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Condensation of 3-Hydroxyimino-2-butanone Hydrazone with 2,4-Pentanedione, Isatin, Ethyl 2-Cyano-3-Ethoxyacrylate, and β-Ketoacid Esters and Anilides

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Abstract—The condensation of 3-hydroxyimino-2-butanone hydrazone with 2,4-pentanediones yields 1,8-dihydroxy-2,3,6-trimethyl-1,4,5-triaza-1,3,5,7-nonatetraene which exists in the iminoenol form. The reactions of the title hydrazone with ethyl 2-cyano-3-ethoxyacrylate, ethyl acetoacetate, methyl 2-oxocyclopentane-carboxylate, and acetoacetanilides occur in a regioselective fashion to afford the corresponfing enamine tautomers; isatin reacts at the 3-oxo group.

Ring–chain isomerism plays an important role in the synthesis, opening, and recyclization reactions of heterocyclic compounds [1]. Ring–chain transformations in the series of 4-hydroxy-3,4-dihydro-1,2,4-triazines [2] and condensation products of hydroxy-iminoacetophenone hydrazone with aldehydes [3] were reported. In continuation of studies performed in [2–12], the present communication deals with the structure and tautomerism of condensation products of 3-hydroxyimino-2-butanone hydrazone (**I**) with ethyl 2-cyano-3-ethoxyacrylate and dicarbonyl compounds. The latter were 2,4-pentanedione, isatin, ethyl acetoacetate, methyl 2-oxocyclopentanecarboxylate, and acetoacetanilides.

The condensation of **I** with an equimolar amount of 2,4-pentanedione readily occurs on heating in dioxane or ethanol. Only one carbonyl group of the initial diketone is involved, and the product is 1,8-dihydroxy-2,3,6-trimethyl-1,4,5-triaza-1,3,5,7-nonatetraene (**II**) (Scheme 1). Theoretically, compound **II** can exist as ketone imine, ketoenamine, and iminoenol tautomer or as a mixture of these. The ketoenamine and iminoenol tautomers can give rise to stereoisomers with respect to the double bond. However, only one iminoenol tautomer was found for compound **II** in the crystalline state. The IR spectrum of a crystalline sample of **II** contains a broadened absorption band with its maximum at 3160 cm^{-1}, which belongs to stretching vibrations of hydroxy groups involved in intramolecular hydrogen bond. The presence of two strong IR bands at 1553 and 1587 cm^{-1} and the absence of multiple bond absorption at higher frequencies are characteristic of conjugated bond system in a chelate structure.

The state of tautomeric equilibrium for compound **II** does not change in going from crystal to solution in DMSO. In the upfield region of the ^{1}H NMR spectrum of **II** four singlets with equal intensities were observed at δ 1.97, 1.99, 2.10, and 2.20 ppm, which belong to the methyl group protons. The downfield region contained two singlets at δ 11.32 and 13.30 ppm, which were assigned to hydroxy protons involved in intramolecular hydrogen bond. The singlet at δ 13.30 ppm belongs to the enolic hydroxy proton. The CH proton at the double bond gives a singlet at δ 5.21 ppm. The spectrum also contained a set of singlets at δ 4.80, 11.19, and 12.08 ppm from the CH= proton and two hydroxy groups of the iminoenol tautomer in which the hydroxy groups form intermolecular hydrogen bonds with the solvent (DMSO). The fraction of the minor isomer is 8%. The observed pattern is explained by formation of a structure possessing an extended conjugation system, which is additionally stabilized by intramolecular H bonding.

It is known that the state of tautomeric equilibrium changes in going from β-diketone acetylhydrazones to β-ketoester hydrazones. The latter exist in crystal and in solution [7, 13–15] as mixtures of the hydrazone and enehydrazine tautomers whose ratio depends on the substituent in the hydrazine fragment. Acyl- and phosphinoylhydrazones derived from β-ketocarboxamides are known [6, 10] to exist in the hydrazone form. In all cases the condensation of 3-hydroxy-imino-2-butanone (**I**) with β-ketoacid esters and

