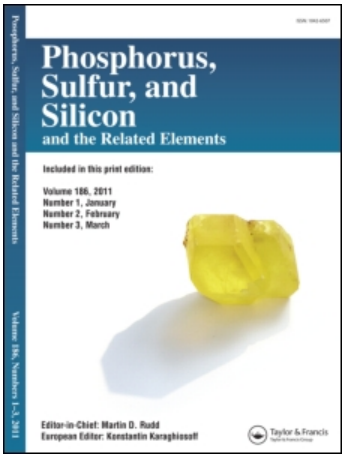

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Zayed, Salem E.(1996) 'KETOKEN GEM-DITHIOLS AND TRITHIONES: SYNTHESIS AND STUDY OF THE BEHAVIOR TOWARDS DIPOLE REAGENTS; SYNTHESIS OF SOME NITROGEN HETEROAROMATICS', Phosphorus, Sulfur, and Silicon and the Related Elements, 108: 1, 7 — 13
To link to this Article: DOI: 10.1080/10426509608029632
URL: http://dx.doi.org/10.1080/10426509608029632

Phosphorus, Sulfur, and Silicon, 1996, Vol. 108, pp. 7–13
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KETOKEN gem-DITHIOLS AND TRITHIONES: SYNTHESIS AND STUDY OF THE BEHAVIOR TOWARDS DIPOLE REAGENTS; SYNTHESIS OF SOME NITROGEN HETEROAROMATICS

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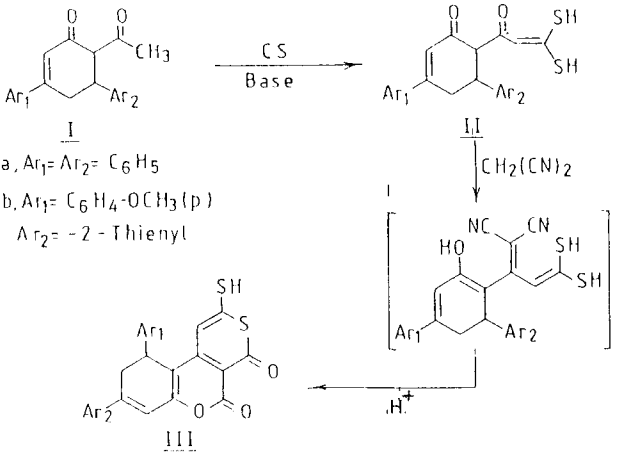
(Received April 9, 1995; in final form July 22, 1995)

The behavior of ketoken gem-dithiols towards active methylene and methyl groups resulted in the formation of thiopyrano-dihydrocaumarine derivatives **IIIa,b** via cyclocondensation reaction between substituted 4-dihydrocyclohexanone **Ia,b**. N-phenylpyrazoline derivative **VI** was also formed through reaction of gem-dithiol **IV** with malonic acid followed by phenyl hydrazine. Pyridopyridazine derivative **XII** could also synthesized. The behavior of thione group in **XV** towards some dipole systems was also investigated to give spiro products **XVIII–XX**.

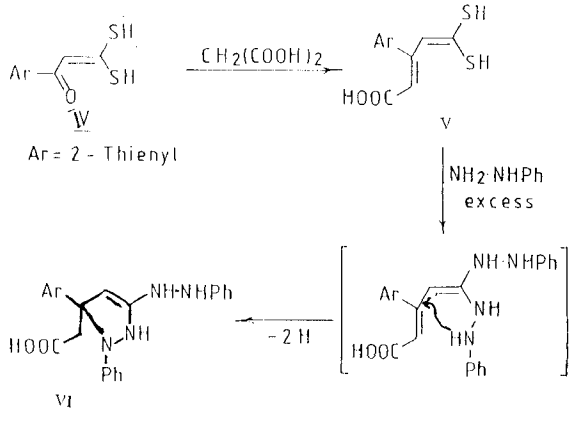
Key words: Ketoken gem dithiols, trithions and dipole reagents, nitrogen heteroaromatics from gem dithiols.

