Studies on the Chemistry of 2,3,5,6-Tetrahydro-6-phenylimidazo[2,1-*b*]-thiazole II. (1) Reaction with Nucleophiles.

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The title compound behaves as an ambident electrophile which reacts with alkylthiols, thiophenols, and sodium diethyldithiocarbamate to give 1-(2-substituted ethyl)-4-phenylimidazolidine-2-thiones by attack at C-2. In contrast, the reaction with pyrrolidine involves attack at the bridgehead carbon atom, followed by elimination of thiirane, to give 4-phenyl-2-(1-pyrrolidino)-imidazoline.

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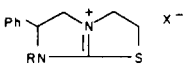
7-Alkyl-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazolium compounds (**1**) and dithiocarbamidium ions behave as ambident electrophiles which react either at the central iminium carbon atom or at the sp^3 carbon α to sulphur, depending on the nucleophile (1,3). It therefore seemed of interest to examine the reactions of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole (**2**) with nucleophiles to determine whether, like the alkylated derivative (**1**), it exhibited ambident character, and whether its reactions might be of synthetic utility in view of the facile elimination of thiirane from 5,6-dihydrothiazolo[2,3-*b*]-thiazolium salts (**3**) when reacted with nucleophiles (4). The only previous report of the reaction of **2** with nucleophiles involves its hydrolysis to the thiol **4** (5). We now report the behaviour of compound **2** with sulphur and nitrogen nucleophiles.



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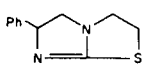

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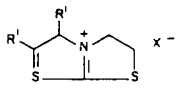

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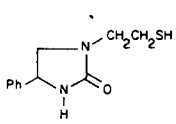

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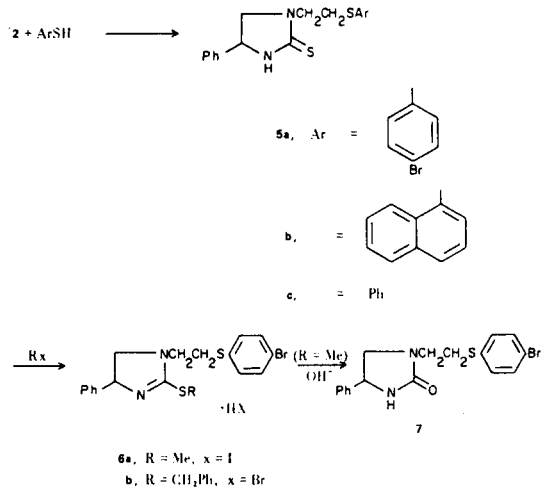
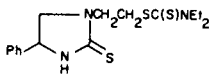
The reaction of the tetrahydroimidazo[2,1-*b*]thiazole **2** with thiophenols occurred readily in 2-ethoxyethanol at reflux, or on heating a mixture of the starting materials in the absence of solvent at 180°. The latter method gave essentially quantitative yields. The products (**5**), derived by attack of the nucleophile at C-2 are analogous to those obtained by treatment of **1** with sulphur nucleophiles (1). The assigned structure is consistent with all physical data and the compounds underwent the expected reactions. Thus treatment of **5a** with iodomethane or benzyl bromide readily gave the *S*-alkylated compounds **6a** and **6b**, and basic hydrolysis of the former gave the imidazolidone **7**. Attempted conversion of **6a** to a 2-aminoimidazoline by reaction with pyrrolidine, however, invariably led to intractable tars.



6a, R = Me, x = I
b, R = CH_2Ph, x = Br

The reaction of sodium diethyldithiocarbamate with **2** similarly led to compound **8**, and reaction with 1,3-propanedithiol gave **9**; a reaction which might be of interest for the preparation of mixed heteroatom crown compounds.



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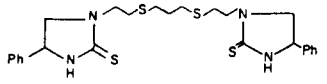

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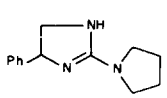
Compound **2** when refluxed in an excess of pyrrolidine gave the 2-pyrrolidinoimidazoline **10** in good yield (79%). The reaction presumably occurs *via* compound **11**, which eliminates thiirane to give **10** (4,6). Surprisingly, other amines (morpholine, diisopropylamine, piperidine) failed to give clean reactions and we were unable to establish the conversion as a general procedure.



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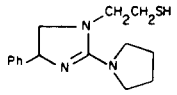

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The behaviour of compound **2** with nucleophiles is similar to that of the quaternary compound **1**. Thus hydroxide ions attack at the bridgehead carbon (1,5),

while sulphur nucleophiles give products derived from attack at C-2. We suggest that similar mechanisms, involving kinetic or thermodynamic control, operate in both series to explain the nature of the products formed (1).

