

2-Benzyl-1,3,4-oxadiazolin-5-one and Related Compounds

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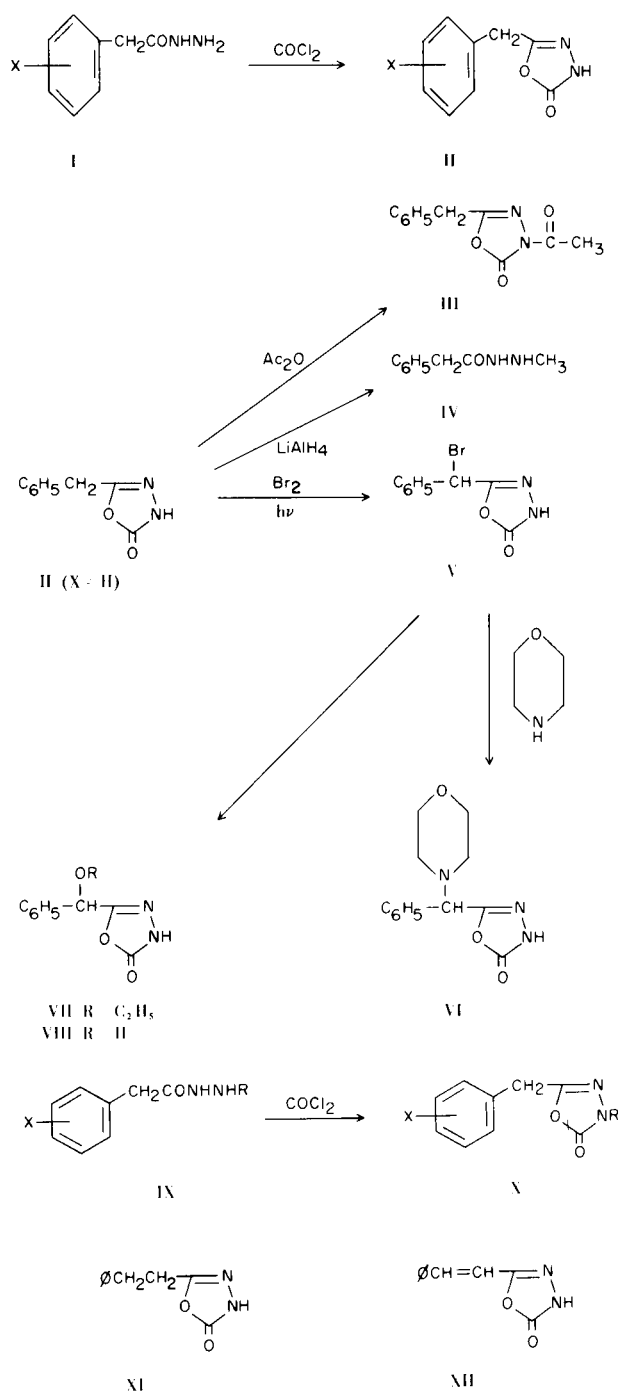
A variety of 2-substituted-1,3,4-oxadiazolin-5-ones have been prepared by the reaction of aliphatic, aromatic, and particularly heterocyclic acid hydrazides with phosgene (I). Very little attention, however, has been given to the use of phenylacetic acid hydrazide and related arylalkyl acid hydrazides in this reaction. We now wish to report on the preparation and reactions of 2-benzyl-1,3,4-oxadiazolin-5-one and some related compounds.

The necessary acid hydrazides were readily prepared by the reaction of ethyl phenylacetates and other esters with an ethanolic solution of hydrazine. These acid hydrazides all possessed absorption in the infrared at 3290-3340 and 1645-1660 cm^{-1} . Hydrazides prepared by this route which had apparently not previously been reported are included in Table I.

Treatment of the hydrazide of phenylacetic acid (I, X = H) with phosgene in methylene chloride gave 2-benzyl-1,3,4-oxadiazolin-5-one (II, X = H). A series of related compounds were prepared by a similar route from other acid hydrazides and are included in Table II. These compounds exhibited absorption in the infrared at 3250-3380 and 1750-1830 cm^{-1} . The nuclear magnetic resonance spectra are consistent with the structures and some typical spectra are included as footnotes to Table II. The mass spectra are also consistent with the structure and will be reported in detail elsewhere.

