[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Chemotherapy of Experimental Tuberculosis. X. Heterocyclic Acyl Derivatives of Substituted Semicarbazides[1]

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A series of heterocyclic acyl derivatives of substituted semicarbazides were prepared for screening as antituberculous agents. Most of the compounds had the general structure $RC(=O)NHNHC(=X)NR^1R^2$ where R was 4-pyridyl, 2-furyl or 2-thenyl, X was O, S or NH and R^1 and R^2 were alkyl groups or H. The reaction of dimethylcarbamyl chloride with isonicotinic acid hydrazide, in pyridine, did not yield the expected 4,4-dimethyl-1-isonicotinyl semicarbazide. Instead, the product was 5-(4-pyridyl)-1,3,4-oxadiazol-2(3H)-one. This unusual reaction was found to occur also with other pyridinecarboxylic acid hydrazides and dialkylcarbamyl chlorides.

In our previous publication[2] we described a series of acid hydrazides, their derivatives and related compounds, prepared in order to establish the structural requirements for antituberculous activity within the isonicotinic acid hydrazide (Nydrazid)[3] lead. As an extension of that work, we have prepared a series of carbamyl derivatives of heterocyclic acyl hydrazides I.

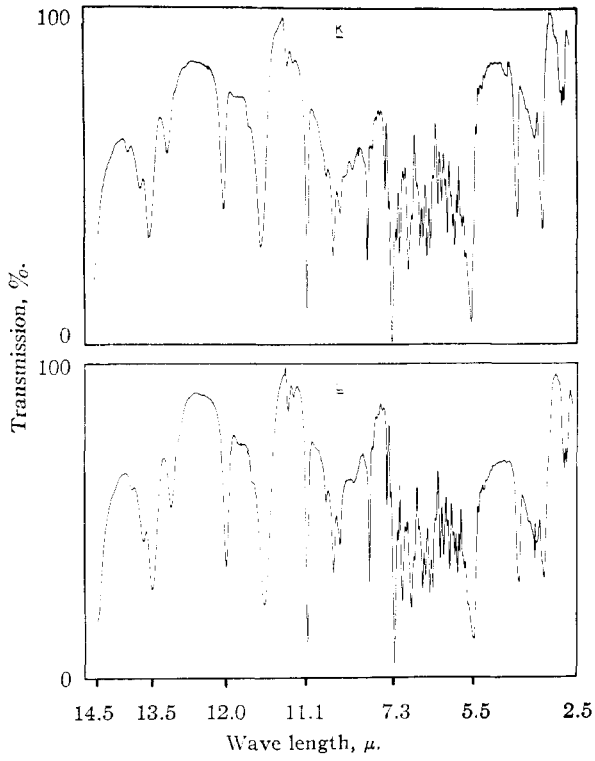
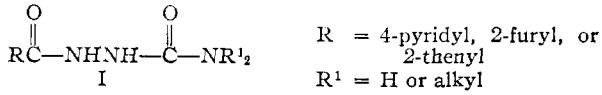


Fig. 1.—Curve K (top) represents the infrared absorption spectrum of 5-(4-pyridyl)-1,3,4-oxadiazol-2(3H)-one prepared by the reaction of isonicotinic acid hydrazide with phosgene. Curve L (bottom) represents the spectrum of the product of the reaction of isonicotinic acid hydrazide with dimethylcarbamyl chloride.



One member of this series, 1-isonicotinylsemicarbazide, already has been described.[2] 4,4-Dimethyl-1-isonicotinylsemicarbazide (II) was prepared by the reaction of dimethylcarbamyl chloride with isonicotinic acid hydrazide in boiling toluene or acetonitrile, or in pyridine at room temperature; the same product was obtained from isonicotinyl chloride and 4,4-dimethylsemicarbazide in boiling acetonitrile. The reaction of dimethylcarbamyl chloride with isonicotinic acid hydrazide in boiling pyridine gave a new product III, $C_7H_5N_3O_2$; III was also obtained from the reaction of diethylcarbamyl chloride with isonicotinic acid hydrazide, indicating that the reaction involved not only the elimination of the elements of HCl, but also those of dimethylamine or diethylamine. The structure of III was established by a comparison with 5-(4-pyridyl)-1,3,4-oxadiazol-2(3H)-one prepared by the reaction of isonicotinic acid hydrazide with phosgene[4]; melting points, mixed melting points and infrared absorption spectra (Fig. 1) were identical.

