Synthesis of 1,2,3-Thiadiazoles

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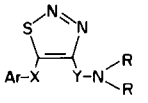
Received July 17, 1975

Several methods were explored for preparing certain 4,5-disubstituted-1,2,3-thiadiazoles. The reaction of phenoxyacetyl chlorides with diazoacetylamides yielded α-diazo-β-ketoacetamides which were cyclized, with hydrogen sulfide and ammonium hydroxide, to 4-carboxamido-5-phenoxymethyl-1,2,3-thiadiazoles. However, treatment of α-diazo-α-benzoylacetamides with hydrogen sulfide and ammonium hydroxide yielded hydrazones rather than thiadiazoles. The reaction of α-[(ethoxycarbonyl)hydrazono]benzenepropanoic acid (**25**) with thionyl chloride yielded 5-phenyl-1,2,3-thiadiazole-4-carbocylic acid (**26a**), the corresponding acid chloride **26b**, and 5-(phenylmethyl)-2*H*-1,3,4-oxadiazine-2,6(3*H*)dione (**27**). The yields of **26a**, **26b**, and **27** were dependent on the reaction conditions employed. Oxadiazine **27** could also be converted to acid chloride **26b** with thionyl chloride. Reduction of 1-([5-(4-chlorophenoxy)methyl-1,2,3-thiadiazol-4-yl]-carbonyl)piperidine (**10b**) with diborane yielded a boron complex which produced 1-([5-((4-chlorophenoxy)methyl)-1,2,3-thiadiazol-4-yl]methyl)piperidine (**31**) upon recrystallization from ethanol.

We recently undertook a synthetic probe to generate 1,2,3-thiadiazoles of general structure **1** for pharmacological evaluation. Our rationale for this study included the



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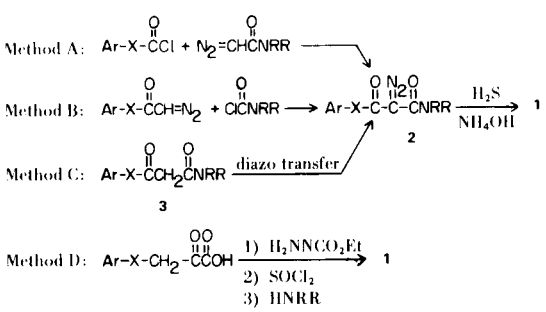
where Ar = phenyl or substituted-phenyl
X and Y = intervening groups, X being optional
R = alkyl group, or
NRR = cyclic amine

observation that although the chemical and patent literature is replete with chemical and biological data on 1,3,4-thiadiazoles, a relatively small amount of biological data has been gathered on 1,2,3-thiadiazoles (1). Some of the biologically active 1,3,4-thiadiazoles contain 2- and 5-substituents which fit the generalized sidechain structures of the 1,2,3-thiadiazole structure **1** at the 4- and 5-positions (2).

Scheme I shows the methods which we considered, at the outset, for the preparation of thiadiazoles of general structure **1** (where Y is C=O). Reactions of α-diazo carbonyl compounds with a carboxylic acid chloride and a carbamoyl chloride are depicted in Methods A and B, respectively, for the preparation of α-diazo-β-ketoamides (general structure **2**) which could then be cyclized with hydrogen sulfide and ammonium hydroxide to the 1,2,3-thiadiazoles (3). Reactions of acyl and aroyl halides with diazoacetic esters and amides to yield α-diazo-β-ketoesters and α-diazo-β-ketoamides, respectively, are well-documented (4). Alternatively, we considered preparing active methylene compounds of general structure **3** (Method C), and then introducing the diazo group. Diazo groups can be transferred to active methylene groups, with the exchange of two hydrogen atoms, from either sulfonyl azides or azidinium salts (5). Finally, we also considered the preparation of 5-aryl-1,2,3-thiadiazole-4-carboxylic acids, which we could modify to the 4-carboxamides, from pyruvic acids (Method D), using the procedure of Hurd and Mori (6). These authors have converted carbethoxyhydrazones of α-keto acids, having a methylene group adjacent to the hydrazone, to 1,2,3-thiadiazole-4-carboxylic acids with thionyl chloride.

