III. Reductions.—Compounds nos. 30, 31, 33 and 38 were reduced catalytically (Adams catalyst) in absolute alcohol at room temperature and *ca.* 4 atmospheres pressure. With compound no. 37 methanol–aqueous hydrochloric acid mixture was used as solvent. The yields in every case ran 76–87%.

Compound 39 was reduced with iron in dilute ammonium chloride. The filtered sludge was extracted with dilute sodium carbonate, and the product precipitated by acidification with hydrochloric acid; yield 51%.

DETROIT 32, MICHIGAN RECEIVED JULY 21, 1950

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

The Chemotherapy of Experimental Tuberculosis. III. The Synthesis of Thiosemicarbazones and Related Compounds[1,2]

BY JACK BERNSTEIN, HARRY L. YALE, KATHRYN LOSEE, MARY HOLSING, JOSEPH MARTINS AND W. A. LOTT

The preparation of a considerable number of thiosemicarbazones and related compounds which were to be tested for antituberculous activity is described. The majority of the compounds prepared were variously substituted derivatives of benzaldehyde thiosemicarbazone. The nuclear substituents included $CH_3CONH\cdot$, $HO_2CCH_2CH_2CONH\cdot$, $(CH_3)_2N\cdot$, $H_2N\cdot$, $O_2N\cdot$, $NC\cdot$, $NaO_3S\cdot$, $C_2H_5O_2S\cdot$, $H_2NO_2S\cdot$, $(C_2H_5)_2NCH_2CH_2O\cdot$; $HO\cdot$, $-OCH_2O-$, $HO_2C\cdot$, $CH_3\cdot$, $C_2H_5O\cdot$, $HO_2CCH_2O\cdot$, $CH_3O\cdot$, n-$C_3H_7O\cdot$, i-$C_3H_7O\cdot$, n-$C_4H_9O\cdot$, i-$C_3H_7\cdot$, t-$C_4H_9\cdot$, Cl and I groups; the lateral substituents included $CH_3\cdot$, $C_2H_5\cdot$, $CH_2{:}CHCH_2\cdot$ n-$C_4H_9\cdot$, i-$C_4H_9\cdot$, and $C_6H_5\cdot$ groups. Thiosemicarbazones were prepared also of a number of substituted cinnamaldehydes and acetophenones. To complete this phase of the chemical study, a number of aliphatic, alicyclic, heterocyclic and α,β-unsaturated aldehydes and ketones were converted to thiosemicarbazones. To ascertain both the extent and limitations of antituberculous activity, a number of related compounds were prepared.

The antituberculous activity, *in vitro*, of certain thiosemicarbazones of aromatic aldehydes and ketones was reported first by Domagk, Behnisch, Mietzsch and Schmidt.[3] In a subsequent paper,[4] these authors indicated qualitative differences in activity among various thiosemicarbazones. Prior to these publications, there had been initiated, in these laboratories, a thorough investigation into the chemotherapy of experimental tuberculosis. As a consequence, when these reports became available to us, we undertook the preparation of a number of thiosemicarbazones and related compounds in an attempt to show quantitatively the relationship between chemical structure and antituberculous activity. While our investigation was in progress, Hoggarth, Martin, Storey and Young[5] published their excellent quantitative *in vivo* evaluation of a considerable number of thiosemicarbazones and related compounds. The *in vitro* and *in vivo* antituberculous activities of some of the compounds prepared in these laboratories have been published recently[2]; this paper is concerned only with their synthesis and characterization.[6]

The majority of the compounds prepared were mono- and poly-substituted derivatives of benzaldehyde 3-thiosemicarbazone. The nuclear substituents included the $CH_3CONH\cdot$, $HO_2CCH_2CH_2CONH\cdot$, $(CH_3)_2N\cdot$, $H_2N\cdot$, $CH_2{:}CHCH_2NHCSNH\cdot$, $NC\cdot$, $NaO_3S\cdot$, $CH_3SO_2\cdot$, $C_2H_5SO_2\cdot$, n-$C_3H_7SO_2\cdot$, $(C_2H_5)_2NCH_2CH_2O\cdot$, $HO_2CCH_2O\cdot$, $CH_3O\cdot$, $C_2H_5O\cdot$, n-$C_3H_7O\cdot$, n-$C_4H_9O\cdot$, $HO\cdot$, $\cdot OCH_2O\cdot$, $HO_2C\cdot$, $CH_3\cdot$, i-$C_3H_7\cdot$, t-$C_4H_9\cdot$, F_3C, Cl and I groups; the lateral substituents included the $CH_3\cdot$, $C_2H_5\cdot$, $CH_2{:}CHCH_2\cdot$, n-$C_4H_9\cdot$, i-$C_4H_9\cdot$ and $C_6H_5\cdot$ groups. Thiosemicarbazones were prepared also of various aliphatic, alicyclic, α,β-unsaturated and heterocyclic carbonyl compounds as well as a number of acetophenones. A number of aldehydes otherwise unavailable were synthesized either by methods previously described in the literature or by methods described in the Experimental part. The carbonyl compounds were condensed with thiosemicarbazide in aqueous ethanol, often in the presence of a small amount of acetic acid. These compounds are listed in Tables I and II.

The amino-substituted benzaldehyde 3-thiosemicarbazones were prepared by the iron and acetic acid reduction of the corresponding nitro compounds. The reaction of 4-aminobenzaldehyde 3-thiosemicarbazone with allyl isothiocyanate gave the 4-allylthiourea derivative and the reaction with succinic anhydride gave the 4-succinoyl derivative.

The substituted thiosemicarbazides were prepared according to the procedure described by Pulvermacher[7] and condensed in similar fashion with the desired aldehydes. These derivatives are to be found in Table III.

A number of miscellaneous compounds structurally related to the thiosemicarbazones were also prepared and these are shown in Table IV. The ferric chloride oxidation[8] of 4-methoxy- and 4-aminobenzaldehyde 3-thiosemicarbazones gave the 5-substituted-2-amino-1,3,4-thiadiazole derivatives; the sodium amalgam reduction of the same thiosemicarbazones gave the correspondingly substituted 1-benzyl-3-thiosemicarbazides. 1-(4-Aminobenzoyl) thiosemicarbazide was prepared by the reduction of the corresponding nitro derivative[9]

(1) Presented before the Division of Medicinal Chemistry, 117th Meeting, American Chemical Society, Philadelphia, Pa., April 9–13, 1950.

(2) The previous papers in this series are: I. Donovick, Pansy, Stryker and Bernstein, *J. Bact.*, **59**, 667 (1950); II. Hamre, Bernstein and Donovick, *ibid.*, **59**, 675 (1950).

(3) Domagk, Behnisch, Mietzsch and Schmidt, *Naturwissenschaften*, **33**, 315 (1946).

(4) Behnisch, Mietzsch and Schmidt, *Angew. Chem.*, **60**, 113 (1948).

(5) Hoggarth, Martin, Storey and Young, *Brit. J. Pharmacol.*, **4**, 248 (1949).

(6) Some of the compounds described in this paper have been mentioned in German Patent Applications J 76,179; 76,180; 76,218; 76,219; 76,679; 76,680; 76,745; 77,783; 77,784; 78,133; 78,134; 78,163; and 78,658. Photostats of these applications are available from the Department of Commerce, Office of Publication, or from the Research Information Service, 509 Fifth Ave., New York 17, N. Y.

(7) Pulvermacher, *Ber.*, **27**, 622 (1894).

(8) Young and Eyre, *J. Chem. Soc.*, **79**, 54 (1901); see also De and Roy Choudhury, *J. Indian Chem. Soc.*, **5**, 269 (1928).

(9) Hoggarth, *J. Chem. Soc.*, 1163 (1949).

TABLE I

NUCLEAR SUBSTITUTED BENZALDEHYDE 3-THIOSEMICARBAZONES

Solvent for crystallization: A, aq. ethanol; B, 95% ethanol; C, abs. ethanol–ether; D, abs. ethanol; E, acetic acid; F, aq. methanol; G, *n*-propanol; H, hexane; I, benzene; J, aq. *n*-propanol; K, water; L, extracted with hot 95% ethanol, but not recrystallized; M, isopropyl alcohol; N, benzene–abs. ethanol; O, reprecipitated; P, benzene–acetone.

