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REACTION OF SPIROCYCLIC ISOPROPYLIDENE MALONATES WITH UREA AND N,N'-DISUBSTITUTED UREAS

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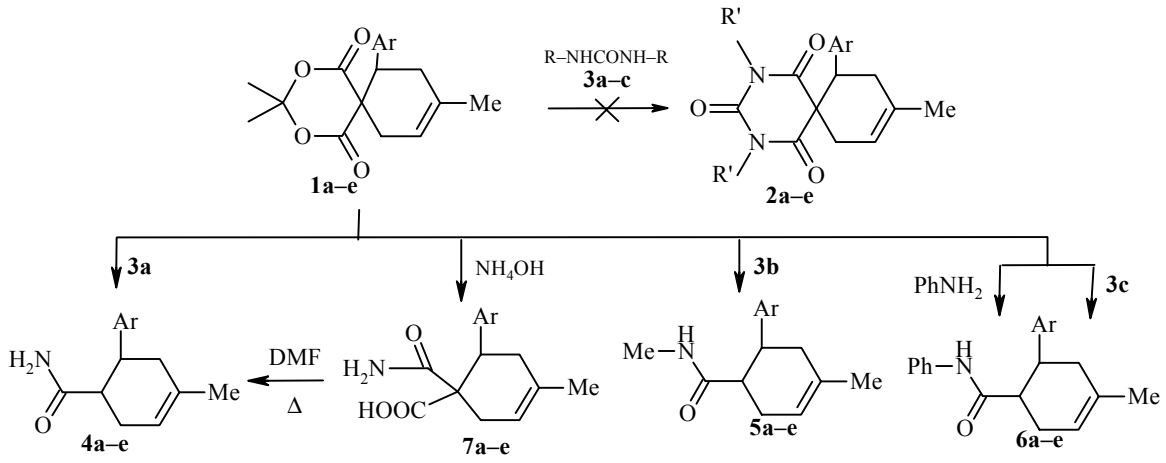
Unsubstituted and N-substituted amides of 2-aryl-4-methyl-4-cyclohexene-1-carboxylic acids are formed during the fusion of 2'-aryl-2,2,4'-trimethyl-1,3-dioxan-5-spirocyclohex-4'-ene-4,6-diones with urea and N,N'-disubstituted ureas.

Keywords: amides, barbituric acid, N,N'-disubstituted ureas, isopropylidene malonate, urea, cyclohexene.

The main method for the production of 5,5-disubstituted barbituric acids, which include a large number of pharmaceutical products [1, 2], involves the reaction of disubstituted malonic acids or their esters with derivatives of urea [1].

The 2'-aryl-2,2,4'-trimethyl-1,3-dioxan-5-spirocyclohex-4'-ene-4,6-diones **1a-e** that we synthesized earlier [3] are derivatives of cyclic esters of malonic acid. We therefore assumed that spirocyclic barbituric acids (2'-aryl-4'-methylhexahydropyrimidine-5-spirocyclohex-4'-ene-2,4,6-triones) **2a-e** would be formed in their reactions with ureas.

However, the spirocyclic isopropylidene malonates **1a-e** did not react with the ureas **3a-c** when boiled in ethanol, dioxan, or DMF.



1, **2**, **4**–**7** **a** Ar = Ph, **b** Ar = C_6H_4F-*p*, **c** Ar = C_6H_4Cl-*p*, **d** Ar = C_6H_4Br-*p*, **e** Ar = $C_6H_4NO_2$-*p*, **3a** R = H, **b** R = Me, **c** R = Ph

