N-Halogen Compounds of Cyanamide Derivatives. VI.[1] The Preparation and Reaction of 2-Carbonimidoyl-3-imino-Δ^4-1,2,4-thiadiazolines

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The reactions of potassium methyl cyanoiminodithiocarbonate (I), potassium methoxy and ethoxythiocarbonylcyanamide (IIa and IIb) with *N*-chloroamidines in various solvents were investigated. Δ^4-1,2,4-Thiadiazolines (TDZ), IIIa—d, were obtained from I in good yields, whereas the 1,3,5-triazines obtained as by-products in addition to TDZ were formed from II and *N*-chlorobenzamidine (NCB) in chloroform and dichloromethane. In the latter reaction, desulfrization occurred completely to give 1,3,5-triazine and/or a chain intermediate to 1,3,5-triazine in dipolar solvents. The TDZ were readily cleft at the N–S link by hydrogen sulfide and recyclized to 1,3,5-triazines. By alkaline hydrolysis, the TDZ were transformed to 2-amino-1,3,5-triazin-4-ols.

1,2,4-Thiadiazole derivatives have been known since 1821,[2] and many of them are important compounds as dyes, medicines, and agricultural chemicals. However, there have been few reports on the preparation of 1,2,4-thiadiazolines, especially on that of Δ^4-1,2,4-thiadiazolines. In our previous works,[3,4] we found that 2-carbonimidoyl-3-imino-5-methylthio-Δ^4-1,2,4-thiadiazolines could easily be prepared by the reaction of *N*-chloroamidino compounds with I and clarified their properties.

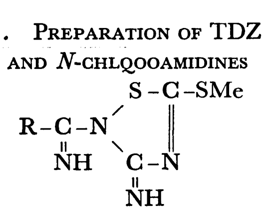
In this paper, we wish to describe the preparation of TDZ using *N*-chloroamidines, I, and II, and the desulfurization in the reaction of II with NCB, together with the reactivities of TDZ in alkaline solutions.

Results and Discussion

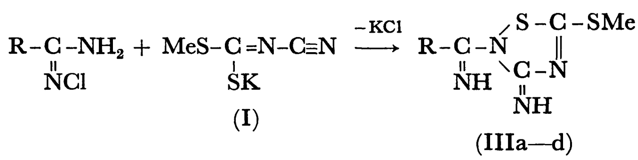
Preparation of Potassium Methoxythiocarbonylcyanamide (IIa). According to the method of preparing IIb,[5] IIa was prepared by the reaction of cyanamide with *O,S*-dimethyl dithiocarbonate in the presence of potassium hydroxide in ethanol. The yield was 40%, and the melting point was 192—195 °C (dp).

Reaction of I with N*-Chloroamidines.* *N*-Chloroamidine reacted exothermically with I in chloroform below 5 °C. After 1—2 h, an active chlorine disappeared and TDZ were formed. In the case of NCB, the yield of the TDZ increased when the solvent was acetonitrile. The structures of the TDZ, IIIa—d, were confirmed by means of elemental analyses and by studies of the IR and mass spectra. The results are summarized in Table 1.

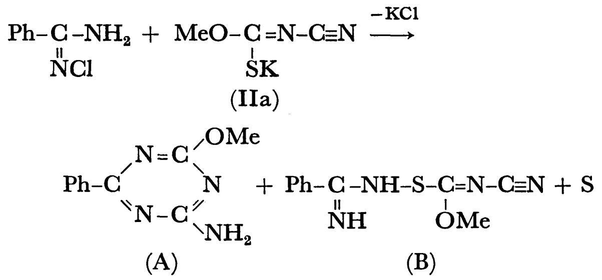
TABLE 1. PREPARATION OF TDZ FROM I AND *N*-CHLQOOAMIDINES



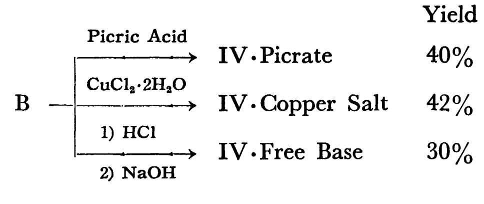
TDZ No	TDZ R	Solvent	Reaction time (min)	Yield (%)
IIIa	Ph	$CHCl_3$	100	64
IIIa	Ph	MeCN	50	76
IIIb	*p*-tol	$CHCl_3$	120	58
IIIc	Bzl	$CHCl_3$	110	57
IIId	Me	$CHCl_3$	180	58



