since the copper salts were either liquids or were very soluble in ligroin. Generally the β -diketones were isolated by fractionation as described above in Method B.

(B) Lithium Amide.—Commercial lithium amide¹³ (0.6 mole) was suspended in 300 ml. of dry ether, and 0.6 mole of ketone in 50 ml. of dry ether was added. After refluxing for 15 minutes, a solution of 0.3 mole of the ester in 50 ml. of ether was added. Refluxing was continued for 3 hours and the reaction mixture was worked up as described above for acylations with sodium amide.

(C) Sodium Hydride.—Acylations with this reagent were carried out by the procedure described previously.³

(13) We are indebted to the Metalloy Corporation, Minneapolis, Minnesota, for a generous supply of lithium amide. Copper Enolate Derivatives.—To a sample of the β -diketone obtained by fractionation (about 5 g.) dissolved in an equal volume of methanol was added 100 ml. of a saturated solution of copper acetate (40 g. of copper acetate hydrate in 350 ml. water), and the mixture allowed to cool. If the copper enolate solidified, it was filtered by suction and recrystallized from 95% ethanol. If the enolate did not solidify, it was extracted from the aqueous portion with ligroin (b.p. 30–60°), the ligroin evaporated and the residue recrystallized from 95% ethanol. A second recrystallization from ethanol yielded pure samples, the melting points of which are given in the notes of Table I. In several instances the enolates were liquid and attempts to obtain solid derivatives failed.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS & CO.]

Some Derivatives of 4-Amino-2-hydroxybenzoic Acid (p-Aminosalicylic Acid)

BY LEONARD DOUB, J. J. SCHAEFER, L. L. BAMBAS AND CONSTANCE T. WALKER

A number of derivatives and analogs of 4-amino-2-hydroxybenzoic acid have been prepared for tuberculostatic test. None of those tested was as active as the parent compound either *in vitro* or *in vivo*.

The versatile intermediates 2-acetoxy-4-nitrobenzoyl chloride and 2-hydroxy-4-nitrobenzimino ether hydrochloride have been prepared and characterized.

Following the announcement by Lehman¹ of the effectiveness of p-aminosalicylic acid (PAS) in tuberculosis we prepared several derivatives of this compound to explore the possibility of improving its activity.²

The N-alkylated compounds (Table I, nos. 8, 9, 10, 11) were prepared by application of a modified Kolbe procedure on the appropriately substituted *m*-aminophenol. The orientation is assumed by analogy with the formation of PAS by the same process. Structure is confirmed in the case of the N-methyl derivative in that the compound from this procedure is identical with that obtained by methylation of PAS.³

The amidines (nos. 18, 19) were made by the catalytic reduction of the corresponding nitro compounds. These latter were in turn prepared from 2-hydroxy-4-nitrobenzonitrile through the imino ether (no. 36).

We were able to prepare in good yield the intermediate 2-acetoxy-4-nitrobenzoyl chloride. Reaction of this with the appropriate amines followed by reduction led to the amides listed in Table I (nos. 12, 13, 14, 15). A number of these are available by reaction of the amines with esters of PAS or 2-hydroxy-4-nitrobenzoic acid.^{4,5} The chloride has the advantage of course that it readily reacts with weak amines and also can be used in Schotten-Baumann procedures. In this respect an attempt was made to prepare in this series the analogs of sulfathiazole and sulfadiazine. Condensation of the acid chloride with the aminoheterocycles was successful (nos. 34, 35) but due to the extraordinary

(5) Schaefer and Doub, THIS JOURNAL, 71, 3564 (1949).

insolubility of the amino compounds the reduction and purification were not completed. It was not determined whether the nitrohydroxybenzoyl moiety was attached to the amino group or the ring nitrogen of the heterocycles.

In an attempt to obtain amides directly from PAS which is more available than the nitro acid, we prepared 4-carbethoxyamino-2-hydroxybenzoyl chloride. This intermediate reacted readily with amines and alcohols (nos. 27, 28, 29) but attempts to hydrolyze preferentially the carbethoxy group were unsuccessful.

The bacteriostatic activities⁶ of the derivatives listed in Table I in no case equal and in only a few cases approach that of the parent PAS. The appreciable activity of no. 8 may be a reflection of the ready metabolism of N-methyl groups generally,^{7,8} whereby PAS is generated. With this exception, substitution of the amino group results in drastic loss of in vitro activity. Similarly it appears that a free hydroxyl group is necessary. Variation of the carboxyl group with the exception of esterification results in greatly reduced activity. The high activity of the glycine amide (no. 14) is only apparent since it is abolished in the presence of serum. It would appear possible that the high activity of the methyl ester (no. 16) might arise because of hydrolysis to PAS in the course of the fourteen-day duration of the in vitro test.

Compounds nos. 2, 5, 6, 8, 12, 16, 17, 21, 22 and 23 were tested in mouse tuberculosis.⁶ These were essentially inactive except with nos. 5 and 17 where some slight activity was evident on the basis of full activity for PAS.

These data taken in conjunction with other re-

(8) Abbott and Lewis, *ibid.*, **131**, 479 (1939).

⁽¹⁾ Lehman, Lancet, 250, 15 (1946).

⁽²⁾ While this work was in progress some of these derivatives, especially esters and amides, have been reported by other workers. Representatives of these classes of compounds have been included in the present report, however, in order to present a more complete picture of the effect of structure on activity.

⁽³⁾ Rosdahl, Svensk Kem. Tid., 60, 12 (1948).

⁽⁴⁾ Jensen, Rosdahl and Ingvorsen, Acta Chem. Scand., 2, 220 (1948).

⁽⁶⁾ The data reported here, both *in vitro* and *in vivo*, were obtained by Dr. Guy P. Youmans, Department of Bacteriology, Northwestern University Medical School. The authors are deeply indebted to him for permission to use his results.

⁽⁷⁾ Gordon and Jackson, J. Biol. Chem., 110, 153 (1935).