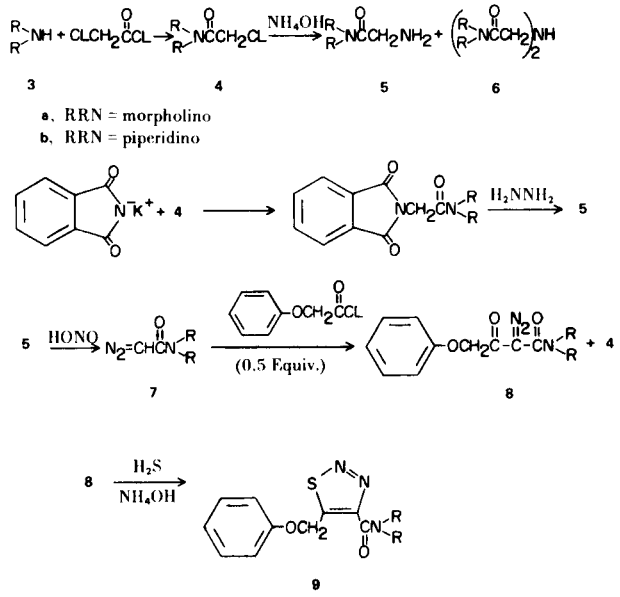
SCHEME I



To pursue Method A we set out to prepare aminoacetamide **5b**, which could be diazotized to the diazoacetamide **7b**. Following a literature procedure for the aminolysis of chloroacetyl-1-piperidine (**7b**) (7), we were able to prepare aminoacetyl-1-piperidine(**5b**), but not consistently. Secondary amine **6b**, resulting from dialkylation, was always a coproduct, and usually was the major product of this reaction in our hands. We therefore used the Gabriel synthesis for the preparation of the aminoacetamides **5a** and **5b**, following the procedure of Speziale and Hamm (8). Diazotiazation of the aminoacetamides **5a** and **5b** proceeded smoothly with nitrous acid to yield the diazoacetamides **7a** and **7b**, which were then acylated with phenoxyacetyl chloride to afford α-diazo-β-ketoamides **8a** and **8b**. Equimolar amounts of chloroacetamides (**4a** and **4b**, respectively) were produced in this reaction, which were carried through the next step. Treatment of the diazo compounds **8a** and **8b** with hydrogen sulfide and a catalytic amount of ammonium hydroxide yielded the 4-carboxamido-5-phenoxymethyl-1,2,3-thiadiazoles **9a** and **9b**, respectively (Scheme II). In similar fashion were prepared the 1,2,3-thiadiazoles **10a**, **10b**-**12a**, **12b**, which are listed in Table I.

We were unable to effect reaction between α-diazoacetamides **7a** and **7b** and benzoyl chlorides [with (9) or without the presence of triethylamine]. Since these attempted acylations were unsuccessful we felt that acylation of α-diazocarbonyl compounds with carbamoyl chlorides (Method B), which are less reactive as acylating agents than benzoyl chlorides, would also be unsuccessful.

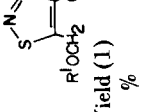
SCHEME II



In addition, since Method A was successful in producing compounds of general structure **1**, we did not pursue Method B.

TABLE I

4-Carboxamido-5-phenoxymethyl-1,2,3-thiadiazoles

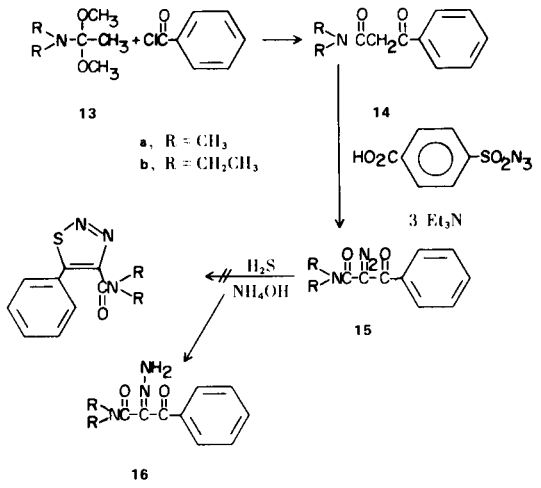


No.	R^1	NRR	M.p. °C	Recryst. Solvent	Yield (1) %	Empirical Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
9a	C_6H_5	4-morpholino	89-90	ethanol-water	40.4	$C_{14}H_{15}N_3O_3S$	55.06	4.95	13.76	55.10	4.98	14.08
9b	C_6H_5	1-piperidino	65-66	ethanol-water	30.2	$C_{15}H_{17}N_3O_2S$	59.38	5.64	13.85	59.60	5.59	14.02
10a	4-ClC_6H_4	4-morpholino	106-108	ethanol-water	35.5	$C_{14}H_{14}ClN_3O_3S$	49.48	4.15	12.36	49.50	4.20	12.41
10b	4-ClC_6H_4	1-piperidino	115	ethanol-water	36.3	$C_{15}H_{16}ClN_3O_2S$	53.33	4.77	12.44	53.20	4.58	12.64
11a	3,4-$Cl_2C_6H_3$	4-morpholino	120-121	ethanol	24.6	$C_{14}H_{13}Cl_2N_3O_3S$	44.92	3.50	11.22	45.10	3.48	11.23
11b	3,4-$Cl_2C_6H_3$	1-piperidino	75-76	ethanol-water	33.3	$C_{15}H_{15}Cl_2N_3O_2S$	48.39	4.06	11.28	48.40	4.08	11.44
12a	4-$CH_3OC_6H_4$	4-morpholino	123-124	ethanol	41.1	$C_{15}H_{17}N_3O_4S$	53.71	5.10	12.52	53.57	5.21	12.36
12b	4-$CH_3OC_6H_4$	1-piperidino	84-85	ethanol	14.1 (2)	$C_{16}H_{19}N_3O_3S$	57.63	5.74	12.60	57.45	5.50	12.54