Reaction of 2-benzyl-1,3,4-oxadiazolin-5-one with acid or base under mild conditions (10%, 100°, 2 hours) gave recovery of starting material in better than 80% recovery. Reaction with selenium dioxide or mercuric oxide also gave an 80-90% recovery of starting material. Reaction of II (X = H) with acetic anhydride gave the 4-acetyl compound III. Reduction of II (X = H) with lithium aluminum hydride gave the ring-opened methylhydrazide IV. The nitro group in 2-(*p*-nitrobenzyl)-1,3,4-oxadiazolin-5-one (II, X = *p*-NO₂) is reduced to an amino group (II, X = *p*-NH₂) by hydrogenation without any reduction of the ring system.

Free-radical bromination of 2-benzyl-1,3,4-oxadiazolin-5-one (II, X = H) gave the α -bromo compound V. Reduction of V with lithium aluminum hydride was accompanied by hydrogenolysis of the bromine to give the same product (IV) as was obtained from II. Reaction of V with morpholine gave the amino derivative VI. Treatment



of V with silver tosylate in refluxing ethanol-acetonitrile gave the ether VII and a trace of the alcohol VIII. This same alcohol (VIII) was the sole product of the reaction in the absence of ethanol. The alcohol VIII was also prepared by reacting the hydrazide of *alpha*-hydroxyphenylacetic acid with phosgene.

Reaction of the hydrazide of phenylacetic acid (I, X = H) with thiophosgene gave 2-benzyl-1,3,4-oxadiazolin-5-thione which had previously (2) been obtained from the hydrazide and carbon disulfide.

Reaction of *N*-substituted hydrazides (IX) with phosgene gave 2-benzyl-4-substituted-1,3,4-oxadiazolin-5-ones (X). Use of the hydrazide of phenylpropionic acid gave the phenethyl product XI. This compound (XI) and its *p*-nitro analogue exhibited reactions similar to those of II with a single exception. Reaction of the *alpha*-bromo derivative of XI with morpholine gave XII through an elimination reaction. XII was also prepared by reaction of the hydrazide of cinnamic acid with phosgene.

EXPERIMENTAL (3)

Preparation of Substituted Phenylacetic Acid Hydrazides (I).

The following is a typical preparation. To a solution of 30.4 mmoles of the substituted ethyl phenylacetate in 20 ml. of ethanol was added 1.04 g. (31.0 mmoles) of 95% hydrazine. The solution was heated on a steam bath for 4 hours and cooled to give the hydrazide. Those hydrazides which apparently have not pre-

viously been reported are included in Table I. Use of methylhydrazine gave the methylhydrazides in Table I. When the hydrazide was refluxed in ethanol with an equimolar quantity of benzyl chloride the benzylhydrazides included in Table I were obtained. Analytical samples were shown to be homogeneous on tlc.

Preparation of 2-Benzyl-1,3,4-oxadiazolin-5-one (II, X = H).

To a solution of 1 g. (6.65 mmoles) of phenylacetic acid hydrazide and 0.525 g. (6.65 mmoles) of pyridine in 75 ml. of methylene chloride was bubbled in phosgene at room temperature until the solution became yellow. The mixture was then washed with large volumes of water and the methylene chloride evaporated to give an oil. Chromatography of the oil on alumina with acetone gave 1.0 g. (86%) of II (X = H), m.p. 50-51.5° from hexane-benzene. This and other related compounds are described in Table I.

Reaction of 2-Benzyl-1,3,4-oxadiazolin-5-one (II, X = H) with

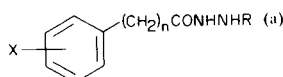
To a solution of 1.0 g. (5.68 mmoles) of II (X = H) in 30 ml. of acetonitrile was added 2.32 g. (22.72 mmoles) of acetic anhydride. The mixture was refluxed for 24 hours, evaporated to dryness and 25 ml. of cold water added. Upon cooling, 0.88 g. (71%) of III was obtained; ir (potassium bromide): 1810, 1750, 1640 cm^{-1} ; nmr (carbon tetrachloride-*d*-chloroform): 7.7 (5Ar), 4.1 (CH₂), 2.65 δ (CH₃).

Anal. Calcd. for C₁₁H₁₀N₂O₃: C, 60.54; H, 4.62; N, 12.83. Found: C, 60.43; H, 4.61; N, 12.76.

In a similar manner 2-(phenethyl)-1,3,4-oxadiazolin-5-one (XI) gave an acetyl derivative, m.p. 93-93.5° from benzene-hexane.

