

REACTIONS OF 1,5-DIKETONES

X.* SYNTHESIS OF 4-KETOHYDROXANTHENES (NEW FORM OF ISOMERIZATION OF 1,5-DIKETONES)

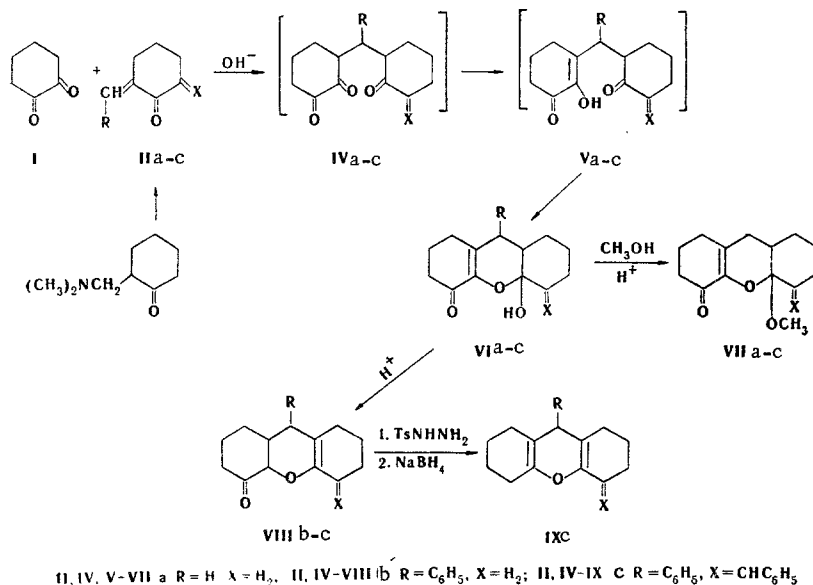
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The corresponding 4-ketohydroxanthenes, which undergo methylation and dehydration, are formed in the condensation of cyclohexane-1,2-dione with 2-dimethylaminomethylcyclohexanone, 2-benzylidenecyclohexanone, and 2,6-dibenzylidenecyclohexanone. 10a-Hydroxy-1,2,3,4,5,6,7,8,8a,10a-decahydro-4-xanthenone exists in tautomeric relationships with 2,2',3-triketoperhydrodiphenylmethane.

It was recently shown that the intermediate 1,5-diketone formed in the Michael condensation of cyclohexanone with 2,6-dibenzylidenecyclohexanone isomerizes to hydroxydecahydroxanthene during the synthesis [1]. It seemed of interest to examine other examples of this cyclization. For this, we studied the addition of cyclohexane-1,2-dione (I), which contains a conjugated carbonyl group, to methylenecyclohexanone (IIa) [this was obtained directly in the reaction mixture from the Mannich base (III)], 2-benzylidenecyclohexanone (IIb), and ketone (IIc). Intermediate IV, which is enolized to V, is apparently obtained initially during the reaction, and V then cyclizes to xanthenone VI.

The structure of VI was confirmed by chemical reactions and spectral data.



Absorption of a conjugated carbonyl group appears at 1680 cm⁻¹ in the IR spectra of the compounds. The presence of an ethylene bond follows from the absorption at 1640 cm⁻¹. A hydroxyl group band is observed

* See [1] for communication IX.

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TABLE 1. 4-Ketohydroxanthenes

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %		Calc., %		Yield, %
			C	H	C	H	
VIa ^a	114—114.5 (Benzene)	C ₁₃ H ₁₈ O ₃	70,0	8,2	70,2	8,2	72
VI ^b	202—203 (Aqueous alcohol)	C ₁₉ H ₂₂ O ₃	76,3	7,6	76,5	7,4	74
VI	205—206 (Ethyl acetate)	C ₂₆ H ₂₆ O ₃	80,6	6,8	80,8	6,8	78
VIIa ^c	130—131 (Ethyl acetate)	C ₁₄ H ₂₀ O ₃	71,0	8,6	71,2	8,5	77
VIIb ^d	134—135 (Alcohol)	C ₂₀ H ₂₄ O ₃	76,9	8,2	76,9	7,7	78
VIIc	138—139 (Alcohol)	C ₂₇ H ₂₈ O ₃	81,3	7,1	81,0	7,0	96
VIII b	154—155 (Alcohol)	C ₁₉ H ₂₀ O ₂	81,3	7,5	81,4	7,2	54
VIII c	151—152 (Alcohol)	C ₂₆ H ₂₄ O ₂	84,6	7,3	84,8	6,6	96

