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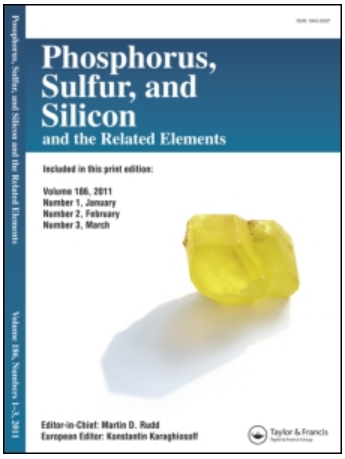

Phosphorus, Sulfur, and Silicon and the Related Elements
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To cite this Article Zayed, Salem E.(1996) 'KETENE GEM-DITHIOLS; A CONVENIENT ONE-STEP PROCEDURE FROM ALIPHATIC ACTIVE METHYLENES: REACTIONS AND SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED THIA- AND AZAHETEROAROMATICS', Phosphorus, Sulfur, and Silicon and the Related Elements, 116: 1, 29 — 37
To link to this Article: DOI: 10.1080/10426509608040466
URL: http://dx.doi.org/10.1080/10426509608040466

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Phosphorus, Sulfur, and Silicon, 1996, Vol. 116, pp. 29–37
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KETENE GEM-DITHIOLS; A CONVENIENT ONE-STEP PROCEDURE FROM ALIPHATIC ACTIVE METHYLENES: REACTIONS AND SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED THIA- AND AZAHETEROAROMATICS

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(Received 15 October 1995; Revised 1 April 1996; In final form 1 April 1996)

It has been reported in the current literature that the isolation of certain ketene gem dithiols has failed due to dimerization. Generation of ketene gem-dithiols via trapping with other reactants led to formation of pyridine VI, pyrroles, pyridothiadiazole and pyrazolone derivatives.

Keywords: Ketene gem-dithiols; sulfur and carbon disulfide with active methylenes; thia and thiaazoheteroaromatics

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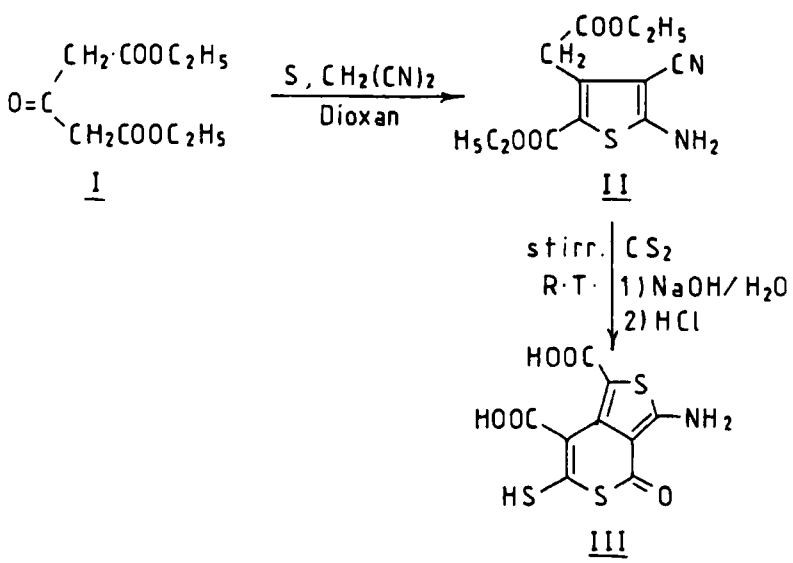
Ketene gem-dithiols derived from reaction of ketones with carbon disulfide in the presence of a base have become a subject of current interest (1,2). Although several publications have appeared regarding their synthesis and structural studies in the recent literature, (3–8) the synthetic utility of these intermediates has not been extensively explored. The objective of the present investigation has been to examine the behavior of aliphatic active methylenes towards elemental sulfur or carbon disulfide. The reactions have now been extended to include 1,3-acetone dicarboxylic acid diethylester, dimethyl succinate and ethyl cyanoacetate. Previous attempts to isolate the ketene-gem dithiols have failed due to the high tendency of most ketene gem dithiols to dimerize or oligomerize. In the present work, they are generated under conditions which permit a trapping reaction.

