Istituto di Chimica Organica dell'Università, Laboratorio del IV° Gruppo di ricerca di strutturistica e spettroscopia molecolare del C.N.R.

Synthesis and Properties of 5-Isoxazolethiols

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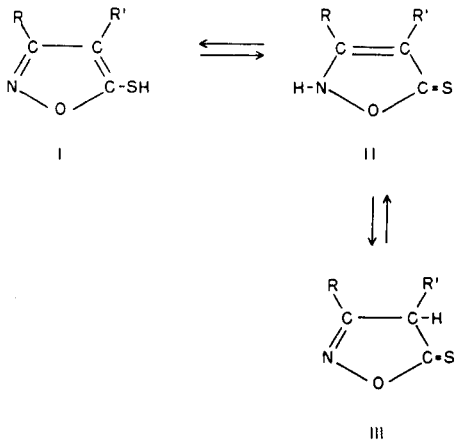
The synthesis of a new class of compounds, the 5-isoxazolethiols, from 5-chloroisoxazoles is described.

The chemical properties and tautomeric behaviour in solution and in solid state are deduced from UV and IR spectra. 5-Ethylthioisoxazoles and 2-methylisoxazoline-5-thiones were also synthesized to support our interpretation.

In a recent paper (1) the preparation of 5-haloisoxazoles has been reported. This synthesis has opened new possibilities in the preparation of 5-isoxazole derivatives; among these we have already discussed (2) that of 5-dimethylaminoisoxazoles, which are important for the knowledge of the tautomeric behaviour of 5-aminoisoxazoles.

This paper mainly concerns the preparation of new products; namely the 5-isoxazolethiols using 5-chloroisoxazoles as starting materials. The UV and IR spectra of these new compounds were also investigated, because of the possibility of 5-isoxazolethiols existing as 2-NH- and 4-H- isoxazolinethione as shown below.



I II III

The compounds studied were those with R=C_6H_5 and R'=H (IV), R=C_6H_5 and R'=CH_3 (V), R=CH_3 and R'=C_6H_5 (VI).

The reaction was carried out by action of potassium hydrosulfide on the chloroisoxazoles in absolute ethanol as solvent. Because of its highly hygroscopic nature, potassium hydrosulfide was prepared directly in the reaction vessel by bubbling anhydrous hydrogen sulfide into a solution of potassium ethoxide.

As we pointed out in a previous paper (1), the reactivity of the 5-chloroisoxazoles depends on the nature and position of the substituent groups; therefore satisfactory yields were obtained by choosing proper concentrations and reaction times. Highest yields were afforded in the preparation of the 3-methyl-4-phenylisoxazole derivatives.

In order to isolate the thiols, it was convenient to purify their potassium salts. For this purpose, when the reaction was completed, the solvent was distilled off and the residue dissolved in anhydrous acetone. By addition of ether to the acetone solutions, highly pure salts were obtained, and from their aqueous solutions, the thiols were obtained by acidification with diluted hydrochloric acid. The thiols were eventually purified by sublimation under reduced pressure; some properties of the prepared compounds are listed in Table I.

The 5-isoxazolethiols are low-melting, colourless products with a characteristic odor. They show definite acidic behaviour and are dissociated in ionized solvents, as is shown by their UV spectra. If kept in air, oxidation occurs most readily and the corresponding disulfides are formed. These can be prepared, in high yields, by treatment of thiols with hydrogen peroxide using acetic acid as solvent.

To study the tautomeric behaviour of 5-isoxazolethiols it was necessary to prepare the alkylated derivatives and compare their UV spectra with those products where tautomerization is possible. 5-Ethylthioisoxazole derivatives were obtained by reaction of potassium ethyl mercaptide and chloroisoxazoles. Compound X had been also prepared by addition of kelene diethylmercaptal to benzonitrile *N*-oxide (3). Some properties of the products are summarized in Table II.

5-Ethylthioisoxazoles are high boiling, colourless products; they are appreciably stable and in air only slowly became pale yellow.

The products corresponding to the 2-*NH*-isoxazo-

line-5-thionic form were obtained by replacing the carbonyl oxygen in the *N*-methylisoxazoline-5-ones by sulfur. The reaction, carried out with phosphorus pentasulfide in xylene, is analogous to that described for the preparation of oxazoline-2-thiones (4), the only difference being the temperature which was kept at 70° to avoid decomposition of the starting material. The yields are listed in Table III.

The *N*-methylisoxazoline-5-thiones are weak bases soluble in concentrated acidic solutions. Because of the high solubility of the starting isoxazolones, the former products were purified from ethanol. At high purity isoxazoline-5-thiones are stable enough and change only after a long standing.

