[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Chemotherapy of Experimental Tuberculosis. VIII. The Synthesis of Acid Hydrazides, their Derivatives and Related Compounds[1,2]

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The preparation of a large number of aliphatic, aromatic and heterocyclic carboxylic acid hydrazides, their derivatives and related compounds which were tested for antituberculous activity is described. The majority of the compounds prepared were derivatives of isonicotinic acid hydrazide.

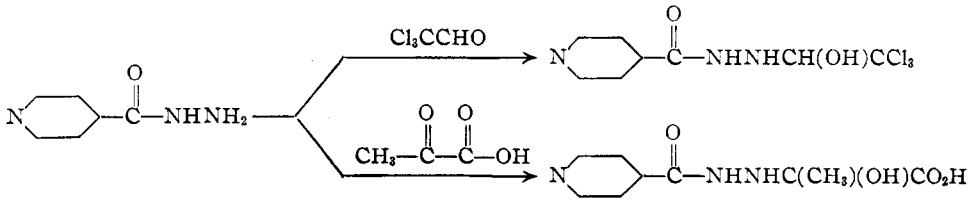
An extensive program has been underway in these laboratories for about five years on the synthesis of a variety of compounds for evaluation as antituberculous agents.[3] At this time we are reporting the synthesis of acid hydrazides, their derivatives and related compounds which were prepared in order to establish the structural requirements for activity within the isonicotinic acid hydrazide (Nydrazid)[4] lead and to discover any new leads.

The acid hydrazides were prepared by refluxing the methyl or ethyl ester with an excess of 85% hydrazine hydrate, either with or without the use of ethanol as additional solvent. In general, the reactions were spontaneous and exothermic and with some methyl esters proceeded to completion without external heating.

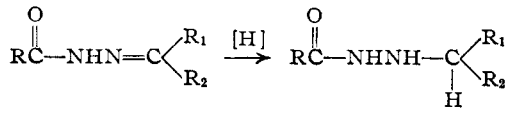
Since no outstanding antituberculous activity was found among the aliphatic, alicyclic and aromatic carboxylic acid hydrazides, the emphasis in this program has been on hydrazides of heterocyclic carboxylic acids. We are now describing the hitherto unreported hydrazides of the following heterocyclic acids: 3-aminoisonicotinic, 2-bromoisonicotinic, 3-chloroisonicotinic, 2,6-diisobutoxyisonicotinic, 2-fluoroisonicotinic, 2-isobutoxyisonicotinic, 3-methylisonicotinic, 2-methyl-3-hydroxy-5-hydroxymethylisonicotinic, isonicotinic-1-oxide, 2-mercaptoisonicotinic-1-oxide, 2-pyridylacetic, 4-pyridylacetic, isonipecotic, 1 acetylisonipecotic, 1-dimethylcarbamylisonipecotic, 1-methylisonipecotic, furanacrylic, 2,5-furandicarboxylic, di-5-nitro-2-furoic, tetrahydro-2-furoic, 3-thiopheneacetic, 3-thiophenecarboxylic, 3,4-dimethyl-2,5-thiophenedicarboxylic, di-2-pyrrolecarboxylic, 1-methyl-2-pyrrolecarboxylic, 3-indoleacetic, 2-pyrrolidone-5-carboxylic, 2,3-pyrazinedicarboxylic, di-4-pyrimidinecarboxylic, cinchoninic, 2-benzimidazolecarboxylic, 2-mercapto-5-imidazolecarboxylic, 2-amino-4-thiazolecarboxylic, 2-benzothiazolecarboxylic, 2-amino-1,3,4-thiadiazole-5-acetic and 2-methyl-5,6-dihydro-4H-pyran-3-carboxylic acid.

In the benzoic acid series, the following new nuclear substituted hydrazides are now being described: 3-amino-, 2,4-dichloro-, 3,4-dichloro-, 4-*t*-butyl-, 2-hydroxyl-4-amino- and 2-hydroxy-5-chlorobenzoic acid. Hydrazides were also prepared from the following acids: 4-chlorophenoxyacetic, 4-hydroxyphenylacetic, ethylmercaptoacetic, sorbic, cyclopentanecarboxylic and cyclohexanecarboxylic acid. All of these compounds along with other pertinent data are given in Table I.

The acid hydrazides reacted with aliphatic or aromatic aldehydes and ketones to give hydrazones. Acyl hydrazones were prepared also with D-ribose, L-arabinose, D-glucose, D-galactose, D-levulose, D-2-aminoglucose, D-maltose, D-glucosone and streptomycin A. All of the hydrazones are listed in Table II. In this large series of compounds, anomalous behavior was noted only with chloral and with pyruvic acid which gave the hydrazine derivatives.



The —C=N— linkage of the hydrazones could be selectively hydrogenated in water, alcohol or acetic acid as solvent with a platinum catalyst, under 50 lb. pressure. This procedure afforded a convenient synthesis of another type of 1,2-disubstituted hydrazine.



Related hydrazines were prepared by the reaction of an acid chloride with 1,1-dimethylhydrazine or phenylhydrazine; by the reaction of a Grignard reagent with an acylhydrazone

(1) Presented before the Division of Medicinal Chemistry at the 122nd Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 14–19, 1952.

(2) The antituberculous activities of various carboxylic acid hydrazides, their derivatives and related compounds are reported in the following papers: V, J. Bernstein, W. A. Lott, B. A. Steinberg and H. L. Yale, *Am. Rev. Tuber.*, **65**, 357 (1952); VI, J. Bernstein, W. P. Jambor, W. A. Lott, F. Pansy, B. A. Steinberg and H. L. Yale, *ibid.*, **67**, 354 (1953); VII, J. Bernstein, W. P. Jambor, W. A. Lott, F. Pansy, B. A. Steinberg and H. L. Yale, *ibid.*, **67**, 366 (1953).

(3) For the previous chemical paper in this series, see J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins and W. A. Lott, THIS JOURNAL, **73**, 906 (1951).

(4) Registered Trade Mark.

TABLE I

ACID HYDRAZIDES

Solvent for crystallization: A, toluene; B, 95% ethanol; C, benzene; D, dimethylformamide; E, water; F, 80% ethanol; G, xylene; H, aq. ethanol; I, butanol; J, abs. ethanol; K, ethyl acetate; L, hexane; M, abs. ethanol–ether; N, *n*-propyl alcohol; O, methanol; P, hexane–ethanol; Q, aq. dimethylformamide; R, 72% *n*-propyl alcohol; S, hexane–benzene; T, acetone; U, 75% methanol; V, acetonitrile; W, methanol–ether; X, isopropyl alcohol; Y, acetic acid; Z, heptane; AA, *n*-propyl alcohol–ether; BB, aq. acetic acid; CC, isopropyl alcohol–hexane; DD, 60% methanol; EE, abs. ethanol–ethyl acetate; FF, toluene–heptane; GG, chloroform.

Acid hydrazide	Yield, %	Solvent	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1-Acetylisonipecotic[a,b]	63	K	124–126	$C_8H_{16}N_2O_2$	51.86	8.05	22.67	51.66	8.14	22.54
β-Alanine··2HCl	61	B	222–224 d.	$C_3H_{11}Cl_2N_3O$			23.87[c]			23.51
3-Aminobenzoic	51	GG	91–92[d]	$C_7H_9N_3O$	55.60	6.00	27.79	55.62	5.92	27.55
2-Amino-4-thiazolecarboxylic	52	B	186–188	$C_4H_6N_4OS$	30.36	3.82	35.41	30.42	3.87	35.64
3-Aminoisonicotinic	62	N	190–192	$C_6H_8N_4O$	47.35	5.30	36.83	47.59	5.00	36.70
2-Amino-1,3,4-thiadiazole-5-acetic	29	E	180–181	$C_4H_7N_5OS$	27.74	4.07	40.45	27.81	4.01	40.48
2-Benzimidazolecarboxylic	85	R	239–240	$C_8H_8N_4O$	54.53	4.58	31.80	54.59	4.93	31.89
2-Benzothiazolecarboxylic[a]	81	N	173–174	$C_8H_7N_3OS$	49.73	3.75	21.75	49.84	3.85	21.96
2-Bromoisonicotinic[a]	62	B	177–178	$C_6H_6BrN_3O$	33.37	2.79	19.45	33.47	2.98	19.30
4-*t*-Butylbenzoic	62	A	118–120	$C_{11}H_{16}N_2O$	68.70	8.39	14.57	69.01	8.15	14.52
3-Chloroisonicotinic	10	N	145–147	$C_6H_6ClN_3O$	42.00	3.52	24.50	42.21	3.64	24.64
4-Chlorophenoxyacetic	97	B	157–158	$C_8H_9ClN_2O_2$	47.89	4.52	13.97	47.92	4.67	14.31
5-Chlorosalicylic	65	R	213–215	$C_7H_7ClN_2O_2$	45.05	3.78	15.02	45.23	4.03	15.14
Cinchoninic	68	G	137–139[f]	$C_{10}H_9N_3O$	64.15	4.85	22.45	63.79	4.96	22.67
Cyclohexanecarboxylic	79	A	154–155	$C_7H_{14}N_2O$	59.12	9.92	19.70	60.05	9.66	19.95
Cyclopentanecarboxylic	34	P	110–111	$C_6H_{12}N_2O$	56.21	9.44	21.86	56.29	9.63	21.81
L-Cysteine	48	[g]	86–89	$C_3H_9N_3OS$	26.65	6.71	31.08	26.33	6.32	30.87
2,4-Dichlorobenzoic	40	H	163–164	$C_7H_6Cl_2N_2O$	41.00	2.95	13.66	41.20	3.18	13.88
3,4-Dichlorobenzoic	46	B	167–168	$C_7H_6Cl_2N_2O$	41.00	2.95	13.66	40.94	3.21	13.54
2,6-Diisobutoxyisonicotinic[a]	74	J	95–97	$C_{14}H_{23}N_3O_3$	59.76	8.24	14.92	59.86	8.40	15.05
1-Dimethylcarbamylisonipecotic[a]	43	P	148–149	$C_9H_{18}N_4O_2$	50.45	8.93	26.15	50.61	8.66	26.00
3,4-Dimethyl-2,5-thiophenedicarboxylic	75	E	247–249	$C_8H_{12}N_4O_2S$	42.09	5.30	[q]	42.16	5.49	
Ethylmercaptoacetic··HCl[a]	26	M	134–135	$C_4H_{11}ClN_2OS$[h]			16.43			16.64
2-Fluoroisonicotinic	60	CC	110–112	$C_6H_6FN_3O$	46.45	3.90	27.09	46.66	3.89	26.83
2-Furanacrylic	69	C	108–110	$C_7H_8N_2O_2$	55.25	5.30	18.42	54.96	5.45	18.61
2,5-Furandicarboxylic	78	N	220–222	$C_6H_6N_4O_3$	39.13	4.38	30.42	38.97	4.33	30.18
2-Hydroxy-4-aminobenzoic	47	B	198–200 d.	$C_7H_9N_3O_2$	50.29	5.42	25.13	50.31	5.63	25.40
4-Hydroxyphenylacetic	56	F	200–202	$C_8H_{10}N_2O_2$	57.82	6.07	16.86	57.89	6.31	17.11
3-Indoleacetic	48	P	138–139	$C_{10}H_{11}N_3O$	63.48	5.86	22.21	63.89	5.91	21.78
2-Isobutoxyisonicotinic[a]	93	E	122–123	$C_{10}H_{15}N_3O_2$	57.39	7.22	20.08	57.70	7.11	20.27
Isonicotinamidoacetic[a]	63	J	189–190	$C_8H_{10}N_4O_2$	49.48	5.19	28.85	49.50	5.49	28.86
Isonicotinic··$CH_3SCH_2CH(NH_2)$-CO_2H salt[a]	95	[e]	227–230 d.	$C_{11}H_{18}N_4O_3S$	46.14	6.34	19.58	46.05	6.15	19.86
Isonicotinic-1-oxide[a]	70	B	218–219 d.	$C_6H_7N_3O_2$	47.05	4.61	27.43	46.94	4.52	27.63
Isonicotinic··4,2-$H_2N(HO)C_6H_3CO_2H$ salt[i]	65	B	142–143 d.	$C_{13}H_{14}N_4O_4$	53.74	4.86	19.31	54.19	5.00	19.87
Isonicotinic··4-$CH_3C_6H_4SO_3H$ salt[a]	75	B	169–170	$C_{13}H_{15}N_3O_4S$	50.48	4.88	13.58	50.54	4.81	13.50
Isonicotinic··CH_3I[a]	77	O	210–212	$C_7H_{10}IN_3O$			15.06[j]			15.23
Isonipecotic··2HCl	35	[g]	242–244 d.	$C_6H_{15}Cl_2N_3O$			19.44[k]			19.27
2-Mercapto-5-imidazolecarboxylic	40	H	280–281	$C_4H_6N_4OS$	30.37	3.82	35.43[o]	30.53	3.89	35.62
2-Mercaptoisonicotinic-1-oxide··H_2-NNH_2 salt[a]	80	[g]	184–185 d.	$C_6H_{11}N_5O_2S$	33.17	5.10	32.24	33.07	5.33	32.50
2-Methyl-5,6-dihydro-4H-pyran-3-carboxylic[a]	30	B	171–173	$C_7H_{12}N_2O$	53.82	7.75	17.94	54.03	7.42	18.10
3-Methyl-2-furoic	77	C	103–105	$C_6H_8N_2O_2$	51.41	5.76	20.00	51.54	5.93	20.26
2-Methyl-3-hydroxy-5-hydroxymethylisonicotinic	50	V	184–186	$C_8H_{11}N_3O_3$	48.72	5.62	21.31	48.84	5.55	21.52
3-Methylisonicotinic[l]	68	P	125–126	$C_7H_9N_3O$	55.60	6.00	27.80	55.49	5.98	27.66
1-Methylisonipecotic	61	C	143–144	$C_7H_{15}N_3O$	53.47	9.61	26.73	53.73	9.40	26.74
1-Methyl-2-pyrrolecarboxylic	15	C	119–121	$C_6H_9N_3O$	51.78	6.52	30.20	51.96	6.76	30.38
2-(4-Nitrobenzenesulfonamido)-4-thiazolecarboxylic··H_2O[a]	60	E	228–229 d.	$C_{10}H_{11}N_5O_6S_2$	33.23	3.07	19.38	33.31	3.46	19.31
5-Nitro-2-furoic	70	B	170–171	$C_5H_5N_3O_4$	35.10	2.95	24.56	35.32	3.17	24.52
Phenoxyacetic	66	E	110–111	$C_8H_{10}N_2O_2$	57.81	6.06	16.86	57.88	6.37	16.99
2-Phenyl-8-chlorocinchoninic	71	O	224–226	$C_{16}H_{12}ClN_3O$	64.62	4.07	14.11	64.78	4.10	13.90
2,3-Pyrazinedicarboxylic	73	[g]	>300	$C_6H_6N_6O_2$			42.86[m]			42.99