TABLE I

p-AMINOSAL

		\mathbf{R}_2							
LICYLIC ACID	DERIVATIVES	R	∕R₃						

	No.	Ri	R₂	R	M.p., ^a °C,	Crystn. solvent	Formula	Carbo Calcd,	n, % Found	Hydro Calco	ogen, % d. Found	Nitrog Calcd.	en, % Foun d	Mg. %	10% serum added
3 No. OH COHT 235 (dec.) .	1	NH2	OH	CO2H ^c	145-146 (dec.)		C7H7NO3	••				9.15	9.14	0.078	(0,156)
4 CHICONH 0H COHP 23 (dec.) Dorane CHINO, 55 4 55 4 57 7 57.3 57.4 <td>2</td> <td>OH</td> <td>OH</td> <td>$\rm CO_2 H^d$</td> <td>217-218 (dec.)</td> <td></td> <td></td> <td>••</td> <td></td> <td></td> <td></td> <td></td> <td>• •</td> <td>10.0</td> <td>_</td>	2	OH	OH	$\rm CO_2 H^d$	217-218 (dec.)			••					• •	10.0	_
5 CHLCONH CHLCO Co.H Cu.H	3	NO2	он	CO ₂ H ^c	235 (dec.)			••						5.0	+
6 CH,CONH CH,CO ₂ CO,H ⁴ 188 -189 (dec.) ACOH Cult,HINO ₀ 5.7. 5.7 5.7	4	CH ₁ CONH	OH	CO ₂ H ^e	233 (dec.)	Dioxane	C ₉ H ₉ NO ₄	55 4	55 4	4.7	4.8	7.2	7.3	10.0	
7 CHRCONNI CHECO, COHI 196 (dec.) MENOA CallaNOA 53.0 54.2 4.0 5.0 5.2 5.4 9 CHANH OH COH 132-134 (dec.) m CallaNOA 62.2 62.4 5.7	5	C ₂ H ₅ CO ₂ NH	OH	CO2H	212 (dec.)	50% EtOH	C10H11NO5	53.3	53.6	4.9	5.1	6.2	6.3	10.0	+
8 CHNH OIL Coll J 125-126 (dec.) m CHIMOS 57.5 57.9 5.4 5.6 0.625 + 9 CH_MCHANH OH COHH 132-134 (dec.) m CHIMOS 62.2 62.4 5.7 5.7 10.0 + 10 CHIMOS OH COHH 132-134 (dec.) m CHIMOS 60.1 62.1 5.7 10.0 + 11 CHIMOS OH CONHCHACHAN 142-145 (dec.) m CHIMOS 67.1 68.4 67.7 5.3 5.3 1.4 1.1 0.312 - 14 NHr OH CONHCHCOH 121-123 Water CHIMOS 68.4 67.7 5.3 5.3 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.6 5.0 5.5 5.7 5.7 5.7 5.7	6	CH ⁸ CONH	CH3CO2	CO2H ^e	188-189 (dec.)	AcOH	C ₁₁ H ₁₁ NO ₅	55.7	55.3	4.7	4.8	5.9	5.9	2.5	+
9 CHi-CHICHNH OH COH 132-134 (dec.) m Cali NO0, 62.2 62.4 5.7 5.7 6.7 7.7 <th7.7< t<="" td=""><td>7</td><td>C₂H₅CO₂NH</td><td>CH₃CO₂</td><td>CO₂H</td><td>166 (dec.)</td><td>MeNO2</td><td>C12H13NO6</td><td>53.9</td><td>54.2</td><td>4.9</td><td>5.0</td><td>5.2</td><td>5.4</td><td></td><td></td></th7.7<>	7	C ₂ H ₅ CO ₂ NH	CH ₃ CO ₂	CO ₂ H	166 (dec.)	MeNO2	C12H13NO6	53.9	54.2	4.9	5.0	5.2	5.4		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	8	CH3NH	он	CO ₂ H ^f	125-126 (dec.)	172	C8H9NO2	57.5	57.9	5.4	5.6			0.625	+
11 $(C_{H1})_{N}$ OH $CO_{H}P$ $142 - 143$ (dec) "" $C_{H}H_{N}O_{1}$ 63 02.9 7.2 7.1 $$ 10° $$ 12 NH ₁ OH $CONH5^{h^{A}}$ $137 - 156$ Water $$	9	CH2=CHCH2NH	ОН	CO2H	132-134 (dec.)	m	C10H11NO3	62.2	62.4	5.7	5.7			10.0	+
12 NH1 OH CONH 6^A 127-198 Water CHIRNO1 06.1 0.2 9 2 1 1. 1.0 1. 13 NH4 OH CONHCHCOPH 121-698 Water CHIRNO1 0.0 6.2 6.7 6.4 15.6 16.0 14 NH4 OH CONHCHCOPH 215 (dec.) Ppt. from Eto CHIRNO1 6.8.4 6.7 5.3 5.3 12.3 12.4 2.5 + 15 NH4 OH CONHCHA 142-142 Water CHIRNO1 8.4 8.3 8.4 9.4 8.4 8.4 8.4 8.4	10	C ₆ H ₅ CH ₂ NH	OH	CO ₂ H	160-161 (dec.)	Dil, MeOH	C14H12NO2	69.1	69.1	5.4	5.5			10.0	+
12 NH ₁ OH CONH f^{A} 157-159 Water	11	(C2H3)2N	он	CO ₂ H ^g	142-145 (dec.)	m	C11H15NO3	63.1	62.9	72	71	• •		10 0	
14NH _F HCIOHCONHCH ₂ Co ₂ H215 (dec.)Ppt. from EtoOCHH ₀ NO,HCI43.843.94.54.54.511.411.10.312-15NH ₁ OHCONHCH ₁ 144-14550% EtOHCuHuNO,68.467.75.35.312.312.42.5+16NH ₁ OHCO ₂ CH ₂ /A121-122WaterCaHuNO,8.48.77.55.05.312.312.42.5+17NH ₁ OHCO ₂ CH ₂ /A114Abs. EtOHCaHuNO,8.47.77.52.5-18NH+CIOHCO ₁ CH ₂ /A114Abs. EtOHCaHuNO,21CI37.537.65.015.818.710.0-19NH ₂ HCIOHC(NII)NH-HCI277.5 (dec.)90% concel. HCICHINO,22CI37.557.15.45.015.710.0-20NH ₃ OHSONH ⁴ 151-15810.0+21NH ₃ CH ₃ OCO ₄ H137-15810.0+23NH ₃ CH ₂ OCO ₄ H139-140.5EtOHCaHuNO,300.059.88.74.74.710.0+24NH ₃ CH ₄ OCO ₄ H137-15810.0+ <td>12</td> <td>NH2</td> <td>OH</td> <td>CONH2^{e,h}</td> <td>157-159</td> <td>Water</td> <td></td> <td>• •</td> <td></td> <td>• • •</td> <td></td> <td></td> <td></td> <td>10.0</td> <td></td>	12	NH2	OH	CONH2 ^{e,h}	157-159	Water		• •		• • •				10.0	
