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A NOVEL SYNTHESIS OF cis-1-[[6-CHLORO-3-[(2-CHLORO-3-THIENYL)METHOXY]-2,3-DIHYDROBENZO[b]THIEN-2-YL]METHYL]1H-IMIDAZOLE. A NEW CLASS OF AZOLE ANTIFUNGAL AGENTS

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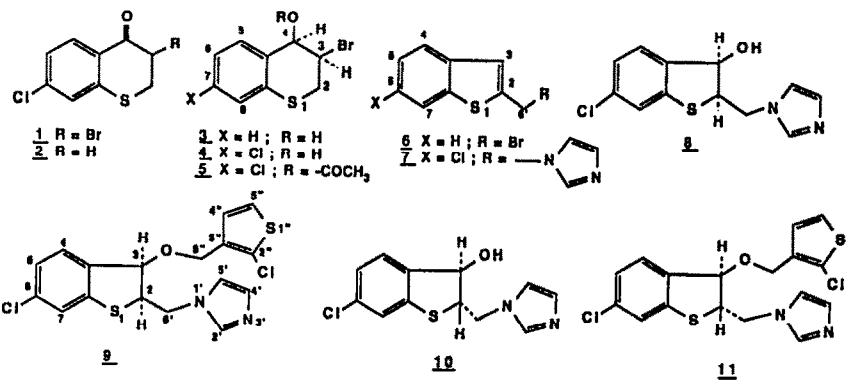
ABSTRACT - Ring contraction of cis-3-bromo-7-chloro-3,4-dihydro-2H-1-benzothiopyran-4-ol 4 in the presence of imidazole results in formation of cis-6-chloro-2,3-dihydro-2-(1H-imidazol-1-ylmethyl) benzo[b]thiophene-3-ol 8 as the major product. The structure of 8 was defined unequivocally by X-ray analysis of a solvated (ethyl acetate) and an unsolvated crystal form. Alkylation of 8 with 3-(bromomethyl)-2-chlorothiophene gave cis-1-[[6-chloro-3-[(2-chloro-3-thienyl)methoxy]-2,3-dihydrobenzo[b]thien-2-yl]methyl]1H-imidazole 9, a representative of a new class of azole antifungal agents.

In recent years, advances in antifungal chemotherapy have been dominated by the single largest class of synthetic antifungal compounds which have as their common feature an imidazole nucleus substituted at the 1-position[1]. As part of a program aimed at synthesis of novel antifungal agents, we explored the ring contraction of cis-3-bromo-7-chloro-3,4-dihydro-2H-1-benzothiopyran-4-ol 4 with imidazole. Cis-3-bromo-3,4-dihydro-2H-1-benzo-thiopyran-4-ol 3 is known to undergo ring contraction in hot dioxane to give 2-(bromo-methyl)benzo[b]thiophene[2] 6 via a thiiranium cation. In this paper, we wish to report that the initially formed thiiranium cation from cis-3-bromo-7-chloro-3,4-dihydro-2H-1-benzothiopyran-4-ol 4 was trapped regioselectively by imidazole to furnish cis-6-chloro-2,3-dihydro-2-(1H-imidazol-1-ylmethyl)benzo[b]thiophene-3-ol 8 as the major product, thus providing an important intermediate for the synthesis of various aryl ethers of 2-(1H-imidazol-1-ylmethyl)dihydrobenzo[b]thiophenes.

RESULTS AND DISCUSSION

The synthesis was initiated with 3-bromo-7-chloro-2,3-dihydro-4H-1-benzothiopyran-4-one 1 which was obtained by bromination of 7-chloro-2,3-dihydro-4H-1-benzothiopyran-4-one 2[3] with bromine in chloroform. Sodium borohydride reduction of the bromoketone 1 in methanol gave the expected cis-3-bromo-7-chloro-3,4-dihydro-2H-1-benzothiopyran-4-ol 4[4,5] which was characterized as its acetate 5. Refluxing cis-bromohydrin 4 and imidazole in acetonitrile for 12 hours, followed by work-up and chromatography, led to cis-6-chloro-2,3-dihydro-2-(1H-imidazol-1-ylmethyl)benzo[b] thiophene-3-ol 8[6] (48%), trans-6-chloro-2,3-dihydro-2-(1H-imidazol-1-ylmethyl)benzo[b]thiophene-3-ol 10 (ca 1%), and 7-chloro-2,3-dihydro-4H-1-benzothiopyran-4-one 2[3] (20%).



