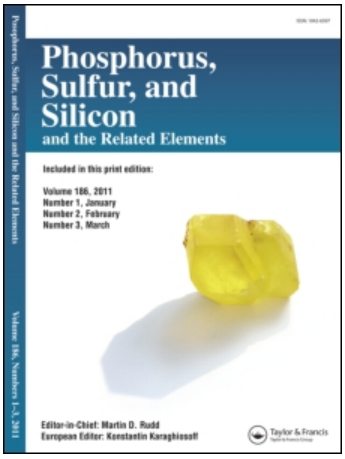

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THIONO COMPOUNDS. 5. PREPARATION AND OXIDATION OF SOME THIONO DERIVATIVES OF IMIDAZOLES

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THIONO COMPOUNDS. 5. PREPARATION AND OXIDATION OF SOME THIONO DERIVATIVES OF IMIDAZOLES[1]

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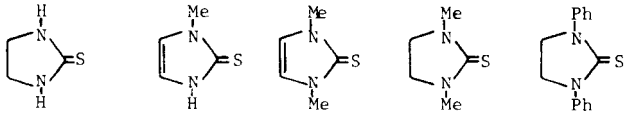
1,3-Dimethyl-3H-imidazole-2-thione (**3**), prepared by a much improved procedure from 1,3-dimethylimidazolium iodide (**6**) with sulfur and an organic base, was oxidized with H_2O_2 in MeOH; three molar proportions of H_2O_2 were consumed, 1,3-dimethylimidazolium picrate (**14**; synthesized independently) was isolated in 61% yield, and 80% of the expected sulfate ion was found. Oxidation of the analogous imidazolidine (**4**), prepared from 1,3-dimethyl-2-imidazolidone (**16**) with Lawesson's reagent (**17**), gave a counterpart picrate (73% from **4**) in a similar but slower reaction. 1,3-Diphenyl-2-imidazolidinethione (**5**) had to be oxidized in DMF–AcOH, with H_2SO_4 catalysis, and only 1,3-diphenyl-2-imidazolidone (**19**, 63%) could be isolated. Understanding is added to the behavior in oxidations of thiono derivatives of imidazoles by these extensions of several earlier studies to different types within the class, i.e., of an N-unsubstituted one (**1**)[15] to the N,N-dimethyl counterpart (**4**), of an N-methyl unsaturated one (**2**)[14] to the N,N-dimethyl counterpart (**3**), and of an N,N-diphenyl unsaturated one (**23**)[13] to the saturated counterpart (**5**). Similarities and differences are discussed relative to members of the class studied previously, along with information that improves understanding of the different courses of reactions various members of the class may follow when they are oxidized.

