Nitrofuryl Heterocycles. II.[1] 2-Alkyl-6-(5-nitro-2-furyl)-3(2H)-pyridazinones and 4,5-Dihydro Derivatives

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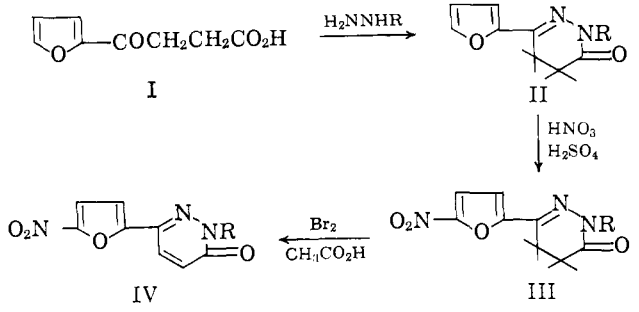
A continuing search for new nitrofuran antimicrobial agents led to the synthesis of 4,5-dihydro-6-(5-nitro-2-furyl)-3(2H)-pyridazinone (IIIa). Because of the significant biological activity of IIIa, additional synthetic work in this area was initiated to study the effect of structure modifications on activity.

Chemistry.—The 4,5-dihydro-3(2H)-pyridazinone ring system is commonly prepared by condensing a γ-keto acid or ester with hydrazine. A survey of the literature revealed that β-(2-furoyl)propionic acid (I) had been prepared in three steps from 2-acetylfuran by Knott.[2] 4,5-Dihydro-6-(2-furyl)-3(2H)-pyridazinone (IIa) was prepared from acid I by Knott and from the ethyl ester of I by Holland and Amstutz.[3] Thus, acid I was condensed with the appropriate alkyl hydrazines to give pyridazinones II (see Scheme I).

SCHEME I



Nitration of II took place readily in mixed acid solution at low temperatures to give III. The nitro group was assigned to the 5-position of the furan ring on the basis of the work of Rinkes,[4] and on the observance of asymmetric and symmetric stretching vibrations of the nitro group at 1515 and 1308 cm^{-1}, respectively, in the infrared.[5] Furthermore, the ultraviolet spectrum of IIIa (λ_{max} 362 mμ) was quite similar to the spectrum of 5-nitro-2-furaldehyde acetylhydrazone (λ_{max} 363 mμ).[6] Finally, the nitration product III was extremely sensitive to aqueous alkali. Nitrofuran derivatives are frequently unstable in the presence of aqueous alkali, giving dark brown solutions or tars.[7] The base lability of III became more apparent when the alkylation of IIIa (R = H) with methyl iodide in methanolic sodium methylate solution was attempted. Only tar was obtained. Therefore, the 2-alkyl derivatives of III were prepared by condensing acid I with the appropriately substituted alkyl hydrazine and nitrating the product.

Overend and Wiggins[8] reported the oxidation of 4,5-dihydro-6-methyl-3(2H)-pyridazinone to 6-methyl-3-(2H)-pyridazinone using bromine in acetic acid solution. A similar oxidation of dihydropyridazinone III gave pyridazinone IV. When pyridazinone IVa (R = H) was treated with an equivalent of sodium hydroxide or methoxide in methanol solution, a sodium salt was formed. This salt was exceptionally stable in aqueous solution. Treatment of this sodium salt with methyl iodide in methanol solution gave the N-methyl derivative IVb (R = CH_3). This product was identical in all respects with the product obtained by the oxidation of IIIb (R = CH_3). On this basis, the methyl group was assigned to the 2-position of the pyridazinone ring. The higher alkyl derivatives of IVa were also prepared by alkylation.

All compounds reported in this paper have been assigned the ketonic structure based on the observance of a strong carbonyl stretching band at 1653–1680 cm^{-1} in the infrared.[5] The physical and analytical properties of these compounds are given in Table I.

Screening Results.—The *in vitro* and *in vivo* antibacterial testing data were determined using the methods described previously.[9] Anticoccidial screening in chickens against a strain of *Eimeria tenella* was carried out as described by Johnson and O'Connor.[10] These data are given in Table II.

As a class of compounds the pyridazinones IV show better antibacterial activity than the dihydropyridazinones III. All of the compounds demonstrated anticoccidial activity against *Eimeria tenella* at dose levels comparable to the level of nitrofurazone,[11] a known coccidiostat. The most active compounds (IIIa and IVa and b) are those in which R = H or CH_3. Therefore, it can be concluded that substitution of alkyl groups at the 2-position (R) does not enhance significantly the anticoccidial activity. Toxicological studies on selected compounds are in progress.

Experimental Section

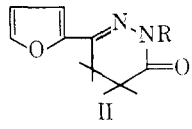
All melting points were determined on a hot stage (Mel-Temp) melting apparatus and are uncorrected.

4,5-Dihydro-6-(2-furyl)-3(2H)-pyridazinone (IIa).—A mixture of 48.0 g (0.28 mole) of β-(2-furoyl)propionic acid[2] and 17.0 g (0.29 mole) of 85% hydrazine hydrate was heated on a steam bath for 75 min. The mixture was poured slowly with stirring into cold aqueous Na_2CO_3 solution. The solids were filtered and recrystallized from water (charcoal) to give the product as colorless needles. Other derivatives of II were prepared from the appropriate alkylhydrazine.

