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2-AMINO-2-THIAZOLINE—VI[1]

THE FORMATION OF A THIAZOLO-S-TRIAZINE FROM 2-AMINO-2-THIAZOLINE

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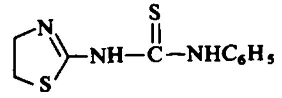
Abstract—The reaction of 2-amino-2-thiazoline (I) with excess phenylisothiocyanate in acetonitrile solution gives hydrogen sulfide, 1-phenyl-3-(2-thiazolin-2-yl)-2-thiourea (II) and a compound, $C_{17}H_{14}N_4S_2$ (III). Hydrolysis of III with conc HCl gave 1-(2-mercaptoethyl)-3-phenyl-2,4,6-trioxohexahydro-s-triazine (IV), aniline hydrochloride and hydrogen sulfide. Dilute hydrochloric acid hydrolysis of III gave one product, 1-(2-mercaptoethyl)-3-phenyl-4-phenylimino-2-thioxo-6-oxohexahydro-s-triazine (VIa). This compound was oxidized to the corresponding disulfide (VII) whose thiocarbonyl group was then replaced by a carbonyl group to give VIII. By comparison of the NMR spectra of the degradation products of III it was possible to assign to it the structure, 2-phenylimino-3-phenyl-4-thioxothiazolo[3.2-a]tetrahydro-s-triazine (IIIa).

2-AMINO-2-THIAZOLINE (I) has been shown[1] to react with one equivalent of phenylisothiocyanate to give 1-phenyl-3-(2-thiazolin-2-yl)-2-thiourea (II).



II

We have found that when I was heated with an excess of phenylisothiocyanate in ethanol, acetonitrile, or preferably, benzene hydrogen sulfide was evolved and from the reaction mixture was obtained some II and another pale yellow crystalline compound, $C_{17}H_{14}N_4S_2$ (III), m.p. 299°. The latter compound can also be made by heating a solution of II with phenylisothiocyanate. The mass spectrum* of III confirmed the molecular formula (molecular ion at *m/e* 338·073). Its IR spectrum showed peaks at 6·15 (C=N) and 8·25 μ.

It was postulated that the bis-(phenylthiocarbamoyl) derivative of I had formed as an intermediate which, subsequently, cyclized with loss of hydrogen sulfide. On this basis, the formulas below were considered to be probable structures for the cyclized product. However, the band at 8·25 μ, tentatively assigned to C=S, suggested that IIIa and IIIb were more likely than IIIc.

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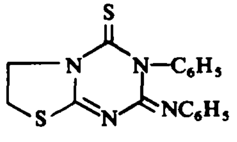
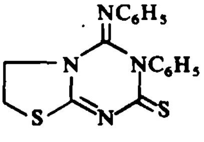
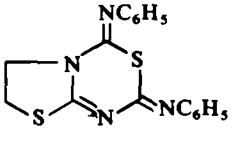
* Mass spectra were measured on an Associated Electrical Industries (U.K.) MS-9 double focusing mass spectrometer. Unless otherwise specified, the ionizing voltage was 70 eV. Accurate measurement of mass to charge ratio was carried out by comparison with a perfluorotributylamine standard.