Substituted benzaldehydes	Yield, %	Solvent	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
Unsubstituted	98	A	158.5–160[a]	$C_8H_9N_3S$								
2-Methyl	98	B	161–164	$C_9H_{11}N_3S$			21.74	16.59			22.01	17.10
3-Methyl[b]	91	N	186–187 (dec.)	$C_9H_{11}N_3S$	55.93	5.74	21.74		55.76	5.63	21.97	
4-Methyl[bb]	79	A	160–161	$C_9H_{11}N_3S$			21.74				21.52	
4-Isopropyl[bb]	98	I	144–145	$C_{11}H_{15}N_3S$	59.70	6.83			59.68	6.85		
4-*t*-Butyl[c,bb]	73	F	152–153	$C_{12}H_{17}N_3S$			17.87	13.63			17.43	13.60
4-Chloro[bb]	53	B	209–210.5 (dec.)	$C_8H_8ClN_3S$	44.97	3.77	19.67		44.93	3.91	19.88	
2,4-Dichloro	91	E	242–244 (dec.)	$C_8H_7Cl_2N_3S$				12.92				12.96
3,4-Dichloro[aa]	61	B	194–195 (dec.)	$C_8H_7Cl_2N_3S$				12.92				12.85
2,6-Dichloro[d]	60	J	235–236.5 (dec.)	$C_8H_7Cl_2N_3S$	38.72	2.84		12.92	38.18	3.18		12.93
3-Hydroxy[e]	76	K	169–170	$C_8H_9N_3OS$	49.21	4.64		16.42	49.28	4.89		16.30
4-Hydroxy	56	M	224–226 (dec.)	$C_8H_9N_3OS$	49.21	4.64	21.52		49.21	4.63	21.27	
2-Ethoxy	69	B	173–174	$C_{10}H_{13}N_3OS$	53.79	5.87	18.82		53.49	5.79	19.43	
4-Ethoxy[f]	37	B	150.5–151.5	$C_{10}H_{13}N_3OS$	53.79	5.87	18.82		53.92	5.98	18.96	
4-*n*-Propoxy[g]	61	B	146–147.5	$C_{11}H_{15}N_3OS$	55.67	6.37	17.71		55.52	6.43	18.03	
4-Iso-propoxy[h]	85	M	154–155	$C_{11}H_{15}N_3OS$	55.67	6.37	17.71		55.60	6.67	17.73	
4-Allyloxy[i]	70	B	156–157	$C_{11}H_{13}N_3OS$	56.15	5.57		13.63	56.66	5.63		13.74
4-*n*-Butoxy[g]	83	B	168.5–170.5	$C_{12}H_{17}N_3OS$	57.34	6.82	16.72		57.51	6.70	17.11	
4-Iso-butoxy[g]	46	A	147–148.5	$C_{12}H_{17}N_3OS$	57.34	6.82		12.76	57.71	6.71		12.80
4-*n*-Amoxy[g]	61	B	133–134	$C_{13}H_{19}N_3OS$	58.84	7.22		12.32	59.23	7.45		12.08
4-(2-Hydroxyethoxy)[j]	60	A	180–181	$C_{10}H_{14}N_3O_2S$	50.19	5.47		13.39	50.26	5.59		13.56
4-(2,3-Dihydroxypropoxy)[k]	75	K	182–183	$C_{11}H_{15}N_3O_3S$	49.05	5.64		11.94	49.55	5.66		11.80
4-(2-Diethylaminoethoxy)[l,bb]	75	B	144–145	$C_{14}H_{22}N_4OS$	57.11	7.54			57.39	7.22		
4-(3-Diethylaminopropoxy)[l]	60	B	198–200	$C_{15}H_{24}N_4OS\cdot HCl$			[y]	9.29				8.98
4-(2-Triethylammoniumethoxy) bromide[j]	40	B	223–224 (dec.)	$C_{16}H_{27}BrN_4OS$	47.63	6.74	[z]		47.30	7.28		
4-Carboxymethoxy[m,bb]	76	B	224–225 (dec.)	$C_{10}H_{11}N_3O_3S$	47.43	4.38			47.45	4.48		
4-Hydroxy-3,5-diiodo	95	B	205–207 (dec.)	$C_8H_7I_2N_3OS$			9.40	7.17			9.02	7.08
4-Methoxy-3,5-diiodo	89	B	211–212	$C_9H_9I_2N_3OS$	23.44	1.97	9.11		23.86	2.09	9.49	
2-Hydroxy-4-nitro[n]	62	E	240–241 (dec.)	$C_8H_8N_4O_3S$	40.00	3.36	23.32	13.34	39.71	3.59	23.56	13.57
3-Hydroxy-4-nitro[o]	70	B	244–245 (dec.)	$C_8H_8N_4O_3S$	40.00	3.36		13.34	39.83	3.37		13.34
3-Hydroxy-6-nitro[p]	66	J	245–246 (dec.)	$C_8H_8N_4O_3S$	40.00	3.36		13.34	39.81	3.47		13.56
4-Hydroxy-3-nitro[p]	40	O	240–241 (dec.)	$C_8H_8N_4O_3S$	40.00	3.36		13.34	40.07	3.34		13.37
2,3-Dihydroxy[b]	90	A	206–207	$C_8H_9N_3O_2S$	45.49	4.30	19.90		45.64	4.54	19.56	
2,4-Dihydroxy	68	G	235–237 (dec.)	$C_8H_9N_3O_2S$	45.49	4.30	19.90		45.31	4.59	19.76	
3,4-Dihydroxy[q]	60	G	227–228 (dec.)	$C_8H_9N_3O_2S$	45.49	4.30	19.90		45.14	4.27	19.40	
2-Hydroxy-3-methoxy[b]	81	E	226–227 (dec.)	$C_9H_{11}N_3O_2S$	47.98	4.92	18.65		48.02	4.81	18.69	
3-Hydroxy-4-methoxy[b]	89	A	152–153	$C_9H_{11}N_3O_2S$	47.98	4.92		14.23	48.01	4.87		14.39
4-Hydroxy-3-methoxy	95	A	191–192	$C_9H_{11}N_3O_2S$	47.98	4.92	18.65		47.75	4.62	18.86	
2,3-Dimethoxy[b]	96	B	225–226 (dec.)	$C_{10}H_{13}N_3O_2S$	50.19	5.47	17.56		50.13	5.56	17.72	
2,4-Diethoxy[r]	56	E	217–218	$C_{12}H_{17}N_3O_2S$	53.76	6.09	15.50		53.91	6.41	15.72	
3,4-Dimethoxy[b]	94	E	200–201	$C_{10}H_{13}N_3O_2S$	50.19	5.47	17.56		50.22	5.63	17.91	
2-Nitro[s,bb]	61	J	247–248 (dec.)	$C_8H_8N_4O_2S$	42.85	3.51		14.30	43.11	3.75		14.53
3-Nitro[bb]	95	L	232–233 (dec.)	$C_8H_8N_4O_2S$			24.99	14.30			25.07	14.76
2-Amino,[t,bb]	33	O	198–199 (dec.)	$C_8H_{10}N_4S$	49.46	5.19		16.50	49.75	5.13		16.42
3-Amino[t,bb]	82	K	153–155	$C_8H_{10}N_4S$			28.84	16.50			29.12	16.75
4-Amino[j,bb]	65	B	197–198 (dec.)	$C_8H_{10}N_4S$	49.46	5.19	28.84		49.57	5.12	28.65	
4-Dimethylamino[bb]	84	B	208–209 (dec.)	$C_{10}H_{14}N_4S$			25.20	14.42			25.24	14.75
4-Acetamido	68	J	223–224 (dec.)	$C_{10}H_{12}N_4OS$	50.83	5.12	23.71		50.57	5.05	23.68	
4-Succinoylamido[j,bb]	63	M	220–221 (dec.)	$C_{12}H_{14}N_4O_3S$			19.04	10.89			18.33	10.57
4-Cyano[b,bb]	95	G	237–238 (dec.)	$C_9H_8N_4S$	52.81	3.94	27.38		53.08	3.97	26.97	
4-Carboxy[u,bb]	50	B	307–308	$C_9H_9N_3O_2S$	48.42	4.06	18.82		48.95	4.24	18.52	
4-Hydroxy-2-sulfonic acid, sodium salt	73	B	.....	$C_8H_8N_3NaO_4S_2$			14.14	21.56			14.14	21.63
4-Sulfamyl[v]	97	E	227–228	$C_8H_{10}N_4O_2S_2$	37.20	3.90	21.69		37.10	4.04	21.38	
4-Ethylsulfonyl[j,bb]	78	J	234–235 (dec.)	$C_{10}H_{18}N_3O_2S_2$	44.26	4.83	15.49		44.14	5.11	15.54	
4-Methylsulfonyl[w]	17	J	245–247	$C_9H_{11}N_3O_2S_2$	42.01	4.18		24.93	42.13	4.02		25.39
4-Propylsulfonyl[x,bb]	82	J	212–213 (dec.)	$C_{11}H_{15}N_3O_2S_2$	46.30	5.31		22.44	46.08	5.51		22.40
2-Methyl-4-methoxy-5-*t*-butyl[q]	84	M	238–240 (dec.)	$C_{14}H_{21}N_3OS$	60.18	7.58		11.40	60.39	7.19		11.30
3-*t*-Butyl-4-ethoxy[q]	84	M	220–222 (dec.)	$C_{14}H_{21}N_3OS$	60.18	7.58		11.40	60.51	7.70		11.33
3-*t*-Butyl-4-methoxy[q]	98	M	225–227 (dec.)	$C_{13}H_{19}N_3OS$	58.82	7.21	15.84	12.08	59.25	7.52	15.80	12.23
2-Methoxy-5-*t*-butyl[q]	78	A	173–175 (dec.)	$C_{13}H_{19}N_3OS$			15.84	12.08			16.07	11.65
2,4-Di-*t*-butyl-5-methoxy[q]	74	B	175–177 (dec.)	$C_{17}H_{27}N_3OS$				9.97				9.70
2-Carboethoxymethoxy[j]	92	M	164–165	$C_{12}H_{15}N_3O_3S$	51.23	5.38		11.40	51.88	5.57		11.22
4-(3-Allyl-2-thioureido)[j]	64	B	195–196 (dec.)	$C_{12}H_{15}N_5S_2$	49.12	5.15		21.86	49.73	4.92		21.63
4-Trifluoromethyl[j]	25	A	167–168	$C_9H_6F_3N_3S$	43.72	3.26		12.96	44.04	3.66		13.08
4-(4-Methoxybenzalamino)	90	B	189–191 (dec.)	$C_{16}H_{16}N_4OS$	61.50	5.16		10.26	61.31	5.31		10.49

