Anal. Calcd. for $C_{12}H_{14}ClN_3$: C, 61.14; H, 5.99; N, 17.83; Cl, 15.04. Found: C, 61.23; H, 6.21; N, 17.80; Cl, 14.90.

3-Cyano-3-phenyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (XXVII). Phenylacetonitrile (4.62 ml., 0.04 mole) was dissolved in 50 ml. of dry toluene in a 500-ml. flask which was equipped with a gas inlet tube, powder funnel, and a mechanical stirrer. To this was added, with stirring in a nitrogen atmosphere, 1.6 g. (0.04 mole) of sodamide which had been pulverized under toluene. Excess toluene was used to wash the sodamide into the flask. The powder funnel was immediately replaced with a condenser equipped with a soda-lime tube. Stirring was continued for 15 min., at which time 9.16 g. of 1-(2-chloroethyl)-2-chloromethylbenzimidazole in 125 ml. of dry toluene was added dropwise over a period of 30 min.[11] The mixture was refluxed for 2 hr., cooled, and another 1.6 g. of pulverized sodamide was added. The mixture was then refluxed for 4 hr., filtered hot, and the filtrate cooled overnight. The precipitate was washed with petroleum ether (b.p. 30–60°) and recrystallized from benzene-hexane, yield 17%, m.p. 215–216.5°.

Anal. Calcd. for $C_{18}H_{15}N_3$: C, 79.09; H, 5.53; N, 15.37. Found: C, 79.06; H, 5.66; N, 15.53.

3-Carboxy-3-phenyl-1,2,3,4-tetrahydropyrido-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole hemihydrate (XXVIII). One gram of 3-cyano-3-phenyl-1,2,3,4-tetrahydropyrido[1,2-a]-benzimidazole was added gradually to a solution of 8 g. of concd. sulfuric acid and 2 g. of water. The solution was heated at 145–150° for 2 hr. The *p*H of the solution was adjusted to about 5 with 40% sodium acetate solution and the solution cooled for 1 hr. The solid so obtained was removed, washed with water, and dried; yield 86%, m.p. 274–276°. It was recrystallized from ethanol-water and dried at 100°/4 mm. for 4 hr., m.p. 285–287° dec.

Anal. Calcd. for $C_{18}H_{16}N_2O_2 \cdot {}^1/_2H_2O$: C, 71.74; H, 5.69; N, 9.30. Found: C, 71.65; H, 5.90; N, 9.46.

3-Carbethoxy-3-phenyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (XXIX). 3-Carboxy-3-phenyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole hemihydrate (1.6 g., 0.0054 mole) was added to 250 ml. of a saturated solution of hydrogen chloride in dry ethanol. The mixture was allowed to stand for 8 days at room temperature with occasional shaking. When all of the solid had dissolved, the alcohol was removed under reduced pressure. The resulting sirup was dissolved in 50 ml. of dry ethanol and the latter removed by distillation. This was repeated until trituration of the oil with diethyl ether produced a solid. The latter was dissolved in water and the solution neutralized with sodium bicarbonate. The oil which formed, on prolonged trituration with water, changed to a solid. In later experiments seeding with crystals shortened this process. The product was recrystallized from hexane; yield 83%, m.p. 146–147.5°.

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.75. Found: C, 74.87; H, 6.26; N, 8.72.

The pharmacological properties of the compounds prepared in this investigation are being studied and the data will be reported elsewhere.

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(11) The free base was prepared from 1-(2-chloroethyl)-2-chloromethylbenzimidazole hydrochloride. The latter was dissolved in water, cooled to 0°, and the solution neutralized with sodium bicarbonate solution. After drying in a vacuum desiccator, the product was recrystallized from hexane, m.p. 102–103°.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF HOFFMAN-LA ROCHE, INC.]

