

SYNTHESIS OF 6-SUBSTITUTED IMIDAZO[4,5-*c*]PYRAZOLE-5-THIONES

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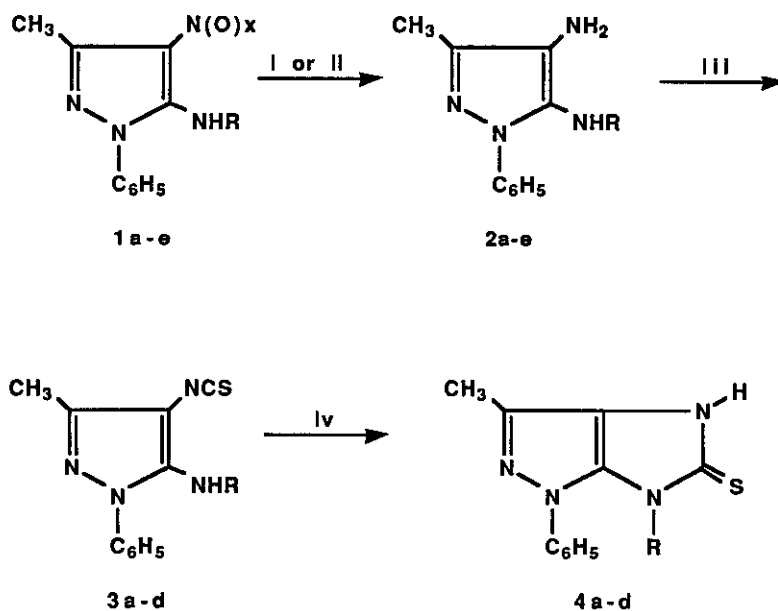
Abstract- Treatment of diaminopyrazole derivatives (**2**) with thiophosgene afforded selectively the isothiocyanatopyrazoles (**3**). Heating of **3** in pyridine gave the imidazo[4,5-*c*]pyrazole-5-thiones (**4**).

There is a paucity on the literature¹⁻⁷ concerning the synthesis and biological activity of imidazo[4,5-*c*]pyrazoles. Apart from a few patents that are claimed to provide particular derivatives employed as photographic couplers, the synthetic approaches up to now available are restricted to the following: a) the Curtius rearrangement followed by cyclization of 4-carbonylazido-5-aminopyrazoles,¹ b) the cyclization of 4-nitro-5-benzylaminopyrazoles,² c) the reaction of 4,5-diaminopyrazoles with carbon disulfide³ or with 2-methoxybenzoic acid⁴ and d) the cycloaddition of diazomethane onto 5-nitroimidazoles.⁵ The only pharmacological evaluation of this class of compounds was made by Barraclough *et al.*⁴ which reported that some imidazo[4,5-*c*]pyrazoles are inotropic agents more potent than the reference sulmazole. In previous researches in this area,⁶ we proved that the intramolecular cyclodehydration of 5-alkylamino-4-nitrosopyrazoles constitutes an efficient method for the synthesis of 5-substituted imidazo[4,5-*c*]pyrazoles. By applying the above procedure, we have prepared a series of homologues which in tests for biological evaluation showed interesting properties as CNS depressants.⁷ In order to better evaluate the structural requirements for activity, a procedure for the regioselective functionalization of position 6 became the target of our synthetic efforts. The present paper describes a general route to imidazo[4,5-*c*]pyrazole-5-thiones in which the nitrogen atom in position 6 can be selectively linked to acyl, aryl and acylamino groups.

The key intermediates to the target products were the isothiocyanates (**3**) (see Scheme). The intermediates (**3a-c**) were prepared from the corresponding nitrosopyrazolylamines (**1a-c**), which were reduced with hydrazine hydrate in the presence of palladized charcoal to the diamines (**2a-c**). These compounds were

isolated as colorless crystalline solids, quite stable if stored at 4°C *in vacuo* over phosphorus pentoxide. The successive treatment of 2a-c with thiophosgene afforded the isothiocyanates (3a-c) as the lone reaction products; the selectivity of the thiophosgene attack is due to the higher nucleophilicity of the pyrazole 4-amino group in comparison with that in position 5.⁸

Scheme



For compounds (1):

	x	R
a	1	H
b	1	COC ₆ H ₅
c	1	CH ₂ C ₆ H ₅
d	2	NHCOC ₆ H ₅
e	2	NH ₂

For compounds (2-4):

	R
a	H
b	COC ₆ H ₅
c	CH ₂ C ₆ H ₅
d	NHCOC ₆ H ₅
e	NH ₂

For x=1: I, 5% C/Pd, N₂H₄; for x=2: II, 5% C/Pd, H₂, 50 psi; III, CSCI₂; IV, Reflux, pyridine.

