INTERACTION OF 1-METHYLTHIO-3,3-DIMETHYL-3,4-DIHYDROISOQUINOLINE WITH β-DICARBOXYLIC ACIDS, β-DICARBONYL COMPOUNDS, AND THEIR ANALOGS

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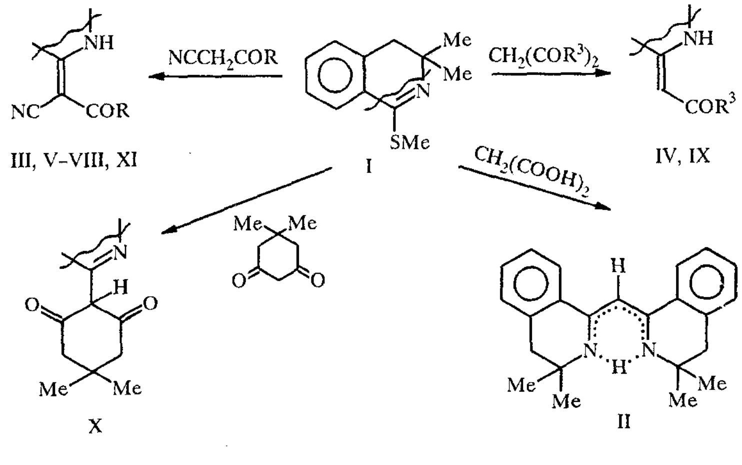
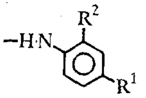
1-Methylthio-3,3-dimethyl-3,4-dihydroisoquinoline interacts as an electrophile with β-dicarbonyl compounds and their analogs to form products in which one or two hydrogen atoms of the β-carbonyl compound are replaced by a 3,3-dimethyl-3,4-dihydroisoquinolyl or 3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidene fragment.

It is known that thioethers of lactims are capable of interaction with nucleophiles, replacing the alkylthio group by the corresponding fragment of the nucleophile [1]. We have shown that 1-methylthio-3,3-dimethyl-3,4-dihydroisoquinoline (I) interacts readily with malonodinitrile to form 3,3-dimethyl-1-dicyanomethylene-1,2,3,4-tetrahydroisoquinoline [2]. Since β-dicarbonyl compounds and related compounds are used widely in the synthesis of many different heterocyclic systems [3], it was of interest to investigate the interaction of the thioether I with β-dicarbonyl compounds.

Reactions of the thioether I with β-dicarbonyl compounds were effected without a solvent at 150°, or with refluxing in acetic acid or DMF. The yields of compounds VI, X, and XI depend on the method selected for the synthesis.



III) R = —OEt. V—VIII,XI) R =  , where V) $R^1 = R^2$ = H; VI) R^1 = H, R^2 = Me; VII) $R^1 = R^2$ = Me; VIII) R^1 = COOEt, R^2 = H; XI) R = —NH_2. IV) R^3 = —OEt; IX) R^3 = Me.

Institute of Technical Chemistry, Ural Branch of the Russian Academy of Sciences, Perm' 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1651-1654, December, 1992. Original article submitted June 26, 1991.

0009-3122/92/2812-1416$12.50

TABLE 1. Characteristics of Compounds II-XI

Compound	Empirical formula	mp, °C*	PMR spectrum, δ, ppm**						Yield, % (method)
			$C_{(3)}$-$(CH_3)_2$, s, 6H	$C_{(4)}$-H_2 s, 2H	N-H, s, 1H	$C_{(8)}$-H, 1H	H arom m, 3H	other protons	
II	$C_{23}H_{26}N_2$	174...176	1,20 (12H)	2,63 (4H)	11,80	7,50 (2H)	6,77...7,23 (6H)	5,67 (1H, s, CH)	72 (A)
III	$C_{16}H_{18}N_2O_2$	138..139	1,20	2,77	10,47	8,37	6,93...7,50	1,27 (3H, t, CH_2CH_3); 4,17 (2H, q, CH_2CH_3)	75 (A)
V	$C_{20}H_{19}N_3O$	174...176	1,24	2,83	11,43	8,40	7,00...7,90 (8H)		87 (C)
VI	$C_{21}H_{21}N_3O$	169...171	1,24	2,82	11,49	8,45	7,10...8,00 (7H)	2,31 (3H, s, CH3–C_{arom})	64 (A) 52 (C)
VII	$C_{22}H_{23}N_3O$	183...185	1,27	2,79	11,45	8,40	6,90...7,80 (6H)	2,25 (6H, br. , sCH3)$_2$–C_{arom})	57 (A)
VIII	$C_{23}H_{23}N_3O_3$	191...193	1,26	2,83	11,39	8,27	7,10...8,06 (7H)	1,37 (3H, t, CH2CH_3); 4,36 (2H, q, CH_2CH_3)	64 (A)
X	$C_{19}H_{23}NO_2$	178...180	0,74	2,14	—	7,76	6,90...7,07	0,95 (6H, s, Me_2–C_4); 2,45 (4H, s, CH_2CO); 6,66 (1H, s, CH)	69 (A)
XI	$C_{14}H_{15}N_3O$	167...169	1,10	2,83	10,47	8,17	7,20...7,60	6,87 (2H, br. s NH_2)	75 (A) 86 (B) 98 (C)

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*Compounds were crystallized from: II) benzene; II) methanol; V—VIII) ethanol; X) petroleum ether; XI) isopropanol.

