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Monoamine Oxidase Inhibitors. III. Structural Variations in 1-Alkyl and 1-Aralkyl-1(or 2)-acylhydrazines

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A number of sugar acyl, 4-hydroxybutyryl and D-pantoyl derivatives of benzylhydrazine, 4-dimethylaminobenzylhydrazine, and α-methylphenethylhydrazine were prepared by the reaction of the corresponding lactones with the substituted hydrazines. Most of these compounds had relatively low toxicity in mice as compared with other hydrazine compounds of comparable monoamine oxidase inhibitory activity. The reaction product of D-ribonolactone with benzylhydrazine was shown to be a N^1,N^2-hydrazine derivative. The most interesting compounds were 1-benzyl-2-(D-ribonoyl)hydrazine, and 1-benzyl-2-(D-pantoyl)hydrazine. Our variation in the structures of active monoamine oxidase inhibitors, such as 1-isopropyl-2-isonicotinoylhydrazine, 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)-hydrazine, and 1-benzyl-2-picolinoylhydrazine, either eliminated or reduced MAO activity. In one case, 1-benzyl-2-picolinoylhydrazine, quaternization with methyl iodide or methyl bromide, increased response to 5-hydroxytryptophan.

Consideration of the clinical results obtained with isopropylisonicotinoyl-hydrazine[1] suggested modifications of this drug so as to obtain (a) a more rapid onset of action; (b) a lower toxicity; and (c) a more specific distribution of the drug in the different tissues. In previous papers,[2,3] we have described classes of compounds fulfilling, at least in part, the requirements (a) and (b), and in this paper are described some further compounds which have been investigated with respect to (c).

(1) Iproniazid (Marsilid®).
(2) T. S. Gardner, E. Wenis, and J. Lee, *J. Med. Pharm. Chem.*, **2**, 133 (1960).
(3) T. S. Gardner, E. Wenis, and J. Lee, *ibid.*, **3**, 241 (1961).

Schwartz[4] has demonstrated that the metabolic degradation of 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine involves primarily the hydrolysis of the acyl residue to yield benzylhydrazine which is the active moiety. This compound in itself is very toxic and undoubtedly the acyl residue contributes to its distribution and detoxification before it is metabolically removed. It was soon found that variation of the acyl residue produced quantitative differences in the distribution of the drug, as judged by its effect on the monoamine oxidase activity of the tissues of the liver, heart or brain. Some of these are shown in Table III.

One of the guiding throughts in the preparation of the majority of these compounds was the introduction of one or more hydroxyl groups in the acyl residue to afford "metabolic hooks" for possible detoxification (Table I). This turned out quite well, since enormous detoxification was obtained without a corresponding loss of activity (Table III, No. 1–13). This is illustrated by the LD_{50} (mice, i.p.) of 1-benzyl-2-D-ribonoylhydrazine (Table III, No. 1), which was not reached at 4000 mg./kg. The compound shows a similar activity and tissue distribution as iproniazid. A quantitatively different distribution was obtained by, for example, another compound (Table III, No. 13).

The effect of some other miscellaneous changes in the acyl residue is shown in Table III (No. 14–28). The toxicity of the compounds, when active, was relatively high, which militated against their further investigation. It might be noted that introduction of a hydroxyl group in the benzyl residue as against the acyl residue did not produce detoxification. Quaternization of the highly active 1-benzyl-2-picolinoylhydrazine as shown in compounds 19 and 20 in Table III, caused a considerable change in direction of activity. The *in vitro* liver activity was doubled, that of the brain halved and the response to 5-hydroxytryptophan tripled, as compared to the non-quaternized parent compound.

The intermediate hydrazones (Table II) were inactive as MAO inhibitors.

Experimental[5,6]

A. General Procedure for the Reaction of Lactones with R-Hydrazines.—The lactone was treated in ethanol solution with an excess of the aralkylhydrazine at 80° for 2 hr. On cooling, the product usually separated and was crystallized

(4) M. A. Schwartz, *J. Pharmacol. Exptl. Therap.*, **130**, 157 (1960); *Proc. Soc. Exper. Biol. Med.*, **107**, 613 (1961); *J. Pharmacol. Exptl. Therap.*, **135**, 1 (1962).

(5) We are indebted to Dr. A. Steyermark and his associates for the microanalyses.

(6) All melting points are corrected.

from water. If crystallization did not take place, the solution was concentrated to a small volume *in vacuo*. In a few cases, equimolar amounts of reactants gave satisfactory yields.

