2-Imidazolines. IV (1). 1-Aryl-2-alkylthio-4,5-diamino-4,5-dihydroimidazoles. Synthesis and Properties

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1,2-Diimmonium salts (**1**) react with *S*-substituted isothioureas (**3**) yielding 2-alkylthio-4,5-diamino-4,5-dihydroimidazoles (**4**), which under mild pyrolytic conditions afforded 2-alkylthio-5-aminoimidazoles (**7**). Imidazolines (**4**) and imidazoles (**7**) were easily desulfurated with Raney nickel affording 4,5-diamino-4,5-dihydroimidazole (**9**) and 5-aminoimidazole (**10**), respectively.

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1,2-Diimmonium salts **1** have proven to be a useful tool for the synthesis of amino-functionalized imidazole derivatives. They react with amidines, guanidines and *o*-methylisoureas affording 2-aryl- or alkyl-, 2-amino- and 2-methoxy-4,5-diamino-2-imidazolines (1,2,3), from which 5-amino- and 4,5-diaminoimidazoles were easily obtained (1,2). The increasing biological interest in compounds incorporating the imidazole ring prompted us to extend this reaction to the preparation of 2-alkylthio derivatives. In this paper we wish to report our findings from this study.

In diimmonium dibromide (**1**, X = O) reacts with *S*-substituted isothioureas (**3**) affording 2-alkylthio-4,5-dimorpholino-2-imidazolines (**4**) with yields of preparative interest. In spite of the increased ring tension of the reaction product, 2-aminothiazolidine (**5**) also reacts with the diimmonium salt affording 5,6-dimorpholino-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole (**6**) in 88% yield. All of the synthesized products show *trans* configurations, as confirmed by the values of the H_4-H_5 coupling constants

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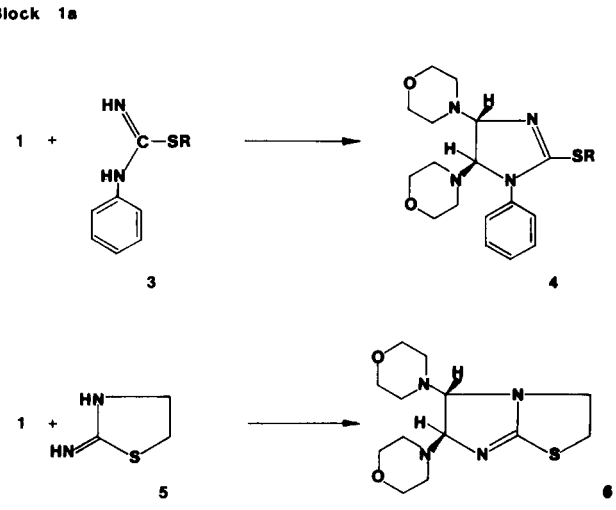

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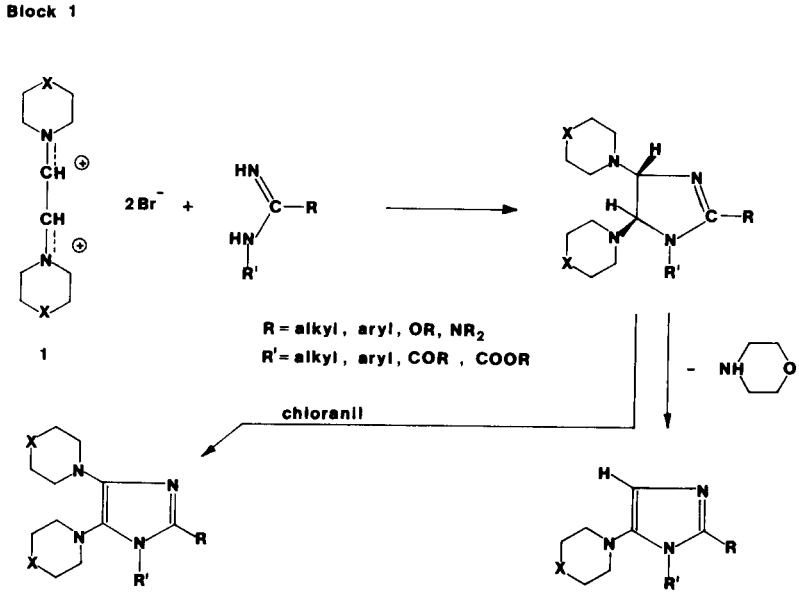