All attempts to obtain 4,4-disubstituted isoxazoline-5-thiones by reaction of phosphorus pentasulfide with the corresponding isoxazoline-5-ions were unsuccessful; however as shown below, these compounds are not necessary for our purposes.

UV Spectra.

Cyclohexane solutions.

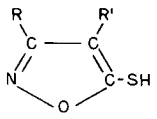
The UV spectra of 5-isoxazolethiols in cyclohexane solutions show broad bands. In addition a sharp band is present near 200-210 mμ which can be assigned to the phenyl group. The position and pattern of the broad band are affected by the nature of the substituents in position 3 and 4 on the ring.

It is also possible to locate a shoulder at about 220 mμ in the spectra of 3-phenyl- and 3-methyl-4-phenyl-5-isoxazolethiols. This shoulder may have remarkable diagnostic value in establishing which tautomeric form is present in the non-polar solvent. A comparison of the spectra of the 2-methylisoxazoline-5-thiones in cyclohexane solution shows the absence of the 2-*NH*-isoxazolinethionic form in the tautomerizable compounds. The spectra of 2-methylisoxazoline-5-thiones are really characterized either by an intense band, with the λ max between 350 and 360 mμ, that can be related to the CH_3-N-C=C-C=S system, or by a band depending on the position of the phenyl group and having the λ max between 245 and 267 mμ.

The lack of absorption beyond 300 mμ in the spectra of the three thiols (Figs. 1,2,3) allows exclusion of the system -NH-C=C-C=S in the solution. Therefore we have to establish whether the absorption could be related to the isoxazole-thiolic form (I) or to the isoxazoline-thionic form (III). However, the 3-methyl-4-phenyl-5-isoxazolethiol structure was readily established. The spectrum of this compound showed a shoulder at about 220 mμ and a large, flat band with the λ max around 242 mμ. This pattern did not agree with the thionic structure III, which does not allow sufficient conjugation. Therefore we concluded that the only form was the isoxazole-thiolic form and consequently the spectrum had to be similar to the corresponding ethylthioisoxazole form. In fact the 3-methyl-4-phenyl-5-ethylthioisoxazole spectrum showed a shoulder at about 220 mμ and two peaks at 236 and 270 mμ respectively (Fig. 2). According to the previous reasoning we could argue that the broad band of the tautomerizable form resulted from the overlapping of two closely positioned bands that are resolved in the spectrum of the corresponding thioether by the effect of the ethyl group.

Likewise the spectrum of 3-phenyl-5-isoxazolethiol (Fig. 1) is clearly understood since it showed a band at 222 mμ and another one at 238 mμ which was slightly more braod toward longer wavelengths. In fact, in spite of the lack of the spectrum of 4,4-disubstituted isoxazoline-thionic form, we can reasonably expect this compound to have an ab-

TABLE I



Compound	R	R'	M.P. °C	Yield %	λ max UV Methanol mμ	log ε	KOH mμ	log ε	Cyclohexane mμ	log ε	$CHCl_3$ mμ	log ε	ν SH cm^{-1} Solid	CCl_4
					206	4.21			208	4.14				
IV	C_6H_5	H	43-44	72	243	4.30	242	4.37	222	4.13	244	4.18	2525	2566
					298	3.73	294	3.93	238	4.16				
					210	4.03			208	4.1				
V	C_6H_5	CH_3	52-54	80	236	4.10	236	4.27	222	4.06	242	3.98	-	2558
					295	3.60	293	3.98						
					208	4.12			212	4.05				
VI	CH_3	C_6H_5	57-58	89	215s	4.05			218s	4.03				
					263	3.90	265s	4.0	242	3.90	240	4.02	2530	2562
					285s	3.78	283	4.10						

sorption between 250 and 260 mμ, as in the corresponding 3-phenyl-4,4-dimethylisoxazoline-5-one (5). On the other hand thiol and 3-phenyl-5-ethylthioisoxazole showed the same spectra in frequency and intensity; this led us to argue that the actual form in the non-polar solvent is the thiolic form even if any contribution by the thionic form (III) could not be completely discarded.

As in the previous instance a shoulder around 260 mμ in the spectrum of ethylthioisoxazole indicates another possible transition, this transition could not be seen in the thiol spectrum, due to the overlap of a higher intensity band.

The interpretation of the 3-phenyl-4-methyl-5-isoxazolethiol spectrum (Fig. 3) seemed more difficult. It showed a broad band with λ max around 222 mμ that overlapped evidently another band at a longer wavelength. The maximum at 226 mμ in the 3-phenyl-4-methyl-5-ethylthioisoxazole spectrum clearly indicated the presence of the thiolic form in the solution of the tautomerizable product. It was not possible, however to distinguish whether the greater width of the band was caused by the overlapping of the transition around 266 mμ that could be seen in the ethylthioisoxazole spectrum or by the coexistence of the thionic form (III) for which an absorption between 250 and 260 mμ was expected.

