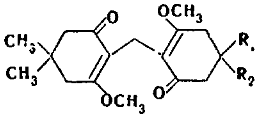
I, II, Va $R=R_1=R_2=H$; b $R=R_1=H$, $R_2=CH_3$; c $R=H$, $R_1=R_2=CH_3$; d $R=C_6H_5$, $R_1=R_2=CH_3$; e $R=C_6H_5$, $R_1=H$, $R_2=CH_3$; f $R=C_6H_5$, $R_1=R_2=H$; h $R=R_2=CH_3$, $R_1=H$; g $R=p\text{-}CH_3OC_6H_4$, $R_1=H$, $R_2=CH_3$; i $R=n\text{-}ClC_6H_4$, $R_1=H$, $R_2=CH_3$; j $R=p\text{-}(NCCH_2CH_2)_2NC_6H_4$, $R_1=R_2=CH_3$



VII a-c, e



VIII a, b



IX

VII a $R=R_1=R_2=H$; b $R=R_1=H$, $R_2=CH_3$; c $R=H$, $R_1=R_2=CH_3$; e $R=C_6H_5$, $R_1=H$, $R_2=CH_3$; VIII a $R=R_1=R_2=H$; b $R=H$, $R_1=R_2=CH_3$; IX $R_1=R_2=CH_3$

All of the structural changes as a result of which the nucleophilicity of the oxygen atom of the OH group or the electrophilicity of the carbon atom of the C=O group are increased stabilize the ring forms and shift the equilibrium in its favor [4]. The spatial drawing together of the reacting groups is very important. Electronic effects with opposing influences stabilize the open form. In monoanion III the electrophilic center for intramolecular addition is the carbon atom of the carbonyl group of the undissociated enol form, in which the electronic shift is less pronounced than in the dissociated form ($\delta^{\oplus} > \delta'^{\ominus}$).

Kondrat'eva and co-workers [5] isolated the monomethyl ether (VIIIb) of the open structure and the dimethyl ether (IX) of bis(1,3-diketo-5,5-dimethyl-2-cyclohexyl)methane with mp 94-95 and 125-125°, respectively. We carried out a similar experiment in a solution of absolute ether and isolated a mixture of products with mp 107-190°. We assume that the mixture consists of monomethyl ether VIIIb, the starting bisdiketone, and cyclic ether Vc (synthesized for the first time), which was obtained by treatment of Ic with diazomethane for 48 h.

Kondrat'eva and co-workers [5] also described a monomethyl ether of bis(1,3-diketo-2-cyclohexyl)methane with open structure VIIIa and mp 156-158°; this product has only the band of a conjugated carbonyl group in its IR spectra. The product that we obtained by methylation of bis(1,3-diketo-2-cyclohexyl)methane (Va) has the same melting point, but bands of unconjugated (1720 cm^{-1}) and conjugated (1654 cm^{-1}) carbonyl groups are observed in its IR spectrum. It might therefore by supposed that product Va has a cyclic structure.

TABLE 2. Spectral Characteristics of 4a-Methoxy-1,2,3,4,4a,5,6,7,8,9a-Decahydroxanthene-1,8-diones (Va-j)

Compound	IR spectrum, * ν_{max}, cm^{-1}									λ_{max}, nm (lg ε)			PMR spectra, δ, ppm			
	C–O	C=O	C=C	C=O	ε	C=O	ε	C=C	ε	50% ethanol	0.1 N HCl in 50% ethanol	0.1 N KOH in 50% ethanol	—CH₃	protons of the decahydroxanthenedione ring	—OCH₃	—C₆H₅
Va	1720 (61)†	1654 (58)	1626 (72)	1724	430	1662	345	1637	560	258 (4,14)	258 (4,13)	282 (4,39)	—	1,68—2,20m ‡, 2,27—2,68 м	3,20 s	—
Vb	1714 (72)	1649 (55)	1621 (55)	1726	445	1663	325	1638	565	259 (4,21)	259 (4,24)	280 (4,43)	1,12 s	1,90—2,70m	3,18 s	—
Vc	1716 (53)	1649 (42)	1623 (60)	1726	305	1661	240	1637	420	260 (4,18)	260 (4,18)	283 (4,41)	1,06—1,14 d	1,70—2,53 m	3,12 s	—
Vd	1719 (53)	1662 (52)	1637 (72)	1728	295	1670	395	1640	490	—	—	—	—	—	—	—
Ve	1710 (69)	1653 (68)	1623 (80)	1720	320	1663	370	1638	580	258 (4,12)	258 (4,14)	236 (4,15) 296 (3,73)	1,10 s	1,80—2,60m	3,08 s	7,08 s
Vf	1716 (51)	1659 (59)	1625 (71)	1727	340	1669	365	1639	505	—	—	—	—	—	—	—
Vh	1712 (61)	1648 (54)	1631 (72)	1725	360	1663	355	1639	575	—	—	—	—	—	—	—
Vg	1714 (67)	1655 (65)	1630 (85)	1724	310	1670	345	1641	595	—	—	—	—	—	—	—
Vi	1718 (54)	1662 (68)	1631 (72)	1725	320	1668	350	1640	565	—	—	—	—	—	—	—
Vj	1725 (33)	1659 (33)	1635 (55)	1726	335	1670	291	1640	583	—	—	—	—	—	—	—