Synthesis of 5-Substituted 3-Isoxazolecarboxylic Acid Hydrazides and Derivatives

THOMAS S. GARDNER, E. WENIS, AND JOHN LEE

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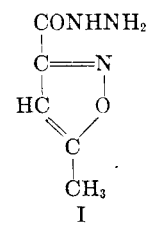
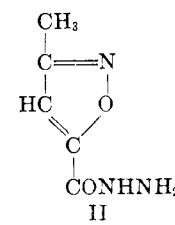
Some 5-substituted 3-isoxazolecarboxylic acid hydrazides have been prepared for investigation of their anti-lepral activity. The 5-methyl, *n*-propyl, and isobutyl compounds showed activity. The 5-methyl compound was superior. Other alkyl residues gave less activity. Aromatic or heterocyclic residues conferred no special activity. Some derivatives and related compounds were prepared.

The development of a reproducible screening procedure for lepraemurium infections in mice by Grunberg and Schnitzer[1] in our chemotherapy laboratories permitted concurrent testing in leprosy of compounds prepared in an anti-tubercular program in progress. 5-Methyl-3-isoxazolecarboxylic acid hydrazide (I),[2] originally found to be inactive in tuberculosis in mice, proved to be active against the lepraemurium infections in mice and rats.

It was therefore thought of interest to examine further hydrazides of this heterocyclic system and some related compounds. The most active compound examined was found to be the initially tested compound (I) which was in the order of ten times the activity of promin in leprosy in both mice and rats. Its position isomer, 3-methyl-5-isoxazolecarboxylic acid hydrazide (II)[3] was inactive.



I



II

In order to determine the effect of isosterism[4] and isomerism, 5-methyl-3-pyrazolecarboxylic acid

(1) E. Grunberg and H. J. Schnitzer, *Ann. N. Y. Acad. Sci.* (*Leprosy*), 54, Art. 1, 107 (1951).

(2) M. Freri, *Gazz. chim. ital.*, 62, 457 (1932).

(3) R. I. Meltzer, P. D. Lewis, F. H. McMillan, J. D. Genzer, F. Leonard, and J. A. King, *J. Am. Pharm. Assoc.* (*Sc. Ed.*), 42, 594 (1953).

TABLE I

ETHYL ACYLPYRUVATES[a]

($RCOCH_2COCOOC_2H_5$)

R	Formula	Cryst. from	M.P.	Yield, %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Pyridyl	$C_{11}H_{11}NO_4$	Ethanol	171–172	50	59.7	5.0	6.3	59.6	5.0	6.2
3-Pyridyl	$C_{11}H_{11}NO_4$	Water	185–187	10			6.3			6.8
4-Pyridyl	$C_{11}H_{11}NO_4$	Water	98–100	5	59.7	5.0	6.3	59.6	5.0	6.2
4-Chlorophenyl	$C_{12}H_{11}ClO_4$	Aqueous ethanol	68–70	68	56.5	4.3	...	56.5	4.1	
2-Furyl	$C_{10}H_{10}O_5$	Ethanol	88–89[b]	85	57.1	4.8	...	57.0	5.0	
2-(5-Methylthienyl)-	$C_{11}H_{12}O_4S$	Methanol	71–72	87	55.0	5.0	...	55.0	5.4	

[a] Many pyruvates could not be distilled and decomposed under high vacuum. Others were not crystallizable from the usual organic solvents. In these cases, the crude pyruvate was used in the preparation of isoxazoles (Table II). [b] Ref. 5 reports m.p. of 72° from dilute alcohol.

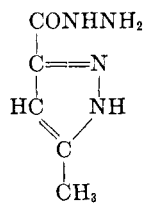
TABLE II

ETHYL 5-R-3-ISOXAZOLECARBOXYLATES[a]

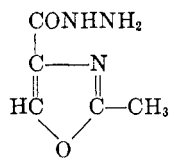
R	Formula	Purification	Yield, %	N Calcd.	N Found
n-Hexyl	$C_{12}H_{19}NO_3$	b.p. 145°/5 mm.	62	6.2	6.0
4-Chlorophenyl	$C_{12}H_9ClNO_3$	m.p. 126–127° (C_2H_5OH)	34	5.7	5.7
n-Pentyl-	$C_{11}H_{17}NO_3$	b.p. 136–140°/2 mm.	30	6.6	6.9
n-Nonyl-	$C_{15}H_{25}NO_3$	m.p. 113–114° (*n*-hexane)	13	5.2	4.9
Isopropyl	$C_9H_{13}NO_3$	b.p. 109–111°/2 mm.	56	7.7	7.8

[a] Some isoxazole esters were unstable and could not be distilled. A few were not susceptible of purification by crystallization from the usual organic solvents. In these cases, the crude material was used for the preparation of the hydrazides.

hydrazide (III) and 2-methyl-4-oxazolecarboxylic acid hydrazide (IV) were prepared. Both were inactive under the test conditions.



