CHEMISTRY OF sym-TETRAZINE

V.* sym-TETRAZINE- AND sym-TRIAZOLINETHIONES

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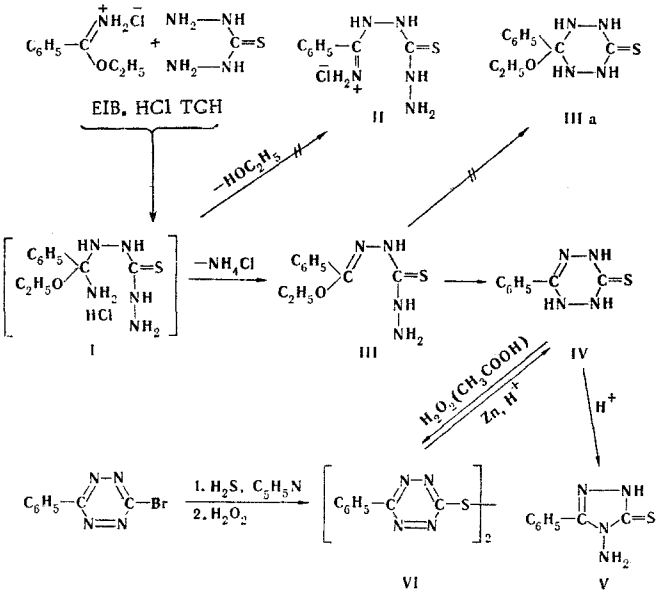
Ethyl benzoate thiocarbohydrazone, which exists in solution with a cis-to-trans isomer ratio of 4.5 : 1, was obtained by reaction of ethyl imidobenzoate hydrochloride with thiocarbohydrazide. In polar solvents the product readily splits out a molecule of alcohol to give 3-phenyl-4-amino-1,2,4-triazoline-5-thione and on oxidation with hydrogen peroxide in glacial acetic acid it is converted to 6,6'-diphenyl-3,3'-biz(sym-tetrazinyl) disulfide, which can be reduced to 6-phenyl-1,2-dihydro-sym-tetrazine-3-thione.

In a search for new methods for the heretofore difficult-to-obtain sym-tetrazinethiones we carried out the reaction of ethyl imidobenzoate hydrochloride (EIB·HCl) with thiocarbohydrazide (TCH). In this case we assumed that the initially formed product of nucleophilic addition (I, see the scheme below) would give, by splitting out of a molecule of alcohol, amidrazone derivative II, which subsequently after splitting out of NH_4Cl, would be converted, depending on elimination of a hydrogen atom from 1-N or 2-N, to 6-phenyl-1,2-dihydro-sym-tetrazine-3-thione (IV) or to 3-phenyl-4-amino-1,2,4-triazoline-5-thione (V). We found that the reaction of ethyl imidobenzoate hydrochloride with thiocarbohydrazide actually leads to the above-mentioned thiones IV and V, but via a different pathway.



A substance with the composition $C_{10}H_{14}N_4OS$, which has ethyl benzoate thiocarbohydrazone structure III (see below), precipitates in ~75% yield when the reaction is carried out in aqueous media. The previously described [2] 3-phenyl-4-amino-1,2,4-triazoline-5-thione (V), the structure of which was confirmed by its conversion to 5-phenyl-1,2,4-triazoline-3-thione, was isolated as a second reaction product in 17% yield from the mother liquor.

*See [1] for communication IV.

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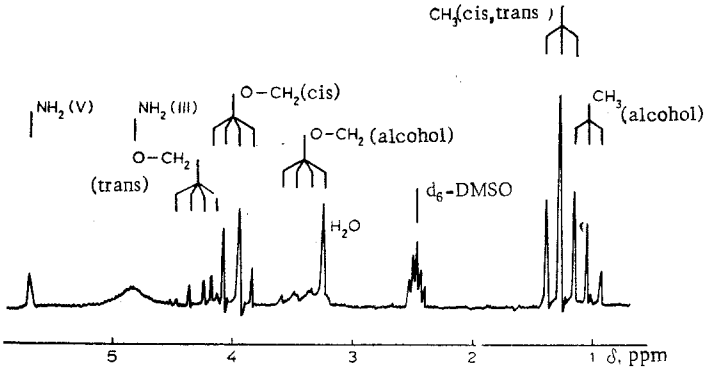

Fig. 1. PMR spectrum of thiocarbohydrazone III in perdeuterodimethyl sulfoxide.

