N-Halogen Compounds of Cyanamide Derivatives. V.[1] The Preparation and Reaction of Δ^4-1,2,4-Thiadiazolines

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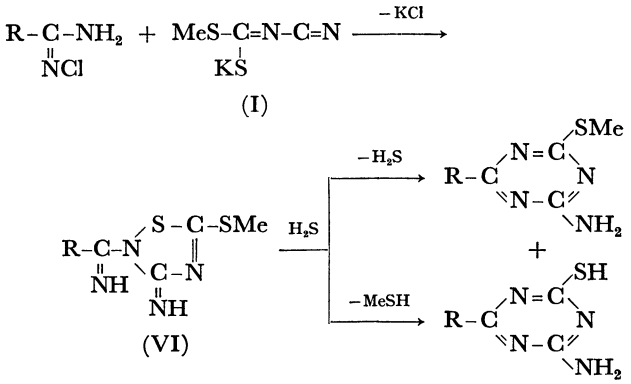
Five new Δ^4-1,2,4-thiadiazolines (TDZ), IIa,b, IIIa,b, and IV, were easily prepared by the reaction of potassium methyl cyanoiminodithiocarbonate (I) with *N*-chloro compounds of *O*-alkylisoureas, guanidines, and guanylurethane. 2-Methoxyimidoyl-3-imino-5-methylthio-TDZ (IIa), with a reactive imidoether group, was converted into the 2-carbamoyl-TDZ derivative (V) by treatment with excess dry hydrogen chloride. The reaction of IIa with aliphatic amines gave 2-amidino-TDZ derivatives (IIIc—e) in good yields in the presence of both free amines and amine hydrochlorides (molar ratio, 2: 1). The mechanism of this amidination was discussed.

In our previous work,[2] it was found that 2-imidoyl-3-imino-5-methylthio-Δ^4-1,2,4-thiadiazolines (VI) could easily be prepared by the reaction of *N*-chloroamidines with I and that VI was readily cleft by reduction at the N–S link and recyclized to two kinds of *s*-triazines.



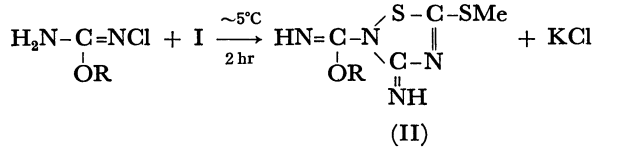
Scheme 1.

In this paper, we wish to report on the synthesis of new TDZ (IIa,b, IIIa,b, and IV) using *N*-chloro compounds of cyanamide derivatives (*O*-alkylisoureas, guanidines, and guanylurethane) and their properties, together with the reaction between IIa and amines to give 2-amidino-TDZ (IIIc—e).

Results and Discussion

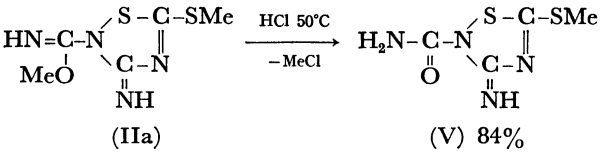
Preparation and Reaction of 2-Alkoxyimidoyl-3-imino-5-methylthio-TDZ (IIa,b). *N*-Chloro-*O*-alkylisoureas readily reacted with I in methylene chloride to form IIa and b. The yield of IIa increased considerably when the solvent was acetonitrile, which is more polar than methylene chloride, while that of IIb did not. The same effect was also observed in the case of *N*-chloroguanidine (Table 3).

Table 1. Preparation of TDZ



R	Solvent	Product	Yield (%)
Me	CH_2Cl_2	IIa	63
	MeCN		79
Et	MeCN	IIb	41

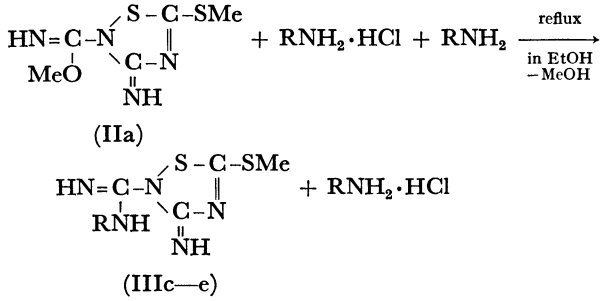
The structures of IIa and b were confirmed by means of elemental analysis and by a study of the IR spectrum. Compounds IIa and b can both be regarded as *N,N*-disubstituted-*O*-alkylisourea with a reactive imidoether group. By the treatment of IIa with excess dry hydrogen chloride in methanol, IIa was further converted into the 2-carbamoyl-TDZ derivative (V).