Reaction of diethyl 1,3-acetone carboxylate I with sulfur and malononitrile in dioxane gave the reported thiophene derivative[9] II. Treatment of II with carbon disulfide in aqueous sodium hydroxide afforded the thiopyrano thiophene derivative III. Formation of III is assumed to proceed via addition of the active methylene in II to carbon disulfide followed by ester hydrolysis and nucleophilic attack of the sulfhydryl group to the cyano group. Reactivity of dimethyl succinate towards elemental sulfur and carbon disulfide in the presence of malononitirile as a trapping reactant has been investigated. Reaction of IV with malononitrile and sulfur in DMF in presence of triethylamine gave 4-amino 2-mercapto 5,6-pyridine dicarboxylic acid dimethylester VI via formation of the unisolable intermediate V. Product VI is assumed to be formed via the effect of elemental sulfur on the cyano and active methylene groups in V to form thioamide and thiol moieties followed by elimination of hydrogen sulfide and aromatization. Structure confirmation of VI is based on the disappearance of the cyano group and appearance of signals characteristic of methyl protons at δ 3.6 & 3.8 ppm. Moreover, reaction of IV with two mols of carbon disulfide and one mol of malononitrile as a trapping reactant gave IX via formation of intermediates VII and VIII. Consequently, reaction of IX with phenyl hydrazine and with thiourea yielded the pyrrole derivative condensed to N-phenylpyrazole and to pyrimidine derivatives X and XI respectively. Presumably the first step in this reaction is the addition of active methylene in dimethyl succinate to carbon disulfide to give the



SCHEME 1

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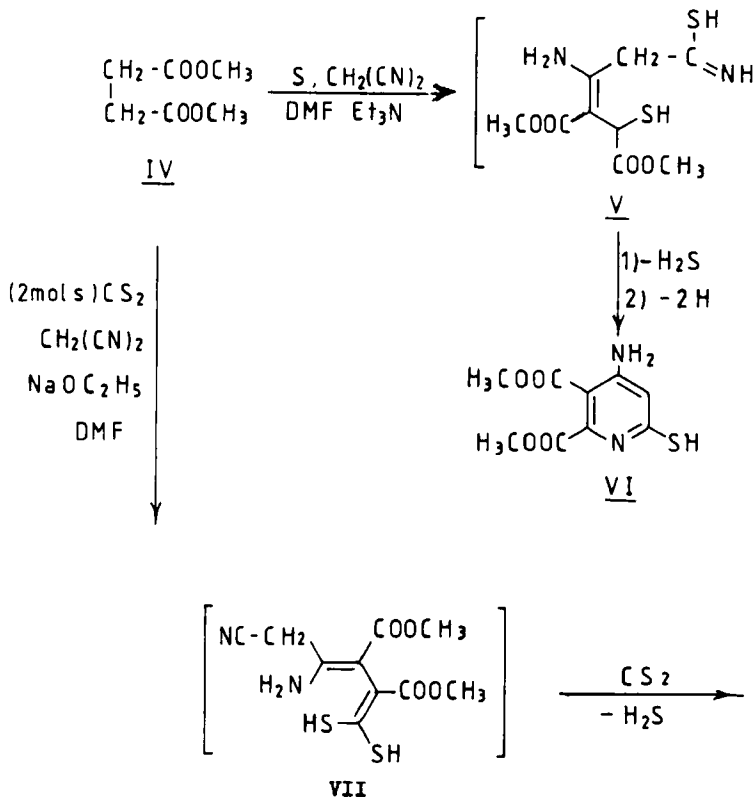