15 NH ₁ OH CONTICH. 144-145 50% EtOH Culture Colligion 68.4 67.7 5.3 5.3 12.3 12.4 2.5 + 16 NH ₁ OH CO/CHr ^J 121-122 Water Culture Cu	13	NH2	OH	CONHC ₂ H ₅ ^h	142-143	Water	C9H12N2O2	60.0	59.9	6.7	6.4	15.6	16.0		
16 NH OH $CO_{C}CH_{1}^{-7}$ 121-122 Water C_{INNO} C_{INNO} C_{INNO} C_{IN} C_{INNO} C_{IN}	14	NH2 HCI	OH	CONHCH2CO2H	215 (dec.)	Ppt. from Et ₂ O	C#H10N2O4HC1	43.8	43.9	4.5	4.5	11.4	11.1	0.312	
17NHOH $CO_{C2H}t^{f,h}$ 114Abs. EOH $CH_{IINO_{1}}$ 50.760.06.16.47.77.52.5-18NH+HCIOH $C(NII)NH_{IH}HCI277-278 (dec.)90% concd. HCICH_{INO_{2}HCI}37.537.650.050.018.818.710.0-20NHOHC(NII)NH_{IH}HCI277 (dec.)90% concd. HCICH_{INO_{2}HCI}37.537.650.050.018.818.710.0-20NHOHSOJH4277 (dec.)10.0-21NHOHSOJH4151-15310.0-23NHCH9OCO1H4233-235 (dec.)CH1NO357.557.15.45.610.0-24NHHanCaH4SOD4H233-235 (dec.)CH1NO357.557.15.45.610.0-25NO3CH2CO3NHOHCOCI115 (dec.)EtcOCH4CINO444.444.52.52.65.85.910.0-26CH4CO3NHOHCOCI115 (dec.)EtcOCH4CINO444.444.52.55.65.85.9$	15	NH ₂	OH	CONHCoH	144-145	50% EtOH	C13H12N2O2	68.4	67.7	5.3	5.3	12.3	12,4	2.5	+
17NH1OH $C_{0}C_{1}H_{1}^{A}$ 114Abs. EtOH $C_{H_{1}NO_{1}}$ 59.760.06.16.47.77.52.5-18NHrHCIOH $C_{(NII)NH_{T}HCI}$ 277.278 (dec.)90% conc. HCI $C_{H_{1}NO_{2}HCI}$ 37.537.65.05.05.05.010.710.0-20NH2OH $C_{(NII)NH_{2}HCI}$ 272 (dec.)90% conc. HCI $C_{H_{1}NO_{2}HCI}$ 42.96.06.010.71.7.010.0-20NH4OHSOAH151-1531.0.0-21NH4OHCO ₂ H ⁴ 151-15810.0-24NH4HaNCallasCO ₂ H233-235 (dec.)""CultipaNoS60.059.84.74.710.0-25NOCOHCOCL115 (dec.)EtoDCultipaNoS60.059.84.74.710.0-26CHaCONHOHCOCL115 (dec.)EtoDCultipaNoS60.059.84.74.710.0-27CHaCONHOHCOCL115 (dec.)EtoHCultipaNoA56.15.75.75.75.85.910.0-28CHaCONHOHCOCL115 (dec.)EtoHCultipaNoA	16	NH ₂	OH	CO ₂ CH ₂ ^f	121-122	Water	C8H9NO2	• •				8.4	8.3	0.625	+
19NHr-HCIOHC(NH)NHC _H /r,HCI272 (dec.)90% concd. HCICallaNo-2HCI42.942.96.06.016.717.010.0-20NHaOHSO _h H ⁴ 151-63 <t< td=""><td>17</td><td>NH2</td><td>OH</td><td>CO₂C₂H₅^{f,h}</td><td>114</td><td>Abs. EtOH</td><td>C₉H₁₁NO₃</td><td>59.7</td><td></td><td>6.1</td><td>6.4</td><td>7.7</td><td>7.5</td><td>2.5</td><td>_</td></t<>	17	NH2	OH	CO ₂ C ₂ H ₅ ^{f,h}	114	Abs. EtOH	C ₉ H ₁₁ NO ₃	59.7		6.1	6.4	7.7	7.5	2.5	_
20NHaOHSOAH ⁴ 275 (dec.)<	18	NHrHCI	OH	C(NII)NH2·HCI	277-278 (dec.)	90% concd. HC1	C7H9N3O·2HC1	37.5	37.6	5.0	5.0	18.8	18.7	10.0	_
21NH1 22OH NH2SONNH2151-153 <th< td=""><td>19</td><td>NH1·HCI</td><td>OH</td><td>C(NH)NHC+H6·HC1</td><td>272 (dec.)</td><td>90% concd. HCl</td><td>C9H13N3O-2HCl</td><td>42.9</td><td>42.9</td><td>6.0</td><td>6.0</td><td>16.7</td><td>17.0</td><td>10.0</td><td>-</td></th<>	19	NH1·HCI	OH	C(NH)NHC+H6·HC1	272 (dec.)	90% concd. HCl	C9H13N3O-2HCl	42.9	42.9	6.0	6.0	16.7	17.0	10.0	-
21NHrOHSONHri151-183 <th< td=""><td>20</td><td>NH2</td><td>OH</td><td>SO₂H⁴</td><td>275 (dec.)</td><td></td><td></td><td>••</td><td></td><td></td><td></td><td></td><td></td><td>10.0</td><td></td></th<>	20	NH2	OH	SO ₂ H ⁴	275 (dec.)			••						10.0	
22NHSH $CO_{0}H^{k}$ 211-213 (dec.)10.023NHCH_{0}OCO_{1}H^{4}157-158CH_{10}NO_{6}57.557.15.45.610.0-24NHHNCAILSCO_H233-252 (dec.)mCultranos60.059.84.710.0-25NOCH_COCOCI56-57ACCl, pet. etherCaH_CINO_644.444.52.52.65.85.926C_H_CO_NHOHCOCCH115 (dec.)EtoOC_0H_0CINO_449.350.04.14.05.85.927C_H_CO_NHOHCOCCH115 (dec.)EtoHCultranos55.25.55.45.95.810.0-28C_H_CO_NHOHCOCH115 (dec.)EtOHCultranos61.064.35.45.95.810.0-29C_H_CO_NHOHCONHCAH187-188Dill. EtOHCultranos51.45.93.810.0	21	NH2	OH	SO2NH2 ^j	151-153									10.0	+