Anal. Calcd. for C₁₂H₁₂N₂O₃: C, 62.06; H, 5.21. Found: C, 62.20; H, 5.08.

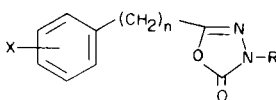
TABLE I



X	n	R	Yield	M.p. (b)	Formula	Analysis					
						Calcd. C	Calcd. H	N	Found C	Found H	N
<i>p</i> -F	1	H	81	125-126 (c)	C ₈ H ₉ FN ₂ O	57.17	5.39		56.88	5.34	
<i>o</i> -Cl	1	H	85	104-106	C ₈ H ₉ ClN ₂ O	52.04	4.91		52.16	4.87	
<i>o</i> -OCH ₃	1	H	82	107-110	C ₉ H ₁₂ N ₂ O ₂	59.99	6.71		60.22	6.74	
<i>m</i> -OCH ₃	1	H	76	86-87	C ₉ H ₁₂ N ₂ O ₂	59.99	6.71		60.13	6.68	
3,4,5-(OCH ₃) ₃	1	H	76	104-106	C ₁₁ H ₁₆ N ₂ O ₄	54.99	6.71		54.93	6.11	
H	1	C ₆ H ₅ CH ₂	75	113-114 (d)	C ₁₅ H ₁₆ N ₂ O	74.97	6.71	11.66	75.10	6.68	11.66
<i>p</i> -NO ₂	1	CH ₃	85	148-149	C ₉ H ₁₁ N ₃ O ₃	51.67	5.30		51.50	5.12	
<i>o</i> -NO ₂	2	H	67	135-137	C ₉ H ₁₁ N ₃ O ₃	51.67	5.30		51.83	5.21	
<i>p</i> -NO ₂	2	H	71	120-122 (c)	C ₉ H ₁₁ N ₃ O ₃	51.67	5.30		51.66	5.33	
H	2	CH ₃	63	85-87 (c)	C ₁₀ H ₁₄ N ₂ O	67.38	7.92	15.72	67.20	7.84	15.15

(a) Other hydrazides used in this work were known compounds. (b) Recrystallized from benzene unless otherwise noted. (c) Sublimed. (d) Recrystallized from benzene-hexane. (e) Recrystallized from hexane.