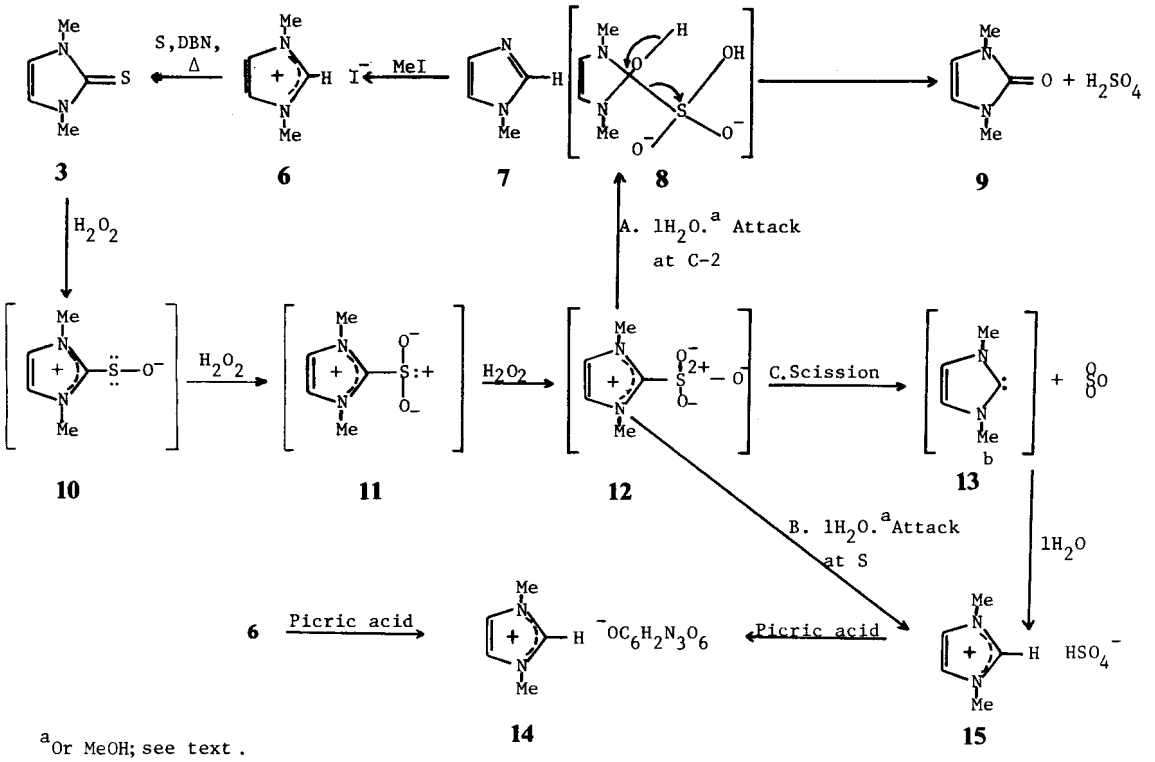
INTRODUCTION

2-Imidazolidinethione (ethylenethiourea, ETU, **1**), a breakdown product of the important fungicides maneb and zineb, produces cancer,[2,3] and although methimazole (1,3-dihydro-1-methyl-2H-imidazole-2-thione; shown as the tautomer **2**) commonly is used to treat thyrotoxicosis it can lead to several adverse effects,[4] including adenomas in the thyroid gland.[5] Reactive intermediates formed during oxidative desulfuration to oxygen counterparts are strongly implicated in the adverse effects inherent in such thiono compounds, since reduction or abolition of adverse effects ordinarily occurs when sulfur is replaced by oxygen.[3] In initiating efforts to learn more about the nature of the reactive species formed by thiono derivatives of imidazoles, and about the nature of their carcinogenic reactions with functional groups of biomacromolecules, we have begun with N,N′-disubstituted imidazole derivatives to obviate complications from tautomerism. This paper reports studies of the preparation and oxidation of **3**–**5** as representatives of the disubstituted class. It thus complements earlier studies of thiono imidazole derivatives.



1 **2** **3** **4** **5**

*Author to whom all correspondence should be addressed.



3 **6** **7** **8** **9** **10** **11** **12** **13** **14** **15**

[a] Or MeOH; see text.

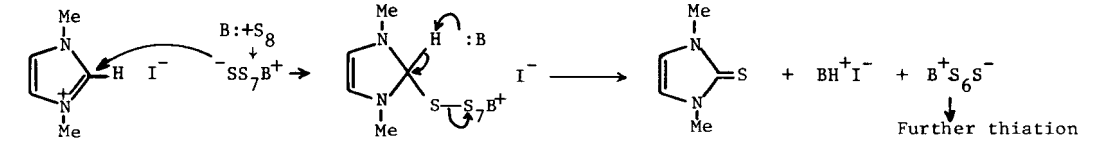
[b] The structure shown for **13** shown for simplicity, represents only one contributor to the resonance hybrid.

SCHEME 1

RESULTS AND DISCUSSION

Preparation

Scheme 1 shows the preparation of the thione **3**. Conversion of the known salt **6** to **3** could be achieved as reported (without details) by stirring **6** with S and K_2CO_3 in MeOH at room temperature, followed by chromatography,[6] although the yield was only 9%. Use of other solvents led to no improvement, although use of more K_2CO_3



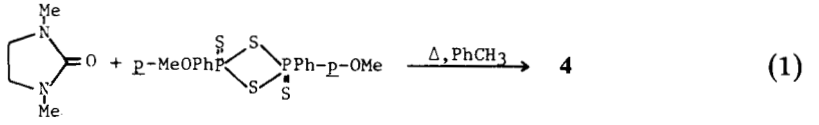
6 **3**

[a] B: = DBU(or DBN). The structure shown for **6** represents one contributor to the resonance hybrid.

SCHEME 2[a]

in refluxing MeOH increased the yield to 47%. On the other hand, reaction of **6** with sulfur and about two molar proportions of DBU in hot MeOH-pyridine led to isolation of **3** in 90% yield without chromatography. The effect of the DBU (or DBN) can be explained by the reactions shown in Scheme 2.

The imidazolidinethione **4** was prepared by thiating the imidazolidone **16** with Lawesson's reagent (**17**; eq. 1). Lawesson's reagent has been used for thiating a few lactams, as well as a wide variety of amides,[7] but so far as we know it has not been used for thiating cyclic ureas such as **16**. Chromatography produced **4** in 70% yield.



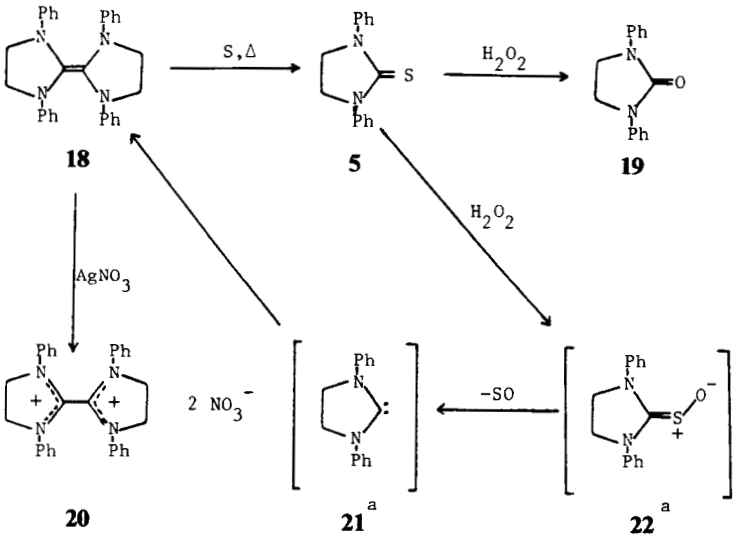
(1)

