Synthesis of 1,2,3-Thiadiazolo[4,5-*d*]pyridazines, A New Heterocyclic Ring System (1)

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A method was developed for the synthesis of 5-carbethoxy-4-formyl-1,2,3-thiadiazole (I), its isomer (II); 5-benzoyl-4-formyl-1,2,3-thiadiazole (III), and its isomer (IV). It was demonstrated that although compounds I, III and IV with hydrazine gave 7*H*-1,2,3-thiadiazolo[4,5-*d*]-pyridazin-7-one (XXII), 7-phenyl-1,2,3-thiadiazolo[4,5-*d*]pyridazine (XXIII) and 4-phenyl-1,2,3-thiadiazolo[4,5-*d*]pyridazine (XXV), respectively; however, compound I gave its corresponding hydrazone (XXIV).

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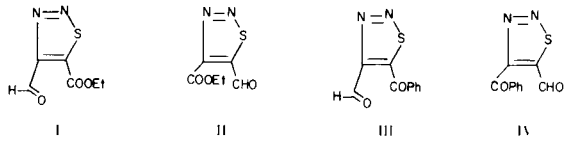
Recently the synthesis of 2,3-diformylbenzo[*b*]furan and its reaction with hydrazine was reported (2). In the present work synthesis of 5-carbethoxy-4-formyl-1,2,3-thiadiazole (I), its isomer 4-carbethoxy-5-formyl-1,2,3-thiadiazole (II), 5-benzoyl-4-formyl-1,2,3-thiadiazole (III), and its isomer 4-benzoyl-5-formyl-1,2,3-thiadiazole (IV) as intermediates in the synthesis of new purine analogues is reported.

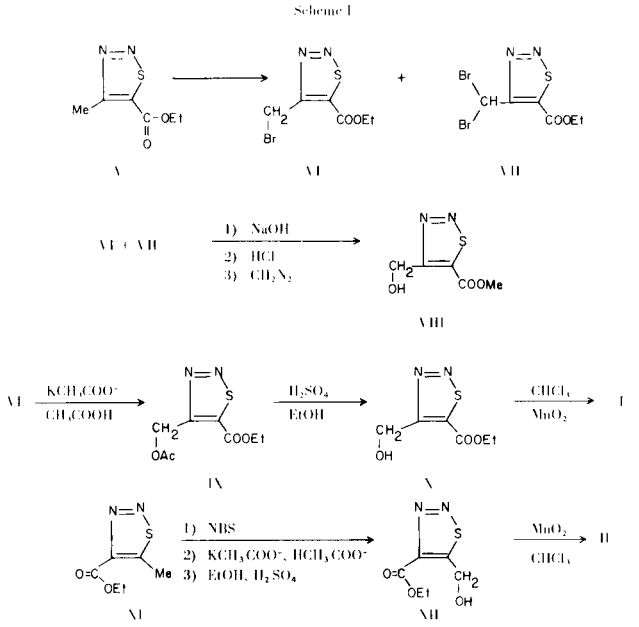


I II III IV

A possible route for the synthesis of compound I would be direct oxidation of 4-methyl-5-carbethoxy-1,2,3-thiadiazole (V). Although, similar oxidation was very successful in the case of 3-methylcoumarilate, as it was reported previously (2), however, in this case under different experimental conditions only starting material was isolated. Finally, this compound could be obtained in good yield as it is shown in Scheme I.

When compound V and 1.1 equivalents of *N*-bromosuccinimide in carbon tetrachloride were irradiated with a 500 W (G. E. photospot) lamp, a mixture of brominated intermediates was obtained. Hydrolysis of this mixture with approximately two equivalents of sodium hydroxide and subsequent esterification with diazomethane afforded, in low yield, 4-hydroxymethyl-5-carbomethoxy-1,2,3-thiadiazole (VIII). However, the corresponding ethyl ester of the latter could be obtained, in two steps, in very high yield as it is shown in Scheme I. Oxidation of the compound X with manganese dioxide gave the desired compound I.

