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REACTIONS OF ENAMINO KETO ESTERS OF 1,2,3,4-TETRAHYDROISOQUINOLINE SERIES WITH NUCLEOPHILES

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It has been shown that the reaction of the methyl ester of 3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-idene)pyruvic acid with thiosemicarbazide in glacial acetic acid leads to heterocyclization with the formation of 3,3-dimethyl-1-(5-thioxo-1,5-dihydro-1,2,4-triazol-3-ylmethylidenecarbonyl)-1,2,3,4-tetrahydroisoquinoline, but the interaction with semicarbazide under the same conditions leads to annelation of the pyrrole ring. On condensation of the enamino keto ester with malonodinitrile, the nitrile of 2-cyano-4-dicyanomethylidene-5-(3,3-dimethyl-1,2,3.4-tetrahydroisoquinolin-1-idene)-3-oxo-pentanoic acid is formed.

Keywords: 3,3-dimethyl-1-(5-thioxo-1,5-dihydro-1,2,4-triazol-3-ylmethylidenecarbonyl)-1,2,3,4-tetrahydroisoquinoline, methyl ester of 3-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-idene)pyruvic acid, nitrile of 2-cyano-4-dicyanomethylidene-5-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-idene)-3-oxo-pentanoic acid, semicarbazide, thiosemicarbazide, annelation of the pyrrole ring, heterocyclization, ester condensation with malonodinitrile.

Enamino keto ester derivatives of 1,2,3,4-tetrahydroquinoline have been obtained previously [1-3]. The properties of the keto ester group of these compounds have been studied little up to the present time. The aim of the present work was to investigate the reactions of enamino keto esters of the 3,3-dialkyl-1,2,3,4-tetrahydroisoquinoline series with nucleophiles.

The initial enamino keto esters **2a,b** were synthesized by the known procedure using dioxopyrrolines **1a,b** as starting materials [1, 2]. It is known that the reaction of compounds **2a,b** with aliphatic amines proceeds on boiling in alcohol with the formation of the corresponding enamino amides [2, 3]. Investigation of the reactions of esters **2a,b** with aromatic amines showed that on boiling in alcohol or glacial acetic acid no aminolysis was observed. However on boiling compound **1a** with thiosemicarbazide in glacial acetic acid a heterocyclization occurred with the formation of ketone **3**, having a triazole system in its structure. Boiling compounds **2a,b** in glacial acid with semicarbazide hydrochloride leads to annelation of the pyrrole ring with the formation of compounds **4a,b**. An intramolecular aminolysis of the ester group therefore occurs in these cases. The observed reaction at the ketone group may be explained by the fact that in acidic medium on going