EXPERIMENTAL

General. Melting points were determined using a Büchi capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 157 spectrometer using sodium chloride plates. Nmr spectra were recorded at 100 MHz using a Varian HA 100D spectrometer. The chemical shift values are expressed as δ values relative to a tetramethylsilane internal standard. Microanalyses were carried out on a Carlo-Erba Elemental Analyser Model 1104. Column chromatography was performed using Woelm neutral alumina (activity 1), or silica gel (60-120 mesh) from B.D.H. Ltd.

1-[2-(4-Bromophenylthio)ethyl]-4-phenylimidazolidine-2-thione (**5a**).

A mixture of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole (**2**) (20.4 g., 0.1 mole) and 4-bromothiophenol (18.9 g., 0.1 mole) was heated at 180° for 4 hours under a nitrogen atmosphere. The reaction mixture was allowed to cool and methanol (40 ml.) added. The white solid obtained on scratching was filtered to give 37.5 g. (95%) of **5a**, m.p. 136-138°. Recrystallisation from toluene/l petroleum b.p. 80-100° raised the m.p. to 138-139°; ir (nujol): 3100 cm^{-1} (NH); nmr (deuteriochloroform + DMSO-d_6): 3.14 δ (t, 2H, CH_2SAr), 3.74 (t, 2H, NCH_2-C-S), 3.48 + 4.04 (q + t, 2H, NCH_2CPh), 4.76 (q, 1H, PhCH), 7.3 (s, 9H, ArH), 8.2 (br., 1H, NH); mass spectrum: m/e 394, 392 (M^+), 216, 214, 200, 146, 135, 91.

Anal. Calcd. for $C_{17}H_{17}BrN_2S_2$: C, 51.9; H, 4.36; N, 7.12; S, 16.3. Found: C, 51.8; H, 4.3; N, 7.0; S, 16.2.

1-[2-(1-Naphthylthio)ethyl]-4-phenylimidazolidine-2-thione (**5b**).

An analogous procedure to that described for the preparation of **5a** gave **5b** as white crystals in 99% yield, m.p. 173-174.5° (unchanged by recrystallisation from ethanol); ir (nujol): 3100 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): 3.26 δ (t, 2H, CH_2SAr), 3.8 (t, 2H, NCH_2-C-S), 3.48 + 4.06 (q + t, 2H, NCH_2CPh), 4.8 (q, 1H, PhCH), 7.26 (s, 5H, phenyl H), 7.46 + 7.76 + 8.27 (m, 7H, naphthyl H), 8.6 (br., 1H, NH); mass spectrum: m/e 364 (M^+), 237, 186.

Anal. Calcd. for $C_{21}H_{20}N_2S_2$: C, 69.2; H, 5.53; N, 7.68; S, 17.6. Found: C, 68.9; H, 5.5; N, 7.4; S, 17.9.

1-[(2-Phenylthio)ethyl]-4-phenylimidazolidine-2-thione (**5c**).

A solution of compound **2** (2.04 g., 0.01 mole) and thiophenol (1.1 g., 0.01 mole) in 2-ethoxyethanol (10 ml.) was heated at reflux under nitrogen for 6 hours. The reaction mixture was poured into aqueous sodium hydroxide (200 ml. of 0.1 *N*) and extracted with methylene chloride. The extracts were washed with water, dried (magnesium sulfate), and evaporated to give 2.4 g. (76%) of **5c**, m.p. 88-89° (from toluene/l. petroleum b.p. 60-80°); ir (nujol): 3100 cm^{-1} (NH), nmr (deuteriochloroform): 3.2 δ (t, 2H, CH_2SPh), 3.82 (t, 2H, NCH_2-C-S), 3.58 + 4.12 (q + t, 2H, NCH_2CPh), 4.80 (q, 1H, PhCH), 6.34 (br., 1H, NH), 7.3 (s, 5H, ArH); mass spectrum: m/e 314 (M^+), 205, 136.

Anal. Calcd. for $C_{17}H_{18}N_2S$: C, 64.9, H, 5.77; N, 8.91, S, 20.4. Found: C, 64.6, H, 5.8; N, 8.9, S, 20.3.

1-[2-(4-Bromophenylthio)ethyl]-2-methylthio-4-phenyl-Δ^2-imidazoline Hydriodide (**6a**).

