NEW METHOD FOR THE SYNTHESIS OF sym-OCTAHYDROXANTHENES AND sym-OCTAHYDROTHIOXANTHENES

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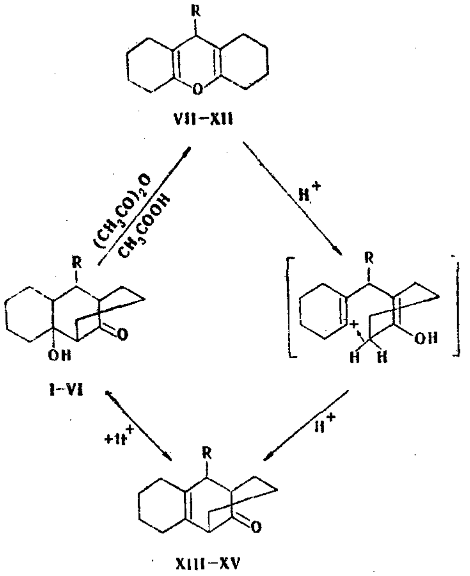
β-Ketols formed as a result of intramolecular cyclization of 1,5-diketones by alkaline condensation of aldehydes with ketones are converted to 9-R-sym-octahydroxanthenes by the action of acids. Treatment of the β-ketols with acids in the presence of hydrogen sulfide leads to the corresponding 9-R-sym-octahydrothioxanthenes. The spectral characteristics of the compounds obtained are given, and some of their properties are described.

Products of intramolecular aldol condensation of the initially formed 1,5-diketones are easily formed in the alkaline condensation of aldehydes with ketones in a ratio of 1 : 2, respectively [1]. For a long time it was assumed that the retroaldol conversion β-ketols is possible only under base-catalysis conditions [2, 3]. In the presence of acids only their dehydration to give β,γ-unsaturated ketones was heretofore known [4]. The presence of a small amount of 9-phenyl-sym-octahydroxanthene (X) in the products of conversion of 4-phenyl-2,3-tetramethylene[3.3.1]bicyclononan-9-on-2-ols (V) in acetic acid was unexpectedly observed in [5]. Considering the highly promising character of the conversion of cyclic β-ketols to six-membered heterocyclic compounds we studied the behavior of β-ketols I-VI with acidic reagents in order to synthesize difficult-to-obtain 9-R-octahydroxanthenes and their sulfur analogs. It was found that refluxing of solutions of ketols I-VI in a mixture of acetic acid and acetic anhydride (1 : 1) leads in all cases to the formation of 9-R-sym-octahydroxanthenes VII-XII. In the case of alkyl-substituted ketols I-III, in addition to the formation of sym-octahydroxanthenes VII-IX, one observes the usual conversion to β,γ-unsaturated ketones XIII-XV [4]:



Under acid-catalysis conditions one evidently observes not only dehydration [4] of ketols I-VI but also, in the case of alkyl-substituted sym-octahydroxanthenes VII-IX, isomerization to α,β-unsaturated ketones XIII-XV.

The relatively high stability of 9-Ar-sym-octahydroxanthenes X-XII with respect to the action of acidic reagents is, in our opinion, the reason for the absence of the corresponding unsaturated ketones in the reaction mixture.

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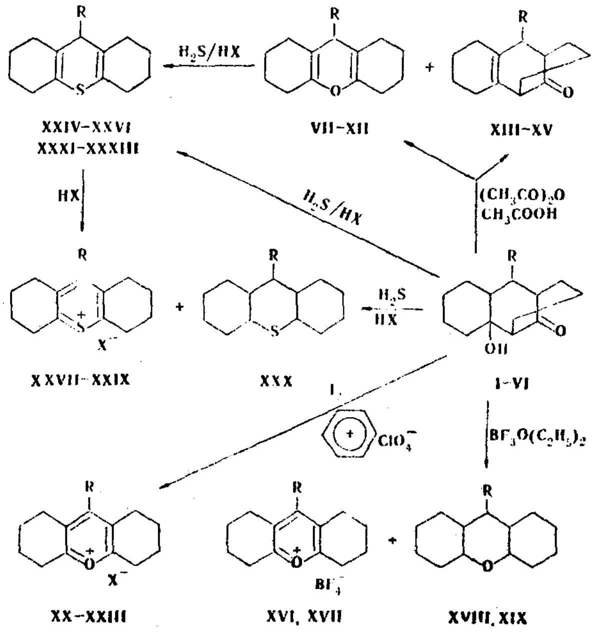

