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The Synthesis of Compounds for the Chemotherapy of Tuberculosis. VI. Hydrazine Derivatives

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A number of hydrazides, hydrazones, and hydrazide-hydrazone compounds were prepared for screening in tuberculosis in mice. Only 2′-isopropylpicolinyl hydrazine and 1,1′-methylene-bis-(picolinyl hydrazide) hydrochloride were of the same order of activity as picolinyl hydrazine. The majority were inactive.

Continuing the investigations previously reported from these laboratories by some of us on heterocyclic thiosemicarbazides,[1] hydroxamic acids,[2] thioamides,[3] and by H. H. Fox on hydrazides,[4] we have prepared some further miscellaneous hydrazides (Table I and Experimental section) and benzylidene hydrazides (Table II). The general method of preparation of the compounds is given in the tables. Where more detailed description was thought desirable, it is given in the Experimental section.

CHEMOTHERAPEUTIC RESULTS

Of special interest were the methylene homolog (4-pyridineacetic acid hydrazide) and ethylene homolog (4-pyridinepropionic acid hydrazide) of isonicotinyl hydrazine. The former still retains some activity when tested in experimental tuberculosis in mice[5] while the higher homolog is inactive under the conditions of the test.

2′-Isopropylpicolinyl hydrazine and 1,1′-methylene - bis - (picolinyl hydrazide) dihydrochloride showed a similar order of activity to the parent picolinyl hydrazine.[4]

The remaining hydrazides, hydrazones, and the mixed hydrazine-hydrazone compounds of Table II were inactive.

Acknowledgment. We are indebted to Drs. E. Grunberg and R. J. Schnitzer for the animal screening of the compounds reported, and to Dr. Al Steyermark and his associates for the microanalyses.

EXPERIMENTAL[6]

1H-imidazo[d]pyridazine-4,7(5H,6H)-dione. Dimethyl 4,5-imidazole carboxylate (25 g.) was refluxed with 9 g. of 85% hydrazine hydrate in propanol-2 for 90 minutes. The solvent was removed under a vacuum and the residue was crystallized from ethanol; yield, 20 g., m.p. >260°.

Anal. Calc'd for $C_5H_4N_4O_2$: N, 36.8. Found: N, 36.7.

4-Hydroxy-3-quinoline carboxylic acid p-tolylsulfonylhydrazide. A solution of 53 g. of crude 4-hydroxy-3-quinolinecarboxylic acid hydrazide, 55 g. of *p*-toluenesulfonic acid chloride, and 250 ml. of pyridine was held at 25° for 24 hours. The pyridine was removed by vacuum-distillation and the residue was dissolved in acetone to which one liter of water was added. The product precipitated out on standing and was recrystallized from ethanol; yield, 81 g., m.p. 247–248°.

Anal. Calc'd for $C_{17}H_{15}N_3O_4S$: C, 57.1; H, 4.2. Found: C, 57.0; H, 4.3.

Attempts to decompose this compound in the McFadyen-Stevens method[7] gave low yields of compounds bound by thiosemicarbazide which we were unable to purify.

Methyl 2-pyridyl ketone hydrazone. A mixture of 40 g. of 2-acetylpyridine and 80 ml. of 85% hydrazine hydrate was refluxed for 1 hour. The excess hydrazine was removed *in vacuo* and the residue was crystallized from ethanol; yield 30 g., m.p. 77–79°.

Anal. Calc'd for $C_7H_9N_3$: C, 62.1; H, 6.7. Found: C, 62.3; H, 6.8.

3,5-Dimethyl-4-pyrazole carboxylic acid hydrazide. A solution of 100 ml. of 85% hydrazine hydrate and 20 g. of ethyl 3,5-dimethyl-4-isoxazole carboxylate was refluxed for 5 hours. Ring opening, rearrangement, and ring closure gave the pyrazole ring derivative which crystallized on cooling from the reaction solution. Recrystallization from water gave a peach-colored compound; yield, 5 g., m.p. 245–246°.

