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Chlorination of Isothiocyanates. V (6). 5-Imino-1,2,4-thiadiazolidin-3-ones

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S-[*N'*-(Chlorocarbonyl)amino]isothiocarbamoyl chlorides (II), obtained from S-chloroisothiocarbamoyl chlorides (I) and isocyanates, react with primary aliphatic and aromatic amines to form the unknown class of 5-imino-1,2,4-thiadiazolidin-3-ones. The structures were confirmed by chemical means and by spectroscopic methods.

N-Alkyl- and *N*-aryl-S-chloroisothiocarbamoyl chlorides (I) (1,2) feature the unique structural arrangement of a sulfenyl chloride and an imidoyl chloride group, whereby the -S-Cl moiety excels the -N=C(CCl)- group in reactivity. The facile addition of compounds I to olefinic (3) and acetylenic (4) double bonds is one of the criteria which classifies them as sulfenyl chloride derivatives.

Recently, we found that – in contrast to common sulfenyl chlorides (5) – compounds I react with isocyanates to form the highly reactive S-[*N'*-(chlorocarbonyl)amino]-isothiocarbamoyl chlorides (II) (6) which were converted to 1,2,4-thiadiazolidine-3,5-diones (III). The reactivity of S-chloroisothiocarbamoyl chlorides toward isocyanates suggests a stronger polarization of the sulfur-chlorine bond in I relative to the known polarity $\delta^+ \text{S} - \delta^- \text{Cl}$ of the regular sulfenyl chlorides (7). As a consequence, ionic scission of the S-Cl linkage, formation of a sulfenium ion – possibly stabilized by resonance forms such as IVa and IVb with IVb making the least contribution –, and reaction of the sulfenium ion with the polar form $\text{R} - \ominus \text{N} = \oplus \text{C} = \text{O}$ of the isocyanate would be facilitated.

N-Alkyl- and *N*-aryl-S-[*N'*-(chlorocarbonyl)amino]isothiocarbamoyl chlorides (II) react readily with aliphatic and aromatic primary amines to afford 5-imino-1,2,4-thiadiazolidin-3-ones (8) (VIa-m) in high yields (Table I). Very small amounts of 1,3-disubstituted ureas, $\text{R}'\text{NHCONHR}''$, and isothiocyanates, RNCS, have been occasionally observed as by-products. The formation of the ureas increases substantially at the expense of VI if both substituents R and R' of the starting compound II represent aromatic groups.

Since the imidoyl chloride group in compounds II is more susceptible to nucleophilic attack than the chlorocarbonyl moiety (6), the reaction of II with primary amines proceeds probably through intermediates V which undergo

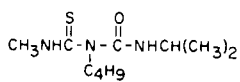
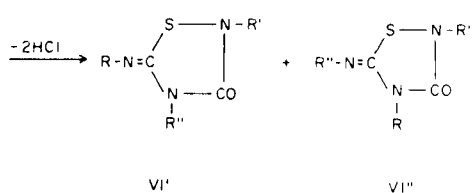
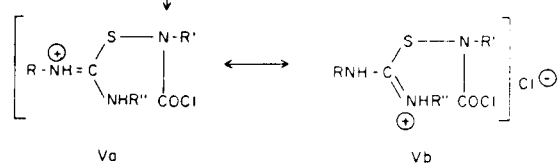
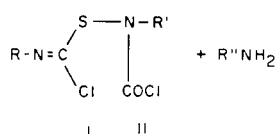
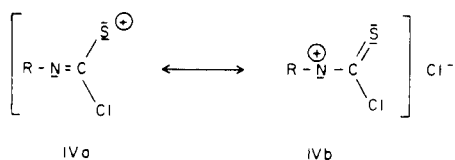
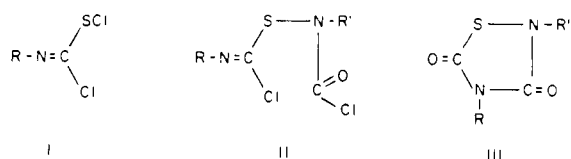
ring closure to form 5-imino-1,2,4-thiadiazolidin-3-ones (VIa-m).

