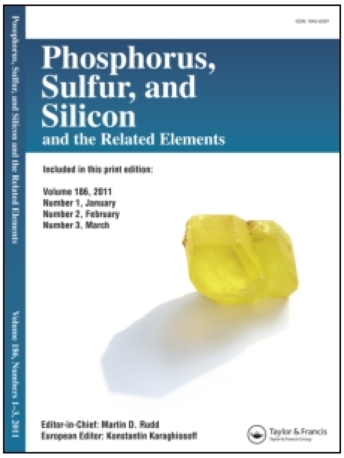

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"Bridgehead Nitrogen Heterocycles: Synthesis and Reactions of S-Triazolothiadiazinyl and S-Triazolothiadiazo-Lylquinoxalines"

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"BRIDGEHEAD NITROGEN HETEROCYCLES: SYNTHESIS AND REACTIONS OF S-TRIAZOLOTHIADIAZINYL AND S-TRIAZOLOTHIADIAZOLYLQUINOXALINES"

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The reaction of 3(4-amino-5-mercapto-1,2,4-triazol-3'-yl)quinoxalin-2(1*H*)-one **4** with phenacyl bromide, 2,3-dichloroquinoxaline, benzoine, chloroacetic acid, and α-chloroacetonitrile to give triazolothiadiazino derivatives **5–10**. Reaction of **4** with phenyl isothiocyanate, aromatic aldehydes, formic acid, aromatic carboxylic acid, benzoyl chloride, and carbon disulphide gave triazolothiadiazino derivatives **11–17**.

Keywords: Quinoxaline; thiadiazino; triazolothiadiazoloquinoxalines

INTRODUCTION

Substituted 1,2,4-*s*-triazoles and N-bridged heterocycles derived from them are among the various heterocycles that have received considerable attention during the last two decades as potential biological active agents.[1–3] A literature survey indicated that triazolo[4,3-a]quinoxaline and quinoxalinecarbonitriles show excellent bactericidal and fungicidal.[4–6] In view of the potential biological activity of the bridgedhead nitrogen heterocycles, it was of interest to us to prepare the title compounds as possible drugs effective aganist tropical disease. [7] The present investigation and, in continuation of our work on the synthesis and reactivity of the qui-

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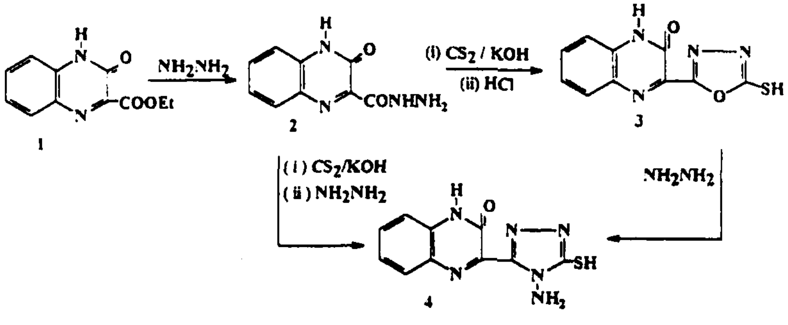
noxaline moiety[8–13] is concerned with the use 3(4-amino-5-mercapto-*s*-triazol-3'-yl)quinoxalin-2(1*H*)-one for the synthesis of many fused quinoxaline heterocycles of a new type. It seemed likely that these compounds would exhibit interesting biological properties.