16 **17**

The 1,3-diphenylthione **5** was prepared by heating the known ylidene **18** with sulfur (Scheme 3).[8] If the oxidation of **5** followed the sequence proposed for methimazole (**2**), i.e. via **22** and **21**,[4] one fate for **21** might be dimerization to **18**. Hence the dinitrate (**20**) of **18** was prepared for identification of **18** as a possible oxidation product of **5**. Owing to initially presumed differences from reported values for melting point and NMR spectra,[9,10] which ultimately were resolved (see Experimental), **20** was carefully characterized (as was **5**, as an added precaution).

Oxidation

Oxidation of the imidazolinethione (**3**) with five molar proportions of H_2O_2 in MeOH gave a product with an NMR spectrum consistent for the HSO_4^- salt **15**



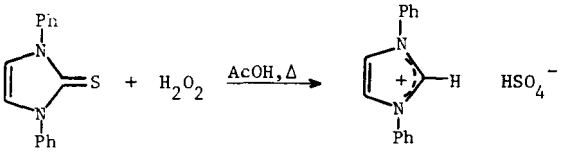
18 **5** **19**

20 **21**[a] **22**[a]

SCHEME 3

[a] One contributor to the resonance hybrid, shown for simplicity.

(Scheme 1).[11] Efforts to isolate and purify **15** led to decomposition, but the corresponding picrate (**14**) could be isolated in an overall yield from **3** of 61%; in a test of the ease of hydrolysis of the picrate **14**, when a solution was basified, let stand for 24 h and reacidified, **14** reprecipitated in 50% yield. The identity of **14** was confirmed by independent synthesis from the iodide **6** and picric acid (Scheme 1). Suszka reported kinetics in acidic solution for the oxidation of **3** (and of methimazole, **2**) to disulfides but isolated no products.[12] Oxidation of **23**, the diphenyl counterpart of **3**, reportedly gave a result like that with **3** (eq. 2);[13] however, the product (**24**) from **23** contrasts markedly with **15** in being a stable salt (mp 168°C),[13] presumably owing to charge delocalization into the phenyl groups.

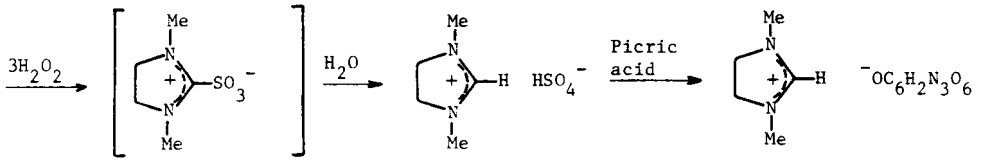


(2)

23 **24**

Study of the stoichiometry of the reaction showed that oxidation of **3** was complete in ca. 0.5 h at ca. 0–5°C, that three molar proportions of H_2O_2 were consumed, and that 80% of one molar proportion of sulfate ion was formed. If one assumes that **3** is rapidly oxidized to the trioxide **12** before C—S cleavage occurs, at least three paths can be envisioned for C—S cleavage of **12** (Scheme 1). Path A, in which H_2O attacks C-2 of the ring, should lead to the imidazolinone **9**. Since there was never any indication of **9**, Path A seems unlikely as a major route. In Path B, which we favor, attack of H_2O on the sulfur atom of **12** should lead to HSO_4^- ion and to acquisition of the remaining proton of H_2O by the ring to give the imidazolium cation of **15**, which was identified as the picrate (**14**). In Path C, spontaneous scission of the C—S bond could produce SO_3; reaction of SO_3 with H_2O present in the 30% H_2O_2 to give H_2SO_4, followed by immediate protonation of the (resonance stabilized) structure **13**, then would lead to HSO_4^- ion and the cation of **15**. However, the stability of complexes such as those of pyridine and trimethylamine with sulfur trioxide make Path C seem less likely than Path B. MeOH also plays a role, along with H_2O (NMR at δ 3.6, $MeOSO_2O^-$). Paths resembling A, B, or C also can be envisioned if only the monoxide **10** is formed prior to C—S cleavage (followed by further oxidation of the sulfur species lost). The same can be said of oxidation only to the dioxide **11** before C—S cleavage. Poulsen, Hyslop, and Ziegler concluded that enzymatic oxidation of methimazole (**2**) produces the sulfinate (i.e., RSO_2^-), which then is hydrolyzed to sulfite ion and N-methylimidazole,[14] but this overall mode of reaction is not open to the N,N-dimethyl counterpart (**3**) since loss of CH_3^+ rather than H^+ would be required.