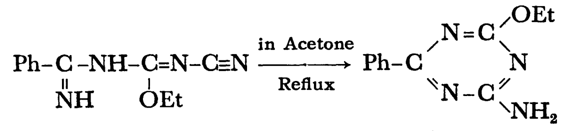
Reaction of IIa and IIb with N*-Chloroamidines.* NCB and IIa reacted readily in chloroform at 10—15 °C. After about 1 h, the active chlorine disappeared and an oily material was obtained instead of the TDZ. A small amount of a crystal (A), the oily material (B), and sulfur could be separated from it.



The A product was 2-amino-4-methoxy-6-phenyl-1,3,5-triazine, whose structure was determined by the elemental analysis and by a study of its IR spectrum, in which the characteristic absorption of 1,3,5-triazine ring was observed at 830 cm^{-1}. The other product, B, which contained sulfur and showed a strong absorption of a nitrile group at 2200 cm^{-1} in the IR spectrum, was supposed to be the open-chain intermediate to the TDZ, the ring closure of B was attempted by acid catalysis. Expectedly, TDZ (IV) could be obtained as corresponding salts by the treatment of B at room temperature using hydrochloric acid, picric acid, and copper (II) chloride.

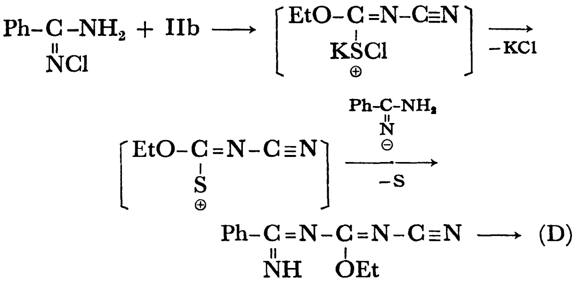


The reaction of NCB with IIb was likewise examined using various kinds of solvents. As is shown in Table 2, a remarkable solvent effect was observed. In dichloromethane, the products were a TDZ (Va) and C, whose IR spectrum showed the absorption of a nitrile group at 2200 cm^{-1}. Only 2-amino-4-ethoxy-6-phenyl-1,3,5-triazine (D) was formed in acetonitrile and ethyl acetate, while C was the sole product in acetone. C was *N*-benzimidoyl-*N'*-cyano-*O*-ethylisourea, whose structure was confirmed by means of elemental analysis, by studies of the IR and mass spectra, and also by the following reaction. C, which was stable at room temperature, was converted into 1,3,5-triazine under reflux in acetone.



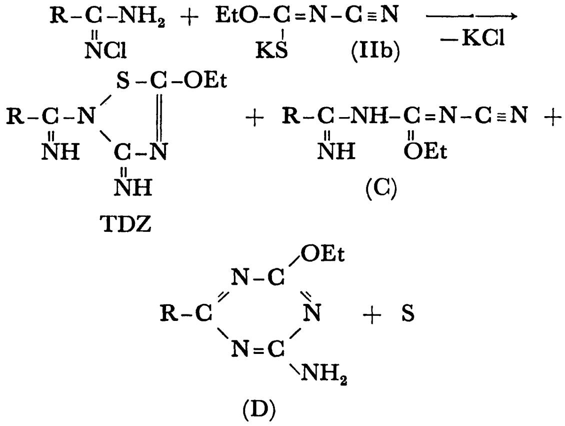
(C) (D) quant.