The stereochemistry of 8 was established unequivocally by single-crystal X-ray analysis. Initially, crystals grown from ethyl acetate were employed. The crystal structure was solved by the heavy-atom approach. Full-matrix least-squares refinement[7] of atomic parameters converged at $R = 0.072$ ($R_w = 0.104$)[8] over 1732 reflections. A view of the solid-state conformation of 8 in these crystals is provided in Figure 1. The dihydrothiophene ring has a conformation intermediate between half-chair and envelope forms[9] with a pseudo-axially oriented methylene group at C(2) and a pseudo-equatorial hydroxy substituent at C(3). The packing of molecules in these crystals is illustrated in Figure 2. Molecules of 8 related by unit translation along c are linked by O-H...N [O(8)...N(3') 2.716(5) Å] hydrogen bonds. Ethyl acetate molecules, disordered over two orientations related by the crystallographic two-fold axis of space group C2/c, are incorporated in cavities generated by the resulting arrangement. Distances between non-hydrogen atoms of 8 and the ethyl acetate molecules exceed 3.18 Å and correspond to weak van der Waals type interactions.

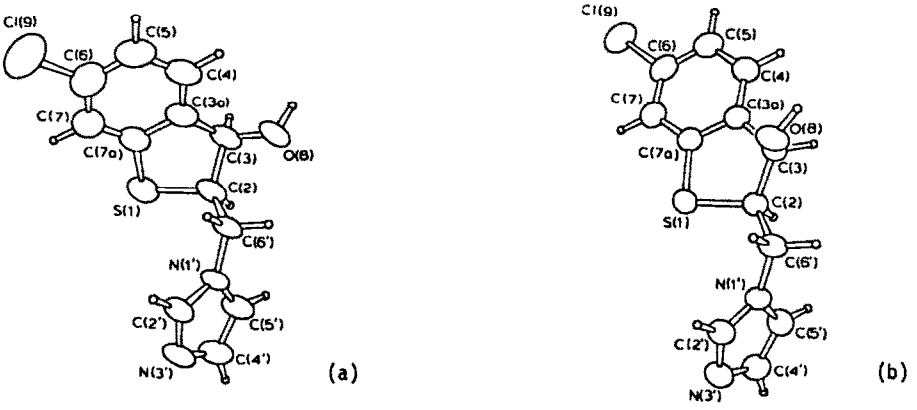


Figure 1. Solid-state conformations of 8 in (a) crystals of 8.1/2 EtOAc, and (b) unsolvated crystals of 8.

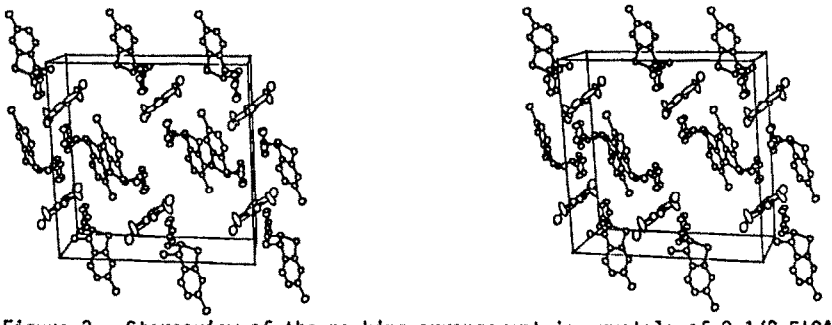


Figure 2. Stereoview of the packing arrangement in crystals of 8.1/2 EtOAc.

