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Notes

1-[[(5-Nitrofuranyl)methylene]amino]-4- and/or -5-substituted 2-Imidazolidinones[1]

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A series of 1-[[(5-nitrofuranyl)methylene]amino]-4- and/or -5-substituted 2-imidazolidinones was prepared utilizing three different reaction sequences. The structure of **4**, the product derived from 4-methyl-2-imidazolidinone (**2a**), was verified by synthesis using an alternate, unequivocal route. The levo isomer *l*-**4** was prepared by a series of reactions starting with L(+)-2-amino-1-propanol (*l*-**10**). All of the nitrofurans were examined for potential use as chemotherapeutic agents for urinary tract infections. Based on the high level of activity in the urine and the in vitro antibacterial activity (MIC), **4**, *l*-**4**, and **16** are considered to be the most active as urinary tract agents.

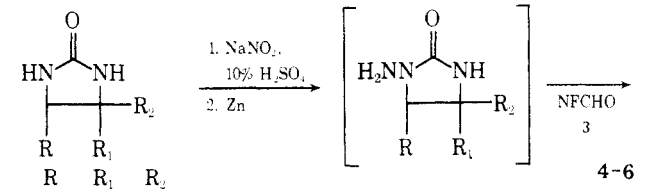
The activity of nifuradene (**1**)[2] (see Table I) as a possible chemotherapeutic agent for urinary tract infections[3] led to the synthesis of a series of N-substituted homologs of **1**.[4] The preparation of homologs of **1** has been expanded to include compounds having substitution on the 2-imidazolidinone ring carbons, e.g., positions 4 and/or 5 of **1**. This paper describes the synthesis, structure determination, and biologic activity of these compounds.

Chemistry. The appropriately substituted 2-imidazolidinones **2** (**a**,[5] **b**,[6] **c**[7]) were nitrosated, reduced, and condensed with 5-nitro-2-furaldehyde (**3**) as previously described[4] to yield **4**, **5**, and **6**, respectively (see Scheme I and Table I). The use of hexahydro-2-benzimidazolinone (**7**)[8] in the place of **2** produced hexahydro-1-[[(5-nitrofuranyl)-methylene]amino]-2-benzimidazolinone (**8**).

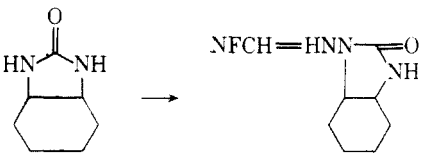
Although the reactions proceeded smoothly, the position of the methyl group(s) in **4** and **5** was questionable. This uncertainty arises from the choice of two nitrogens for the position of nitrosation. Thus, for example, when **2a** was nitrosated, attack at the 1 position would ultimately yield **4** and attack at position 3 would lead to **15**. Therefore, it was necessary to establish unequivocally the position of the methyl group in **4**. The unambiguous synthesis of **4** was carried out as shown in Scheme II. Benzaldehyde semicarbazone (**9**) was heated with 2-amino-1-propanol (**10a**) in 2-ethoxyethanol to yield benzaldehyde 4-(2-hydroxypropyl)semicarbazone (**11a**). The treatment of **11a** with $SOCl_2$ resulted in a water-soluble hydrochloride which was assigned the structure **12a** on the basis of previous work involving the chlorination of 5-nitro-2-furaldehyde 2-(2-hydroxyalkyl)semicarbazones with $SOCl_2$.[9] When **12a** was heated in an inert solvent, rearrangement occurred to yield benzaldehyde 4-(2-chloropropyl)semicarbazone (**13a**). Cyclization of **13a** was achieved in DMF using NaH as the condensing agent to give 1-benzylideneamino-4-methyl-2-imidazolidinone (**14a**). The acid hydrolysis of **14a** in the presence of **3** produced **4**. The two compounds were identical in all respects, e.g., mixture melting point and ir and NMR spectra.