Scheme I

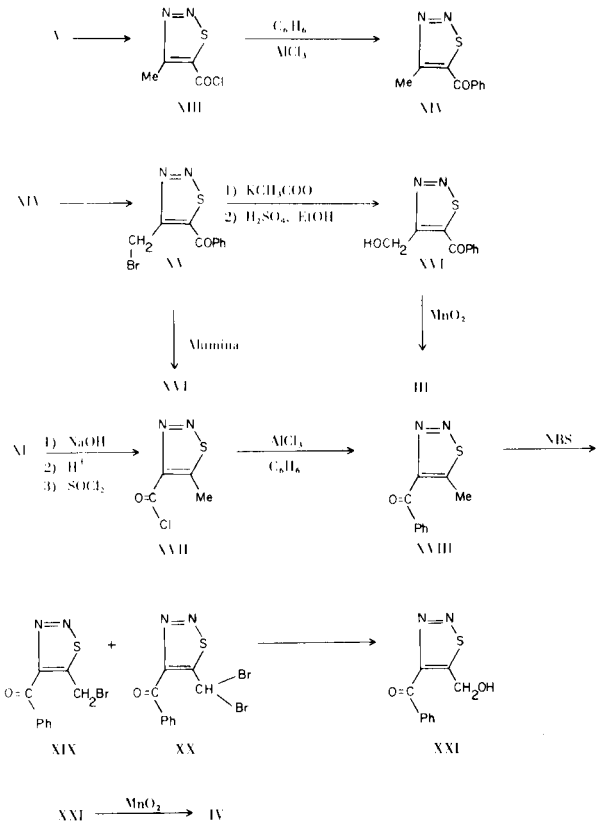


The synthesis of compound II in impure state and low yield was reported (3). However, this method cannot be regarded as a preparative procedure. The synthesis of this compound in moderate yield is summarized in Scheme I.

The synthesis of compound III was easily achieved from 4-methyl-5-cabethoxy-1,2,3-thiadiazole (V). The latter could be obtained, in high yield, following our general method for the preparation of 1,2,3-thiadiazoles which is an oxidative cyclization of methyl or methylene keton semicarbazones with thionyl chloride (4). The latter method is a modification of Hurd and Mori's method (5). Hydrolysis of compound V followed by the

reaction with thionyl chloride afforded 4-methyl-1,2,3-thiadiazole-5-carboxy chloride (XIII). The reaction of XIII with benzene in the presence of two equivalents aluminium chloride gave 4-methyl-5-benzoyl-1,2,3-thiadiazole (XIV) in high yield. Compound XIV could be transfered to 4-hydroxymethyl-5-benzoyl-1,2,3-thiadiazole (XVI) by similar steps of reaction which was discussed above, or in better yield by chromatography, on activated alumina, of brominated intermediate XV (See Scheme II). Manganese dioxide oxidation of XVI afforded the desired compound III.

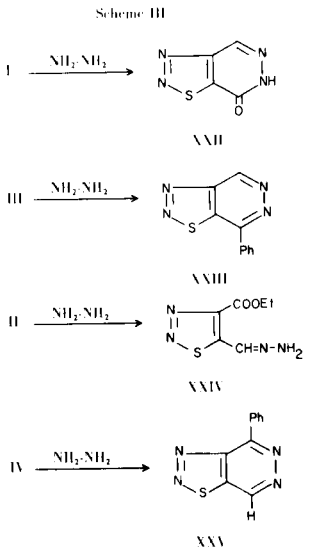
Scheme II



By the above procedure, starting from 5-methyl-4-carbethoxy-1,2,3-thiadiazole (XI) compound IV was obtained (See Scheme II).