TABLE I (*Continued*)

Acid hydrazide	Yield, %	Solvent	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Pyridylacetic	44	N	120–122	$C_7H_9N_3O$	55.60	6.00	27.80	55.65	6.30	27.90
4-Pyridylacetic	40	C	85–86	$C_7H_9N_3O$	55.60	6.00	27.80	55.49	6.24	27.64
4-Pyrimidinecarboxylic	32	B	144–145	$C_5H_6N_4O$	43.47	4.38	40.56	43.49	4.49	40.72
2-Pyrrolecarboxylic	65	B	227–228	C_5H_7NO	47.99	5.64	33.58	48.22	5.91	33.33
2-Pyrrolidone-5-carboxylic	80	EE	107–109 d.	$C_5H_9N_3O_2$	41.95	6.33	29.35	41.67	6.38	29.13
β-Resorcylic	67	B	239–240	$C_7H_6N_2O_3$	50.00	4.80	16.66	50.28	4.68	16.70
Sorbic··HCl·H_2O	16	M	185–188 d.	$C_6H_{13}ClN_2O_2$	39.89	7.25	15.51	39.99	7.47	15.25
Tetrahydro-2-furoic	75		Oil[n]	$C_5H_{10}N_2O_2$	46.15	7.75	21.54	46.19	7.64	21.36
Tetrahydro-2-thiophenecarboxylic	18	C	81–83	$C_5H_{10}N_2OS$			19.17[p]			19.29
3-Thiophenacetic	55	C	83–84	$C_6H_6N_2OS$	46.13	5.16	17.94	46.44	5.29	18.11
3-Thiophenecarboxylic	50	C	122–123	$C_5H_6N_2OS$	42.23	4.25	19.70	42.10	4.35	19.65

[a] See Experimental part. [b] Prepared by the reaction of methyl 1-acetylisonipecotate and hydrazine, employing the General Procedure for the preparation of hydrazides. [c] *Anal.* Calcd.: Cl, 40.27. Found: Cl, 40.66. [d] A. Struve and R. Radenhausen, *J. prakt. Chem.*, [2] **52**, 241 (1895), report a m.p. of 77°. [e] Freeze-dried material. [f] E. Thielepape, *Ber.*, **59B**, 127 (1922), reports a m.p. of 154.5°. [g] Not recrystallized. [h] *Anal.* Calcd.: Cl, 20.78. Found: Cl, 20.77. [i] The preparation was similar to that of *p*-toluenesulfonic acid salt. [j] *Anal.* Calcd.: I, 45.46. Found: I, 45.85. [k] *Anal.* Calcd.: Cl, 32.76. Found: Cl, 32.78. [l] The 3-methylisonicotinic acid was generously supplied by Reilly Tar and Chemical Co. [m] *Anal.* Calcd.: neut. equiv. (titration in glacial acetic acid with $HClO_4$), 196.17. Found: neut. equiv., 184.4. [n] B.p. 125–160° (1 mm.). [o] *Anal.* Calcd.: S, 20.22. Found: S, 20.06. [p] *Anal.* Calcd.: S, 21.93. Found: S, 22.00. [q] *Anal.* Calcd.: S, 14.05. Found: S, 14.16.

TABLE II

HYDRAZONES

Hydrazone	Method	Yield, %	Solvent[a]	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Acetaldehyde isonicotinyl	[b]	35	P	175–176	$C_8H_9N_3O$	58.88	5.56	25.75	59.10	5.60	25.60
4-Acetamidobenzaldehyde 2-furoyl	C(a)[b]	75	Y	>300	$C_{14}H_{13}N_3O_3$	61.98	4.83	15.49	61.76	5.01	15.77
4-Acetamidobenzaldehyde isonicotinyl	C(a)	89	D	292–294	$C_{15}H_{14}N_4O_2$	63.82	4.98	19.85	64.18	5.29	19.41
Acetone 2-furoyl	B	75	C	92–94	$C_8H_{10}N_2O_2$	57.81	6.07	16.86	57.87	6.06	16.80
Acetone isonicotinyl	B[b]	83	T	159–160	$C_9H_{11}N_3O$	61.00	6.26	23.72	61.17	6.15	23.73
Acetone isonicotinyl-1-oxide	B	46	T	184–186	$C_9H_{11}N_3O_2$	55.95	5.74	21.75	55.94	5.91	21.43
Acetone nicotinyl	B	73	T	141–142	$C_9H_{11}N_3O$	61.00	6.26	23.72	61.32	6.22	23.75
Acetone picolinyl	B	68	S	95–96	$C_9H_{11}N_3O$	61.00	6.26	23.72	61.06	6.48	23.60
Acetone 2-thiophenecarboxyl	B	85	Z	105–106	$C_8H_{10}N_2OS$			15.34[l]			15.51
Acetylacetone monoisonicotinyl	A	49	T	131–133	$C_{11}H_{13}N_3O_2$	60.26	5.92	19.16	60.38	6.03	18.97
Acetylacetone bis-(isonicotinyl)	[b]	44	E	254–256	$C_{17}H_{18}N_4O_2$	60.34	5.36	24.84	60.02	5.14	24.70
D-2-Aminoglucose isonicotinyl··HCl	D	89	[c]	124–127 d.	$C_{12}H_{19}ClN_4O_5$			16.74[d]			16.10
4-Isoamoxybenzaldehyde isonicotinyl	C(a)	17	U	172–173	$C_{18}H_{21}N_3O_2$	69.43	6.80	13.49	69.40	6.94	13.31
L-Arabinose isonicotinyl	C(b)	50	K	169–170	$C_{11}H_{15}N_3O_5$	49.07	5.61	15.60	49.10	5.96	15.61
Benzaldehyde isonicotinyl	A	89	K	193–194	$C_{13}H_{11}N_3O$	69.32	4.92	18.66	69.65	4.99	18.60
4-Isobutoxybenzaldehyde isonicotinyl	C(a)	75	K	177–178	$C_{17}H_{19}N_3O_2$	68.67	6.44	14.13	68.95	6.43	13.93
Isobutyraldehyde 2-furoyl	A	74	A	100–101	$C_9H_{12}N_2O_2$	59.98	6.71	15.55	60.29	6.69	15.35
Isobutyraldehyde isonicotinyl	A[b]	74	C	135–136	$C_{10}H_{13}N_3O$	62.81	6.85	21.97	62.75	6.96	21.75
Isobutyraldehyde 2-thiophenecarboxyl	A	71	C	113–114	$C_9H_{12}N_2OS$			14.35[m]			14.58
Cyclohexanone isonicotinyl	A	75	E	163–164	$C_{12}H_{15}N_3O$	66.33	6.95	19.34	66.21	6.93	19.51
Cyclohexanone 2-thiophenecarboxyl	A	90	O	142–143	$C_{11}H_{14}N_2OS$			12.60[n]			12.77
4-Diethylaminobenzaldehyde isonicotinyl	C(a)	68	H	180–181	$C_{17}H_{20}N_4O$	68.88	6.80	18.91	68.94	6.63	18.68
Diethyl ketone isonicotinyl	B	91	S	85–87	$C_{11}H_{15}N_3O$	64.36	7.37	20.48	64.24	7.17	20.23
4-Dimethylaminobenzaldehyde isonicotinyl	C(a)	57	K	200–201	$C_{15}H_{16}N_4O$	67.14	6.01	20.88	67.40	5.97	20.79
Dimethylglyoxal bis-(isonicotinyl)	A	60	[e]	>300	$C_{16}H_{16}N_6O_2$	59.25	4.97	25.91	59.60	4.83	25.49
D-Galactose isonicotinyl	C(b)	21	K	161–163 d.	$C_{12}H_{17}N_3O_6$	48.15	5.72	14.04	48.22	5.90	13.96
D-Glucose 4-aminobenzoyl	C(b)	40	[f]	180–181	$C_{13}H_{19}N_3O_6$	49.84	6.11	13.42	49.62	6.37	13.51
D-Glucose benzoyl	C(b)	42	O	187–189 d.	$C_{13}H_{18}N_2O_6$	52.35	6.08	9.39	52.21	6.08	9.12
D-Glucose 2-furoyl	C(b)[b]	24	O	174–175 d.	$C_{11}H_{16}N_2O_7$	45.82	5.59	9.72	46.14	5.69	9.53
D-Glucose isonicotinyl	C(b)	48	O	162–163	$C_{12}H_{17}N_3O_6$	48.15	5.73	14.04	48.70	6.12	13.65
D-Glucose 3-nitrobenzoyl	C(b)	22	O	169–170	$C_{14}H_{21}N_3O_9$	44.80	5.64	11.20	44.65	5.09	11.67
D-Glucose 2-thiophenecarboxyl	C(b)	36	O	190–192 d.	$C_{11}H_{16}N_2O_6S$	43.40	5.30	9.21	43.56	5.40	9.37
D-Glucosone bis-(isonicotinyl)	C(b)	16	O	204–206 d.	$C_{18}H_{20}N_6O_6$	51.91	4.84	20.18	51.47	4.65	19.90
Glyoxal bis-(isonicotinyl)	A	89	[f]	>300	$C_{14}H_{12}N_6O_2$	56.74	4.08	28.36	56.83	4.26	28.17
Hendecanal isonicotinyl	[b]	52	M	82–83	$C_{17}H_{27}N_3O$	70.55	9.41	14.52	70.85	9.39	14.23
Δ9-Hendecenal isonicotinyl	A	25	T	67–68	$C_{17}H_{25}N_3O$	71.04	8.75	14.62	71.47	8.74	14.72
Heptaldehyde isonicotinyl	A	60	S	96–97	$C_{13}H_{19}N_3O$	66.92	8.21	18.01	67.23	8.14	17.78
Heptaldehyde isonicotinyl-1-oxide	A	28	P	146–147	$C_{13}H_{19}N_3O_2$	62.62	7.68	16.85	63.10	7.88	16.45
Heptaldehyde 2-thiophenecarboxyl	A	63	Z	84–85	$C_{12}H_{18}N_2OS$			11.75[o]			11.81
D-Levulose isonicotinyl··$2H_2O$	C(b)	60	AA	64–67 d.	$C_{12}H_{21}N_3O_8$	42.98	6.31	12.53	43.58	6.27	12.26
D-Maltose isonicotinyl··H_2O	D	88	[c]	80–85	$C_{18}H_{29}N_3O_{12}$	45.09	6.10	8.77	45.41	6.73	8.37
Methyl amyl ketone isonicotinyl	B	24	S	82–83	$C_{13}H_{19}N_3O$	66.92	8.21	18.01	67.15	8.28	17.78
Methyl amyl ketone 2-thiophenecarboxyl	B	80	C	100–101	$C_{12}H_{18}N_2OS$			11.75[p]			11.43
3-Methylcyclohexanone isonicotinyl	A	67	E	133–134	$C_{13}H_{17}N_3O$	67.50	7.41	18.17	67.70	7.59	18.03
4-Methylcyclohexanone isonicotinyl	A	66	H	174–175	$C_{13}H_{17}N_3O$	67.50	7.41	18.17	67.73	7.61	18.20
4-[N-Methyl-N-(diethylaminoethyl)]-aminobenzaldehyde isonicotinyl	C(a)	53	H	80–81	$C_{20}H_{29}N_5O_2$	64.66	7.87	18.86	65.16	7.96	18.86

