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THE REACTION OF 1,2-DITHIOLIUM SALTS WITH AMMONIA

A GENERAL SYNTHESIS OF ISOTHIAZOLES. SCOPE AND MECHANISM

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Abstract—4-Phenyl-1,2-dithiolium perchlorate reacts with ammonia in ethanol to yield 4-phenylisothiazole. The reaction is general for dithiolium salts. When unsymmetrical dithiolium salts are treated with ammonia, the major product and, under many conditions, the only product is the 5-substituted isothiazole. Of the four possible mechanisms for these reactions, an addition-elimination mechanism has been shown to be correct. Treatment of dithiolium salts with hydroxylamine gives a mixture of isoxazoles and isothiazoles.

LEAVER and Robertson,[2] in 1960, noted the formation of 3,5-diphenylisothiazole on treatment of 3,5-diphenyl-1,2-dithiolium perchlorate with ammonia in ethanol. We wish to report that this reaction is general and constitutes a practical synthesis of isothiazoles from the now readily available 1,2-dithiolium salts.[3-5]

When this work was begun, there were no general syntheses of isothiazoles in the literature, though the parent compound had been prepared by Adams and Slack[6,7] by a tedious thirteen step procedure. Since the completion of this work, however, a number of useful syntheses of isothiazoles have appeared in the literature.[8-12] The present procedure is the most practical laboratory synthesis of simple isothiazoles, though the process of Hübenett *et al.*,[8] which requires the simultaneous passage of

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[2] D. Leaver and W. A. H. Robertson, *Proc. Chem. Soc.* 252 (1960).

[3] E. Klingsberg, *J. Amer. Chem. Soc.* **83**, 2934 (1961).

[4] E. Klingsberg and A. M. Schreiber, *J. Amer. Chem. Soc.* **84**, 2941 (1962).

[5] E. Klingsberg, *J. Org. Chem.* **28**, 529 (1963).

[6] A. Adams and R. Slack, *Chem & Ind.* 1232 (1956).

[7] A. Adams and R. Slack, *J. Chem. Soc.* 3061 (1959).

[8] F. Hübenett and F. H. Flock, *Angew. Chem.* **74**, 653 (1962); F. Hübenett and Hd. Hofmann, *Ibid.* **75**, 420 (1963); F. Hübenett, F. H. Flock, W. F. Hansel, H. Heinze and Hd. Hofmann, *Ibid.* **75**, 1189 (1963).

[9] F. Wille, L. Capeller and A. Steiner, *Angew. Chem.* **74**, 467 (1962).

[10] W. R. Hatchard, *J. Org. Chem.* **29**, 660, 665 (1964); and earlier Refs.

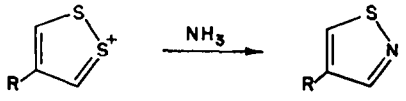
[11] J. Goerdeler and H. Horn, *Chem. Ber.* **96**, 1551 (1963); and earlier Refs.

[12] R. B. Woodward, G. P. Volpp and J. Z. Gougoutas, unpublished results; see R. B. Woodward, *Harvey Lectures* 1963–64, Series 59 p. 31, Academic Press New York (1965) and J. Z. Gougoutas, Thesis, Harvard University, May (1964).

an alkene, sulfur dioxide, and ammonia over an aluminum oxide catalyst at high temperature, is more economical industrially.

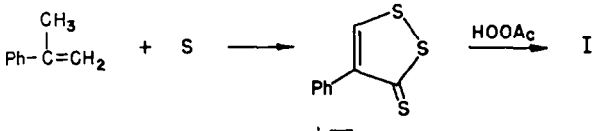
A number of reasons prompted us to undertake the present work. First, we required a practical synthesis of 3- and 5- unsubstituted isothiazoles and isothiazolium salts, compounds we wished to use as substrates in a study of the acidity of protons in heterocyclic systems.[13,14] We also hoped that 3-unsubstituted isothiazolium salts would prove as useful as the synthetically important 3-unsubstituted isoxazolium salts. These isoxazolium salts have been utilized as precursors in the synthesis of a wide variety of heterocycles[15,16] and as reagents for the practical synthesis of peptides.[17] Finally, we were interested in the ring opening mechanisms of dithiolium salts as part of a general study of the base-induced ring scission reactions of five-membered ring heterocyclic salts.[13,15,16,18–20]

Synthetic studies. 4-Phenylisothiazole (II) was prepared in 88% yield by treatment of 4-phenyl-1,2-dithiolium perchlorate (I) with ammonia in ethanol. Dithiolium



I II

salts are easily prepared in high yield. For example, I is made by boiling the industrial monomer, α-methylstyrene, with sulfur followed by titration of the product trithione (III) with peracetic acid.[21,3] A few experiments were carried out to determine the

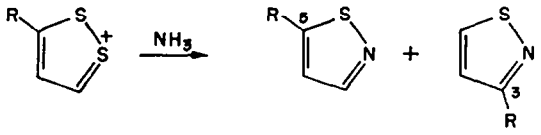


III

optimum experimental conditions for the formation of II; it was found that the highest yields of II were obtained when a saturated solution of anhydrous ammonia gas in ethanol was added to the dithiolium perchlorate (I). The mixture was then stirred while additional ammonia was bubbled through it. Lower yields were obtained when other anions or different solvents were used. 4-Phenylisothiazole was easily isolated by vacuum distillation after removal of the by-product ammonium salts by filtration.

A number of other isothiazoles were prepared by variations of the above procedure (Table 1). It was found that the major product, and under many conditions, the only product formed on treatment of an unsymmetrical dithiolium salt (IV) with ammonia is the 5-substituted isothiazole (V). Further, it was discovered that in this

[13] R. A. Olofson, W. R. Thompson and J. S. Michelman, *J. Amer. Chem. Soc.* **86**, 1865 (1964).
[14] R. A. Olofson, J. M. Landesberg and K. N. Houk, unpublished results.
[15] R. B. Woodward and R. A. Olofson, *J. Amer. Chem. Soc.* **83**, 1007 (1961).
[16] R. B. Woodward and R. A. Olofson, unpublished results.
[17] R. B. Woodward, R. A. Olofson and H. Mayer, *J. Amer. Chem. Soc.* **83**, 1010 (1961).
[18] R. A. Olofson and J. S. Michelman, *J. Amer. Chem. Soc.* **86**, 1863 (1964).
[19] J. M. Landesberg and R. A. Olofson, *Tetrahedron* **22**, 2129 (1966).
[20] R. A. Olofson *et al.*, unpublished results.
[21] E. K. Fields, *J. Amer. Chem. Soc.* **77**, 4255 (1955).



