

## Chemistry of Ketoacetals: II. $\beta,\beta'$ -Ketodiacetal and $\beta,\beta'$ -Hydroxydiacetals in Reactions with Ammonia and Amines

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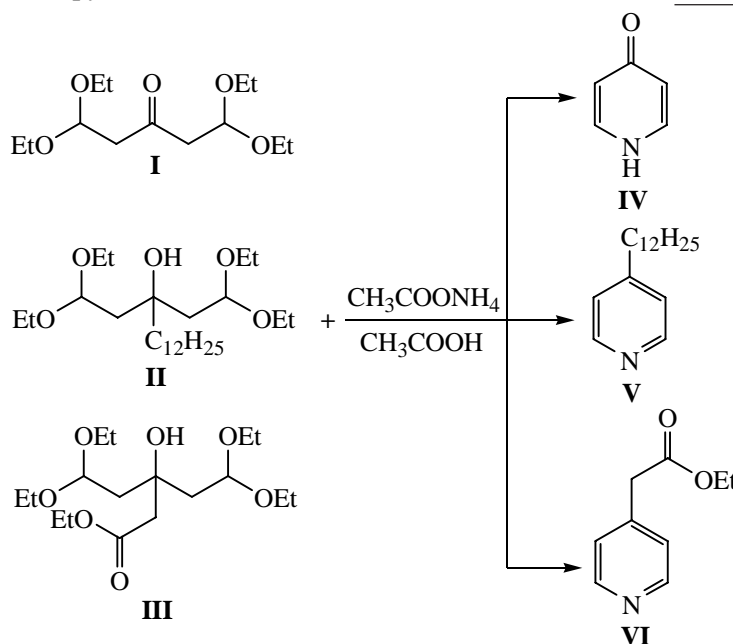
**Abstract**— $\beta,\beta'$ -Ketodiacetal and  $\beta,\beta'$ -hydroxydiacetals react with ammonium acetate in acetic acid to afford substituted pyridine, and with aromatic amines in the presence of hydrochloric acid form substituted pentamethine salts.

Ketoacetals and hydroxyacetals long attracted attention of researchers as polyfunctional synthons in the organic synthesis and as precursors of biologically active compounds [1, 2]. The presence of several electrophilic sites of various activity suggests numerous possibilities for these compounds in reactions with nucleophiles. We formerly developed procedures for preparation of  $\beta,\beta'$ -ketodiacetal [3] and  $\beta,\beta'$ -hydroxydiacetals [4] that made it possible to study their chemical properties. Here we report on the study of reactions of ketodiacetals and hydroxydiacetals with ammonia and amines..

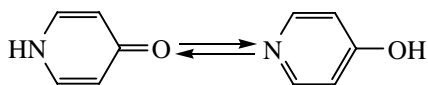
It is known that treating glutaconic aldehyde acetal with ammonium acetate affords pyridine but it has been

stated in [5] that this method is not suitable for the other dialdehydes. We found that the treatment of diacetals **I–III** with a solution of ammonium acetate in acetic acid at heating to 90–100°C resulted both in substitution of the ethoxy groups for amino group and also in elimination of ether and hydroxy groups affording  $\gamma$ -substituted pyridines **IV–VI**.

The occurring aromatization was confirmed by the analysis of  $^1\text{H}$  NMR spectra of compounds obtained where the proton signals were observed in the region 6.5–8.5 ppm characteristic of aromatic compounds. The type of signals in all cases was similar: doublets with a coupling constant around 6 Hz characteristic of pyridine rings.



The IR spectra also possess a characteristic pattern. In the IR spectrum of pyridone **IV** absorption bands are observed in the region 3210–2830  $\text{cm}^{-1}$  corresponding to the stretching vibrations of NH (or OH), a vibration band of the carbonyl group at 1642  $\text{cm}^{-1}$ , and a band at 1526  $\text{cm}^{-1}$  belonging to vibrations of the C=C bonds in pyridine. The complex pattern of the IR spectrum in the region 3210–2830  $\text{cm}^{-1}$  may originate from the known existence of tautomerism in  $\gamma$ -pyridones [6].



