Intramolecular Oxidative Cyclizations in Heteroarylthioureas: A Versatile Pathway to Bridgehead Heterocyclic Systems

Ana Castro and Ana Martinez*

Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain

Received November 2, 1998

Intramolecular oxidations in *N*-alkyl-*N'*-heteroarylthioureas represent a facile and versatile synthetic pathway to fused heterocyclic systems including the bridgehead ones. This kind of heterocycles are the main feature in commom biologically active compounds.

J. Heterocyclic Chem., **36**, 991 (1999).

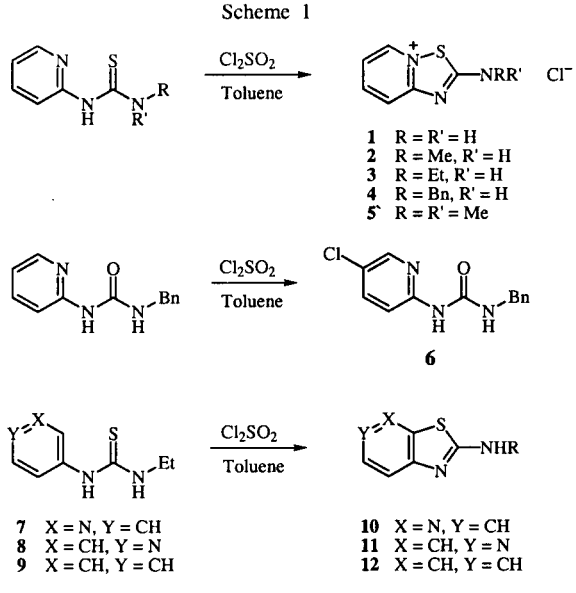
In our search of efficient synthetic pathways for biologically active compounds, [1,2] which involves in some cases enzymatic mediated synthesis [3,4], we have recently shown the high reactivity of 1,2,4-thiadiazolo-[2,3-*a*]pyridinium salts against electrophiles, which provides and efficient synthetic route to several heterocycles such as thiazolines, thiadiazolines and thiadiazolidin-3-ones carrying pyridylimino substituents [5]. Thiadiazolo heteroarylium salts are prepared by a facile oxidation reaction of heteroarylthioureas [6]. Whereas the oxidation of *N*-arylthioureas has been studied in some detail by a number of workers [7], the oxidation of *N*-heteroarylthioureas has received scant attention. Here, we report the regioselective intramolecular oxidation found in several heteroarylthioureas and their application to the synthesis of biologically active compounds.

1,2,4-Thiadiazolo[2,3-*a*]pyridinium salts are easily obtained from *N*-(2-pyridyl)-*N'*-alkylthioureas by treatment with sulphuryl chloride in toluene at room temperature [6] (Scheme 1). *N*-(2-pyridyl)- or *N*-(2-pyridyl)-*N'*-dialkylthioureas can be also used as starting material for the obtention of bridgehead heterocyclic salts (Scheme 1). Under these conditions, only one compound was detected as a white solid which precipitates from reaction medium. The isolated organic salts **1-5** are very stable and only in basic media show a high reactivity [8]. In the intramolecular oxidative cyclization the sulfur d orbitals are involved. When the analogous ureas (*i.e.* *N*-(2-pyridyl)-*N'*-benzylurea) are treated under the same conditios, no reaction was observed and only after 10 hours of toluene reflux, the compound chlorinated in the pyridine ring of **6** was isolated.

With the aim to study the scope of this reaction, *N*-(3-pyridyl)-, *N*-(4-pyridyl)- and *N*-(phenyl)-*N'*-ethylthioureas **7-9** were treated with oxidizing agents as sulphuryl chloride, thionyl chloride or sulfur chloride in toluene. In all cases, only one product of intramolecular oxidative cyclization was obtained, and the corresponding bicyclic derivatives of thiazolopyridine or benzothiazoles **10-12** were isolated in good yields (Scheme 1).

From the thiourea cyclization two products can be obtained, but none of the compound resulting from oxidation between sulfur and the aromatic carbon was detected.

