of tan solid, mp 234–235°.[21] This material was suspended in 20 ml of glacial HOAc and heated to 60° and 4.0 g (0.028 mole) of freshly distilled quinaldine and 5 ml of Ac_2O were added. The mixture was heated at reflux for 4 hr and cooled over a week-end, and 100 ml of Et_2O was added. After filtering and drying, 5 g (61%) of product, mp 269–272°, was obtained. A sample was recrystallized from EtOH–Me_2CO (1:1) with added DMF to increase the solubility; mp 273–274°. *Anal.* ($C_{16}H_{13}N_3OS$) C, H, N, S.

2-[2-(2-Amino-5-thiazolyl)vinyl]quinoline (31).—A suspension of 0.4 g (1.35 mmoles) of **15** in a mixture of 2 ml of glacial HOAc and 2 ml of concentrated HCl was heated at reflux for 2 hr to give a clear, dark solution. The solution was evaporated to dryness, and the residue was dissolved in 100 ml of H_2O and treated with saturated $NaHCO_3$ until gas evolution stopped. The precipitate was collected, washed (H_2O), and dried to give 0.275 g (80%) of yellow crystals, mp 244–246°. *Anal.* ($C_{14}H_{11}N_3S$) C, H, N, S.

Attempts to convert the NH_2 group to NO_2 by diazotization in the presence of Cu and excess $NaNO_2$ gave traces of a semisolid which had an ir spectrum showing NO_2 bands (1510 and 1340 cm^{-1}), which was similar to the spectrum of **12**. A virtually identical spectrum was obtained from a crude solid which had been isolated from an attempt to condense 2-nitro-5-thiazolecarboxaldehyde with quinaldine in refluxing HOAc–Ac_2O.

(21) H. Taniyama, B. Yasui, and F. Inoue [*J. Pharm. Soc. Jap.*, **73**, 276 (1953)] report mp 207° dec.

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Synthesis of 3-[(5-Nitrofurfurylidene)amino]hydantoins and N-Ethoxycarbonylamino Acid Nitrofurfurylidenehydrazides

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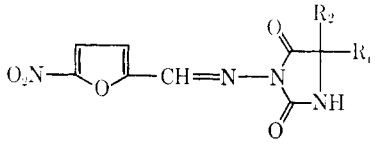
Some 3-[(5-nitrofurfurylidene)amino]hydantoins and some N-ethoxycarbonylamino acid nitrofurfurylidenehydrazides have been synthesized for antibacterial screening. Improved procedures for the preparation of 3-aminohydantoins have been developed.

In view of the chemotherapeutic properties of 1-[(5-nitrofurfurylidene)amino]hydantoins,[1] we synthesized and screened several 3-[(5-nitrofurfurylidene)amino]hydantoins (I). Three examples of N-ethoxycarbonylamino acid 5-nitrofurfurylidenehydrazides (II), open-chain forms of the hydantoins, were also prepared for antibacterial screening.



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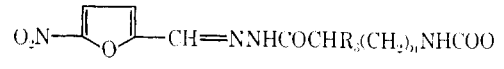
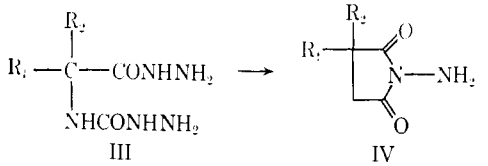


II, $n = 0, 1$

The synthesis of several 5,5-disubstituted 3-aminohydantoins (IV) by heating aqueous solutions of N-carboxy-α-amino acid dihydrazides (III) at atmospheric pressure has been reported by Taub[2] (method B).



III IV

Earlier, Schlögl, *et al.*,[3,4] had found this method unsatisfactory for the synthesis of monosubstituted hydantoins; yields decreased as the size of the substituent decreased, and they were unable to prepare the unsubstituted 3-aminohydantoin or its 5-hydroxymethyl analog. We also were unable to prepare either the unsubstituted or the 5-methyl compound by heating aqueous solutions of dihydrazides.

More recently another synthesis of 5,5-disubstituted 3-aminohydantoin from 5,5-disubstituted hydantoins and hydrazine hydrate was devised by Davidson.[5] The applicability of this method to the preparation of 5-monosubstituted 3-aminohydantoins or to unsubstituted 3-aminohydantoin was not mentioned. These methods, then, are of limited value for the preparation of 3-aminohydantoins.