Recrystallization of 8 from several other solvents yielded a second, unsolvated crystal form. The crystal structure of this form was solved by direct methods.[7] Full-matrix least-squares adjustment of atomic parameters converged at $R = 0.036$ ($R_w = 0.059$) over 1844 reflections. The solid-state conformation of 8 is presented in Figure 1, and the packing of these units in the crystal is shown in Figure 3. In this crystal form, molecules of 8 related by unit translations along both the a and c axes are associated by O-H...N hydrogen bonds involving the same centers [O(8)...N(3') 2.784(3) Å] as in the solvated form obtained from ethyl acetate. The dihydrothiophene ring is again in a conformation intermediate between half-chair and envelope forms, but the dispositions of the methylene and hydroxy substituents at C(2) and C(3), respectively, are interchanged, i.e. the former is pseudo-equatorial while the latter is pseudo-axial.

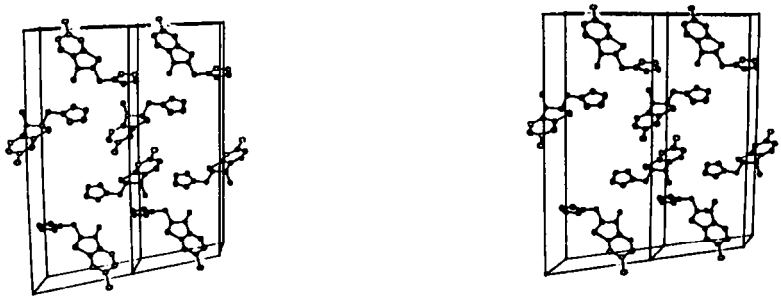
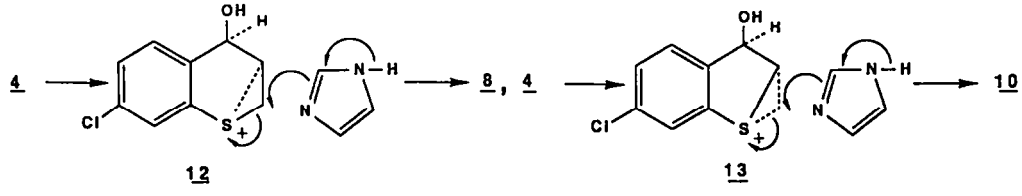


Figure 3. Stereoview of the arrangement of molecules in crystals of 8.

NMR spectroscopy established the relative stereochemistry of trans 10. Comparison of ^{1}H NMR data for cis 8 and trans 10 indicated that the non-equivalent methylene protons ($H_{6"A}$ and $H_{6"B}$) experience a greater deshielding effect ($\Delta\delta$ = 0.38 vs 0.12 ppm) in the former than in the latter ($\delta H_A H_B$ = 4.14 and 4.52 in 8 vs 4.22 and 4.34 ppm in 10) as a consequence of the different influences exerted by their hydroxy groups. The very similar magnitudes of the observed coupling constants between the C(2) and C(3) protons (J = 5.9 and 6.0 Hz) accord well with values computed by use of the Karplus equation[10] in conjunction with dihedral angles of ca. 30° and 130° derived by inspection of molecular models of 8 and 10, respectively; the corresponding solid-state values from the X-ray studies of 8 are 39° in the solvated and 33° in the unsolvated crystal forms. Comparison of the upfield region (δ 40 - 80 ppm) of the ^{13}C NMR spectra of 8 and 10 indicated that all carbons (δCH_2 45.3→48.3, CH-S 55.3→58.5, and CH-O 74.7→77.3 ppm, respectively) were shifted downfield in 10, indicative of trans stereochemistry with a minimum number of steric interactions. Furthermore, both cis 8 and trans 10 when treated with PBr_3 in pyridine at room temperature gave 1-[(6-chlorobenzo[b]thien-2-yl)methyl]1H-imidazole 7.