Oxidation of **4**, the ring-saturated counterpart of **3**, appears to follow the same course as **3** (eq. 3). However, the HSO_4^- salt (**26**) analogous to **15** seemed even less stable than **15**. The ^1H and ^{13}C spectra of the product were consistent for the presence of **26** (signals for CH_3, CH_2, and CH), although the ^1H spectra indicated a content only of about 70–76% of **26**.



25 **26** **27** (3)

The ^1H and ^{13}C NMR spectra indicated the presence not only of HSO_4^- but also of $MeOSO_2O^-$. The methyl sulfate anion, $MeOSO_2O^-$, may have resulted from attack of MeOH on **25** since it did not appear in the ^1H spectrum when d_4-MeOH was used. This result and the similar one mentioned with **3** are significant to our long-term objectives of learning about the reactions of reactive intermediates with biomacromolecules, since they indicate that a nucleophile such as MeOH (and hence important nucleophilic groups of biomacromolecules) can react with species such as **12** and **25** or their less oxidized counterparts.

Picric acid converted the HSO_4^- salt **26** to a picrate (**27**), which had properties consistent with **27** (^1H and ^{13}C NMR, FAB-MS, elemental analysis). The overall yield of the picrate **27** from the thione **4** was 73%. In some oxidations, N,N′-dimethylethylenediamine dipicrate (**28**) also was isolated in ca. 10% yield; this diamine differed from the impurity mentioned and presumably arose from hydrolysis of **26** or **27**.

Titration of residual peroxide showed that **4** consumed three equivalents of H_2O_2 and that the oxidation is considerably slower than that of **3** (ca. 5 h at ca. 25°C for **4** vs. ca. 0.5 h at 0–5°C for **3**); 84% of one molar proportion of sulfate ion was precipitated as barium sulfate. Use of only one equivalent of H_2O_2 led merely to oxidation of about a third of the **4**, and no intermediates could be observed.

Marshall and Singh concluded that oxidation of ethylenethiourea (**1**) with 3 equiv. of H_2O_2 proceeds through the sulfenate (i.e., RSO^-) and sulfinate to the sulfonate, which they dimethylated with CH_2N_2 to give the salt **25**,[15a] the ring-saturated counterpart of **12** (Scheme 1). We saw no indication of the sulfonate **25**, however.

A reviewer kindly called our attention to a later paper by Marshall.[15b] The results, taken with those of Poulsen *et al.*,[14] may indicate that of the monoxide, dioxide, or trioxide options mentioned above for the key intermediate, the dioxide is the most important. The sulfinate in D_2O gave an EPR signal about 25% of that from one equivalent of sodium dithionite,[15b] indicating presence of the radical anion $\cdot SO_2^-$, which accordingly was invoked in the mechanism of the oxidation. Hence $\cdot SO_2^-$ may well play a role, at least to some extent, in eq. 3 and presumably in Scheme 1 as well (perhaps by electron transfer from $\cdot SO_2^-$ to the ring, accompanied by reaction with solvent to give outcomes like those shown). The formation of $\cdot SO_2^-$ from acidified sodium formaldehyde sulfoxylate, $HOCH_2SO_2Na$,[15c] also is relevant in indicating facile formation of $\cdot SO_2^-$.

In the oxidation of 1,3-diphenyl-2-imidazolidinethione (**5**), sparing solubility precluded use of the usual medium, MeOH. A solution of **5** in DMF consumed no more H_2O_2 than DMF alone. Hence the relative ease of oxidation of the compounds studied appears to be **3** > **4** > **5**. The resistance of **5** is reminiscent of the greater

stability mentioned for the 1,3-diphenyl salt counterpart of the 1,3-dimethyl salts **15** and **26**. Use of 1 : 1 DMF–AcOH, with catalysis by H_2SO_4, led to conversion of **5** to **19** in 63% yield (Scheme 3); the major product with the ring-unsaturated counterpart (**23**), it may be recalled, is the salt **24**.[13] Since the nature of the medium precluded following the consumption of H_2O_2 or determination of the sulfur balance, little more can be said about the oxidation of **5** except that there was no indication of the violet color that would point to involvement of the dimer **18** (**18** becomes violet upon exposure to air,[9] with the ultimate formation of **19**).[16]

In summary, the N,N-disubstituted compounds **3–5** show both significant differences from each other and from thiono derivatives of imidazoles studied previously, as well as similarities. From the standpoint of adverse biological effects, the reactions of MeOH with species like **12** and **25** or the dioxide equivalents hints that similar reactions may be significant for other thiono imidazole derivatives in attack by important nucleophilic groups of biomacromolecules.

