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Synthesis of 3-(Aminoalkyl)-1-[(5-nitrofurfurylidene)amino]hydantoins

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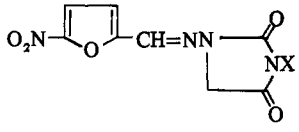
Received November 6, 1972

The success of 1-[(5-nitrofurfurylidene)amino]hydantoin (Ia)[1,†] as an antibacterial agent has prompted the synthesis of analogs substituted in the 3 position with aminoalkyl groups (Ib). *In vitro* screening data against three organisms are presented.



Ia, X = H
b, X = $(CH_2)_nNRR'$

Chemistry. The most direct approach to the preparation of these analogs would be treatment of the sodium salt of nitrofurantoin with aminoalkyl halides. Unfortunately, this method is not applicable because of the sensitivity of nitrofurans to alkaline reagents. For this reason four different approaches were developed. The method used for each compound is designated in Table I.

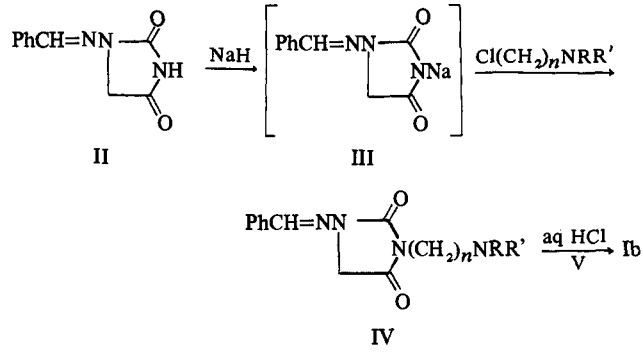
In method A, the sodium salt (III) of 1-benzylideneaminohydantoin (II)[2] was treated with the appropriate aminoalkyl chloride. The benzylidene group was then removed by acid hydrolysis and replaced by the 5-nitrofurfurylidene group by treatment with 5-nitro-2-furaldehyde (V) as shown in Scheme I.

Most of the aminoalkyl halides used in method A either were commercially available or have been reported in the literature. The preparation of 3-chlorobutyl-*N*,*N*-dimethylamine, the intermediate for **28**, and 3-chloropropyl-*N*-methyl-*N*-isopropylamine, the intermediate for **6**, is described in the Experimental Section.

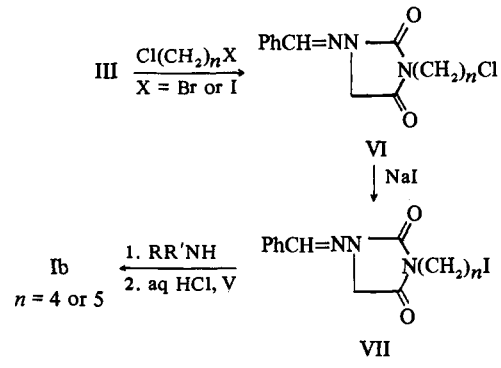
When the aminoalkyl side chain contains four or five carbon atoms (n = 4 or 5, Ib), method A cannot be used because the required chlorobutyl- or chloropentylamines cyclize rapidly upon neutralization of their salts to form quaternary salts which are too stable to function as alkylating agents. Therefore, method B (Scheme II) was used for the preparation of those analogs in which n = 4 or 5. Compound III was treated with an alkyl chlorobromide or chloroiodide. With the former the product was the chloroalkyl intermediate VI; this proved unreactive toward most amines and was therefore converted to the iodo compound VII with sodium iodide. When an alkyl chloroiodide was used the product was a mixture of chloro- and iodoalkyl intermediates (the latter formed by exchange of VI with the sodium iodide liberated). Treatment of the mixture with more sodium iodide completed the conversion to VII. Reaction of VII with various amines followed by hydrolysis and treatment with V then gave the desired products.

Two of the compounds (**34** and **35**) were made by heating II with the appropriate vinylpyridine in pyridine solution, followed by removal of the benzylidene group, and treatment with V as shown in Scheme III (method C).