(1) Overall yield from diazoamide. (2) Isolated by column chromatography.

In pursuing Method C, we prepared *N,N*-dimethyl- and *N,N*-diethyl-(α-benzoyl)acetamides **14a** and **14b**, respectively, by acylating the amide acetals **13a** and **13b** with benzoyl chloride (10). Treatment of the active methylene compounds **14a** and **14b** with *p*-carboxybenzensulfonyl azide (11) and triethylamine afforded the respective diazo compounds **15a** and **15b**. These compounds appeared to evolve nitrogen gas upon standing and were therefore only characterized spectrally. Treatment of **15a** and **15b** with hydrogen sulfide and a catalytic amount of ammonium hydroxide produced the hydrazones **16a** and **16b**, respectively, rather than 1,2,3-thiadiazoles. See Scheme III.

SCHEME III



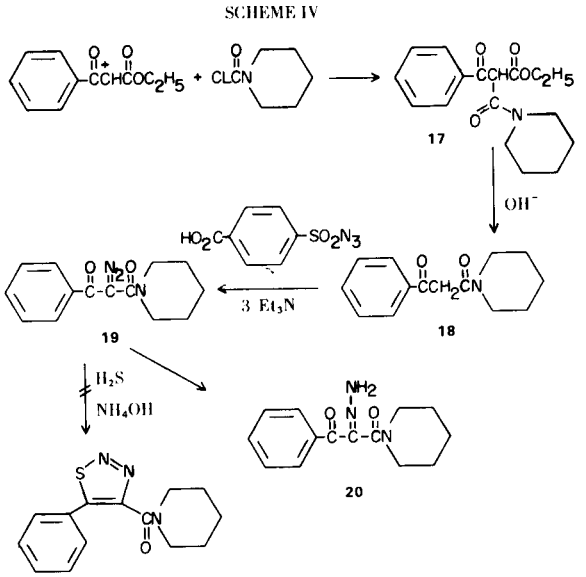
Another approach to the synthesis of *N,N*-dialkyl-(α-benzoyl)acetamides is shown in Scheme IV. Acylation of ethyl benzoylacetate thallium (I) salt with 1-piperidinecarbonyl chloride yielded the C-acylated compound **17**, which was hydrolyzed to 1-[(α-benzoyl)acetyl]piperidine (**18**). Reaction of **18** with *p*-carboxybenzenesulfonyl azide and triethylamine yielded the diazo compound **19**, which was treated with hydrogen sulfide/ammonium hydroxide. Again, the product of this reaction was the hydrazone **20** rather than a 1,2,3-thiadiazole.

It is interesting to consider possible explanations for diazo compounds **15a**, **15b** and **19** undergoing reduction to hydrazones, rather than cyclization to 1,2,3-thiadiazoles, with hydrogen sulfide/ammonium hydroxide. If one assumes that the first step in the mechanism of 1,2,3-thiadiazole formation from α-diazoketones is the attack by hydrosulfide ion at the ketone carbonyl carbon atom and that reduction and cyclization reactions are competitive, then it can be inferred that thiadiazole formation in compounds of general structure **8** will be favored, with respect to structures **15a**, **15b**, and **19**, since the carbonyl groups in compounds **8** should be more susceptible to nucleophilic attack.

Staudinger (3b) has shown that methyl (α-benzoyl-α-diazo)acetate (**21**) cyclizes to 4-carbomethoxy-4-phenyl-1,2,3-thiadiazole (**22**) with hydrogen sulfide/ammonium hydroxide. Since **21** is structurally very similar to compounds **15a**, **15b**, and **19**, it is not immediately obvious that they should react differently. Perhaps resonance structure **23** is significant for the amides **15a**, **15b**, and **19**, and serves to decrease the reactivity of the carbonyl carbon atom toward nucleophilic attack with respect to ester **21**, where an analogous resonance structure should not be important. See Scheme V.