Scheme 1



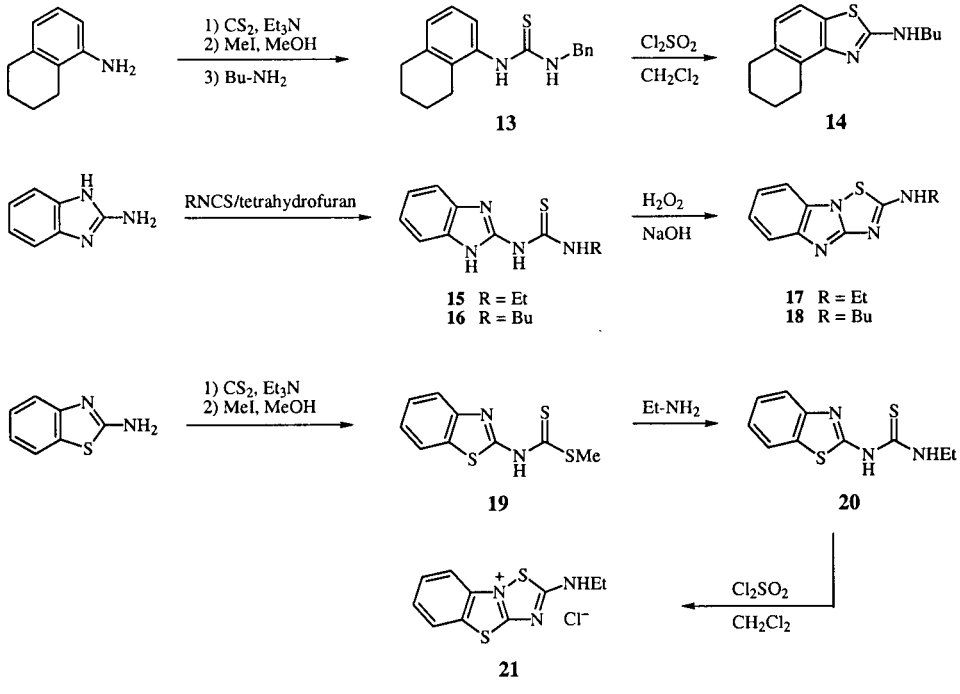
The regioselectivity found in this oxidative cyclizations shows that, if geometric requirements are present, the sulfur-nitrogen bond is formed preferently to sulfur-carbon one. Additionally, the carbon atom closer to an electronegative nucleous is the more appropiate for the regioselective formation of a sulfur-carbon bond.

The structure of all compounds were unequivocally elucidated on basis to their analytical and spectroscopic (^{1}H and ^{13}C nmr) data which are collected in the Experimental.

This kind of intramolecular cyclization was applied to the sythesis of new tricyclic derivatives (Scheme 2). The first one was the synthesis of thiazolonaphthalene compounds. Thus, 1-amino-5,6,7,8-tetrahydronaphthalene was treated with carbon disulfide, methyl iodide and 1-butylamine to yield in a three step reaction, the *N*-butyl-*N'*-(5,6,7,8-tetrahydronaphth-1-yl)thiourea **13**. Intramolecular oxidative cyclization was acomplished by treatment with sulphuryl chloride in dichloromethane, yielding the tricyclic compound **14**. On the other hand, starting from 2-aminobenzimidazole, *N*-alkyl-*N'*-(2-benzimadazolyl)thioureas were obtained by reaction with the corresponding alkyl isothiocyanates. In this case, cyclization to the bridgehead tricyclic

systems was performed by treatment of the heteroarylthioureas **15-16** with hydrogen peroxide in alkaline aqueous solution. The new thiadiazolobenzimidazole derivatives **17-18** were obtained in good yields. These new compounds were used as starting materials in the synthesis of new phosphodiesterase 4 inhibitors related to losartan [9] and new muscarinic agonists related to besipirdine [10].

Scheme 2



Finally, *N*-ethyl-*N'*-(2-benzothiazolyl)thiourea was obtained from 2-aminobenzothiazole following the same three step reaction mentioned above. The thioesther derivative **19** could be isolated in aceptable yield. Intramolecular oxidative cyclization of thiazolylthiourea **20** with sulphuryl choride provides regio selectively the new bridgehead charged system **21** derived from thiadiazolobenzothiazole.

In this paper, intramolecular regioselective oxidations in *N*-alkyl-*N'*-heteroarylthioureas has been revised, showing their efficient application in the synthesis of fused heterocyclic systems including the bridgehead systems.

EXPERIMENTAL

Melting points were determined with a Reichert-Jung Thermovar apparatus and are uncorrected. Reagents and solvents were purchased from common commercial suppliers and used without further purification. Flash column chomatography was carried out at medium pressure using silica gel (E. Merck, Grade 60, particle size 0.040-0.063 mm, 230-240 mesh ASTM) with the indicated solvent as eluent. The nmr spectra were recorded on Bruker AM-200 or Varian Gemini-200 spectrometers working at 200 and 50 MHz for ^1H and ^{13}C respectively. Chemical shifts are reported in δ values (ppm) relative to internal tetramethylsilane and J values are reported in Hertz. Elemental analyses were performed by the analytical departament at C.N.Q.O. (CSIC).

2-Amino-1,2,4-thiadiazolo[2,3-a]pyridinium Chloride (**1**).