The isothiocyanate (3d) was obtained starting from nitropyrazolylhydrazine (1e), prepared according to the literature method.⁹ Compound (1e) was acylated with benzoyl chloride to the hydrazide (1d) which was hydrogenated in the presence of palladized charcoal to give the *N*-(4-amino-5-pyrazolyl)-*N'*-benzoylhydrazine (2d). Since 2d was unstable during the usual work-up for isolation, it was directly reacted with thiophosgene

to give selectively the isothiocyanate (3d). Finally, when 1e was submitted to catalytic reduction and then treated with thiophosgene under the same conditions followed for the synthesis of 3d, the reaction product was the 4-isothiocyanato-3-methyl-1-phenyl-1*H*-pyrazol-5-ylamine (3a), identical to the product obtained from the reaction of 2a with thiophosgene.

The intramolecular cyclization of all isothiocyanates (3a-d) was performed by heating under reflux in pyridine; the yields of the target imidazo[4,5-c]pyrazole-5-thiones (4a-d) ranged from good to quantitative. The proposed structures were supported by analytical and spectral data. A particular attention was paid to the product (4d), given that its nmr spectra could not exclude the structure of pyrazolo[4,3-*e*][1,2,4]triazine-5-thione deriving from a hypothetical alternative cyclization of 3d. For the definitive assignment, a single-crystal X-ray analysis was performed on a sample of 4d recrystallized from methanol-hexane. It is worthwhile noting that the melting point of our product (4a) resulted quite different from that reported by other authors,³ who claimed to have obtained the same compound by reacting 2a with carbon disulfide: anyway the structure proposed by these authors was not supported by spectral data.

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded from potassium bromide discs on a Perkin-Elmer 299B spectrophotometer. The ¹H nmr and ¹³C nmr spectra were recorded on a Bruker AC 200 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as internal standard. Column chromatography was performed using Merck silica gel (70-230 mesh); for flash chromatography technique silica gel (230-400 mesh) was employed. Compounds (1c), (1e) and (2b) were prepared according to the reported procedures.^{6,9,10}

Procedure for the synthesis of diamines (2a,c).

99% Hydrazine hydrate (0.98 ml, 20 mmol) and 5% palladized charcoal (0.30 g) were added to a solution of each nitrosopyrazolylamine (1a,c) (4 mmol) in methanol (50 ml). After heating under reflux for 5 min, the catalyst was removed and the filtrate was evaporated to dryness *in vacuo*. The resulting solid was purified by flash chromatography or by recrystallization from the indicated solvent.

3-Methyl-1-phenyl-1*H*-pyrazol-4,5-yl diamine (2a).

Colorless crystals, yield 89%, mp 120.5-121.5°C (ligroin) (lit.,³ 119-121°C); ir (KBr): 3350-3100 (br), 1650, 1600, 1500 cm⁻¹; ¹H nmr (DMSO-*d*₆) δ: 2.02 (s, 3H, Me), 3.19 (br s, 2H, NH₂), 4.57 (br s, 2H, NH₂), 7.18-7.63 (m, 5H, Ph).

4-Amino-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzylamine (2c).

Colorless crystals from flash chromatography (eluent: 8:2 ethyl acetate/petroleum ether); yield 78%, mp 82-83°C (ethyl acetate/petroleum ether); ir (KBr): 3400, 3320, 1610, 1510 cm⁻¹; ¹H nmr (DMSO-*d*₆) δ: 2.04 (s, 3H, Me), 3.42 (br s, 2H, NH₂), 3.87 (d, J=6.8 Hz, 2H, CH₂), 4.87 (t, J=6.8 Hz, 1H, NH), 7.20-7.72 (m, 10H, 2Ph). Anal. Calcd for C₁₇H₁₈N₄: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.60; H, 6.47; N, 20.28.

Procedure for the synthesis of isothiocyanates (3a-c)

Thiophosgene (0.23 ml, 3 mmol) was added dropwise to a suspension or solution of **2a-c** (3 mmol) in water (15 ml). After 2 h stirring at room temperature, the white precipitate was collected, washed with water and dissolved in ethyl acetate. After drying over anhydrous magnesium sulfate, the solvent was removed to give a solid which was recrystallized from the indicated solvent.

4-Isothiocyanato-3-methyl-1-phenyl-1*H*-pyrazol-5-ylamine (3a).

Pale yellow crystals, yield 86%, mp 163-164°C (ethyl acetate/petroleum ether); ir (KBr): 3410, 3290, 3100 (br), 2150, 1640, 1600, 1530, 1500 cm⁻¹; ¹H nmr (DMSO-d₆) δ: 2.14 (s, 3H, Me), 6.10 (br s, 2H, NH₂), 7.34-7.50 (m, 5H, Ph). Anal. Calcd for C₁₁H₁₀N₄S: C, 57.37; H, 4.38; N, 24.33, S, 13.92. Found: C, 57.22; H, 4.42; N, 24.21, S, 13.80.