In view of the two possible forms Va and Vb of the intermediates, the ring closure reaction can conceivably progress in two ways – if R and R'' are not identical – and, hence, yield two isomeric 5-imino-1,2,4-thiadiazolidin-3-ones (VI' and VI''), which indeed have been observed (Table I).

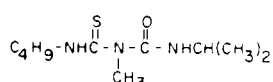
The assignments of structure to compounds VIa-m are based on chemical reactions as well as instrumental analysis. Hydrogenolysis of the distilled reaction mixture being composed of VIa and VIb by lithium aluminum hydride resulted in reductive cleavage of the S-N linkage and formation of 1-methyl-3-butyl-5-isopropyl-2-thiobiuret (VIIa) as principal reaction product in 73% yield. The structure of compound VIIa is supported by the results of elemental analysis, molecular weight determination, and by nuclear magnetic resonance and mass spectroscopy (see Experimental Part). The formation of VIIa rather than VIIb serves as evidence that the major component of the reaction mixture obtained from II (R = C₄H₉, R' = *i*-C₃H₇) and methylamine is 2-isopropyl-4-butyl-5-methylimino-1,2,4-thiadiazolidin-3-one (VIa). The H¹ nuclear magnetic resonance spectrum of VIa shows a single peak at 2.98 ppm for the exocyclic methylimino group, and a triplet at 3.71 ppm for the α -methylene of the butyl group in 4-position. In contrast, the methyl group of the isomer VIb, which represents the minor component of the reaction mixture, appears as a singlet at 3.19 ppm while the α -methylene of the butyl group was now detected as a triplet at 3.03 ppm.

A comparison of the chemical shifts measured for VIa and VIb with those obtained for the other 5-alkylimino-4-alkyl-1,2,4-thiadiazolidin-3-ones led to the structure assignments for compounds VIc-h (Tables I and II).

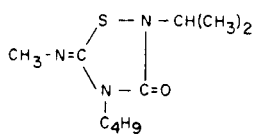
The structures of compounds VIj, VIk and VII, which



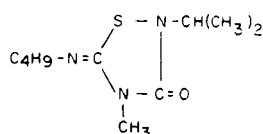
VIIa



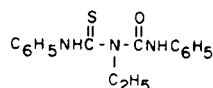
VIIb



VIa



VIb



VIII

from 6.80 to 7.56 ppm (multiplet). In conjunction with the proton resonance spectrum of *N*-phenyl-*S*-chloroiso-thiocarbamoyl chloride (I; R = C₆H₅), which exhibits only a multiplet extending from 6.79 to 7.50 ppm, one is prompted to associate the single peak at 7.42 ppm with a phenyl group attached to the ring nitrogen atom in 4-position, and the multiplet with the protons of an exocyclic phenylimino moiety. This conclusion proves to be valid if applied to compound VIj, for instance. The nmr spectrum of VIj serves evidence for the presence of an exocyclic butylimino group ($\delta_{\text{-CH}_2\text{N=}}$ 3.03, triplet) and a phenyl ring in 4-position, giving rise to a proton resonance at 7.42 ppm of unit multiplicity as expected. In contrast to VIj, compounds VIk and VII have exocyclic phenylimino groups and the alkyl or cycloalkyl moieties attached to the nitrogen atom in 4-position (Table II).

The structure assignments for compounds VII-l are confirmed by the formation of 1-phenyl-3-ethyl-5-phenyl-2-thiobiuret (VIII) as principal reaction product in the lithium aluminum hydride-reduction of compound VIk.

The infrared spectra of compounds VI feature strong absorptions for C=O at 5.80-5.90 μ and for C=N at 6.06-6.12 μ .

The structures assigned to compounds VI are also in agreement with the ultraviolet absorption spectra obtained for VIi-l. From Table III one recognizes that only those compounds bearing exocyclic phenylimino groups in 5-position, have absorption maxima at about 270 $m\mu$. This bathochromic shift is caused by the conjugation of the >C=N- chromophore with the π -electron system of the aromatic nucleus.

