Diheterocyclic Compounds from Dithiocarbamates and Derivatives Thereof. V. 4,4'-Dioxo-2,2'-dithioxo(dioxo)-6,6'-biquinazolines

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The title compounds **3**, **5** and **9** were synthesized in a one step procedure from dithiocarbamates **2** or dithiocarbonimidates **7** in medium to high yields. The usefulness of **2** and **7** as synthetic equivalents of unstable or unavailable isocyanates and isothiocyanates is also discussed.

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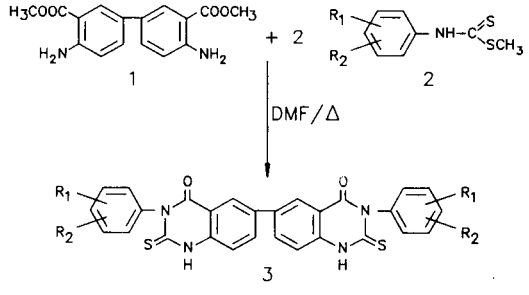
One of the most usual routes to 4-oxo-2-thioxoquinazolines and 2,4-dioxoquinazolines involves the reaction of anthranilic acid with isothiocyanates [1] or isocyanates [2] respectively. We have previously reported the usefulness of dithiocarbamates and dithiocarbonimidates as synthetic equivalents of isothiocyanates [3] and taking advantage of this we have developed a general method for the preparation of 4-oxo-2-thioxoquinazolines [4] and 2,4-dioxoquinazolines [5].

In this paper we report the reactivity of dithiocarbamic and dithiocarbonimidic acid esters with 4,4'-diamino-3,3'-biphenylylenedicarboxylic acid derivatives, namely **1**, **4** and **6**.

Thus, the reaction of dimethyl 4,4'-diamino-3,3'-biphenylylenedicarboxylate **1** [6] with methyl *N*-aryldithiocarbamates **2** [7] in refluxing dimethylformamide afforded compounds **3** in moderate to good yields (Scheme I) (Table 1).

Scheme I



Compound	a	b	c	d	e	f
R_1	H	H	H	H	H	3-CH_3
R_2	H	2-CH_3	4-CH_3	4-OCH_3	4-Cl	5-CH_3

The structure of compounds **3** was confirmed by an independent synthesis from arylisothiocyanates and 4,4'-diamino-3,3'-biphenylylenedicarboxylic acid **4** [6] as well as from their spectroscopical data. The ir spectra exhibited the C=O stretching band at 1710-1660 cm^{-1} and the

Table 1

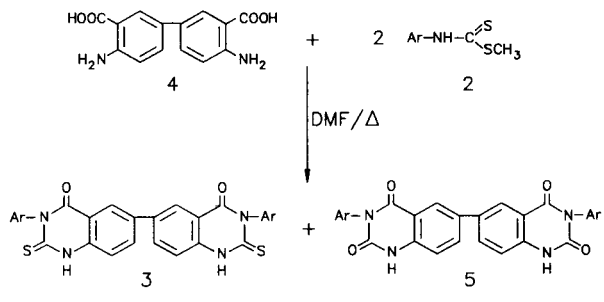
3,3'-Diaryl-4,4'-dioxo-2,2' dithioxo-6,6'-biquinazolines

Compound	mp (°C) (Recrystalization solvent)	Yield (%)
3a	>300 (DMF/EtOH)	74
3b	>300 (DMF)	46
3c	>300 (DMSO)	58
3d	>300 (DMF)	64
3e	>300 (DMSO)	46
3f	>300 (DMF)	61

^{1}H-nmr spectra showed a broad N-H singlet at δ 11-13 ppm as expected for such structures.

On the other hand, when dithiocarbamates **2** were made to react with **4** a partial decomposition was observed, hydrogen sulfide being evolved, and the reaction yielded a mixture of **3** and 2,2',4,4'-tetraoxo-6,6'-biquinazolines **5** (Scheme II). This was not observed in the reactions of **2** with anthranilic acids, which under the same conditions yielded 4-oxo-2-thioxoquinazolines as major products [4].