In a similar manner the use of L(+)-2-amino-1-propanol (*l*-**10**) resulted in the synthesis of *l*-**4**, the L(−) isomer of **4**. That the integrity of the asymmetric center was maintained was evidenced by the optical activity of the intermediates *l*-**11**–*l*-**14**. By the utilization of **10b,c**, compounds **15**

Scheme I



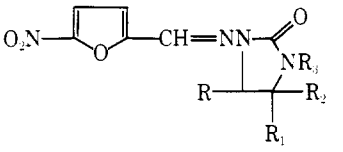
	R	R_1	R_2
2a	H	CH_3	H
2b	H	CH_3	CH_3
2c	CH_3	CH_3	H



7 8

NF = O_2N–

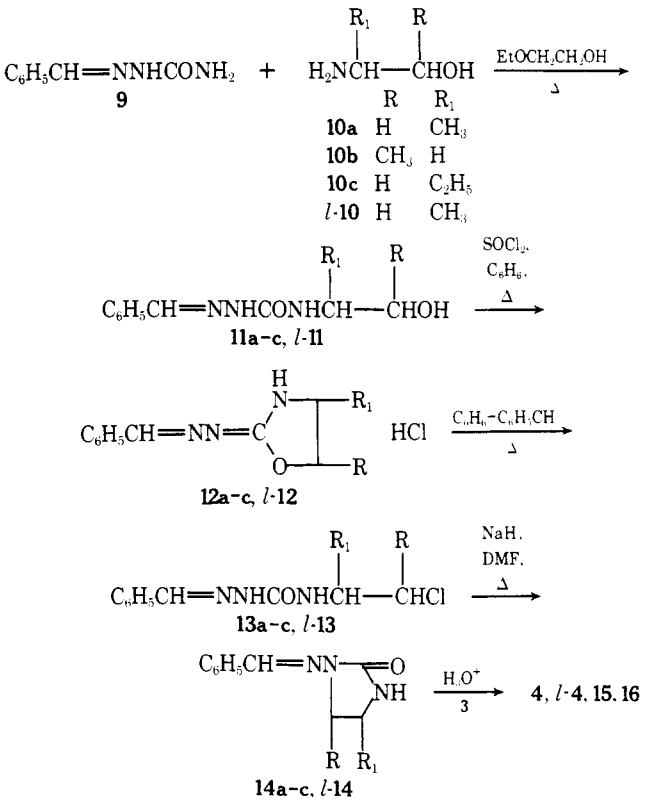
Table I. 1-[[(5-Nitrofuranyl)methylene]amino]-4- and/or -5-substituted 2-Imidazolidinones



No.	R	R_1	R_2	R_3	Yield, %	Mp, °C	Formula	Min inhibitory concn, μg/ml,[a] Es-2[b]	% of dose excreted in rat urine in 24 hr[c]
1[d]	H	H	H	H				0.4	5
4[e]	H	CH_3	H	H	83	240–240.5 dec	$C_9H_{10}N_4O_4$	0.8	41
l-4[f]	H	CH_3	H	H	78	224–225	$C_9H_{10}N_4O_4$	0.75	21
5	H	CH_3	CH_3	H	84	273–274 dec	$C_{10}H_{12}N_4O_4$	3	1.2
6	CH_3	CH_3	H	H	47	177–180 dec	$C_{10}H_{12}N_4O_4$	1.5	4.8
8	$-CH_2CH_2CH_2CH_2-$		H	H	63	193–194 dec	$C_{12}H_{14}N_4O_4$	3	5.8
15	CH_3	H	H	H	56	223–225 dec	$C_9H_{10}N_4O_4$	1.5	3
16	H	C_2H_5	H	H	91	203–205	$C_{10}H_{12}N_4O_4$	0.75	15.1
17	H	CH_3	H	CH_2OH	78	175 dec	$C_{10}H_{12}N_4O_5$	1.5	7.8
18	H	CH_3	H	$CH_2C{\equiv}CH$	46	191–192	$C_{12}H_{12}N_4O_4$	3.1	1

[a]Lowest concentration of compound which prevents visible growth following 24-hr incubation at 37°. [b]The Norwich Pharmacal Co. number, Es-2 = *Escherichia coli*. [c]Calculated on the basis of antibacterial equivalents, 10 mg/kg dose. [d]See ref 4. [e]Yield by method a; 84% by method b. [f]$[\alpha]^{20}D$ −55.47° (*c* 0.112, DMF).