As part of continuing work[1–3] the use of ketoken and keten gem-dithiols in synthesis in the preparation of heterocyclic systems was studied. The key substrates **IIa,b**; **V**; **VIII** and **XV** are available from the reaction of methyl ketones, active methylene and methyle groups with carbon disulfide in the presence of base[4–6] and **XIV** or **XIII** with phosphorus pentasulfide.[4,7,8]

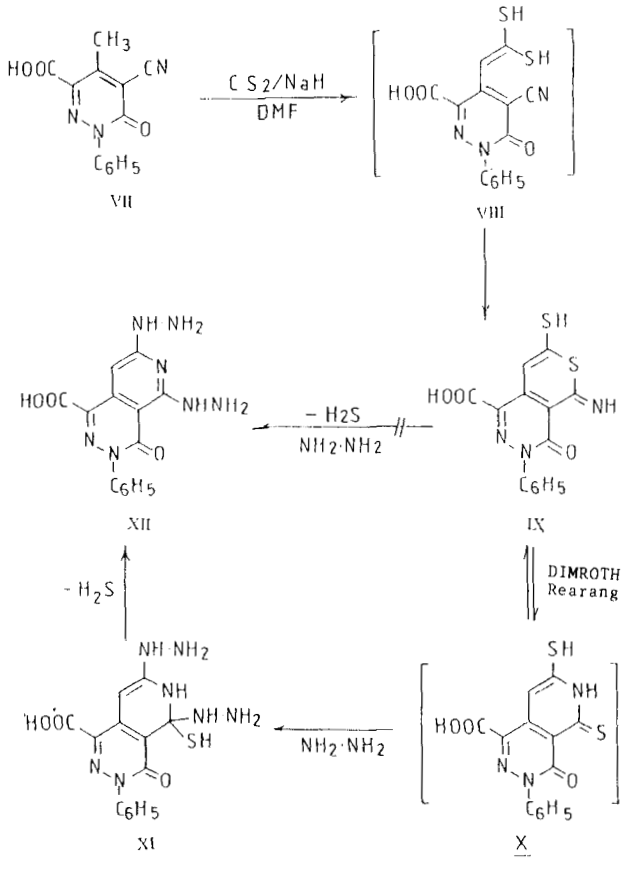
The products thiopyrano-5-dihydrocoumarine **III**, pyrazoline **VI** and pyridopyridazine **XII** could be prepared smoothly in few steps and high yields. similar products are known to possess potent effects.[9,10] Among the precursors 6-acetyl-3,5-disubstituted arylcyclohexenones **Ia–c** were prepared via cyclocondenstion of the required chalcones with acetylacetone in methanol containing sodium methoxide.[11,12] Reaction of the precursors **Ia–b** with carbon disulfide in benzene in presence of sodium *tert.*butoxide yielded the gem-dithiols **IIa,b** 3,3′-Dimercapto 1-(2-thienyl)2-propen-1-one **IV** was also obtained by the same procedure using 2-acetylthiophene. In the present work, the behavior of **IIa,b** and **IV** towards active methylene compounds was investigated. **IIa,b** reacted smoothly with malononitrile in ethanol in the presence of triethylamine and yielded products **IIIa,b**. These products were assumed to have formed via condensation of the methylene group at malononitrile with the carbonyl group followed by nucleophilic attack of thiol and hydroxyl groups on two carbonitrile groups to give the isolable products **IIIa,b** (Scheme I). 3,3′-Dimercapto 1-(2-thienyl)2-propen-1-one **IV** when reacted with malonic acid in methanolic so-