Thiocarbohydrazone III undergoes cyclization when it is heated in polar solvents [H_2O, C_2H_5OH, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and $C_2H_5NO_2$] and especially readily in acids (HCl, CH_3COOH) with splitting out of a molecule of alcohol to give triazolinethione V. This transformation can be followed distinctly from the change in the PMR spectrum in perdeuterodimethyl sulfoxide. Signals of ethanol at 1.08 (t, CH_3) and 3.46 ppm (q, CH_2O) appear even at room temperature. The formation of triazolinethione V is detected from the increase in the signals at 5.80 (NH_2) and 14.85 ppm (NH), which coincide with the signals of V obtained by an independent method. Splitting out of a molecule of alcohol from thiocarbohydrazone III is accelerated to such an extent in CF_3COOH solution that triazolinethione V is formed quantitatively even when III is dissolved in this solvent. Triazolinethione V p-nitrophenylhydrazone was also obtained in an attempt to protect the free hydrazine group in III by reaction with p-nitrobenzaldehyde.

Signals of two different CH_2O groups at 4.31 and 4.01 ppm, protons of the thiocarbohydrazide residue at 4.90 ppm (NH_2), the superposition of three broad NH signals at 9.15, 9.55, and 9.75 ppm (2H), and a complex multiplet of aromatic protons at 7.3-7.8 ppm are observed in the PMR spectrum of III in $(CD_3)_2SO$. The doubling of the CH_2O signals is evidently due to the presence in solution of a second isomer. Thione–thiol tautomerism does not exist for III, since the characteristic SH bands at 2500-2600 cm^{-1} are completely absent in the IR spectrum of the compound in DMSO. It is known [3] that thiocarbohydrazides can exist in the cyclic form, for example, in the form of covalent alcoholate IIIa. However, the assumption of the equilibrium existence of isomer IIIa is not in agreement with the high chemical shifts of the CH_2O protons, which are characteristic for an ester grouping (structure III) in contrast to the ether grouping (structure IIIa).

The data from the PMR spectra of III can be satisfactorily explained by assuming cis–trans isomerism relative to the C=N bond, which is well known for many hydrazones [4]. A cis configuration with less bulky substituents attached to the carbon atom usually predominates [5]. Thus the less intense quartet of CH_2O protons at 4.31 ppm can be assigned to the trans isomer, and the more intense quartet at 4.01 ppm can be assigned to the cis isomer (Fig. 1). Judging from the relative intensities of the components of the CH_2O quartets, the ratio of the isomers in solution is 1 : 4.5.

When thiocarbohydrazone III is oxidized with hydrogen peroxide in glacial acetic acid, it undergoes tetrazine ring closure to give purple-red crystals of 6,6'-diphenyl-3,3'-bis(sym-tetrazinyl) disulfide (VI) in good yield. The electronic spectrum of VI contains two absorption bands characteristic for tetrazine compounds at 290 and 534 nm.

In conformity with the disulfide structure, the IR spectrum does not contain vibrations of a thioamide group or absorption bands of NH and SH groups. At the same time, the spectrum contains a strong narrow band at 550 cm^{-1}, which is related to the stretching vibrations of an S–S grouping [6]. The disulfide structure was confirmed by alternative synthesis. A compound identical to disulfide VI was obtained when hydrogen sulfide was bubbled through a pyridine solution of 6-phenyl-3-bromo-sym-tetrazine (VII) and hydrogen peroxide was subsequently added to the mixture. Yellow crystals of 6-phenyl-1,2-dihydrotetrazine-3-thione (IV) were obtained when the disulfide was reduced with zinc dust in glacial acetic acid. This compound does not add a molecule of alcohol either in the cold or when it is heated, from which it follows that it is not converted to covalent alcoholate IIIa. This may serve as another piece of evidence against the existence in solution of ring isomer IIIa along with the chain form. In acidic media the dihydro compound is readily isomerized with ring contraction, as in the case of other dihydrotetrazines [7], to triazole derivative V. This sort of conversion of

III to V is also observed when it is heated in alcohol and other solvents. Dihydro compound IV is rapidly oxidized to disulfide VI under the influence of hydrogen peroxide.