Scheme II



and **16** (see Scheme II and Tables I and II), respectively, were prepared.

Having established that nitrosation of **2a** occurred at the less hindered nitrogen, it has been assumed that nitrosation of **2b** would follow the same course since position 3 is more hindered and give the product having the structure of **5** (Table I). It is interesting to note that nitrosation of the nitrogen adjacent to the substituted carbon is not impossible since **2c** and **7** do yield **6** and **8**, respectively, although the yields are considerably lower.

The treatment of **4** with 5% HCHO gave the *N*-hydroxymethyl compound **17**. The alkylation of **14a** by propargyl bromide was carried out as previously described[4] to give the intermediate benzylideneamino compound which was transformed into **18** by acid hydrolysis in the presence of **3**.

Biologic Activity. Compounds were tested for in vitro antibacterial activity by procedures described previously for the determination of minimal inhibitory concentration (MIC).[10] The urinary antibacterial activity was determined by serial tube dilution[11] or cup plate bioassay.[12] Following peroral dosing of the compound at 10 mg/kg to four rats as a suspension in 1% carboxymethylcellulose, the percent of the dose excreted in rat urine over the 24-hr period was calculated as antibacterial equivalents of parent compound.

The antibacterial activity and urinary excretion data are presented in Table I. This series of compounds demonstrated a high order of in vitro antibacterial activity against *Escherichia coli*.

Although peroral administration of a number of the compounds in this series resulted in urinary excretion of antibacterial activity, only **4**, *l*-**4**, and **16** were excreted at levels higher than 15% of the administered dose (as antibacterial equivalents). High urine concentration of antibacterial activity often indicates potential usefulness of the compound as a urinary tract antibacterial agent. Based on the high level of activity in the urine and the in vitro antibacterial activity (MIC), **4**, *l*-**4**, and **16** are considered to be the most active as urinary tract agents.

Experimental Section

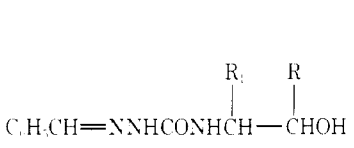
The melting points were taken in an open capillary tube on a Mel-Temp melting point apparatus and are corrected. The physical constants of all the final products are listed in Table I. The physical constants for the intermediates **11**–**14** are listed in Table II. The analytical results for C, H, and N of all of the compounds prepared were within ±0.4% of the theoretical values. The optical rotation measurements were obtained on a Perkin-Elmer polarimeter Model 141.

4-Methyl-1-[[(5-nitrofuranyl)methylene]amino]-2-imidazolidinone (4). (a) Compound **2a**[5] (73.0 g, 0.73 mol) was nitrosated, reduced with Zn dust, and condensed with **3** (93.0 g, 0.66 mol) as previously described by Snyder et al.[4] The product was recrystallized from $MeNO_2$ (charcoal).

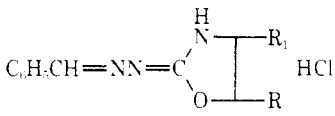
In a similar manner, **2b**,[6] **2c**,[7] and **7**,[8] respectively, yielded **5** which was purified by recrystallization from $MeNO_2$ (charcoal), **6** which was recrystallized from *i*-PrOH (charcoal), and **8** which was purified by recrystallization from *i*-PrOH (charcoal).