The stereochemistry of cis 8 is influenced by the mechanism of ring contraction. Intramolecular participation of the ring sulfur presumably takes place from the backside of the C-3 --- Br bond in cis-bromohydrin 4 to give thiiranium cation 12. Subsequent ring contraction with simultaneous attack by imidazole at the primary center (methylene group) results in a cis relationship on the newly created dihydrobenzothiophene ring. The mode of formation of trans compound 10 is less clear. It is possible, however, that by an SN_1 process, cis-bromohydrin 4 could give thiiranium cation 13 which would then open in a like manner to produce trans 10. Formation of 7-chloro-2,3-dihydro-4H-1-benzothiopyran-4-one 2 may be explained by simple dehydrobromination of cis-bromohydrin 4, or, more probably, by loss of the benzylic proton from cation 12 or 13.



Treatment of 8 and 10 with NaH in DMF at room temperature, followed by alkylation with 3-(bromomethyl)-2-chlorothiophene gave cis- and trans-1-[[6-chloro-3-[(2-chloro-3-thienyl) methoxy]-2,3-dihydrobenzo[b]thien-2-yl]methyl]1H-imidazoles, 9 and 11, respectively.

In an extension of this work, various substituted cis-6-chloro-2,3-dihydro-2-(1H-imidazol-1-ylmethyl)benzo[b]thiophene-3-ols were reacted with aryl halides to generate 3-aryl ethers of 2-(1H-imidazol-1-ylmethyl)dihydrobenzo[b]thiophenes. Cis compounds showed excellent broad spectrum antifungal activity in both in vitro and in vivo studies, but trans products were less active. The biological profile of these novel antifungal compounds obtained by the ring contraction of cis-3-bromo-3,4-dihydro-2H-1-benzothiopyran-4-ol with azoles will be reported elsewhere.

EXPERIMENTAL

All mps were determined on a Unimelt capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-200 spectrometer using Me_4Si as internal standard, and ^{13}C NMR spectra were recorded on a Varian XL-100 spectrometer. Mass spectra were obtained on Varian Mat CH-5 instrument.

3-Bromo-7-chloro-2,3-dihydro-4H-1-benzothiopyran-4-one 1. To a solution of 2 (10 g, 50.3 mmol) in $CHCl_3$ (200 mL) was added bromine (2.6 mL, 50.3 mmol), and the mixture was stirred for 2 hr at room temperature. The mixture was washed with 10% Na_2SO_3 and water, and then dried over anhydrous $MgSO_4$. Concentration *in vacuo* afforded 1 (12.6 g, 90%) as colourless needles, m.p. 109-110° (from cyclohexane). ^{1}H NMR ($CDCl_3$): δ 3.40 (dd, J = 14.0, 7.5 Hz, H-2_A), 3.68 (dd, J = 14.0, 3.5 Hz, H-2_B), 4.90 (dd, J = 7.5, 3.5 Hz, H-3), 7.15 (dd, J = 8.0, 2.0 Hz, H-6), 7.25 (d, J = 2.0 Hz, H-8), and 8.04 (d, J = 8.0 Hz, H-5). (Found: C, 39.02; H, 2.03; Br, 29.0; Cl, 13.03; S, 11.88. Calc. for $C_9H_6BrClOS$: C, 38.94; H, 2.18; Br, 28.79; Cl, 12.77; S, 11.55%).

Cis-3-bromo-7-chloro-3,4-dihydro-2H-1-benzothiopyran-4-ol 4. To a suspension of 1 (12.6 g, 45.4 mmol) in MeOH (100 mL) at 0° was added $NaBH_4$ (1.71 g, 45.4 mmol), and the reaction mixture was allowed to rise slowly to room temperature over a period of 3 hr. The mixture was subsequently poured into water (2 L) and filtered to give 4 as a colourless solid (10.7 g, 84%), m.p. 141-142°. (Found: C, 38.6; H, 2.69; Br, 28.72; Cl, 12.58; S, 11.40. Calc. for $C_9H_8BrClOS$: C, 38.65; H, 2.88; Br, 28.57; Cl, 12.67; S, 11.46%).