Methanol solutions.

Even in these solutions the position of phenyl group had a remarkable influence on the λ max and the shape of the bands; we could observe three bands at 200-210, 236-244 and 295-298 mμ in the spectra of the 3-phenyl-substituted thiols. The introduction of a methyl group in position four caused as previously noted (6) a slight blue-shift that was larger for the central band. It was possible to locate two maxima at 206 and 263 mμ and a shoulder at about 280 mμ in the 3-methyl-4-phenyl-5-isoxazolethiol spectrum (Fig. 6). The remarkable red-shift in the absorption of the thiols in methanol solution compared to cyclohexane solution might suggest a tautomeric equilibrium shift or a solvent effect. Neither possibility, however, could satisfactorily explain this change. If the thionic form (II) were present in methanol, the last band should be beyond 300 mμ since 2-methylisoxazoline-5-thiones showed a maximum between 335 and 345 mμ in methanol. On the other hand, if the band at 280-298 mμ, even if it were overlapped, was the same as the thiol band at ~260 mμ in cyclohexane solution which exhibits a shift for solvent effect, then a solvent shift would be expected in the spectra of 5-ethylthioisoxazole; however, no wavelength change from non-polar to polar solvent was observed.

The spectral behaviour of these products in methanol suggests that thiols in a proton acceptor solvent are dissociated. Therefore the band at 290-298 mμ suggests the presence of a mercaptide ion.

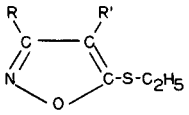
This hypothesis was supported by the fact that the pattern of the spectra of the thiols in methanol was completely analogous to those in potassium hydroxide solutions (Figs. 4,5,6). The spectra in chloroform solution gave further support; in fact in this strongly polar, but not proton acceptor solvent, the spectra showed an absorption shift with respect to cyclohexane of less than 10 mμ toward the longer wavelengths.

I.R. Spectra.

In the solid state, 3-phenyl- (Fig. 7) and 3-methyl-4-phenyl-5-isoxazolethiol (Fig. 8) are in thiolic form, as shown by the occurrence of a characteristic SH-stretching mode band at about 2550 cm^{-1}.

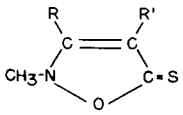
In the solid spectrum of 3-phenyl-4-methyl-5-isoxazolethiol (Fig. 9), no absorption in the region of SH-stretching was detectable, whereas a broad band between 3200 and 2800 cm^{-1} was observed. This band could easily be explained as a NH-stretching vibration. Therefore the IR spectrum clearly shows

TABLE II



Compound	R	R'	B.P. °C (mm.)	Yield %	λ max UV Methanol mμ	log ε	Cyclohexane mμ	log ε
					208	4.24	210	4.11
X	C_6H_5	H	106-108 (0.1)	61	222s	4.14	222s	4.15
					238	4.20	236	4.22
					260s	3.87	260s	3.78
					208	4.10	208	4.06
XI	C_6H_5	CH_3	112-113 (0.1)	53	218s	4.0	216s	4.08
					232	3.98	226	4.1
					268	3.76	266	3.78
					210	4.1	210	4.04
XII	CH_3	C_6H_5	96-98 (0.05)	66	220s	4.0	220s	3.98
					234	3.95	236	3.92
					270	3.90	270	3.90

TABLE III



Compound	R	R'	M.P. °C	Yield %	λ max UV Methanol mμ	log ε	Cyclohexane mμ	log ε
XIII	C_6H_5	H	140-141	60	248	4.16	253	4.12
					345	4.23	360	4.10
XIV	C_6H_5	CH_3	120-122	55	243	3.95	245	4.02
					347	4.22	354	4.05
XV	CH_3	C_6H_5	150-152	65			267	3.79
					272	3.84	285s	3.68
					335	4.26	349	3.94

