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The exposure of *dl*-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole (tetramisole) to lithium diisopropylamide in tetrahydrofuran ruptures the thiazole ring to give, following the introduction of primary or secondary alkyl halides, 1-(2'-alkylthio)ethyl-4-phenylimidazoles. Conclusive evidence for the thiazole ring opening was obtained by a single crystal x-ray diffraction study of 1-(2'-*p*-bromobenzylthio)ethyl-4-phenylimidazole.

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dl-2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*]thiazole (1) (tetramisole) is a broad spectrum anthelmintic which has found application in veterinary medicine (1). Recently, levamisole (*l*-tetramisole) was reported to potentiate the immune system in man (2) and to prolong significantly the disease-free interval in patients with lung or breast cancer when administered in conjunction with other protocols (3). These reports prompted us to synthesize various analogs and derivatives of tetramisole. In the course of this investigation, we observed an unusual fragmentation of the thiazole ring using an aprotic base, lithium diisopropylamide. The product of this reaction was different from the products of aqueous basic hydrolysis of levamisole reported by Dickinson, Hudson and Taylor (4).

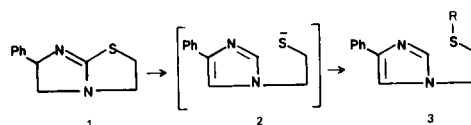
The exposure of tetramisole (1) to two equivalents of lithium diisopropylamide in THF and the subsequent introduction of various alkyl halides led to the isolation of 1-(2'-alkylthio)ethyl-4-phenylimidazoles 3 in good yield (Table I). Both primary and secondary alkyl halides

Table I

The Conversion of Tetramisole to
1-(2'-Alkylthio)ethyl-4-phenylimidazoles 3

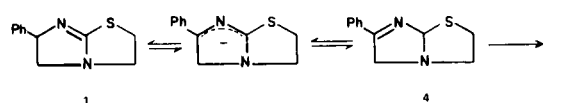
Alkyl Halide	Isolated Yield of 3, %
a (CH ₃) ₂ CHBr	80
b CH ₂ =CHCH ₂ Br	69
c <i>n</i> -C ₄ H ₉ Br	55
d cyclopentyl bromide	59
e C ₆ H ₅ CH ₂ Cl	69
f <i>p</i> -BrC ₆ H ₄ CH ₂ Br	42
g C ₆ H ₅ COCH ₂ Br	63

proved effective in trapping the intermediate thiolate anion 2. The products were readily identified on the basis of their nmr and ultraviolet spectra which closely resembled those of 4(5)-phenylimidazole. Particularly diagnostic was the disappearance of the C-5 methylene proton signals in the nuclear magnetic resonance spectrum of 1 and the appearance of low field multiplets characteristic of aro-



matic protons in the imidazoles 3.

The mechanism of the ring opening 1 → 2 has not been studied in detail. Since Baklien has reported that levamisole will racemize to tetramisole in the presence of amine bases (5), it is possible that an equilibrium exists between tetramisole and its conjugated isomer 4. The 1,4-elimination of thiolate anion from 4 to give 2 is then driven by the aromatization of the imidazoline ring to give an imidazole.



Conclusive evidence for the thiazole ring opening was obtained by a single crystal x-ray diffraction study of 1-(2'-*p*-bromobenzylthio)ethyl-4-phenylimidazole (3f). The intramolecular bond distances and angles (as well as the numbering scheme for this molecule) are displayed in Figure 1. Most of the bond lengths of the compound are

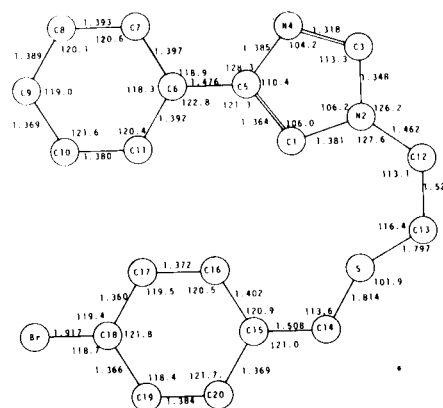


Figure 1. Intramolecular Bond Distances and Angles. The average estimated standard deviation in bond length is 0.007 Å and in bond angle is 0.6°.