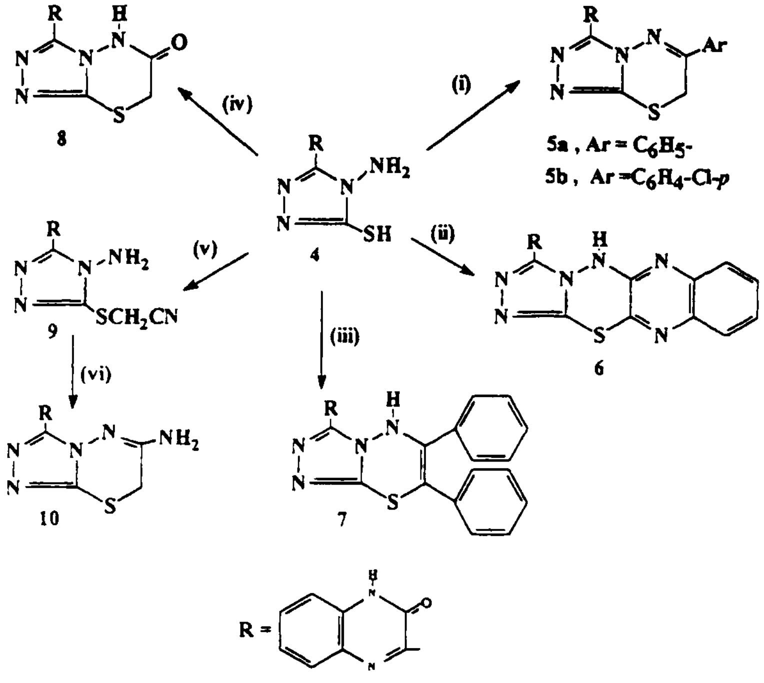
RESULTS AND DISSCUTION

The synthetic route to the bridgedhead nitrogen heterocycles is shown in Schemes 2 and 3. Conversion of **1** to hydrazide **2** was accomplished according to a reported method[8]. The starting compound 3(4'-amino-5'-mercapto-*s*-triazol-3'-yl)quinoxalin-2(1*H*)-one **4** was synthesised by the reaction of carbohydrazide **2** and carbon disulphide in the presence of potassium hydroxide and subsequent cyclization in presence of hydrazine hydrate. Treatment of carbohydrazide **2** with carbon disulphide in alkaline medium afforded, after acidic treatment, 3(3'-mercapto-1,2,4-oxadiazol-5'-yl)quinoxalin-2(1*H*)-one[12] **3**, which upon treatment with hydrazine hydrate, yielded **4** (Scheme 1).



SCHEME 1

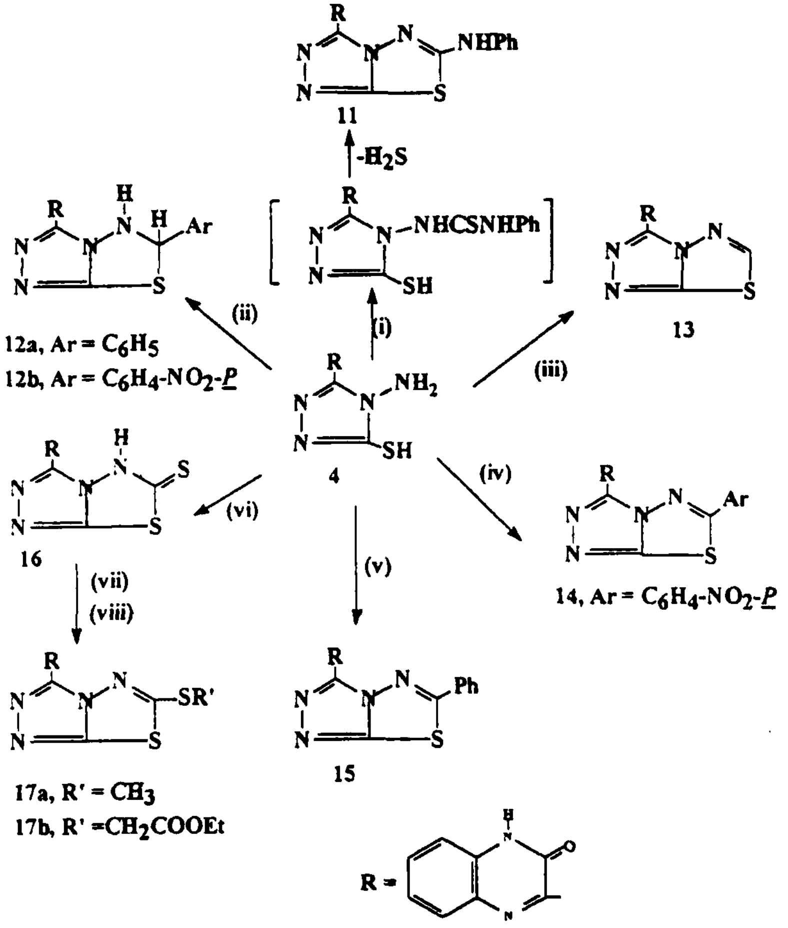
The cyclization of thiole **4** with phenacyl bromide and K_2CO_3 in DMF, or 2,3-dichloroquinoxaline and fused sodium acetate, or benzoine in KOH solution, or chloroacetic acid in presence of fused sodium acetate gave triazolothiadiazinylquinoxalinone derivatives **5–8**. Cyclocondensation of compound **4** with α-chloroacetonitrile gave cyanomethylthio derivative **9** which upon cyclization using conc H_2SO_4, yielded aminotriazolothiadiazinylquinoxalinone derivative **10** (Scheme 2).