B. Reduction of Acylhydrazones by Lithium Aluminum Hydride.—Acyl hydrazone (0.50 mole) was added in finely pulverized form to a solution of lithium aluminum hydride (19 g.) in dry ether (3 l.). Addition of the powder required about 2 hr. The reaction solution was stirred for 4 hr., stood overnight, and then the excess lithium aluminum hydride was destroyed by cautious addition of ethyl acetate (150 ml.) with stirring. The stirring was continued for 0.5 hr. and ice water (100 ml.) was then dropped in over a period of 15 min. After stirring for a further 0.5 hr., the suspension was filtered; the ether was removed *in vacuo*, and the residue crystallized from methanol or ethanol.

1-Benzyl-2-(D-ribonoyl)hydrazine (No. 1).—1-Benzylidene-2-(D-ribonoyl)hydrazine (27 g.) was dissolved in ethanol (200 ml.) and water (100 ml.). To this solution was added 10% palladium on charcoal (2 g.), and the mixture reduced under 35 kg./cm.^{2} of hydrogen at 30°. A theoretical uptake of hydrogen was obtained. The recovered solution was concentrated to a small volume (200 ml.) and benzene (1 l.) was added and evaporated to dryness. The solid residue was dissolved in hot water (300 ml.), decolorized by activated carbon (Norite-A, 10 g.) and on cooling, the crude product crystallized. The procedure was repeated and then to obtain a colorless product, the material was recrystallized twice more from hot water (5.4 g. yield), m.p. 157–158° (10°/min. rate of heating). Under the same conditions, 1-benzyl-2-ribonoylhydrazine (Table I, No. 1) prepared from the lactone had a m.p. of 157–158° and unchanged mixture m.p. The rotation of the sample prepared by reduction was $[\alpha]^{25}D$ + 19.2° (*c*, 5; 0.1 *N* HCl). The D-lactone procedure gave a product $[\alpha]^{25}D$ + 19.2° (*c*, 5; 0.1 *N* HCl) and $[\alpha]^{25}D$ + 19.8° (*c*, 5; 0.28 *N* HCl).

1-Benzylidene-2-(D-ribonoyl)hydrazine has a characteristic ultraviolet absorption band at about 280–290 mμ, which disappears on reduction. The ultraviolet and infrared absorption spectra of 1-benzyl-2-(D-ribonoyl)hydrazine prepared by both processes were identical, thus establishing the acylation at N-2 with lactone.[7]

1-Benzyl-2-(cyanoacetyl)hydrazine (No. 18).—Ethyl cyanoacetate (57 g.) and benzylhydrazine (70 g.) were heated at 100° for 1 hr. After 4 days at 4°, a colorless compound crystallized and was recrystallized from ethanol; yield, 15 g., m.p. 203–204°.

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.5; H, 5.9. Found: C, 63.7; H, 5.9.

1-Benzyl-2-picolinoylhydrazine Methiodide Hemihydrate[8] (No. 19).—Ethyl picolinate methiodide (27 g.) was heated at 100° with benzylhydrazine (16.5 g.) in water (50 ml.) for 5 min. The solution was then concentrated to an oil *in vacuo* using ethanol to expedite removal of excess water. The oil crystallized from ethanol; yield, 25 g., m.p. 118–120°.

Anal. Calcd. for $C_{14}H_{16}IN_3O \cdot 0.5\ H_2O$: C, 44.5; H, 4.5. Found: C, 44.9; H, 5.3.

This compound was not very stable. In boiling water, iodine was evolved on addition of nitric acid.

1-Benzyl-2-picolinoylhydrazine Methyl Bromide Hydrate[8] (No. 20).—1-Methyl-2-carbomethoxypyridinium bromide (70 g.), water (50 ml.) and benzyl-

(7) F. Micheel, "Chemie der Zucker und Polysaccharide," Akad. Verlagsgesellschaft m.b.H., Leipzig, 1939, p. 34.

(8) T. S. Gardner, J. Lee, and E. Wenis, U. S. Patent 2,597,882, Oct. 25, 1960.