SCHEME I



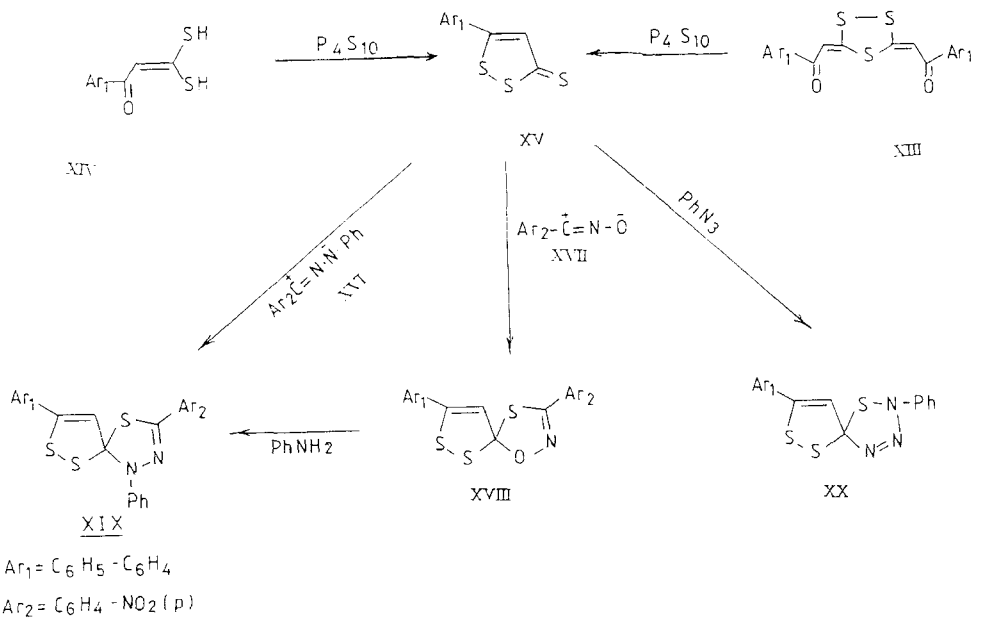
SCHEME II



SCHEME III

dium methoxide yielded **V** through condensation of active methylene in malonic acid with ketogroup in **IV**. Treating **V** with excess phenyl hydrazine resulted in elimination of hydrogen sulfide followed by intramolecular neucleophilic attack on Michael system and finally 3-phenyl hydrazino 5-(2-thienyl)N-phenyl pyrazole 5-acetic acid **VI** was obtained (Scheme II). Spectral data ruled out the possibility of formation of other products. A trials to investigate the reactivity of the methyl group at C_4 neighboring two carbonitriles in N-phenylpyridazine derivative **VII** towards addition to carbon disulfide using different bases has failed. In the case of sodium hydride in DMF, the unisolable intermediate gem-dithiol **VIII** formed followed by addition of sulfohydryl group to carbonitrile to give **IX** and finally 2-mercapto thiopyran-6-imino (4:3-c)N-phenyl-3-carboxy pyridazin-6-one **IX** has been obtained and under Dimroth rearrangement it converted to intermediate **X**. Reaction of **X** with hydrazine hydrate in ethanol resulted in formation of **XII** via intermediate **XI** (Scheme III).

The precursor **XV** (prepared from 3,3-dimercapto 1-(4-biphenyl)2-propen-1-one **XIV** through sulfurization using phosphorus pentasulfide or via sulfurization of the disaurine **XIII**) has been utilized to investigate its behavior towards dipole systems derived from **XVI** and **XVII**. It has been found that these dipoles behave by addition



SCHEME IV

to the more electron rich thione group and gave the spiro 5[(2-*p*-nitrophenyl)4-phenyl-1,3,4-thiadiazole]5-[3-diphenyl-1,2 dithiacyclopenten] **XIX** and the spiro 5-[(2-*p*-nitrophenyl) 1,3,4-thiaisoxazole[-5-(3-biphenyl 1,2-dithiacyclopenten] **XVIII**. The spiro product **XIX** could also be obtained via reacting **XVIII** with aniline in ethanol through ring opening followed by recyclization and loss of water, and the product was found to be identical with **XIX**. Structure assignment of the products **XVIII** and **XIX** was based on ^{1}H NMR where a singlet signal appeared at δ 6.9 ppm which indicates the presence of a proton at C-4 in trithione moiety. Behavior of the trithione **XV** towards phenylazide was also investigated in ether and sodium bicarbonate at room temperature. Phenyl azide behaves by the same way on addition to the thione group to give the spiro compound 5(2-phenyl 1,2,3,4-thiatriazine)5-(3-biphenyl 1,2-dithiacyclopenten) **XX**. Structure confirmation of **XX** was proved by ^{1}H NMR where a singlet signal appeared at δ 6.9 ppm and not at 4.4 (quat. carbon C_4). (Scheme IV).

EXPERIMENTAL

All melting points are uncorrected. Elemental analysis were determined at the microanalysis unit, Cairo University, I.R. spectra on Shimadzu instrument (4000–650 cm^{-1}), ^{1}H NMR spectra were measured on Gemini 200 MHz Vrian ($CDCl_3$). Mass spectra on Shimadzu SQ 1000.

