REACTIONS INVOLVING THE FORMATION AND RECYCLIZATION OF HETEROCYCLES

IX.* RECYCLIZATION OF 5-ARYL-1,3,4-OXADIAZOLE-2-THIONES UNDER THE INFLUENCE OF HYDRAZINES

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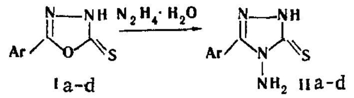
The reaction of 5-aryl-1,3,4-oxadiazole-2-thiones with hydrazine and hydrazides proceeds with recyclization of the oxadiazole ring to a triazole ring. Depending on the nature of the aryl residue, adducts of 5-aryl-1,3,4-oxadiazole-2-thiones with hydrazine can be isolated in a number of cases. 6-Aryl-2-methyldihydro-1,2,4,5-tetrazine-3-thiones are formed with methylhydrazine as a result of recyclization.

In studying the recyclization of five-membered heterocycles under the influence of hydrazines we assumed that hydrazine acts on azolidones and oxazolones as a two-center reagent of the type that involves quasi-1,2-addition to the heterocycle. Depending on the relative positions of the electrophilic centers in the heteroring, triazolone, triazolethione [2], or triazinone [1] derivatives, respectively, are formed in the process. However, it is known [3] that such aromatic five-membered heterocycles as aminooxadiazoles are recyclized to aminotriazoles during reaction with hydrazine. We became interested in other oxadiazole derivatives activated by electronegative substituents in the two-position of the heteroring. Since oxadiazolones are cleaved by the action of hydrazine [4], we decided to study oxadiazolethiones.

The hydrazination of oxadiazolethiones has received very little study. According to a patent [5], the reaction of 5-isonicotinyl-1,3,4-oxadiazole-2-thione with hydrazine hydrate leads to a compound with empirical formula $C_8H_8N_4S$ having one of two possible isomeric structures – 5-isonicotinyl-3-mercapto-4-amino-1,2,4-triazole or 6-isonicotinyl-1,2-dihydro-1,2,4,5-tetrazine. In order to ascertain the peculiarities of the recyclization of oxadiazolethiones under the influence of hydrazine and to definitively establish the structures of the final products, we investigated the reaction of aryloxadiazolethiones with hydrazine and its derivatives in various media under various temperature conditions.

The reaction of 5-aryl-1,3,4-oxadiazole-2-thiones (I) with hydrazine while refluxing in organic solvents is completed by recyclization to 5-aryl-4-amino-1,2,4-triazole-3-thiones (II):



I a-d II a-d

a $Ar = C_6H_5$; b $Ar = p\text{-}CH_3OC_6H_4$;
c $Ar = p\text{-}O_2NC_6H_4$; d $Ar = \gamma\text{-}C_5H_4N$

A more detailed investigation of the rearrangement of oxadiazolethiones demonstrated that at room temperature adducts IIIa, IIIc, and IIId are formed with hydrazine; these adducts have a high specific electrical conductivity (of the order of the electrical conductivities for organic salts) and a number of properties that make it possible to consider them to be compounds of ionic character. Thus, acidification precipitates the starting oxadiazole, while the action of benzaldehyde at room temperature gives benzalazine.

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*See [1] for communication VIII.

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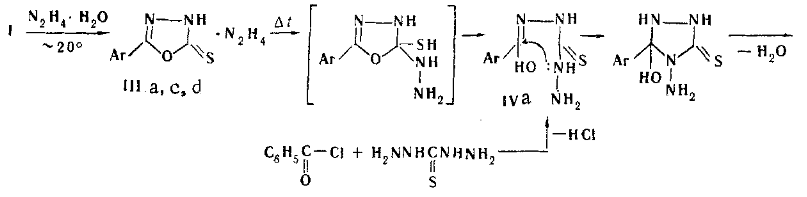
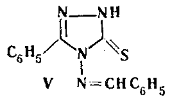
In contrast to the azolidone analogs, the hydrazino salts of oxadiazolethiones are completely stable on storage and even on brief heating; this makes it possible to crystallize them from alcohol solutions. Their stability depends to a considerable degree on the nature of the substituents in the aryl residue. The stronger the electron-acceptor substituent, the more stable the adducts [for example, with 5-(p-nitrophenyl)-1,3,4-oxadiazole-2-thione] prove to be. A salt of this type cannot be isolated at all in the presence of a strong electron–donor substituent [for example, with 5-(p-methoxyphenyl)-1,3,4-oxadiazole-2-thione].