(b) Compound **14a** (1.0 g, 0.005 mol) was dissolved in a mixture

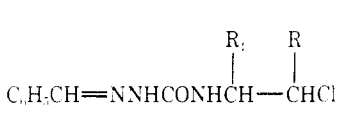
Table II. Intermediates 11-14



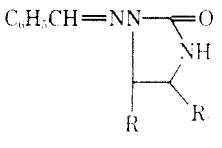
11



12



13



14

Compd no.	R	R_1	Yield, %	Mp, °C	Formula	Recrysn solvent
11a	H	CH_3	53	118–120	$C_{11}H_{15}N_3O_2$	$MeNO_2$
11b	CH_3	H	50	142–143	$C_{11}H_{15}N_3O_2$	$MeNO_2$
11c	H	C_2H_5	58	135–136	$C_{12}H_{17}N_3O_2$	$MeNO_2$
l-11	H	CH_3[a]	47	141–142	$C_{11}H_{15}N_3O_2$	$MeNO_2$
12a	H	CH_3	72	101–105	$C_{11}H_{13}N_3O \cdot HCl$	MeOH–Et_2O
12c	H	C_2H_5	68	130–132	$C_{12}H_{15}N_3O \cdot HCl$	MeOH–Et_2O
l-12	H	CH_3[b]	64	129–130	$C_{11}H_{13}N_3O \cdot HCl$	MeOH–Et_2O
13a	H	CH_3	100	109–110	$C_{11}H_{14}ClN_3O$	Hexane
13b	CH_3	H	55[c]	104–106	$C_{11}H_{14}ClN_3O$	Hexane
13c	H	C_2H_5	94	94–96	$C_{12}H_{16}ClN_3O$	Hexane
l-13	H	CH_3[d]	100	129–130	$C_{11}H_{14}ClN_3O$	Hexane
14a	H	CH_3	61	191–193	$C_{11}H_{13}N_3O$	$MeNO_2$
14b	CH_3	H	45	149–151	$C_{11}H_{13}N_3O$	$MeNO_2$
14c	H	C_2H_5	83	195–197	$C_{12}H_{15}N_3O$	C_6H_6–hexane
l-14	H	CH_3[e]	61	227–228	$C_{11}H_{13}N_3O$	$MeNO_2$

[a] $[\alpha]^{20}D$ +24.3° (*c* 1.03, MeOH). [b] $[\alpha]^{20}D$ +49.8° (*c* 1.04, MeOH). [c] Yield from **11b**. [d] $[\alpha]D$ +66.5° (*c* 1.08, MeOH). [e] $[\alpha]D$ −7.53° (*c* 1.61, MeOH).

of 10% H_2SO_4 and MeOH and heated on the steam bath for 10 min. A solution of **3** (0.7 g, 0.005 mol) in a minimum amount of MeOH was added and the mixture was heated for 1 hr, cooled, and filtered to yield 1.0 g of **4**.

In a similar manner, *l*-**14** gave *l*-**4**. The use of **14b,c** in the above reaction yielded **15**, recrystallized from an aqueous DMF–*i*-PrOH mixture, and **16** purified by recrystallization from $MeNO_2$, respectively.

Benzaldehyde 4-(1-Hydroxy-2-propyl)semicarbazone (11a). A mixture of **9** (48.9 g, 0.30 mol), **10a** (23.0 g, 0.30 mol), and 2-ethoxyethanol (150 ml) was placed in a flask and heated at reflux for 4 hr. The solvent was removed in vacuo and the residue was diluted with H_2O. The product crystallized to yield 35 g of **11a**.

In a similar manner, **10b, 10c,** and *l*-**10** gave **11b, 11c,** and *l*-**11**, respectively.

2-[(Benzylideneamino)imino]-4-methyloxazolidine Hydrochloride (12a). Compound **11a** (35.0 g, 0.158 mol) was placed in a flask with benzene (470 ml) and the mixture was heated to reflux. The heat was removed and $SOCl_2$ (44 ml) was added dropwise over a period of 10–15 min. The reaction mixture was stirred for 1 hr and then cooled. The solid was filtered, washed with Et_2O, and dried at 65° to yield 27.0 g of **12a**.

In a similar manner **11b, 11c,** and *l*-11 gave **12b, 12c,** and *l*-**12**, respectively; however, **12b** was very hygroscopic and was used with no further purification.

Benzaldehyde 4-(1-Chloro-2-propyl)semicarbazone (13a). Compound **12a** (27.0 g, 0.11 mol) was suspended in a mixture of benzene (420 ml) and toluene (180 ml) and refluxed for 12 hr. The solvents were removed under reduced pressure. The solid residue was washed with H_2O, filtered, and dried to yield 27.0 g of **13a**.

Compounds **13b, 13c,** and *l*-13 were prepared in a similar manner from **12b, 12c,** and *l*-**12**, respectively.

