Synthesis of 3-Aryl-2,4-dioxo-1,2,3,4-tetrahydroquinazolines and 2-Arylamino-4-oxo-4*H*-3,1-benzoxazines from Methyl *N*-Aryldithiocarbamates

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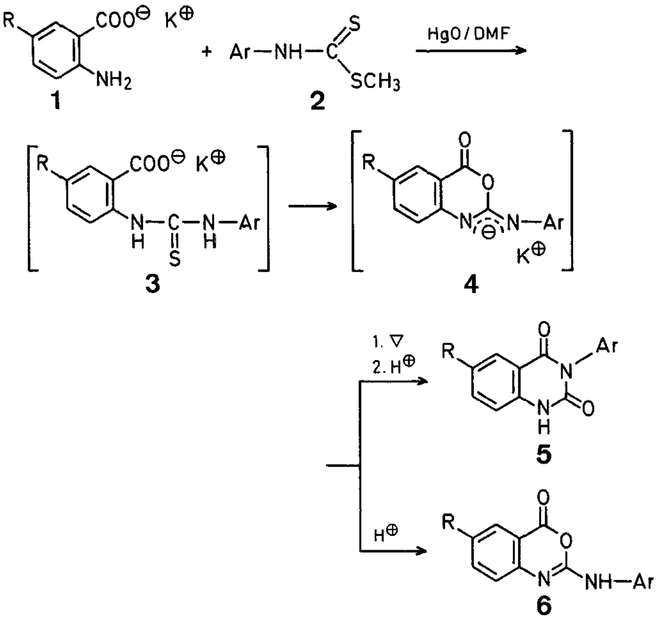
Recently, we have reported the preparation of methyl *N*-aryldithiocarbamates[1] and their applications to the synthesis of several types of heterocyclic rings[2,3]. As a continuation of this work, the synthesis of the title compounds was undertaken. These, in turn, have previously been prepared by a variety of methods, all of them using anthranilic acid or isatoic anhydride as starting materials. Thus, 3-aryl-2,4-dioxo-1,2,3,4-tetrahydroquinazolines have been obtained by reaction of anthranilic acid (or its methyl ester) with isocyanates[4,5,6], anthranilamides with urea[7], and isatoic anhydride with *N,N'*-diarylureas[8] or isothioureas[9]. On the other hand, the synthesis of the isomeric 2-arylamino-4-oxo-4*H*-3,1-benzoxazines has not been described in detail[5,10,11] with one exception[6].

We now report that both the above-mentioned isomers can be easily obtained from methyl *N*-aryldithiocarbamates **2**, depending on the reaction conditions utilized. When compounds **2** are reacted with 5-substituted potassium anthranilates **1** in the presence of 1.5 mol of red mercury(II) oxide below room temperature in dimethylformamide, benzoxazinones **6** can be isolated after acidification (Table 2). However, when the mixture is heated under reflux, the isomeric quinazolinediones **5** are obtained after acidic work-up (Table 1)



These are probably formed via the anion of the corresponding benzoxazinone **4** which, at elevated temperatures, is assumed to rearrange into the more stable quinazolinedione anion.

The structures for **5** and **6** are supported by their I.R. and ^{1}H-N.M.R. spectra which are in good agreement with the reported values[6].

Melting points were determined using a Büchi 510 and are uncorrected. I.R. spectra were recorded on a Perkin-Elmer 283 instrument. ^{1}H-N.M.R. spectra were obtained on a Perkin-Elmer R-12-B spectrometer with TMS as internal reference. Mass spectra were recorded using a Hewlett-Packard 5930-A spectrometer.

3-Aryl-2,4-dioxo-1,2,3,4-tetrahydroquinazolines 5; General Procedure: To a suspension of the potassium anthranilate **1** (0.005 mol) and red mercury(II) oxide (1.5 g, 0.0075 mol) in dimethylformamide (15 ml) with vigorous stirring at room temperature, is added a solution of methyl *N*-aryldithiocarbamate **2** (0.005 mol) in dimethylformamide (15 ml). The mixture is refluxed for 13 h, cooled, and filtered. The solution thus obtained is poured into water (300 ml), cooled in an ice-bath, and acidified (pH = 3–4) with concentrated hydrochloric acid. The precipitate formed is isolated by suction, dried, and the crude product **5** is purified by recrystallization (Table 1).