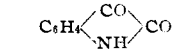
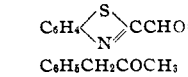
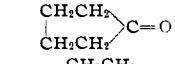
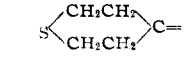
[a] Freund and Schander, *Ber.*, **35**, 2602 (1902), report a m.p. of 160°. [b] Obtained from Monsanto Chemical Co., St. Louis, Mo. [c] Lewinson, *Riechstoff Ind. Kosmetik*, **13**, 81 (1938). [d] Obtained from National Aniline Division, Allied Chemical and Dye Corp., Buffalo, N. Y. [e] *Org. Syntheses*, **25**, 55 (1945). [f] Kostanecki and Schneider, *Ber.*, **29**, 1892 (1896). [g] Stoermer and Wodarg, *ibid.*, **61**, 2323 (1928). [h] Weygand and Gabler, *J. prakt. Chem.*, **155**, 332 (1940). [i] Claisen and Eisleb, *Ann.*, **401**, 107 (1913). [j] See Experimental part. [k] This preparation was similar to that employed in preparing the 2-isomer. See Yale, Pribyl, Braker, Bergeim and Lott, THIS JOURNAL, **72**, 3710 (1950). It was obtained in 30% yield, m.p. 82–84°. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.01; H, 5.94. [l] Prepared in 70% yield, b.p. 168° (6 mm.),

by the procedure described for the alkoxybenzaldehydes (see Experimental part). *Anal.* Calcd. for $C_{13}H_{19}NO_2$: N, 6.33. Found: N, 6.17. Diethylaminopropoxybenzaldehyde was similarly prepared in 67% yield, b.p. 175° (5 mm.). *Anal.* Calcd. for $C_{14}H_{21}NO_2$: N, 5.97. Found: N, 5.99. [m] Elkan, *Ber.*, **19**, 3041 (1886). [n] Segesser and Calvin, THIS JOURNAL, **64**, 825 (1942). [o] (a) *Org. Syntheses*, **25**, 55 (1945); (b) Friedlander and Schenk, *Ber.*, **47**, 3043 (1914). [p] Brühl, *ibid.*, **28**, 2393 (1895). [q] Obtained from Givaudan-Delawanna, Inc., New York, N. Y. [r] Tiemann and Lewy, *Ber.*, **10**, 2215 (1877). [s] Thiele and Winter, *Ann.*, **311**, 356 (1900). [t] 2-Aminobenzaldehyde thiosemicarbazone and 3-aminobenzaldehyde thiosemicarbazone were prepared as described in the Experimental part by the reduction of the corresponding nitro derivatives. [u] The procedure of Gabriel and Thieme, *Ber.*, **52**, 1089 (1919), was employed in the hydrolysis of the 4-cyanobenzaldehyde to the 4-carboxybenzaldehyde. [v] Hoelschet, *Helv. Chim. Acta*, **12**, 678 (1929). [w] 4-Methylsulfonylbenzaldehyde diacetate was prepared by the chromic acid oxidation of 4-methylsulfonyltoluene. It was obtained in 53% yield, m.p. 137–138.5°, after recrystallization from 95% ethanol. *Anal.* Calcd. for $C_{12}H_{14}O_6S$: C, 50.34; H, 4.93. Found: C, 50.68; H, 4.71. [x] 4-Propylsulfonylbenzaldehyde diacetate, prepared in 52% yield by the chromic acid oxidation of 4-*n*-propylsulfonyltoluene, melted at 108–109°, after recrystallization from 95% ethanol. *Anal.* Calcd. for $C_{14}H_{18}O_6S$: C, 53.50; H, 5.77. Found: C, 53.64; H, 5.74. [y] *Anal.* Calcd.: Cl, 10.27. Found: Cl, 10.38. [z] *Anal.* Calcd.: Br, 19.81. Found: Br, 19.89. [aa] *Anal.* Calcd.: Cl, 29.24. Found: Cl, 29.14. [bb] Compound described in German Patent Application; see ref. 6.

TABLE II

MISCELLANEOUS THIOSEMICARBAZONES

See Table I for solvent designations.