SCHEME 2

ketene gem dithiol followed by nucleophilic attack of the malononitrile cyano group on the second methylene group in dimethyl succinate and finally elimination of hydrogen sulfide to give VIII in which the cyanomethylene side chain at C-2 adds to carbon disulfide to give IX. Appearance of peaks characteristic for CN and ester carbonyl and methyl groups on subjecting IX to ir. and ^{1}H.NMR spectra confirmed the structure of IX. The structure of IX was chemically established by its reaction with phenyl hydrazine to give 4-(3-amino-5-mercapto N-phenyl pyrazole) 2-mercapto 3,4-pyrrole dicarboxylic acid dimethyl ester X. Furthermore reaction of IX with thiourea in ethanol and sodium ethoxide afforded 3-(2-mercapto 3,4-pyrrole dimethyl carboxylate)-4-amino-2,5-dimercapto pyrimidine XI. Reaction of IV with carbon disulfide in the presence of acetonitrile as a trapping reagent, in place of malonitrile, facilitates formation of another polyfunctionally substituted pyrrole derivative XII. XII is assumed to be formed via formation of the intermediate XI_A and elimination of hydrogen

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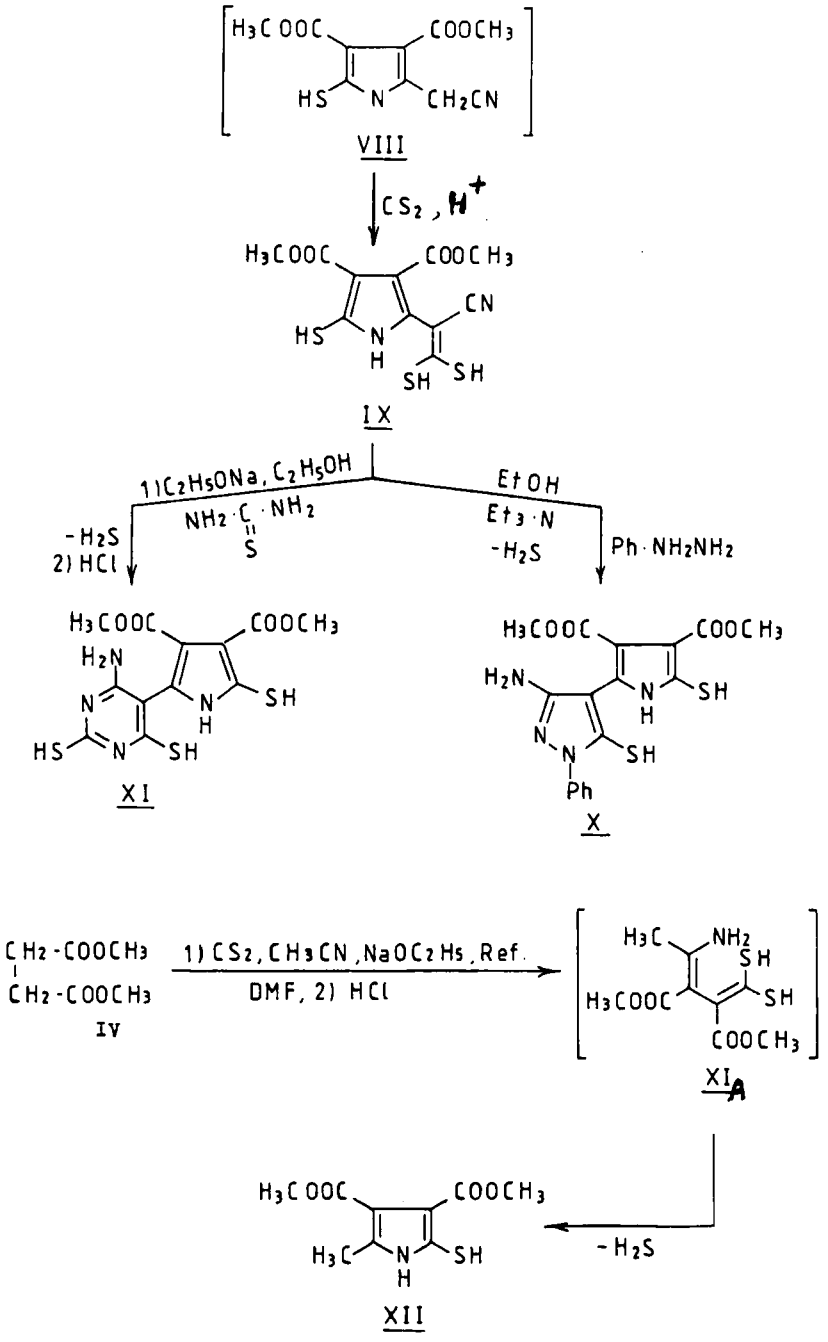

