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DI-6R,7R[1]-4(3H)-OXO-2-QUINAZOLINYL-SUBSTITUTED CYCLOBUTANES FROM PINIC AND *sym*-HOMOPINIC ACIDS

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The corresponding diamides were obtained from reaction of cis-3-carboxy-2,2-dimethylcyclobutylacetic acid (pinic acid) and of cis/trans-3-(carboxymethyl)-2,2-dimethylcyclobutyl-acetic acid (homopinic acid) dichlorides with two equivalents of 5-bromo-, 4-chloro-, and 4,5-dimethoxyanthranilic acids. Treatment of them with formamide leads to the formation of the corresponding 2,2-dimethyl-3-[4(3H)-oxo-2-quinazolinyl]methyl-1-[4(3H)-oxo-2-quinazolinyl]cyclobutanes and 2,2-dimethyl-1,3-di[4(3H)-oxo-2-quinazolinylmethyl]cyclobutanes.

Keywords: N-acyl derivatives of 5-bromo-, 4-chloro-, and 4,5-dimethoxyanthranilic acids, *sym*-homopinic acid, di-6,7-substituted 4(3H)-oxo-2-quinazolinyl derivatives of cyclobutane, pinic acid.

In continuation of studies [1-3] on the synthesis of 4(3H)-quinazolinones with a cyclobutyl substituent at position 2, we have obtained the corresponding diamides **4a-c**, **5a-c** (Table 1) by the reactions of 4,5-substituted anthranilic acids (**1a-c**) with the pinic (**2**) [4] and *sym*-homopinic (**3**) acid dichlorides [5,6]. Heating the N-acyl anthranilic acids **4a-c**, **5a-c** and formamide in a molar ratio of 1:6 to 1:8 at 180-190°C leads to the formation of the di-[4(3H)-oxo-2-quinazolinyl derivatives **6a-c**, **7a-c** (Table 1). The di-4(3H)-quinazolinones **6a-c**, **7a-c** are soluble with difficulty in organic solvents, and decompose at the melting point.

On heating diamides **4** and **5** in formamide a side reaction occurs leading to the formation of 4(3H)-quinazolinones **8a-c** in 11-22% yield.

The structure of the synthesized compounds was confirmed by data of IR and ^{1}H NMR spectra (Table 2). The proton signals of the geminal α- and β-methyl groups were readily identified in the ^{1}H NMR spectra of all compounds **4-7** at δ 0.85-1.35 and 0.81-1.05 ppm respectively [7]. The diamides **5a,b** were a mixture of *cis/trans* isomers, which was indicated by the appearance of additional signals for the geminal methyl groups at 1.04-1.06 ppm [5,8]. Low field signals were detected in the ^{1}H NMR spectra of compounds **4** and **5** for amide NH protons (δ 11-12 ppm) and strongly broadened signals for the carboxyl group protons in the range 6.5-9.5 ppm. Triplet signals were also identified in the spectra of compounds **4a-c** for the $C_{(3)}$-H methine protons (δ 2.86-2.93 ppm, ^3J = 9 Hz). Bands were clearly displayed in the IR spectra of diamides **4** and **5** for $\nu_{C=O}$ absorption (1702-1672 and 1670-1642 cm^{-1}), a band characteristic of δ_{NCHO} absorption (1532-1580 cm^{-1}), intense absorption for the NH bond (3108-3345 cm^{-1}), and also a broad band for the absorption of the carboxyl group at 2500-2600 cm^{-1}. The amide functions of the quinazolinone were displayed in the IR spectra of compounds **6** and **7** ($\nu_{C=O}$ 1650-1676, ν_{NH} 3123-3183 cm^{-1}). The protons of the NH groups of compounds **6** and **7** in the ^{1}H NMR spectra were detected as broadened signals in the range 9.59-12.38 ppm.