Thus, it was found that desulfurization took place completely in the above three solvents. On the other hand, no desulfurization was observed in the case of *N*-chloroacetamidine, and the corresponding TDZ (Vb) was obtained in a low yield. This desulfurization may occur by means of the oxidation with a positive chlorine from NCB and may be accelerated in polar solvents.



(C)

Table 2. Reaction of IIb with *N*-chloroamidines



(IIb) TDZ (C) (D)

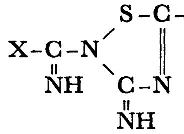
R	Solvent	Reaction time (min)[a]	Product (%)			
			TDZ	C	D	S
Ph	CH_2Cl_2	60 (40)	47	18	—	+
	AcOEt	90 (60)	—	—	62	++
	MeCN	35 (15)	—	—	78	++
	Me_2CO	60 (40)	—	98	—	++
Me	MeCN	270	38	—	—	—

a) Active chlorine disappeared.

The decay time of an active chlorine decreased considerably in acetonitrile, as is shown in Table 2.

The TDZ derivatives thus prepared are mono acidic bases, and their basicity is weaker than that of the starting compounds, amidino compounds. Therefore, a TDZ ring seems to be an electron-withdrawing group. A copper salt, whose color is blue or green, is formed from TDZ and copper (II) chloride, but its structure has not yet been established. The physical properties and analytical data of TDZ and the copper salts are summarized in Tables 3 and 4.

Table 3. Physical properties and analytical data of TDZ



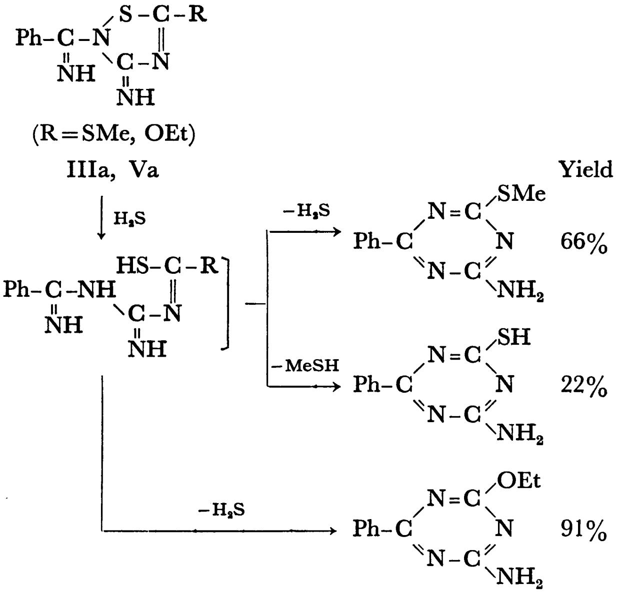
No.	X	Y	Free base Mp (°C)	Found (Calcd) % C	H	N	UV Spectra $\lambda_{max}^{H_2O}$ ($\varepsilon \times 10^{-4}$)	Picrate Mp (°C)	Found (Calcd) % C	H	N
IIIa	Ph	SMe	138—139	47.68 (47.98)	3.87 (4.03)	22.56 (22.38)	256 (3.2)	192—194 (Dp)	40.08 (40.09)	2.62 (2.73)	20.19 (20.46)
IIIb	*p*-tol	SMe	181—182	49.78 (49.98)	4.51 (4.58)	21.19 (21.19)	263 (3.5)	204—205 (Dp)	41.53 (41.39)	2.94 (3.06)	19.57 (19.87)
IIIc	Bzl	SMe	148—149 (Dp)	49.80 (49.98)	4.45 (4.58)	20.85 (21.18)	247 (2.8)	183—185	41.55 (41.39)	2.95 (3.06)	19.52 (19.87)
IIId	Me	SMe	155—158	31.63 (31.90)	4.22 (4.28)	29.59 (29.76)	243 (2.3)	—	—	—	—
IV	Ph	OMe	124—128	51.08 (51.27)	4.32 (4.30)	23.51 (23.91)	278 (1.3)	183—185	41.91 (41.47)	2.64 (2.83)	21.29 (21.16)
Va	Ph	OEt	138—139	52.74 (53.21)	4.70 (4.87)	22.38 (22.56)	278 (1.2)	193—195	42.98 (42.77)	3.08 (3.19)	20.22 (20.54)
Vb	Me	OEt	80— 81	36.76 (36.91)	5.36 (5.68)	28.29 (28.70)[a]	271 (0.9)	148—149	34.53 (34.70)	3.15 (3.15)	23.65 (23.61)

