Diheterocyclic Compounds from Dithiocarbamates and Derivatives Thereof. VI. Unsymmetrical N^1,N^4-Bis(2-benzazolyl)sulphanilamides

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The title compounds **9** are readily synthesized from dithiocarbamic acid derivative **5** by stepwise formation of the heterocyclic rings. Differences in reactivity of dithiocarbamates and dithiocarbonimidates make group protection unnecessary.

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We have previously reported the synthesis of bisbenzazoles from either aromatic [1] or heterocyclic [2] dithiocarbamates and dithiocarbonimidates using the corresponding diamines as starting materials. Nevertheless, these methods did not allow the preparation of unsymmetrical bisheterocycles because of the symmetry of the starting diamines.

Recently, we have reported a new methodology for a stepwise synthesis of bisheterocycles with two different heterocyclic rings attached to the central benzene ring in a protocol which involves the use of 4-nitroaniline as starting material, where the nitro group acts as a masked amino group [3].

We describe here a new approach to unsymmetrical bisbenzazoles which makes use of the different reactivity of the two -NH_2 moieties in sulphanilamide **1**, providing in this way a new entry to bis(benzazolyl)sulphanylamides **9**.

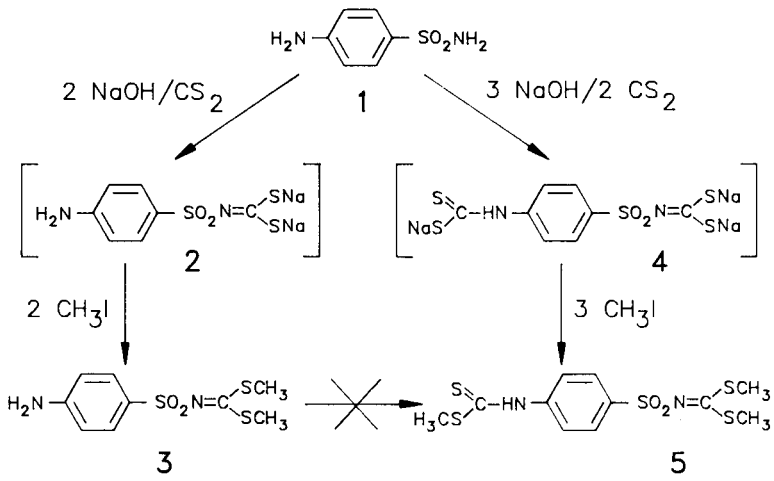
Thus, when **1** was sequentially treated with sodium hydroxide, carbon disulfide and iodomethane under the usual conditions [4] either dimethyl *N*-(4-aminophenylsulphonyl)dithiocarbonimidate **3** or dimethyl *N*-(4-methylthiothiocarbonylaminophenylsulphonyl)dithiocarbonimidate **5** was obtained depending on the stoichiometry (Scheme I). It is noteworthy that while compound **5** is readily obtained from **1** it cannot be synthesized from dithiocarbonimidate **3**.

Compound **3** was unreactive towards *o*-substituted anilines under a variety of conditions; however, when the nucleophilicity of *o*-aminothiophenol **6a** or *o*-aminophenol **6b** was enhanced by the addition of a base [5], 2-(4-aminophenylamino)benzazoles **7** were obtained in good yields (Scheme II) and in a very direct way when compared with previously reported methods which involved masking [6] or protection [7,8] of the amino group. Reaction of **3** with *o*-phenylenediamine could not be performed since the addition of sodium hydroxide caused, in this case, the hydrolysis of dithiocarbonimidate.

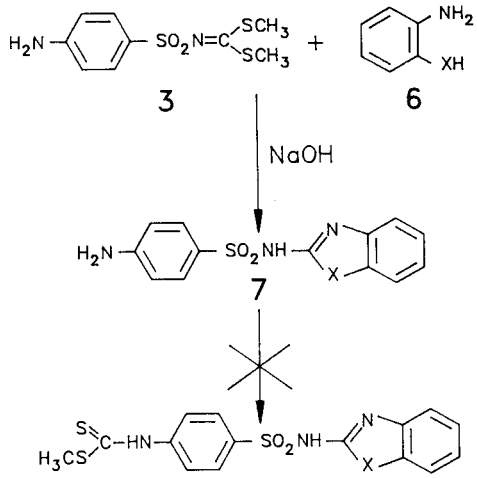
Attempts to transform the amino group of **7** in a dithiocarbamate group resulted in complex mixtures and hence this route to bisbenzazoles had to be abandoned.

