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REACTION OF 2-SUBSTITUTED 7,7-DIMETHYL-5-OXO-5,6,7,8-TETRAHYDROQUINOLINE-4-CARBOXYLIC ACIDS WITH HYDRAZINE. SYNTHESIS OF 5-SUBSTITUTED 8,8-DIMETHYL-3,7,8,9-TETRAHYDRO-2*H*-PYRIDO-[4,3,2-*de*]CINNOLIN-3-ONES

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The reaction of 2-substituted 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-4-carboxylic acids with hydrazine was studied. This reaction gave 5-substituted 8,8-dimethyl-3,7,8,9-tetrahydro-2H-pyrido-[4,3,2-de]cinnolin-3-ones in good yields. A possible reaction mechanism was discussed using nonempirical quantum-chemical calculations.

Keywords: 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-4-carboxylic acids, 8,8-dimethyl-3,7,8,9-tetrahydro-2*H*-pyrido[4,3,2-*de*]cinnolin-3-ones, hydrazine.

The reaction of 1,4-dicarbonyl compounds with hydrazines is a convenient method for the construction of pyridazine ring [1]. If the dicarbonyl fragment is a part of a cyclic system as, for example, in alkyl 5-oxo-5,6,7,8-tetrahydroquinoline-4-carboxylates, the reactions with hydrazines may give fused heterocyclic compounds containing a pyridazine ring [2].

Heating equimolar amounts of 2-substituted 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-4-carboxylic acids **1a-g** [3] with hydrazine in ethanol at reflux gives the corresponding 5-alkyl- or 5-aryl-8,8-dimethyl-3,7,8,9-tetrahydro-2*H*-pyrido[4,3,2-*de*]cinnolin-3-ones **7a-g**. These products are colorless or slightly colored crystalline compounds with high melting points, soluble in hot DMF and DMSO, and poorly soluble in acetonitrile, ethanol, acetone, and water.

The yields, melting points, and elemental analysis results for 2*H*-pyrido[4,3,2-*de*]cinnolin-3-ones **7a-g** are given in Table 1. The structures of these derivatives were established using IR, ^{1}H NMR, and ^{13}C NMR spectroscopy (Tables 2 and 3). The assignment of the signals in the ^{1}H and ^{13}C NMR spectra was carried out by means of heteronuclear 2D ^{1}H-^{13}C gHSQC and gHMBC experiments.

In particular, C-3 atoms in the 2D gHMBC spectra give cross peaks with the pyridine ring protons, while

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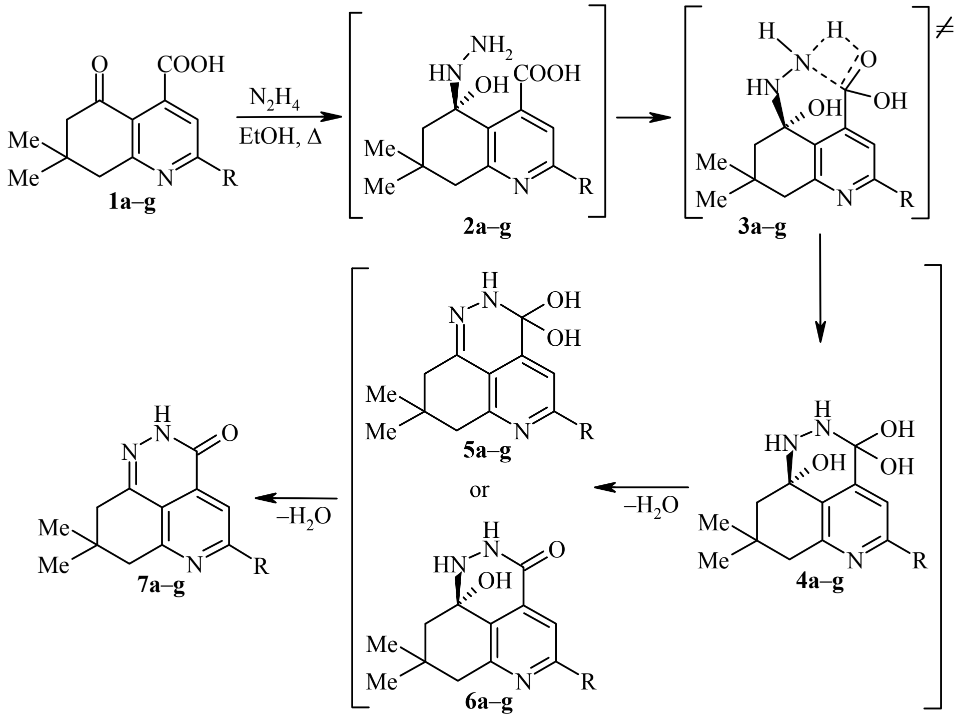

a R = *t*-Bu, **b** R = Ph, **c** R = 4-MeC_6H_4, **d** R = 4-$MeOC_6H_4$, **e** R = 4-BrC_6H_4,
f R = 2,4,5-$Me_3C_6H_2$, **g** R = 1-naphthyl

C-5 atoms give cross peaks with protons of the R substituents. In turn, C-9b atoms are coupled with H-4, H-7, and H-9 protons, while C-9a atoms are coupled with H-4 and H-7 protons. The signals for C-7 and C-9 atoms were assigned using the 2D gHSQC spectra according to the direct spin-spin coupling constants of bound hydrogen and carbon atoms.