Cis-4-(acetoxy)-3-bromo-7-chloro-3,4-dihydro-2H-1-benzothiopyran 5. Acetic anhydride (1.5 mL) was added to a solution of 4(1 g, 3.5 mmol) in pyridine (10 mL). After stirring it overnight, the reaction mixture was poured into ice and extracted with $CHCl_3$. The organic solution was washed with dilute aqueous HCl and water, and then dried over $MgSO_4$. Evaporation of the solvent gave 5 (1.05 g, 91%) as colourless needles, m.p. 95-96° (from hexane). ^{1}H NMR ($CDCl_3$): δ 2.1 (s, OAc), 3.17 (ddd, J = 12.0, 3.5, 1.0 Hz, H-2_A), 3.78 (dd, J = 12.0, 12.0 Hz, H-2_B), 4.59 (ddd, J = 12.0, 3.5, 2.5 Hz, H-3), 6.19 (dd, J = 2.5, 1.0 Hz, H-4), 7.05 (dd, J = 8.0, 2.0 Hz, H-6), 7.10 (d, J = 2.0 Hz, H-8), 7.30 (d, J = 8.0 Hz, H-5). (Found: C, 41.25; H, 3.15; Br, 24.78; Cl, 11.30; S, 10.10. Calc. for $C_{11}H_{10}BrClO_2S$: C, 41.07; H, 3.13; Br, 24.84; Cl, 11.02; S, 9.96%).

Ring contraction of cis-3-bromo-7-chloro-3,4-dihydro-2H-1-benzothiopyran-4-ol in the presence of imidazole. Compound 4 (10.7 g, 38.3 mmol) and imidazole (13.0 g, 191 mmol) were refluxed in MeCN (500 mL) for 5 hr. After dilution with $CHCl_3$ (1 L), the mixture was washed with water (3 x 1 L), dried over anhydrous $MgSO_4$, and then concentrated *in vacuo* to give a yellow viscous oil. Purification by silica gel chromatography, eluting with $CHCl_3$ furnished 7-chloro-2,3-dihydro-4H-1-benzothiopyran-4-one 2 [1.52 g, 20%, m.p. 64° (lit.[3] m.p. 64-65.5°)]. Further elution with $CHCl_3$-2% MeOH, gave cis-6-chloro-2,3-dihydro-2-(1H-imidazol-1-ylmethyl)benzo[b] thiophene-3-ol 8 (4.86 g, 48%) and trans-6-chloro-2,3-dihydro-2-(1H-imidazol-1-ylmethyl)benzo[b] thiophene-3-ol 10 (0.12 g, 1%).

Compound 8. Colourless needles, m.p. 164-165° (MeCN, MeOH, or CH_2Cl_2). ^{1}H NMR (360 MHz, DMSO-d_6: δ 4.14 (dd, J = 13.0, 9.0 Hz, H-$6'_A$), 4.52 (dd, J = 13.0, 5.0 Hz, H-$6'_B$), 4.29 (m, J = 9.0, 6.0, 5.9 Hz, H-2), 5.18 (t, J = 6.0 Hz, H-3), 6.75 (d, J = 6.0 Hz, OH), 7.31 (d, J = 8.0 Hz, H-4), 7.15 (dd, J = 8.0, 2.0 Hz, H-5), 7.34 (d, J = 2.0 Hz, H-7), 7.65 (bs, H-2'), 6.88 (bs, H-4'), and 7.22 (bs, H-5'). ^{13}C NMR (DMSO-d_6): δ 45.3 (C-6'), 55.3 (C-2), 74.7 (C-3), aromatic carbons at 122.1, 126.6, 128.3 (3 x =CH), and 133.3, 137.7, 140.6 (3 x C*), and imidazole carbons at 119.5, 124.5, 137.7. (Found: C, 53.84; H, 3.91; Cl, 13.27; N, 10.59; S, 11.86. Calc. for $C_{12}H_{11}ClN_2OS$: C, 54.01; H, 4.14; Cl, 13.29; N, 10.50; S, 12.02%).