EXPERIMENTAL

Melting points were determined by using a Thomas-Hoover stirred-liquid apparatus and are corrected. NMR spectra, reported in parts per million (δ), were obtained with a JEOL Model JNM-MH-100 spectrometer (^1H) or JEOL FX90Q spectrometer operating at 22.64 MHz (^{13}C) with Me_4Si as an internal standard or in D_2O with DSS, $Me_3Si(CH_2)_3SO_3Na$; spectra are for ^1H unless ^{13}C is specified. IR spectra were obtained by using KBr pellets with a Perkin-Elmer Model 727 spectrometer. Elemental analyses were performed by Galbraith Laboratories, and mass spectra by the Midwest Center for Mass Spectrometry, University of Nebraska-Lincoln. Moist extracts were dried by using Na_2SO_4, and solvent was removed in concentrations by using a rotary-flask evaporator under vacuum. TLC was performed on Eastman Chromagram Catalog No. 13181 with visualization by UV or I_2 vapor, and 80–200 mesh silica gel (Fisher Scientific Co.) was used for column chromatography. The H_2O_2 used was 34 ± ca. 1%; molar amounts specified were based on titration.[17] Sulfur used was a resublimed grade (Fisher Scientific Co.). Pyridine and MeCN were reagent grades dried over 3 A Molecular Sieve. All other materials were commercial products unless otherwise specified.

1,3-Dimethyl-2(3H)-imidazolethione (**3**). 1,3-Dimethylimidazolium iodide (**6**) was prepared as reported from 1-methylimidazole (62 mmol) and MeI (153 mmol) in EtOAc (30 mL);[18a] the progress of the reaction was followed conveniently by TLC.[19] The yield of **6** was 92%: mp 87–88°C (lit.[18a] mp 86.5–88°C); NMR (Me_2SO-d_6) δ 9.20 (s, 1 H), 7.78 (s, 2 H), 3.92 (s, 6 H). For clarification of a reported result, it should be added that values previously were reported for the NMR of **6** in D_2O of 7.48, 4.81, and 4.01 ppm (ratio 1 : 2 : 6).[18a] Aged solutions of our **6** showed similar peaks, but a *fresh* solution showed peaks at *8.74*, 7.49, and 3.98 ppm (ratio ca. 1 : 2 : 6). The peak at 8.74 ppm disappeared in D_2O overnight, and the DOH peak at 4.69 ppm increased somewhat. Hence, a H—D exchange reaction of **6** in D_2O presumably accounts for the previous report of a peak at 4.81 but not at 8.74 (cf. ref 18b).

In the best conversion of the salt **6** to the thione **3**, a solution of 3.00 g (13.4 mmol) of **6** and 4.54 g (29.8 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 25 mL of MeOH and 3.2 g of pyridine was stirred with 0.65 g (20.3 mmol) of sulfur at 65–68°C for 6 h. The mixture then was diluted with H_2O (100 mL) and extracted with $CHCl_3$ (3 × 70 mL). The organic extract was washed with 8% aqueous HCl, H_2O, dried, and concentrated to give a solid, which after one recrystallization from acetone amounted to 1.54 g (90%) of **3**: mp 183–184°C; lit.[6] mp 181–182°C, NMR ($CDCl_3$) δ 6.74 (s, 2 H), 3.64 (s, 6 H); lit.[6] NMR δ 6.75 (s), 3.58 (s).

Use of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in a similar way, but with MeOH as a solvent at 65–68°C for 3 h, gave **3** in 85% yield (mp 181–183°C), although reaction at 25–30°C for 5 h gave **3** in only 22% yield after recrystallization from Me_2CO (mp 181–182°C).

Initially, an undetailed reported procedure was used.[6] Thus a mixture of the salt **6** (3.36 g, 15.0 mmol), K_2CO_3 (0.5 g, 3.62 mmol) and sublimed sulfur (0.95 g, 29.7 mmol) was stirred in MeOH (35 mL) for 18 h at 25–30°C. Filtration, concentration, column chromatography (silica gel), and recrystallization then led only to 0.18 g (9%) of **3**, mp 181–182°C. Substitution of CS_2, a better solvent for sulfur, gave much the same result as MeOH, as did pyridine; use of pyridine in MeOH at ca. 25°C, without K_2CO_3, gave no **3**. With use of 14 mmol of the salt **6**, 19 mmol of K_2CO_3, and 46 mmol of sulfur in refluxing MeOH, however, the yield of **3** improved to 47% (mp 183–184°C).

1,3-Dimethyl-2-imidazolidinethione (**4**). A mixture of 1,3-dimethyl-2-imidazolidone (**16**, 11.4 g, 99.9 mmol), 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's Reagent, **17**, 24.2 g, 59.8 mmol) and toluene (100 mL) was stirred at the reflux temperature under Ar for 4.5 h. The mixture then was cooled, mixed with H_2O, and extracted with $CHCl_3$ (3 × 75 mL). The crude **4** obtained by washing the extract with H_2O, drying, and concentration was subjected to flash chromatography on 225 g of silica gel in a 50-mm × 23-cm column with a 1 : 1 mixture of hexane–EtOAc for elution. The thione **4**, obtained from early fractions and recrystallized (Me_2CO), amounted to 9.15 g (70%): mp 111–113°C; lit.[20] mp 109–111°C; NMR ($CDCl_3$) δ 3.56 (s, 4 H), 3.16 (s, 6 H); NMR lit.[20] δ 3.52 (s), 3.07 (s); IR 2950, 2875, 1500, 1490, 1450, 1430, 1380, 1330, 1285, 1220, 1115, 1065, 1015, 960, 620 cm^{-1}. Anal. Calcd for $C_5H_{10}N_2S$: C, 46.12; H, 7.74; N, 21.51. Found: C, 46.26; H, 7.79; N, 21.48.