23NH1CH4OCO2hH157-158C4H9NO257.557.15.45.610.0-24NH1H1NC3H4SCO2H233-235 (dec.)mCH4U112N2OS60.059.84.710.0+25NO2CH4CO2,COCI56-57ACCI, pet. etherCH4U12N2OS60.059.84.74.710.0+26CH4CO2NHOHCOCI56-57ACCI, pet. etherCH4U2NO449.350.04.14.05.85.927CH4CO2NHOHCO2CH115 (dec.)EtsOC14H9CINO449.350.04.14.05.85.928C4H2O2NHOHCO2CH4139-140.5EtOHC14H14NO456.956.86.06.05.55.6 </td <td>22</td> <td>NH2</td> <td>SH</td> <td>CO_2H^k</td> <td>211-213 (dec.)</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>10.0</td> <td>_</td>	22	NH2	SH	CO_2H^k	211-213 (dec.)									10.0	_
111 111000110^{10} 253^{-253} (dc.) 253^{-253} (dc.) 1100010^{-1} 110000^{-1} 11000^{-1}	23	NH ₂	CH ₂ O	CO ₂ H ¹	157-158		C8H9NO3	57.5	57.1	5.4	56			10 0	-
25NO1CHaCO2COCI56-57AcCl, pet. etherCaHaCINO444.444.52.52.65.85.926CHLCO2NHOHCOCI115 (dec.)EtdOClaHaCINO449.350.04.14.05.85.927CHLCO2NHOHCOCCH1139-140.5EtOHClaHaCINO449.350.04.14.05.85.928C2H4CO2NHOHCO2C2H4139-140.5EtOHClaHaNO455.25.65.65.55.45.629CHLCO2NHOHCONCLGH4187-188DIL ECOHClaHaNO464.064.35.45.59.39.55.030NO4OHCONHCH2CO2H211-213 (dec.)WaterCaHaNO451.451.451.43.11.71.5	24	NH ₂	H2NC4H4S	CO ₂ H	233-235 (dec.)	771	C12H12N2O2S	60.0	59.8	4.7	4.7			10.0	+
26 $C_{4H_4CO_2NH}$ OH $COCl$ 115 (dec.) $EtgO$ $C_{10}H_{10}CINO_4$ 49.3 50.0 4.1 4.0 5.8 5.9 \dots \dots 27 $C_{4H_4CO_3NH}$ OH $C_{02}C_{4H_4}$ $139-140.5$ EtOH $C_{11H_{11}NO_6}$ 55.2 55.0 5.5 5.4 5.9 5.8 10.0 $ 28$ $C_{2H_4CO_2NH}$ OH $C_{02}C_{2H_4}$ $146-148$ EtOH $C_{12H_{11}NO_6}$ 56.9 56.8 $60.$ $60.$ 5.5 5.6 \ldots \ldots 29 $C_{2H_4CO_2NH}$ OH $CONHC_4H_4$ $187-188$ Dil. EtOH $C_{4H_4NO_4}$ 51.4 51.4 5.5 9.3 9.5 5.0 \ldots \ldots 30 NO_1OH $CONHC_2H_4$ $157-158$ 50% EtOH $C_{4H_4NO_4}$ 51.4 51.1 4.8 4.8 \ldots \ldots \ldots \ldots \ldots 31 NO_1OH $CONHCHC_2O_2H$ $211-213$ (dec.)Water $C_{4H_4NO_4$ 46.2 44.9 3.4 3.6 11.7 11.5 \ldots <td>25</td> <td>NO2</td> <td>CH2CO2</td> <td>COCI</td> <td>56-57</td> <td>AcCl, pet. ether</td> <td>C₂H₆CINO₅</td> <td>44.4</td> <td>44.5</td> <td>2.5</td> <td>2.6</td> <td>5.8</td> <td></td> <td></td> <td></td>	25	NO2	CH2CO2	COCI	56-57	AcCl, pet. ether	C ₂ H ₆ CINO ₅	44.4	44.5	2.5	2.6	5.8			
27 $C_{4}H_{6}CO_{2}NH$ OH $CO_{2}CH_{1}$ 139-140.5EtOH $C_{11}H_{14}NO_{6}$ 55.255.05.55.45.95.810.0-28 $C_{4}H_{6}CO_{2}NH$ OH $CO_{2}CH_{1}$ 146-148EtOH $C_{12}H_{14}NO_{6}$ 56.956.86.06.05.55.629 $C_{4}H_{6}CO_{2}NH$ OHCONHC_{4}H_{6}187-188Dil. EtOH $C_{14}H_{16}N_{2}O_{4}$ 64.064.35.45.59.89.55.030NO_1OHCONHC_4H_{6}157-15850% EtOH $C_{4}H_{10}N_{2}O_{4}$ 41.49.44.81.71.5<	26	C ₂ H ₅ CO ₂ NH	OH	COCI	115 (dec.)	Et ₂ O	C10H10CINO4	49.3	50.0	4.1	4.0	5.8	5.9		
29C4H4CO2NHOHCONHC4H5187-188Dil. EtOHC1eH14N2O464.064.35.45.59.39.55.030NO2OHCONHC2H6157-15850% EtOHC2H16N2O451.451.14.84.8<	27	C ₂ H ₅ CO ₂ NH	OH	CO ₂ CH ₁	139-140.5	EtOH	C11H13NO5	55.2	55.0	5.5	5.4	5.9	5.8	10.0	
30 NO1OHCONHCH6 $157-158$ 50% EtOHCoH10N2O4 51.4 51.1 4.8 4.8 \ldots <	28	C ₂ H ₆ CO ₂ NH	он	CO ₂ C ₂ H ₆	146-148	EtOH	C12H15NO5	56.9	56.8	6.0	6.0	5.5	5.6		
31NO2OHCONHCH2CO2H211-213 (dec.)WaterCaHaN2O445.044.93.43.611.711.532NO3OHCONHCH(CO2H)CH2CO2H171-172 (dec.)EtaO PhHC12H12N2O346.246.33.93.8<	29	C ₂ H ₅ CO ₂ NH	он	CONHC6H5	187-188	Dil. EtOH	C16H16N2O4	64.0	64.3	5.4	5.5	9.3	9.5	5.0	••
31NO2OHCONHCH2CO2H211-213 (dec.)WaterC0HsN2O6 45.0 44.9 3.4 3.6 11.7 11.5 \dots \dots 32NO3OHCONHCH(CO2H)CH2CH2CO3H $171-172$ (dec.)EtsO PhHCuH12N2O6 46.2 46.3 3.9 3.8 \dots \dots \dots \dots \dots 33NO3OHCONHCH5 $234-235$ (dec.) 50% EtOHCuH19N2O4 60.5 60.4 3.9 3.8 \dots \dots \dots \dots \dots 34NO3OHCO(HAN3) 289 (dec.)PhNC2 $C_{11H8N4O4}$ 50.8 50.7 3.1 3.2 21.5 21.2 \dots \dots 35NO2OHCO(C4H4N3) 289 (dec.)PhNC2 $C_{00H7N4O45}$ 45.3 45.5 2.7 2.7 21.5 21.2 \dots \dots 36NO2OHC(NH)OCH4sHc1C1190 (dec.) \dots $C_{00H7N4O45}$ 45.8 43.7 4.5 4.6 11.4 11.5 \dots \dots 37NO2OHC(NH)NH2 300 (dec)See prep. $C_{11}T_{N3O4}$ 46.4 46.6 3.9 3.8 23.2 23.3 10.0 $-$ 38NO3OHC(NH)NHC2H5 $218-220$ (dec.) 50% EtOH $C_{11}H_{0}N_{0}O5$ 51.7 51.9 5.5 20.1 20.6 10.0 $-$ 39NO3 p - p - $O_{2}N-C_{4}H-S$ CO3H $214-216$ MeOH $C_{11}H_{0}N_{0}O5$ 48.8 <	30	NO ₁	OH	CONHC ₂ H ₅	157-158	50% EtOH	CoH10N2O4	51.4	51.1	4.8	4.8				