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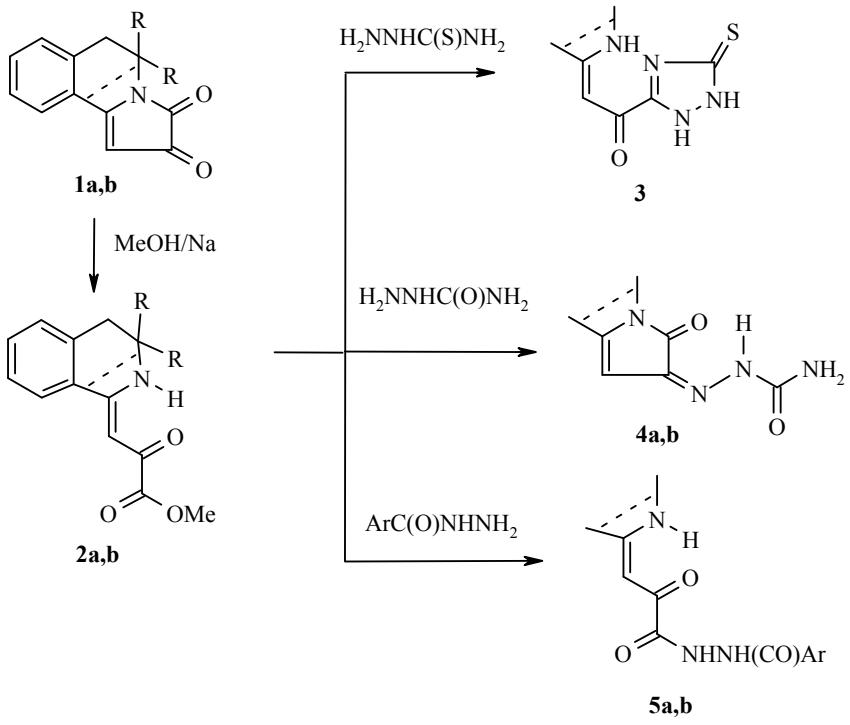
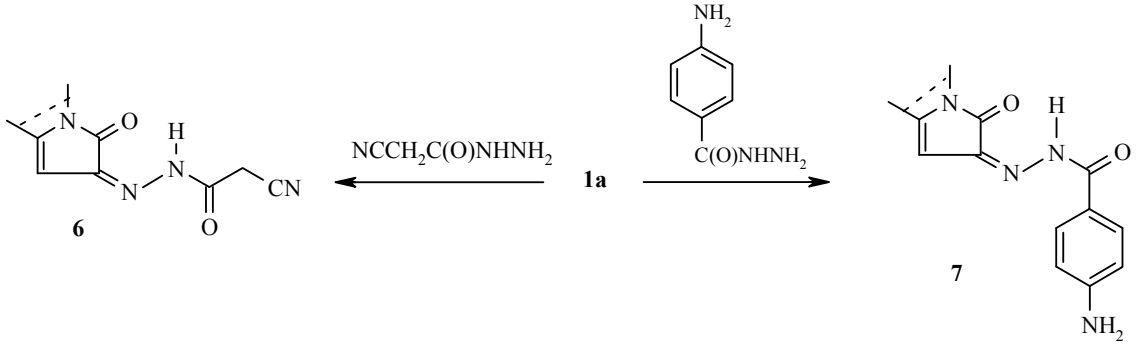
from the enamine form to a protonated imino form the ketone group is more electrophilic in relation to semicarbazide than the ester. Under analogous conditions ester **2** interacts with isonicotinic acid hydrazide with the formation of diacylhydrazide **5a**. Compound **5b** is formed on boiling ester **2a** with *p*-aminobenzoic acid hydrazide in 2-propanol.



1,2,4 a R = Me, **b** 2R = spirocyclopentyl; **3** R = Me; **5 a,b** R = Me, **a** Ar = 4-Py, **b** Ar = 4-$H_2NC_6H_4$

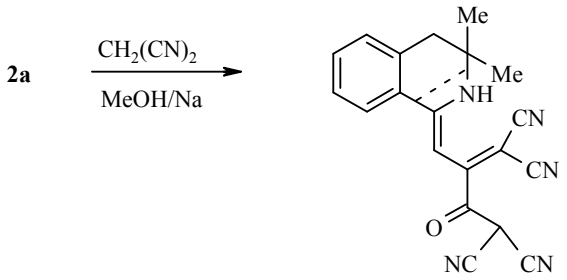
On interacting ester **2a** with other hydrazides, such as cyanoacetylhydrazide and benzoic acid hydrazide in boiling glacial acetic acid or 2-propanol, no new products were isolated, which may be explained by the weak nucleophilic properties of the reactants used.



It is known that 2,3-dioxopyrrolo[2,1-*a*]isoquinolines frequently play the role of acylating reagents, interacting with N-nucleophiles with opening of the pyrrole ring [4-7]. It therefore seemed of interest to study the acylation reaction of hydrazides with these reagents with the aim of obtaining substances analogous to

compounds **5a,b** in structure. The investigations showed that on boiling dioxopyrroline **1a** with the hydrazides of cyanoacetic and *p*-aminobenzoic acids reaction proceeds according to the previously known scheme with the formation of the corresponding hydrazones **6** and **7**, i.e. without opening of the pyrroledione ring [5].

Condensation of ester **2a** with malonodinitrile leads to the tetracyano ketone **8**.