1,3-Diphenyl-2-imidazolidinethione (**5**). 2-(1,3-Diphenyl-2-imidazolidinylidene)-1,3-diphenylimidazolidine (**18**) was prepared from recrystallized 1,2-dianilinoethane and triethyl orthoformate;[21] after the **18** had been washed with xylene and dried, melting points were in the range of 279–284°C dec; lit.[21] mp 285°C dec; IR 2850, 1585, 1485, 1460, 1370, 1360, 1320, 1300, 1180, 1065, 1025, 1005, 730, 680 cm^{-1}.

For possible identification of **18** in studies of the thione **5**, the dinitrate (**20**) was prepared from **18** (according to details kindly provided by Prof. D. M. Lemal) by adding $AgNO_3$ (0.680 g, 4.00 mmol) in MeCN (20 mL) to a suspension of **18** (0.888 g, 2.00 mmol) in MeCN with vigorous stirring. After 15 min of stirring, filtration, concentration of the filtrate to ca. half volume, chilling, and filtration gave 1.04 g (91%) of canary-yellow **20**: mp 205–207°C dec., immersed at ca. 160°C with an increase of ca. 2°C/min (lit.[9] mp 242–243°C); ^1H NMR (D_2O, DSS as internal standard) δ 7.55 and 7.14 (two sets of multiplets, 10 H), 4.86 (s, 4 H) [lit.[10] ^1H NMR (D_2O, TMS as *external* standard) δ 7.7 (center of complex multiplet), 5.27 (s); relative areas, 5 : 2]; ^{13}C NMR δ 146.08, 133.95, 131.51, 131.37, 121.41, 53.63. Variations in reaction periods from 15 min to 48 h invariably gave **20** with a melting point in the range of 195–208°C dec. In view of these apparent differences from earlier observations,[9,10] a sample of **20** was recrystallized to a constant mp of 198–205°C from MeCN and analyzed: ^1H and ^{13}C NMR as with our results above for **20**; IR 3025, 1580, 1570, 1490, 1380, 1360, 1340, 1330, 1300, 755, 710, 690 cm^{-1}. Anal. Calcd for $C_{30}H_{28}N_6O_6$: C, 63.38; H, 4.93; N, 14.79; O, 16.88. Found: C, 63.21; H, 5.09; N, 14.56; O, 17.14.

The apparent discrepancy in melting points evidently is due to a remarkable variability, previously encountered,[22] and in NMR to the difference in standards. The melting point does not seem to be significantly affected by the temperature of immersion or the rate of heating. Identity of the two materials finally was established by comparison of melting points (present 188–191°C dec; previous,[22] 184–187°C dec; mixture, 186–190°C dec; all simultaneously inserted at 160°C and heated at an increase of 2–3°C/min) and by identity of ^1H NMR spectra under our conditions.

In a modified conversion of the ylidene **18** to the thione **5**,[8] 6.60 g (14.8 mmol) of **18** was heated under reflux with 1.10 g (34.4 mmol) of sulfur in 100 mL of pyridine under Ar with vigorous stirring for 7 h. Crude **5**, obtained by removing the pyridine under vacuum, was washed with Et_2O and recrystallized from MeOH; yield of **5**, 6.97 g (93%); mp 188–189.5°C (lit.[8] mp, 187–188°C); NMR ($CDCl_3$) δ 7.68–7.28 (m, 10 H), 4.15 (s, 4 H); IR 3050, 2980, 2900, 1598, 1500, 1462, 1420, 1398, 1340, 1290, 1270, 750, 690 cm^{-1}. Because of the initially perplexing problem with the dinitrate **20**, an elemental analysis of the **5** also was obtained to assure its identity. Anal. Calcd for $C_{15}N_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01. Found: C, 70.77; H, 5.60; N, 10.90.

Oxidation of 1,3-Dimethyl-3H-imidazole-2-thione (**3**)

a. Oxidation. During 5 min, 0.26 mL (2.60 mmol) of H_2O_2 was added to a solution of 64.0 mg (0.50 mmol) of the thione **3** in 3 mL of MeOH with stirring at ca. 0–5°C. After 1 h of stirring at 5°C and 7 h at ca. 25°C, TLC showed absence of **3**. Residual H_2O_2 and H_2O were removed by storage overnight over anhydrous Na_2SO_3 and Na_2SO_4 (negative to KI-starch paper). Filtration and concentration gave 100 mg of **15** having an NMR spectrum ($CDCl_3$) consistent with *1,3-dimethylimidazolium hydrogen sulfate* (**15**): δ 9.32 (s, 1 H), 7.66 (s, 2 H), 3.98 (s, 6 H); a singlet at δ 3.60 (ca. 1.5 H) was attributable to $MeOSO_2O^-$ and a broad signal at ca. δ 6.7 (ca. $\frac{1}{2}$H) to HSO_4^-. This product was converted to *1,3-dimethylimidazolium picrate* (**14**) by dissolution in 1 mL of EtOH and addition of a solution of 120 mg (0.52 mmol) of picric acid in 3 mL of EtOH. The yellow precipitate was dissolved by boiling, and the crystalline **14** that separated on cooling was recrystallized from EtOH to give 0.10 g (61% from **3**); mp 150–152°C; NMR (Me_2SO-d_6) 9.23 (s, 1 H), 8.76 (s, 2 H), 7.82 (s, 2 H), 3.96 (s, 6 H); IR 3150, 3060, 1620, 1600, 1565, 1545, 1490, 1430, 1360, 1320, 1300, 1260, 1160, 1065, 920, 900, 780, 760, 740, 700. Anal. Calcd for $C_{11}H_{11}N_5O_7$: C, 40.61; H, 3.41; N, 21.54. Found: C, 40.34; H, 3.48; N, 21.30.