I, VII, XIII, XVI, XVIII, XX, XXII, XXIV, XXVII—XXX R=H; II, VIII, XIV, XVII, XIX, XXI, XXIII, XXV $R=CH_3$; III, IX, XV, XXVI $R=H—C_3H_7$; IV, X, XXXI $R=C_6H_5$; V, XI, XXXII $R=C_6H_4Cl$-p; VI, XII, XXXIII $R=C_6H_4Br$-p; XX, XXI, XXVII $X=ClO_4$; XXII, XXIII $X=I_5$; XXVIII X=Cl; XXIX $X=BF_4$

Treatment of acetic acid solutions of ketols I-II with boron trifluoride etherate leads to the formation of 9-R-sym-octahydroxanthylium tetrafluoroborates XVI and XVII and 9-R-perhydroxanthenes XVIII and XIX. The latter reaction constitutes evidence for disproportionation of the intermediate 4H-pyrans [6].

The reactions of ketols I and II with tropylium perchlorate and iodine in acetic acid lead to the quantitative formation of 9-R-sym-octahydroxanthylium perchlorates XX and XXI and periodides XXII and XXIII.

We studied the reactions of ketols I-III with hydrogen sulfide and acids ($HClO_4$, HCl, and $BF_3 \cdot Et_2O$) in acetic acid. Under these conditions ketols I-III are converted smoothly to the corresponding sulfides XXIV-XXVI at temperatures that do not exceed 20-22°C, whereas products of disproportionation of sym-octahydrothioxanthene XXIV were also isolated from the reaction mixture in the case of ketol I. Depending on the acid used, sym-octahydrothioxanthylium perchlorate XXVII, chloride XXVIII, tetrafluoroborate XXIX, and perhydrothioxanthene XXX were obtained.

Aryl-substituted β-ketols IV-VI on reaction with $HClO_4$, HCl, and $BF_3 \cdot O(C_2H_5)_2$ and hydrogen sulfide were not converted to the corresponding 9-Ar-sym-octahydrothioxanthenes XXXI-XXXIII under the conditions sufficient for the conversion of alkyl-substituted ketols I-III to 9-R-sym-octahydrothioxanthenes XXIV-XXVI. The

TABLE 1. Conditions and Results of the Reaction of Ketols I-VI with Acidic Reagents in Acetic Acid with and without the Participation of Hydrogen Sulfide

Starting ketol	Reagents	Reaction temp., °C	Reaction time, h	Reaction products (yields, %)
I	$CH_3COOH/(CH_3CO)_2O$	115—120	2	VII (30), XIII (65)
II	$CH_3COOH/(CH_3CO)_2O$	115—120	2	VIII (45), XIV (44)
III	„ „	115—120	3	IX (50), XV (24)
IV	„ „	115—120	6	X (91)
V	„ „	115—120	6	XI (90)
VI	„ „	115—120	6	XII (74)
I	$BF_3 \cdot Et_2O$	20—22	3	XVI (52), XVIII (19)
II	$BF_3 \cdot Et_2O$	20—22	6	XVII (27), XIX (10)
I	Tropylium perchlorate	20—22	48	XX (91)
II	Tropylium perchlorate	20—22	48	XXI (80)
I	I_2	20—22	8	XXII (51)
II	I_2	20—22	8	XXIII (51)
I	H_2S/HCl	18—20	48	XXVIII (40), XXX (20)
I	$H_2S/HClO_4$	18—20	24	XXVII (59), XXX (21)
I	H_2S/BF_3Et_2O	18—20	24	XXIX (54), XXX (25)
II	H_2S/HCl	18—20	24	XXV (71)
III	H_2S/HCl	18—20	24	XXVI (60)

TABLE 2. Characteristics of the 9-R-sym-Octahydroxanthenes and 9-R-sym-Octahydrothioxanthenes