III



IV

Variation in the 5-position of I, where the substituent was aliphatic, aromatic, or heterocyclic, was therefore undertaken. These compounds are shown in Table III. For the preparation of these materials, the isoxazole esters (Table II) were produced in most cases by the action of buffered hydroxylamine solutions on the acylpyruvate esters (Table I). When the acyl groups in the pyruvates were 2-thienylcarbonyl or 5-methyl-2-thienylcarbonyl, a modified procedure was found to be necessary in order to obtain the isoxazole ring structure. In these cases, the intermediate α-oximes [$RCOCH_2C(NOH)COOC_2H_5$] were prepared and the final ring closure to obtain the isoxazole was achieved at low temperature in the presence of ethanolic hydrogen chloride. The α-oxamino structure has been arbitrarily assigned to the above α-oximes in analogy with the demonstrated α-structure for ethyl 2-furoylpyruvate α-oxime.[5]

Attempts to prepare either the α-oxime or the isoxazole ring using the substituted acylpyruvate esters in which the acyl group was picolinoyl, nicotinoyl, or isonicotinoyl, failed.

In the case of ethyl acetylpyruvate, ring closure with buffered hydroxylamine solutions gave a major amount of ethyl 5-methyl-3-isoxazolecarboxylate and a minor amount of the isomeric ethyl 3-methyl-5-isoxazolecarboxylate. With the higher acylpyruvates under the same conditions, only the 3-carboxylic esters were isolated.

The esters were transformed in the usual manner to the hydrazides by the action of hydrazine hydrate. The known tendency of isoxazole rings to open and transform to pyrazole rings in the presence of hydrazine was in general avoided by the use of solvents from which the hydrazides crystallize easily and by operating at room temperature.

In attempts to modify the structure I by incorporating the hydrazine moiety into a cyclic structure such as VII, I was treated with phosgene in chlorobenzene at reflux temperature. This gave only the bis compound (V). Using chloroform and phosgene at 30°, a crystalline compound, probably VI, was obtained and this, on boiling in chlorobenzene, gave the desired oxadiazole derivative (VII).

(4) H. Erlenmeyer and M. Leo, *Helv. Chim. Acta*, **16**, 896 (1933).

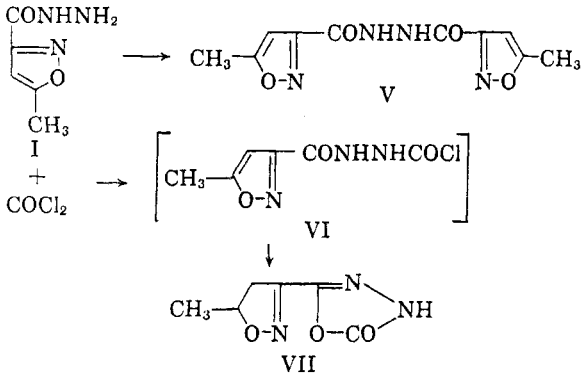
(5) C. Musante and S. Fatutta, *Gazz. chim. ital.*, **88**, 879 (1958).

TABLE III[a]