33 NO1 OH CONHCaH5 234-235 (dec.) 50% EtOH ClaHioN204 60.5 60.4 3.9 3.9 2.5 34 NO2 OH CO(CaHAN3) 289 (dec.) PhNC2 ClaHioN204 60.5 60.4 3.9 3.9 2.5 35 NO2 OH CO(CaHAN3) 289 (dec.) PhNO2 CloH7N304S 45.3 45.5 2.7 2.7 15.1 15.4 2.5 + 36 NO2 OH C(NH)OC2H5HCI 190 (dec.) ClaHiN3020 HCI 43.8 43.7 4.5 4.6 11.4 11.5 37 NO2 OH C(NH)NH4 300 (dec.) See prep. CH1N304 46.4 46.6 3.9 3.8 23.2 23.3 10.0 - 38 NO2 OH C(NH)NH4 300 (dec.) See prep. CH1N304 46.4 46.6 3.9 3.8 23.2 23.3 10.0 - 38 NO2 OH C(NH)NHC2H3	31	NO2	OH	CONHCH2CO2H	211-213 (dec.)	Water	CoH8N2O6	45.0	44.9	3.4	3.6	11.7			
33 NO1 OH CONHCeH5 $234-235$ (dec.) 50% EtOH ClisHisN2O4 60.5 60.4 3.9 3.9 \ldots 2.5 \ldots 34 NO1 OH CO(CtHN3) 289 (dec.) PhNC3 ClisHisNAO4 50.8 50.7 3.1 3.2 21.5 21.2 \ldots \ldots 35 NO2 OH CO(CaH1N2S) 306 (dec.) PhNC3 ClisHisNAO4 50.8 50.7 3.1 3.2 21.5 21.2 \ldots \ldots 36 NO2 OH CO(CaH1N2S) 306 (dec.) PhNC3 ClisHisNAO4 45.8 45.5 2.7 2.7 15.1 15.4 2.5 $+$ 36 NO2 OH C(NH)OCH4+CI 190 (dec.) \ldots CaHn3O4+CI 43.8 43.7 4.5 4.6 11.4 11.5 \ldots \ldots 37 NO2 OH C(NH)NH2 $218-220$ (dec.) 50% EtOH CaHn3O5 48.8 49.0 2.5 2.6 8.8 8.8 8.8	32	NO ₂	ОН	CONHCH(CO ₂ H)CH ₂ CH ₂ CO ₂ H	171-172 (dec.)	Et ₂ O PhH	C12H12N2O8	46.2	46.3	3.9	3.8		• •		
35NO2OH $CO(C_{4}H_{1}N_{2}S)$ 306 (dec.)PhNO2 $C_{10}H_{7}N_{3}O_{4}S$ 45.345.52.72.715.115.42.5+36NO2OH $C(NH)OC_{2}H_{5}$ +HC1190 (dec.) $C_{4}H_{10}N_{2}O_{4}$ +HC143.843.74.54.611.411.537NO2OH $C(NH)NH_{4}$ 300 (dec).See prep. $C_{7}H_{7}N_{3}O_{4}$ 46.446.63.93.823.223.310.0-38NO2OH $C(NH)NHC_{2}H_{5}$ 218-220 (dec.)50% EtOH $C_{4}H_{11}N_{5}O_{4}$ 51.751.95.35.520.120.610.0-39NO2 p -ON-C_{4}H_{2}SCO2H214-216MeOH $C_{13}H_{6}N_{2}O_{5}$ 48.849.02.52.68.88.840NO2CHCOH156.5P.4P.4P.4P.4P.4P.4P.4P.4P.4P.4	33	NO	он	CONHC6H5	234-235 (dec.)	50% EtOH	C18H10N2O4	60.5	60.4	3.9	3.9			2.5	
36 NO2 OH C(NH)OC2H5+HC1 190 (dec.) C4H10N2O4+HC1 43.8 43.7 4.5 4.6 11.4 11.5 37 NO2 OH C(NH)NHa 300 (dec). See prep. CrH7N3O1 46 46.6 3.9 3.8 23.2 23.3 10.0 - 38 NO2 OH C(NH)NHC2H5 218-220 (dec.) 50% EtOH C4H11N3O1 51.7 51.9 5.3 5.5 20.1 20.6 10.0 - 39 NO2 p -ON-C4H4-S CO2H 214-216 MeOH C1146N2O5 48.8 49.0 2.5 2.6 8.8 8.8 40 NO2 CH CO CO H 156 FE PU CU NO 48.8 49.0 2.5 2.6 8.8 8.8	34	NO ₁	OH	CO(C4H4N3)	289 (dec.)	PhNC ₂	C11H8N4O4	50.8	50.7	3.1	3.2	21.5	21.2		
37 NO2 OH C(NH)NH2 300 (dec). See prep. C/H/N3O1 46 4 46.6 3.9 3.8 23.2 23.3 10.0 $-$ 38 NO2 OH C(NH)NHC2H3 218-220 (dec.) 50% EtOH C4H1N3O2 51.7 51.9 5.3 5.5 20.1 20.6 10.0 $-$ 39 NO2 p -O2N-C4H4-S CO2H 214-216 MeOH C13HaN3O5 48.8 49.0 2.5 2.6 8.8 8.8 40 NO2 CH CO CO H 156 FE PUL CU NO2 48.8 49.0 2.5 2.6 8.8 8.8	35	NO2	OH	$CO(C_3H_1N_2S)$	306 (dec.)	PhNO ₂	C10H7N3O4S	45.3	45.5	2.7	2.7	15.1	15.4	2.5	+
37 NO2 OH $C(NH)NH_1$ 300 (dec). See prep. $C_1H_7N_3O_1$ 46 4 46.6 3.9 3.8 23.2 23.3 10.0 - 38 NO2 OH $C(NH)NHC_2H_3$ 218-220 (dec.) 50% EtOH $C_8H_{11}N_3O_3$ 51.7 51.9 5.3 5.5 20.1 20.6 10.0 - 39 NO2 p -O2N-C4H4-S CO2H 214-216 MeOH C13H6N20S 48.8 49.0 2.5 2.6 8.8 8.8 40 NO2 CH CO CO H 156 F.6 PH C13H6N20S 48.8 49.0 2.5 2.6 8.8 8.8	36	NO ₂	он							4.5	4.6	11.4	11.5		-
38 NO1 OH $C(NH)NHC_2H_6$ 218-220 (dec.) 50% EtOH $C_{4}H_{11}N_4O_6$ 51.7 51.9 5.3 5.5 20.1 20.6 10.0 - 39 NO2 p -O2N-C_4H4-S CO2H 214-216 MeOH C14H4N20S 48.8 49.0 2.5 2.6 8.8 8.8 40 NO2 CH CO CO H 156 F. DU CU NO2 48.8 49.0 2.5 2.6 8.8 8.8	37	NO2	ОН	C(NH)NH						3.9	3.8	23.2	23.3		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	38	NO	ОН												-
	39	NO ₃	p-O2N-C6H4-S								2.6	8.8			
	40	NO ₂	CH ₃ CO ₁	CO ₂ H	156-156.5	PhH	C9H7NO6		48.3		3.3		••		••

