Synthesis of Substituted *N*-(2,4-Dioxo-1,2,3,4-tetrahydroquinazolinyl)benzamides and *N*-(2-Thiono-4-oxo-1,2,3,4-tetrahydroquinazolinyl)benzamides

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Substituted *N*-(2,4-dioxo-1,2,3,4-tetrahydroquinazolinyl)benzamides (**3a-g**) and substituted *N*-(2-thiono-4-oxo-1,2,3,4-tetrahydroquinazolinyl)benzamides (**4a-g**) were synthesized in one step from the reaction of methyl anthranilate with 2-aryl-1,3,4-oxadiazolin-5-ones (**1a-g**) and 2-aryl-1,3,4-oxadiazoline-5-thiones (**2a-g**), respectively, in *m*-cresol at 150-160°. Alternative routes leading to the formation of **3a** and **4a** are also reported.

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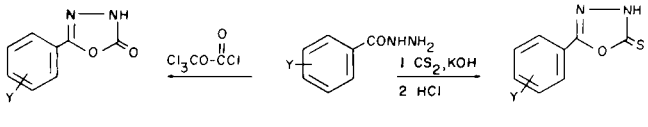
2-Substituted-1,3,4-oxadiazolin-5-ones (1-4) and 2-substituted-1,3,4-oxadiazoline-5-thiones (5-7) are of considerable interest for their pharmacological properties. It has been reported that these heterocyclic compounds react with nucleophilic reagents such as amines and hydrazines to give ring-opening addition products (8-10). As part of our investigation of the synthetic utility of these oxadiazoles, we wish to report here the synthesis of substituted *N*-(2,4-dioxo-1,2,3,4-tetrahydroquinazolinyl)benzamides (**3a-g**) and substituted *N*-(2-thiono-4-oxo-1,2,3,4-tetrahydroquinazolinyl)benzamides (**4a-g**) from the reaction of methyl anthranilate with 2-aryl-1,3,4-oxadiazolin-5-ones (**1a-g**) and 2-aryl-1,3,4-oxadiazoline-5-thiones (**2a-g**), respectively.

Compounds **1a-g** were conveniently prepared by treating the appropriate hydrazides with trichloromethyl chloroformate in dioxane. Compounds **2a-g** were prepared as previously reported by condensing the hydrazides with carbon disulfide in ethanolic potassium hydroxide followed by acidification with hydrochloric acid (11) (Scheme 1, Table 1).

Scheme 1

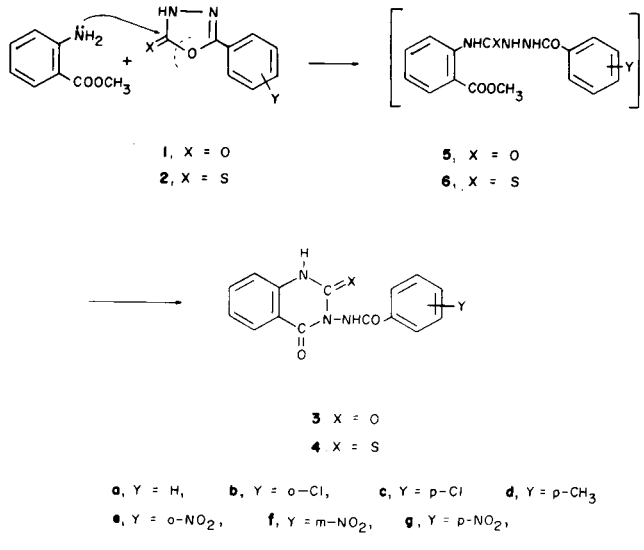


1 **2**

a, Y = H, **b**, Y = o-Cl, **c**, Y = p-Cl, **d**, Y = p-CH_3, **e**, Y = o-NO_2, **f**, Y = m-NO_2, **g**, Y = p-NO_2,

Treatment of **1a-g** and **2a-g** with methyl anthranilate in *m*-cresol at 150-160° for 5 hours afforded **3a-g** and **4a-g**, respectively, in 48-81% yields after purification (Scheme 2, Table 2). The structure of all compounds was confirmed by elemental analyses and spectral data.