Anal. Calc'd for $C_6H_{10}N_4O$: C, 46.6; H, 6.5; N, 36.3. Found: C, 45.7; H, 6.5; N, 36.2.

Nicotinaldehyde hydrazone hydrochloride stannous chloride complex. A mixture of 3-cyanopyridine (60 g.), 550 g. of anhydrous fused $SnCl_2$, and 1500 ml. of the dry diethyl ether of diethylene glycol was saturated with hydrogen chloride gas. After complete solution and standing for 18 hours, 2 liters of 80° water containing 40 g. of hydrazine hydrate was added. On cooling, 161 g. of the tin complex crystallized. The product was recrystallized from boiling water; yield, 161 g., m.p. 218–222° (dec.).

Anal. Calc'd for $C_6H_7N_3 \cdot HCl \cdot SnCl_2$: N, 12.1. Found: N, 12.2.

Nicotinaldehyde hydrazone hydrochloride. Nicotinaldehyde hydrazone hydrochloride stannous chloride complex (174 g.) was dissolved in 2 liters of hot water and the tin was removed with hydrogen sulfide. The solution freed of SnS was concentrated to 500 ml., brought with ammonium

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[1] Gardner, Smith, Wenis, and Lee, *J. Org. Chem.*, **16**, 1121 (1951); Fox, *J. Org. Chem.*, **17**, 555 (1952); Gardner, Smith, Wenis, and Lee, *J. Am. Chem. Soc.*, **74**, 2106 (1952); Gardner, Wenis, and Lee, *J. Org. Chem.*, **20**, 976 (1955); Grunberg and Leiwant, *Proc. Soc. Exptl. Biol. Med.*, **77**, 47 (1951).

[2] Gardner, Wenis, and Lee, *J. Am. Chem. Soc.*, **73**, 5455 (1951).

[3] Gardner, Wenis, and Lee, *J. Org. Chem.*, **19**, 753 (1954).

[4] Fox and Gibas, *J. Org. Chem.*, **17**, 1653 (1952); Fox, U. S. Patent 2,596,069 (May 6, 1952).

[5] Grunberg and Schnitzer, *Quart. Bull. Sea View Hosp.* **13**, 3 (1952).

[6] All melting points are corrected.

[7] McFadyen and Stevens, *J. Chem. Soc.*, 584 (1936).