^a Uncorrected. The decomposition points listed are extremely dependent on the rate of heating. These were obtained by immersing the capillary tube in the preheated-bath at approximately 10° below the melting point and bringing up to temperature rapidly. ^b This information kindly supplied by Dr. Guy P. Youmans, Department of Bacteriology, Northwestern University Medical School, Chicago, Illinois. The concentration given is that determined by serial dilution in media which just prevents growth of the tubercle bacil-lus strain H37Rv. + Denotes active; - denotes inactive, depending upon whether complete inhibition of growth occurs at 10 mg. % concentration. ^c Seidel and Bittner, Monalsk., 23, 415 (1902); Kondo, et al., J. Pharmacol. Soc. (Japan), 483, 355 (1922). ^d "Organic Syntheses," Coll. Vol. II, second edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 557. ^e Reference 11. ^f Reference 3. ^g Heyden, German Patent 50,835 (1890). ^k Reference 4. ⁱ Thorpe and Williams, Biochem. J., 35, 61 (1941). ^j Supplied by Dr. H. S. Mosher, Department of Chemistry, Stanford University, Palo Alto, California. ^k Feldt and Fritzsche, U. S. Patent 1,207,284 (1917). ^l Froelicher and Cohen, J. Chem. Soc., 131 (1909) ^c Theorem and double other billion of the second 121, 1652 (1922). " These compounds, due to instability or other reasons, were prevared for analysis by repeated solution in bicarbonate and precipitation by acid. followed by careful washing in water.

