

## INTERACTION OF HYDRAZIDES OF 2-ARYL-4-METHYL-4-CYCLOHEXENE- 1,1-DICARBOXYLIC ACIDS WITH CERTAIN HETEROCYCLIC ALDEHYDES

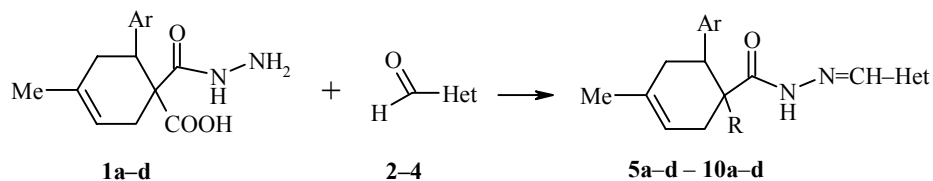
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*Monohydrazides of 2-aryl-4-methyl-4-cyclohexene-1,1-dicarboxylic acids react with 2-thiophene-, 3-pyridine-, and 4-pyridinecarbaldehydes to form the corresponding acylhydrazones of hydrazides of mono- or dicarboxylic acids of the cyclohexene series depending on the temperature.*

**Keywords:** hydrazones, monohydrazides of 2-aryl-4-methyl-4-cyclohexene-1,1-dicarboxylic acids, 3-pyridinecarbaldehyde, 4-pyridinecarbaldehyde, 2-thiophenecarbaldehyde.

While continuing investigations on monohydrazides of 2-aryl-4-methyl-4-cyclohexene-1,1-dicarboxylic acids **1** [1-3] and with the aim of synthesizing biologically active compounds from them, in the present work we have studied in more detail the reaction of hydrazides **1a-d** with 2-thiophene-, 3-pyridine-, and 4-pyridinecarbaldehydes **2-4** respectively.

The reactions of hydrazides with aldehydes are widely used for obtaining acylhydrazones, the most valuable property of which is their high physiological activity. Amongst them herbicides, insecticides, fungicides, and plant growth regulators are found [4]. Acylhydrazones display spasmolytic and hypotensive activity, and act on leukemia, sarcoma, and other malignant neoplasms [4-6].



**1, 5-10a-d** Ar = 4- $\text{XC}_6\text{H}_4$ ; **a** X = H, **b** X = F, **c** X = Cl, **d** X =  $\text{NO}_2$ ; **2, 5, 8** Het = 2-thienyl;  
**3, 6, 9** Het = 3-pyridyl; **4, 7, 10** Het = 4-pyridyl; **5-7** R = COOH; **8-10** R = H

The reaction of hydrazides **1a-d** with aldehydes **2-4** was carried out using equimolar quantities of these reactants in ethanol or dioxane at room temperature or in DMF on boiling. Irrespective of the reaction temperature and solvent used the primary amino group of the hydrazide fragment and the carbonyl group of the aldehyde participated in the reaction in all cases. Acylhydrazones **5a-d** to **7a-d**, derivatives of hydrazides of dicarboxylic acids of the cyclohexene series, were formed at room temperature. On boiling the same reactants in DMF decarboxylation took place, consequently hydrazones of hydrazides of the corresponding monocarboxylic acids, **8a-d** to **10a-d** were isolated as products.

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Differences in the reactivity of hydrazides **1** were noted at room temperature. In the case of compounds **1b,c** the reaction was complete after 1-2 h and the yields of products **5b,c** to **7b,c** were 72-93%. High yields of compounds **5a-7a** (73-93%) from hydrazide **1a** were achieved after 3-10 h, and of compounds **5d-7d** (75-93%) from hydrazide **1d** after 4-20 h. In all cases products **8a-d** to **10a-d** were obtained in 63-90% yield after boiling in DMF for 2 h (see Table 1 and Experimental).