***N*-(4-Isothiocyanato-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)benzamide (3b).**

Colorless crystals, yield 94%, mp 165-166°C (ethyl acetate/petroleum ether); ir (KBr): 3200 (br), 2100, 1650, 1590, 1500 cm⁻¹; ¹H nmr (DMSO-d₆) δ: 2.31 (s, 3H, Me), 7.48-7.91 (m, 10H, 2Ph), 10.72 (br s, 1H, NH). Anal. Calcd for C₁₈H₁₄N₄OS: C, 64.65; H, 4.22; N, 16.75, S, 9.59. Found: C, 64.60; H, 4.32; N, 16.64, S, 9.48.

4-Isothiocyanato-3-methyl-1-phenyl-1*H*-pyrazol-5-ylbenzylamine (3c).

Colorless crystals, yield 84%, mp 66-67°C (methanol/water); ir (KBr): 3250, 2100, 1600, 1540, 1500 cm⁻¹; ¹H nmr (CDCl₃) δ: 2.26 (s, 3H, Me), 4.15 (br t, 1H, NH), 4.43 (d, J=7.0 Hz, 2H, CH₂), 7.27-7.42 (m, 10H, 2Ph). Anal. Calcd for C₁₈H₁₆N₄S: C, 67.48; H, 5.03; N, 17.49, S, 10.01. Found: C, 67.60; H, 5.12; N, 17.64, S, 9.88.

Synthesis of *N*-(3-methyl-4-nitro-1-phenyl-1*H*-pyrazol-5-yl)-*N'*-benzoylhydrazine (1d).

A solution of benzoyl chloride (0.35 ml, 3 mmol) in ethyl acetate (20 ml) was added dropwise to a mixture of **1e** (0.70 g, 3 mmol) in ethyl acetate (120 ml) and sodium hydrogen carbonate (0.25 g, 3 mmol) in water (25 ml). After 1 h stirring at room temperature the organic phase was washed with water and then dried over anhydrous magnesium sulfate. The solvent was evaporated to leave a crude white product which was recrystallized from toluene. Yield 0.89 g, 88%, mp 169-171°C; ir (KBr): 3350, 3220 (br), 1680, 1600, 1530 cm⁻¹; ¹H nmr (DMSO-d₆) δ: 2.42 (s, 3H, Me), 7.13-7.43 (m, 10H, 2Ph), 9.40 (br s, 1H, NH), 10.35 (br s, 1H, NH). Anal. Calcd for C₁₇H₁₅N₅O₃: C, 60.53; H, 4.48; N, 20.76. Found: C, 60.70; H, 4.47; N, 20.68.

Synthesis of *N*-(4-isothiocyanato-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-*N'*-benzoylhydrazine (3d).

N-(3-Methyl-4-nitro-1-phenyl-1*H*-pyrazol-5-yl)-*N'*-benzoylhydrazine (**1d**) (1.01 g, 3 mmol) in methanol (11 ml) was hydrogenated under 50 psi in the presence of 5% Pd/C (0.23 g) for 5 h. The mixture was rapidly filtered through Celite and the solvent evaporated. The crude product was suspended in water (15 ml) and thiophosgene (0.23 ml, 3 mmol) was added dropwise to the suspension. After 2 h stirring at room temperature, the white precipitate was collected, washed with water and dissolved in ethyl acetate. After drying over anhydrous magnesium sulfate, the solvent was removed to give a solid which was recrystallized from the indicated solvent.

Pale yellow crystals, yield 75%, mp 189°C (ethyl acetate/petroleum ether); ir (KBr): 3210, 2100, 1650, 1550 cm⁻¹; ¹H nmr (DMSO-d₆) δ: 2.18 (s, 3H, Me), 7.35-7.90 (m, 10H, 2Ph), 8.58 (br s, 1H, NH), 10.70 (br s,

1H, NH). Anal. Calcd for C₁₈H₁₅N₅OS: C, 61.88; H, 4.33; N, 20.04, S, 9.18. Found: C, 61.70; H, 4.37; N, 20.08, S, 9.10.

Reduction and treatment with thiophosgene of 1e.

A solution of 3-methyl-4-nitro-1-phenyl-1*H*-pyrazol-5-ylhydrazine (1e) (0.70 g, 3 mmol) in methanol (50 ml) was hydrogenated for 1 h and treated with thiophosgene (0.23 ml, 3 mmol) under the same conditions followed for the synthesis of 3d.

Pale yellow crystals, yield 52%, mp 163-164°C (ethyl acetate/petroleum ether). The product was identical to compound (3a) obtained from the reaction of 2a with thiophosgene.