Treatment of I with Hydrazine in ethanol gave a new heterocyclic ring system 7*H*-1,2,3-thiadiazolo[4,5-*d*]-pyridazin-7-one (XXII). Compound III and IV with hydrazine gave 7-phenyl-1,2,3-thiadiazolo[4,5-*d*]pyridazine (XXIII), and 4-phenyl-1,2,3-thiadiazolo[4,5-*d*]pyridazine (XXV), respectively. However, II with hydrazine gave the hydrazone XXIV (See Scheme III). The latter could not be cyclized under different experimental conditions. In all cases either the starting material or a complex mixture of products was obtained.

Scheme III



EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were obtained on a Leitz Model III spectrograph. Nmr spectra were determined using T-60A spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT CH-5 in Aryamehr Technical University.

4-Methyl-5-carbethoxy-1,2,3-thiadiazole (V).

This compound was prepared from ethyl acetoacetate semicarbazone and thionyl chloride according to the literature (4), b.p. 122-124° (15 mm Hg).

Reaction of 4-Methyl-5-carbethoxy-1,2,3-thiadiazole (V) with *N*-Bromosuccinimide.

A mixture of V (17.2 g., 0.1 mole) and *N*-bromosuccinimide (19.6 g., 0.11 mole) in 300 ml. of carbon tetrachloride was irradiated with a 500 W (G. E. photospot) lamp while heating and stirring at reflux temperature for 4 hours. The reaction mixture was cooled and filtered. The solvent was evaporated and the residue was distilled under reduced pressure to give 4-bromomethyl-5-carbethoxy-1,2,3-thiadiazole (VI, 20 g., 80%), b.p. 120-122° (2 mm Hg); nmr (carbon tetrachloride): 5,13 (s, 2H, CH_2Br), 4.71 (q, 2H, OCH_2) and 1.71 (t, 3H, CH_3).

Anal. Calcd. for $C_6H_7BrN_2O_2S$: C, 28.69; H, 2.79; N, 11.16. Found: C, 28.71; H, 2.63; N, 11.23.

The residue of distillation was crystallized from ether-hexane to give 2.6 g. (8%) of compound VII; m.p. 91-92°; nmr (carbon tetrachloride): 7.63 (s, 1H, $CHBr_2$), 4.52 (q, 2H, OCH_2); and 1.45 (t, 3H, CH_3).

Anal. Calcd. for $C_6H_6Br_2N_2O_2S$: C, 21.82; H, 1.82; N, 8.48. Found: C, 21.65; H, 1.69; N, 8.53.

4-Hydroxymethyl-5-carbomethoxy-1,2,3-thiadiazole (VIII).

A mixture of VI (25.1 g., 0.1 mole) an sodium hydroxide (8 g., 0.2 mole) in 200 ml. of water was refluxed for two hours. After cooling it was acidified with hydrochloric acid and the solvent was distilled under reduced pressure. The residue was treated with diazomethane in ether and filtered. The solvent was evaporated and the residue was distilled under reduced

pressure to give 2 g. (8%) of VIII, b.p. 118-120° (1 mm Hg); nmr (deuteriochloroform): 5.62 (s, 2H, CH_2O), 4.83 (broad s, 1H, OH), 4.02 (s, 3H, OCH_3).

Anal. Calcd. for $C_5H_6N_2O_3S$: C, 34,48; H, 3.45; N, 16.09. Found: C, 34.49; H, 3.26; N, 16.24.

4-Acetoxymethyl-5-carbethoxy-1,2,3-thiadiazole (IX).

A mixture of VI (25.1 g., 0.1 mole) and potassium acetate (49 g., 0.5 mole) in 500 ml. of acetic acid was refluxed for 3 hours. The reaction mixture was cooled and filtered. The solvent was evaporated under reduced pressure. The residue was dissolved in chloroform. The chloroform was washed with water, dried and evaporated. The residue was distilled under reduced pressure to give 22 g. (96%) of IX, b.p. 119-120° (1 mm Hg); nmr (deuteriochloroform): 5,67 (s, 2H, CH_2OAc), 4.40 (q, 2H, OCH_2), 2.11 (s, 3H, CH_3-CO), and 1.43 (t, 3H, CH_3).