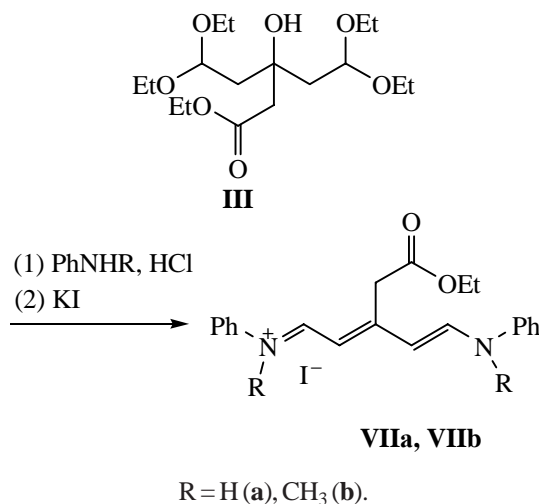
The IR spectrum of pyridine **VI** hydrochloride may be regarded as representative. It contains characteristic vibration bands of the ester group (C=O at 1725, C–O–C at 1200–1100  $\text{cm}^{-1}$ ), bands belonging to vibrations of the C=C in the aromatic system at 1606, and 1502  $\text{cm}^{-1}$ , a band of the out-of-plane bending vibrations of CH at 800  $\text{cm}^{-1}$  revealing the presence of two contiguous hydrogen atoms and thus indicating that the compound possesses a *para*-substituted benzene ring (for the heteroatom in pyridines may be regarded as a substituent in the ring), a band characteristic of aromatic amine salt at 2000  $\text{cm}^{-1}$  corresponding to the C–N+H group vibrations, and also a wide band of “ammonium” salt of N+–H vibrations in the region 2700–2500  $\text{cm}^{-1}$ .

The yields of compounds obtained are sufficiently high, the initial compounds are available, the substituents structure in the arising structures is versatile, therefore  $\beta,\beta'$ -ketodiacetal and  $\beta,\beta'$ -hydroxydiacetals are convenient and accessible synthons for preparation of  $\gamma$ -substituted pyridines with various substituents in the  $\gamma$ -position of the ring.

A dissimilar behaviour was observed in reactions of the  $\beta,\beta'$ -hydroxydiacetals with aromatic amines. It was previously shown [4] that the treatment of mesoalkyl-substituted  $\beta,\beta'$ -hydroxydiacetals (among them also **II**) with *N*-methylanilinium hydrochloride in alcoholic solution afforded mesoalkyl-substituted pentamethine salts possessing an absorption maximum in ethanol at 476.2 nm. Hydroxyacetal **III** behaved in the same way.

On prolonged storage at room temperature of the alcoholic solution of 1,1,5,5-tetraethoxy-3-ethoxycarbomethyl-3-pentanol (**III**) and aniline hydrochloride a pentamethine salt **VIIa** formed with an ester group in a *meso*-position and having an absorption band in the visible region. The structure of compound obtained is confirmed by the

electron absorption spectrum with a maximum in the long-wave region at 463 nm characteristic of this chromophore system, and by  $^1\text{H}$  NMR spectrum where alongside the proton signals characteristic of the aromatic moiety and polymethine chain in the region 6.5–8.0 ppm appear the proton resonances belonging to the ethoxy group (4.25 and 1.2 ppm) of the ester fragment. A similar result was obtained at treating hydroxydiacetal **III** with *N*-methylaniline hydrochloride. Pentamethine salt **VIIb** isolated from this reaction mixture possessed an absorption band at 490 nm (in 2-propanol solution).



Different reaction routes with ammonia (providing substituted pyridine) and aromatic amines (affording polymethine salts) may be due to the contribution of the phenyl rings at the nitrogen atoms to the stabilization of the conjugated polyene **VII** system.

Therefore the study performed demonstrated that the *meso*-substituted  $\beta,\beta'$ -hydroxydiacetals can serve as initial compounds for preparation of *meso*-substituted pentamethine salts or  $\gamma$ -substituted pyridines depending on the character of amine used and on the condensation conditions.

## EXPERIMENTAL

$^1\text{H}$  NMR spectra were registered on spectrometers Bruker-200SY and Bruker-300SY (Germany) at operating frequencies 200 and 300 MHz respectively from solutions in  $\text{CDCl}_3$ . The residual proton signals of the solvent served as internal reference. IR spectra were recorded on a spectrophotometer Shimadzu IR-435 (Japan) from thin film of substances. Electronic spectra of compounds were taken on spectrophotometer Jasco-UV 7800 from solutions in alcohol. The reaction progress

was monitored and the compounds obtained were identified by TLC on Silufol UV-254 plates (Czechia) in the solvent system ethyl acetate–petroleum ether, 2:1, for compound **VI**, and ethyl acetate for compound **IV**; development under UV irradiation, in iodine vapor, or by heating to 120–140°C for 2–3 min.

**1,1,5,5-Tetraethoxy-3-pentanone (I)** and **1,1,5,5-tetraethoxy-3-dodecyl-3-pentanol (II)** were obtained by procedures described in [4], **1,1,5,5-tetraethoxy-3-ethoxycarbomethyl-3-pentanol (III)** was prepared as in [7].