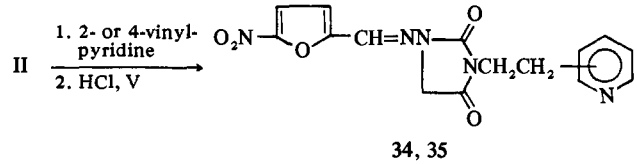
Scheme I



Scheme II



Scheme III

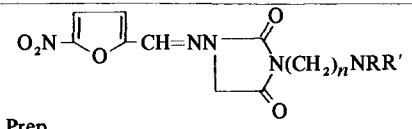


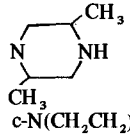
34, **35**

The primary aminoalkyl analogs (R = R′ = H, formula Ib) were prepared by reduction of the appropriate nitriles (method D, Scheme IV). These nitriles (VIII), in all cases except one, were made by reaction of III with ω-halonitriles; for the trimethylene compound acrylonitrile was used. The most effective conditions found for the reduction were Raney nickel catalyst in acetic anhydride solution with sodium acetate.[3] The acetylated amines IX, which were formed in good yields, were then hydrolyzed and treated with V which reacted preferentially with the ring amino group. This point was determined by treatment of **36**

†The Norwich Pharmacal Company's registered trademarks are Furadantin and Macrodantin; the generic name is nitrofurantoin.

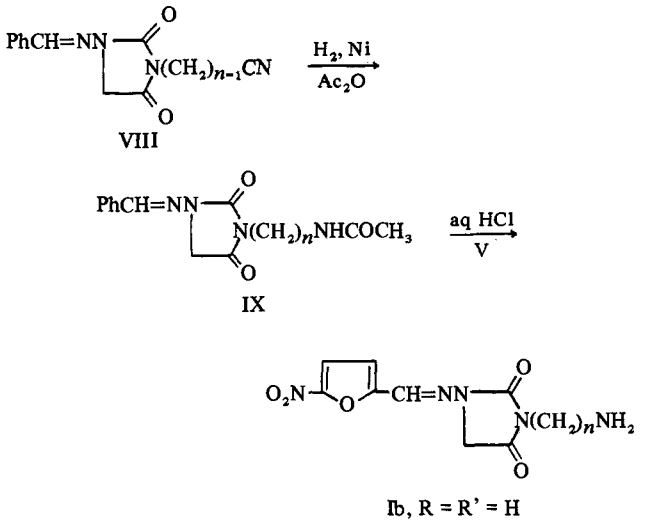
Table 1. 3-(Aminoalkyl)-1-[(5-nitrofurfurylidene)amino]hydantoins