Tuberculostatic activity^b in synthetic media

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ports which have appeared⁹ point up the decided structural specificity associated with PAS activity. Considering further that this action apparently is shown only against tubercle bacilli¹⁰ it constitutes a remarkable example of specificity in chemotherapy.

Experimental

All melting points uncorrected.

4-Acetamino-2-hydroxybenzoic Acid.—4-Acetamino-2-acetoxybenzoic acid¹¹ (9.4 g.) was dissolved in 100 ml. of N After standing ten minutes the solution was fil-NaOH. tered, cooled, and acidified strongly with dilute hydrochloric acid. The solid was filtered off and dried over phosphorus pentoxide at *ca*. 1 mm. pressure for sixty hours; yield, 7.6 g., 98%; m.p. 231-232° dec.

2-Acetoxy-4-nitrobenzoic Acid.-2-Hydroxy-4-nitrobenzoic acid (80 g.) was suspended in 100 ml. of acetic anbenzoic acid (80 g.) was suspended in 100 ml. of acetic an-hydride. This was slowly brought to boil and refluxed until the solution was clear. After the addition of charcoal the solution was filtered through a sintered glass filter. The filtrate on cooling deposited light yellow crystals; filtered, yield 53 g., m.p. $152-154^{\circ}$. The filtrate was concentrated to half its volume and then diluted with water until cloudy, cooled, filtered; yield 12 g., m.p. $151-154^{\circ}$; combined yield 65 g., 66%. yield 65 g., 66%

2-Acetoxy-4-nitrobenzoyl Chloride .--- Phosphorus pentachloride (25 g.) was suspended in 103 ml. of acetyl chloride. 2-Acetoxy-4-nitrobenzoic acid (20 g.) was added in ca. 5-g. portions. Reaction ensued immediately after each addition. After all of the acid was added, the mixture was refluxed 1 hour. After cooling to room temperature, 100 ml. of dry petroleum ether was added. The solution was cooled in a Dry Ice-alcohol-bath; crystals formed on scratching. Filtered and washed with petroleum ether; yield 1st crop, 14 g., m.p. 57°. To the filtrate 50 ml. of petroleum ether

14 g., m.p. 57°. To the hitrate 50 ml. of petroleum ether was added and again cooled in a Dry Ice-bath, filtered; yield 5 g., m.p. 55-57°; combined yield 19 g., 88%. **4-Nitro-2-(4'-nitrophenylmercapto)-benzoic Acid.**—2-Amino-4-nitrobenzoic acid¹² (37 g.) was diazotized by the invert method with 15 g. of sodium nitrite in 100 ml. of concd. hydrochloric acid. This was added to a warm solu-tion prepared from 60 g. of sodium *c*-nitrophenol and tion prepared from 60 g. of sodium p-nitrothiophenol and 100 g. of sodium hydroxide in 500 ml. of water. The resulting solution was heated to boiling to complete reaction, The cooled and the precipitate removed by filtration. product was purified by solution in water, filtering from insoluble material, and reprecipitation with excess concd. hydrochloric acid. This product was dissolved in dilute bi-carbonate solution and the preceding purification repeated. The resulting precipitate was crystallized from dilute meth-anol. The yield of light yellow crystalline solid was 6.8 g. 4-Carbethoxyamino-2-hydroxybenzoic Acid.—PAS (75

g.) was suspended in 300 ml. of water, 40 g. of sodium hy-droxide in 200 ml. of water was added, and the solution cooled to 5° . Ethyl chlorocarbonate (125 g.) was added slowly with intermittent addition of 10 N NaOH as needed to keep slightly alkaline to phenolphthalein. The temperature was kept below 10° by external cooling and by addition of ice if necessary. This was diluted to 1 liter and warmed to approximately 20° to obtain a clear solution. On acidifying strongly the product precipitated, was filtered off and washed with water; yield 116 g. (quantitative), m.p. 202-204° dec.

4-Carbethoxyamino-2-hydroxybenzoyl Chloride.-4-Carbethoxyamino-2-hydroxybenzoic acid (225 g.) was suspended in 100 ml. of thionyl chloride and slowly heated on a steam-bath until clear, then refluxed until no more gas The solution, after the addition of charcoal, was evolved. was filtered, then cooled to crystallization and filtered; yield 175 g., 72%; m.p. 108-110° (dec.). A second crop was obtained by evaporation to dryness, dissolving in ether, treatment with charcoal, filtering and again evaporating to dryness; yield 60 g., 25%; m.p. 106-110° (dec.). 2-Acetoxy-4-carbethoxyaminobenzoic Acid.--2-Hy-

droxy-4-carbethoxyaminobenzoic acid (50 g.) was heated on the steam-bath with 250 ml. of acetic anhydride containing 1 ml. of pyridine until a clear solution was formed; cooled to crystallization, filtered; yield 58 g. (quantita-tive); m.p. 164-165° (dec.).

2-Hydroxy-4-nitrobenzimino Ethyl Ether Hydrochloride. -2-Hydroxy-4-nitrobertzonitrile¹⁸ (3.3 g.) was dissolved in 10 ml. of absolute ether and 3 ml. of absolute ethyl alcohol containing 1.8 g. of anhydrous hydrogen chloride. This was allowed to stand in a refrigerator $(ca. 4^{\circ})$ for 5 days, filtered, and washed with anhydrous ether; yield 4.5 g., 91%; m.p. 190° (dec.).

