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RESEARCH ON 1, 2, 4-TRIAZOLES

V. 4-Phenyl-2, 2, 4-Triazolinethione-3 Alkylation Products*

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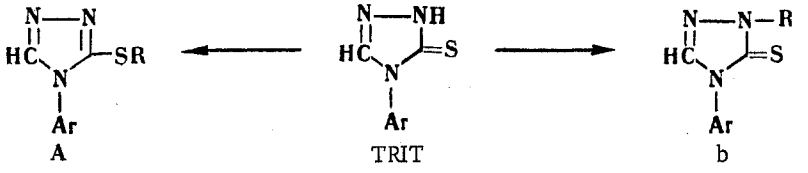
Alkylation of 4-phenyl-1, 2, 4-triazolinethione-3 with halogen compounds gives sulfides, which oxidize to sulfones. Unlike the corresponding tetrazole derivatives they do not exhibit antitubercular activity. The oxidation of 4-phenyl-3-carboxymethylthio-1, 2, 4-triazole is investigated. Permanganate oxidation is accompanied by decarboxylation and formation of 4-phenyl-1, 2, 4-triazolylmethylsulfone-3, while oxidation with hydrogen peroxide gives 4-phenyl-1, 2, 4-triazolinone-3. It is found that treatment of 4-phenyl-3-carboxymethylthio-1, 2, 4-triazole with acetic anhydride gives di(4-phenyl-3-methylenethio-1, 2, 4-triazoline)ketone, possibly via formation of an anhydro- derivative.

Some tetrazole sulfides and sulfones, prepared from 1-aryltetrazolinethiones-5 (TETT), exhibit antitubercular activity in vitro [1]. Consequently it was of interest to synthesize and test the antitubercular activities of their analogs, 4-aryl-1, 2, 4-triazole sulfides and sulfones. The literature describes 4-phenyl-3-methylthio- and 4-phenyl-3-carboxymethylthio-1, 2, 4-triazole (IIa, IV) (see diagram). These were prepared by reacting the appropriate halogen compounds with 4-phenyl-1, 2, 4-triazolinethione-3 (TRIT) [2]. In the present work a number of new compounds (see table) have been prepared by this method. Because of the dual reactivity of the thioamide group in TRIT [3], the products can have sulfide structure A or thione structure B.



The compounds prepared oxidize to sulfones, whence their sulfide structure A. In agreement with this, in the UV absorption spectra of the compounds λ_{max} is displaced towards the shorter wavelengths compared with λ_{max} for TRIT, but the spectrum curves differ in shape from those for TRIT and derivatives of it of known thione structure [4] (see figure).

Oxidation of 4-phenyl-3-carboxymethylthio-1, 2, 4-triazole (IV) by potassium permanganate in glacial acetic acid gives, instead of the expected sulfone acid V (see diagram), a good yield of 4-phenyl-1, 2, 4-triazolylmethylsulfone (IIIa). In all probability, oxidation first gives the sulfone acid V, and then, under the reaction conditions, decarboxylates. This is apparently because the acetic acid portion in sulfone acid V is joined to the strongly electronegative triazolylsulfonyl group.

