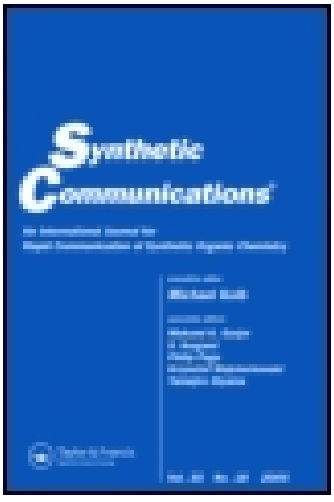

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Synthesis of Ethyl 8-Aryl-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo-[3,4-*c*][1,4]thiazine-5-carboxylates by Ring-Expansion Rearrangement

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Abstract: The title compounds were prepared by the ring–ring interconversion of ethyl 5-nitroso-6-arylimidazo[2,1-*b*]thiazole-3-carboxylates with hydrochloric acid. The effect of electron-withdrawing substituent in the thiazole ring on the general applicability of the ring–ring interconversion has been also evaluated.

Keywords: imidazo[2,1-*b*]thiazole, oxazolothiazines, ring–ring interconversion

INTRODUCTION

A literature survey reveals that both oxadiazole and thiazine derivatives exhibit pharmacological activities wherein oxadiazoles displayed antibacterial, antitubercular, anticancer, anti-inflammatory, and anti-HIV activities[1,2] and thiazines showed fungicidal[3] activity and are a constituent of cephalosporine antibiotics.[3] Oxadiazolothiazines are known to act as myocardial calcium channel modulators.[4] They exhibited potential antitumor and fungicidal action also. In view of this and in continuation of our work on fused heterocyclic systems containing nitrogen and sulfur,[5,6] we are reporting a new simple route for the synthesis of novel oxadiazolothiazines. The present work also explains the reactivity of 3-ethoxycarbonyl-5-nitroso-6-arylimidazo[2,1-*b*]thiazoles with hydrochloric acid in ethanol.

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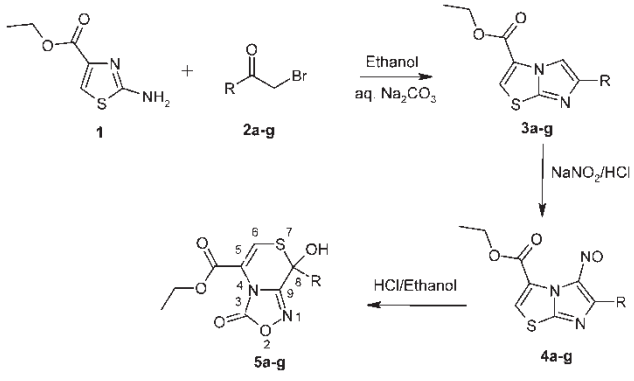
DISCUSSION

The reaction of 2-aminothiazole-4-carboxylate with α-haloketones in boiling ethanol for 14 h afforded the desired 3-ethoxycarbonyl-6-arylimidazo[2,1-*b*]thiazolium bromide in good yields, which on neutralization gave corresponding free bases (**3a**–**g**). The π electron charge data of imidazothiazole system clearly tells us that all electrophilic substitution reactions take place at C-5 and not at C-2. These findings prompted us to study the effect of the ethoxycarbonyl group during ring–ring interconversion of 3-ethoxycarbonyl-5-nitroso-6-arylimidazo[2,1-*b*]thiazoles (**4a**–**g**) into ethyl 8-aryl-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo[3,4-*c*][1,4]thiazine-5-carboxylates (**5a**–**g**).

The required 3-ethoxycarbonyl-5-nitroso-6-aryl-imidazo[2,1-*b*]thiazoles (**4a**–**g**) were prepared by nitrosation of corresponding imidazothiazoles (**3a**–**g**). The IR spectrum of nitroso compound showed $\nu_{C=O}$ for ester in the range 1720–1710 cm^{-1} along with ν_{NO} in the range of 1540–1530 cm^{-1}. The ^1H NMR spectra showed the presence of aromatic protons in the range of δ 8.50–7.60, and the absence of C5-H around δ 7.40 confirmed the nitrosation at 5-position of imidazo[2,1-*b*]thiazole.