That the formation of 5-(4-pyridyl)-1,3,4-oxadiazol-2(3H)-one by the reaction of isonicotinic acid hydrazide with a dialkylcarbamyl chloride in boiling pyridine occurs stepwise was demonstrated in the following manner: When isonicotinic acid hydrazide and dimethylcarbamyl chloride reacted in pyridine at room temperature, 4,4-dimethyl-1-isonicotinylsemicarbazide was isolated in 60% yield. When this product was refluxed in pyridine for 15 hours, 83% of theoretical of dimethylamine (characterized as N,N-dimethyl-*p*-toluenesulfonamide) was obtained; from the pyridine, 5-(4-pyridyl)-1,3,4-oxadiazol-2(3H)-one was isolated in 97% yield.

It was shown that the reaction of dimethylcarbamyl chloride with nicotinic acid hydrazide, picolinic acid hydrazide and cinchoninic acid hydrazide led, respectively, to 5-(3-pyridyl)-, 5-(2-pyridyl)- and 5-(4-quinolyl)-1,3,4-oxadiazol-2(3H)-one. In addition, 1-isonicotinyl-2-isopropylhydrazine and dimethylcarbamyl chloride gave 3-isopropyl-5-(4-pyridyl)-1,3,4-oxadiazol-2-one.

5-(2-Furyl)- and 5-(2-thenyl)-1,3,4-oxadiazol-2-

(1) Presented before the Division of Medicinal Chemistry at the 124th Meeting of the American Chemical Society, Chicago, Illinois, September 6–11, 1953.

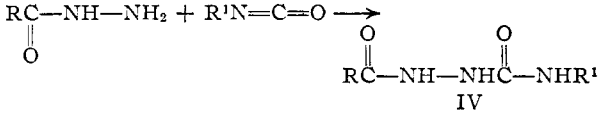
(2) For the previous chemical paper in this series, see H. L. Yale, K. A. Losee, J. Martins, M. Holsing, F. M. Perry and J. Bernstein, THIS JOURNAL, **75**, 1933 (1953).

(3) Registered Trade Mark.

(4) A. Dornow and K. Bruncken, *Chem. Ber.*, **82**, 121 (1949), prepared 5-(3-pyridyl)-1,3,4-oxadiazol-2(3H)-one by the reaction of nicotinic acid hydrazide with phosgene.

(3H)-one were prepared by the reaction of 2-furoic acid hydrazide and 2-thiophenecarboxylic acid hydrazide with phosgene.

The acid hydrazides reacted smoothly with ethyl isocyanate, allyl isocyanate and octadecyl isocyanate in acetonitrile to give derivatives of the general structure IV.

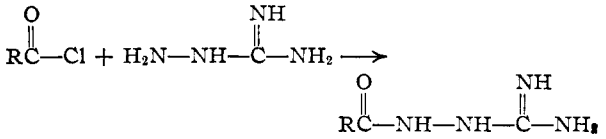


IV

1-Acyl-3-thiosemicarbazides were prepared by the condensation of the acyl halide with thiosemicarbazide in pyridine.[2] 4,4-Dimethyl-1-(2-furoyl)-3-thiosemicarbazide and 4,4-dimethyl-1-(2-thenoyl)-3-thiosemicarbazide were prepared by the condensation of the corresponding acid chloride with 4,4-dimethyl-3-thiosemicarbazide in pyridine; 1-isonicotinyl-, 1-(2-furoyl)- and 1-(2-thenoyl)-4,4-diethyl-3-thiosemicarbazide were prepared by the reaction of the corresponding acid chloride with 4,4-diethyl-3-thiosemicarbazide in pyridine; 4,4-diethyl-1-isonicotinyl-3-thiosemicarbazide also was prepared from isonicotinic acid hydrazide and diethylthiocarbamyl chloride in boiling acetonitrile.