β-Phenylpyruvic acid (**24**) was the starting material chosen for exploring Method D (Scheme VI). The carbethoxyhydrazone, **25**, of **24**, when treated with thionyl chloride, yielded three products. 5-Phenyl-1,2,3-thiadiazole-4-carboxylic acid (**26a**), the corresponding acid chloride (**26b**), and oxadiazine **27** were produced in varying proportions, depending on the specific reaction conditions employed. Treatment of **22** with excess thionyl chloride for 15 hours at 25° yielded a mixture of **26a** and **27**. If the same reaction procedure was employed, followed by brief heating, a mixture of **26b** and **27** resulted. Treatment of **25** with excess thionyl chloride at 60-70° for one hour afforded a 57% yield of **27**. The acid chloride **26b** was not characterized as were the acid **26a** and oxadiazine **27**, but

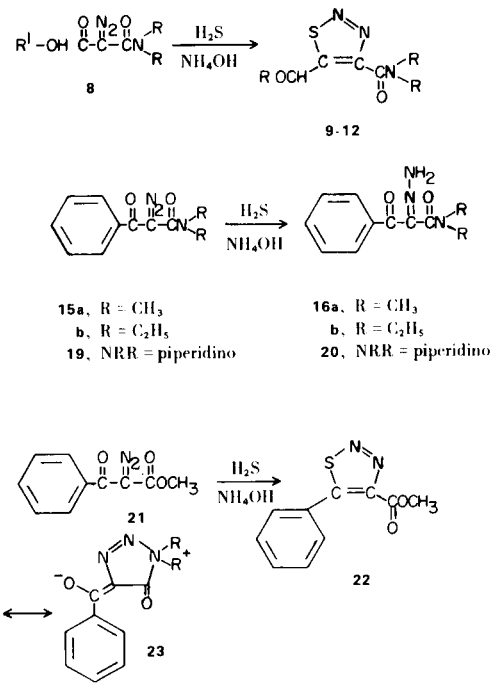
SCHEME IV



was derivatized with morpholine to yield the desired end-product **28**. It was interesting to note that thiadiazole **26a**, on exposure to sunlight, turned green, while **28** turned pink. The thiadiazoles in Table I were also light-sensitive.

We next determined that oxadiazine **27** could be cleanly converted to acid chloride **26b** when treated with thionyl chloride at reflux for 15 hours. In spite of this interesting result, we do not think that **27** is necessarily a reaction intermediate, since the vigorous conditions

SCHEME V



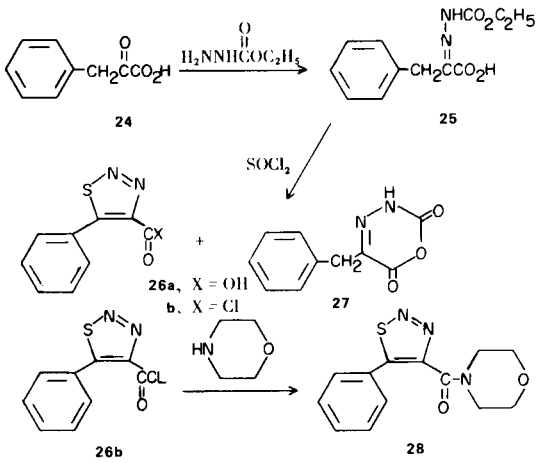
required to produce **26b** in this reaction were not necessary in other reactions which yielded **26b**, and since only acid chloride **26b** (and not free acid **26a**) should be produced from **27**. In Scheme VII are shown proposed mechanisms for the conversion of oxadiazine **27** to **26b**, and the conversions of carboethoxyhydrazone **25** to **26a**, **26b**, and **27**.

It is interesting to compare the reactions of the carbethoxyhydrazones of β-phenylpyruvic acid (**25**) and pyruvic acid (**29**) with thionyl chloride, with respect to oxadiazine formation. Hurd and Mori (6) report that only a small quantity of oxadiazine **30** is formed from the reaction of **29** with thionyl chloride. One would expect that with hydrazones **25** and **29**, the syn-isomers would lead to 1,2,3-thiadiazole formation and the anti-isomers to oxadiazine formation. Perhaps in both cases the syn-isomers are initially produced from the reactions of the pyruvic acids with carbethoxyhydrazine, and that during the reaction with thionyl chloride, only hydrazone **25** is appreciably isomerized to the anti-isomer. Isomerization of the oximes could occur as shown *via* an enamine intermediate. The benzyl compound **25** should be more susceptible to this isomerization than the methyl compound **29**, since the benzyl protons are more acidic than the methyl protons. See Scheme VIII.