(i) $ArCOCH_2Br$ / K_2CO_3 (ii) 2,3-Dichloroquinoxaline (iii) Benzoine / KOH
(iv) $ClCH_2COOH$ / NaOAc (v) $ClCH_2CN$ / Na_2CO_3 (vi) H_2SO_4

SCHEME 2

Treatment of thiol **4** with phenyl isothiocyanate in abs ethanol at room temp. afforded an uncyclized substituted thiourea derivative, which, upon refluxing, cyclized into triazolothiadiazolylquinoxalinone derivative **11**. The reaction of **4** with aromatic aldehydes in dry benzene furnished 3-(5,6-dihydro, 6-substituted-s-triazolo[3,4-b][1,3,4]thiadiazol-3′-yl)quinoxalin-2(1*H*)-one **12**. The cyclocondensation of compound **4** with formic acid in dichlorobenzene, or aromatic carboxylic acids in the presence of $POCl_3$ or benzoyl chloride in DMF afforded triazolothiadiazolyl derivatives **13–15**. Cyclyization of triazole **4** with carbon disulphide in the presence of alc KOH gave the thione derivative **16** which was alkylated with methyl iodide and/or ethyl chloroacetate to yield S-alkyl derivatives **17a,b** (Scheme 3).



(i) PhNCS (ii) ArCHO (iii) HCOOH (iv) ArCOOH
(v) PhCOCl (vi) CS_2 / KOH (vii) CH_3I / NaOAc (viii) $ClCH_2COOEt$

SCHEME 3

EXPERIMENTAL

Melting points were determined on a Gallen Kamp melting point apparatus and were uncorrected. IR spectra were recorded on a Pye-Unicam SP^3-100 spectrophotometer using the KBr waver technique. ^{1}HNMR spectra were measured on a Varian 390 90 MHz NMR spectrometer in the suitable deuterated solvent, using TMS as internal standard. Elemental analyses were performed on a Perkin-Elmer 240C microanalyzer, and all compounds gave results in an acceptable range. Spectral data of compounds **4–17** are listed in Table I.

