Reaction of 2,5-Dimethyl-3,4-dinitrothiophen with Secondary Amines. Formation and Crystal Structure Analysis of 2,5-Dimethyl-*trans*-2,3-dimorpholino-4-nitro-2,3-dihydrothiophen [1]

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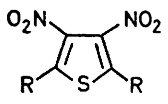
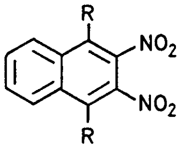
2,5-Dimethyl-3,4-dinitrothiophen (2) reacts with both morpholine and piperidine, in neat amine, to yield 2,5-dimethyl-*trans*-2,3-dimorpholino- (5a) and 2,5-dimethyl-*trans*-2,3-dipiperidino-4-nitro-2,3-dihydrothiophen (5b). The structure of (5a) has been unambiguously determined by *X*-ray analysis. In the crystal (monoclinic space group $P2_1/n$, a = 14.126, b = 11.103, c = 10.821 Å, β = 96.66°, Z = 4; R = 0.041 over 1 898 observed reflections) the dihydrothiophen ring is puckered. The two C–S bond lengths are significantly different (1.89 and 1.73 Å, respectively). Steric hindrance is reflected by some short intra- and inter-molecular contacts. A reaction scheme is proposed.

AROMATIC dinitro-derivatives where the nitro-groups are present in vicinal but slightly conjugated positions generally react with nucleophiles in peculiar and unexpected ways. The behaviour of 3,4-dinitrothiophens (1) and (2) and of 2,3-dinitronaphthalenes (3) and (4) is indicative.



(1) R = H
(2) R = CH_3



(3) R = H
(4) R = CH_3

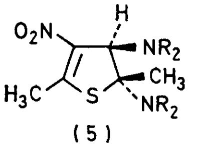
Compound (1) reacts with arenethiolates and secondary amines (*e.g.* piperidine) to give 2-arylthio-4-nitrothiophens (*cine*-substitution reaction) [2] and 1,4-dipiperidino-2,3-dinitrobutadiene (ring-opening reaction),[3] respectively, whereas compound (2) by treatment with arenethiolates furnishes 2-arylthiomethyl-5-methyl-4-nitrothiophens (*tele*-substitution reaction).[4] Compound (3) reacts with arenethiolates to give 2-arylthio-3-nitronaphthalenes (S_NAr reaction) [5] and with piperidine to give 1-piperidino-3-nitronaphthalene (*cine*-substitution reaction) [6] whereas compound (4) by treatment with piperidine furnishes 1-piperidinomethyl-4-methyl-3-nitronaphthalene (*tele*-substitution reaction) [7] and by treatment with arenethiolates a mixture of 2-arylthio-1,4-dimethyl-3-nitronaphthalenes and of 1-arylthiomethyl-4-methyl-3-nitronaphthalenes (competition between S_NAr and *tele*-substitution reactions, respectively).[8]

We report now the results obtained from the reaction of (2) with both morpholine and piperidine and the crystal structure of the product with morpholine.

RESULTS AND DISCUSSION

Upon carrying out the reaction between (2) and morpholine or piperidine in ethanol under the same experimental conditions used for (1),[3] only unidentifiable tarry material was obtained. On the other hand, when (2) was dissolved in neat amine at room temperature the rapid formation of just one product was observed. From the reaction with morpholine a yellow compound (5a) corresponding to the formula $C_{14}H_{23}N_3O_4S$ was isolated in nearly quantitative yield. As analytical and ^{1}H n.m.r. data did not give unequivocal information, a single crystal *X*-ray structure determination was performed. This allowed compound (5a) to be identified as 2,5-dimethyl-*trans*-2,3-dimorpholino-4-nitro-2,3-dihydrothiophen.†

Analogously, the compound obtained from the reaction of (2) with piperidine was identified as 2,5-dimethyl-*trans*-2,3-dipiperidino-4-nitro-2,3-dihydrothiophen (5b) on the basis of the striking similarity of its ^{1}H n.m.r. spectrum to that of (5a).