TABLE I

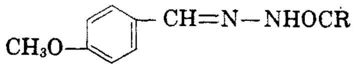
HYDRAZINE DERIVATIVES R—NHNH₂

R—	Formula	Cryst. from	M.p., °C.	Yield, %	Color	Analyses					
						Calc'd			Found		
						C	H	N	C	H	N
4-Amino-2-chlorobenzoyl-	$C_7H_8ClN_3O$	Ethanol	179–180	70	Colorless	—	—	22.7	—	—	23.0
1-Phenyl-5-oxo-2-pyrazoline-3-carbonyl-	$C_{10}H_{10}N_4O_2$	Dil. ethanol	235–236	10	Reddish-brown	55.0	4.6	—	54.6	4.7	—
3,5-Diiodo-4-hydroxybenzoyl-	$C_7H_6I_2N_2O_2$	Ethanol	192–194	40	Colorless	—	—	7.0	—	—	6.8
2-Mercapto-4-imidazolecarbonyl-HCl	$C_4H_6N_4OS \cdot HCl$	Dil. ethanol	>250	54	Colorless	24.7	3.6	—	24.8	3.7	—
5-Amino-2-methyl-4-oxazolecarbonyl-	$C_5H_8N_4O_2$	Dil. ethanol	256–257	50	Buff	—	—	35.9	—	—	36.3
2-Amino-4,5-thiazole dicarbonyl-di-	$C_5H_8N_6O_2S$	Water	>300	40	Colorless	—	—	38.9	—	—	38.6
2-Hydroxy-3-cyano-6-methylisonicotinyl-	$C_8H_8N_4O_2$	[a]	>270	70	Yellow	50.0	4.2	—	50.1	4.5	—
4-Hydroxy-3-quinolinecarbonyl-	$C_{10}H_9N_3O_2$	Ethanol	>270	65	Colorless	59.0	4.5	20.7	58.7	4.3	20.5
2-Chloro-6-nitro-4-quinolinecarbonyl-	$C_{10}H_7ClN_4O_3$	Ethanol	>250	40[b]	Yellow	45.1	2.6	—	45.5	2.7	—
4-Pyridineacryloyl-HCl	$C_8H_9N_3O \cdot HCl$	[c,d]	140–143 (dec.)	95	Lt. yellow	—	—	21.0	—	—	21.9
4-Pyridinepropionyl-2HCl[d]	$C_8H_{11}N_3O \cdot 2HCl$	Dil. ethanol	224–225	75	Colorless	40.2	5.5	—	40.3	5.4	—
4-Pyridineacetyl-2HCl[d,e]	$C_7H_9N_3O \cdot 2HCl$	Ethanol	213–215	52	Colorless	—	—	18.8	—	—	19.2[f]
6-Ethylmercaptonicotinyl-	$C_8H_{11}N_3OS$	Methanol	126–127	70	Yellow	48.7[g]	5.6	21.6	49.0	5.6	21.3
(2-Methyl-3-hydroxy-4-aminomethyl-5-pyridinemethyl)-HBr	$C_8H_{14}N_4O \cdot HBr$	Dil. ethanol	167–169 (dec.)	71	Buff	[h]	—	—	—	—	—
4-Carboxynicotinyl-	$C_7H_7N_3O_3$	Dil. ethanol	>300	68	Yellow	—	—	7.7	—	—	7.7[i]
6-Methyl-2,4-pyridinedicarbonyl-di-	$C_8H_{11}N_5O_2$	Ethanol	239–240 (dec.)	94	Colorless	—	—	6.7	—	—	6.7[i]
6-Methyl-2-hydroxynicotinyl-	$C_7H_9N_3O_2$	[j]	>300	86	Colorless	50.1	5.4	8.4	49.6	4.8	7.6[i]
1,6-Dihydro-3-methyl-6-oxo-pyridazine-acetyl-	$C_7H_{10}N_4O_2$	Ethanol	199–201	91	Colorless	46.2	5.5	—	46.3	5.2	—
1,6-Dihydro-6-oxo-1-methyl-3-pyridazine-carbonyl	$C_6H_8N_4O_2$	Water	227–228	90	Colorless	42.9	4.8	—	42.8	4.8	—
1,6-Dihydro-6-oxo-pyridazine-3-carbonyl-1-acetyl-di-	$C_7H_{10}N_6O_3$	Water	227–228	95	Ivory	37.1	4.5	—	37.4	4.4	—
1,6-Dihydro-6-oxo-1-pyridazineacetyl-	$C_6H_8N_4O_2$	Water	208–209	77	Colorless	42.9	4.8	—	42.9	4.4	—
3-Pyridineacetyl-2HCl	$C_7H_9N_3O \cdot 2HCl$	Dil. ethanol	212–213	86	Colorless	37.6[k]	—	18.7	38.1	—	17.9
2-Hydroxy-4-ethoxymethyl-6-methyl-nicotinyl-	$C_{10}H_{15}N_3O_3$	Water	220–222	69	Colorless	—	—	18.7	—	—	18.1

[a] The free base was desalted using a 5% acetic acid solution. [b] Prepared from the acid chloride and hydrazine in pyridine. [c] The acrylic salt was purified by extraction with ethanol. [d] The free base has been reported. [Katritzky, *J. Chem. Soc.*, 4038 (1954)]. [e] The free base has been reported. [Yale, Losee, Perry, and Bernstein, *J. Am. Chem. Soc.*, **76,** 2208 (1954)]. [f] Calc'd for the dihydrochloride: Cl, 31.7. Found: Cl, 31.2. [g] Calc'd: S, 16.2. Found: S, 15.8. [h] Calc'd: Br, 30.3. Found: Br, 29.7. [i] One nitrogen by Kjeldahl. [j] The sodium salt was precipitated using carbon dioxide. [k] Carbon was obtained by a wet combustion procedure. Calc'd: Cl, 31.7. Found: Cl, 31.1.

