STUDIES IN THE FIELD OF 2,1,3-THIA- AND -SELENADIAZOLES

LI. Amination of Chloronitrobenzo-2,1,3-thiadiazoles*

V. G. Pesin, V. A. Sergeev, and M. G. Nikulina

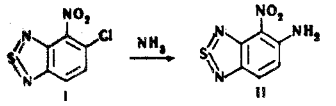
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 2, pp. 249–253, 1968

UDC 547.794.543.422

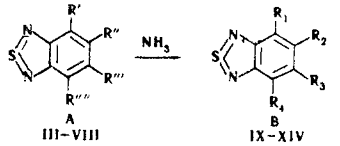
The thiadiazole ring activates a chlorine atom in the ortho or para positions with respect to the nitro group in the nucleophilic amination of chloronitrobenzo-2,1,3-thiadiazoles. The action of ammonia on a chlorobenzo-2,1,3-thiadiazole activated by a nitro group in ethylene glycol readily leads to the replacement of the chlorine by an amino group. The resulting aminonitrobenzo-2,1,3-thiadiazoles have been reduced to the corresponding diamines and these have been converted into pyrazine, quinoxaline, thiadiazole, and acetic acid derivatives.

It has been shown previously [2, 3] that the thiadiazole ring, by drawing off electrons from a benzene ring, favors nucleophilic exchange reactions. In the present work we studied the reaction of chloronitrobenzo-2,1,3-thiadiazoles with ammonia.

When ammonia was passed into a solution of 5-chloro-4-nitro-2,1,3-thiadiazole (I) in boiling ethylene glycol for 10-15 min, a high yield of 5-amino-4-nitro-2,1,3-thiadiazole (II) was obtained.



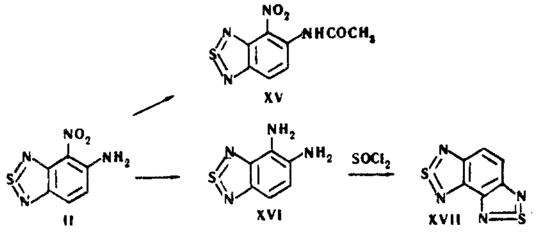
Under analogous conditions, 7-chloro-4-nitro-, 4-chloro-5, 7-dinitro-, 4,7-dichloro-5-nitro-, 5,7-dichloro-4-nitro, 5,6-dichloro-4-nitro-, and 4,6-chloro-5,7-dinitrobenzo-2,1,3-thiadiazoles (III-VIII) are converted in high yields into 7-amino-4-nitro-, 4-amino-5,7-dinitro-, 4-amino-7-chloro-5-nitro-, 5-amino-7-chloro-4-nitro-, 5-amino-6-chloro-4-nitro-, and 4,6-diamino-5,7-dinitrobenzo-2,1,3-thiadiazoles (IX-XIV), respectively.



A—B

R′	R″	R‴	R⁗	R_1	R_2	R_3	R_4
NO_2	H	H	Cl	NO_2	H	H	NH_2
Cl	NO_2	H	NO_2	NH_2	NO_2	H	NO_2
Cl	NO_2	H	Cl	NH_2	NO_2	H	Cl
NO_2	Cl	H	Cl	NO_2	NH_2	H	Cl
NO_2	Cl	Cl	H	NO_2	NH_2	Cl	H
Cl	NO_2	Cl	NO_2	NH_2	NO_2	NH_2	NO_2

o-Nitrobenzene, p-chloronitrobenzene, and 2,5-dichloronitrobenzene do not react with ammonia under analogous conditions. This comparison clearly shows the activating influence of the thiadiazole ring on nucleophilic exchange reactions. The aminonitro derivative II was converted into the acetylamino derivative XV and 4,5-diaminobenzo-2,1,3-thiadiazole (XVI); the latter was converted with thionyl chloride in pyridine into 4,5-(2′,1′,3′-thiadiazolo)benzo-2,1,3-thiadiazole (XVII).



---

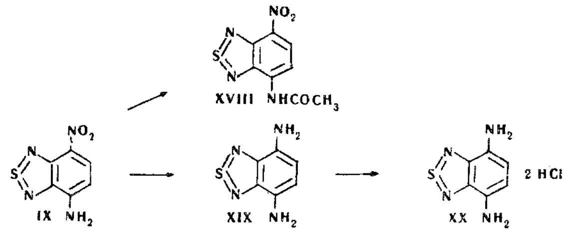
*For communication L, see [1].