Scheme 2



1, X = O
2, X = S

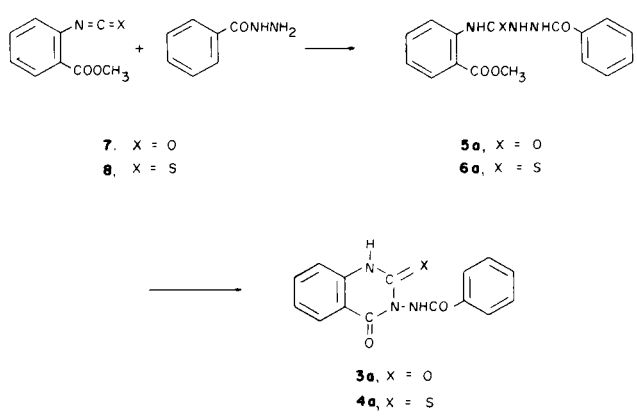
5, X = O
6, X = S

3 X = O
4 X = S

a, Y = H, **b**, Y = o-Cl, **c**, Y = p-Cl, **d**, Y = p-CH_3, **e**, Y = o-NO_2, **f**, Y = m-NO_2, **g**, Y = p-NO_2,

The formation of **3a-g** and **4a-g** presumably proceeds through nucleophilic attack of the amino nitrogen of methyl anthranilate on (thio) carbonyl C-5 of **1a-g** and **2a-g** to give acylsemicarbazides (**5a-g**) and acylthiosemicarbazides (**6a-g**), respectively (10). Subsequent ring

Scheme 3



7, X = O
8, X = S

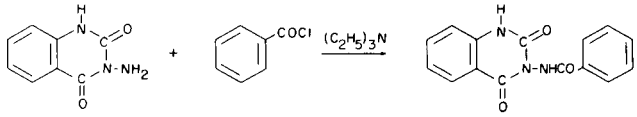
5a, X = O
6a, X = S

3a, X = O
4a, X = S

closure accompanied with the elimination of methanol completes the quinazoline structure. Attempts to isolate intermediates **5a-g** and **6a-g** by lowering the reaction temperature below the level described above gave only recovered starting materials. However, **5a** (Y = H) and **6a** (Y = H) could be prepared by treating benzoyl hydrazide with 2-carbomethoxyphenyl isocyanate (**7**) and 2-carbomethoxyphenyl isothiocyanate (**8**), respectively, in tetrahydrofuran at 0°-room temperature (Scheme 3).

6a was readily cyclized to **4a** by refluxing in acetonitrile while the conversion of **5a** to **3a** required heating to 150-160° in *m*-cresol. Compound **3a** was also prepared by simple condensation of 3-amino-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**9**) with benzoyl chloride in tetrahydrofuran at 0° in the presence of triethylamine (Scheme 4).

Scheme 4



9 **3a**

EXPERIMENTAL

Melting points were determined with a Mel-temp melting point apparatus and are uncorrected. The ir spectra were recorded on a JASCO IRA-1 spectrophotometer and the nmr spectra were recorded on a JEOL JNM-PMX 60 spectrometer and are reported in ppm from TMS.

The following starting materials were obtained according to the literature method: 2-carbomethoxyphenyl isocyanate (**7**), bp 102.5°/1.5 mm (lit (14) bp 80°/0.05 mm); 2-carbomethoxyphenyl isothiocyanate (**8**), bp 124-125°/3 mm (lit (15) bp 100-102°/0.35 mm); and 3-amino-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (**9**), mp 281-283° (lit (16) mp 281-284°).

2-Phenyl-1,3,4-oxadiazolin-5-one (**1a**).

To a stirred solution of trichloromethyl chloroformate (4.6 ml, 0.038 mole) in dioxane (30 ml) was added dropwise a solution of benzoyl hydrazide (6.8 g, 0.05 mole) in dioxane (30 ml) at room temperature. After the addition, the reaction mixture was heated to reflux for 4 hours. The solvent was removed under reduced pressure and the residue was recrystallized from water to yield 7.3 g (90%) of **1a** as colorless needles, mp 138-139° (lit (12) mp 137-138°).

Compounds **1b-g** were prepared in a similar manner and are summarized in Table 1.