(5)
a; R_2N = morpholino
b; R_2N = piperidino

The behaviour of (2) with morpholine and piperidine is therefore very different from that observed for the reaction of the same substrate with arenethiolates. This result confirms that the reactivity of compounds (1)—(4) is strongly influenced by the type of nucleophilic reagent used.

The most interesting point of the studied reaction is the high stereospecificity observed. Although at present no direct evidence has been collected on the mechanism of formation of (5a and b), we think that the reaction proceeds through an initial reversible addition of a molecule of amine to the 2,3 bond of (2) to give the intermediate (6) from which the final products are formed [equation (1)].

The stereochemical result observed implies that, if the proposed equation (1) occurs, all the intermediate stages

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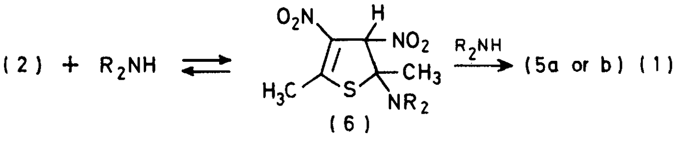
† The present work reports for the first time (to our knowledge) the geometry of the 2,3-dihydrothiophen ring in the crystal phase.

must be stereospecific. The formation of (6) should be favoured *inter alia* by the strong double-bond character of the αβ bonds in the thiophen ring.

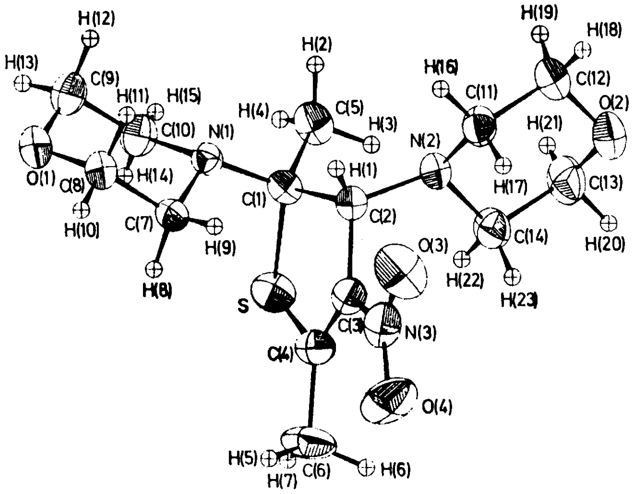
The formation of compounds (5a and b) from (2) matches those of *trans*-4,5-dimethoxy-1-methyl-3-nitro-2-pyrroline form the reaction of 1-methyl-3,4-dinitropyrrole with sodium methoxide [9] and of 2,3-bisarylthio-4-nitro-2,3-dihydrothiophen from the reaction of (1) with sodium arenethiolates.[2b] However, both these dihydroheterocyclic derivatives have been found to rearomatize easily into *cine*-substitution products. Any attempt to rearomatize (5a and b) to thiophen derivatives, instead, proved futile leading to untreatable tarry material, probably as a result of disruptive ring-opening reactions.



(6)

R_2NH = morpholine, piperidine

The crystal structure of (5a) indicates that the 2,3-dihydrothiophen ring is not planar: deviations as high as 0.16 Å are found between the least-squares plane [10] through the five atoms, and atoms C(1) and C(2). By leaving out C(1) the planarity is enhanced, the deviations being within 0.02 Å; correspondingly the deviation of the C(1) atom from the mean plane is 0.42 Å. The torsion angles along the ring range from +20 to −24°. The two carbon–sulphur bond distances are quite different, S–C(1) 1.892(3), S–C(4) 1.727(3) Å. The last figure is a normal value for an S–C(sp^2) bond length; according to Cox and Jeffrey,[11] for a C–S distance of 1.73 Å the mobile bond order is 0.50. Slightly shorter C–S bond distances [1.715(2), 1.716(2) Å] have been found for the starting compound (2).[12] On the other hand the S–C(1) bond distance exceeds significantly the value of 1.81 Å proposed for an S–C(sp^3) bond length.[11,13] However, in the present case the long C(1)–S bond, possibly together with the rather long C(1)–C(2) bond distance, might offer a justification for the ease of ring-opening reactions.