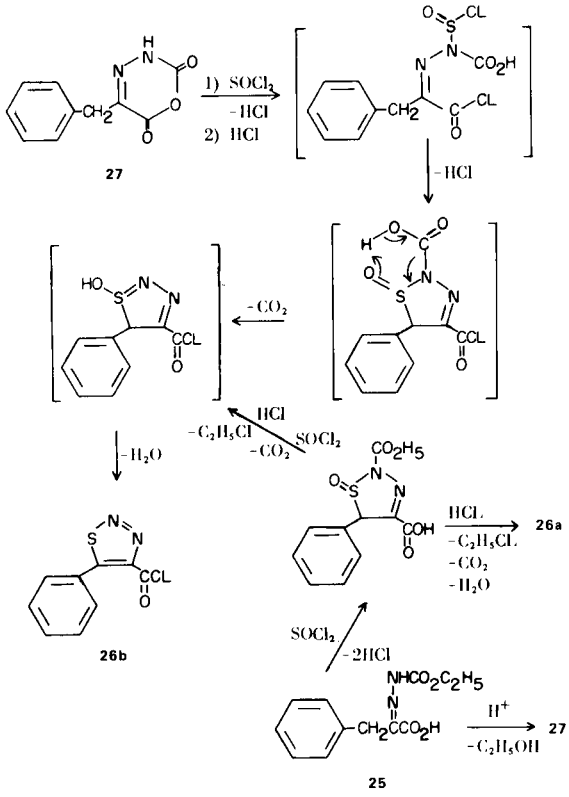
One of our original goals was to prepare a compound of general structure **1** where Y was a methylene group. To this end, thiadiazole **10b** was treated with diborane (Scheme IX). We initially isolated a reduced material which appeared to be a complex between a boron species and the thiadiazole ring of the reduced material. The complex (m.p. 100-103°) when recrystallized from ethanol, yielded amine **31** (m.p. 80-81°).

The infrared spectrum of the complex displayed four distinct diazo bands. The nmr spectrum of the complex was identical to that of **31**, except for chemical shift differences. The mass spectra of **31** and the complex were identical.

SCHEME VI

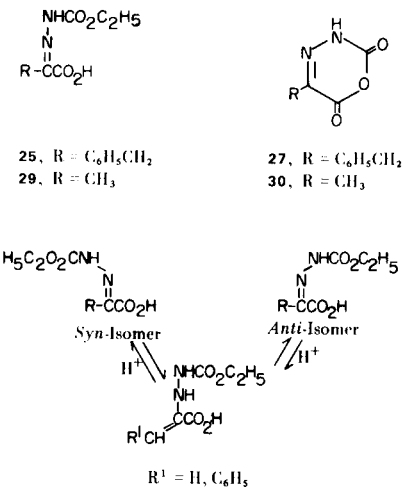


SCHEME VII

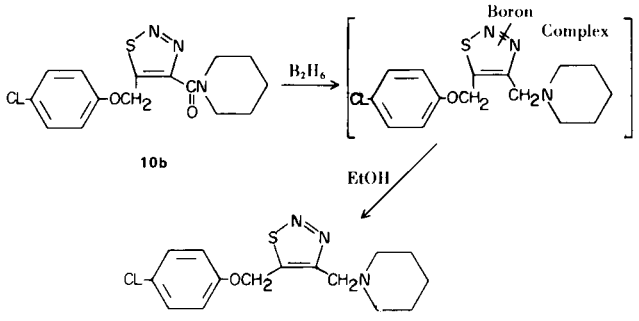


In summary, we have shown that 1,2,3-thiadiazoles of general structure **1** can be prepared by Methods A and D.

SCHEME VIII



SCHEME IX



Method B was not explored, and Method C led to hydrazones rather than 1,2,3-thiadiazoles. Another potential route to 4-carboxamido-5-aryl-1,2,3-thiadiazoles of which we were aware but did not pursue would involve the appropriate transformations of 4-carboalkoxy-5-aryl-1,2,3-thiadiazoles, which could be conveniently prepared by the method of Staudinger (3b).

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 727 Spectrophotometer, nmr spectra on a Varian T-60 nmr spectrometer, and mass spectra on a Hitachi RMU-6D mass spectrometer (70 eV). Combustion analyses for C, H, and N were performed by Dow Analytical Laboratories and Galbraith Laboratories, Inc., of Knoxville, Tennessee.

Materials.

4-(Aminoacetyl)morpholine hydrochloride (**5a**), m.p. 239-241° [lit. (8) m.p. 240-243°], and 1-(aminoacetyl)piperidine hydrochloride (**5b**), m.p. 177-181° [lit. (7) m.p. 185-186°], were prepared by the method of Speziale and Hamm (8). *N,N*-Dimethyl(β-benzoyl)-acetamide (**14a**), m.p. 79-81° [lit. (10) m.p. 84.5-85°] (12), and *N,N*-diethyl-(α-benzoyl)acetamide (**14b**), b.p. 160-170° (0.90 m.m) (12), were prepared by the method of Oishi, *et al.* (10). 1-Piperidinecarbonyl chloride, b.p. 78° (1.1 m.m.), was prepared from piperidine and excess phosgene in toluene.