X-R-Y-ISOXAZOLECARBOXYLIC ACID HYDRAZIDES

Name	Formula	Cryst. from	M.P.	Yield, %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
5-Methyl-3-[b]	$C_5H_7N_3O_2$	Propanol-2	142–143	90	42.6	5.0	—	42.5	4.8	—
3-Methyl-5-	$C_5H_7N_3O_2$	Ethanol	136–137	53						
5-Phenyl-3-	$C_{10}H_9N_3O_2$	Propanol-2	145–146	31			20.7			20.5
5-*n*-Hexyl-3-	$C_{10}H_{17}N_3O_2$	*n*-Hexane	79–80	62	56.9	8.1	20.0	57.1	7.6	21.0
5-Ethyl-3-HCl	$C_6H_9N_3O_2 \cdot HCl$	Ethanol-ether	157–158	42	37.6	5.2	21.9	37.6	5.2	22.5
5-Isobutyl-3-	$C_8H_{13}N_3O_2$	*n*-Hexane	60–61	13	52.4	7.2	23.0	53.3	7.4	23.2
5-*n*-Propyl-3-	$C_7H_{11}N_3O_2$	*n*-Hexane	90–91	36	49.7	6.6	24.8	49.8	6.5	24.6
5-(*p*-Tolyl)-3-	$C_{11}H_{11}N_3O_2$	Propanol-2	149–150	53			19.4			19.3
5-(4-Chlorophenyl)-3-	$C_{10}H_8N_3O_2Cl$	Propanol-2 + ether	202–203	73			17.7			17.4
5-(*n*-Pentyl)-3-	$C_9H_{15}N_3O_2$	Methanol	85–86	50			21.3			21.1
5-(*n*-Nonyl)-3	$C_{13}H_{23}N_3O_2$	[c]	Amorphous	71			16.6			16.4
5-Isopropyl-3-	$C_7H_{11}N_3O_2$	Propanol-2	65–66	27			24.9			25.4
5-(2-Furyl)-3-	$C_8H_7N_3O_3$	Propanol-2	137–138	25			21.8			21.5

[a] All of the hydrazides in this table were colorless with the exception of the isobutyl which has a very pale yellow color. [b] Freri[2] reports a m.p. 131–132°. We have prepared this compound by the ethyl acetylpyruvate procedure and also by oxidation of acetonylacetone using nitric acid. Both procedures give identical products. [c] The product was not crystallizable from the usual organic solvents. On vacuum drying, a colorless, tacky amorphous solid was obtained.



Chemotherapeutic findings. 5-Methyl-3-isoxazolecarboxylic acid hydrazide (I) was found to be in the order of ten times the activity of promin in *M. lepraemurium* infections in mice and rats. 5-Isobutyl-3-isoxazolecarboxylic acid hydrazide and 5-*n*-propyl-3-isoxazolecarboxylic acid hydrazide were found to be several times more active than promin in mice.

That the activity is intimately connected with the hydrazide structure is supported by the finding that 5-methyl-3-isoxazolecarbohydroxamic acid hydrate,[6] 5-methyl-3-isoxazolethiocarboxamide,[7] 5-methyl-3-isoxazolecarboxamide[7] and 1-(5-methyl-3-isoxazoylformyl)-2-(4-methoxybenzylidene)hydrazine,[8] were inactive.

The following substitutions in I on N^2 in the hydrazine moiety decreased activity: acetyl; benzenesulfonyl; glucuronyl; *N*-acetyl-*dl*-methionioyl; isonicotinyl; and the bis compound, 5-methyl-3-isoxazolylcarbonyl (V).

(6) T. S. Gardner, E. Wenis, and F. A. Smith, *J. Am. Chem. Soc.*, **73**, 5455 (1951).

(7) T. S. Gardner, E. Wenis, and J. Lee, *J. Org. Chem.*, 19, 753 (1954).

(8) T. S. Gardner, F. A. Smith, E Wenis, and J. Lee, *J. Org. Chem.*, 21, 530 (1956).

EXPERIMENTAL[9]

General procedure A. *Preparation of $RCOCH_2COCOOC_2H_5$ compounds.* One mole of sodium was dissolved in 250 ml. of anhydrous ethanol. To this ice-cooled solution of sodium ethoxide a solution of 1 mole of diethyl oxalate and 1 mole of a methyl ketone ($RCOCH_3$) was slowly added with stirring. The paste formed was permitted to stand at 25° for 15 hr. or more and warmed at 80° on a steam bath for 0.5 hr. The pasty mass was cooled and dilute sulfuric acid added until *p*H 2 was obtained. The separated oil was extracted with ether and purified by distillation or crystallization, according to the type of compound. Sometimes the crude substituted pyruvate was used without further purification. In the case of the pyridine methyl ketones, after acidification, ammonium hydroxide was used to bring the *p*H up to about 7.5 before ether extraction.