TABLE II[a]

1-RCO-2-(4-METHOXYBENZYLIDENE)HYDRAZINES



RCO—	Formula	Cryst. from	M.p., °C.	Yield, %	Color	Analyses Nitrogen Calc'd	Analyses Nitrogen Found
4-Amino-2-methyl-5-pyrimidylcarbonyl-	$C_{14}H_{15}N_5O_2$	Ethanol	227–228	79	Colorless	24.5	24.1
5-Methyl-3-isoxazolecarbonyl-	$C_{13}H_{13}N_3O_3$	Ethanol	188–189	87	Creamy white	16.2	16.0
4-Amino-2-hydroxybenzoyl-	$C_{15}H_{15}N_3O_3$	Water	217	28	Lt. brown	14.7	14.6
Nicotinyl-	$C_{14}H_{13}N_3O_2$	Water	115	50	Colorless	16.5	16.0
Pyrazinylcarbonyl-	$C_{13}H_{12}N_4O_2$	Ethanol	223–224	84	Pale cream	21.9	22.0
Picolinyl-	$C_{14}H_{13}N_3O_2$	Ethanol	144–145	95	Colorless	16.5	16.6

[a] All compounds in Table II were prepared by heating the hydrazide with *p*-methoxybenzaldehyde in an appropriate solvent, usually ethanol-water.

hydroxide to *p*H 7, and the separated oil was extracted with ether. The ether was removed and the oily residue was dissolved in ethanol containing hydrogen chloride gas. Addition of ether precipitated an oil which crystallized on standing. Recrystallization from ethanol gave a yellow product; yield, 19 g., m.p. 132–134°.

Anal. Calc'd for $C_6H_7N_3{\cdot}HCl$: C, 45.6; H, 5.1. Found: C, 45.3; H, 5.2.

Nicotinaldehyde-2-pyridyl hydrazone trihydrochloride stannous chloride complex. A solution of 3-cyanopyridine (48 g.), reduced by the Stephen procedure as described above, and hydrolyzed in hot water in the presence of 70 g. of 2-pyridylhydrazine, gave 300 g. of wet, crude tin complex. A small quantity of the crude complex was recrystallized as a pale yellow compound from hot water; m.p. 195–197°.

Anal. Calc'd for $C_{11}H_{10}N_4{\cdot}3HCl{\cdot}SnCl_2$: C, 19.3; H, 1.9; N, 8.2. Found: C, 20.2; H, 2.1; N, 8.0.

Microanalysis of this type of compound by the usual method ruins the combustion tube and the wet combustion method for carbon is recommended.

Nicotinaldehyde 2-pyridylhydrazone. The crude nicotinaldehyde 2-pyridylhydrazone obtained (300 g. wet) was freed of tin as previously described for nicotinaldehyde hydrazone above. The acid solution precipitated a white product on adjustment to *p*H 7 with concentrated ammonium hydroxide. The colorless compound was recrystallized from aqueous ethanol; yield, 47 g.; m.p. 177–179°.

Anal. Calc'd for $C_{11}H_{10}N_4$: C, 66.6; H, 5.1. Found: C, 66.3; H, 5.1.

Ethyl isonicotinate diiodide. Potassium iodate (18 g.) in 160 ml. of water was dropped into a solution of 37.7 g. of ethyl isonicotinate and 63 g. of iodine in 200 ml. of ethanol.[8] To complete the reaction, the solution was heated at reflux for two hours. On cooling, the red periodide crystallized which was recrystallized from ethanol; yield, 30 g., m.p. 108–109° (dec.). This compound decomposed in boiling ethanol, liberated iodine on drying in a vacuum, and liberated iodine slowly at 25°.