Further, the 3-ethoxycarbonyl-5-nitroso-6-arylimidazo[2,1-*b*]thiazoles (**4a**–**g**) were rearranged (Scheme 1) to ethyl 8-aryl-8-hydroxy-3-oxo-8*H*[1,2,4]-oxadiazolo[3,4-*c*][1,4]thiazine-5-carboxylates (**5a**–**g**) by the action of hydrochloric acid in ethanol at 80°C. The same reaction when carried out at room temperature did not afford the rearranged product, but when the temperature was raised to 80°C, a smooth rearrangement took place, giving ethyl 8-aryl-8-hydroxy-3-oxo-8*H*[1,2,4]-oxadiazolo[3,4-*c*][1,4]thiazine-5-carboxylates (**5a**–**g**). The presence of electron-withdrawing carbethoxy group hinders the reaction at room temperature, hence requiring drastic conditions.

The structures of various ethyl 8-aryl-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo[3,4-*c*][1,4]thiazine-5-carboxylates (**5a**–**g**) were established by their



Scheme 1. R = a) Ph; b) 4-NO_2Ph; c) 4-CH_3Ph; d) 4-ClPh; e) 4-BrPh; f) 2-thienyl; g) 3-coumarinyl.

analytical and spectral data. The presence of a lactone carbonyl band around 1795–1785 cm^{-1} with the ester carbonyl group at 1720–1715 cm^{-1} and $\nu_{O\text{-}H}$ around 3325 cm^{-1} in the IR spectra was major evidence for the formation of oxadiazolothiazine ring. The ^1H NMR spectra of the rearranged products showed a broad singlet in the range δ 1.6–2.5 (exchangeable with D_2O) for hydroxyl group and a singlet at δ 7.96 for C6-H. Finally ^{13}C NMR and mass spectra confirmed the structures of the rearranged products. The ^{13}C NMR of **5e** displayed the lactone and ester carbonyl carbons at δ 186 and δ 178.2 respectively. Further, the mass spectra of the compound confirms the structure; namely **5e** showed m/z: M^+(398) and M^++2 (400).

EXPERIMENTAL

The melting points were determined in a capillary apparatus to open capillaries and are uncorrected. IR spectra were recorded on Nicolet Impact-410 FT-IR spectrophotometer, using the KBr pellet technique. ^1H NMR and ^{13}C NMR experiments were performed at 300 MHz on a Bruker AC-300F spectrometer (TMS as internal standard). Mass spectra were recorded on an EI-70 EV instrument. Elemental analyses were carried out using Heraus CHN rapid analyzer; the results were in satisfactory agreement with the calculated values. Various 2-bromoketones (**1a–g**),[7–11] ethyl 2-aminothiazole-4-carboxylate (**2**),[12,13] and the compounds **3a–d**[14] were prepared as described in the literature.

Preparation of Ethyl 6-arylimidazo[2,1-*b*]thiazole-3-carboxylates (3a–g), General Procedure

A mixture of ethyl 2-aminothiazole-4-carboxylate **1** (1.72 g, 0.01 mol) and α-haloketone **2a–g** (0.01 mol) in ethanol (60 mL) was heated to reflux on a steam bath for 14 h. The mixture was concentrated under reduced pressure, and the separated hydrobromide was filtered, washed with cold ethanol, and dried. The neutralization of the hydrobromide with aqueous sodium carbonate solution afforded the corresponding free base (**3**), which was purified by recrystallization in ethanol.

Physicochemical and Spectral Data

Ethyl 6-(4-bromophenyl)imidazo[2,1-*b*]thiazole-3-carboxylate (3e): Pale yellow solid, yield 52%, mp 145–146°C; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.42 (s, 1H, C5-H), 8.30 (d, $J = 8.6$ Hz, 2H, ArH), 8.24 (s, 1H, C2-H), 7.76 (d, $J = 8.6$ Hz, 2H, ArH), 4.42 (q, $J = 7.1$ Hz, 2H, CH_2 of ester), 1.36 (t, $J = 7.2$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{14}H_{11}BrN_2O_2S$: C, 47.88; H, 3.16; N, 7.98. Found: C, 47.92; H, 3.09; N, 8.06%.

Ethyl 6-(2-thienyl)imidazo[2,1-*b*]thiazole-3-carboxylate (3f): Yellow solid, yield 60%, mp 155–156°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.38 (s, 1H, C5-H), 7.89 (s, 1H, C2-H), 7.46–6.90 (m, 3H, thienyl), 4.30 (q, $J = 6.9$ Hz, 2H, CH_2 of ester), 1.32 (t, $J = 7.0$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{12}H_{10}N_2O_2S_2$: C, 51.79; H, 3.59; N, 10.07. Found: C, 51.66; H, 3.48; N, 10.15%.