b. Independent synthesis of the picrate **14**. A saturated solution of 2.35 g (10.3 mmol) of picric acid in 47 mL of EtOH was mixed with one of 1,3-dimethylimidazolium iodide (**6**, 2.30 g, 10.3 mmol) in EtOH (3 mL). The mixture was warmed gently to effect a clear solution. Yellow crystalline **14** which separated on

cooling was removed, washed with EtOH, and dried under vacuum to give 1.91 g (57%) of **14**; mp 150–152°C, undepressed by **14** obtained under *a*; NMR and IR spectra congruent with the previous **14**.

c. Stoichiometric studies. A solution of 0.384 g (3.00 mmol) of **3** in 20 mL of MeOH was cooled to 0–5°C, and 1.60 mL (16.0 mmol) of H_2O_2 was added ("time zero") with good stirring, which was continued throughout. After 1 h, the cooling bath was removed. Aliquots were titrated as usual for H_2O_2.[17] After subtraction of consumption in a control with 1.6 mL of H_2O_2 in 20 mL of MeOH, the consumption of mol H_2O_2 per mol of **3** after "time zero" (h in parentheses) was as follows: 2.99 (0.5), 3.00 (1), 3.1 (2.5), 3.1 (4.5), 3.1 (6.5), 3.2 (24).

After a similar reaction (88.8 mg of **3**, 0.69 mmol; 0.37 mL of H_2O_2, 3.70 mmol) had proceeded for 24 h after discontinuation of cooling, the mixture was diluted with 20 mL of deionized H_2O, warmed, and 10% aqueous $BaCl_2$ was added until precipitation of $BaSO_4$ ceased. After digestion, filtration, and ignition in the usual way, 0.1292 g of $BaSO_4$ was obtained (80% of expectation for **3**).

Oxidation of 1,3-Dimethyl-2-imidazolidinethione (**4**)

a. Oxidation. During ca. 5 min, 2.00 mL (20.0 mmol) of H_2O_2 was added to a solution of 520 mg (3.99 mmol) of the thione **4** in 10 mL of MeOH with cooling at ca. 5°C and good stirring. Cooling was discontinued after 10 min, and stirring then was continued for 6 h (TLC then indicated absence of **4**). As with **3**, the mixture was kept overnight over Na_2SO_3–Na_2SO_4 (negative to KI-starch paper). Filtration and concentration then gave a crude product (700 mg), which was immediately dissolved in $CDCl_3$; insoluble solid (ca. 30 mg) was removed. In the filtrate, the ratio of the NMR integrals assigned to *1,3-dimethyl-2-imidazolinium hydrogen sulfate* (**26**) (and the $MeOSO_2O^-$ salt) to all integrals indicated the mixture to be ca. 70–76% of **26**: ^1H NMR δ 8.80 (s, 1 H), 3.98 (s, 4 H), 3.27 (s, 6 H); a singlet at δ 3.72 (ca. 1.5 H, not exchangeable with D_2O) is attributable to $MeOSO_2O^-$, and one at δ 7.1–7.3 (ca. $\frac{1}{2}$H), not seen in D_2O, is attributable to HSO_4^-; ^{13}C NMR δ 159.79, 50.83, 34.85 [with smaller signals at 54.41 (presumably $MeOSO_2O^-$) and 48.67 δ]. Evaporation of $CDCl_3$ and redissolution of the product led to marked changes in the NMR spectra that indicated **26** would be best isolated as a derivative. Efforts to purify **26** by chromatography (silica gel, reversed-phase silica gel, alumina) led to destruction of the **26**. Oxidation of **4** in Me_2CO gave much the same result as in MeOH.