Anal. Calcd. for $C_8H_{10}N_2O_4S$: C, 41.74; H, 4.35; N, 12.17. Found: C, 41.59; H, 4.23; N, 12.01.

4-Hydroxymethyl-5-carbethoxy-1,2,3-thiadiazole (X).

A solution of IX (23 g., 0.1 mole) in 400 ml. of absolute ethanol and 4 ml. of concentrated sulfuric acid was allowed to stand at room temperature overnight. It was concentrated under reduced pressure and treated with ice-water. The organic compound was extracted with chloroform. The chloroform was dried, (sodium sulfate), filtered and evaporated. The residue was distilled under reduced pressure to give 17 g. (90%) of X, b.p. 122-124° (1 mm Hg); nmr (deuteriochloroform): 5.20 (broad s, 2H, CH_2OH), 4.40 (q, 2H, OCH_2), 4.10 (broad s, 1H, OH) and 1.43 (t, 3H, CH_3).

Anal. Calcd. for $C_6H_8N_2O_3S$: C, 38.30; H, 4.26; N, 14.89. Found: C, 38.45; H, 4.05; N, 14.96.

5-Carbethoxy-4-formyl-1,2,3-thiadiazole (I).

A mixture of X (3.76 g., 0.02 mole) and manganese dioxide (30 g.) in 150 ml. of chloroform was stirred overnight. The reaction mixture was filtered and evaporated. The residue was distilled under reduced pressure to give 3.35 g. (90%) of I: b.p. 106-108° (1 mm Hg); nmr (deuteriochloroform): 10.53 (s, 1H, CHO), 4.46 (q, 2H, OCH_2), and 1.46 (t, 3H, CH_3).

Anal. Calcd. for $C_6H_6N_2O_3S$: C, 38.71; H, 3.23; N, 15.05. Found: C, 38.59; H, 3.41; N, 15.22.

5-Methyl-4-carbethoxy-1,2,3-thiadiazole (XI).

A solution of 2-oxobutyric acid (51 g., 0.5 mole) in absolute ethanol (70 ml.), benzene (70 ml.) and one ml. of absolute ethanol-saturated with hydrochloric acid was refluxed for 3 hours. One hundred ml. of solution was distilled. To the residue a solution of semicarbazide hydrochloride (55.25 g., 0.5 mole) and sodium acetate (80 g.) in 300 ml. of water was added. The precipitate was filtered, washed with water and dried to give 77.6 g. (83%) of 2-oxobutyric acid ethyl ester semicarbazone, m.p. 141-142°.

Anal. Calcd. for $C_7H_{13}N_3O_3$: C, 44.92; H, 6.95; N, 22.46. Found: C, 45.03; H, 6.78; N, 22.63.

The reaction of the above semicarbazone with thionyl chloride under the conditions which were published previously (4) gave the desired compound XI in 80% yield m.p. 34-35° [lit. (6) 35°].

5-Hydroxymethyl-4-carbethoxy-1,2,3-thiadiazole (XII).

Compound XI (17.2 g., 0.1 mole) was borminated with *N*-bromosuccinimide (19.6 g., 0.1 mole) under similar conditions which were specified for compound V. 5-Bromomethyl-4-carbethoxy-1,2,3-thiadiazole was distilled at 130° (5 mm Hg). To this fraction in acetic acid (150 ml.), potassium acetate (39 g.) was added. The mixture was refluxed for 3 hours. After cooling the precipitate was filtered. The filtrate was evaporated. To the residue a soluiton of 300 ml. of absolute ethanol and 3 ml. of concentrated sulfuric acid was added. It was allowed to stand overnight. The solvent was evaporated. To the residue a solution of saturated sodium bicarbonate in water, ice and chloroform was added. The chloroform was dried (sodium sulfate) and filtered. The filtrate was evaporated and the residue was crystallized from ethyl acetate to give 9.4 g. (50%) of compound XII, m.p. 129-130°; nmr (deuteriochloroform): 5.36 (d, 2H, $J_{CH2/OH} = 6$ Hz, CH_2OH), 4.51 (q, 2H, CH_2O), 4.02 (t, 1H, OH, $J_{OH/CH2} = 6$ Hz), and 1.46 (t, 3H, CH_3).