Scheme 2.

The reaction of IIa with amines was likewise examined. The reaction of IIa with amines in ethanol under reflux gave 2-amidino-3-imino-5-methylthio-TDZ (IIIc—e). It was found that IIIc—e were obtained as free bases in good yields in the presence of both free amines and amine hydrochlorides (molar ratio,

Table 2. Reaction of IIa with amines



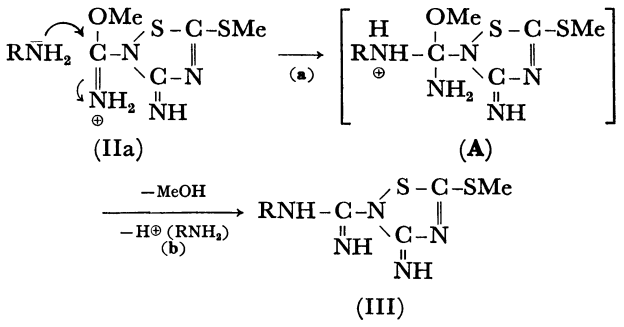
R	Free amine[a]	Amine salt[a]	R. Time (hr)	Product (Yield %)
Me	2	1	4.0	IIIc (80)
Et	1	0	4.0	(0)
	0	1	4.0	IIId (0)
	2	1	4.0	(97)
Bzl	1	0	2.5	IIIe (0)
	2	1	3.0	(75)
Ph	2	1	3.0	V (80)

a) Molar ratio.

2: 1). It is notable that no substitution reaction occurred in the absence of either free amine or amine hydrochloride. In the case of such a weak base as aniline, no substitution reaction occurred and V was obtained. The basicity of IIa seems to be stronger than that of aniline, so IIa may take hydrogen chloride from aniline hydrochloride to form V, thus evolving methyl chloride.

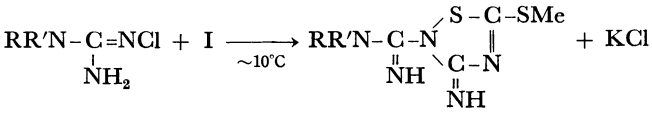
As is shown in Table 2, the methylthio group of IIa was found not to be reactive.

The mechanism of this amidination, judging from the above results, is as follows. Free amine attacks the protonated imidoether group of IIa to form a tetrahedral addition intermediate (**A**)—Step (**a**). Then, the elimination of methanol and a proton from A gives IIIc—e as a free base—Step (**b**). The first step and the second step seem to be subjected to acid catalysis (HCl) and base catalysis (free amine) respectively



Scheme 3.

Table 3. Preparation of TDZ



(III)

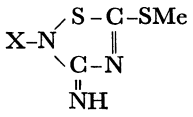
R	R′	Solvent	R. Time (hr)	Product	Yield (%)
H	H	CH_2Cl_2	2	IIIa	55
		MeCN	1		91
		MeCN	1	IIIb	44

(Scheme 3).

Preparation of Other TDZ. 2-Amidino-TDZ (IIIa,b). In a manner similar to that described above, *N*-chloroguanidines and I gave IIIa, and b. The yield of IIIa in acetonitrile increased considerably, as had been observed in the case of IIa. The low yield of IIIb may be attributable to the steric hyndrance of the piperidyl group. Since IIIa is too weak a base, IIIa could not be subjected to benzoylation by benzoyl chloride.

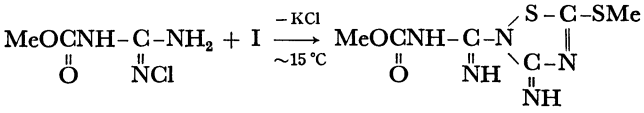
2-N-Carbethoxyamidino-TDZ (IV). In a similar manner, *N*-chloroguanylurethane and I gave IV in a good yield (85%). Its NMR spectrum showed three singlet signals, at δ 2.70 (SMe), 3.67 (OMe), and 8.50 (NH, broad). In the mass spectrum, the parent peak, *m/e* 247, and other fragment peaks appeared appropriately. It would be expected that the elimination of