a) Calcd for $C_6H_4N_4SO \cdot 1/2\ H_2O$: S content 16.75% (16.42%).

TABLE 4. PHYSICAL PROPERTIES AND ANALYTICAL DATA OF COPPER SALTS OF TDZ
TDZ·$CuCl_2$·$(H_2O)_n$

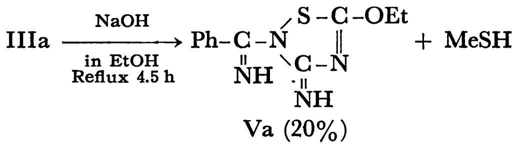
TDZ No.	Dp (°C)	Color	n	N Found (Calcd %)
IIIa	246	Yellowish green	1	13.89(13.89)
IIIb	253	Green	1	13.40(13.47)
IIIc	172—174	Dark blue	2	12.86(12.91)
IV	266	Green	1	14.46(14.48)
Va	270	Blue	2	13.46(13.40)

TDZ was readily cleft at the N–S link by hydrogen sulfide, and the elimination of methanethiol or hydrogen sulfide from the intermediate gave 1,3,5-triazines. Although 5-methylthio-TDZ gave two kinds of 1,3,5-triazines, 5-ethoxy-TDZ gave only one kind of 1,3,5-triazine.

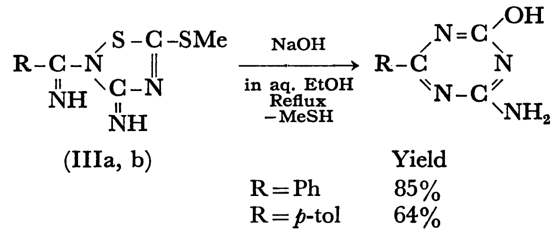


The low stability of TDZ seems to be related to its structure, in which the aromatic character is absent.

5-Methylthio-TDZ, IIIa was treated with ethanolic sodium hydroxide to give 5-ethoxy-TDZ, Va in a low yield.



We found that the ring cleavage of TDZ by alkaline hydrolysis gave rise to 1,3,5-triazine, also. The TDZ were refluxed with sodium hydroxide in aqueous alcohol to give 2-amino-1,3,5-triazin-ol in high yields.



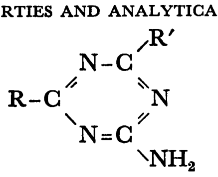
However, the detailed mechanism of the transformation has not yet been made clear.

The physical properties and analytical data of 1,3,5-triazines are summarized in Table 5.

Experimental

Materials. Potassium Methyl Cyanoiminodithiocarbonate (I): To a stirred solution of cyanamide (8.40 g, 20 mmol) and potassium hydroxide (22.40 g, 40 mmol) in water–acetone (60—30 ml), we gradually added, drop by drop, carbon disulfide (15.20 g, 20 mmol) at 0—5 °C. After the addition, the mixture was stirred at room temperature for 1.5 h; it was cooled below 5 °C again, and then methyl iodide was added, drop by drop. After the addition, the mixture was stirred at room temperature for 2 h. The residue obtained by the removal of the solvent was extracted with hot ethanol (80 ml). After the extract had been concentrated under reduced pressure, the crude product of I was obtained (24 g, 71%). Re-