IV V VI

TABLE 1

Reaction temp	Dithiolium salt	Isothiazole	Yield
Room temp	4-phenyl	4-phenyl	88%
r.t.	4-*p*-tolyl	4-*p*-tolyl	89%
r.t.	4-methyl	4-methyl	50%
r.t.	3-phenyl	5-phenyl	49%
		3-phenyl	7%
−5°	3-phenyl	5-phenyl	54%
r.t.	3-*p*-anisyl	5-*p*-anisyl	61%
		3-*p*-anisyl	7%
−5°	3-*p*-anisyl	5-*p*-anisyl	67%
r.t.	3-*p*-nitrophenyl	5-*p*-nitrophenyl	38%
80°	3,5-diphenyl	3,5-diphenyl	50%

TABLE 2

Reaction temp	Dithiolium perchlorate (g)	Solvent (ml)	Relative ratio (%) 5-Isomer	3-Isomer	Total yield
Isothiazoles from 3-phenyl-1,2-dithiolium perchlorate in ethanol:					
−5°	4·0	150	>99	<1	—
−5°	6·0	200	>99	<1	54%
−5°	10·0	200	>99	<1	—
20°	10·0	200	87	13	57%
30°	10·0	200	90	10	—
40°	10·0	200	91	9	50%
50°	10·0	200	94	6	50%
60°	10·0	200	94	6	44%
80°	10·0	200	98·5	1·5	48%
80°	9·0	200	>99	<1	50%
80°	11·0	200	98	2	—
Isothiazoles from 3-phenyl-1,2-dithiolium perchlorate in acetonitrile:					
−5°	10·0	200	98	2	47%
20°	10·0	200	87	13	47%
40°	10·0	200	87	13	45%
100°	10·0	200	87	13	43%
Isothiazoles from 3-*p*-anisyl-1,2-dithiolium perchlorate in ethanol:					
−5°	6·0	200	>99	<1	67%
20°	28·5	400	89	11	68%
80°	6·0	200	>99	<1	58%

reaction the product ratio of 3-substituted to 5-substituted isothiazole is not only strongly dependent on temperature, but is dependent on temperature in a remarkable manner. As is shown in Table 2, the amount of 3-substituted isothiazole in the product mixture is at a maximum when the reaction is carried out at an intermediate temperature.

Isothiazole structure proofs. Analyses, IR, UV (Table 3), and NMR (Table 3) spectral data are in accord with the isothiazole structures proposed for the reaction

TABLE 3

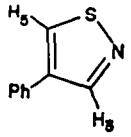
Isothiazole		UV Spectra λ_{max} mμ (ε); cyclohexane	NMR Spectra ($CDCl_3$) Chemical shift, τ	Multiplicity	Protons
VII	4-Methyl	250 (5,500)	1·67	singlet	1
			1·73	singlet	1
			7·73	singlet	3
VIII	4-*p*-Tolyl	272 (11,300)	1·15	singlet	1
		242 (9,200)	1·35	singlet	1
			2·33–2·87	quartet, A_2B_2	4
			7·63	singlet	3
IX	3-Phenyl	291 (6,500)	1·20	doublet, J = 5·0 c/s	1
		283 (9,800) shoulder	2·27	doublet, J = 5·0 c/s	6
		270 (15,100)	1·68–2·62	multiplet	
		239 (6,600) shoulder			
X	4-Phenyl	266 (13,900)	1·40	singlet	1
		242 (12,400)	1·57	singlet	1
			2·33–3·00	multiplet	5
XI	5-Phenyl	266 (7,900)	1·52	doublet, J = 2·0 c/s	1
			2·27–2·77	multiplet	6
XII	3-*p*-Anisyl	303 (7,500) shoulder	1·23	doublet, J = 5·0 c/s	1
		280 (17,800)	1·77–3·07	quartet, A_2B_2	4
		246 (6,400) shoulder	2·35	doublet, J = 5·0 c/s	1
			6·09	singlet	3
XIII	5-*p*-Anisyl	285 (8,400)	1·42	doublet, J = 2·0 c/s	1
			2·13–3·07	quartet, A_2B_2	4
			2·55	doublet, J = 2·0 c/s	1
			6·05	singlet	3
XIV	5-*p*-Nitro phenyl	299 (8,000)	1·30	doublet, J = 2·0 c/s	1
		223 (4,500)	1·38–2·20	quartet, A_2B_2	4
			2·28	doublet, J = 2·0 c/s	1

products. In addition, a sample of the known 4-methyl-isothiazole was obtained[8,22] and was shown to be identical with our product resulting from the action of ammonia on 4-methyl-1,2-dithiolium hydrogen sulfate.

Additional experiments were required to distinguish between the 3- and the 5-arylisothiazoles obtained from the reaction of unsymmetrical dithiolium salts with ammonia. From Table 3 it is seen that isothiazoles, IX and XII, have much more complex UV spectra than their respective isomers, XI and XIII: this suggests that they belong in the same series. Also, the nitrophenylisothiazole (XIV) has a UV spectrum similar to XI and XIII so these three compounds must belong in the same series. This conclusion is confirmed by a study of the NMR spectra of these compounds (Table 3). The coupling constant for the vicinal isothiazole ring protons in IX and XII is 5·0 c/s while the similar coupling constant in XI, XIII and XIV is 2·0 c/s.

[22] We wish to thank Dr. F. Hübenett and Dr. F. Flock for a generous sample of this compound and for communicating some of their results to us prior to publication.

The absolute assignment of IX and XII, as 3-isomers and the other three compounds as 5-isomers depends on the observations of Woodward *et al.*[12] who showed that isothiazoles with a proton in the 5-position undergo exchange of this proton for deuterium in the presence of methoxide in deutero-methanol. In order to use this observation in the structure assignment, it was first necessary to determine the lability of the 3-proton of the isothiazole ring in deuterated base. This was accomplished by studying the exchange of 4-phenylisothiazole (II). Only the lowest field proton in II

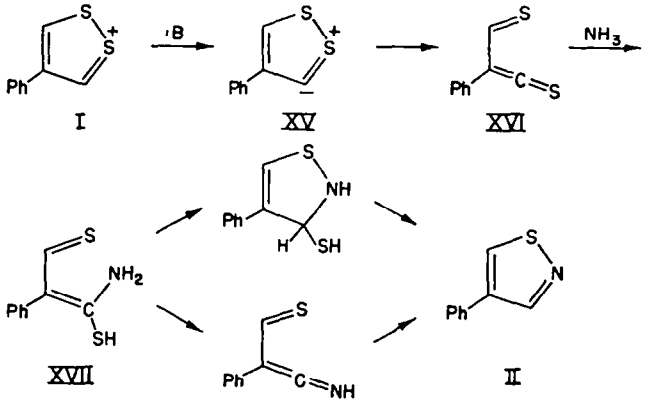


II

undergoes exchange with 1·13N sodium methoxide in deutero-methanol. The other isothiazole proton does not exchange under conditions many times more stringent. That the exchanging proton is H_5 is confirmed by a close scrutiny of the NMR spectrum of II. Of the two low field signals due to the isothiazole protons, the higher field peak is shorter and broader than the other as would be expected from a small coupling constant with an N^{14} nucleus on the adjacent carbon. Therefore, the lowest field, tallest peak corresponds to the base labile proton and must be caused by the proton on the carbon next to sulfur. Protons on carbon next to nitrogen are stable under the exchange conditions. The isothiazoles, IX and XII, undergo exchange of a single proton with 1·13N sodium methoxide in deutero-methanol; these compounds must be 3-arylisothiazoles. Since isothiazoles, XI, XIII and XIV, are unaffected even under more drastic conditions, these compounds must be 5-arylisothiazoles.