SCHEME 2 (Continued)

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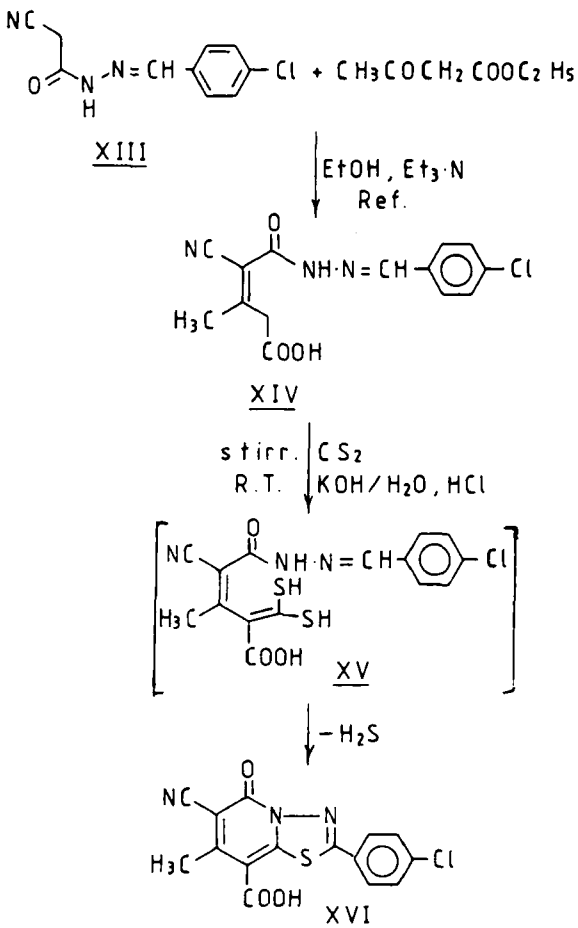
sulfide. Reactivity of the methylene group neighboring the electron donor moiety in conjugated system XIV towards carbon disulfide is also subjected to investigation. Reaction of XIV with carbon disulfide in aqueous alkali yielded the polyfunctionally substituted 1,3,4 thiadiazolopyridine derivative XVI. This product is probably formed via addition of carbon disulfide to the methylene group in dimethyl succinate to give the unisolable intermediate XV, then elimination of hydrogen sulfide followed by cyclization and finally XVI is formed.

The reactivity of the methylene group, neighboring to the withdrawing group, towards carbon disulfide is also investigated. XVII was reacted with carbon disulfide in aqueous alkali and obtained 3-amino-2-mercapto-N-phenyl pyrazol-