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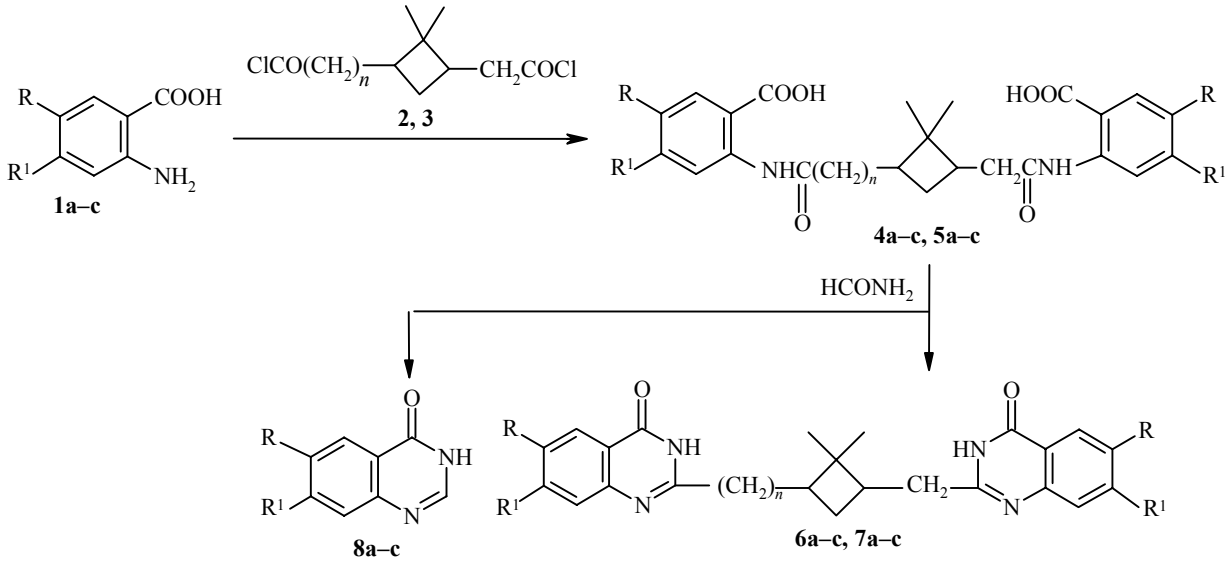

1, 4–8 a R = Br, R^1 = H; **b** R = H, R^1 = Cl; **c** R = R^1 = MeO; **2, 4, 6** *n* = 0; **3, 5, 7** *n* = 1

TABLE 1. Characteristics of the Synthesized Compounds **4-8***

Compound	Empirical formula	Found, % / Calculated, %				(mp, °C (solvent for crystallization)	Yield, %
		C	H	Hal	N		
4a	$C_{23}H_{22}Br_2N_2O_6$	47.15 / 47.45	4.02 / 3.81	27.14 / 27.48	4.55 / 4.81	228-230 $MeNO_2$	85.6
4b	$C_{23}H_{22}Cl_2N_2O_6$	56.19 / 55.99	4.40 / 4.49	14.27 / 14.37	5.61 / 5.68	229-231 $MeNO_2$	74.4
4c	$C_{27}H_{32}N_2O_{10}$	54.38 / 59.55	5.81 / 5.92		5.02 / 5.14	264-265 $MeNO_2$	76.8
5a	$C_{24}H_{24}Br_2N_2O_6$	48.58 / 48.34	4.01 / 4.06	26.85 / 26.80	4.59 / 4.70	221-222 MeCN	84.9
5b	$C_{24}H_{24}Cl_2N_2O_6$	56.66 / 56.81	4.70 / 4.77	13.72 / 13.97	5.63 / 5.52	231-232 MeCN	86.0
5c	$C_{28}H_{34}N_2O_{10}$	60.11 / 60.21	6.06 / 6.13		4.89 / 5.01	243-245 BuOH	81.6
6a	$C_{23}H_{20}Br_2N_4O_2$	50.59 / 50.76	3.62 / 3.70	29.65 / 29.36	10.11 / 10.29	334-335 DMF–H_2O, 4:1	49.6
6b	$C_{23}H_{20}Cl_2N_4O_2$	60.85 / 60.67	4.29 / 4.43	15.89 / 15.57	11.93 / 12.30	314-316 $MeNO_2$	47.5
6c	$C_{27}H_{30}N_4O_6$	63.88 / 64.02	5.91 / 5.97		10.90 / 11.06	300-302 $MeNO_2$	46.5
7a	$C_{24}H_{22}Br_2N_4O_2$	51.51 / 51.63	3.90 / 3.97	28.33 / 28.63	10.14 / 10.04	309-311 MeCN	48.2
7b	$C_{24}H_{22}Cl_2N_4O_2$	61.19 / 61.41	4.61 / 4.72	15.25 / 15.11	11.79 / 11.94	296-298 $MeNO_2$	51.5
7c	$C_{28}H_{32}N_4O_6$	64.73 / 64.60	6.23 / 6.20		10.63 / 10.76	311-313 DMF–H_2O, 1:1	50.0
8c	$C_{10}H_{10}N_2O_3$	58.11 / 58.25	4.79 / 4.88		13.65 / 13.58	285-287 $MeNO_2$	54.6

* Compounds **4a-c** to **7a-c** decompose.