b. 1,3-Dimethyl-2-imidazolinium picrate (**27**). Oxidation of **4** was performed as described under *a* with 260 mg (2.00 mmol) of **4** and 1.00 mL (10.0 mmol) of H_2O_2 in 7 mL of MeOH. The crude **26** (400 mg; equivalent to the 700 mg in Part *a*) was immediately dissolved in 2 mL of EtOH and the solution was filtered. The filtrate was added to a saturated solution of 800 mg of picric acid (3.49 mmol) in EtOH (15 mL). After the mixture had been boiled for 7 min and then kept at 5°C for a day, filtration removed 0.48 g (73% overall from **4**) of **27**, mp 95–98°C. Recrystallization from EtOH gave yellow crystalline **27** with a constant mp of 100–103°C; ^1H NMR (Me_2SO-d_6) δ 8.82 (s, 2 H), 8.56 (s, 1 H), 3.98 (s, 4 H), 3.21 (s, 6 H); ^{13}C NMR (Me_2SO-d_6) δ 160.77, 158.39, 141.75, 125.07, 124.20, 50.23, 34.00; IR 3110, 1662, 1605, 1565, 1540, 1495, 1420, 1360, 1330, 1265, 1165, 1140, 1080, 1010, 960, 780, 720, 700 cm^{-1}; FAB-MS m/z, positive ion 99 (calcd 99), negative ion 228 (calcd 228). Anal. Calcd for $C_{11}H_{13}N_5O_7$: C, 40.37; H, 4.00; N, 21.40. Found: C, 40.31; H, 4.00, N, 21.32.

In other reactions, *N,N'-dimethylethylenediamine dipicrate* (**28**) sometimes was obtained as a first crop in recrystallization (yields, ca. 10%). Recrystallization (Me_2CO) gave yellow crystals: NMR (Me_2SO-d_6) δ 8.82 (s, 4 H), 3.30 (s, 4 H), 2.74 (s, 6 H), identical with that of authentic **28** prepared from N,N'-dimethylethylenediamine (0.2 g) and picric acid (1 g) in EtOH (19 mL) in 89% yield: mp 217–220°C, undepressed by mixture with the authentic **28** (mp 218–221°C; lit.[23] mp 215–216°C). Anal. (authentic **28**). Calcd for $C_{16}H_{18}N_8O_{14}$: C, 35.17; H, 3.32. Found: C, 35.36; H, 3.36.

c. Stoichiometric studies. The progress of oxidation of **4** was followed essentially in the manner used for **3**, except that for this slower reaction the cooling bath was removed 15 min after "time zero" when the H_2O_2 was added; 130 mg (1.00 mmol) of **4**, 10 mL of MeOH, and 0.75 mL of H_2O_2 (7.5 mmol) were used. The consumption, expressed as before after "time zero" was (h in parentheses): 1.65 (0.5), 2.35 (1), 2.73 (2.5), 3.00 (5.5), 3.05 (21), 3.05 (51).

For the gravimetric determination of sulfate ion, 130 mg (1.00 mmol) of **4** in 2 mL of MeOH was oxidized, essentially as described under *a*, with 0.60 mL (6.00 mmol) of H_2O_2. When TLC after 10 h showed no **4**, the procedure used with **3** led to 0.1953 g of $BaSO_4$ (84% of expectation for **4**).

In exploration of the possibility that intermediates might be evident with less than three molar proportions of H_2O_2, 65.0 mg (0.50 mmol) of **4** in 5 mL of MeOH was oxidized with 0.05 mL (0.50 mmol) of H_2O_2 essentially as described under *a*. After the 6-h period, TLC indicated unreacted **4**; no H_2O_2 remained (KI-starch paper). Isolation of the product as before was followed by dissolution in $CDCl_3$ and filtration. NMR then showed the signals at δ 3.58 and 3.19 for the thione **4** and at δ 4.01 and 3.29 for the oxidation product **26**; the ratio of the first set of integrals (**4**) to the second (**26**) was ca. 2 : 1.

Oxidation of 1,3-diphenyl-2-imidazolidinethione (**5**). When a solution of 127 mg (0.50 mmol) of **5** in 5 mL of DMF at ca. 25°C was treated with 0.50 mL (5.00 mmol) of H_2O_2, comparison after 7 h with a control where **5** was omitted showed no difference in H_2O_2 consumption upon titration as usual for H_2O_2.[17] Accordingly, a solution of 762 mg (3.00 mmol) of **5** in 25 mL of DMF containing 25 mL of AcOH and 2 drops of concd. H_2SO_4 was treated with 2.3 mL (23.0 mmol) of H_2O_2 with cooling and stirring. After 48 h at ca. 25°C, solid **19** that had appeared was separated, washed with Et_2O, and dried. The yield of 1,3-diphenyl-2-imidazolidone (**19**) was 452 mg (63%): mp 214–216°C (lit. mp 209–210°C,[16] 218.5–219.5°C);[24] NMR ($CDCl_3$) δ 7.62–7.03 (m, 10 H), 3.92 (s, 4 H); MS m/z 238 (calcd 238); IR 3055, 3000, 2905, 1660, 1590, 1480, 1450, 1400, 1325, 1300, 1225, 1200, 1180, 1160, 1120, 1100, 1075, 1010, 890, 740, 690, 670 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.54; H, 5.84; N, 11.76.

A control solution (omission of **5**) consumed so much H_2O_2 that following the course of reaction in the manner used with **3** and **4** seemed infeasible; no attempt was made to determine sulfate ion owing to the indeterminate fate of the H_2SO_4 added.

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