General procedure B. *Preparation of ethyl 5-R-3-isoxazole carboxylates.*[10] The following modified procedure was used. To 1 mole of ethyl RCO-pyruvate (procedure A) in five volumes of ethanol were added 1 mole of hydroxylamine hydrochloride and 0.95 mole of sodium carbonate anhydrous in five volumes of water. The mixture was permitted to stand 15 hr. and then acidified to *p*H 2 with sulfuric acid. The separated oil was extracted with ether and after removal of the ether, the residual oil was heated on the steam bath at 80–90° for 0.5 hr. in order to complete the ring closure to form the isoxazole. The product was purified by distillation or crystallization according to the type of compound. In a few cases, the crude isoxazole was used in procedure C.

General procedure C. *Preparation of 5-R-3-isoxazolecarboxylic acid hydrazide.* One mole of ethyl 5-R-isoxazole-3-carboxylate was treated with 2–3 moles of hydrazine hydrate in isopropyl alcohol. Reaction usually went to completion at 25° in 24 hr. In a few cases, the solution was warmed at 80° for 0.5 hr. The excess hydrazine and solvent were removed under vacuum and the residue crystallized from an appropriate solvent.

Ethyl α-isonitroso-γ-oxo-2-thiophenebutyrate. Ethyl 2-thenoylpyruvate (380 g.) was dissolved in 1.0 l. of ethanol. This solution was mixed with a solution of water (400 ml.) containing 117 g. of hydroxylamine hydrochloride and 168 g. of sodium carbonate. The final solution was permitted to

(9) All melting points are corrected.

(10) H. Keskin, *Rev. fac. sci. univ. Istanbul*, **11A**, 1 (1946).

stand at 25° for 14 hr. The solution was brought to *p*H 2 with dilute sulfuric acid and extracted several times with ether. The combined ether extracts were washed once with cold water. The ether was removed under vacuum and the residue was crystallized from propanol-2; yield, 160 g., m.p. 99–100°.

Anal. Calcd. for $C_{10}H_{11}NO_4S$: C, 49.8; H, 4.6; N, 5.8. Found: C, 50.5; H, 4.6; N, 6.2.

The monooxime $[(C_4H_3S)COCH_2C(NOH)COOC_2H_5]$ shows a slight tendency for ring closure to the isoxazole under the mild acidic conditions of recovery.

Ethyl-5-(2-thienyl)-3-isoxazole carboxylate. Ethyl α-isonitroso-γ-oxo-2-thiophenebutyrate (75 g.) was dissolved in ethanol (150 ml.) to which was added 150 ml. of 4*N* hydrogen chloride in ethanol. The solution was kept at 4° for 15 hr. The product crystallized under these conditions and was recrystallized as a colorless compound from ethanol; yield, 62 g., m.p. 53–54°.

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.8; H, 5.0. Found: C, 54.2; H, 4.2.

5-(2-Thienyl)-3-isoxazolecarboxylic acid hydrazide. Ethyl-5-(2-thienyl)-3-isoxazole carboxylate (25 g.) in 375 ml. of propanol-2 was treated with 10 g. of 85% hydrazine hydrate at 25° and immediately cooled to 4° for 15 hr. The hydrazide was recovered by filtration and recrystallized as a colorless compound from propanol-2; yield, 17 g., m.p. 143–144°.

Anal. Calcd. for $C_8H_7N_3O_2S$: N, 20.1. Found: N, 20.5.

In another experiment, crystallization from ethanol gave a m.p. of 138°.

Anal. Calcd. for $C_8H_7N_3O_2S$: C, 45.9; H, 3.4; S, 15.3; N, 20.1. Found. C, 46.0; H, 3.1; S, 15.4; N, 21.5.

If an excess of hydrazine is used, or if the reaction is run in a concentrated solution, or if the reaction is heated, the isoxazole ring is opened and a pyrazole is obtained.

Ethyl α-isonitroso-γ-oxo-2-(5-methylthiophene)butyrate. The methylthiophene compound was prepared in the same manner as the thiophene derivative described above. On crystallization from methanol, a colorless monooxime $[(CH_3C_4H_2S)COCH_2C(NOH)COOC_2H_5]$ was obtained, m.p. 115–116°.

Anal. Calcd. for $C_{11}H_{13}NO_4S$: C, 51.7; H, 5.1. Found: C, 51.7; H, 5.1.

