UDC. 547.79 + 542.959 + 543.422

STUDIES IN THE 1,2,4-TRIAZOLE SERIES. III*. AMINOMETHYLATION OF 4-PHENYL-1,2,4-TRIAZOLINETHIONE-3

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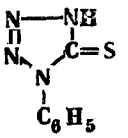
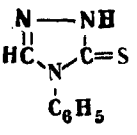
Khimiya geterotsiklicheskikh soedinenii, Vol. 1, No. 1, pp. 133-138, 1965

In a study of the aminomethylation of 4-phenyl-1,2,4-triazolinethione-3 (TRIT) it is ascertained that the reaction involves the nitrogen atom of the thioamide group. Salts of TRIT with secondary amines are obtained. It is shown that replacement of N (2) in 1-phenyltetrazolinethione-5 by the = CH— of TRIT leads to a decrease in the acidity of the thione and an increase in the stability of the hydroxymethyl and chloromethyl derivatives.

The aminomethylation of 1-aryltetrazolinethiones-5 (TETT) has previously been described, and it has been shown to involve a nitrogen atom of the thioamide group [3]. In continuance of that work, a study has been made of the aminomethylation of a compound, 4-phenyl-1,2,4-triazolinethione-3 (TRIT), with one nitrogen atom less in the ring than TETT.



TETT



TRIT

Reducing the number of nitrogen atoms in the ring leads to a lowering of the acidity (k_a for TETT: 9×10^{-4}, k_a for TRIT: 7.6×10^{-8}** [4] of the thiones. It was of interest to ascertain to what extent this is reflected in the mode of aminomethylation and the properties of the reaction products.

The aminomethylation products (Mannich bases), 4-phenyl-, p-chlorophenyl-, p-ethoxyphenyl-1,2,4-triazolinethione-3, crystallize well. The starting 4-substituted triazolinethiones-3 (I) were synthesized according to [5]. Like TETT, TRIT is a thione, not a thiol, as is shown by the IR spectrum of the compound both in the crystalline state and in chloroform. The SH absorption band in the region 2500-2600 cm^{-1} was absent, while a 3116 cm^{-1} band, belonging to the valence vibration of the NH group, and a 1332 cm^{-1} band, corresponding to vibration of the C=S group in the thiomide group [6], were observed. Considering these results, and those of the previous work on TETT, it may be assumed that in aminomethylation TRIT will react not at the sulfur in the thiol form, but at the NH of the thiomide group II in the thione form. As will be shown below, this assumption is correct.

On heating the Mannich base with 10% acetic acid it is hydrolyzed to amine and hydroxymethyl derivative III, identical with the product of the reaction between TRIT and formaldehyde. Reaction of III with thionyl chloride gives the chloromethyl compound IV, reduced by zinc dust to the methyl derivative V. In respect to its m.p. (110°-111°) and UV spectrum (λ_{max} 265 mμ) this compound differs from the 4-phenyl-3-methylthio-1,2,4-triazole (VI) described in the literature [5] (m.p. 76°, λ_{max}220 mμ). On comparing the spectra of the two methyl compounds (see figure), it can be seen that the compound obtained from the chloromethyl derivative IV has a maximum further into the long wavelength region, and therefore a thione structure. The UV spectrum of the methyl derivative coincides exactly with that of the starting TRIT, which undoubtedly has a thione structure. Hence it can be concluded that the chloromethyl and hydroxymethyl derivatives, and hence the Mannich bases, also have the thione structures II, III, IV, V. Thus there is a perfect resemblance between TETT and TRIT with regard to aminomethylation; at the same time the replacement of one nitrogen atom in the ring of TETT by a CH group in the case of TRIT is indicated not only by a decrease in acidity, but also by the properties of the compounds obtained. Thus, the hydroxymethyl compound III is quite stable, while the corresponding 4-hydroxymethyl-TETT slowly decomposes in air, splitting off formaldehyde. The chloromethyl derivative of TRITT IV is also a very stable compound, but the corresponding chloromethyl derivative of TETT is extremely unstable and cannot be isolated in the pure form.