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TABLE 1. The Characteristics of Compounds **4a-e** and **5a-e**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Hal		
4a	$C_{14}H_{17}NO$	78.17 / 78.10	7.90 / 7.96	6.39 / 6.51		125-127	55.6
4b	$C_{14}H_{16}FNO$	72.21 / 72.08	6.72 / 6.91	5.86 / 6.00	8.22 / 8.14	139-140	70.2
4c	$C_{14}H_{16}ClNO$	67.17 / 67.33	6.33 / 6.46	5.47 / 5.61	14.31 / 14.20	150-151	67.6
4d	$C_{14}H_{16}BrNO$	56.90 / 57.16	4.84 / 4.76	5.39 / 5.48	27.26 / 27.16	127-129	60.0
4e	$C_{14}H_{16}N_2O_3$	57.80 / 57.93	5.21 / 5.56	9.49 / 9.65		160-161	71.4
5a	$C_{15}H_{19}NO$	71.69 / 71.79	7.20 / 7.39	5.49 / 5.40		165-166	58.3
5b	$C_{15}H_{18}FNO$	75.16 / 75.28	7.28 / 7.34	5.71 / 5.66	7.57 / 7.68	181-183	74.1
5c	$C_{15}H_{18}ClNO$	70.49 / 70.58	6.91 / 6.88	5.13 / 5.31	13.27 / 13.44	159-161	57.1
5d	$C_{15}H_{18}BrNO$	61.71 / 61.60	6.01 / 5.89	4.71 / 4.54	25.78 / 25.93	167-168	59.8
5e	$C_{15}H_{18}N_2O_3$	60.90 / 61.17	5.76 / 5.96	9.03 / 9.21		232-235	60.0

The reaction of the compounds in methanol or ethanol in the presence of sodium methoxide or sodium ethoxide according to the usual procedures [4-6] led to the formation of mixtures of products, from which it was not possible to isolate individual products. Various modifications of the methods also did not give positive results.

TABLE 2. The Spectral Characteristics of Compounds **4a-e** and **5a-e**

Compound	^{1}H NMR spectrum, δ, ppm, CCSS, *J* (Hz)
4a	1.64 (3H, s, CH_3); 2.26-2.37 (4H, m, $2CH_2$); 2.48 (1H, m, CH); 3.33 (1H, m, CH); 5.42 (1H, m, =CH); 6.71 (1H, br. s, NH); 7.22 (5H, m, C_6H_5); 11.5 (1H, br. s, NH)
4b	1.64 (3H, s, CH_3); 2.00-2.22 (4H, m, $2CH_2$); 2.68 (1H, m, CH); 3.33 (1H, m, CH); 5.42 (1H, m, =CH); 6.68 (1H, br. s, NH); 6.91-7.31 (4H, m, C_6H_4); 7.52 (1H, br. s, NH)
4c	1.75 (3H, s, CH_3); 2.27-2.53 (4H, m, $2CH_2$); 2.79 (1H, m, CH); 3.52 (1H, m, CH); 5.35 (2H, br. s, NH_2); 5.59 (1H, m, =CH); 7.20 (4H, m, C_6H_4)
4d	1.68 (3H, s, CH_3); 2.17-2.37 (4H, m, $2CH_2$); 2.71 (1H, m, CH); 3.34 (1H, m, CH); 5.20 (1H, m, =CH); 5.43 (2H, br. s, NH_2); 7.02-7.37 (4H, m, C_6H_4)
4e	1.75 (3H, s, CH_3); 2.08-2.37 (4H, m, $2CH_2$); 2.75 (1H, m, CH); 3.55 (1H, m, CH); 5.51 (1H, m, =CH); 6.06 (2H, br. s, NH_2); 7.42 (2H, d, *J* = 8, C_6H_4); 8.11 (2H, d, *J* = 8, C_6H_4)
5a	1.71 (3H, s, CH_3); 2.08-2.37 (4H, m, $2CH_2$); 2.58 (3H, d, *J* = 5, CH_3); 2.60 (1H, m, CH); 3.40 (1H, m, CH); 5.02 (1H, d, *J* = 5, NH); 5.44 (1H, m, =CH); 7.13 (5H, m, C_6H_5)
5b	1.72 (3H, s, CH_3); 2.07-2.27 (4H, m, $2CH_2$); 2.60 (3H, d, *J* = 5, CH_3); 2.62 (1H, m, CH); 3.39 (1H, m, CH); 5.02 (1H, d, *J* = 5, NH); 5.43 (1H, m, =CH); 6.68-7.37 (4H, m, C_6H_4)
5c	1.64 (3H, s, CH_3); 1.93-2.17 (4H, m, $2CH_2$); 2.40 (3H, d, *J* = 5, CH_3); 2.71 (1H, m, CH); 3.37 (1H, m, CH); 5.15 (1H, d, *J* = 5, NH); 5.47 (1H, c, =CH); 7.06 (4H, m, C_6H_4)
5d	1.71 (3H, s, CH_3); 2.00-2.33 (4H, m, $2CH_2$); 2.62 (3H, d, *J* = 5, CH_3); 2.64 (1H, m, CH); 3.42 (1H, m, CH); 5.20 (1H, d, *J* = 5, NH); 5.48 (1H, m, =CH); 7.04 (2H, d, *J* = 8, C_6H_4); 7.42 (2H, d, *J* = 8, C_6H_4)
5e	1.77 (3H, s, CH_3); 2.13-2.44 (4H, m, $2CH_2$); 2.70 (3H, d, *J* = 5, CH_3); 2.73 (1H, m, CH); 3.62 (1H, m, CH); 5.28 (1H, d, *J* = 5, NH); 5.55 (1H, m, =CH); 7.33 (2H, d, *J* = 8, C_6H_4); 8.08 (2H, d, *J* = 8, C_6H_4)