within the range of expected values (6). The Br-C (18) distance is slightly elongated over the value of $1.85 \pm (1)$ Å given in Sutton. All three ring systems are planar within experimental error (7). The dihedral angle between the imidazole ring and the attached phenyl ring is 4.0° which is indicative of some conjugation between these two aromatic moieties. Consistent with this suggestion, the C(5)-C(6) bond is shorter than a typical carbon-carbon bond. A calculation of the bond order of this bond using the equation $D(n') = 1.54 - 0.71 \log(n')$ (where $D(n')$ = bond length under consideration and n' = bond order) gives a value of 1.23. The slight twist of the phenyl ring with respect to the imidazole ring can be explained by the intermolecular contacts between C(8) of the phenyl ring and C(19), H(1C19), C(20) and H(1C20) in an adjacent molecule which were determined to be 3.71, 3.08, 3.68 and 2.98 Å, respectively.

The two most significant features of the molecular packing of **3f** are the weak interactions between N(4) and H(1C3) in adjacent molecules and the stacking of the chain C(12)-N(2)-C(3)-N(4). A portion of the unit cell

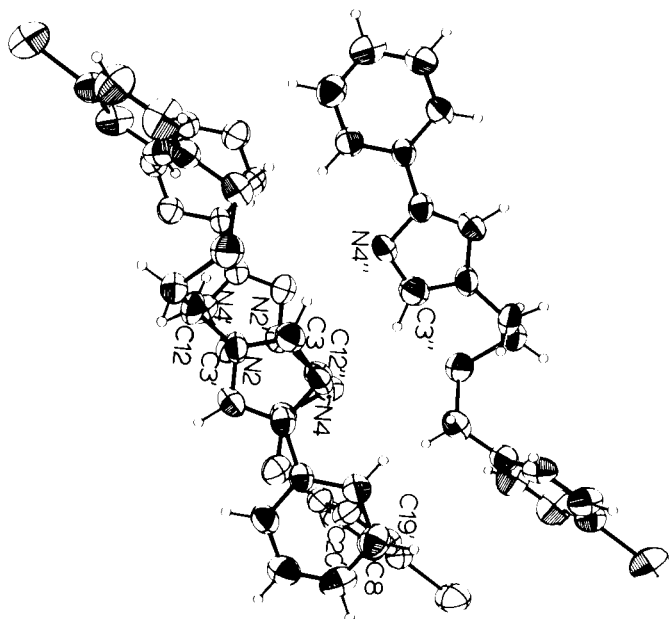


Figure 2. A portion of the unit cell of 1-(2'-*p*-bromobenzylthio)ethyl-4-phenylimidazole (**3f**). Molecules shown are at x, y, z : 1.0- $x, -y, 1.0-z$ ($'$), 1.0- $x, 1.0-y, 1.0-z$ ($'$).

illustrating these features is displayed in Figure 2. Although not a typical hydrogen bond (8), the N(4)...H(1C3)-C(3) interaction is similar to the interactions described for O...H-C bonds (9). The stacking of the C(12)-N(2)-C(3)-N(4) moieties in symmetry related molecules is such that each carbon is stacked directly above a nitrogen atom and vice versa. The spacing between each pair of atoms is 3.41 Å. This stacking interaction is of the dipole-induced dipole type found for base stacking in nucleic acid constituents (10).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were taken on a Beckman Acculab 4 spectrophotometer as potassium bromide pellets or liquid films, and ultraviolet spectra were recorded on a Beckman Model 25 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian EM-360 spectrometer with tetramethylsilane as an internal standard. The mass spectra were obtained with a Varian MAT CH-5 instrument. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Georgia. Column chromatography was performed using J. T. Baker aluminum oxide (JT0537-01).

The following is a typical experimental procedure.

1-(2'-Isopropylthio)ethyl-4-phenylimidazole (**3a**).