Anal. Calcd. for $C_6H_8N_2O_3S$: C, 38.30; H, 4.26; N, 14.89. Found: C, 38.16; H, 4.39; N, 14.70.

4-Carbethoxy-5-formyl-1,2,3-thiadiazole (II).

Compound XII was oxidized with manganese dioxide, under similar conditions as for the oxidation of X, to II in 90% yield, b.p. 107-108° (1 mm Hg); nmr (deuteriochloroform): 10.57 (s, 1H, CHO), 4.53 (q, 2H, OCH_2), and 1.52 (t, 3H, CH_3).

Anal. Calcd. for $C_6H_6N_2O_3S$: C, 38.71; H, 3.23; N, 15.05. Found: C, 38.82; H, 3.15; N, 14.98.

4-Methyl-1,2,3-thiadiazole-5-carboxy Chloride (XIII).

A mixture of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid (7) (14.4 g., 0.1 mole) and 50 ml. of thionyl chloride was refluxed for 4 hours. The excess of the thionyl chloride was evaporated and the residue was distilled under reduced pressure to give 14.5 g. (89%) of XIII, b.p. 94-96° (15 mm Hg).

Anal. Calcd. for $C_4H_3ClN_2OS$: C, 29.54; H, 1.85; N, 17.23. Found: C, 29.39; H, 1.74; N, 17.37.

4-Methyl-5-benzoyl-1,2,3-thiadiazole (XIV).

A mixture of XIII (16.25 g., 0.1 mole) and aluminium chloride (26.6 g., 0.2 mole) in 200 ml. of dry benzene was stirred and refluxed for 6 hours. The mixture was cooled and the complex was decomposed with ice-water and hydrochloric acid. The benzene was dried (sodium sulfate), filtered and evaporated. The residue was distilled under reduced pressure to give 18.5 g. (90%) of XIV, b.p. 140-142° (1 mm Hg), m.p. 51-52° (ether-hexane); nmr (deuteriochloroform): 7.87-7.26 (m, 5H, Ar-H), 2.73 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.92; N, 13.73. Found: C, 58.69; H, 3.95; N, 13.82.

4-Bromomethyl-5-benzoyl-1,2,3-thiadiazole (XV).

A mixture of XIV (20.4 g., 0.1 mole) and *N*-bromosuccinimide (19.6 g., 0.11 mole) in 400 ml. of carbon tetrachloride was irradiated with a 500 W lamp while heating and stirring for 48 hours. The reaction mixture was cooled and filtered. The solvent was evaporated and the residue was distilled to give XV (11.4 g., 40%); b.p. 165-170° (1 mm Hg), nmr (deuteriochloroform): 8-7.3 (m, 5H, ArH), 4.93 (s, 2H, CH_2).

Anal. Calcd. for $C_{10}H_7BrN_2OS$: C, 42.40; H, 2.47; N, 9.89. Found: C, 42.58; H, 2.53; N, 10.11.

4-Hydroxymethyl-5-benzoyl-1,2,3-thiadiazole (XVI).