A slight tendency to ring close to form the isoxazole takes place in this compound also.

Ethyl 5-(5-methyl-2-thienyl)-3-isoxazole carboxylate. Ethyl α-isonitroso-γ-oxo-2-(5-methylthiophene butyrate prepared from 195 g. of ethyl-(5-methyl-2-thenoyl)pyruvate was treated with 10*N* hydrochloride in ethanol at 4°, as described above for the thienyl compound. The recovered pale yellow product was recrystallized from methanol; yield, 101 g., m.p. 45–46°.

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.7; H, 4.7. Found: C, 55.8; H, 4.9.

5-(5-Methyl-2-thienyl)-3-isoxazolecarboxylic acid hydrazide. Ethyl 5-(5-methyl-2-thienyl)-3-isoxazole carboxylate (101 g.) was treated with 22 g. of hydrazine at 4° in 1.2 l. of propanol-2. The almost colorless product was recrystallizable from methanol, ethanol, or propanol-2; yield, 60 g., m.p. 157–158°.

Anal. Calcd. for $C_9H_9N_3O_2S$: N, 18.8. Found. N, 18.4.

5-Methyl-3-isoxazole-carboxylic acid chloride. This compound has been prepared by action of phosphorus pentachloride on the sodium salt of 5-methyl-3-isoxazole carboxylic acid.[11] Thionyl chloride does not react with the free acid but reacts readily with the sodium salt of the acid. After reaction has been completed by refluxing for 16 hr., dilution of the thionyl chloride with dry ether and filtration removes most of the sodium chloride. The solution was concentrated in a vacuum to the acid chloride which may be distilled at 88° at 18 mm. to give a yield of 85–90%. The acid chloride solidified at 4° and could be stored for months without change. However, we have found that the acid chloride may decompose violently on distillation and for this reason distillation has been abandoned. Instead, the crude acid chloride was heated to 90° under vacuum for 0.5 hr.

5-Methyl-3-isoxazolecarboxylic acid-2'-acetylhydrazine. A solution of pyridine (300 ml.) containing 40 g. of 5-methyl-3-isoxazolecarboxylic acid chloride and 15 g. of acetic acid hydrazide was warmed to 80° for 2 hr. The solution was concentrated to a solid under a vacuum, and water added to the residue. The separated solid was crystallized from hot water and then from ethanol; yield, 17 g., m.p. 224–225°.

Anal. Calcd. for $C_7H_9N_3O_3$. N, 22.9. Found. N, 22.6.

1-(5-Methyl-3-isoxazolylcarbonyl)-2-(benzenesulfonyl)hydrazine. A solution of 34 g. of 5-methyl-3-isoxazolecarboxylic acid hydrazide in 500 ml. of benzene was cooled in an ice bath to 15°. Benzenesulfonyl chloride (40 ml.) was dropped in while the solution was rapidly stirred. After final addition of the acid chloride, the solution was heated to 70° and permitted to stand at 25° for 24 hr. Concentration in a vacuum gave an oil which was crystallized as a colorless product from a methanol-water solution; yield, 54 g., m.p. 142°; a mixed m.p. with the parent hydrazide (143°) was 105°.

Anal. Calcd. for $C_{11}H_{11}N_3O_4S$: N, 14.9. Found: N, 14.7.

N²-(5-Methyl-3-isoxazolylcarbonyl)hydrazone of D-*glucuronolactone.* A hot solution of methanol (1 l.) containing 44 g. of D-glucuronolactone was mixed with 35 g. of 5-methyl-3-isoxazolecarboxylic acid hydrazide and heating continued for 10 min. On cooling, the colorless product separated and was recrystallized from methanol; yield, 22 g., m.p. 105–106°.

Anal. Calcd. for $C_{11}H_{13}N_3O_7$: N, 14.0. Found: N, 13.5.

1-(N-Acetyl-dl-methioninoyl)-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine. A dry pyridine solution (250 ml.) of 51 g. of *N*-acetyl-*dl*-methioninoyl hydrazide (m.p. 96°) was dropped into a solution of 100 ml. of pyridine and 40 g. of 5-methyl-3-isoxazole carboxylic acid chloride. After warming to 60° and standing 24 hr., the solution was concentrated to a solid. The solid residue was crystallized from an ethanol-benzene solution and then from aqueous methanol by slow removal of the methanol. A final recrystallization from aqueous methanol gave a very pale, yellow product; yield, 20 g., m.p. 194–195°.