N-(2-Pyridyl)thiourea [11] (0.46 g, 3.0 mmoles) was dissolved in dry toluene (20 ml) and stirred at room temperature during the dropwise addition of sulphuryl chloride (0.4 g, 3.0 mmoles). After 4 hours the product was collected by filtration and recrystallized from ethyl acetate/hexane to give **1** (0.49 g, 87%), mp 222-224° dec; ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 7.30 (t, $J_{H5,H6}$ = 8.0 Hz, 1H, H-5 pyr), 7.65 (dd, $J_{H3,H4}$ = 8.5 Hz, $J_{H3,H5}$ = 1.3 Hz, 1H, H-3pyr), 8.03 (td, $J_{H4,H5}$ = 8.0 Hz, $J_{H4,H6}$ = 1.4 Hz, 1H, H-4pyr), 9.04 (d, $J_{H5,H6}$ = 8.0 Hz, 1H, H-6 pyr), 9.74 (bs, 2H, NH_2); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 116.4, 116.5, 134.8, 140.4, 156.5 (C-3, C-5, C-4, C-6 and C-2 pyridine moiety), 172.8 (C-2 thiadiazole moiety).

Anal. Calcd. for $C_6H_6N_3ClS$: C, 38.41; H, 3.22; N, 22.39; S, 17.09; Cl, 18.89. Found: C, 38.11; H, 3.54; N, 22.69; S, 16.86; Cl, 18.52.

2-Dimethylamino-1,2,4-thiadiazolo[2,3-*a*]pyridinium Chloride (**5**).

N-(2-Pyridyl)-*N'*,*N'*-dimethylthiourea [11] (0.09 g, 0.5 mmole) was dissolved in dry toluene (15 ml) and stirred at room temperature during the dropwise addition of sulphuryl chloride (0.06 g, 0.5 mmole). The reaction mixture was stirred at room temperature for 12 hours. The product was collected by filtration and recrystallized from ethyl acetate/hexane to give **5** (0.07 g, 68%), mp 142-144°; ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 3.22 (s, 3H, NCH_3), 3.36 (s, 3H, NCH_3), 7.45 (t, $J_{H5,H6}$ = 7.6 Hz, 1H, H-5pyr), 7.84 (d, $J_{H3,H4}$ = 7.6 Hz, 1H, H-3 pyr), 8.17 (t, $J_{H4,H5}$ = 7.6 Hz, 1H, H-4 pyr), 9.27 (d, $J_{H5,H6}$ = 7.6 Hz, 1H, H-6 pyr); ^{13}C nmr

(hexadeuterated dimethyl sulfoxide): δ ppm 40.76, 42.22 (NCH_3), 117.3, 117.8, 136.9, 142.1, 159.6 (C-3, C-5, C-4, C- 6 and C-2 pyridine moiety), 172.2 (C-2 thiadiazole moiety).

Anal. Calcd. for $C_8H_{10}N_3ClS$: C, 44.55; H, 4.67; N, 19.48; S, 14.86; Cl, 16.44. Found: C, 44.32; H, 4.82; N, 19.7 1; S, 14.63; Cl, 16.24.

N-Benzyl-*N'*-(5-chloropyrid-2-yl)urea (**6**).

N-benzyl-*N'*-(2-pyridyl)urea [12] (1 g, 4.4 mmoles) was dissolved in dry toluene (30 ml) and stirred at room temperature during the dropwise addition of sulphuryl chloride (0.7 g, 5.3 mmoles). The reaction mixture was refluxed for 10 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was recrystallized from water/methanol to give **6** (0.7 g, 61%), mp 152°; ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 4.55 (d, $J_{CH2,NH}$ = 5.8 Hz, 2H, CH_2Ph), 6.78 (d, $J_{H6,H4}$ = 2.6 Hz, 1H, H-3), 7.20-7.32 (m, 5H, H-Ph), 7.44 (dd, $J_{H6,H4}$ = 2.6 Hz, $J_{H3,H4}$ = 8.8 Hz, 1H, H-4), 8.02 (d, $J_{H6,H4}$ = 2.6 Hz, 1 H, H-6), 9.50 (bs, 1H, NH), 9.55 (bt, 1H, NH); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 56.6 (*N*-CH_2), 113.4 (C-3), 123.8 (C-5), 127.1 (C*p*), 127.2 (C*o*), 128.5 (C*m*), 138.0 (C-4), 139.1 (C*i*), 144.3 (C-6), 151.9 (C-2), 156.6 (C=O).

Anal. Calcd. for $C_{13}H_{12}N_3OCl$: C, 59.66; H, 4.62; N, 16.06; Cl, 13.55. Found: C, 59.84; H, 4.55; N, 16.33; Cl, 13.32.

