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RESEARCHES ON 1,2,4-TRIAZOLES

VIII. Preparation and Properties of 4-(α-Pyridyl)-1,2,4-triazoline-3-thione*

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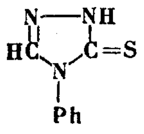
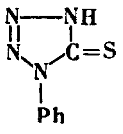
A new method of preparing 1,2,4-triazolinethione derivatives by directly sulfurating the corresponding triazoles is described. 4-(α-Pyridyl)-1,2,4-triazoline-3-thione undergoes aminomethylation, cyanoethylation, and pyridylethylation at the nitrogen of the thioamide group. Replacement of the phenyl group in 4-phenyl-1,2,4-triazolinethione by α-pyridyl, gives a compound closely resembling 1-phenyltetrazoline-5-thione in its properties.

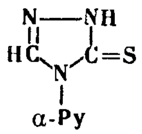
We previously showed [1] that replacement of one CH group in the ring of 4-phenyl-1,2,4-triazoline-3-thione (I) by nitrogen, to give 1-phenyltetrazoline-5-thione (II), gives rise to an increase in acidity and real change in chemical properties.



I



II



III

It was of interest to ascertain to what extent replacement of a CH group by a nitrogen atom in the phenyl ring, and not in the heterocyclic ring, of the thione I, i.e., by replacing phenyl by pyridyl, affected the properties of the compound. It could be assumed that this kind of substitution would lead to the resultant triazole compound III approximating in properties to 1-phenyltetrazoline-5-thione (II) because of inter-ring conjugation. We synthesized 4-(α-pyridyl)-1,2,4-triazoline-3-thione (III). According to a patent [2], that compound can be prepared by condensing 4-(α-pyridyl) thiosemicarbazide with ethyl formate in the presence of sodium ethoxide. We have prepared it by another method, sintering 4-(α-pyridyl)-1,2,4-triazole [4] with sulfur.**

As was assumed, 4-(α-pyridyl)-1,2,4-triazoline-3-thione (III) resembles 4-phenyl-1,2,4-triazoline-3-thione (I) in chemical properties [5-7]. It can be aminomethylated, cyanoethylated, and pyridylethylated, and it reacts with formaldehyde. The UV absorption spectra curves of the compounds prepared, and the positions of the maxima agree with that of the starting compound III. It was previously shown [5], that 4-phenyl-1,2,4-triazoline-3-thione has a typical thione structure, and in the reactions mentioned, reacts at the NH of the thioamido group, with retention of the triazoline skeleton. This is confirmed by comparing the UV spectra of the compounds with that of the starting thione. However, if methyl iodide is used, the reaction involves sulfur, and the triazole sulfide VIII is formed. The structure of this compound follows from its readily undergoing oxidation with permanganate, to give the sulfone, and to its UV spectrum having λ_{max} almost coincident with that of 4-(α-pyridyl)-1,2,4-triazole (fig.).

The behavior of hydroxymethyl compound VII is noteworthy. Boiled in aqueous solution, it splits off formaldehyde, unlike 4-phenyl-2-hydroxymethyl-1,2,4-triazoline-3-thione, which is stable under those conditions [5]. In this connection, VII behaves like 1-phenyl-4-hydroxymethyltetrazoline-5-thione.

The pyridyl group exhibits a clear-cut effect in triazole compounds, sulfides VIII, and sulfones IX. In those compounds, the degree of polarization of C—S single bond (magnitude of the δ^+ charge on the carbon) is increased due to the electron-withdrawing action of the pyridyl group. This appears as increased reactivity of the compounds in hydrolysis and hydrazinolysis. For inspection, comparative results for reactions of compounds I, II, and III are shown in the table.