Procedure for the synthesis of imidazo[4,5-*c*]pyrazole-5-thiones (4a-d).

A solution of each 4-isothiocyanatopyrazole(3)(1 mmol) in pyridine (35 ml) was heated under reflux until the intramolecular cyclization was completed (1 h for 3a and 3c, 3 h for 3d and 6 h for 3b). The solvent was removed under reduced pressure to give a solid which was purified by flash chromatography or by recrystallization from the indicated solvent.

3-Methyl-1-phenylimidazo[4,5-*c*]pyrazole-5-thione (4a).

Colorless crystals, yield 95% , mp 233°C (ethyl acetate/petroleum ether); ir (KBr): 3100 (br), 1590, 1510, 1480 cm⁻¹; ¹H nmr (DMSO-d₆) δ: 2.26 (s, 3H, Me), 7.23-7.75 (m, 5H, Ph), 12.47 (br s, 1H, NH), 13.39 (br s, 1H, NH); ¹³C nmr (DMSO-d₆) δ: 11.74 (q, J=128.4 Hz, Me), 117.14 (d, J=163.1 Hz, Ph), 120.17 (s, C-3a), 125.16 (d, J=162.7 Hz, Ph), 129.39 (d, J=162.5 Hz, Ph), 130.21 (s, C-3), 135.33 (s, C-6a), 137.87 (s, Ph), 169.01 (CS). Anal. Calcd for C₁₁H₁₀N₄S: C, 57.37; H, 4.38; N, 24.33, S, 13.92. Found: C, 57.30; H, 4.42; N, 24.18, S, 13.84.

6-Benzoyl-3-methyl-1-phenylimidazo[4,5-*c*]pyrazole-5-thione (4b).

Colorless crystals from column chromatography (eluent: 8:2 ethyl acetate/petroleum ether); yield 62%, mp 243-244°C (ethyl acetate/petroleum ether); ir (KBr): 3450 (br), 3250 (br), 1700, 1640, 1550 cm⁻¹; ¹H nmr (DMSO-d₆) δ: 2.12 (s, 3H, Me), 7.31-7.85 (m, 10H, 2Ph), 10.40 (br s, 1H, NH). Anal. Calcd for C₁₈H₁₄N₄OS: C, 64.65; H, 4.22; N, 16.75, S, 9.59. Found: C, 64.55; H, 4.29; N, 16.54, S, 9.38.

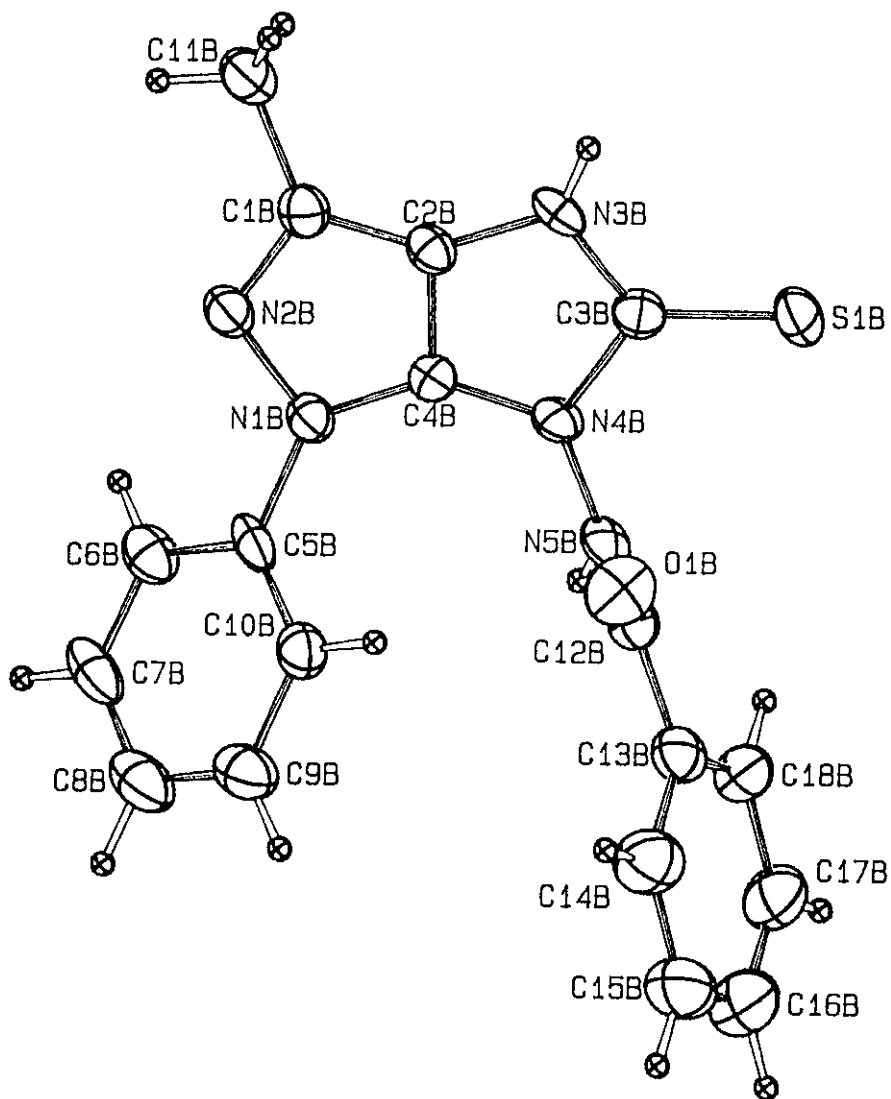
6-Benzyl-3-methyl-1-phenylimidazo[4,5-*c*]pyrazole-5-thione (4c).