3,5-Diaryl-6-acetyl cyclohexen 5-ones **Ia, Ib.** Equimolar ratios of acetylacetone, the appropriate chalcone and sodium methoxide (0.01 mol) in methanol were heated at 120°C for 3 hours. After cooling, the separated yellow oil obtained was washed with water, extracted with ether and triturated with methanol. The yellow solid obtained were collected from methanol to give **Ia** and **Ib**, respectively.

Ia, separated in form of pale yellow crystals, m.p. 112°C (78%). Analysis calcd. for $C_{20}H_{18}O_2$ (290.34) Calcd. C, 82.73; H, 6.25%. Found C, 82.8; H, 6.2%.

I.R./cm^{-1} 1630 (C=O), 1660 (CH_3C=O).

Ib, separated in form of yellow crystals, m.p. 82°C (68%). Analysis calcd. for $C_{19}H_{18}SO_3$ (326.32). Calcd. C, 69.93; H, 5.56; S, 9.8%. Found C, 70.0; H, 5.5; S, 9.9%.

I.R./cm^{-1}; 1620 (C═O), 1645 C═O, CH_3).
^{1}H NMR δ 2.6 (s, 3H, CH_3); 2.7 (s, 3H, $COCH_3$), 6.5–6.7 (d,d, 2H, H-5 H-6 cyc.), 1.39 (d, 2H, CH_2), 6.8 (s, 1H, CH═C) 7.0–7.3 (m, 3H, thioph.); 3.2 (s, 3H, OCH_3) 7.4–8.2 (m, 4H, C_6H_4).

3,5-Diaryl(3,3-dimercaptoethenylcarbonyl)-2-cyclohexen-1-ones **IIa,b**: To sodium *tert.* butoxide (0.01 mol) in benzene was added carbon disulfide (0.012 mol) and the cyclohexenones **Ia,b** with vigorous shaking at room temperature. After addition, the reaction mixtures were shaken for an additional half hour and left in an ice-bath for 3 hours. The reaction mixtures were then poured into ice-cold water. The benzene layers were extracted and the aqueous layer washed twice with ether. Acidification of the water layer with cold conc. sulfuric acid afforded a solid product. Reprecipitation via solubility in aqueous sodium bicarbonate and regeneration with conc. hydrochloric acid yielded pure products **IIa** and **IIb**.

IIa, separated in form of a yellow product, mp. 146°C (67%). Analysis calcd. for $C_{21}H_{18}S_2O_2$ (366.35). Calcd. C, 68.85; H, 4.95; S, 17.47%. Found C, 68.9; H, 5.0; S, 17.5%.

I.R./cm^{-1} 1660 (C═O, cyc.), 1635 (C═O), 2535 (SH).
^{1}H NMR 7.1 (s, 1H, CH═CH), 7.2–8.1 (m, 10H, 2, C_6H_5), 6.5–6.7 (d,d, 2H, H-5, H-6 cyc.), 1.44 (d, 2H, CH_2-cyc.) 13.6 (s, 2H, 2-SH).

IIb was obtained as a yellow compound, m.p. 122°C (64%). Analysis calcd. for $C_{20}H_{18}S_3O_3$ (402.33). Calcd. C, 59.70; H, 4.50; S, 23.86%. Found. C, 59.7; H, 4.5; S, 23.9%.

^{1}H NMR δ 6.95 (s, 1H, CH═C); 7.3–8.2 (m, 4H-C_6H_4), 7.0–7.25 (m, 3H, thioph.). 6.5–6.7 (d,d, 2H, H-5, H-6 cyc.) 1.4 (d, 2H, CH_2) 3.4 (s, 3H, OCH_3) 13.5 (s, 2H, 2SH).

2-Mercaptothiopyran 6-one [3:2-b] 6-dihydro-5,7-diarylcaumarine **IIIa,b**: To **IIa, b** (0.01 mol) in ethanol (100 ml) and triethylamine (1 ml), mononitrile (0.01 mol; 0.66 gm) was added and the reaction mixtures were heated under reflux for 3 hours. After cooling, the separated solid products **IIIa,b** were collected and recrystallized form D.M.F. **IIIa** formed as yellow crystals, m.p. 184°C (62%). Analysis calcd. for **IIIa** $C_{24}H_{16}O_3S_2$ (416.36). Calcd. C, 69.23; H, 3.87; S, 15.37%. Found C, 69.2; H, 3.9; S, 15.4%.