Allyl isothiocyanate and the acid hydrazides reacted in boiling acetonitrile to give the corresponding 1-acyl-4-allyl-3-thiosemicarbazide derivatives.

The condensation of the acyl halides with aminoguanidine hydrochloride in pyridine gave the corresponding acylamidoguanidine derivatives.[5]



Acknowledgment.—The authors are indebted to Mr. W. A. Lott for his stimulating direction and encouragement throughout this investigation. Our appreciation is extended to Dr. Nettie Coy and her associates for the infrared absorption spectra and their interpretation. The microanalyses were carried out by Mr. Joseph Alicino and his associates.

Experimental Part

All melting points are uncorrected.

The following typical procedures are examples of the methods used to prepare representative types of the several groups of compounds reported in Table I.

Method A. Reaction of an Acid Chloride and Semicarbazide Hydrochloride in Pyridine. 1-(2-Furoyl)-semicarbazide.—To a stirred suspension of 37.2 g. (0.33 mole) of semicarbazide hydrochloride in 300 ml. of pyridine at 0° was added dropwise 43.5 g. (0.33 mole) of 2-furoyl chloride. After stirring for three hours, the reaction was kept overnight. The pyridine was removed *in vacuo* and the residue stirred with 200 ml. of water. The solid which separated was filtered and recrystallized from water to give 23 g. (41% yield) of product, m.p. 189–190° dec.

Method B. Reaction of a Hydrazide and an Alkylisocyanate in Acetonitrile. 4-Ethyl-1-isonicotinylsemicarbazide.—To a stirred solution of 27.4 g. (0.2 mole) of isonicotinic acid hydrazide in 600 ml. of hot dry acetonitrile was added dropwise a solution of 14.2 g. (0.2 mole) of ethyl isocyanate (Monsanto) in 100 ml. of dry acetonitrile. Within a few minutes a solid began to separate. The reaction mixture was refluxed and stirred for two hours, cooled and filtered. The solid was recrystallized from water to give 32 g. (77% yield) of product, m.p. 228–229°.

Method C. Reaction of a Hydrazide and a Dialkylcarbamyl Chloride in Toluene. 4,4-Dimethyl-1-isonicotinylsemicarbazide.—To a stirred solution of 10.8 g. (0.1 mole) of dimethylcarbamyl chloride (Monsanto) in 600 ml. of boiling toluene was added in small portions, 13.7 g. (0.1 mole) of isonicotinic acid hydrazide. The reaction mixture was refluxed and stirred for two hours, cooled and the solid filtered. The solid was refluxed with 750 ml. of acetonitrile and filtered hot. The solid which separated on cooling was filtered. The extraction was repeated twice, using the same acetonitrile. The combined solids were recrystallized from methyl ethyl ketone to give 4 g. (19% yield) of product, m.p. 197–198° dec.

Method D. Reaction of a Hydrazide and a Dialkylcarbamyl Chloride in Acetonitrile. 4,4-Dimethyl-1-(2-furoyl)-semicarbazide.—To a stirred solution of 32 g. (0.25 mole) of 2-furoic acid hydrazide in 250 ml. of hot acetonitrile was added dropwise a solution of 26.9 g. (0.25 mole) of dimethylcarbamyl chloride in 100 ml. of acetonitrile. The reaction mixture was refluxed and stirred for two hours. A solid began to separate after 15 minutes. The cooled reaction mixture was filtered, and the solid recrystallized from isopropyl alcohol to give 21 g. (36% yield) of product, m.p. 213–214°.

Method E. Reaction of an Acid Chloride and a Dialkylsemicarbazide in Acetonitrile. 4,4-Dimethyl-1-(2-thenoyl)-semicarbazide.—To a stirred solution of 5.2 g. (0.05 mole) of 4,4-dimethylsemicarbazide in 250 ml. of hot dry acetonitrile was added dropwise 7.4 g. (0.05 mole) of 2-thenoyl chloride. The reaction mixture was refluxed for four hours with continued stirring, and then cooled. The solid was filtered and recrystallized from isopropyl alcohol to give 6.3 g. (56% yield) of product, m.p. 213–214° dec.