Anal. Calc'd for $C_8H_9I_2NO_2$: I, 62.7. Found: I, 62.4.

Trihydrazine dihydriodide. Ethyl isonicotinate diiodide (26 g.) was treated at 25° with 25 g. of 85% hydrazine hydrate in 400 ml. of propanol-2. An immediate reaction occurred with separation of the white cyclic compound previously prepared by another method by Curtius and Schulz[9] having a m.p. of 90°. Our colorless product was recrystallized from propanol-2-methanol; yield, 16 g.; m.p. 91–92° (dec.). On heating on a spatula the compound exploded with a white flash and evolution of iodine vapors. The compound also decomposed on standing at 0° and due to its instability was not investigated further. Good analyses were difficult to obtain as vacuum-drying resulted in decomposition with loss of iodine.

Anal. Calc'd for $(N_2H_4)_3{\cdot}2HI$: N, 23.9; I, 72.2. Found: N, 22.8; I, 71.8.

The hydrazine salt of 2,5-pyridine dicarboxylic acid monohydrazide. Isocinchomeronic acid monoethyl ester (9.5 g.), 85% hydrazine hydrate, and 15 ml. of ethanol were refluxed 1 hour. The colorless hydrazine salt crystallized (9.1 g.), m.p. after repeated crystallizations from aqueous ethanol, 178–179° (dec.).

Anal. Calc'd for $C_7H_7N_3O_3{\cdot}N_2H_4$: C, 39.4; H, 5.2. Found: C, 39.6; H, 4.8.

5-Hydroxy-7-methylpyrido[3,4d]pyridazine-1,4(2H,3H)-dione. 2-Hydroxy-6-methylcinchomeronic acid diethyl ester (16 g.), 85% hydrazine hydrate (28 g.), and water (28 ml.) were heated together 1–2 hours at 80° and diluted with 1000 ml. of water. After filtering and concentrating, 4.8 g. of a yellow product was obtained on cooling. Concentration and dilution of the mother liquor with alcohol gave an additional 3.7 g. of product. The combined fractions were purified by leaching several times with hot water, m.p. >300°.

Anal. Calc'd for $C_8H_7N_3O_3$: N, 21.8. Found: N, 21.4.

1,6-Dihydro-1-isopropylideneamino-6-oxo-nicotinic acid hydrazide or 1-(1-amino-1,6-dihydro-6-oxonicotinyl)-2-isopropylidene hydrazine. Methyl coumalate (40 g.), 42% hydrazine hydrate (40 ml.), and water (300 ml.) were reacted together first in the cold and then briefly at 50°. After filtering, the cooled solution was concentrated *in vacuo* to a syrup. On refluxing with acetone and chilling, 20.0 g. of product separated which was triturated with hot nitromethane to give 8.3 g. of a light yellow product, m.p. 153° (dec.).

Anal. Calc'd for $C_9H_{12}N_4O_2$: C, 51.9; H, 5.8. Found: C, 51.3; H, 5.3.

2-Aminothiazole[4,5d]pyridazine-4,7-(5H,6H)dione. Diethyl 2-amino-4,5-thiazole-dicarboxylate (27.5 g.), 85% hydrazine hydrate (46 g.), and 46 ml. of water were heated

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[8] Sheahan, Wilkinson, and MacLagan, *Biochem. J.*, **48**, 188 (1951).

[9] Curtius and Schulz, *J. prakt. Chem.*, [2], **42**, 521 (1890); Mellor, J. W., *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, **8**, 324–5, Longmans, Green & Co., New York, 1928. (Note: Mellor structural formula is incorrect).

together at 80° for 2 hours. Heating was continued for one-half hour after adding additional 85% hydrazine hydrate (23 g.). The reaction mixture was dissolved in 650 ml. of water from which upon cooling 19.8 g. of a yellow product separated. It was leached several times with boiling water; 9.4 g. remained undissolved, m.p. >330°.

Anal. Calc'd for $C_5H_4N_4O_2S$: N, 30.8. Found: N, 31.3.