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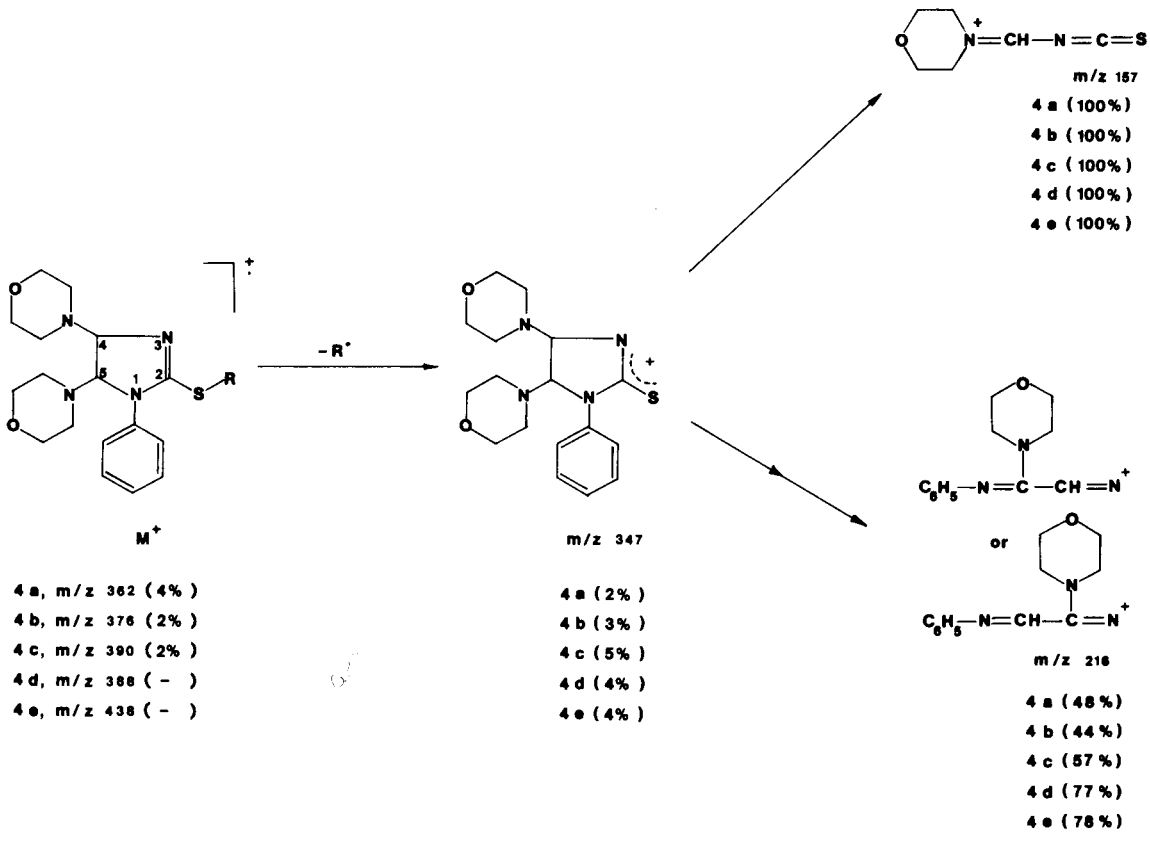
with range between 3 and 5 Hz.

The mass fragmentation pattern of 2-alkylthioimidazolines (**4a-e**) is depicted in the following Scheme, in which are also reported the relative intensities of the ions. The molecular ion is of low intensity or totally absent. The splitting of the group bonded to the sulphur atom gives rise to the ion at m/z 347. The subsequent cleavage of the bonds N_1-C_2 and C_4-C_5 gives the ion at m/z 157, which is always the base peak; whereas the simultaneous elimination of C_5 and morpholine gives the ion at m/z 216. All of these fragmentation processes are confirmed by the presence of the corresponding metastable peaks, observed with the linked scan technique (4).