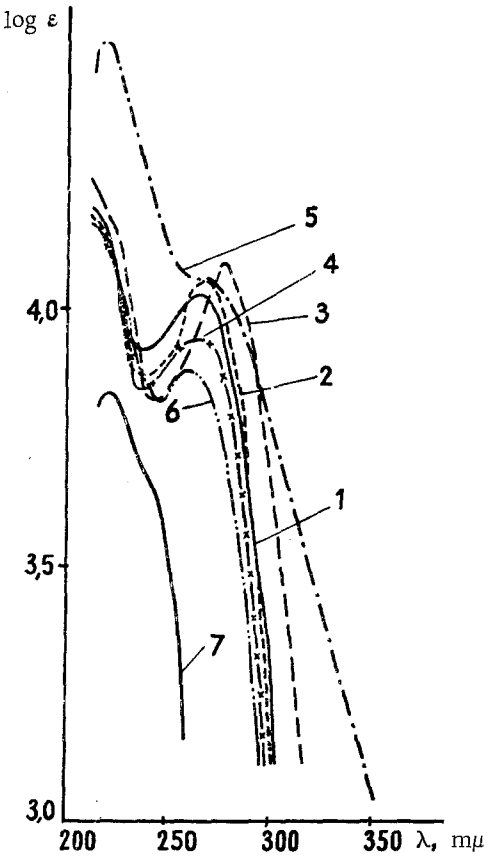
It was also intended to prepare Mannich bases IIa and IIb by reacting the chloromethyl derivative IV with piperidine or morpholine. However, in both cases the reaction gave the same compound. It is actually obtained by reacting TRIT with the chloromethyl derivative IV. These results and the analytical data enabled sulfide structure VII to be

*For preceding papers see [1] and [2].

**The k_a values were determined by V. F. Degtyarevyi (Ordzhonikidze All-Union Chemical-Pharmaceutical Scientific Research Institute.

ascribed to the compound obtained. A similar reaction of the chloromethyl derivative with thione was first observed in the benzothiazolinethione-2 series [7].

Aminomethylation with excess of secondary amine gives compounds, which, from their properties and composition, must be regarded as salts of TRIT with the bases or salt-type complexes VIII. The very same salts are formed by treating



UV spectra (in ethanol), concentration 10^{-3} mole/*l*, SF-4 instrument: 1. 4-Phenyl-1, 2, 4-triazolinethione-3 (Ia); 2. 2-Hydroxymethyl-4-phenyl-1, 2, 4-triazolinethione-3 (III); 3. 2-Chloromethyl-4-phenyl-1, 2, 4-triazolinethione-3 (IV); 4. 2-Methyl-4-phenyl-1, 2, 4-triazolinethione-3 (V); 5. 2-N-Diethylaminomethyl-4-p-chlorophenyl-1, 2, 4-triazolinthione-3 (IId); 6. The salt piperidine-4-phenyl-1, 2, 4-triazoline-3 (VIIIa); 7. 3-Methylthio-4-phenyl-1, 2, 4-triazole (VI).

the Mannich base with excess amine, and they can also be obtained by mixing equimolecular quantities of the bases with TRIT. On reaction with formaldehyde the salts again give the Mannich base. The salts are readily soluble in water, and even in the cold are decomposed by 3% acetic acid with separation of TRIT. Their UV spectra have λ_{max} and λ_{min} coincident with the spectrum of TRIT. All this indicates that in salt formation TRIT reacts in the thione form at the NH of the thioamide group, and not in the thiol form at the SH group. The low melting points of the salts, and their high solubilities in hot benzene are noteworthy. Further research is necessary for complete clarification of the problem of their structure.

