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RESEARCH ON 1, 2, 4-TRIAZOLES

IV. Cyanoethylation of 4-Phenyl-1, 2, 4-Triazolinethione-3*

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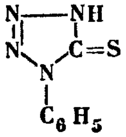
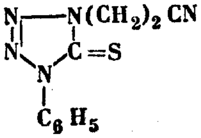
Cyanoethylation of 4-aryl-1, 2, 4-triazolinethiones-3 takes place at the nitrogen atom of the thioamide group, to give N-cyanoethyl derivatives. β-Chloropropionitrile reacts at the nitrogen atom of the thioamide groups, but β-chloropropionic acid reacts at its sulfur atom, giving a sulfide. The results of cyanoethylation enable conclusions to be drawn regarding the shift of the reaction center from sulfur to nitrogen on passing from a tetrazole to a triazole derivative.

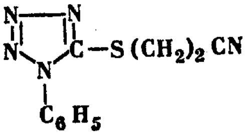
To determine the effect of replacing one nitrogen atom in a tetrazole ring by a CH group, a comparison of tetrazole and 1, 2, 4-triazole derivatives was undertaken, in particular of 1-phenyltetrazolinethione-5 (TETT) (I) with 4-phenyl-1, 2, 4-triazolinethione-3 (TRIT) (II) [1], and a study was planned of the cyanoethylation of those compounds. It had previously been shown that TETT reacts in two ways with acrylonitrile, giving the isomeric N- and S-cyanoethyl compounds IIIa and IIIb [2].



I



IIIa



IIIb

The present work shows that TRIT reacts with acrylonitrile mainly or entirely at the NH group in the ring, to give a good yield of 4-phenyl-2-β-cyanoethyl-1, 2, 4-triazolinethione-3 (IVa), and that here the S-isomer, 4-phenyl-3-β-

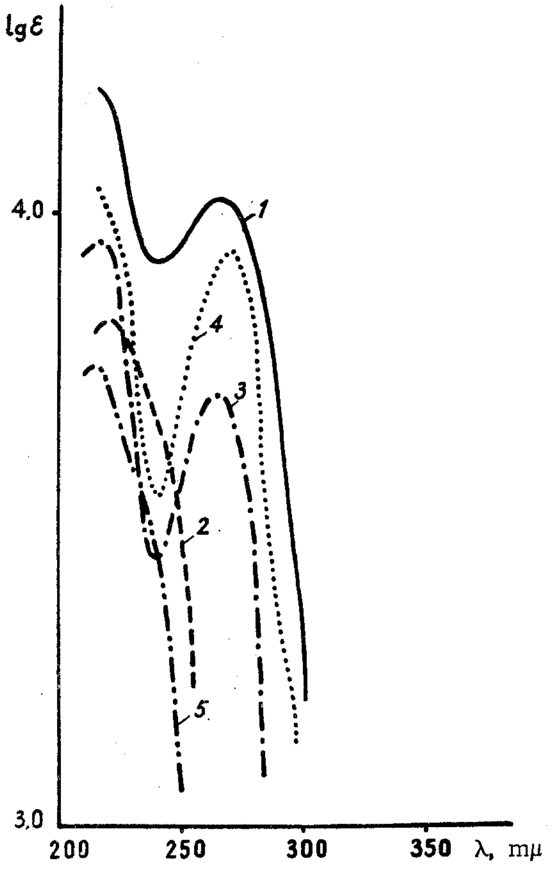


Fig. 1. UV absorption spectra (in ethanol), concentration 10^{-3} M, SF-4 instrument: 1) 4-phenyl-2-methyl-1, 2, 4-triazolinethione-3; 2) 4-phenyl-3-methylthio-1, 2, 4-triazole; 3) 4-phenyl-2-β-cyanoethyl-1, 2, 4-triazolinethione-3 (IVa); 4) 4 phenyl-2-β-carboxyethyl-1, 2, 4-triazolinethione-3 (Va); 5) 4-phenyl-3-β-carboxyethyl-1, 2, 4-triazole (VI).