IIIa

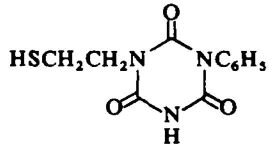


IIIb



IIIc

Hydrolysis of III with hydrochloric acid (1:1) for several days gave aniline hydrochloride (approximately one equivalent), hydrogen sulfide and a compound, $C_{11}H_{11}N_3O_3S$ (IV), whose IR absorption at 3·90 μ and positive nitroprusside test indicated that the S atom was in a thiol group. The spectrum also showed two strong peaks of approximately equal intensity in the carbonyl region (5·75 and 6·00 μ) which can be ascribed[2] to amide I bands of a system —CO—NH—CO—. A small peak was present in the IR spectrum at 3·11 μ, indicative of N–H absorption while the NMR spectrum had a broad band centered at δ_{NH} 11·7. The mass spectrum of IV showed no ion at *m/e* 135. An ion with this mass to charge ratio (Ph—N=C=S$^+$) has been found in the spectra of compounds, such as II, which contain the structural unit, Ph—N—C—S, and consequently such a unit was tentatively considered to be absent from IV. The mass spectrum contains a molecular ion of low abundance at *m/e* 265 and, as the base peak of the spectrum, an ion* at *m/e* 119 ($C_7H_5NO^+$) which is considered to be Ph—N=C=O$^+$, since it breaks down in stepwise fashion to give ions at *m/e* 103 ($C_7H_5N^+$), 91 (PhN^+), and 77 (Ph^+). The expected metastable ions for these three fragmentations are also observed. On the basis of this evidence, IV was assigned the cyanuric acid structure shown below. Because IV retains one phenyl group and does not have a heterocyclic sulfur atom, structure IIIc, in which the two phenylimino groups should be hydrolyzed with approximately equal ease, was ruled out. Compound IV was oxidized to the corresponding disulfide (V), $C_{22}H_{20}N_6O_6S_2$, which showed a broad band centered at δ 11·8 for the protons attached to the ring N atoms. The NMR spectrum of cyanuric acid determined in dimethylsulfoxide-d_6 had a peak centered at δ 11·1 due to the three protons on nitrogen.



IV

Hydrolysis of III with dilute hydrochloric acid for a few hours, in contrast, was not accompanied by hydrogen sulfide evolution, nor by aniline hydrochloride formation. The white compound obtained, $C_{17}H_{16}N_4OS_2$ (VI), showed a weak absorption in the IR at 3·90 μ ascribed to the presence of a thiol group which was confirmed by a positive nitroprusside test. Only one carbonyl peak was present which appeared at 5·90 μ while the absorption at 6·22 μ was attributed to C=N and a peak at 8·43 μ was

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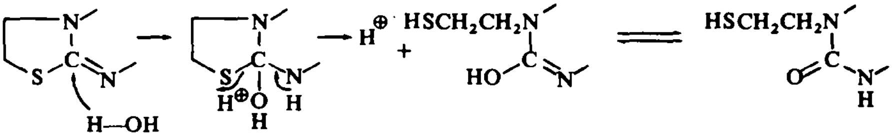
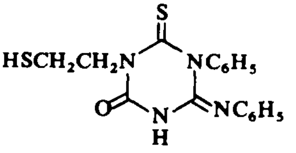
* The masses of all ions to which formulas are assigned have been accurately measured and agree with the calculated masses within 10 parts per million.

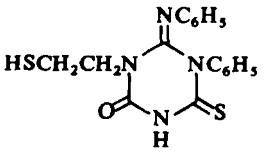
attributed to C=S. The mass spectrum of VI had a very small molecular ion at *m/e* 356. That this was, in fact, a molecular ion was demonstrated when its abundance relative to that of the base peak was found to increase upon lowering the ionizing voltage. An ion at *m/e* 135 showed fragmentation ions at *m/e* 103, 91 and 77 and thus indicated the presence of a Ph—N—C—S rather than a Ph—N—C—O (*m/e* 119) moiety in the molecule. The NMR spectrum of VI showed a band at δ 8·25 corresponding to N—H. The mechanism postulated for this acid-catalyzed hydrolysis of III is shown below. At this stage, two structures, VIa and VIb, can be proposed



for the hydrolysis product. These are derived from either IIIa or IIIb, respectively.