2-Phenyl-1,3,4-oxadiazoline-5-thione (**2a**).

This compound was prepared by the method described by Young and Wood (11). To a solution of benzoyl hydrazide (6.8 g, 0.05 mole) and potassium hydroxide (2.9 g, 0.05 mole, dissolved in water (10 ml)) in ethanol (200 ml) was added carbon disulfide (3.6 ml, 0.06 mole) and the reaction mixture was heated to reflux for 7 hours. After concentration of

Table I

2-Aryl-1,3,4-oxadiazolin-5-ones (**1a-g**) and 2-Aryl-1,3,4-oxadiazoline-5-thiones (**2a-g**)

Compound No.	Y	Mp °C	Recrystallization Solvent	Yield %	Formula		Analysis % C	H	N
1a (a)	H	138-139	Water	90	$C_8H_6N_2O_2$	Calcd.	59.25	3.73	17.28
						Found	59.16	3.57	17.48
1b (b)	*o*-Cl	165-166	Methanol	88	$C_8H_5ClN_2O_2$	Calcd.	48.87	2.56	14.25
						Found	48.68	2.43	14.48
1c	*p*-Cl	234-235	Ethanol	74	$C_8H_5ClN_2O_2$	Calcd.	48.87	2.56	14.25
						Found	49.06	2.40	14.02
1d	*p*-CH_3	170-171	Ethanol	83	$C_9H_8N_2O_2$	Calcd.	61.35	4.58	15.90
						Found	61.07	4.73	15.85
1e	*o*-NO_2	161-162	Ethanol	68	$C_8H_5N_3O_4$	Calcd.	46.38	2.43	20.29
						Found	46.55	2.29	20.46
1f (c)	*m*-NO_2	190-192	Ethanol	75	$C_8H_5N_3O_4$	Calcd.	46.38	2.43	20.29
						Found	46.31	2.26	20.21
1g (d)	*p*-NO_2	251-253	Dioxane/Water	52	$C_8H_5N_3O_4$	Calcd.	46.38	2.43	20.29
						Found	46.29	2.53	20.36
2a (e)	H	219-220	Methanol	72	$C_8H_6N_2OS$	Calcd.	53.91	3.39	15.72
						Found	53.86	3.41	15.61
2b	*o*-Cl	174-175	Chloroform	62	$C_8H_5ClN_2OS$	Calcd.	45.18	2.37	13.18
						Found	45.32	2.23	13.29
2c (f)	*p*-Cl	174-175	Chloroform	62	$C_8H_5ClN_2OS$	Calcd.	45.18	2.37	13.18
						Found	45.19	2.26	13.26
2d	*p*-CH_3	217-218	Methanol	56	$C_9H_8N_2OS$	Calcd.	56.23	4.19	14.58
						Found	56.36	4.01	14.45
2e	*o*-NO_2	151-152	Benzene	65	$C_8H_5N_3O_3S$	Calcd.	43.04	2.26	18.83
						Found	43.29	2.02	19.08
2f	*m*-NO_2	168-169	Ethanol	63	$C_8H_5N_3O_3S$	Calcd.	43.04	2.26	18.83
						Found	43.13	2.07	18.94
2g (g)	*p*-NO_2	203-205	Methanol	63	$C_8H_5N_3O_3S$	Calcd.	43.04	2.26	18.83
						Found	43.16	2.19	18.62

(a) Lit (12), mp 137-138°. (b) Lit (10), mp 168-169°. (c) Lit (1), mp 192°. (d) Lit (1), mp 249-251°. (e) Lit (11), mp 219-220°. (f) Lit (11), mp 176.5-178°. (g) Lit (13), mp 207-209°.

the solution to a small volume, the residue was dissolved in water (20 ml) and acidified with concentrated hydrochloric acid under cooling in an ice bath. The resulting precipitation was collected, washed with water, and recrystallized from methanol to yield 6.4 g (72%) of **2a** as colorless needles, mp 219-220° (lit (11) mp 219-220°).

Compounds (**2b-g**) were prepared according to the procedure described above and are compiled in Table 1.

N-(2,4-Dioxo-1,2,3,4-tetrahydroquinazolinyl)benzamide (3a).

Method A. From **1a**.