Compound	mp, °C	IR spectrum (C=C), cm^{-1}	H^9 spectrum, δ, ppm	Found, %			Empirical formula	Calc., %		
				C	H	S		C	H	S
IX	28—30	1692, 1730	2,37m	82,70	10,42	—	$C_{16}H_{24}O$	82,75	10,34	—
X[7]	98—99	1690, 1728	3,33s	85,88	8,35	—	$C_{19}H_{22}O$	85,71	8,27	—
XI	96—98	1690, 1630	3,31s	75,69	7,29	—	$C_{19}H_{21}OCl$	75,81	6,98	—
XII	98—99	1690, 1728	3,32s	66,07	6,11	—	$C_{19}H_{21}OBr$	66,08	6,08	—
XXV	61—62	1640, 1665	2,33q	76,43	9,11	14,59	$C_{14}H_{20}S$	76,30	9,25	14,46
XXVI†	—	1645, 1665	2,36m	77,60	9,63	12,79	$C_{16}H_{24}S$	77,42	9,68	12,90
XXXI	111—113	1653, 1678	3.38s	80.69	7,82	11,48	$C_{19}H_{22}S$	80,85	7,80	11,34
XXXII	115—116	1650, 1678	3,35s	71,81	6.60	10.41	$C_{19}H_{21}ClS$	72,03	6,63	10,11
XXXIII	116—117	1650, 1678	3,35s	57,70	5,27	8,28	$C_{19}H_{21}BrS$	58,01	5,34	8,11

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*The compounds were crystallized from ethanol (IX and XXV) and acetonitrile (X-XII and XXXI-XXXIII).

†This compound had bp 136-140°C (2 mm) and n_D^{20} 1.5546.

conversion of 9-Ar-substituted ketols IV-VI to the corresponding sulfides XXXI-XXXIII was accomplished in two steps. Ketols IV-VI were converted to 9-Ar-sym-octahydroxanthenes X-XII by the method described above, and the latter were converted smoothly to 9-Ar-sym-octahydroxanthenes XXXI-XXXIII in 96, 94, and 80% yields, respectively, by the action on them of acetic acid solutions of hydrogen sulfide and hydrogen chloride at 95-110°C.

Thus carbocyclic compounds of the 4-R-2,3-tetramethylene[3.3.1]bicyclononan-9-on-2-ol series are capable under acid-catalysis conditions of undergoing conversion to a six-membered heterocyclic compound that includes a 4H-pyran ring, whereas the product contains a 4H-thiopyran ring when the reaction is carried out in the presence of hydrogen sulfide.

We share the opinion of Tilichenko and coworkers [5] that prior retroaldol cleavage of β-cycloketols I-VI to the corresponding bicyclic 1,5-diketones occurs in this case.

The compositions and structures of the compounds obtained are confirmed by the results of elementary and spectral analysis and, in a number of cases, by comparison of the physical constants with those of genuine samples [7-11].

The IR spectra of 9-R-sym-octahydroxanthenes IX-XII and their sulfur analogs XXIV-XXVI and XXXI-XXXIII contain, respectively, two bands at 1690-1730 and 1650-1690 cm^{-1}, which are due to the vibrations of the C=C bonds of the 4H-pyran and 4H-thiopyran rings; this is in agreement with the data in [11] (Table 2).

The PMR spectra of IX-XII, XXIV-XXVI, and XXXI-XXXIII (Table 2) are in agreement with the 4H-pyran and 4H-thiopyran structures. Thus the spectrum of sulfide XXV contains a signal of three protons of a methyl group in the form of a doublet at δ 0.95 ppm (J=6.9 Hz) and a signal of a hydrogen atom in the C^9 position in the form of a quartet centered at δ 2.33 ppm (J=6.9 Hz); this is undoubtedly evidence in favor of the 4H structure of the heteroring. The protons in the C^9 positions of X-XII and XXXI-XXXIII give signals in the form of singlets at 3.31-3.35 ppm. The correctness of the assignment of the signals is confirmed by the literature analogies [7].

EXPERIMENTAL

Ketols I-VI were obtained by alkaline condensation of cyclohexanone with the corresponding aldehydes [4, 13]. Monitoring of the conversion of ketols I-VI [4, 13] and the determination of the individuality of the products were accomplished by gas-liquid chromatography (GLC) with an LKhM-8MD chromatograph with a flame-ionization detector; the column was 2-m long with a diameter of 3 mm and was filled with 10% Apiezon-L on Chromaton N-AW-DMCS, and the carrier gas was argon. The IR spectra of suspensions of the compounds in mineral oil and hexachlorobutadiene were recorded with a UR-20 spectrometer with a KBr prism. The PMR spectra of 30% solutions of the compounds in CCl_4 were obtained with a Tesla BS-477 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