TABLE II



X	n	R	Yield	M.p. (a)	Formula	Analysis					
						Calcd.		Found		N	
						C	H	N	C	H	N
H	1	H	86	50-52 (b,c)	C ₉ H ₈ N ₂ O ₂	61.34	4.58	15.91	61.38	4.51	15.80
<i>m</i> -Cl	1	H	60	79-80	C ₉ H ₇ ClN ₂ O ₂	51.32	3.35	13.30	51.15	3.32	13.22
<i>p</i> -Cl	1	H	80	112-115	C ₉ H ₇ ClN ₂ O ₂	51.32	3.35	13.30	51.20	3.45	13.41
<i>p</i> -F	1	H	58	94-96 (d)	C ₉ H ₇ FN ₂ O ₂	55.67	3.63	14.43	55.71	3.66	14.37
<i>o</i> -OCH ₃	1	H	79	62-64	C ₁₀ H ₁₀ N ₂ O ₃	58.25	4.89	13.59	58.18	4.88	13.59
<i>m</i> -OCH ₃	1	H	69	59-61	C ₁₀ H ₁₀ N ₂ O ₃	58.25	4.89	13.59	58.33	4.93	13.59
<i>p</i> -OCH ₃	1	H	91	108-109 (d)	C ₁₀ H ₁₀ N ₂ O ₃	58.25	4.89	13.59	57.92	4.83	13.43
<i>o</i> -CH ₃	1	H	92	84-85	C ₁₀ H ₁₀ N ₂ O ₂	63.15	5.30	14.73	63.29	5.39	14.59
<i>p</i> -CH ₃	1	H	84	96-98	C ₁₀ H ₁₀ N ₂ O ₂	63.15	5.30	14.73	63.13	5.32	14.62
<i>o</i> -NO ₂	1	H	71	130-131 (d,e,f)	C ₉ H ₇ N ₃ O ₄	48.87	3.19	19.00	48.77	3.19	18.81
<i>m</i> -NO ₂	1	H	66	162-163 (d,e,f)	C ₉ H ₇ N ₃ O ₄	48.87	3.19	19.00	48.89	3.22	18.83
<i>p</i> -NO ₂	1	H	79	158-161 (d)	C ₉ H ₇ N ₃ O ₄	48.87	3.19	19.00	49.02	3.25	18.89
3,4,5-(OCH ₃) ₃	1	H	58	138-140	C ₁₂ H ₁₄ N ₂ O ₅	54.13	5.30	10.52	53.80	5.20	10.36
H	1	CH ₃	40	46-48 (h)	C ₁₀ H ₉ N ₃ O ₂	63.14	5.29	14.73	63.33	5.34	14.60
<i>p</i> -NO ₂	1	CH ₃	80	111-113 (i)	C ₁₀ H ₉ N ₃ O ₂	51.06	3.86	17.87	51.15	3.81	17.63
H	1	C ₆ H ₅	68	67-68 (j,k,b)	C ₁₅ H ₁₂ N ₂ O ₂	71.41	4.79		71.31	4.70	
H	1	C ₆ H ₅ CH ₂	76	48-50 (b,l)	C ₁₆ H ₁₄ N ₂ O ₂	72.16	5.30	10.52	72.07	5.28	10.58
H (α-OH)	1	H	63	145-147 (d,m)	C ₉ H ₈ N ₂ O ₃	56.25	4.19	14.58	56.46	4.26	14.22
H	2	H	76	99-100	C ₁₀ H ₁₀ N ₂ O ₂	63.14	5.30	14.73	63.14	5.31	14.77
<i>p</i> -OCH ₃	2	H	74	138-140 (d)	C ₁₁ H ₁₂ N ₂ O ₃	59.99	5.49		59.81	5.38	
<i>o</i> -NO ₂	2	H	71	92-94 (d)	C ₁₀ H ₉ N ₃ O ₄	51.07	3.86		51.12	3.90	
<i>p</i> -NO ₂	2	H	68	158-160	C ₁₀ H ₉ N ₃ O ₄	51.07	3.86		51.18	3.84	
H	2	CH ₃	65	40-42 (b,n)	C ₁₁ H ₁₂ N ₂ O ₂	64.69	5.92	13.72	64.50	5.91	13.57
H	2	H	57	191-193 (p)	C ₁₀ H ₈ N ₂ O ₂	63.82	4.29	14.89	63.54	4.25	14.75

(a) Recrystallized from benzene-hexane unless otherwise noted. (b) Recrystallized from hexane. (c) Nmr (DMSO-d₆): 7.75 (5Ar, NH), 4.15 δ (CH₂). (d) Recrystallized from benzene. (e) Hydrazone did not give correct analysis but gave expected product with phosgene. (f) Nmr (DMSO-d₆): 7.8-8.7 (4Ar), 4.4 (CH₂), 12.8 δ (NH). (g) Nmr (DMSO-d₆): 8.4-9.1 (4Ar), 4.55 (CH₂), 13.3 δ (NH). (h) Nmr (carbon tetrachloride-DMSO-d₆): 7.45 (5Ar), 3.9 (CH₂), 3.3 δ (CH₃). (i) R. F. Meyer and B. L. Cummings, *J. Heterocyclic Chem.*, **1**, 186 (1964) report m.p. 113-114° from ArCH₂CONHN(CH₃)₂ and phosgene. (j) H. Rupe and H. Labhardt, *Ber.*, **33**, 233 (1900) report m.p. 68°. (k) Nmr (carbon tetrachloride): 7.6-8.1 (10Ar), 3.95 δ (CH₂). (l) Nmr (carbon tetrachloride): 7.4-7.5 (10Ar), 3.8 (CH₂), 4.8 δ (CH₂). (m) Prepared from hydrazone of α-hydroxyphenylacetic acid. See experimental section for alternative method of preparation. (n) Nmr (DMSO-d₆): 7.4 (4Ar), 2.9 (2CH₂), 3.4 δ (CH₃). (o) CH=CH not (CH₂)₂. Prepared from hydrazone of cinnamic acid. See experimental section for alternative method of preparation. (p) Recrystallized from benzene-ethyl acetate-hexane.

Reaction of 2-Benzyl-1,3,4-oxadiazolin-5-one (II, X = H) with Lithium Aluminum Hydride.