To a solution of 30 mmoles of lithium diisopropylamide in 20 ml. of anhydrous tetrahydrofuran at 0° under a nitrogen atmosphere was added 3.0 g. (15 mmoles) of tetramisole (**1**) in 10 ml. of tetrahydrofuran. The red solution was stirred for 5 minutes at 0° . To this solution was added 3.7 g. (30 mmoles) of 2-bromopropane in 10 ml. of tetrahydrofuran. The yellow solution was stirred an additional 15 minutes and quenched with water. The product was extracted into dichloromethane and, following drying, was concentrated and chromatographed using a solvent progression of 1:1 petroleum ether-chloroform to chloroform on a 2.5 cm. diameter column at 20-60 psi to afford 2.9 g. (80%) of **3a**, m.p. $82-83^\circ$; ir (potassium bromide): 3120, 1605 and 1555 cm^{-1} ; uv max (95% ethanol): 256 nm ($\epsilon, 14,800$); nmr (deuteriochloroform): δ 1.10 (d, 6, $J = 7 \text{ Hz}$, $\text{CH}(\text{CH}_3)_2$), 2.65 (septet, 1, $J = 7 \text{ Hz}$, $\text{CH}(\text{CH}_3)_2$), 2.65 (m, 2, $\text{NCH}_2\text{CH}_2\text{S}$), 3.85 (m, 2, $\text{NCH}_2\text{CH}_2\text{S}$), and 7.0-8.0 (m, 7, aromatic H); ms: (70 eV) m/e (relative intensity) 246 (M^+ , 100), 203 (25), 172 (63), 103 (63), and 61 (81).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{S}$: C, 68.29; H, 7.32; N, 11.38. Found: C, 68.06; H, 7.34; N, 11.35.

1-(2'-Allylthio)ethyl-4-phenylimidazole (**3b**).

This compound had m.p. 37° ; ir (potassium bromide): 3080, 2930, 1632, 1605 and 1500 cm^{-1} ; uv max (95% ethanol): 258 nm ($\epsilon, 14,500$); nmr (deuteriochloroform): δ 2.77 (m, 2, $\text{NCH}_2\text{CH}_2\text{S}$), 3.00 (d, 2, $J = 7 \text{ Hz}$, $\text{SCH}_2\text{CH}=\text{CH}_2$), 4.07 (m, 2, $\text{NCH}_2\text{CH}_2\text{S}$), 4.8-6.1 (m, 3, vinyl H), and 7.1-7.9 (m, 7, aromatic H); ms: (70 eV) m/e (relative intensity) 284 (M^+ , 6), 244 (100), 203 (30), 172 (43), 104 (30), and 77 (22).

Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{S}$: C, 68.85; H, 6.55; N, 11.48. Found: C, 68.70; H, 6.61; N, 11.45.

1-(2'-Butylthio)ethyl-4-phenylimidazole (**3c**).

This compound had m.p. $34-35^\circ$; ir (potassium bromide): 3120, 1615 and 1565 cm^{-1} ; uv max (95% ethanol): 256 nm ($\epsilon, 14,100$); nmr (deuteriochloroform): δ 0.9-1.5 (m, 7, $\text{SCH}_2(\text{CH}_2)_2\text{CH}_3$), 2.42 (m, 2, $\text{SCH}_2(\text{CH}_2)_2\text{CH}_3$), 2.80 (m, 2, $\text{NCH}_2\text{CH}_2\text{S}$), 4.03 (m, 2, $\text{NCH}_2\text{CH}_2\text{S}$), and 7.2-8.0 (m, 7, aromatic H); ms: (70 eV) m/e (relative intensity) 260 (M^+ , 86), 203 (9), 172 (30), 117 (100), and 61 (49).

Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{S}$: C, 69.23; H, 7.69; N, 10.77. Found: C, 69.09; H, 7.72; N, 10.76.

1-(2'-Cyclopentylthio)ethyl-4-phenylimidazole (**3d**).