Products of the Amination of Chloronitrobenzo-2,1,3-thiadiazoles

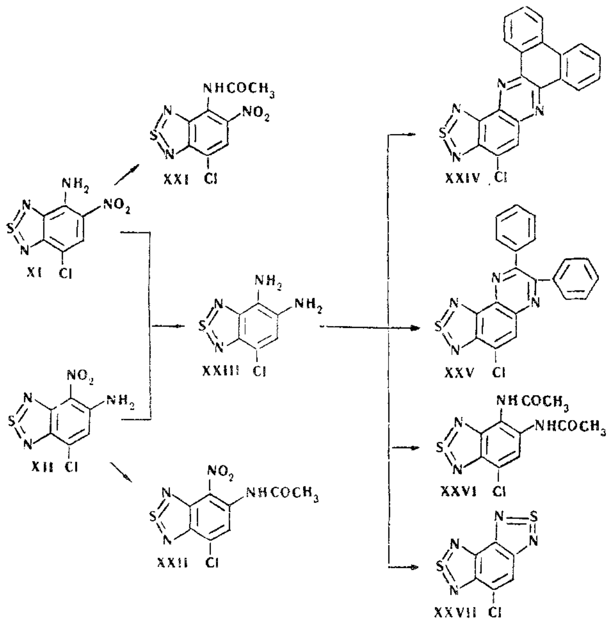
Initial chloronitrobenzo-2,1,3-thiadiazole, g	Ethylene glycol, ml	Compound obtained, g	Color of the crystals, mp, °C, solvent for crystallization	Empirical formula	S, %		Yield, %
					found	calculated	
I; 3.20	20	II; 2.55	Yellow-green, 280–281[1*], ethylene glycol				87.6
III; 3.20	10	IX; 2.50	Dark yellow 300 (decomp), nitrobenzene	$C_6H_4N_4O_2S$[2*]	15.84 19.97	16.33	86.2
IV; 2.00	20	X; 1.66	Dark yellow, 228–229[3*], ethylcellosolve				90,0
V; 2.50	40	XI; 1.95	Yellow, 228–230, ethylene glycol	$C_6H_3ClN_4O_2S$[4*]	13.71 13.75	13.88	85.0
VI; 2.82	20	XII; 2.33	Yellow-green, 282 (decomp.), 50% ethanol	$C_6H_3ClN_4O_2S$	13.44 13.27	13.88	91.0
VII; 2.16	20	XIII; 1.75	Yellow-green, 204–205, 30% acetic acid	$C_6H_3ClN_4O_2S$	13.95 14.00	13.88	88.0
VIII; 0.75	20	XIV; 0.60	Brown, >300, diethyleneglycol	$C_6H_4N_6O_4S$[5*]	12.43 12.50	12.50	92.0

[1*] A mixture with authentic 5-amino-4-nitrobenzo-2,1,3-thiadiazole [2, 3] gave no depression of the melting point. [2*] Found, %: N 28.62, 28.78. Calculated, %: N 28.56. [3*] A mixture with authentic 4-amino-5,7-dinitrobenzo-2,1,3-thiadiazole [3] gave no depression of the melting point. [4*] Found, %: Cl 14.90, 15.46. Calculated, %: Cl 15.40. [5*] Found, %: N 33.30, 33.35. Calculated, %: N 38.21.

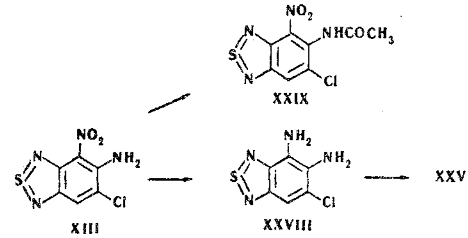
The aminonitro derivative **IX** was converted into the acetylamino derivative **XVIII** and into 4,7-diaminobenzo-2,1,3-thiadiazole, the base **XIX**, and the hydrochloride **XX**:



The aminonitrobenzothiadiazoles **XI** and **XII** were converted, respectively, into the acetylamino derivatives **XXI** and **XXII** and into 4,5-diamino-7-chlorobenzo-2,1,3-thiadiazole (**XXIII**); the latter by reaction with phenanthrenequinone, benzil, acetic anhydride, and thionyl chloride yielded, respectively, the pyrazine, acetic acid, and thiadiazole derivatives **XXIV–XXVII**.



Compound **XXVII** was also obtained from the isomeric 4,5-diamino-6-chlorobenzo-2,1,3-thiadiazole (**XXVIII**) which, in its turn, was obtained by reduction of the aminonitrobenzothiadiazole (**XIII**); the action of acetic anhydride on the latter gave the acetyl derivative **XXIX**.