Numbering of atoms and molecular geometry of (5a) with temperature ellipsoids at 0.30 probability. Hydrogen atoms, treated as isotropic, are on an arbitrary scale

The puckering of the dihydrothiophen ring allows C(1) and C(2) to deviate moderately from eclipsing, the torsion angle C(5)–C(1)–C(2)–N(2) being just −14° (synperiplanar).[14] Evidence of steric hindrance in compound (5a) is also given by a short 1,5 intramolecular contact, *i.e.* C(6) ··· O(4) 2.81 Å. The strain is partially relieved by the large bond angle C(3)–C(4)–C(6). Both C(6) and O(4) on the other hand are engaged in short intermolecular distances, such as C(6) ··· O(1) (at $3/2 - x$, $-1/2 + y$, $1/2 - z$) 3.27 and C(7) ··· O(4) (at $2 - x$, $1 - y$, $1 - z$) 3.20 Å. Another tight intermolecular contact is C(5) ··· C(12) (at $2 - x$, $-y$, $-z$) 3.59 Å. All these are significantly shorter than the sum of the van der Waals radii.[15]

The 3-NO_2 group is planar within 0.01 Å; the torsion angle C(4)–C(3)–N(3)–O(4) is *ca.* 8°. The geometry of the morpholine rings is normal; the absolute values of the torsion angles along each ring range between 57 and 59°. The two morpholino groups are *trans* to each other, the N(1)–C(1)–C(2)–N(2) torsion angle being −138° (anticlinal).[14]

EXPERIMENTAL

^{1}H N.m.r. spectra were taken on a Varian XL 100 instrument using Me_4Si as internal standard. Molecular weights were determined in toluene solution with a Mechrolab vapour pressure osmometer. Organic extracts were rotoevaporated at reduced pressure below 40 °C. *X*-Ray diffraction data were measured with Cu-K_α radiation on a Philips PW 1 100 four-circle diffractometer equipped with graphite monochromator. All calculations were performed on a CII-10070 computer.

Reaction of 2,5-*Dimethyl*-3,4-*dinitrothiophen with Amines*.—Compound (2) (0.5 g) was dissolved in neat amine (10 mol. equiv.) at room temperature. After a few minutes the solution was diluted with light petroleum (b.p. 30—50 °C), filtered from the insoluble amine nitrite, washed with water to remove the excess amine, and dried. The residue obtained by evaporation of the solvent was purified by crystallization.

From the reaction with morpholine for 20 min 2,5-*dimethyl*-trans-2,3-*dimorpholino*-4-*nitro*-2,3-*dihydrothiophen* (5a) was isolated in nearly quantitative yield, m.p. 131—132° [from light petroleum (b.p. 60—80°)]; δ(CCl_4) 4.12br (1 H, s), 3.62 (8 H, m), 2.70 (m) and 2.49 (s) (partly overlapped, 11 H in all), and 1.62br (3 H, s) (Found: C, 51.35; H, 6.85; N, 12.9. $C_{14}H_{23}N_3O_4S$ requires C, 51.05; H, 7.0; N, 12.75%)

From the reaction with piperidine for 5 min 2,5-*dimethyl*-trans-2,3-*dipiperidino*-4-*nitro*-2,3-*dihydrothiophen* (5b) was obtained, m.p. 95° [from light petroleum (b.p. 30—50°)]; δ(CCl_4) 4.16br (1 H, s), 2.72 and 2.48 (overlapping m, 11 H in all), 1.58br (3 H, s), and 1.49 (12 H, m) (Found: C, 59.4; H, 8.2; N, 13.05. $C_{16}H_{27}N_3O_2S$ requires C, 59.1; H, 8.3; N, 12.9%).