N-Ethyl-*N'*- (4-pyridyl) Thiourea (**8**).

A solution of ethyl thioisocyanate (1.7 g, 20 mmoles) and 4-aminopyridine (1.8 g, 20 mmoles) in toluene (50 ml) was refluxed for 24 hours. After cooling to room temperature, the solvent was evaporated *in vacuo* and the solid residue was recrystallized from ethyl acetate to give 8 (1.4 g, 42%) as white needles, mp 102°; ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 1.62 (t, J_{CH2CH3} = 7.1 Hz, 3H, CH_2CH_3), 3.57 (m, J_{CH2CH3} = 7.1 Hz, 2H, CH_2CH_3), 7.25 (m, 1 H, NH), 7.47 (d, $J_{H2,H3}$ = 6.3 Hz, 2H, H-2, H-6), 8.29 (d, $J_{H6,H5}$ = 6.3 Hz, 2H, H-3, H-5), 10.39 (bs, 1H, NH); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 13.6 (CH_3), 39.3 (CH_2), 115.3 (C-2, C-6), 147.2 (C1), 149.1 (C-3, C-5) 179.9 (C=S).

Anal. Calcd. for $C_8H_{11}N_3S$: C, 53.01; H, 6.12; N, 23.18; S, 17.69. Found: C, 53.30; H, 6.04; N, 23.38; S, 17.95.

2-Aminoethylthiazolo[5,4-*b*]pyridine (**10**).

To a solution of *N*-ethyl-*N'*-(3-pyridyl)thiourea [13] (0.25 g, 1.4 mmoles) in toluene (25 ml), sulphuryl chloride (0.18 g, 1.4 mmoles) was added dropwise. The reaction mixture was stirred at room temperature for 24 hours. The solid was collected by filtration and dissolved in water. The aqueous solution was neutralized with sodium bicarbonate and extracted with ethyl acetate (3 x 25 ml). The organic phase was dryed over sodium sulphate, the solvent was eliminated under reduced pressure and the solid was recrystallized from ethyl acetate/hexane to give **10** (0.24 g, 88%), mp 143° dec; ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 1.14 (t, J_{CH2CH3} = 7.1 Hz, 3H, CH_2CH_3), 3.56 (m, J_{CH2CH3} = 7.1 Hz, 2H, CH_2CH_3), 7.42 (dd, $J_{H6,H5}$ = 8.3 Hz, $J_{H6,H4}$ = 4.7 Hz, 1H, H-6), 7.92 (d, $J_{H4,H6}$ = 4.7 Hz, 1H, H-4), 8.32 (d, $J_{H5,H6}$ = 8.3 Hz, 1H, H-5), 10.27 (m, 1H, NH); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 15.3 (CH_3), 35.0 (CH_2), 123.9 (C-5), 126.7 (C-4), 136.8 (C-6), 140.2 (C-3a), 142.8 (C-7a), 156.2 (C-2).

Anal. Calcd. for $C_8H_9N_3S$: C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.42; H, 5.01; N, 23.78; S, 17.80.

2-Aminoethylthiazolo[4,5-*c*]pyridine (**11**).

To a solution of thiourea **7** (0.5 g, 2.8 mmoles) in toluene (25 ml), sulphuryl chloride (0.41 g, 3 mmoles) was added dropwise. The reaction mixture was stirred at room temperature for 24 hours. The solid was collected by filtration and recrystallized from ethyl acetate/hexane to give **11** (0.42 g, 85%) as yellow needles, mp 155° dec; ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 1.10 (t, J_{CH2CH3} 7.1 Hz, 3H, CH_2CH_3), 3.42 (m, J_{CH2CH3} = 7.1 Hz, 2H, CH_2CH_3), 8.30 (d, $J_{H4,H5}$ 6.7 Hz, 1H, H-4), 8.62 (d, $J_{H7,H5}$ = 1.4 Hz, 1H, H-7), 8.71 (d, $J_{H5,H4}$ = 6.7 Hz, $J_{H7,H5}$ = 1.4 Hz, 1H, H-5), 9.83 (m, 1H, NH); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 14.9 (CH_3), 34.1 (CH_2), 112.1 (C-4), 113.4 (C-5), 126.7 (C-4), 141.1 (C-7), 153.5 (C-7a), 154.1 (C-3a), 154.4 (C-2).

Anal. Calcd. for $C_8H_9N_3S$: C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.32; H, 5.16; N, 23.51; S, 17.63.

2-Aminoethylbenzothiazole (**12**).