Scheme II

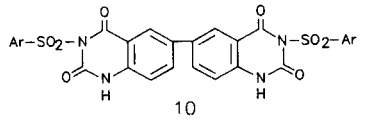


A different approach to the synthesis of **5**, which also makes use of dithiocarbamates **2** as starting materials, was used. Thus, when compounds **2** were made to react with dipotassium salt **6** in the presence of red mercury(II) oxide, compounds **5** were obtained in good yields (Scheme III) (Table 2). Dipotassium salt **6** was generated *in situ* by the addition of aqueous potassium hydroxide to a solution of diacid **4**. The reactions depicted in Scheme III took

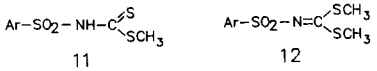
In a similar way, attempts were made to synthesize arylsulfonylquinazolones **10** by both the methods described above. The reaction of dithiocarbamates **11** with dipotassium salt **6** and red mercury(II) oxide under a variety of conditions resulted in decomposition products while dithiocarbonimidates **12** were not electrophilic enough to react with **6**, and under harsh conditions extensive decomposition was also observed.

This was not entirely unexpected since compounds **11** and **12** when treated with potassium anthranilate, only yielded 2,4-dioxoquinazolines in low yields [12].

Figure



10



11 12

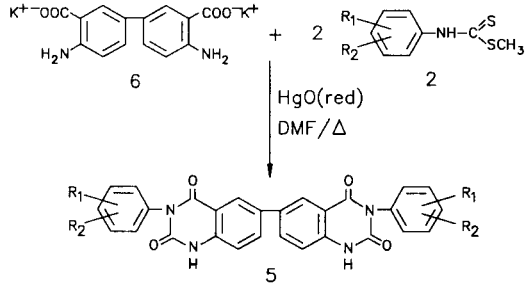
As reported [13], *N*-aryldithiocarbamates **2** are useful reagents to introduce arylamino groups while dithiocarbonimidates **7** are usually preferred when 2-benzothiazolylamino groups are to be introduced. Arenesulfonamide derivatives which allowed the synthesis of 2-aminobenzoazoles [13] and simple 2,4-dioxoquinazolines [12] were not suitable reagents for the preparation of biquinazolones **10**.

To sum up, the methods herein reported allow the synthesis of compounds **3**, **5** and **9** in a one-pot procedure involving the use of dithiocarbamates and dithiocarbonimidates which, in turn, are readily available from aromatic or heterocyclic amines. Furthermore, these methods avoid the use of unstable or unavailable isocyanates and isothiocyanates.

place in 12-14 hours in dimethylformamide.

The ir spectra of compounds **5** showed the C=O stretching bands at 1740-1700 and 1675-1640 cm^{-1} respectively in agreement with the values reported for 2,4-dioxoquinazolines [8], while in their ^{1}H-nmr spectra a broad N-H singlet appeared at δ 11-12 ppm [9].

Scheme III



R_1, R_2: as in Scheme I

Table 2

3,3'-Diaryl-2,2',4,4'-tetraoxo-6,6'-biquinazolines

Compound	mp (°C) (Recrystalization solvent)	Yield (%)
5a	>300(DMSO)	77
5b	>300 (MeOH/$CHCl_3$)	70
5c	>300(DMSO)	66
5d	>300(DMF)	72
5e	>300(DMF)	92
5f	>300 (DMF)	52

Table 3

3,3'-Bis(2-benzothiazolyl)-2,2',4,4'-tetraoxo-6,6'-biquinazolines

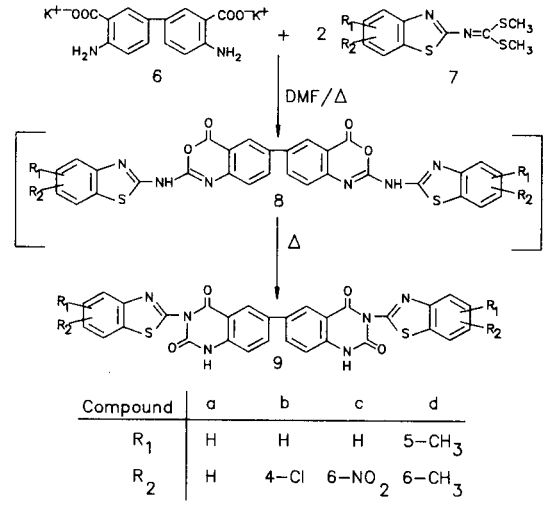
Compound	mp (°C) (Recrystalization solvent)	Yield (%)
9a	>300 (DMF)	40
9b	>300 (DMF)	70
9c	>300 (DMSO)	70
9d	>300 (DMF)	63