1-Benzylideneamino-4-methyl-2-imidazolidinone (14a). (a) Compound **13a** (9.6 g, 0.04 mol) was dissolved in DMF. Sodium hydride as 56% oil dispersion (1.7 g, 0.04 mol) was added and the mixture was heated at 100–110° for 3 hr. The DMF was removed under reduced pressure and the residue diluted with Et_2O. The solid was collected, washed with H_2O, and dried to yield 5.0 g of **14a**.

The cyclization of **13b, 13c,** and *l*-13 in a similar manner gave **14b, 14c,** and *l*-14, respectively.

(b) Compound **2a** was nitrosated, reduced with Zn dust, and condensed with PhCHO as previously described by Snyder et al.[4] to yield **14a** in a 60% yield.

3-Hydroxymethyl-4-methyl-1-[[(5-nitrofuranyl)methylene]amino]-2-imidazolidinone (17). Compound **4** (59.5 g, 0.25 mol) was added to a stirred 5% aqueous HCHO solution (ca. 2000 ml). The suspension was heated at reflux with stirring for 15 min. Upon cooling the yellow solution in an ice bath, the product crystallized to yield 50.0 g. An analytical sample was prepared by recrystallization from MeOH (charcoal).

4-Methyl-1-[[(5-nitrofuranyl)methylene]amino]-3-(2-propynyl)-2-imidazolidinone (18). Compound **14a** (102.0 g, 0.5 mol) was alkylated in DMF using NaH and propargyl bromide as previously described by Snyder et al.[4] The crude benzylideneamino intermediate was hydrolyzed in acidic aqueous MeOH in the presence of **3** (72.0 g, 0.5 mol) to yield 63.5 g of **22**. The crude product was recrystallized from aqueous DMF (charcoal).

Acknowledgments. The authors gratefully acknowledge the aid of Mr. Frederick Abbott and Mr. Edwin Woodrick in the preparation of chemical intermediates. Mr. Grant Gustin, Mr. Warren Smith, and Mr. Marvin Tefft performed the microanalyses. Microbiologic data were obtained through the assistance of Mr. Richard Dobson and Mr. Patrick Moynihan. Miss Esther Nohle and Mr. Donald Humphrey assisted in obtaining the urinary excretion data.

References and Notes

(1) After the completion of this work, a patent application was filed April 3, 1967, for 4-methyl-1-(5-nitrofurfurylideneamino)-2-imidazolidinone. U.S. Patent No. 3,407,195 was issued Oct 22, 1968; *Chem. Abstr.*, **70,** 77763d (1969).
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Inhibitors of Polyamine Biosynthesis. 3. (±)-5-Amino-2-hydrazino-2-methylpentanoic Acid, an Inhibitor of Ornithine Decarboxylase

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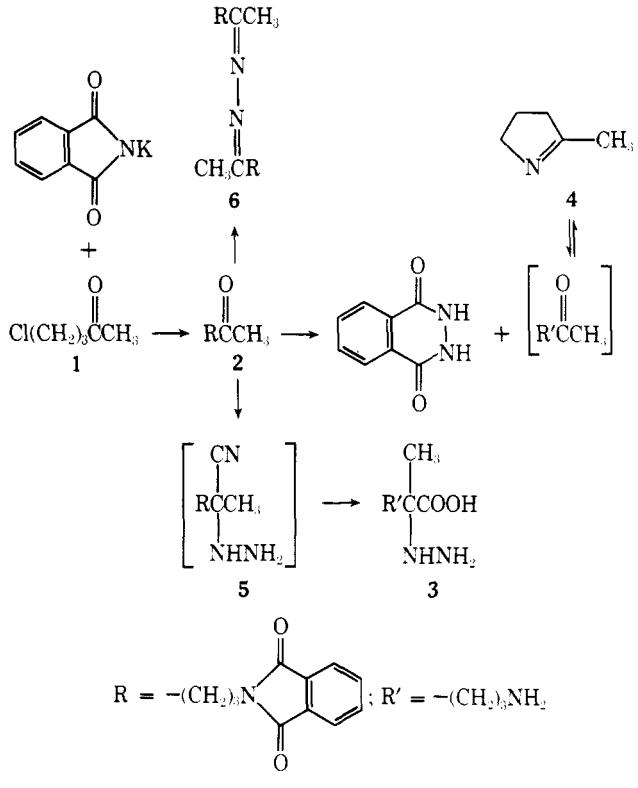
(±)-5-Amino-2-hydrazino-2-methylpentanoic acid [α-hydrazino-α-methyl-(±)-ornithine] was obtained from 1-phthalimidopentan-4-one by treatment with hydrazine and KCN followed by acid hydrolysis. The title compound was found in vitro to be a potent competitive inhibitor of ornithine decarboxylase obtained from the prostate glands of rats. This inhibition was abolished at high concentrations of pyridoxal phosphate. The title compound also blocked the increase in putrescine levels normally observed in bovine lymphocytes transformed by conconavalin A.