TABLE I[a]

HYDRAZINES (R′—NHNHCOR″)

No.	R′	R″CO—	Formula	$[\alpha]^{25}D$ 0.1 *N* HCl	M.p., °C.	Yield, %	Analyses, % Calcd. C	Calcd. H	Found C	Found H
1	Benzyl	D-Ribonoyl	$C_{12}H_{18}N_2O_6$	+20 (*c*, 6)	155–156[b]	60–80	53.3	6.7	53.4	6.7
2	Benzyl	D-Arabonoyl	$C_{12}H_{18}N_2O_6$	−31.0 (*c*, 2)	155–157	89	53.3	6.7	53.4	6.9
3	Benzyl	D-Gluconoyl	$C_{13}H_{20}N_2O_6$	+17.5 (*c*, 2)	181–182	78	52.0	6.7	52.3	6.8
4	Benzyl	D-Galactonoyl	$C_{13}H_{20}N_2O_6$	+19.0 (*c*, 2)	204–205	93	52.0	6.7	52.4	6.9
5	Benzyl	Pantoyl[c]	$C_{13}H_{20}N_2O_5$	+18.0 (*c*, 6)	84–85[d]	45–70	61.9	8.0	61.7	8.1
6	Benzyl	4-Hydroxybutyryl·HCl	$C_{11}H_{16}N_2O_2 \cdot HCl$	—	111–112[e]	34	53.8	7.0	53.6	6.9
7	4-Dimethylaminobenzyl	D-Ribonoyl	$C_{14}H_{23}N_3O_5$	+22.5 (*c*, 0.8)	155–157	66	53.7	7.4	53.6	7.3[f]
8	4-Dimethylaminobenzyl	D-Gluconoyl	$C_{15}H_{25}N_3O_6$	+21.2 (*c*, 8)	155–157	62	52.5	7.3	52.7	7.2[g]
9	4-Dimethylaminobenzyl	Pantoyl[c]	$C_{15}H_{25}N_3O_5$	−3.5 (*c*, 2)	104–105[d]	50	60.9	8.5	60.9	8.3
10	4-Dimethylaminobenzyl	4-Hydroxybutyryl	$C_{13}H_{21}N_3O_2$	—	70–72[d]	45	62.1	8.4	62.0	8.3
11	α-Methylphenethyl	D-Ribonoyl	$C_{14}H_{22}N_2O_5$	−2 (*c*, 2)	171–173	70	56.4	7.4	56.1	7.3
12	α-Methylphenethyl	D-Gluconoyl	$C_{15}H_{24}N_2O_6$	+9.5 (*c*, 2)	204–205	60	54.8	7.4	55.1	7.3
13	α-Methylphenethyl	4-Hydroxybutyryl·HCl	$C_{13}H_{20}N_2O_2 \cdot HCl$	—	117–118	29[e]	57.2	7.7	57.6	7.8
14	Isopropyl	5-Methyl-3-pyrazolylcarbonyl[h]	$C_8H_{14}N_4O$		166–168	8	52.7	7.7	53.2	7.6
15	2-Furfuryl	5-Methyl-3-isoxazolylcarbonyl[h]	$C_{10}H_{11}N_3O_3$		88–89[i]	11	54.3	5.5	54.3	4.8
16	Benzyl	5-Hexyl-3-isoxazolylcarbonyl[h]	$C_{17}H_{23}N_3O_2$		62–63[j]	34	67.7	7.6	67.8	7.7
17	Benzyl	2-Furoyl[h]	$C_{12}H_{12}N_2O_2 \cdot HCl$		208–214 dec.	37	57.2	5.2	57.7	5.3

[a] All carbohydrate acid derivatives were prepared by the general procedure A described in the experimental section. Yields are based on the lactone, and all compounds were crystallized from water unless noted otherwise. All compounds were colorless. [b] All melting points are corrected. This compound melted at 148–150° at 3°/min. rate of heating. [c] D-Pantoyl or D-(+)-(2,4-dihydroxy-3,3-dimethylbutyryl). [d] Crystallized from ethyl acetate. [e] Crystallized from ethanol. [f] Calcd. N, 13.4. Found: N, 13.3. [g] Calcd. N, 12.3. Found: N, 12.7. [h] Prepared by procedure B. Yields are based on the hydrazide. The compounds were colorless and crystallized from ethanol unless otherwise noted. [i] Crystallized from water. [j] Pale yellow leaflets.