To a solution of *N*-ethyl-*N'*-phenylthiourea [14] (0.3 g, 1.2 mmoles) in toluene (20 ml), sulphuryl chloride (0.02 g, 1.2 mmoles) was added dropwise. The reaction mixture was stirred at room temperature for 24 hours. The solid was collected by filtration and dissolved in water. The aqueous solution was neutralized with sodium bicarbonate and extracted with ethyl acetate (3 x 25 ml). The organic phase was dried over sodium sulphate, the solvent was eliminated under reduced pressure and the solid was recrystallized from ethyl acetate/hexane to give **12** (0.15 g, 72%), mp 92-94° (lit [15] 93-94°); ^1H nmr (hexadeuterated dimethyl sulfoxide): 1.27 (t, J_{CH2CH3} = 7.1 Hz, 3H, CH_2CH_3), 3.38 (m, J_{CH2CH3} = 7.1 Hz, 2H, CH_2CH_3), 6.90 (m, 1H, NH), 7.18 (m, $J_{H6,H7}$ = 8.0 Hz, $J_{H6,H4}$ = 1.4 Hz, 1H, H-6), 7.27 (m, $J_{H7,H5}$ = 1.4 Hz, $J_{H5,H4}$ = 7.7 Hz, 1H, H-5), 7.43 (d, $J_{H7,H6}$ = 8.0 Hz, 1H, H-7), 7.56 (dd, $J_{H4,H5}$ = 7.7 Hz, $J_{H6,H4}$ = 1.4 Hz, 1H, H-4); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 14.5 (CH_3), 40.1 (CH_2), 117.9 (C-6), 120.6 (C-7), 120.9 (C-5), 125.6 (C-4), 129.9 (C-3a), 152.0 (C-7a), 168.0 (C-2).

Anal. Calcd. for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.72; S, 17.99. Found: C, 60.38; H, 5.43; N, 15.62; S, 18.02.

N-Butyl-*N'*-(5,6,7,8-tetrahydronaphth-1-yl)thiourea (**13**).

A suspension of 1-aminotetraline (2.94 g, 20 mmoles), carbon disulfide (1.12 ml, 20 mmoles) and triethylamine (2.8 ml, 20 mmoles) was stirred at room temperature for 12 hours. After that time, methanol (25 ml) and methyl iodide (1.24 ml, 20 mmoles) were added. A white solid precipitated. The reaction mixture was stirred at room temperature for an additional 7 hours. Afterwards, the white solid was collected by filtration, dissolved in tetrahydrofuran (25 ml), and butylamine (1.4 g, 20 mmoles) was added to this solution. This new reaction mixture was stirred at room temperature for 20 hours. The solvent was eliminated under reduced pressure, and the residue was recrystallized from water to yield the thiourea **13** (5.1 g, 98%), mp 93-95°; ^1H nmr (deuterated chloroform): δ ppm 0.84 (t, $J_{CH2,CH3}$ = 7.3 Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.23 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.46 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.72 (m, 4H, CH_2), 2.59 (m, 2H, CH_2), 2.74 (m, 2H, CH_2), 3.53 (q, 2H, $NCH_2CH_2CH_2CH_3$), 5.67 (bs, 1H, NH), 7.01-7.14 (m, 2H, H-Ar), 7.67 (bs, 1H, NH); ^{13}C nmr (deuterated chloroform): δ ppm 13.6 (CH_3), 19.8, 22.4, 24.8, 29.5, 3 1.0 (CH_2), 45.0 (NCH_2), 124.4 (C-2), 126.3 (C-4), 129.2 (C-3), 134.0 (C-7a), 134.7 (C-4a), 139.8 (C-1), 180.5 (C=S).

Anal. Calcd. for $C_{15}H_{22}N_2S$: C, 68.66; H, 8.45; N, 10.68; S, 12.22. Found: C, 68.48; H, 8.43; N, 10.62; S, 12.02.

2-Butylamino-6,7,8,9-tetrahydronaphtho[1,2-*d*]thiazole (**14**).

Sulphuryl chloride (0.4 g, 3 mmoles) was added dropwise to a solution of heteroarylthiourea **13** (0.8 g, 3 mmoles) in dichloromethane (25 ml). After magnetic stirring 30 minutes at room temperature, the solution was washed with water (25 ml). The organic phase was separated and dried over sodium sulphate. The solvent was eliminated *in vacuo* and the residue was crystallized from water to give the fused heterocycle **14** (0.7 g, 93%) as a white crystalline solid, mp 103°; ^{1}H nmr (deuterated chloroform): δ ppm 0.86 (t, $J_{CH2,CH3}$ = 7.1 Hz, 3H, $NCH_2CH_2CH_2CH_3$), 1.35 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.56 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.93 (m, 4H, CH_2), 2.74 (m, 2H, CH_2), 2.94 (m, 2H, CH_2), 3.25 (q, 2H, $NCH_2CH_2CH_2CH_3$), 5.62 (bs, 1H, NH), 6.75 (d, $J_{H8,H9}$ = 8.1 Hz, H-8), 7.27 (d, $J_{H8,H9}$ = 8.1 Hz, H-9); ^{13}C nmr (deuterated chloroform): δ ppm 13.7 (CH_3), 19.9, 23.0, 23.1, 25.9, 29.5, 31.6 (CH_2), 45.5 (NCH_2), 117.4 (C-8), 122.5 (C-9), 127.7 (C-3b), 134.6 (C-7a), 150.9 (C-9a), 167.6 (C-3a), 172.4 (C-2).