EXPERIMENTAL

Starting materials. 5-Chloro-4-nitro- and 5, 7-dichloro-4-nitrobenzo-2, 1, 3-thiadiazoles (I and VI) were obtained as described previously [4]. 7-Chloro-4-nitro-, 4-chloro-5, 7-dinitro-, and 4, 7-dichloro-5-nitrobenzo-2, 1, 3-thiadiazoles (III–V) were also obtained by methods described previously. The preparation of 5, 6-dichloro-4-nitro and 4, 6-dichloro-5, 7-dinitrobenzo-2, 1, 3-thiadiazoles (VII and VIII) has also been described previously [1].

Amination of the chloronitrobenzo-2, 1, 3-thiadiazoles. Ammonia was passed into a solution of a chloronitrobenzo-2, 1, 3-thiadiazole in boiling ethylene glycol at 180–200° C for 10–15 min (the solution rapidly darkened). After cooling, the reaction mixture was diluted with an equal volume of water, and the precipitate was filtered off, washed with water, dried, and recrystallized from a suitable solvent (see table).

4, 5-Diaminobenzo-2, 1, 3-thiadiazole (XVI). a) Ten grams of 10% solution of sodium hydrogen sulfide was added to a suspension of 0.5 g of 5-amino-4-nitrobenzo-2, 1, 3-thiadiazole (II) in 10 ml of water and the mixture was boiled until a clear red solution had been formed. This was cooled and the red crystals that deposited were filtered off and washed with a small amount of water. Yield 0.25 g (60%), mp 168–170° C; a mixture with an authentic sample [6] gave no depression of the melting point.

b) With stirring, a solution of 30 g of potassium hydroxide in 100 ml of ethanol was gradually added to a mixture of 6 g of 5-nitrobenzo-2, 1, 3-thiadiazole, 15 g of hydroxylamine hydrochloride, and 100 ml of ethanol; the mixture was stirred for 1 hr, 400 ml of water was added, it was heated to 70° C, and 60 g of sodium dithionite was added in portions. After heating to the boil, the mixture was cooled and extracted with dichloroethane, and subsequent distillation of the solvent yielded 3.85 g of a substance (70%, calculated on the 5-nitrobenzo-2, 1, 3-thiadiazole) showing no depression of the melting point in admixture with that obtained by method (a).

4-Acetylamino-7-chloro-5-nitrobenzo-2, 1, 3-thiadiazole (XXI). Two drops of concentrated sulfuric acid was added to a suspension of 0.9 g of 4-amino-7-chloro-5-nitrobenzo-2, 1, 3-thiadiazole (XI) in 10 ml of acetic anhydride at 100° C, with stirring, and the solid matter rapidly dissolved. After cooling, the reaction mixture was diluted with an equal volume of water. The crystals that deposited were filtered off, washed with water, and dried. Yield 0.74 g (72%). After recrystallization from 50% acetic acid, mp 210–212° C. Found, %: Cl 12.70, 12.96; S 11.63, 11.64. Calculated for $C_8H_5ClN_4O_3S$, %: Cl 13.03; S 11.74.

5-Acetylamino-6-chloro-4-nitrobenzo-2, 1, 3-thiadiazole (XXIX) was obtained from 0.2 g of 5-amino-6-chloro-4-nitrobenzo-2, 1, 3-thiadiazole (XIII) in a similar manner to compound **XXI**. The yield was 0.18 g (78.5%). After recrystallization from 50% methanol, yellow crystals with mp 104–105° C. Found, %: S 11.41, 11.46. Calculated for $C_8H_5ClN_4O_3S$, %: S 11.74.

5-Acetylamino-7-chloro-4-nitrobenzo-2, 1, 3-thiadiazole (XXII) was obtained from 0.4 g of 5-amino-7-chloro-4-nitrobenzo-2, 1, 3-thiadiazole (XII) in a similar manner to compound **XXI**. Yield 0.35 g (74.5%). After recrystallization from 50% ethanol, lustrous light brown crystals with mp 183–185° C. Found, %: S 11.13, 11.30. Calculated for $C_8H_5ClN_4O_3S$, %: S 11.74.

5-Acetylamino-4-nitrobenzo-2, 1, 3-thiadiazole (XV) was obtained from 1 g of 5-amino-4-nitrobenzo-2, 1, 3-thiadiazole (II) in a similar manner to compound **XXI**. Yield 0.97 g (80%). After recrystallization from water, colorless crystals with mp 145–147° C. A mixture with an authentic sample of XV [6] gave no depression of the melting point. Found, %: S 13.63, 13.71. Calculated for $C_8H_6N_4O_3S$, %: S 13.44.