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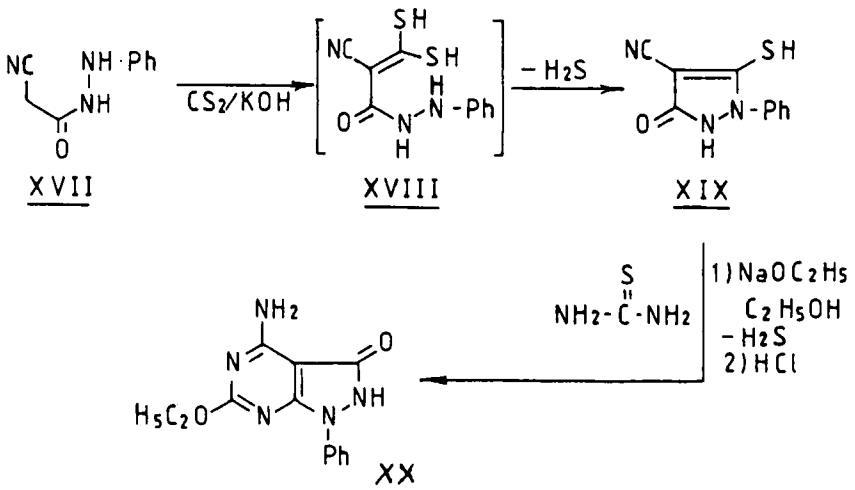

SCHEME 4

5-one XIX. Reaction of XIX with thiourea in ethanolic sodium ethoxide gave XX on prolonged heating. Appearance of signals characteristic for O-CH_2-CH_3 is an evidence for structure confirmation of XX.

Experimental

All melting points are uncorrected and were measured on an electrothermal melting point apparatus. IR spectra were recorded on Schimadzu No. 200-91506 instrument, ^{1}H.NMR signals were measured on Varian Gemini-200-200 MHz Varian (DMSO) and mass spectra on Schimadzu SQ1000. Microanalysis data were measured in the microanalysis unit, at Cairo University.

2-Mercapto 3-Carboxythiopyran-6-one [4:3-c] 2-Amino-5-Carboxy Thiophene III

To II (0.01 mol; 2.82 gm) in aqueous sodium hydroxide (5 gm/100 ml) was added carbon disulfide (0.015 mol; 1.14 g.) while stirring at room temperature. After complete addition of carbon disulfide, stirring was continued until complete solubility of II and appearance of a dark red colored solution. (~ 6 hours). On acidification with conc. hydrochloric acid and leaving aside overnight, a green solid product was obtained. Purification by solubility in aqueous sodium bicarbonate and neuteralization with dilute hydrochloric acid afforded green crystals. (86%) m.p. > 320°C. Analysis Calcd. for $C_9H_5NS_3O_5$ (303.09). Calcd., C, 35.66; H, 1.66; N, 4.62; S, 31.67%. Found C, 35.7; H, 1.7; N, 4.6; S, 31.5%.

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IR/cm^{-1}, 1610 (C═O) 1685 (C═O, COOH), 3175 (OH, COOH), 3520 (NH_2). ^{1}H.NMR. δ 4.8 (b, 2H.NH_2), 10.9 (s, 1H. OH, COOH) and 12.3 (s, 1H. OH-COOH, Thiophene C-2). 2.6 (s, 1H, SH).

4-Amino 2-Mercaptopyridine-5,6-Dicarboxylic Dimethyl Ester VI

A mixture of an equimolar ratio from dimethyl succinate, elemental sulfur and malononitrile (0.01 mol) in dioxane (100 ml) and triethylamine (1/2 ml) was heated under reflux until evolution of hydrogen sulfide ceased (~ 3 hours). After cooling, the separated solid product was filtered and purified by dissolving in sodium bicarbonate followed by neutralization with cold dilute hydrochloric acid; m.p. 196°C (67%). Analysis calcd. for $C_9H_{10}N_2SO_4$ (242.15). Calcd. C, 44.64; H, 4.16; N, 11.56; S, 13.21%. Found: C, 44.6; H, 4.2; N, 11.6; S, 13.2%. IR/cm^{-1} 3440 (NH_2), 1695 & 1710 (C═O, $COOCH_3$), ^{1}H.NMR δ 3.6, 3.8 (s, 6H. $2CH_3$, ester), 4.9 (s, b, 2H, NH_2), 6.8 (1H, H-3 pyrid) 2.1 (s, 1H, SH).