TABLE II[a]

HYDRAZONES (R = NNHCOR')

No.	R·	R'CO—	Formula	Yield, %	M.p., °C.	—Calcd.— C	H	—Found— C	H
1	Benzylidene	N-Acetyl-*dl*-methionoyl	$C_{14}H_{19}N_3O_2S$[b]	79[c]	147–150	57.3	6.5	57.1	6.6
2	Benzylidene	2-Furoyl	$C_{12}H_{10}N_2O_2$	71	225–226	67.3	4.7	67.4	4.7
3	Benzylidene	5-Hexyl-3-isoxazolyl-carbonyl	$C_{17}H_{21}N_3O_2$	82	140–141	68.2	7.0	68.4	7.2
4	2-Furfurylidene	5-Methyl-3-isoxazolyl-carbonyl	$C_{10}H_9N_3O_3$	62	192–193	54.8	4.1	54.2	4.0
5	Isopropylidene	5-Methyl-3-pyrazolyl-carbonyl-[d]	$C_8H_{12}N_4O$	90[e]	224–225	53.3	6.6	52.7	6.0
6	Isopropylidene	4-Pyridylacetyl	$C_{10}H_{13}N_3O$	28[e,f]	135–137	62.8	6.9	62.8	7.1
7	Benzylidene	D-Arabonyl[g,h]	$C_{13}H_{16}N_2O_5$	50	208–210[i,j]	—	—	—	—
8	4-Dimethylamino-	D-Ribonoyl[k]	$C_{14}H_{21}N_3O_5$	45	188–192[l,m,n] dec.	53.9	6.8	53.8	7.0
9	benzylidene	D-Gluconoyl[k]	$C_{15}H_{23}N_3O_6$	17	182–184[l,m,n]	52.7	6.8	52.5	7.0
10	α-Methylphenethyl-	D-Ribonoyl[g,o]	$C_{15}H_{22}N_2O_6$	15	137–138[n,o]	56.7	6.8	56.5	6.8
11	idene	D-Gluconoyl[g,o]	$C_{15}H_{22}N_2O_6$	22	142–144[n,p]	55.2	6.8	55.0	7.6

[a] All melting points are corrected and all compounds were crystallized from propanol-2 unless otherwise noted; also, all compounds were colorless unless otherwise noted. [b] Attempts to reduce this material resulted in mixtures of undetermined composition. [c] The carbonyl reagent and the hydrazide were heated together in a suitable solvent, usually propanol-2 unless otherwise noted. [d] The hydrazide was heated in acetone. [e] Recrystallized from acetone. [f] The starting compound, 4-pyridylacetic acid hydrazide, was reported by A. R. Katritzky, *J. Chem. Soc.*, 4038 (1954), to have an indefinite m.p. due to solvation Also, it has been reported to melt at 85–86° from benzene [H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry, and J. Bernstein, *J. Am. Chem. Soc.*, **75**, 1933 (1953)]. We obtained a product of m.p. of 94–95° from propanol-2 giving the expected analysis. [g] The aldehyde and acid hydrazide were condensed by heating in water. [h] Condensations in alcoholic solution gave poor yields. [i] The L-isomer has been reported to melt at 208° [W. J. Van Marle, *Rec. trav. chim.*, **39**, 549 (1920)]. [j] Recrystallized from water. [k] The aldehyde and acid hydrazide were condensed by heating in ethanol and water using *p*-toluenesulfonic acid as a catalyst. [l] Yellow. [m] Recrystallized from ethanol. [n] *p*-Toluenesulfonic acid was used as a catalyst. Caution: lachrymatory. [o] Cream colored. [p] Recrystallized from aqueous ethanol· mixture m.p. with D-gluconoylhydrazine (m.p. 142–144°) was 124–128°.

TABLE III[a]