No.	n	NRR'	Prep method[a]	Yield, %[b]	Mp, °C	Recrystn solvent[c]	Formula	Analyses[d]
1[f]	3	NH-*i*-Pr	A	30	247–248 dec	C–H	$C_{14}H_{19}N_5O_5 \cdot HCl$	C, H, N
2[f]	2	NMe_2	A	67	dec >200	A–C	$C_{12}H_{15}N_5O_5 \cdot HCl \cdot {}^2/_3H_2O$	C, H, N, Cl, H_2O
3[f]	3	NMe_2	A	54	238–241 dec	A–C	$C_{13}H_{17}N_5O_5 \cdot HCl \cdot 0.5H_2O$	C, H, Cl
4[f]	4	NMe_2	B	28	233–255 dec	A–C	$C_{14}H_{19}N_5O_5 \cdot HCl$	C, H, N
5	5	NMe_2	B	41	199–201	A–C	$C_{15}H_{21}N_5O_5 \cdot HCl \cdot 0.5H_2O$	C, H, N
6	3	NMe-*i*-Pr	A	32	213–215	A	$C_{15}H_{21}N_5O_5 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
7[f]	2	NEt_2	A	43	227–230 dec	A–C	$C_{14}H_{19}N_5O_5 \cdot HCl \cdot H_2O$	C, H, Cl
8[f]	3	NEt_2	A	63	238–239 dec	A–C	$C_{15}H_{21}N_5O_5 \cdot HCl$	C, H, Cl
9	4	NEt_2	B	26	185–188	A	$C_{16}H_{23}N_5O_5 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
10	5	NEt_2	B	28	169–171	A–C	$C_{17}H_{25}N_5O_5 \cdot HCl$	C, H, N
11	3	NEtBu	A	42	185–187	A	$C_{17}H_{25}N_5O_5 \cdot HCl$	C, H, N, Cl
12[f]	2	N-*i*-Pr_2	A	35	230–240 dec	B	$C_{16}H_{23}N_5O_5 \cdot HCl$	C, H, Cl
13[f]	3	N-*i*-Pr_2	A	39	224–227	A–C	$C_{17}H_{25}N_5O_5 \cdot HCl$	C, H, Cl, N[e]
14	3	NPr_2	A	90	141–143	B–G	$C_{17}H_{25}N_5O_5 \cdot HCl$	C, H, N, Cl
15	4	NPr_2	B	52	167–170	A	$C_{18}H_{27}N_5O_5 \cdot HCl \cdot 0.5H_2O$	C, H, N
16	3	HN-*c*-C_6H_{11}	A	31	260–263 dec	A–C	$C_{17}H_{23}N_5O_5 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
17	3	c-NC_5H_{10}	A	72	280–283 dec	A–C	$C_{16}H_{21}N_5O_5 \cdot HCl \cdot 0.5H_2O$	C, H, N
18[f]	4	c-NC_5H_{10}	B	56	229–233 dec	A	$C_{17}H_{23}N_5O_5 \cdot HCl \cdot 0.5H_2O$	C, H, Cl
19[g]	2	c-$N(CH_2CH_2)_2O$	A	58	230–235 dec	F–C	$C_{14}H_{17}N_5O_6 \cdot HCl$	C, H, Cl
20	3	c-$N(CH_2CH_2)_2O$	A	60	272–274 dec	A–C	$C_{15}H_{19}N_5O_6 \cdot HCl$	C, H, N
21	4	c-$N(CH_2CH_2)_2O$	B	48	225–230 dec	A–C	$C_{16}H_{21}N_5O_6 \cdot HCl$	C, H, N
22	5	c-$N(CH_2CH_2)_2O$	B	66	190–195	A–C	$C_{17}H_{23}N_5O_6 \cdot HCl$	C, H, N
23	6	c-$N(CH_2CH_2)_2O$	A	13	177–180	A	$C_{18}H_{25}N_5O_6 \cdot HCl$	C, H, Cl
24	3	c-NC_4H_8	A	40	270–273	E–C	$C_{15}H_{19}N_5O_5 \cdot HCl$	C, H, N, Cl
25	4		B	31	271–275 dec	A–C	$C_{18}H_{26}N_6O_5 \cdot 2HCl$	C, H, N, Cl
26	4	c-$N(CH_2CH_2)_2NCH_2CH_2OH$	B	31	dec >250	A	$C_{18}H_{26}N_6O_6 \cdot 2HCl$	C, H, Cl
27	4	$N(CH_2CH_2OH)_2$	B	29	134–138	A–C	$C_{16}H_{23}N_5O_7 \cdot HCl$	C, H, N, Cl
28	$-C(CH_3)HCH_2CH_2-$	NMe_2	A	20	175–177	A	$C_{14}H_{19}N_5O_5 \cdot HCl \cdot 0.5H_2O$	C, H, N
29[h]	2	$NHCO_2Et$		78	176–177	D	$C_{13}H_{15}N_5O_7$	C, H, N
30	5	$NHCO_2Et$		74	152–154	A	$C_{16}H_{21}N_5O_7$	C, H, N
31	2	$NHNMe_2$	A	12	186–188	C	$C_{12}H_{16}N_6O_5 \cdot HI$	C, H, N
32	3	$NHNMe_2$	B	46	166–171	C	$C_{13}H_{18}N_6O_5 \cdot HI \cdot 0.5H_2O$	C, H, N, I
33	4	$NHNMe_2$	B	42	210–212	C	$C_{14}H_{20}N_6O_5 \cdot HI$	C, H, N
34[i]	2	4-Pyridyl	C	62	210–212 dec	D–B	$C_{15}H_{13}N_5O_5$	C, H, N
35	2	2-Pyridyl	C	70	218–221	E	$C_{15}H_{13}N_5O_5$	C, H, N
36	2	NH_2	D	24	dec >230	A–C	$C_{10}H_{11}N_5O_5 \cdot HCl$	C, H, N
37	3	NH_2	D	24	dec >240	A–C	$C_{11}H_{13}N_5O_5 \cdot HCl$	C, H, N
38	4	NH_2	D	28	206–210	A–C	$C_{12}H_{15}N_5O_5 \cdot HCl$	C, H, N
39	5	NH_2	D	28	222–224	A–C	$C_{13}H_{17}N_5O_5 \cdot HCl$	C, H, N