The formation of the corresponding triazolethiones (IIa, IIc, and IId) is observed when the adducts are refluxed in organic solvents. Since 5-aryl-4-amino-1,2,4-triazole-3-thione is also obtained from specially synthesized 1-benzoylthiocarbohydrazide (IVa) under adequate conditions, the mechanism of the recyclization of oxadiazolethiones can be represented by the scheme

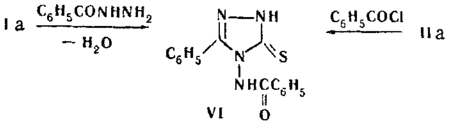


The structures of the final reaction products as aminotriazolethiones are confirmed by analytical data (with respect to elementary and functional compositions). The characteristic band of the mercapto group is not observed in their IR spectra (in KBr pellets), and a thione structure, at least in the solid state, should be preferred for them. They do not give a positive reaction for the hydrazine group with Fehling's solution and do not react with benzaldehyde in alcohol as do thiosemicarbazide derivatives. Benzylidene derivative V is obtained only when the starting components are refluxed in acetic acid containing sodium acetate:

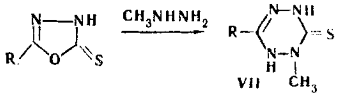

V

Since tetrazines can also be converted to aminotriazoles by heating in acid media [6], a test experiment with refluxing of the starting IIa in acetic acid was specially set up. The stability of IIa under these conditions excludes a tetrazine structure for the recyclization products.

The recyclization of oxadiazolethione Ia under the influence of benzhydrazide proceeds under comparatively severe conditions by refluxing the components in dimethylformamide. Since a product that is identical to that obtained in the benzoylation of aminotriazolethione IIa is formed, it can unambiguously be asserted that it has the 5-phenyl-4-benzamido-1,2,4-triazole-3-thione (VI) structure:

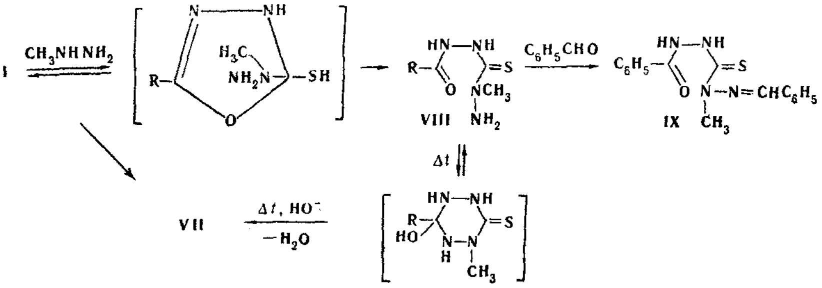


An investigation of the recyclization of oxadiazolethiones under the influence of methylhydrazine seemed of interest. If it is considered that methylhydrazine in reactions with azolidones always attacks the most electrophilic center of the heteroring with the methylated nitrogen atom [2], one might expect that compounds with a tetrazine structure would be obtained in the case of oxadiazolethiones. The formation of aminotriazolethiones is impossible for this sort of direction of attack of the heteroring by methylhydrazine. Prolonged refluxing of oxadiazolethiones in organic solvents with excess methylhydrazine actually leads to recyclization of the oxadiazole ring to a tetrazine ring:



The characteristic band of the mercapto group is not observed in the IR spectra (in KBr pellets) of tetrazine VII.

An intermediate product of recyclization of an oxadiazolethione (R = C_6H_5) – 1-benzoyl-4-methylthiocarbohydrazide (VIII) – can be isolated by brief heating. The structure of this compound is in agreement with the analytical data and the chemical properties. The formation of benzylidene derivative IX attests to the presence of a primary amino group. As might have been expected in accordance with the presuppositions set forth in [7], carbohydrazide VIII splits out a molecule of water during refluxing in an alkaline medium to give 6-phenyl-2-methyldihydro-1,2,4,5-tetrazine-3-thione (VIIa), identical to the sample obtained above by direct recyclization; this unambiguously proves the structure of the latter. The proposed mechanism of these transformations can be expressed by the following scheme:



Thus the participation of both reaction centers of the hydrazine in the recyclization of such heterocycles as oxadiazolethiones is observed when there is a substituent attached to the α-nitrogen atom of the hydrazine added to the heteroring under sufficiently severe conditions. However, if this nitrogen atom is unsubstituted, the formation of a triazole system is preferred, and hydrazine acts as a one-center reagent.