A solution of compound XV (14.2 g., 0.05 mole), potassium acetate (19.6 g., 0.2 mole) in 150 ml. acetic acid was refluxed for 3 hours. The mixture was cooled and filtered. The solvent was evaporated under reduced pressure. To the residue a solution of sodium bicarbonate, ice and chloroform was added. The chloroform was evaporated. To the residue absolute ethanol (200 ml.) and concentrated sulfuric acid (2 ml.) was added and allowed to

stand at room temperature for 24 hours. The solvent was evaporated under reduced pressure. To the residue a solution of sodium bicarbonate in ice-water and chloroform was added. The chloroform was evaporated and the residue was distilled under reduced pressure to give 9 g. (82%) of compound XVI, b.p. 170-174° (1 mm Hg); nmr (deuteriochloroform): 8.06-7.36 (m, 5H, Ar-H), 5.26 (s, 1H, CH_2O), 3.63 (broad s, 1H, OH).

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.55; H, 3.64; N, 12.73. Found: C, 54.72; H, 3.75; N, 12.63.

5-Benzoyl-4-formyl-1,2,3-thiadiazole (III).

Compound XVI was oxidized with manganese dioxide, under similar conditions as specified for compound X, to III in 85% yield, m.p. 78-79° (chloroform-hexane); nmr (deuteriochloroform): 10.30 (s, 1H, CHO), and 8.0-7.37 (m, 5H, ArH).

5-Methyl-1,2,3-thiadiazole-4-carboxy Chloride (XVII).

Compound XI was hydrolyzed to its corresponding acid according to the literature (7). The acid was transfered to XVII under similar conditions as specified for the preparation of XIII, b.p. 74-76° (1 mm Hg).

Anal. Calcd. for $C_4H_3ClN_2OS$: C, 29.53; H, 1.85; N, 17.23. Found: C, 29.45; H, 1.97; N, 17.41.

5-Methyl-4-benzoyl-1,2,3-thiadiazole (XVIII).

Compound XVIII was prepared from XVII, benzene and aluminium chloride under similar conditions as for preparation of compound XIV, b.p. 136-138° (1 mm Hg), m.p. 44-45° (ether-hexane); nmr (deuteriochloroform): 8.35-8.03 (m, 2H, ArH), 7.66-7.30 (m, 3H, ArH), and 2.83 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_8N_2OS$: C, 58.82; H, 3.92; N, 13.73. Found: C, 58.94; H, 3.86; N, 13.87.

5-Hydroxymethyl-4-benzoyl-1,2,3-thiadiazole (XXI).

Compound XVIII was brominated with 1.1 equivalents of *N*-bromosuccinimide under similar conditions as specified for the bromination of XIV. The crude product was chromatographed on activated alumina (Merck, activity II-III). 5-Dibromomethyl-4-benzoyl-1,2,3-thiadiazole (XX) was eluted with petroleum ether-chloroform (90:10) in 10% yield, m.p. 78-79° (ether-hexane).

Anal. Calcd. for $C_{10}H_6Br_2N_2OS$: C, 33.15; H, 1.66; N, 7.73. Found: C, 33.31; H, 1.45; N, 7.89.

The second fraction which was eluted with petroleum ether-chloroform (50:50) was the starting ketone (XVIII).

Finally the desired compound XXI was eluted with chloroform-methanol (90:10) in 25% yield, m.p. 109-110° (ethyl acetate-hexane); nmr (deuteriochloroform): 8.56-8.26 (m, 2H, ArH), 7.83-7.38 (m, 3H, ArH), 5.37 (d, 2H, CH_2O, $J_{CH2/OH}$ = 4 Hz), and 3.80 (t, 1H, OH, J = 4 Hz).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.54; H, 3.64; N, 12.73. Found: C, 54.71; H, 3.79; N, 12.61.

4-Benzoyl-5-formyl-1,2,3-thiadiazole (IV).

Compound XXI was oxidized with manganese dioxide, under similar conditions as specified for the oxidation of X, to IV in 85% yield, m.p. 100-101° (carbon tetrachloride); nmr (deuteriochloroform): 10.35 (s, 1H, CHO), 8.53-8.27 (m, 2H, ArH), and 7.83-7.37 (m, 3H, ArH).