Aldehydes or Ketone	Yield, %	Solvent	M.p., °C.	Empirical formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
$CH_3CH_2CH_2CH{=}C(C_2H_5)CH{=}O$	55	B	158–160	$C_9H_{17}N_3S$	54.23	8.60	16.09		54.28	8.14	16.29	
$C_6H_5CH{=}C(C_6H_{11}\text{-}n)CH{=}O$	87	I	133–134	$C_{18}H_{21}N_3S$	65.41	7.68	15.26		65.45	7.68	15.27	
p-$C_2H_5C_6H_4CH{=}CHCH{=}O$[a]	66	B	174–176	$C_{12}H_{13}N_3OS$	57.81	6.06	16.86		58.08	6.16	16.83	
p-$(CH_3)_2NC_6H_4CH{=}CHCH{=}O$[b]	62	L	211–212 (dec.)	$C_{12}H_{16}N_4S$	58.03	6.49	22.56		58.00	6.50	22.17	
$C_4H_3O{-}CH{=}CHCHO$	96	J	155–156 (dec.)	$C_8H_9N_3OS$	49.21	4.65		16.42	49.18	4.76		16.08
α-Naphthaldehyde[c]	7.5	J	225–226	$C_{12}H_{11}N_3S$	63.00	4.84		13.98	63.07	4.90		14.08
α-Furaldehyde	95	A	149–150	$C_6H_7N_3OS$	42.59	4.23	24.89		42.61	4.10	24.85	
α-$C_4H_3S{-}CHO$	75	B	186–187	$C_6H_7N_3S_2$	38.79	3.81	22.67		38.53	3.87	22.37	
	70	B	247–249 (dec.)	$C_9H_8N_4OS$	49.13	3.66		14.55	48.76	3.90		14.46
4-quinolinecarboxaldehyde[d]	98	C	237–238 (dec.)	$C_{11}H_{10}N_4S$	57.36	4.38	24.33		57.56	4.96	24.58	
6-quinolinecarboxaldehyde[e]	45	J	246–247 (dec.)	$C_{11}H_{10}N_4S$	57.36	4.38	24.33	13.92	57.16	4.38	24.11	14.00
7-Quinolinecarboxaldehyde[e]	67	J	223–224 (dec.)	$C_{11}H_{10}N_4S$	57.36	4.38		13.92	57.07	4.22		13.86
(*p*-OHC—$C_6H_4)_2SO_2$[f,i]	61	K	264–267 (dec.)	$C_{16}H_{16}N_6O_2S_3$	45.69	3.83		22.87	46.25	4.15		22.63
	16	E	242–243 (dec.)	$C_9H_8N_4S_2$	45.74	3.41		27.13	45.54	3.81		27.47
$C_6H_5CH_2COCH_3$	88	B	145–147	$C_{10}H_{13}N_3S$	57.94	6.32	20.27		58.12	6.56	20.17	
	88	A	157–159	$C_6H_{11}N_3S$			26.73	20.39			26.36	20.40
	70	B	143–144	$C_6H_{11}N_3S_2$	38.07	5.86	22.20	33.87	38.36	5.81	22.39	33.48
-$C_2H_5{-}C_6H_4{-}COCH_3$	41	J	133.5–135.5	$C_{11}H_{15}N_3S$	59.70	6.83		14.48	59.48	6.55		14.07
p-HO—C_6H_4—$COCH_3$	50	G	200–201 (dec.)	$C_9H_{11}N_3OS$	51.65	5.30		15.32	51.53	5.37		15.27
p-$C_2H_5O{-}C_6H_4{-}COCH_3$	64	D	158–159	$C_{11}H_{15}N_3OS$	55.67	6.37		13.51	55.78	6.39		13.43
p-$NH_2{-}C_6H_4{-}COCH_2CH_3$	30	A	139–140	$C_{10}H_{14}N_4S$	54.03	6.35		14.42	54.17	6.30		14.45

[a] The procedure of Scholtz and Wiedemann, *Ber.*, **36**, 845 (1903), was employed for condensing anisaldehyde and acetaldehyde. The 4-methoxycinnamaldehyde distilled at 127–130° (9 mm.). *Anal.* Calcd. for $C_{11}H_{12}O_2$: C, 75.00; H, 6.82. Found: C, 75.55; H, 6.84. [b] Möhlau and Adam, *Z. Farbenind.*, **5**, 377 (1906); [*Chem. Zentr.*, **78**, I, 107 (1907)]. [c] Mayer and Sieglitz, *Ber.*, **58**, 1846 (1922). [d] Kaplan, THIS JOURNAL, **63**, 2654 (1941). [e] Rodinov and Berkengeim, *J. Gen. Chem.* (*U. S. S. R.*), **14**, 330 (1944); [*C. A.*, **39**, 4076 (1945)]. [f] See Experimental part. [g] Borsche and Doeller, *Ann.*, **537**, 61 (1938). [h] Bennett and Scorah, *J. Chem. Soc.*, 194 (1927). [i] Compound described in German Patent Application; see ref. 6.

with ammonium sulfide. The reaction between 4-acetamidobenzaldehyde, 1-acetyl-2-thiohydantoin and sodium acetate in glacial acetic acid gave apparently 5 - (4 - acetamidobenzal) - 2 - thiohydantoin, due probably to hydrolysis of the 1-acetyl group during the isolation of the product.[10] The procedure of Hüter[11] was utilized in the preparation of 1-(4-methoxyphenethyl)-2-thiourea and 1-(4-nitrophenethyl)-2-thiourea. This involved procedure was used, since other methods which were expected to yield the mono-substituted thiourea gave instead the 1,3-disubstituted-2-thiourea. 1-(4-Nitrophenethyl)-2-thiourea was reduced to 1-(4-aminophenethyl)-2-thiourea by means of iron and acetic acid; neither of the other methods tried, aqueous ammonium sulfide or catalytic reduction over platinum or palladium, was successful.

(10) See Johnson and Nicolet, THIS JOURNAL, **33**, 1973 (1911).

(11) Hüter, *Chem. Ber.*, **3**, 273 (1947).

In view of the promising antituberculous activities in the mouse of some of these compounds,[2] further synthetic investigations along these lines are being pursued in these laboratories.

Acknowledgment.—The authors are indebted to Dr. F. Y. Wiselogle for his stimulating interest throughout this investigation. The microanalyses were carried out by Mr. J. F. Alicino.

Experimental Part[12]

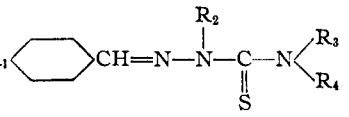
Thiosemicarbazones.—The general methods employed in the preparation of the thiosemicarbazones will be illustrated by the following typical examples.

(1) **4-Nitrobenzaldehyde 3-Thiosemicarbazone.**—A solution of 30.2 g. (0.2 mole) of 4-nitrobenzaldehyde in 300 ml. of warm 95% ethanol and a solution of 18.2 g. (0.2 mole) of thiosemicarbazide in 300 ml. of warm water were mixed. The product separated immediately. When the reaction mixture had cooled to room temperature, it was

(12) All temperatures are uncorrected.