4-Acetylamino-7-nitrobenzo-2, 1, 3-thiadiazole (XVIII) was obtained from 1 g of 4-amino-7-nitrobenzo-2, 1, 3-thiadiazole (IX) in a similar manner to compound **XXI**. Yield 0.97 g (80%). After recrystallization from ethanol, yellow crystals with mp ~180° C. A mixture with an authentic sample [6] gave no depression of the melting point.

4, 5-(2', 1', 3'-Thiadiazolo)benzo-2, 1, 3-thiadiazole (XVII). With stirring, a solution of 5 ml of thionyl chloride in 3 ml of chloroform was added to a solution of 1 g of 4, 5-diaminobenzo-2, 1, 3-thiadiazole (XVI) in 5 ml of pyridine and 17 ml of chloroform. After 15 minutes' heating in the boiling water bath, the reaction mixture was evaporated to dryness and the residue was treated with 15 ml of cold water. The gray precipitate was filtered off, washed with water, and dried. Yield 1.16 g (100%). After recrystallization from water, colorless needles, mp 173–175° C, giving no depression of the melting point in admixture with an authentic sample [6].

4, 5-Diacetylamino-7-chlorobenzo-2, 1, 3-thiadiazole (XXVI). A mixture of 1.37 g of 4, 5-diamino-7-chlorobenzo-2, 1, 3-thiadiazole

(XXIII) in 4 ml of acetic anhydride was heated in the boiling water bath for 5 min, and then 10 ml of water was added and it was heated to the boil and cooled. The yellow precipitate that deposited was filtered off and dried. Yield 1.29 g (66.4%). After recrystallization from methylcellosolve it formed a yellow powder with mp 232–233° C sparingly soluble in water. Found, %: Cl 11.82; S 11.54. Calculated for $C_{10}H_9ClN_4O_2S$, %: Cl 12.48, S 11.25.

4, 5-(2', 3'-Diphenylpyrazino-5', 6')-7-chlorobenzo-2, 1, 3-thiadiazole (XXV). With stirring, a solution of 0.5 g of benzil in 4 ml of ethanol was added to a solution of 0.5 g of 4, 5-diamino-7-chlorobenzo-2, 1, 3-thiadiazole (XXIII) in 6 ml of ethanol; then 50 ml of water was added and the mixture was heated to the boil and cooled, and the gray-green precipitate that had deposited was filtered off, washed with water, and dried. Yield 0.7 g (77.8%) in the form of a brown powder with mp 221° C; after a benzene solution had been passed through activated alumina and the eluate had been evaporated, it formed lemon-yellow crystals with mp 225–227° C sparingly soluble in water and giving a red color in concentrated sulfuric acid. Found, %: N 15.18, 15.18; S 8.59, 8.62. Calculated for $C_{20}H_{11}ClN_4S$, %: N 14.95; S 8.54.

4, 5-(5', 6', 7', 8'-Dibenzoquinoxalino-2', 3')-7-chlorobenzo-2, 1, 3-thiadiazole (XXIV). A solution of 0.96 g of phenanthrenequinone in 96 ml of acetic acid was added to a solution of 1.03 g of 4, 5-diamino-7-chlorobenzo-2, 1, 3-thiadiazole (XXIII) in 10 ml of acetic acid. The yellow-green precipitate that deposited was filtered off, washed with acetic acid, and dried. Yield 1.39 g (72.2%). After recrystallization from nitrobenzene and washing with ethanol it formed a light brown powder with mp 338° C which was subjected to additional purification by the passage of a benzene solution through activated alumina and evaporation of the eluate to dryness. The residue consisted of lemon-yellow crystals with mp 340° C sparingly soluble in water, ethanol, and pyridine; in concentrated sulfuric acid they became crimson. Found, %: Cl 9.67, 9.84; S 8.50, 8.58. Calculated for $C_{20}H_9ClN_4S$, %: Cl 9.53; S 8.59.

4, 5-(2', 1', 3'-Thiadiazolo)-6(7)-chlorobenzo-2, 1, 3-thiadiazole (XXVII). A solution of 1 g of 4, 5-diamino-6-chloro- (XXVIII) or 4, 5-diamino-7-chlorobenzo-2, 1, 3-thiadiazole (XXIII) in 4 ml of pyridine was carefully treated with 2 ml of thionyl chloride.