In an effort to elucidate the role of polyamines in proliferating tissues we have embarked on a program for the synthesis of specific inhibitors of the enzyme ornithine decarboxylase which is thought to be the rate-limiting step in the synthesis of the polyamines. In previous communications from this laboratory we have described the synthesis of α-alkyl- and α-aralkyl-(±)-ornithines and their evaluation as inhibitors of this enzyme.[1,2] The present report describes the synthesis of (±)-5-amino-2-hydrazino-2-methylpentanoic acid [α-hydrazino-α-methyl-(±)-ornithine] and its evaluation as an inhibitor of ornithine decarboxylase in vitro and in transforming lymphocytes. This ornithine analog was studied on the premise that since both α-methyl-(±)-ornithine and α-hydrazino-(±)-ornithine were found to be effective inhibitors of ornithine decarboxylase, the combination of these modifications might provide more potent inhibitor of this enzyme. Furthermore, α-methyl-α-hydrazino analogs of other amino acids were found to be potent inhibitors of their decarboxylases.[3]

Results and Discussion

The target compound was obtained using a modification of the Strecker synthesis as shown in Scheme I. 5-Chloro-2-pentanone (1) was treated with potassium phthalimide to provide **2** in moderate yields. Treatment of **2** with hydrazine and KCN at room temperature, followed by heating under reflux, provided phthalhydrazide in quantitative yields and a complex mixture of crude products which was treated in situ with concentrated hydrochloric acid. Purification of the product by ion-exchange resin provided the crude target compound **3** in 40% yield and a volatile compound which was identified as 2-methyl-Δ^1-pyrroline (**4**) in 50% yield. The separation of compound **4** was accomplished by treatment of the crude product after acid hydrolysis with Na_2CO_3 followed by steam distillation. The amine was separated from the distillate as the hydrochloride and picrate salts. The formation of compound **4** could be attributed to the facile cleavage of the phthalimide-protecting group prior to the formation of the hydrazinonitrile **5**. This was shown to be the case since mixing equimolar amounts of hydrazine and **2** at room temperature produced phthalhydrazide, unreacted **2**, and bis(1-methyl-4-phthalimidobutyl)hydrazone (**6**) in 40, 40, and 10% yields, respectively. The formation of **6** in the presence of limiting concentration of hydrazine dictated the use of an excess of hydrazine in subsequent reactions. Scheme I represents a proposed overall scheme for the formation of the isolated and identified compounds. In an attempt to improve the yields of **3**, compound **2** was initially treated with $NaHSO_3$ followed by treatment with KCN and hydrazine. This, however, did not increase the yield of **3**.

Scheme I



The 10,000g supernatant from extracts of prostate glands of rats was dialyzed for 12 hr and then used as the source of the enzyme ornithine decarboxylase for studies of the inhibition by **3**·HCl of the enzymatic decarboxylation of L-ornithine. The activity of ornithine decarboxylase was measured by determining the amount of $^{14}CO_2$ released from [^{14}C]carboxyl-(±)-ornithine in the presence of pyridoxal phosphate. Corrections were made for the nonenzymatic production of $^{14}CO_2$ by running controls which were identical with the experimental runs except that the tissue extracts were replaced with the homogenization solution. The activity of prostatic ornithine decarboxylase was found