TABLE II (*Continued*)

Hydrazone	Method	Yield, %	Solvent[a]	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Methyl ethyl ketone isonicotinyl	B	80	L	75–77	$C_{10}H_{13}N_3O$	62.80	6.85	21.98	63.19	7.27	21.66
Methylglyoxal bis-(isonicotinyl)	A	55	[e]	>300	$C_{14}H_{14}N_6O_2$	58.11	4.55	27.11	57.65	4.84	26.84
Pyruvic acid 2-furoyl	A	85	E	168–169 d.	$C_8H_8N_2O_4$	48.97	4.11	14.29	49.01	4.38	14.56
D-Ribose isonicotinyl	D	64	[c]	[q]	$C_{11}H_{15}N_3O_5$	49.07	5.61	15.60	48.83	6.13	15.29
Streptomycin A 4-aminobenzoyl-·3HCl	D	86	[c]	198–200 d.	$C_{28}H_{49}Cl_3N_{10}O_{12}$			16.99[g]			15.37
Streptomycin A benzoyl-·3HCl	D	88	[c]	195–197 d.	$C_{28}H_{48}Cl_3N_9O_{12}$			15.58[h]			14.65
Streptomycin A isonicotinyl-·3HCl	D[b]	100	[c]	202–204 d.	$C_{27}H_{47}Cl_3N_{10}O_{12}$			17.29[i]			16.23
Streptomycin A 3-nitrobenzoyl-·3HCl	D	84	[c]	184–186 d.	$C_{28}H_{47}Cl_3N_{10}O_{14}$			16.38[j]			15.06
Streptomycin A 2-thiophenecarboxyl-·3HCl	D	85	[c]	198–200 d.	$C_{26}H_{46}Cl_3N_9O_{12}S$			15.46[k]			15.10
Succinaldehyde bis-(isonicotinyl)	[b]	37	K	202–203	$C_{16}H_{16}N_6O_2$	59.25	4.97	25.91	59.20	5.06	26.16
4-Thiacyclohexanone isonicotinyl	A	68	K	176–177	$C_{11}H_{12}N_2OS$	56.14	5.56	17.88	55.85	5.63	18.12

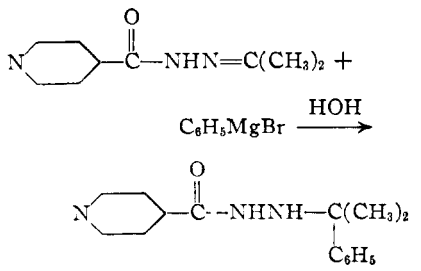
[a] See Table I. [b] See Experimental Part. [c] Freeze-dried material. [d] *Anal.* Calcd.: Cl, 10.59. Found: Cl, 10.14. [e] Reprecipitated. [f] Not recrystallized. [g] *Anal.* Calcd.: Cl, 12.91. Found: Cl, 12.14. [h] *Anal.* Calcd.: Cl, 13.14. Found: Cl, 12.06. [i] *Anal.* Calcd.: Cl, 13.13. Found: Cl, 12.21. [j] *Anal.* Calcd.: Cl, 12.45. Found: Cl, 12.27. [k] *Anal.* Calcd.: Cl, 13.05. Found: Cl, 12.13. [l] *Anal.* Calcd.: S, 17.60. Found: S, 17.71. [m] *Anal.* Calcd.: S, 16.33. Found: S, 16.42. [n] *Anal.* Calcd.: S, 14.42. Found: S, 14.54. [o] *Anal.* Calcd.: S, 13.45. Found: S, 13.06. [p] *Anal.* Calcd.: S, 13.45. Found: S, 13.28. [q] Very hygroscopic; m.p. could not be determined.