EXPERIMENTAL

5-Phenyl-1,3,4-oxadiazole-2-thione (Ia). A mixture of 5 g of 5-phenyl-1,3,4-oxadiazole-2-one and 3.5 g of phosphorus pentasulfide in 30 ml of dioxane containing several drops of water was refluxed for 2 h. The unchanged solid material was filtered, and the filtrate was evaporated on a water bath. The residue was treated with water and filtered to give 3.5 g (64%) of a product with mp 210° (from aqueous alcohol). Compound Ia, obtained by another route, had mp 212° [8]. Neither sample depressed the melting point of the other.

1-Benzoylthiocarbohydrazide (IVa). A solution of 4 ml of benzoyl chloride in 30 ml of dioxane was added dropwise with vigorous stirring in the course of 30 min to a solution of 4.24 g (0.04 mole) of thiocarbohydrazide in 30 ml of 3 N potassium hydroxide. The reaction mixture was acidified with acetic acid, and the resulting precipitate was filtered and crystallized from 40 ml of ethanol to give 4.2 g (50%) of colorless needles that were insoluble in water, were soluble on heating in alcohol, and melted at 143-145° (decomp., from alcohol). Found %: S 15.2. $C_8H_{10}N_4OS$. Calculated %: S 15.0. The mother liquor was treated with water, and 3 g (24%) of dibenzoylthiocarbohydrazide with mp 171° (from aqueous alcohol) was obtained by filtration. Found %: S 10.2. $C_{15}H_{14}N_4O_2S$. Calculated %: S 10.2.

Adduct of 5-Phenyl-1,3,4-oxadiazole-2-thione with Hydrazine (IIIa). Hydrazine hydrate (0.85 ml) was added to a solution of 3 g (0.017 mole) of oxadiazole Ia in 50 ml of dioxane to precipitate 3.2 g (92%) of colorless crystals with mp 131-132° (decomp., from dioxane) that were soluble in water, less soluble in alcohol, and soluble on heating in dioxane. Found %: N 26.8; S 15.2. $C_8H_{10}N_4OS$. Calculated %: N 26.7; S 15.2.

Adduct of 5-Nitrophenyl-1,3,4-oxadiazole-2-thione with Hydrazine (IIIc). This was similarly obtained in 95% yield and had mp 149° (decomp.). Found %: N 27. $C_8H_9N_5O_3S$. Calculated %: N 27.4.

Adduct of 5-Isonicotinyl-1,3,4-oxadiazole-2-thione with Hydrazine (IIId). This was similarly obtained in 90% yield and had mp 226° (from alcohol). Found %: N 33.3. $C_7H_9N_5OS$. Calculated %: N 33.2.

All of the adducts obtained gave the starting oxadiazoles on treatment with aqueous hydrochloric acid and gave benzalazine and the starting oxadiazole on treatment with benzaldehyde.

5-Phenyl-4-amino-2,3-dihydro-1,2,4-triazole-3-thione (IIa). A. Adduct IIIa was refluxed in butanol for 30-40 min. The mixture was cooled, and the precipitate was filtered to give 80% of colorless crystals with mp 210° (from ethanol) that were insoluble in water and soluble on heating in alcohol. Found %: C 50.0; H 4.3; N 29.0; S 16.6. $C_8H_8N_4S$. Calculated %: C 50.0; H 4.2; N 29.2; S 16.7.

B. A 0.5 g sample (2.4 mmole) of thiocarbohydrazide IVa was refluxed in 2.5 ml of pyridine for 3 h. The mixture was treated with water, and the resulting precipitate was filtered to give 0.3 g (65%) of a product with mp 209° (from ethanol).

C. Triazole IIa was similarly obtained by refluxing benzoylthiocarbohydrazide IVa in dimethylformamide (43% yield), in amyl alcohol (60% yield), xylene (with a Dean–Stark trap, 55% yield), and in acetic acid (75% yield).