TABLE 5. PHYSICAL PROPERTIES AND ANALYTICAL DATA OF 1,3,5-TRIAZINES



R	R′	Free base Mp (°C)	Free base Found (Calcd) % C	H	N	Picrate Mp (°C)	Picrate Found (Calcd) % C	H	N
Ph	MeO	161—164	57.10 (56.86)	5.07 (5.25)	26.63 (26.53)[a]	—	—	—	—
Ph	EtO	153—154	58.93 (58.68)	5.89 (5.78)	24.89 (24.88)[b]	193—195	45.66 (45.85)	3.30 (3.40)	22.04 (22.02)
Ph	OH	327—328 (320—321)[b] (dp)	57.53 (57.44)	4.24 (4.28)	30.09 (29.77)	278—280	43.27 (43.17)	2.62 (2.66)	23.52 (23.50)
p-tol	OH	320 (dp)	59.03 (59.40)	4.91 (4.98)	27.72 (27.71)	295 (Dp)	44.11 (44.56)	3.02 (3.04)	22.53 (22.73)

a) Calcd for $C_{10}H_{10}N_4O \cdot 1/2H_2O$. b) Calcd for $C_{11}H_{12}N_4O \cdot 1/2H_2O$.

crystallization from ethanol gave pure I; mp 213—214 °C (214—216 °C).[7]

Potassium Methoxythiocarbonylcyanamide (IIa): According to the method of preparing potassium ethoxythiocarbonylcyanamide (IIb),[5] IIa was prepared by the reaction of cyanamide with *O*,*S*-dimethyl dithiocarbonate and potassium hydroxide in ethanol. Two recrystallizations from ethanol gave pure IIa (yield 40%, dp 192—195 °C). Found: C, 23.30; H, 1.96; N, 18.14%. Calcd for $C_3H_3N_2OSK$: C, 23.36; H, 1.96; N, 18.16%.

The *N*-chloroamidines were prepared by a previously described method.[8]

Reaction of I with N-*Chloroamidines.* *2-Benzimidoyl-3-imino-5-methylthio-TDZ (IIIa)*: To a stirred suspension of I (3.40 g, 20 mmol) in acetonitrile (20 ml), we gradually added a solution of NCB (3.09 g, 20 mmol) in acetonitrile (20 ml), the temperature being kept below 10 °C. After about 50 min of continued stirring, the solvent was removed by distillation under reduced pressure. The titled compound was obtained by washing the residue with water to remove potassium chloride; 3.78 g, 76%, mp 129—135 °C. Pure IIIa: mp 138—139 °C (from acetone). The above reaction, when carried out in chloroform by a similar method, gave IIIa in a 64% yield.

*2-*p*-Toluimidoyl-3-imino-5-methylthio-TDZ (IIIb)*: To a stirred mixture of I (5.95 g, 35 mmol) and chloroform (55 ml) we gradually added, drop by drop, a solution of *N*-chloro-*p*-toluamidine (5.90 g, 35 mmol) in chloroform (55 ml). After about 2 h of continued stirring, the active chlorine disappeared and potassium chloride was precipitated. After the salt had been removed by filtration, the filtrate was concentrated. When the residue was washed with a small amount of acetone, 4.90 g of crude IIIb remained; 53%, mp 181—182 °C. Recrystallization from acetone gave pure IIIb; mp 181—182 °C. To the washings, we added a methanolic solution of copper (II) chloride. The copper salt of IIIb thus precipitated was collected by filtration; dp 253 °C. The yield was 5%.

Similarly, reactions with other *N*-chloroamidines were carried out.