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2-Mercapto-5-(2,2-Dimercapto 1-Cyanoethylene) Pyrrole 3,4-Dicarboxylic Acid Dimethyl Ester IX

To an equimolar ratio of dimethyl succinate, malononitrile (0.01 mol) in DMF and sodium methoxide (100 ml/0.23 gm Na) carbon disulfide (0.02 mol) was added. Heating the reaction mixture under reflux until complete ceasing of hydrogen sulfide (4 hours) and neutralization with cold dilute hydrochloric acid obtained a yellow product IX. Recrystallization of IX from benezene gave brown crystals (77%), m.p. 112°C, Analysis calcd. for $C_{11}H_{10}N_2S_3O_4$ (330.17). Calcd. C, 40.01; H, 3.05; N, 8.48; S, 29.07%. Found C, 40.0; H, 3.0; N, 8.5; S, 29.0%. IR/cm^{-1} 2220 (CN), 1710 (C═O, ester), ^{1}H.NMR δ 3.6 (s, 3H-CH_3-ester) 3.7 (s, 3H-CH_3, ester), 8.5 (s, 1H, NH), 12.2 (s, 2H, 2SH) 1.8 (s, 1H, SH-pyrr. C_2)

4-(3-Amino- 5-Mercapto-N-Phenyl Pyrazole) 5-Mercatpo-Pyrrole 3,4-Dicarboxylic acid dimethyl ester X

To IX (0.01 mol; 3.3 gm) in ethanol (100 ml) and triethylamine (0.2 ml) was added phenyl hydrazine (0.01 mol, 1.08 ml) while stirring at room temperature. Then the reaction mixture was heated under reflux for 4 hours. After cooling, the separated solid product was filtered and recrystallized from ethanol in the form of brown crystals (77%) m.p. 212°C. Analysis calcd. for $C_{17}H_{16}N_4S_2O_4$ (404.29). Calcd. C, 50.50; H, 3.98; N, 13.85; S, 15.82%. Found C, 50.5; H, 4.0; N, 13.9; S, 16.0%. IR/cm^{-1} 1715 (C═O, ester) ^{1}H.NMR δ 3.6 (s, 3H, CH_3

ester) 3.7 (s, 3H, CH_3-ester), 5.6 (b, 2H, NH_2), 7.4–7.8 (m, 5H, C_6H_5) 12.9 (s, 1H, NH), 1.6 & 1.7 (s, s, 2H, 2 SH).

5-(5-Mercapto-3,4-Pyrroledicarboxylic Acid Dimethyl ester)4-Amino-2,6 Dimercapto Pyrimidine XI

A mixture of IX (0.01 mol, 3.3 gm) and thiourea (0.01 mol; 0.76 gm) in ethanolic sodium ethoxide (0.23 gm/100 ml) was heated under reflux for 3 hours. After cooling and neutralization with cold dilute hydrochloric acid, the separated solid was collected and recrystallized from DMF to give XI (63%), in the form of yellow crystals, m.p. 276°C. Analysis calcd. for $C_{12}H_{12}N_4S_3O_4$ (372.21). Calcd. C, 38.72; H, 3.24; N, 15.05; S, 25.79%. Found C, 38.7; H, 3.2; N, 15.0; S, 25.8%. IR/cm^{-1} 1700 (C═O), ^{1}H.NMR δ 3.7 (s, 3H, CH_3), 3.6 (s, 3H, CH_3), 5.2 (s. 2H, NH_2); 8.7 (s, 1H, NH), 1.8 (s, 1H, SH), 1.2 (s, 2H, 2 SH, pyrimid. C_2 & C_6)