TABLE 2. Spectral Characteristics of Compounds **4-8**

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm, SSCC (*J*), Hz
4a	1698, 1666, 1600, 1574, 1504; 3345, 2610	0.93 (3H, s, β-CH_3); 1.29 (3H, s, α-CH_3); 2.06 (2H, m, CH_2); 2.43 (3H, center m, CH_2–CH); 2.89 (1H, t, ^3J = 9.0, CH); 7.71 (2H, dd, ^3J = 9, ^4J = 2, $2C_6H_3$); 8.03 (1H, d, ^4J = 2, C_6H_3); 8.05 (1H, d, ^4J = 2, C_6H_3); 8.45 (1H, d, ^3J = 9, C_6H_3); 8.53 (1H, d, ^3J = 9, C_6H_3); 10.96 (2H, br. s, 2NH)
4b	1680, 1642, 1600, 1580, 1514; 3260, 3125; 2627	0.94 (3H, s, β-CH_3); 1.29 (3H, s, α-CH_3); 2.07 (2H, m, CH_2); 2.49 (3H, center m, CH_2–CH); 2.93 (1H, t, ^3J = 9, CH); 5.54 (1H, br. s, 2OH); 7.18 (2H, dd, ^3J = 9, ^4J = 1.5, C_6H_3); 7.99 (2H, d, ^3J = 9, $2C_6H_3$); 8.62 (1H, d, ^4J = 1.5, C_6H_3); 8.73 (1H, d, ^4J = 1.5, C_6H_3); 11.21 (1H, br. s, NH); 11.3 (1H, br. s, NH)
4c	1672, 1614, 1532; 3195	1.05 (3H, s, β-CH_3); 1.35 (3H, s, α-CH_3); 2.15-2.58 (5H, m, –CH_2CHCH_2–); 2.86 (1H, t, ^3J = 9, CH); 3.87 (6H, s, $2CH_3O$); 3.95 (6H, s, $2CH_3O$); 7.55 (2H, s, $2C_6H_2$); 8.48 (1H, s, C_6H_2); 8.53 (1H, s, C_6H_2); 8.69 (2H, br. s, 2OH); 11.33 (1H, br. s, NH); 11.46 (1H, br. s, NH)
5a	1702, 1668, 1602, 1578, 1518; 3119, 2590	0.99 and 1.06 (3H, s, β-CH_3); 1.06 and 1.11 (3H, s, α-CH_3); 1.43-2.59 (8H, m, –$CH_2CHCH_2CHCH_2$–); 7.55 (2H, dd, ^3J = 9, ^4J = 2, $2C_6H_3$); 8.21 (2H, d, ^4J = 2, C_6H_3); 8.66 (2H, d, ^3J = 9, $2C_6H_3$); 10.47 (2H, br. s, 2NH); 11.33 (2H, br. s, 2OH)
5b	1702, 1670, 1601, 1580, 1524; 3108, 2620	0.96 and 1.04 (3H, s, β-CH_3); 1.04 and 1.05 (3H, s, α-CH_3); 2.34 (8H, center m, –$CH_2CHCH_2CHCH_2$–); 6.20 (2H, br. s, 2OH); 7.20 (2H, dd, ^3J = 9, ^4J = 2, $2C_6H_3$); 8.01 (2H, d, ^3J = 9, $2C_6H_3$); 8.63 (2H, d, ^4J = 2, $2C_6H_3$); 11.23 (2H, br. s, 2NH)
5c	1678, 1636, 1620, 1532, 1510;3108, 2620	0.96 (3H, s, β-CH_3); 1.04 (3H, s, α-CH_3); 2.34 (8H, center m, –$CH_2CHCH_2CHCH_2$–); 3.76 (6H, s, $2CH_3O$); 3.79 (6H, s, $2CH_3O$); 7.47 (2H, s, C_6H_2); 8.29 (2H, s, C_6H_2); 9.20 (2H, br. s, 2OH); 11.54 (2H, br. s, 2NH)
6a	1674, 1617; 3134	0.81 (3H, s, β-CH_3); 1.25 (3H, s, α-CH_3); 1.77-2.94 (6H, m, –$CHCH_2CHCH_2$–); 7.54 (1H, d, ^3J = 9, C_6H_3); 7.58 (1H, d, ^3J = 9, C_6H_3); 7.84 (2H, dd, ^3J = 9, ^4J = 2, C_6H_3); 8.16 (2H, d, ^4J = 2, C_6H_3); 12.14 (1H, br. s, NH); 12.38 (1H, br. s, NH)
6b	1660, 1556, 1606, 1500; 3171, 3123	0.83 (3H, s, β-CH_3); 1.27 (3H, s, α-CH_3); 2.01-3.61 (6H, m, –$CHCH_2CHCH_2$–); 7.46 (2H, dd, ^3J = 9, ^4J = 2, $2C_6H_3$); 7.60 (1H, d, ^4J = 2, C_6H_3); 7.66 (1H, d, ^4J = 2, C_6H_3); 8.16 (2H, d, ^3J = 9, C_6H_3); 11.16 (2H, br. s, 2NH)
6c	1656, 1614, 1522, 1490; 3167	0.83 (3H, s, β-CH_3); 1.25 (3H, s, α-CH_3); 1.98-3.08 (6H, m, –$CHCH_2CHCH_2$–); 3.87 (6H, s, $2CH_3O$); 3.92 (6H, s, $2CH_3O$); 7.10 (1H, s, C_6H_2); 7.16 (1H, s, C_6H_2); 7.45 (2H, s, C_6H_2); 11.85 (1H, br. s, NH); 12.09 (1H, br. s, NH)
7a	1676, 1618, 1557; 3163	1.01 (6H, α-, β-CH_3); 1.48-2.74 (8H, m, –$CH_2CHCH_2CHCH_2$–); 7.49 (2H, d, ^3J = 9, C_6H_2); 7.87 (2H, dd, ^3J = 9, ^4J = 2, C_6H_2); 8.16 (2H, d, ^4J = 2, C_6H_2); 12.34 (2H, br. s, 2NH)
7b	1672, 1614, 1532; 3183	1.01 (3H, s, β-CH_3); 1.04 (3H, s, α-CH_3); 1.58-2.63 (8H, m, –$CH_2CHCH_2CHCH_2$–); 7.45 (2H, dd, ^3J = 9, ^4J = 2, $2C_6H_2$); 7.63 (2H, d, ^4J = 2, $2C_6H_2$); 8.13 (2H, d, ^3J = 9, $2C_6H_2$); 12.05 (2H, br. s, 2NH)
7c	1656, 1612, 1522, 1490; 3167	0.82 (3H, s, β-CH_3); 0.85 (3H, s, α-CH_3); 1.45-2.27 (8H, m, –$CH_2CHCH_2CHCH_2$–); 3.09 (6H, s, $2CH_3O$); 3.14 (6H, s, $2CH_3O$); 5.65 (2H, s, C_6H_2); 5.94 (2H, s, $2C_6H_2$); 9.59 (2H, s, 2NH)
8c	1711, 1682, 1640, 1600, 1505; 3180, 3120	3.38 (3H, s, CH_3O); 3.94 (3H, s, CH_3O); 7.15 (1H, s, C_6H_2); 7.47 (1H, s, C_6H_2); 8.01 (1H, s, =CH–); 11.42 (1H, br. s, NH)