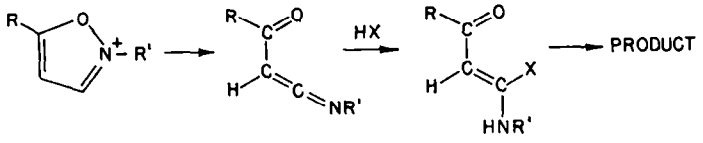
Possible reaction mechanisms. There are four reasonable mechanisms for the formation of 4-phenylisothiazole from the dithiolium salt and ammonia.

Mechanism A:



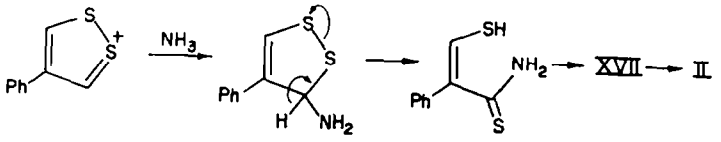
The first mechanism involves initial abstraction of the proton on the carbon next to sulfur yield the ylide (XV) which can undergo ring scission to the thioketene (XVI). This species would be expected to add ammonia at the electrophilic carbon to give XVII which could undergo ring closure and loss of hydrogen sulfide either directly

or via the ketenimine (XVIII). A number of precedents exist for this mechanism. The lability of protons next to positively charged atoms in heterocyclic salts is well known.[23,13] Further, the ring cleavage mechanism postulated has been already demonstrated in the ring scission reactions of isoxazolium salts:[15]



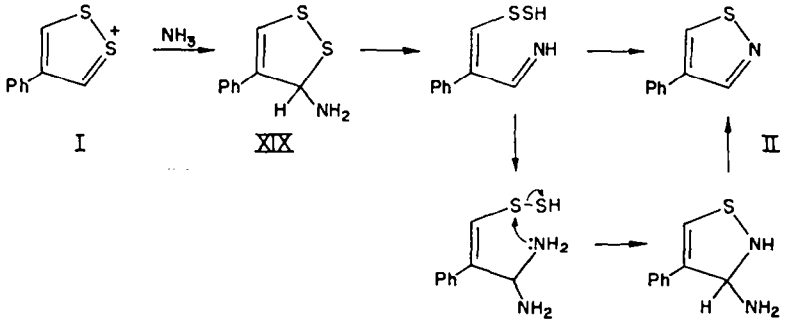
The cyclization mechanism is the one required in the isothiazole synthesis of Woodward *et al.*[12]

Mechanism B:



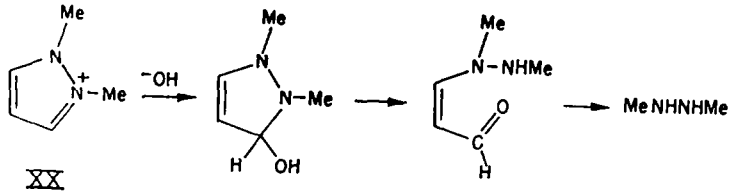
In mechanism B ammonia is added to the dithiolium salt to neutralize the positive charge. This is followed by removal of a proton from the tetrahedral intermediate (XIX) and ring scission to yield XVII which can undergo ring closure via the alternatives of path A. There are many analogies for formation of a pseudobase (XIX) by addition of ammonia to the dithiolium salt. There are, however, no analogies for the ring opening reaction of XIX and any driving force for this reaction must derive from some special property of sulfur in such a system.

Mechanism C:



In mechanism C we have a simple addition-elimination mechanism followed by ring closure via displacement of sulfhydride ion by some nucleophilic nitrogen species. The best analogy for the ring scission is the formation of dimethylhydrazine on treatment of 1,2-dimethylpyrazolium iodide (XX) with potassium hydroxide.[24] The

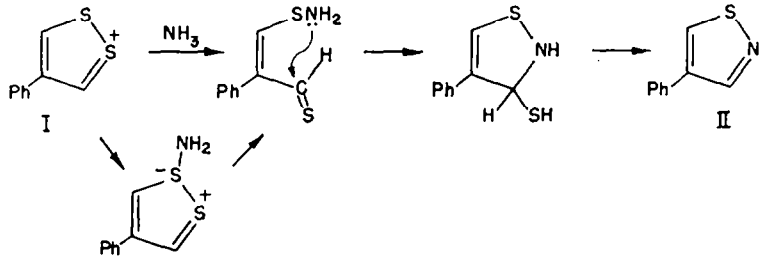
[23] R. Breslow, *J. Amer. Chem. Soc.* **80**, 3719 (1958).
[24] L. Knorr and A. Köhler, *Chem. Ber.* **39**, 3257 (1906).



XX

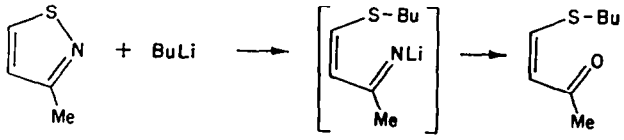
ring closure step is also not lacking in precedents since reactions involving the nucleophilic scission of sulfur-sulfur bonds are widely known and well documented.[25–29]

Mechanism D:

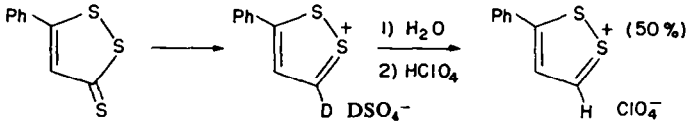


I II

The final mechanism involves neutralization of the positive charge on sulfur by displacement followed by ring closure by an addition-elimination path. Few examples exist for a displacement on sulfur in a pseudoaromatic system. The best analogies are found in some work by Woodward[12] and by Slack[30] involving such a displacement on an isothiazole ring:



Mechanistic studies Mechanisms A and B are incapable of explaining the formation of 3,5-diphenylisothiazole or the other 3-arylisothiazoles since the precursor dithiolium salts do not have protons in the required positions. In order to further rule out these mechanisms in the formation of the 4- and 5-substituted isothiazoles, the following experiments were performed. 3-Phenyl-1, 2-dithiolium-5-d deuterosulfate (XXII) was prepared by treatment of the trithione (XXI) with D_2O_2 in deutero-acetic acid.

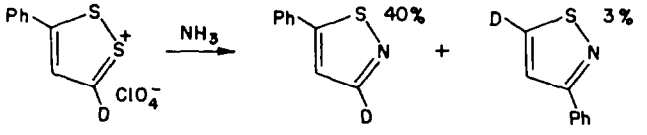


XXI XXII

[25] A. J. Parker and N. Kharasch, *Chem. Revs.* **59**, 583 (1959).
[26] W. A. Pryor, *Mechanisms of Sulfur Reactions* pp. 59–64. McGraw-Hill, New York (1962).
[27] O. Foss, *Ionic Scission of the Sulfur-Sulfur Bond*, in *Organic Sulfur Compounds*, Vol. I; pp. 83–96. Pergamon Press, London (1960).
[28] D. F. Twiss and F. A. Jones, Brit. Pat. 413296 (1934).
[29] M. Busch, *Chem. Ber.* **29**, 2127 (1896).
[30] M. P. L. Caton, D. H. Jones, R. Slack and K. R. H. Wooldridge, *J. Chem. Soc.* 446 (1964).