This compound had m.p. $56-57^\circ$; ir (potassium bromide): 3095, 1600 and 1550 cm^{-1} ; uv max (95% ethanol): 258 nm ($\epsilon, 16,000$); nmr (deuteriochloroform): δ 1.2-2.2 (m, 8, cyclopentyl CH_2), 2.7-3.4 (m, 1, CH_2SCH), 2.85 (m, 2, $\text{NCH}_2\text{CH}_2\text{S}$), 4.10 (m, 2, $\text{NCH}_2\text{CH}_2\text{S}$), and 7.1-7.9 (m, 7, aromatic H); ms: (70 eV) m/e (relative intensity) 272 (M^+ , 11), 249 (52), 204 (52),

148 (36) and 69 (100).

Anal. Calcd. for $C_{16}H_{20}N_2S$: C, 70.59; H, 7.35; N, 10.29.
Found: C, 70.57; H, 7.35; N, 10.31.

1-(2'-Benzylthio)ethyl-4-phenylimidazole (**3e**).

This compound had m.p. 83-84°; ir (potassium bromide): 3090, 1598 and 1548 cm^{-1} ; uv max (95% ethanol): 257 nm (ϵ , 18,000); nmr (deuteriochloroform): δ 2.72 (m, 2, NCH_2CH_2S), 3.58 (s, 2, SCH_2Ph), 3.90 (m, 2, NCH_2CH_2S), and 7.1-7.9 (m, 12, aromatic H); ms: (70 eV) m/e (relative intensity) 294 (M^+ , 78), 203 (70), 176 (25), 172 (33), and 91 (100).

Anal. Calcd. for $C_{18}H_{18}N_2S$: C, 73.47; H, 6.12; N, 9.52.
Found: C, 73.40; H, 6.19; N, 9.52.

1-(2'-p-Bromobenzylthio)ethyl-4-phenylimidazole (**3f**).

This compound had m.p. 85.5-87°; ir (potassium bromide): 3100, 1602 and 1485 cm^{-1} ; uv max (95% ethanol): 257 nm (ϵ , 19,000); nmr (deuteriochloroform): δ 2.65 (m, 2, NCH_2CH_2S), 3.43 (s, 2, SCH_2Ar), 3.93 (m, 2, NCH_2CH_2S), and 6.9-7.9 (m, 11, aromatic H); ms: (70 eV) m/e (relative intensity) 374 (M^+ , 52), 372 (52), 203 (100), 172 (50), 171 (52), and 169 (52).

Anal. Calcd. for $C_{18}H_{17}BrN_2S$: C, 57.91; H, 4.56; N, 7.51.
Found: C, 57.99; H, 4.61; N, 7.54.

1-(2'-Phenacylthio)ethyl-4-phenylimidazole (**3g**).

This compound had ir (thin film): 3050, 1660, 1590 and 1570 cm^{-1} ; uv max (95% ethanol): 258 nm (ϵ , 20,900); nmr (deuteriochloroform): δ 2.90 (m, 2, NCH_2CH_2S), 3.65 (s, 2, SCH_2CO), 4.10 (m, 2, NCH_2CH_2S) and 7.1-8.1 (m, 12, aromatic H); ms: (70 eV) m/e (relative intensity) 322 (M^+ , 79), 248 (16), 203 (16), 179 (23), 172 (35), 105 (100), 91 (39), and 77 (77).

Crystal Data.

Crystals of 1-(2'-p-bromobenzylthio)ethyl-4-phenylimidazole (**3f**) were grown from chloroform using the vapor diffusion method with petroleum ether as the second solvent. The unit cell is monoclinic. The cell dimensions, determined by least-squares fit of the cell parameters to fifteen carefully measured reflections, are $a = 15.227$ (4), $b = 5.629$ (2), $c = 19.596$ (6) Å and $\beta = 91.48$ (2)°. The volume is 1679 (1) Å³. The measured density of the crystals, determined by pycnometry using zinc iodide solution, is 1.48 g/cm³. Assuming four molecules in the unit cell, the calculated density is 1.477 g/cm³. From precision photographs and the absences observed in the measurement of the sphere of reflection, the space group is $P2_1/c$. The systematic absences are (0, k, 0) with $k = 2n+1$ and (h, 0, l) with $l = 2n+1$.

Intensity Measurements.