It is interesting to notice the versatility of dithiocarbamates **2** which can either behave as synthetic equivalents of isothiocyanates to yield **3** or, under desulfurizing conditions, yield compounds **5** which would otherwise require the use of unstable arylisocyanates.

A different approach was used in the synthesis of 3,3'-bis(2-benzothiazolyl)-2,2',4,4'-tetraoxo-6,6'-biquinazolines **9** which takes advantage of the high electrophilicity of dimethyl *N*-(2-benzothiazolyl)dithiocarbonimidates **7** (Scheme IV).

The reaction is supposed to involve the formation of benzoxazin-4-ones **8** [10] which at the reaction temperature (refluxing dimethylformamide) rearrange to **9** and cannot be isolated. The use of dithiocarbonimidates **7** constitutes a suitable method for the synthesis of 2,4-dioxoquinazolines, specially if we consider that 2-benzothiazolylisocyanates are unavailable [11].

Scheme IV



Compound	a	b	c	d
R_1	H	H	H	5-CH_3
R_2	H	4-Cl	6-NO_2	6-CH_3

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer FT 1600 instrument. The nmr spectra were recorded on a Bruker WP 80 CW spectrometer with TMS as internal reference.

Synthesis of 3,3'-diaryl-4,4'-dioxo-2,2'-dithioxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazolines **3**.

General Procedure.

To a solution of 1 mmole of dimethyl 4,4'-diamino-3,3'-biphenylylenedicarboxylate **1** in 5 ml of dimethylformamide a solution of 2 mmole of methyl *N*-aryldithiocarbamate **2** in 5 ml of dimethylformamide was added dropwise. The mixture thus obtained was refluxed until no more methylmercaptane was evolved (24-26 hours). After cooling, the mixture was filtered and the precipitate thus obtained was washed with ethanol, dried and recrystallized.

3,3'-Diphenyl-4,4'-dioxo-2,2'-dithioxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**3a**).

This compound had ir: 1660 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.0 (s, 1H), 8.3-8.0 (m, 2H), 7.6-7.2 (m, 6H).

Anal. Calcd. for $C_{28}H_{18}N_4O_2S_2$: C, 66.39; H, 3.58; N, 11.06. Found: C, 66.50; H, 3.43; N, 10.92.

3,3'-Bis(2-methylphenyl)-4,4'-dioxo-2,2'-dithioxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**3b**).

This compound had ir: 1705 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.0 (s, 1H), 8.3-8.1 (m, 2H), 7.6 (d, 1H, J = 8), 7.4-7.2 (m, 4H), 2.1 (s, 3H).

Anal. Calcd. for $C_{30}H_{22}N_4O_2S_2$: C, 67.40; H, 4.15; N, 10.48. Found: C, 67.52; H, 4.08; N, 10.37.

3,3'-Bis(4-methylphenyl)-4,4'-dioxo-2,2'-dithioxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**3c**).

This compound had ir: 1705 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 13.1 (s, 1H), 8.3-8.0 (m, 2H), 7.5 (d, 1H, J = 8), 7.3-7.0 (m, 4H), 2.4 (s, 3H).

Anal. Calcd. for $C_{30}H_{22}N_4O_2S_2$: C, 67.40; H, 4.15; N, 10.48. Found: C, 67.59; H, 4.04; N, 10.33.

3,3'-Bis(4-methoxyphenyl)-4,4'-dioxo-2,2'-dithioxo-1,1',2,2',3,3',-4,4'-octahydro-6,6'-biquinazoline (**3d**).

This compound had ir: 1710 cm^{-1}; ^{1}H-nmr: insoluble in all the usual solvents.