**$\gamma$ -Pyridone (IV)**. In a reaction flask 0.2 g (0.76 mmol) of compound **I** was mixed with a solution of 0.12 g (1.53 mmol) of ammonium acetate in 1.5 ml of glacial acetic acid. The mixture was heated for 30 min at 90–100°C and then cooled to room temperature. Acetic acid was removed by azeotropic distillation with carbon tetrachloride. The residue was subjected to thin layer chromatography on a plate with aluminum oxide, eluent ethyl acetate. Yield 0.055 g (76%),  $R_f$  0.30, mp 146–148°C (publ.: mp 148.5°C [8]).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.1 (1H, the signal position considerably changed depending on the solvent where the substance was recorded), 6.39 br.d (2H,  $J$  6.24 Hz), 7.74 br.d (2H,  $J$  6.24 Hz).

**$\gamma$ -Dodecylpyridine (V)** was obtained in a similar way from 0.21 g (0.486 mmol) of compound **II** and solution of 0.075 g (0.97 mmol) of ammonium acetate in 1 ml of glacial acetic acid. The residue after evaporating the solvents was mixed with 5 ml of 21% HCl solution in anhydrous ether. The separated crystals were filtered off, washed with anhydrous ether and benzene. The free base was obtained by adding 0.015 g of NaOH in 6 ml of methanol. Yield 0.046 g (39%), mp 124–125°C (for hydrochloride).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.89 t (3H,  $J$  7.96 Hz), 1.25–1.57 m (20 H), 2.55 t (2H,  $J$  7.62 Hz), 7.19 d (2H,  $J$  5.50 Hz), 8.39 d (2H,  $J$  5.50 Hz). Found, %: C 70.35; H 10.40; N 5.03.  $\text{C}_{17}\text{H}_{29}\text{N} \cdot \text{HCl}$ . Calculated, %: C 71.88; H 10.68; N 4.93.

**$\gamma$ -Ethoxycarbomethylpyridine (VI)** was obtained in a similar way from 0.24 g (0.69 mmol) of compound **III** and solution of 0.11 g (1.35 mmol) of ammonium acetate in 1.5 ml of glacial acetic acid. The solution was heated for 1 h 45 min. The residue after evaporating the solvents was subjected to chromatography on a column packed with aluminum oxide, gradient elution with a mixture of petroleum ether with ethyl acetate, from 10:1

to 4:1. Yield 0.05 g (46%),  $R_f$  0.37, mp 161–163°C (for hydrochloride) {publ: mp (for hydrochloride) 165–168, 162–163.5°C [9]}. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 2500–2700 ( $\text{N}^+-\text{H}$ ), 2000 ( $\text{C}-\text{N}^+\text{H}$ ), 1725 ( $\text{C}=\text{O}$ ), 1606, 1502 ( $\text{C}=\text{C}_{\text{arom}}$ ), 1100–1200 ( $\text{C}-\text{O}-\text{C}$ ), 800 (bending  $\text{C}_{\text{arom}}-\text{H}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.26 t (3H,  $J$  6.82 Hz), 3.62 s (2H), 4.17 q (2H,  $J$  6.82 Hz), 7.25  $\delta$  (2H,  $J$  5.56 Hz), 8.56 d (2H,  $J$  5.56 Hz).

**[5-(*N*-Phenylamino)-3-ethoxycarbomethyl-2,4-pentadienylidene]-*N*-anilinium iodide (VIIa)** was prepared from 0.0643 g (0.185 mmol) of compound **III**, 0.048 g (0.367 mmol) of aniline hydrochloride in 1.2 ml of anhydrous ethanol in 4 days at room temperature. Then the solution was poured on ice acidified with 5% solution of HCl, and 0.060 g of potassium iodide was added. The separated crystals were filtered off, washed with water and petroleum ether. Yield 0.0472 g (60.5%), mp 123–125°C,  $\lambda_{\text{max}}$  463 nm (2-propanol).

**[5-(*N*-Methyl-*N*-phenylamino)-3-ethoxycarbomethyl-2,4-pentadienylidene]-*N*-methylanilinium iodide (VIIb)** was similarly obtained from 0.3 g (0.856 mmol) of compound **III**, 0.246 g (1.7 mmol) of *N*-methyl-aniline hydrochloride in 1.2 ml of anhydrous ethanol in 14 h at room temperature. Yield 0.030 g (51%),  $\lambda_{\text{max}}$  490 nm (2-propanol). The hygroscopicity of the product prevented measuring of the melting point.

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