EXPERIMENTAL

Melting points were determined in a modified Thiele Apparatus; melting and boiling points are not corrected. The H^1 nmr spectra were obtained on a Varian A-60 instrument, and the chemical shift data are expressed in parts per million relative to tetramethyl silane. Ultraviolet spectra were recorded by a Cary Spectrophotometer, Model 14. Spectrograde acetonitrile was used as solvent. Infrared spectra were taken on a Perkin-Elmer Infracord spectrophotometer 137B. Vapor phase chromatography column used: 6 ft., 0.25" O.D., aluminum 0.032" wall, 30% SE 30 Chromosorb W (60-80 mesh).

Starting Materials.

S-[*N'*-(Chlorocarbonyl)amino]isothiocarbamoyl chlorides (II) were synthesized by addition of *S*-chloroiso-thiocarbamoyl chlorides (I) to isocyanates as recently described (6).

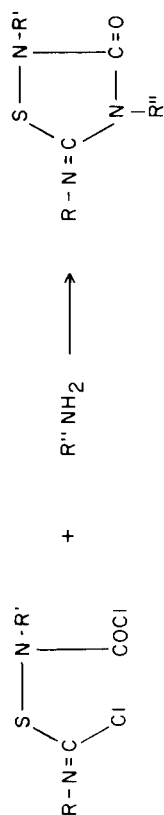
2-Ethyl-4-phenyl-5-butylimino-1,2,4-thiadiazolidin-3-one (VIj). (General Procedure for the Preparation of Compounds VIa-m).

To a stirred slurry of 73.0 g. (0.26 mole) of *N*-phenyl-*S*-[*N'*-(chlorocarbonyl)ethylamino]isothiocarbamoyl chloride in 350 ml. of sodium dried ether was added dropwise a solution of 64.0 g. (0.88 mole) of butylamine in 50 ml. of dry ether. The very exothermic reaction was controlled at 5-10° by an external wet ice bath. After completion of addition, the reaction mixture was brought to room temperature and stirred for additional 3 hours.

contain a phenyl group either in 4-position or linked to the imino-nitrogen were resolved in a similar fashion. Resonance of the aromatic protons of the two phenyl groups in VIi (9) was observed at 7.42 ppm (singlet) and

TABLE I

Synthesis of 5-Imino-1,2,4-thiadiazolidin-3-ones (VI) from 5-[Chloro-carbonyl]amino isothiocarbonyl Chlorides and Primary Amines



R	Starting Materials		Reaction Products		R''	Empirical Formula	Isomer Ratio	Yield, %	Mp, °C	Bp, °C (mm)	n _D ²⁰ (°C)	Calculated, %						
	R'	R''	R	R'								C	H	Cl	N	S	C	H
C ₄ H ₉	i-C ₃ H ₇	CH ₃	i-C ₃ H ₇	i-C ₃ H ₇	C ₄ H ₉	C ₁₀ H ₁₉ N ₃ OS	8.5/1.5	83	99 (0.45)	1.5071 (25)	52.38	8.35	18.33	13.96	52.06	8.4	18.42	13.69
C ₄ H ₉	C ₄ H ₉	CH ₃	C ₄ H ₉	i-C ₃ H ₇	CH ₃	C ₁₁ H ₂₁ N ₃ OS	6.7/3.3	52	111 (0.5)	1.5060 (23)	54.29	8.71	17.35	13.15	53.90	9.09	17.07	13.15
C ₂ H ₅	C ₈ H ₁₇	C ₄ H ₉	C ₈ H ₁₇	C ₄ H ₉	C ₄ H ₉	C ₁₆ H ₃₁ N ₃ OS	7/3	60	150 (0.3)	1.4941 (24)	61.32	9.98	13.40	10.21	60.98	9.98	13.13	10.18
C ₂ H ₅	C ₆ H ₅	C ₄ H ₉	C ₄ H ₉	C ₆ H ₅	C ₄ H ₉	C ₁₄ H ₁₉ N ₃ OS	6.3/3.7	68	150-2 (0.4)	1.5729 (23)	60.63	6.91	15.15	11.54	60.99	7.11	14.89	11.67
C ₄ H ₅	C ₂ H ₅	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅	C ₆ H ₅	C ₁₆ H ₁₅ N ₃ OS	—	82	89.5-90.5	—	64.64	5.09	14.13	10.76	64.52	4.94	14.43	10.72
C ₆ H ₅	C ₂ H ₅	C ₄ H ₉	C ₄ H ₉	C ₂ H ₅	C ₆ H ₅	C ₁₄ H ₁₉ N ₃ OS	n.d.	83	41.5-42.5	—	60.63	6.91	15.15	11.54	60.62	7.37	15.54	11.24
C ₂ H ₅	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅	C ₁₆ H ₁₅ N ₃ OS	n.d.	51	55-56	—	64.64	5.09	14.13	10.76	64.71	5.36	14.10	10.72
C ₆ H ₁₁	i-C ₃ H ₇	C ₆ H ₅	C ₆ H ₅	i-C ₃ H ₇	C ₆ H ₁₁	C ₁₇ H ₂₃ N ₃ OS	n.d.	81	101-102	—	64.33	7.25	13.24	10.08	64.59	7.25	13.22	10.38
C ₆ H ₅	p-Cl-C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	p-Cl-C ₆ H ₄	C ₆ H ₅	C ₂₀ H ₁₄ ClN ₃ OS	—	6	134-135	—	63.24	3.72	9.35	11.07	62.93	4.11	8.97	11.17

