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Monoamine Oxidase Inhibitors—I. 1-Alkyl and 1-Aralkyl-2-(picolinoyl and 5-methyl-3-isoxazolylcarbonyl)hydrazines

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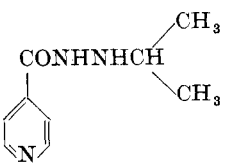
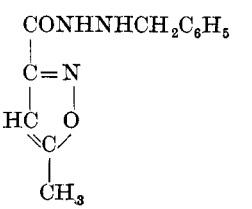
In the course of the clinical investigation of 1-isopropyl-2-isonicotinoylhydrazine (I),* a compound prepared by Fox[1] of these laboratories in an antituberculosis drug programme, a marked central activity, manifested in improvement of appetite and attitude, was noted.[2] This led to the successful investigation of the compound in psychotic depression.[3] Further interest in the compound was stimulated by the reports of its pain-blocking effect in angina pectoris[4, 5] which were amply confirmed and mark a new approach to the management of this disease. Clinical experience with this valuable drug indicated that it should be handled with considerable skill since the margin between therapeutic efficiency and side effects (chiefly hepatotoxicity and orthostatic hypotension) was not great.



(I)

(II)



(III)

Almost simultaneously with these clinical findings,[2] the powerful monoamine oxidase inhibiting effect of iproniazid was demonstrated by Zeller *et al.*[6, 7] and numerous publications have attempted to link this activity with the therapeutic results.[8]

* Iproniazid; Marsilid ®

It was therefore of interest to examine related hydrazine structures for their effect on monoamine oxidase *in vitro* and *in vivo*. In the latter case, the quantitative effect on the enzyme in various organs was of interest since it might be related to the effectiveness of a drug in different disorders or to its toxic effects.

This led, in the first place, to the examination in our pharmacology laboratories of a large number of hydrazines previously synthesized in an antituberculosis drug programme and this resulted *inter alia* in the preparation of a new series of derivatives of hydrazides where the acyl group was a picolinoyl or an isoxazolyl residue. These are (in part) reported in this first paper. In the interim, reports by other workers on the syntheses of hydrazides for similar purposes have appeared.[9-11]

The syntheses of the compounds reported here present no special difficulties. The following reaction scheme was generally employed.

$$RCHO + NH_2NHCOR' \longrightarrow RCH{=}NNHCOR' \quad \text{(IV)}$$

$$\xrightarrow[\text{or (b) } LiAlH_4 \text{ or (c) Na(or K)}BH_4]{H_2 \text{ (a) 10\% Pd–C}} RCH_2NHNHCOR' \quad \text{(V)}$$

R = alkyl or aralkyl R′ = picolinoyl or 5-methyl-3-isoxazolylcarbonyl

The acyl hydrazones (IV) and the acyl-, alkyl- or aralkylhydrazines (V) prepared are listed in Tables I and II. For the last step in the synthesis, procedure (a) generally gave the best yields (R′ = picolinoyl) and platinum was inferior to palladium as a catalyst. Hydrogenation with Pd–C was found to be improved by the addition of acetic acid. When R′ was 5-methyl-3-isoxazolylcarbonyl, catalytic procedures could not be used on account of the easy hydrogenolysis of the ring and either procedure (b) or (c) was employed. An alternative procedure of condensing the alkyl- or aralkylhydrazine with a carboxylic ester was also successfully employed. This generally gave better yields when the procedures were worked out and was also more attractive and economical for large-scale production.

Table I.[a,b] Hydrazones (R′=NNHCOR″)