A possible scheme for the formation of cinnolinones **7a-g** assumes an attack on the ketone carbonyl group of acids **1a-g** by a hydrazine nitrogen atom and cyclization of the resultant intermediates **2a-g** due to reaction of the primary amino group and carboxyl carbon atom, to give intermediates **4a-g**. The tricyclic intermediates **4a-g** then undergo dehydration to yield the reaction products **7a-g**.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **7a-g**

Compound	Empirical formula	Found, % / Calculated, % C	Found, % / Calculated, % H	Found, % / Calculated, % N	Mp, °C	Yield, %
7a	$C_{16}H_{21}N_3O$	70.49 70.82	7.75 7.80	15.39 15.48	212-213	74
7b	$C_{18}H_{17}N_3O$	74.08 74.21	5.73 5.88	14.24 14.42	282-284	71
7c	$C_{19}H_{19}N_3O$	74.61 74.73	6.20 6.27	13.57 13.76	280-281	99
7d	$C_{19}H_{19}N_3O_2$	70.97 71.01	5.85 5.96	12.90 13.07	261-262	94
7e	$C_{18}H_{16}BrN_3O$	58.40 58.39	4.17 4.36	11.43 11.35	316-318	90
7f	$C_{21}H_{23}N_3O$	75.67 75.65	6.93 6.95	12.54 12.60	231-232	92
7g	$C_{22}H_{19}N_3O$	77.29 77.40	5.51 5.61	12.18 12.31	233-234	84

TABLE 2. IR and ^{1}H NMR Spectra of Cinnolinones **7a-g**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)					
		2-NH	H-4	7-CH_2	8-CH_3	9-CH_2	R
7a	3156 (N-H), 1666 (C=O), 1596 (C=S, C=N)	12.46	7.84	2.97	1.04	2.69	1.39 (9H, s, $C(CH_3)_3$)
7b	3152 (N-H), 1668 (C=O), 1592 (C=S, C=N)	12.60	8.34	3.05	1.11	2.76	7.51-7.57 (3H, m, H Ph); 8.21-8.23 (2H, m, H Ph)
7c	3156 (N-H), 1668 C=O), 1596 (C=S, C=N)	12.52	8.26	3.03	1.06	2.72	2.38 (3H, s, 4'-CH_3); 7.34 (2H, d, *J* = 8.4, H Ar); 8.09 (2H, d, *J* = 8.4, H Ar)
7d	3153 (N-H), 1666 (C=O), 1589 (C=S, C=N)	12.49	8.22	3.01	1.06	2.71	3.85 (3H, s, OCH_3); 7.07 (2H, d, *J* = 9.0, H Ar); 8.16 (2H, d, *J* = 9.0, H Ar)
7e	3156 (N-H), 1668 (C=O), 1590 (C=S, C=N)	12.57	8.35	3.07	1.07	2.76	7.73 (2H, d, *J* = 8.4, H Ar); 8.18 (2H, d, *J* = 8.4, H Ar)
7f	3162 (N-H), 1657 (C=O), 1587 (C=S, C=N)	12.56	7.89	3.00	1.06	2.72	2.25 (6H, s, 4',5'-CH_3); 2.31 (3H, s, 2'-CH_3); 7.07 (1H, s, H-3'); 7.29 (1H, s, H-6')
7g	3147 (N-H), 1654 (C=O), 1589 (C=S, C=N)	12.63	8.06	3.07	1.11	2.78	7.74-7.50 (4H, m, H Ar); 8.11-8.01 (3H, m, H Ar)