Anal. Calcd. for $C_{12}H_{18}N_4O_4S$: N, 17.8; S, 10.2. Found: N, 17.3; S, 10.2.

5-Methyl-3-isoxazolecarboxylic acid hydrazide copper complex. Twenty grams of 5-methyl-3-isoxazolecarboxylic acid hydrazide was added to 1 l. of a 10% copper sulfate solution at 25°. Complete solution took place at first and in a few minutes a blue-green precipitate separated. The copper complex was purified by sludging with ethanol twice. This reaction in hot water undergoes oxidation with separation of cuprous oxide or free copper. The blue-green complex does not melt at 250°; yield, 25 g.

Anal. Calcd. for $C_5H_7N_3O_2 \cdot {}^1/_2H_2O \cdot {}^1/_2CuSO_4$: C, 26.1; H, 3.5; N, 17.2; Cu, 13.8. Found: C, 25.9; H, 3.7; N, 17.9; Cu, 13.9.

1-Isonicotinoyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine. Isonicotinoylhydrazine (30 g.) and 30 g. of 5-methyl-3-isoxazolecarboxylic acid chloride were allowed to react in 300 ml. of dry pyridine. The solution was heated to 70° for 2 hr. and after standing 24 hr. at 25°, was concentrated to a solid; addition of water and filtration gave a crude material which was recrystallized from water first and then ethanol, as a colorless product; yield, 9 g., m.p. 175–176°.

Anal. Calcd. for $C_{11}H_{10}N_4O_3$: C, 53.7; H, 4.1; N, 22.8. Found: C, 53.8; H, 4.1; N, 23.0.

1,2-Bis(5-methyl-3-isoxazolylcarbonyl)hydrazine (V). Carbonyl chloride was passed into a solution of 70 g. of 5-methyl-3-isoxazolecarboxylic acid hydrazide in 500 g. of hot chlorobenzene for 1.5 hr. After 15 min., a white precipitate began to form. After cooling, the colorless product was separated by filtration and was recrystallized from ethanol; yield, 30 g., m.p. 222–223°.

(11) A. Quilico and J. Panizzi, *Gazz. chim. ital.*, 68, 625 (1938).

Anal. Calcd. for $C_{10}H_{10}N_4O_4$: C, 48.0; H, 4.0; N, 22.4. Found: C, 48.3; H, 4.2; N, 22.9.

This compound has been reported with m.p. 218–219°, as a byproduct in the Curtius diazotization[12] of 5-methyl-3-isoxazolecarboxylic acid hydrazide using sodium nitrite in 80% acetic acid at 0°.

Oxidation of 5-methyl-3-isoxazolecarboxylic acid hydrazide with potassium ferricyanide gave the same bis compound in regard to melting point and undepressed mixed melting point. The expected oxadiazole was obtained by a variation as described below.

5-(5-Methyl-3-isoxazolyl)-1,3,4-oxadiazole-2(3H)-one (VII). A solution of chloroform (1 l.) containing 52 g. of 5-methyl-3-isoxazolecarboxylic acid hydrazide was saturated with carbonyl chloride for 4 hr. at 30°. The colorless product (65 g.) that separated was filtered off and recrystallized from ethanol; yield, 47 g., m.p. 183–184°. This compound gave a positive chloride test and on drying was partially converted to the oxadiazole. This intermediate is probably 1-(5-methyl-3-isoxazolylcarbonyl)-2-chlorocarbonylhydrazine (VI). Analyses were not obtainable due to loss of hydrochloride to give the oxadiazole. Ring closure was completed by heating the intermediate (65 g. from two experiments) in chlorobenzene at reflux temperature. Hydrogen chloride was evolved and the oxadiazole was obtained; yield, 20 g., m.p. 225–226°. Mixed m.p. with 1,2-bis(5-methyl-3-isoxazolylcarbonyl)hydrazine formed in the one step reaction in chlorobenzene was 208°.