**The PMR spectra of compounds III, V—VIII, X, and XI were taken in $CDCl_3$, that of II in C_6D_6.

Fusion of malonic acid with the thioether I gave a single product, bis(3,3-dimethyl-3,4-dihydro-1-isoquinolyl)methane (II). Such a course of the reaction is explained by the facile decarboxylation of the intermediate product (3,3-dimethyl-1,2,3,4-tetrahydro-1-isoquinolylidene)malonic acid (subsequently termed 3,3-dimethyl-1,2,3,4-tetrahydroisoquinolylidene, or simply isoquinolylidene); this leads to the formation of 1,3,3-trimethyl-3,4-dihydroisoquinoline, which, upon interaction with I, gives compound II. The presence of 1,3,3-trimethyl-3,4-dihydroisoquinoline in the reaction mass, this compound being formed in the course of the reaction, was verified by TLC with a reference spot as described in [4].

In the PMR spectrum of compound II, in place of the signal of the exomethylene group, we observe two signals of protons at 5.67 and 11.80 ppm (Table 1), indicating an enaminoazomethine structure with an intramolecular hydrogen bond. However, the methyl and methylene groups of different rings give identical, unbroadened signals, indicating equalization of electron density in the real molecule (as shown in the scheme).

The derivatives of malonic acid also differ in the character of thermal breakdown. Thus, from the reaction of malonic ester and the thioether I without solvent, the only product of the interaction is the ethyl ester of the 1-isoquinolylideneacetic acid IV, the constants of which are in agreement with those reported in [5]. Under the same conditions, cyanoacetic ester gives the ethyl ester of the 1-isoquinolylidenecyanoacetic acid III; and, according to TLC data obtained with known reference spots, the reaction products contain as impurities the nitrile of the 1-isoquinolylideneacetic acid and compound IV (the same results were obtained when the reaction was carried out by refluxing in acetic acid or DMF).

Amides of cyanoacetic acid proved to be more heat-stable: Reactions of various cyanoacetamides with the thioether I gave the corresponding anilides of the 1-isoquinolylidenecyanoacetic acid V—VIII with high yields. Similar results were obtained in the reaction of the thioether I with cyanoacetamide.

Thermal splitting is also observed in the interaction of the thioether I with acetoacetic ester or acetylacetone. With the acetoacetic ester, according to TLC data with reference spots that are described in [5, 6], a mixture of the ester IV and compound IX is formed. The latter is the sole product of the reaction of the thioether I with acetylacetone. The reaction of the thioether I with dimedone yields 1-(4′,4′-dimethylcyclohexa-2′,6′-dion-1′-yl)-3,3-dimethyl-3,4-dihydroisoquinoline (X).

In the PMR spectra of all compounds other than X, we observe signals of the N—H protons in the 10.47—11.80 ppm region, indicating that these compounds exist in the enamine form. The PMR spectrum of compound X exhibits a signal at 6.6 ppm, but no signal in the 10—12 ppm region. Also, the two methylene groups of the dimedone ring give a single signal, the intensity of which corresponds to four protons. These two facts indicate that compound X exists in the azomethine form.

EXPERIMENTAL

The PMR spectra were taken in an RYa-2310 spectrometer, internal standard HMDS. The course of the reaction was monitored by means of TLC on Silufol UV-336 plates (development by chloroaniline solution) in a 9:1 chloroform—acetone system.

The elemental analyses matched the calculated data.

Interaction of 1-Methylthio-3,3-dimethyl-3,4-dihydroisoquinoline with β-Dicarboxylic Acids, β-Dicarbonyl Compounds, and Their Analogs

A. Equivalent quantities of the thioether I and a β-dicarbonyl compound were heated in an oil bath at 150°C until the thioether I had disappeared, according to TLC. After cooling, the mixture was treated with pentane or hexane, and the solidified mass was crystallized.

B. A 0.01-mole quantity of the thioether I and 0.01 mole of a β-dicarbonyl compound were dissolved in 25—30 ml of DMF and refluxed until the thioether I had disappeared according to TLC. Then the reaction mixture was poured into 100 ml of water, acidified with HCl to acid reaction, and extracted with ether; the aqueous layer was made alkaline by adding an ammonia solution. The precipitate was filtered off and crystallized.

C. A 0.01-mole quantity of the thioether I and a β-dicarbonyl compound were dissolved in 30 ml of acetic acid, refluxed until the thioether I had disappeared according to TLC, and poured into 100 ml of water; the precipitate was filtered off and crystallized.

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