Anal. Calcd. for $C_{15}H_{20}N_2S$: C, 69.19; H, 7.74; N, 10.76; S, 12.31. Found: C, 69.48; H, 7.54; N, 10.92; S, 12.67.

N-Ethyl-*N'*-(2-benzimidazolyl)thiourea (**15**).

Ethyl isothiocyanate (0.87 g, 10 mmoles) was added to a solution of 2-aminobenzimidazole (1.33g, 10 mmoles) in tetrahydrofuran (40 ml). The reaction mixture was refluxed for 20 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure, and the residue was recrystallized from methanol/water to give the thiourea **15** (0.85 g, 40%), mp 175-177°; ^{1}H nmr (deuterated chloroform): δ ppm 1.25 (t, $J_{CH2,CH3}$ = 6.3 Hz, 3H, CH_3), 3.61 (q, 2H, NCH_2), 7.12 (m, 2H, H-4, H-7), 7.29 (m, 2H, H-5, H-6) 10.09 (bs, 1H, NH); ^{13}C nmr (deuterated chloroform): δ ppm 13.9 (CH_3), 40.0 (NCH_2), 113.2 (C-4, C-7), 122.4 (C5, C-6), 135.0 (C-3a, C-7a), 148.3 (C-2), 178.2 (C=S).

Anal. Calcd. for $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43; S, 14.55. Found: C, 54.13; H, 5.83; N, 25.62; S, 14.74.

N-Butyl-*N'*-(2-benzimidazolyl)thiourea (**16**).

Butyl isothiocyanate (1.7 g, 10 mmoles) was added to a solution of 2-aminobenzimidazole (1.3 g, 10 mmoles) in tetrahydrofuran (40 ml). The reaction mixture was refluxed for 42 hours. After that time, the solvent was eliminated under reduced pressure, and the residue recrystallized from methanol/water to give thiourea **16** (0.89 g, 36%), mp 135-137°; ^{1}H nmr (deuterated chloroform): δ ppm 0.89 (t, $J_{CH2,CH3}$ = 7.2 Hz, 3H, CH_3), 1.39 (m, 2H, CH_2CH_3), 1.62 (m, 2H, NCH_2CH_2), 3.63 (q, 2H, NCH_2), 5.51 (bs, 1H, NH), 7.11 (m, 2H, H-4, H- 7), 7.29 (m, 2H, H-5, H-6) 10.42 (bs, 1H, NH); ^{13}C nmr (deuterated chloroform): 8 ppm 13.7 (CH_3), 20.1, 30.8 (CH_2), 45.1 (NCH_2), 113.4 (C-4, C-7), 122.5 (C-5, C-6), 132.3 (C-3a, C-7a), 148.3 (C-2), 17 8.6 (C=S).

Anal. Calcd. for $C_{12}H_{16}N_4S$: C, 58.04; H, 6.49; N, 22.56; S, 12.91. Found: C, 57.91; H, 6.43; N, 22.32; S, 12.78.

2-Ethylamino[1,2,4]thiadiazolo[2,3-*a*] benzimidazole (**17**).

Hydrogen peroxide (1 ml) was added dropwise to a solution of thiourea **15** (0.4 g, 2 mmoles) in sodium hydroxide 2*N* (25 ml) previously cooled at 0° by an external ice-bath. The reaction mixture was stirred at 0° for 2 hours. After that time, the solution was neutralized with concentrated hydrogen chloride. A white solid appeared that was collected by filtration, recrystallized from methanol/water to give compound **17** (0.43 g, 99%), mp >220°; ^{1}H nmr (deuterated chloroform): δ ppm 1.05 (t, $J_{CH2,CH3}$ = 6.1 Hz, 3H, CH_3); 3.17 (m, 2H, NCH_2), 7.19 (m, 2H, H-5, H-8), 7.44 (m, 2H, H-6, H-7); ^{13}C nmr (deuterated chloroform): δ ppm 15.5 (CH_3), 35.2 (CH_2), 113.7 (C-5, C-8), 124.0 (C-6, C-7), 131.7 (C-4a, C-8a), 146.3 (C-2), 153.4 (C-3a).