In order to discover the fine details of the reaction of acids **1a-g** with hydrazine, we carried out nonempirical quantum-chemical calculations for the total energy (E_{tot}), bond lengths, atomic charges, and bond orders in the intermediates **2b** and **4b-6b**, activated complex **3b**, and cinnolinone **7b** by the LCAO MO SCF method in the 6-31G(d) basis. These calculations indicate that the distance between the reaction sites ($l_{N\cdots C}$), the amino group nitrogen atom and the carboxyl carbon atom in compound 2**b** is 2.711 Å, while the distance between an NH_2 group hydrogen atom and the carbonyl oxygen atom of the carboxyl group ($l_{H\cdots O}$) is 2.779 Å. The decrease in the $l_{N\cdots C}$ interatomic distance is accompanied by an increase in the N–H bond length and decrease in the corresponding $l_{H\cdots O}$ interatomic distance. The $l_{N\cdots C}$ distance in activated complex **3b** is contracted to 1.538 Å, the N–H bond length is extended from 1.002 Å in intermediate **2b** to 1.231 Å, while the $l_{H\cdots O}$ interatomic distance is 1.311 Å. Further approach of the nitrogen and carbon atoms leads to cleavage of the N–H bond, i.e., proton transfer from the nitrogen atom to the oxygen atom with formation of a stable intermediate **4b**. The subsequent transformation of intermediate **4b** into the reaction product **7b** may proceed either through intermediates **5b** or **6b**. Calculations indicate that the intermediate **5b** has lower total energy (E_{tot} = -1005.7685 a.u.) than intermediate **6b** (E_{tot} = -1005.7585 a.u.). Thus, the formation of intermediate **5b** is more likely and, correspondingly, our quantum-chemical calculations are in accord with the proposed reaction scheme.

Hence, the reaction studied is a convenient and efficient method for the preparation of fused tricyclic heterocyclic compounds containing a pyridazine fragment, by means of the reaction of 2-substituted 7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-4-carboxylic acids with hydrazine.

EXPERIMENTAL

The IR spectra were recorded on a Bruker IFS 66ps spectrometer for vaseline mulls. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solution with HMDS as internal standard (δ 0.059 ppm) on a Varian Mercury 300 plus spectrometer at 300 and 75 MHz, respectively. Elemental analysis was carried out on a LECO CHNS-932 analyzer. The melting points were determined on a PTP instrument. The purity of the products was

TABLE 3. ^{13}C NMR Spectra of Compounds **7a–g**

Compound	Chemical shifts, δ, ppm											
	C-3	C-3a	C-4	C-5	C-6a	C-7	C-8	8-CH_3	C-9	C-9a	C-9b	R
7a	158.8	132.6	110.1	170.4	158.4	45.5	31.8	27.4	41.9	144.0	117.7	29.6 ($C(\underline{C}H_3)_3$); 37.6 ($\underline{C}(CH_3)_3$)
7b	158.6	133.2	111.4	156.8	159.6	45.5	31.8	27.4	41.8	143.9	118.8	126.8 (C-2',6'); 128.7 (C-3',5'); 129.6 (C-4'); 137.5 (C-1')
7c	158.7	133.2	110.9	156.8	159.6	45.5	31.9	27.4	41.8	143.9	118.5	20.6 (4'-CH_3); 126.8 (C-2',6'); 129.4 (C-3,5); 134.8 (C-1'); 139.5 (C-4')
7d	158.7	133.2	110.3	156.6	159.5	45.5	31.8	27.4	41.9	143.9	118.1	55.2 (4-OCH_3); 114.2 (C-3',5'); 128.4 (C-2',6'); 130.0 (C-1'); 160.8 (C-4')
7e	158.5	133.3	111.6	155.5	159.7	45.4	31.8	27.3	41.8	143.8	119.0	123.3 (C-4'); 128.8 (C-2',6'); 131.6 (C-3',5'); 136.7 (C-1')
7f	158.6	132.5	115.0	160.1	158.9	45.4	31.8	27.4	41.9	143.9	117.9	19.4 (2'-CH_3); 18.4 (4'-CH_3); 18.7 (5'-CH_3); 130.7 (C-6'); 132.0 (C-3'); 132.6 (C-1'); 133.5 (C-2'); 136.3 (C-4'); 136.7 (C-5')
7g	159.2	132.8	116.3	158.6	159.5	45.4	31.9	27.5	41.9	144.0	118.6	124.9; 125.2; 125.9; 126.5; 127.9; 128.2; 129.2; 130.3; 133.4; 137.0

products was checked by HPLC on an Agilent 1260 chromatograph equipped with a 250×4.6 mm Zorbax Eclipse XDB-C18 column (5 μm particle size) using gradient elution with 50-100% acetonitrile in water over 20 min at 30°C. The flow rate was 1 ml/sec. Detection was carried out at 254 and 300 nm.

The quantum-chemical calculations were carried out using the Firefly software suite [14] adapted for a Toshiba Portege M400 personal computer.

5-Substituted 8,8-dimethyl-3,7,8,9-tetrahydro-2*H*-pyrido[4,3,2-*de*]cinnolin-3-ones 7a-g (General Method). A mixture of corresponding quinolinecarboxylic acid **1a-g** (6 mmol) and 64% hydrazine hydrate (0.6 g, 12 mmol) was heated at reflux in ethanol (30 ml) for 2 h. The reaction mixture was cooled. The precipitate formed was filtered off and washed on the filter with hot ethanol.

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