Method F. Reaction of an Acid Chloride and Thiosemicarbazide in Pyridine. 1-(2-Furoyl)-3-thiosemicarbazide.—To a stirred suspension of 46 g. (0.5 mole) of 3-thiosemicarbazide in 200 ml. of pyridine at 0° was added dropwise 62.5 g. (0.5 mole) of 2-furoyl chloride. After stirring for one hour at 0°, the mixture solidified. The next day, 800 ml. of water was added; a clear solution was formed initially, but in a few minutes a solid began to separate. This solid was filtered. Concentration of the filtrate to one-half volume gave additional solid. The combined solids were recrystallized from 80% ethanol to give 47 g. (50% yield) of product, m.p. 204–205° dec.

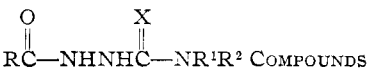
Method G. Reaction of a Hydrazide and an Alkylisothiocyanate in Acetonitrile. 4-Allyl-1-isonicotinyl-3-thiosemicarbazide.—To a stirred solution of 27.4 g. (0.2 mole) of isonicotinic acid hydrazide in 600 ml. of hot acetonitrile was added dropwise a solution of 19.8 g. (0.2 mole) of allyl isothiocyanate in 100 ml. of acetonitrile. When about half of the allyl isothiocyanate had been added, a solid began to separate. The reaction mixture was stirred and refluxed for two hours and cooled. The solid was filtered and washed successively with water and 95% ethanol to give 43 g. (90% yield) of product, m.p. 215–216° dec.

Method H. Reaction of an Acid Chloride and a Dialkylthiosemicarbazide in Pyridine. 4,4-Diethyl-1-isonicotinyl-3-thiosemicarbazide.—To a stirred suspension of 12 g. (0.08 mole) of 4,4-diethyl-3-thiosemicarbazide in 125 ml. of pyridine at 0° was added in small portions 12 g. (0.08 mole) of isonicotinyl chloride. After standing overnight, the reaction mixture was concentrated *in vacuo*, and the residue triturated with 150 ml. of water. The solid formed was filtered and recrystallized from water to give 8 g. (40% yield) of product, m.p. 178–179° dec.

Method I. Reaction of a Hydrazide and a Dialkylthiocarbamyl Chloride in Acetonitrile. 4,4-Diethyl-1-isonicotinyl-3-thiosemicarbazide.—To a stirred solution of 41.1 g. (0.3 mole) of isonicotinic acid hydrazide in 1 liter of hot dry acetonitrile was added slowly a suspension of 45.4 g. (0.3 mole) of diethylthiocarbamyl chloride (Sharples) in 200 ml. of dry acetonitrile. A solid began to separate in a few minutes. The reaction mixture was refluxed and stirred for two hours, 700 ml. of acetonitrile was distilled and the mixture cooled. The solid which separated was filtered and stirred up with 250 ml. of water; the insoluble material was filtered and recrystallized from 35% ethanol to give 7 g. (9% yield) of product, m.p. 185–186° dec.

(5) The structure of these compounds has been demonstrated recently by B. Hoggarth, *J. Chem. Soc.*, 612 (1950), who obtained identical products from the reaction of (1) S-methylisothiourea and benzoic acid hydrazide and (2) benzoyl chloride and aminoguanidine bicarbonate in pyridine.

TABLE I



RC—NHNHC—NR¹R² COMPOUNDS

Solvents for crystallization: A, water; B, methanol–ether; C, 35% ethanol; D, 80% ethanol; E, 95% ethanol; F, absolute ethanol; G, isopropyl alcohol; H, methyl ethyl ketone.