On the other hand, compound **5** had already two dithiocarbamic acid derivatives in its structure and could lead to unsymmetrical bisbenzazoles if these groups showed a different reactivity.

Scheme I

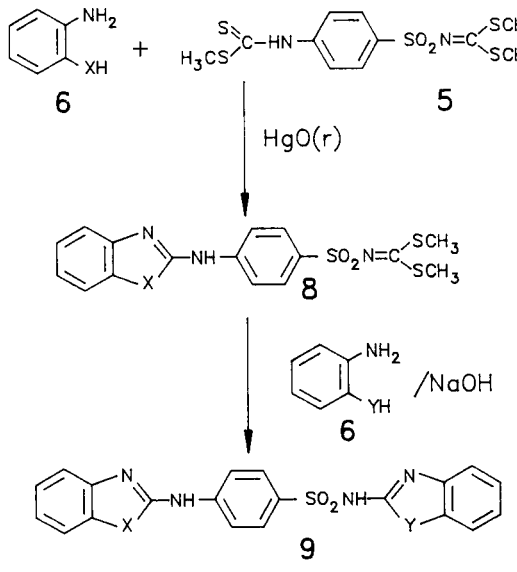


Scheme II



X	S	O
6,7	a	b

Scheme III



X = S, O, NH; Y = S, O.

In fact, when **5** was allowed to react with *o*-substituted anilines **6** in the presence of red mercury(II) oxide at 60-70°, the reaction occurred selectively at the dithiocarbamate centre, the dithiocarbonimidate group remaining unaltered (Scheme III). Reaction at higher temperatures resulted in partial decomposition, 2-mercaptobenzoazoles being formed [9], whilst below 60° extremely long reaction times were required.

Compounds **8** thus obtained showed a similar reactivity to **7** and reacted with *o*-aminothiophenol or *o*-aminophenol in basic medium affording unsymmetrical N^1,N^4-bis(2-benzazolyl)sulphanylamides **9** in yields ranging from 50 to 90% (Table).

Table

N^1,N^4-Bis(2-benzazolyl)sulphanilamides and their precursors

Compound	X	Y	Mp (°C) (Rec.)	Yield (%)
8a	S		182-184 (EtOH)	87
8b	O		218-220 (CH_3CN)	78
8c	NH		172-174 (EtOH)	84
9a	S	S	225-227 (EtOH)	50
9b	O	S	220-222 (CH_3CN)	70
9c	NH	S	248-250 (CH_3CN)	73
9d	S	O	228-232 (CH_3CN)	85
9e	O	O	228-230 (EtOH)	90
9f	NH	O	203-205 (EtOH)	70

To sum up, we have reported a three step synthesis of unsymmetrical bisbenzazoles taking advantage of the different reactivity of the dithiocarbamate and the dithiocarbonimidate groups in order to selectively construct the two heterocyclic rings. The usefulness of dithiocarbamates and dithiocarbonimidates in heterocyclic synthesis [10] makes this a suitable method to be employed in the synthesis of a wide variety of unsymmetrical systems.

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 ^{1}H nmr spectra were recorded on a Bruker WP 80 CW spectrometer with TMS as internal reference. Mass spectra were recorded on a HP 5995 spectrometer.

Dimethyl *N*-(4-Aminophenylsulphonyl)dithiocarbonimidate **3**.

To a solution of sulphanilamide **1** (17.2 g, 0.1 mole) in DMF (75 ml), aqueous 20 *M* sodium hydroxide (5.5 ml, 0.11 mole) was added with stirring at room temperature. After 10 minutes carbon disulfide (3.5 ml, 0.055 mole) was added and stirring was continued for 30 minutes. Then aqueous 20 *M* sodium hydroxide (3 ml, 0.06 mole) and carbon disulfide (1.8 ml, 0.0275 mole) were added. This operation was finally repeated 10 minutes later.

After 30 minutes the reaction was placed in an ice bath, methyl iodide (12.75 ml, 0.2 mole) was added dropwise and stirring was continued for 2 hours. The mixture was then poured into ice-cooled water (1000 ml) and the precipitate thus obtained was filtered, washed with water, dried and recrystallized from ethanol, yield (60%), mp 180-182°. The compound had ir (potassium bromide): 3460, 3370, 1590, 1480, 1140 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.5 (d, 2H, J = 8), 6.6 (d, 2H, J = 8), 6.0 (s, 2H), 2.5 (s, 6H); ms: (m/z) 276 (M^+, 12%), 156 (97%), 108 (58%), 92 (100%), 65 (94%), 46 (46%).