Table 1. 3-Aryl-2,4-dioxo-1,2,3,4-tetrahydroquinazolines **5a–r**

Product	R	Ar	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	M.S. (70 eV) *m/e* (M$^+$, rel. intens. %)	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
5a	H	C_6H_5	76	279–281° (ethanol)	280–282°[4]	238 (24)	3200–3080 (NH) 1725, 1660 (C=O)	6.9–8.0 (m, 9 H); 11.5 (s, 1 H, NH)
5b	H	2-H_3C—C_6H_4	73	241–243° (acetonitrile)	244–245°[7]	252 (34)	3200–3150 (NH) 1730, 1650 (C=O)	2.05 (s, 3 H); 7.1–8.0 (m, 8 H); 11.55 (s, 1 H, NH)
5c	H	4-H_3C—C_6H_4	80	266–267° (acetonitrile)	265–266°[4]	252 (46)	3200–3150 (NH) 1730, 1650 (C=O)	2.35 (s, 3 H); 6.95–7.95 (m, 8 H); 11.5 (s, 1 H, NH)
5d	H	4-H_3CO—C_6H_4	96	297–299° (ethanol)	293–294°[7]	268 (39)	3200–3140 (NH) 1730, 1650 (C=O)	3.75 (s, 3 H); 6.85–7.95 (m, 8 H); 11.4 (s, 1 H, NH)
5e	H	2,5-di-H_3C—C_6H_3	60	230–232° (ethanol)	—[b]	266 (48)	3250 (NH) 1720, 1670 (C=O)	2.0 (s, 3 H); 2.3 (s, 3 H); 7.0–8.1 (m, 7 H); 11.55 (s, 1 H, NH)
5f	H	2-H_3C, 3-Cl—C_6H_3	70	247–249° (ethanol)	$C_{15}H_{11}ClN_2O_2$ (286.7)	286 (17)	3200–3150 (NH) 1730, 1650 (C=O)	2.1 (s, 3 H); 7.1–8.1 (m, 7 H); 11.3–11.8 (br. s, 1 H, NH)
5g	CH_3	C_6H_5	83	>300° (ethanol)	296–297°[13]	252 (32)	3220 (NH) 1730, 1650 (C=O)	2.35 (s, 3 H); 7.1–7.9 (m, 8 H); 11.3–11.7 (br. s, 1 H, NH)
5h	CH_3	2-H_3C—C_6H_4	75	281–283° (ethanol)	$C_{16}H_{14}N_2O_2$ (266.3)	266 (33)	3230 (NH) 1730, 1650 (C=O)	2.1 (s, 3 H); 2.35 (s, 3 H); 7.1–7.9 (m, 7 H); 11.4 (s, 1 H, NH)
5i	CH_3	4-H_3C—C_6H_4	93	286–288° (ethanol)	289–290°[14]	266 (19)	3220 (NH) 1730, 1650 (C=O)	2.3 (s, 3 H); 2.35 (s, 3 H); 7.0–7.8 (m, 7 H); 11.2–11.6 (br. s, 1 H, NH)
5j	CH_3	4-H_3CO—C_6H_4	80	>300° (acetonitrile)	$C_{16}H_{14}N_2O_3$ (282.3)	282 (100)	3260–3190 (NH) 1730, 1650 (C=O)	2.35 (s, 3 H); 3.8 (s, 3 H); 6.9–7.8 (m, 7 H); 11.4 (s, 1 H, NH)
5k	CH_3	2,5-di-H_3C—C_6H_3	83	>300° (ethanol)	$C_{17}H_{16}N_2O_2$ (280.3)	280 (10)	3200 (NH) 1720, 1660 (C=O)	2.0 (s, 3 H); 2.3 (s, 3 H); 2.35 (s, 3 H); 7.1–7.9 (m, 6 H); 11.4–11.8 (br. s, 1 H, NH)
5l	CH_3	2-H_3C, 3-Cl—C_6H_3	73	298–300° (ethanol)	$C_{16}H_{13}ClN_2O_2$ (300.7)	300 (30)	3220–3100 (NH) 1730, 1650 (C=O)	2.05 (s, 3 H); 2.35 (s, 3 H); 7.1–7.9 (m, 6 H); 11.5 (s, 1 H, NH)
5m	Cl	C_6H_5	73	>300° (ethanol)	308–309°[15]	272 (27)	3240–3190 (NH) 1735, 1650 (C=O)	7.1–7.9 (m, 8 H); 11.4–11.8 (br. s, 1 H, NH)
5n	Cl	2-H_3C—C_6H_4	83	270–271° (ethanol)	$C_{15}H_{11}ClN_2O_2$ (286.7)	286 (38)	3240–3140 (NH) 1735, 1650 (C=O)	2.05 (s, 3 H); 7.2–7.95 (m, 7 H); 11.45 (s, 1 H, NH)