TABLE III

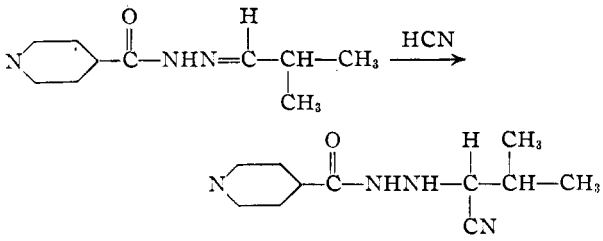
HYDRAZINES

Hydrazine	Method	Yield, %	Solvent[a]	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1,2-Bis-(ethylmercaptoacetyl)	[b]	32	B	128–130	$C_8H_{16}N_2O_2S_2$			11.85[n]			12.23
1,2-Bis-(isonicotinyl)	[c]	37	N	253–255	$C_{12}H_{10}N_4O_2$	59.50	4.16	23.13	59.33	4.05	23.43
1,2-Bis-(sorboyl)	E	55	[d]	>300	$C_{12}H_{16}N_2O_2$	65.43	7.32	12.72	65.34	7.46	12.80
1,2-Bis-(2-thiophenecarboxyl)	E[c]	33	E	256–257	$C_{10}H_8N_2O_2S_2$			11.10[o]			10.93
1-(2-Furoyl)-2-acetyl	D	68	W	149–150	$C_7H_8N_2O_3$	50.00	4.79	16.66	49.79	5.01	16.89
1-(2-Furoyl)-2,2-dimethyl-·HCl	[e]	24	I	205–207 d.	$C_7H_{11}ClN_2O_2$			14.70[o]			14.96
1-(2-Furoyl)-2-(1,1-dimethyl-1-cyanomethyl)	I	76	A	133–135	$C_9H_{11}N_3O_2$	55.95	5.74	21.75	55.92	5.71	21.95
1-(2-Furoyl)-2-formyl	F	81	V	144–146	$C_6H_6N_2O_3$	46.75	3.93	18.18	46.56	4.07	18.45
1-(2-Furoyl)-2-isopropyl	G(a)	16	Z	82–84	$C_8H_{12}N_2O_2$	57.12	7.20	16.66	56.81	7.17	17.01
1-Isonicotinyl-2-acetyl-·HCl	D[c]	56	W	208–209	$C_8H_{10}ClN_3O_2$			19.48[f]			19.35
1-Isonicotinyl-2-(4-aminobenzenesulfonyl)	[c]	44	X	220–222	$C_{13}H_{13}N_4O_3S$	49.31	4.14	[m]	49.36	4.23	
1-Isonicotinyl-2-benzyl	G(a)	53	P	120–121	$C_{13}H_{13}N_3O$	68.70	5.77	18.49	68.82	6.08	18.81
1-Isonicotinyl-2-(2-butyl)-·2HCl	G(a)	78	W	218–220	$C_{10}H_{17}Cl_2N_3O$			15.79[g]			15.99
1-Isonicotinyl-2-carbethoxy-·HCl	C[c]	26	M	202–203 d.	$C_9H_{12}ClN_3O_3$	43.99	4.92	17.10	43.48	4.98	17.56
1-Isonicotinyl-2-(1-carboxy-1-hydroxyethyl)	[e]	75	[d]	213–214	$C_9H_{11}N_3O_4$	47.99	4.92	18.65	48.38	5.15	18.58
1-Isonicotinyl-2-cyclohexyl	G(b)[e]	50	E	146–147	$C_{12}H_{17}N_3O$	65.71	7.81	19.16	65.22	7.79	18.83
1-Isonicotinyl-2-(1-cyano-4-methylcyclohexyl)	I	65	A	159–161	$C_{14}H_{18}N_4O$	65.10	7.02	21.69	64.94	6.85	21.41
1-Isonicotinyl-2-(1-cyano-2-methylpropyl)	I	91	A	142–143	$C_{11}H_{14}N_4O$	60.51	6.47	25.67	60.51	6.77	25.79
1-Isonicotinyl-2-(1-cyanothiacyclohexyl)	I	71	K	182–184 d.	$C_{12}H_{14}N_4OS$	54.93	5.38	21.36	55.11	5.45	21.29
1-Isonicotinyl-2-(1,1-dimethylbenzyl)	[c]	31	FF	109–111	$C_{15}H_{17}N_3O$	70.56	6.71	16.47	70.75	6.99	16.73
1-Isonicotinyl-2-dimethylcarbamyl	C	35	E	270–271 d.	$C_9H_{12}N_4O_2$	51.96	5.81	26.91	51.82	5.73	26.48
1-Isonicotinyl-2-(1,1-dimethyl-1-cyanomethyl)	I[c]	72	V	123–124	$C_{10}H_{12}N_4O$	58.80	5.93	27.43[i]	58.87	5.88	27.40
1-Isonicotinyl-2-formyl	F[c]	95	V	96–98	$C_7H_7N_3O_2$	50.90	4.27	25.45	51.18	4.20	25.50
1-Isonicotinyl-2-(2-furoyl)-·HCl	A[c]	60	O	254–255 d.	$C_{11}H_{10}ClN_3O_3$			15.70[j]			15.95
1-Isonicotinyl-2-(1-hydroxy-2,2,2-trichloroethyl)	A	72	E	124–125	$C_8H_8Cl_3N_3O_2$	33.77	2.83	14.77	34.15	2.96	14.57
1-Isonicotinyl-2-isopropyl[k]	G(a),H[c]	55	P	111–112	$C_9H_{13}N_3O$	60.32	7.31	23.45	60.06	7.04	23.27
1-Isonicotinyl-2-lauroyl	B[c]	47	P	118–119	$C_{18}H_{29}N_3O_2$	67.83	9.18	13.15	67.73	8.99	12.91
1-Isonicotinyl-2-(3-methylcyclohexyl)-·2-HCl	G(a)	59	M	231–233 d.	$C_{13}H_{21}Cl_2N_3O$	50.98	6.91	13.72	51.23	6.70	13.58
1-Isonicotinyl-2-(4-nitrobenzenesulfonyl)	C[c]	80	X	216–217	$C_{12}H_{10}N_4O_5S$	44.71	3.13	[p]	44.85	3.32	
1-Isonicotinyl-2-phenyl	[c]	14	E	185–186 d.	$C_{12}H_{11}N_3O$	67.59	5.20	19.71	67.55	5.35	19.59
1-Isonicotinyl-2-(3-pentyl)-·2HCl	G(a)	74	[d]	223–224	$C_{11}H_{19}Cl_2N_3O$			15.00[l]			15.27
1-(Isonicotinyl-1-oxide)-2-acetyl	D	38	B	213–214 d.	$C_8H_9N_3O_3$	49.23	4.65	21.53	49.11	4.80	21.50
1-(Isonicotinyl-1-oxide)-2-(1-carboxy-1-hydroxyethyl)		81	[h]	223–224 d.	$C_9H_{11}N_3O_6$	44.73	4.55	17.41	45.06	4.71	17.53
1-(Isonicotinyl-1-oxide)-2-(1,1-dimethyl-1-cyanomethyl)	I	85	X	150–151 d.	$C_{10}H_{12}N_4O_2$	54.52	5.49	25.44	54.60	5.57	25.34
1-(Isonicotinyl-1-oxide)-2-lauroyl	B	51	P	146–147	$C_{18}H_{29}N_3O_3$	64.44	8.71	12.52	64.59	8.64	12.73
1-(2-Thiophenecarboxyl)-2-(1,1-dimethyl-1-cyanomethyl)	I	91	A	147–148	$C_9H_{11}N_3OS$	51.67	5.30	20.09	51.75	5.30	19.82

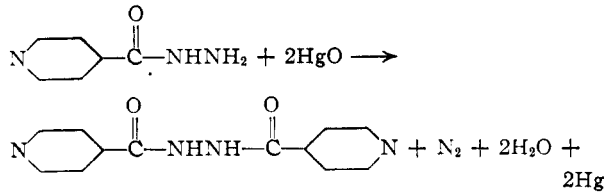
[a] See Table I. [b] Obtained as a residue from the distillation of ethylthioacetic acid hydrazide (see Table I). [c] See Experimental Part. [d] Not recrystallized. [e] *Anal.* Calcd.: Cl, 18.60. Found: Cl, 18.27. [f] *Anal.* Calcd.: Cl, 16.44. Found: Cl, 16.43. [g] *Anal.* Calcd.: Cl, 26.64. Found: Cl, 26.97. [h] Reprecipitated material. [i] *Anal.* Calcd.: neut. equiv., 204.23. Found: neut. equiv., 203.0. [j] *Anal.* Calcd.: Cl, 13.25. Found: Cl, 13.01. [k] Hydrochloride, m.p. 224–225° (dec.) (from abs. ethanol). *Anal.* Calcd. for $C_9H_{15}Cl_2N_2O$: C, 42.86; H, 5.99; N, 16.66. Found: C, 43.00; H, 6.02; N, 16.63. [l] *Anal.* Calcd.: Cl, 25.31. Found: Cl, 25.08. [m] *Anal.* Calcd.: S, 10.97. Found: S, 10.67. [n] *Anal.* Calcd.: S, 27.13. Found: S, 26.53. [o] *Anal.* Calcd.: S, 25.41. Found: S, 24.79. [p] *Anal.* Calcd.: S, 9.95. Found: S, 9.73.



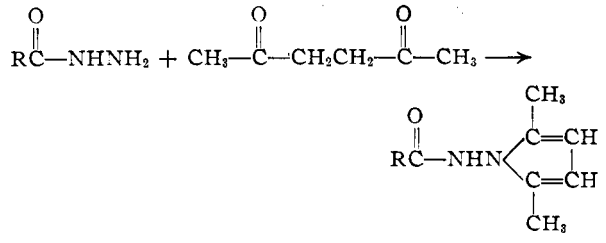
and by the addition of hydrogen cyanide to an acylhydrazone



Diacylhydrazine derivatives were prepared by the reaction of an acid hydrazide with an acid chloride or acid anhydride or by the reaction of an acid chloride with hydrazine. Ethyl ethylmercaptoacetate and hydrazine gave 1,2-bis-(ethylmercaptoacetyl)-hydrazine as well as ethylmercaptoacetic acid hydrazide. The 1-acyl-2-formylhydrazines were prepared by the reaction of an acid hydrazide and 98–100% formic acid. 1,2-Bis-(isonicotinyl)-hydrazine was prepared by the oxidation of isonicotinic acid hydrazide with mercuric oxide.[5] The hydrazines are listed in Table III.



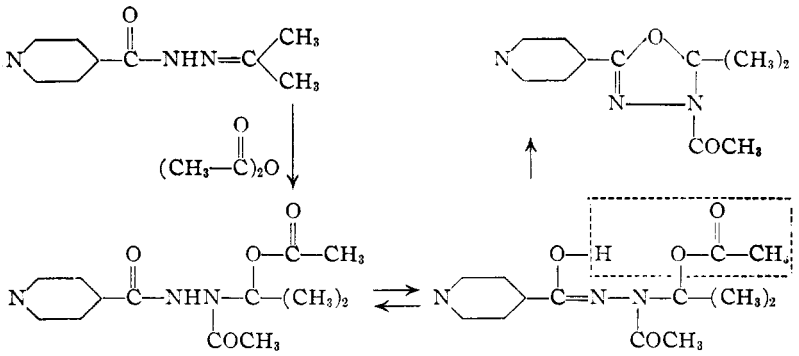
The reaction of acetonylacetone or succinaldehyde and the acid hydrazides led to an interesting group of pyrrole derivatives.



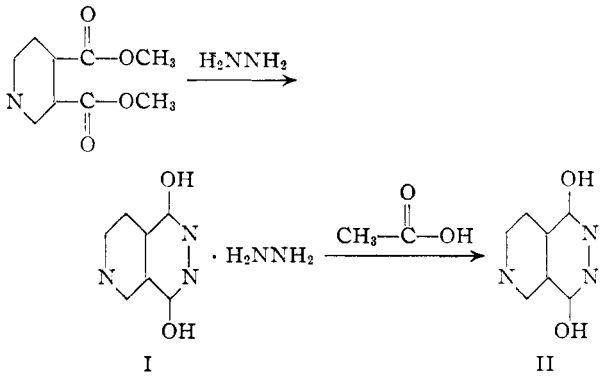
The reaction of acetone isonicotinylhydrazone with acetic anhydride led to 2,2-dimethyl-3-acetyl-5-(4-pyridyl)-1,3,4-oxadiazoline. The mechanism of this reaction is probably as shown[6]

(5) J. A. Gautier, *Compt. rend.*, **222** 394 (1946), employed this procedure to oxidize nicotinic acid hydrazide to 1,2-bis-(nicotinyl)-hydrazine.

(6) J. B. Ekeley, M. C. Swisher and C. C. Johnson, *Gazz. chim. ital.*, **62**, 81 (1932), have shown that benzal anil and acetic anhydride form $C_6H_5CH(O_2CCH_3)N(COCH_3)C_6H_5$.

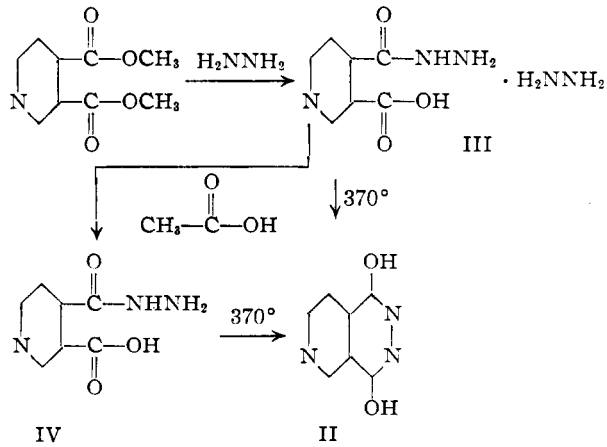


Pyrido(3,4-*d*)pyridazine-1,4-diol (II) was prepared by refluxing a mixture of dimethyl cinchomeronate and hydrazine hydrate in methanol. II was first obtained as the hydrazine salt (I).[7]



The preparation of a number of additional compounds, 2-furoic acid azide, O-(2-furoyl)-acetone oxime, isonicotinohydroxamic acid, O-isonicotinylacetone oxime hydrochloride, isonicotinylsemicarbazide, 3-(4-pyridyl)-5-pyrazolone, streptomycin A hydrazone and methyl 4-pyridyl ketone hydrazone, is also described. These miscellaneous derivatives are listed in Table IV.

(7) H. Meyer and J. Mally, *Monatsh.*, **33**, 393 (1912), have described the preparation of II by the pyrolysis at 370° of 3-carboxyisonicotinic acid hydrazide (IV) or its hydrazine salt (III). According to these authors, III was formed by refluxing dimethyl cinchomeronate and hydrazine hydrate in ethanol. They proposed the following mechanism:



IV behaved like a monobasic acid and was identified only by a neutralization equivalent, using phenolphthalein as indicator.