HYDRAZINE DERIVATIVES (R'—NHNHCOR") PHARMACOLOGICAL DATA

No.	R'	R"	Monoamine oxidase inhibition in rats[b] Liver[c,f] *in vitro*	Brain[d,f] *in vivo*	5-HTP[h] potentiation in mice[g]	Toxicity[i] 24 hr. I.P. LD_{50} in mice, mg./kg.
Standard	Iproniazid[e] (isopropyl)	Isonicotinoyl	1.0	1.0	1.0	1100±50
1	Benzyl	D-Ribonoyl (Ro 5-1162)	1.7	0.5	1.0	>4000
2	Benzyl	D-Arabonoyl	0.7	1.0	<1.0	>400
3	Benzyl	D-Gluconoyl	2.0	1.1	<1.0	>400
4	Benzyl	D-Galactonoyl	0.7	0.3	<1.0	>400
5	Benzyl	Pantoyl (Ro 5-1221)	0.3	1.0	1.0	>400
6	Benzyl	4-Hydroxybutyryl	14.0	42.0	40.0	132 ± 8
7	4-Dimethylaminobenzyl	D-Ribonoyl	0.4	<0.25	<1.0	>400
8	4-Dimethylaminobenzyl	D-Gluconoyl	1.0	0.25	<1.0	>400
9	4-Dimethylaminobenzyl	Pantoyl	10.2	<0.25	<1.0	>400
10	4-Dimethylaminobenzyl	4-Hydroxybutyryl	0.2	—	1.0	>400
11	α-Methylphenethyl	D-Ribonoyl	0.2	0.5	<1.0	>400
12	α-Methylphenethyl	D-Gluconoyl	0.7	0.25	<1.0	>400
13	α-Methylphenethyl	4-Hydroxybutyryl·HCl	4.0	36.0	60.0	173 ± 13
14	Isopropyl	5-Methyl-3-pyrazolylcarbonyl	0.5	—	4.0	371
15	Furfuryl	5-Methyl-3-isoxazolylcarbonyl	0.1	0.6	<1.0	112
16	Benzyl	5-Hexyl-3-isoxazolylcarbonyl	0.7	5.5	7.5	>400
17	Benzyl	2-Furoyl HCl	3.0	6.0	1.5	275 ± 32
18	Benzyl	Cyanoacetyl	0.01		<1.0	>400
19	Benzyl	Picolinoylmethyl iodide·$^1/_2H_2O$	14.0	13.0	30.0	250 ± 35
20	Benzyl	Picolinoylmethyl bromide·H_2O	14.0	13.0	30.0	236 ± 19
21	3-Hydroxybenzyl	H	1.3	1.5	<1.0	154 ± 9
22	4-Isopropylbenzyl	H	10.0	17.0	60.0	190 ± 8

TABLE III (*Continued*)

23	Benzyl	3-Methyl-5-isoxazolylcarbonyl	3.0	17.0	7.5	278 ± 36
24	β-Hydroxyethyl	5-Methyl-3-isoxazolylcarbonyl	5.0	3.5	2.0	292
25	Isopropyl	4-Pyridylacetyl	Inactive	—		>400

[See Note *j* for data on 1,1-substituted compounds (No. 26–28).]

[a] The pharmacological data were obtained under the direction of Dr. L. O. Randall, Director of the Pharmacological Laboratories. The monoamide 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 2. [c] A Warburg determination of oxygen uptake on rat liver mitochondria. [d] Run on rat brain 1 hr. after intraperitoneal administration of the drug. This procedure is based on the work of A. N. Davison [*Biochem. J.*, **67**, 312 (1957)]. [e] In each test, iproniazid[1] was used as a standard and arbitrarily assigned value 1. Therefore, all other compounds were related to iproniazid and a compound having a MAO of 8.0 *in vivo* means that it is 8 times as active as iproniazid. The use of percentages has been avoided by nearly all workers in this field as such usage would be confusing. [f] On a molar basis. [g] On a weight basis. [h] 5-HTP is 5-hydroxytryptophan. [i] Toxicity work was carried out by Dr. E. Keith and his associates of the Pharmacological Laboratories. [j] 1,1-Acyl aralkyl hydrazines had these activities on tests as described in Table III.

Compound 26.—1-Benzyl-1-(5-methyl-3-isoxazolylcarbonyl)hydrazine

MAO *in vitro*	11.0	5-HTP	30.0
MAO *in vivo*	8.0	Toxicity	172 ± 9

Compound 27.—1-(4-Dimethylaminobenzyl)-1-(5-methyl-3-isoxazolylcarbonyl)hydrazine

MAO *in vitro*	0.002	5-HTP	6.0
MAO *in vivo*	2.3	Toxicity	232 ± 20

Compound 28.—1-(4-Dimethylaminobenzyl)-1-acetylhydrazine

MAO *in vitro*	Inactive at 10^{-3} molar concn.
5-HTP	1.0
Toxicity	400

hydrazine (43 g.) were boiled for 5 min. On concentration *in vacuo*, an amorphous residue was obtained. The residue was dissolved in ethanol (500 ml.) and reconcentrated *in vacuo*. The residue so obtained was again dissolved in ethanol (200 ml.) and on cooling, the product separated. Recrystallization from ethanol was repeated twice. A colorless product was obtained; yield 58 g., m.p. 90–92°.

Anal. Calcd. for $C_{14}H_{15}BrN_2O \cdot H_2O$: C, 49.4; H, 5.3; N, 12.3; Br, 23.5. Found: C, 49.6; H, 5.2; N, 12.3; Br, 24.2.

The colorless compound changes in a few days to a lower m.p. form having a light yellow color, m.p. 78°, analyzing at C, 49.6; H, 5.2. This lower melting form sometimes reverts to the unstable 92° form on crystallizing from ethanol. However, in a few days, the 92° form again reverts to the 78° type. This compound is slightly hygroscopic.