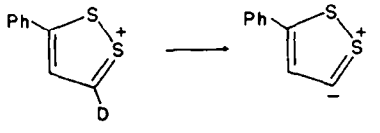
This compound was dissolved in water containing enough base to decompose part of it[3] and the remaining dithiolium salt was isolated as the perchlorate by precipitation with perchloric acid (60% recovery). The NMR spectrum of this reisolated material showed that half the deuterium in XXII had been exchanged for protium under these conditions. Another experiment in which undeuterated 3-phenyl-1,2-dithiolium bisulfate was similarly treated in *heavy* water resulted in the replacement of half of the protium in the 3-position of the reisolated dithiolium salt by deuterium. These results verify the first step of Mechanism A and testify to its reversibility.

However, on treatment of the dithiolium salt (XXIII) with ammonia in ethanol the product isothiazoles (XXIV) contained 90% of their deuterium. Since most of



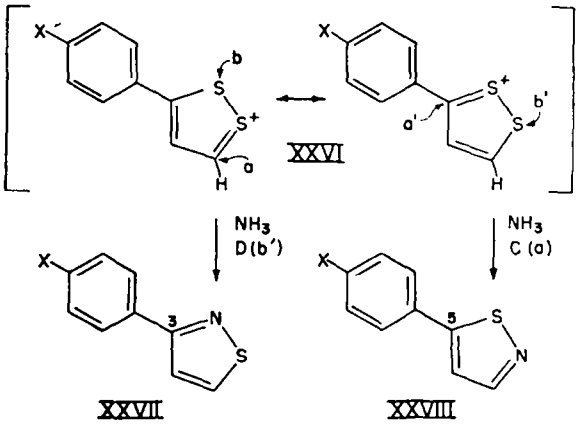
XXIII XXIV

the initial deuterium content is found in XXIV and since both mechanisms A and B require obligatory deuterium exchange with the undeuterated solvent, these two mechanisms are then unambiguously ruled out. The small amount of protium found in the isothiazoles (XXIV) undoubtedly occurs via the ylide (XXV) which results from a side reaction. This reaction has approximately the same rate as the main reaction, but has nothing to do with the formation of isothiazoles.



XXV

The remaining mechanistic pathways, the addition-elimination path C and the displacement mechanism D, are very similar; the main difference between them is the order in which the various steps are carried out. It is possible to choose between these pathways, however, if one considers the course of the reaction when one starts with an unsymmetrical dithiolium salt (XXVI).



XXVI

XXVII XXVIII

If the addition-elimination path C is operative, ammonia can add at *a* or *a'*. If we postulate that steric effects are the major ones operating in deciding the position of attack, we would expect addition at *a* since *a'* has a large substituent. If mechanism C is the reaction path then we would expect the 5-substituted isothiazole (XXVIII) to be the major product.

On the other hand, if the displacement mechanism D is operative, one would expect attack at *b'* to be favored over *b*, since *b* is an *ortho*-position in what is essentially a biphenyl system; then the major product should be the 3-substituted isothiazole (XXVII).

Tables 1 and 2 show that the only product found at low temperature is XXVIII; this strongly suggests that the replacement of sulfur by nitrogen in the formation of isothiazoles from dithiolium salts proceeds by the addition-elimination mechanism C. A number of control experiments were carried out to prove that the isothiazoles were stable and not interconvertible under the reaction and isolation conditions.

In order to test our assumption that steric effects are the most important effects in determining the isomer obtained in these reactions, the electronic character of the dithiolium salt (XXVI) was varied widely without appreciably changing the magnitude of the steric effect. This was accomplished by varying the *para*-substituents on the benzene ring from methoxy to nitro, from electron releasing to electron withdrawing. In both cases the 5-arylisothiazole was obtained at low temperature, thus providing experimental verification for our postulate.

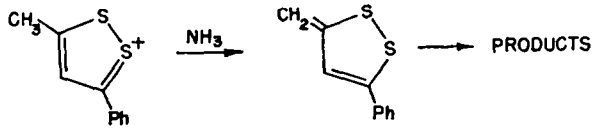
The change in isomer ratio with temperature in these reactions deserves some comment. We would argue that at low temperatures steric effects are important. As one raises the temperature, however, more energy is put into the system and a statistical distribution of isomers is approached. As the temperature is raised further, two comparable intermediates have quite different activation energies for some side reaction, and the intermediate which would normally lead to the 3-substituted isothiazole is preferentially shunted off and destroyed. The fact that this extraordinary temperature dependence is not found when the reaction is run in acetonitrile suggests that the side reaction involves a hydroxylic solvent.

In conclusion it should be said that although these final arguments are attractive they are not absolutely conclusive. It is, however, clear that the predominant, if not the only mechanism, for the formation of isothiazoles from dithiolium salts is the addition-elimination path C.[31]

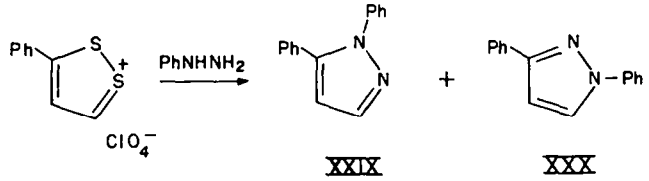
Reactions of dithiolium salts with other nucleophiles

Klingsberg[3,5] has discovered that dithiolium salts react with N,N'-disubstituted hydrazines to yield pyrazolium salts and with monosubstituted hydrazines to give pyrazoles. We have repeated the reaction of 3-phenyl-1,2-dithiolium perchlorate with

[31] 3-Methyl-5-phenyl-1,2-dithiolium perchlorate gives a purple compound on treatment with ammonia in ethanol rather than the expected isothiazole mixture.[3] This is probably due to the fact that the favored reaction in this case involves initial abstraction of the methyl proton as diagrammed below:

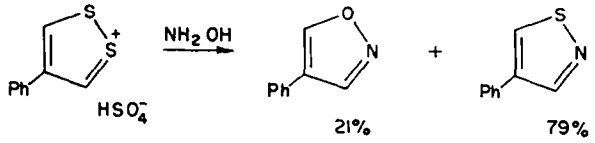


phenyl-hydrazine[3] and discovered that the pyrazole mixture obtained contained 1,5-diphenylpyrazole (XXIX) and 1,3-diphenylpyrazole (XXX) in the ratio of 75% to 25%. This result does not allow us to draw any concrete mechanistic conclusions though it suggests that an initial addition-elimination step is again involved in the mechanism.



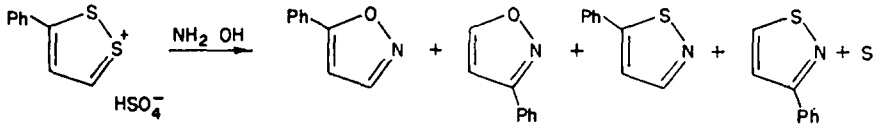
XXIX XXX

Finally, we have studied the reaction of dithiolium salts with hydroxylamine and obtained the results outlined below:



21% 79%

TOTAL YIELD = 11%



9.5% 84% 6% 0.5%

TOTAL YIELD = 17%

We expected to obtain the isoxazoles but it is difficult to visualize a mechanism for the formation of isothiazoles without involving ammonia or some reaction equivalent in this potential oxidation-reduction system. The major reactions in these equations are probably the formation of 4- and 5-phenylisoxazole, respectively; it has been shown that 3-unsubstituted isoxazoles are not stable under the reaction conditions (Experimental). Further study of the mechanisms of these reactions is required.