Table 4. Physical properties and analytical data of Δ^4-1,2,4-thiadiazolines

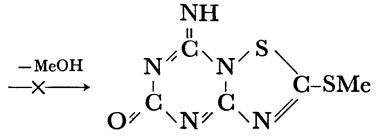


Compoud No.	X	Free base Mp (°C)	Free base Anal (Calcd %) C	H	N	IR (KBr) (cm^{-1}) C=N	C=O	Picrate Mp (°C)	Picrate Anal (Calcd %) C	H	N
IIa	MeO–C(=NH)–	112—115	29.43	3.96	27.55	1650	—	143—145	29.78	2.74	22.96
			(29.40)	(3.95)	(27.43)	1610	—		(30.49)	(2.56)	(22.62)
IIb	EtO–C(=NH)–	108—109	33.11	4.56	25.70	1640	—	184	32.20	2.74	21.92
			(33.01)	(4.62)	(25.66)	1610			(32.22)	(2.93)	(21.91)
IIIa	H_2N–C(=NH)–	225—228	25.55	3.72	37.08	1660	—	230	28.78	2.41	27.14
			(25.39)	(3.73)	(37.00)	1620		(Dp)	(28.71)	(2.41)	(26.78)
IIIb		139	42.37	5.98	27.13	1630	—	179—180	37.02	3.78	32.94
			(42.00)	(5.89)	(27.21)				(37.03)	(3.73)	(23.03)
IIIc	MeHN–N(=NH)–	183—184	29.10	4.65	34.40	1620	—	196—197	30.18	2.81	25.90
			(29.54)	(4.46)	(34.45)				(30.56)	(2.80)	(25.91)
IIId	EtHN–C(=NH)–	165—166	33.36	5.11	31.89	1620	—	170—172	32.53	3.07	24.91
			(33.16)	(5.10)	(32.23)				(32.29)	(3.16)	(25.10)
IIIe	BzlNH–C(=NH)–	167—169	47.10	4.71	25.06	1620	—	148—153	40.10	3.03	22.04
			(47.29)	(4.69)	(25.07)			(Dp)	(40.16)	(3.17)	(22.06)
IV	MeCNH–C(=O)–NH	190	28.80	3.63	28.57	1640	1720	—	—	—	—
		(Dp)	(29.10)	(3.67)	(28.32)	1620					
V	NH_2–C(=O)–	237—238	25.60	3.15	29.34	1670		—	—	—	—
			(25.25)	(3.18)	(29.45)						

methanol from IV would give rise to the formation of a condensed ring. However, no product due to such a condensation was formed, and decomposition only took place when IV was heated gradually at 190 °C.



(IV) 80%



Scheme 4.

The physical properties and analytical data of the products are summarized in Table 4.

Compounds IIa, IIIa, and IV display approximately similar UV spectra (Fig. 1), perhaps because of their structural resemblance.[3]

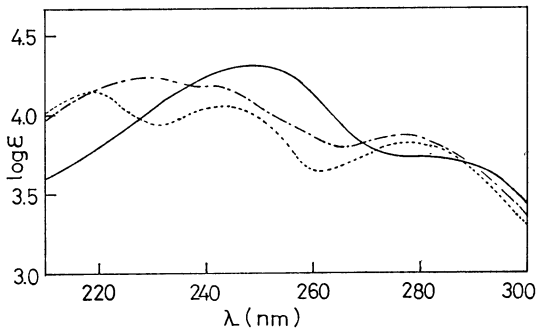


Fig. 1. Ultraviolet absorption of TDZ in water.
——: IIa, ——: IIIa, ----: V.

Experimental

The melting points are uncorrected. The IR spectra were taken with a Hitachi EPI-S 2 spectrophotometer. The NMR spectrum was recorded at 90 MHz in DMSO-d_6, with TMS as the internal standard, using a Hitachi R-22 spectrometer. The mass spectrum was taken with a JEOL JMS-D100 mass spectrometer. The UV spectra were taken with a Hitachi 624 spectrophotometer.

N-Chloro Compounds. *N*-Chloro-*O*-methylisourea,[4] *N*-chloro-*O*-ethylisourea,[4] *N*-chloroguanidine,[5] *N*-chloro-*N'*, *N'*-pentamethyleneguanidine,[6] and *N*-chloroguanylurethane were prepared by a previously described method.[7] *N*-chloroguanylurethane; yield, 80%; dp 124—125 °C; active chlorine 22.40% (calcd for $C_3H_6N_3O_2Cl$ 23.40%).