Thus replacement of a CH group in the phenyl group of 4-phenyl-1,2,4-triazoline-3-thione by a nitrogen atom (i.e., replacement of phenyl by pyridyl) gives rise to a change in properties similar to that called forth by replacement

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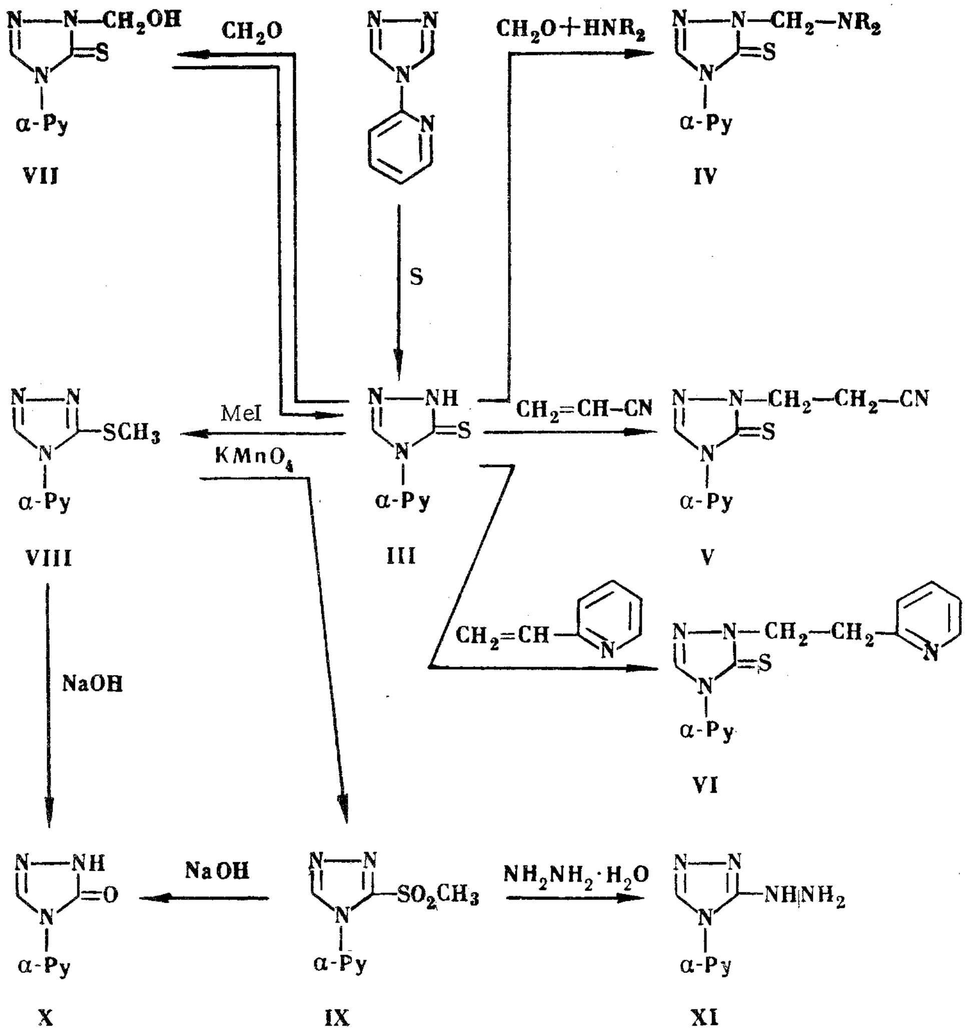
*For Part VII see [1].

**A similar reaction leading to formation of a cyclic thioamide is known in the case of the preparation of benzimidazole-2-thione from benzimidazole [3]. We successfully applied direct introduction of sulfur into the heterocyclic ring to other 1,2,4-triazoles (phenyl, p-tolyl).



HNR_2 = piperidine, morpholine

of the CH group by nitrogen in the triazole ring of the same compound. This shows up clearly on comparing sulfides and sulfones of 4-(α-pyridyl)-1, 2, 4-triazole and 1-phenyltetrazole.