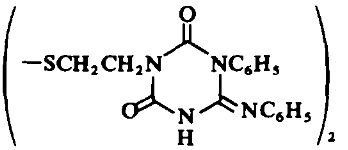


VIa



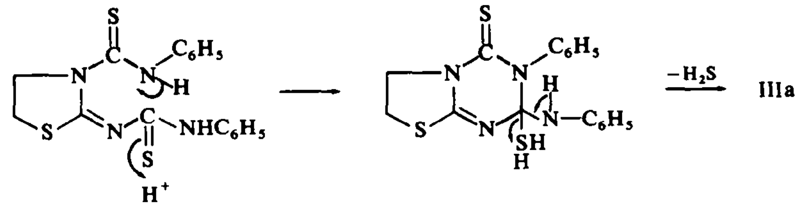
VIb

Oxidation of VI to the disulfide, $C_{34}H_{30}N_8O_2S_4$ (VII), gave a compound whose NMR spectrum showed an N—H band at δ 8·25, unchanged from that of VI. In order to distinguish between VIa and VIb, the disulfide, VII, was treated with alkaline hydrogen peroxide thereby converting the thiocarbonyl to a carbonyl group. If structure VIa were correct, the functional groups adjacent to the N—H would remain unchanged, i.e. —CO—NH—C=N—, while in VIb the —CO—NH—CS— would become —CO—NH—CO—. The new compound formed, $C_{34}H_{30}N_8O_4S_2$ (VIII), showed in its IR spectrum loss of the peak at 5·90 μ and appearance of new ones in that region at 5·80 μ and 6·01 μ. The peak at 8·48 μ (C=S) was also missing. These spectral changes confirmed that a second carbonyl group had been generated. The mass spectrum of VIII showed a small molecular ion at *m/e* 678 and a base peak at *m/e* 119

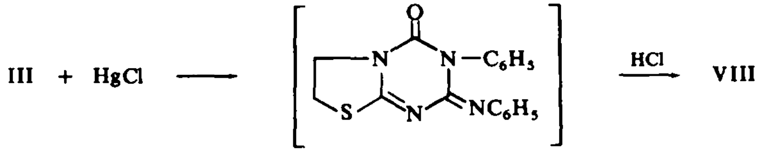


VIII

($C_7H_5NO^+$) which collapsed in the usual manner (q.v.) to give the ions at *m/e* 103, 91 and 77. No fragment was observed at *m/e* 135 ($C_6H_5NCS^+$). The NMR spectrum of VIII showed a singlet at δ 8·25, as in VI and VII. On the basis of this evidence, compound VI is assigned structure VIa. It follows from this that structure IIIb for the diadduct is untenable and the product of the reaction of excess phenylisothiocyanate with I is, therefore, 2-phenylimino-3-phenyl-4-thioxothiazolo-[3.2-a]tetrahydro-s-triazine (IIIa). The suggested pathway for its formation from the intermediate bis-(phenylthiocarbamoyl) derivative of I is shown below.



The disulfide, VIII, is also formed directly from III on heating with $HgCl_2$ in aqueous N,N-dimethylformamide. Mercuric sulfide precipitates rapidly in the reaction and this fact, coupled with the known relatively slow rate of opening of the 5-membered ring in III, suggests that this hydrolysis step is preceded by conversion of the thiocarbonyl group of III to a carbonyl group giving the probable intermediate, IX. This compound is converted to VIII by acid hydrolysis and subsequent aerial oxidation.



IX

The major peaks in the high resolution mass spectrum of III are given in Table 1. The base peak of the spectrum is that at *m/e* 337, formed by loss of hydrogen from the molecular ion at *m/e* 338. By analogy with the fragmentation[3] of I this hydrogen is

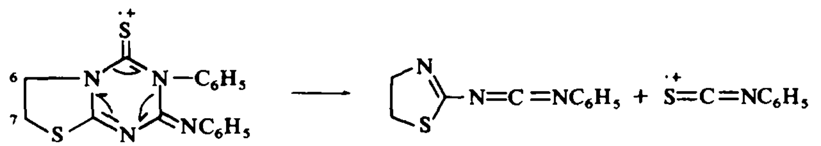
Table 1. High resolution mass spectrum of III[a]

m/e (found)	Relative abundance[b]	Empirical formula	*m/e* (calcd.)
338·073	55	$C_{17}H_{14}N_4S_2$	338·066
337·060	100	$C_{17}H_{13}N_4S_2$	337·058
298·032	20	$C_{14}H_{10}N_4S_2$	298·035
203·053	12	$C_{10}H_9N_3S$	203·052
202·046	19	$C_{10}H_8N_3S$	202·044
175·022	13	$C_8H_5N_3S$	175·020
144·058	51	$C_8H_6N_3$	144·056
135·015	20	C_7H_5NS	135·014
103·043	29	C_7H_5N	103·042
91·0432	12	C_6H_5N	91·0420
77·0393	94	C_6H_5	77·0391

[a] All ions with abundance of greater than 10% of that of the base peak are included above *m/e* 70.

