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The addition of dimethyl acetylenedicarboxylate to 3-methyl-1,2,4-triazole-5-thione (**1**), both in alcoholic medium and in inert solvents, has been investigated. When **1** was allowed to react with diethyl azodicarboxylate a disulfide **5** was obtained.

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In recent years there has been an increased interest in the synthesis of heterocyclic compounds containing sulphur and nitrogen in order to study the pharmacological properties of the resulting compounds.

In preceding reports we have described the reaction between diethyl azodicarboxylate and 2-thioxoquinazolines [1] and the addition of acetylenic esters to thioureas [2]. The reactions of thiosemicarbazides substituted with acetylenic esters have been reported to give 1,3-thiazin-4-one derivatives [3] and thiazolotriazin-3,7-diones [4]. With a view to extending the synthetic utility of dimethyl acetylenedicarboxylate (DMAD) to cyclic models of thiosemicarbazides we have investigated the addition of DMAD to 3-methyl-1,2,4-triazole-5-thione and we herein report our results. When compound **1** was allowed to react with DMAD in boiling methanol only one product was obtained that showed to be adduct **3**, the reaction being complete within a few hours (Scheme 1).

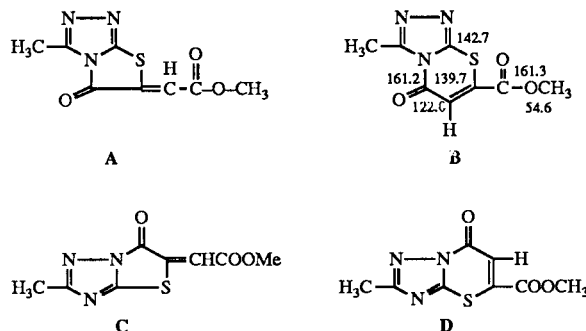
Scheme 1



By carrying out the reaction in an inert solvent such as tetrahydrofuran or acetonitrile the reaction does not occur or poor yields are obtained either at room temperature or under reflux conditions. The ir spectrum (nujol) of **3** showed two carbonyl absorptions at 1720 (ester CO) and 1705 cm^{-1} (amide CO) but no NH bands. The ^1H -nmr spectrum (deuteriochloroform) exhibited signals corresponding to one methyl ester group at δ_{H} 4.07 (s, 3H, OCH_3) and a vinyl proton at δ_{H} 7.68 (s, 1H, $>\text{C}=\text{CH}$), besides that of the substituent at C^3 (δ_{H} 2.60, s, 3H, CH_3); no signals ex-

changeable with deuterium oxide were present. These data indicated that a cyclization process had occurred to give a heterocyclic condensed system. The mass spectrum showed a molecular ion peak at m/z 225 (47%) corresponding to 1:1 molar adduct which condensed by methanol elimination; conventional "simple" fragmentations, such as loss of OMe (m/z 194 (8%)) and CO_2Me (m/z 166 (100%)) confirmed the gross structural features. Significant peaks occurred at m/z 139 (7%), 116 (11%), 86 (5%), 85 (30%), 59 (20%) and 57 (25%). These data were consistent with all four of the possible condensed structures **A**, **B**, **C**, and **D** but were not sufficient to distinguish between them. A method of distinguishing five member (**A** and **C** type) and six member (**B** and **D** type) adducts from thiols and DMAD, based on the marked difference of the chemical shifts of the carbon atoms in the ^{13}C -nmr spectra has been reported [4,5]. The analysis of the ^{13}C -nmr chemical shifts of the spectrum of compound **3** allowed us to assign to it the six member condensed ring structure, **B** or **D** type (Scheme 2).