TABLE I Spectroscopic data of compounds 4–17

Comp. No	*IR(λCm^{-1}); 1HNMR (δ ppm)*
4	3410, 3220 (NH, NH$_2$), 1660 (C=O), 1230, 1060 (C=S); (DMSO-d$_6$): δ 7.2–8.0 (m, 4H, Ar-H), δ 8.5 (s, 2H, NH$_2$), δ 11.5 (s, 1H, NH of quinoxaline ring).
5a	3220 (NH), 1660 (C=O); (CDCl$_3$): δ 4.3 (s, 2H, CH$_2$), δ 7.3–8.1 (m, 9H, Ar-H), δ 11.3 (s, 1H, NH).
5b	3260 (NH), 1670 (C=O): (CDCl$_3$): δ 4.5 (s, 2H, CH$_2$), δ 7.4–8.2 (m, 8H, Ar-H), δ 11.4 (s, 1H, NH).
6	3240–3180 (NH), 1670 (C=O), 1620 (C=N); (CF$_3$COOD): δ 7.4–7.9 (m, 4H, Ar-H).
7	3260–3210 (NH), 1680 (C=O), 1610 (C=N); (DMSO-d$_6$): δ 7.2–8.3 (m, 14H, Ar-H), δ 11.4 (s, 1H, NH of quinoxaline ring).
8	3240, 3200 (NH), 1660, 1680 (C=O): (CDCl$_3$): δ 4.6 (s, 2H, CH$_2$), δ 7.5–8.1 (m, 4H, Ar-H), δ 11.4 (s, 1H, NH of quinoxaline ring).
9	3420, 3260 (NH, NH$_2$), 2220 (CN), 1670 (C=O); (CDCl$_3$): δ 5.9 (s, 2H, CH$_2$), δ 7.2–8.11 (m, 4H, Ar-H), δ 11.6 (s, 1H, NH of quinoxaline ring).
10	3460, 3210 (NH, NH$_2$), 1670 (C=O); (CF$_3$COOD): δ 4.4 (s, 2H, CH$_2$), δ 7.28–8.1 (m, 4H, Ar-H).
11	3280, 3180 (NH), 1660 (C=O); (DMSO-d$_6$): δ 7.4–7.9 (m, 9H, Ar-H), δ 9.6 (s, 1H, NH), δ 11.4 (s, 1H, NH of quinoxaline ring).
12a	3250, 3170 (NH), 2950 (CH), 1660 (C=O); (DMSO-d$_6$): δ 7.3–8.2 (m, 9H, Ar-H), δ 9.1 (s, 1H, CH), δ 10.5, δ 11.4 (s, 1H, 2NH).
12b	3220, 3190 (NH), 2950 (CH), 1680 (C=O); (DMSO-d$_6$): δ 7.2–8.10 (m, 8H, Ar-H), δ 9.1 (s, 1H, CH), δ 10.3, δ 11.4 (s, 1H, 2NH).
13	3220 (NH), 2960 (CH), 1675 (C=O); (DMSO-d$_6$): δ 7.4–8.3 (m, 4H, Ar-H), δ 9.5 (s, 1H, CH), δ 11.4 (s, 1H, NH).
14	3230 (NH), 1660 (C=O); (CDCl$_3$): δ 7.3–8.2 (m, 8H, Ar-H), δ 11.4. (s, 1H, NH).
15	3240 (NH), 1650 (C=O); (DMSO-d$_6$): δ 7.1–8.1 (m, 9H, Ar-H), δ 11.3 (s, 1H, NH of quinoxaline ring).
16	3280, 3200 (NH), 1660 (C=O), 1230, 1120 (C=S); (DMSO-d$_6$): δ 7.5–8.0 (m, 4H, Ar-H), δ 9.9, δ 11.4 (s, 1H, 2NH).
17a	3190 (NH), 1670 (C=O); (CDCl$_3$): δ 2.3 (s, 3H, CH$_3$), δ 7.4–8.2 (m, 4H, Ar-H), δ 11.3 (s, 1H, NH of quinoxaline ring).
17b	3210 (NH), 1720, 1660 (2C=O); (CDCl$_3$): δ 1.3–1.75 (t, 3H, CH$_3$), δ 3.6–4.0 (q, 2H, CH$_2$), δ 7.4–8.1 (m, 4H, Ar-H), δ 11.4 (s, 1H, NH of quinoxaline ring).

3-(4′-Amino-5′-mercapto-s-triazol-3′-yl)quinoxalin-2(1H)-one (4)

A suspension of oxadiazole 3 (0.01 mol) in hydrazine hydrate (0.015 mol)was refluxed for 4 hr. It was then cooled and poured on crushed ice. The solid that separated out was filtered, washed with water, and crystallized from ethanol as red crystals, m.p. 285°C, yield 82 %; $C_{10}H_8N_6OS$ (260).

3-(7H,6-phenyl-s-triazolo[3,4-*b*][1,3,4]thiadiazin-3′-yl)quinoxalin-2(1H) -one (5a)

A solution of 4 (0.01 mol), phenacyl bromide (0.01 mol), and anhydrous K_2CO_3 (3 g) in DMF (20 ml) was refluxed for 3 hr, and the reaction mixture was cooled and poured into ice-cold water. The solid thus separated was filtered, washed with water, dried and recrystallized from ethanol as brownish crystals, m.p. 225 °C, yield 75 %; $C_{18}H_{12}N_6OS$ (360).

3-(7H, 6′-*p*-Chlorophenyl-s-triazolo[3,4-*b*][1,3,4]thiadiazin-3′-yl) quinoxalin-2(1H)one (5b)

A solution of 4 (0.01 mol), p-chlorophenacyl bromide (0.01 mol), and anhydrous K_2CO_3 (3 g) in DMF (20 ml) was refluxed for 3 hr, and the reaction mixture was cooled and poured into ice-cold water. The solid thus separated was filtered, washed with water, dried and recrystallized from ethanol as deep red crystals, m.p. 204 °C, yield 69 %; $C_{18}H_{11}N_6OSCl$ (394.5).