Fig. 1

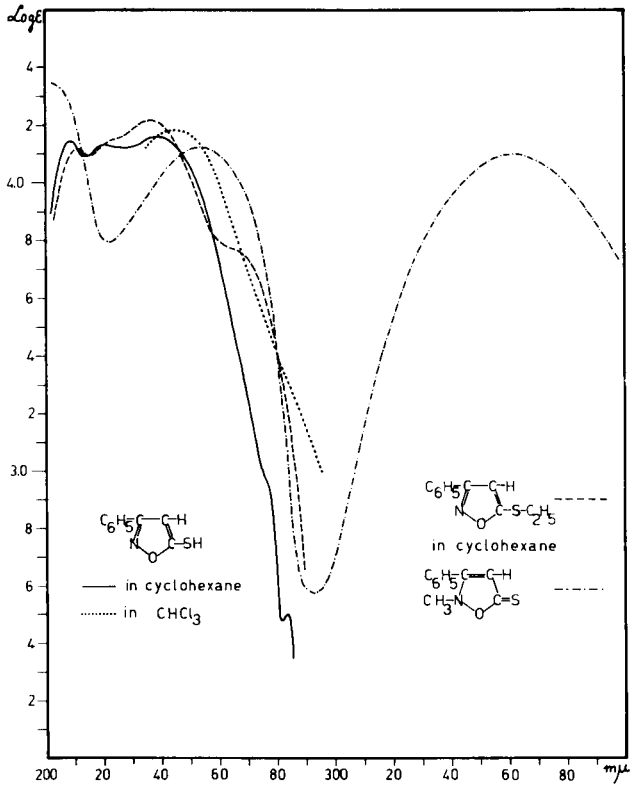


Fig. 2

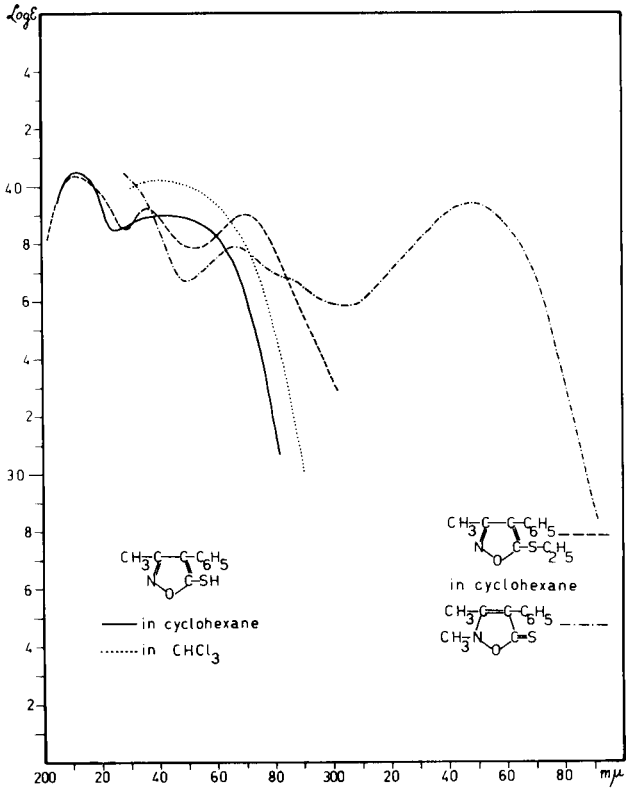


Fig. 3

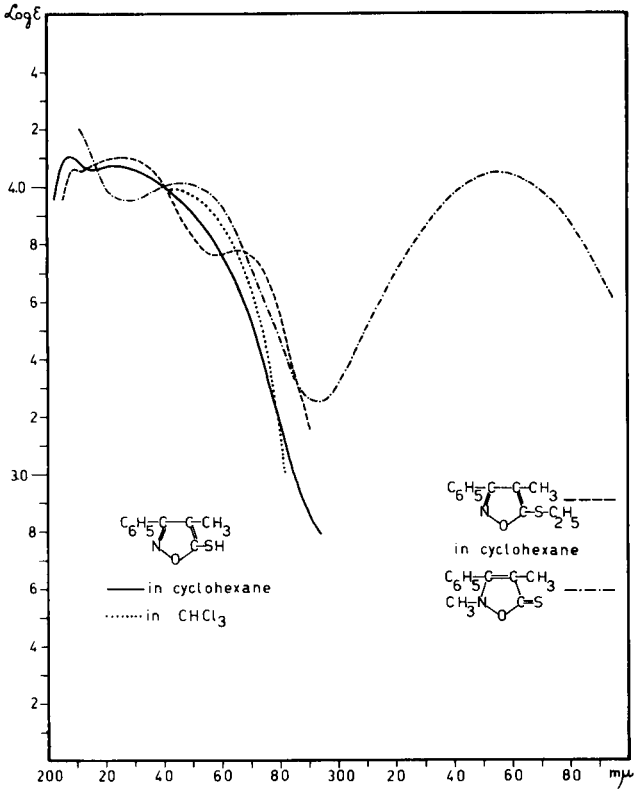


Fig. 4

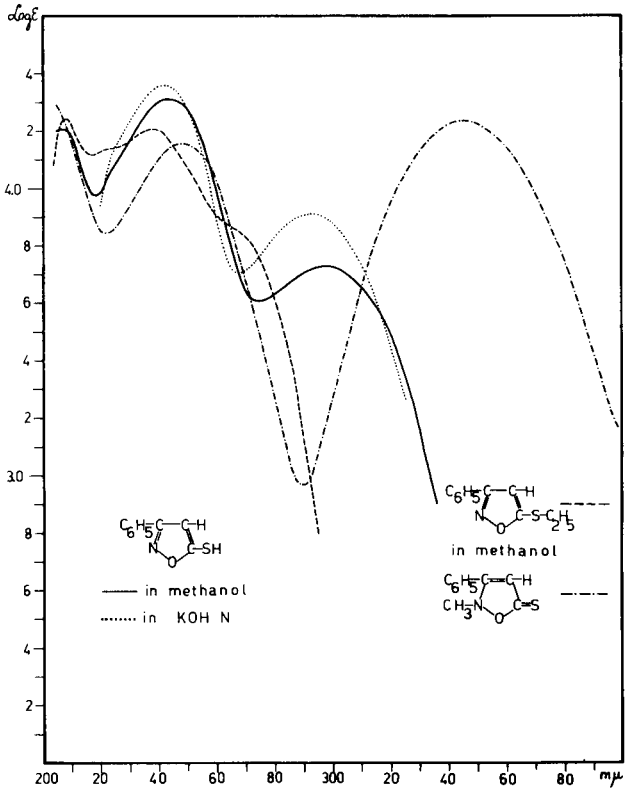


Fig. 5

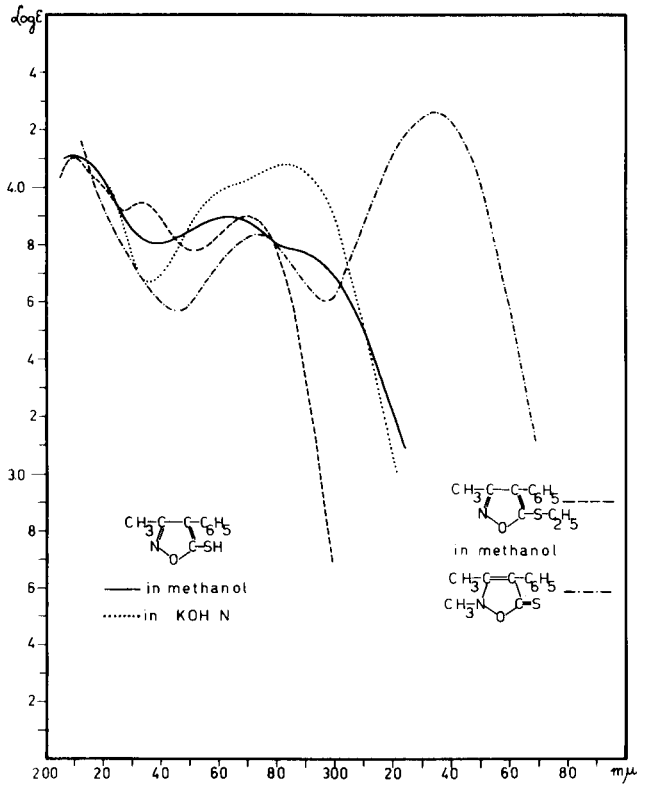
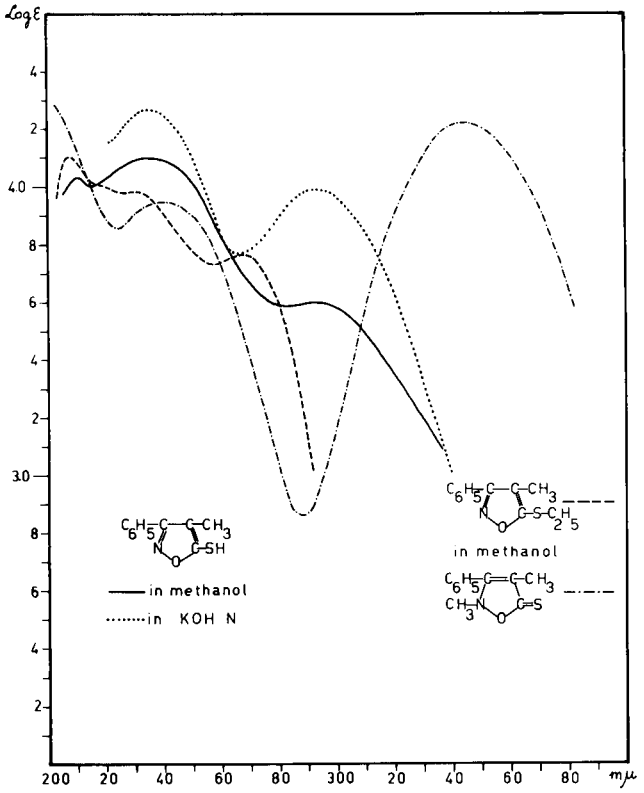


Fig. 6



that the compound exists in the crystalline state in the thionic form (II). In carbon tetrachloride solution all isoxazolethiols show an SH-stretching band; therefore in agreement with the results of the electronic spectra the thiolic form is present in the solution.