TABLE 1. Characteristics of the Synthesized Compounds **5a-d** to **10a-d**

Compound	Empirical formula	Found, %				mp, °C	Yield, %
		Calculated, %					
		C	H	N	Cl		
<b>5a</b>	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> S	65.38	5.36	7.46		163-165	82
		65.20	5.47	7.60			
<b>5b</b>	C <sub>20</sub> H <sub>19</sub> FN <sub>2</sub> O <sub>3</sub> S	62.19	5.01	7.19		160-161	94
		62.16	4.96	7.25			
<b>5c</b>	C <sub>20</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>3</sub> S	59.81	4.86	6.80	8.69	179-181	92
		59.60	4.95	6.95	8.80		
<b>5d</b>	C <sub>20</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> S	58.05	4.65	10.01		213-215	90
		58.10	4.63	10.16			
<b>6a</b>	C <sub>21</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub>	69.70	5.75	10.71		198-200	72.7
		69.41	5.82	11.56			
<b>6b</b>	C <sub>21</sub> H <sub>20</sub> FN <sub>3</sub> O <sub>3</sub>	66.08	5.20	11.21		201-202	92
		66.13	5.29	11.02			
<b>6c</b>	C <sub>21</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>3</sub>	63.51	5.18	10.41	8.80	204-206	92
		63.40	5.07	10.56	8.91		
<b>6d</b>	C <sub>21</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub>	61.59	4.76	13.60		209-210	93
		61.76	4.94	13.72			
<b>7a</b>	C <sub>21</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub>	69.31	5.73	11.50		187-188	72
		69.41	5.82	11.56			
<b>7b</b>	C <sub>21</sub> H <sub>20</sub> FN <sub>3</sub> O <sub>3</sub>	66.01	5.20	10.98		174-175	79
		66.13	5.29	11.02			
<b>7c</b>	C <sub>21</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>3</sub>	63.28	4.98	10.41	8.80	179-180	89
		63.40	5.07	10.56	8.91		
<b>7d</b>	C <sub>21</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub>	61.69	4.88	13.64		190-192	75
		61.76	4.94	13.72			
<b>8a</b>	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> OS	70.21	6.11	8.54		180-181	83
		70.34	6.21	8.63			
<b>8b</b>	C <sub>19</sub> H <sub>19</sub> FN <sub>2</sub> OS	66.59	5.48	8.01		195-196	86
		66.64	5.59	8.18			
<b>8c</b>	C <sub>19</sub> H <sub>19</sub> ClN <sub>2</sub> OS	63.48	5.27	7.49	9.71	194-195	86
		63.59	5.34	7.81	9.88		
<b>8d</b>	C <sub>19</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> S	61.68	5.02	11.29		225-228	65
		61.77	5.18	11.37			
<b>9a</b>	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O	75.15	6.54	12.98		188-190	86
		75.21	6.63	13.16			
<b>9b</b>	C <sub>20</sub> H <sub>20</sub> FN <sub>3</sub> O	71.36	5.88	12.36		194-195	76
		71.20	5.97	12.45			
<b>9c</b>	C <sub>20</sub> H <sub>20</sub> ClN <sub>3</sub> O	67.95	5.61	11.70	9.01	198-200	63
		67.89	5.70	11.88	9.17		
<b>9d</b>	C <sub>20</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub>	65.99	5.42	15.02		201-202	70
		65.92	5.53	15.37			
<b>10a</b>	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O	75.17	6.58	12.89		176-178	90
		75.21	6.63	13.16			
<b>10b</b>	C <sub>20</sub> H <sub>20</sub> FN <sub>3</sub> O	71.13	5.77	12.11		191-193	62
		71.20	5.97	12.45			
<b>10c</b>	C <sub>20</sub> H <sub>20</sub> ClN <sub>3</sub> O	67.71	5.57	11.72	9.29	180-182	70
		67.89	5.70	11.88	9.17		
<b>10d</b>	C <sub>20</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub>	65.80	5.45	15.26		183-185	72
		65.92	5.53	15.37			

The structure and composition of the obtained compounds were confirmed by data of  $^1\text{H}$  NMR spectra and the results of elemental analysis.

TABLE 2.  $^1\text{H}$  NMR Spectral Characteristics of Compounds **5a-d** to **10a-d**