TABLE III

LATERALLY SUBSTITUTED BENZALDEHYDE 3-THIOSEMICARBAZONES



See Table I for Solvent Designations

R_1	R_2	R_3	R_4	Yield, %	Solvent	M.p., °C.	Empirical formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
H	H	H	C_4H_9-iso	91	A	126–127	$C_{12}H_{17}N_3S$	61.25	7.28		13.63	61.30	7.32		13.51
C_4H_7-iso	H	H	C_4H_9-iso	66	B	129–130	$C_{16}H_{23}N_3S$	64.94	8.36		11.56	64.79	8.12		11.78
HO	H	H	C_4H_9-iso	86	A	185–186	$C_{12}H_{17}N_3OS$	57.35	6.82		12.76	57.11	6.47		12.51
CH_3O	H	H	C_4H_9-*n*	87	A	128.5–129.5	$C_{13}H_{19}N_3OS$	58.83	7.22		12.08	58.74	7.41		12.00
CH_3O	H	H	C_4H_9-iso	81	B	139–140	$C_{13}H_{19}N_3OS$	58.83	7.22		12.08	59.05	7.36		11.95
C_3H_7O-*n*	H	H	C_4H_9-iso	90	B	151–153	$C_{15}H_{23}N_3OS$	61.40	7.90		10.93	61.68	7.82		10.95
C_3H_7O-*n*	CH_3	H	C_4H_9-iso	67	B	79–80	$C_{16}H_{25}N_3OS$	62.51	8.20		10.43	62.81	7.92		10.51
$(C_2H_5)_2N$-CH_2CH_2O	H	H	C_4H_9-iso	48	C	106–120	$C_{18}H_{30}N_4OS$·HCl			[a]	8.29				8.41
$(CH_3)_2N$	H	H	C_4H_9-*n*	98	B	179–181	$C_{14}H_{22}N_4S$	60.40	7.96	20.13		60.20	8.00	20.15	
$(CH_3)_2N$	H	H	C_4H_9-iso	98	B	169–170	$C_{14}H_{22}N_4S$	60.40	7.96	20.13		60.84	8.31	20.31	
$(CH_3)_2N$	CH_3	H	C_4H_9-iso	50	B	124–126	$C_{15}H_{24}N_4S$	61.61	8.27		10.97	61.74	8.40		10.77
CH_3CONH	H	H	CH_3	98	D	234–235	$C_{11}H_{14}N_4OS$	52.78	5.64	22.38		52.68	5.57	22.51	
CH_3CONH	H	H	$CH_2CH{=}CH_2$	96	E	234–235	$C_{13}H_{16}N_4OS$	56.50	5.84	20.27		56.43	5.55	20.06	
CH_3CONH	H	H	C_4H_9-*n*	98	B	165–166	$C_{14}H_{20}N_4OS$	57.50	6.89	19.16		57.19	7.15	19.23	
CH_3CONH	H	H	C_4H_9-iso	98	B	151–152 (dec.)	$C_{14}H_{20}N_4OS$·$\frac{1}{2}H_2O$	55.79	7.02	18.59	[b]	55.93	7.16	18.87	
CH_3CONH	H	H	C_6H_5	97	B	209–210	$C_{16}H_{16}N_4OS$	61.51	5.20	17.93		61.31	5.14	17.93	
CH_3CONH	CH_3	H	CH_3[c]	63	E	115–117 (dec.)	$C_{12}H_{16}N_4OS$·H_2O	51.03	6.43	19.81	[d]	51.09	6.12	19.61	
CH_3CONH	CH_3	H	C_4H_9-iso	83	A	147–148	$C_{16}H_{22}N_4OS$·H_2O	55.53	7.46		9.88	55.71	7.08		10.12
CH_3CONH	H	C_2H_5	C_2H_5[e]	93	D	162–164 (dec.)	$C_{14}H_{20}N_4OS$	57.50	6.89	19.16		57.96	7.14	19.18	
$C_2H_5SO_2$	H	H	C_4H_9-*n*	45	G	148–149	$C_{14}H_{21}N_3O_2S_2$	51.35	6.47		19.58	51.67	6.47		19.90
$C_2H_5SO_2$	H	H	C_4H_9-iso	62	G	197–198.5	$C_{14}H_{21}N_3O_2S_2$	51.35	6.47		19.58	51.67	6.27		19.49
CH_3CONH	H	H	C_7H_{15}-*n*	85	H	120–121	$C_{17}H_{28}N_4OS$	61.04	7.80		9.58	61.01	7.93		9.47
CH_3CONH	H	H	$CH_2CHC_2H_5$ | C_2H_5	31	A	149–150	$C_{16}H_{24}N_4OS$	59.98	7.55		10.01	60.07	7.87		10.21

[a] *Anal.* Calcd.: Cl, 9.16. Found: Cl, 9.20. [b] *Anal.* Calcd.: H_2O, 3.0. Found: H_2O, 3.1. [c] 2,4-Dimethylthiosemicarbazide was prepared according to the method reported by Cattelain, *Bull. soc. chim.*, **12**, 46 (1945) who reported a m.p. of 116.5°. Busch, *et al.*, *Ber.*, **37**, 2318 (1904) have reported a m.p. of 137–138°. Our product had a m.p. of 136–138°. *Anal.* Calcd. for $C_3H_9N_3S$: N, 35.25. Found: N, 34.88. [d] *Anal.* Calcd.: H_2O, 6.4. Found: H_2O, 6.7. [e] 4,4-Diethylthiosemicarbazide was prepared as described by Jensen, *J. prakt. Chem.*, **159**, 189 (1941).

filtered to give 38 g. (85% yield) of 4-nitrobenzaldehyde 3-thiosemicarbazone, m.p. 232–233° (dec.). It was recrystallized from 3 l. of glacial acetic acid to give 29 g. (65% yield) of material with the same m.p.

(2) **α-Amylcinnamaldehyde 3-Thiosemicarbazone.**—A solution of 48 g. (0.2 mole) of α-amylcinnamaldehyde in 350 ml. of 95% ethanol and a solution of 18.2 g. (0.2 mole) of thiosemicarbazide in 250 ml. of water were mixed, 10 ml. of glacial acetic acid was added and the mixture refluxed for 3 hours. On cooling, a crystalline solid separated and was filtered. It weighed 48 g. (87% yield) and melted at 127–132°. The crude product was recrystallized from 400 ml. of benzene to give 39 g. of pure α-amylcinnamaldehyde 3-thiosemicarbazone, m.p. 133–134°. An additional crystallization was without effect on the m.p.

(3) **4-Ethylsulfonylbenzaldehyde 3-Thiosemicarbazone.**—**4-(Ethylsulfonyl)-toluene**[13] was converted to **4-(ethylsulfonyl)-benzaldehyde diacetate** by means of chromic acid.[14] The diacetate was obtained in 55.2% yield, m.p. 109–110°, after recrystallization from 95% ethanol. *Anal.* Calcd. for $C_{13}H_{16}O_6S$: C, 51.99; H, 5.37. Found: C, 52.21; H, 5.75. A mixture of 130 g. (0.43 mole) of the diacetate, 335 ml. of water, 335 ml. of 95% ethanol and 33.5 ml. of concentrated sulfuric acid was refluxed 0.5 hr., cooled and neutralized with 10% sodium hydroxide solution. To this mixture was added a solution of 39.6 g. (0.44 mole) of thiosemicarbazide in 425 ml. of hot water, the mixture refluxed for several minutes, cooled and filtered. The yield of crude material was 107 g. (91%). For recrystallization, 300 g. of the crude product was dissolved in 15 l. of boiling 72% aqueous *n*-propanol, decolorized with carbon, and filtered. The recovery was 235 g. (78%) of material, m.p. 234–5° (dec.).

For identification, the intermediate 4-(ethylsulfonyl)-benzaldehyde was isolated from the hydrolysis mixture. It melted at 99–100°, after recrystallization from 95% ethanol, and was apparently a monohydrate. *Anal.* Calcd. for $C_9H_{10}O_3S$·H_2O: C, 50.10; H, 5.56. Found: C, 50.29; H, 5.38.

(4) **4-Aminobenzaldehyde 3-Thiosemicarbazone.**—To a stirred and refluxing mixture of 450 g. of iron filings, 960 ml. of water and 12.8 ml. of glacial acetic acid was added 143 g. (0.64 mole) of 4-nitrobenzaldehyde 3-thiosemicarbazone in small portions. When the addition was complete, the mixture was stirred and refluxed for 4 hours, 100 ml. of 30% sodium hydroxide was added, the mixture refluxed for an additional 5 minutes and filtered through a steam-heated Büchner funnel. The filtrate was cooled and acidified with 10% hydrochloric acid to give 111.9 g. of crude 4-aminobenzaldehyde 3-thiosemicarbazone, m.p. 197–198° (dec.). After one recrystallization from isopropyl alcohol, there was obtained 87 g. of pure material, m.p. 197–198° (dec.).

A number of attempts to reduce the nitro derivative catalytically were unsuccessful.

Aldehydes.—The preparation of a number of aldehydes will be described, either because they are new or because a special synthetic method was employed.

2-(Carboethoxymethoxy)-benzaldehyde.—To a solution of 23 g. (1.0 mole) of sodium in 1000 ml. of absolute ethanol was added 122 g. (1.0 mole) of salicylaldehyde. The mixture was stirred for 15 minutes, 167 g. (1.0 mole) of ethyl bromoacetate added and the stirring and refluxing continued for 4 hours. The alcohol was distilled and the residue stirred with ether and filtered. The filtrate was concentrated and the residual liquid distilled to give 85 g. of 2-(carboethoxymethoxy)-benzaldehyde, b.p. 148–153° (3 mm.). This material crystallized on standing and was recrystallized from hexane, m.p. 45–46°.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.86; H, 5.42.

(13) Otto, *Ber.*, **13**, 1272 (1880).

(14) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., 1944, p. 242.