Anal. Calcd. for $C_{30}H_{22}N_4O_4S_2$: C, 63.59; H, 3.91; N, 9.89. Found: C, 63.74; H, 3.99; N, 10.01.

3,3'-Bis(4-chlorophenyl)-4,4'-dioxo-2,2'-dithioxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**3e**).

This compound had ir: 1710 cm^{-1}; ^{1}H-nmr: insoluble in all the usual solvents.

Anal. Calcd. for $C_{28}H_{16}Cl_2N_4O_2S_2$: C, 58.44; H, 2.80; N, 9.74. Found: C, 58.58; H, 2.94; N, 9.65.

3,3'-Bis(3,5-dimethylphenyl)-4,4'-dioxo-2,2'-dithioxo-1,1',2,2',3,3',-4,4'-octahydro-6,6'-biquinazoline (**3f**).

This compound had ir: 1710 cm^{-1}; ^{1}H-nmr: insoluble in all the usual solvents.

Anal. Calcd. for $C_{32}H_{26}N_4O_2S_2$: C, 68.30; H, 4.66; N, 9.96. Found: C, 68.41; H, 4.78; N, 9.76.

Synthesis of 3,3'-diaryl-2,2',4,4'-tetraoxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazolines **5**.

General Procedure.

To a solution of 2 mmoles of 4,4'-diamino-3,3'-biphenylylenedicarboxylic acid **4** in 5 ml of dimethylformamide, 0.4 ml of aqueous 10 *N* potassium hydroxide was added. The solution was stirred at room temperature for 15 minutes, and then 6 mmoles of red mercury(II) oxide and 4 mmoles of methyl *N*-aryldithiocarbamate **2** were added. The mixture was refluxed for 13 hours and then filtered in cold. The filtrate was poured into 100 ml of ice-cooled water and neutralized with acetic acid. The precipitate thus obtained was filtered, washed with water and recrystallized from the appropriate solvent.

3,3'-Diphenyl-2,2',4,4'-tetraoxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**5a**).

This compound had ir: 1715, 1660 cm^{-1}; ^{1}H-nmr (TFA): δ 8.52 (s, 1H), 8.2 (dd, 1H, J = 8, J' = 2), 7.7-7.3 (m, 6H).

Anal. Calcd. for $C_{28}H_{18}N_4O_4$: C, 70.88; H, 3.82; N, 11.81. Found: C, 71.11; H, 3.75; N, 11.65.

3,3'-Bis(2-methylphenyl)-2,2',4,4'-tetraoxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**5b**).

This compound had ir: 1715, 1665 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.7 (s, 1H), 8.3-7.9 (m, 2H), 7.5-7.2 (m, 5H), 2.0 (s, 3H).

Anal. Calcd. for $C_{30}H_{22}N_4O_4$: C, 71.70; H, 4.41; N, 11.15. Found: C, 71.93; H, 4.28; N, 11.01.

3,3'-Bis(4-methylphenyl)-2,2',4,4'-tetraoxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**5c**).

This compound had ir: 1715, 1660 cm^{-1}; ^{1}H-nmr (TFA): δ 8.6 (s, 1H), 8.2 (d, 1H, J = 8), 7.5-7.2 (m, 5H), 2.4 (s, 3H).

Anal. Calcd. for $C_{30}H_{22}N_4O_4$: C, 71.70; H, 4.41; N, 11.15. Found: C, 71.84; H, 4.51; N, 11.07.

3,3'-Bis(4-methoxyphenyl)-2,2',4,4'-tetraoxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**5d**).

This compound had ir: 1720, 1665 cm^{-1}; ^{1}H-nmr (TFA): δ 8.6 (s, 1H), 8.2 (d, 1H, J = 8), 7.6 (d, 1H, J = 8), 7.5-7.2 (m, 4H), 4.0 (s, 3H).

Anal. Calcd. for $C_{30}H_{22}N_4O_6$: C, 67.41; H, 4.15; N, 10.48. Found: C, 67.54; H, 4.04; N, 10.55.

3,3'-Bis(4-chlorophenyl)-2,2',4,4'-tetraoxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**5e**).