Scheme 1.
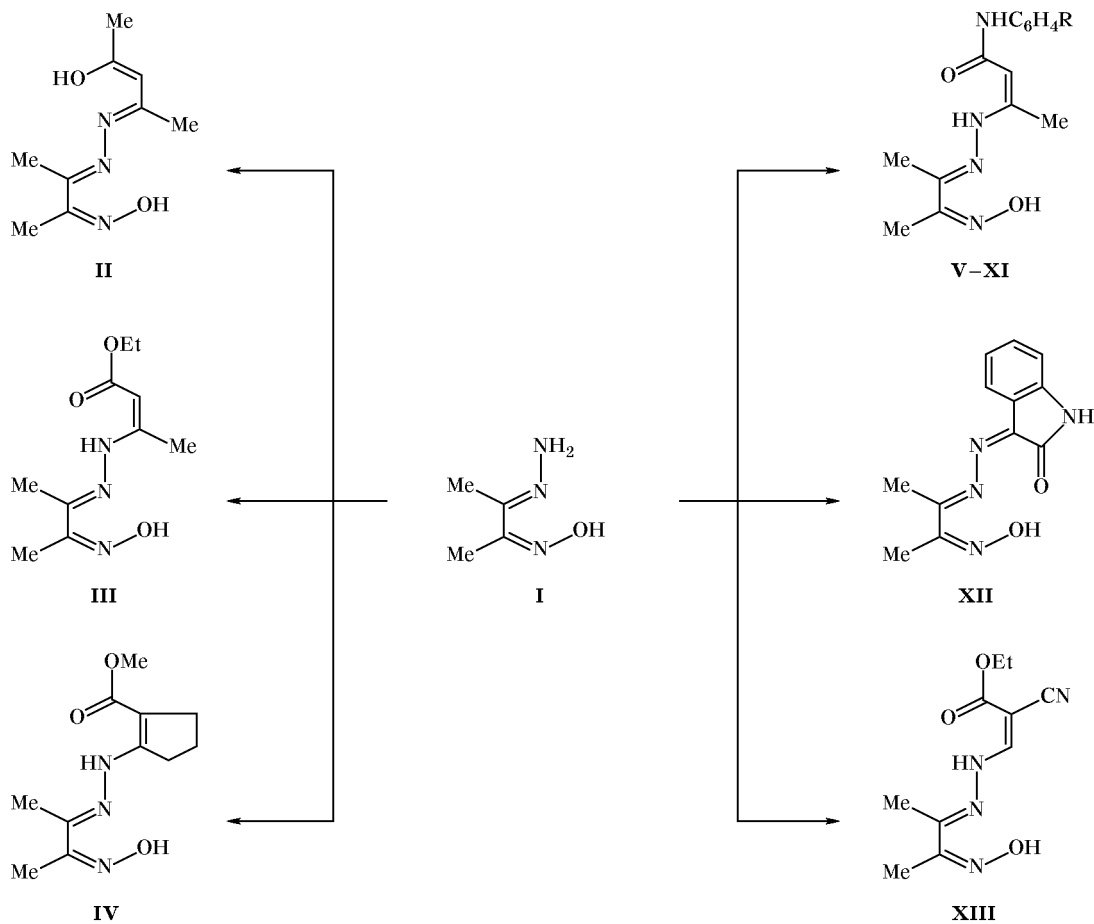
V, R = H; **VI**, R = 4-Cl; **VII**, R = 2-Cl; **VIII**, R = 4-Br; **IX**, R = 2-Br; **X**, R = 4-Me; **XI**, R = 2-MeO.

anilides involves only the ketone group of the latter. The isolated products, compounds **III–XI** are enamine tautomers stabilized by intramolecular hydrogen bond. Neither the presence of a cyclic fragment in β-keto-ester nor the nature of substituent in the aromatic ring of β-ketoanilides affects the tautomeric equilibrium. As β-ketoesters we used ethyl acetoacetate and cyclic methyl 2-oxocyclopentanecarboxylate. Compounds **III–XI** (Table 1) are stable colored (from yellow to brown) finely crystalline substances, poorly soluble in hexane, carbon tetrachloride, and water and soluble in acetone, dioxane, diethyl ether, DMSO, and DMF. Their purity was checked by TLC. Compounds **III** and **IV** showed in the high-frequency region of the IR spectra two broadened absorption bands at 3185–3193 and 3250–3260 cm^{-1} which correspond to stretching vibrations of the NH and OH groups. No absorption was observed in the multiple bond region above 1640 cm^{-1}, indicating the absence of nonconjugated ester carbonyl; therefore, the imino structure can be ruled out. Two strong absorption bands at 1533–1560 and 1560–1610 cm^{-1} belong to stretching vibrations of the conjugated bond system in H-chelate ring. The ester carbonyl group which is conjugated with the double C=C bond and is involved in intramolecular hydrogen bond gives a strong absorption band at 1610–1640 cm^{-1}. The IR spectra of anilides **V–XI** are analogous to those of esters **III** and **IV**. A conclusion can be drawn that the nature of the carbonyl component in the condensation products of 3-hydroxy-imino-2-butanone hydrazone with β-ketoacid deriva-tives does not determine the structure of the major tautomer. These compounds exist in crystal as *cis*-enamine tautomers stabilized due to formation of extended conjugation system and intramolecular hydrogen bond. The same follows from the ^{1}H NMR spectra (Table 2). The upfield region of the ^{1}H NMR spectrum of **III** contains three singlets at δ 2.00, 2.08, and 2.17 ppm and a triplet at δ 1.23 ppm from the methyl protons. Methylene protons of the ethoxy