Ethyl 6-(3-coumarinyl)imidazo[2,1-*b*]thiazole-3-carboxylate (3 g): Yellow solid, yield 64%, mp 170–172°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.52 (s, 1H, coumarinyl C4-H), 7.46 (s, 1H, C2-H), 7.00–6.75 (m, 4H, coumarinyl), 4.35 (q, $J = 6.9$ Hz, 2H, CH_2 of ester), 1.34 (t, $J = 7.0$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{17}H_{12}N_2O_4S$: C, 60.00; H, 3.53; N, 8.23. Found: C, 60.24; H, 3.48; N, 8.35%.

Preparation of Ethyl 5-nitroso-6-arylimidazo[2,1-*b*]thiazole-3-carboxylates(4a–g), General Procedure

Ethyl 6-arylimidazo[2,1-*b*]thiazole-3-carboxylate (**3a–g**, 0.01 mol) was dissolved in acetic acid (20 mL) and treated with sodium nitrite solution (1.45 g, 0.021 mol, in 10 mL of water) at 0–5°C. The mixture was stirred for 30 min at room temperature. It was then neutralized with sodium hydroxide solution (2 N), and the solid that separated was collected by filtration and crystallized from ethanol.

Data

Ethyl 5-nitroso-6-phenylimidazo[2,1-*b*]thiazole-3-carboxylate (4a): Yellow solid, yield 56%, mp 152–154°C; IR (KBr) νcm^{-1}: 1710 (C═O), 1530 (N═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.32–7.50 (m, 5H, ArH), 7.41 (s, 1H, C2-H), 4.32 (q, $J = 7.2$ Hz, 2H, CH_2 of ester), 1.35 (t, $J = 7.2$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{14}H_{11}N_3O_3S$: C, 55.81; H, 3.65; N, 13.95. Found: C, 55.45; H, 3.72; N, 13.83%.

Ethyl 5-nitroso-6-(4-nitrophenyl)imidazo[2,1-*b*]thiazole-3-carboxylate (4b): Yellow solid, yield 55%, mp 168–169°C; IR (KBr) νcm^{-1}: 1720 (C═O), 1545 (N═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.40 (d, $J = 8.6$ Hz, 2H, ArH), 7.61 (d, $J = 8.6$ Hz, 2H, ArH), 7.50 (s, 1H, C2-H), 4.41 (q, $J = 6.9$ Hz, 2H, CH_2 of ester), 1.26 (t, $J = 7.0$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{14}H_{10}N_4O_5S$: C, 48.55; H, 2.89; N, 16.18. Found: C, 48.16; H, 2.85; N, 16.30%.

Ethyl 5-nitroso-6-(4-methylphenyl)imidazo[2,1-*b*]thiazole-3-carboxylate (4c): Yellow solid, yield 54%, mp 156–158°C; IR (KBr) νcm^{-1}: 1715 (C═O), 1535 (N═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.25 (d, $J = 8.2$ Hz,

2H, ArH), 7.43 (d, $J = 8.2$ Hz, 2H, ArH), 7.34 (s, 1H, C2-H), 4.26 (q, $J = 7.2$ Hz, 2H, CH_2 of ester), 2.11 (s, 3H, CH_3), 1.34 (t, $J = 7.0$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.14; H, 4.12; N, 13.33. Found: C, 57.53; H, 4.18; N, 13.24%.

Ethyl 5-nitroso-6-(4-chlorophenyl)imidazo[2,1-*b*]thiazole-3-carboxylate (4d): Yellow solid, yield 56%, mp 129–130°C; IR (KBr) νcm^{-1}: 1720 (C═O), 1540 (N═O); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.41 (d, $J = 8.4$ Hz, 2H, ArH), 7.52 (d, $J = 8.4$ Hz, 2H, ArH), 7.43 (s, 1H, C2-H), 4.30 (q, $J = 7.2$ Hz, 2H, CH_2 of ester), 1.32 (t, $J = 7.2$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{14}H_{10}ClN_3O_3S$: C, 50.07; H, 2.98; N, 12.51. Found: C, 49.69; H, 3.15; N, 12.43%.

Ethyl 5-nitroso-6-(4-bromophenyl)imidazo[2,1-*b*]thiazole-3-carboxylate (4e): Yellow solid, yield 52%, mp 145–146°C; IR (KBr) νcm^{-1}: 1715 (C═O), 1536 (N═O); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.50 (d, $J = 8.5$ Hz, 2H, ArH), 7.62 (d, $J = 8.5$ Hz, 2H, ArH), 7.41 (s, 1H, C2-H), 4.42 (q, $J = 6.9$ Hz, 2H, CH_2 of ester), 1.23 (t, $J = 6.8$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{14}H_{10}BrN_3O_3S$: C, 44.21; H, 2.63; N, 11.05. Found: C, 44.58; H, 2.66; N, 11.18%.