Peaks arising from the loss of morpholine from the molecular ion are also present, but their origin is clearly due to a thermal decomposition, because their intensity increases with the source temperature. This is in line with their chemical behaviour. Actually, 1-phenyl-2-alkylthioimidazolines (**4a-e**) under mild conditions lose the amino group bonded on C_4, affording the corresponding 5-morpholinoimidazoles (**7a-e**) in almost quantitative

SCHEME



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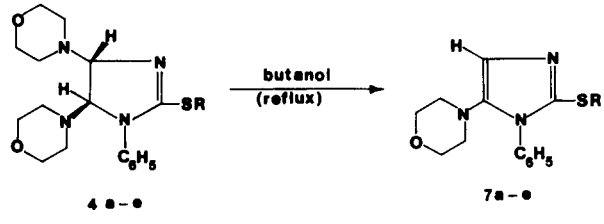
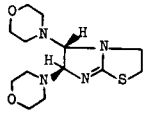
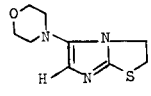


yields. The bicyclo derivative (**6**) under the same deamination conditions gives only poor yields of 5-morpholino-2,3-dihydroimidazo[2,1-*b*]thiazole (**8**), which was identified by analytical and spectral data. No effort was made to increase the yield of **8**. The main characteristics of products **4**, **6**, **7** and **8** are summarized in Table 1.

For testing a new entry to 4,5-diaminoimidazolines and 5-aminoimidazoles unsubstituted at C_2, compounds **4a** and **7a** were reacted with Raney nickel in refluxing ethanol. 1-Phenyl-4,5-dimorpholinoimidazoline **9** and 1-phenyl-5-aminoimidazole **10** were thus obtained. The latter compound was also obtained from the dihydro derivative **9** under the usual deamination conditions.

The oxidation of alkylthio group to alkylsulfinyl- and alkylsulfonyl groups was attempted both on 4,5-diamino imidazolines **4** and on 5-aminoimidazoles **7**. In the first case the deamination process always precedes the sulfur oxidation. In the second case the reaction was successfully

Table 1

Product No.	R	Yield (%)	M.p. (°C) (from)	H_4 and H_5 Pmr (deuteriochloroform)	C	H	N
4a	CH_3	85	169-171 (ethanol)	4.50, 4.75 (J = 3.0 Hz)	59.50 (59.67)	7.30 (7.18)	15.31 (15.47)
4b	C_2H_5	88	158-160 (ethanol)	4.45, 4.72 (J = 3.0 Hz)	60.65 (60.64)	7.58 (7.45)	14.97 (14.89)
4c	n-C_3H_7	78	112-114 (ethanol)	4.50, 4.73 (J = 3.0 Hz)	61.29 (61.54)	7.80 (7.69)	14.26 (14.36)
4d	CH_2-CH=CH_2	75	168 (ethanol)	4.90, 5.15 (J = 3.0 Hz)	61.49 (61.86)	7.31 (7.22)	14.30 (14.43)
4e	CH_2-C_6H_5	80	143-145 (ethanol)	4.48, 4.73 (J = 3.2 Hz)	65.78 (65.75)	6.72 (6.85)	12.61 (12.79)
6		88	124 (acetone)	4.20, 4.85 (J = 5.0 Hz)	52.26 (52.35)	7.60 (7.38)	18.60 (18.79)
7a	CH_3	90	118-120 (isopropyl ether)	6.65	61.12 (61.09)	6.30 (6.18)	15.09 (15.27)
7b	C_2H_5	88	88-89 (isopropyl ether)	6.60	62.40 (62.28)	6.75 (6.57)	14.76 (14.53)
7c	n-C_3H_7	92	99-101 (isopropyl ether)	6.60	63.51 (63.37)	7.04 (6.93)	13.78 (13.86)
7d	CH_2-CH=CH_2	86	111-113 (isopropyl ether)	6.65	63.59 (63.79)	6.47 (6.31)	13.87 (13.95)
7e	CH_2-C_6H_5	90	124-126 (isopropyl ether)	6.70	68.19 (68.38)	6.15 (5.88)	12.09 (11.97)
8		8	128-130 (isopropyl ether)	6.38	51.02 (51.18)	6.18 (6.16)	20.07 (19.91)