Reaction of Ketol III with Acetic Acid and Acetic Anhydride. A 5-g (0.02 mole) sample of ketol III was dissolved in 50 ml of a hot mixture of acetic acid and acetic anhydride (1:1), and the solution was refluxed for 3 h. It was then cooled, and the resulting crystalline precipitate was removed by filtration, washed with acetic acid, and dried to give 2 g of 9-propyl-sym-octahydroxanthene (IX). The mother liquor was diluted with water and extracted with ether. The ether extract was washed with water and dried over Na_2SO_4, and the solvent was removed by distillation. Treatment of the oily residue with hot ethanol gave 0.47 g of IX and 1.3 g (24%) of unsaturated ketone XV. The overall yield of IX was 2.47 g (50%).

The reactions of ketols I, II, and IV-VI with acetic acid and acetic anhydride were carried out similarly. In the case of ketols I and II the yields of reaction products were estimated by GLC. 9-Aryl-sym-octahydroxanthenes XXXIV-XXXVI were isolated preparatively (Table 1).

Reaction of Ketol I with Boron Trifluoride Etherate. A 10-g (0.8 mole) sample of $BF_3 \cdot Et_2O$ was added in the course of an hour to 5.2 g (0.025 mole of the ketol) I in 20 ml of acetic acid. After 3 h, the mixture was diluted with ether, and the crystalline precipitate of sym-octahydroxanthylium tetrafluoroborate XVI was separated to give 3.6 g of a product with mp 90-91°C (from alcohol). Found: C 56.41; H 6.10%. $C_{13}H_{17}BF_4O$. Calculated: C 56.52; H 6.15%. Vacuum distillation of the mother liquor gave 0.921 g of perhydroxanthene XVIII with bp 97-98°C (4 mm) and n_D^{25} 1.4951 [8].

The reaction of ketol II with $BF_3 \cdot Et_2O$ under similar conditions gave salt XVII and 9-methylperhydroxanthene XIX with bp 177-179°C (11 mm) and n_D^{20} 1.4980. Found: C 80.56; H 11.50%. $C_{14}H_{24}O$. Calculated: C 80.76; H 11.05%. 9-Methyl-sym-octahydroxanthylium tetrafluoroborate XVIII had mp 102-104°C (alcohol). Found: C 57.72; H 6.45%. $C_{14}H_{19}BF_4O$. Calculated: C 57.93; H 6.55%.

Reaction of Ketol with Tropylium Perchlorate. A 1.25-g (6.7 mmole) sample of tropylium perchlorate was added to 1.4 g (6.7 mmole) of ketol I in 20 ml of acetic acid, and the mixture was stirred for 48 h. It was then treated with ether to precipitate 1.31 g (66%) of colorless crystals of sym-octahydroxanthylium perchlorate XX with mp 172-173°C (alcohol) [9].

The reaction of ketol II with tropylium perchlorate proceeded similarly, and 9-methyl-sym-octahydroxanthylium perchlorate (XXI), with mp 130-131°C [9], was obtained.

Reaction of Ketol I with Iodine. An ether solution of 19.95 g (0.15 mole) of iodine was added to 5.2 g (0.025 mole) of ketol I in 50 ml of acetic acid, and the mixture was stirred for 8 h. The resulting crystalline precipitate was removed by filtration, washed with ether, and dried to give 10.8 g (50%) of sym-octahydroxanthylium pentaiodide (XXII) with mp 112-114°C (from acetonitrile). Found: C 19.02; H 2.02%. $C_{13}H_{17}OI_5$. Calculated: C 20.05; H 2.26%. Found: C 19.86; H 2.16%. $C_{14}H_{19}OI_5$. Calculated: C 20.05; H 2.26%.

Pentaiodide XXIII, with mp 103-104°C (acetonitrile), was similarly obtained from ketol II. Found: C 19.86; H 2.16%. $C_{14}H_{19}OI_5$. Calculated: C 20.05; H 2.26%.