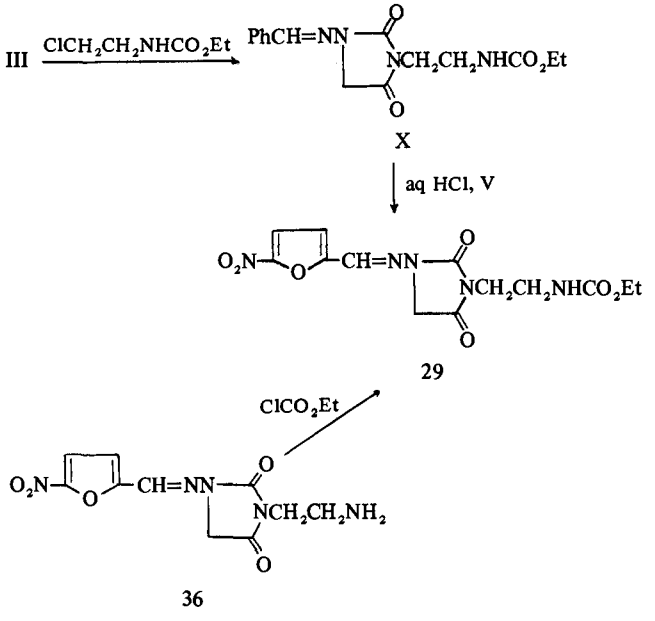
[a]See text and Experimental Section. [b]Recrystallized products. [c]A, EtOH; B, MeOH; C, H_2O; D, $MeNO_2$; E, DMF; F, Me_2CO; G, Et_2O; H, *i*-PrOH. [d]Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [e]N: calcd, 16.84; found, 16.40. [f]J. G. Michels, U. S. Patent 3,075,973 (1963); *Chem. Abstr.*, 57, 16625*f* (1962). [g]J. G. Michels, U. S. Patent 3,075,974 (1963); *Chem. Abstr.*, 57, 16626*c* (1962). [h]J. G. Michels, U. S. Patent 3,075,972 (1963); *Chem. Abstr.*, 57, 13724*f* (1962). [i]J. G. Michels, U. S. Patent 3,097,202 (1963); *Chem. Abstr.*, 57, 16625*a* (1962).

Scheme IV



with ethyl chloroformate which gave **29**. Compound **29** was also prepared from the benzylidene intermediate X as shown in Scheme V, thereby establishing the structure of **36**. Compound **30** was prepared by treatment of **39** with ethyl chloroformate.

Scheme V



Biologic Activity. The compounds were tested for antibacterial activity *in vitro* by reported procedures.[4] Although no real trend is apparent, inspection of Table II shows that compounds with an alkyl chain of 3–5 carbon atoms appear most active against *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus pyogenes*. The piperidino, morpholino, and pyrrolidino analogs, however, all have about the same order of activity regardless of chain length. None of the compounds prepared were significantly more active than nitrofurantoin, even though water solubility was greatly improved in most cases. Therefore, attempts to correlate activity with other parameters, such as partition coefficients, were not undertaken.

Experimental Section

The general procedures given here are representative of those used for the preparation of the compounds described in this paper.