To a solution of 0.43 g. (11.36 mmoles) of lithium aluminum hydride in 20 ml. of anhydrous ether was added 1.0 g. (5.68 mmoles) of II (X = H) dissolved in 60 ml. of anhydrous ether. The mixture was refluxed for 6 hours, cooled and hydrolyzed with water and alkali. Evaporation of the ethereal layer gave 0.48 g. of solid which was chromatographed on alumina with ether-benzene to give 0.45 g. (47%) of the hydrazone IV, m.p. 124.5-125° from benzene-hexane. Reported (4) m.p. 126-127°; ir (potassium bromide): 3300, 1640 cm⁻¹.

Anal. Calcd. for C₉H₁₂N₂O: C, 65.83; H, 7.37; N, 17.06. Found: C, 66.11; H, 7.36; N, 17.01.

In a similar manner XI gave C₆H₅CH₂CH₂CONHNHCH₃, m.p. 83-85° from benzene-hexane, identical with the compound in Table I.

Anal. Calcd. for C₁₀H₁₄N₂O: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.20; H, 7.84; N, 15.25.

Reduction of 2-(*p*-Nitrobenzyl)-1,3,4-oxadiazolin-5-one (II, X = *p*-nitro).

To a solution of 1.23 g. (5.56 mmoles) of II (X = *p*-nitro) in 60 ml. of absolute methanol was added 0.055 g. of platinum oxide and the mixture was reduced at 34 psi of hydrogen. The mixture was filtered and evaporated to dryness to give 1.1 g. of solid. Chromatography on silica gel with ether gave 1.0 g. (93%) of

2-(*p*-aminobenzyl)-1,3,4-oxadiazolin-5-one (II, X = *p*-amino), m.p. 138-140°. Treatment with hydrogen chloride gave the hydrochloride, m.p. 217-219° from benzene-methanol; ir (potassium bromide): 3250, 2575, 1780-1760, 1625 cm⁻¹.

Anal. Calcd. for C₉H₁₀ClN₃O₂: C, 47.48; H, 4.43; N, 18.46; Cl, 15.58. Found: C, 47.59; H, 4.40; N, 18.54; Cl, 15.61.

In a similar manner the *p*-nitro analogue of XI gave 2-(*p*-aminophenethyl)-1,3,4-oxadiazolin-5-one, m.p. 297-300° from ethyl acetate.

Anal. Calcd. for C₁₀H₁₁N₃O₂: C, 58.53; H, 5.40. Found: C, 58.57; H, 5.42.

Reaction of 2-Benzyl-1,3,4-oxadiazolin-5-one (II, X = H) with Bromine.

To a solution of 1.42 g. (8.05 mmoles) of II (X = H) in 60 ml. of benzene was added 1.29 g. (8.05 mmoles) of bromine in 25 ml. of benzene. The mixture was irradiated using a sunlamp and refluxed for 5 hours. Upon cooling and filtering 1.63 g. of solid was obtained. Chromatography on silica gel with benzene gave 1.58 g. (77%) of 2-(α -bromobenzyl)-1,3,4-oxadiazolin-5-one (V), m.p. 95-98° from benzene; ir (potassium bromide): 3300, 1780, 1750, 1610 cm⁻¹; nmr (DMSO-d₆): 7.5-8.0 (5Ar, NH), 6.2 δ (CH).

Anal. Calcd. for C₉H₇BrN₂O₂: C, 42.38; H, 2.77; N, 10.98; Br, 31.33. Found: C, 42.43; H, 2.80; N, 10.95; Br, 30.97.

In a similar manner XI gave an α -bromo derivative, m.p. 125-127° from benzene-hexane.

Anal. Calcd. for C₁₀H₉BrN₂O₂: C, 44.63; H, 3.37. Found: C, 44.80; H, 3.19.

Reaction of V with Lithium Aluminum Hydride.

To a slurry of 0.37 g. (9.8 mmoles) of lithium aluminum hydride in 40 ml. of anhydrous ether was added 1.0 g. (3.92 mmoles) of V in 40 ml. of anhydrous ether. The mixture was refluxed for 4 hours, cooled and hydrolyzed with water and alkali. The organic layer was evaporated to give 0.31 g. (46.5%) of the hydrazide IV, m.p. 124.5-125° from benzene-hexane. This was identical with the material noted above.

Reaction of V with Morpholine.