Anal. Calcd. for $C_9H_{12}N_2O_2S_3$: C, 39.11; H, 4.38; N, 10.14. Found: C, 39.37; H, 4.26; N, 10.28.

Dimethyl *N*-(4-Thiomethylthiocarbonylaminophenylsulphonyl)dithiocarbonimidate **5**.

To a solution of sulphanilamide **1** (17.2 g, 0.1 mole) in DMF (90 ml) aqueous 20 *M* sodium hydroxide (7.5 ml, 0.15 mole) was

added with stirring at room temperature. After 10 minutes carbon disulfide (6.4 ml, 0.1 mole) was added and stirring was continued for 15 minutes. Aqueous 20 *M* sodium hydroxide (3.75 ml, 0.075 mole) and carbon disulfide (3.2 ml, 0.05 mole) were successively added. After 30 minutes the reaction was placed in an ice bath, methyl iodide (19.12 ml, 0.3 mole) was added dropwise and stirring was continued for 2 hours. The mixture was poured into ice-cooled water (1000 ml) and the precipitate thus obtained was filtered, washed with water, dried and recrystallized from ethanol, yield (55%), mp 140-142°. This compound had ir (potassium bromide): 3200, 1590, 1460, 1135 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.9 (s, 1H), 8.0-7.8 (m, 4H), 2.5 (s, 6H), 2.3 (s, 3H); ms: m/z 318 (M^+-CH_3SH, 12%), 271 (26%), 245 (22%), 198 (100%), 134 (78%); 47 (79%).

Anal. Calcd. for $C_{11}H_{14}N_2O_2S_5$: C, 36.04; H, 3.85; N, 7.64. Found: C, 36.21; H, 4.02; N, 7.86.

Synthesis of N^1-(2-Benzazolyl)sulphanilamides **7**.

General Procedure.

A solution of the corresponding **6** (0.02 mole) in DMF (100 ml) was treated with aqueous 5 *M* sodium hydroxide (8 ml, 0.04 mole) at room temperature and the mixture was stirred for 15 minutes. Then a solution of **3** (5.2 g, 0.02 mole) in DMF (100 ml) was added dropwise and the mixture was refluxed until no more methylmercaptan was evolved (8 hours). After cooling, the mixture was neutralized with acetic acid and poured into ice-cooled water (800 ml). The precipitate thus obtained was filtered, washed with water, dried and recrystallized from an appropriate solvent.

N^1-(2-benzothiazolyl)sulphanilamide **7a**.

This compound was obtained in 71% yield, mp >300° dec, lit [6] 304-305°; ir (potassium bromide): 3460, 3360, 1630, 1470, 1140 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.0-7.0 (m, 6H), 6.6 (d, 2H, J = 8), 5.9 (s, 2H).

Anal. Calcd. for $C_{13}H_{11}N_3O_2S_2$: C, 51.13; H, 3.63; N, 13.76. Found: C, 51.27; H, 3.79; N, 13.85.

N^1-(2-Benzoxazolyl)sulphanilamide **7b**.

This compound was obtained in 75% yield, mp 280-284° dec; ir (potassium bromide): 3460, 3360, 1550, 1460, 1140 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.9-7.0 (m, 6H), 6.6 (d, 2H, J = 8), 5.9 (s, 2H).

Anal. Calcd. for $C_{13}H_{11}N_3O_3S$: C, 53.97; H, 3.83; N, 14.52. Found: C, 54.09; H, 3.76; N, 14.36.

Synthesis of Dimethyl *N*-[4-(2-Benzazolylamino)phenylsulphonyl]dithiocarbonimidates **8**.

General Procedure.

To a suspension of **6** (4 mmoles) and red mercury(II) oxide (4 mmoles) in DMF (15 ml) at 70°, **5** (1.46 g, 4 mmoles) in DMF (15 ml) was added dropwise and the mixture was maintained at 70° for 24 hours. After cooling the mixture was filtered off, and the filtrate was cooled in an ice bath and poured into water (300 ml). The precipitate thus obtained was filtered, washed with hydrochloric acid (*ca* 3%) dried and recrystallized.

Dimethyl *N*-[4-(2-Benzothiazolylamino)phenylsulphonyl]dithiocarbonimidate **8a**.

This compound had ir (potassium bromide): 3450-3290, 1570, 1450, 1145 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 10.9 (s, 1H), 8.2-7.6 (m, 4H), 7.5-7.1 (m, 4H), 2.5 (s, 6H).

Anal. Calcd. for $C_{16}H_{15}N_3O_2S_4$: C, 46.92; H, 3.69; N, 10.26. Found: C, 47.06; H, 3.81; N, 10.39.