D. Hydrazine hydrate (1.5 ml) was added to a solution of 1.78 g (0.01 mole) of oxadiazole Ia in 10 ml of dioxane, and the mixture was refluxed for 3 h. The solvent was evaporated, and the precipitate was treated with water and filtered to give 1.15 g (55%) of a product with mp 210° (from ethanol). This product did not depress the melting point of the preceding samples.

5-(p-Methoxyphenyl)-4-amino-2,3-dihydro-1,2,4-triazole-3-thione (IIb). This was similarly obtained in 63% yield and had mp 187° (from methanol). Found %: S 14.7. $C_9H_{10}N_4OS$. Calculated %: S 14.4.

5-(p-Nitrophenyl)-4-amino-2,3-dihydro-1,2,4-triazole-3-thione (IIc). Adduct IIIc was refluxed in butanol for 3 h. The solvent was removed by vacuum distillation, and the residue was treated with water and filtered to give 78% of yellow crystals with mp 209° (from aqueous dioxane) that were soluble in dioxane and alcohol and insoluble in water. Found %: N 30.1. $C_8H_7N_5O_2S$. Calculated %: N 29.5.

5-Isonicotinyl-4-amino-2,3-dihydro-1,2,4-triazole-3-thione (IId). This was similarly obtained in 74% yield and had mp 238-242° (decomp., from aqueous dimethylformamide) [mp 240° (decomp.) [5]].

5-Phenyl-4-benzamide-2,3-dihydro-1,2,4-triazole-3-thione (VI). A. A 0.8 g (6 mmole) sample of benzhydrazide was added to a solution of 0.9 g (5 mmole) of oxadiazole Ia in 5 ml of dimethylformamide, and the solution was refluxed for 2 h. The mixture was then cooled, treated with water, and filtered to give 1.1 g (74%) of colorless crystals with mp 243-244° (from aqueous methanol) that were soluble in alcohol and insoluble in water. Found %: C 60.8; H 4.4; S 10.7. $C_{15}H_{12}N_4OS$. Calculated %: C 60.8; H 4.1; S 10.8.

B. Benzoyl chloride (1.2 ml) was added dropwise with stirring to a solution of 1.92 g (0.01 mole) of triazole IIa in 5 ml of pyridine. The mixture was refluxed for 5 h, cooled, treated with water, and filtered to give 2.1 g (72%) of a product with mp 242° (from aqueous alcohol). The product did not depress the melting point of the previous sample.

1-Benzoyl-4-methylthiocarbohydrazide (VIII). Methylhydrazine (2 ml) was added to a suspension of 3.56 g (0.02 mole) of oxadiazole Ia in 50 ml of n-propanol, and the mixture was refluxed for 5 h with periodic washing of the methylhydrazine from the condenser walls with small portions of propanol. The mixture was cooled, and the precipitate was filtered to give 1.2 g (27%) of colorless, needlelike crystals with mp 203° (from dioxane) that were insoluble in alcohol and slightly soluble on heating in dioxane. Found %: C 48.2; H 5.5; N 24.8; S 14.5. $C_9H_{12}N_4OS$. Calculated %: C 48.2; H 5.4; N 25.0; S 14.3.

6-Phenyl-2-methyl-1,4-dihydro-1,2,4,5-tetrazine-3-thione (VIIa). A. The filtrate obtained in the previous experiment was evaporated on a water bath. The residue was treated with 30 ml of 5% hydrochloric acid. The resulting oily product crystallized, and the crystals were filtered, washed with water, and dried in vacuo to give 1.9 g (46%) of colorless crystals with mp 135-136° (from ethanol) that were insoluble in water and soluble on heating in alcohols. Found %: C 52.6; H 5.0; N 27.2; S 15.7. $C_9H_{10}N_4S$. Calculated %: C 52.4; H 4.9; N 27.2; S 15.5.