R′	R″CO	Formula	Cryst. from	m.p. °C	% Yield[c]	Analysis			
						Calcd.		Found	
						C	H	C	H
Propylidene	Picolinoyl	$C_9H_{11}N_3O$	Ethanol	70– 71	50	61·0	6·2	61·2	5·8
Cyclohexylidene	,,	$C_{12}H_{15}N_3O$	,,	148–150	86	66·3	7·0	66·2	6·7
4-Methoxybenzylidene	,,	$C_{14}H_{13}N_3O_2$	,,	145–146	88	65·9	5·1	66·0	5·3
2-Hydroxybenzylidene[d]	,,	$C_{13}H_{11}N_3O_2$		175–176	72	64·7	4·6	65·0	5·0
Ethylidene	5-Methyl-3-isoxazolylcarbonyl	$C_7H_9N_3O_2$	Ethanol	159–160	85	50·3	5·4	49·4	5·6
Propylidene	,,	$C_8H_{11}N_3O_2$	,,	137–138	80	53·0	6·1	52·9	5·9
Isopropylidene[e]	,,	$C_8H_{11}N_3O_2$	Acetone or Ethanol	106–109	83	53·0	6·1	53·1	5·8
Butylidene	,,	$C_9H_{13}N_3O_2$	Ethanol	138–139	90	55·4	6·7	55·1	6·7
n-Amylidene	,,	$C_{10}H_{15}N_3O_2$	,,	114–115	42	57·4	7·2	57·5	6·9
Isoamylidene	,,	$C_{10}H_{15}N_3O_2$	,,	125–126	64	57·4	7·2	57·2	7·0
n-Heptylidene	,,	$C_{12}H_{19}N_3O_2$	,,	114–115	95	60·8	8·1	61·0	8·1
n-Nonylidene	,,	$C_{14}H_{23}N_3O_2$	,,	117–118	96	63·4	8·7	63·7	8·5
Benzylidene	,,	$C_{12}H_{11}N_3O_2$	,,	199–200	85	62·9	4·8	62·9	5·0
4-Methoxybenzylidene	,,	$C_{13}H_{13}N_3O_2$	,,	187–188	88	60·2	5·1	60·0	5·1
2-Chlorobenzylidene	,,	$C_{12}H_{10}ClN_3O_2$	,,	172–173	97	54·6	3·8	55·0	3·8
4-Isopropylbenzylidene	,,	$C_{15}H_{17}N_3O_2$	,,	170–172	76	66·3	6·3	66·4	6·2
Phenethylidene	,,	$C_{13}H_{13}N_3O_2$	,,	157–158	63	64·2	5·4	64·1	5·6
α-Methylphenethylidene	,,	$C_{14}H_{15}N_3O_2$	,,	126–127	81	65·3	5·9	65·4	5·6
2-Hydroxybenzylidene	,,	$C_{12}H_{13}N_3O_3$	,,	220–221	91	58·8	4·5	59·5	4·6

[a] Most hydrazones tested were colourless compounds and were crystallized from ethanol with a few exceptions listed.
[b] All hydrazones were prepared by heating the appropriate aldehyde or ketone with the acid hydrazide in ethanol or isopropyl alcohol.
[c] Yields were calculated on the acid hydrazides used.
[d] Crystallized from isopropyl alcohol. [e] Prepared by heating in acetone solution. Recrystallized from acetone or ethanol.

Table II.[a] Hydrazines (R′—NHNHCOR″)

R′	R″CO	Formula	Procedure	m.p. °C.	% yield	Analysis			
						Calcd.		Found	
						C	H	C	H
Ethyl	Picolinoyl	$C_8H_{11}N_3O$	A or B	[b]	30–60	58·2	6·7	57·9	7·2
n-Propyl	,,	$C_9H_{13}N_3O$	A[c]	[d]	30–40	60·3	7·3	60·5	6·8
n-Butyl	,,	$C_{10}H_{15}N_3O$	A	[e]	41	62·1	7·8	62·2	8·1
Cyclohexyl	,,	$C_{12}H_{17}N_3O$	A[f]	136–137	60	65·7	7·8	65·2	7·7
Benzyl	,,	$C_{13}H_{13}N_3O$	A	86– 87	82	68·7	5·8	69·1	6·0
4-Methoxybenzyl	,,	$C_{14}H_{15}N_3O_2$	A	62– 64	14	65·4	5·8	66·1	5·7
2-Hydroxybenzyl	,,	$C_{13}H_{13}N_3O$	A	152–153	38	64·2	5·4	63·9	5·1
Ethyl	5-Methyl-3-isoxazolyl-carbonyl	$C_7H_{11}N_3O_2$	B	80– 81[g]	22	49·7	6·6	49·4	6·4
n-Propyl	,,	$C_8H_{13}N_3O_2$	B	48– 50	48	52·4	7·2	52·5	7·0
Isopropyl	,,	$C_8H_{13}N_3O_2$	B or C	85– 87	B–10 C–50/70	52·4	7·2	52·8	7·5
n-Heptyl	,,	$C_{12}H_{21}N_3O_2$	B	57– 58[h]	10	60·2	8·8	61·3	9·0
n-Nonyl	,,	$C_{14}H_{25}N_3O_2$	B	42– 44[i]	8	[j]			
Benzyl	,,	$C_{12}H_{13}N_3O_2$	B and C	105–106	[k,l]	62·4	5·7	62·7	6·0
4-Methoxybenzyl	,,	$C_{13}H_{15}N_3O_3$	B	88– 89	60	59·8	5·8	60·1	5·9
2-Chlorobenzyl	,,	$C_{12}H_{12}ClN_3O_2$	B	100–101	16	54·3	4·6	54·6	4·3
4-Isopropylbenzyl	,,	$C_{15}H_{19}N_3O_2$	B	107–108	50	65·9	7·0	65·6	6·7
α-Methylphenethyl	,,	$C_{14}H_{17}N_3O_2$	B or C	86– 87	[m]	64·9	6·6	64·4	6·0