3-Hydroxybenzylhydrazine (No. 21).—3-Hydroxybenzaldehyde (61 g.) and 85% hydrazine hydrate (60 g.) in propanol-2 (1.2 l.) were hydrogenated at 35 kg./cm.^{2} at 30° using 10% palladium on carbon (10 g.) as a catalyst. The recovered solution was concentrated under vacuum to a solid. The solid residue was crystallized from ethanol; yield, 33 g., m.p. 114–115°.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.8; H, 7.2. Found: C, 60.6; H, 7.3.

4-Isopropylbenzylhydrazine (No. 22).—4-Isopropylbenzaldehyde (100 g.) and 85% hydrazine hydrate (80 g.) in ethanol (1.2 l.) were hydrogenated at 35 kg./cm.^{2} using 10% palladium on carbon (10 g.) as a catalyst. The temperature spontaneously rose to 70°. The recovered solution was concentrated and the residual oil distilled through a 15 cm. Vigreux column and the fraction boiling at 115–119° (4–6 mm.) collected. This fraction was redistilled at 100–105° (2 mm.); $n^{26}D$ 1.5351; yield, 69 g.

Anal. Calcd. for $C_{10}H_{16}N_2$: N, 17.1. Found: N, 16.8.

1-Benzyl-2-(3-methyl-5-isoxazolylcarbonyl)hydrazine (No. 23).—Methyl 3-methyl-5-isoxazolecarboxylate (50 g.) and benzylhydrazine (42 g.) were slowly heated from 60 to 92° for 0.5 hr. The cooled melt was dissolved in methanol and on cooling of the methanol solution, the product crystallized. The recovered crystals were washed with ice water and recrystallized from ethanol; yield 16 g., m.p. 93–94°.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.4; H, 5.7. Found: C, 62.6; H, 5.5.

1-(β-Hydroxyethyl)-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine (No. 24).—β-Hydroxyethylhydrazine (40 g.), b.p. 155–160° (3 mm.) and ethyl 5-methyl-3-isoxazolecarboxylate (78 g.) in propanol-2 (1000 ml.) were heated at 80° for 15 min. The solution darkened rapidly. It was concentrated to about 75 ml. and on standing at 4° some crystallization took place. The crystals thus obtained were used to seed an alcohol–ether solution (100 ml.) of the oily residue. The product crystallized and was recrystallized twice from ethanol and once from hot water; yield 18 g., m.p. 119–120°.

Anal. Calcd. for $C_7H_{11}N_3O_3$: C, 45.4; H, 5.9; N, 22.6. Found: C, 45.3; H, 5.2; N, 22.2.

1-Isopropyl-2-(4-pyridylacetyl)hydrazine (No. 25).—1-Isopropylidene-2-(4-pyridylacetyl)hydrazine (19 g.) was dissolved in ethanol (175 ml.) and hydrogenated at 25° with platinum oxide (0.5 g.) under 3.5 kg./cm.^{2} pressure. The recovered colorless product was crystallized from acetone; yield 5 g., m.p. 94–95°.

Anal. Calcd. for $C_{10}H_{15}N_3O$: C, 62.6; H, 7.8. Found: C, 61.8; H, 7.6.

A mixture m.p. with the starting compound was 67–69°.

1-Benzyl-1-(5-methyl-3-isoxazolylcarbonyl)hydrazine (No. 26).—5-Methyl-3-

isoxazolecarboxylic acid hydrazide (14.2 g.) was added to concentrated hydrochloric acid (20 ml.) and water (200 ml.). On stirring, a clear solution was obtained. To this chilled solution was added a solution of sodium nitrite (15 g.) in water (50 ml.). The white azide separated and was filtered off. It was washed with cold water and finally a dilute solution (5%) of sodium bicarbonate. The wet azide was dissolved in ether (50 ml.) at 0° and to this solution benzylhydrazine (12.2 g.) in ether (200 ml.) was added. The temperature of the ether solution rose; it first became turbid, and then clear with continued stirring. The clear solution was filtered and then permitted to stand at 25° overnight. The ether was removed under vacuum and the residue was crystallized from methanol; crude yield 25 g. A second recrystallization from methanol gave a pure, colorless product; yield, 15 g. m.p. 69–71°.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.4; H, 5.7; N, 18.2. Found: C, 62.5; H, 5.4; N, 18.1.