Potassium methyl cyanoiminodithiocarbonate (I) was prepared according to the method of Timmons *et al.*[8]

2-Methoxyimidoyl-3-imino-5-methylthio-Δ⁴-1,2,4-thiadiazoline (IIa). To a stirred mixture of I (10.20 g, 60 mmol) and methylene chloride (55 ml), we added a solution of *N*-chloro-*O*-methylisourea (5.97 g, 55 mmol) in methylene chloride (45 ml). The temperature was maintained below 5 °C during the reaction. After about 2 hr of continued stirring, the mixture was refluxed for 0.3 hr. After the precipitated salt had been removed by filtration, the filtrate was concentrated. Washing the residue with ether afforded IIa (7.10 g, 63%, mp 110—112 °C). Recrystallization from methanol gave a pure product; mp 112—115 °C. The above reaction, when carried out in acetonitrile by a similar method, gave IIa in a 79% yield.

2-Ethoxyimidoyl-3-imino-5-methylthio-Δ⁴-1,2,4-thiadiazoline (IIb). Using the same procedure, the crude product of IIb was obtained as an oily material from *N*-chloro-*O*-ethylisourea. The oily material was crystallized from aqueous methanol, and the yield was 41% (mp 99—100 °C). Recrystallization from aqueous methanol yielded an analytical sample; mp 108—109 °C.

2-Carbamoyl-3-imino-5-methylthio-Δ⁴-1,2,4-thiadiazoline (V). A slow stream of dry hydrogen chloride was passed through a solution of IIa (2.04 g, 10 mmol) in methanol at 50 °C for 2 hr. The white crystalline precipitate (V, 1.34 g) was collected by filtration, and the filtrate was concentrated. Washing the residue with a small amount of methanol or acetone gave V (0.25 g). The total yield was 84%; dp 237 °C. Recrystallization from DMF–methanol gave pure V; dp 237—238 °C.

Reaction of IIa with Amines. *2-N-Methylamidino-3-imino-5-methylthio-Δ⁴-1,2,4-thiadiazoline (IIIc)*: A solution of IIa (2.04 g, 10 mmol), 40% aqueous methylamine (20 mmol) and methylamine hydrochloride (0.68 g, 10 mmol) in ethanol (25 ml) was refluxed for 4 hr. After cooling, a crystalline precipitate was collected by filtration (IIIc, 1.45 g; mp 170—174 °C). After the concentration of the filtrate, the washing of the residue with water afforded IIIc (0.20 g, mp 170—174 °C). The total yield was 81%. Recrystallization from methanol gave pure IIIc; mp 183—184 °C.

Similarly, reactions with other amines were carried out. The products and reaction conditions are given in Table 2.

2-Amidino-3-imino-5-methylthio-Δ⁴-1,2,4-thiadiazoline (IIIa). To a stirred suspension of I (2.38 g, 14 mmol) in acetonitrile (30 ml), we gradually added *N*-chloroguanidine (1.31 g, 14 mmol). The temperature was maintained below 10 °C during the reaction. After about 1 hr of continued stirring, an insoluble matter (IIIa and KCl) was separated by filtration. Washing the solid with water (to remove KCl) and acetone afforded IIIa (2.41 g; 91%; dp 214—215 °C). Recrystallization from DMF gave pure IIIa; dp 225—228 °C. The above reaction, undertaken in methylene chloride in a similar manner, gave IIIa in a 55% yield.

2,N,N-Pentamethyleneamidino-3-imino-4-methylthio-Δ⁴-1,2,4-thiadiazoline (IIIb). To a stirred solution of I (1.19 g, 7 mmol) in acetonitrile (8 ml), we added a solution of *N*-chloro-*N',N'*-pentamethyleneguanidine (1.13 g, 7 mmol) in acetonitrile (10 ml). After 1 hr of continued stirring below 10 °C, an insoluble matter was separated by filtration. The oily material obtained by concentrating the filtrate was dissolved in 2 M hydrochloric acid and (5 ml) and methanol (5 ml). After stirring the solution for 0.5 hr at room temperature, IIIb was precipitated by making the solution neutral (0.80 g; 44%; mp 130—132 °C). Recrystallization from methanol gave pure IIIb; mp 139 °C.

2-N-Carbethoxyamidino-3-imino-5-methylthio-Δ⁴-1,2,4-thiadiazoline (IV). To a stirred suspension of I (2.72 g, 16 mmol) in acetonitrile we gradually added *N*-chloroguanylurethane (2.42 g, 16 mmol), the temperature being kept below 15 °C. After about 1 hr of continued stirring, the mixture was refluxed for 0.1 hr. After the insoluble matter had then been separated by filtration, washing with water and ether afforded IV (3.30 g; 85%; dp 190 °C). Recrystallization from ethyl acetate–DMF (2: 1) gave pure IV; dp 190 °C.

We wish to thank Dr. Ichikawa of our laboratory for his invaluable discussions.

References

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