[a] Most compounds in this table were colourless and crystallized from ethanol, unless otherwise noted.

[b] b.p. 118–120°C/2 mm; n_D^{22} 1·5455.

[c] PtO_2 also may be used in procedure (a) for this compound.

[d] b.p. 140–150°C/1–2 mm; n_D^{21} 1·5682.

[e] b.p. 165–175°C/1–2 mm; n_D^{22} 1·5268.

[f] This compound was prepared by procedure (a) with PtO_2.

[g] Crystallized from methanol.

[h] Crystallized from petroleum ether (b.p. 30–60°).

[i] Amorphous yellow precipitate from petroleum ether (b.p. 30–60°C).

[j] Calcd. for $C_{14}H_{25}N_3O_2$: N, 15·8. Found: N, 16·2.

[k] May also be prepared by the reaction of benzylhydrazine on the methyl, ethyl, or phenyl esters in yields of 70%, 65%, and 35% respectively.

[l] 55% yield using KBH_4 and purification through the hydrochloride salt.

[m] Procedure (b) using ethyl ether as a solvent, yield 22%; or tetrahydrofuran, yield 28%. Procedure (c) using $NaBH_4$, yield 77%, and KBH_4, yield 60%.

Pharmacological

The *in vitro* and *in vivo* monoamine oxidase screening tests, and the 5-hydroxytryptophan potentiation test were related to the activity of iproniazid. In all cases, iproniazid was arbitrarily given the value of one, and the compounds screened were thus more active than iproniazid with a rating greater than one, or less active with a rating less than one. With this method of rating, the activity and toxicity of the structures appear to be a function of both the acyl and alkyl or aralkyl groups. Generally, maintaining the acyl group constant, the activity with an alkyl group rises to a maximum at three or four carbon atoms and declines to markedly lower activity at seven to nine carbon atoms. With an aralkyl group, when the alkylene chain has one carbon atom (benzyl), the activity is maximal. Substitution of the benzyl group with halogen, alkyl, alkoxyl or hydroxyl groups as far as carried out did not improve the activity (Table III). The changes in the acyl group generally favour the 5-methyl-3-isoxazolylcarbonyl over the picolinoyl derivatives with respect to activity and in general the therapeutic ratio favoured the isoxazolyl compounds. The pharmacological[12, 13] and subsequent clinical trials[14] with the most promising compounds in both series (II and III) clearly demonstrated the superiority of isocarboxazid both in activity and in the relative infrequency of side effects, and it has been introduced into clinical practice.

Experimental*†

Procedure (a). Reduction of Acylhydrazones using palladium

The acylhydrazone (0·50 moles) previously prepared, or prepared *in situ* by mixing equivalent quantities of the alkylhydrazine and the desired aldehyde or ketone, was dissolved in ethanol (1 l.) and 10 per cent palladium (15 g on carbon catalyst) was added. The solution was reduced under 500 lb/in^2 of hydrogen, usually at 50° and occasionally at 80°. After absorption of the theoretical amount of hydrogen, the solution was cooled and the catalyst removed by filtration. Occasionally the reduced product

* All melting points are corrected.