R	R¹	R²	X	Empirical formula	Method[a]	Yield, %	M.p., °C.	Solvent	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Furyl	H	H	O	$C_6H_7N_3O_3$	A	41	189–190 dec.	A	42.61	4.17	24.85	43.18	4.55	24.64
2-Thenyl	H	H	O	$C_6H_7N_3O_2S$	A	80	215–216	A	...	...	22.69[b]	...	...	22.45
4-Pyridyl	C_2H_5	H	O	$C_9H_{12}N_4O_2$	B	77	228–229	A	51.91	5.81	26.91	52.03	5.68	26.90
2-Furyl	C_2H_5	H	O	$C_8H_{11}N_3O_3$	B	58	191–193	E	48.72	5.62	21.31	48.59	5.68	21.53
2-Thenyl	C_2H_5	H	O	$C_8H_{11}N_3O_2S$	B	80	185–186	E	45.05	5.20	19.70	45.05	5.03	19.79
4-Pyridyl	$CH_2CH{=}CH_2$	H	O	$C_{10}H_{12}N_4O_2$	B	50	188–190	A	54.54	5.50	25.45	55.06	5.23	25.31
2-Furyl	$CH_2CH{=}CH_2$	H	O	$C_9H_{11}N_3O_3$	B	47	150–152	A	51.68	5.30	20.09	51.74	5.32	20.28
2-Thenyl	$CH_2CH{=}CH_2$	H	O	$C_9H_{11}N_3O_2S$	B	62	164–166	A	47.99	4.92	18.66	48.01	4.99	18.56
4-Pyridyl	$(CH_2)_{17}CH_3$	H	O	$C_{23}H_{44}N_4O_2$	B	92	173–175	E	69.40	10.25	12.95	69.41	9.39	12.81
2-Furyl	$(CH_2)_{17}CH_3$	H	O	$C_{24}H_{45}N_3O_3$	B	88	141–143	E	68.38	10.28	9.97	68.98	10.11	9.78
2-Thenyl	$(CH_2)_{17}CH_3$	H	O	$C_{24}H_{45}N_3O_2S$	B	88	127–129	E	...	...	9.60[c]	...	...	9.71
4-Pyridyl	CH_3	CH_3	O	$C_9H_{12}N_4O_2$	C	19	197–198 dec.	H	51.91	5.81	26.91	52.02	5.74	26.67
4-Pyridyl	CH_3	CH_3	O	$C_9H_{12}N_4O_2{\cdot}HCl$	E	50	180–182	B	...	...	22.90[d]	...	...	22.76
2-Furyl	CH_3	CH_3	O	$C_8H_{11}N_3O_3$	D	36	213–214	G	48.72	5.62	21.31	48.89	5.57	21.32
2-Thenyl	CH_3	CH_3	O	$C_8H_{11}N_3O_2S$	E	56	213–214	G	...	...	19.71[e]	...	...	19.63
2-Furyl	H	H	S	$C_6H_7N_3O_2S$	F	50	204–205 dec.	D	38.91	3.81	22.69	39.14	3.71	22.73
2-Thenyl	H	H	S	$C_6H_7N_3OS_2$	F	37	202–203 dec.	A, E	35.81	3.51	20.88	35.96	3.67	21.12
4-Pyridyl	$CH_2CH{=}CH_2$	H	S	$C_{10}H_{12}N_4OS$	G	90	215–216 dec.	*f*	50.81	5.12	23.71	51.07	4.97	23.42
2-Furyl	$CH_2CH{=}CH_2$	H	S	$C_9H_{11}N_3O_2S$	G	71	169–170	G, A	...	...	18.66[g]	...	...	18.84
2-Thenyl	$CH_2CH{=}CH_2$	H	S	$C_9H_{11}N_3OS_2$	G	75	198–199 dec.	E	...	...	17.42[h]	...	...	17.60
2-Furyl	CH_3	CH_3	S	$C_8H_{11}N_3O_2S$	H	34	174–175 dec.	H	45.05	5.20	19.70	45.27	5.32	19.83
2-Thenyl	CH_3	CH_3	S	$C_8H_{11}N_3OS_2$	H	14	153–155	H	41.90	4.84	18.33	42.37	4.99	17.90
4-Pyridyl	C_2H_5	C_2H_5	S	$C_{11}H_{16}N_4OS$	I	9	185–186 dec.	C	...	...	22.20[i]	...	...	22.06
4-Pyridyl	C_2H_5	C_2H_5	S	$C_{11}H_{16}N_4OS$	H	40	178–179 dec.	A	52.35	6.39	22.20	52.51	6.23	21.93
2-Furyl	C_2H_5	C_2H_5	S	$C_{10}H_{15}N_3O_2S$	H	25	117–119	A	49.77	6.27	17.42	49.74	5.99	17.15
2-Thenyl	C_2H_5	C_2H_5	S	$C_{10}H_{15}N_3OS_2$	H	24	115–116	A	46.65	5.88	16.33	46.95	5.80	16.42
4-Pyridyl	H	H	NH	$C_7H_9N_5O$	J	29	271–272	A	46.90	5.06	39.08	46.60	5.34	38.84
2-Furyl	H	H	NH	$C_6H_8N_4O_2{\cdot}HCl$[j]	J	19	256–257 dec.	F	...	...	27.38[k]	...	...	27.66
2-Thenyl	H	H	NH	$C_6H_8N_4OS$[l]	J	29	215–216 dec.	E	39.12	4.38	30.42	38.90	4.14	30.30