EXPERIMENTAL (7)

3-Phenyl-5-isoxazolethiol (IV).

A solution of potassium (2.2 g.) dissolved in 15 ml. of anhydrous ethanol was saturated with dry hydrogen sulfide which was bubbled into the reaction flask. 3-Phenyl-5-chloroisoxazole (3.9 g.) dissolved in a minimum amount of anhydrous ethanol was then added and refluxed for 12 hours.

The solvent was distilled off and the residue was extracted in the Sohxlet extractor with 200 ml. of anhydrous acetone. The acetone was distilled again and the residue was washed with anhydrous ether. A pale brown product (3.38 g.) was eventually obtained. Purification was carried out by dissolving the product in a minimum amount of anhydrous ethanol followed by precipitation by addition of anhydrous ether while cooling. The potassium salt of the thiol was slightly yellow, m.p. 243° dec. A saturated solution of the salt in water was acidified with dilute hydrochloric acid to *p*H 5, treated with animal charcoal then filtered and acidified to *p*H 1-2 while cooling in an ice-water bath. A flaky white compound was separated, washed with water and quickly dried under reduced pressure. The product was then purified by sublimation (0.05 mm Hg at 25°); characteristic citron odor, m.p. 43-44°.

Anal. Calcd. for C_9H_7NOS: C, 61.0; H, 4.0; N, 7.9; S, 18.1. Found: C, 61.1; H, 4.0; N, 8.1; S, 17.5.

3-Phenyl-4-methyl-5-isoxazolethiol (V).

Following the method described for IV, 3-phenyl-4-methyl-5-chloroisoxazole (4 g.) and potassium (2.2 g.) gave the corresponding salt of the thiol (3.85 g.). The product was then dissolved in acetone and precipitated by the addition of anhydrous ether, m.p. 260-264° dec.

The thiol V was isolated as in the case described for IV. After sublimation under reduced pressure (0.05 mm Hg at 35°) a white compound was obtained, m.p. 52-54°.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.8; H, 4.7; N, 7.3; S, 16.8. Found: C, 62.6; H, 4.7; N, 7.4; S, 17.0.

3-Methyl-4-phenyl-5-isoxazolethiol (VI).

3-Methyl-4-phenyl-5-chloroisoxazole (4 g.) was allowed to react with potassium (2.2 g.) to give the corresponding potassium salt (4.2 g.), m.p. 210-215° dec. Compound VI was then isolated by acidification with dilute hydrochloric acid as described for IV and purified by sublimation under reduced pressure at 40°, m.p. 57-58°.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.8; H, 4.7; N, 7.3; S, 16.8. Found: C, 63.1; H, 4.7; N, 7.5; S, 17.1.

Bis-(3-phenylisoxazol-5-yl) disulphide (VII).

Hydrogen peroxide (30%) (7.6 ml.) was added dropwise to a saturated solution of IV in glacial acetic acid. The yellow crystals were separated and crystallized from methanol, m.p. 116-118°. By dilution of the solution more of the disulphide separated giving almost a quantitative yield.

Anal. Calcd. for $C_{18}H_{12}N_2O_2S_2$: C, 61.4; H, 3.4; N, 7.9; S, 18.2. Found: C, 61.5; H, 3.3; N, 8.2; S, 18.2.

Bis-(3-phenyl-4-methylisoxazol-5-yl) disulphide (VIII).

The reaction conditions described for VII were followed; the disulphide was prepared from 3 g. of V and crystallized from petroleum ether to give a yellow product, m.p. 91-93°.

Anal. Calcd. for $C_{20}H_{16}N_2O_2S_2$: C, 63.2; H, 4.2; N, 7.4; S, 16.8. Found: C, 63.0; H, 4.2; N, 7.3; S, 16.8.

Bis-(3-methyl-4-phenylisoxazol-5-yl) disulphide (IX).