Experimental

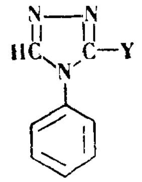
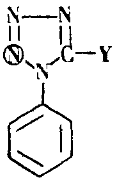
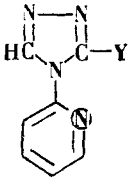
4-(α-Pyridyl)-1, 2, 4-triazoline-3-thione (III). 15 g 4-(α-pyridyl)-1, 2, 4-triazole was heated at 210°-215° C with 15 g elemental sulfur for 10 min. After cooling 200 ml water was added, the mixture heated to boiling, and filtered. The operation was repeated, so long as the filtrate on cooling continued to give a precipitate of compound III. Yield 4.9 g (28%) III, mp 222°-223° C, long needles ex water. Evaporation of the filtrate gave 6.4 g starting 4-(α-pyridyl)-1, 2, 4-triazole, which could be used for further reaction.

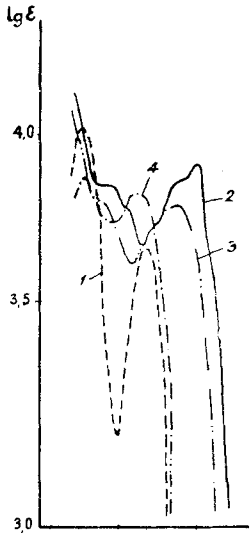
4-Phenyl-1, 2, 4-triazoline-3-thione. Prepared by melting sulfur with 4-phenyl-1, 2, 4-triazole [9] at 190°-200° C, for 3 min, yield 54%, mp 168° C.

4-p-Tolyl-1, 2, 4-triazoline-3-thione. Prepared by melting with sulfur 4-p-tolyl-1, 2, 4-triazole [9], temperature 220°-230° C, for 45 min. Yield 86%, mp 163°-164° C (plates ex water). Found: N 22.28; S 16.37%. Calculated for $C_9H_9N_3S$: N 21.97; S 16.77%.

4-(α-Pyridyl)-2-N-piperidinomethyl-1, 2, 4-triazoline-3-thione (IV). 0.21 ml formalin was added dropwise to a solution of 0.36 g thione III and 0.25 ml piperidine in 3 ml MeOH. After stirring for a short time, the Mannich base was precipitated, the mixture was heated to boiling, diluted with 10 ml water, and then cooled and filtered. Yield 0.55 g (99%), oblong prisms ex water, mp 117°-118° C. Found: N 25.76; S 12.03%. Calculated for $C_{13}H_{17}N_5S$: N 25.43; S 11.46%. 4-(α-Pyridyl)-2-N-morpholinomethyl-1, 2, 4-triazoline-3-thione, in 97% yield, mp 133°-134° C (needles ex water). Found: N 24.97; S 11.63%. Calculated for $C_{12}H_{15}N_5OS$: N 25.25; S 11.56%.

4-(α-Pyridyl)-2-hydroxymethyl-1, 2, 4-triazoline-3-thione (VII). 0.18 g thione III was boiled with 0.2 ml formaldehyde solution, and 2 ml water. The precipitate obtained after cooling, derivative VII, was diluted with water, Comparison of Properties of Compounds I–III

	Y=SCH_3	Y=SO_2CH_3
	Not hydrolyzed by alkali [8] Does not undergo hydrazinolysis	Hydrolyzed by alkali to 4-phenyl-1,2,4-triazoline-3-thione Does not undergo hydrazinolysis under ordinary conditions
	Hydrolyzed by alkali to 1-phenyltetrazolin-5-one Does not undergo hydrazinolysis	Hydrolyzed by alkali to 1-phenyltetrazolin-5-one Readily undergoes hydrazinolysis
	Hydrolyzed by alkali to 4-(α-pyridyl)-1,2,4-triazolin-3-one Does not undergo hydrazinolysis	Hydrolyzed by alkali to 4-(α-pyridyl)-1,2,4-triazolin-3-one Readily undergoes hydrazinolysis



UV spectra in EtOH, C 10^{-3} M, SF-4 instrument: 1) 4-(α-pyridyl)-1,2,4-triazole; 2) 4-(α-pyridyl)-1,2,4-triazoline-3-thione; 3) 4-(α-pyridyl)-2-N-piperidinomethyl-1,2,4-triazoline-3-thione (IV); 4) 4-(α-pyridyl)-3-methylthio-1,2,4-triazole (VIII).

and filtered off, yield 0.18 g (85%), mp 122°–123° C (prisms ex water). Found: N 27.40; S 15.88%. Calculated for $C_8H_8N_4OS$: N 26.91; S 15.40%.