EXPERIMENTAL

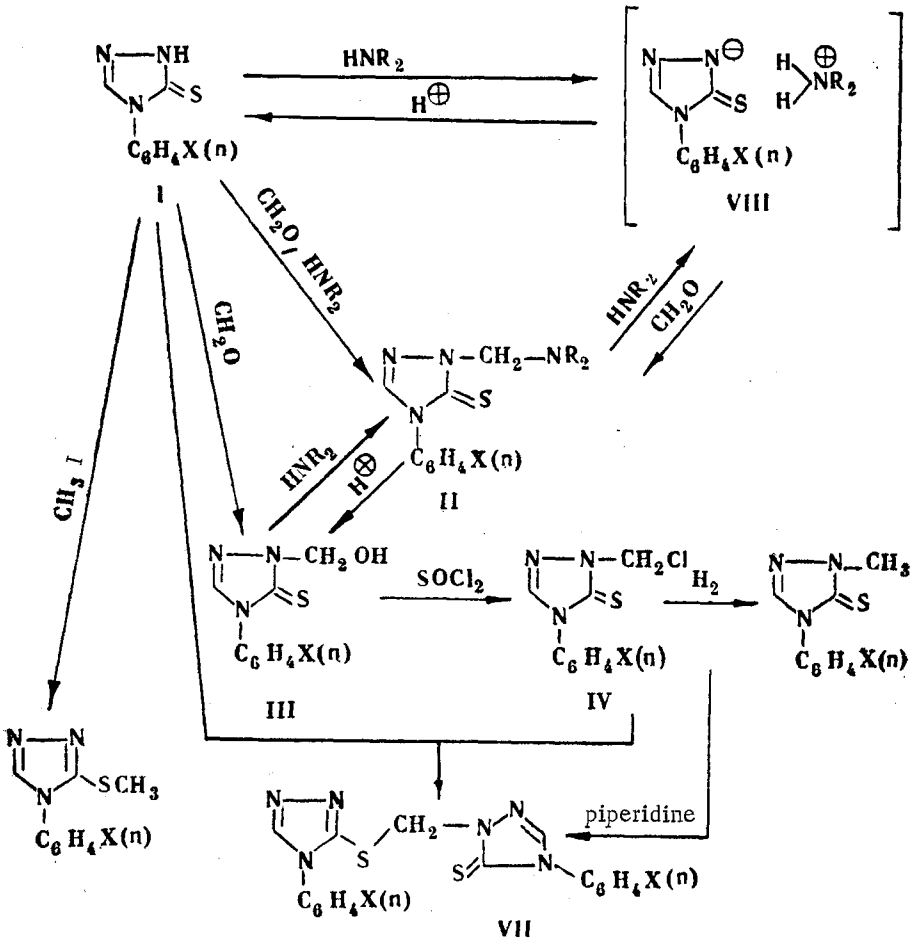
4-Aryl-1, 2, 4-triazolines-3 are prepared from the corresponding 4-substituted thiosemicarbazides by condensation with ethyl formate in the presence of sodium methoxide [5]. All these thiones crystallize well from water. 4-Phenyl-1, 2, 4-triazolinethione-3 (Ia), m.p. 169-170°, needles. 4-p-Chlorophenyl-1, 2, 4-triazolinethione-3 (Ib), m.p. 213-214°, prisms. 4-p-Ethoxyphenyl-1, 2, 4-triazolinethione-3 (Ic), m.p. 184-185°, needles. The products are insoluble in benzene, but dissolve in alcohol, ether, and chloroform on heating. IR spectrum of thione Ia cm^{-1}: 1332 s (C=S); 1496 s (N—C=S); 2748 w; 2832 w; 2912 s (CH); 3001 s (CH); 3074 m (CH); 3116 s (NH) (s = strong, w = weak, m = medium).