EXPERIMENTAL

All m.ps were taken in soft glass capillary tubes in a Thomas–Hoover m.p. apparatus using a calibrated thermometer. The IR spectra were run on a Perkin–Elmer Model 21 Double Beam Recording Spectrophotometer equipped with NaCl optics, and bands in the 5–7 μ region were calibrated against the 5·88 μ band of atmospheric water vapor; the UV spectra were run on a Cary Model 11 Recording Spectrophotometer. NMR spectra were measured on a Varian A-60 Spectrometer. VPC was carried out on an F&M model 609 flame ionization gas chromatograph using disc chart integration; compound ratios as determined from the integrated peak areas were always checked against mixtures of known composition. The heavy water used in the exchange experiments had an isotopic purity of greater than 99·75%.

4-Phenyl-1,2-dithiolium hydrogen sulfate. This salt was prepared in 91% yield according to the method of Klingsberg[8] from 4-phenyl-1,2-dithiol-3-thione;[21] m.p. 233–234° (dec) (lit.[8] 230–232°).

4-Phenyl-1,2-dithiolium perchlorate. 4-Phenyl-1,2-dithiolium hydrogen sulfate, 63·1 g (0·229 mole), was dissolved in 1300 ml 0·1N H_2SO_4 and the insoluble decomposition products removed by filtration. Precipitation of the perchlorate salt occurred immediately when 36 g of 70% perchloric

acid was slowly stirred into the solution. This was filtered, washed with distilled water, and dried. The product was then dissolved in warm acetone and precipitated with ether yielding 65·4 g (91%) of a pale yellow solid; m.p. 209–210° (dec) (lit.[3] 210–212°).

3-Phenyl-1,2-dithiolium hydrogen sulfate. This salt was also prepared in 91% yield according to the method of Klingsberg[3] from 5-phenyl-1,2-dithiol-3-thione[3]; m.p. 203–205° (dec.) (lit.[3] 205–207°).

3-Phenyl-1,2-dithiolium perchlorate. The exchange of anions was accomplished by adding 25 g of 70% perchloric acid to a solution of 46·2 g (0·167 mole) of 3-phenyl-1,2-dithiolium hydrogen sulfate in 1200 ml 0·1N H_2SO_4. The solid which precipitated, 44·2 g (96%), was recrystallized from acetone–ether; m.p. 178–179° (dec.) (lit.[3] 180–182·5).

3-p-Anisyl-1,2-dithiolium hydrogen sulfate. 5-*p*-Anisyl-1,2-dithiol-3-thione,[22] 43·8 g (0·183 mole), was dissolved in 1500 ml acetone and titrated over a 15 min period with 160 g commercial 40% peracetic acid with external cooling. The precipitate which separated was filtered off, washed with cold acetone, and dried yielding 42·5 g (76%) of a yellow solid which crystallized from EtOH as yellow needles; m.p. 232–234° (dec.). In 0·1N HCl the compound showed absorption maxima at 407 mμ (ε 20,000) and 244 mμ (ε 7,500). (Found: C, 39·15, 39·62; H, 3·48, 3·44; S, 30.43, 31·01. $C_{10}H_{10}S_2O_5$ requires: C, 39·20; H, 3·28; S, 31·39%.)

3-p-Anisyl-1,2-dithiolium perchlorate. This salt was prepared in the same way as the 4-phenyl isomer from 41·5 g (0·136 mole) 3-*p*-anisyl-1,2-dithiolium hydrogen sulfate in 1500 ml 0·1N H_2SO_4 by addition of 25 g 70% perchloric acid. The crude product was dissolved in warm acetone and precipitated with ether yielding 34·5 g (83%) of a yellow solid; m.p. 226–227° (dec). In 0·1N HCl the compound showed absorption maxima at 407 mμ (ε 21,000) and 244 mμ (ε 7,100). Found C, 38·94; H, 3·11; S, 21·07. $C_{10}H_9S_2ClO_5$ requires: C, 38·90; H, 2·93; S, 20·76%.)

3-p-Nitrophenyl-1,2-dithiolium bromide. This salt was prepared in 18% yield from 3-phenyl-1, 2-dithiolium hydrogen sulfate according to the method of Klingsberg;[3] m.p. 224–226° dec.) (lit.[3] 220–222°).

4-p-Tolyl-1,2-dithiolium perchlorate. 4-*p*-Tolyl-1,2-dithiol-3-thione,[21] 59·0 g (0·263 mole), was dissolved in 1400 ml acetone and titrated with 180 g commercial 40% peracetic acid (15 min) with external cooling. The reaction mixture containing the precipitated bisulfate salt was cooled for an additional 15 min, then filtered, washed with cold acetone, and dried. A yellow solid, 69·0 g (91%), was collected but no satisfactory analytical results could be obtained on recrystallization; m.p. 263–265° (dec). The bisulfate salt was transformed in 80% yield into the perchlorate salt in the usual manner. The perchlorate salt was recrystallized from acetone–ether, m.p. 233–234·5° (dec). In 0·1N HCl the salt showed absorption maxima at 361 mμ (ε 750) and 249 mμ (ε 11,400). (Found: C, 41·03; H, 3·06; S, 21·81. $C_{10}H_9S_2ClO_4$ requires: C, 41·03, H, 3·10; S, 21·90%.)

3-Phenyl-1,2-dithiolium-5-d-deuterosulfate. 5-Phenyl-1,2-dithiol-3-thione,[3] 5·0 g (0·024 mole), was dissolved in 300 ml warm monodeutero-acetic acid (prepared by heating 306 g Ac_2O with 60 g of D_2O). The stirred solution was cooled in an ice bath and 20 ml of 25% D_2O_4 in D_2O[23] was added over a 15 min period. The solution was stirred for an additional 20 mins in the ice bath and then filtered to remove a small amount of insoluble material. Ether was added to the filtrate to precipitate the deutero-sulfate salt which was then filtered off, washed with ether, and dried; 1·6 g (25%) of the deuterated compound was obtained; m.p. 203–205° (dec.) (undeuterated salt m.p. 203–205°, dec.).

3-Phenyl-1,2-dithiolium-5-d perchlorate. The procedure used for the undeuterated salt was followed; yield, 73%; m.p. 178–179° (dec.) (undeuterated salt m.p. 178–179°, decomp.); IR (KBr pellet) showed a C–D stretch at 4.38 μ.

NMR spectra of the deuterated and undeuterated dithiolium perchlorates were measured in acetonitrile and are compared as follows:

5-h isomer:	−0·20 τ (doublet, J = 5·0 c/s, 1 proton)
	1·20 τ (doublet, J = 5·0 c/s, 1 proton)
	1·83–2·67 τ (multiplet, 5 protons).
5-d isomer:	1·17 τ (singlet, 1 proton)
	1·83–2·67 τ (multiplet, 5 protons).

The UV spectra of the deuterated and undeuterated isomers are identical with maxima at 356 and 287 mμ as reported by Klingsberg[3] for the bisulfate salt.

[22] B. Böttcher and A, Lüttringhaus. *Liebigs Ann.* **557**, 89 (1947).
[23] C. Martius and G. Schorre, *Liebigs. Ann.* **570**, 140 (1950).