General Method for 4-Carboxamido-5-phenoxymethyl-1,2,3-thiadiazoles **9-12**.

To a 0.0200-mole quantity of the aminoacetamide hydrochloride dissolved in 80 ml. of 2*N* sodium acetate solution was added a solution of 20.0 g. of sodium nitrite in 40 ml. of water at 5-7°. A 1 l. volume of methylene chloride and 8 ml. of acetic acid were added and the two-phase reaction mixture was stirred for 4 hours at room temperature. The layers were separated and the organic layer was washed with 5% sodium bicarbonate solution, dried (sodium sulfate) and concentrated to a yellow oil, which displayed diazo stretching in the ir at 2110 cm^{-1}.

A solution of the diazo compound in 50 ml. of methylene chloride was added to a solution of the phenoxyacetyl chloride (half-molar amount) in 100 ml. of methylene chloride. After 15 hours at room temperature the yellow solution was washed with 5% sodium bicarbonate solution, dried (sodium sulfate) and concentrated to a yellow oil, which was an equimolar mixture of α-diazo-β-ketoamide and chloroacetamide; ir: 2120 and 1650 cm^{-1}.

A solution of this mixture in 100 ml. of ethanol and 2 ml. of 2% ammonium hydroxide solution was saturated with hydrogen sulfide and aliquots were monitored by ir until the diazo band had disappeared. The solution was then concentrated, reconstituted in methylene chloride, washed with water, dried (sodium sulfate), concentrated, and recrystallized from the solvent(s) specified in Table I.

Hydrazones **16a** and **16b**.

To a solution of 8.42 g. (0.0440 mole) of **14a** in 120 ml. of acetonitrile was added 10.0 g. (0.0440 mole) of *p*-carboxybenzenesulfonyl azide (Eastman). To the cooled mixture was added 13.4 g. (0.132 mole) of triethylamine. Solution resulted immediately. After 90 minutes, the mixture was filtered to remove *p*-carboxybenzenesulfonamide. The filtrate was concentrated, reconstituted in methylene chloride, and the solution was washed with 0.5 *N* sodium hydroxide solution, water, and dried (sodium sulfate). The resulting yellow oil, whose ir spectrum displayed diazo stretching at 2120 cm^{-1}, was dissolved in 100 ml. of ethanol and 2 ml. of 2% ammonium hydroxide solution and saturated with hydrogen sulfide. Reaction progress was monitored by the disappearance of the diazo band in the ir spectra of concentrated aliquots. The mixture was concentrated, reconstituted in methylene chloride, and the solution was washed with water and dried (sodium sulfate). The solution was concentrated and the residue was recrystallized from ethanol to yield a first crop of elemental sulfur and subsequently 5.00 g. (52% from **14a**) of α-hydrazono-α-benzoyl-*N,N*-dimethylacetamide (**16a**), m.p. 158-160°; ir (Nujol): 3380 (NH), 3200 (NH), 1625 (C=O) cm^{-1}; nmr (dimethyl sulfoxide-d_6): δ 8.43 (s, 2H, NH_2), 7.95-7.30 (m, 5H, aromatic), 2.94 (s, 3H, CH_3), 2.80 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.36; H, 6.10; N, 19.39.

In similar fashion was prepared α-hydrazono-α-benzoyl-*N,N*-diethylacetamide, **16b**, from **14b** in 45% overall yield, m.p. 141-142°; ir (Nujol): 3440 (NH), 3190 (NH), 1625 (C=O), 1610 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.25 (s, 2H, NH_2), 3.42 (q, J = 7 Hz, 2H, CH_2), 3.12 (q, J = 7 Hz, 2H, CH_2), 1.15 (t, J = 7 Hz, 3H, CH_3), 1.03 (t, J = 7 Hz, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.10; H, 6.85; N, 17.15.

1-[(α-Hydrazono-α-benzoyl)acetyl]piperidine (**20**).

