# *v*-Triazolines. Part XIX [1]. Thiocino[4,5-*d*]-1,2,3-triazole and Thiocino[4,5-*d*]isoxazole Derivatives



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5-Amino-2,3,6,7-tetrahydrothiocines were reacted with arylazides yielding 1-aryl-9a-amino-1,3a,4,5,7,8,9,9a-octahydrothiocino[4,5-*d*]-1,2,3-triazoles which could be deaminated to 1-aryl-1,4,5,7,8,9-hexahydrothiocino-[4,5-*d*]-1,2,3-triazoles. Similarly, the above enamines yielded, with nitrile oxides, 3-aryl-9a-amino-3a,4,5,8,9,9a-hexahydrothiocino[4,5-*d*]isoxazoles which were transformed with acids into 3-aril-4,5,8,9-tetrahydrothiocino-[4,5-*d*]isoxazoles.

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The thiocino[4,5-*d*]-1,2,3-triazole and thiocino[4,5-*d*]isoxazole ring systems have not been described previously.

Our continuing interest in the preparation of new heterocyclic compounds containing an azole ring condensed with a thiacycloalcane moiety is supported both by their potential activity as biologically active substances and their concern for the chemistry of cycloaddition and cycloreversion reactions [2].

Some representative examples of the above heterocycles have been obtained by 1,3-dipolar cycloaddition reactions of arylazides and nitrile oxides, respectively, to 5-amino-2,3,6,7-tetrahydrothiocines **2a-c** (Scheme 1).

Enamines **2a-c** were readily obtained by reacting 5-thiocanone **1** with the appropriate secondary amine and titanium(IV) chloride, according to a well established procedure [3]. The starting ketone was made readily available by a modification of the literature procedures. The structure of the enamines is clearly confirmed by their $^1$H-nmr spectrum in which the enamine hydrogen is associated with a multiplet in the expected range of $\delta$ 4.12-4.65.

Enamines **2a-c** readily reacted with arylazides, neat or in benzene solution, affording the 1-aryl-9a-amino-1,3a,-4,5,7,8,9,9a-octahydrothiocino[4,5-*d*]-1,2,3-triazoles **3a-e**. Yields, analytical and physical data of the compounds **3a-e** are listed in Table I. The structure of compounds **3a-e** are confirmed by the presence of a signal (multiplet) in their $^1$H-nmr spectra at $\delta$ 4.62-4.75, which is associated with $H_{3a}$. This chemical shift value is in good agreement with that expected for hydrogen atoms in position 4 of 5-

Scheme 1

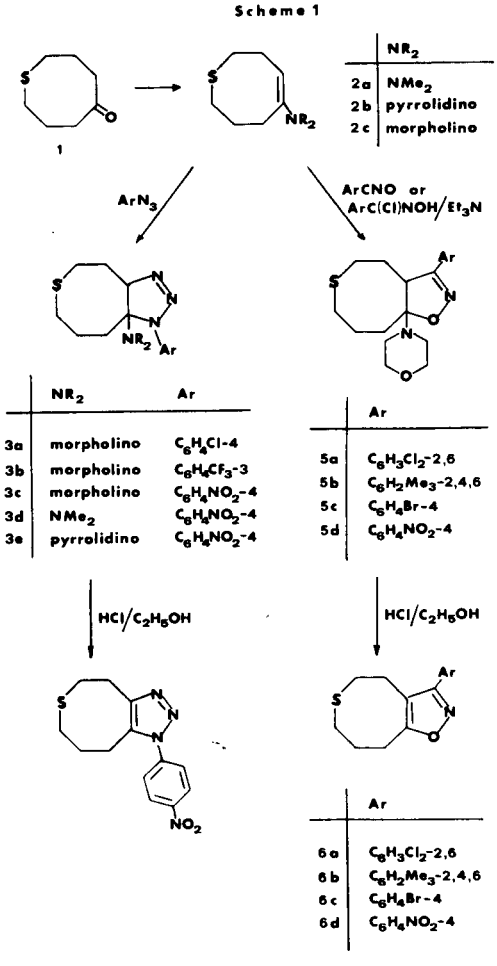


Table I

| Compound | Mp (°C) | Recrystallization solvent | Yield (%) | $^1$H-nmr $\delta$ H-3a [c] | Formula | Required (%) C | H | N | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | 100 | *i*-Pr$_2$O | 85 | 4.62 | $C_{17}H_{23}ClN_4OS$ | 55.65 | 6.25 | 15.3 | 55.5 | 6.3 | 15.2 |
| **3b** | Oil [a] | [b] | 87 | 4.70 | $C_{18}H_{23}F_3N_4OS$ | 54.0 | 5.75 | 14.0 | 55.85 | 5.45 | 14.3 |
| **3c** | 158 | *i*-Pr$_2$O | 90 | 4.75 | $C_{17}H_{23}N_5O_2S$ | 54.1 | 6.1 | 18.55 | 53.9 | 6.1 | 18.4 |
| **3d** | 145 | AcOEt | 76 | 4.68 | $C_{15}H_{21}N_4O_2S$ | 53.75 | 7.15 | 20.9 | 53.45 | 6.85 | 20.75 |
| **3e** | 117 | *i*-Pr$_2$O | 56 | 4.65 | $C_{17}H_{23}N_4O_2S$ | 56.5 | 6.35 | 19.4 | 56.3 | 6.45 | 19.1 |
| **4** | 197 | EtOH | 75 (A) 59 (B) | | $C_{13}H_{14}N_4O_2S$ | 53.8 | 4.8 | 19.3 | 53.65 | 4.8 | 19.1 |

[a] Undistillable owing to decomposition. [b] Purified by several extractions with *n*-pentane. [c] Multiplet.