Aminomethylation. 0.005 mole 4-phenyl-1, 2, 4-triazolinethione-3 (TRIT) is dissolved in 5 ml methanol and mixed with 0.006 mole secondary amine, then 0.008 mole formaldehyde is added dropwise. Solution is accompanied by evolution of heat. After standing 3 hr the solution is vacuum-distilled to remove methanol, and the precipitate formed filtered off. The products are dissolved in cold alcohol, benzene, ether, chloroform, or carbon tetrachloride in the cold. They are insoluble in water, slightly soluble in petroleum ether, but crystallize well from it (Table 1).

2-Hydroxymethyl-4-phenyl-1, 2, 4-triazolinethione-3 (III). 4.5 g TRIT are dissolved in 30 ml hot ethanol, and 4.5 ml formalin added. The mixture is boiled 20 min, and after evaporating off part of the ethanol, the precipitate formed is filtered off. Colorless needles, yield 31.84 g (73%), m.p. 103-104° (from ether). Readily soluble in alcohol and chloroform, insoluble in benzene and petroleum ether. Found: N 20.56%. Calculated for $C_9H_9N_3OS$: N 20.28%.

2-Chloromethyl-4-phenyl-1, 2, 4-triazolinethione-3 (IV). A solution of 1.04 g (0.005 mole) III in 25 ml dry chloroform and 3.6 ml (0.05 mole) thionyl chloride are heated for 1 hr at 60°. Solvent and excess thionyl chloride are then removed in a vacuum, about 15 ml dry benzene is twice poured onto the residue, and then taken off in a vacuum.

Yield 0.5 g (44%), colorless needles m.p. 131-132° (from benzene), soluble in chloroform and benzene, insoluble in ether, and petroleum ether. Found: C 47.75; H 3.49; Cl 15.46; N 18.40; S 14.48%. Calculated for $C_9H_8ClN_3S$: C 47.89; H 3.55; Cl 15.75; N 18.63; S 14.18%.



I: a) X = H, b) C = Cl(p), c) X = OC_2H_5(p). II: a) X = H, NR_2 = piperidino; b) X = H, NR_2 = morpholino; c) X = Cl(p), NR_2 = piperidono; d) X = Cl(p), NR_2 = diethylamino; e) X = Cl(p), NR_2 = pyrrolidino; f) X = OC_2H_5(p), NR_2 = piperidino; g) X = OC_2H_5(p), NR_2 = morpholino. III, IV, V, VI, VII: X = H. VIII: a) X = H, NR_2 = piperidino; b) X = H, NR_2 = morpholino; NR_2 = diethylamino; d) X = Cl(p), NR_2 = piperidino.

2-Methyl-4-phenyl-1, 2, 4-triazolinethione-3 (V). A mixture of 0.45 g (0.002 mole) chloromethyl derivative IV dissolved in 13 ml glacial acetic acid with 13 ml benzene is vigorously stirred, and 2 g zinc dust added over 20 min, the temperature being not over 30°. The mixture is then stirred for 15 min more, filtered, and the residue washed with water. The benzene solution is separated, and the aqueous layer extracted with benzene. The combined extracts are washed with water and dried over sodium sulfate. The solvent is then distilled off. Yield 0.3 g (78%), m.p. 110-111° (from water). The reaction product dissolves in methanol, benzene, chloroform, and ether. Found: N 22.02%. Calculated for $C_9H_9N_3S$: 22.00%.

Hydrolysis of 2-N-morpholinomethyl-4-phenyl-1, 2, 4-triazolinethione-3 (IIb). 0.3 g base IIb is stirred for 30 min at 50° with 10 ml 10% acetic acid. The mixture is filtered, and after standing needles of the hydroxymethyl derivative III are deposited, m.p. 103-104°, yield 0.2 g (89%).

Aminolysis of 2-N-piperidinomethyl-4-phenyl-1, 2, 4-triazolinethione-3 (IIa). 0.27 base IIa is heated to boiling with 1 ml piperidine. On cooling a crystalline precipitate of the piperidine salt of TRIT (VIIIa) comes down. It is filtered off, and washed with ether. Yield 0.1 g (40%), m.p. 131-132° (prisms from benzene).

