UDC 547.79 + 543.422 + 542.95

SYNTHESIS OF SOME NITRO AND AMINO DERIVATIVES OF 1, 2, 4-TRIAZOLE-5-THIONES AND 1, 2, 4-TRIAZOLES

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 2, No. 1, pp. 117-121, 1966

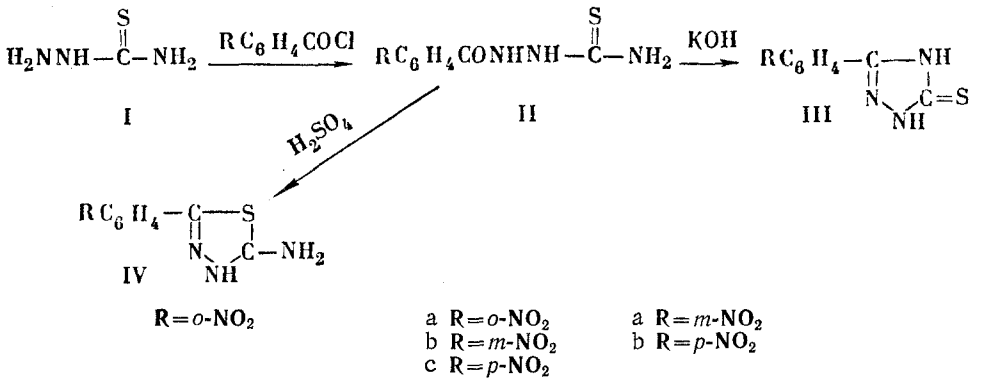
Isomeric 3-(nitrophenyl)-1, 2, 4-triazole-5-thiones are synthesized by cyclizing 1-nitrobenzoylthiosemicarbazides. 1-(4-Nitrophenyl)-1, 2, 4-triazole-3-thione is prepared by condensing 4-(4-nitrophenyl) thiosemicarbazide with formic acid. Oxidation converts the triazolethiones to nitrophenyltriazoles, and the latter are reduced to aminophenyltriazoles.

Aminodiphenyl and its structural analogs containing heterocyclic rings, are characterized by a marked tuberculostatic activity [1, 2]. Compounds in which the aminophenyl group is linked to a triazole ring, evoke a definite interest in that direction.

Continuing research on the connection between structure and tuberculostatic activity of compounds of the triazole series [3], we have synthesized certain isomeric aminophenyl-1, 2, 4-triazoles.

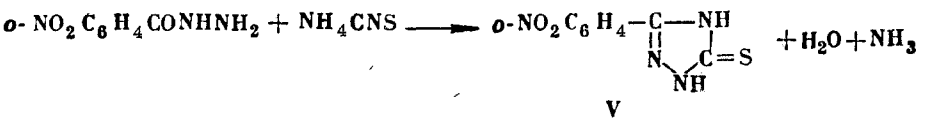
For synthesis of 3-(aminophenyl)-1, 2, 4-triazoles, we used as intermediates the corresponding 3-(nitrophenyl)-1, 2, 4-triazolethiones, from which the sulfur was eliminated by oxidation, and the resultant 3-(nitrophenyl)-1, 2, 4-triazoles were reduced using Adam's platinum catalyst.

3-(3- and 4-Nitrophenyl)-1, 2, 4-triazole-5-thiones (IIIa, b) are synthesized thus:



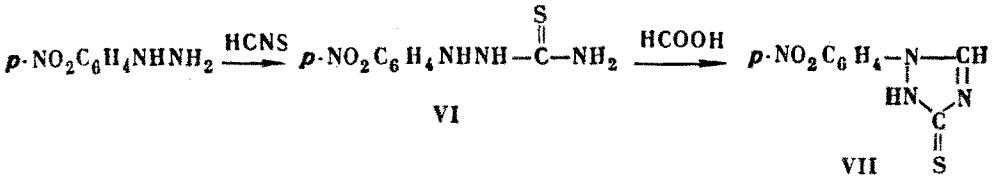
Acylation of thiosemicarbazide I with the acid chlorides of nitrobenzoic acids using the method of [4], gives 1-(2-, 3- and 4-nitrobenzoyl) thiosemicarbazides (IIa, IIb, IIc). Acylsemicarbazides IIb, IIc are further converted to the corresponding triazolethiones (IIa, b) by boiling them with solutions of alkalies. IIa does not give 3-(2-nitrophenyl)-1, 2, 4-triazole-5-thione under those conditions. Use of more concentrated alkali solutions than for the m and p isomers, and increasing the reaction time, leads to decomposition and resinification of the starting compound IIa. It is of interest that in concentrated sulfuric acid IIa readily undergoes thiadiazole ring closure to give 2-amino-5-(2-nitrophenyl-1, 3, 4-thiadiazole (IV).