TABLE IV

MISCELLANEOUS RELATED COMPOUNDS

See Table I for Solvent Designations

Compound	Yield, %	Solvent	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
p-$CH_3CONH—C_6H_4—CH{=}NNHC(NH)NH_2 \cdot HCl$[a]	71	D	263–264	$C_{10}H_{14}ClN_5O$			27.39	*g*			27.31	
p-$CH_3CONH—C_6H_4—CH{=}NNHCSSCH_3$[b]	95	E	221–222 (dec.)	$C_{11}H_{13}N_3OS_2$	49.41	4.90	15.71		49.40	5.20	15.32	
p-$CH_3CONH—C_6H_4—CH{=}C(C{=}O)NHC(=S)$[c]	87	L	>285	$C_{12}H_{11}N_3O_2S$			16.08	12.27[e]			15.73	12.31
p-$CH_3CONH—C_6H_4—CH{=}NNHC(SCH_3){=}NH \cdot HI$[d]	69	K	233–234 (dec.)	$C_{11}H_{15}IN_4OS$	34.92	3.99	14.81		34.42	3.96	14.49	
p-$CH_3CONH—C_6H_4—CH{=}NNHC(SC_4H_9\text{-}i){=}NH$[a]	66	A	150–151	$C_{14}H_{20}N_4OS$	57.50	6.89		10.96	58.02	7.03		10.64
p-$C_3H_7O—C_6H_4—CH{=}NNHC(SC_4H_9\text{-}i){=}NH \cdot HCl$[a]	61	K	204–205 (dec.)	$C_{15}H_{24}ClN_3OS$	54.61	7.33	[f]		54.69	7.17		
p-$CH_3O—C_6H_4—CH_2NHNHCSNH_2$[a]	71	B	137–138	$C_9H_{13}N_3OS$	51.16	6.20		15.18	51.35	6.33		15.03
p-$H_2N—C_6H_4—CH_2NHNHCSNH_2$[a]	34	D	153–154	$C_8H_{12}N_4S$	48.96	6.17		16.34	48.72	5.70		16.19
p-$CH_3O—C_6H_4—CH{=}NNHC(=N)S{>}C_6H_4\text{-}o$[g]	51	B	188–189	$C_{15}H_{13}N_3OS$	63.58	4.62	14.83		63.43	4.72	14.97	
p-$(CH_3)_2N—C_6H_4—CH{=}NNHC(=N)S{>}C_6H_4$[g]	56	G	231–233	$C_{16}H_{16}N_4S$	65.21	5.63	18.54		64.84	5.44	18.91	
p-$CH_3CONH—C_6H_4—CH{=}NNHC(=N)S{>}C_6H_4$[g]	30	E	299–300 (dec.)	$C_{16}H_{14}N_4OS$	61.91	4.55	18.05		62.18	4.47	17.82	
p-$CH_3O—C_6H_4CH_2CH_2NHCSNH_2$[a]	31	M	160–162	$C_{10}H_{14}N_2OS$			13.32	15.25			13.06	15.32
$(p\text{-}CH_3O—C_6H_4—CH_2CH_2NH)_2CS$[a]	50	M	123–125	$C_{19}H_{24}N_2O_2S$	66.25	7.02		9.31	66.29	6.55		9.38
p-$O_2N—C_6H_4—CH_2CH_2NHCSNH_2$[a]	53	M	193–195	$C_9H_{11}N_3O_2S$			18.65	14.23			18.48	14.37
$(p\text{-}O_2N—C_6H_4—CH_2CH_2NH)_2CS$[a]	37	M	141–142	$C_{17}H_{18}N_4O_4S$	54.53	4.85		8.56	54.53	5.08		8.39
p-$H_2N—C_6H_4—CH_2CH_2NHCSNH_2$[a]	56	K	155–156	$C_9H_{13}N_3S$			21.52	16.42			21.29	16.68
p-$CH_3CONH—C_6H_4—C(=N—N{=}C(S)—NH_2)$[a]	30	B	237–238 (dec.)	$C_{10}H_{10}N_4OS$			23.91	13.68			23.65	13.51
p-$CH_3O—C_6H_4—C(=N—N{=}C(S)—NH_2)$[a]	35	K	185–187	$C_9H_9N_3OS$	52.16	4.38		15.47	51.99	4.41		15.25

[a] See Experimental part. [b] Methyl dithiocarbazinate was prepared according to the method described by Losanitch, *J. Chem. Soc.*, 119, 764 (1921). [c] *Anal.* Calcd.: N-Acetyl, 16.47. Found: N-Acetyl, 15.87. [d] For the preparation of S-methylthiosemicarbazide, see Freund and Paradies, *Ber.*, **34**, 3114 (1901). [e] *Anal.* Calcd.: Cl, 10.75. Found: Cl, 10.54. [f] The preparation of 2-benzothiazolyl hydrazine is described in U. S. Patent 2,073,600. [g] *Anal.* Calcd.: Cl, 13.86. Found: Cl, 13.86.

4-Trifluoromethylbenzaldehyde. 4-Cyanobenzotrifluoride.—A solution of 7.0 g. (0.1 mole) of sodium nitrite in 40 ml. of water was added to a solution of 16.1 g. (0.1 mole) of *p*-aminobenzotrifluoride[15] in 17.5 ml. of concentrated hydrochloric acid and 500 ml. of water, at 0°. The cooling-bath was removed and the mixture stirred until the temperature rose to 15°. It was then added dropwise to a solution of cuprous cyanide prepared from 25 g. of copper sulfate pentahydrate, 28 g. of potassium cyanide and 150 ml. of water, maintained at 70°, and then stirred an additional half-hour at 70°. The mixture was steam distilled and the distillate extracted with ether. The dried ether solution was concentrated to give a residue which crystallized on cooling. It weighed 4.0 g. and was recrystallized from hexane to give 2.5 g. of **4-cyanobenzotrifluoride**, m.p. 36–37°. *Anal.* Calcd. for $C_8H_4F_3N$: N, 8.18. Found: N, 8.62. Into a suspension of 28.9 g. (0.15 mole) of anhydrous stannous chloride,[16] in 350 ml. of dry ether was bubbled a rapid stream of hydrogen chloride until two layers formed (about 6 hours). 4-Cyanobenzotrifluoride, 17.1 g. (0.1 mole) in 50 ml. of dry ether was added rapidly while stirring. Hydrogen chloride gas was then passed in for an additional hour and the reaction mixture allowed to stand overnight. The lower layer was separated and poured into warm water. The oil which separated was extracted with ether. The dried ether solution was concentrated and the residual oil distilled to give 4.5 g. (26% yield) of the **aldehyde**, b.p. 80–81° (25 mm.). The aldehyde was unstable and no satisfactory analyses could be obtained. The thiosemicarbazone was prepared in the usual manner and gave satisfactory analyses.

4-Hydroxyethoxybenzaldehyde.—To a solution prepared from 61 g. (0.5 mole) of 4-hydroxybenzaldehyde, 20 g. (0.5 mole) of sodium hydroxide and 200 ml. of water was added 40 g. (0.5 mole) of ethylene chlorohydrin and the mixture heated on the steam-bath for 7 hours. After 4 hours of heating an oil had separated. The mixture was made strongly alkaline and extracted with ethyl acetate. The ethyl acetate extracts were washed with saturated sodium chloride solution, dried, concentrated under reduced pressure and the residue dissolved in about 1 l. of ether. The aldehyde crystallized on standing and was filtered. It weighed 25 g. (30% yield) and melted at 33°.[17]

4-Formylphenoxyethyl Triethylammonium Bromide 3-Thiosemicarbazone.—4-Diethylaminoethoxybenzaldehyde, 37 g. (0.19 mole), 33 g. (0.26 mole) of ethyl bromide and 200 ml. of absolute ethanol were refluxed 20 hours, after which the ethanol was distilled. The aldehyde could not be induced to crystallize; hence 17.3 g. (0.19 mole) of thiosemicarbazide in 300 ml. of water was added, the mixture was decolorized with Darco, residual ethanol removed under reduced pressure and the aqueous solution freeze-dried. The residue weighed 57 g. (75% yield). After one recrystallization from 95% ethanol, there was obtained 30 g. (40% yield) of the product, m.p. 223–224° (dec.).