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The formation of structure **8** may be explained by the high CH acidity of malonodinitrile, and also the stability of the resulting structure due to the conjugation chain of the enamine fragment with acceptor nitrile groups.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3*	$C_{15}H_{16}N_4OS$	59.8 / 60.0	5.3 / 5.4	18.8 / 18.7	230-232	35
4b	$C_{17}H_{18}N_4O_2$	65.7 / 65.8	5.7 / 5.8	18.1 / 18.0	220-222	52
5a	$C_{20}H_{20}N_4O_3$	65.8 / 65.9	5.4 / 5.5	15.4 / 15.3	240-242	48
5b	$C_{21}H_{22}N_4O_3$	66.5 / 66.6	5.8 / 5.9	14.9 / 14.8	238-240	55
6	$C_{17}H_{16}N_4O_2$	66.1 / 66.2	5.1 / 5.2	18.3 / 18.2	222-224	75
7	$C_{21}H_{20}N_4O_2$	69.8 / 69.9	5.5 / 5.6	15.8 / 15.7	296-298	82
8	$C_{20}H_{15}N_5O$	70.3 / 70.4	4.3 / 4.4	20.4 / 20.5	208-10	75

*Found, %: S 10.6; calculated, %: S 10.7.

TABLE 2. IR Spectra of the Synthesized Compounds

Compound	ν, cm^{-1}
3	1610 (CO), 1640 (C=N), 3150, 3250, 3300 (NH)
4a	1700 (CO lactam), 1730 (CO semicarbazone), 3180 (NH chelate), 3330 and 3400 (NH_2)
4b	1700 (CO lactam), 1730 (CO semicarbazone), 3180 (NH chelate), 3330 and 3400 (NH_2)
5a	1600 (CO, chelate), 1650 and 1690 (NCO), 3150 (NH ring, chelate), 3350 (NH hydrazide)
5b	1600 (CO, chelate), 1650 and 1690 (NCO), 3150 (NH ring, chelate), 3350 (NH hydrazide)
6	1675 (CO hydrazide), 1720 (CO lactam, chelate), 3140 (NH, chelate), 2260 (CN)
7	1670 (CO hydrazide), 1700 (CO lactam, chelate), 3200 (NH, hydrazide), 3300 and 3400 (NH_2)
8	1600 (CO, conj.), 1620 (C=C, conj.), 3210 (NH ring), 2300-2310 (CN)

TABLE 3. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm					
	R_2	2H-4, s	1-CH= s	Aromatic protons	NH ring	Other protons
3	1.3 (6H, s)	2.9	6.2	7.1-7.9 (4H)	9.0	6.0 (s, NH); 6.1 (s, NH)
4a	1.3 (6H, s)	2.8	6.7	7.0-7.6 (4H)	—	10.3 (s, NH); 6.6 (2H, br. s, NH_2)
4b	1.3 (8H, s)	2.8	6.7	7.0-7.7 (4H)	—	10.3 (s, NH); 6.5 (2H, br. s, NH_2)
5a	1.3 (6H, br. s)	2.8	6.8	7.1-7.9 (8H)	13.7	8.8 (2H, s, CONHNHCO)
5b	1.2 (3H, s); 1.3 (3H, s)	2.8	6.2	7.2-7.9 (8H)	13.6	11.4 (2H, s, CONHNHCO)
6	1.3 (6H, s)	2.8	6.7	7.1-7.8 (4H)	—	4.1 (2H, s, CH_2CN); 11.6 (s, CONH)
7	1.3 (6H, s)	2.8	6.4	6.4-7.9 (8H)	—	3.7 (2H, s, H_2NAr); 13.5 (s, CONH)
8	1.3 (6H, s)	2.8	6.2	7.0-8.0 (4H)	12.1	3.8 (s, $CH(CN)_2$)

The characteristics of the synthesized compounds are given in Table 1, with data of IR spectra and ^{1}H NMR spectra in Tables 2 and 3. The compounds obtained were colored crystalline substances.

The tricyclic lactams **4**, **6**, and **7** have an orange color, ketones **3**, **5** a yellow color, and tetranitrile **8** forms black crystals. Compound **4a**, according to data of ^{1}H NMR, TLC, and mixed melting test, tallies with the semicarbazide obtained by us previously in [8].

Singlets are present in the ^{1}H NMR spectra of ketones **3, 5, 8** (Table 2), unlike the spectra of the initial dioxopyrrolines, for the protons of the NH groups of the isoquinoline ring (9.0-13.7 ppm). In the case of diacylhydrazides **5a,b** the displacement towards low field (13.6 and 13.7 ppm) may be explained by the possibility of forming a six-membered H-chelate ring. In the spectrum of compound **3** there were two singlets for the NH group protons of the thiazole fragment (6.0 and 6.1 ppm). The condensed structure of compounds **4a,b** was confirmed by the presence of singlet signals for the NH group protons of the hydrazone (10.3) and NH_2CO (6.6 and 6.5 ppm) [8]. The spectra of hydrazones **6, 7** contain only one singlet for the protons of the NH group at low field (11.6 and 13.5 ppm), which points in favor of the condensed tricyclic structure.