A 32.7-g. (0.0827 mole) quantity of ethyl benzoylacetate thallium (I) salt (Aldrich) and 12.2 g. (0.0827 mole) of 1-piperidinecarbonyl chloride in 100 ml. of tetrahydrofuran were heated

at reflux for 14 hours. The mixture was filtered and the filtrate was fractionally distilled to yield 4.85 g. (19%) of ethyl α-benzoyl-β-oxo-(1-piperidino)propionate (**17**); b.p. 205° (2.0 mm); ir (neat): 1725 (broad C=O), 1635 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 7.94-7.43 (m, 5H, aromatic), 6.38 (s, 1H, CH), 4.30 (q, J = 7 Hz, 2H, OCH_2), 3.93-3.40 (m, 4H, CH_2NCH_2), 1.95-1.50 [m, 6H, $NCH_2(CH_2)_3$], 1.31 (t, J = 7 Hz, 3H, OCH_2CH_3); ms: m/e 303 (M^+).

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.23; H, 7.01; N, 4.64.

A 13.9-g. (0.0417 mole) quantity of crude **17** was mixed with 40 ml. of 4*N* sodium hydroxide, 50 ml. of water, and 200 ml. of dimethoxyethane and heated at reflux for 5 hours. The mixture was diluted with water (250 ml.), acidified with concentrated hydrochloric acid, and extracted with methylene chloride. The combined extracts were dried (sodium sulfate) and concentrated to yield 13.6 g. of crude ketoamide **18**. This material was dissolved in acetonitrile (100 ml.) and 6.81 g. (0.0300 mole) of *p*-carboxybenzenesulfonyl azide and 9.12 g. (0.0900 mole) of triethylamine were added. After 15 hours the mixture was partitioned between dilute sodium hydroxide solution and methylene chloride. The organic layer was dried (sodium sulfate) and concentrated to leave 12.7 g. of crude **19**, whose ir spectrum displayed diazo stretching at 2120 cm^{-1}. Diazo compound **19** was dissolved in 100 ml. of ethanol and 2 ml. of 2% ammonium hydroxide solution and saturated with hydrogen sulfide. After 15 hours, a 0.75-g. quantity of sulfur was removed by filtration. The filtrate was concentrated, reconstituted in methylene chloride, and filtered to remove 0.56 g. of *p*-carboxybenzenesulfonamide. The filtrate was concentrated and triturated with hexane to afford 2.21 g. [20% from ethyl benzoylacetate thallium (I) salt] of **20**, m.p. 145-148°, m.p. 157-159° (methylene chloride-hexane); ir (Nujol): 3380 (NH), 3200 (NH), 1640 (C=O), 1600 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.10-7.77 (m, 2H, aromatic), 7.63-7.30 (m, 3H, aromatic), 7.17 (broad s, 2H, NH_2, exchangeable with deuterium oxide), 3.70 (m, 2H, CH_2N), 3.27 (m, 2H, CH_2N), 1.64 (m, 6H, remaining piperidino protons); ms: m/e 259 (M^+).

Anal. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.84; H, 6.61; N, 16.21. Found: C, 64.70; H, 6.59; N, 16.31.

α-[(Ethoxycarbonyl)hydrazono]benzenepropanoic Acid (**25**).

A 25.0-g. (0.152 mole) quantity of β-phenylpyruvic acid (Sigma) and 15.8 g. (0.152 mole) of carbethoxyhydrazine (Aldrich) in 200 ml. of benzene were heated at reflux for 4 hours. Water from the condensation reaction was collected in a Dean-Stark trap. The benzene solution was concentrated and cooled to yield 32.5 g. (85%) of **25**, m.p. 148-149°; ir (Nujol): 3300-2500 (OH), 3240 (NH), 1735 (ester C=O), 1710 (acid C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 12.40 and 11.13 (two singlets, 1H, NH), 11.63 (broad s, 1H, OH), 7.43 (s, 5H, aromatic), 4.57-3.80 (m, 4H, both CH_2 groups), 1.27 (t, J = 7 Hz, 3H, CH_3); ms: m/e 250 (M^+).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.30; H, 5.67; N, 11.01.

Reactions of **25** with Thionyl Chloride.

A 16.6-g. (0.0663 mole) quantity of **25** and 20 ml. of thionyl chloride were heated at 60-70° for 1 hour. The solution was cooled, and the solid was collected and washed with ether to afford 7.67 g. (57%) of 5-(phenylmethyl)-2*H*-1,3,4-oxadiazine-2,6(3*H*)dione (**27**), m.p. 176-178° (chloroform); ir (Nujol): 3300 (NH), 1790 (C=O), 1730 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 12.30 (s, 1H, NH, exchangeable with deuterium oxide), 7.10 (s, 5H, aromatic), 3.77 (s, 2H, CH_2); ms: m/e 204 (M^+).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.66; H, 4.04; N, 13.83.