Iodomethane (1.56 g., 0.011 mole) was added to a suspension of compound **5a** (3.93 g., 0.01 mole) in acetone (25 ml.) and the mixture stirred at room temperature overnight. Filtration gave 4.7 g. (88%) of **6a** as a white crystalline solid, m.p. 144-145.5° (attempted recrystallisation from ethanol led to some decomposition), ir (nujol): 1550 cm^{-1} (C=N); nmr (DMSO-d_6): 2.7 δ (s, 3H, SCH_3), 3.37 (t, 2H, CH_2SAr), 3.68 (t, 2H, CH_2-C-S), 3.84 + 4.50 (q + t, 2H, NCH_2CPh), 5.35 (q, 1H, PhCH), 7.4 (m, 9H, ArH), mass spectrum: m/e 406 (weak), 392, 216.

Anal. Calcd. for $C_{18}H_{20}BrIN_2S_2$: C, 40.6, H, 3.77; N, 5.23, S, 12.0. Found: C, 40.2, H, 3.6, N, 5.1, S, 12.1.

2-Benzylthio-1-[2-(4-bromophenyl)ethyl]-4-phenyl-Δ^2-imidazoline Hydrobromide (**6b**).

An analogous procedure to that described for **6a** gave **6b** as white crystals, m.p. 142-146° in 74% yield, ir (nujol): 1550 cm^{-1} (C=N), nmr (deuteriochloroform): 3.08 δ (t, 2H, CH_2SAr), 3.58 (m, 3H, $CHNCH_2$-C-S), 4.3 (t, 1H, PhCCHN-), 4.89 (q (AB), 2H, SCH_2Ph), 5.32 (q, 1H, PhCH), 7.24 (m, 10H, ArH); mass spectrum: m/e 484, 482 (M^+), 216, 214.

Anal. Calcd. for $C_{24}H_{24}Br_2N_2S_2$: C, 51.1; H, 4.29; N, 4.96; S, 11.4. Found: C, 50.9; H, 4.1; N, 4.9; S, 11.5.

1-[2-(4-Bromophenylthio)ethyl]-4-phenylimidazolidin-2-one (**7**).

A solution of **6a** (5.35 g., 0.01 mole) in methanol/water (50/10 ml.) containing sodium hydroxide (2.0 g., 0.05 mole) was refluxed for 48 hours, during which time a clear oil separated. The reaction mixture was diluted with water and the methanol evaporated under reduced pressure. Extraction of the residual liquid with chloroform gave, after drying (magnesium sulfate) and evaporation, 3.6 g. (96%) of **7** as a white solid, m.p. 90-93°. Recrystallisation of a portion from light petroleum, b.p. 80-100°, raised the m.p. to 96.5-97.5°; ir (nujol): 3100 cm^{-1} (NH), 1670 (C=O); nmr (deuteriochloroform): 2.93-3.50 δ (m, 5H), 3.78 (t, 1H, PhCCHN-), 4.66 (t, 1H, PhCH), 5.4 (br., 1H, NH), 7.3 (m, 9H, ArH); mass spectrum: m/e 378, 376 (M^+), 216, 214.

Anal. Calcd. for $C_{17}H_{17}BrON_2S$: C, 54.1; H, 4.54; N, 7.42; S, 8.49. Found: C, 54.1; H, 4.5; N, 7.4; S, 8.7.

2-(4-Phenyl-2-thioxo-1-imidazolidinyl)ethyl *N,N*-Diethyldithiocarbamate (**8**).

A mixture of **2** (2.04 g., 0.01 mole) and sodium diethyldithiocarbamate (2.25 g., 0.01 mole) in dry DMF (10 ml.) was heated at 80-100° for 48 hours. The reaction mixture was poured into water (150 ml.) and extracted with methylene dichloride (2 x 150 ml.). The extracts were washed, dried (magnesium sulfate), and evaporated to give a yellow oil which was purified by chromatography on a column of silica gel (400 g.). Elution with ethyl acetate gave 2.8 g. (79%) of **8** as a fawn solid, m.p. 123-125°. Recrystallisation of a portion from aqueous ethanol raised the m.p. to 126-127°; ir (nujol): 3100 cm^{-1} (NH); nmr (deuteriochloroform): 1.2 δ (t, 6H, C-CH_3), 3.25-4.32 (m, 10H, $CH_2N + CH_2S$), 6.7 (br., 1H, NH), 4.74 (q, 1H, PhCH), 7.25 (s, 5H, ArH); mass spectrum: m/e 353 (M^+), 237, 205, 178.