Anal. Calcd. for $C_{10}H_{10}N_4S$: C, 55.03; H, 4.62; N, 25.67; S, 14.69. Found: C, 55.32; H, 4.43; N, 25.34; S, 14.21.

2-Butylamino[1,2,4]thiadiazolo[2,3-*a*]benzimidazole (**18**).

Hydrogen peroxide (1 ml) was added dropwise to a solution of thiourea **16** (0.5 g, 2 mmoles) in sodium hydroxide 2*N* (5 ml) previously cooled at 0° by an external ice-bath. The reaction mixture was stirred at 0° for 2 hours. After that time, the solution was neutralized with concentrated hydrogen chloride. A white solid appeared that was collected by filtration, recrystallized from methanol/water to give compound **18** (0.42 g, 84%), mp 132°; ^{1}H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 0.86 (t, $J_{CH2,CH3}$ = 7.1 Hz, 3H, CH_3), 1.30 (m, 2H, CH_2CH_3), 1.42 (m, 2H, NCH_2CH_2), 3.15 (m, 2H, NCH_2), 7.00 (m, 2H, H-5, H-8), 7.32 (m, 2H, H-6, H-7); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 13.8 (CH_3), 19.6, 31.5 (CH_2), 40.7 (NCH_2), 113.2 (C-5, C-8), 122.6 (C-6, C-7), 132.6 (C-4a, C-8a), 146.4 (C-2), 153.4 (C-3a).

Anal. Calcd. for $C_{12}H_{14}N_4S$: C, 58.51; H, 5.73; N, 22.74; S, 13.02. Found: C, 58.73; H, 5.78; N, 23.01; S, 12.94.

S-Methyl *N*-(2-Benzothiazolyl)dithiocarbamate (**19**).

A suspension of 2-aminobenzothiazole (1.50 g, 10 mmoles), carbon disulfide (0.76 ml, 10 mmoles) and triethylamine (1.4 ml, 10 mmoles) in ethyl ether (25 ml) was stirred at room temperature for 24 hours. The solvent was eliminated under reduced pressure and the yellow solid obtained was dissolved in methanol (25 ml). Methyl iodide (0.7 ml, 10 mmoles) was added to this solution. The reaction mixture was stirred at room temperature for an additional 24 hours. The solvent was evaporated *in vacuo* and the residue was crystallized from water to yield the thioesther **19** (0.8 g, 50%), mp 80-81°; ^{1}H nmr (deuterated chloroform): δ ppm 3.46 (s, 3H, SCH_3), 5.69 (bs, 1H, NH), 7.11 (t, $J_{H5,H4}$ = 8.0 Hz, 1H, H-5), 7.29 (t, $J_{H6,H7}$ = 8.5 Hz, 1H, H-6), 7.57 (d, $J_{H6,H7}$ = 8.5 Hz, 1H, H-7), 7.61 (d, $J_{H5,H4}$ = 8.0 Hz, 1H, H-4); ^{13}C nmr (deuterated chloroform): δ ppm 22.4 (SCH_3), 119.3 (C-7), 120.8 (C-4), 122.4 (C-6), 124.3 (C-5), 130.4 (C-7a), 152.3 (C-3a), 166.1 (C-2), 174.1 (C=S).

Anal. Calcd. for $C_9H_8N_2S_3$: C, 44.97; H, 3.35; N, 11.65; S, 40.02. Found: C, 45.28; H, 3.43; N, 11.62; S, 40.12.

N-Ethyl-*N'*-(2-benzothiazolyl)thiourea (**20**).

Ethylamine (0.15 g, 3.5 mmoles) was added to a solution of thiocarbamate **19** (0.85 g, 3.5 mmoles) in tetrahydrofuran (25 ml). The reaction mixture was stirred at room temperature for 24 hours. The solvent was eliminated under reduced pressure, and the residue was recrystallized from methanol/water to yield the thiourea **20** (0.7 g, 85%), mp 190-192°; ^{1}H nmr (deuterated chloroform): δ ppm 1.34 (t, $J_{CH2,CH3}$ = 7.3 Hz, 3H, CH_3), 3.78 (q, $J_{CH2,CH3}$ = 7.3 Hz, 2H, CH_2), 7.20 (t, $J_{H5,H4}$ = 7.7 Hz, 1H, H-5), 7.34 (t, $J_{H6,H7}$ = 7.9 Hz, 1H, H-6), 7.61 (d, $J_{H6,H7}$ = 7.9 Hz, 1H, H-7), 7.65 (d, $J_{H5,H4}$ = 7.7 Hz, 1H, H-4), 11.08 (bs, 1H, NH); ^{13}C nmr (deuterated chloroform): δ ppm 13.9 (CH_3), 40.5 (CH_2), 120.5 (C-7), 121.1 (C-4), 124.2 (C-6), 125.3 (C-5), 129.8 (C-7a), 149.4 (C-3a), 160.3 (C-2), 177.5 (C=S).