The material set forth above provides a basis for the following conception of the III → VI reaction (see the scheme above). 6-Phenyl-1,2-dihydrotetrazine-3-thione (IV) is initially formed as a result of intramolecular attack by the NH_2 group of III at the C = N carbon atom, possibly through a step involving the extremely unstable covalent alcoholate IIIa. Under the reaction conditions IV undergoes rapid isomerization to triazolinethione V but in the presence of an oxidizing agent gives 6-phenyl-3-mercaptotetrazine, which is subsequently oxidized to disulfide VI.*

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EXPERIMENTAL

The UV spectra of dimethylformamide (DMF) solutions of the compounds were recorded with a Specord UV-vis spectrometer. The IR spectra of mineral oil (NaCl prism) and perfluorocarbon oil (LiF prism) suspensions of the crystalline compounds were recorded with a UR-20 spectrophotometer. The PMR spectra of $(CD_3)_2SO$ solutions of the compounds were recorded with a Perkin–Elmer R 12B spectrometer with hexamethyldisiloxane as the internal standard.

Ethyl Benzoate Thiocarbohydrazone (III) and 3-Phenyl-4-amino-1,2,4-triazoline-5-thione (V). An 11.1-g (60 mmole) sample of ethyl imidobenzoate hydrochloride was added all at once to a boiling solution of 6 g (57 mmole) of thiocarbohydrazine in 120 ml of water, after which the mixture was cooled rapidly, and the resulting colorless precipitate was removed by filtration, washed with water, and air dried to give 10 g (74%) of a product with mp 154-155 deg C [alcohol with DMF (1 : 1)]. Crystallization must be carried out as rapidly as possible in view of the conversion of III to triazolinethione V on heating. Found: C 50.5; H 5.9; N 23.3; S 13.6%. $C_{10}H_{14}N_4OS$. Calculated: C 50.4; H 5.9; N 23.5; S 13.5%. IR spectrum: 3258 m (NH_2), 3174 w (NH), 2970 w (aromatic CH), 1622 m (NH_2, C_6H_5), 1508-1542 vs (C = N, aromatic C = C), 1448-1467 s br (N–C–S), 1313 s (N–C–S), 1260-1274 m br (C = S), 1101 s, 1074 m, 1017 s, 927 w, 776 m (C_6H_5), and 698 s cm^{-1} (C_6H_5).†

The aqueous mother liquor obtained after separation of III was evaporated to 50-60 ml, and the concentrate was allowed to stand for 24 h for completion of crystallization. The colorless precipitate of 3-phenyl-4-amino-1,2,4-triazoline-5-thione (V) was removed by filtration to give 1.85 g (17%) of shiny plates from ethanol with mp 208-209 deg C (mp 204-206 deg C [2]). Found: C 50.2; H 4.3; N 29.4; S 16.8%. $C_8H_8N_4S$. Calculated: C 50.0; H 4.2; N 29.1; S 16.7%. IR spectrum: 3300 m (NH_2), 3195 w, 3105 m br (NH), 2934 w (aromatic CH), 1639 s, 1536 s narrow, 1503 vs narrow (C = N, aromatic C = C), 1457-1472 s (N–C–S), 1323 vs (N–C–S), 1237 w (C = S), 790 s (C_6H_5), 690 s (C_6H_5), 603 m, and 508 w cm^{-1}.

Compound V was also obtained: a) in 60% yield by heating 0.5 g (2.3 mmole) of III in 10 ml of 2 N HCl for 2 h; b) in almost quantitative yield by heating 6-phenyl-1,2-dihydrotriazine-3-thione (IV) in 2 N HCl.