Table II. Antibacterial Activity

No.	MIC,[a] μg/ml *Staph. aureus*	*E. coli*	*Strept. pyogenes*
1	100	12.5	25
2	206	206	>206
3	12.5	12.5	6
4	25	6	3
5	28	14	7
6	7	14	5
7	>200	>200	>200
8	12.5	25	6
9	25	12.5	6
10	25	12.5	6
11	25	12.5	25
12	>198	>198	>198
13	25	12.5	12.5
14	25	12.5	25
15	25	25	25
16	12.5	6	6
17	12.5	6	12.5
18	12.5	6	12.5
19	12.5	50	200
20	12.5	6	50
21	12.5	6	50
22	12.5	6	25
23	12.5	12.5	12.5
24	12.5	6	12.5
25	100	50	25
26	100	50	12.5
27	>200	100	100
28	6	6	6
29	7	15	30
30	10[b]	0	7
31	>200	>200	>200
32	>200	>200	>200
33	>200	>200	>200
34	3	6	12.5
35	6	6	8
36	100	100	25
37	200	50	25
38	>200	100	50
39	>200	100	50
Nitrofurantoin	12.5	6	3

[a] Minimal inhibitory concentration, tube dilution method.[4] [b] Zone diameters in millimeters, including the 3-mm tablet; negative reactions recorded as 0.

Analyses, yields, and other data are recorded in Table I. Melting points, determined with a Fisher-Johns hot stage apparatus, are uncorrected.

3-(2-Dimethylaminoethyl)-1-[(5-nitrofurfurylidene)amino]-hydantoin Hydrochloride (2, Method A). A solution of 50 g (0.25 mol) of 1-benzylideneaminohydantoin (II)[2] in 1250 ml of DMF was treated with 11 g of 55% NaH dispersion in mineral oil. When salt formation was complete, 26.7 g (0.25 mol) of 2-dimethylaminoethyl chloride was added and the mixture was heated at 110–115° overnight. The DMF was distilled under reduced pressure and the residue was steam-distilled in the presence of HCl. When evolution of PhCHO ceased, a solution of 35 g (0.25 mol) of 5-nitro-2-furaldehyde (V) in 100 ml of EtOH was added. After standing for about 1 hr, the solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The yellow residue was boiled with 250 ml of EtOH while H_2O was added gradually; 100 ml was required for complete solution. After adding charcoal and boiling, the mixture was filtered and cooled to give 58 g of 2.

1-[(5-Nitrofurfurylidene)amino]-3-(4-piperidinobutyl)hydantoin Hydrochloride (18, Method B). To 252 g (1.28 mol) of II in 8 l. of DMF was added in portions 56.8 g (1.30 mol) of a 55% dispersion of NaH in mineral oil. When the reaction was complete, 223 g (1.30 mol) of 1-bromo-4-chlorobutane was added and the mixture was heated at 100–105° for 5 hr. The white solid which separated during the heating period was filtered, washed with DMF, and dried. This material [3,3'-tetramethylenebis(1-benzylideneamino)hydantoin] weighed 128 g and was discarded.

The filtrate was evaporated to dryness under reduced pressure. The residue was triturated with H_2O, filtered, washed with H_2O,

EtOH, and then Et_2O, and air-dried; 249 g (66%) of crude 1-benzylideneamino-3-(4-chlorobutyl)hydantoin was obtained. Recrystallization from 1 l. of $MeNO_2$ gave 87 g of product, mp 148–150°. Concentration of the filtrate gave an additional 71 g: mp 146–148°; total yield 158 g.

A solution of 50 g (0.17 mol) of 1-benzylideneamino-3-(4-chlorobutyl)hydantoin in 200 ml of piperidine was heated on the steam bath for 2 hr and evaporated to dryness *in vacuo*. The residue was triturated with H_2O, filtered, washed with H_2O, and dissolved in 10% aqueous HCl. The solution was filtered through Celite and steam distilled until no more PhCHO was evolved. A solution of 24 g of V in MeOH was added. The solution was then evaporated to dryness *in vacuo*. The residue was crystallized from EtOH giving 40 g of 18.