The reaction mixture was heated in the boiling water bath for 5 min, cooled, diluted with an equal volume of water, and acidified with concentrated hydrochloric acid; the yellow-brown precipitate that deposited was filtered off, washed with water, and dried. Yield 0.7 g (51%). A toluene solution of the substance obtained was passed through activated alumina and the eluate evaporated to dryness to give colorless lustrous crystals with mp 162.5–163° C. Found, %: Cl 15.33, 15.35; S 27.83, 27.92. Calculated for $C_6HClN_4S_2$, %: Cl 15.54; S 28.01.

4, 7-Diaminobenzo-2, 1, 3-thiadiazole (XIX). A suspension of 3 g of 4-amino-7-nitrobenzo-2, 1, 3-thiadiazole (IX) in 70 ml of hot water (70–80° C) was treated with 8 g of sodium dithionate, and the mixture was heated to the boil and filtered hot. After cooling, the dark red crystals that deposited from the filtrate were filtered off, washed with water, and dried. Yield 1.5 g (60%). After recrystallization from water, mp 128–130° C. Found, %: N 33.64, 33.67; S 19.03, 19.40. Calculated for $C_6H_6N_4S$, %: N 33.73; S 19.28.

4, 7-Diaminobenzo-2, 1, 3-thiadiazole dihydrochloride (XX). When hydrogen chloride was passed into an ethereal or ethanolic solution of 4, 7-diaminobenzo-2, 1, 3-thiadiazole (XIX), the dihydrochloride was obtained in the form of sand-colored crystals with mp 230° C (decomp) readily soluble in water. Yield 80–90%. Found, %: N 22.97, 23.12; S 13.27, 13.49. Calculated for $C_6H_6N_4S \cdot 2HCl$, %: N 23.43; S 13.38.

4, 5-Diamino-6-chlorobenzo-2, 1, 3-thiadiazole (XXVIII). With stirring, 6.25 g of sodium dithionite was added in portions to 1.15 g of 5-amino-6-chloro-4-nitrobenzo-2, 1, 3-thiadiazole (XIII) and then the mixture was heated to the boil and cooled, and the cherry-red precipitate was filtered off, washed with water, and dried. Dichloroethane extraction of the filtrate yielded a further small amount of dark red substance. The total yield was 0.72 g (55.4%). After recrystallization from water the substance formed a brick-red powder with mp 136–138° C, readily soluble in ethanol. Found, %: N 27.92, 28.14. Calculated for $C_6H_5ClN_4S$, %: N 27.93.

4, 5-Diamino-7-chlorobenzo-2, 1, 3-thiadiazole (XXIII). a) With stirring, 7 g of sodium dithionite was gradually added to 2.3 g of 4-amino-7-chloro-5-nitro- (XI) or 5-amino-7-chloro-4-nitrobenzo-2, 1, 3-thiadiazole (XII) in 35 ml of boiling ethylene glycol, and then 35 ml of water was added. The mixture was heated to the boil, cooled, and diluted with 30 ml of water. The dark red precipitate was filtered off and washed with water. Yield 1.4 g. Chloroform extraction of the filtrate gave another 0.3 g of red powder. The total yield was 1.7 g (85%); mp 177° C (decomp, from water). Found, %: Cl 17.64, 17.77; S 15.94, 15.97. Calculated for $C_6H_5ClN_4S$, %: Cl 17.71; S 15.96.

b) With stirring, 8 g of iron filings and 4.6 g of finely ground 4-amino-7-chloro-5-nitro- (XI) or 5-amino-7-chloro-4-nitrobenzo-2, 1, 3-thiadiazole (XII) were added successively to a boiling solution of 100 ml of 2% acetic acid. After boiling for 5 minutes the mixture was cooled, the solid matter filtered off, and the filtrate extracted with chloroform. Evaporation of the chloroform yielded dark red crystals with mp ~170° C readily soluble in ethanol and sparingly soluble in water. Yield 1.4 g (40%).

REFERENCES

1. V. G. Pesin, V. A. Sergeev, and A. G. Nesterova, KhGS [Chemistry of Heterocyclic Compounds], 95, 1968.
2. V. G. Pesin and A. M. Khaletskii, ZhOKh, **32**, 3284, 1962.
3. V. G. Pesin, A. M. Khaletskii, and V. A. Sergeev, KhOKh, **34**, 261, 1964.
4. V. G. Pesin and A. M. Khaletskii, ZhOKh, **27**, 2599, 1957.
5. V. G. Pesin, A. M. Khaletskii, and V. A. Sergeev, ZhOKh, **33**, 1759, 1963.
6. V. G. Pesin, A. M. Khaletskii, and V. A. Sergeev, ZhOKh, **32**, 181, 1962.

25 April 1966

Leningrad Chemical and
Pharmaceutical Institute