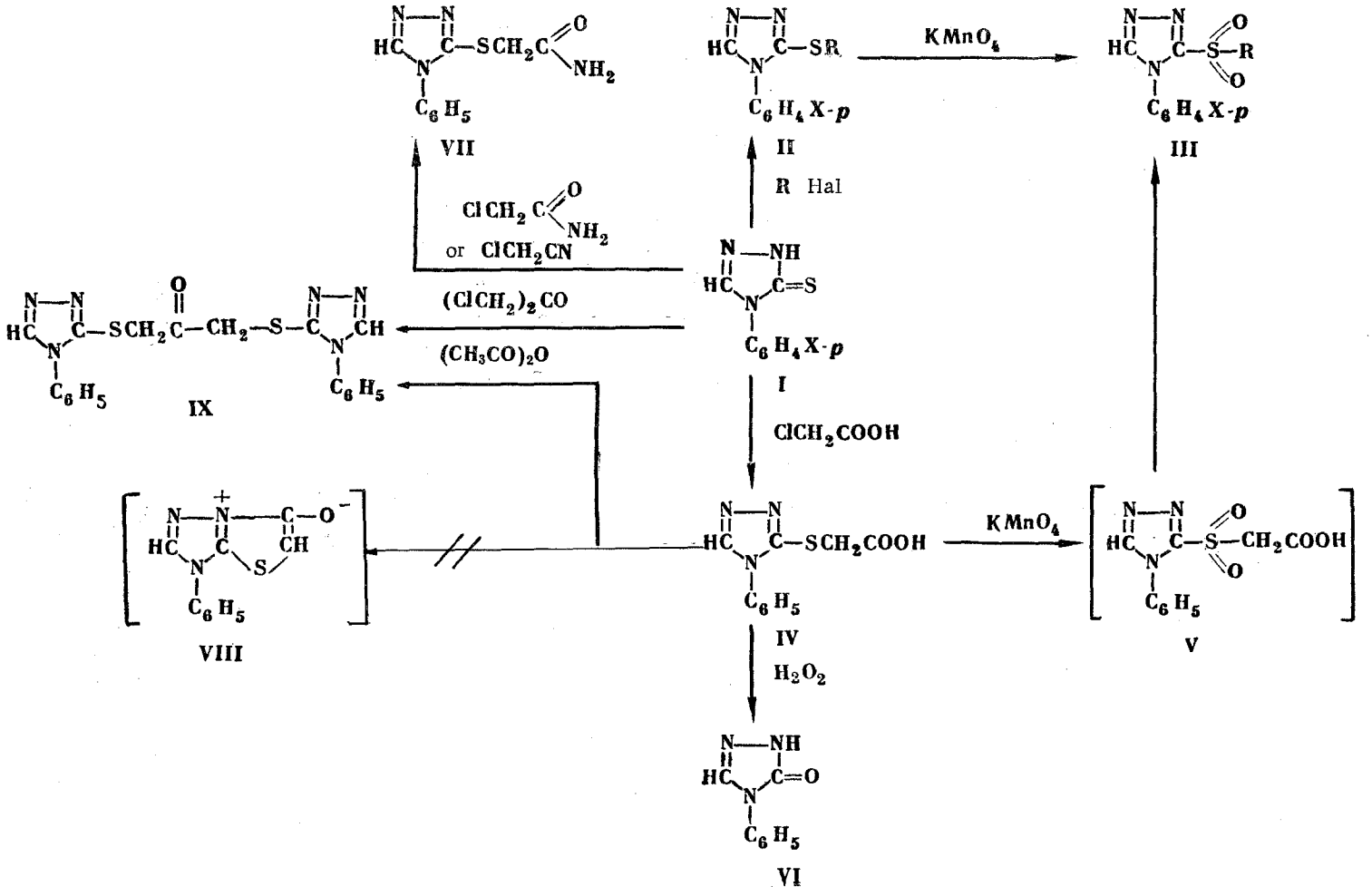
The sulfide acid IV was oxidized under different conditions, by hydrogen peroxide in glacial acetic acid, when it gave 4-phenyl-1, 2, 4-triazolinone-3 (VI). Evidently, here, oxidation is accompanied by hydrolytic splitting off of the sulfur-containing group. It was established that methyl sulfone IIIa is completely stable towards hydrogen peroxide in glacial acetic acid, consequently it can be assumed that when IV is oxidized with hydrogen peroxide, what is first formed is not a methylsulfone, but in all probability, a sulfoxide, $SO{-}CH_2COOH$, which subsequently undergoes hydrolysis**.

It was of interest to prepare the sulfide and sulfone containing the cyanomethyl group $-CH_2CN$, but it proved impossible, since the nitrile hydrates during the reaction gave 4-phenyl-3-carbamylthio-1, 2, 4-triazole (VII). The same compound was obtained by reacting TRIT with chloroacetamide. The amide readily hydrolyzes to acid IV, and on oxidation gives the methylsulfone IIIa.

In conclusion, the preparation of the anhydro- compound VIII was planned, resembling the compounds prepared by the action of acetic anhydride on 3-carboxymethylthioimidazoles [5, 6]. This kind of compound could be of interest in connection with testing its physiological action. However, an anhydro- compound is not formed when the carboxymethyl compound IV is reacted with acetic anhydride, and instead di(4-phenyl-3-methylenethio-1, 2, 4-triazolyl)ketone (IX) is formed. The structure of ketone IX was confirmed by comparison with the ketone prepared from symmetric dichloroacetone and TRIT; the two had identical melting points and UV spectra.

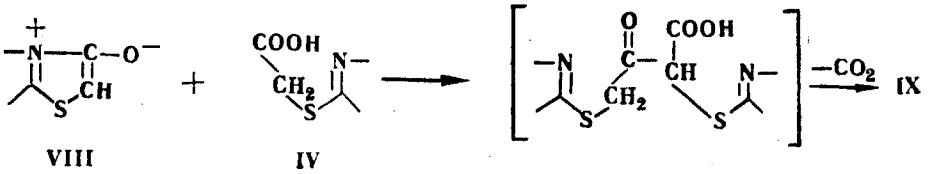
*For Part IV see [3].

**The behavior of 4-phenyl-3-carboxymethylthio-1, 2, 4-triazole on oxidation with potassium permanganate and hydrogen peroxide corresponds to that of 1-phenyl-5-carboxymethylthiotetrazole (observed by V. L. Nirenburg).