Colorless crystals, yield 89% , mp 201-202°C (ethyl acetate/petroleum ether); ir (KBr): 3100 (br), 1610, 1580, 1520, 1480 cm⁻¹; ¹H nmr (DMSO-d₆) δ: 2.26 (s, 3H, Me), 5.36 (s, 2H, CH₂), 6.66-7.41 (m, 10H, 2Ph), 12.61 (br s, 1H, NH). Anal. Calcd for C₁₈H₁₆N₄S: C, 67.48; H, 5.03; N, 17.49, S, 10.01. Found: C, 67.30; H, 5.12; N, 17.48, S, 9.88.

6-Benzamido-3-methyl-1-phenylimidazo[4,5-*c*]pyrazole-5-thione (4d).

Pale yellow crystals from flash chromatography (eluent: 3:7 ethyl acetate/petroleum ether); yield 77%, mp 206-207°C (ethyl acetate/petroleum ether); ir (KBr): 3450 (br), 3000 (br), 1700, 1600, 1470 cm⁻¹; ¹H nmr (DMSO-d₆) δ: 2.32 (s, 3H, Me), 7.22-7.85 (m, 10H, 2Ph), 11.93 (br s, 1H, NH), 13.05 (br s, 1H, NH); ¹³C nmr (DMSO-d₆) δ: 11.58 (q, J=128.0 Hz, Me), 117.15 (s, C-3a), 121.01 (d, J=163.1 Hz, Ph), 126.76 (d, J=162.3 Hz, Ph), 127.49 (d, J=162.5 Hz, Ph), 128.67 (d, J=163.4 Hz, Ph), 129.10 (d, J=161.2 Hz, Ph), 130.98 (s, C-3), 131.02 (s, Ph), 132.62 (d, J=162.8 Hz, Ph), 134.98 (s, C-6a), 137.22 (s, Ph), 165.61 (s, CONH), 170.64 (s, CS). Anal. Calcd for C₁₈H₁₅N₅OS: C, 61.88; H, 4.33; N, 20.04, S, 9.18. Found: C, 61.74; H, 4.42; N, 19.88, S, 9.04.