4-Phenylisothiazole. 4-Phenyl-1,2-dithiolium perchlorate, 35·3 g (0·127 mole), was placed in a 500 ml 3-neck round-bottomed flask equipped with a slip-seal stirrer, gas inlet tube, and reflux condenser fitted with a drying tube. A solution of 400 ml of abs EtOH saturated with ammonia gas was slowly added with stirring; the gas inlet tube was connected and anhydrous ammonia bubbled through the solution. Bubbling was continued for 30 min at room temp and 1 hr at reflux. The reaction mixture was cooled, placed in a beaker, and 200 ml ether added to precipitate the ammonium perchlorate which was then removed by filtration. The solvent was evaporated at reduced pressure and the residue ($b.p._{0.6mm}$ 100–103°) was distilled giving 18·0 g (88%) of a yellow oil which solidified on cooling. For analysis the product was crystallized from 50:50 ether–pet. ether; white needles, m.p. 35·5–36·5°; λ_{max} 266 mμ (ε 13,900), 242 mμ (ε 12,400) in cyclohexane. (Found: C, 66·69, 67·09; H, 4·37, 4·77; N, 8·44, 8·33; S, 19·66, 19·85. C_9H_7NS requires: C, 67·03; H, 4·38; N, 8·69; S, 19·89%.)

Other procedures were also examined for the synthesis of 4-phenylisothiazole. A tabulation follows:

Anion of dithiolium salt	Solvent mixture	Yield
HSO_4^-	Pyridine–NH_3	58%
HSO_4^-	95% EtOH–NH_4OH	60%
HSO_4^-	Dioxane–NH_3	53%
HSO_4^-	EtOH–NH_3	73%
HSO_4^-	Acetonitrile–NH_3	39%
HSO_4^-	Nitromethane–NH_3	53%
ClO_4^-	Nitromethane–NH_3	29%
HSO_4^-	conc NH_4OH	30%
HSO_4^-	liq. NH_3	40%
ClO_4^-	EtOH–NH_3	88%

The isothiazole could also be isolated by extraction and crystallization without distillation but the above procedure proved more convenient.

A different type of procedure was also studied. A saturated solution of $AcONH_4$ in AcOH (10 ml) was added to a boiling solution of 4-phenyl-1,2-dithiolium perchlorate (1·5 g) in AcOH (50 ml) and boiling was continued for 10 min. The solution was cooled, filtered, and evaporated to yield a viscous residue which was partitioned between ether and water. Evaporation of the ether yielded a brown oil which solidified on treatment with light petroleum. Purification was achieved by treatment of the solid, dissolved in AcOH with perchloric acid (0·2 ml, 70%), and precipitation with ether, thereby affording 4-phenylisothiazolium perchlorate (0·6 g); m.p. 152–153°. (Found: Cl, 13·8; N, 5·3; S, 12·3. $C_9H_8ClNO_4S$ requires: Cl, 13·6; N, 5·4; S, 12·2%.)

Treatment of this salt with sodium hydroxide gave 4-phenyl-isothiazole.

4-p-Tolylisothiazole. Adaptation of the procedure devised for the synthesis of 4-phenylisothiazole with 4-*p*-tolyl-1,2-dithiolium perchlorate, 46·2 g (0·158 mole), yielded 89% of a yellow oil, b.p. 1·3 mm 125–130°, which solidified on cooling. The product was recrystallized from ether; white needles, m.p. 76·5–77·5°; λ_{max} 272 mμ (ε 11,300) and 242 mμ (ε 9,200) in cyclohexane. (Found: C, 68·36; H, 5.29; N, 8·07. $C_{10}H_9NS$ requires: C, 68·54; H, 5·18; N, 7·99%.)

3,5-*Diphenylisothiazole.* Ammonia was passed into a solution of 3,5-diphenyl-1,2-dithiolium perchlorate[3,24] (0·6 g) in 40 ml of boiling EtOH which first became dark red and then pale orange. After 20 min the solution was concentrated to 2 ml, diluted with 50 ml of 2N NaOH, and extracted with ether. Evaporation of the ether gave 3,5-diphenylisothiazole, 0·2 g (50%); plates, m.p. 81° (from light petroleum); λ_{max} 277 mμ (ε 22,000), 251 mμ (ε 26,000), and 207 mμ (ε 25,000) in EtOH. (Found: C, 76·05; H, 4·6; N, 5·5; S, 13·5. $C_{15}H_{11}NS$ requires: C, 75·95; H, 4·6; N, 5·9; S, 13·5%.)

4-*Methylisothiazole.* 4-Methyl-1,2-dithiolium hydrogen sulfate was prepared by titrating an externally cooled solution of 14·9 (0·101 mole) 4-methyl-1,2-dithiol-3-thione[25] in 250 ml acetone

[24] D. Leaver, W. A. H. Robertson, and D. M. McKinnon. *J. Chem. Soc.* 5104 (1962).

[25] R. S. Spindt, D. R. Stevens, and W. E. Baldwin, *J. Amer. Chem. Soc.* 73, 3693 (1951).

with 45 g 40% peracetic acid (15 min). The precipitate which separated was filtered off, washed with cold acetone, and dried giving 14 g (65%) of a yellow solid which was quite unstable and had no definite m.p. This crude solid was treated with 50 ml of a saturated ethanolic ammonia solution and the reaction carried out as above. The EtOH was removed by fractional distillation through a 10 inch packed column yielding 3·2 g (50%) 4-methylisothiazole as a pale yellow oil, b.p. 760 mm 146–147° (lit.[8] 147°). The procedure is not a very practical one; the product still contains a trace of EtOH. The product is, however, identical with authentic material as adjudged from a comparison of IR spectra.[22]

3-Phenylisothiazole; 5-phenylisothiazole. 3-Phenyl-1,2-dithiolium perchlorate, 33·7 g (0·121 mole), was treated with ammonia in 400 ml EtOH. Distillation yielded 11·0 g (56%) of a yellow oil, $b.p._{0.7mm}$ 98–105°, which solidified on cooling, m.p. 39–44°. Analysis by VPC showed the presence of only two products. Two columns were used: an 8′ silicone gum rubber on Chromosorb P (Column A) and an 8′ Flourosilicone on Chromosorb P (Column B). Both columns gave identical percentage ratios: 13% 3-phenylisothiazole and 87% 5-phenylisothiazole.

Column	Temp	He flow ml/min	3-Phenyl Ret. time	%	5-Phenyl Ret. time	%
A	150°	110	22 min	13	24 min	87
B	180°	60	16 min	13	20 min	87

The isomers were separated on a large scale by chromatography on alumina (Merck; 30 g of alumina per gram of mixture) and eluted in 50 ml fractions with 5% benzene in pet. ether. 3-Phenylisothiazole was eluted first as a yellow oil which did not solidify (VPC analysis showed that the compound was not contaminated with the 5-isomer).

This compound was analyzed as its N-ethyl-3-phenylisothiazolium fluororate (*vide infra*).

5-Phenylisothiazole eluted as a white solid. An analytical sample was prepared by recrystallization of this material from 50% MeOH–water, m.p. 46–47°. (Found: C, 67·10; H, 4·51; N, 8·56; MW, 161 (mass spectroscopy). C_9H_7NS requires: C, 67·03; H, 4·38, N, 8·69%; MW, 161.)