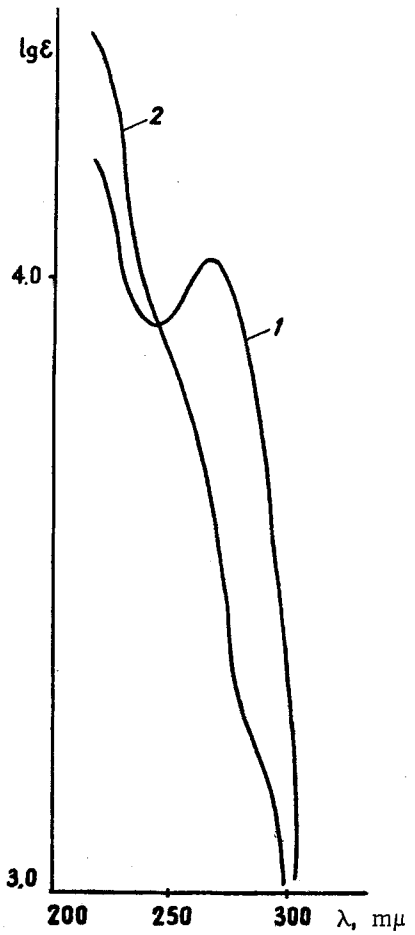
I: a) X = H; b) X = Cl; c) X = OC_2H_5;
II or III: a) X = H, R = CH_3; b) X = H, R = $CH_2C_6H_5$; c) X = H, R = $CH_2C_6H_4NO_2$-p; or X = Cl, R = CH_3; d) X = OC_2H_5, R = CH_3.

Apparently in the formation of ketone IX, the action of acetic anhydride on the carboxymethyl compound IV first gives rise to an unstable anhydro- compound, which reacts with the acid IV which has not yet reacted, to give a product which decarboxylates to the ketone IX



VIII IV

Unlike 4-phenyl-3-carboxymethylthio-1, 2, 4-triazole, (IV), 1-phenyl-5-carboxymethylthiotetrazole is unchanged even after four hrs refluxing with acetic anhydride, and this is probably connected with the nitrogen atom here having lost its capacity to appear in the ammonium form.



UV absorption spectra (in ethanol), concentration 10^{-3} M, SF-4 instrument: 1) 4-phenyl-1, 2, 4-triazoline-thione-3 (Ia); 2) 4-phenyl-3-benzylthio-1, 2, 4-triazole (IIb).

TRIT and some of the sulfides and sulfones made from it were tested for antitubercular activity, and unlike their tetrazole analogs, they were inactive*.

From observations made in the present and previous work [3, 4], it is apparent that on passing from an azole with 4 nitrogen atoms in the ring to one with 3 (from TETT to TRIT), real, qualitative differences in chemical properties and biological activity appear, though certain azole features are retained.

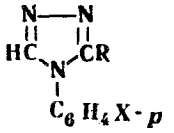
Experimental

4-p-Ethoxyphenyl-3-methylthio-1, 2, 4-triazole (IIe). 3 ml methyl iodide was added to a solution of 6. 6 g 4-p-ethoxyphenyl-1, 2, 4-triazolinethione-3 (Ic) in 6 ml 30% sodium hydroxide and 70 ml ethanol. The solution was refluxed for a few minutes, cooled, and 300 ml water added. Yield 7 g (see table). The rest of the sulfides were prepared in exactly the same way, save in the case of the condensation product from TRIT and p-nitrobenzylchloride, where reaction took place even in the cold. IR spectrum of 4-phenyl-3-methylthio-1, 2, 4-triazole (IIa) (s = strong, m = medium): 3080 m (CH aromat), 1599 m (CH aromat), 1505 s (–C=N–), 1416 s, 1321 m, 1269 s, 1242 m, 1167 m, 1006 m, 845 m, 766 s (CH aromat), 697 s (CH aromat) cm^{-1}.

4-Phenyl-1, 2, 4-triazolylmethylsulfone-3 (IIIa). 7% potassium permanganate solution was added, with stirring, to a solution of 3. 8 g IIa in 20 ml acetic acid, at 35-40°, until a sample drop placed on filter paper gave a red color which did not disappear. The solution was cooled to 10-15°, and a 40% sodium bisulfite solution added until the solution was decolorized. The yellowish precipitate of sulfone was filtered off and recrystallized from water. The other sulfones were prepared similarly. The sulfones were colorless crystalline compounds which could be crystallized from water or alcohol (see table).

4-Phenyl-3-carbamylthio-1, 2, 4-triazole (VII). 1. 77 g TRIT and 0. 65 g chloroacetonitrile were dissolved in 5 ml 2 N sodium hydroxide plus 5 ml ethanol, and the whole heated to boiling, when it turned red. It was cooled, and the crystalline precipitate VII which formed was filtered off and recrystallized from water; yield 36% (see table). The product dissolved on heating with water, alcohol, acetone, chloroform, and dichloroethane, and was insoluble in benzene, carbon tetrachloride, and petroleum ether. The same product mp 178-180° was obtained in 97% yield by reacting TRIT with chloroacetamide under conditions similar to those described above.