TABLE IV

MISCELLANEOUS COMPOUNDS

Compound	Yield, %	Solvent[a]	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4-Amidinopyridine·HCl[b]	32	M	230–232	C_6H_8ClN			26.66[c]			26.59
1-Benzamido-2,5-dimethylpyrrole	64	U	184–185	$C_{13}H_{14}N_2O$	72.87	6.58	13.05	72.94	6.68	13.23
2,2-Dimethyl-3-acetyl-5-(4-pyridyl)-1,3,4-oxadiazoline[d]	95	Z	109–111	$C_{11}H_{13}N_3O_2$	60.25	5.98	19.17[e]	60.23	6.37	18.52
1-(2-Furamido)-2,5-dimethylpyrrole	41	H	159–160	$C_{11}H_{12}N_2O_2$	64.68	5.92	13.72	64.84	6.18	13.75
2-Furoic acid azide[d]	22	L	62–63	$C_5H_3N_3O_2$	43.80	2.21	30.65	43.68	2.38	30.96
O-(2-Furoyl)-acetone oxime[d]	53	L	34–35[f]	$C_8H_9NO_3$	57.48	5.43	8.38	57.41	5.31	8.61
Hydrazonium isonicotinate[d]	74	[g]	130 d.	$C_6H_9N_3O_2$			27.09[h]			26.98
1-Isonicotinamido-2,5-dimethylpyrrole[d]	44	E	147–148 d.	$C_{12}H_{13}N_3O$	66.95	6.09	19.52	66.68	5.88	19.36
1-(Isonicotinamido)-pyrrole[d]	14	E	167–169	$C_{10}H_9N_3O$	64.15	4.84	22.44	64.47	4.96	22.53
Isonicotinohydroxamic acid[d]	54	E	163–164 d.	$C_6H_6N_2O_2$	52.17	4.38	20.28	51.98	4.47	20.08
O-Isonicotinylacetone oxime·HCl[d]	58	J	196–197	$C_9H_{11}ClN_2O_2$	50.35	5.17	13.05	50.53	5.22	12.77
Isonicotinylsemicarbazide[d]	30	E	241–242	$C_7H_8N_4O_2$	46.66	4.48	31.10	46.86	4.32	31.00
Isonicotinylthiosemicarbazide[i]	24	E	230–231	$C_7H_8N_4OS$	42.84	4.11	28.55	42.78	4.10	28.39
Methyl 4-pyridyl ketone hydrazone[d]	59	S	114–116	$C_7H_9N_3$	62.18	6.71	31.19	62.14	6.88	31.01
Pyrido(3,4-d)pyridazine-1,4-diol[d]	80	D	>300	$C_7H_5N_3O_2$	51.52	3.09	25.76	51.60	3.24	25.71
3-(4-Pyridyl)-5-pyrazolone[d]	90	X	286–287 d.	$C_8H_7N_3O$	59.63	4.38	26.08	59.45	4.65	26.14
Streptomycin A hydrazone[d]	85	[j]	180–185 d.	$C_{21}H_{44}Cl_3N_9O_{11}$	35.77	6.29	17.88	35.11	6.97	17.50
1-(2-Thiophenecarboxamido)-2,5-dimethylpyrrole	45	DD	197–199	$C_{11}H_{12}N_2OS$			12.73[k]			12.65

[a] See Table I. [b] The method employed was that of H. J. Barber and R. Slack, THIS JOURNAL, 66, 1607 (1944). [c] *Anal.* Calcd.: Cl, 22.50. Found: Cl, 22.35. [d] See Experimental Part. [e] *Anal.* Calcd.: N-acetyl, 19.63. Found: N-acetyl, 20.19. [f] B.p. 118–122° (1.8 mm.). [g] Not recrystallized. [h] *Anal.* Calcd.: neut. equiv. (titration in glacial acetic acid with $HClO_4$), 155.15. Found: neut. equiv., 158.2. [i] Resolidifies and melts again at 286–288° (dec.). The latter m.p. is attributed to the formation of 3-mercapto-5-(4-pyridyl)-1,2,4-triazole by loss of water. The chemistry of this and related compounds will be described in a forthcoming publication from these laboratories. [j] Freeze-dried material. [k] *Anal.* Calcd.: S, 14.56. Found: S, 14.47.

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Experimental Part

Hydrazides (Table I)

A. General Procedure.—A mixture of 0.1 mole of a methyl (or ethyl) ester and 0.15 mole of 85% hydrazine hydrate in 200 ml. of ethanol was refluxed for six hours. The ethanol, water and excess hydrazine hydrate were removed *in vacuo*, and the residual solid recrystallized.

B. Miscellaneous Procedures. Ethylmercaptoacetic Acid Hydrazide Hydrochloride.—To 16 g. (0.27 mole) of 85% hydrazine hydrate, warmed on a steam-bath, was added 40 g. (0.27 mole) of ethyl ethylmercaptoacetate and the mixture refluxed for two days. The mixture was concentrated *in vacuo*, and distilled to give an oil, and a non-volatile residue. The oil, b.p. 150–170° (12 mm.), was identified as ethylmercaptoacetic acid hydrazide.

Anal. Calcd. for $C_4H_{10}N_2OS$: N, 20.88; S, 23.89. Found: N, 20.80; S, 23.25.

The hydrochloride was formed by adding ethereal hydrogen chloride to the free base. The crude hydrochloride was filtered, dissolved in 150 ml. of hot absolute ethanol and the solution allowed to come to room temperature. The solid which separated was filtered. One hundred and fifty ml. of anhydrous ether was added to the ethanol filtrate. The trace of solid which separated was filtered, and the filtrate was diluted with 1 l. of anhydrous ether to give 12.2 g. (26% yield) of product, m.p. 134–135°.

The non-volatile residue from the distillation of the ethylmercaptoacetic acid hydrazide was identified as 1,2-bis-(ethylmercaptoacetyl)-hydrazine (see Table III).

Isonicotinic Acid Hydrazide Methiodide.—A solution was made of 29.3 g. (0.1 mole) of ethyl isonicotinate methiodide in 50 ml. of methanol at room temperature. To this solution, without cooling but with constant shaking, was added 6.0 ml. (0.1 mole) of 85% hydrazine hydrate, dropwise. Spontaneous warming occurred and within a few minutes bright orange crystals separated. The mixture was kept for three hours, the solid was filtered and recrystallized from methanol to give 20.5 g. (77% yield) of product, m.p. 210–212°.

Isonicotinic Acid Hydrazide, Methionine Salt.—A solution of 29.8 g. (0.2 mole) of DL-methionine and 27.4 g. (0.2 mole) of isonicotinic acid hydrazide in 800 ml. of water was clarified and freeze-dried to give 55 g. (96% yield) of product, m.p. 227–230°.

Isonicotinic Acid Hydrazide, *p*-Toluenesulfonic Acid Salt.—A solution of 27.4 g. (0.2 mole) of isonicotinic acid hydrazide in 500 ml. of hot 95% ethanol was mixed with a solution of 38 g. (0.2 mole) of *p*-toluenesulfonic acid monohydrate in 300 ml. of hot 95% ethanol. A solid separated immediately. The mixture was cooled, the solid was filtered and recrystallized from 95% ethanol to give 47 g. (75% yield) of product, m.p. 169–170°.

2-Mercaptoisonicotinic Acid-1-oxide Hydrazide, Hydrazine Salt.—A mixture of 12 g. (0.07 mole) of methyl 2-mercaptoisonicotinate-1-oxide (see part C) and 240 ml. (4.0 moles) of 85% hydrazine hydrate was heated for two hours on the steam-bath. The reaction mixture was concentrated *in vacuo* and the residue triturated with 150-ml. of 95% ethanol until crystallization occurred. The solid was filtered and washed twice with 250-cc. portions of boiling 95% ethanol to give 12 g. (80% yield) of product, m.p. 184–185° (dec.).

C. Intermediates for Hydrazides. Methyl 1-Acetylisonipecotate.—Methyl isonipecotate (from 27 g. (0.15 mole) of methyl isonipecotate hydrochloride) and 40 ml. of acetic anhydride were heated on the steam-bath for two hours. The mixture was concentrated *in vacuo* and the residue fractionated to give 17 g. (61% yield) of product, b.p. 121° (2 mm.).

Anal. Calcd. for $C_9H_{15}NO_3$: N, 7.55. Found: N, 7.84.

Ethyl 2-Benzothiazolecarboxylate.—A mixture of 125 g. (1.0 mole) of 2-aminobenzenethiol and 292 g. (2.0 moles) of ethyl oxalate was refluxed for seven hours. The solid which separated on cooling was filtered and recrystallized from hexane to give 82 g. (40% yield) of product, m.p. 60–62°.

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.96; H, 4.38. Found: C, 58.15; H, 4.54.

2-Isobutoxyisonicotinic Acid.—To a solution of 10.6 g. (0.46 g. atom) of sodium in 500 ml. of anhydrous isobutyl alcohol was added a solution of 47 g. (0.23 mole) of 2-bromoisonicotinic acid in 500 ml. of anhydrous isobutyl alcohol. The mixture was refluxed for 48 hours. The isobutyl alcohol was distilled and the residue dissolved in 400 ml. of water. The aqueous solution was acidified with 10% hydrochloric acid and the solid filtered. This material was recrystallized from aqueous ethanol to give 26 g. (54% yield) of product, m.p. 136–138°.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.70. Found: C, 61.16; H, 6.31.

Methyl 2-Isobutoxyisonicotinate.—The isobutoxyisonicotinic acid was converted to the methyl ester by reaction with diazomethane in the usual manner. The product was obtained in 61% yield, b.p. 114° (5 mm.). The ester was unstable and gave unsatisfactory analyses; the hydrazide, however, was readily formed and was a stable compound.

2,6-Diisobutoxyisonicotinic Acid.—A mixture of 17 g. (0.74 g. atom) of sodium in 100 ml. of anhydrous isobutyl alcohol and 35 g. (0.18 mole) of 2,6-dichloroisonicotinic acid was refluxed for 64 hours. The excess isobutyl alcohol was distilled and the residue dissolved in water. The aqueous solution was acidified with 10% hydrochloric acid. The precipitated acid was filtered and recrystallized from aqueous ethanol to give 20 g. (44% yield) of product, m.p. 149–150°.

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92. Found: C, 63.86; H, 7.80.

Methyl 2,6-Diisobutoxyisonicotinate.—2,6-Diisobutoxyisonicotinic acid was esterified in the usual manner with saturated methanolic hydrogen chloride. The yield of ester was 70%, b.p. 146° (1 mm.).

Anal. Calcd. for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.23. Found: C, 63.94; H, 8.48.

Methyl 1-Dimethylcarbamylisonipecotate.—A solution of 34.4 g. (0.32 mole) of dimethylcarbamyl chloride in 50 ml. of anhydrous ether was added dropwise to an ethereal solution of 45.8 g. (0.32 mole) of methyl isonipecotate and 32.3 g. (0.32 mole) of N-methylmorpholine. A crystalline product (N-methylmorpholine hydrochloride) separated immediately. The mixture was kept overnight at room temperature. The solid was filtered and the filtrate was concentrated and distilled to give 28.8 g. (42% yield) of product, b.p. 141–142° (2 mm.).