X-*Ray Analysis of* (5a).—The compound crystallizes in the monoclinic space group $P2_1/n$ with a = 14.126(2), b = 11.103(2), c = 10.821(1) Å, β = 96.66(1)°, U = 1 686 Å^3,

$Z = 4$, $D_c = 1.297$ g cm^{-3}. Aborption coefficient for X-rays, μ(Cu-K_{α}) = 18 cm^{-1}. Cell dimensions were obtained from 12 reflections (plus their equivalents) for λ 1.541 78 Å. A crystal of dimensions 0.29 × 0.32 × 0.48 mm (elongated along y) was examined by means of oscillation, Weissenberg, and precession photographs. Intensities were collected in the range $3 \leqslant \theta \leqslant 67°$ (θ–2θ scan mode, scan width 1.40°, scan speed 0.04 ° s^{-1}). Two reference reflections were monitored periodically to test crystal decomposition or movement. A total of 2 990 independent reflections was collected; of these, 1 899 having $|F_o| > \sigma(F_o)$ were considered as observed. Lorentz and polarization factors were applied; the absorption correction was evaluated[16] by means of 90 ψ-scan data from five strong $0k0$ and $0k1$ reflections. The structure was solved by direct methods with the SHELX 76 system of programs,[17] kindly supplied by Dr. G. M. Sheldrick. After a trial, the solution was achieved by redoubling the dimension of the main array A to 28 000. This allowed the program to retain nearly 5 500 phase relationships which were used to determine 582 signs. The ' best ' E map showed all the non-hydrogen atoms unambiguously.

TABLE 1

Fractional co-ordinates (× 10^4), with estimated standard deviations in parentheses

	x	y	z
S	7 758(0)	3 053(1)	2 729(1)
C(1)	8 660(2)	3 022(2)	1 566(2)
C(2)	9 624(2)	2 739(2)	2 374(2)
C(3)	9 506(2)	3 145(2)	3 676(2)
C(4)	8 616(2)	3 281(2)	3 978(3)
C(5)	8 350(2)	2 041(3)	620(3)
C(6)	8 282(3)	3 598(4)	5 201(3)
C(7)	9 026(2)	5 209(2)	1 760(2)
C(8)	9 244(2)	6 281(3)	984(3)
C(9)	8 146(3)	5 634(4)	−630(3)
C(10)	7 909(2)	4 547(3)	87(3)
C(11)	10 922(2)	1 299(3)	2 126(3)
C(12)	11 065(2)	12(3)	1 739(3)
C(13)	9 805(3)	−626(3)	2 769(4)
C(14)	9 623(2)	638(3)	3 187(3)
N(1)	8 737(1)	4 178(2)	953(2)
N(2)	9 926(1)	1 481(2)	2 284(2)
N(3)	10 350(2)	3 368(2)	4 507(3)
O(1)	8 448(2)	6 626(2)	144(2)
O(2)	10 773(2)	−814(2)	2 619(2)
O(3)	11 108(2)	3 376(3)	4 074(3)
O(4)	10 287(2)	3 575(3)	5 611(2)

TABLE 2

Hydrogen fractional co-ordinates (× 10^3), obtained from a difference synthesis and unrefined

	x	y	z
H(1)	1 016	322	205
H(2)	873	203	−8
H(3)	839	127	113
H(4)	776	213	27
H(5)	843	435	540
H(6)	855	303	585
H(7)	766	353	511
H(8)	856	540	236
H(9)	961	502	227
H(10)	943	699	157
H(11)	982	608	47
H(12)	863	540	−115
H(13)	762	591	−109
H(14)	751	485	61
H(15)	764	396	−38
H(16)	1 116	192	153
H(17)	1 137	149	287
H(18)	1 174	−12	174
H(19)	1 066	−15	90
H(20)	963	−121	335
H(21)	940	−78	200
H(22)	896	78	321
H(23)	999	75	405

Refinement was accomplished by full-matrix least-squares process[17] on isotropic and then anisotropic C, N, O, and S atoms. The function minimized was $\Sigma w(\Delta F)^2$, with weights $w = [\sigma^2(F_o) + 0.05\, F_o^{\,2}]^{-1}$. After some cycles a difference synthesis allowed all the hydrogen atoms to be located; they were considered as isotropic with a temperature factor U_H of 0.07 Å^2 and included in the structure factor calculations. In the last cycles, zero weight was given to the very strong 112 reflection, as presumably affected by extinction. At the end of the refinement the factor $R = \Sigma|\Delta F|/\Sigma|F_o|$ converged to 0.041 for the 1 898 observed reflections; in the final cycle most shifts were $< 0.01\sigma$, the maximum shift being 0.03σ. A final difference synthesis was essentially featureless, the electron density values being ± 0.25 eÅ^{-3}.