*The testing was done at the Chertkova Sverdlovsk Tuberculosis Institute, and we take this opportunity to express our sincere thanks.

Sulfides and Sulfones 

Compound no.	X	R	Crystal form	Mp, °C, Solvent	Formula	Found, %	Calculated, %	Yield, %
IIb	H	$SCH_2C_6H_5$	Prisms	93—94, benzene—petroleum ether	$C_{15}H_{13}N_3S$	N 15.38; S 11.80	N 15.72; S 11.99	94
IIc	H	$SCH_2C_6H_4NO_2$	Yellow plates	137—138, benzene—petroleum ether	$C_{15}H_{12}N_4O_2S$	N 17.60	N 17.94	97
IId	Cl	SCH_3	Needles	174—175, water	$C_9H_8ClN_3S$	Cl 15.60	Cl 15.70	91
IIe	OC_2H_5	SCH_3	Needles	89— 90, water	$C_{11}H_{13}N_3OS$	N 17.69	N 17.86	99
VII	H	$SCH_2C(=O)NH_2$	Needles	178—180, water	$C_{10}H_{10}N_4OS$	C 51.52; H 4.72; N 24.05; S 13.75	C 51.26; H 4.30; N 23.92; S 13.69	97
IIIa	H	SO_2CH_3	Needles	149—150, water	$C_9H_9N_3O_2S$	N 18.41; S 14.02	N 18.82; S 14.36	39
IIIb	H	$SO_2CH_2C_6H_5$	Plates	118—120, water	$C_{15}H_{13}N_3O_2S$	N 13.84; S 10.38	N 14.04; S 10.71	15
IIIc	H	$SO_2CH_2C_6H_4NO_2$	Needles	185—186, ethanol	$C_{15}H_{12}N_4O_4S$	N 16.63; S 9.07	N 16.27; S 9.31	75
IIId	Cl	SO_2CH_3	Needles	183—185, methanol, water	$C_9H_8ClN_3O_2S$	N 16.00	N 16.30	50
IIIe	OC_2H_5	SO_2CH_3	Plates	165—166.5, water	$C_{11}H_{13}N_3O_3S$	N 15.68	N 15.72	70

Oxidation of 4-phenyl-3-carboxymethylthio-1, 2, 4-triazole (IV).

a) With potassium permanganate. 0. 22 g acid IV was oxidized in the way described above for sulfides. After decolorizing with sodium bisulfite, the solution was extracted 3 times with benzene. The benzene solution was dried over sodium sulfate, and the benzene distilled off to give 0. 17 g (82%) sulfone IIIa.

b) With hydrogen peroxide. 0.47 g acid IV was refluxed for ten hr with 6 ml glacial acetic acid and 1. 6 ml 30% hydrogen peroxide. The solution was then evaporated, and the precipitate crystallized from water. Yield of 4-phenyl-1, 2, 4-triazolinone-3 (VI) 0. 23 g (70%), mp 185-186° (plates). Mixed mp with an authentic specimen of the triazolone VI of mp 186°, undepressed. IR spectrum: (s = strong, vs = very strong, m = medium): 3200 m (NH), 3121 m, 3078 m, 2993 m, (CH aromat), 1706 vs (C=O), 1593 m (CH aromat), 1561 s, 1499 s (—C=N—) cm^{-1}.

Di(4-phenyl-3-methylenethio-1, 2, 4-triazolyl)ketone (IX)

a) 0. 7 g IV was refluxed for 20 min in 4 ml acetic anhydride, and the substance which precipitated on cooling was filtered off and recrystallized from water; yield 0. 4 g (66%), mp 167-168° (yellow plates). The product was readily soluble in alcohol, acetone, chloroform, and benzene on heating, but insoluble in ether and petroleum ether. Found: C 56. 37; H 4. 22; N 20. 43; S 15. 56%. Calculated for $C_{19}H_{16}N_6OS_2$: C 55. 86; H 3. 94; N 20. 57; S 15. 70%.

b) 0. 47 g acid IV was dissolved in 3 ml hot pyridine, 0. 5 ml acetic anhydride added, and the whole heated on a steam bath for a few minutes, after which the brown solution was evaporated on the same bath. Yield 0. 33 g (81%).

c) 1. 77 g TRIT was heated with 0. 65 g symm.-dichloroacetone in 6 ml ethanol. The solution was cooled, 100 ml water added, and the gradually solidifying precipitate filtered off; yield 1. 9 g (93%), mp 167-168° (from water). The mixed mp of the two products prepared by the different routes was undepressed.

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