We have developed a reliable procedure for the preparation of 5-monosubstituted 3-aminohydantoins (IV, R_1 = H), which consists of heating under reflux a dilute solution of the dihydrazide (III) in DMF. The compounds prepared in this way are listed in Table I (method A). This method is applicable for either large or small substituents, as well as the unsubstituted compound.

Although the procedure of Taub[2] was used for preparation of the dimethyl and methylethyl compounds (Table I, method B), we found that the low yield of the latter compound could be doubled by a third procedure (method C).[3] This consisted of heating under reflux an ethanol solution of ethyl N-ethoxycarbonyl-DL-iso-

(1) (a) M. Abrams and B. Prophete, *Missouri Med.*, **51**, 280 (1954); (b) K. J. Hayes, U. S. Patent 2,610,181 (1952); *Chem. Abstr.*, **47**, 6980*i* (1953); (c) J. G. Michels, U. S. Patent 3,075,973 (1963).

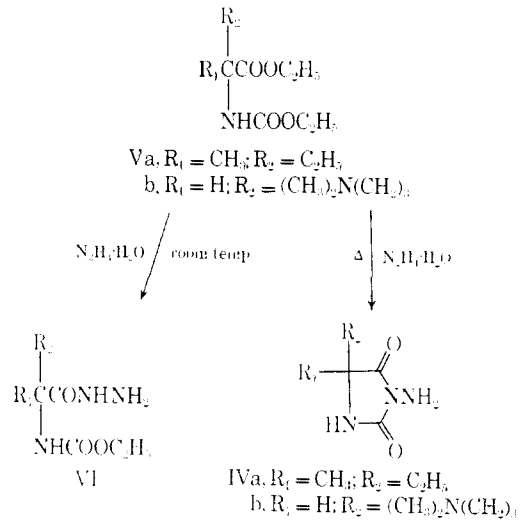
(2) W. Taub, U. S. Patent 2,767,193 (1956); *Chem. Abstr.*, **51**, 5841*h* (1957).

(3) K. Schlögl and G. Korger, *Monatsh. Chem.*, **82**, 799 (1951); *Chem. Abstr.*, **47**, 7511*a* (1953).

(4) K. Schlögl, J. Derkosch, and E. Wawersich, *Monatsh. Chem.*, **85**, 607 (1954); *Chem. Abstr.*, **49**, 9511*d* (1955).

(5) J. S. Davidson, *J. Chem. Soc.*, 4646 (1964).

valinate (Va) and hydrazine hydrate. Method C was also used for the preparation of 5-(3-dimethylaminopropyl)-3-aminohydantoin (IVb) from the corresponding ester (Vb). Thus, cyclization at relatively low temperatures is possible for both mono- and disubstituted precursors, depending on the nature of the substituents.

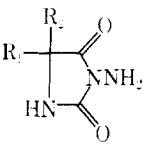


The dihydrazides III used as starting compounds for methods A and B were prepared by treatment of the appropriate amino acid esters with ethyl chloroformate, followed by prolonged heating with hydrazine hydrate.[4] When the hydrazine reaction was carried out at room temperature, the N-ethoxycarbonylamino acid hydrazide VI resulted.[2-4]

The 3-aminohydantoins IV, with one exception, reacted readily with 5-nitro-2-furaldehyde in aqueous alcohol to give the hydantoins I (Table II). The exception was the *p*-hydroxybenzyl derivative, where condensation was effected in aqueous DMF solution yielding a DMF complex. The DMF was removed by heating the complex under reduced pressure, affording the desired 5-nitrofurfurylidene derivative. Similarly the hydrazones II (Table II) were prepared by treating the hydrazides VI with 5-nitro-2-furaldehyde.

The hydantoin structure, for the compounds described in this paper, was further supported by the ir

TABLE I

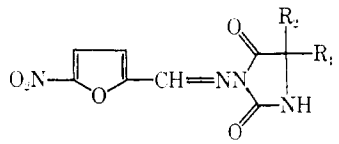


IV

R_1	R_2	Method	Mp, °C[a]	% yield[b]	Formula[c]
H	H	A	197–198.5	60[e]	$C_4H_5N_3O_2$
CH_3	H	A	133–135 (135–136)[d]	63[e]	$C_5H_7N_3O_2$
$(CH_3)_2CH$	H	A	140–141.5 (141–142)[d]	62[e]	$C_7H_{11}N_3O_2$
$HOCH_2$	H	A	120–122	20[e]	$C_4H_5N_3O_3$
p-$HOC_6H_4CH_2$	H	A	212–214 (215–216)[d]	74[e]	$C_{10}H_{11}N_3O_3$
CH_3	CH_3	B	179–180 (184)[d]	72	$C_5H_9N_3O_2$
C_2H_5	CH_3	B	149–150 (157)[d]	53	$C_6H_{11}N_3O_2$
C_2H_5	CH_3	C	148–150	26	

[a] Melting points were determined on a Fisher-Johns (hot stage) apparatus and are uncorrected. [b] Recrystallized product. [c] Based on dihydrazide. [d] Reference 4. [e] Where the formula is given, the compounds were analyzed for C, H, N and analytical results were within ±0.4% of calculated values.