I.R./cm^{-1}, 2535 (SH), 1680, 1710 (C═O).
^{1}H NMR δ 7.0 (s, CH═C—thiopyr.) 6.8–6.9 (d,d 2H, H-5, H-8 cyclohex.), 1.42 (d, 2H, CH_2 cyclohex).

3,3-Dimercapto 1-(2-thienyl) 2-propen-1-acrylic acid **V**: a mixture of 3,3-dimercapto 1-(2-thienyl)2-propene-1-one (0.01 mol; 2.02 gm) and molonic acid (0.01 mol; 1.04 gm) in methanol (100 ml) and sodium methoxide (0.68 gm) was heated under reflux for 5 hours. After cooling and neutralization with cold dilute hydrochloric acid a solid product was separated. Recrystallization from DMF gave a yellowish red product, m.p. 114°C. Analysis Calcd. for $C_9H_8S_3O_2$ (244.14). Calcd., C, 44.27; H, 3.3; S, 39.32%. Found C, 44.3; H, 3.3; S, 39.5%.

I.R./cm^{-1} 1685 (C═O), 3210 (OH).
^{1}H NMR δ 6.9 (s, 1H, CH═C); 7.0 (s, 1H, CH—COOH), 14.1 (s, 1H, OH), 7.0–7.2 (m, 3H, thiophene).

3-Phenyl hydrazino-5 (2-thienyl)-N-phenylpyrazole, 5-acetic acid **VI**: To **V** (0.01 mol; 2.02 g) in ethanol (75 ml). Phenyl hydrazine (5 ml) was added and the reaction mixture was heated under reflux until complete ceasing of hydrogen sulfide (~3 hours). After evaporation of the solvent to its third of volume and left aside to cool, the separated solid product was collected so formed. Recrystallization from benzene gave yellowish red crystals of m.p. 210°C. (decompos.) (72%). Analysis calcd. for $C_{21}H_{20}N_4SO_2$ (392.39). Calcd. C, 64.28; H, 5.13; N, 14.27; S, 8.15%. Found C, 64.3; H, 5.1; N, 14.3; S, 8.2%.

I.R./cm^{-1} 1695 (C═O), 3400 (NH), 3210 (OH, COOH).
^{1}H NMR δ 6.8 (s, 1H, C_4-H) 8.1–8.43 (b, 3H, 3NH), 12.9 (s, b, 1H, OH, COOH). 4.1 (d, 2H, CH_2) 7.1–7.3 (m, 3H, Thioph.), 7.5–8.2 (m, 10H, $2C_6H_5$)

2-Mercapto-6-imino-thiopyran-7-one [3,2-b] N-phenyl-3-carboxypyridazin-6-one **IX**: To **VII** (0.01 mol, 2.55 gm) in anhydrous DMF (100 ml). Sodium hydride (0.012 mol; 0.29 gm) was added while stirring at room temperature, then carbon disulfide (0.012 mol; 0.9 gm) was added. The stirring was continued for three hours, followed by heating under reflux for 3 hours. After cooling and neutralization with cold dilute hydrochloric acid, the separated yellow product was collected and recrystallized from benzene to give **IX** (76%) m.p. 162°C. Analysis calcd. for $C_{14}H_9N_3S_2O_3$ (331.21). Calcd. C, 50.76; H, 2.73; N, 12.68; S, 28.98%. Found C, 50.8; H, 2.7; N, 12.7; S, 29.0%.

I.R./cm^{-1}, 2545 (SH); 1645 (C=O, carboxyl), 1595 (C=O), 1610 (C=O—N—Ar) 3150 (—OH, COOH).
^{1}H NMR δ 13.2 (s, 1H, SH); 12.2 (s, 1H, OH, COOH) 7.3–8.1 (m, 5H, C_6H_5), 5.9 (d, 1H—CH=C—SH, cyclic).

2,6-Dihydrazino-pyrido-[3,2-b] N-phenyl-3-carboxypyridazin-6-one **XII**: To **IX** (0.01 mol; 3.31 gm) in ethanol (100 ml), hydrazine hydrate (0.25 mol, 8 gm) was added portionwise while stirring at room temperature. After complete addition the reaction mixture was heated under reflux until complete ceasing of hydrogen sulfide (ca. 3 hours) evolution. Pouring the reaction mixture into cold water gave a water soluble product. Extraction with benzene and distillation of excess benaene, then addition of pet. ether 40/60 afforded white needles, (82%) m.p. 197°C. Analysis calcd. for $C_{14}H_{13}N_7O_3$ (327.27). Calcd. C, 51.38, H, 4.00; N, 29.95%. Found C, 51.4; H, 3.9; N. 29.9%.