† We are indebted to Dr. A. Steyermark and his associates for the microanalyses.

Table III.[a] (R′—NHNHCOR″). Pharmacological Data

R′	R″CO	Monoamine oxidase inhibition in rats[b]		5-HTP[h] potentiation in mice[g]	Toxicity[l] 24 h I.P. LD50 in mice mg/kg
		Liver *in vitro*[c, f]	Brain *in vivo*[d, f]		
Iproniazid[e] Isopropyl	Isonicotinoyl	1·0	1·0	1·0[c]	1100 ± 50
Ethyl (as phosphate)	Picolinoyl	5·0	5·0	4·6	265 ± 21
n-Propyl	,,	1·0		2·0	290 ± 8
Isopropyl[i]	,,	2·0	9·0	6·0	275 ± 9
n-Butyl	,,	0·6	2·0	5·7	[m]
Cyclohexyl	,,	0·2		8·0	225
Phenyl[j]	,,	0·3	inactive	6·0	> 400
Benzyl (Ro 5–0700)	,,	7·0	25·0	10·0	235 ± 38
4-Methoxybenzyl[k]	,,	0·16	1·0	2·0	> 400
2-Hydroxybenzyl	,,	1·0	< 1·0	< 1·0	> 400
Methyl	5-Methyl-3-isoxazolyl-carbonyl	1·0		< 1·0	108 ± 2
Ethyl	,,	3·0	8·0	8·0	200 ± 12
n-Propyl	,,	3·0	21·0	3·5	234 ± 47
Isopropyl	,,	2·0	16·0	6·0	> 400
n-Butyl	,,	5·0	12·5	8·0	342
n-Amyl HCl	,,	1·8	0·7		355 ± 5

Isoamyl HCl	,,	1·8	2·0	4·0	>400
n-Heptyl	,,	inactive		<1·0	185
n-Nonyl	,,	0·8		<1·0	350
Benzyl (Ro 5–0831/1)	,,	7·0	33·0	20·0	138±13
4-Methoxybenzyl HCl	,,	1·7	3·0	8·0	219±47
2-Chlorobenzyl	,,	0·9	1·4	4·0	180
4-Isopropylbenzyl	,,	0·8	0·7	4·0	335±20
Phenethyl HCl	,,	2·2	2·3	6·0	260±30
α-Methyl-phenethyl	,,	2·5	4·0	5·0	150±13
2-Hydroxybenzyl HCl	,,	1·0	0·6	<1·0	>400

See Notes *n* and *o* for additional values on bis compounds.

[a] The pharmacological data was obtained under the direction of Dr. L. O. Randall, Director of the Pharmacological Laboratories. The monoamine oxidase inhibition was determined by Mrs. Carol Callahan, and the 5-hydroxytryptophan potentiation was determined by Mrs. B. H. Kappell.

[b] The methods are described in detail in reference 13.

[c] A Warburg determination of oxygen uptake on rat liver mitochrondia.[13]

[d] Run on rat brain 1 h after I.P. administration of the drug.[13] This procedure is based on the work of A. N. Davison [*Biochem. J.*, **67**, 312 (1957)].

[e] In each test, iproniazid was used as a standard and arbitrarily assigned a value of one. Therefore, all other compounds were related to iproniazid and a compound having an MAO of 8·0 *in vivo* means that it is eight times as active as iproniazid. The use of percentages has been avoided by nearly all workers in this field on the basis that such usage would be confusing.

[f] On a molar basis.

[g] On a weight basis.

[h] 5-HTP is 5-hydroxytryptophan.

[i] T. S. Gardner, E. Wenis, and John Lee, *J. org. Chem.*, **21**, 530 (1956).

[j] For comparative purposes, 1-phenyl-2-picolinoyl hydrazine was prepared. [H. Meyer and J. Mally, *Monatsh.*, **33**, 393 (1912)].

[k] With a slight excess of HCl in solution.

[l] Toxicity work was carried out by Dr. E. Keith and his associates of the Pharmacological Laboratories.