(2-Oxo-1H-quinoxalin-3′-yl)-5H-s-triazolo[3′,4′:2,3][1,3,4]-thiadiazino [5,6-*b*]quinoxaline (6)

A mixture of triazolethiol 4 (0.01 mol), 2,3-dichloroquinoxaline (0.01 mol), and fused sodium acetate (0.02 mol) in abs ethanol (50 ml) was refluxed on a steam-bath for 4 hr, and cooled. The resulting solid was washed thoroughly with water and crystallized from ethanol as yellow crystals, m.p. >300 °C, yield 73 %; $C_{18}H_{10}N_8OS$ (386).

3-(5H-6,7-Diphenyl-s-triazolo[3,4-*b*][1,3,4]thiadiazin-3′-yl)quinoxalin-2(1H)-one (7)

A mixture of triazolethiol 4 (0.01 mol), and benzoine (0.01 mol) in ethanol (40 ml) was heated to get a clear solution. To the hot solution was added an aqueous 2*N* KOH solution (3 ml). The resulting mixture was refluxed with stirring for about half an hour. The yellow precipitate thus separated out was filtered, washed with water and crystallized from ethanol, m.p. 295°C, yield 71%; $C_{24}H_{16}N_6OS$ (436).

3-(6-Oxo-(5H,7H)-s-triazolo[3,4-*b*][1,3,4]thiadiazin-3'-yl)quinoxalin-2 (1H)-one (8)

A mixture of triazole **4** (0.01 mol), chloroacetic acid (0.01 mol), and fused sodium acetate (0.01 mol) in abs ethanol (40 ml) was heated under reflux for 6 hr, and then cooled in ice. The solid thus separated was filtered, washed thoroughly with water, and crystallized from ethanol as yellowish crystals, m.p. 227°C, yield 65 %; $C_{12}H_8N_6O_2S$ (300).

3-(6-Amino-5-cyanomethylthio-s-triazolo-3'-yl)quinoxalin-2(1H)-one (9)

A sample of thiol **4** (0.01 mol) dissolved in abs ethanol (30 ml) was mixed with (0.02 mol) of α-chloroacetonitrile and heated for 4 hr. The solvent was removed, and the residue was dissolved in water (25 ml). After neutralization with 10% aqueous Na_2CO_3, a precipitate formed and was filtered, washed thoroughly with cold water, and crystallized from ethanol as orange red crystals, m.p. 215 °C, yield 77 %; $C_{12}H_9N_7OS$ (299).

3-(6-Amino-7H-s-triazolo[3,4-*b*][1,3,4]thiadiazin-3'-yl)quinoxalin-2 (1H)-one (10)

A sample of compound **9** in H_2SO_4 (20 ml) was left for 3 hr at room temperature. It was then diluted with water and neutralized with 20% ammonium hydroxide. The precipitated product was filtered and crystallized from ethanol as deep red crystals, m.p. 252°C, yield 67 %; $C_{12}H_9N_7OS$ (299).

3-(6-Phenylamino-s-triazolo[3,4-*b*][1,3,4]thiadiazol-3'-yl)quinoxalin-2 (1H)-one (11)

To a solution of **4** (0.01 mol) in abs ethanol (20 ml) added phenyl isothio-cyanate (0.01 mol), and the mixture was stirred for 3 hr. The stirred solution was then refluxed for 2 hr. After cooling, the precipitated product was filtered and crystallized from ethanol as pale yellow crystals, m.p. 276°C, yield 72 %; $C_{17}H_{11}N_7OS$ (361).

3-(5,6-Dihydro, 6-phenyl-s-triazolo[3,4-*b*][1,3,4]thiadiazol-3'-yl) quinoxalin-2(1H)-one (12a)

3-(5,6-Dihydro,6-*p*-nitrophenyl-s-triazolo[3,4-*b*][1,3,4]-thiadiazol-3'-yl)-quinoxalin-2(1H)-one (12b)

A mixture of triazolethiol 4 (0.01 mol) and benzaldehyde (or p-nitro benzaldehyde) (0.01 mol) in dry benzene (30 ml) was refluxed on a steam-bath for 5 hr. The reaction mixture was then concentrated to half its volume and kept in an ice-bath. The solid thus separated was filtered and crystallized from ethanol

*12*a: as pale yellow crystals, m.p. 265 °C, yield 62 %; $C_{17}H_{12}N_6OS$ (348).