*Of suspensions in mineral oil and $2.5 \cdot 10^{-2}$ M solutions in dioxane (layer thickness l = 0.011 cm).

†The absorption intensity in percent is indicated in parentheses.

††Complex multiplet; s is singlet and d is doublet.

We isolated only cyclic monomethyl ethers of bis(1,3-diketo-2-cyclohexyl)methane. For example, only cyclic monomethyl ether Vj was obtained by diazomethane methylation of open-form Ij and cyclic form IIj of p-[N,N-bis(β-cyanoethyl)aminophenyl]bis(1,3-diketo-5,5-dimethyl-2-cyclohexyl)methane [6]. In all likelihood the electronic effect of the methyl group, which increases the nucleophilicity of the oxygen atom in the methoxy group, promotes the formation of cyclic form V, and this stabilizes the cyclic form or shifts the equilibrium in its favor.

When cyclic monomethyl ethers V are heated to their melting points methanol is split out and octahydroxanthene-1,8-diones (VI) are formed. The starting bis(1,3-diketo-2-cyclohexyl)methanes (I and II) also form octahydroxanthene-1,8-dione derivatives [1, 6].

The cyclic monomethyl ethers have interesting behavior in alkali solution. Characteristic (for octahydroxanthene-1,8-dones) absorption maxima at 236 and 296 nm [7] are observed in the UV spectra of Ve obtained from cyclic bis(1,3-diketo-2-cyclohexyl)methane (IIe). The pyran ring undergoes cleavage after some time to give dianion VIIe, which has only one intense maximum at 292-294 nm [8, 9]. Cyclic monoethers Va-c, obtained from open bis(1,3-diketo-2-cyclohexyl)methanes Ia-c, do not form octahydroxanthene-1,8-diones in alkaline media but undergo saponification with cleavage of the pyran ring to give the corresponding **dianions** (VIIa-c).

Methylation with methanol in acidic media [10, 11] is not suitable for the preparation of methyl ethers of bis(1,3-diketo-2-cyclohexyl)-methanes. In this case, a water molecule is split out from I and II, and this leads to octahydroxanthene-1,8-diones. We were also unable to obtain methyl ethers of bis(1,3-diketo-2-cyclohexyl)methanes by methylation with dimethyl sulfate and methyl iodide in alkaline media.

EXPERIMENTAL

The IR spectra were recorded with an IKF-14 spectrometer. The UV spectra of 50% ethanol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of $CDCl_3$ solutions were obtained with a Perkin—Elmer R12A spectrometer with an operating frequency of 60 MHz at 37° with tetramethylsilane as the internal standard.

4a-Methoxy-1,2,3,4,4a,5,6,7,8,9a-decahydroxanthene-1,8-diones (Va-j). A 0.005-mole sample of bis(1,3-diketo-2-cyclohexyl)methanes (I or II) was treated at 20° with a solution of 0.4-0.9 g (0.01-0.02 mole) of diazomethane in 20-40 ml of absolute ether. The mixture was allowed to stand at room temperature for 48 h, after which the precipitates were removed by filtration, and Va-j were recrystallized from benzene–heptane (Table 1). The filtrate was evaporated to dryness, and the residue was recrystallized to give another 5-15% of Va-j.

Octahydroxanthene-1,8-dione Derivatives (VI). A 0.3-0.5-g sample of Vb,c,f-i was heated in a small flask with a gas-outlet tube on an oil bath at the compound's melting point for 10-15 min. The evolved vapors were passed into a test tube containing cold water, and the presence of methanol was proved by the Eegriwe reaction [12]. The corresponding octahydrozanthene-1,8-diones, which were identified from their melting points and IR spectra [1], remained in the flask.

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