A mixture of methyl anthranilate (1.51 g, 0.01 mole) and **1a** (1.62 g, 0.01 mole) in *m*-cresol (10 ml) was heated at 150-160° for 5 hours. After cooling, the reaction mixture was poured into ether (50 ml). The crude product, which precipitated as a tan yellow product, was collected, washed well with ether and recrystallized from ethanol/water to give 2.25 g (80%) of **3a** as white needles, mp 281-282°; ir (potassium bromide): 3250, 3160 (NH), 1730 (quinazoline 4-C=O), 1660 cm^{-1} (quinazoline 2-C=O and amide C=O); nmr (DMSO-d_6): 7.09-8.00 (m, 9H, C_6H_4 and C_6H_5), 11.35 ppm (broad s, 2H, NH).

Method B. From **7**.

A solution of benzoyl hydrazide (1.36 g, 0.01 mole) in dry tetrahydrofuran (30 ml) was slowly added to a stirred solution of **7** (1.77 g, 0.01 mole) in the same solvent (30 ml) at 0°. After stirring at 0° for 30 minutes and then at room temperature for 3 hours, the solvent was removed under reduced pressure and the residue was triturated with dry ether. The solid was collected and washed with ether to give 3.00 g (96%) of **5a**. Careful recrystallization from methanol afforded colorless needles, mp 152-153° (rapid heating); ir (potassium bromide): 3220 (NH), 1680 (ester C=O), 1645 cm^{-1} (semicarbazide and benzoyl C=O); nmr (DMSO-d_6): 3.76 (s, 3H, OCH_3), 6.88-7.97 (m, 9H, C_6H_4 and C_6H_5), 8.95 (broad s, 1H, NH), 10.45 ppm (broad s, 2H, NH).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.29; H, 4.66; N, 13.50.

Heating **5a** (1.57 g, 0.005 mole) in *m*-cresol (5 ml) at 150-160° for 2 hours gave 1.31 g (93%) of crude **3a**. This material was recrystallized from ethanol/water and identical in physical (mp, mixed mp) and spectral characteristics with a sample of **3a** prepared from **1a**.

Method C. From **9**.

To a stirred solution of **9** (1.77 g, 0.01 mole) and triethylamine (1.11 g, 0.011 mole) in tetrahydrofuran (40 ml) was added dropwise a solution of benzoyl chloride (1.41 g, 0.01 mole) of tetrahydrofuran (40 ml) at 0° over a period of 20 minutes. After the reaction was continued at 0° for 30 minutes, the reaction mixture was allowed to stand at room temperature for 3 hours. After the precipitated triethylamine hydrochloride was filtered off, the solution was concentrated to give a viscous material which crystallized by adding a small amount of ether. There was collected 2.61 g (93%) of **3a**, mp 281-282°, mixed melting point with a sample of **3a** prepared from **1a** 281-282°.

Compounds **3b-g** were prepared by the reaction of the appropriate compound **1** with methyl anthranilate as described above for **3a** (Method A) and are presented in Table 2.

N-(2-Thiono-4-oxo-1,2,3,4-tetrahydroquinazolinyl)benzamide (**4a**).

Method A. From **2a**.

Table 2

Substituted *N*-(2,4-Dioxo-1,2,3,4-tetrahydroquinazolinyl)benzamides (**3a-g**) and *N*-(2-Thiono-4-oxo-1,2,3,4-tetrahydroquinazolinyl)benzamides (**4a-g**) (a)