Anal. Calcd. for $C_{10}H_{18}N_2O_3$: N, 13.14. Found: N, 12.88.

Ethyl Isonicotinamidoacetate Hydrochloride.—To a stirred suspension of 34.6 g. (0.25 mole) of glycine ethyl ester hydrochloride in 200 ml. of pyridine, at 0°, was added, in small portions, 35.4 g. (0.25 mole) of sublimed isonicotinyl chloride. The mixture was stirred for five hours at room temperature, kept overnight, and the excess pyridine was removed *in vacuo*. The residue crystallized on cooling and was recrystallized from absolute ethanol to give 13 g. (25% yield) of product, m.p. 218–219° (dec.).

Anal. Calcd. for $C_{10}H_{13}ClN_2O_3$: Cl, 14.49; N, 11.45. Found: Cl, 14.31; N, 11.26.

Methyl Isonicotinate-1-oxide.—A solution of 27.4 g. (0.2 mole) of methyl isonicotinate in 200 ml. of glacial acetic acid was treated dropwise with 35 g. of 40% peracetic acid in glacial acetic acid (Buffalo Electrochemical Company). The mixture was heated for five hours on the steam-bath and kept overnight. The acetic acid was removed *in vacuo* and the residue recrystallized from 95% ethanol–ether to give 24 g. (80% yield) of product, m.p. 118–119°.

Anal. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.14. Found: C, 55.07; H, 4.75; N, 9.07.

Methyl 2-Bromoisonicotinate.—A suspension of 46 g. (0.23 mole) of 2-bromoisonicotinic acid in 500 ml. of ether was treated dropwise with 12 g. (0.24 mole) of diazomethane in 200 ml. of ether. Nitrogen was evolved and the acid dissolved. The mixture was kept overnight, treated with 5 ml. of acetic acid, decolorized with Darco and filtered. The ethereal filtrate was washed with 5% sodium carbonate solution, dried and concentrated to give 38.5 g. (78% yield) of product, m.p. 35–36°. An analytical sample was recrystallized from hexane and melted at 36–37°.

Anal. Calcd. for $C_7H_6BrNO_2$: N, 6.48. Found: N, 6.27.

Methyl 2-Bromoisonicotinate-1-oxide.—A mixture of 78 g. (0.35 mole) of methyl 2-bromoisonicotinate, 78 g. of 40% peracetic acid in glacial acetic acid (Buffalo Electrochemical Company) and 500 ml. of glacial acetic acid was heated for two hours on the steam-bath. The solution was then concentrated *in vacuo* (water-bath at 40°) and the viscous residue triturated with a mixture of 50 ml. of absolute ethanol and 300 ml. of dry hexane to give 43 g. (53% yield) of product, m.p. 113–115°. One recrystallization from absolute ethanol raised the m.p. to 123–124°.

Anal. Calcd. for $C_7H_6BrNO_3$: C, 36.23; H, 2.61; N, 6.04. Found: C, 36.23; H, 2.77; N, 6.02.

Methyl 2-Isothioureidoisonicotinate-1-oxide Hydrobromide.—A mixture of 43 g. (0.2 mole) of methyl 2-bromoisonicotinate-1-oxide, 15.2 g. (0.2 mole) of thiourea and 600 ml. of anhydrous methanol was refluxed for 0.5 hour. The methanol was removed *in vacuo* to give 35 g. (57% yield) of product, m.p. 145–146° (dec.).

Anal. Calcd. for $C_8H_{10}BrN_3O_3S$: N, 13.63; Br, 25.93. Found: N, 13.00; Br, 25.89.

Methyl 2-Mercaptoisonicotinate-1-oxide.—A solution consisting of 35 g. (0.11 mole) of methyl 2-isothioureidoisonicotinate-1-oxide hydrobromide, 20 g. (0.2 mole) of sodium carbonate and 500 ml. of water was allowed to stand at room temperature for 15 minutes, decolorized with Darco and filtered. The filtrate was made acid to congo red with 20% hydrochloric acid. The precipitated solid was filtered and washed with water to give 12 g. (60% yield) of product, m.p. 94–95°. A recrystallization from water did not affect the melting point.

Anal. Calcd. for $C_7H_7NO_3S$: C, 45.39; H, 3.89; N, 7.56. Found: C, 45.29; H, 3.85; N, 7.52.

Methyl 2-Methyl-5,6-dihydro-4H-pyran-3-carboxylate.—A mixture of 46 g. (2.0 g. atom) of sodium in 700 ml. of absolute methanol and 116 g. (1 mole) of methyl acetoacetate was heated to reflux and maintained at reflux while 202 g. (1 mole) of trimethylene bromide was added over a period of three hours. The mixture was stirred and refluxed for eight hours, the sodium bromide was filtered and washed with methanol. The combined filtrates were concentrated *in vacuo*, the residue was dissolved in 2 l. of water and the aqueous solution was extracted with five 600-ml. portions of ether. The dried ether extracts were concentrated and the residue distilled. The fraction, b.p. 35–70° (2 mm.), was redistilled through a 12-cm. packed column to give 40 g. (26% yield) of product, b.p. 67–69° (2 mm.).

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.25; H, 7.75. Found: C, 61.77; H, 7.85.

2-(4-Nitrobenzenesulfonamido)-4-carbethoxythiazole Dihydrate.—To a stirred solution of 116 g. (0.67 mole) of ethyl 2-amino-4-thiazolecarboxylate in 900 ml. of pyridine at room temperature was added dropwise a solution of 150 g. (0.67 mole) of 4-nitrobenzenesulfonyl chloride in 250 ml. of pyridine. The mixture was heated on the steam-bath for 1.5 hours and then concentrated *in vacuo*. The residue was poured on ice and the aqueous solution was acidified with 20% hydrochloric acid. The crude acid which separated was filtered and suspended in 1.5 l. of water. An excess of 6 *N* sodium hydroxide was added to dissolve the acid. The alkaline solution was decolorized with Darco, filtered and the filtrate was acidified with 20% hydrochloric acid. The solid which separated was filtered and recrystallized from aqueous ethanol to give 132 g. (55% yield) of product, m.p. 254–257° (dec.).

Anal. Calcd. for $C_{12}H_{11}N_3O_6S_2 \cdot 2H_2O$: C, 36.64; H, 3.84; N, 10.68. Found: C, 36.69; H, 3.09; N, 10.43.

Hydrazones (Table II)

A. General Procedures. Method A. Reaction of an Aldehyde (or Ketone) and an Aqueous Solution of a Hydrazide. Isobutyraldehyde Isonicotinylhydrazone.—To a solution of 41.1 g. (0.3 mole) of isonicotinic acid hydrazide in 300 ml. of water was added, with shaking, 21.6 g. (0.3 mole) of freshly distilled isobutyraldehyde. The product separated as an oil which solidified on continued shaking. The reaction mixture was kept overnight. The solid was filtered and recrystallized from benzene to give 42.5 g. (74% yield) of product, m.p. 135–136°.

Method B. Reaction of a Hydrazide and a Ketone (Excess Ketone as Solvent). Acetone Isonicotinylhydrazone.—A mixture of 27.4 g. (0.2 mole) of isonicotinic acid hydrazide and 500 ml. of acetone was refluxed for one hour and filtered hot. The crystalline product which separated on cooling was recrystallized from acetone to give 29 g. (83% yield) of product, m.p. 159–160°.

With the higher molecular weight ketones it was generally necessary to concentrate the reaction mixture to obtain the product.

Method C. Reaction of an Aldehyde (or Ketone) and a Hydrazide in Aqueous Ethanol. (a) 4-Acetamidobenzaldehyde 2-Furoylhydrazone.—To a solution of 25.2 g. (0.2 mole) of 2-furoic acid hydrazide in 200 ml. of warm water was added a solution of 32.6 g. (0.2 mole) of recrystallized 4-acetamidobenzaldehyde in 250 ml. of warm 50% ethanol. The solution was heated on the steam-bath for about five minutes when a precipitate separated. This solid was filtered and recrystallized from glacial acetic acid to give 39 g. (65% yield) of product, m.p. > 300°.

(b) D-Glucose 2-Furoylhydrazone.—To a solution of 36 g. (0.2 mole) of anhydrous D-glucose in 20 ml. of warm water was added 400 ml. of warm absolute ethanol. To this solution was added 25.2 g. (0.2 mole) of 2-furoic acid hydrazide and the reaction mixture refluxed for eight hours. The crystalline product which separated on cooling was filtered and recrystallized from methanol to give 14 g. (24% yield) of product, m.p. 174–175° (dec.).

Method D. Reaction of Aqueous Solutions of a Hydrazide and an Aldehyde (or Ketone). Isolation by Freeze-drying. Streptomycin A Isonicotinylhydrazone Trihydrochloride.—A solution of 5.5 g. (0.04 mole) of isonicotinic acid hydrazide and 27.7 g. (0.04 mole) of streptomycin A trihydrochloride in 200 ml. of water was kept overnight, clarified and freeze-dried to give 30.7 g. (100% yield) of product, m.p. 202–204° (dec.).

B. Miscellaneous Procedures. Acetaldehyde Isonicotinylhydrazone.—To a solution of 54.8 g. (0.4 mole) of isonicotinic acid hydrazide in 500 ml. of water was added 22 g. (0.5 mole) of acetaldehyde. The mixture was kept for several hours and the water was evaporated. The residue was recrystallized from 95% ethanol–hexane to give 23 g. of product, m.p. 175–176°.

Acetylacetone Di-(isonicotinylhydrazone).—A mixture of 21.9 g. (0.1 mole) of acetylacetone monoisonicotinylhydrazone, 13.7 g. of isonicotinic acid hydrazide and 75 ml. of water was warmed on the steam-bath until a solution was formed. On cooling, a solid separated. It was filtered and recrystallized from water to give 15 g. (44% yield) of product, m.p. 254–256°.

Succinaldehyde Di-(isonicotinylhydrazone).—To a suspension of 64 g. (0.4 mole) of 2,5-diethoxytetrahydrofuran (Carbide and Carbon Chemicals Co.) in 150 ml. of water was added 25 ml. of 20% hydrochloric acid and the mixture allowed to stand for two hours with occasional shaking. The solution was neutralized with calcium carbonate, the excess calcium carbonate filtered and the filtrate added to a solution of 54.8 g. (0.4 mole) of isonicotinic acid hydrazide in 500 ml. of water. The solid which separated was filtered, washed with 95% ethanol and with ether and recrystallized from 95% ethanol to give 24 g. (37% yield) of product, m.p. 202–203°.

Hendecanal Isonicotinylhydrazone.—A mixture of 38.4 g. (0.15 mole) of 9-hendecenal isonicotinylhydrazone, 0.2 g. of platinum oxide and 300 ml. of 95% ethanol was reduced under 50 lb. of hydrogen at room temperature. The catalyst was filtered and the filtrate concentrated. The residue was recrystallized from 95% ethanol–ether to give the product, m.p. 82–83°.