Compound V gave bright-yellow fine crystals of a hydrazone with mp 225-227 deg C (from ethanol) on reaction with p-nitrobenzaldehyde. Found: C 55.2; H 3.5; N 21.5; S 9.7%. $C_{15}H_{11}N_5O_2S$. Calculated: C 55.4; H 3.4; N 21.5; S 9.9%. This hydrazone was identical to the compound obtained from III by heating in ethanol with p-nitrobenzaldehyde.

Deamination of V with sodium nitrite in glacial acetic acid by the method in [2] gave crystals with mp 254-256 deg C (mp 256 deg [2]). Found: C 54.3; H 3.5; N 23.5; S 18.0%. $C_8H_7N_3S$. Calculated: C 54.2; H 4.0; N 23.2; S 18.1%.

6,6'-Diphenyl-3,3'-bis(sym-tetrazinyl) Disulfide (VI) [10]. A) A 1.5-ml sample of 30% hydrogen peroxide was added with stirring to a suspension of 1.65 g (7.4 mmole) of III in 8 ml of glacial acetic acid. At the end of the reaction, the temperature was raised to 60-70 deg C. The purple-red precipitate was removed by filtration and washed with water, alcohol, and ether to give 1 g (76%) of prisms with mp 200-201 deg C [from alcohol–DMF (1 : 1)]. Found: C 50.7; H 2.8; N 29.5; S 16.8%; M 370 (by the Rast method). $C_{16}H_{10}N_8S_2$. Calculated: C 50.8; H 2.7; N 29.6; S 16.9%; M 378. IR spectrum: NH and SH bands at 2400-3500 are absent; 1600 w (C = N, aromatic C = C), 1466 m narrow, 1422 m narrow, 1346 vs (N–C–S), 1186 s (tetrazine?), 1165 m, 1072 m,

*The reaction of an iminoester with thiocarbohydrazide, as a result of which 4-amino-3-R-triazoline-5-thione (R = $C_{17}H_{35}$) was isolated, has been described in the patent literature [8]. The preparation of the corresponding tetrazinethione is not mentioned (see [9]).

†The authors thank I. I. Mudretsova for recording the IR spectra.

900 m, 762 s (C_6H_5), 690 s (C_6H_5), and 562-570 s cm^{-1} (S–S). UV spectrum, λ_{max} (log ε): 290 (4.60) and 534 nm (2.45).

B) Hydrogen sulfide was bubbled through a solution of 0.95 g (4.0 mmole) of 6-phenyl-3-bromotetrazine (VII) [11] in pyridine until the red color of VII vanished, after which 5 ml of 15% hydrogen peroxide was added. The red precipitate was removed by filtration and crystallized from alcohol–DMF (1 : 1) to give 0.2 g (26%) with mp 198-202 deg C. No melting-point depression was observed for a mixture of this compound with a sample of the compound obtained from thiocarbohydrazone III.

A suspension of the disulfide in alcohol became colorless when it was shaken with zinc dust, but the compound was rapidly reoxidized to the red disulfide in air. This transformation can be repeated many times.

6-Phenyl-1,2-dihydro-sym-tetrazine-3-thione (IV). Zinc dust was added in portions to a suspension of 0.5 g (1.3 mmole) of disulfide VI in 20 ml of glacial acetic acid until the red color disappeared. The excess zinc was removed by filtration, crushed ice was added to the filtrate, and the resulting precipitate was separated and washed with water and alcohol to give 0.25 g (49%) of yellow plates with mp 201-203 deg C (from ethanol). Found: C 50.0; H 4.1; N 29.1%. $C_8H_8N_4S$. Calculated: C 50.0; H 4.2; N 29.2%. IR spectrum: 3276 m, 3160 m (NH), 2920 w (aromatic CH), 1645 m, 1605 w, 1552-1580 m (C=N, aromatic C=C), 1470 s, 1410-1428 vs (N–C–S), 1308-1327 s (N–C–S), 1246 vs (C=S), 1100 m, 1032 m, 780 s narrow (C_6H_5), 690 vs (C_6H_5), 610-620 m br, and 507 m cm^{-1}.

The product was soluble in 2 N NaOH. The resulting yellowish solution gradually turned red (because of formation of the disulfide). Conversion to the disulfide is accomplished rapidly if hydrogen peroxide is added to a solution of the compound in glacial acetic acid.

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