X-Ray Crystallographic Analysis



An ORTEP¹⁴ view of molecule displaying the thermal ellipsoids at 30% probability

Table 1. Final fractional atomic coordinates

Atom	x	y	z
S (1A)	0.16048 (6)	0.1328 (2)	0
O (1A)	0.2924 (2)	0.3665 (6)	0.0738 (2)
N (1A)	0.3650 (2)	0.2679 (6)	- 0.1089 (2)
N (2A)	0.3599 (2)	0.3188 (6)	- 0.1687 (2)
N (3A)	0.2101 (2)	0.2508 (6)	- 0.1049 (2)
N (4A)	0.2775 (2)	0.1890 (6)	- 0.0348 (2)
N (5A)	0.3009 (2)	0.1082 (6)	0.0162 (2)
C (1A)	0.2998 (2)	0.3260 (2)	- 0.1827 (2)
C (2A)	0.2680 (2)	0.2832 (7)	- 0.1295 (2)
C (3A)	0.2156 (2)	0.1912 (8)	- 0.0488 (2)
C (4A)	0.3090 (2)	0.2482 (7)	- 0.0859 (3)
C (5A)	0.4235 (2)	0.2572 (7)	- 0.0812 (3)
C (6A)	0.4720 (2)	0.1906 (8)	- 0.1141 (3)
C (7A)	0.5289 (2)	0.1828 (9)	- 0.0867 (3)
C (8A)	0.5355 (2)	0.2391 (9)	- 0.0287 (3)
C (9A)	0.4875 (3)	0.3048 (9)	0.0037 (3)
C (10A)	0.4295 (2)	0.3166 (8)	- 0.0217 (3)
C (11A)	0.2771 (3)	0.3716 (10)	- 0.2441 (3)
C (12A)	0.3046 (2)	0.2039 (9)	0.0699 (3)
C (13A)	0.3264 (2)	0.0794 (9)	0.1201 (3)
C (14A)	0.3653 (3)	0.1554 (11)	0.1637 (3)
C (15A)	0.3884 (3)	0.0378 (13)	0.2098 (3)
C (16A)	0.3725 (4)	- 0.1484 (14)	0.2091 (3)
C (17A)	0.3336 (4)	- 0.2167 (13)	0.1681 (3)
C (18A)	0.3111 (3)	- 0.1043 (10)	0.1229 (3)
H (3A)	0.181 (2)	0.288 (6)	- 0.127 (2)
H (5A)	0.317 (1)	0.012 (4)	0.011 (1)
S (1B)	0.08812 (6)	0.4051 (2)	- 0.17571 (8)
O (1B)	- 0.0360 (2)	0.0940 (6)	- 0.2343 (2)
N (1B)	- 0.1157 (2)	0.2419 (6)	- 0.0684 (2)
N (2B)	- 0.1105 (2)	0.1919 (7)	- 0.0077 (2)
N (3B)	0.0386 (2)	0.2864 (6)	- 0.0702 (2)
N (4B)	- 0.0292 (2)	0.3322 (6)	- 0.1413 (2)
N (5B)	- 0.0521 (2)	0.3843 (6)	- 0.1969 (2)
C (1B)	- 0.0511 (2)	0.1943 (8)	0.0048 (3)
C (2B)	- 0.0179 (2)	0.2428 (7)	- 0.0458 (2)
C (3B)	0.0333 (2)	0.3404 (8)	- 0.1286 (2)
C (4B)	- 0.0591 (2)	0.2701 (7)	- 0.0909 (2)
C (5B)	- 0.1753 (2)	0.2388 (8)	- 0.0952 (3)
C (6B)	- 0.2249 (2)	0.2999 (9)	- 0.0625 (3)
C (7B)	- 0.2811 (2)	0.2883 (9)	- 0.0877 (3)
C (8B)	- 0.2892 (3)	0.2239 (9)	- 0.1454 (3)
C (9B)	- 0.2398 (3)	0.1640 (8)	- 0.1784 (3)
C (10B)	- 0.1825 (2)	0.1702 (8)	- 0.1529 (2)
C (11B)	- 0.0290 (3)	0.1572 (11)	0.0674 (3)
C (12B)	- 0.0542 (2)	0.2504 (8)	- 0.2416 (2)
C (13B)	- 0.0822 (2)	0.3217 (9)	- 0.2986 (3)
C (14B)	- 0.1144 (3)	0.1957 (10)	- 0.3330 (3)
C (15B)	- 0.1456 (3)	0.2594 (14)	- 0.3846 (3)
C (16B)	- 0.1422 (3)	0.4406 (14)	- 0.4011 (3)
C (17B)	- 0.1094 (3)	0.5614 (12)	- 0.3679 (3)
C (18B)	- 0.0793 (3)	0.5082 (11)	- 0.3160 (3)
H (3B)	0.071 (2)	0.255 (5)	- 0.059 (2)
H (5B)	- 0.081 (2)	0.466 (7)	- 0.198 (2)