[m] 72 h LD50 in mice, I.V. 68 mg/kg.

[n] A N_1 bis-compound obtained as a by-product in an attempt to prepare 1-methyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine was 1-methyl-1,2-bis-(5-methyl-3-isoxazolylcarbonyl)hydrazine; monoamine oxidase inhibition, *in vitro*, 0·15; *in vivo*, 0·4; 24 h LD50 in mice, I.P. 235±13.

[o] A bis-compound obtained as a by-product in an attempt to prepare 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine was 1-benzyl-1,2-bis(5-methyl-3-isoxazolylcarbonyl)hydrazine; monoamine oxidase inhibition, *in vitro*, 5; *in vivo*, 7; 5–HTP, 3. 24 h LD50 in mice, I.P., 228±5 mg/kg.

crystallized, in which case the mixture was heated to dissolve the product before filtration; the filtrate was evaporated to dryness *in vacuo* and the residue crystallized from ethanol or isopropyl alcohol.

Procedure (b). Reduction of Acylhydrazones by Lithium Aluminium Hydride

Acyl hydrazone (0·50 moles) was added in finely pulverized form to a solution of lithium aluminium hydride (19 g) in dry ether (3 l.). Addition of the powder required about 2 h. The reaction solution was stirred for 4 h, stood overnight, and then the excess $LiAlH_4$ was destroyed by cautious addition of ethyl acetate (150 ml) with stirring. The stirring was continued for ½ h and ice water (100 ml) was then dropped in over a period of 15 min. After stirring for a further ½ h, the suspension was filtered; the ether was removed *in vacuo*, and the residue crystallized from methanol or ethanol.

Procedure (c). Reduction by Sodium or Potassium Borohydride

Acyl hydrazone (0·50 moles) was dissolved in a mixture of methanol (1700 ml) and water (300 ml) using a good mechanical stirrer. Over a period of ½ h, sodium borohydride (40 g), or potassium borohydride (55 g), was added portionwise as the temperature of the solutions rose to about 50°. After the final addition of the borohydride, stirring was continued for ½ h, then acetic acid (50 g) was added and stirring continued for an additional ½ h in order to destroy the excess of borohydride. The solvents were removed *in vacuo* and toluene or benzene (500 ml) was added and distilled off *in vacuo* in order to remove the final traces of water. The residue was extracted with boiling ethyl ether three times using 1 l. of ether for each extraction. To the combined ether extracts 10 N HCl in ethanol (125 ml) was added, and the mixture cooled in a solid CO_2–acetone bath for about 2 h to crystallize the hydrochloride. The hydrochlorides were recrystallized from ethanol. For the preparation of the free bases, the crude hydrochloride was dissolved or suspended in water (500 ml) and made basic to pH 10 with ammonium hydroxide. Solid bases were filtered off, washed with water and recrystallized,

usually from ethanol. Otherwise, the base was extracted with ether, dried and on concentration the base crystallized.

2-Ethyl-1-picolinoylhydrazine phosphate hydrate. Pure distilled 2-ethyl-1-picolinoylhydrazine (Table II) (5·0 g) was added to ethanol (50 ml). To this solution, 85 per cent phosphoric acid (5 ml) was added. On cooling at 4° for 14 h, the phosphate crystallized as a colourless compound, and was recrystallized from ethanol; m.p. 126–127° (3·0 g yield).

Anal. Calcd. for $C_8H_{11}N_3O.H_2O$: C, 36·5; H, 5·4. Found: C, 36·9; H, 5·4.

1-n-Butyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine hydrochloride. 1-Butylidene-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine (Table I) (98·0 g) was reduced with $LiAlH_4$ by procedure (b). A gel was obtained on removal of the ether. It was extracted with boiling benzene (1·5 l.) and the benzene extract concentrated to an amorphous residue. This residue was dissolved in ethanol (100 ml) to which was added 10 N HCl in ethanol (20 ml) and on addition of ether, the product separated and was crystallized from ethanol; m.p. 155–156° (3·5 g yield).

Anal. Calcd. for $C_9H_{15}N_3O_2.HCl$: C, 46·2; H, 6·8. Found: C, 45·9; H, 6·7.