Ethyl 5-nitroso-6-(2-thienyl)imidazo[2,1-*b*]thiazole-3-carboxylate (4f): Yellow solid, yield 50%, mp 144–146°C; IR (KBr) νcm^{-1}: 1710 (C═O), 1540 (N═O); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.48 (s, 1H, C2-H), 7.00–6.75 (m, 3H, thienyl), 4.35 (q, $J = 7.2$ Hz, 2H, CH_2 of ester), 1.34 (t, $J = 7.3$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{12}H_9N_3O_3S_2$: C, 52.36; H, 3.27; N, 15.27. Found: C, 52.70; H, 3.38; N, 15.42%.

Ethyl 5-nitroso-6-(3-coumarinyl)imidazo[2,1-*b*]thiazole-3-carboxylate (4g): Yellow solid, yield 50%, mp 140–142°C; IR (KBr) νcm^{-1}: 1720 and 1745 (C═O), 1535 (N═O); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.54 (s, 1H, coumarinyl C4-H), 7.53 (s, 1H, C2-H), 7.46–7.08 (m, 4H, coumarinyl), 4.35 (q, $J = 7.2$ Hz, 2H, CH_2 of ester), 1.34 (t, $J = 7.2$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{17}H_{11}N_3O_5S$: C, 55.28; H, 2.98; N, 11.38. Found: C, 55.66; H, 3.06; N, 11.51%.

Preparation of Ethyl 8-aryl-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo [3,4-*c*][1,4] thiazine-5-carboxylates (5a–g), General Procedure

To a stirring solution of ethyl 5-nitroso-6-arylimidazo[2,1-*b*]thiazole-3-carboxylate (**4**, 0.01 mol) in ethanol (10 mL), hydrochloric acid (0.73 g, 0.02 mol) was added dropwise and heated to 80°C, until completion of

reaction. Removal of solvent gave the product, which was purified by recrystallization from ethanol.

Data

Ethyl 8-phenyl-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo[3,4-*c*][1,4]thiazine-5-carboxylate (5a): Pale yellow granules, yield 50%, mp 185–187°C; IR (KBr) νcm^{-1}: 1720 (C═O, ester), 1785 (C═O, lactone), 3340 (br, OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20–7.90 (m, 5H, ArH), 7.80 (s, 1H, C6-H), 4.40 (q, $J = 6.9$ Hz, 2H, CH_2 of ester), 1.60 (br s, 1H, D_2O exchangeable, 1H, OH), 1.35 (t, $J = 6.9$ Hz, 3H, CH_3 of ester); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.5, 168.1, 155.4, 148.2, 129.3, 128.2, 124.5, 121.7, 118.8, 116.0, 61.7, 13.6. Anal. calcd. for $C_{14}H_{12}N_2O_5S$: C, 52.50; H, 3.75; N, 8.75. Found: C, 52.12; H, 3.68; N, 8.62%.

Ethyl 8-(4-nitrophenyl)-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo-[3,4-*c*][1,4]-thiazine-5-carboxylate (5b): Intense yellow solid, yield 56%, mp 192–194°C; IR (KBr) νcm^{-1}: 1715 (C═O, ester), 1790 (C═O, lactone), 3330 (br, OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.35 (d, $J = 8.4$ Hz, 2H, ArH), 7.95 (s, 1H, C6-H), 7.60 (d, $J = 8.4$ Hz, 2H, ArH), 4.50 (q, $J = 6.7$ Hz, 2H, CH_2 of ester), 1.70 (br s, 1H, D_2O exchangeable, OH), 1.41 (t, $J = 6.7$ Hz, 3H, CH_3 of ester); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.0, 172.4, 158.8, 153.5, 131.6, 129.8, 124.0, 122.8, 119.4, 117.2, 62.5, 13.0. Anal. calcd. for $C_{14}H_{11}N_3O_7S$: C, 46.02; H, 3.01; N, 11.50. Found: C, 46.41; H, 2.93; N, 11.38%.