4,4′-Sulfonyldibenzaldehyde Bis-(3-thiosemicarbazone).—**4,4′-Sulfonyldibenzaldehyde tetraacetate** was obtained by chromic acid oxidation of 4,4′-ditolylsulfone. The diacetate was obtained in 17.8% yield, m.p. 140–141°, after recrystallization from 95% ethanol. *Anal.* Calcd. for $C_{22}H_{22}O_{10}S$: S, 6.70. Found: S, 6.45. The diacetate was further identified by hydrolysis to the **aldehyde monohydrate**, which melted at 180°.[18] To a stirred, hot mixture of 400 ml. of glacial acetic acid and 18.2 g. (0.2 mole) of thiosemicarbazide was added dropwise a solution of 20 g. (0.073 mole) of the aldehyde in 800 ml. of 95% ethanol and 100 ml. of glacial acetic acid. When the addition was complete, the mixture was refluxed an additional 2 hours and filtered hot. The solid was washed successively with boiling glacial acetic acid, boiling water, boiling 95% ethanol and finally anhydrous ether. The solid weighed 16.8 g. and decomposed at 264–267°.

4-Alkylthiosemicarbazides.—The intermediate **alkyl isothiocyanates** required were prepared according to the literature method.[19] The condensation of the alkyl isothiocyanates and hydrazine or methylhydrazine was carried out as described by Pulvermacher.[7] The new substituted thiosemicarbazides prepared during this investigation are given in Table V.

TABLE V

ALKYL THIOSEMICARBAZIDES

4-Alkyl	2-Alkyl	M.p., °C.	Yield, %	Analyses, % Calcd. C	Calcd. H	Found C	Found H
n-Butyl	.....	73–74	63	40.77	8.90	40.71	8.87
i-Butyl	.....	77–78	80	40.77	8.90	41.14	8.80
i-Butyl	Methyl	75–76	63	44.67	9.37	44.80	9.22
2-Ethylbutyl	.....	69–70	75	59.98	7.55	60.07	7.87
n-Heptyl	.....	52–53	100	61.04	7.80	61.01	7.93

1-(4-Aminophenyl)-4-isobutylthiosemicarbazide. 1-(4-Nitrophenyl)-4-isobutylthiosemicarbazide.—To a cold suspension of 33 g. (0.22 mole) of 4-nitrophenylhydrazine in 1500 ml. of absolute ethanol was added dropwise and with stirring 22 g. (0.2 mole) of isobutyl isothiocyanate in 35 ml. of absolute ethanol, maintaining the temperature at 10–15° during the addition. The mixture was stirred at room temperature for 60 hours. The insoluble material was filtered to give 26.3 g. of solid, m.p. 209–210°. The filtrate after being concentrated gave an additional 14.3 g. of solid. The combined solids were recrystallized from 95% ethanol to give 23 g. (43% yield) of pure product, m.p. 210–211°. *Anal.* Calcd. for $C_{11}H_{16}N_4O_2S$: C, 49.24; H, 6.01. Found: C, 49.58; H, 6.00. 1-(4-Nitrophenyl)-4-isobutylthiosemicarbazide, 21 g. (0.079 mole), in a mixture of 250 ml. of 15% sodium hydroxide solution and 210 ml. of 20% ammonium sulfide solution was stirred and heated to boiling for 3 hours, during which time a solid separated. The volume was kept constant by the addition of water. The solid was filtered from the hot solution, washed once with 300 ml. of hot water and recrystallized from 50% ethanol to give the amino compound.

4-Acetamidobenzaldehyde S-Isobutylthiosemicarbazone. S-Isobutylthiosemicarbazide dihydrochloride was prepared according to the method described by Baird.[20] A solution of 25 g. (0.114 mole) of the hydrochloride in 100 ml. of water and a solution of 18.6 g. (0.114 mole) of 4-acetamidobenzaldehyde in 200 ml. of 95% ethanol were mixed and the *p*H adjusted to about 6 by the addition of 10% sodium hydroxide solution. The mixture was refluxed one-half hour, made exactly neutral and the precipitated solid filtered. It weighed 30 g., m.p. 148–150°. After two recrystallizations from aqueous ethanol there was obtained the pure product.

4-Propoxybenzaldehyde S-Isobutylthiosemicarbazide Hydrochloride.—This preparation was carried out as with the corresponding acetamido compound with the exception that the reaction mixture, subsequent to the refluxing period, was acidified with 20% hydrochloric acid to precipitate the product as the hydrochloride.

1-(4-Aminobenzoyl)-3-thiosemicarbazide.—A mixture of 26 g. 1-(4-nitrobenzoyl)-3-thiosemicarbazide[9] and 175 ml. of 20% aqueous ammonium sulfide solution was heated at the boiling point for 1.5 hours, keeping the volume constant by the addition of water. The hot solution was filtered. On cooling, the product separated and was filtered. After one recrystallization from boiling water there was obtained 14.7 g. of the pure product.

1-(4-Aminobenzyl)-3-thiosemicarbazide.—To a stirred mixture of 22 g. (0.11 mole) of 4-aminobenzaldehyde, 3-thiosemicarbazone in 1100 ml. of 95% ethanol at 50–60°, was added in about 4 hours, 236 g. of 10% sodium amalgam, while a slow stream of carbon dioxide was passed through the mixture. This carbon dioxide atmosphere and consequent formation of sodium carbonate is essential; a nitrogen atmosphere will not function as a substitute. The mixture was stirred an additional hour at 50–60° and filtered hot, with suction. The filtrate was concentrated to dryness and the residual solid recrystallized from absolute ethanol.

1-(4-Methoxybenzyl)-3-thiosemicarbazide.—This compound was prepared similarly to the above 4-aminobenzyl derivative.

4-(3-Allyl-2-thioureido)-benzaldehyde 3-Thiosemicarbazone.—A refluxing solution of 13.7 g. (0.075 mole) of 4-aminobenzaldehyde 3-thiosemicarbazone in 600 ml. of methanol was treated with 7.5 g. (0.075 mole) of allyl isothiocyanate in 32 ml. of methanol, and the mixture refluxed

(15) Drake, *et al.*, THIS JOURNAL, **68**, 1602 (1946).

(16) Metal and Thermit Corp., New York, N. Y.

(17) Gattermann, *Ann.*, **357**, 353 (1907), prepared the aldehyde by another method and reported a m.p. of 34°.

(18) Genvresse, *Bull. soc. chim.*, [3] 11, 505 (1894), reports a m.p. of 179°.

(19) *Org. Syntheses*, **21**, 81 (1941).

(20) Baird, *J. Chem. Soc.*, 2527 (1927).

for 16 hours. The solvent was distilled and the residue crystallized from 1 l. of 95% ethanol.

4-Succinoylamidobenzaldehyde 3-Thiosemicarbazone.—4-Aminobenzaldehyde 3-thiosemicarbazone, 19.4 g. (0.1 mole), 10 g. (0.1 mole) of succinic anhydride and 200 ml. methyl ethyl ketone, were stirred and refluxed for 6 hours, allowed to cool and filtered. The solid was dissolved in 250 ml. of 4% aqueous ammonia, treated with carbon and filtered. The filtrate was acidified with 10% hydrochloric acid, and the precipitated solid filtered. It was recrystallized from 80% isopropyl alcohol to give 18.5 g. of pure product.

Bis-(4-acetamidobenzaldehyde) 3-Thiocarbazone.—A solution of 30.8 g. (0.19 mole) of 4-acetamidobenzaldehyde in 300 ml. of water and 50 ml. of 95% ethanol were mixed with 10 g. (0.095 mole) of thiocarbohydrazide[21] in 150 ml. of hot water. An oil separated. Upon the addition of 300 ml. of 95% ethanol, the oil solidified. The product was filtered and weighed 39 g. (99% yield). It melted at 177–184°, resolidified, then melted and decomposed at 240–242°. After one crystallization from glacial acetic acid there was obtained 15 g. (39% yield) of product which melted and decomposed at 242–244° with no physical change at a lower temperature.