Table II

| Compound | Mp (°C) | Recrystallization solvent | Yield (%) | Formula | Required (%) C | H | N | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | 145 | EtOH | 65 | $C_{18}H_{22}Cl_2N_2O_2S$ | 53.85 | 5.5 | 7.0 | 54.0 | 5.35 | 6.8 |
| **5b** | 157 | EtOH | 30 | $C_{21}H_{30}N_2O_2S$ | 67.35 | 8.05 | 7.5 | 67.1 | 8.05 | 7.3 |
| **5c** | 155-156 | EtOH | 17 | $C_{18}H_{23}BrN_2O_2S$ | 52.55 | 5.60 | 6.81 | 52.61 | 5.54 | 6.66 |
| **5d** | 215 | MeOH | 25 | $C_{18}H_{23}N_3O_4S$ | 57.4 | 5.9 | 11.15 | 57.2 | 5.75 | 11.1 |
| **6a** | 130 | — | 98 | $C_{14}H_{13}Cl_2NOS$ | 53.5 | 4.15 | 4.45 | 53.25 | 3.95 | 4.15 |
| **6b** | 120 | MeOH | 97 | $C_{17}H_{21}NOS$ | 71.05 | 7.35 | 4.85 | 70.7 | 7.4 | 4.65 |
| **6c** | 120 | — | 55 | $C_{14}H_{14}BrNOS$ | 51.85 | 4.35 | 4.3 | 52.05 | 4.55 | 4.1 |
| **6d** | 140 | MeOH [a] | 91 | $C_{14}H_{14}N_2O_3S$ | 57.9 | 4.85 | 9.65 | 58.15 | 5.1 | 9.5 |

[a] Several washings.

amino-4,5-dihydro-1,2,3-triazoles [4].

Compounds **3a-c** could be easily deaminated to the corresponding triazole derivative **4**. The enamine elimination was obtained by refluxing the triazoline compounds with hydrogen chloride in ethanol solution. Product 4 was also obtained in a single step by refluxing a benzene solution of 5-thiocanone, morpholine and 4-nitrophenylazide. For data of **4** see Table I.

The cycloaddition reaction of nitrile oxides to enamine **2c** was performed by generating the dipole in the reaction medium through the action of triethylamine in the corresponding hydroxamoyl chlorides (4-nitro- and 4-bromobenzonitrile oxides) or by using the stable nitrile oxides (2,6-dichloro- and 2,4,6-trimethylbenzonitrile oxides) in the isolated form.

The reaction proceeded at a moderate rate at room temperature and the reaction mixture was elaborated after 24-72 hours yielding the adducts **5a-d**. Their analytical data and physical properties are listed in Table II.

As usual [5], the secondary amine elimination from the 5-aminoisoxazoline nucleus was obtained by an acidic catalyst (hydrogen chloride in ethanol) and the corresponding thiocino[4,5-*d*]isoxazole derivatives **6a-d** were formed in satisfactory yield (Table II).

## EXPERIMENTAL

Melting points are uncorrected. The $^1$H-nmr spectra were recorded at 60 MHz using Varian 360-A spectrometer. The chemical shift values are expressed in $\delta$, relative to tetramethylsilane as internal standard. The tlc was run on silica gel plates.

5-Thiocanone (**1**).

This procedure is a modification of the literature method [6]. 1,7-Dibromo-4-heptanone was prepared by self-condensing $\gamma$-butyrolactone as described in the literature [7] and reacting the crude reaction product with 48% hydrogen bromide. The reaction mixture was refluxed for 30 minutes, cooled and extracted several times with ether. The ethereal solution was dried over calcium chloride and evaporated. The residue was distilled yielding 1,7-dibromo-4-heptanone (22%), bp 115° at 0.3 torr, lit [8] 137-138° at 3 torr. 1,7-Dibromo-4-heptanone (12 g, 0.044 mole) and anhydrous sodium sulphide (6 g, 0.077 mole) were refluxed in an ethanol solution (500 ml) for 48 hours. The solvent was evaporated and the residue taken up with water and diethyl ether. The ethereal layer was evaporated yielding an oily residue, which was distilled under reduced pressure affording 2.5 g of pure 5-thiocanone (40%), bp 100° at 0.2 torr; ir (neat): 1684 cm$^{-1}$ (C=O).