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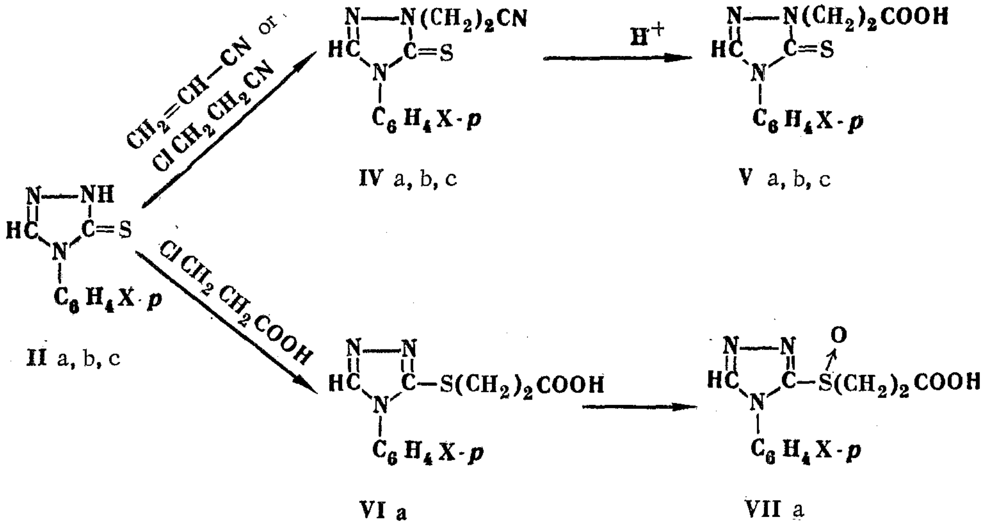
*For Part III see [1].

cyanoethylthio-1, 2, 4-triazole cannot be isolated. The structure of the nitrile follows from the fact that its UV spectrum corresponds well with that of TRIT, whose thione structure was previously demonstrated [1] (Fig. 1). Hydrolysis of the nitrile gives the acid V, whose spectrum was also found to correspond completely with that of TRIT.



a) X=H; b) X=Cl; c) X=OC_2H_5

We decided to prepare (for comparison) the missing S-isomer by reacting TRIT with β-chloropropionitrile, since this halogenonitrile and TETT gave the sulfide IIIb. It was shown that when TRIT reacts with β-chloropropionitrile, the compound formed is identical with the N-isomer IVa. It must be assumed that the S-isomer is formed in the first stage of the reaction, that it is unstable and readily de-cyanoethylates, and that the molecule of acrylonitrile which splits off, adds to the amide nitrogen atom in the ring, giving the more stable N-nitrile IVa. A similar course for the reaction, involving de-cyanoethylation, was observed with TETT, the only difference being that there the S-isomer could be separated [2]. The indicated assumption concerning the course of reaction is supported by the fact that β-chloropropionic acid, as when its reacts with TETT, does not react at the nitrogen atom, but at the sulfur, giving sulfide VIa. It is of interest that the melting points of acid V, prepared by saponifying the N-cyanoethyl derivative, and of the isomeric acid VI made by reacting TRIT with β-chloropropionic acid, are very close together (143-146°). However, the mixed mp is depressed 15°. Both compounds differ in crystalline form, and sharply differ in UV spectra, the spectrum of the acid V agreeing with that of TRIT, while the spectrum of the acid VI resembling that of the sulfide 4-phenyl-3-methylthio-1, 2, 4-triazole, prepared as described in [3] (Fig. 1). Alkaline permanganate oxidation of acid VI gives the sulfoxide VII. Furthermore, the characteristic thioamide band in the region 1520-1560 cm^{-1} is common to the IR spectra of the nitriles and acids corresponding to them, but the band is lacking in the IR spectrum of acid VI (Fig. 2).