To a solution of 2.0 g. (7.83 mmoles) of V in 40 ml. of methylene chloride was added 1.36 g. (15.66 mmoles) of morpholine in 20 ml. of methylene chloride. The mixture was stirred at room temperature for 1 hour and poured onto crushed ice. The layers were separated and the organic layer was evaporated to dryness to give 1.82 g. of an oil. Chromatography on silica gel with ether gave 1.77 g. (87%) of VI, m.p. 173-174° from benzene; ir (potassium bromide): 1810, 1780, 1640 cm⁻¹; nmr (DMSO-d₆): 7.7-7.9 (5Ar, NH), 4.8 (CH), 3.7-3.9 (2CH₂), 2.45-2.6 δ (2CH₂).

Anal. Calcd. for C₁₃H₁₅N₃O₃: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.66; H, 5.72; N, 15.86.

A benzene solution of VI was treated with hydrogen chloride to give the hydrochloride, m.p. 151-153° from benzene-methanol.

Anal. Calcd. for C₁₃H₁₆ClN₃O₃·½H₂O: C, 50.89; H, 5.58; N, 13.69; Cl, 11.56. Found: C, 51.33; H, 5.74; N, 13.43; Cl, 11.56.

Reaction of 2-(α -Bromophenethyl)-1,3,4-oxadiazolin-5-one with Morpholine.

In a similar manner the α -bromo analogue of XI and morpholine gave XII, m.p. 191-193° from benzene-hexane. This product

was identical in all respects with the one in Table II from the hydrazide of cinnamic acid and phosgene. A trace of the homologue of VI was also obtained, m.p. 208-212° from benzene-hexane.

Anal. Calcd. for C₁₄H₁₇N₃O₃: C, 61.08; H, 6.23; N, 15.26. Found: C, 60.22; H, 6.13; N, 15.33.

Reaction of V with Silver Tosylate.

To 13.4 g. (48 mmoles) of silver tosylate in 90 ml. of acetonitrile was added 12.23 g. (48 mmoles) of V in 20 ml. of ethanol. The mixture was heated on a steam bath for 1 hour, filtered and evaporated to dryness. The remaining oil was heated with 10% sodium hydroxide for 1 hour, neutralized with hydrochloric acid and extracted with chloroform. Evaporation of the organic layer to dryness gave an oil. Chromatography of the oil on silica gel with chloroform gave 8.8 g. of an oil which crystallized from ligroin. Recrystallization from ligroin gave 8.5 g. (78%) of VII, m.p. 65-67°; ir (potassium bromide): 3250, 1800, 1780, 1630 cm⁻¹; nmr (carbon tetrachloride): 12.3 (NH), 7.7-7.9 (5Ar), 5.45 (CH), 3.8 (q, CH₂), 1.4 δ (t, CH₃).

Anal. Calcd. for C₁₁H₁₂N₂O₃: C, 59.99; H, 5.49. Found: C, 59.82; H, 5.51.

Continuation of the chromatography with ethyl acetate gave 0.8 g. (9%) of VIII, m.p. 145-147° from benzene; ir (potassium bromide): 3200-3350, 1750-1770, 1630 cm⁻¹; nmr (DMSO-d₆): 12.7 (NH), 7.5-7.9 (5Ar), 6.7 (OH), 5.8 δ (CH).

Anal. Calcd. for C₉H₈N₂O₃: C, 56.24; H, 4.19; N, 14.58. Found: C, 56.46; H, 4.26; N, 14.22.

A similar reaction in which V was added in methylene chloride instead of ethanol gave an 86% yield of VIII identical with the sample noted above. This compound was also prepared as noted in Table II from the hydrazide of α -hydroxyphenylacetic acid and phosgene.

Preparation of 2-Benzyl-1,3,4-oxadiazolin-5-thione.

A solution of 1.0 g. (6.65 mmoles) of phenylacetic acid hydrazide (I, X = H), 0.525 g. (6.65 mmoles) of pyridine, and 0.7 g. (6.65 mmoles) of thiophosgene in 100 ml. of methylene chloride was refluxed for 1 hour. The mixture was washed with large volumes of water and the organic layer was evaporated to dryness to give 1.2 g. of an oil. Chromatography of the oil on silica gel with methylene chloride gave 0.42 g. (33%) of the thione, m.p. 122-124° from hexane-benzene. Reported (2) m.p. was 130-131°; ir (potassium bromide): 1625, 3350, 1350 cm⁻¹.

Anal. Calcd. for C₉H₈N₂OS: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.18; H, 4.23; N, 14.58.

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