Piperidine salt of TRIT (VIIIa). 0.885 g TRIT are mixed with 10 ml benzene and 0.52 ml piperidine. The mixture is heated for a few minutes until solution is complete; the solution cooled, the crystalline precipitate filtered off, washed with ether, and crystallized from benzene. Yield 1.15 g, or 88% (Table 2).

(3-Thione-4-phenyl-1, 2, 4-triazolinyl-2)methyl(4-phenyl-1, 2, 4-triazolin-3 sulfide (VII).

a) 0.22 g chloromethyl derivative IV and 0.18 g TRIT are dissolved with heating in 5 ml ethanol and 0.5 ml 2 N alkali. The solution is boiled 10 min, after which it is cooled and 20 ml water added, resulting in precipitation of VII.

Yield 0.32 g (89%), m.p. 166-167° (prisms, from benzene).

b) 0.45 g chloromethyl derivative IV and 0.4 ml piperidine are mixed with 4 ml ethanol, and the whole boiled 5 min, after which the solution is cooled and diluted with 20 ml water. The precipitate is filtered off. Yield 0.27 g (74%), m.p. 166-167°. Found: N 22.95; S 17.49%. Calculated for $C_{17}H_{14}N_6S_2$: N 22.84; S 17.00%.

TABLE 1

Aminomethylation products

Compound	Name	M.p., °C	Empirical formula	N, %		Yield, %
				Found	Calculated	
IIa	2-N-Piperidinomethyl-4-phenyl-1, 2, 4-triazolinethione-3	97— 98*	$C_{14}H_{18}N_4S$	20.30	20.42	91
IIb	2-N-morpholino-4-phenyl-1, 2, 4-triazolinethione-3	141—142	$C_{13}H_{16}N_4OS$	20.49	20.30	99
IIc	2-N-Piperidinomethyl-4-p-chlorophenyl-1, 2, 4-triazolinethione-3	134—135 (plates)	$C_{14}H_{17}ClN_4S$	17.76	18.13	77
IId	2-N-Diethylaminomethyl-4-p-chlorophenyl-1, 2, 4-triazolinethione-3	72— 73*	$C_{13}H_{14}ClN_4S$	18.47	18.90	91
IIe	2-N-Pyrrolidinomethyl-4-p-chlorophenyl-1, 2, 4-triazolinethione-3	91— 92*	$C_{13}H_{15}ClN_4S$	18.67	19.00	96
IIf	2-N-Piperidinomethyl-4-p-chlorophenyl-1, 2, 4-triazolinethione-3	72— 73	$C_{16}H_{22}N_4OS$	17.89	17.63	31
IIg	2-N-Morpholinomethyl-4-p-chlorophenyl-1, 2, 4-triazolinethione-3	100—101	$C_{15}H_{20}N_4O_2S$	17.43**	17.50	80

*Needles, otherwise plates.

**Found: C 56.63; H 6.37%. Calculated: C 56.20; H 6.25%.

TABLE 2

Amine salts of 4-phenyl-1, 2, 4-triazolinethione-3

Compound	Amine	T. пл., °C	Empirical formula	N, %		Yield, %
				Found	Calculated	
VIIIa	Piperidine	131—132, pr*	$C_{13}H_{18}N_4S$	21.82**	21.40	88
VIIIб	Morpholine	121—122, pl	$C_{12}H_{16}N_4OS$	21.21	21.20	70
VIIIв	Diethylamine	131—132, i	$C_{12}H_{18}N_4S$	22.60	22.40	72
VIIIг	Piperidine	142—143, pr	$C_{13}H_{17}ClN_4S$	18.61	18.88	71

*pr = prisms; pl = plates; i = needles.

**Found: C 59.87; H 6.71%. Calculated: C 59.53; H 6.87%.

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29 December 1963

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