Compound	Chemical shifts, $\delta$ , ppm*
<b>5a</b>	1.66 (3H, s, Me); 1.81-3.91 (5H, m, 2CH <sub>2</sub> , CH); 5.41 (1H, m, =CH); 7.05-8.67 (9H, m, Ar, N=CH); 11.14 (1H, br. s, NH); 12.58 (1H, br. s, COOH)
<b>5b</b>	1.65 (3H, s, Me); 1.82-3.78 (5H, m, 2CH <sub>2</sub> , CH); 5.39 (1H, m, =CH); 7.11-8.47 (8H, m, Ar, N=CH); 11.06 (1H, br. s, NH); 12.61 (1H, br. s, COOH)
<b>5c</b>	1.66 (3H, s, Me); 1.77-3.89 (5H, m, 2CH <sub>2</sub> , CH); 5.44 (1H, m, =CH); 7.01-8.53 (8H, m, Ar, N=CH); 11.14 (1H, br. s, NH); 12.56 (1H, br. s, COOH)
<b>5d</b>	1.63 (3H, s, Me); 1.84-3.95 (5H, m, 2CH <sub>2</sub> , CH); 5.44 (1H, m, =CH); 6.96-8.47 (8H, m, Ar, N=CH); 10.84 (1H, br. s, NH); 12.01 (1H, br. s, COOH)
<b>6a</b>	1.67 (3H, s, Me); 2.11-3.96 (5H, m, 2CH <sub>2</sub> , CH); 5.44 (1H, m, =CH); 7.07-8.84 (10H, m, Ar, N=CH); 11.30 (1H, br. s, NH); 12.25 (1H, br. s, COOH)
<b>6b</b>	1.61 (3H, s, Me); 1.85-3.83 (5H, m, 2CH <sub>2</sub> , CH); 5.39 (1H, m, =CH); 6.84-8.62 (9H, m, Ar, N=CH); 11.18 (1H, br. s, NH); 11.99 (1H, br. s, COOH)
<b>6c</b>	1.80 (3H, s, Me); 2.09-3.98 (5H, m, 2CH <sub>2</sub> , CH); 5.57 (1H, m, =CH); 7.04-8.78 (9H, m, Ar, N=CH); 11.43 (1H, br. s, NH); 12.00 (1H, br. s, COOH)
<b>6d</b>	1.61 (3H, s, Me); 1.89-3.98 (5H, m, 2CH <sub>2</sub> , CH); 5.30 (1H, m, =CH); 7.11-8.58 (9H, m, Ar, N=CH); 11.09 (1H, br. s, NH); 11.37 (1H, s, COOH)
<b>7a</b>	1.60 (3H, s, Me); 1.90-3.83 (5H, m, 2CH <sub>2</sub> , CH); 5.40 (1H, m, =CH); 7.20-8.60 (10H, m, Ar, N=CH); 11.46 (1H, br. s, NH); 11.97 (1H, br. s, COOH)
<b>7b</b>	1.68 (3H, s, Me); 1.90-3.89 (5H, m, 2CH <sub>2</sub> , CH); 5.49 (1H, m, =CH); 7.03-8.51 (9H, m, N=CH); 11.56 (1H, br. s, NH); 12.18 (1H, br. s, COOH)
<b>7c</b>	1.56 (3H, s, Me); 1.87-3.81 (5H, m, 2CH <sub>2</sub> , CH); 5.21 (1H, m, =CH); 6.93-8.47 (10H, m, Ar, N=CH, COOH); 11.31 (1H, s, NH)
<b>7d</b>	1.63 (3H, s, Me); 1.91-3.93 (5H, m, 2CH <sub>2</sub> , CH); 5.41 (1H, m, =CH); 7.17-8.47 (10H, m, Ar, N=CH, COOH); 11.42 (1H, br. s, NH)
<b>8a</b>	1.71 (3H, s, Me); 2.09-2.78 (4H, m, 2CH <sub>2</sub> ); 3.64 (2H, m, 2CH); 5.48 (1H, m, =CH); 6.89-7.38 (8H, m, Ar); 7.56 (1H, s, N=CH); 10.18 (1H, s, NH)
<b>8b</b>	1.69 (3H, s, Me); 2.02-2.75 (4H, m, 2CH <sub>2</sub> ); 3.52 (2H, m, 2CH); 5.46 (1H, m, =CH); 6.56-7.26 (7H, m, Ar); 7.59 (1H, m, N=CH); 9.17 (1H, br. s, NH)
<b>8c</b>	1.74 (3H, s, Me); 1.89-2.88 (4H, m, 2CH <sub>2</sub> ); 3.54 (2H, m, 2CH); 5.43 (1H, m, =CH); 6.89-7.37 (7H, m, Ar); 7.71 (1H, m, N=CH); 9.75 (1H, br. s, NH)
<b>8d</b>	1.83 (3H, s, Me); 1.98-2.79 (4H, m, 2CH <sub>2</sub> ); 3.56 (2H, m, 2CH); 5.37 (1H, m, =CH); 6.86-7.94 (8H, m, Ar, N=CH); 9.24 (1H, br. s, NH)
<b>9a</b>	1.69 (3H, s, Me); 1.69-2.60 (4H, m, 2CH <sub>2</sub> ); 3.59 (2H, m, 2CH); 5.39 (1H, m, =CH); 6.75-8.65 (10H, m, Ar, N=CH); 9.72 (1H, br. s, NH)
<b>9b</b>	1.89 (3H, s, Me); 2.16-2.95 (4H, m, 2CH <sub>2</sub> ); 3.72 (2H, m, 2CH); 5.54 (1H, m, =CH); 6.69-8.84 (9H, m, Ar, N=CH); 10.16 (1H, br. s, NH)
<b>9c</b>	1.74 (3H, s, Me); 2.09-2.55 (4H, m, 2CH <sub>2</sub> ); 3.59 (2H, m, 2CH); 5.39 (1H, m, =CH); 6.91-8.43 (9H, m, Ar, N=CH); 9.57 (1H, br. s, NH)
<b>9d</b>	1.75 (3H, s, Me); 2.11-2.51 (4H, m, 2CH <sub>2</sub> ); 3.71 (2H, m, 2CH); 5.56 (1H, m, =CH); 7.26-8.75 (9H, m, Ar, N=CH); 9.55 (1H, br. s, NH)
<b>10a</b>	1.76 (3H, s, Me); 2.08-2.57 (4H, m, 2CH <sub>2</sub> ); 3.45-3.67 (2H, m, 2CH); 5.35 (1H, m, =CH); 6.82-8.60 (10H, m, Ar, N=CH); 10.36 (1H, br. s, NH)
<b>10b</b>	1.76 (3H, s, Me); 2.05-2.86 (4H, m, 2CH <sub>2</sub> ); 3.63 (2H, m, 2CH); 5.41 (1H, m, =CH); 6.45-8.40 (9H, m, Ar, N=CH); 9.94 (1H, br. s, NH)
<b>10c</b>	1.76 (3H, s, Me); 2.07-2.71 (4H, m, 2CH <sub>2</sub> ); 3.52 (2H, m, 2CH); 5.39 (1H, m, =CH); 6.95-8.51 (9H, m, Ar, N=CH); 9.86 (1H, br. s, NH)
<b>10d</b>	1.72 (3H, s, Me); 1.98-2.86 (4H, m, 2CH <sub>2</sub> ); 3.65 (2H, m, 2CH); 5.37 (1H, m, =CH); 7.06-8.51 (9H, m, Ar, N=CH); 9.75 (1H, br. s, NH)