I.R./cm^{-1} 3480–3320 (NH + NH_2). 1635 (N—C=O); 1710 (C=O) 3215 (OH, COOH).
^{1}H NMR δ 6.6 (s, 1H, H-3 pyridine), 10.8 (s, OH, COOH), 4.4–4.6 (s, 2H, 2NH) 8.4–8.6 (d, 4H, 2NH_2) 7.6–8.2 (m, 5H, C_6H_5).

3,3-Dimercapto 1(-4-biphenyl)2-propen-1-one[1,3,4] **XIV**: This product is prepared as usual via reaction of 4-acetylbiphenyl with carbon disulfide in presence of a base.

1,2-Dithiacyclopenten 3-(4-biphenyl)5-thione[1,3,4] **XV**: Sulfurization of **XIV** with phosphorous pentasulfide in dry benzene gave **XV**.

Disaurine **XIII** is prepared through either boiling **XIVa** in glacial acetic acid or leaving at room temperature for 3 weeks.

Preparation of the dipoles **XVI** and **XVII**: Reaction of equimolar ratio of *p*-nitrobenzoyl chloride with phenylhydrazine and/or hydroxylamine hydrochloride in dry benzene afforded the corresponding amides which on refluxing with thionylchloride in dry benzene gave the required α-chloro compounds. On treating with triethylamine in dry ether the required freshly prepared **XVI** and **XVII** respectively was obtained.

3-(4-Biphenyl 1,2-dithiacyclopenten)-5-spiro-2-(p-nitrophenyl)4-phenyl,1,3,4-thiadiazole **XIX** *and 3 (4-biphenyl)-1,2-dithiacyclopenten-2(p-nitrophenyl)-5-spiro-1,3,4-thiaisoxazole* **XVIII**: To **XV** (0.01 mol, 2.86 gm) in dry benzene (100 ml) was added to **XVI** (0.01 mol) and/or to **XVII** (0.01 mol) with stirring at room temperature. After stirring for 2 hours, the filtrates were distilled to give products **XIX** and **XVIII**, respectively.

Product **XIX** was separated in form of pale yellow neddles from benzene (89%) m.p. 189°C. Analysis calcd. for $C_{28}H_{19}N_3S_3O_2$ (525.45). Calcd. C, 64.00; H, 3.64; N, 7.99; S, 18.27%. Found C, 64.0; H, 3.6; N, 8.0; S, 18.3%. ^{1}H NMR δ 7.0 (s, 1H, CH-cyclopent.), 7.6–8.2 (m, 18H, Aromatic protons).

Product **XVIII** was obtained as yellow crystals from benzene, (91%) m.p. 231°C. Analysis calcd. for $C_{22}H_{14}N_2S_3O_3$ (450.33). Calcd. C, 58.67; H, 3.13; N, 6.22; S, 21.31%. Found C, 58.7; H, 3.1; N 6.2; S, 21.2%. ^{1}H NMR δ 6.9 (s, 1H, CH cyclopent.), 7.4–8.3 (m, 13H, aromatic protons).

3-(4-biphenyl)-1,2-dithiacyclopenten-5-spiro-2-phenyl 1,2,3,4-thiatriazine **XX**: To **XV** (0.01 mol, 2.86 gm) in ether (100 ml) was added phenylazide (0.01 mol) [prepared from diazodization of phenylhydrazine followed by treating with $NaHCO_3$ in ether] with stirring at room temperature for 4 hours. Distillation of ether left orange yellow crystals. Recrystallization from benzene gave deep yellow needles m.p. 103°C. Analysis calcd. for $C_{21}H_{15}N_3S_3$ (405.37). Calcd. C, 62.22; H, 3.72; N, 10.37; S, 23.68%. Found C, 62.2; H, 3.7; N, 10.4; S 23.7%.

^{1}H NMR δ 7.0 (s, 1H, CH cyclopent.) 7.4–8.3 (m, 14H, aromatic protons).

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