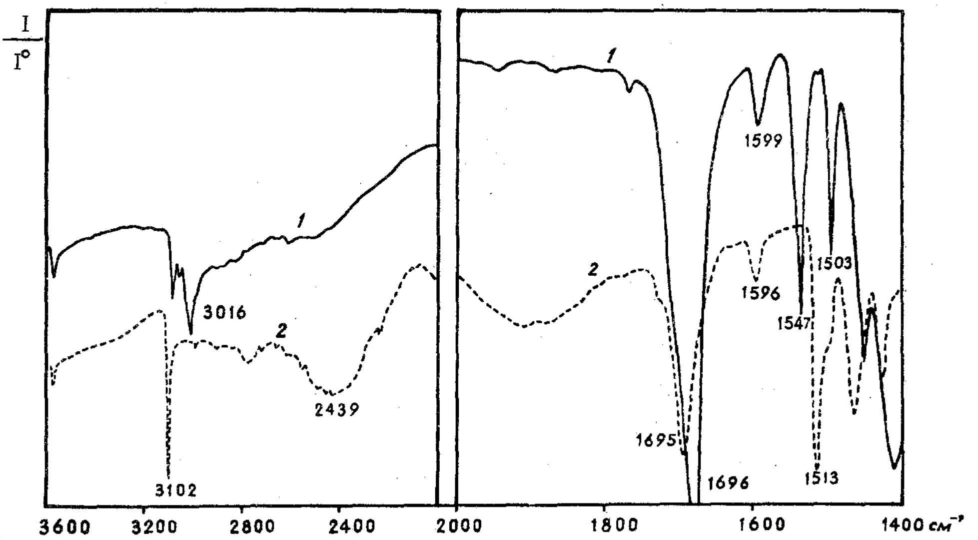


Fig. 2. IR spectra in the region 1400-3600 cm^{-1}, UR-10 instrument: 1) 4-phenyl-2-β-carboxyethyl-1, 2, 4-triazolinethione-3 (Va); 2) 4-phenyl-3-β-carboxyethylthio-1, 2, 4-triazole (VI).

Cyanoethylation Products, and Their Hydrolysis Products

Compound no.	Compound	Mp, °C, solvent, and crystal form	UV spectra		N—C=S band in the IR spectrum, cm⁻¹	Formula	N, %		Yield, %
			λ_{max}	lg ε			Found	Calculated	
IVa	4-Phenyl-2-β-cyanoethyl-1, 2, 4-triazolinethione-3	108—110; Methanol, leaflets	265	3.71	1523	$C_{11}H_{10}N_4S$	24.56	24.36	74
IVb	4-p-Chlorophenyl-2-β-cyanoethyl 1, 2, 4-triazolinethione-3.	157—158; Methanol, prisms	275	3.72	1534	$C_{11}H_9ClN_4S$	20.92	21.15	76
IVc	4-p-Ethoxyphenyl-2-β-cyanoethyl 1, 2, 4-triazolinethione-3.	126—128; Methanol, needles	270	3.99	1534	$C_{13}H_{14}N_4OS$	20.00*	20.43	74
Va	4-Phenyl-2-β-carboxyethyl-1, 2, 4-triazolinethione-3	143—145; Water, leaflets	270	3.94	1547	$C_{11}H_{11}N_3O_2S$	16.86**	16.88	93
Vb	4-p-Chlorophenyl-2-β-carboxyethyl-1, 2, 4-triazolinethione-3	161—162; Water, leaflets	270	3.74	1548	$C_{11}H_{10}ClN_3O_2S$	14.78	14.82	75
Vc	4-p-Ethoxyphenyl-2-β-carboxyethyl-1, 2, 4-triazolinethione-3	152—154; Water, needles	262	4.00	1533	$C_{13}H_{15}N_3O_3S$	14.48***	14.33	86

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*Found: S 11. 75%. Calculated S: 11. 68%.

**Found: C 53. 20; H 4. 80%. Calculated for C: 53. 00; for H: 4. 42%.

***Found: S 11. 07%. Calculated for S: 10. 81%.

From our results, it can be concluded that the negative charge in the TRIT anion is more concentrated on the ring amide nitrogen atom than it is with TETT, where the anion's negative charge is more uniformly distributed between all the atoms of the nitrogen ring and the sulfur.

Experimental

Cyanoethylation. 0.02 mole 4-aryl-1, 2, 4-triazolinethione-3 (II) was refluxed with 1.3 ml (0.02 mole) freshly-distilled acrylonitrile in 15 ml anhydrous dioxane. The catalyst was 0.33 g freshly-prepared sodium ethoxide in 3.5 ml dry ethanol. The mixture was refluxed for 4 hr, cooled, and poured onto 100 g ice. The crystalline precipitate formed was filtered off and recrystallized. Acidification of the filtrate gave a crystalline precipitate of unreacted thione II (see table). The cyanoethylation products were colorless compounds which crystallized well from water or methanol. They readily dissolved when heated with benzene, chloroform, acetone, dichloroethane, and ether, but were insoluble in petroleum ether and carbon tetrachloride.