1-[(5-Nitrofurfurylidene)amino]-3-[2-(2-pyridyl)ethyl]-hydantoin (35, Method C). A mixture of 157 g (0.77 mol) of II, 500 ml of pyridine, and 90 g of distilled 2-vinylpyridine was heated under reflux for 30 hr and then poured into 3.5 l. of H_2O. The white crystalline product was filtered, washed with H_2O, and dried at 110° to give 225 g of 1-benzylideneamino-3-[2-(2-pyridyl)ethyl]hydantoin. This was steam distilled with 400 ml of H_2O and 80 ml of concentrated H_2SO_4 to remove all of the PhCHO. After treatment with charcoal and filtering, 100 g of V in MeOH was added. The solution was extracted with Et_2O to remove any unreacted V. After cooling, the product was filtered, dissolved in warm dilute aqueous HCl, treated with charcoal, filtered, and made alkaline with NH_4OH. The crude product was filtered and washed with H_2O and EtOH. Recrystallization from DMF gave 185 g of 35.

3-(5-Aminopentyl)-1-[(5-nitrofurfurylidene)amino]hydantoin Hydrochloride (39, Method D). To a solution of 177 g (0.87 mol) of II in 1.5 l. of DMF was added 38 g (0.87 mol) of a 52.6% dispersion of NaH in mineral oil in portions. After heating on the steam bath with stirring for 25 min, 103 g (0.87 mol) of 5-chlorovaleronitrile was added during 10 min. The mixture was then heated under reflux for 44 hr. The insoluble NaCl was filtered and the filtrate was concentrated nearly to dryness. The residue was triturated with 500 ml of hot EtOH, cooled, and filtered. Recrystallization from 250 ml of EtOH and 700 ml of $MeNO_2$ gave 130 g of 1-benzylideneamino-3-(4-cyanobutyl)hydantoin, mp 164–167°.

A mixture of 12 g (0.042 mol) of this nitrile, 5.7 g of NaOAc, 165 ml of Ac_2O, and *ca.* 2 g of Raney nickel catalyst No. 28 (W. R. Grace Co.) was shaken with H_2 in a Parr apparatus at 40 psig and 50°. The reduction stopped after a pressure drop of 6 psig (calcd 7). After cooling in an ice bath, the product (with the catalyst) was filtered and washed with H_2O. The above procedure was repeated three times and the combined products were recyrstallized from 1.2 l. of EtOH to give 33 g of 3-(5-acetamidobutyl)-1-benzylideneaminohydantoin, mp 182–184°.

A mixture of 79 g (0.24 mol) of the above amide and 1.2 l. of 10% HCl was steam distilled for 8 hr. The solution was then concentrated to *ca.* 400 ml and cooled, and a solution of 34 g (0.24 mol) of V in 100 ml of EtOH was added. After thorough cooling the product was collected, washed with cold EtOH, and recrystallized from EtOH to give 76 g of 39.

3-Chlorobutyl-*N*,*N*-dimethylamine. A solution of 71 g (0.8 mol) of 4-amino-2-butanol, 220 g of HCOOH, and 160 ml of 37% HCHO solution was heated under reflux for 21 hr and allowed to stand overnight. Then 80 ml of concentrated HCl was added and the solution was evaporated under reduced pressure to a yellow viscous residue which was dissolved in water and made alkaline with aqueous NaOH. This solution was extracted with several portions of $CHCl_3$. Distillation of the $CHCl_3$ under reduced pressure left 62 g of 4-dimethylamino-2-butanol as a pale yellow liquid.