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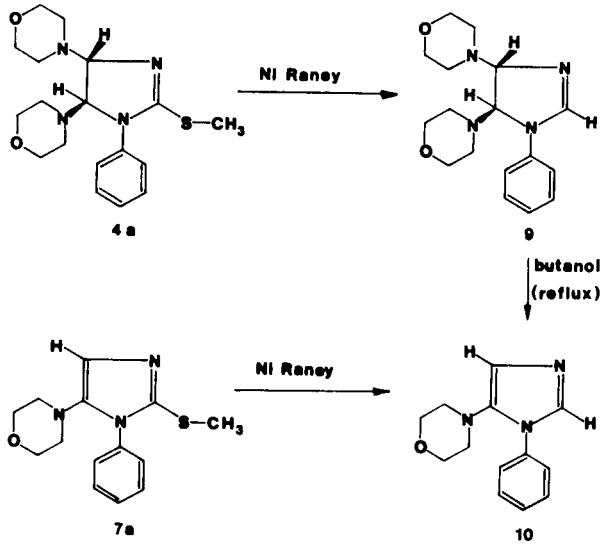

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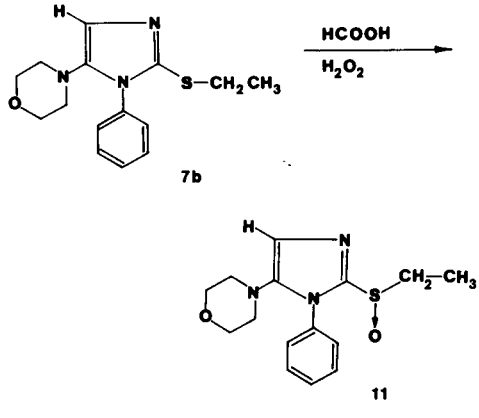

accomplished with formic acid/hydrogen peroxide to form the sulfinyl derivative **11**, but all efforts to obtain the sulfonyl derivative failed. Only meaningless reaction mixtures were obtained under all the oxidation conditions tested.

EXPERIMENTAL

Melting points were determined using a Büchi capillary melting point apparatus and are uncorrected. Nmr spectra were recorded using a Varian 360-A spectrometer. The chemical shift values are expressed as δ values relative to a tetramethylsilane internal standard. Mass spectra were recorded with a Varian MAT 311-A mass spectrometer at an electron energy of 70 eV. The direct insertion technique was used with a probe temperature of 50-90° and an ion source temperature of 180-200°. Column chromatography was performed using Merck silica gel (60-120 mesh) and thin layer chromatography was run on silica gel GF 254 plates.

Preparation of the Diimmonium Salt (**1**).

The salt was prepared by the method described in reference 2 in a 25-50 mmoles scale and was used immediately after preparation.

S-Substituted Isothioureas (**3a-e**).

N-Phenylthiourea (15.2 g., 0.10 moles) was refluxed in ethanol (100 ml.) in the presence of an equimolecular amount of the appropriate alogenide (methyl iodide, ethyl iodide, *n*-propyl iodide, allylbromide and benzyl chloride, respectively) until no starting product was detectable by tlc.

The reaction mixture was cooled at room temperature, the solvent removed under reduced pressure and the residue basified with a saturated solution of sodium bicarbonate. The separated isothiourea was extracted with chloroform, the organic layer dried over sodium sulfate and the solvent evaporated under reduced pressure. The crude isothioureas thus obtained were employed without further purification.

2-Alkylthio-4,5-dimorpholino-4,5-dihydroimidazoles (**4a-e** and **6**).