1-(4-Dimethylaminobenzyl)-1-(5-methyl-3-isoxazolylcarbonyl)hydrazine (No. 27).—5-Methyl-3-isoxazolecarboxylic acid hydrazide (28 g.) in concentrated hydrochloric acid (400 ml.) and ice water (400 ml.) was diazotized by the slow addition of sodium nitrite (30 g.) in cold water (100 ml.). One hour was required for this step, the suspension meanwhile being stirred slowly. The separated azide was removed by filtration, washed with cold water, 5% sodium bicarbonate solution, and with cold water. The wet azide was dissolved in ether (2 l.) at 0° and dimethylaminobenzylhydrazine (33 g.) added. The ether solution became cloudy and warm. The suspension was stirred for 1 hr. and filtered. The recovered solid was recrystallized from methanol; yield, 23 g., m.p. 124–125°. Recrystallization from hot water did not change the melting point.

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: N, 20.4. Found: N, 20.8.

1-(4-Dimethylaminobenzyl)-1-acetylhydrazine (No. 28).—4-Dimethylaminobenzylhydrazine (27 g.) was cautiously treated with acetic anhydride (26 g.). On warming at 80°, a vigorous reaction took place and after 0.5 hr. at 80°, the solution was poured into 1 l. of ice water. A colorless precipitate separated and was crystallized from hot water; yield 5 g., m.p. 126–127°.

Anal. Calcd. for $C_{11}H_{17}N_3O$: C, 63.7; H, 8.3. Found: C, 63.8; H, 8.0.

The assignment of structure was based on a previously established reaction mechanism for acetic anhydride and methyl hydrazine.[9]

1-(4-Dimethylaminobenzyl)-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine Dihydrochloride.[10]—1-(4-Dimethylaminobenzyl)-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine (10 g.) was dissolved in warm acetone. To this solution was slowly added with stirring 6 *N* hydrogen chloride in methanol (6.5 ml.). A colorless precipitate formed and stirring was continued for 0.5 hr. The recovered product was dried *in vacuo* at 25°; yield, 12.5 g., m.p. 136–138°.

Anal. Calcd. for $C_{14}H_{18}N_4O_2 \cdot 2HCl$: C, 48.4; H, 15.8; Cl, 20.5. Found: C, 48.6; H, 5.9; Cl, 19.8.

This salt could not be recrystallized without decomposition.

Methyl Picolinate Methobromide (or 1-Methyl-2-carbomethoxypyridinium Bromide).[8]—Methyl picolinate (86 g.) and methyl bromide (170 g.) in methanol (500 ml.) were heated in a shaking autoclave at 80–100° for 4 hr. under 35 kg./cm.[2]

(9) R. L. Hinman and D. Fulton, *J. Am. Chem. Soc.*, **80**, 1895 (1958); B. Forsgren and J. Sandstrom, *Acta Chem. Scand.*, **14**, 789 (1960); T. Folpmers, *Rec. trav. chim.*, **34**, 34 (1915).

(10) This salt was prepared by Mr. H. Newmark and Dr. E. H. Gans of the Applied Research Laboratories of Hoffmann-La Roche Inc., Nutley, N. J.

of nitrogen. On concentration to 200 ml. and cooling, a colorless product separated. It was recrystallized from ethanol; yield, 70 g., m.p. 173–174°. The compound turns yellow on exposure to air for a few days.

Anal. Calcd. for $C_8H_{10}BrNO_2$: N, 6.0. Found: N, 6.2.

Methyl Picolinate Methochloride (or (1-Methyl-2-carbomethoxypyridinium Chloride).—Methyl picolinate (86 g.) and methyl chloride (170 g.) in methanol (400 g.) were treated in the same manner as for the methyl bromide. The product was recrystallized from acetone-ethanol; yield, 17 g., m.p. 117–118°.

Anal. Calcd. for $C_8H_{10}ClNO_2$: N, 7.5. Found: N, 7.6.

1 - (β - Hydroxyethylidene) - 2 - (5 - methyl - 3 - isoxazolylcarbonyl)hydrazine.—5-Methyl-3-isoxazolecarboxylic acid hydrazide (7 g.), glycolaldehyde diethyl acetal (7 g.) and *p*-toluenesulfonic acid (100 mg.) were dissolved in ethanol (50 ml.) containing concentrated hydrochloric acid (0.6 ml.) in water (1 ml.). On standing at 25° for 48 hr., a small quantity of the starting hydrazide crystallized out. The solution was heated to 80° for 10 min. The color of the solution darkened rapidly. The solution was cooled to 25° and 2 vol. of ether added. An amorphous solid separated which crystallized at 4°. The solid material was washed with ether and extracted with hot water. The crude material had m.p. 214–215°. The product was recrystallized from ethanol to yield a buff-colored compound; yield, 300 mg., m.p. 220–221°. A sample was dissolved in ethanol and treated with activated carbon to give a colorless product, m.p. 220–221°.