TABLE 3

Bond lengths (Å) with estimated standard deviations in parentheses

S–C(1)	1.892(3)	N(1)–C(7)	1.469(3)
S–C(4)	1.727(3)	C(7)–C(8)	1.509(4)
C(1)–C(2)	1.563(3)	C(8)–O(1)	1.415(3)
C(2)–C(3)	1.506(4)	O(1)–C(9)	1.419(4)
C(3)–C(4)	1.345(4)	C(9)–C(10)	1.494(5)
C(1)–C(5)	1.523(4)	C(10)–N(1)	1.470(3)
C(1)–N(1)	1.455(3)	N(2)–C(11)	1.451(3)
C(2)–N(2)	1.467(3)	C(11)–C(12)	1.509(4)
C(3)–N(3)	1.428(4)	C(12)–O(2)	1.418(4)
C(4)–C(6)	1.497(4)	O(2)–C(13)	1.411(4)
N(3)–O(3)	1.218(4)	C(13)–C(14)	1.506(5)
N(3)–O(4)	1.230(4)	C(14)–N(2)	1.452(4)
	Mean C–H	1.0	

TABLE 4

Bond angles (°) with estimated standard deviations in parentheses

S–C(1)–C(2)	104.0(2)	C(7)–N(1)–C(10)	108.0(2)
C(1)–C(2)–C(3)	106.2(2)	N(1)–C(7)–C(8)	110.1(2)
C(2)–C(3)–C(4)	118.0(2)	C(7)–C(8)–O(1)	111.9(3)
C(3)–C(4)–S	112.6(2)	C(8)–O(1)–C(9)	109.4(2)
C(4)–S–C(1)	93.3(1)	O(1)–C(9)–C(10)	113.0(3)
S–C(1)–C(5)	107.3(2)	C(9)–C(10)–N(1)	110.2(3)
S–C(1)–N(1)	112.2(2)	C(2)–N(2)–C(11)	115.7(2)
N(1)–C(1)–C(2)	109.1(2)	C(2)–N(2)–C(14)	117.3(2)
N(1)–C(1)–C(5)	110.8(2)	C(11)–N(2)–C(14)	110.8(2)
C(5)–C(1)–C(2)	113.4(2)	N(2)–C(11)–C(12)	109.1(2)
C(1)–C(2)–N(2)	113.3(2)	C(11)–C(12)–O(2)	111.5(3)
C(3)–C(2)–N(2)	114.3(2)	C(12)–O(2)–C(13)	110.1(2)
C(2)–C(3)–N(3)	117.8(3)	O(2)–C(13)–C(14)	112.0(3)
C(4)–C(3)–N(3)	124.2(3)	C(13)–C(14)–N(2)	109.0(3)
C(3)–C(4)–C(6)	129.9(3)	C(3)–N(3)–O(3)	117.7(3)
S–C(4)–C(6)	117.5(3)	C(3)–N(3)–O(4)	119.7(3)
C(1)–N(1)–C(7)	116.5(2)	O(3)–N(3)–O(4)	122.5(3)
C(1)–N(1)–C(10)	116.1(2)		
Means: C–C–H	110	N–C–H	110
O–C–H	108	H–C–H	109

Final atomic co-ordinates are listed in Tables 1 and 2. Bond distances and bond angles are reported in Tables 3 and 4, respectively. Mean values for e.s.d.s are 0.004 Å, 0.3°, and 0.5°, respectively for bond lengths, bond angles, and torsion angles not involving hydrogen atoms. Observed and calculated structure factors together with the thermal parameters are available as Supplementary Publication No.

22866 (13 pp.).* A view of the molecular structure in the crystal[18] is shown in the Figure.

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* For details of the Supplementary Publications Scheme see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1979, Index issue.

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