Dimethyl *N*-[4-(2-Benzoxazolylamino)phenylsulphonyl]dithiocarbonimidate **8b**.

This compound had ir (potassium bromide): 3450-3200, 1569, 1474, 1140 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.1 (s, 1H), 7.9-7.8 (m, 4H), 7.7-7.2 (m, 4H), 2.5 (s, 6H).

Anal. Calcd. for $C_{16}H_{15}N_3O_3S_3$: C, 48.84; H, 3.84; N, 10.68. Found: C, 49.02; H, 4.01; N, 10.49.

Dimethyl *N*-[4-(2-Benzimidazolylamino)phenylsulphonyl]dithiocarbonimidate **8c**.

This compound had ir (potassium bromide): 3400-3000, 1580, 1470, 1150 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.2-7.2 (m, 5H), 2.5 (s, 3H).

Anal. Calcd. for $C_{16}H_{16}N_4O_2S_3$: C, 48.95; H, 4.10; N, 14.27. Found: C, 49.11; H, 4.21; N, 14.38.

Synthesis of N^1,N^4-Di(2-benzazolyl)sulphanilamides **9**.

General Procedure.

A solution of the corresponding **6** (1 mmole) in DMF (5 ml) was treated with aqueous 5 *M* sodium hydroxide (0.4 ml, 2 mmoles) at room temperature and the mixture was stirred for 15 minutes. Then a solution of the appropriate **8** (1 mmole) in DMF (5 ml) was added dropwise and the reaction mixture was refluxed until no more methylmercaptane was evolved (24 hours). After cooling the mixture was treated with acetic acid and poured into ice-cooled water (100 ml). The precipitate thus obtained was filtered, washed with ether, dried and recrystallized.

N^1,N^4-Di(2-benzothiazolyl)sulphanilamide **9a**.

This compound had ir (potassium bromide): 3500-3200, 1540, 1460, 1140 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.2 (s, 1H), 8.0-7.0 (m, 13H).

Anal. Calcd. for $C_{20}H_{14}N_4O_2S_3$: C, 54.78; H, 3.22; N, 12.78. Found; C, 54.56; H, 3.38; N, 12.91.

N^1-(2-Benzothiazolyl)-N^4-(2-benzoxazolyl)sulphanilamide **9b**.

This compound had ir (potassium bromide): 3500-2700, 1640, 1560, 1460, 1140 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.1 (s, 1H), 8.0-7.0 (m, 13H).

Anal. Calcd. for $C_{20}H_{14}N_4O_3S_2$: C, 56.86; H, 3.34; N, 13.26. Found: C, 57.01; H, 3.47; N, 13.14.

N^1-(2-Benzothiazolyl)-N^4-(2-benzimidazolyl)sulphanilamide **9c**.

This compound had ir (potassium bromide): 3600-2500, 1550, 1460, 1140 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.2 (s, 1H), 8.0-7.0 (m, 14H).

Anal. Calcd. for $C_{20}H_{15}N_5O_2S_2$: C, 56.99; H, 3.59; N, 16.62. Found: C, 57.16; H, 3.46; N, 16.52.

N^1-(2-Benzoxazolyl)-N^4-(2-benzothiazolyl)sulphanilamide **9d**.

This compound had ir (potassium bromide): 3600-2500, 1640, 1625, 1530, 1140 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 10.8 (s, 1H), 8.0-7.0 (m, 13H).

Anal. Calcd. for $C_{20}H_{14}N_4O_3S_2$: C, 56.86; H, 3.34; N, 13.26. Found: C, 56.98; H, 3.29; N, 13.39.

N^1,N^4-Di(2-benzoxazolyl)sulphanilamide **9e**.

This compound had ir (potassium bromide): 3500-3000, 1550,

1460, 1140 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 11.1 (s, 1H), 8.1-7.0 (m, 13H).

Anal. Calcd. for $C_{20}H_{14}N_4O_4S$: C, 59.11; H, 3.47; N, 13.79. Found: C, 59.38; H, 3.29; N, 13.92.

N^1-(2-Benzimidazolyl)-N^4-(2-benzoxazolyl)sulphanilamide **9f**.

This compound had ir (potassium bromide): 3500-2500, 1660, 1580, 1470, 1150 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.1 (s, 1H), 8.1-7.0 (m, 14H).

Anal. Calcd. for $C_{20}H_{15}N_5O_3S$: C, 59.25; H, 3.73; N, 17.27. Found: C, 59.41; H, 3.60; N, 17.13.

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