Table 1. (Continued)

Product	R	Ar	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	M.S. (70 eV) m/e (M$^+$, rel. intens. %)	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
5o	Cl	4-H_3C—C_6H_4	84	291–293° (ethanol)	$C_{15}H_{11}ClN_2O_2$ (286.7)	286 (36)	3250 (NH) 1720, 1670 (C═O)	2.35 (s, 3H); 7.1–7.9 (m, 7H); 11.55 (s, 1H, NH)
5p	Cl	4-H_3CO—C_6H_4	88	294–296° (ethanol)	—[c]	302 (25)	3200–3130 (NH) 1725, 1670 (C═O)	3.85 (s, 3H); 7.0–8.0 (m, 7H); 11.65 (s, 1H, NH)
5q	Cl	2,5-di-H_3C—C_6H_3	74	>300° (acetonitrile)	$C_{16}H_{13}ClN_2O_2$ (300.7)	300 (57)	3190 (NH) 1720, 1670 (C═O)	2.05 (s, 3H); 2.35 (s, 3H); 7.1–8.1 (m, 6H); 11.8 (s, 1H, NH)
5r	Cl	2-H_3C, 3-Cl—C_6H_3	89	277–279° (ethanol)	$C_{15}H_{10}Cl_2N_2O_2$ (321.1)	320 (87)	3220–3140 (NH) 1735, 1655 (C═O)	2.1 (s, 3H); 7.2–8.0 (m, 6H); 11.8 (s, 1H, NH)

[a] Satisfactory microanalyses obtained: C ±0.31, H ±0.27, N ±0.29.
[b] Ref.[12], melting point not reported.
[c] Ref.[16], melting point not reported.

Table 2. 2-Arylamino-4-oxo-4*H*-3,1-benzoxazines **6**

Product	R	Ar	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	M.S. (70 eV) m/e (M$^+$)	I.R. (Nujol), ν [cm^{-1}]			^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
							NH	C═O	C═N	
6a	H	C_6H_5	63	191–193° (benzene)	192–193°[10]	238	3290	1745	1640	6.9–8.1 (m, 9H); 10.3 (s, 1H, NH)
6b	H	2-H_3C—C_6H_4	52	153–155° (benzene)	156–158°[6]	252	3285	1750	1640	2.25 (s, 3H); 7.0–8.0 (m, 8H); 9.5 (s, 1H, NH)
6c	H	4-H_3C—C_6H_4	72	195–197° (benzene)	196–198°[6]	252	3285	1730	1635	2.25 (s, 3H); 7.0–8.0 (m, 8H); 10.1 (s, 1H, NH)
6d	H	4-H_3CO—C_6H_4	69	193–195° (acetonitrile)	$C_{15}H_{12}N_2O_3$ (268.3)	268	3290	1740	1625	3.75 (s, 3H); 6.8–8.0 (m, 8H); 10.1 (s, 1H, NH)
6g	CH_3	C_6H_5	81	203–205° (benzene)	$C_{15}H_{12}N_2O_2$ (252.3)	252	3280	1740	1635	2.35 (s, 3H); 7.0–7.9 (m, 8H); 10.2 (s, 1H, NH)
6h	CH_3	2-H_3C—C_6H_4	90	209–211° (benzene)	$C_{16}H_{14}N_2O_2$ (266.3)	266	3310	1740	1635	2.25 (s, 3H); 2.3 (s, 3H); 6.9–7.8 (m, 7H); 9.3–9.5 (br. s, 1H, NH)
6i	CH_3	4-H_3C—C_6H_4	88	217–219° (benzene)	$C_{16}H_{14}N_2O_2$ (266.3)	266	3290	1740	1635	2.3 (s, 3H); 2.35 (s, 3H); 7.1–7.8 (m, 7H); 10.0–10.4 (br. s, 1H, NH)
6j	CH_3	4-H_3CO—C_6H_4	84	213–215° (benzene)	$C_{16}H_{14}N_2O_3$ (282.3)	282	3300	1740	1635	2.3 (s, 3H); 3.71 (s, 3H); 6.8–7.7 (m, 7H); 9.9 (s, 1H, NH)
6m	Cl	C_6H_5	60	222–223° (acetonitrile)	$C_{14}H_9ClN_2O_2$ (272.7)	272	3280	1745	1650	7.0–7.9 (m, 8H); 9.8 (s, 1H, NH)
6o	Cl	4-H_3C—C_6H_4	78	224–226° (acetonitrile)	$C_{15}H_{11}ClN_2O_2$ (286.7)	286	3280	1735	1630	2.35 (s, 3H); 7.1–8.0 (m, 7H); 9.9 (s, 1H, NH)