Reaction of IIa with NCB. *Cyclization by Picric Acid*: To a stirred suspension of IIa (4.62 g, 30 mmol) in chloroform (40 ml), we added, drop by drop, a solution of NCB (4.62 g, 30 mmol) in chloroform (20 ml). After 1 h of stirring, the reaction mixture was poured into water (25 ml). The organic layer was separated, and then the aqueous layer was extracted twice with 5 ml portions of chloroform. After the combined chloroform extracts had been dried over sodium sulfate, filtered off, and concentrated under reduced pressure, an oily material remained. On standing for 5 days at room temperature, part of 2-amino-4-methoxy-6-phenyl-1,3,5-triazine (A) crystallized out of the oil. On the addition of a small amount of ethyl acetate, the resulting A was separated by filtration (0.83 g, 13%). The oily product (B) obtained by the concentration of the filtrate was dissolved in ether, and a saturated ethereal solution of picric acid was added. The picrate of 2-benzimidoyl-3-imino-5-methoxy-TDZ (IV) thus precipitated was collected and recrystallized from water; mp 183—185 °C. The yield was 5.53 g (40%). When A was recrystallized from methanol, a small amount of sulfur was separated. Purified A; mp 161—164 °C.

Cyclization by Copper(II) Chloride: A (0.80 g, 13%) and B were obtained by the same procedure as above. The copper salt of IV was precipitated on the addition of a methanolic solution of copper(II) chloride ($CuCl_2 \cdot 3H_2O$) to a methanolic solution of B. The yield was 4.83 g (42%); dp 266 °C.

Cyclization by Hydrochloric Acid: To a methanolic solution of A, we added 15 ml of 2 M hydrochloric acid, and then the mixture was stirred for 20 min at room temperature. After the addition of 2 M sodium hydroxide to make the reaction mixture neutral, the methanol was almost entirely removed by concentration. The oily material thus obtained was left for a while, whereupon, crystals (IV) were obtained as a free base. The yield was 2.11 g (30%); mp 124—128 °C (from acetone-water).

Reaction of IIb with NCB. *The Reaction in Dichloromethane*: To a stirred suspension of IIb (10.08 g, 60 mmol) in dichloromethane (60 ml), we added, drop by drop, a solution of NCB (9.27 g, 60 mmol) in dichloromethane (60 ml) below 10 °C. After about 1 h of continued stirring, the reaction mixture was poured into 30 ml of water; then sulfur was separated. The organic layer was separated, and the aqueous layer was extracted twice with 10 ml portions of dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and concentrated. To the residual oily material, we added a small amount of ethyl acetate and rubbed the sirup with a grass rod. The resulting crystals were filtered off and recrystallized from ethanol to give 2-benzimidoyl-3-imino-5-ethoxy-TDZ (Va); mp 138—139 °C. The yield was 6.16 g (41%). The filtrate and mother liquor were then combined, and an ethanolic solution of copper(II) chloride was added. The copper salt of Va thus precipitated was collected by filtration (1.50 g, 6%, dp 270 °C). By removing the copper from the filtrate, 2-amino-4-ethoxy-6-phenyl-1,3,5-triazine (D) was obtained; 2.34 g (18%); mp 153—154 °C (from ethanol).

The Reaction in Acetonitrile: The reaction (15 mmol scale) in 30 ml of acetonitrile was carried out according to the same procedure. Desulfurization occurred at the time of the addition of NCB, and after about 15 min the active chlorine disappeared. The insoluble matter was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. D was obtained by washing the residual crystals with ether: 2.37 g, 73%, mp 153—156 °C. To the washings, we added a saturated ethereal solution of picric acid. The picrate of D was thus precipitated; 0.37 g (5%), dp 193 °C. The total yield was 78%.

The reaction in ethyl acetate was carried out similarly.

The Reaction in Acetone-Formation of N-*Benzimidoyl*-N′-*cyano*-O-*ethylisourea (C)*: According to the same procedure, the reaction (17 mmol scale) in acetone (34 ml) was carried out. The insoluble matter was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue, C, was washed with petroleum ether and a small amount of ether. The yield of C was 3.60 g (98%); mp 120 °C. Recrystallization from ethanol gave pure C; mp 125—126 °C. IR spectrum (cm^{-1}): 3200, 3300 (νNH); 2200 (νC≡N); 1600 (νC=N). Found: C, 60.93; H, 5.58; N, 25.41%. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91%.