4-(4-Methoxybenzal)-aminobenzaldehyde 3-Thiosemicarbazone.—A mixture of 9.7 g. (0.05 mole) of 4-aminobenzaldehyde 3-thiosemicarbazone, 250 ml. of 95% ethanol and 6.8 g. of anisaldehyde was refluxed 2 hours and allowed to cool. The yield of crude product was 16.7 g., m.p. 185° (dec.). It was recrystallized from 95% ethanol and then melted at 189–191° (dec.).

5-(4-Acetamidobenzal)-2-thiohydantoin.—A mixture of 6 g. (0.037 mole) of 4-acetamidobenzaldehyde, 6 g. (0.038 mole) of 1-acetyl-2-thiohydantoin, 14 g. of anhydrous sodium acetate and 38 ml. of glacial acetic acid was refluxed for 4 hours and then poured into 250 ml. of water. The orange colored product was insoluble in all of the usual solvents; as a consequence, it was washed thoroughly with hot 95% ethanol. The yield of product was 8.4 g. Analyses indicated that an acetyl group had been hydrolyzed off, apparently from the thiohydantoin portion of the molecule.

N-(2-Benzothiazolyl)-N′-(4-methoxybenzal)-hydrazone.—To 16.5 g. (0.1 mole) of 2-benzothiazolylhydrazine[22] in 800 ml. of hot 95% ethanol was added a solution of 13.6 g. of anisaldehyde in 50 ml. of hot 95% ethanol. The mixture was refluxed 10 minutes and cooled. The solid which separated was recrystallized from 95% ethanol.

4-Acetamidobenzaldehyde Azine.—A solution of 8.15 g. (0.05 mole) of 4-acetamidobenzaldehyde in 100 ml. of 95% ethanol and a solution of 2.5 g. (0.05 mole) of hydrazine hydrate in 50 ml. of water were mixed and refluxed for 2.5 hours. The solid which separated on cooling was recrystallized from 75% ethanol to give 1.3 g. of product.

2-Amino-5-(4-methoxyphenyl)-1,3,4-thiadiazole.—A mixture of 16.7 g. (0.08 mole) of 4-methoxybenzaldehyde 3-thiosemicarbazone, 3600 ml. of water and 60 g. of ferric chloride pentahydrate was stirred and heated at 80–90° for one-half hour, then filtered hot.[8] The filtrate was concentrated under reduced pressure and the residue made alkaline with 10% aqueous ammonia. The insoluble material was filtered and dried; subsequently, it was thoroughly extracted with boiling 95% ethanol. The extract was concentrated to dryness and the residue recrystallized from boiling water to give the desired product.

Guanidoiminomethyl-4-acetanilide Hydrochloride.—A solution of 32.6 g. (0.2 mole) of 4-acetamidobenzaldehyde in 300 ml. of water and 50 ml. of 95% ethanol was mixed with an aqueous solution of 27.2 g. (0.2 mole) of aminoguanidine bicarbonate and 22.4 g. (0.4 mole) of potassium hydroxide. The hot mixture was treated with carbon and filtered. The solid which separated on cooling was filtered to give 31 g. (71% yield) of the **bicarbonate monohydrate**, m.p. 236–238°. After one crystallization from water there was obtained 26 g., m.p. 236–237°. *Anal.* Calcd. for $C_{10}H_{13}N_5O \cdot H_2O \cdot 0.5H_2CO_3$: C, 47.13; H, 5.96; N, 26.39. Found: C, 46.88; H, 5.99; N, 26.04. A solution of 25 g. of the bicarbonate in 200 ml. of water was treated with 10% hydrochloric acid until the solution was acid to congo red. On cooling and filtering, there was obtained 21 g. of crude guanidoiminomethyl 4-acetanilide hydrochloride, m.p. 263–264°. After crystallization from absolute ethanol, there was obtained 18 g. of pure product.

1-(4-Nitrophenethyl)-2-thiourea.—A concentrated aqueous solution of 10 g. of 4-nitrophenylamine hydrochloride[23] was made strongly alkaline with 50% sodium hydroxide solution and the free base (8.5 g.) isolated in the usual manner. The method employed in the preparation of the thiourea is that of Hüter.[11] To a solution of 8.5 g. of the base in 600 ml. of absolute ethanol and 19.5 ml. of water was added the suspension made by dissolving 15 g. of mercuric acetate in 300 ml. of boiling absolute ethanol, cooling and adding 9.9 ml. of water. The combined mixture was diluted with 9.9 ml. of water, and the whole added dropwise to 185 ml. of stirred and refluxing carbon disulfide. After the addition was complete, the refluxing and stirring were continued for 3 hours. After cooling, the mixture was treated with Hyflo and filtered. The filtrate was concentrated on the steam-bath. The crude **isothiocyanate** thus obtained was shaken for 24 hours with 30 ml. of concentrated aqueous ammonia and 30 ml. of saturated methanolic ammonia. The pale gray colored solid was filtered and recrystallized twice from isopropyl alcohol to give the product.

1,3-Bis-(4-nitrophenethyl)-2-thiourea.—To an ice-cooled mixture of 11.2 g. of sodium hydroxide, 35 ml. of water and 10.5 g. of carbon disulfide was added 28 g. (0.138 mole) of 4-nitrophenethylamine hydrochloride, during 2 hours. An additional 65 ml. of water was then added, the whole stirred and heated at 50° for 3.5 hours, cooled to 35° and treated with 14 ml. of ethyl chlorocarbonate. The heavy oil that separated was insoluble in ether or carbon tetrachloride.

Concentrated aqueous ammonia (60 ml.) was added periodically during about 8 hours of heating on the steam-bath. The oil which separated did not solidify. Upon stirring this oil with 100 ml. of boiling methanol, a light colored solid separated. The hot mixture was filtered to give 7 g. of crude product, which was purified by recrystallization from isopropyl alcohol.

1-(4-Aminophenethyl)-2-thiourea.—To a stirred refluxing mixture of 180 g. of iron filings, 585 ml. of water and 50 ml. of glacial acetic acid was added 20 g. (0.089 mole) of 1-(4-nitrophenethyl)-2-thiourea in small portions. After the mixture was stirred and refluxed for 4 hours, it was cooled and filtered. The insoluble material was extracted with 1 l. of 95% ethanol and filtered hot. The filtrate was concentrated and the residual liquid diluted with water to give the crude product. It was recrystallized from boiling water to give the pure product.

1-(4-Methoxyphenethyl)-2-thiourea.—Mixture A (1.6 g. of 4-methoxyphenethylamine,[24] 107 ml. of absolute ethanol and 3.5 ml. of water) and Mixture B (2.7 g. of mercuric acetate dissolved in 53 ml. of boiling absolute ethanol, the solution cooled and treated with 1.7 ml. of water) were mixed, 1.7 ml. of water was added and the whole added dropwise to 32.8 ml. of carbon disulfide which was stirred and refluxed. After the addition was complete, the mixture was stirred and refluxed 3 hours, filtered, the filtrate concentrated and treated with 10 ml. of concentrated aqueous ammonia and 10 ml. of saturated methanolic ammonia. The solid which formed was filtered and twice recrystallized from isopropyl alcohol.

1,3-Bis-(4-methoxyphenethyl)-2-thiourea.—A mixture of 4.2 g. of 4-methoxyphenethylamine, 100 ml. of 95% ethanol and 100 ml. of carbon disulfide was refluxed 6 hours, the solvents distilled and the residual oil treated with 5 ml. of concentrated aqueous ammonia and 5 ml. of saturated methanolic ammonia. The solid product was filtered and recrystallized from isopropyl alcohol to give the product.

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(21) Autenrieth and Hefner, *Ber.*, **58**, 2154 (1925).

(22) Colonna, *Pubbl. ist. chim. ind. Univ. Bologna*, 3 (1943); [*C. A.*, **41**, 754 (1947)].

(23) Goss, Hanhart and Ingold, *J. Chem. Soc.*, 250 (1927).

(24) Prepared in 53% yield by the lithium aluminum hydride reduction of 4-methoxy-ω-nitrostyrene. Nystrom and Brown, THIS JOURNAL, **70**, 3738 (1948), have reported that nitrostyrene is reduced by lithium aluminum hydride to β-phenethylamine.