IR spectrum of compound IVa (s = strong, m = medium): 3148 m (CH aromat.), 2254 m (C≡N), 1596 m (CH aromat.), 1523 s (N—C=S), 1496 s, 1429 m, 1412 s, 1344 s, 1301 s, 1245 m, 1222 s, 1183 m, 1135 m, 1066 m, 972 s, 845 m, 793 s, 762 s (CH aromat.), 693 s, 686 s (CH aromat.) cm^{-1}.

4-Phenyl-2-β-cyanoethyl-1, 2, 4-triazolinethione-3 (IVa). 0.4 ml β-chloropropionitrile was added to 0.7 g (0.04 mole) TRIT dissolved in 2.5 ml 2 N sodium hydroxide in 2.5 ml ethanol, and the whole refluxed for 30 min, cooled and the precipitate of nitrile formed filtered off. Yield: 0.55 g (58%), mp 108-110° (from methanol). Acidification of the filtrate with acetic acid precipitated 0.29 g (41%) of the starting TRIT.

4-Aryl-2-β-carboxyethyl-1, 2, 4-triazolinethione-3 (V). 0.002 mole 4-aryl-2-β-cyanoethyl-1, 2, 4-triazolinethione-3 (IV) was heated for 15 min with 10 ml concentrated hydrochloric acid. The voluminous precipitate of N-acid which precipitated after cooling was filtered off, washed with cold water, and crystallized from water (see table). Acid V was a colorless crystalline compound, readily soluble in methanol, acetone, and chloroform, but insoluble in benzene, petroleum ether, dichloroethane, and carbon tetrachloride.

IR spectrum of compound Va (s = strong, m = medium, v = very) 3016 m (CH aromat.), 1696 vs (C=O); 1599 m (CH aromat), 1547 s (N—C=S), 1503 s (C=N), 1425 s, 1344 s, 1328 s, 1277 s, 1213 s, 1180 m, 1134 m, 947 m, 755 s (CH aromat.), 687 s (CH aromat.), 570 s, cm^{-1}.

4-Phenyl-3-β-carboxyethylthio-1, 2, 4-triazole (VI). 1.4 g (0.008 mole) TRIT and 0.88 g (0.008 mole) β-chloropropionic acid were dissolved in 8 ml 2 N sodium hydroxide solution, refluxed for 40 min, cooled, and neutralized with hydrochloric acid. The precipitate of acid VI (prisms) was filtered off and washed with cold water. Yield: 1.80 g (90%) mp 143-146° (from water). Found: 16.75%. Calculated for $C_{11}H_{11}N_3O_2S$: N 16.88%. UV spectrum: λ_{max} 216 mμ; log ε 3.74.

IR spectrum (s = strong, m = medium): 3102 s (CH aromat.), 2439 wide, m (COOH associated), 1695 s (C=O), 1596 m (CH aromat.), 1513 s (C=N), 1464 m, 1428 m, 1334 m, 1301 m, 1263 m, 1225 m, 1157 m, 813 m, 765 m (CH aromat.), 694 s (CH aromat.), 657 m, 553 m, 509 m cm^{-1}.

The presence of a wide band in the 2439 cm^{-1} region, characteristic of an associated carboxyl group, is here explicable by transfer of a proton to the ring nitrogen atom, with a tendency to form an internal salt.

4-Phenyl-3-β-carboxyethylsulfoxy-1, 2, 4-triazole (VII). 0.5 g (0.002 mole) 4-phenyl-3-β-carboxyethylthio-1, 2, 4-triazole (VIa) was dissolved in 12 ml 10% sodium carbonate, maintained at 60-65°, and a 7% potassium permanganate solution added in small amounts, until a drop placed on filter paper showed a red color which did not disappear. After cooling a small amount of 40% sodium bisulfite solution was then added to destroy the excess permanganate, the manganese dioxide filtered off, and washed with water. The filtrate was neutralized with 2 N hydrochloric acid, and the solution evaporated on a steam bath. The precipitate obtained was recrystallized from water. Yield 0.25 g (47%), mp 158-159° (plates). Found: C 49.47; H 4.19; N 15.74%. Calculated for $C_{11}H_{11}N_3O_3S$: C 49.80; H 4.15; N 15.84%.

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