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SYNTHESIS OF N'-CYCLOHEXENECARBONYL-SUBSTITUTED HYDRAZIDES OF 2-AMINOBENZOIC ACIDS AND PREPARATION OF 3-CYCLOHEXENYL-AMIDO-1,2-DIHYDROQUINAZOLIN-4-ONES BASED ON THEM

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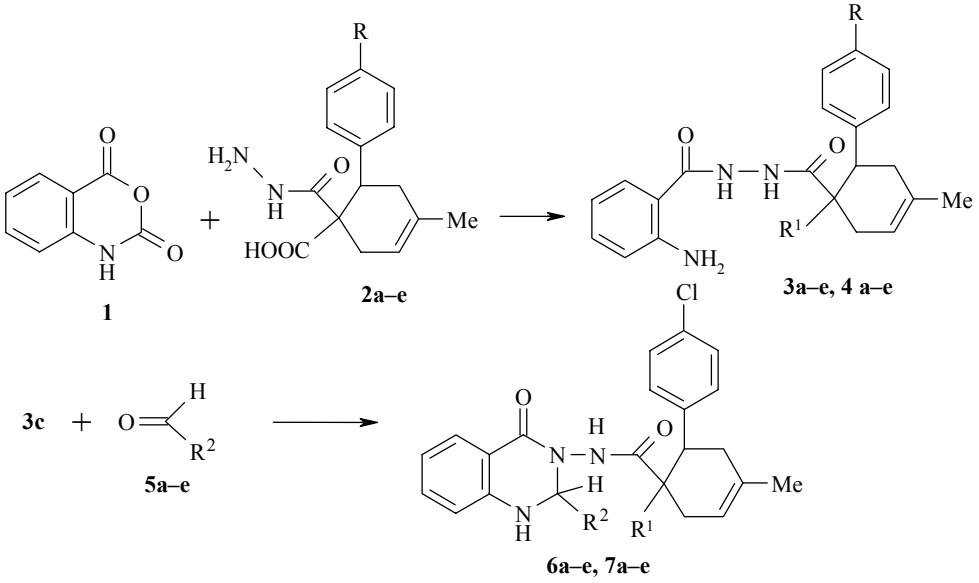
N'-Cyclohexenecarbonyl-substituted hydrazides of 2-aminobenzoic acids were obtained from the reaction of isatoic anhydride with monohydrazides of cyclohexenedicarboxylic acid. Reaction of the 2-aminobenzoic acid hydrazides with substituted benzaldehydes gave 3-cyclohexenylamido-1,2-dihydroquinazolin-4-ones.

Keywords: benzaldehyde, isatoic anhydride, cyclohexenedicarboxylic acid, 3-cyclohexenylamido-1,2-dihydroquinazolin-4-ones, N'-cyclohexenecarbonyl-substituted hydrazides.

Among the derivatives of dihydroquinazolin-4-ones (DHQ) are compounds with sedative effects on the central nervous system [1,2] and also antiepileptic activity [3].



2–4 a R = H, **b** R = F, **c** R = Cl, **d** R = Br, **e** R = NO_2; **3a–e** R^1 = COOH; **4a–e** R^1 = H; **5–7 a** R^2 = 4-FC_6H_4, **b** R^2 = 4-ClC_6H_4, **c** R^2 = 2-OHC_6H_4, **d** R^2 = 4-$Et_2NC_6H_4$, **e** R^2 = 4-NCC_6H_4; **6a–e** R^1 = COOH; **7a–e** R^1 = H

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Recently [4] a method was proposed for the synthesis of little known derivatives of DHQ with amide residues in position 3 by the reaction of carbonyl compounds with N-acyl-substituted hydrazides of anthranilic acid, obtained by reaction of isatoic anhydride **1** with acyl hydrazines. We have used this scheme with monohydrazides of 2-arylcyclohexenyl-1,1-dicarboxylic acids **2a-e**, which we had synthesized previously [5]. The hydrazides **3a-e** were obtained in 60-70% yields by boiling an ethanol solution of the components. Increasing the reaction temperature – by boiling the components in acetic acid – led only to partial decarboxylation to give mixtures of **3a-e** and **4a-e** in a ratio of ~3-5 : 1, and on boiling in DMF a still more complex mixture of products was obtained. The pure products of decarboxylation **4a-e** were obtained only by boiling individual compounds **3a-e** in DMF solution.

We demonstrated the possibility of using the hydrazides **3**, which we had made, to synthesize derivatives of DHQ, by using the reaction of compound **3c** with benzaldehydes **5a-e.** It was established that when the components were boiled for a relatively short time (10-60 min) in ethanol the quinazolinones **6a-e** were formed in 75-83% yields, while the products of decarboxylation **7a-e** were produced in 59-74% yields on boiling the components in DMF for 2 h.