\* The  $^1\text{H}$  NMR spectra taken in  $\text{CDCl}_3$  (for compounds **8a-d**, **9a-d**, and **10a-d**) and in  $\text{DMSO-d}_6$  (for compounds **5a-d**, **6a-d**, **7a-d**).

## EXPERIMENTAL

The  $^1\text{H}$  NMR spectra were taken on a Bruker WH 90/DS (90 MHz) instrument, internal standard was HMDS. The homogeneity of the obtained compounds was checked by TLC on Silufol plates in the solvent systems: chloroform–acetone–glacial acetic acid, 9:1:1 (for compounds **5a-d** and **8a-d**), and chloroform–methanol–glacial acetic acid, 9:1:1 (for **6a-d**, **7a-d**, **9a-d**, and **10a-d**).

The characteristics of the synthesized compounds are given in Tables 1 and 2.

**2-Thiophenecarbaldehyde (2-Aryl-1-carboxy-4-methyl-4-cyclohexene-1-carbonyl)hydrazones (5a-d).** Mixture of hydrazide **1a-d** (1.5 mmol) and aldehyde **2** (1.5 mmol) in ethanol (10 ml) was stirred at room temperature [in the case of hydrazide **1a** glacial AcOH (3 drops) was added to the reaction mixture]. The reaction time was 10 (for hydrazide **1a**), 1 (for **1b,c**), and 20 h (for **1d**). Products **5a-d** were filtered off, compound **5a** was recrystallized from ethanol–water, 1:1, compounds **5b,c** were washed on the filter with ethanol, and with ether, and compound **5d** was recrystallized from dilute AcOH.

**3-Pyridinecarbaldehyde (2-Aryl-1-carboxy-4-methyl-4-cyclohexene-1-carbonyl)hydrazones (6a-d).** Equimolar quantities of hydrazide **1a-d** and aldehyde **3** were stirred at room temperature in solution in dioxane (**1a,d**) or ethanol (**1b,c**) for 3 (**1a**), 2 (**1b,c**), and 4 h (**1d**). Products **6a-d** were filtered off, washed on the filter with ethanol, and with ether. Hydrazone **6a** was recrystallized from methanol–water, 1:1.

**4-Pyridinecarbaldehyde (2-Aryl-1-carboxy-4-methyl-4-cyclohexene-1-carbonyl)hydrazones (7a-d)** were obtained analogously to hydrazones **6a-d**, stirring hydrazide **1a-d** and aldehyde **4** in ethanol (hydrazides **1a-c**) or dioxane (hydrazide **1d**) for 10 (**1a**), 1 (**1b,c**), and 3 h (**1d**). Products **7a-d** were filtered off, hydrazone **7a** was washed further on the filter with ethyl acetate. In the case of hydrazone **7d** the reaction mixture was poured into water, the product was filtered off, and recrystallized from ethanol–water, 1:1.

**(2-Aryl-4-methyl-4-cyclohexene-1-carbonyl)hydrazones of 2-Thiophenecarbaldehyde (8a-d), 3-Pyridinecarbaldehyde (9a-d) and 4-Pyridinecarbaldehyde (10a-d).** Mixture of hydrazide **1a-d** (2 mmol) and aldehyde **2**, **3**, or **4** was boiled in DMF (5 ml) for 2 h. The reaction mixture was cooled, poured into water, and products **8a-d** to **10a-d** were filtered off. Hydrazone **9d** was recrystallized from ethanol, **9b** from methanol, and **8b,c** and **10b** from methanol–water, 1:1.

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