Reaction of Ketol I with Hydrogen Sulfide and Acids. A suspension of 5.2 g (0.025 mole) of ketol I in 50 ml of acetic acid was saturated with hydrogen sulfide at 20-22°C in the course of 1.5 h, after which it was saturated with a mixture of H_2S and HCl gases in the course of 2 h [in the case of the reaction with perchloric acid and boron trifluoride etherate 5.4 g (0.053 mole) of 70% perchloric acid or 10 g (0.07 mole) of boron trifluoride etherate was added in the course of 2 h as saturation with hydrogen sulfide was continued]. The reaction mixture was allowed to stand for 24-48 h, after which the corresponding sym-octahydrothioxanthylium salts XXVII-XXIX were precipitated with ether. With respect to their melting points and IR spectra, salts XXVII and XXVIII were identical to genuine samples [10]. Perchlorate XXVII had mp 120-122°C (water), chloride XXVIII had mp 94-95°C (acetonitrile – ether), and tetrafluoroborate XXIX had mp 98-99.5°C (acetic acid – ether). Found: C 53.32; H 6.64; S 10.70%. $C_{13}H_{17}SBF_4$. Calculated: C 53.43; H 5.83; S 10.59%. The yields of the compounds are presented in Table 1.

The mother liquor was washed with water and dried over Na_2SO_4, and the solvent was removed by distillation. The oily residue was recrystallized from methanol to give perhydrothioxanthene XXX with mp 70-72°C [10].

Sulfides XXV and XXVI (Tables 1 and 2) were similarly obtained by reaction of ketols II and III with hydrogen sulfide and hydrogen chloride.

9-Phenyl-sym-octahydrothioxanthene (XXVIII). A suspension of 5.32 g (0.02 mole) of 9-phenyl-sym-octahydroxanthene X in 50 ml of acetic acid was saturated with hydrogen sulfide in the course of 1 h, after which 4 ml of concentrated hydrochloric acid was added, and the temperature of the mixture was raised to 95-100°C as saturation of the solution with hydrogen sulfide was continued. After 3 h, the solution was cooled and filtered to give 5.41 g (96%) of 9-phenyl-sym-octahydrothioxanthene XXXI with mp 111-113°C [11].

9-R-sym-Octahydrothioxanthenes XXXII and XXXIII were similarly obtained in 94 and 80% yields, respectively, from 9-R-sym-octahydroxanthenes XI and XII.

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CONDENSATION OF 4-BENZAMIDO-3-OXOTHIOPHAN WITH ACROLEIN. SYNTHESIS OF 1-BENZAMIDO-4-HYDROXY-6-THIABICYCLO[3.2.1]-OCTAN-8-ONE AND 6-BENZOYL-7-HYDROXY-2-THIA-6-AZASPIRO[4.4]-NONAN-4-ONE

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It is shown that acrolein adds to the 4 position (rather than to the 2 position) of 4-benzamido-3-oxothiophan under the influence of catalysts with basic character; the aldehyde group of the intermediate compound reacts with the amino group (if the reaction is carried out in chloroform) to give 6-benzoyl-7-hydroxy-2-thia-6-azaspiro[4.4]nonan-4-one or (if the reaction is carried out in a mixture of alcohol and chloroform) 1-benzamido-4-hydroxy-6-thiabicyclo-[3.2.1]octan-8-one as a result of intramolecular aldol condensation.

We have previously shown [1] that substituted 3-oxothiophans are capable of undergoing the Michael reaction with α,β-unsaturated ketones. In the present research we investigated the reaction of 4-benzamido-3-oxothiophan (I) with acrolein. Electrophilic attack on acylaminooxothiophan I by the β-carbon atom of the double bond of the unsaturated aldehyde may take place at the carbon atoms in both the 2 and 4 positions of the thiophan ring.

The reaction of acrolein with acylaminooxothiophan I was carried out in chloroform or in a mixture of chloroform and methanol in the presence of a basic catalyst (piperidine, diethylamine, sodium methoxide, or potassium hydroxide) at 0 to −50°C. It was established that the addition may proceed in different directions depending on the composition of the medium.

1-Benzamido-4-hydroxy-6-thiabicyclo[3.2.1]octan-8-one (III) was isolated in the condensation of I with acrolein in a mixture of chloroform and methanol. The characteristic bands of an amide [3400 (ν_{NH}) and 1600 cm^{-1} (ν_{CO})] and of an oxo group (1740 cm^{-1}), as well as the band of a free hydroxyl group (3580 cm^{-1}), are observed in the IR spectrum of III. The formation of oxime IV also constitutes evidence in favor of the presence

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