[a] See Experimental part. [b] *Anal.* Calcd.: S, 17.31. Found: S, 17.28. [c] *Anal.* Calcd.: S, 7.33. Found: S, 7.17. [d] *Anal.* Calcd.: Cl, 14.49. Found: Cl, 14.52. [e] *Anal.* Calcd.: S, 15.04. Found: S, 14.73. [f] Not recrystallized. [g] *Anal.* Calcd.: S, 14.23. Found: S, 14.22. [h] *Anal.* Calcd.: S, 26.58. Found: S, 26.61. [i] *Anal.* Calcd.: S, 12.71. Found: S, 12.87. [j] Free base, m.p. 209° dec. *Anal.* Calcd. for $C_6H_8N_4O_2$: C, 42.86; H, 4.80; N, 33.32. Found: C, 43.16; H, 4.59; N, 33.37. [k] *Anal.* Calcd.: Cl, 17.33. Found: Cl, 17.02. [l] Hydrochloride, m.p. 255–256° dec. *Anal.* Calcd. for $C_6H_8N_4OS{\cdot}HCl$: N, 25.39; Cl, 16.07. Found: N, 25.56; Cl, 16.23.

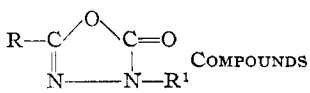
Method J. Reaction of an Acid Chloride and Aminoguanidine Hydrochloride in Pyridine. 2-Thenoylamidoguanidine.—To a stirred suspension of 28 g. (0.25 mole) of aminoguanidine hydrochloride in 100 ml. of pyridine at 0° was added dropwise 36.6 g. (0.25 mole) of 2-thenoyl chloride. After one hour of stirring, the reaction mixture solidified. The next day, the mixture was stirred up with 200 ml. of acetonitrile and filtered. The insoluble material was washed again with acetonitrile. A small amount was recrystallized from absolute ethanol to give the **hydrochloride**, m.p. 255–256° dec. The crude hydrochloride was dissolved in water, filtered from a small amount of insoluble material, and the filtrate neutralized with solid sodium bicarbonate. The precipitated solid was filtered and recrystallized from 95% ethanol to give 13.2 g. (29% yield) of product, m.p. 215–216° dec.

The following typical procedures are examples of the methods used to prepare the compounds reported in Table II.

Method K. Reaction of a Hydrazide with Phosgene. 5-(4-Pyridyl)-1,3,4-oxadiazol-2(3H)-one.—To a stirred solution of 13.7 g. (0.1 mole) of isonicotinic acid hydrazide in 150 ml. of water at 0° was added slowly 10 g. (0.1 mole) of phosgene in 50 ml. of toluene. The product separated directly and the reaction mixture was kept overnight. The solid was filtered and recrystallized from water to give 9 g. (55% yield) of product, m.p. 274–276° dec.