1-n-Amyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine hydrochloride. 1-*n*-Amylidene-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine (Table I) (46·0 g) was reduced by procedure (b) using $LiAlH_4$. The ether layer was evaporated to give a solid residue, which on treatment with ethanol (100 ml) and 10 N hydrogen chloride in ethanol (23 ml) gave a colourless hydrochloride, which was recrystallized from ethanol; m.p. 155–157° (16·0 g yield).

Anal. Calcd. for $C_{10}H_{17}N_3O_2.HCl$: C, 48·5; H, 7·3. Found: C, 48·4; H, 7·2.

1-Isoamyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine hydrochloride. 1-Isoamylidene-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine (Table I) (71 g) was reduced with $LiAlH_4$ using procedure (b). The product was purified and crystallized as described for the normal isomer above; m.p. 185–186° (12·0 g yield).

Anal. Calcd. for $C_{10}H_{17}N_3O_2.HCl$: C, 48·5; H, 7·3. Found: C, 48·5; H, 7·3.

1-Phenethyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine hydrochloride. 1-Phenethylidene-2-(5-methyl-3-isoxazolylcarbonyl)-

hydrazine (Table I) (83 g) was reduced with $LiAlH_4$ using procedure (b). The product recovered from the ether was dissolved in ethanol solution (100 ml) and the hydrochloride formed by the addition of 10 N HCl in ethanol (20 ml). The colourless salt which separated was recrystallized from ethanol; m.p. 187–189° (24 g yield).

Anal. Calcd. for $C_{13}H_{15}N_3O_2.HCl$: C, 55·5; H, 5·7. Found: C, 55·7; H, 5·7.

1-(2-Hydroxybenzyl)-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine hydrochloride. A solution of 1-(2-hydroxybenzylidene)-2-(5-methyl-3-isoxazolylcarbonyl)-hydrazine (Table I) (30 g) in methanol (500 ml) was heated under reflux with stirring and sodium borohydride (20 g) ($NaBH_4$) was added portionwise. Heating was continued for 24 h then the solution was cooled and acetic acid (50 ml) added. The solvent was removed *in vacuo* and the residue extracted three times with 100 ml portions of ethanol. On addition of 10 N HCl in ethanol (30 ml), the hydrochloride crystallized. It was recrystallized from ethanol and petroleum ether; m.p. 157–159° (18 g yield).

Anal. Calcd. for $C_{12}H_{13}N_3O.HCl$: C, 50·7; H, 5·0. Found: C, 50·0; H, 5·3.

1-Benzyl-2-picolinoylhydrazine hydrobromide. 1-Benzyl-2-picolinoylhydrazine (Table II) (3 g) was dissolved in ethanol (20 ml) and to this solution 8 N HBr in ethanol (3 ml) was added. On addition of ether, the salt separated and was recrystallized from ethanol–ether; m.p. 163–164° (2·5 g yield).

Anal. Calcd. for $C_{13}H_{13}N_3O.HBr$: C, 50·6; H, 4·5; Br, 25·5. Found: C, 50·3; H, 4·5; Br, 25·8.

Attempts to prepare the hydrochloride salt gave a crystalline material whose analysis indicated about $1\frac{1}{2}$ molecules of hydrogen chloride.

1-Benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine hydrochloride. To a solution of 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)-hydrazine (Table II) (50 g) in hot ethanol (90 ml), 10 N HCl in ethanol (28 ml) was added. On cooling to 30° and dilution with ether (300 ml), a granular hydrochloride was obtained which was recrystallized from ethanol; m.p. 190–192° (55 g yield).

Anal. Calcd. for $C_{12}H_{13}N_3O_2.HCl$: C, 53·8; H, 5·3; Cl, 13·3. Found: C, 54·1; H, 5·4; Cl, 13·2.

1-(4-Methoxybenzyl)-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine hydrochloride. 1-(4-Methoxybenzyl)-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine (Table II) (25 g) was dissolved in ethanol (150 ml) and 10 N HCl in èthanol (25 ml) added. On addition of ether (100 ml), the hydrochloride separated and was recrystallized as a colourless compound from ethanol–ether; m.p. 166–167° (16 g yield).