Anal. Calcd. for $C_{10}H_6N_2O_2S$: C, 55.05; H, 2.75; N, 12.84. Found: C, 55.23; H, 2.69; N, 12.66.

7*H*-1,2,3-Thiadiazolo[4,5-*d*]pyridazin-7-one (XXII).

A solution of compound I (186 mg., 1 mmole) and hydrazine hydrate 50 mg. (1 mmole) in 15 ml. of ethanol was refluxed for 3 hours. The solvent was evaporated and the residue was crystallized from ethanol to give 145 mg. (94%) of XXII, m.p. 246-248°; ir (potassium bromide); 3160 (NH), 1680 (C=O); mass spectrum: m/e 154 (M^+), 126, 99, 69, 56 and 44.

Anal. Calcd. for $C_4H_2N_4OS$: C, 31.17; H, 1.20; N, 26.26. Found: C, 31.05; H, 1.35; N, 26.18.

Reaction of 4-carbethoxy-5-formyl-1,2,3-thiadiazole (II) with hydrazine.

A solution of II (186 mg., 1 mmole) and hydrazine hydrate (50 mg., 1 mmole) in 15 ml. of ethanol was refluxed for 3 hours. The solvent was evaporated and the residue was crystallized from ethanol to give 150 mg. (75%) of hydrazone XXIV, m.p. 145-146°; nmr (trifluoroacetic acid): 4.40 (q, 2H, OCH_2), and 1.33 (t, 3H, CH_3); mass spectrum: m/e 200; ir (potassium bromide): 1725 cm^{-1} (ester).

Anal. Calcd. for $C_6H_8N_4O_2S$: C, 36.00; H, 4.00; N, 28.00. Found: C, 36.18; H, 3.91; N, 27.96.

7-Phenyl-1,2,3-thiadiazolo[4,5-*d*]pyridazine (XXIII).

A solution of III (2.18 g., 0.01 mole) and hydrazine hydrate (0.5 g., 0.01 mmole) in 100 ml. of ethanol was refluxed for 3 hours. The solvent was evaporated and the residue was crystallized from ethanol to give 2 g. (93%) of XXIII, m.p. 126-127°; nmr (deuteriochloroform): 10.29 (s, 1H, H_4), 8.33-8.03 (m, 2H, Ar-H), and 7.86-7.50 (m, 3H, Ar-H); ir (potassium bromide): 1518, 1490, 1445, 1392, 1360, 1290, 1200, 998, 952, 905, 855, 840, 788, 756, 760 and 700 cm^{-1}; mass spectrum: m/e 214.

Anal. Calcd. for $C_{10}H_6N_4S$: C, 56.07; H, 2.80; N, 26.17. Found: C, 56.01; H, 2.95; N, 26.32.

4-Phenyl-1,2,3-thiadiazolo[4,5-*d*]pyridazine (XXV).

A solution of IV (218 mg., 1 mmole) and hydrazine hydrate (50 mg., 1 mmole) in 10 ml. of ethanol was refluxed for 4 hours. The solvent was evaporated and the residue was crystallized from ethanol to give 200 mg. (92%) of XXV, m.p. 162-163°; ir (potassium bromide): 1535, 1498, 1456, 1392, 1360, 1290, 1184, 1035, 1010, 1000, 920, 866, 800, 786, 760, and 690 cm^{-1}; nmr (deuteriochloroform): 10.06 (s, 1H, H_7); 9.03-8.66 (m, 2H, ArH) and 7.90-7.60 (m, 3H, ArH); mass spectrum: m/e 214.

Anal. Calcd. for $C_{10}H_6N_4S$: C, 56.07; H, 2.80; N, 26.17. Found: C, 56.21; H, 2.94; N, 26.23.

REFERENCES AND NOTES

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