In the spectrum of diacylhydrazide **5b** the methyl groups are displayed as two singlets, which may be explained by the influence of the primary amino group of the aromatic ring, and makes a difference to their magnetic enviroment.

The mass spectrum of compound **3** contains a peak* for the molecular ion of 300 $[M]^+$ (27), and also a peak for the 3,3-dimethyl-1-methylidenecarbonyl-1,2,3,4-tetrahydroisoquinoline fragment at 200 (35), characteristic for compounds having this fragment in their structure [4-7]. In the mass spectrum of tricyclic ketone **4a** a peak was observed for the molecular ion at 284 $[M]^+$ (12), and also a peak corresponding to cleavage of the semicarbazide fragment 211 $[M]^+$ (17). The mass spectrum of hydrazide **7** contains a peak for the molecular ion at 360 $[M]^+$ (12), and a peak corresponding to the elimination of $NHC(O)C_6H_4NH_2$ at 225 (4). For the spectrum of tetranitrile **8a** the molecular ion peak is a characteristic at 341 $[M]^+$ (36), as is a fragment caused by removal of a methyl group at 326 (100).

*Here and subsequently values of m/z (I_{rel}, %) are given for peaks.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Tesla BS 567A instrument (100 MHz) in $CDCl_3$ (compounds **3** and **5a**) and DMSO-D_6 (remaining compounds), internal standard was HMDS (δ 0.05 ppm). The IR spectra were obtained on a Specord M-80 spectrometer in nujol. The mass spectra were recorded on a Finigan MAT INCOS 50 instrument (70 eV, EI). Tests on the purity of the substances obtained were effected by TLC on Silufol UV-254 plates in the system acetone–ethanol–chloroform, 1:3:6, visualization in UV light and iodine vapor.

Compound **8** was recrystallized from benzene, the remainder from acetonitrile.

3,3-Dimethyl-1-(5-thioxo-1,5-dihydro-1,2,4-triazol-3-ylmethylidenecarbonyl)-1,2,3,4-tetrahydroisoquinoline (3), 5,5-(R)$_2$-3-oxo-2-semicarbazono-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolines (4a,b) and N-Isonicotinoylhydrazide of 3-3,3-Dimethyl-2,3,5,6-tetrahydroisoquinolin-1-idene)pyruvic Acid (5a) (General Method). A mixture of keto ester **2a,b** (10 mmol) and the appropriate nucleophile (15 mmol) was boiled in glacial acetic acid (30 ml) (check by TLC). The solution was cooled to 20°C, diluted with water (100 ml), the precipitated solid was filtered off, dried, and recrystallized.

N-(*p*-Aminobenzoyl)hydrazide of 3-(3,3-Dimethyl-1,2,3,4-tetrahydroisoquinolin-1-idene)pyruvic Acid (5b). A mixture of keto ester **2a** (2.59 g, 10 mmol) with *p*-aminobenzoic acid hydrazide (2.26 g, 15 mmol) in the presence of a catalytic amount (2-3 crystals) of *p*-TsOH in 2-propanol (30 ml) was boiled for 2.5 h (check by TLC). The compounds were then isolated analogously to compounds **3**, **4a,b**, and **5a**.

2-(N-Cyanoacetylhydrazono)-5,5-dimethyl-3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline (6) and 2-[N-(*p*-Aminobenzoyl)hydrazono]-3-oxo-2,3.5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline (7) (General Method). A solution of a mixture of dioxopyrroline **1a** and the appropriate hydrazide (15 ml) in 2-propanol (25 ml) was boiled for 40 min. Further isolation was analogous to compounds **3-5a**.

2-Cyano-4-dicyanomethylidene-5-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-idene)-3-oxopentanoic Acid Nitrile (8). Sodium (0.1 g) and malonodinitrile (1.65 g, 25 mmol) were added to a solution of keto ester **2a** (2.59 g, 10 mmol) in absolute methanol (20 ml). The reaction mixture was boiled for 30 min until development of a dark-cherry color, diluted with water (100 ml), acidified with acetic acid solution dropwise until precipitation of a dark-raspberry colored solid, which was filtered off, dried, and recrystallized.

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