Method L. Reaction of a Hydrazide and a Dialkylcarbamyl Chloride in Pyridine. 5-(4-Pyridyl)-1,3,4-oxadiazol-

TABLE II



COMPOUNDS

R	R¹	Empirical formula	Method[a]	Yield, %	M.p., °C.	Solvent	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4-Pyridyl	H	$C_7H_5N_3O_2$	L	41	273–275 dec.	A	51.54	3.09	25.77[b]	51.72	3.11	25.84
4-Pyridyl	H	$C_7H_5N_3O_2$	K	55	274–276 dec.	A	51.54	3.09	25.77	51.60	3.30	25.88
3-Pyridyl	H	$C_7H_5N_3O_2$	L	36	198–200	H	51.54	3.09	25.77	51.80	3.23	25.80
2-Pyridyl	H	$C_7H_5N_3O_2$	L	14	190–192	H	51.54	3.09	25.77	51.86	3.35	26.31
4-Quinolyl	H	$C_{11}H_7N_3O_2$	L	33	277–278 dec.	E	61.95	3.31	19.71	62.47	3.78	19.53
4-Pyridyl	$CH(CH_3)_2$	$C_{10}H_{11}N_3O_2$	L	39	129–131	A	58.51	5.40	20.48	58.22	5.47	20.48
2-Furyl	H	$C_6H_4N_2O_3$	K	51	115–117	A	47.38	2.65	18.42	47.60	2.75	18.56
2-Thenyl	H	$C_6H_4N_2O_2S$	K	60	129–130	A	42.86	2.40	16.67	42.93	2.77	16.63

[a] See Experimental part. [b] *Anal.* Calcd.: O, 19.62; Found, O, 19.6. The authors wish to acknowledge the coöperation of Mr. Oliver Sundberg, Calco Chemical Division, American Cyanamid Co., Bound Brook, N. J., for the determination of oxygen.

2(3H)-one.—To a stirred suspension of 27.4 g. (0.2 mole) of isonicotinic acid hydrazide in 300 ml. of pyridine was added 21.5 g. (0.2 mole) of dimethylcarbamyl chloride, at room temperature. The temperature rose to 35°; after stirring for one-half hour, a clear solution had formed. This mixture was refluxed for 2.5 hours and allowed to cool. The crystalline solid was filtered. The filtrate was concentrated to dryness *in vacuo*, the residue was stirred with water and filtered to give additional material. The combined solids were recrystallized from water to give 17 g. (41% yield) of product, m.p. 273–275° dec.; a mixed m.p. with the product from K was 273–275° dec.

The same product was obtained by the reaction of isonicotinic acid hydrazide and diethylcarbamyl chloride in pyridine as described in method L. The yield was 37%, m.p. 275–276° dec.; a mixed m.p. with the product from K was 274–276° dec.

The Stepwise Formation of 5-(4-Pyridyl)-1,3,4-oxadiazol-2(3H)-one.—To a stirred suspension of 13.7 g. (0.1 mole) of isonicotinic acid hydrazide in 150 ml. of pyridine at room temperature was added dropwise 10.8 g. (0.1 mole) of dimethylcarbamyl chloride. The reaction mixture was stirred for six hours at room temperature and kept overnight. A clear solution formed after 0.5 hour stirring. The pyridine was removed *in vacuo*, keeping the water-bath temperature below 40°. The semisolid residue was washed with acetonitrile, filtered and recrystallized from acetonitrile to give 12.5 g. (60% yield) of product, m.p. 197–198° dec. A mixed m.p. with 4,4-dimethyl-1-isonicotinylsemicarbazide was 197–198° dec.