TABLE II

R_1 or R_3	R_2 or *a*	Mp, °C[a]	Yield, %	Formula[c]	MIC, mg/100 ml: *E. coli* Es-2[g]	*S. typhosa* SaD-13	*P. vulgaris* Pr-12	*P. aeruginosa* Ps-10	*S. pyogenes* StA-1	*S. agalactiae* StB-12	*S. aureus* Mi-6	*E. faecalis* Er-1	ED_{50} (mice), mg/kg oral[d]: *S. aureus* Mi-12	*S. typhosa* SaD-13
														
I														
H	H	224–226	73[e]	$C_9H_8N_4O_5$	50	50	>200	>200	100	100	100	100	>210	>210
CH_3	H	155–158	74[h]	$C_9H_8N_4O_5 \cdot 0.5H_2O$	50	50	>200	>300	100	100	30	100	>210	>210
$(CH_3)_2CH$	H	187–189	78[h]	$C_{11}H_{12}N_4O_5$	50	30	>200	>200	50	100	10	100	>210	>210
$HOCH_2$	H	197–200	83[h]	$C_9H_8N_4O_6$	100	50	>200	>300	100	200	100	200	>210	>210
p-$HOC_6H_4CH_2$	H	192–195	77[e]	$C_{15}H_{12}N_4O_6$	60	30	>230	>230	60	110	30	60	>210	210
p-$HOC_6H_4CH_2$–DMF complex	H	192–194.5 dec	77[h]	$C_{15}H_{12}N_4O_6 \cdot C_3H_7NO$										
$(CH_3)_2N(CH_2)_3$	H	205–207 dec	23[e]	$C_{12}H_{17}N_5O_5 \cdot HCl$	100	200	>200	>200	100	200	200	200	210	>210
CH_3	CH_3	235–237	73[h]	$C_{10}H_{10}N_4O_5$	30	30	200	>200	50	100	10	50	>210	>210
C_2H_5	CH_3	189–192	93[h]	$C_{11}H_{12}N_4O_5$	20	20	130	>150	30	60	20	60	210	>210
														
II														
H	0	176–177.5	83[g]	$C_{10}H_{12}N_4O_5$	13	25	200	>200	100	100	13	25	>210	105
CH_2OH	0	145–148	75[d]	$C_{10}H_{14}N_4O_7$	18[f]	13	9	0	22	14	19	26	96	96
H	1	165–167	63[g]	$C_{10}H_{14}N_4O_6$	10	30	>200	>200	50	200	10	50	168	168
1-(5-Nitrofurfurylideneamino)hydantoin[f]					6	6	200	>190	3	6	12	6		34[h]

[a] See ref *a*, Table I. [b] Recrystallized; based on the aminohydantoin. [c] Based on Vb. [d] Recrystallized; based on hydrazide. [e] See ref *e*, Table I. [f] Furadantin®; it is used here as a standard of reference. [g] Norwich Pharmacal Co. strain number. [h] Published ED_{50} value for *S. typhosa*.[10] [i] Impregnated paper disks (30 μg). Zone diameters in millimeters include the 6-mm disk, except negative reactions are recorded as 0.

spectra[6] of all products (Tables I and II), with absorptions at 5.60–5.65 and 5.80–5.85 μ assigned to the carbonyl groups.

The compounds in Table II were screened for antibacterial activity by reported methods.[7] Most of the hydantoins I showed slight *in vitro* activity against gram-positive and gram-negative organisms. Very limited activity was observed for these compounds (I) when tested against *Salmonella typhosa* and *Staphylococcus aureus* infections in mice.