n.d. = not determined, however the other isomer was detected in the crude reaction mixture in small amounts (by NMR).

TABLE II

Proton NMR of 5-Imino-1,2,4-thiadiazolidin-3-ones (VI) Chemical Shift δ in ppm

Compound	R	δ	Multiplicity	R''	δ	Multiplicity	R'	δ	Multiplicity					
VIa	CH ₃	2.98	1	α -CH ₂	3.71	3	CH ₃	1.25	2					
				CH ₂ CH ₂	1.10-2.00	m (b)	CH	4.62	7					
				CH ₃	0.93	3 (a)								
VIb	α -CH ₂ CH ₂ CH ₂ CH ₃	3.01 1.11-2.19 0.92	3 m (b) 3 (a)	CH ₃	3.19	1	CH ₃ CH	1.25 4.62	2 7					
VIc	α -CH ₂ CH ₂ CH ₂ CH ₃	3.01 1.11-2.19 0.92	3 m (b) 3 (a)	CH ₃	3.18	1	CH ₃ CH ₂ CH ₂ α -CH ₂	0.92 1.11-2.19 3.56	3 (a) m (b) 3					
VI d	CH ₃	2.95	1	α -CH ₂	3.69	3	CH ₃	0.92	3 (a)					
				CH ₂ CH ₂	1.11-2.19	m (b)	CH ₂ CH ₂	1.11-2.19	m (b)					
				CH ₃	0.92	3 (a)	α -CH ₂	3.56	3					
VIe	α -CH ₂ CH ₂ CH ₂ CH ₃	3.00 1.08-2.00 0.92	3 m (b) 3 (a)	CH ₂ CH ₃	3.76 1.08-2.00	4 3	CH ₃ (CH ₂) ₆ α -CH ₂	0.89 1.08-2.00 3.52	3 (a) m (b) 3					
VI f	CH ₂ CH ₃	3.04 1.08-2.00	4 3	α -CH ₂ CH ₂ CH ₂ CH ₃	3.71 1.08-2.00 0.92	3 m (b) 3 (a)	CH ₃ (CH ₂) ₆ α -CH ₂	0.89 1.08-2.00 3.52	3 (a) m (b) 3					
VI g	α -CH ₂ CH ₂ CH ₂ CH ₃	3.06 1.10-2.00 0.94	3 m (b) 3 (a)	CH ₂ CH ₃	3.86 1.28	4 3	C ₆ H ₅	7.08-7.68	m (b)					
VI h	CH ₂ CH ₃	3.13 1.28	4 3	α -CH ₂ CH ₂ CH ₂ CH ₃	3.81 1.10-2.00 0.94	3 m (b) 3 (a)	C ₆ H ₅	7.08-7.68	m (b)					
VI i	C ₆ H ₅	6.80-7.56	m (b)	C ₆ H ₅	7.42	1	CH ₃	1.16	3					
							CH ₂	3.56	4					
VI j	α -CH ₂ CH ₂ CH ₂ CH ₃	3.03 1.11-1.73 0.91	3 m (b) 3 (a)	C ₆ H ₅	7.39	1	CH ₃ CH ₂	1.28 3.66	3 4					
VI k	C ₆ H ₅	6.90-7.67	m (b)	CH ₂	4.02	4	C ₆ H ₅	6.90-7.67	m (b)					
				CH ₃	1.43	3								
VII	C ₆ H ₅	6.63-7.53	m (b)	CH	4.11-4.92	m (b)	CH ₃ CH	1.19 4.11-4.92	2 m (b)					
				(CH ₂) ₅	1.09-3.00	m (b)								