Anal. Calcd. for $C_6H_5N_3O_3$: C, 43.1; H, 3.0; N, 25.2. Found: C, 43.1; H, 3.1; N, 25.3.

During this work a few 5-substituted pyrazole carboxylic acid hydrazides were prepared, sometimes inadvertently. They are included for completeness of the investigation.

5-(2-Thienyl)-3-pyrazolecarboxylic acid hydrazide. Ethyl-5-(2-thienyl)-3-isoxazolecarboxylate (81 g.) and 162 g. of 85% hydrazine hydrate in 200 ml. of isopropyl alcohol were allowed to react at 25°. A crystalline mass separated which was crystallized from hot water, m.p. 164–165°; recrystallization from water gave a compound, m.p. 176–177°, and two recrystallizations from methanol gave the final, very pale yellow product, the pyrazole, m.p. 215–216°; yield, 28 g.

Anal. Calcd. for $C_8H_8N_4OS$: C, 46.1; H, 3.8; N, 26.9; S, 15.4. Found: C, 45.9; H, 3.5; N, 26.7; S, 15.3.

The same compound was prepared by the direct reaction of hydrazine hydrate and ethyl (2-thienylcarbonyl)pyruvate.

5-(2-Furyl)-3-pyrazolecarboxylic acid hydrazide.[5] If 1*M* excess of hydrazine is used in this reaction, only oxalic acid dihydrazide is obtained by chain scission of the ethyl (2-furylcarbonyl)pyruvate, even at 4°. However, if stoichiometric quantities of hydrazine are used, the desired product is obtained with only traces of easily separated oxalic acid dihydrazide as byproducts.

Ethyl (2-furoyl)pyruvate (50 g.), 50 g. of 85% hydrazine hydrate, and 30 ml. of isopropyl alcohol were refluxed for 3 hr. Concentration under vacuum gave a solid residue which was extracted with 100 ml. of boiling isopropyl alcohol. The insoluble residue was oxalic acid dihydrazide which crystallized from boiling water; m.p. 241–242°. The isopropyl alcohol extract on concentrating to half volume and chilling, gave the desired pyrazole; yield, 8.5 g., m.p. 202–203°.

Anal. Calcd. for $C_8H_8N_4O_2$: N, 29.2. Found: N, 29.0.

2-Methyl-4-oxazolecarboxylic acid hydrazide. Ethyl 2-methyl-4-oxazolecarboxylate (35 g.), 17 g. of 85% hydrazine hydrate, and 400 ml. of isopropyl alcohol were permitted to react at 25° for 6 hr. and at 4° for 48 hr. The crude material (18 g.) was recrystallized twice from isopropyl alcohol to give a colorless product; yield, 16 g., m.p. 99–100°.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.6; H, 5.0. Found: C, 43.0; H, 4.7.

The compound is very soluble in both water and ethanol.

5-Cyclohexyl-3-pyrazolecarboxylic acid hydrazide. Crude ethyl (cyclohexylcarbonyl)pyruvate, prepared by the reaction of 153 g. of diethyl oxalate and 132 g. of methyl cyclohexyl ketone using sodium ethylate as a catalyst, was allowed to react with 100 g. of 85% hydrazine hydrate in 200 ml. of isopropyl alcohol. A vigorous reaction took place and after standing at 4° for 14 hr., the product crystallized and was recrystallized from propanol-2 as a colorless product; yield, 66 g., m.p. 173–174°.

Anal. Calcd. for $C_{10}H_{16}N_4O$: N, 26.9. Found: N, 27.1.

This compound was also prepared by the reaction of 85% hydrazine hydrate in propanol-2 on ethyl 5-cyclohexyl-3-isoxazolecarboxylate at 80° for 15 min. Additional evidence for the assignment of structure was obtained by heating 5-cyclohexyl-3-pyrazolecarboxylic acid hydrazide in acetone to give 1-isopropylidene-2-(5-cyclohexyl-3-pyrazolecarbonyl)hydrazine. Recrystallizing the product so obtained from acetone, gave the compound, m.p. 237–238°.

Anal. Calcd. for $C_{13}H_{20}N_4O$: C, 62.9; H, 8.1; N, 22.6. Found: C, 62.9; H, 7.8; N, 23.0.

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