5-Dimethylamino-2,3,6,7-tetrahydrothiocine (**2a**).

5-Thiocanone (3.6 g, 0.025 mole) and dimethylamine (6.75 g, 0.150 mole) were dissolved in a pentane-benzene mixture (50 ml, 15:1). The solution was cooled to −10°, under nitrogen, and titanium tetrachloride (0.013 mole) was dropped under vigorous stirring. The reaction mixture was stirred at room temperature for 24 hours. The solution was filtered and the solvent evaporated and the residue was distilled under reduced pressure yielding 2.45 g of pure **2a** (57%), bp 80-85°/0.2 torr; nmr (deuteriochloroform): $\delta$ 4.35 (m, =CH-, 1H).

*Anal.* Calcd. for $C_9H_{17}NS$: C, 63.1; H, 10.0; N, 8.2. Found: C, 63.3; H, 10.25; N, 8.1.

5-Pyrrolidino-2,3,6,7-tetrahydrothiocine (**2b**).

This compound was prepared as described for **2a** above, giving 2.96 g of pure **2b** (60%), bp 100°/0.2 torr; nmr (deuteriochloroform): $\delta$ 4.12 (m, =CH-, 1H).

*Anal.* Calcd. for $C_{11}H_{19}NS$: C, 66.95; H, 9.7; N, 7.1. Found: C, 67.35; H, 9.85; N, 7.5.

5-Morpholino-2,3,6,7-tetrahydrothiocine (**2c**).

This compound was prepared as described for **2a** above, giving 2.83 g of pure **2c** (53%), bp 110°/0.2 torr; nmr (deuteriochloroform): $\delta$ 4.62 (m, =CH-, 1H).

*Anal.* Calcd. for $C_{11}H_{19}NOS$: C, 61.95; H, 9.0; N, 6.55. Found: C, 61.6; H, 8.9; N, 6.3.

1-Aryl-9a-morpholino-1,3a,4,5,7,8,9,9a-octahydrothiocino[4,5-*d*]-1,2,3-triazoles **3a,b**.

The enamine **2c** (0.5 g, 2.5 mmoles) and the appropriate azide (2.5 mmoles) were mixed and kept at 10° until complete reaction (tlc). The oily crude material was taken up with *n*-pentane yielding an essentially pure product which was subjected to further purification as indicated in Table I.

1-(4-Nitrophenyl)-9a-amino-1,3a,4,5,7,8,9,9a-octahydrothiocino[4,5-*d*]-1,2,3-triazoles **3c-e**.

The enamine **2** (2.5 mmoles) was added to a benzene solution (5-10 ml) of 4-nitrophenylazide (2.5 mmoles) and stirred, under nitrogen, at room temperature for 30 minutes. The precipitate that formed was filtered with suction and recrystallized (Table I).

1-(4-Nitrophenyl)-1,4,5,7,8,9-hexahydrothiocino[4,5-*d*]-1,2,3-triazole (**4**).

Method a.

The triazolines **3c-e** (1.5 mmoles) were dissolved in ethanol (20 ml). An ethanolic solution of hydrogen chloride (3.0 mmoles) was added and the

reaction mixtures were refluxed for 2 hours. The solvent was evaporated and the triazole was recrystallized (Table I).

Method b.

A benzene solution (20 ml) of 5-thiocanone (0.144 g, 10 mmoles), morpholine (0.087 g, 10 mmoles) and 4-nitrophenylazide (0.164 g, 10 mmoles) was refluxed for 2 hours. The precipitate was filtered and recrystallized (Table I).

3-Aryl-9a-morpholino-3a,4,5,8,9,9a-hexahydrothiocino[4,5-*d*]isoxazoles **5a,b**.

An acetonitrile solution (50 ml) of the nitrile oxide (20 mmoles) was mixed with the enamine **2c** (4.27 g, 20 mmoles) dissolved in anhydrous acetonitrile (40 ml). The reaction mixture was stirred at room temperature for 24 hours. The solution was then evaporated and the residue recrystallized (Table II).

3-Aryl-9a-morpholino-3a,4,5,8,9,9a-hexahydrothiocino[4,5-*d*]isoxazoles **5c,d**.

The enamine **2c** (3.48 g, 18 mmoles) was dissolved in anhydrous acetonitrile (100 ml). Triethylamine (1.82 g, 18 mmoles) was added, followed by the dropwise addition of the hydroxamoyl chloride (18 mmoles), dissolved in the minimum amount of acetonitrile. After 24-36 hours the solution was concentrated and the residue crystallized (Table II).

3-Aryl-4,5,8,9-tetrahydrothiocino[4,5-*d*]isoxazoles **6a-d**.

The isoxazolines **5a-d** (12 mmoles) were added to 10% hydrochloric acid (10-15 ml). Ethanol (50-60 ml) was then added and the mixture was refluxed for 24 hours. The solution was then evaporated and the precipitate was washed with sodium hydrogen carbonate solution, then with water and dried over phosphorus pentoxide. The dried product was essentially pure and was recrystallized to obtain analytically pure samples (Table II).

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