[b] Expressed as a percentage of the base peak (*m/e* 337).

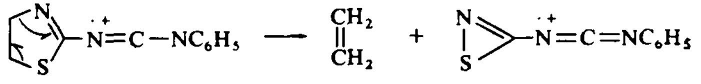
presumed to have been lost from position 6 or 7 of III. A prominent metastable ion accompanying this fragmentation is observed at *m/e* 336·1. In the remainder of the spectrum, the ions at *m/e* 135, 103, 91 and 77 are clear evidence of the formation and subsequent fragmentation of $PhNCS^+$. This reveals a significant part of the skeleton of III in that it may be presumed to arise by the common "retro-Diels–Alder" type of cleavage,[4] thus:



X

As is usual, the phenylisothiocyanate retains most of the charge, but the charged ion $C_{10}H_9N_3S^+$ is observed, although it loses hydrogen readily, presumably in the same way as does the molecular ion (q.v.) to give the more abundant ion at *m/e* 202 ($C_{10}H_8N_3S^+$).

The structures of the remaining ions in the mass spectrum of III are not clear. That at *m/e* ($C_8H_5N_3S^+$) might be considered to be formed by the loss of C_2H_4 from X, a fragmentation that has previoulsy been established[3] for substituted 2-amino-2-thiazolines.



X

The structure of III was confirmed by X-ray crystallographic analysis (cf. Fig. 1).*

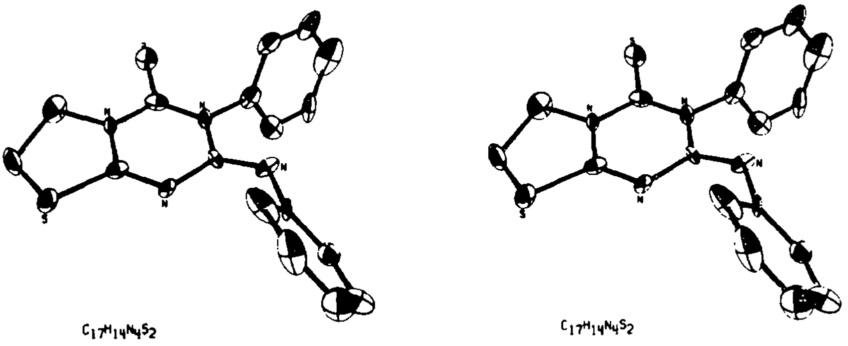


FIG. 1 Stereostructure of III. The ellipsoids of average vibrational motion are indicated at the atomic positions. (The three-dimensional effect is most easily observed if these structures are viewed through standard stereoscopic glasses.)

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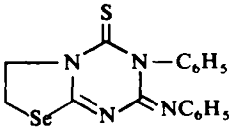
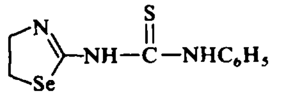
* We thank Dr. Jerome Karle, *et al.* Naval Research Laboratories, Washington, D.C. for the X-ray crystallographic analysis of III.[5]

A selenium analog of III, 2-phenylimino-3-phenyl-4-thioxoselenazolo[3.2-a]-tetrahydro-s-triazine (XI), was prepared by refluxing 1-phenyl-3-(2-selenazolin-2-yl)-2-thiourea (XII) with excess phenylisothiocyanate in benzene solution. The infrared spectrum of XI was nearly identical to that of III.