B. A mixture of 1.78 g (0.01 mole) of oxadiazole Ia and 0.75 ml of methylhydrazine in 8 ml of ethanol was heated in a sealed ampule at 100° for 6 h. The ampule was opened, and the contents were poured into a dish and evaporated to one-third the original volume on a water bath. The mixture was cooled, and the precipitate was filtered and washed with a small amount of alcohol. The mother liquor (M) was cooled to stand for the subsequent operations. The precipitate was treated with 3 ml of boiling ethanol, and the undissolved residue, which was thiocarbohydrazide VIII, was filtered to give 0.05 g (2%) of a product with mp 201-203° (from dioxane) that did not depress the melting point of the sample obtained above. The filtrate was cooled to give 0.35 g of colorless crystals with mp 135° that did not depress the melting point of tetrazine VIIa obtained in the previous experiment. The mother liquor M was treated with 10 ml of water. The initially isolated oil crystallized; the mixture was filtered, and the solid was washed with a small amount of alcohol to give 0.2 g of a product with mp 134-135° (from ethanol) that did not depress the melting point of tetrazine VIIa obtained above. The overall yield was 0.55 g (27%). The mother liquor was acidified with 10 ml of 5%

hydrochloric acid, and the resulting precipitate was filtered to give 0.55 g (31%) of a product with mp 208-210° (from aqueous alcohol) that did not depress the melting point of the starting oxadiazole Ia.

C. A solution of 0.45 g (1.9 mmole) of thiocarbohydrazide VIII was refluxed in 3 ml of piperidine for 1 h, after which the solution was evaporated on a water bath. The residue was treated with 5 ml of 5% hydrochloric acid. The resulting oily product crystallized, and the crystals were filtered and washed with water and a small amount of alcohol to give 0.2 g (50%) of a product with mp 134-135° (from ethanol) that did not depress the melting point of the corresponding samples obtained in the previous experiments.

6-Isonicotinyl-2-methyl-1,4-dihydro-1,2,4,5-tetrazine-3-thione (VIId). A mixture of 1.79 g (0.01 mole) of oxadiazole Id and 0.75 ml of methylhydrazine was heated in 10 ml of n-propanol at 150-160° for 6 h in a sealed ampule. A homogeneous solution was formed. The ampule was then cooled and opened, and the solid was removed by filtration to give 1.4 g (68%) of colorless needles with mp 171-172° (from alcohol) that were insoluble in water and soluble on heating in alcohols. Found %: C 46.5; H 4.5; N 33.7; S 15.6. $C_8H_9N_5S$. Calculated %: C 46.4; H 4.3; N 33.8; S 15.5.

1-Benzoyl-4-methyl-5-benzylidenethiocarbohydrazide (IX). Benzaldehyde (0.1 ml) was added to a suspension of 0.22 g (1 mmole) of thiocarbohydrazide VIII in 3 ml of ethanol, and the mixture was heated until a homogeneous solution formed (about 5 min). The mixture was then cooled, 5 ml of water was added, and the resulting precipitate was filtered to give 0.25 g (80%) of a product with mp 149-150° (from aqueous ethanol). Found %: N 18.0. $C_{16}H_{16}N_4OS$. Calculated %: N 17.8.

5-Phenyl-4-benzylideneamino-2,3-dihydro-1,2,4-triazole-3-thione (V). A 0.38 g (2 mmole) sample of triazole IIa was dissolved by heating in 3 ml of glacial acetic acid, 0.1 g of anhydrous sodium acetate and 0.21 ml of benzaldehyde were added, and the mixture was refluxed for 30 min. It was then cooled, and the resulting precipitate was washed with alcohol to give 0.5 g (90%) of colorless crystals with mp 178° (from methanol) that were soluble on heating in alcohols and insoluble in water. Found %: N 19.8. $C_{15}H_{12}N_4S$. Calculated %: N 20.0.

LITERATURE CITED

1. O. P. Shvaika and G. P. Klimisha, Dopovidi Akad. Nauk Ukr. RSR, B, 350 (1970).
2. O. P. Shvaika, S. N. Baranov, and V. N. Artemov, Dokl. Akad. Nauk SSSR, 186, 1102 (1969).
3. G. Blankenstein and K. Möckel, Z. Chem., 2, 69 (1962).
4. A. Stempel, J. Zelauskas, and J. A. Aeschlimann, J. Org. Chem., 20, 412 (1955).
5. H. B. König and H. A. Offe, West German Patent No. 953,801 (1956); Chem. Abstr., 53, 4309 (1959).
6. A. Pinner, Ann., 297, 221 (1897).
7. O. P. Shvaika, Dopovidi Akad. Nauk Ukr. RSR, B, 1028 (1968).
8. R. W. Young and K. H. Wood, J. Am. Chem. Soc., 77, 400 (1955).