To prepare 3-(2-nitrophenyl)-1, 2, 4-triazole-5-thione (V), we utilized the reaction between o-nitrobenzohydrazide and ammonium thiocyanate. Such condensations are disclosed in the patent literature [5].

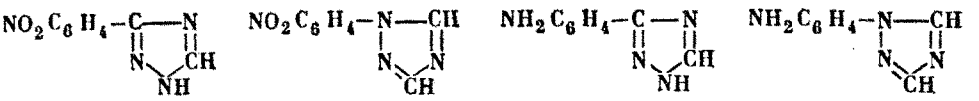


When o-nitrobenzohydrazide and ammonium thiocyanate are fused together at 170-175°, V is formed in 61% yield.

For the biological tests it was important to obtain an aminophenyltriazole minus a mobile hydrogen atom, e.g., 1-(4-aminophenyl)-1, 2, 4-triazole (XI). For this purpose the corresponding triazolethione VII was synthesized as follows:



VI VII



VIII IX X XI

The nitrophenyl-1, 2, 4-triazoles VIII, IX, prepared by oxidizing thiones IIIa, b, V, VII with hydrogen peroxide, were further catalytically reduced to the corresponding amines X, XI (Table 1).

Table 1

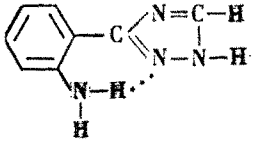
Aminophenyl-1, 2, 4-Triazoles

Compound	Mp, °C (ex H_2O)	Found, %**		
		C	H	N
3-(4-Aminophenyl)-1, 2, 4-triazole	202—203	60.26	4.99	35.04
3-(3-Aminophenyl)-1, 2, 4-triazole	179—180*	60.49	5.08	35.02
3-(2-Aminophenyl)-1, 2, 4-triazole	148	60.08	5.27	34.32
1-(4-Aminophenyl)-1, 2, 4-triazole	142	59.65	5.07	34.45

*Ex EtOH.

**Calculated for $C_8H_8N_4$: C 59.99; H 5.03; N 34.98%.

3-(4-Nitro- and 3-nitrophenyl)-1, 2, 4-triazole-5-thiones (IIIa, b), and 3-(4-nitro- and 3-nitrophenyl)-1, 2, 4-triazoles (VIII), are insoluble in organic solvents of low polarity, but on the other hand, the 2-nitro derivatives of the above compounds are readily soluble even in ether. In all cases it is the ortho isomer which has the lowest melting point. 3-(2-Aminophenyl)-1, 2, 4-triazole is readily soluble in ether, while the corresponding meta and para isomers of X are practically insoluble. In this latter case the behavior of the ortho isomer of X is readily understood, if one considers the ease of formation of an intramolecular hydrogen bond between the hydrogen of the amino group, and a nitrogen atom in



XII

the triazole ring (XII). The red shift [6] of the K band in the UV spectrum of aminophenyltriazoles (Table 2) also indicates this. It is known that mutual conjugation of two aromatic rings leads to formation of a K band ($\pi \rightarrow \pi^*$ transition) in the 240-250 mμ region. The simplest example is diphenyl (absorption band at 251 mμ [7]); 3-phenyl-1, 2, 4-triazole has an absorption band at 241.5 mμ [8].

Introduction of the amino or nitro group at the para position in the benzene ring gives rise to a marked bathochromic shift of this band. With the para, meta, and ortho series of isomers, the band is displaced towards the short wave region (red shift).

Regarding the anomalous solubility of o-nitrophenyl derivatives of triazole VIII and triazolethione V in nonpolar solvents, obviously here reaction of the nitro group with the triazole ring is of a different character, as hydrogen bonding is improbable (7-membered ring). Clarification of the fine structure of these compounds requires additional physical-chemical research.