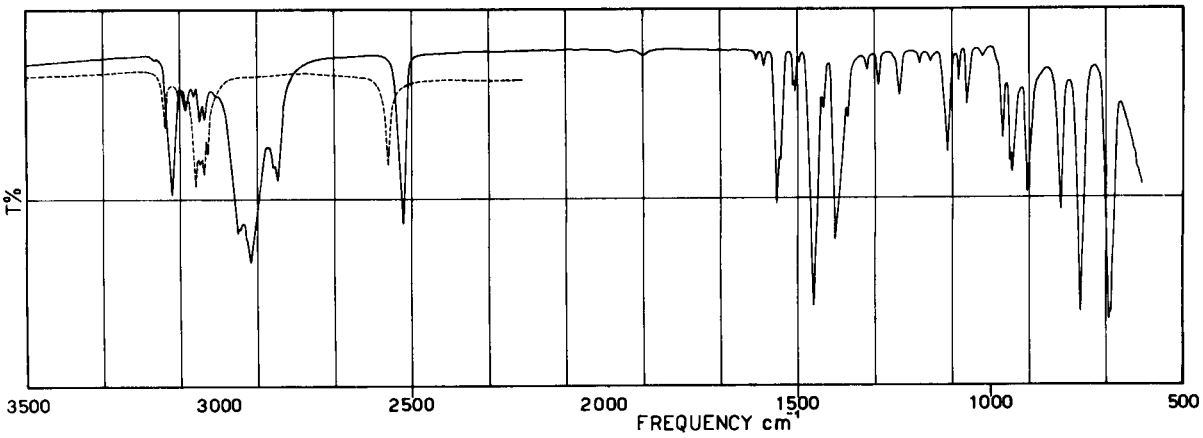


Fig. 7. IR spectrum of 3-phenyl-5-isoxazolethiol; _____ in Nujol
---------- in CCl_4

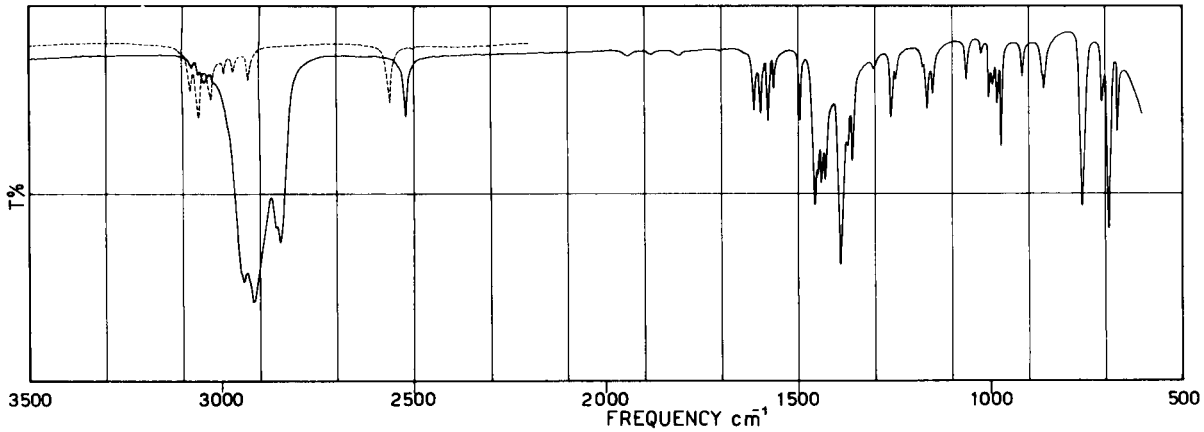


Fig. 8. IR spectrum of 3-methyl-4-phenyl-5-isoxazolethiol; _____ in Nujol
---------- in CCl_4

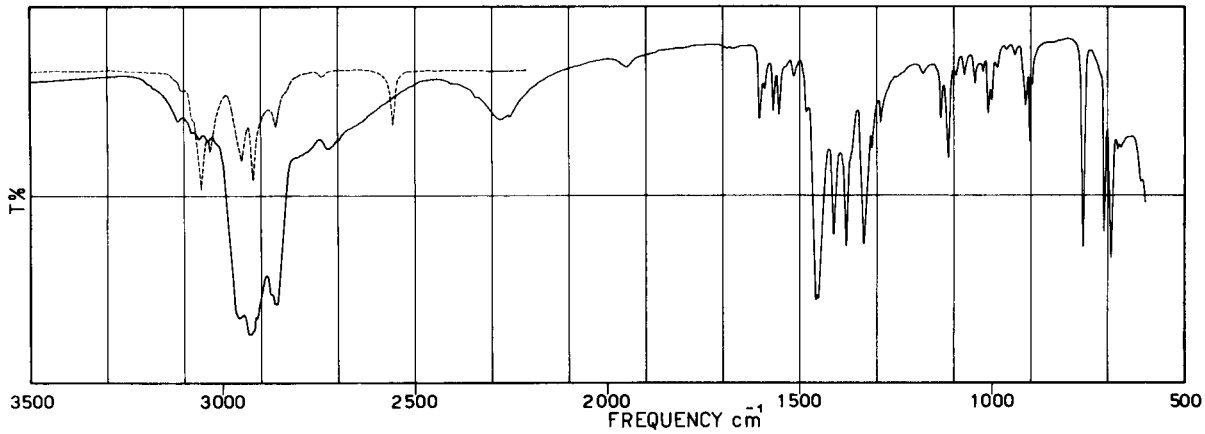


Fig. 9. IR spectrum of 3-phenyl-4-methyl-5-isoxazolethiol; _____ in Nujol
---------- in CCl_4

Yellow crystals obtained as above were crystallized from aqueous acetone, m.p. 107°.