To a well stirred suspension of diimmonium salt **1** (3.59 g., 10 mmoles) in dry dichloromethane (50 ml.), cooled at −20°, a solution of isothiourea **3** (8 mmoles) and triethylamine (20 mmoles) in 50 ml. of dichloromethane was added dropwise. After stirring at room temperature for 60 minutes, the reaction mixture was washed with water, the organic layer dried over sodium sulfate and freed from the solvent under reduced pressure. The residue was crystallized from the suitable solvent or chromatographed on a silica gel column to give products **4** and **6** (Table 1).

2-Alkylthio-5-morpholinoimidazoles (**7a-e**).

Imidazolines **4a-e** (20 mmoles) were refluxed in 25 ml. of 1-butanol until no more product was detectable by tlc. The solvent was evaporated under reduced pressure and the residue crystallized to give imidazoles (**7a-e**) (Table 1).

1-Phenyl-4,5-dimorpholino-4,5-dihydroimidazole (**9**).

1-Phenyl-2-methylthio-4,5-dimorpholino-4,5-dihydroimidazole **4a** (1.0 g., 2.76 mmoles) and 1.0 g. of Raney nickel were refluxed in 25 ml. of ethanol under vigorous stirring for 48 hours. The reaction mixture was cooled and freed from Raney nickel by suction, ethanol was evaporated under *vacuo* and the residue crystallized from ethyl ether, yield 63%, m.p. 80-82°; nmr (deuteriochloroform): 2.53 (m, 8H, CH_2-N-CH_2), 3.60 (m, 8H, CH_2-O-CH_2), 4.55 (s, 2H, H_4 and H_5, J = 3.5 Hz measured in DMSO-d_6), 7.18 (m, 10H, aromatics), 7.58 (s, 1H, H_2); ms: m/z 316 (46, M^+), 203 (13), 191 (100), 148 (17), 127 (33), 115 (13), 104 (14), 86 (30), 77 (22).

Anal. Calcd. for $C_{17}H_{24}N_4O_2$: C, 64.56; H, 7.59; N, 17.72. Found: C, 64.60; H, 7.41; N, 17.49.

1-Phenyl-5-morpholinoimidazole (**10**).

1-Phenyl-2-methylthio-5-morpholinoimidazole **7a** (1.0 g., 3.64 mmoles) was reacted in the same manner described for imidazoline **4a**. After the usual working up, imidazole **10** was obtained as white crystals melting at 90-91° (isopropyl ether), yield 75%; nmr (deuteriochloroform): 2.82 (m, 4H, CH_2-N-CH_2), 3.66 (m, 4H, CH_2-O-CH_2), 6.66 (d, 1H, H_4, J ≅ 0.5 Hz), 7.5 (m, 6H, aromatics and imidazole H_2); ms: m/z 229 (67, M^+), 171 (45), 170 (55), 104 (34), 91 (31), 77 (100).

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.12; H, 6.55; N, 18.34. Found: C, 68.02; H, 6.70; N, 18.15.

1-Phenyl-2-ethylsulfinyl-5-morpholinoimidazole (**11**).

To 1-phenyl-2-ethylthio-5-morpholinoimidazole (**7b**) (0.5 g., 173 mmoles) dissolved in 18 ml. of formic acid, 0.17 ml. of hydrogen peroxide (36%) were added at 10-15° under stirring. The stirring was continued for 4 hours, the reaction mixture was then poured in 20 ml. of water, neutralized with sodium bicarbonate and extracted twice with ethyl ether. After drying over sodium sulfate the ether was evaporated and the residue crystallized from diisopropyl ether yielding sulfoxide **11** as white crystals (75%), m.p. 111-113°; nmr (deuteriochloroform): 1.23 (t, 3H, CH_3), 2.72 (m, 4H, CH_2-N-CH_2), 3.28 (q, 2H, CH_2), 3.51 (m, 4H, CH_2-O-CH_2), 6.72 (s, 1H, H_4), 7.5 (m, 5H, aromatics); ms: m/z 305 (10, M^+), 289 (20), 276 (81), 260 (15), 244 (30), 202 (25), 114 (40), 77 (100).

Anal. Calcd. for $C_{15}H_{19}N_3O_2S$: C, 59.02; H, 6.23; N, 13.77. Found: C, 59.17; H, 6.09; N, 13.89.

REFERENCES AND NOTES

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