Table 2

Absorption Bands of Some 1, 2, 4-Triazole Derivatives in the 200-300 mμ Region

Compound	λ_{max}, mμ	ε	λ_{max}, mμ	ε
3-(4-Aminophenyl)-1, 2, 4-triazole	—	—	271	16900
3-(3-Aminophenyl)-1, 2, 4-triazole	—	—	224	23300
3-(2-Aminophenyl)-1, 2, 4-triazole	—	—	216	25100
			310	2800
3-(4-Nitrophenyl)-1, 2, 4-triazole	217	10420	292	14106
3-(3-Nitrophenyl)-1, 2, 4-triazole	—	—	236	21400
3-(2-Nitrophenyl)-1, 2, 4-triazole	—	—	211	13720
3-(4-Nitrophenyl)-1, 2, 4-triazole-5-thione	255	17160	305	8260
3-(4-Nitrophenyl)-1, 2, 4-triazole-5-thione	250	21200	—	—
3-(2-Nitrophenyl)-1, 2, 4-triazole-5-thione	217	22600	250	22000

Experimental

1-(2-Nitrobenzoyl) thiosemicarbazide (II). 54.1 g (0.29 mole) o-nitrobenzoyl chloride was added with stirring and cooling (0°) to 26.6 g (0.29 mole) thiosemicarbazide suspended in 150 ml dry pyridine. Stirring was continued for another 4 hr (until solution of the thiosemicarbazide was complete). The solution was kept for 12 hr at room temperature, then poured, with stirring into water (2000 ml). Stirring was continued for a further 2 hr, until the oily precipitate formed had solidified completely, and the latter was then filtered off.

Yield of IIa, 54 g (75%). After recrystallizing from AcOH (1 g from 20 ml), mp 256° (block). Found: N 23.49%. Calculated for $C_8H_8N_4O_3S$: N 23.32%.

Exactly the same method was used to prepare the p-isomer, IIa, mp 218-219° (ex water) (219° [4]), and the m-isomer IIb, mp 193-194° (decomp, ex H_2O). The following analysis given is for the m-isomer. Found: N 23.10%. Calculated for $C_8H_8N_4O_3S$: N 23.32%.

3-(4-Nitrophenyl)-1, 2, 4-triazole-5-thione (IIIb). 20 g (0.083 mole) IIc and 7.2 g (0.13 mole) KOH were dissolved in 100 ml water, and refluxed for 1 hr, cooled, acidified with AcOH, and the precipitate filtered off, yield 18.0 g (97.3%). After recrystallizing from water (1 g from 270 ml), mp 244° (decomp). Found: N 25.14%. Calculated for $C_8H_6N_4O_2S$: N 25.20%.

3-(3-Nitrophenyl)-1, 2, 4-triazole-5-thione (IIIa). IIb was cyclized similarly. Compound IIIa has mp 240° (decomp, ex H_2O). Found: N 25.57%. Calculated for $C_8H_6N_4O_2S$: N 25.20%.

2-Amino-5-(2-nitrophenyl)-1, 3, 4-triazole (IV). 1.7 g (7 mmole) 1-(2-nitrobenzoyl) thiosemicarbazide (II) was added in small portions to 10 ml concentrated H_2SO_4, left till solution was complete, then poured into 50 ml ice water. The precipitate was filtered off (1.25 g, 80.0%), treated with 200 ml hot water, filtered off, and dried in a vacuum desiccator over KOH, mp 249°. Found: N 24.88%. Calculated for $C_8H_6N_4O_2S$: N 25.20%.

3-(2-Nitrophenyl)-1, 2, 4-triazole-5-thione (V). 20 g (0.11 mole) o-nitrobenzohydrazide and 30 g (0.4 mole) ammonium thiocyanate were heated together at 170-175° for 5 min. The resultant mass was dissolved in 100 ml hot water, and acidified to pH 3 with HCl. Yield of V, 15.0 g (61.2%). After recrystallization from water (1 g from 100 ml), it had mp 219-220° (decomp). Found: C 43.20; H 2.86; N 25.23%. Calculated for $C_8H_6N_4O_2S$: C 43.24; H 2.72; N 25.20%.