A 10.0-g. (0.0399 mole) quantity of **25** in 20 ml. of thionyl chloride was stirred at 25° for 15 hours. The clear solution was concentrated and the semisolid was partitioned between ethyl acetate and sodium bicarbonate solution. The organic layer was dried (sodium sulfate) and concentrated to yield 3.95 g. (48%) of crude oxadiazine **27**. The aqueous layer was acidified, extracted with methylene chloride, and the organic extract was dried (sodium sulfate) and concentrated to yield 4.04 g. (49%) of crude 5-phenyl-1,2,3-thiadiazole-4-carboxylic acid (**26a**), m.p. 156-157° (ethanol); ir (Nujol): 3300-2300 (OH), 1690 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 7.77 (s); ms: m/e 206 (M^+).

Anal. Calcd. for $C_9H_6N_2O_2S$: C, 52.41; H, 2.92; N, 13.58. Found: C, 52.40; H, 2.96; N, 13.77.

A 10.0-g. (0.0399 mole) quantity of **25** in 20 ml. of thionyl chloride was stirred at 25° for 15 hours and then heated on the steambath for 20 minutes. The solution was cooled, triturated with hexane, and filtered to remove 5.00 g. (61%) of crude oxadiazone **27**. The filtrate was concentrated to leave 3.41 g. (38%) of crude 5-phenyl-1,2,3-thiadiazole-4-carboxylic acid chloride (**26b**) as an oil; ir (neat): 1735 (C=O) cm^{-1}.

To a solution of 3.41 g. (0.0152 mole) of **26b** in 100 ml. of benzene was added 8 ml. of morpholine. After 3 hours, the mixture was washed with water, dilute acid, and sodium bicarbonate solution. The solution was dried (sodium sulfate) and concentrated to yield 2.16 g. of oil which, when triturated with ether, afforded 1.66 g. (40%) of 4-[(5-phenyl-1,2,3-thiadiazol-4-yl)carbonyl]morpholine (**28**), m.p. 105-105.5° (ethanol); ir (Nujol): 1640 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 7.42 (s, 5H, aromatic), 3.94-3.55 (m, 4H, CH_2OCH_2), 3.55-3.00 (m, 4H, CH_2NCH_2).

Anal. Calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.72; H, 4.76; N, 15.26. Found: C, 56.50; H, 4.85; N, 15.23.

Conversion of Oxadiazine **27** to Amide **28**.

A 5.30-g. (0.0260 mole) quantity of crude **27** in 15 ml. of thionyl chloride was heated at reflux for 15 hours. The solution was evaporated to yield 6.4 g. of red oil, whose ir spectrum was identical to that of **26b**. To a solution of this red oil in 50 ml. of benzene was added 10.0 ml. of morpholine. After 2 hours, the mixture was washed with water, dilute acid, and sodium bicarbonate solution. The benzene solution was dried (sodium sulfate) and concentrated to yield 6.1 g. of oil which, when triturated with ether, afforded 2.20 g. (31% from **27**) of amide **28**.

1-([5-((4-Chlorophenoxy)methyl)-1,2,3-thiadiazol-4-yl]methyl)-piperidine (**31**).

To 20 ml. (0.0190 mole) of diborane in tetrahydrofuran (Alfa) under a nitrogen atmosphere was added 3.37 g. (0.0100 mole) of **10b**. The solution was heated at reflux for 8 hours, cooled, and carefully diluted with 50 ml. of water. The solution was extracted with methylene chloride and the extracts were dried (sodium sulfate) and concentrated to yield 3.59 g. of oil which solidified to a white solid (boron complex of **31**), m.p. 100-103°; ir (Nujol): 2430, 2400, 2340, 2300 cm^{-1}; nmr (deuteriochloroform): δ 7.27-6.60 (m, 4H, aromatic), 5.55 (s, 2H, OCH_2), 4.24 (s, 2H, CH_2-piperidine), 3.16-2.75 (m, 4H, CH_2NCH_2), 2.15-1.38 (m, 6H, remaining piperidino protons); ms: m/e 323 (parent ion).

Anal. Found for complex: C, 52.80; H, 6.13; N, 12.75.

Recrystallization of the complex from ethanol yielded **31** as a white solid, m.p. 80-81°; ir (Nujol): 1490, 1240, 815 cm^{-1}; nmr (deuteriochloroform): δ 7.18-6.48 (m, 4H, aromatic), 5.34 (s, 2H, OCH_2), 3.90 (s, 2H, CH_2-piperidino), 2.50-2.00 (m, 4H, CH_2NCH_2), 1.67-1.13 (m, 6H, remaining piperidino protons); ms: m/e 323 (M^+).

Anal. Calcd. for $C_{15}H_{18}ClN_3OS$: C, 55.63; H, 5.60; N, 12.97. Found: C, 55.50; H, 5.70; N, 13.03.

Acknowledgment.

We are grateful to Professor J. H. Looker of the University of Nebrasks for inspiring a portion of this work.

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