XI



XII

It was found that when II was heated in benzene solution for 120 hr hydrogen sulfide was slowly evolved and on cooling there precipitated ca. 37% of the theoretical yield of III. While I was also expected in this "disproportionation" only a polymeric mass devoid of I was found in the filtrate. Compound I was demonstrated to partially decompose when boiled in acetonitrile for 120 hr. That the 2-thiocarbamoyl moiety of II was labile was demonstrated[1] by the reaction of II with benzylamine to give 1-benzyl-3-phenyl-2-thiourea in good yield.

$$\text{II} \longrightarrow [\text{I}] + [\text{PhNCS}]$$
$$\text{II} + [\text{PhNCS}] \longrightarrow H_2S + \text{III} + [\text{I}]$$

An attempt to make the 1-naphthyl analog of III by the reaction of I with excess 1-naphthylisothiocyanate in refluxing benzene or acetonitrile gave only the mono-adduct, 1-(1-naphthyl)-3-(2-thiazolin-2-yl)-2-thiourea (XIII), in high yield. Similarly, the reaction of II with excess 1-naphthylisothiocyanate gave only XIII as the major product. When XIII was treated with excess phenylisothiocyanate in other effort to prepare a mixed analog of III, only III itself and 1-naphthylisothiocyanate were isolated. The exchange between a thiourea and an aromatic isothiocyanate was reported earlier by Zetzsche and Fredrich.[6]

EXPERIMENTAL

M.ps were determined on a Fisher-Johns m.p. apparatus and are uncorrected. Microanalyses were performed by Mr. Joseph F. Alicino, Metuchen, N.J. IR spectra were determined as KBr pellets on a Beckman IR-5 spectrometer. NMR spectra were run on 15–20% solns of the compound in DMSO-d_6 on a Varian A-60 spectrometer using TMS as the internal standard.

2-Phenylimino-3-phenyl-4-thioxothiazolo [3.2-a] tetrahydro-s-triazine (III). A soln of 2·52 g (0·025 mole) of I and 10·3 g (0·075 mole) phenylisothiocyanate in 20 ml benzene was heated under reflux for 1·6 hr. Crystals separated from the hot soln in the course of the reaction and H_2S was evolved. The mixture was cooled to room temp and the crystals were collected by filtration and washed with ether to give 7·02 g (83%) of III, m.p. 297–298° dec. A second crop of crystals, consisting mainly of II, was also obtained. A small portion of the III was recrystallized from N,N-dimethylformamide to give an analytical sample which melted at 299° dec; IR 6·15 (C═N) and 8·25 μ (C═S). (Found: C, 60·44; H, 4·33; N, 16·64; S, 19·29. $C_{17}H_{14}N_4S_2$ requires: C, 60·33; H, 4·17; N, 16·55; S, 18·95%).

A total of 1·17 g of II (from acetonitrile), m.p. 148–149°, was also obtained from this reaction.

Hydrolysis of III *to* IV. A mixture of 33·8 g (0·1 mole) of III and 600 ml conc HCl diluted with an equal volume of water was heated under reflux for 72 hr, during which time H_2S was evolved. The colorless soln was evaporated to dryness under reduced press and the residue was treated twice with water and taken to dryness each time to remove the excess HCl. The residue was extracted with 100 ml water and the water-insoluble product was collected by filtration. The filtrate contained aniline hydrochloride. The crude IV (24·4 g) was recrystallized from EtOH to give 19·0 g (71%) of the product as white crystals, m.p. 149–150°. The compound gave a positive nitroprusside test for a thiol. Its IR spectrum showed peaks at 3·90 (SH), 5·75 and 5·95 (C═O), 6·90 μ (amide II). (Found: C, 49·79; H, 4·32; N, 15·61; S, 12·12. $C_{11}H_{11}N_3O_3S$ requires: C, 49·80; H, 4·18; N, 15·84; S, 12·09%).