Compound 10. Colourless needles, m.p. 110-111° (EtOAc). ^{1}H NMR (360 MHz, DMSO-d_6): δ 4.22 (dd, J = 14.0, 8.0 Hz, H-$6'_A$), 4.34 (dd, J = 14.0, 6.0 Hz, H-$6'_B$), 4.06 (m, J = 8.0, 6.0, 6.0 Hz, H-2), 4.97 (t, J = 6.0 Hz, H-3), 5.98 (d, J = 6.0 Hz, OH), 7.31 (d, J = 8.0 Hz, H-4), 7.16 (dd, J = 8.0, 2.0 Hz, H-5), 7.35 (d, J = 2.0 Hz, H-7), 7.68 (bs, H-2'), 6.9 (bs, H-4'), and 7.36 (bs, H-5'). ^{13}C NMR (DMSO-d_6): δ 48.3 (C-6'), 58.5 (C-2), 77.3 (C-3), aromatic carbons at 121.8, 126.9, 128.4 (3 x =CH) and 133.5, 139.9, 140.8 (3 x C*), and imidazole carbons at 119.5, 124.5,

137.5. (Found: C, 53.92: H, 3.98: Cl, 13.09: N, 10.36: S, 11.7. Calc. for $C_{12}H_{11}ClN_2OS$: C, 54.01: H, 4.14: Cl, 13.29: N, 10.50: S, 12.02%).

1-[(6-chlorobenzo[b]thien-2-yl)methyl]1H-imidazole 7. PBr_3 (0.11 mL, 1.2 mmol) was added to a cooled (0-5°) solution of 8 or 10 (0.15 g, 0.56 mmol) in pyridine (2 mL), and the mixture was stirred at room temperature for 2 hr. The mixture was then extracted with $CHCl_3$ (50 mL) and washed with water (2 x 50 mL). The $CHCl_3$ layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford a colourless solid (0.12 g, 86%). Recrystallization from MeCN gave 7 as colourless needles, m.p. 113°. ^1H NMR (100 MHz, $CDCl_3$): δ 5.35 (bs, H-6'), 7.65 (d, J = 9.0 Hz, H-4), 7.30 (dd, J = 9.0, 2.0 Hz, H-5), 7.75 (d, J = 2.0 Hz, H-7), 7.10 (s, H-3), 7.60 (bs, H-2'), 7.10 (bs, H-5'). (Found: C, 57.83: H, 3.71: Cl, 14.15: N, 11.02: S, 12.29. Calc. for $C_{12}H_9ClN_2S$: C, 57.94: H, 3.64: Cl, 14.25: N, 11.26: S, 12.89%).

Cis-1-[[6-chloro-3-[(2-chloro-3-thienyl)methoxy]-2,3-dihydrobenzo[b]thien-2-yl]methyl]1H-imidazole 9. To a suspension of NaH (50% dispersion) (0.4 g, 8.25 mmol) in dry DMF (20 mL) was added compound 8 (2.0 g, 7.5 mmol) and the mixture was stirred for 1 hr. 3-(bromomethyl)-2-chlorothiophene (1.75 g, 8.25 mmol) was then added, and stirring was continued for an additional 1 hr. The reaction mixture was extracted with CH_2Cl_2 (500 mL) and washed with water (3 x 500 mL). The extract was dried over $MgSO_4$, and subsequently evaporated in vacuo to give an oily residue which was crystallized from cyclohexane to afford 9 (2.04 g, 61%), m.p. 99-101°. ^1H NMR ($CDCl_3$): δ 4.04 (m, H-6'), 4.50 (m, H-2), 4.55 (br dd, H-6"), 5.53 (d, J = 5.0 Hz, H-3), 6.93 (t, J = 1.0 Hz, H-4'), 7.07 (t, J = 1.0 Hz, H-5'), 7.52 (t, J = 1.0 Hz, H-2'), 7.05 (d, J = 6.0 Hz, H-4"), 7.20 (d, J = 6.0 Hz, H-5"), 7.13 (dd, J = 8.0, 2.0 Hz, H-5), 7.26 (d, J = 8.0 Hz, H-4), 7.23 (d, J = 2.0 Hz, H-7). ^{13}C NMR ($CDCl_3$): δ 45.8 (C-6'), 54.6 (C-2), 64.3 (C-6"), 83.1 (C-3), aromatic carbons at 123.3, 126.2, 127.2 (3x = CH) and 134.5, 136.2, 140.0 (3 x C*), imidazole carbons at 119.2, 123.7, 137.7, and thiophene carbons at 123.3, 129.6 (2x =CH), and 129.6, 135.4 (2 x C*). (Found: C, 51.33: H, 3.43: Cl, 18.06: N, 7.06: S, 16.32. Calc. for $C_{17}H_{14}Cl_2N_2OS_2$: C, 51.4: H, 3.55: Cl, 17.84: N, 7.05: S, 16.14%).