(a) Perturbed triplet. (b) Multiplet.

Butylamine hydrochloride (74.0 g.) was separated by suction filtration, and the solvent was removed from the filtrate *in vacuo* at 20-25°. The residual tan colored oil was dissolved in 900 ml. of pentane: the solution was decanted from little insoluble oil and stored at -30° for 18 hours. Rapid filtration through a pre-cooled Büchner funnel afforded 79.0 g. (83% yield) of pure VIj, m.p. 41-42°. A second recrystallization from hexane raised the melting point to 41.5-42.5°.

The reactions of compounds II with aromatic primary amines are only slightly exothermic, and are carried out at 25-35°.

Compounds VIj, VII and VI m were recrystallized from hexane,

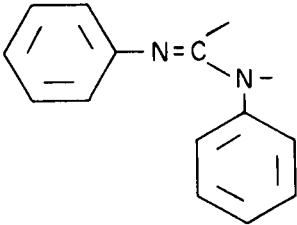
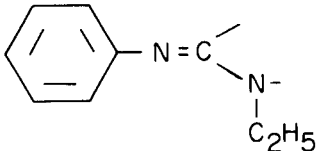
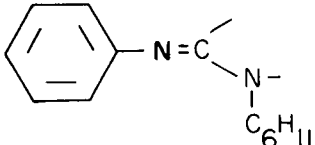
VI i from a 60/40 mixture of *n*-heptane and toluene, and VI k from cyclohexane.

The liquid representatives VI a-h were purified by distillation *in vacuo* over a 36" spinning band column. The crude reaction product containing VI g and VI h decomposed on heating, but the isomer mixture VI g/VI h could be distilled after these compounds had been separated as hydrochlorides and reconverted to the free bases. None of these operations, however, provided for isomer separation which was eventually done for analytical purposes by vapor phase chromatography.

1-Methyl-3-butyl-5-isopropyl-2-thiobiuret (VII a).

TABLE III

Ultraviolet Absorptions of Selected 5-Imino-1,2,4-thiadiazolidin-3-ones (VI) in the Range from 250 $m\mu$ to 400 $m\mu$

Compound	Structure Segment	λ max in $m\mu$
VIi		270
VIj	$C_4H_9-N=C$ (with methyl group on C) and a benzene ring attached to the nitrogen atom.	
VIk		272, 249
VII		272

To a stirred solution of 48.0 g. (0.21 mole) of an isomer mixture composed of 44.0 g. of 2-isopropyl-4-butyl-5-methylimino-1,2,4-thiadiazolidin-3-one (VIa) and 4.0 g. of VIb in 100 ml. of tetrahydrofuran was added at 5-10° a solution of 8.0 g. of lithium aluminum hydride in 250 ml. of tetrahydrofuran over a period of 1.5 hours. The reaction mixture was then refluxed for 3.5 hours, cooled to 0°, and the metal-organic complex and excessive lithium aluminum hydride decomposed with 35 ml. of water.