Table 2. Bond distances (Å) with esds in parentheses

Molecule A		Molecule B	
S(1A)-C(3A)	1.673 (5)	S(1B)-C(3B)	1.657 (5)
O(1A)-C(12A)	1.199 (8)	O(1B)-C(12B)	1.201 (7)
N(1A)-N(2A)	1.376 (6)	N(1B)-N(2B)	1.394 (6)
N(1A)-C(4A)	1.336 (6)	N(1B)-C(4B)	1.352 (6)
N(1A)-C(5A)	1.423 (7)	N(1B)-C(5B)	1.435 (6)
N(2A)-C(1A)	1.354 (6)	N(2B)-C(1B)	1.331 (6)
N(3A)-C(2A)	1.400 (6)	N(3B)-C(2B)	1.387 (6)
N(3A)-C(3A)	1.318 (6)	N(3B)-C(3B)	1.353 (6)
N(3A)-H(3A)	0.85 (4)	N(3B)-H(3B)	0.78 (4)
N(4A)-N(5A)	1.368 (6)	N(4B)-N(5B)	1.380 (6)
N(4A)-C(3A)	1.392 (6)	N(4B)-C(3B)	1.400 (6)
N(4A)-C(4A)	1.391 (8)	N(4B)-C(4B)	1.368 (6)
N(5A)-C(12A)	1.374 (8)	N(5B)-C(12B)	1.379 (7)
N(5A)-H(5A)	0.78 (3)	N(5B)-H(5B)	0.86 (5)
C(1A)-C(2A)	1.402 (6)	C(1B)-C(2B)	1.380 (8)
C(1A)-C(11A)	1.483 (8)	C(1B)-C(11B)	1.491 (9)
C(2A)-C(4A)	1.342 (7)	C(2B)-C(4B)	1.360 (6)
C(5A)-C(6A)	1.374 (7)	C(5B)-C(6B)	1.377 (8)
C(5A)-C(10A)	1.389 (9)	C(5B)-C(10B)	1.377 (8)
C(6A)-C(7A)	1.388 (7)	C(6B)-C(7B)	1.355 (7)
C(7A)-C(8A)	1.352 (9)	C(7B)-C(8B)	1.369 (9)
C(8A)-C(9A)	1.357 (8)	C(8B)-C(9B)	1.375 (9)
C(9A)-C(10A)	1.393 (8)	C(9B)-C(10B)	1.378 (8)
C(12A)-C(13A)	1.502 (9)	C(12B)-C(13B)	1.492 (8)
C(13A)-C(14A)	1.398 (9)	C(13B)-C(14B)	1.376 (9)
C(13A)-C(18A)	1.360 (9)	C(13B)-C(18B)	1.392 (10)
C(14A)-C(15A)	1.416 (11)	C(14B)-C(15B)	1.407 (10)
C(15A)-C(16A)	1.379 (13)	C(15B)-C(16B)	1.351 (14)
C(16A)-C(17A)	1.338 (11)	C(16B)-C(17B)	1.344 (11)
C(17A)-C(18A)	1.375 (11)	C(17B)-C(18B)	1.378 (10)

Crystal data for 4d. C₁₈H₁₅N₅O₅S, M = 349.42, orthorhombic, space group: *Pca2₁* (No. 29), *a* = 21.923(3), *b* = 7.167(2), *c* = 22.117(2) Å, V = 3475(1) Å³ (by least-squares refinement on diffractometer angles for 25 automatically centered reflections, λ = 0.71069 Å), Z = 8, (two molecule in the asymmetric unit), D_x = 1.33 g/cm⁻³, μ(MoK_α) = 1.92 cm⁻¹, T = 295 K, crystal dimensions: 0.19 x 0.19 x 0.45 mm.

Data collection, analysis and refinement. A Enraf-Nonius CAD-4 diffractometer was used, with graphite-monochromated MoK_α radiation and ω/2θ scan technique. 3877 unique reflections measured (2 ≤ θ ≤ 27°), giving 1935 with I ≥ 3σ(I). Solution by direct methods (SIR88)¹¹ and Fourier synthesis. Hydrogen atoms of the amino groups found in difference-Fourier maps. Two-blocks matrix least-squares refinement. The weighting scheme w = 4Fo²/[σ²(Fo²) + (0.03Fo²)²] gave satisfactory agreement analysis. Goodness of fit = 1.45. Final R = 0.044 and Rw = 0.048. All calculations were performed by the MolEN¹² and PARST¹³ programs.