[a] Satisfactory microanalyses obtained: C ±0.27, H ±0.28, N ±0.34.

2-Arylamino-4-oxo-4*H*-3,1-benzoxazines 6; General Procedure:

To a suspension of the potassium anthranilate **1** (0.005 mol) and red mercury(II) oxide (1.5 g, 0.0075 mol) in dimethylformamide (15 ml) kept at 5–10 °C, is added dropwise with stirring a solution of methyl *N*-aryldithiocarbamate **2** (0.005 mol) in dimethylformamide (15 ml). After the mixture is stirred for 4–6 h, the suspension is filtered, and the filtrate so obtained is poured into water (300 ml), cooled in an ice-bath, and acidified (pH = 6) with concentrated hydrochloric acid. The precipitate is isolated by filtration, dried, and recrystallized (Table 2).

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[1] J. Garin, V. Martinez, J. Mayoral, E. Melendez, F. Merchán, *Synthesis* **1981**, 961.

[2] J. Mayoral, E. Melendez, F. Merchán, J. Sanchez, *Synthesis* **1981**, 962.

[3] F. Merchán, J. Garin, V. Martinez, E. Melendez, *Synthesis* **1982**, 482.

[4] B. Taub, J. B. Hino, *J. Org. Chem.* **26**, 5238 (1961).

[5] M. Kurihara, N. Yoda, *Tetrahedron Lett.* **1965**, 2597.

[6] E. P. Papadopoulos, C. D. Torres, *J. Heterocyclic Chem.* **19**, 269 (1982).

[7] S. Toyoshima, K. Shimada, S. Hamano, T. Ogo, *J. Pharm. Soc. Jpn.* **85**, 502 (1965); *C. A.* **63**, 7009 (1965).

[8] T. Kappe, W. Steiger, E. Ziegler, *Monatsh. Chem.* **98**, 214 (1967).

[9] E. Ziegler, W. Steiger, T. Kappe, *Monatsh. Chem.* **99**, 1499 (1968).

[10] G. Doleschall, K. Lempert, *Tetrahedron Lett.* **1963**, 1195.

[11] J. C. Sheehan, G. D. Daves, Jr., *J. Org. Chem.* **29**, 3599 (1964).

[12] L. Giral, *German Patent (DOS)* 2652144 (1978), Merck; *C. A.* **89**, 43496 (1978).

[13] S. Murahashi, S. Horie, *Ann. Rept. Sci. Works, Fac. Sci. Osaka Univ.* **7**, 89 (1959); *C. A.* **54**, 24785 (1960).

[14] T. L. Cairns, D. D. Coffman, W. W. Gilbert, *J. Am. Chem. Soc.* **79**, 4405 (1957).

[15] R. L. Jacobs, *J. Heterocyclic Chem.* **7**, 1337 (1970).

[16] V. N. Choubey, *U. A. R. J. Chem.* **14**, 407 (1971); *C. A.* **77**, 88423 (1972).