^aThe phenylhydrazone had mp 104–106°C (from alcohol). Found: N 9.3%. C₁₉H₂₄N₂O₂. Calculated: N 9.0%. The tritosylhydrazone had mp 109–110°C (from methanol). Found: N 11.7%. C₃₄H₄₂N₆O₆S₃. Calculated: N 11.6%. ^bThe tosylhydrazone had mp 172–173°C (decomp., from aqueous dioxane). Found: N 6.4%. C₂₆H₃₁N₂O₃S. Calculated: N 6.0%. ^cCH₃O: Found: 13.3%. Calculated 13.1%. ^dCH₃O: Found: 10.0%. Calculated: 9.9%. ^eThe tosylhydrazone had mp 201–202°C (decomp., from chloroform–methanol). Found: N 5.7%. C₃₃H₃₂N₂O₃S. Calculated: N 5.2%.

at 3400–3600 cm⁻¹. The benzyl proton in the PMR spectrum of product VIb gives a doublet centered at 3.18 ppm (*J*=11 Hz).

Compounds VI readily undergo Helferich methylation to give methoxy derivatives VII. A band at 2845 cm⁻¹, which can be assigned to the vibrations of C–H bonds of a methoxy group [2], appears in their IR spectra in place of hydroxyl group absorption. The absorption of the carbonyl group and of the double bond does not change in character. A singlet at 3.05 ppm, which corresponds to a CH₃O group, appears in the PMR spectra of VII.

The ease of dehydration increases in the order VIa–c. Compound VIc is converted almost quantitatively to 9-phenyl-5-benzylidene-1,2,3,4,5,6,7,8-octahydro-4-xanthenone (VIIIc) on refluxing in benzene for 1 h in the presence of catalytic amounts of *p*-toluenesulfonic acid. Compound VIb is converted to 9-phenyl-1,2,3,4,5,6,7,8-octahydro-4-xanthenone (VIIIb) (50%) in 4 h; water is not isolated from VIa under similar conditions.

Compounds VIa and IVa are apparently tautomers. In fact, while the IR spectrum of a KBr pellet of the compound corresponds to structure VIa, an intense band at 1710 cm⁻¹ of an unconjugated carbonyl group of open structure IVa appears in the spectrum of a solution in chloroform along with the frequencies enumerated above. The UV spectra of a cyclohexane solution has one maximum at 262 nm. This also corresponds to structure IVa, inasmuch as the cyclic form should absorb like acetal VIIa, the UV spectrum of which contains a single maximum at 217 nm. Compound VIa reacts with 3 mole of tosylhydrazine and forms a tritosylhydrazone. Although a few spots (in addition to the spots of the starting substances), which apparently correspond to intermediate products, are detected during thin-layer chromatography (TLC) of a mixture of VIa with tosylhydrazine, only chromatographically individual tritosylhydrazone crystallizes out from the mixture. This also indicates equilibrium VIa ⇌ IVa; several mono- and ditosylhydrazones can be formed from the latter compound, but they are apparently quite soluble in methanol. The reaction therefore goes to completion, and the insoluble tritosylhydrazone crystallizes out.

Ketol VIb forms the expected monotosylhydrazone. The reaction of VIc with tosylhydrazine is accompanied by dehydration to give the tosylhydrazone of VIIIc (confirmed by alternative synthesis from VIIIc).