Anal. Calcd. for $C_{20}H_{16}N_2O_2S_2$: C, 63.2; H, 4.2; N, 7.4; S, 16.8. Found: C, 63.3; H, 4.5; N, 7.7; S, 16.7.

3-Phenyl-5-ethylthioisoxazole (X).

3-Phenyl-5-chloroisoxazole (2 g.) and sodium ethyl mercaptide (0.94 g.) dissolved in 30 ml. of anhydrous ethanol were refluxed for 4 hours. The precipitate was filtered off and washed with anhydrous ethanol; on evaporation of the solvent an oily brown liquid was obtained together with a small amount of unreacted mercaptide. Anhydrous ether and animal charcoal were then added to the mixture. After filtration and distillation of the solvent, a yellow oily product was separated, 1.4 g., b.p. 98-100° at 0.05 mm Hg. On cooling the oil solidified into white needles. After further distillation a colourless liquid was obtained, b.p. 106-108° at 0.1 mm Hg, m.p. 28°.

Anal. Calcd. for $C_{11}H_{11}NOS$: C, 64.4; H, 5.4; N, 6.8. Found: C, 64.1; H, 5.3; N, 7.0.

3-Phenyl-4-methyl-5-ethylthioisoxazole (XI).

3-Phenyl-4-methyl-5-chloroisoxazole (2 g.) and sodium ethyl mercaptide (1.75 g.) were refluxed for 24 hours in the minimum amount of anhydrous ethanol. Following the procedure described for X an oily liquid was separated, b.p. 112-113° at 0.1 mm Hg.

Anal. Calcd. for $C_{12}H_{13}NOS$: C, 65.7; H, 6.0; N, 6.4; S, 14.6. Found: C, 66.0; H, 6.0; N, 6.1; S, 14.7.

3-Methyl-4-phenyl-5-ethylthioisoxazole (XII).

3-Methyl-4-phenyl-5-chloroisoxazole (2 g.) and sodium ethyl mercaptide (0.87 g.) were refluxed overnight in anhydrous ethanol. Following the procedure described for X a colourless product was isolated, b.p. 96-98° at 0.05 mm Hg.

Anal. Calcd. for $C_{12}H_{13}NOS$: C, 65.7; H, 6.0; N, 6.4; S, 14.6. Found: C, 65.5; H, 5.8; N, 6.5; S, 14.3.

2-Methyl-3-phenylisoxazoline-5-thione (XIII).

2-Methyl-3-phenylisoxazoline-5-one (8) (8 g.) and phosphorus pentasulfide (20.4 g.) in 600 ml. of xylene were heated at 70° for 24 hours with vigorous stirring. The solvent was then distilled off under reduced pressure and a red coloured sticky precipitate was obtained. The product was shaken with two portions of concentrated hydrochloric acid (50 ml.) and filtered. The solution was decolourized with animal charcoal and after filtration a bright-yellow solution was obtained; on cooling after dilution with water a yellow solid compound precipitated. The product was washed several times with water and eventually dried under reduced pressure. There was obtained pale yellow needles, m.p. 140-141°, after repeated crystallization from ethanol.

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.8; H, 4.7; N, 7.3; S, 16.7. Found: C, 62.7; H, 5.0; N, 7.2; S, 16.4.

2,4-Dimethyl-3-phenylisoxazoline-5-thione (XIV).

2,4-Dimethyl-3-phenylisoxazoline-5-one (8) (5 g.) and phosphorus pentasulfide (11.8 g.) in xylene were heated at 70° for 24 hours with vigorous stirring. Following the method described for XIII a yellow product was isolated, m.p. 115-120°. After several crystallizations from ethanol pale yellow flakes were obtained, m.p. 120-122°.

Anal. Calcd. for $C_{11}H_{11}NOS$: C, 64.4; H, 5.4; N, 6.8; S, 15.6. Found: C, 64.0; H, 5.7; N, 6.9; S, 15.2.

2,3-Dimethyl-4-phenylisoxazoline-5-thione (XV).

Compound XV was obtained from 2,3-dimethyl-4-phenylisoxazoline-5-one (8) (7.75 g.) and phosphorus pentasulfide (18.5 g.) by heating in xylene at 70° for 24 hours while stirring. Operating as above 5.45 g. of a yellow product was isolated, m.p. 138-140°. After several recrystallizations from ethanol white needles were obtained, m.p. 150-152°.

Anal. Calcd. for $C_{11}H_{11}NOS$: C, 64.4; H, 5.4; N, 6.8; S, 15.6. Found: C, 64.6; H, 5.5; N, 6.9; S, 15.3.

Acknowledgment.

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