EXPERIMENTAL

The IR spectra were taken on a Specord IR 75 instrument for suspensions of substances in nujol (1500-1800 cm^{-1}) and in hexachlorobutadiene (2000-3600 cm^{-1}). The frequencies of the stretching vibrations of C–H bonds at 2800-3050 cm^{-1} are not given.

The ^1H NMR spectra were recorded on a Bruker WH-90/DS (90 MHz) in DMSO-d_6 solution, internal standard was TMS. A check on the purity of products was effected by TLC on Silufol UV-254 plates in the system $CHCl_3$–C_2H_5OH, 9:1. Visualization was with UV light or chlorine with subsequent treatment with KI–benzidine reagent. The acid chlorides of *cis*-3-carboxy-2,2-dimethylcyclobutylacetic (pinic) (**2**) and *cis/trans*-3-(carboxymethyl)-2,2-dimethylcyclobutylacetic (*sym*-homopinic) (**3**) acids were obtained by the procedure of [4-6]. The diamides of pinic and *sym*-homopinic acids were synthesized by the methods of [4,6,8].

The physicochemical and spectral characteristics of compounds **4-8** are given in Tables 1 and 2.

The yield of the known quinazolone **8c** obtained by the method of [9] is given in Table 1. Yields of the reaction side products **8a-c** are given in the experimental section.