The 5-nitrofurfurylidenehydrazides II showed slight to fair *in vitro* antibacterial activity, with limited activity against *Salmonella typhosa* and *Staphylococcus aureus* infections in mice. These compounds II exhibited parasiticidal activity[8] in chicks against *Eimeria tenella* and *Histomonas meleagridis* when mixed in feed at 0.001 and 0.002% of the ration, by the method of Johnson.[9]

In conclusion, the antibacterial properties of both the 3-[(5-nitrofurfurylidene)amino]hydantoins (I) and the 5-nitrofurfurylidenehydrazides (II) were inferior to those of the 1-[(5-nitrofurfurylidene)amino]hydantoins.[10]

Experimental Section

3-Aminohydantoin (Method A).—A mixture of N-carboxyglycine dihydrazide (70 g, 0.48 mole) and DMF (2290 ml) was heated to boiling in 0.5 hr, with mechanical stirring. The reaction solution was refluxed for 2.8 hr. The solution was evaporated under reduced pressure, and the solid residue was washed with EtOH (50 ml). Recrystallization from 25% EtOH (185 ml) gave white crystals.

3-[(5-Nitrofurfurylidene)amino]hydantoin.—A solution of 5-nitro-2-furaldehyde (47.0 g, 0.33 mole) in EtOH (350 ml) was added gradually to a solution of 3-aminohydantoin (38.4 g, 0.33 mole) in H_2O (500 ml) at 25°, with mechanical stirring. The mixture was stirred for 1.3 hr, then cooled in an ice bath. The resultant pale yellow, crystalline solid was collected and washed (H_2O), mp 217–222°, yield 33.8 g. A second crop (34.9 g, mp 223–225°) was isolated. The combined product was recrystallized from $MeNO_2$ (1800 ml).

5-Ethyl-5-methyl-3-aminohydantoin (Method C).—A solution of ethyl N-ethoxycarbonyl-DL-isovalinate (250 g, 1.15 moles), in hydrazine hydrate (570 ml, 11.4 moles) and EtOH (3300 ml), was refluxed for 82 hr. The solution was evaporated under reduced pressure, and the semicrystalline residue was triturated with Et_2O (400 ml). The filtered product, mp 120–140°, was washed with Et_2O. Recrystallization from a mixture of H_2O (4 ml) and EtOH (120 ml) gave a white, crystalline solid.

5-Ethyl-5-methyl-3-[(5-nitrofurfurylidene)amino]hydantoin was prepared by the same procedure as described for 3-[(5-nitrofurfurylidene)amino]hydantoin.

N-Ethoxycarbonylglycine 5-Nitrofurfurylidenehydrazide.—To a solution of N-ethoxycarbonylglycine hydrazide (40.5 g, 0.25 mole) in 50% EtOH (100 ml) was gradually added a solution of 5-nitro-2-furaldehyde (35.0 g, 0.25 mole) in EtOH (100 ml). The product was collected and washed with 70% EtOH; mp 174–176°, yield 66.2 g (93%). Recrystallization from EtOH (3600 ml) gave yellow crystals.

Acknowledgments.—The authors wish to thank Mr. Grant Gustin and Mr. Marvin Tefft for the elemental analyses, and Mr. Raymond Freedman for the microbiologic testing data.

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1,2,4-Oxadiazolylpyridinium Salts. Oral Hypoglycemic Agents

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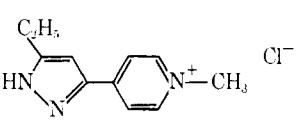
A series of 1,2,4-oxadiazolylpyridinium quaternary salts has been synthesized. These compounds display interesting hypoglycemic activity in mice.

4-[3(5)-Pyrazolyl]pyridinium salts (**1**, for instance) have been found to display interesting oral hypoglycemic activity in alloxan-diabetic mice.[1] As an initial development of this lead, the pyrazole ring was replaced by an isoxazole ring to obtain some novel isoxazolylpyridinium salts[2] which also exhibited interesting hypoglycemic activity in laboratory animals.[3] 1-Methyl-4-(3-methyl-5-isoxazolyl)pyridinium chloride (**2**) has been chosen for extensive evaluation as a potential antidiabetic agent.[4] As a further development of the lead, we now describe the synthesis and hypoglycemic activity of a number of new 1,2,4-oxadiazolylpyridinium salts, **5**, for instance.



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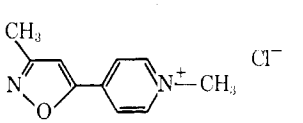

2

The synthesis of unsymmetrically substituted 1,2,4-oxadiazoles by the condensation of an amidoxime with Ac_2O has been described.[5,6] Thus the reaction of Ac_2O with isonicotinamidoxime (**3**)[7] provided 4-(5-methyl-

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