For proof of the structure of VIIIc, its tosylhydrazone was reduced with sodium borohydride to give 9-phenyl-4-benzylidene-1,2,3,4,5,6,7,8-octahydroxanthene (IXc) which was identical to a previously synthesized sample [1].

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in deuteriochloroform were recorded with a ZKR-60 spectrometer (on the δ scale with respect to tetramethylsilane). The UV spectra of 0.001% solutions of the compounds in cyclohexane were recorded with a Specord spectrophotometer (layer thickness 1 cm). The identical character of the compounds obtained and of genuine samples were established from the absence of a depression during melting of mixtures of the samples and from the identical character of the IR spectra. Data on the synthesized compounds are presented in Table 1.

10a-Hydroxy-1,2,3,4,5,6,7,8,8a,10a-decahydro-4-xanthenone (VIa). A 56-g (0.5 mole) sample of ketone I was mixed with 40 ml of 6 N NaOH and with a heated (up to the boiling point) solution of 24 g (0.125 mole) of hydrochloride III in 250 ml of alcohol, and the mixture was then refluxed for 20 min, cooled with ice, and neutralized to pH 7 with concentrated HCl. The alcohol was removed by distillation, and the residue was diluted with 200 ml of water and acidified to pH 5 with HCl. The resulting oil was extracted with benzene, and the extract was washed with water, dried with Drierite, and evaporated to half its original volume. A total of 20 g of VIa crystallized out from the solution.

10a-Hydroxy-9-phenyl-1,2,3,4,5,6,7,8,8a, 10a-decahydro-4-xanthenone (VIb). A 3.4-g (0.03 mole) sample of ketone I and 5.6 g (0.03 mole) of IIb were refluxed in 30 ml of 0.15 N alcoholic KOH for 6 h. The VIb that precipitated on cooling of the mixture was removed by filtration. Compound VIb was similarly obtained when the mixture was refluxed for 45 min.

10a-Methoxy-1,2,3,4,5,6,7,8,8a,10a-decahydro-4-xanthenone (VIIa). A 1.0-g sample of VIa was mixed with 10 ml of 0.25% HCl in absolute methanol, and the mixture was refluxed for 1.5 h. It was then cooled and neutralized (at 0°) with sodium bicarbonate solution to precipitate 0.35 g of acetal VIIa. The filtrate remaining after separation of the precipitate was extracted with ether, and the extract was dried with Drierite and evaporated to give an additional 0.5 g VIIa. Compounds VIIb, c were similarly obtained.

9-Phenyl-1,2,3,4,5,6,7,8-octahydro-4-xanthenone (VIIIb). A mixture of 4.0 g of xanthene VIb, 100 ml of benzene, and 70 mg of p-toluenesulfonic acid was refluxed in a flask equipped with a Dean-Stark trap for 4 h, during which 0.18 ml of water (calculated value 0.24 ml) separated. A total of 1.8 g of the starting ketol crystallized out when the mixture was cooled. The filtrate was washed with sodium bicarbonate solution and water, 85 ml of benzene was removed by distillation, and 2.0 g of VIIIb crystallized out from the residue. Compound VIIIc was similarly obtained.

Tosylhydrazones. The tosylhydrazones were obtained by mixing methanol solutions of the compounds and tosylhydrazine. The reaction products crystallized out while the mixtures were allowed to stand.

9-Phenyl-4-benzylidene-1,2,3,4,5,6,7,8-octahydroxanthene (IXc). A 1.0-g sample of tosylhydrazone of VIIIc and 2.0 g of sodium borohydride were refluxed in 50 ml of methanol for 15 h, after which the mixture was acidified with dilute HCl, and the precipitate was removed by filtration and washed with methanol. The filtrate was evaporated, and the residue (0.6 g) was purified by chromatography on a plate containing Al_2O_3 (activity II) in petroleum ether-ethyl acetate (7:1) to give 0.09 g of IXc with mp 111-113° (from alcohol) (mp 111-113° [1]).

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