1-(4-Nitrophenyl) thiosemicarbazide (VI). 22.95 g (0.15 mole) p-nitrophenylhydrazine was suspended in 700 ml water, the mixture acidified with 15 ml concentrated HCl, and 13.7 g (0.18 mole) ammonium thiocyanate added. The solution was evaporated to dryness in a porcelain basin on a water bath, then the heating continued for half an hour longer, 300 ml water added, and the whole again evaporated to dryness. The resultant dry residue was treated with 250 ml hot water. The undissolved p-nitrophenylthiosemicarbazide VI was filtered off, yield 29 g (91.5%), after recrystallizing from AcOH (1 g from 10 ml) it had mp 207° (decomp). Found: N 26.28%. Calculated for $C_7H_8N_4O_2S$: N 26.39%.

1-(4-Nitrophenyl)-1, 2, 4-triazole-5-thione (VII). 20.4 g (0.1 mole) VI and 100 ml 85% formic acid were refluxed together for 14 hr, the unreacted acid neutralized with a saturated NaOAc solution. The nitrophenyltriazolethione which separated after neutralizing was filtered off, yield, 20 g (93.6%). Compound VII was purified by washing it a few times with hot water, mp 226° (decomp). Found: N 25.49%. Calculated for $C_8H_6N_4O_2S$: N 25.21%.

Nitrophenyl-1, 2, 4-triazoles. a) 3-(4-Nitrophenyl)-1, 2, 4-triazole (VIII). 11.1 g (0.05 mole) IIIb was heated with 50 ml AcOH until dissolved, and 25 ml perhydrol added from a dropping funnel to the hot solution, after which the whole was left for half an hour. The AcOH was distilled off under reduced pressure, the resultant dry residue dissolved in 300 ml water, and the solution filtered. On cooling, 4.9 g (51.5%) nitrophenyltriazole separated from the filtrate. After recrystallization from water (1 g from 140 ml), it had mp 222°. Found: N 29.72%. Calculated for $C_8H_6N_4O_2S$: N 29.45%.

b) 3-(3-Nitrophenyl)-1, 2, 4-triazole (VIII). 5.6 g (25 mmole) thione IIIa was suspended in 56 ml AcOH, the mixture heated to boiling, and 14 ml perhydrol added dropwise, when the thione dissolved. The AcOH was dissolved off under reduced pressure, 30 ml water added to the residue, the mixture heated, neutralized with a saturated Na_2CO_3 solution, and filtered. On cooling 4.65 g (98%) 3-(3-nitrophenyl)-1, 2, 4-triazole (VIII) was precipitated, and after recrystallizing from water (1 g from 130 ml), it had mp 213°. Found: N 29.24%. Calculated for $C_8H_6N_4O_2$: N 29.34%.

c) 3-(2-Nitrophenyl)-1, 2, 4-triazole (VIII) produced by method b by oxidizing 3-(2-nitrophenyl)-1, 2, 4-triazole-5-thione (V) mp 167°C from water. Found: N 29.69%. Calculated for $C_8H_6N_4O_2$: N 29.34%.

d) 1-(4-Nitrophenyl)-1, 2, 4-triazole (IX). Compound IX was prepared from 1-(4-nitrophenyl)-1, 2, 4-triazole-5-thione (VII) by method b. It had mp 189° (ex water). Found: N 28.83%. Calculated for $C_8H_6N_4O_3$: N 29.34%.

3-(Aminophenyl)-1, 2, 4-triazoles (Table 1). 0.95 g (5 mmole) 3-(4-nitrophenyl)-1, 2, 4-triazole (VIII) was dissolved in 65 ml EtOH, and added to reduced Adam's catalyst (20 mg) in 5 ml EtOH. The theoretical amount of H_2 was absorbed in 6-7 hr (magnetic stirrer). The solution was then filtered, and evaporated to dryness, the residue dissolved in 30 ml hot water, and filtered. From the filtrate separated 0.5 g (61%) 3-(4-aminophenyl)-1, 2, 4-triazole (X), mp 202-203°. The other nitrophenyl triazoles were similarly reduced.

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3 February 1965

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