2-Hydroxy-4-nitrobenzamidine Hydrochloride.—2-Hy-droxy-4-nitrobenzimino ethyl ether hydrochloride (12.5 g.) was added to 25 ml. absolute ethanol containing 3 g. of anhydrous ammonia. The temperature was kept below 40° and the solution was allowed to stand two days, evaporated to dryness under vacuum, and crystallized from 50% hy-drochloric acid; yield 10 g., 91%, m.p. above 300°. For analysis a sample of the hydrochloride was dissolved in water and precipitated with amonia hydroxide. The free base was washed several times with water and dried. The product melted above 300° and was a deep red compound, very insoluble in all common solvents

N-Ethyl-2-hydroxy-4-nitrobenzamidine.-Imino ether hydrochloride (12.5 g.) was added to 25 ml. of absolute ethyl alcohol containing 25 ml. of ethylamine and allowed to stand two days. This was evaporated to dryness under vacuum, dissolved in water, treated with charcoal and filtered. The solution, on being made alkaline to pH 9

nitered. The solution, on being made alkaline to pH 9 with ammonium hydroxide and cooling, deposited crystals. These were filtered off and recrystallized from dilute alcohol; yield 9 g., 85%, m.p. 222-223° (dec.). General Procedures. I. Kolbe-Schmidt Synthesis.
(a) Aqueous Modification.—The following procedure for the preparation of PAS is convenient in that the use of pressure is avoided. The yield is moderate compared to that obtainable by application of carbon dioxide pressure. obtainable by application of carbon dioxide pressure.

m-Aminophenol (436.5 g.) and 2 kg. of potassium bicar-bonate, after mixing, were covered with 5.2 l. of water in a closed flask fitted with a condenser, an inlet tube, and an exit tube. Under a slight positive exit pressure (30 cm. water) carbon dioxide was bubbled through the solution. The mixture was heated on the steam-bath (internal temperature 96°) for 90 hours; cooled and acidified with a large excess of concd. HCl; yield of white-to-gray hydrochloride, 38-41%; m.p. 221-223° (dec.) (rapid heating). The use of 30-50 p.s.i. carbon dioxide pressure led to 50-60% yields of comparable material.

Application of this procedure to the appropriately sub-stituted *m*-aminophenol led to low yields (5-20%) of compounds nos. 8, 10, 11 (isolated as free compound, not as hydrochloride). The intermediate m-allylaminophenol for no. 9, prepared by the action of allyl bromide on *m*-amino-phenol, could not be obtained in a state of satisfactory purity. The crude oil was submitted to this Kolbe procedure giving an acid which after extensive purification amounted to ca. 5% yield over-all.

In every case above the majority of unreacted m-aminophenol could be recovered by extraction.

I (b)—Compound 10 was obtained by the usual Kolbe-Schmidt process using the dry solium salt of *m*-benzyl-aminophenol at 130° under 1500 p.s.j. carbon dioxide pres-sure for twelve hours; yield *ca*. 10%. II. Formation of Amides.—The very reactive acid chlo-rides (2-acetoxy-4-nitrobenzoyl chloride and 4-carbethoxy-

amino-2-hydroxybenzoyl chloride) were readily converted to amides or esters by following usual procedures depending upon the amine or alcohol used: (a) By reaction with large excess of amine or alcohol. Compounds nos. 27, 28, 29, 30 and 33; yields essentially quantitative except no. 29 gave 63%. (b) By the Schotten-Baumann procedure with the acid chloride dissolved in ether or chloroform: compounds nos. 31 and 32; 98 and 74% yield, respectively. (c) By nos. 31 and 32; 98 and 74% yield, respectively. (c) By reaction with equivalent amounts of amine (aminohetero-cycles) in pyridine: compounds nos. 34 and 35; yields 42 and 87%, respectively. (d) With compound no. 33 the acetoxy group was not removed when the reaction mixture may diluted with water prior to exiding the acetox. was diluted with water prior to acidification. A step was introduced involving solution in excess dilute sodium hy-droxide at room temperature. The compound dissolved immediately with loss of this group, and acidification re-covered the hydroxyl compound.

(13) Borsche, Ann., 390, 1 (1912).

⁽⁹⁾ Lehman, Svenska Läkartidn., 43, 2029 (1946)

⁽¹⁰⁾ Sievers, *ibid.*, **43**, 2041 (1946).
(11) Drain, et al., J. Chem. Soc., 1498 (1949).

⁽¹²⁾ Blanksma and Hoegen, Rec. trav. chim., 65, 333 (1946).

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 , $HO_2CCH_2CH_2CONH$, $(CH_3)_2N$, H_2N , O_2N , NC, NaO_3S , $C_2H_5O_2S$, H_2NO_2S , $(C_2H_5)_2NCH_2CH_2O$, HO, $-OCH_2O-$, HO_2C , CH_3 , C_2H_5O , HO_2CCH_2O , CH_4O , $n-C_2H_7O$, $i-C_2H_7O$, $n-C_4H_9O$, $i-C_3H_7$, $t-C_4H_9$, Cl and I groups; the lateral substituents included CH_3 , C_2H_8 , CH_5 , CH_5 , CH_2 ; $CHCH_2$: $n-C_4H_9$, $i-C_4H_9$, and C_6H_5 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.⁸ 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 Young⁵ 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 recently²; 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 CH₃CONH·, HO₂CCH₂CH₂-CONH·, (CH₃)₂N·, H₂N·, CH₂:CHCH₂NHCSNH·, NC·, NaO₃S·, CH₃SO₂·, C₂H₅SO₂·, n-C₃H₇SO₂·,

(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 aud 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. $(C_2H_5)_2NCH_2CH_2O$, HO_2CCH_2O , CH_3O , C_2H_5O , $n-C_3H_7O$, $n-C_4H_9O$, HO, OCH_2O , HO_2C , CH_3 , $i-C_3H_7O$, $n-C_4H_9O$, HO, OCH_2O , HO_2C , CH_3 , $i-C_3H_7$, $i-C_4H_9$, F_3C , Cl and I groups; the lateral substituents included the CH_3 , C_2H_5 , CH_2 : $CHCH_2$, $n-C_4H_9$, $i-C_4H_9$ and C_6H_5 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 3thiosemicarbazone 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 Pulvermacher⁷ 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 oxidation⁸ of 4-methoxy- and 4aminobenzaldehyde 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 derivative⁹

(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).