Table 1. Characteristics of Compounds **3**, **4**, **6** and **7**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	Hal	N		
3a	$C_{22}H_{23}N_3O_4$	66.96 / 67.16	5.77 / 5.89		11.34 / 10.68	192-193	62.1
3b	$C_{22}H_{22}FN_3O_4$	64.26 / 64.22	5.19 / 5.39	4.65 / 4.62	10.21 / 10.21	200-202	73.2
3c	$C_{22}H_{22}ClN_3O_4$	61.99 / 61.76	5.06 / 5.18	8.88 / 8.29	9.70 / 9.82	188-191	70.0
3d	$C_{22}H_{22}BrN_3O_4$	55.54 / 55.94	4.77 / 4.69	16.91 / 16.92	8.72 / 8.90	195-197	68.3
3e	$C_{22}H_{22}N_4O_6$	60.30 / 60.27	5.08 / 5.06		12.87 / 12.78	178-180	63.1
4a	$C_{21}H_{23}N_3O_2$	71.97 / 72.18	6.65 / 6.63		12.03 / 12.03	92-95	53.4
4b	$C_{21}H_{22}FN_3O_2$	68.51 / 68.65	6.01 / 6.04	4.69 / 5.17	11.42 / 11.44	104-107	56.8
4c	$C_{21}H_{22}ClN_3O_2$	65.69 / 65.71	5.62 / 5.78	9.17 / 9.24	10.93 / 10.95	128-130	60.3
4d	$C_{21}H_{22}BrN_3O_2$	58.98 / 58.89	5.06 / 5.18	18.64 / 18.66	9.73 / 9.81	171-175	57.8
4e	$C_{21}H_{22}N_4O_4$	63.72 / 63.94	5.62 / 5.62		14.30 / 14.20	156-158	58.2
6a	$C_{29}H_{25}ClFN_3O_4$	65.41 / 65.24	4.90 / 4.72		8.02 / 7.87	220-223 (dec.)	76.3
6b	$C_{29}H_{25}Cl_2N_3O_4$	63.50 / 63.28	4.50 / 4.58	13.03 / 12.88	7.42 / 7.63	248-250 (dec.)	81.6
6c	$C_{29}H_{26}ClN_3O_5$	65.81 / 65.72	5.00 / 4.93	7.00 / 6.66	8.04 / 7.90	253-255 (dec.)	80.1
6d	$C_{33}H_{35}ClN_4O_4$	67.83 / 67.51	6.06 / 6.01	6.15 / 6.03	9.72 / 9.54	190-193 (dec.)	75.0
6e	$C_{30}H_{25}ClN_4O_4$	66.82 / 66.60	4.83 / 4.66	6.83 / 6.55	10.58 / 10.36	239-240 (dec.)	83.1
7a	$C_{28}H_{25}ClFN_3O_2$	68.82 / 68.64	5.38 / 5.14		8.73 / 8.58	143-145	58.8
7b	$C_{28}H_{25}Cl_2N_3O_2$	66.72 / 66.71	5.12 / 4.98	7.12 / 7.00	8.62 / 8.30	160-161	60.2
7c	$C_{28}H_{26}ClN_3O_3$	58.04 / 57.98	5.43 / 5.37	7.41 / 7.27	7.17 / 7.06	168-170	63.0
7d	$C_{32}H_{35}ClN_4O_2$	71.02 / 70.77	6.73 / 6.50	6.78 / 6.53	10.58 / 10.32	123-125	62.4
7e	$C_{29}H_{25}ClN_4O_2$	69.92 / 70.08	5.18 / 5.07	7.30 / 7.13	11.40 / 11.27	203-205	74.2

The composition and structures of all the compounds synthesized were confirmed by elemental analysis (Table 1) and ^{1}H NMR spectroscopy (Table 2) and in the case of the derivatives of 1,2-dihydroquinazolin-4-ones **6a-e** and **7a-e** by comparison of their ^{1}NMR spectra with those of analogous compounds reported elsewhere [1, 6-7].