Anal. Calcd. for $C_{16}H_{23}N_3S_3$: C, 54.3; H, 6.56; N, 11.9; S, 27.2. Found: C, 54.1; H, 6.7; N, 11.8; S, 27.6.

4,4′-Diphenyl-1,1-trimethylenebis(thioethylene)diimidazolidine-2-thione (**9**).

A solution of **2** (8.16 g., 0.04 mole) and 1,3-propanedithiol (2.16 g., 0.02 mole) in glycol (10 ml.) was heated overnight at 180° under nitrogen. The orange glass obtained on cooling the reaction mixture was dissolved in hot acetone (50 ml.) and poured into dilute hydrochloric acid (120 ml. of 2*N*). The mixture was extracted with methylene chloride and the extracts washed once

with an equal volume of water, dried (magnesium sulfate), concentrated and added to a column of alumina (400 g.). Elution with ethyl acetate gave a yellow oil which was slightly impure by tlc. A second purification by column chromatography gave 6.2 g. (60%) of **9** as a hygroscopic light-yellow solid, m.p. 43-46°; nmr (deuteriochloroform): 1.88 δ (m, 2H, CCH_2C), 2.68 (m, 8H, CH_2S-), 3.70 (m, 6H, S-C-CH_2N + PhCCHN), 4.10 (t, 2H, PhCCNH), 4.87 (t, 2H, PhCH), 6.82 (s, 2H, NH), 7.3 (s, 10H, ArH); mass spectrum: m/e 312, 237, 205, 191.

Anal. Calcd. for $C_{25}H_{32}N_4S_4$: C, 58.1; H, 6.24; N, 10.8; S, 24.8. Found: C, 57.8; H, 6.3; N, 10.4; S, 24.5.

4-Phenyl-2-(1-pyrrolidino)imidazoline Hydrochloride (**10**).

Compound **2** hydrochloride (2.4 g., 0.01 mole) was suspended in pyrrolidine (4.25 g., 0.06 mole) and the mixture heated at reflux for 24 hours under nitrogen. Evaporation of excess amine left a dark oil which, on trituration with acetone, gave 1.8 g. of **10** as a granular white solid, m.p. 200-202°. The residual material was taken up in hydrochloric acid (4*N*) and washed with methylene chloride. The aqueous solution was basified with sodium hydroxide and extracted with methylene chloride. Evaporation of the dried (magnesium sulfate) extracts left an oil which on treatment with acetone and ethereal hydrogen chloride gave a further 0.2 g. of **10** (combined yield 79%). Recrystallisation of a portion from ethanol raised the m.p. to 203-204°; ir (nujol): 1670 cm^{-1} (C=N); nmr (DMSO-d_6): 1.65-2.05 δ (m, 4H, pyrrolidine CH_2C-N), 3.15-4.05 (m, 6H, CH_2N), 4.9 (t, 1H, PhCH), 7.3 (s, 5H, ArH), 8.7 (br., 1H, NH); mass spectrum: m/e 205, 204 (M^+), 187, 185 (M-C_2H_4).

Anal. Calcd. for $C_{13}H_{18}ClN_3$: C, 62.0; H, 7.21; N, 16.7. Found: C, 61.8; H, 7.4; N, 16.8.

REFERENCES AND NOTES

(1) Part I. D. C. H. Bigg, A. W. Faull and S. R. Purvis, *J. Heterocyclic Chem.*, in press.

(2) Present address: L.E.R.S., 31 Ave. Paul Vaillant-Couturier, Bagneux 92220, France.

(3) T. Nakai, Y. Ueno and M. Okawara, *Bull. Chem. Soc. Japan*, **43**, 156, 3175 (1970); T. Nakai and M. Okawara, *ibid.*, **43**, 1864, 3528, 3882 (1970); K. Hiratani, T. Nakai and M. Okawara, *ibid.*, **46**, 3872 (1973); *ibid.*, **47**, 398 (1974).

(4) H. Ohtsuka, H. Toyofuku, T. Miyasaka and K. Arakawa, *Chem. Pharm. Bull.*, **23**, 3234 (1975); H. Ohtsuka, T. Miyasaka and K. Arakawa, *ibid.*, **23**, 3243, 3254 (1975).

(5) A. H. M. Raeymaekers, F. T. N. Allewijn, J. Vandenberk, P. J. A. Demoen, T. T. T. Van Offenwert and P. A. J. Janssen, *J. Med. Chem.*, **9**, 545 (1966).

(6) R. Feinauer, *Angew. Chem., Int. Ed. Engl.*, **5**, 894 (1966).