Reaction of IIb with N-*Chloroacetamidine.* According to the same procedure, a reddish brown reaction mixture was obtained. The insoluble matter was removed by filtration, and the concentration of the filtrate afforded a reddish brown oily material, which was then dissolved in hot water and treated with charcoal. The addition of a saturated aqueous solution of picric acid to it afforded the picrate of 2-acetimidoyl-3-imino-5-ethoxy-TDZ (Vb). The yield was 7.93 g (38%); mp 144—148 °C. Recrystallization from water gave pure Vb; mp 148—149 °C. The free base of Vb was obtained by the treatment of the picrate with concd hydrochloric acid; mp 80—81 °C (from dichloromethane–petroleum ether).

Reduction of TDZ by Hydrogen Sulfide. *Reduction of IIIa*: Hydrogen sulfide was passed through a solution of IIIa (2.00

g, 8 mmol) in ethanol–chloroform (40—40 ml). The solution was left at room temperature for about 1 h and the resulting precipitate (P-1) was separated by filtration. After the filtrate had been evaporated to dryness, the residual yellowish crystals were dissolved in 5% ammonium hydroxide (20 ml), and then the insoluble matter was removed by filtration. The filtrate was neutralized with 3 M acetic acid, and the precipitate (P-1) was separated by filtration. The matter insoluble in ammonium hydroxide was extracted with hot ethanol (20 ml), and the residual sulfur was removed by filtration. After cooling, the precipitate (P-2) was obtained. P-1 was 2-amino-4-mercapto-6-phenyl-1,3,5-triazine; yield 0.36 g (22%); dp 278 °C (from DMF–water). P-2 was 2-amino-4-methylthio-6-phenyl-1,3,5-triazine; 1.15 g, 66%, mp 170—172 °C (from acetone).

Reduction of Va: In the same way, hydrogen sulfide was passed through. The precipitated sulfur was removed by filtration, and the filtrate was evaporated to dryness. The recrystallization of the residue from ethanol gave pure D; 91%, mp 153—154 °C.

Reaction of IIIa with Potassium Hydroxide in Ethanol. IIIa (2.50 g, 10 mmol) and potassium hydroxide were refluxed in ethanol (20 ml) for 4.5 h. Methanethiol was evolved and an insoluble matter was precipitated after about 1 h of reflux. The unidentified precipitate was removed by filtration, and the concentration of the filtrate gave an oily material. It was dissolved in chloroform; the subsequent removal of an insoluble matter by filtration and the concentration of the filtrate gave a sirup. It was solidified by treatment with a small amount of ether, and the solid was collected by filtration. Two recrystallizations from ethanol gave Va; 0.23 g (9%). The addition of a saturated ethereal solution of picric acid to an ethereal solution of the filtrate gave the picrate of Va; 0.51 g (11%). The total yield of Va was 20%. A mixed-melting-point determination with the authentic sample prepared from IIb and NCB showed no depression.

Reaction of IIIa with Sodium Hydroxide in Aqueous Ethanol. A mixture of IIIa (2.50 g, 10 mmol) and 3 M sodium hydroxide (30 ml)–ethanol (30 ml) was refluxed for 1.5 h. TDZ, IIIa was thus gradually dissolved, with the evolution of methanethiol. When the reaction mixture was evaporated under reduced pressure to remove almost all the ethanol and was neutralized with 3 M hydrochloric acid, the resulting precipitate, 2-amino-4-hydroxy-6-phenyl-1,3,5-triazine, was filtered out; yield, 1.60 g (85%): dp 327—328 °C (from DMF–ethanol).

Reaction of IIIb with Sodium Hydroxide in Aqueous Ethanol. 2-Amino-4-hydroxy-6-*p*-tolyl-1,3,5-triazine was obtained by a similar method. The yield was 64%, dp 327—329 °C (from DMF–water).

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