We found that the malonates **1a-e** reacted with the ureas **3a-e** at the melting point of their mixture with the formation not of the barbituric acid derivatives **2** but of 2-aryl-4-methylcyclohex-4-ene-1-carboxamides **4a-e** or their N-methyl or N-phenyl derivatives **5a-e** and **6a-e** respectively. The formation of these products is probably due to decomposition of the ureas **3a-c** at the melting point of the reaction mixture to ammonia or amines, which react with the malonates **1a-e** to form the familiar monoamides of cyclohexenecarboxylic acids **7a-e** [7]. The latter then undergo decarboxylation to the amides **4a-e** and **5a-e** and the previously described amides **6a-e** {obtained by the prolonged boiling of **1a-e** and aniline in DMF [7]}.

The structure of the synthesized compounds **4a-e** and **5a-e** is confirmed by the results from elemental analysis (Table 1) and the ^{1}H NMR spectra (Table 2). In the case of the products **4a-e** it was also confirmed by decarboxylation of the monoamides **7a-e** (by boiling in DMF).

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker WH/90DS instrument (90 MHz) with deuterochloroform and DMSO as solvents and HMDS as internal standard. The individuality of the obtained compounds was checked by TLC on Silufol plates in the following solvent systems: 9:1:1 chloroform–acetone–glacial acetic acid for compounds **4a-e**; 24:2:1 chloroform–methanol–glacial acetic acid for compounds **5a-e** and **6a-e**.

Amides of 2-Aryl-4-methylcyclohex-4-en-1-carboxylic Acids (4a-e), N-Methylamides of 2-Aryl-4-methylcyclohex-4-ene-1-carboxylic Acids (5a-e), and N-Phenylamides of 2-R-4-Methylcyclohex-4-ene-1-carboxylic Acids (6a-e) (General Procedure). A mixture of equimolar amounts of the spirocyclic isopropylidene malonate **1a-e** and the urea **3a-c** was kept at the melting point for 2 h (during the synthesis of compounds **5a**, **b**), 2.5 h (**4a**, **c** and **5c**, **d**), 3 h (**4b**, **d**, **e**), and 4 h (**6a-e**).

The amides **4a-e**–**6a-e** were isolated from the reaction mixture by the addition of water followed by filtration. They were purified by recrystallization from methanol (**4a**), a 1:1 mixture of methanol and water (**4b-e**), acetonitrile (**5a-d**), or a 1:1 mixture of ethanol and water (**5e**, **6a-e**).

The properties and chemical characteristics of compounds **6a-e** agree with those for previously obtained samples [7].

Compounds **4a-e** were also synthesized by boiling the monoamides **7a-e** (obtained by the method in [7]) for 2 h in DMF followed by addition to iced water, filtration, and drying. Compounds **4a-e** were chromatographically uniform without recrystallization.

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