A solution of this product in 500 ml of $CHCl_3$ was cooled in an ice bath and 54 ml (40% excess) of $SOCl_2$ was added dropwise with stirring at a rate such that the temperature never exceeded 10°. The ice bath was removed and stirring was continued until room temperature was reached. The solution was then heated under reflux until evolution of HCl ceased (*ca.* 6 hr). After distillation of most of the $CHCl_3$ under reduced pressure, the solid was filtered and washed with Et_2O. Recrystallization from EtOH gave 50 g of white solid. A solution of this hydrochloride in water was made alkaline with aqueous NaOH and extracted with several portions of Et_2O. After drying over $MgSO_4$ and removal of the Et_2O, distillation of the residue gave 32 g of 3-chloro-1-dimethylaminobutane, bp 34–36° (5 mm).‡

3-Chloropropyl-*N*-isopropyl-*N*-methylamine. A solution of 58 g (0.5 mol) of 3-isopropylaminopropanol, 90 ml of 88% HCO_2H, and 52 ml of 37% HCHO was heated under reflux for 17 hr and cooled, and 30 ml of concentrated HCl was added. The solvent was distilled at atmospheric pressure until a temperature of 110° was reached. The remaining solution was poured into 50 ml of ice–water, made strongly alkaline with aqueous KOH, and extracted several times with Et_2O. The combined extracts were dried over K_2CO_3, the Et_2O was distilled, and the residue was distilled under reduced pressure giving 56 g of 3-(isopropylmethylamino)-1-propanol, bp 95–99° (25–27 mm).

This material was treated with $SOCl_2$ as in the previous example. Recrystallization of the product from EtOAc gave 63 g of 3-chloropropyl-*N*-isopropyl-*N*-methylamine·HCl, mp 58–61°.

The free base was liberated as above; 10 g of the salt gave 6 g of amine, bp 40–41° (4 mm).

Ethyl *N*-[5-[1-(5-Nitrofurfurylideneamino)-2,4-dioxo-3-imidazolyl]pentyl]carbamate (30). A solution of 7.8 g (0.068 mol) of $Na_2CO_3·H_2O$ in 65 ml of H_2O was added dropwise to a mixture of 46.8 g (0.13 mol) of 39 and 500 ml of H_2O at 4–6°. Then 12.5 ml (0.13 mol) of $ClCO_2Et$ was added dropwise at 4–6°. After stirring for 10 min, an additional 5.1 g (0.041 mol) of $Na_2CO_3·H_2O$ in 40 ml of H_2O was added at 5°. Then 400 ml of water was added and the mixture was stirred and cooled for 40 min. The product was filtered, washed with water, air-dried, and recrystallized from 1100 ml of EtOH to give 38 g (74%) of 30.

Acknowledgment. We wish to thank Mr. Grant Gustin and Mr. Marvin Tefft for the elemental analyses, Mr. Raymond Freedman for the microbiological testing data, and Mrs. Valerie Streichert for assistance in preparing many of the compounds.

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‡Reference 5 gives bp 38–39° (10 mm).

Synthesis of 5′-Phosphates of the Naturally Occurring 6-Ureidopurine Ribonucleosides and Their Analogs†

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Received March 26, 1973

N-(Purin-6-ylcarbamoyl)-L-threonine ribonucleoside (PCTR,‡ **1a**), a hyper-modified nucleoside, has been isolated and characterized from tRNA of many organisms.[1,2] It also occurs as a free nucleoside in human and rat urine.[3] It has been shown to be an anticodon adjacent nucleotide in yeast $tRNA^{Ile}$[4] and in *Escherichia coli* $tRNA^{Ser}$, $tRNA^{Met}$, $tRNA^{Lys}$,[5] and $tRNA^{Asn}$.[6] A glycine analog, *N*-(purin-6-ylcarbamoyl)glycine ribonucleoside (PCGR, **1b**), has been isolated from yeast tRNA.[7] Recently the syntheses of PCTR, PCGR, and their analogs have been reported.[8,9]

†Presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971. Supported by NSF Grant GB 29394 and U. S. PHS Grant 2-MO1-RR00262-07.

‡Abbreviations used are as follows: PCTR, *N*-(purin-6-ylcarbamoyl)-L-threonine ribonucleoside; PCGR, *N*-(purin-6-ylcarbamoyl)-glycine ribonucleoside; PCTRP, *N*-(purin-6-ylcarbamoyl)-L-threonine ribonucleoside 5′-phosphate; PCGRP, *N*-(purin-6-ylcarbamoyl)glycine ribonucleoside 5′-phosphate.