Anal. Calcd. for $C_{13}H_{15}N_3O_3.HCl$: Cl, 11·9. Found: Cl, 11·7.

1-Methyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine. Ethyl 5-methyl-3-isoxazolecarboxylate (32 g) and methylhydrazine (9 g) in ethanol (200 ml) were heated at 60° for 1 h. The excess solvent and methylhydrazine were removed by distillation at 20 mm. On addition of ethanol (50 ml), the product crystallized and was recrystallized from ethanol as a colourless compound; m.p. 93–94° (2·5 g yield).

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46·5; H, 5·8; N, 27·2. Found: C, 46·4; H, 5·4; N, 27·2.

1-Methyl-1,2-bis(5-methyl-3-isoxazolylcarbonyl)hydrazine. Methyl hydrazine (23 g) was dissolved in dry pyridine (800 ml). The solution was cooled to 0° in an ice bath and to this solution 5-methyl-3-isoxazolylcarbonyl chloride (73 g) was carefully added dropwise, since the reaction is quite vigorous. After stirring for 24 h, a solution of 10 per cent water in acetone (100 ml) was added and the solvents were then removed *in vacuo*. The solid residue was dissolved in chloroform and the chloroform solution extracted twice with 10 per cent sodium bicarbonate solution and finally with ice-water. The chloroform was removed *in vacuo* and the residue was crystallized from methanol four times, giving colourless crystals, m.p. 131–132° (3·5 g yield).

Anal. Calcd. for $C_{10}H_{12}N_4O_4$: C, 50·0; H, 4·6; N, 21·2. Found: C, 49·6; H, 4·4; N, 21·4.

1-Benzyl-1,2-bis(5-methyl-3-isoxazolylcarbonyl)hydrazine. Benzylhydrazine (12 g) was dissolved in dry ether (300 ml). To this solution was added 5-methyl-3-isoxazolylcarbonyl chloride (14·6 g) in dry ether (100 ml) when refluxing spontaneously occurred. A precipitate separated and the suspension was stirred overnight. The separated precipitate was crystallized from ethanol, then washed with dilute ammonium hydroxide solution and recrystallized from ethanol; m.p. 155–156° (10·0 g yield).

Anal. Calcd. for $C_{17}H_{16}N_4O_4$: C, 60·0; H, 4·7. Found: C, 60·3; H, 4·7.

The same compound was prepared by the reaction of 5-methyl-3-isoxazolylcarbonyl chloride on 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine in ether solution.

Phenyl 5-methyl-3-isoxazolecarboxylate. 5-Methyl-3-isoxazolylcarbonyl chloride (29 g) was dissolved in dry ether (500 ml). To this solution was added dry pulverized sodium phenoxide (23 g). The suspension was stirred for 14 h, filtered, and the ether removed. The solid residue was distilled at 160–165°/2 mm. The distillate was recrystallized from ether, giving colourless crystals; m.p. 49–50° (27 g yield).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65·0; H, 4·5. Found: C, 65·0; H, 4·5.

4-Nitrophenyl 5-methyl-3-isoxazolecarboxylate. Sodium 4-nitrophenoxide (40 g) was added to dry ether (1 l.) containing 5-methyl-3-isoxazolylcarbonyl chloride (36 g). The suspension was stirred and heated at reflux for 2 h, then filtered and the solvent removed. On cooling, the product crystallized and was recrystallized from ether, giving a cream coloured powder, m.p. 134–135° (11·5 g yield).

Anal. Calcd. for $C_{11}H_8N_2O_5$: C, 53·2; H, 3·3. Found: C, 53·4; H, 3·1.

Summary. In the search for improved monoamine oxidase inhibitors, a number of alkyl and aralkyl derivatives of picolinoyl hydrazine and 5-methyl-3-isoxazolylcarbonylhydrazine have been made. 1-Benzyl-2-(5-methyl-3-isoxazolylcarbonyl)-hydrazine (III)* and 1-benzyl-2-picolinoylhydrazine (II), showed the most interesting activities.

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* Isocarboxazid; Marplan$^{T.M.}$

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