Trans-1-[[6-chloro-3-[(2-chloro-3-thienyl)methoxy]-2,3-dihydrobenzo[b]thien-2-yl]methyl]-1H-imidazole 11. Compound 11 was prepared from 10 according to the procedure described for compound 9, yielding colourless needles, m.p. 81-82° (cyclohexane). ^1H NMR ($CDCl_3$): δ 4.07 (m, H-6'), 4.07 (m, H-2), 4.49 (br dd, H-6"), 4.75 (d, J = 2.0 Hz, H-3), 7.0, 7.12, 7.52 (3 x imidazole-H), 6.9, 7.51 (d, J = 6.0 Hz, 2 x thiophene-H), 7.15 (dd, J = 8.0, 2.0 Hz, H-5), 7.28 (d, J = 8.0 Hz, H-4), 7.30 (d, J = 2.0 Hz, H-7). ^{13}C NMR ($CDCl_3$): δ 49.8 (C-6'), 55.4 (C-2), 63.1 (C-6"), 84.4 (C-3), all aromatic carbons at 123.0, 125.5, 127.7 (x2), 130.1, 134.6, 134.7, 137.4, 138, 142.7, and imidazole carbons at 118.8, 123.5, 137.4. (Found: C, 51.32: H, 3.47: Cl, 17.76: N, 7.36: S, 16.01. Calc. for $C_{17}H_{14}Cl_2N_2OS_2$: C, 51.4: H, 3.55: Cl, 17.84: N, 7.05: S, 16.14%).

Crystallographic Characterization of 8. For X-ray analysis, 8 was recrystallized initially from EtOAc and subsequently from MeOH, MeCN, and CH_2Cl_2. Crystals from EtOAc became opaque fairly rapidly in the open air, indicating that they probably contained solvent molecules which were lost quite readily, and, accordingly, those used for the X-ray study were sealed inside thin-walled glass capillaries to minimize the rate of deterioration during data collection. Crystallization from MeOH, MeCN, or CH_2Cl_2 afforded a second, more stable solvent free form.

Crystal Data. $C_{12}H_{11}ClN_2OS.\ C_4H_8O_2$ (8.¼EtOAc), M = 310.8, monoclinic, a = 18.054(2) Å, b = 8.961(1) Å, c = 18.445(2) Å, β = 92.69 (1)°, V = 2980.8 Å^3, Z = 8, $D_{calc.}$ = 1.385 g cm^{-3}, μ (Cu-Kα radiation, λ = 1.5418 Å) = 36.1 cm^{-1}. Space group Cc(C_s^4) or C2/c(C_{2h}^6) from the systematic absences: hkℓ when h + k ≠ 2n, h0ℓ when ℓ ≠ 2n; shown to be the latter by structure solution and refinement. Sample dimensions: 0.14 x 0.30 x 0.90 mm.

$C_{12}H_{11}ClN_2OS$ (8), M = 266.75, monoclinic, a = 5.451(1) Å, b = 26.024(3) Å, c = 11.467(1) Å, β = 131.87(1)°, V = 1211.3 Å^3, Z = 4, $D_{calc.}$ = 1.463 g cm^{-3}, μ(Cu-Kα radiation) = 42.9 cm^{-1}. Space group $P2_1/c(C_{2h}^5)$ uniquely from the systematic absences: 0k0 when k ≠ 2n, h0ℓ when ℓ ≠ 2n. Sample dimensions: 0.10 x 0.22 x 0.60 mm.