Compound No.	Y	Mp (b) °C	Yield %	Formula		Analysis % C	H	N
3a	H	281-282	80	$C_{15}H_{11}N_3O_3$	Calcd.	64.05	3.94	14.94
					Found	64.06	3.80	14.93
3b	*o*-Cl	287-288	81	$C_{15}H_{10}ClN_3O_3$	Calcd.	57.06	3.19	13.31
					Found	57.33	3.11	13.56
3c	*p*-Cl	350-352	76	$C_{15}H_{10}ClN_3O_3$	Calcd.	57.06	3.19	13.31
					Found	57.08	3.15	13.11
3d	*p*-CH_3	338-339	79	$C_{16}H_{13}N_3O_3$	Calcd.	65.07	4.44	14.23
					Found	65.17	4.32	14.10
3e	*o*-NO_2	320-321	72	$C_{15}H_{10}N_4O_5$	Calcd.	55.22	3.09	17.18
					Found	55.50	3.01	17.38
3f	*m*-NO_2	302-303	62	$C_{15}H_{10}N_4O_5$	Calcd.	55.22	3.09	17.18
					Found	55.11	3.06	17.35
3g	*p*-NO_2	361-362	65	$C_{15}H_{10}N_4O_5$	Calcd.	55.22	3.09	17.18
					Found	55.06	2.98	17.22
4a	H	264-265 dec	75	$C_{15}H_{11}N_3O_2S$	Calcd.	60.59	3.73	14.14
					Found	60.67	3.78	14.08
4b	*o*-Cl	292-293 dec	73	$C_{15}H_{10}ClN_3O_2S$	Calcd.	54.30	3.04	12.67
					Found	54.04	3.06	12.46
4c	*p*-Cl	266-267 dec	73	$C_{15}H_{10}ClN_3O_2S$	Calcd.	54.30	3.04	12.67
					Found	54.07	2.94	12.46
4d	*p*-CH_3	275-276 dec	73	$C_{16}H_{13}N_3O_2S$	Calcd.	61.72	4.21	13.50
					Found	61.64	4.06	13.35
4e	*o*-NO_2	280-281 dec	48	$C_{15}H_{10}N_4O_4S$	Calcd.	52.62	2.94	16.37
					Found	52.32	2.88	16.59
4f	*m*-NO_2	271-273 dec	79	$C_{15}H_{10}N_4O_4S$	Calcd.	52.62	2.94	16.37
					Found	52.81	2.88	16.27
4g	*p*-NO_2	284-286 dec	71	$C_{15}H_{10}N_4O_4S$	Calcd.	52.62	2.94	16.37
					Found	52.48	2.74	16.28

(a) All compounds were prepared according to Method A in Experimental. (b) All compounds were recrystallized from ethanol/water.

A mixture of methyl anthranilate (1.51 g, 0.01 mole) and **2a** (1.78 g, 0.01 mole) in *m*-cresol (10 ml) was heated at 150-160° for 5 hours and worked up as reported for **3a** (Method A). Recrystallization from ethanol/water afforded 2.23 g (75%) of **4a** as colorless needles, mp 264-265° dec; ir (potassium bromide): 3240, 3180 (NH), 1715 (quinazoline C=O), 1660 cm^{-1} (amide C=O); nmr (DMSO-d_6): 7.27-8.09 (m, 9H, C_6H_4 and C_6H_5), 11.41 (s, 1H, NH), 13.14 ppm (broad s, 1H, NH).

Method B. From **8**.

To a stirred solution of **8** (1.93 g, 0.01 mole) in tetrahydrofuran (20 ml), benzoyl hydrazide (1.36 g, 0.01 mole) was added in one portion at room temperature. The reagents dissolved and within 1 minute a white precipitate separated. After stirring for 10 minutes, the product was collected to give 3.22 g (98%) of **6a** which was used in the next step without further purification, mp 165-166° dec (rapid heating); ir (potassium bromide): 3200, 3150 (NH), 1685 (ester C=O), 1660 cm^{-1} (benzoyl C=O); nmr (DMSO-d_6): 3.74 (s, 3H, OCH_3), 7.06-8.06 (m, 9H, C_6H_4 and C_6H_5), 8.87 (broad s, 1H, NH), 10.00 (broad s, 1H, NH), 10.73 ppm (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{15}N_3O_3S$: C, 58.34; H, 4.59; N, 12.76. Found: C, 58.23; H, 4.36; N, 12.43.

Refluxing **6a** (1.65 g, 0.005 mole) in acetonitrile (10 ml) for 2 hours gave 1.46 g (98%) of **4a**, recrystallized from ethanol/water as colorless needles melting at 264-265° dec (identified by mp, mixed mp and spectral comparison with a sample of **4a** prepared from **2a**).

Compounds **4b-g** were prepared by the reaction of the appropriate compound **2** with methyl anthranilate as described above for **4a** (Method A) and are listed in Table 2.

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