Anal. Calcd. for $C_{10}H_{11}N_3$ S 2: C, 50.61; H, 4.67; N, 17.70; S, 27.02. Found: C, 50.48; H, 4.43; N, 17.62; S, 26.87.

2-Aminoethyl[1,2,4]thiadiazolo[3,2-*b*]benzothiazolium Chloride (**21**).

Sulphuryl chloride (0. 13 g, 1 mmole) was added dropwise to a solution of thiourea 20 (0.15 g, 1 mmole) in dichloromethane (20 ml). The reaction mixture was stirred at room temperature for 24 hours. The solvent was eliminated under reduced pressure and the residue was recristallyzed from ethyl acetate to yield compound **21** (0.07 g, 41%) as a white crystalline solid, mp 110°; ^{1}H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 1.01 (t, $J_{CH2,CH3}$ = 7.2 Hz, 3H, CH_3), 3.12 (q, $J_{CH2,CH3}$ = 7.2 Hz, 2H, CH_2), 7.17 (t, $J_{H7,H8}$ = 7.8 Hz, 1H, H-7), 7.32 (t, $J_{H6,H5}$ = 7.9 Hz, 1H, H-6), 7.55 (d, $J_{H6,H5}$ = 7.9 Hz, 1H, H-5), 7.74. (d, $J_{H7,H8}$ = 7.7 Hz, 1H, H-8); ^{13}C nmr (hexadeuterated diimethylsulfoxide): δ ppm 15.5 (CH_3), 35.2 (CH_2), 119.4 (C-5), 122.2 (C-8), 124.1 (C-6), 127.0 (C-7), 130.9 (C-4a), 147.0 (C-8a), 154.2 (C-3a), 161.5 (C-2).

Anal. Calcd. for $C_{10}H_{10}N_3S_2Cl$: C, 44.19; H, 3.71; N, 15.46; S, 23.59; Cl, 13.04. Found: C, 43.87; H, 3.89; N, 15.21; S, 23.88; Cl, 12.94.

Acknowledgement.

This work was financially supported by CYCIT (project no. SAF 96/107).

REFERENCES AND NOTES

[1] A. Castro, A. Martinez, I. Cardelús, and J. Llenas, *Bioorg. Med. Chem.*, **2**, 179 (1995).

[2] A. Martinez, A. Castro, I. Cardelús, J. Llenas, and J. M. Palacios, Bioorg. Med. Chem., 5, 1274 (1997).

[3] A. I. Esteban, O. Juanes, S. Conde, and A. Martinez, Tetrahedron, 50, 13865 (1994).

[4] S. Conde, P. Lopez-Serrano, M. Fierros, M. I. Biezma, and M. I. Rodriguez, and A. Martinez, Tetrahedron, 53, 11745 (1997).

[5] A. Martinez, A. Castro, M. Martinez-Ripoll, I. Fonseca, F. H. Cano, and A. Albert, Heterocycles, 43, 2657 (1996).

[6] A. Martinez and A. Castro, Heterocycles, 38, 1737 (1994).

[7] T. Griffin, T. Woods, and D. Klayman, Adv. Heterocyclic Chem., 18, 99 (1975).

[8] A. Martinez, A. Castro, and J. P. Fayet, J. Heterocyclic Chem., 34, 337 (1997).

[9] V. Segarra, M. I. Crespo, F. Pujol, J. Beleta, T. Domenech, M. Miralpeix, J. M. Palacios, A. Castro, and A. Martinez, Bioorg. Med. Chem. Letters, 8, 505, (1998).

[10] I. Dorronsoro, M. I. Rodriguez-Franco, and A. Martinez, Abstract P-51, X Congreso de la Sociedad Española de Química Terapéutica, Oviedo, September 1997.

[11] M. Nagano, M. Oshige, T. Kinoshita, T. Matoui, and J. Tobitska, Chem. Pharm. Bull., 25, 993 (1974).

[12] G. E. Novikov, K. D. Shvestsova, N. N. Melnikov, and A. P. Makykhin, Khim. Geterotsikl. Soedin., 263 (1967); Chem. Abstr., 70, 77727v.

[13] S. Tanaka, Agric. Biol. Chem., 41, 1953 (1977).

[14] J. Ettlinger and H. Lundeen, J. Am. Soc., 78, 1952 (1956).

[15] H. Farooq, J. Indian Chem., 10, 189 (1933).