After filtration and evaporation of the solvent, the residual oil was dissolved in ether and the ethereal solution dried over calcium chloride. Evaporation of the ether *in vacuo* (receiver in Dry-Ice; no heat source applied to distillation flask) afforded 23.8 g. (54% yield) of VII, m.p. 43-45°. Recrystallization from hexane raised the melting point to 45-46°. The nmr spectrum (in deuteriochloroform) consists of the following resonances: 0.97 (CH_3 -butyl, perturbed triplet), 1.20-2.00 ($-CH_2CH_2$ -butyl, broad hump), 4.27 (CH_2-N -butyl, triplet), 3.10 (CH_3CH_2NH , doublet, $J = 4.40$ Hz), 11.33 (NH_2NHCS- , broad hump), 1.22 (CH_3 -isopropyl, doublet $J = 6.3$ Hz), 3.99 (CH -isopropyl, multiplet), 5.21 ($NH-NHCO-$, broad hump (10)). The mass spectrum shows no molecular ion at 231 m/e , but two major fragments in the higher mass region at 146 m/e (containing sulfur and two nitrogen atoms) representing $CH_3NHC(S)NHC_4H_9$, and at 158 m/e (containing two nitrogen atoms but no sulfur) representing $C_4H_9NHC(O)NHCH(CH_3)_2$. The IR spectrum of VIIa shows strong absorptions for two different NH-groups at about 3350 cm^{-1} and 3125 cm^{-1} , and for an amide-type carbonyl at about 1650 cm^{-1} .

Anal. Calcd. for $C_{10}H_{21}N_3OS$: C, 51.92; H, 9.15; N, 18.17; S, 13.84; mol. wt. 231. Found: C, 51.96; H, 9.20; N, 17.92; S, 13.91; mol. wt. 223.

1,5-Diphenyl-3-ethyl-2-thiobiuret (VIII).

2-Phenyl-4-ethyl-5-phenylimino-1,2,4-thiadiazolidin-3-one (VIk) (39.0 g.) and lithium aluminum hydride (approximately 9 g.) were allowed to react in tetrahydrofuran as described above. The reaction mixture was treated with 150 ml. of water, filtered and the solvent evaporated. The remaining aqueous solution was extracted with ether, and then acidified with 10% sulfuric acid to precipitate VIII, which was separated by ether extraction and purified by recrystallization from methanol. Obtained were 12 g. of pure VIII, m.p. 102.5-103° (white silky needles).

Anal. Calcd. for $C_{16}H_{17}N_3OS$: C, 64.20; H, 5.73; N, 14.04; S, 10.69. Found: C, 64.35; H, 5.65; N, 13.84; S, 10.61.

Concentration of the ether extract prior to acidification left 7.0 g. of an oily mixture composed of 1-ethyl-3-phenylurea, *N*-methylaniline and some 1,3-diphenylurea.

Acknowledgment.

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- (3) G. Ottmann and H. Hooks, *Angew. Chem.*, **78**, 210 (1966); *Angew. Chem. Intern. Ed. Engl.*, **5**, 250 (1966).
- (4) G. Ottmann and H. Hooks, unpublished work.
- (5) We are not aware of any literature report describing attempted reactions between sulfonyl chlorides and isocyanates. We have, therefore, ascertained in case of *p*-chlorophenylsulfenyl chloride and phenylisocyanate, that there is no reaction between these two classes of compounds both in solution and in the undiluted state (temperature range checked: 0-100°).

(6) G. Ottmann and H. Hooks, *Angew. Chem.*, **78**, 681 (1966); *Angew. Chem. Intern. Ed. Engl.*, **5**, 672 (1966).

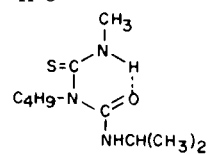
(7) N. Kharash, "Organic Sulfur Compounds", Vol. I, Pergamon Press Ltd., London 1961, p. 375-396.

(8) 5-Imino-1,2,4-thiadiazolidin-3-ones have not been described previously except 2-phenyl-4*H*-5-phenylimino-1,2,4-thiadiazolidin-3-one ($R'' = H$) which was obtained by cyclization of 1,5-diphenyl thiobiuret (C. P. Joshua, *Indian J. Chem.*, **1**, 391 (1963)).

(9) The position of these two phenyl groups can be derived from the synthesis with reasonable certainty.

(10) Strong hydrogen bonding in compound VIIa is responsible

for the 6.34 δ chemical shift difference of the NH proton resonances in $\begin{array}{c} | \text{H} \\ \text{N}-\text{C}- \\ | \text{H} \end{array}$ and $\begin{array}{c} | \text{H} \\ \text{N}-\text{C}- \\ | \text{O} \end{array}$.



VIIa

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