Intensity measurements were made on a crystal of dimensions 0.64 x 0.19 x 0.19 mm. mounted parallel to the needle axis and aligned on a Syntex P1 auto diffractometer equipped with a graphite monochromator. Using Mo $K\alpha$ radiation ($\lambda = 0.71069$ Å), measurements were made with the θ -2 θ scanning technique as programmed by Syntex. The scan speed was varied from 24°/minute for reflections with more than 1500 counts in a 2 second scan to 2°/minute for reflections with 30 counts in a 2 second scan. By examining reciprocal space at high 2 θ , it was determined that background was at least 15 counts/second and, hence, reflections with less than 30 counts in a two second scan were not measured. The scan ranges were calculated to start 1° below 2 θ for $K\alpha_1$ and end 1° above 2 θ for $K\alpha_2$. Background measurements were made at the beginning and end of each scan period for a period equal to the scan time. The background, collected using the stationary crystal-stationary counter technique, was assumed to be linear between the two measured points.

Of the 5487 reflections surveyed within a single quadrant to 2 $\theta = 60^\circ$, 2168 reflections had at least 30 counts in a 2 second scan and were measured. The data was monitored after every 100 measurement cycles by four reference standards. The references showed no significant variation over the course of the experiment. The data was processed in the usual way with values of I_{obsd} and $\sigma(I_{obsd})$ corrected for Lorentz and polarization effects. No correction was made for absorption ($\mu(MoK\alpha) = 27.1 cm^{-1}$) since the transmission coefficients (11) varied from only 0.592 to 0.650. Of the 2168 reflections measured, 1209 were determined to have intensity significantly above background and were used in the refinement. A reflection was taken as significant when $F_o^2 > 3.0 * \sigma(F_o^2)$ and $\sigma(F_o^2) = [TSC + BACK + \{P*(TSC-BACK)\}^2]^{1/2} * RLP$. TSC is the total counts collected during the measurement scan and BACK is the total number of counts accumulated during the background measurements. P, a damping factor to downweight stronger intensities, was given a value of 0.04 (12). RLP, the reciprocal of the Lorentz and polarization correction, was defined as

$$0.5 \left(\frac{2.0 * \sin \theta \cos \theta}{1.0 + \cos^2 2\theta_{mono} + \cos^2 2\theta} \right) + 0.5 \left(\frac{\cos 2\theta_{mono} + \cos^2 2\theta}{1.0 + \cos 2\theta_{mono}} \right)$$

where θ_{mono} is the monochromator angle.

Solution and Refinement.

The structure was solved using heavy atom techniques. A difference electron density summation based on the positions of the bromine and sulfur atoms revealed the position of 11 of the 20 light atoms. A second difference map based on the positions of these 13 atoms revealed the rest of the molecule. Initial isotropic full-matrix least-squares refinement of the model with all light atoms included as carbons converged at $R = \Sigma[|F_o| - |F_c|] / \Sigma|F_o| = .107$. Upon examination of the resulting bond lengths and isotropic thermal parameters, the two nitrogen atoms were identified. Further refinement with the bromine and sulfur atoms treated anisotropically and the light atoms included with the proper atom type converged with $R = .064$. From a difference map based on this calculation, the positions of all seventeen hydrogens were determined. The hydrogen atoms were added to the model in fixed positions with isotropic thermal parameters 1.0 greater than those of the atom to which they were attached, and all non-hydrogen atoms were refined anisotropically. At convergence, $R = .0381$ and $wR = [\Sigma w(|F_o| - |F_c|)^2 / \Sigma w|F_o|^2]^{1/2} = .0426$. The standard deviation of an observation of unit weight was 1.29. A final difference map had no significant residual density. The scattering curves used were those for neutral atoms (13). Except for the data reduction program which was written in this laboratory based on routines supplied by Syntex Analytical Instruments, all programs used were those contained in J. A. Ibers' Northwestern Crystallographic Computing Packages. The weighting scheme used in all refinements was based on counting statistics where, $w = 1/\sigma^2(F_o) = 4.0(F_o^2)/\sigma^2(F_o^2)$.

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