4,5,7-Trimethylpyrido[3,4-d]pyridazin-1(2H)-one. Ethyl 2,6-dimethyl-3-acetyl-4-pyridinecarboxylate (21.7 g.), 85% hydrazine hydrate (16.5 g.), and 16 cc. of ethanol were heated at 80° for 15 minutes. The colorless product crystallized immediately; yield, 9.5 g., m.p. 235–237°.

Anal. Calc'd for $C_{10}H_{11}N_3O$: C, 63.5; H, 5.9; N, 22.2. Found: C, 63.9; H, 5.5; N, 22.7.

Hydrazone of 3-hydroxy-5-hydroxymethyl-2-methyl isonicotinaldehyde hydrochloride. Pyridoxal (from 100 g. of pyridoxine) was converted *in situ* to the hydrazone by buffering with sodium acetate (239 g.) and addition of 85% hydrazine hydrate (84 g.). After warming for 30 minutes at 80° and cooling, the product crystallized; yield, 61.1 g. A 25-g. portion was converted to the hydrochloride by solution in 1.5 equivalents of 1 *N* hydrochloric acid, decolorizing with charcoal and concentrating to a smaller volume; yield, 19.0 g. of a yellow product, m.p. >285°.

Anal. Calc'd for $C_8H_{11}N_3O_2 \cdot HCl$: Cl, 16.8. Found: Cl, 16.7.

2'-Isopropyl-1-picolinylhydrazine. 2-Isopropylidene-1-picolinylhydrazine (25 g.), m.p. 105–106°,[10] prepared by the reaction of acetone on picolinylhydrazine, was reduced in ethanol using platinum oxide as a catalyst and hydrogen at 500 p.s.i. at 25°. The catalyst was removed by filtration and the solution was concentrated to an oil. The oily residue was washed with *n*-hexane. This residue was semi-crystalline and was crystallized from *n*-hexane. The colorless product, $RCONHNHCH(CH_3)_2$, was soluble in water; yield, 9.5 g., m.p. 75–77°.

Anal. Calc'd for $C_9H_{13}N_3O$: N, 23.6. Found: N, 23.1.

1,1'-Methylenebis(2-picolinylhydrazine)dihydrochloride. Picolinylhydrazine (20 g.), 200 ml. of water, and 10 ml. of 37% formaldehyde solution were mixed. A small amount of precipitate formed at first but redissolved. The solution was concentrated to a syrup and dissolved in ethanol; on addition of HCl-ethanol and ether a colorless product crystallized; yield, 8 g., m.p. 205–206°.

Anal. Calc'd for $C_{13}H_{14}N_6O_2 \cdot 2HCl$: C, 43.5; H, 4.5; Cl, 19.8. Found: C, 43.5; H, 4.7; Cl, 19.5.

The *free base* was soluble in water. Oxidation of the dihydrochloride with alkaline hydrogen peroxide solution used up five equivalents of base which confirms the structure, $RCONHNHCH_2NHNHCOR \cdot 2HCl$.

4-Oxo-4H-pyran-2-carboxylic acid hydrazide monohydrate. Coumalic acid (28 g.) was converted to the acid chloride using hot thionyl chloride. The solid was obtained by washing the residue from the reaction with benzene-petroleum ether (1:3) yield, 8.5 g., m.p. 65–70°. The acid chloride thus obtained was reacted with 99% hydrazine (4 g.) in dry ether, initially at 4°, followed by gradually raising the reaction temperature to the reflux temperature for 1 hour. The solution was concentrated to a solid and the residue was extracted with warm concentrated hydrochloric acid. The filtered acid solution was neutralized with ammonium hydroxide to *p*H 4. The pale yellow product separated; yield, 21.7 g., m.p. >300°.

Anal. Calc'd for $C_6H_6N_2O_3 \cdot H_2O$: C, 41.9; H, 4.7. Found: C, 41.7; H, 4.5.

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[10] Offe, Seifken, and Domagk, *Z. Naturforsch.*, **76**, 462 (1952).