Ethyl 8-(4-methylphenyl)-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo[3,4-*c*][1,4] thiazine-5-carboxylate (5c): Pink solid, yield 52%, mp 180–182°C; IR (KBr) νcm^{-1}: 1722 (C═O, ester), 1791 (C═O, lactone), 3341 (br OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.30 (d, $J = 8.0$ Hz, 2H, ArH), 7.85 (s, 1H, C6-H), 7.65 (d, $J = 8.0$ Hz, 2H, ArH), 4.42 (q, $J = 7.2$ Hz, 2H, CH_2 of ester), 2.30 (s, 3H, CH_3), 1.75 (br s, 1H, D_2O exchangeable, OH), 1.45 (t, $J = 7.4$ Hz 3H, CH_3 of ester). Anal. calcd. for $C_{15}H_{14}N_2O_5S$: C, 53.89; H, 4.19; N, 8.38. Found: C, 53.62; H, 4.32; N, 8.23%.

Ethyl 8-(4-chlorophenyl)-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo[3,4-*c*][1,4] thiazine-5-carboxylate (5d): Red solid; mp 200–201°C; yield 50%; IR (KBr) νcm^{-1}: 1725 (C═O, ester), 1788 (C═O, lactone), 3329 (br, OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.40 (d, $J = 8.1$ Hz, 2H, ArH), 7.96 (s, 1H, C-6H), 7.69 (d, $J = 8.2$ Hz, 2H, ArH), 4.52 (q, $J = 7.2$ Hz, 2H, CH_2 of ester), 1.72 (br s, 1H, D_2O exchangeable, OH), 1.38 (t, $J = 7.0$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{14}H_{11}ClN_2O_5S$: C, 47.39; H, 3.10; N, 7.89. Found: C, 47.05; H, 3.22; N, 7.72%.

Ethyl 8-(4-bromophenyl)-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo[3,4-*c*][1,4] thiazine-5-carboxylate (5e): Red solid, yield 50%, mp 205–206°C; IR (KBr) νcm^{-1}: 1727(C═O, ester), 1795 (C═O, lactone), 3335 (br, OH); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.37 (d, $J = 8.0$ Hz, 2H, ArH), 8.08 (s, 1H, C6-H), 7.63 (d, $J = 8.2$ Hz, 2H, ArH), 4.49 (q, $J = 7.1$ Hz, 2H, CH_2 of ester), 1.68 (br s, 1H, D_2O exchangeable, OH), 1.42 (t, $J = 7.1$ Hz, 3H, CH_3 of ester); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.0, 178.2, 157.7, 151.0, 132.2, 131.8, 130.0, 125.5, 122.4, 120.0, 63.4, 14.5. Anal. calcd. for $C_{14}H_{11}BrN_2O_5S$: C, 42.10; H, 2.75; N, 7.01. Found: C, 42.53; H, 2.66; N, 7.16%. MS (m/z): M^+ (398) and $M^+ + 2$ (400).

Ethyl 8-(2-thienyl)-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo[3,4-*c*][1,4] thiazine-5-carboxylate (5f): Red solid, yield 46%, mp 210–211°C; IR (KBr) νcm^{-1}: 1720 (C═O, ester), 1787 (C═O, lactone), 3328 (br, OH); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.10 (s, 1H, C6-H), 6.90–6.60 (m, 3H, thienyl), 4.50 (q, $J = 6.8$ Hz, 2H, CH_2 of ester), 1.58 (br s, 1H, D_2O exchangeable, OH), 1.32 (t, $J = 7.0$ Hz 3H, CH_3 of ester). Anal. calcd. for $C_{12}H_{10}N_2O_5S_2$: C, 44.17; H, 3.06; N, 8.58. Found: C, 44.40; H, 3.12; N, 8.65%.

Ethyl 8-(3-coumarinyl)-8-hydroxy-3-oxo-8*H*[1,2,4]oxadiazolo[3,4-*c*][1,4] thiazine-5-carboxylate (5g): Red solid, yield 42%, mp 196–198°C; IR (KBr) νcm^{-1}: 1721 (C═O, ester), 1790, 1750 (C═O, lactone), 3330 (br, OH); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.56 (s, 1H, coumarinyl C4-H), 8.30 (s, 1H, C6-H), 8.16–7.69 (m, 4H, coumarinyl), 4.35 (q, $J = 6.8$ Hz, 2H, CH_2 of ester), 1.55 (br s, 1H, D_2O exchangeable, OH), 1.35 (t, $J = 6.8$ Hz, 3H, CH_3 of ester). Anal. calcd. for $C_{17}H_{12}N_2O_7S$: C, 56.35; H, 3.31; N, 7.73. Found: C, 56.99; H, 3.62; N, 7.44%.

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