4-Bromo-2-carboxyphenylamide of 3-(4-Bromo-2-carboxyphenylaminocarbonyl)-2,2-dimethylcyclobutylacetic Acid (4a). A solution of pinic acid dichloride **2** (1.0 g, 4.5 mmol) in absolute dioxane (20 ml) was added slowly with stirring to a solution of 5-bromoanthranilic acid **1a** (1.94 g, 9 mmol) and triethylamine (2.0 ml, 14.3 mmol) in absolute dioxane (30 ml) at 20°C. The mixture was stirred for 3 h, the precipitate of triethylamine hydrochloride was filtered off, and washed with dioxane (3 × 10 ml). The filtrate was evaporated on a rotary evaporator in a water-pump vacuum, and the residue recrystallized.

The Diamides 4b,c were obtained analogously from anthranilic acids **1b,c** by reaction with pinic acid dichloride **2**.

1,3-Di-(4-bromo-2-carboxyphenylaminocarbonylmethyl)-2,2-dimethylcyclobutane (5a). A solution of *sym*-homopinic acid dichloride **3** (0.82 g, 3.5 mmol) in absolute dioxane (20 ml) was added slowly with stirring to a solution of 5-bromoanthranilic acid **1a** (1.54 g, 7.1 mmol) and triethylamine (1.0 ml, 7.1 mmol) in absolute dioxane (30 ml) at 20°C, and the mixture stirred for 2 h. The precipitate was filtered off, washed with dioxane (3 × 10 ml), the filtrate evaporated on a rotary evaporator in a water-pump vacuum, and the residue of **5a** was recrystallized.

The Diamides 5b,c were obtained analogously from amines **1b,c** by reaction with *sym*-homopinic acid dichloride **3**.

3-[6-Bromo-4(3H)-oxo-2-quinazolinyl]-1-[6-bromo-4(3H)-oxo-2-quinazolinyl]methyl-2,2-dimethylcyclobutane (6a). A mixture of diamide **4a** (0.84 g, 1.65 mmol) and formamide (1 ml, 7.14 mmol) was heated at 180-185°C for 2 h in a small flask with a reflux condenser. The mixture was cooled, and suspended in water (30 ml) containing sodium bicarbonate (0.6 g, 7.14 mmol). The precipitate of **6a** was filtered off, washed with water (3 × 20 ml), dried in the air, and recrystallized.

After removing **6a** the aqueous solution was acidified with dilute (1:1) hydrochloric acid to pH 5-6, extracted with chloroform (3 × 20 ml), and the extract dried over magnesium sulfate. The solvent was distilled on a rotary evaporator in a water-pump vacuum. The residue was recrystallized from nitromethane and **6-bromo-4(3H)-quinazolinone 8a** (0.16 g, 21.6%) was obtained; mp 264-266°C (decomp.); lit. mp 261-267°C (decomp.) [9]. No depression of melting point was observed on mixing with a known synthesized sample.

The **diquinazolinyl derivatives 6b,c** and the corresponding **quinazolones 8b,c** were obtained analogously from diamides **4b,c**.

7-Chloro-4(3H)-quinazolinone (8b). Yield 19.9%; mp 243-244°C (decomp.) (acetonitrile); lit. mp 242-245°C [9]. No depression of melting point was observed on mixing with a known synthesized sample.

6,7-Dimethoxy-4(3H)-quinazolinone (8c). Yield 11.4%; mp 285-287°C (decomp.) (nitromethane). No depression of melting point was observed on mixing with a known synthesized sample. The identical known quinazolinone **8c** was obtained by the procedure of [9].

1,3-Di-[6-bromo-4(3H)-oxo-2-quinazolinylmethyl]-2,2-dimethylcyclobutane (7a). A mixture of diamide **5a** (0.35 g, 0.59 mmol) and formamide (0.45 g, 5 mmol) was heated at 186±2°C in a small flask with a reflux condenser. The mixture was cooled, and suspended in water (30 ml) containing sodium bicarbonate (0.2 g, 2.38 mmol). The precipitate of **7a** was filtered off, washed with water (3 × 20 ml), dried in the air, and recrystallized.

After separating **7a** the aqueous solution was acidified with dilute (1:1) hydrochloric acid to pH 5-6, extracted with chloroform (3 × 20 ml), and the extract dried over magnesium sulfate. The solvent was distilled on a rotary evaporator in a water-pump vacuum. The residue was recrystallized from nitromethane and quinazolinone **8a** (0.05 g, 18.9%) was obtained.

The **diquinazolinyl derivatives 7b,c** and the corresponding **quinazolinones 8b,c** were obtained analogously from diamides **5b,c**. The yield of **8b** was 16.2%, and of **8c** 12.5%.

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