Table 2. ^{1}H NMR Spectra of the Compounds Synthesized **3**, **4, 6**, and **7**

Com-pound	Chemical shifts, δ, ppm, SSCC (*J*, Hz)
3a	1.64 (3H, s, CH_3); 1.73-3.26 (4H, m, $2CH_2$); 3.91 (1H, m, CH); 5.42 (1H, m, =CH); 6.46-7.54 (12H, m, Ar, NH_2, COOH); 9.67 (2H, br. s, 2NH)
3b	1.57 (3H, s, CH_3); 1.81-3.36 (4H, m, $2CH_2$); 3.89 (1H, m, CH); 5.42 (1H, m, =CH); 6.48 (11H, m, Ar, NH_2, COOH); 9.66 (1H, br. s, NH);12.51 (1H, br. s, NH)
3c	1.61 (3H, s, CH_3); 1.72-3.24 (4H, m, $2CH_2$); 3.90 (1H, m, CH); 5.41 (1H, m, =CH); 6.51-7.54 (11H, m, Ar, NH_2, COOH); 9.67 (1H, br. s, NH);10.10 (1H, br. s, NH)
3d	1.57 (3H, s, CH_3); 1.76-3.22 (4H, m, $2CH_2$); 3.86 (1H, m, CH); 5.38 (1H, m, =CH); 6.33-7.52 (11H, m, Ar, NH_2, COOH); 9.73 (1H, br. s, NH);10.12 (1H, br. s, NH)
3e	1.65 (3H, s, CH_3); 1.78-3.36 (4H, m, $2CH_2$); 4.02 (1H, m, CH); 5.44 (1H, m, =CH); 6.41-8.04 (11H, m, Ar, NH_2, COOH); 9.76 (1H, br. s, NH); 9.98 (1H, br. s, NH)
4a	1.64 (3H, s, CH_3); 2.04 (2H, m, CH_2); 2.53 (2H, m, CH_2); 2.75 (1H, m, CH); 3.36 (1H, m, CH); 5.38 (1H, m, =CH); 6.17 (2H, br. s, NH_2); 6.25-7.42 (9H, m, Ar); 9.62 (1H, br. s, NH); 9.71 (1H, br. s, NH)
4b	1.76 (3H, s, CH_3); 1.82-2.56 (4H, m, $2CH_2$); 2.86 (1H, m, CH); 3.31 (1H, m, CH); 4.96 (2H, br. s, NH_2); 5.06 (1H, m, =CH); 6.38-7.48 (8H, m, Ar); 8.34 (1H, br. s, NH); 8.76 (1H, br. s, NH)
4c	1.68 (3H, s, CH_3); 2.04-2.58 (4H, m, $2CH_2$); 2.81 (1H, m, CH); 3.36 (1H, m, CH); 5.01 (2H, br. s, NH_2); 5.44 (1H, m, =CH); 6.62-7.71 (8H, m, Ar); 8.53 (1H, br. s, NH); 9.02 (1H, br. s, NH)
4d	1.64 (3H, s, CH_3); 2.04-2.56 (4H, m, $2CH_2$); 2.78 (1H, m, CH); 3.31 (1H, m, CH); 5.41 (1H, m, =CH); 6.12 (2H, br. s, NH_2); 6.29-7.41 (8H, m, Ar); 9.75 (1H, br. s, NH); 10.21 (1H, br. s, NH)
4e	1.69 (3H, s, CH_3); 2.24-2.46 (4H, m, $2CH_2$); 2.91 (1H, m, CH); 3.54 (1H, m, CH); 5.57 (1H, m, =CH); 5.62 (2H, br. s, NH_2); 6.71-8.07 (8H, m, Ar); 8.24 (1H, br. s, NH); 9.28 (1H, br. s, NH)
6a	1.58 (3H, s, CH_3); 1.61-2.72 (4H, m, $2CH_2$); 3.69 and 4.30 (1H, two m, CH); 4.94 and 5.16 (1H, two m, =CH); 5.91 and 5.99 (1H, two s, C(2)H); 6.69-7.61 (13H, m, Ar, NH); 9.80 9.85 (1H, two br. s, NH); 12.64 (1H, br. s, COOH)
6b	1.51 (3H, s, CH_3); 1.71-2.42 (4H, m, $2CH_2$); 3.68 and 3.78 (1H, two m, CH); 5.03 and 5.26 (1H, two m, =CH); 5.88 and 6.05 (1H, two s, C(2)H); 6.74-7.79 (13H, m, Ar, NH); 9.88 and 9.99 (1H, two br. s, NH); 10.22 (1H, br. s, COOH)
6c	1.49 (3H, s, CH_3); 1.64-2.67 (4H, m, $2CH_2$); 3.32 and 3.69 (1H, two m, CH); 4.93 and 5.22 (1H, two m, =CH); 6.14 and 6.21 (1H, two s, C(2)H); 6.61-7.75 (13H, m, Ar, NH); 9.56 and 9.62 (1H, two br. s, NH); 9.86 (1H, br. s, OH); 12.53 (1H, br. s, COOH)
6d	1.13 and 1.18 (6H, two t, $J = 7$, $2CH_3$); 1.76 (3H, s, CH_3);1.91-2.71 (4H, m, $2CH_2$); 3.34 (4H, m, $2CH_2$); 3.36 and 3.64 (1H, two m, CH); 5.11 and 5.36 (1H, two m, =CH); 6.02 (1H, s, C(2)H); 6.48-7.82 (14H, m, Ar, 2NH); 9.51 (1H, br. s, COOH)
6e	1.58 (3H, s, CH_3); 1.69-2.61 (4H, m, $2CH_2$); 3.32 and 3.69 (1H, two m, CH); 4.94 and 5.19 (1H, two m, =CH); 5.94 and 6.03 (1H, two s, C(2)H); 6.72-7.81 (13H, m, Ar, NH); 9.86 and 9.94 (1H, two br. s, NH); 12.61 (1H, br. s, COOH)
7a	1.61 (3H, s, CH_3); 1.93-2.41 (4H, m, $2CH_2$); 2.69-3.29 (2H, m, 2CH); 5.36 (1H, m, =CH); 6.04 (1H, s, C(2)H); 6.53-7.87 (14H, m, 2NH)
7b	1.64 (3H, s, CH_3); 1.93-3.26 (6H, m, $2CH_2$, 2CH); 5.36 (1H, m, =CH); 6.02 and 6.06 (1H, two s, C(2)H); 6.51-7.89 (14H, m, Ar, 2NH)
7c	1.64 (3H, s, CH_3); 1.87-3.31 (6H, m, $2CH_2$, 2CH); 5.25 and 5.29 (1H, two m, =CH); 6.16 and 6.18 (1H, two s, C(2)H); 6.62-7.93 (15H, m, Ar, 2NH, OH)
7d	1.05 and 1.13 (6H, two t, $J = 7$, $2CH_3$); 1.67 (3H, s, CH_3); 1.81-3.31 (6H, m, $2CH_2$, 2CH); 5.37 (1H, m, =CH); 5.67 and 5.81 (1H, two s, C(2)H); 6.33-7.65 (14H, m, Ar, 2NH)
7e	1.67 (3H, s, CH_3); 1.95-3.38 (6H, m, $2CH_2$, 2CH); 5.37 (1H, m, =CH); 6.11 (1H, s, C(2)H); 6.58-7.96 (14H, m, Ar, 2NH)

EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ (**4b,c, 6d, 7a-c,e**) or DMSO-d_6 solutions (**3a-e, 4a,d,e, 6a-c,e, 7d)** with TMS as internal standard were recorded on WH-90DS (90 MHz) instrument.

Purity of the compounds synthesized was monitored by TLC on Silufol plates with the eluents dichloromethane-methanol, 0.5:5 (for **3a-e** and **4a-e**) and benzene-acetone-glacial acetic acid, 100:50:2 (for **6a-e** and **7a-e**).

N'-[1-Hydroxycarbonyl-4-methyl-2-(4-R-phenyl)cyclohex-4-enyl-1-carbonyl]hydrazides of 2-Aminobenzoic Acid 3a-e. A solution of anhydride **1** (1.54 g, 5 mmol) and an equimolar quantity of a monohydrazide of cyclohexenedicarboxylic acid **2a-e** in ethanol (30 ml) was boiled for 5 h. Half of the ethanol was evaporated, an equal volume of water was added, and the mixture was kept for ~10 h. The product was filtered off and recrystallized from 1:1 aqueous ethanol.

N'-[4-methyl-2-(4-R-phenyl)cyclohex-4-enyl-1-carbonyl]hydrazides of 2-Aminobenzoic Acid 4a-e. N'-hydrazides **3a-e** (5 mmol) were boiled in DMF (15 ml) for 2 h. The reaction mixture was cooled, poured into water, filtered, and recrystallized from dilute ethanol (3:1).

2-Aryl-3-[2-(4-chlorophenyl)-1-hydroxycarbonyl-4-methylcyclohex-4-en-1-ylamido]-1,2-dihydroquinazolin-4(3H)-ones 6a-e. A solution of the N'-hydrazide **3c** (0.7 mmol) and the corresponding benzaldehyde **5a-e** (0.9 mmol) was boiled in ethanol (5 ml) for 10 (**6c,e**), 20 (**6a,b**), or 60 min (**6d**). The mixture was cooled, kept for ~8-10 h, and the precipitate was filtered off and washed on the filter with ethanol. Compounds **6a-c,e** were chromatographically pure without recrystallization. Compound **6d** was recrystallized from 1:1 aqueous ethanol.

2-Aryl-3-[2-(4-chlorophenyl)-4-methyl-4-cyclohex-4-en-1-ylamido]-1,2-dihydroquinazolin-4(3H)-ones 7a-e. A solution of the N'-hydrazide **3c** (0.7 mmol) and the corresponding benzaldehyde **5a-e** (0.9 mmol) was boiled in DMF (5 ml) for 2 h. The mixture was cooled, poured into water, and filtered. The precipitate was recrystallized from 1:1 aqueous ethanol.

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