4-(α-Pyridyl)-2-cyanoethyl-1,2,4-triazoline-3-thione (V). 0.89 g thione III was boiled with 0.1 ml Et_3N and 0.6 ml acrylonitrile in 10 ml MeOH. The precipitate formed after cooling and diluting with water was filtered off, and recrystallized from water. Yield 1.09 g (quantitative), mp 101°–102° C (prisms). Found: N 30.35; S 13.87. Calculated for $C_{10}H_9N_5S$: N 30.28; S 13.86%.

4-(α-Pyridyl)-2-[2-(α-pyridyl) ethyl]-1,2,4-triazoline-3-thione (VI). 0.89 g thione III was heated for 4 hr, at 110° C, with 0.8 ml freshly-distilled α-vinylpyridine and 0.32 ml AcOH. After cooling and adding ether, the precipitate formed was filtered off, and washed with petrol ether, yield 1.4 g (99%), mp 90°–91° C (needles ex water). Found: N 24.67; S 11.23%. Calculated for $C_{14}H_{13}N_5S$: N 24.72; S 11.32%. Hydrochloride, mp 180°–181° C (prisms ex EtOH on precipitating with Et_2O). Picrate, mp 167°–168° C (prisms ex benzene).

4-(α-Pyridyl)-3-methylthio-1,2,4-triazole (VIII). 0.89 g thione III was boiled for 10 min with 0.35 ml MeI and 0.6 ml 30% NaOH in 3 ml MeOH. The solution was evaporated, VIII extracted with $CHCl_3$, and crystallized ex heptane, yield 0.9 g (94%), mp 93°–94° C (long interlocking needles). Found: N 29.02; S 16.70%. Calculated for $C_8H_8N_4S$: N 29.15; S 16.68%.

4-(αλPyridyl)-3-methylsulfonyl-1,2,4-triazole (IX). 1.31 g VIII was dissolved in 15 ml AcOH, heated to 60° C, and 7% $KMnO_4$ solution added until a drop on filter paper gave a permanent pink color. After cooling, the solution was decolorized with $NaHSO_3$, and the sulfone extracted with $CHCl_3$. After evaporating off the chloroform, the residue weighed 1.3 g (85%), mp 119°–121° C (prisms ex water). Found: N 25.54; S 13.84%. Calculated for $C_8H_8N_4O_2S$: N 24.99; S 14.30%.

4-α-Pyridyl-1,2,4-triazolin-3-one (X). a) 0.2 g VIII was refluxed for 10 hr with 5 ml 30% NaOH solution, until the emulsion of melted sulfide disappeared. After neutralizing, the solid was filtered off, and recrystallized from water. Yield 0.07 g (41%), mp 244-245° C (long needles). Found: N 34.54%. Calculated for $C_7H_6N_4O$: N 34.56.

b) 0.5 g IX was boiled for 10 min in 10 ml 2 N NaOH solution, and after cooling, the solution was neutralized with HCl. The precipitate was filtered off, weight 0.35 g (98%), mp 244°-245° C.

4-(α-Pyridyl)-3-hydrazino-1,2,4-triazole (XI). 0.5 g IX was boiled for a few minutes with 3 ml hydrazine hydrate, a needle-shaped precipitate forming even in the hot solution. After cooling, the precipitate was filtered off, and recrystallized from water. Yield 0.39 g (99%), mp 213°-214° C (decomp). The product was unstable, and became colored on standing. Found: N 47.41%. Calculated for $C_7H_8N_6$: N 47.70%.

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