Oxidation of IV *to* V. To 0·26 g (1·0 mmole) of IV in 5 ml $CHCl_3$ was added 3 ml MeOH and 0·5 ml MeOH and 0·5 ml 28% NH_4OH. H_2O_2 (30%) was added dropwise until the nitroprusside test became negative. The soln was permitted to remain at room temp for ca. 2 hr and was evaporated to dryness under reduced press to give V, m.p. 251° dec. Recrystallization was effected from acetonitrile-water to give 0·15 g (58%) of V, m.p. 260° dec; the IR spectrum was identical to that of IV except that there was no peak at 3·90 μ. (Found: C, 50·17; H, 4·10; N, 15·88; S, 12·01. $C_{22}H_{20}N_6O_6S_2$ requires: C, 49·99; H, 3·81; N, 15·91; S, 12·13%).

Hydrolysis of III *to* VI. A mixture of 33·8 g (0·1 mole) of III and 30 ml conc HCl diluted with 750 ml water was heated under reflux with stirring until the yellow solid was converted into a white insoluble product (ca. 2·5 hr). Excessive heating caused the thiocarbonyl group to be hydrolyzed, as indicated by the evolution of H_2S. The mixture was cooled and filtered to give 29·5 g (83%) of VI, m.p. 154–158°. Recrystallization of the product from MeCN–EtOH gave crystals, m.p. 158°, which gave a positive nitroprusside test. The IR spectrum of VI showed peaks at 3·90 (SH), 5·90 (C═O), 6·21 (C═N), 6·90 (amide II) and 8·43 μ (C═S). (Found: C, 57·04; H, 4·82; N, 15·76; S, 17·94. $C_{17}H_{16}N_4OS_2$ requires: C, 57·27; H, 4·53; N, 15·71; S, 17·99%).

Oxidation of VI *to* VII. To 3·56 g (0·01 mole) of VI in 30 ml, 40 ml MeOH and 3 ml 28% NH_4OH was added dropwise with stirring 30% H_2O_2 until the nitroprusside test became negative. The soln became cloudy and on cooling, a white ppt formed. The disulfide was collected by filtration giving 3·3 g (94%) white crystals, m.p. 170–175°. Recrystallization of the VII from $CHCl_3$–EtOH raised its m.p. to 177–179°; IR spectrum was identical to that of the VI except that there was no peak at 3·90 μ. (Found: C, 56·93; H, 4·47; N, 15·82; S, 17·85. $C_{34}H_{30}N_8O_2S_4$ requires: C, 57·44; H, 4·25; N, 15·76; S, 18·04%).

Formation of VIII

A. *From* VII. In a soln of 0·6 g (15 mmoles) NaOH in 50 ml 90% EtOH was dissolved 1·02 g (1·43 mmoles) of VII. To the magnetically stirred soln was added dropwise 3·75 ml 30% H_2O_2 and the mixture was stirred an additional 2 hr. Na_2SO_4 was removed by filtration and the filtrate was concentrated to ca. ¼ of the volume under reduced press. The addition of water caused the separation of fine white crystals. The cooled mixture was filtered and the product was washed with water to give 0·55 g (57%) of VIII, m.p. 240–241°. The compound after recrystallization from $CHCl_3$–EtOH melted at 242–244°. The IR spectrum showed peaks at 5·80 and 6·00 (C═O), 6·21 (C═N) and 6·90 μ (amide II). (Found: C, 60·34; H, 4·40; N, 17·85; S, 9·62. $C_{34}H_{30}N_8O_4S_2$ requires: C, 60·16; H, 4·45; N, 16·51; S, 9·45%).

B. *From* III. To a warm soln of 1·36 g (4 mmoles) of III in 50 ml N,N-dimethylformamide was added a soln of 1·63 g (6 mmoles) $HgCl_2$ in 10 ml hot water. The mixture was heated on a steam bath and stirred periodically for 3 hr. The HgS which precipitated was filtered from the hot soln and 75 ml water was added to the filtrate causing separation of the white product. After the mixture was cooled, the solid was collected by filtration, air-dried and recrystallized from $CHCl_3$–MeOH to give 0·85 g (63%) of VIII, m.p. 240–244°. Its IR spectrum was identical to the product made by Method A.