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.9; H, 4.9. Found: C, 46.1; H, 4.9.

5-Amino-1-benzyl-3-methylpyrazole Hydrochloride.—Benzylhydrazine (31 g.) and 5-methyl-3-isoxazolecarboxylic acid (32 g.) were heated at reflux temperature in xylene for 4 hr. As cyclization took place, the water formed (4.0 ml.) was collected in a Barrett distilling column (calcd. H_2O, 4.5 ml.). The solution was concentrated to an oily residue which was dissolved in ethanol and an excess of 10 *N* hydrogen chloride in ethanol added. A solid hydrochloride separated and was washed with ether and then dissolved in water (200 ml.) at 60°. The solution was cooled to 25° and an excess of ammonia added. The base separated as an oil which was dissolved in ether. The ether was extracted with water, the ether layer was concentrated to an oil which was recrystallized from a solution of ether to which hexane was added; yield 23 g., m.p. 43–44°. The base (10 g.) was dissolved in ethanol (30 ml.) and 10 *N* HCl in ethanol (20 ml.) was added. The hydrochloride separated and was recrystallized from ethanol; yield 11 g., m.p. 226–228°.

Anal. Calcd. for $C_{11}H_{13}N_3HCl$: C, 59.1; H, 6.3; N, 18.8; Cl, 15.8; Van Slyke amino group, N, 6.3. Found: C, 59.2; H, 6.4; N, 18.6; Cl, 16.0; Van Slyke amino group, N, 5.8.

Fusion of benzylhydrazine (6 g.) and 5-methyl-3-isoxazolecarboxylic acid (6 g.) led to elimination of carbon dioxide. The evolved carbon dioxide was absorbed in 100 ml. of 1.0 *N* sodium hydroxide solution in water (300 ml.). Differential titration using phenolphthalein and methyl red as indicators gave 0.04 mole of carbon dioxide (calcd., 0.05 mole). The assignment of structure is made by analogy with the reaction of phenylhydrazine and 5-phenyl-3-isoxazolecarboxylic acid,[11] for which the structure of 1-phenyl-3-methyl-5-aminopyrazole is established.

Methylhydrazine Sulfate.—To a mixture of 85% hydrazine hydrate (200 g.) and 37% formaldehyde solution (81 g.) in ethanol (1 l.) was added 10% palla-

(11) S. Cusmano, *Gazz. chim. ital.*, **69**, 594 (1939).

dium on charcoal (15 g.), and this mixture hydrogenated at 70° for 2 hr. at 35 kg./cm.^{2} A slightly greater than theoretical uptake of hydrogen was obtained. The catalyst was filtered off and the solution concentrated to an oil *in vacuo*. The residual oil was distilled through a 15 cm. Vigreux column at atmospheric pressure. The fraction distilling at 85–95° was collected, cooled, and an excess of sulfuric acid was added. A white solid crystallized; yield, 90 g., m.p. 133–140° (dec.). Two recrystallizations from 80% ethanol–water gave the pure compound, m.p. 143–144°.

Anal. Calcd. for $CH_6N_2 \cdot H_2SO_4$: C, 8.3; H, 5.6; N, 19.4; S, 22.2. Found: C, 8.4; H, 5.4; N, 19.6; S, 21.9.

Reduction of Nitrofurans. I. Aminofurans

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A number of 2-substituted 5-nitrofurans have been reduced catalytically to the corresponding aminofurans. The aminofurans are relatively stable solids which can be acetylated with acetic anhydride, or condensed with 5-nitro-2-furaldehyde. Several new 2-substituted 5-aminothiophene compounds have been prepared.

The reduction of a number of nitrofurans by various body tissues and bacteria has been studied by several workers.[1] In this paper we present some studies on the chemical reduction of selected nitrofurans.

Prior to this work only three 5-nitrofuran derivatives have been reduced unequivocally to the corresponding aminofurans by chemical means. Reduction of ethyl and of β-diethylamino 5-nitro-2-furoates has been effected with aluminum amalgam[2] and with hydrogen over platinum.[3] Reduction of 5-nitro-2-furaldehyde semicarbazone (I) with Raney nickel[4] in water gave a solid which was identified as 4-cyano-2-oxobutyraldehyde semicarbazone (III), with 5-amino-2-furaldehyde semicarbazone (II) being postulated as the intermediate. However, reduction of I in absolute alcohol with palladium on charcoal

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