Scheme 2

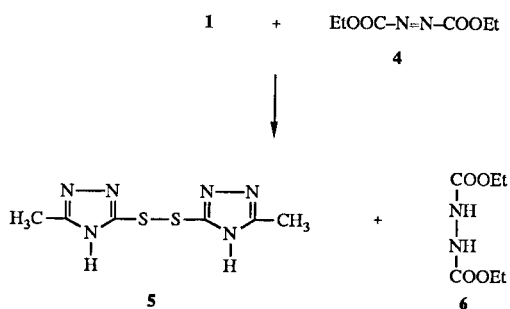


In fact, the vinyl C-H carbon resonance in **A** or **C** similar structures is shown to be at higher fields (δ_{C} 112.9) than in six member ring structures such as **B** or **D** (δ_{C}

122.0, assigned from our uncoupled spectrum); the ester carbonyl carbon atom was at higher fields (δ_c 161.3) than in five member adducts (δ_c 165.7) [5]. Moreover, the amide-carbonyl carbon atom in the **A** or **C** type structures appears at higher fields (δ_c 157.2) than in **B** or **D** (δ_c 161.2). Furthermore, the carbon atoms bonded to a sulphur atom are shown to be at lower fields in **A** or **C** type structures. An immediate decision between structures **B** and **D** in favour of the former can be reached by comparison of the ^{13}C chemical shift value of the carbonyl carbon's ring for our product with those of similar compounds having in their cyclic structure the $>\text{N}-\text{CO}-\text{C}=\text{sequence}$ (δ_c 161.2 in structure **B** and δ_c 158.3 in similar structures with an $=\text{N}-(\text{N})-\text{CO}-\text{sequence}$ [6], so that the values of ^{13}C chemical shifts found for adduct from **1** and DMAD fit well with structure **B**. Then, the compound **3** is identified as methyl 3-methyl 5-oxo-5*H*-s-triazolo[3,4-*b*]-[1,3]thiazine-7-carboxylate (**B**). Successively, in order to obtain new heterocyclic compounds, **1** was allowed to react with diethyl azodicarboxylate (**4**).

It is known [7] that substituted thioureas react with diethyl azodicarboxylate to give an intermediate which undergoes thermal decomposition affording carbodiimides; on the other hand, azoesters generally react with dienes *via* three pathways: the addition-abstraction reaction, an oxidation-reduction reaction and a Diels-Alder addition reaction [8]. In an earlier paper we reported that two of these routes take place when 1,2,3,4-tetrahydro-2-thioxoquinazolin-4-one was allowed to react with diethyl azodicarboxylate [1]. We have shown that the products obtained could arise from a 1:1 adduct (thermally unstable), such as diethyl (3,4-dihydro-4-oxo-2-quinazolinyl)thiobicarbamate isolated in the course of the reaction. On the other hand, it is claimed that mercaptans reacting with azoesters are transformed into the corresponding disulphides [9,10]. When compound **1** was allowed to react with **4**, only compounds **5** and **6** were obtained under the various reaction conditions (Scheme 3). We carried out the reaction both in an alcoholic medium and in an inert solvent such as acetonitrile or tetrahydrofuran both at reflux and at room temperature. At the lower temperature (0-10°) the reaction led to the same products but with very low yields.

Scheme 3



Compound **5** is a colourless crystalline solid, $\text{C}_4\text{H}_8\text{N}_6\text{S}_2$, mp 215-216°. It shows infrared broad bands at 3200 cm^{-1} (NH). Its $^1\text{H-nmr}$ spectrum (DMSO- d_6) exhibits a singlet at δ_H 2.3 (6H, 2 CH_3) and a broad singlet centered at δ_H 12.9 which was exchanged with deuterium oxide (NH). The mass spectrum showed a molecular ion peak at m/z 228 (76%) and fragments of importance from the standpoint of structural conformation which occur at m/z 142 (29%), 115 (100%), 83 (26%). The isotopic cluster at m/z 228 and 230 (9.7%) indicates two sulphur atoms in the molecule. These data allow a definite assignment of the structure of 3,3'-dithiobis[5-methyl-4*H*-1,2,4-triazole]. This product was obtained with other triazole disulphide derivatives by reaction of **1** with oxidizing agents [11]. Such derivatives were useful as DOPA-decarboxylase inhibitors at 35-85 μM and hypotensives at 50-100 mg/Kg. In our experiment the reaction produced the disulfide **5** in one step and with a high yield.

EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. The ir spectra were recorded using a Perkin-Elmer 1720 Fourier transform spectrophotometer as nujol mulls. The $^1\text{H-nmr}$ spectra were recorded at 60 MHz on a Varian EM-360 instrument with tetramethylsilane as internal standard as deuteriochloroform or DMSO- d_6 solutions. The $^{13}\text{C-nmr}$ spectra were recorded at 62.9 MHz with broad band decoupling on a Bruker AC 250 as spectrometer in deuteriochloroform solutions. Mass spectra were recorded on a Jeol JMS-10SG-2 mass spectrometer. Elemental analyses were carried out by the Kurt Eder service (Geneve, Switzerland). The tlc for confirming compound purity utilized 0.25 mm silica gel plates (Merck) with fluorescent indicator and methylene chloride-ethyl acetate (6:4) as the solvent system. 3-Methyl-1,2,4-triazole-5-thione was prepared by a literature method [12]. Its purity was checked by tlc and it was identified on the basis of its spectroscopic properties.

Methyl 3-Methyl-5-oxo-5*H*-s-triazolo[3,4-*b*][1,3]thiazine-7-carboxylate (**B**).

A solution of **2** (1.70 g, 0.012 mole) in 3 ml of methanol was added dropwise to a stirred solution of **1** (1.44 g, 0.012 mole) in 20 ml of methanol. The mixture was refluxed for 3 hours and then allowed to stand for 3 hours at room temperature, during which time crystals separated. The resulting solid material was filtered, washed with methanol, dried and purified by chromatography over a column of silica gel (methylene chloride/ethyl acetate 7:3 as eluent). The product obtained crystallized from ethyl acetate in a yield of 2.1 g (75%) of **3** as colorless crystals, mp 151-152°.

Anal. Calcd. for $\text{C}_8\text{H}_7\text{N}_3\text{O}_3\text{S}$: C, 42.67; H, 3.11; N, 18.67; S, 14.22. Found: C, 42.78; H, 3.34; N, 18.41; S, 13.94.

When compound **1** was allowed to react with DMAD in tetrahydrofuran or acetonitrile with the above procedure at room temperature, the reaction does not occur. When the mixture was refluxed for 3 hours and then allowed to stand for 3 hours at room temperature, the same crude **3** was obtained in poor yield. The product was isolated and purified under the conditions prev-

iously described (reaction between **1** and **2** in methanol) and melted at 151-152° undepressed with a sample of **3**. The infrared spectra of the two samples were identical.

3,3'-Dithiobis[5-methyl-4*H*-1,2,4-triazole] (**5**).

A solution of **4** (0.75 g, 0.0043 mole) in 5 ml of acetonitrile was gently added to a stirred solution of **1** (0.5 g, 0.0043 mole) in 20 ml of acetonitrile. The mixture was refluxed and stirred for 3 hours and then set aside overnight during which time the crystals separated. The resulting crude mass was collected, washed with cold acetonitrile, and recrystallized from ethyl acetate to yield 0.87 g (88%) of **5** as crystals.

Anal. Calcd. for C₆H₈N₆S₂: C, 31.58; H, 3.51; N, 36.84; S, 28.07. Found: C, 31.61; H, 3.64; N, 36.78; S, 27.87.

The acetonitrilic mother liquors of the reaction, after removal of compound **5** were concentrated in a rotary evaporator to about 10 ml to afford a crude product. Recrystallization from benzene yielded colorless crystals (0.76 g, 85%), mp 131-132°, identified as **6** by comparison of the ir spectrum with that of an authentic pure sample obtained from ethyl chloroformate and hydrazine hydrate [13]. The melting point was not depressed when mixed. The same products **5** and **6** were obtained when the reaction above mentioned, was repeated whether at reflux or at room temperature using methanol or tetrahydrofuran as solvent.

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