3-p-Anisylisothiazole; 5-p-anisylisothiazole. 3-*p*-Anisyl-1,2-dithiolium perchlorate, 28·5 g (0·092 mole), when treated with ammonia in EtOH, yielded 12·0 g (68%) of a yellow oil, $b.p._{0.65mm}$ 133–135°, which solidified on cooling, m.p. 72–78°. VPC revealed the presence of only two products.

Column	Temp	He flow ml/min	3-*p*-Anisyl Ret. time	%	5-*p*-Anisyl Ret. time	%
A	200°	125	27 min	11	33 min	89
B	215°	110	13 min	11	16 min	89

The isomers were separated by chromatography on alumina (Merck; 35 g per gram of isothiazoles) and eluted in 50 ml fractions with 50% benzene–pet ether. 3-*p*-Anisylisothiazole eluted first as a white solid and was recrystallized from 1:3 benzene–pet. ether, white needles, m.p. 56–57·5°. (Found: C, 62·72; H, 4·71; S, 17·09. $C_{10}H_9NSO$ requires: C, 62·80; H, 4·74; S, 16·77%.)

5-*p*-Anisylisothiazole also eluted as a white solid and was recrystallized from 1:3 benzene–pet ether, white needles, m.p. 81–82°. (Found: C, 62·81; H, 4·80; N, 7·26. $C_{10}H_9NSO$ requires: C, 62·80; H, 4·74; N, 7·32%.)

5-p-Nitrophenylisothiazole. 3-*p*-Nitrophenyl-1,2-dithiolium bromide,[8] 8·0 g (0·025 mole), was treated with ammonia in 150 ml EtOH giving 2·0 g (38%) of a yellow oil, $b.p._{0.2mm}$ 135–145°, which solidified on cooling, m.p. 114–126°. VPC analysis showed the presence of only one product.

Column	Temp	He flow ml/min	Ret. time
A	190°	100	44 min
B	200°	120	74 min

The product was purified by fractional crystallization from 1:3 benzene–pet. ether (traces of S were removed) yielding buff needles, m.p. 122–123°. (Found: C, 52·17: H, 2·88, N, 13·64. $C_9H_8N_2SO_2$ requires: C, 52·42; H, 2·92; N, 13·58%.)

Control experiments: isothiazole synthesis. A. A sample of mixed phenylisothiazoles, 4·53 g 5-phenylisothiazole (85%) and 0·79 g 3-phenylisothiazole (15%), was distilled, b.p.$_{0.7mm}$ 98–105°; 5·1 g (96%) was recovered. VPC (Column B; 180°; He flow, 60 ml/min) indicated an isomer distribution of 85% 5-phenylisothiazole and 15% 3-phenylisothiazole.

B. 3-Phenyl-1,2-dithiolium perchlorate, 10·0 g (0·0358 mole), was treated with ammonia in 200 ml of EtOH while the system was thermostated to 20 ± 1°·VPC on the crude mixture (prior to solvent removal but after filtration of insoluble salts) showed an isomer distribution of 87% 5-phenylisothiazole and 13% 3-phenylisothiazole. 5-Phenylisothiazole, 2·0 g, was added to the mixture; the VPC of the solution showed a new isomer distribution of 93% to 7% (predicted 92% to 8%). Two ml of 22% ammonium sulfide was then added and ammonia gas allowed to bubble through the refluxing solution for 30 min. VPC of the cooled solution showed no change in the isomer distribution. After the usual purification procedure, 4·9 g of mixed isothiazoles was obtained, again with no change in isomer ratio.

C. Mixtures of known isothiazole composition were passed through VPC Column B under exact conditions for analysis of the unknowns to check the accuracy of the relative percentages obtained from the integrated peak areas.

	Isothiazoles		% Found by VPC	
(1)	6·5 mg 3-phenyl	9·1%	9·7	9·8
	64·9 mg 5-phenyl	90·9%	90·3,	90·2
(2)	15·7 mg 3-phenyl	14·8%	14·6	14·8
	90·5 mg 5-phenyl	85·2%	85·4,	85·2
(3)	2·4 mg 3-*p*-anisyl	9·4%	10·9	
	23·2 mg 5-*p*-anisyl	90·6%	89·1	
(4)	2·5 mg 3-*p*-anisyl	7·9%	9·6%	
	29·3 mg 5-*p*-anisyl	92·1%	90·4%	

A greater degree of tailing in the *p*-anisyl compounds was responsible for the decreased accuracy here.

Temperature dependence studies. All runs were carried out in exactly the same way. A sample procedure is described below for the reaction giving 3- and 5-phenylisothiazole.

3-Phenyl-1,2-dithiolium perchlorate, 10·0 g (0·0358 mole), was placed in a 250 ml 3-neck round-bottomed flask equipped with a slip-seal stirrer, gas inlet tube, and reflux condenser fitted with a drying tube. A solution of 200 ml of abs EtOH saturated with ammonia and kept at 20° was slowly added with stirring; the gas inlet tube was connected and anhydrous ammonia bubbled through for 3·5 hr while contents were thermostated at 20 ± 1°. The reaction mixture was allowed to cool, poured into a beaker, and 200 ml of ether added to precipitate the ammonium perchlorate which was then removed by filtration. The solvent was evaporated at reduced press. and distillation of the residue, b.p.$_{0.7mm}$ 98–105°, gave 3·3 g (57%) of a yellow oil which solidified on cooling. A small sample was dissolved in chloroform and analyzed by VPC (Column B, 180°, He flow, 60 ml/min). For the complete results see Table 2.

Reaction of 3-phenyl-1,2-dithiolium-5-d perchlorate with ammonia. The deuterated dithiolium salt, 3·7 g (0·013 mole), was treated with ammonia in 50 ml abs EtOH. The reaction was carried out in the usual way yielding 0·9 g (43%) of mixed isothiazoles. VPC (Column B) showed two compounds to be present: 6% 3-phenylisothiazole and 94% 5-phenylisothiazole. Chromatography through 35 g of Merck alumina with a 5% benzene in pet. ether solution gave a few milligrams of 3-phenylisothiazole-5-d as a crude red oil and 0·8 g 5-phenylisothiazole-3-d which was crystallized from MeOH–water as white needles, m.p. 46·5–47·5°. The red oil showed only one high boiling product by VPC which corresponded to 3-phenylisothiazole in retention time. A number of peaks due to low boiling components were present.

NMR spectra of both compounds showed the presence of about 10% of the undeuterated material. A band at 4·43 μ (CCl_4) caused by the C–D stretching vibration was present in the IR spectrum of 5-phenylisothiazole-3-d.

Exchange reactions of dithiolium salts. A. A buffer solution at pH 9·1 was prepared by making distilled water 0·1 M in boric acid and 0·1 M in $Na_2B_4O_7$. Three ml of the buffer was added to 0·153 g 3-phenyl-1,2-dithiolium-5-d deuterosulfate. The contents were stirred with glass rod for 1 min and then acidified with 5 drops 70% perchloric acid. A yellow solid precipitated which was filtered off and washed with ether. Partially deuterated 3-phenyl-1,2-dithiolium perchlorate, 0·091 g (60%), was recovered; m.p. 177–179° (dec.) (lit.[8] 180–182·5°) after recrystallization from acetone–ether. The NMR showed that about 50% of the deuterium had been exchanged for protium: –0·20 τ, doublet (0·5 protons); 1·17 τ, triplet (1 proton); 1·83–2·67 τ, multiplet (5 protons) in acetonitrile.