Table 1. Yields, melting points, R_f values, and elemental analyses of 3-hydroxyimino-2-butanone hydrazone derivatives **II–XIII**

Comp. no.	Yield, %	mp, °C	R_f (system)	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
II	73	185–188	0.49 (A)	54.79	7.71	21.28	$C_9H_{15}N_3O_2$	54.81	7.66	21.30
III	64	141–143	0.78 (B)	52.88	7.53	18.55	$C_{10}H_{17}N_3O_3$	52.85	7.54	18.49
IV	66	166–168	0.44 (A)	55.17	7.20	17.49	$C_{11}H_{17}N_3O_3$	55.22	7.16	17.56
V	97	140–142	0.47 (A)	61.35	6.66	20.40	$C_{14}H_{18}N_4O_2$	61.30	6.61	20.42
VI	77	197–199	0.78 (B)	54.41	5.52	18.11	$C_{14}H_{17}ClN_4O_2$	54.46	5.55	18.15
VII	87	186–188	0.50 (A)	54.43	5.57	18.17	$C_{14}H_{17}ClN_4O_2$	54.46	5.55	18.15
VIII	81	192–194	0.38 (A)	47.66	4.88	15.89	$C_{14}H_{17}BrN_4O_2$	47.61	4.85	15.86
IX	83	197–199	0.42 (A)	47.54	4.83	15.92	$C_{14}H_{17}BrN_4O_2$	47.61	4.85	15.86
X	77	140–142	0.50 (A)	62.52	7.04	19.43	$C_{15}H_{20}N_4O_2$	62.48	6.99	19.43
XI	79	190–192	0.39 (A)	59.25	6.61	18.36	$C_{15}H_{20}N_4O_3$	59.20	6.62	18.41
XII	65	240[a]	0.73 (B)	58.96	4.99	23.00	$C_{12}H_{12}N_4O_2$	59.01	4.95	22.94
XIII	55	184–186	0.78 (B)	50.43	5.95	23.49	$C_{10}H_{14}N_4O_3$	50.41	5.92	23.52

[a] With decomposition.

Table 2. ^{1}H NMR spectra of 3-hydroxyimino-2-butanone hydrazone derivatives **II–IV**, **VI**, **XIII**

Comp. no.	OH	NH	CH	CH$_3$	CH$_2$ (C$_6$H$_4$)
II	12.08 s, 13.30 s	11.19 s, 11.32 s	4.80 s, 5.21 s	1.97 s, 1.99 s, 2.10 s, 2.20 s	
III	11.55 s	11.18 s	4.66 s	1.23 s, 2.00 s, 2.08 s, 2.17 s	4.08 s
IV	11.25 s	10.40 s		1.97 s, 2.03 s, 3.67 s	1.88 s, 2.55 s, 2.86 s
VI	12.29 s	9.52 s, 11.08 s	4.86 s	2.01 s, 2.10 s, 2.18 s	(7.20 d, 7.61 d)
XIII	11.55 s, 11.70 s	10.94 s, 11.55 d	7.68 s, 8.22 s	1.30 t, 1.33 t, 1.98 s, 2.06 s, 2.10 s, 2.17 s	4.20 t, 4.26 t

group give a quadruplet at δ 4.08 ppm. One-proton singlets in the downfield region, δ 11.18 and 11.55 ppm, belong to the NH and OH protons. Compound **III** in solution exists exclusively as the *cis*-enamine tautomer, for its ^{1}H NMR spectrum lacks signal from methylene protons of β-dicarbonyl fragment. The spectra of enamines **IV** and **VI** are similar to that of **III**.

Regardless of the solvent nature, isatin reacts with 3-hydroxyimino-2-butanone through the carbonyl group in position *3* of the heteroring, yielding the corresponding hydrazone **XII**. The product is stabilized by intramolecular hydrogen bond. It shows in the IR spectrum two bands at 1587 and 1607 cm^{-1}, belonging to the conjugated bond system; the lactam carbonyl group gives a strong band at 1697 cm^{-1}. The shift of this band is explained not only by conjugation, but also by participation of the carbonyl group in H bond formation. The high-frequency region of the spectrum contains a sharp peak at 3300 cm^{-1} (OH) and a broadened band at 3153 cm^{-1} (NH).