Table 3. Bond angles ($^{\circ}$) with esds in parentheses

Molecule A		Molecule B	
C(4A)-N(1A)-C(5A)	131.2 (5)	C(4B)-N(1B)-C(5B)	133.3 (5)
N(2A)-N(1A)-C(5A)	120.1 (4)	N(2B)-N(1B)-C(5B)	117.9 (4)
N(2A)-N(1A)-C(4A)	108.6 (4)	N(2B)-N(1B)-C(4B)	108.5 (4)
N(1A)-N(2A)-C(1A)	108.0 (4)	N(1B)-N(2B)-C(1B)	106.1 (4)
C(2A)-N(3A)-C(3A)	109.7 (4)	C(2B)-N(3B)-C(3B)	111.1 (4)
C(3A)-N(4A)-C(4A)	107.4 (4)	C(3B)-N(4B)-C(4B)	108.6 (4)
N(5A)-N(4A)-C(4A)	127.8 (4)	N(5B)-N(4B)-C(4B)	129.8 (4)
N(5A)-N(4A)-C(3A)	123.6 (4)	N(5B)-N(4B)-C(3B)	121.6 (4)
N(4A)-N(5A)-C(12A)	121.6 (4)	N(4B)-N(5B)-C(12B)	117.6 (4)
N(2A)-C(1A)-C(11A)	123.0 (4)	N(2B)-C(1B)-C(11B)	120.6 (4)
N(2A)-C(1A)-C(2A)	106.5 (4)	N(2B)-C(1B)-C(2B)	110.5 (4)
C(2A)-C(1A)-C(11A)	130.6 (4)	C(2B)-C(1B)-C(11B)	128.8 (5)
N(3A)-C(2A)-C(1A)	144.4 (4)	N(3B)-C(2B)-C(1B)	147.5 (5)
C(1A)-C(2A)-C(4A)	108.1 (4)	C(1B)-C(2B)-C(4B)	106.3 (4)
N(3A)-C(2A)-C(4A)	107.3 (4)	N(3B)-C(2B)-C(4B)	106.0 (4)
N(3A)-C(3A)-N(4A)	107.6 (4)	N(3B)-C(3B)-N(4B)	105.3 (4)
S(1A)-C(3A)-N(4A)	123.9 (4)	S(1B)-C(3B)-N(4B)	126.6 (4)
S(1A)-C(3A)-N(3A)	128.5 (4)	S(1B)-C(3B)-N(3B)	128.2 (4)
N(4A)-C(4A)-C(2A)	108.0 (4)	N(4B)-C(4B)-C(2B)	109.0 (4)
N(1A)-C(4A)-C(2A)	108.8 (4)	N(1B)-C(4B)-C(2B)	108.6 (4)
N(1A)-C(4A)-N(4A)	142.9 (5)	N(1B)-C(4B)-N(4B)	142.0 (4)
N(1A)-C(5A)-C(10A)	118.5 (4)	N(1B)-C(5B)-C(10B)	119.5 (4)
N(1A)-C(5A)-C(6A)	119.2 (5)	N(1B)-C(5B)-C(6B)	119.8 (5)
C(6A)-C(5A)-C(10A)	122.3 (4)	C(6B)-C(5B)-C(10B)	120.6 (4)
C(5A)-C(6A)-C(7A)	118.6 (6)	C(5B)-C(6B)-C(7B)	118.8 (6)
C(6A)-C(7A)-C(8A)	119.9 (5)	C(6B)-C(7B)-C(8B)	121.5 (5)
C(7A)-C(8A)-C(9A)	121.4 (5)	C(7B)-C(8B)-C(9B)	119.9 (6)
C(8A)-C(9A)-C(10A)	121.1 (6)	C(8B)-C(9B)-C(10B)	119.4 (6)
C(5A)-C(10A)-C(9A)	116.7 (5)	C(5B)-C(10B)-C(9B)	119.7 (5)
O(1A)-C(12A)-N(5A)	122.3 (6)	O(1B)-C(12B)-N(5B)	122.8 (5)
N(5A)-C(12A)-C(13A)	111.2 (5)	N(5B)-C(12B)-C(13B)	112.4 (5)
O(1A)-C(12A)-C(13A)	126.5 (6)	O(1B)-C(12B)-C(13B)	124.7 (5)
C(12A)-C(13A)-C(18A)	122.0 (5)	C(12B)-C(13B)-C(18B)	122.9 (5)
C(12A)-C(13A)-C(14A)	118.2 (6)	C(12B)-C(13B)-C(14B)	117.0 (6)
C(14A)-C(13A)-C(18A)	119.8 (6)	C(14B)-C(13B)-C(18B)	120.0 (6)
C(13A)-C(14A)-C(15A)	118.9 (7)	C(13B)-C(14B)-C(15B)	119.0 (7)
C(14A)-C(15A)-C(16A)	118.5 (6)	C(14B)-C(15B)-C(16B)	120.3 (6)
C(15A)-C(16A)-C(17A)	121.5 (8)	C(15B)-C(16B)-C(17B)	120.1 (7)
C(16A)-C(17A)-C(18A)	120.5 (8)	C(16B)-C(17B)-C(18B)	122.2 (7)
C(13A)-C(18A)-C(17A)	120.8 (6)	C(13B)-C(18B)-C(17B)	118.3 (7)

Table 4. Bond distances (\AA) and angles ($^{\circ}$) for inter- and intramolecular hydrogen bonds with esd in parentheses

	D---A ^a	H---A	Angle	Sym.Op. ^b
N(3A)-H(3A)---S(1B)	3.290 (5)	2.45 (4)	171 (4)	0
N(3B)-H(3B)---S(1A)	3.281 (5)	2.51 (4)	166 (4)	0
N(5A)-H(5A)---N(2B)	2.946 (6)	2.20 (3)	160 (2)	I
N(5B)-H(5B)---N(2A)	2.939 (6)	2.12 (5)	159 (4)	II

^a D=donor; A=acceptor.^b Symmetry Operations: (0) x,y,z; (I) x+1/2,-y,z; (II) x-1/2,1-y,z.

ACKNOWLEDGEMENTS

The Authors are grateful to Dr. A Casolari and P. Orlandini for carrying out nmr spectra. Research work supported by grants of MURST (40%), Italy.

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Received, 28th October, 1994