B. Another buffer solution at pD 8·9 was prepared by making D_2O 0·1 M in boric acid and 0·1 M in $Na_2B_4O_7$. 3-Phenyl-1,2-dithiolium hydrogen sulfate, 0·151 g, was reacted for 1 min with 3·0 ml of the buffer. After acidification with perchloric acid, partially deuterated dithiolium perchlorate was recovered, 0·092 g (60%), m.p. 177–179° (dec.). The NMR spectrum showed that about 50% of the lowest field proton had been exchanged for deuterium.

Deuterium exchange reactions of isothiazoles. The exchange reactions were run directly in NMR tubes and monitored on a Varian A-60. Sodium metal, 0·48 g, was reacted with 20 g of CH_3OD, and the resulting 1·13N $NaOCH_3$ solution (standardized with 0·1N HCl to the phenolphthalein end point) in deutero-MeOH was used as the solvent.

Approximately 0·1 g isothiazole was added to one ml of this solution in a 7 cm test tube. After mixing, the single phase system was transferred to an NMR tube and the solution kept at 40° for 12 hr. The NMR spectra were then taken using tetramethylsilane as an internal standard. NMR spectra were also taken of the unexchanged isothiazoles in MeOD

Isothiazole	No. of protons exchanged	τ value of exchanged proton
4-methyl	1	1·60 (MeOD)
4-phenyl	1	1·15 (MeOD)
4-*p*-tolyl	1	1·10 (MeOD)
3-phenyl	1	1·20 (MeOD)
5-phenyl	0	(MeOD)
3-*p*-anisyl	1	1·23 ($CDCl_3$)
5-*p*-anisyl	0	(MeOD)
5-*p*-nitrophenyl	0	($CDCl_3$)

3-*p*-Anisylisothiazole and 5-*p*-nitrophenylisothiazole are not very soluble in MeOD containing NaOMe so a different exchange procedure was used. About 0·05 g of the isothiazole was kept at 40° in one ml of the NaOMe solution for 13 hr; extraction with CCl_4 followed by evaporation yielded solids. NMR spectra of these were taken in $CDCl_3$.

4-Phenylisothiazole-5-d was recovered from the NMR tube by acidifying the mixture with aqueous HCl and extracting the resulting solution with chloroform. Removal of the solvent gave 4-phenyl-isothiazole-5-d, m.p. 36–37° after recrystallization from ether–pet. ether. A band at 4·32 μ (CCl_4) caused by the C-D stretching vibration was present in the IR spectrum.

These exchange reactions have been shown to be first order in methoxide and first order in substrate. A kinetic study has been carried out.[14]

1,5-Diphenylpyrazole; 1,3-diphenylpyrazole. 3-Phenyl-1,2-dithiolium hydrogen sulfate was treated with phenylhydrazine according to the procedure of Klingsberg.[8] The chloroform extract was used directly for analysis by VPC. (Column A, 205°C, He flow, 110 ml/min). 1,5- and 1,3-diphenylpyrazoles were identified by comparison of retention times with pure material.[19]

Pyrazole	Ret. time	Rel % in mixture
1,5-diphenyl	15 min	75
1,3-diphenyl	31 min	35

Reaction of 4-phenyl-1,2-dithiolium hydrogen sulfate with hydroxylamine.[36] 4-Phenyl-1,2-dithiolium hydrogen sulfate, 27·6 g (0·10 mole), was treated with an ethanolic solution of hydroxylamine prepared from 21·4 g (0·31 mole) hydroxylamine hydrochloride and 300 ml of 1·03N EtONa (0·31 mole). The solution was refluxed for ½ hr and then stirred for an additional 1½ hr at room temp. The solution was then poured into a beaker containing 200 ml ether, the insoluble material was filtered off, and the solvent removed under vacuum. Distillation of the residue gave a yellow oil, $b.p._{0.1mm}$ 70–75°, which solidified on cooling; 1·57 g, no definite m.p. VPC (Column A, 150°, He flow, 90 ml/min.) showed the presence of 4-phenylisoxazole and 4-phenylisothiazole.

Compound	Ret. time	Rel % in mixture
4-phenylisoxazole	13 min	21
4-phenylisothiazole	24·5 min	79

A sample of the mixture, 0·65 g, was placed on 20 g of silica gel and was eluted with 50% benzene–pet. ether. 4-Phenylisoxazole eluted first as an off-white solid, m.p. 44–46° (lit.[37] m.p. 46°); NMR: 1·55 τ (singlet, 1 proton); 1·72 τ (singlet, 1 proton); 2·67–3·00 τ (multiplet, 5 protons).

5-Phenylisothiazole was eluted as a white solid, m.p. 35–36° identical with authentic material.

Reaction of 3-phenyl-1,2-dithiolium hydrogen sulfate with hydroxylamine.[36] 3-Phenyl-1,2-dithiolium hydrogen sulfate, 20·0 g (0·0723 mole), was treated with an ethanolic solution of hydroxylamine, prepared from 11·4 g (0·165 mole) hydroxylamine hydrochloride and 150 ml of 1·10N EtONa (0·165 mole). Distillation of the residue yielded 1·83 g (17% based on phenylisoxazole) of yellow oil, $b.p._{0.05mm}$ 40–45°, which partly solidified on cooling. Chloroform was added, and the solid, which was identified as S, was removed by filtration. The chloroform solution was analyzed directly by VPC (Column A, 150°, He flow, 90 ml/min) and four peaks caused by high boiling materials were present. These were identified by comparing retention times with pure authentic samples.

Compound	Ret. time	Rel % in mixture
3-phenylisoxazole[38]	12·0 min	84·0
5-phenylisoxazole[39]	14·5 min	9·5
3-phenylisothiazole	24·5 min	0·5
5-phenylisothiazole	27·5 min	6·0

Control for hydroxylamine reactions. 5-Phenylisoxazole, 5·0 g (0·036 mole), in 300 ml EtOH was added to a solution of 3-phenyl-1,2-dithiolium hydrogen sulfate, 10·0 g (0·036 mole), and ethanolic hydroxylamine from 11·4 g (0·165 mole) hydroxylamine hydrochloride and 62·5 ml 2·64N EtONa (0·165 mole). The reaction was carried out as before yielding 2·5 g of a light yellow oil, $b.p._{0.15mm}$ 73–75°, after distillation. This material was subjected to VPC analysis.

Compound	Rel % in mixture	Rel % in mixture*
3-phenylisoxazole[38]	75·0	13·0
5-phenylisoxazole[39]	17·5	86·0
3-phenylisothiazole	0·5	0·1
5-phenylisothiazole	7·0	1·0

* expected if no decomposition of the 5-phenylisoxazole.

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[36] An attempt to carry out this reaction with 4-phenyl-1,2-dithiolium perchlorate led to an explosion during the initial distillation. Evidently the work up procedure is not very efficient in the removal of some perchlorate salt.

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