*12*b: as red crystals, m.p. 283°C, yield 68 %; $C_{17}H_{11}N_7O_3S$ (393).

3-(6H-s-Triazolo[3,4-*b*][1,3,4]thiadiazol-3'-yl)quinoxalin-2(1H)-one (13)

A mixture of 4 (0.01 mol) and formic acid (0.01 mol) in dichlorobenzene (30 ml) was refluxed for 1 hr. Excess solvent was evaporated under reduced pressure. To the reaction mixture, was added ethanol (10 ml), and then it was poured over crushed ice. The solid obtained was filtered and dried. It was treated with conc H_2SO_4 (10 ml) in the cold whereby a pasty mass was obtained. It was poured into water, and the solid obtained was filtered and crystallized from ethanol as yellowish crystals, m.p. 214 °C, yield 61%; $C_{11}H_6N_6OS$ (270).

3-(6-*p*-Nitrophenyl-s-triazolo[3,4-*b*][1,3,4]thiadiazol-3'-yl)quinoxalin-2(1H)-one (14)

A mixture of thiol 4 (0.01mol) and p-nitrobenzoic acid in $POCl_3$ (15 ml) was heated on a steam-bath for 4 hr. The reaction mixture was cooled, poured onto ice, and neutralized with aqueous K_2CO_3solution (10%). The solid, thus separated was filtered, washed thoroughly with cold water, and crystallized from ethanol as yellow crystals, m.p. 252 °C, yield 65 %; $C_{17}H_9N_7O_3S$ (391).

3-(6-Phenyl-s-triazolo[3,4-*b*][1,3,4]thiadiazol-3′-yl)quinoxalin-2(1H)-one (15)

A solution of **4** (0.01 mol) and benzoyl chloride (0.01 mol) in DMF (25 ml) was refluxed for 4 hr. The reaction mixture was cooled, poured over crushed ice and neutralized with $NaHCO_3$ (10% solution). The solid thus separated was filtered, washed with water, and recrystallized from ethanol as yellow crystals, m.p. 240 °C, yield 74 %; $C_{17}H_{10}N_6OS$ (346).

3-(5H-6-thio-s-triazolo[3,4-*b*][1,3,4]thiadiazol-3′-yl)quinoxalin-2(1H)-one (16)

To a solution of **4** (0.01 mol) in ethanolic KOH solution (2 g in 35 ml) was added dropwise carbon disulphide (0.02 mol) with stirring. The reaction mixture was heated on a steam-bath for 8 hr until the evolution of H_2S ceased. The reaction mixture was concentrated to one- fourth of its volume and was poured into ice and acidified with dilute Hcl. The precipitate thus obtained was filtered, washed with water and recrystallized from ethanol as pale red crystals, m.p. 225°C, yield 80 %; $C_{11}H_6N_6OS_2$ (302).

3-(6-Methylthio-s-triazolo[3,4-*b*][1,3,4]thiadiazol-3′-yl)quinoxalin-2 (1H)-one (17a)

A mixture of thione **16** (0.01 mol), methyl iodide (0.02 mol) and fused sodium acetate (3 g) in ethanol (30 ml) was refluxed for 2 hr. The solid thus separated was filtered and recrystallized from ethanol as colourless crystals, m.p. 185 °C yield 76%; $C_{12}H_8N_6OS_2$ (316).

3-(6-Carboethoxymethylthio-s-triazolo[3,4-*b*][1,3,4]thiadiazol-3′-yl) quinoxalin-2(1H)-one (17b)

A mixture of thione **16** (0.01 mol), ethyl chloroacetate (0.01 mol), and fuse sodium acetate (3 g) in ethanol (30 ml) was refluxed for 2 hr. The solid thus separated was filtered and recrystallized from ethanol as colourless crystals, m.p. 162°C, yield 82%; $C_{15}H_{12}N_6O_3S_2$ (388).

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