1-*Phenyl*-3-(2-*selenazolin*-2-*yl*)-2-*thiourea* (XII). 2-Amino-2-selenazoline hydrobromide (2·29 g, 0·01 mole) was converted to the free base by adding it to a soln of 0·40 g (0·01 mole) NaOH hydroxide in 15 ml EtOH. The mixture was stirred and the NaBr which formed was removed by filtration. To the filtrate was added 1·35 g (0·01 mole) phenylisothiocyanate and the soln was heated for 0·5 hr. Cooling caused 1·53 g (54%) of XII, m.p. 145–149°, to separate from soln. Recrystallization from MeOH raised the m.p. of the pale yellow crystals to 151–152°. (Found: C, 42·06; H, 4·11; N, 14·72; S, 11·17; Se, 27·86. $C_{10}H_{11}N_3SSe$ requires: C, 42·25; H, 3·90; N, 14·78; S, 11·28; Se, 27·78%).

2-*Phenylimino*-3-*phenyl*-4-*thioxoselenazolo* [3.2-a] *tetrahydro*-s-*triazine* (XI). A soln of 2·84 g (0·01 mole) of XII and 4·05 g (0·03 mole) phenylisothiocyanate in 40 ml MeCN was heated under reflux for 72 hr during which time H_2S was evolved. The soln was cooled resulting in the crystallization of 1·12 g (29%) of XI, m.p. 283–285° dec. An analytical sample, m.p. 289–290° dec, was prepared by recrystallization from N,N-dimethylformamide. (Found: C, 52·79; H, 3·55; N, 14·74; S, 8·48; Se, 20·66. $C_{17}H_{14}N_4SSe$ requires: C, 52·98; H, 3·66; N, 14·54; S, 8·32; Se, 20·49%).

"Disproportionation" of II. A soln of 2·37 g (0·01 mole) of II in 25 ml benzene was heated under reflux for 5 days during which time H_2S was slowly evolved. After cooling to room temp, the mixture was filtered giving III and some II. The yellow crystals were treated with hot MeCN to remove the II leaving 0·62 g (37% conversion) of III, m.p. 298–299° dec.

Reaction of I *with excess* 1-*naphthylisothiocyanate.* A soln of 2·52 g (0·025 mole) of I in 25 ml benzene was heated under reflux for 24 hr with 13·89 g (0·075 mole) 1-naphthylisothiocyanate. The mixture was cooled and the crystals which formed were filtered off and washed with ether giving 6·64 g (93%) of XIII, m.p. 178–179°. Recrystallization from MeCN raised the m.p. of the compound to 181–182°. (Found: C, 58·61; H, 4·70; N, 14·53; S, 22·01. $C_{14}H_{13}N_3S_2$ requires: C, 58·51; H, 4·56; N, 14·62; S, 22·31%).

Reaction of II *with* 1-*naphthylisothiocyanate.* A soln of 1·19 g (0·005 mole) of II and 5·55 g (0·015 mole) 1-naphthylisothiocyanate in 25 ml benzene was heated under reflux for 24 hr. The soln was permitted to stand several days at room temp during which time crystals slowly formed. The crude XIII was removed by filtration and recrystallized from MeCN to give 0·53 g (34%) of the thiourea, m.p. 181–182°. The IR spectrum of the material was identical to that of the product obtained in the reaction of I and 1-naphthylisothiocyanate, described above.

Reaction of 1-(1-*naphthyl*)-3-(2-*thiazolin*-2-*yl*)-2-*thiourea* (XIII) *with phenylisothiocyanate.* A soln of 2·87 g (0·01 mole) of XIII and 4·05 g (0·03 mole) phenylisothiocyanate in 50 ml benzene was heated under reflux for 120 hr. Crystals of III which formed were filtered off from the mixture cooled to room temp. The product was washed with benzene to give 2·24 g (66%) of III, m.p. 290–292°. The IR spectrum of the material was identical to that of a sample of III prepared from I and phenylisothiocyanate, as described earlier.

From the mother liquors was isolated 0·53 g of 1-naphthylisothiocyanate which after recrystallization from MeCN melted at 57–58°; lit.[7] m.p. 58°.

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