Preliminary unit-cell parameters and space group information were obtained from

boscillation, Weissenberg, and precession photographs. Intensity data ($hk\pm\ell$) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu-Kα radiation, incident-beam graphite mono-chromator: ω-2θscans, $\theta_{max.} = 67^{\circ}$). Crystal and instrument stability, monitored periodically throughout by remeasuring the intensities of 4 reference reflections, showed insignificant variation (-1.6% over 33 hr for 8.½EtOAc: +0.7% over 23 hr for 8). From totals of 2647 and 2158 unique measurements for 8.½EtOAc and 8, respectively, after averaging equivalent forms, those 1732 and 1844 reflections with $I > 3.0\sigma(I)$ were retained for the structure analyses. In addition to the usual Lorentz and polarization corrections, empirical absorption corrections, based on the ϕ-dependence of the intensities of several reflections with x ca. 90°, were also applied to these data. Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 25 reflections ($40^{\circ} < \theta < 65^{\circ}$ for 8.½EtOAc; $58^{\circ} < \theta < 67^{\circ}$ for 8) widely separated in reciprocal space.

The crystal structure of 8.½EtOAc was solved by the heavy-atom approach.[7] Approximate sulphur and chlorine atom coordinates were derived from a Patterson map, and the remaining non-hydrogen atoms of 8 were located in a weighted F_o Fourier synthesis phased by these two atoms. Several rounds of full-matrix least-squares adjustment of positional and anisotropic thermal parameters were followed by evaluation of a difference Fourier synthesis which revealed, in the vicinity of the crystallographic C_2 axis of space group C2/c, a set of maxima which could be interpreted in terms of atoms of an ethyl acetate molecule disordered over two orientations. Parameters for the ethyl acetate atoms were then included as variables in the next series of least-squares calculations following which it was verified that positions calculated for the hydrogen atoms of 8 coincided with significant positive regions in a difference Fourier synthesis. With the inclusion of these hydrogen atoms at their calculated positions, several further rounds of least-squares refinement of non-hydrogen atom parameters led to convergence at $R = 0.072$ ($R_w = 0.104$).

Direct methods[7] were used to solve the crystal structure of the unsolvated crystal form. Approximate non-hydrogen atom positions were obtained from an E-map. Hydrogen atoms were all located in a difference Fourier synthesis evaluated after several cycles of full-matrix least-squares adjustment of non-hydrogen atom positional and anisotropic thermal parameters, and, with their inclusion at their calculated positions in the later iterations, the refinement converged at $R = 0.036$ ($R_w = 0.059$).

Anisotropic temperature factor parameters, hydrogen atom parameters, and atomic co-ordinates have been deposited with the Cambridge Crystallographic Data Centre. Neutral atom scattering factors used in the structure-factor calculations were taken from ref. 11. In the least-square iterations, $\Sigma w\Delta^2$ [$w = 1/\sigma^2(|F_o|)$; $\Delta = |F_o| - |F_c|$] was minimized.

REFERENCES AND NOTES

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6. All new compounds reported here are racemic, but only one enantiomer is shown throughout for convenience.
7. Crystallographic calculations were performed on a PDP11/44 computer by use of the Enraf-Nonius SDP suite of programmes. The direct methods programme MULTAN11/80 was employed.
8. $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$.
9. Endocyclic torsion angles, ω_{ij}(°), in the dihydrothiophene ring of 8 in crystals of 8.½EtOAc, with, in parentheses, corresponding values in unsolvated crystals of 8, follow: $\omega_{1,2}$ -30.9(26.6), $\omega_{2,3}$ 37.3(-32.0), $\omega_{3,3a}$ -27.8(23.7), $\omega_{3a,7a}$ 4.5(-4.0), $\omega_{1,7a}$ 16.2(-13.5).
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