Enol ethers (or alkyl alkenyl ethers) are widely used in organic synthesis due to the presence of highly nucleophilic double bond and alkoxy group

which can readily be converted into carbonyl group. Introduction of other functional groups into molecules of alkyl alkenyl ethers extends their synthetic potential as a result of activation of each functional group. 3-Hydroxyimino-2-butanone hydrazone was also brought into reaction with ethyl 2-cyano-3-ethoxy-acrylate. The latter contains two electrophilic centers which can compete for the nucleophile. However, the condensation occurred regioselectively at the ethoxy-methylene group to afford product **XIII**. Its IR spectrum contained broadened bands at 3210 and 3280 cm⁻¹ belonging to stretching vibrations of the OH and NH groups and a strong band at 2212 cm⁻¹ from the cyano group. In the region of double bond vibrations three bands were present at 1620, 1687, and 1710 cm⁻¹. The two latter correspond to stretching vibrations of the ester carbonyl group, indicating that compound **XIII** exists as a mixture of two stereo-isomers. The high-frequency band (1710 cm⁻¹) belongs to the isomer whose carbonyl group is not involved in intramolecular hydrogen bond. The strong band at 1610 cm⁻¹ should be assigned to stretching vibrations of the conjugated bond system. The ¹H NMR spectrum of **XIII** (Table 2) contains a double set of signals, in keeping with the presence of two stereoisomers of the enamine tautomer. In the downfield region of the spectrum a singlet at δ 11.70 ppm from the hydroxy proton and two doublets at δ 8.22 and 11.55 ppm from the CH and NH protons are observed. Spin–spin coupling in the =CHNH fragment suggests coplanar arrangement of multiple bonds, stabilized by intramolecular hydrogen bond. The structure of that isomer is shown in Scheme 1; its fraction is 40%. The second stereoisomer of **XIII** is characterized by three one-proton singlets located more upfield, at δ 7.68, 10.94, and 11.55 ppm (CH, NH, and OH groups, respectively). The conjugated bond sequence O=C–C=C in the second isomer is turned through some angle about the C–N bond. As a result, intramolecular hydrogen bond becomes weaker, proton chemical shifts becomes lower, and stretching vibration frequency of the ester carbonyl group increases. It should be noted that the state of tautomeric equilibrium does not change in going from crystal to solution, but solvation favors formation of another rotamer of the enamine tautomer.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer in mineral oil. The ¹H NMR spectra were obtained on a Bruker AM-300 instrument in DMSO-d_6; the chemical shifts were measured relative to hexamethyldisiloxane as internal reference. Thin-layer chromatography was performed on Silufol UV-254 plates; the following solvent systems were used as eluent: 2-propanol–benzene, 1:4 (A) and 1:3 (B); the spots were visualized with iodine vapor.

1,8-Dihydroxy-2,3,6-trimethyl-1,4,5-triaza-1,3,5,7-nonatetraene (II) and ethyl 8-hydroxy-3,6,7-trimethyl-4,5,8-triaza-2,5,7-octatrienoate (III). 2,4-Pentanedione or ethyl acetoacetate, 20 mmol, was added to a warm solution of 2.3 g of 3-hydroxyimino-2-butanone hydrazone (**I**) in 20 ml of dioxane or ethanol. The mixture was heated on a water bath for 0.5 h, and the solvent was distilled off under reduced pressure (water-jet pump). The residue was recrystallized from dioxane and washed with carbon tetrachloride.

Methyl 2-(2-hydroxyimino-1-methylpropylidene-hydrazino)-1-cyclopentenecarboxylate (IV) was synthesized by the above procedure from 2.3 g of hydrazone **I** in 20 ml of dioxane and 20 mmol of methyl 2-oxocyclopentanecarboxylate.

8-Hydroxy-3,6,7-trimethyl-4,5,8-triaza-2,5,7-octatrienoic acid anilides V–XI were synthesized following the general procedure from 2.3 g of hydrazone **I** in 20 ml of dioxane and an equimolar amount of the corresponding acetoacetanilide.

Ethyl 2-cyano-8-hydroxy-6,7-dimethyl-4,5,8-triaza-2,5,7-octatrienoate (XIII) and N-(2-hydroxy-imino-1-methylpropylidene)-N'-(2-oxo-2,3-dihydro-indol-3-ylidene)hydrazine (XII) were synthesized as described above for compounds **II** and **III** from 2.3 g of hydrazone **I** in 20 ml of dioxane and 20 mmol of ethyl 2-cyano-3-etoxyacrylate or isatin, respectively.

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