Five grams (0.024 mole) of the 4,4-dimethyl-1-isonicotinylsemicarbazide obtained above in 100 ml. of pyridine was refluxed while nitrogen, at the rate of about five bubbles per second, was passed through the solution. The exit gases were bubbled through water to absorb the dimethylamine. The formation of dimethylamine occurred as follows: during the first 2.5 hours, 0.009 mole; during the next six hours, 0.009 mole; and during the following seven hours, 0.002 mole; the total was 0.020 mole or 83% of the theoretical. The dimethylamine was characterized subsequently as N,N-dimethyl-*p*-toluenesulfonamide, m.p. 79–80°; a mixed m.p. with an authentic specimen showed no depression.

The pyridine solution remaining after the removal of dimethylamine was concentrated *in vacuo*. The residual solid was triturated with 50 ml. of water and filtered to give 3.8 g. (97% yield) of product, m.p. 271–272° dec. Recrystallization from water raised the melting point to 273–274° dec.; a mixed m.p. with 5-(4-pyridyl)-1,3,4-oxadiazol-2(3H)-one showed no depression.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthetic Hypotensive Agents. I. Some Powerful New Autonomic Ganglionic Blocking Agents Derived from Nicotine

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While searching for new useful hypotensive drugs among ganglionic blocking agents it was felt that valuable agents might be obtained by modifying the nicotine molecule. Catalytic hydrogenation of nicotine salts, the dihydrochloride and a series of di-quaternary alkiodides, gave a di-secondary amine and a series of di-tertiary amines, respectively. Reaction of one of the di-tertiary amine reduction products with several alkyl halides gave a new series of di-quaternary ammonium salts. All of these compounds are derivatives of 3-(4'-aminobutyl)-piperidine, and all, the di-secondary and the di-tertiary amines as well as the di-quaternary ammonium salts, possess marked hypotensive action. Several members of the various series have powerful and useful activities in this sense.

In seeking for useful new hypotensive agents among possible ganglionic blocking agents it was felt that exploitation of the readily available and pharmacologically very active nicotine might furnish valuable compounds. Nicotine was deemed a starting intermediate worthy of chemical modification for several reasons. Firstly, it is itself endowed with strong pharmacological actions, although it is too toxic for any great usefulness as a drug. Secondly, as an undesired by-product of the great tobacco industry it is quite readily available in moderate quantities, and finds its main use only as an insecticide. Thirdly, much of our recent work has centered around salts of di- or polyfunctional organic bases, of which nicotine is a di-basic representative. It was believed that by suitable chemical transformations some derivatives of nicotine might be obtained in which certain of the intense pharmacological effects of nicotine might be retained or enhanced while its toxicity might be considerably diminished. All of these expectations have been realized to a very satisfactory degree.

In the first attempts to modify the chemical structure and pharmacological properties of nicotine, the latter was treated with a series of alkyl halides to give the di-quaternary ammonium salts. Of the series of alkyl halides used for quaternization methyl iodide gave a nearly quantitative yield of the di-methiodide, ethyl iodide gave about a 60% yield of crystalline di-ethiodide, *n*-propyl iodide gave a 10 to 20% recovery of crystalline di-propiodide, while no crystalline solid has so far been isolated from the reaction with *n*-butyl iodide. In each of the cases where the yield of crystalline product was considerably less than 100% the calculated amount of an ether insoluble oil was recovered. Since these non-crystalline fractions are ether insoluble and are salt-like in nature they may represent either mixtures of mono- and di-quaternary salts, or possibly mixtures of stereoisomers which interfere with further crystallization of solid products.

The crystalline di-quaternary salts (I of Chart I) were subjected to catalytic hydrogenation in methanol solution using Adams catalyst at room temperature and three atmospheres overpressure of hydrogen. As platinum is usually an inferior debenzylation catalyst compared with palladized charcoal it was anticipated that only the pyridine ring of the di-salts would be reduced to piperidine, leaving the pyrrolidine ring intact, and giving products of structure III (Chart I). In agreement with this idea the first few hydrogenations showed an absorption of three moles of hydrogen per mole of di-salt. Nevertheless all subsequent reductions showed an uptake of four moles of hydrogen per mole of salt, corresponding presumably to a pre-