Hydrazines (Table III)

A. General Procedures. 1. 1,2-Diacylhydrazines. Method A. Reaction of a Hydrazide and an Acid Chloride in Acetonitrile. 1-Isonicotinyl-2-(2-furoyl)-hydrazine Hydrochloride.—To a stirred refluxing suspension of 10 g. (0.07 mole) of isonicotinic acid hydrazide in 250 ml. of acetonitrile was added dropwise 9.6 g. (0.074 mole) of 2-furoyl chloride in 50 ml. of acetonitrile. The mixture was refluxed for one hour and cooled. The solid which separated was filtered and recrystallized from methanol to give 11.8 g. (60% yield) of product, m.p. 254–255° (dec.).

Method B. Reaction of a Hydrazide and an Acid Chloride in an Acetonitrile–N-methylmorpholine Mixture. 1-Isonicotinyl-2-lauroylhydrazine.—To a stirred refluxing suspension of 27.4 g. (0.2 mole) of isonicotinic acid hydrazide, 450 ml. of acetonitrile and 20.2 g. (0.2 mole) of N-methylmorpholine was added 43.6 g. (0.2 mole) of lauroyl chloride in 100 ml. of acetonitrile. The stirring and refluxing was continued for two hours and the mixture allowed to cool. The solid which separated was filtered and washed with 2 l. of water. After one recrystallization from 20% ethanol and a second recrystallization from 95% ethanol–hexane, the yield of product was 30 g. (45%), m.p. 118–119°.

Method C. Reaction of a Hydrazide and an Acid Chloride in Pyridine. 1-Isonicotinyl-2-carbethoxyhydrazine Hydrochloride.—A stirred suspension of 27.4 g. (0.2 mole) of isonicotinic acid hydrazide in 300 ml. of pyridine was treated dropwise with 21.6 g. (0.2 mole) of ethyl chlorocarbonate. During the addition, the temperature was maintained at 30–40°; subsequently, the mixture was heated on the steam-bath for one hour. The pyridine was removed *in vacuo* and the viscous residue was dissolved in 500 ml. of warm absolute ethanol. The filtered solution was cooled and treated with excess ethereal hydrogen chloride. The crude hydrochloride was filtered and recrystallized from absolute ethanol–ether to give 12.5 g. (26% yield) of product, m.p. 202–203° (dec.).

Method D. Reaction of a Hydrazide and an Acid Anhydride. 1-Isonicotinyl-2-acetylhydrazine Hydrochloride.—A mixture of 25 g. (0.18 mole) of isonicotinic acid hydrazide, 15 ml. (0.18 mole) of acetic anhydride and 200 ml. of acetic acid was refluxed for three hours. The acetic acid was removed *in vacuo*. The oily residue was dissolved in warm methanol and the solution was decolorized with Darco and filtered. The filtrate was treated with ethereal hydrogen chloride and the solid which separated was filtered and recrystallized from methanol–ether to give 22 g. (56% yield) of product, m.p. 208–209° (dec.).

Method E. Reaction of an Acid Chloride and Hydrazine. 1,2-Bis-(2-thiophenecarboxyl)-hydrazine.—This compound was obtained in an attempt to prepare the mono derivative. To a stirred mixture of 27 ml. (0.44 mole) of 85% hydrazine hydrate and 300 ml. of ether was added dropwise, at 5°, 64 g. (0.44 mole) of 2-thiophenecarboxylic acid chloride in 200 ml. of anhydrous ether. A solid separated immediately. The mixture was kept overnight and the solid was filtered. This material was recrystallized from water to give 18.4 g. (33% yield) of product, m.p. 256–257°.

Method F. Reaction of a Hydrazide and Formic Acid. 1-Isonicotinyl-2-formylhydrazine.—A mixture of 25 g. (0.18 mole) of isonicotinic acid hydrazide and 25 ml. of 98–100% formic acid was heated to boiling and allowed to cool. The crystalline product which separated was filtered and recrystallized from acetonitrile to give the product, m.p. 96–98°.

2. 1-Acyl-2-mono- or Dialkylhydrazines. Method G. Reduction of a Hydrazone. (a) 1-Isonicotinyl-2-isopropylhydrazine.—A mixture of 17.7 g. (0.1 mole) of acetone isonicotinylhydrazone in 125 ml. of absolute ethanol and 0.1 g. of platinum oxide was reduced at 60° under 50 lb. of hydrogen. The catalyst was filtered and the filtrate concentrated *in vacuo*. The residue was recrystallized from 95% ethanol–hexane to give 10 g. (55% yield) of product, m.p. 111–112°.

In a number of instances the hydrazine derivatives were obtained as oils. These were converted to the crystalline dihydrochlorides.

(b) **1-Isonicotinyl-2-cyclohexylhydrazine.**—A mixture of 2 g. (0.01 mole) of cyclohexanone isonicotinylhydrazone, 100 ml. of water and 0.1 g. of platinum oxide was reduced at 75° under 50 lb. of hydrogen. The warm solution was filtered. The solid which separated on cooling was filtered to give 0.7 g. (30% yield) of product, m.p. 145–146°.

Method H. Reduction of a Hydrazide–Aldehyde (or Ketone) Mixture. 1-Isonicotinyl-2-isopropylhydrazine.—To a solution of 13.7 g. (0.1 mole) of isonicotinic acid hydrazide in 150 ml. of hot 95% ethanol was added 5.8 g. (0.1 mole) of acetone and 0.1 g. of platinum oxide and the mixture reduced at 60–70° under 50 lb. of hydrogen. The catalyst was filtered and the filtrate concentrated *in vacuo*. Trituration of the residue with anhydrous ether gave a solid which was filtered and recrystallized from 95% ethanol–hexane to give 7.0 g. of product, m.p. 111–112°. This compound was identical with the one prepared by the catalytic reduction of acetone isonicotinylhydrazone.

Method I. Reaction of a Hydrazone and Hydrogen Cyanide. 1-Isonicotinyl-2-(1,1-dimethyl-1-cyanomethyl)-hydrazine.—A mixture of 45 g. (0.25 mole) of acetone isonicotinylhydrazone and 250 ml. of liquid hydrogen cyanide was kept at room temperature for four days. The excess hydrogen cyanide was evaporated. The oily residue crystallized slowly when kept in the cold. The crude product was recrystallized from isopropyl alcohol to give 37.0 g. (72% yield) of product, m.p. 123–124°.

B. Miscellaneous Procedures. 1,2-Bis-(isonicotinyl)-hydrazine.—To 27.4 g. (0.2 mole) of isonicotinic acid hydrazide suspended in 250 ml. of 95% ethanol at room temperature was added all at once 43.3 g. (0.2 mole) of powdered yellow mercuric oxide. The color gradually darkened until after about 20 minutes, the reaction turned black with the evolution of heat. When the mixture had cooled, Hyflo was added, and the mixture filtered through Hyflo. The insoluble material was extracted with 100 ml. of 10% hydrochloric acid, filtered and the filtrate made slightly alkaline with 10% sodium hydroxide. Acidification with acetic acid gave a solid, m.p. 250°. It was recrystallized from *n*-propyl alcohol to give 9 g. (37% yield) of product, m.p. 253–255° (lit. 254–255°).[8]

1-(2-Furoyl)-2,2-dimethylhydrazine Hydrochloride.—To a stirred mixture of 100 ml. of ether and 6.0 g. (0.1 mole) of 1,1-dimethylhydrazine, at 0°, was added 13.1 g. (0.1 mole) of 2-furoyl chloride in 100 ml. of anhydrous ether. The cold reaction mixture was concentrated *in vacuo* (finally in a desiccator over phosphorus pentoxide at 5°) and the residual solid, 18 g., was recrystallized from butanol to give 7.3 g. (38% yield) of product, m.p. 207–209° (dec.).

1-Isonicotinyl-2-(4-aminobenzenesulfonyl)-hydrazine.—1-Isonicotinyl-2-(4-nitrobenzenesulfonyl)-hydrazine (see Table III) was prepared from isonicotinic acid hydrazide and *p*-nitrobenzenesulfonyl chloride in pyridine.[9] A mixture of 30 g. of 1-isonicotinyl-2-(4-nitrobenzenesulfonyl)-hydrazine, 450 ml. of glacial acetic acid and 3 g. of 5% palladium-on-charcoal was reduced at 100° under 50 lb. of hydrogen. The acetic acid solution was filtered from the catalyst while hot. The solid which separated on cooling was filtered and recrystallized from glacial acetic acid. The compound crystallized with one molecule of acetic acid and melted at 220–222°.

Anal. Calcd. for $C_{14}H_{16}N_4O_6S$: N, 15.90. Found: N, 15.93.

The solvate-free compound was obtained by heating for two hours at 120° and 5 mm. The yield was 12 g. (44%), m.p. 220–222°.

1-Isonicotinyl-2-(1-carboxy-1-hydroxyethyl)-hydrazine.—To a solution of 27.4 g. (0.2 mole) of isonicotinic acid hydrazide in 500 ml. of hot 95% ethanol was added 17.6 g. (0.2 mole) of pyruvic acid. Sufficient heat was evolved to cause the solution to reflux. The solid which separated as the reaction mixture was allowed to cool to room temperature was filtered to give 34 g. (75% yield) of product, m.p. 213–214° (dec.).

1-(Isonicotinyl-1-oxide)-2-(1-carboxy-1-hydroxyethyl)-hydrazine.—The preparation of this compound was similar to the above example except that isonicotinic acid-1-oxide hydrazide was used. The yield of product, m.p. 223–224° (dec.), was 81%.

1-Isonicotinyl-2-(1,1-dimethylbenzyl)-hydrazine.—To 17.7 g. (0.1 mole) of acetone isonicotinylhydrazone suspended in 250 ml. of anhydrous benzene was added, dropwise, with stirring, 150 ml. of an ether solution containing 0.25 mole of phenylmagnesium bromide. The reaction mixture was stirred and refluxed for five hours, cooled and hydrolyzed with water. The hydrolyzed mixture was washed with three 750-ml. portions of chloroform (vigorous shaking gives stable emulsions) and the combined chloroform extracts were dried and concentrated. The residue solidified on cooling and was recrystallized from toluene–heptane to give 8 g. (31% yield) of product, m.p. 109–111°.

1-Isonicotinyl-2-phenylhydrazine.—A stirred suspension of 30 g. (0.21 mole) of sublimed isonicotinyl chloride in 500 ml. of anhydrous benzene was treated, dropwise, with 22.7 g. (0.21 mole) of phenylhydrazine in 150 ml. of anhydrous benzene. The mixture was refluxed for two hours and the solid product filtered. The solid was dissolved in water and the aqueous solution made slightly alkaline with 10% sodium hydroxide. The solid which separated was filtered and recrystallized from water to give 6.2 g. (14% yield) of product, m.p. 185–186° (dec.).

Miscellaneous Compounds (Table IV)

2,2-Dimethyl-3-acetyl-5-(4-pyridyl)-1,3,4-oxadiazoline.—A mixture of 10 g. (0.06 mole) of acetone isonicotinylhydrazone and 10 ml. of acetic anhydride was refluxed for one hour. The excess acetic anhydride and acetic acid were removed *in vacuo* and the solid residue recrystallized from heptane to give 11.7 g. (95% yield) of product, m.p. 109–111°.