This compound had ir: 1740, 1640 cm^{-1}; ^{1}H-nmr: insoluble in all the usual solvents.

Anal. Calcd. for $C_{28}H_{16}Cl_2N_4O_4$: C, 61.89; H, 2.97; N, 10.31. Found: C, 61.76; H, 3.04; N, 10.12.

3,3'-Bis(3,5-dimethylphenyl)-2,2',4,4'-tetraoxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**5f**).

This compound had ir: 1700, 1675 cm^{-1}; ^{1}H-nmr (TFA): δ 8.6 (s, 1H), 8.2 (d, 1H, J = 8), 7.5 (d, 1H, J = 8), 7.2 (s, 1H), 6.9 (s, 2H), 2.3 (s, 6H).

Anal. Calcd. for $C_{32}H_{26}N_4O_4$: C, 72.44; H, 4.94; N, 10.56. Found: C, 72.68; H, 5.00; N, 10.64.

Synthesis of 3,3'-Bis(2-benzothiazoly)-2,2',4,4'-tetraoxo-1,1',2,2',-3,3',4,4'-octahydro-6,6'-biquinazolines **9**.

General Procedure.

To a solution of 2 mmoles of 4,4'-diamino-3,3'-biphenylylenedicarboxylic acid **4** in 5 ml of dimethylformamide, 0.4 ml of aqueous 10 *N* potassium hydroxide was added. The solution was stirred at room temperature for 15 minutes and then 4 mmoles of dimethyl *N*-(2-benzothiazolyl)dithicarbonimidate **7** in 5 ml of di-

methylformamide were added dropwise. The mixture thus obtained was refluxed until no more methylmercaptane was evolved (6-7 hours), cooled at room temperature and then 2 ml of acetic acid were added. The precipitate thus obtained was filtered, washed with ethanol, dried and recrystallized from the appropriate solvent.

3,3'-Bis(2-benzothiazolyl)-2,2',4,4'-tetraoxo-1,1',2,2',3,3',4,4'-octahydro-6,6'-biquinazoline (**9a**).

This compound had ir: 1715, 1665 cm^{-1}; ^1H-nmr: insoluble in all the usual solvents.

Anal. Calcd. for $C_{30}H_{16}N_6O_4S_2$: C, 61.22; H, 2.74; N, 14.28. Found: C, 61.43; H, 2.61; N, 14.35.

3,3'-Bis(4-chloro-2-benzothiazolyl)-2,2',4,4'-tetraoxo-1,1',2,2',3,3',-4,4'-octahydro-6,6'-biquinazoline (**9b**).

This compound had ir: 1730, 1680 cm^{-1}; ^1H-nmr (TFA): δ 8.7 (s, 1H), 8.2-7.6 (m, 5H).

Anal. Calcd. for $C_{30}H_{14}Cl_2N_6O_4S_2$: C, 54.80; H, 2.15; N, 12.78. Found: C, 54.73; H, 2.02; N, 12.58.

3,3'-Bis(6-nitro-2-benzothiazolyl)-2,2',4,4'-tetraoxo-1,1',2,2',3,3',-4,4'-octahydro-6,6'-biquinazoline (**9c**).

This compound had ir: 1740, 1700 cm^{-1}; ^1H-nmr: insoluble in all the usual solvent.

Anal. Calcd. for $C_{30}H_{14}N_8O_8S_2$: C, 53.10; H, 2.08; N, 16.51. Found: C, 53.24; H, 2.25; N, 16.42.

3,3'-Bis(5,6-dimethyl-2-benzothiazolyl)-2,2',4,4'-tetraoxo-1,1',2,2'-3,3',4,4'-octahydro-6,6'-biquinazoline (**9d**).

This compound had ir: 1740, 1675 cm^{-1}; ^1H-nmr (TFA): δ 8.7 (s, 1H), 8.0-7.8 (m, 4H), 2.5 (s, 6H).

Anal. Calcd. for $C_{34}H_{24}N_6O_4S_2$: C, 63.34; H, 3.75; N, 13.04. Found: C, 63.20; H, 3.58; N, 13.17.

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