5-Mercapto 2-methyl pyrrole 3,4-dicarboxylic acid dimethyl ester XII

To dimethyl succinate (0.01 mol; 1.64 gm) in DMF (100 ml) acetonitrile (0.01 mol; 0.41 gm) and sodium ethoxide (0.68 gm) were added and the reaction mixture was heated under reflux for 4 hours. After cooling and neutralization with cold dilute hydrochloric acid, the separated solid product was collected and recrystallized from methanol to give XII as faint yellow crystals, (69%) m.p. 112°C. Analysis calcd. for $C_9H_{11}NSO_4$ (229.15). Calcd. C, 47.17; H, 4.83; S, 13.96%. Found, C. 47.2; H, 4.8; S, 13.0%. IR/cm^{-1} 1710 (C═O, ester). ^{1}H.NMR δ 3.7 (s, 3H-CH_3-ester) 3.6 (s, 3H, CH_3 ester) 3.5 (s, 3H, CH_3), 8.9 (s, 1H, NH), 2.2 (s, 3H, CH_3).

5(p-Chlorophenyl) 1,3,4-thiadiazolo [3:2-a] 5-cyano-4- methyl-5-carboxy pyridin-2-one XVI

A mixture of XIV (0.01 mol; 3.06 gm), KOH (3 gm/100 ml H_2O) and carbon disulfide (0.013 mol, 0.78 gm) was stirred at room temperature until complete solubility and the solution becomes dark red. Filtration and neutralization with cold conc. HCl gave a yellow solid product. Recrystallization from benzene gave a pale yellow product of m.p. 184°C. Analysis calcd. for $C_{15}H_8N_3SO_3Cl$ (345.67). Calc. C, 52.12; H, 2.33 N, 12.15; S, 9.25%. Found. C, 52.1; H, 2.3; N, 12.1; S, 9.2. IR/cm^{-1} 2235 (CN), 1685 (C═O), 1610 (C═O). ^{1}H.NMR, δ, 2.4 (s, 3H, CH_3), 7.4–7.9 (m, 4H, C_6H_4), 10.8 (s, 1H-OH, COOH),

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N-phenyl-4-cyano 5-mercapto pyrazol 3-one XIX

A mixture of cyano acetophenylhydrazone XVII (0.01 mol; 1.75 gm) and carbon disulfide (0.015 mol, 1.14 gm) in aqueous potassium hydroxide (2 gm/100 ml H_2O) was stirred at room temperature until complete solubility. Neutralization of the filtrate with cold conc. hydrochloric acid gave a yellow solid product XIX m.p. 184°C. Analysis calcd. for $C_{10}H_7N_3SO$ (217.17). Calcd. C, 55.30; H, 3.24; N, 5.16; S, 14.73%. Found C, 55.3; H, 3.2; N, 5.2; S, 14.8%. IR/cm^{-1}. 2240 (CN), 1590 (C═O). ^{1}H.NMR δ 7.4–7.9 (m, 5H, C_6H_5), 9.6 (s, 1H.NH), 2.0 (s, 1H, SH).

N-Phenyl pyrazol 3-one [4:3-c] 4-amino 2-ethoxy pyrimidine XX:

An equimolar ratio from XIX and thiourea (0.01 mol) in ethanolic sodium ethoxide (0.3 gm Na/100 ml ethanol) was heated under reflux for 8 hours. After cooling, the separated pale yellow product was filtered and recrystallized from benzene to give XX (77%) m.p. 146°C. Analysis calcd. for $C_{13}H_{13}N_5O_2$ (271.25). Calcd. C, 57.56; H, 4.83; N, 25.81%. Found C, 57.6; H, 4.8; N, 25.8%. ^{1}H.NMR δ 1.6 (t, 3H, CH_3), 4.2 (q 2H, CH_2) 8.3 (d, 2H, NH_2), 7.3–7.8 (m, 5H, C_6H_5), 8.8 (s, 1H, NH).

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