2-Furoic Acid Azide.—An ice-cooled solution of 29.0 g. (0.22 mole) of 2-furoic acid hydrazide in 220 ml. of 2 *N* hydrochloric acid was treated, dropwise, with stirring, with a solution of 17.5 g. (0.25 mole) of sodium nitrite in 150 ml. of water. The temperature was maintained at 0°. The solid which separated was filtered and recrystallized from 75 ml. of hexane to give 6.5 g. (22% yield) of product, m.p. 62–63°.

O-(2-Furoyl)-acetone Oxime.—A stirred solution of 51.2 g. (0.77 mole) of acetone oxime in 700 ml. of anhydrous benzene was treated, dropwise, with 100 g. (0.77 mole) of 2-furoyl chloride. The mixture was stirred for 30 minutes and refluxed until no more hydrogen chloride was evolved (about 12 hours). The benzene was evaporated and the residue distilled to give 90 g. (70% yield) of product, b.p. 118–122° (18 mm.). The distillate solidified and was recrystallized from hexane to give the crystalline product, m.p. 34–35°.

Hydrazonium Isonicotinate.—A mixture of 36.9 g. (0.3 mole) of isonicotinic acid and 27 g. (0.45 mole) of 85% hydrazine hydrate was warmed until a clear solution formed. The solution was cooled and the water allowed to evaporate at room temperature. The anhydrous salt melts at 130°; it dissociates into isonicotinic acid and hydrazine when heated at 80° *in vacuo*.

1-Isonicotinamido-2,5-dimethylpyrrole.—A mixture of 25 g. (0.18 mole) of isonicotinic acid hydrazide and 100 ml. of acetonylacetone was heated on the steam-bath for one hour. A clear solution formed during this heating period. The solution was cooled and diluted with 125 ml. of water. The solid which separated was filtered and recrystallized from water to give 16 g. (41% yield) of product, m.p. 147–148° (dec.).

1-(Isonicotinamido)-pyrrole.—Freshly distilled succinaldehyde, 22 g. (0.2 mole), was added dropwise to a solution of 34.2 g. (0.25 mole) of isonicotinic acid hydrazide in 250 ml. of acetic acid at 50°. The mixture was heated on the steam-bath for one hour. The acetic acid was removed *in vacuo* and the residue treated with 150 ml. of water. The solid which separated was filtered and recrystallized from water to give 5 g. (14% yield) of product, m.p. 167–169°.

Isonicotinohydroxamic Acid.[10]—To a warm solution of 13.9 g. (0.2 mole) of hydroxylamine hydrochloride in 80 ml. of methanol was added a warm solution of 19 g. (0.3 mole) of 85% potassium hydroxide in 40 ml. of methanol followed by 15.1 g. (0.1 mole) of ethyl isonicotinate. The warm mixture was filtered rapidly, the insoluble salt washed with a little methanol and the combined filtrates kept at room temperature for four days. The crystalline potassium salt was filtered and weighed 1.05 g. It dissolved rapidly in a mixture of 5 ml. of water and 0.5 ml. of glacial acetic acid, and immediately thereafter the free acid separated. This was dissolved by warming and the hydroxamic acid was allowed to crystallize. It was filtered and recrystallized from water to give the product, m.p. 163–164° (dec.) (the melting point varies with the rate of heating). The methanolic filtrate was concentrated to dryness at room temperature *in vacuo* and the residual solid worked up as above. The combined yield was 7.5 g. (54%).

O-Isonicotinylacetone Oxime Hydrochloride.—A mixture of 28.4 g. (0.2 mole) of sublimed isonicotinyl chloride, 14.6 g. (0.2 mole) of acetone oxime and 700 ml. of anhydrous benzene was refluxed two hours and kept overnight. The solid was filtered and recrystallized from absolute ethanol to give 25 g. (58% yield) of product, m.p. 196–197°.

Isonicotinyl Semicarbazide.—To a stirred suspension of 38.6 g. (0.35 mole) of powdered semicarbazide hydrochlo-

(8) Prepared from isonicotinic acid hydrazide and isonicotinyl chloride by R. Graf, *J. prakt. Chem.*, **138**, 289 (1933).

(9) This method was used by E. Hoggarth, *J. Chem. Soc.*, 1163 (1949), to prepare 4-nitrobenzoylthiosemicarbazide.

(10) T. S. Gardner, E. Wenis and F. A. Smith, THIS JOURNAL, **73**, 5455 (1951), reported the preparation of the hydrochloride.

ride in 300 ml. of pyridine, at 0°, was added, in small portions, 49 g. (0.35 mole) of sublimed isonicotinyl chloride. The mixture was stirred two hours and kept overnight at room temperature. It was then poured into 700 ml. of water, the mixture was cooled and the solid filtered. This material was recrystallized from water to give 19 g. (30% yield) of product, m.p. 241–242°.

Pyrido(3,4-d)pyridazine-1,4-diol, Hydrazine Salt.—To a solution of 48 g. (0.24 mole) of dimethyl cinchomeronate in 960 ml. of methanol was added dropwise 360 ml. (6.0 moles) of 85% hydrazine hydrate. Subsequently, the mixture was refluxed for six hours, cooled and the solid filtered. The yield was 58.5 g., m.p. > 300°. An analytical sample was recrystallized from 95% ethanol to give the **hydrazine salt**, m.p. > 300°.

Anal. Calcd. for $C_7H_9N_5O_2$: C, 43.07; H, 4.65; N, 35.90. Found: C, 43.40; H, 4.98; N, 34.57.

The hydrazine salt was dissolved in warm water and the solution acidified with acetic acid. The solid which separated was filtered and recrystallized from dimethylformamide to give 31.5 g. (80% yield) of product, m.p. > 300.

3-(4-Pyridyl)-5-pyrazolone.—To 19.3 g. (0.1 mole) of ethyl isonicotinylacetate in 25 ml. of *n*-propyl alcohol was added 6 ml. (0.1 mole) of 85% hydrazine hydrate. When the mixture was warmed slightly a vigorous reaction occurred. The mixture was refluxed for four hours and cooled. The solid was filtered and recrystallized from glacial acetic acid to give 14.5 g. (90% yield) of product, m.p. 286–287° (dec.).

Streptomycin A Hydrazone.—A solution of 69 g. (0.1 mole) of streptomycin A trihydrochloride in 500 ml. of water was treated with a solution of 6 g. (0.1 mole) of 85% hydrazine hydrate in 100 ml. of water. The combined solutions were kept overnight, clarified and freeze-dried to give 60 g. (85% yield) of product, m.p. 180–185°.

Methyl 4-Pyridyl Ketone Hydrazone.—A mixture of 9.2 g. (0.08 mole) of methyl 4-pyridyl ketone and 18.0 ml. (0.3 mole) of 85% hydrazine hydrate was refluxed for seventy minutes and cooled. The precipitated solid was filtered and recrystallized from benzene–hexane to give 9 g. (59% yield) of product, m.p. 114–116°.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PITMAN-MOORE CO.]

Hypotensive Alkaloids from *Veratrum album* Protoveratrine A, Protoveratrine B and Germitetrine B[1a]

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An investigation of the hypotensive alkaloids of *Veratrum album* has resulted in the finding that protoveratrine prepared from this source is a mixture of two alkaloids and in the isolation of a new hypotensive alkaloid, named germitetrine B, from the "amorphous alkaloid" fraction. One of the alkaloids, protoveratrine A, was found to conform to the accepted structure of protoveratrine except that it yielded two instead of one mole of acetic acid on hydrolysis. Protoveratrine B was found to yield protoverine, 2-methylbutyric acid, 2,3-dihydroxy-2-methylbutyric acid and two moles of acetic acid on hydrolysis. Germitetrine B was found to yield germine, 2-methylbutyric acid, 2,3-dihydroxy-2-methylbutyric acid and two moles of acetic acid.

The original purpose of the work reported here was to prepare protoveratrine for clinical testing and then to search for alkaloids responsible for the hypotensive activity of the so-called "amorphous alkaloid" fraction from *Veratrum album*. Paper chromatographic methods developed to aid in following the fractionation of the "amorphous alkaloids" soon revealed that protoveratrine, itself, as prepared by the technique of Craig and Jacobs,[2,3] was, in fact, a mixture of two alkaloids. This necessitated a reinvestigation of the chemistry of protoveratrine.

Such mixtures of two alkaloids were encountered in protoveratrine from all six lots of *Veratrum album* roots and rhizomes examined. The proportion of protoveratrine B varied from 0.36 to 0.58 among these six different lots. No significant variation was noted among different preparations from the same lot of roots and rhizomes. Attempts to separate the two alkaloids by fractional crystallization were unsuccessful. To purify protoveratrine for analysis, Craig and Jacobs[2,3] had used crystallization by addition of ammonia to a solution of the acetate in alcohol and crystallization from chloroform–ether. Carrying out serial fractional crystallizations by these two techniques and examining the successive crops and mother liquors by paper chromatography at each step, we obtained no evidence of separation of the two alkaloids. Fractional crystallization from acetone likewise gave no indication of separation. In their paper, Jacobs and Craig[3] call attention to their dissatisfaction with the analytical results they obtained. A mixture of alkaloids such as we have found would explain their apparently low carbon analyses.

Separation of protoveratrine into protoveratrines A and B[4] on a macro scale was accomplished by a

(1) (a) Paper read before the Medicinal Chemistry Division of the American Chemical Society at the Atlantic City Meeting, September, 1952. (b) Indiana Central College, Indianapolis, Indiana.

(2) L. C. Craig and W. A. Jacobs, *J. Biol. Chem.*, **143**, 427 (1942).

(3) W. A. Jacobs and L. C. Craig, *ibid.*, **149**, 271 (1943).

(4) Following the suggestion of Dr. W. A. Jacobs of Rockefeller Institute for Medical Research these alkaloids have been given names to indicate their being part of the recognized clinical entity "protoveratrine" instead of following the alternative procedure of modifying the parent trivial name to indicate partially the structure. In the paper read at the American Chemical Society meeting protoveratrine A was referred to simply as "protoveratrine" and protoveratrine B was termed "oxyprotoveratrine X."

NOTE ADDED IN PROOF.—Since the submission of this paper for publication, two pertinent articles have appeared in print. M. W. Klohs, *et al.*, THIS JOURNAL, **74**, 5107 (1952), describe an alkaloid which they call neoprotoveratrine and which they isolated from *Veratrum viride*. W. L. Glen, G. S. Meyers, *et al.*, *Nature*, **170**, 932 (1952), have announced the separation of a crude crystalline fraction from *Veratrum album* and its separation by countercurrent distribution into alkaloids they describe as protoveratrine, veratetrine, and germitetrine. We have now exchanged samples with both groups and find protoveratrine B, veratetrine and neoprotoveratrine chromatographically identical. In personal communications, Dr. G. S. Meyers reports protoveratrine B and veratetrine identical (including infrared), and Dr. M. W. Klohs reports protoveratrine B and neoprotoveratrine identical. The "protoveratrine" reported by both of these groups is presumably protoveratrine A. By countercurrent distribution techniques, they separated the alkaloids corresponding to protoveratrines A and B before attempting to obtain pure crystalline materials.