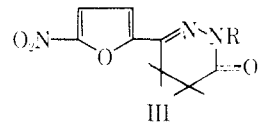
4,5-Dihydro-6-(5-nitro-2-furyl)-3(2H)-pyridazinone (IIIa).—To 400 ml of concentrated H_2SO_4 chilled to 5° was added in small portions with stirring 51.5 g (0.31 mole) of IIa. The resulting solution was chilled to 0° by means of an ice–salt bath. The temperature was kept below 5° while a solution of 50 ml of concentrated HNO_3 (sp gr 1.42) in 100 ml of concentrated H_2SO_4 was added dropwise during 0.5 hr. Stirring in the cold was continued for 15 min after which time the mixture was poured slowly with vig-

(1) For the previous paper in this series see H. R. Snyder, Jr., and L. E. Benjamin, *J. Med. Chem.*, **9**, 402 (1966).
(2) E. B. Knott, *J. Chem. Soc.*, 1190 (1947).
(3) D. G. Holland and E. D. Amstutz, *Rec. Trav. Chim.*, **83**, 1047 (1964).
(4) I. V. Rinkes, *ibid.*, **51**, 349 (1932).
(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp 203, 297.
(6) F. F. Ebetino, J. J. Carroll, and G. Gever, *J. Med. Pharm. Chem.*, **5**, 513 (1962).
(7) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p 149.
(8) W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 242 (1947).
(9) F. F. Ebetino, W. F. Carey, and B. F. Stevenson, *J. Med. Chem.*, **6**, 633 (1963).
(10) C. A. Johnson and J. O'Connor, *Poultry Sci.*, **44**, 578 (1965).
(11) Furacin®.

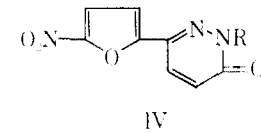
TABLE I



II



III



IV

No.	R	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
IIa	H	144–145[a]	78	$C_8H_8N_2O_2$	58.53	58.62	4.91	4.89	...	...
b	CH_3	90.5–91.5	79	$C_9H_{10}N_2O_2$	60.66	60.71	5.66	5.68	15.72	15.75
c	C_2H_5	65–66	97	$C_{10}H_{12}N_2O_2$	62.48	62.51	6.29	6.37	14.58	14.65
d	$(CH_2)_2CH_3$	73–74	72	$C_{11}H_{14}N_2O_2$	64.06	63.99	6.84	6.78	13.58	13.54
IIIa	H	249.5–250	42	$C_8H_7N_3O_3$	45.94	45.81	3.37	3.26	20.09	20.04
b	CH_3	198–199	42	$C_9H_9N_3O_4$	48.43	48.43	4.06	4.03	18.83	18.80
c	C_2H_5	134.5–135.5	20	$C_{10}H_{11}N_3O_4$	50.63	50.75	4.67	4.74	17.72	17.71
d	$(CH_2)_2CH_3$	101–102	31.5	$C_{11}H_{13}N_3O_4$	52.58	52.64	5.22	5.22	16.73	16.62
IVa	H	303–304	94	$C_8H_5N_3O_4$	46.38	46.43	2.43	2.65	20.29	20.16
b	CH_3	232	89[b]	$C_9H_7N_3O_4$	48.87	49.05	3.19	3.21	19.00	18.88
c	C_2H_5	149–149.5	39.5[c]	$C_{10}H_9N_3O_4$	51.06	51.06	3.86	3.86	17.87	17.88
d	$(CH_2)_2CH_3$	106.5–107.5	32.5[c]	$C_{11}H_{11}N_3O_4$	53.01	53.10	4.45	4.57	16.86	16.77

[a] Lit.[2] mp 145°. [b] By oxidation. [c] By alkylation.

TABLE II

BIOLOGICAL ACTIVITY OF 2-ALKYL-6-(5-NITRO-2-FURYL)-3(2H)-PYRIDAZINONE AND 4,5-DIHYDRO DERIVATIVES

No.	ED_{50} (mice, mg/kg)/MIC (μg/ml) *Staphylococcus aureus*	*Salmonella typhosa*	Effective dose, % in feed *Eimeria tenella*
IIIa	50/6	100/3	0.0055
b	>200/25	>200/6	0.0055
c	100/12.5	>100/6.2	0.0055
d	>200/12.5	−/50	0.011
IVa	146/3	112/1.5	0.0055
b	59/25	87/1.5	0.0055
c	57/12	66/3	0.011
d	70/12	63/6	0.011
Nitrofurazone[a]	50/12.5	100/3	0.0055

[a] See ref 11.

orous stirring into 3 l. of cracked ice and water. The crude product was collected by filtration and washed thoroughly with water. Recrystallization from glacial acetic acid (charcoal) gave the product as short yellow needles. Other derivatives of III were prepared similarly.

6-(5-Nitro-2-furyl)-3(2H)-pyridazinone (IVa).—A mixture of 41.8 g (0.2 mole) of IIIa in 200 ml of glacial acetic acid was heated to 90°. Bromine (2 ml) was added with stirring. When HBr evolution began, the remaining bromine (total of 32 g, 0.2 mole) was added at such a rate as to maintain a temperature of 90–95°. When the addition was completed, the mixture was heated at 100° for 30 min. The mixture was cooled, diluted with water, and filtered, and the residue was washed thoroughly with water. The yield of crude product melting at 293–295° was 39.0 g (94%). Four recrystallizations from dimethylformamide (charcoal) gave pale yellow crystals. IVb was prepared similarly.

2-Ethyl-6-(5-nitro-2-furyl)-3(2H)-pyridazinone (IVc).—A mixture of 50.0 g (0.24 mole) of IVa and 13.0 g (0.24 mole) of sodium methoxide in 1000 ml of methanol was refluxed with stirring for 3 hr. Ethyl iodide (50 ml) was added and refluxing was continued overnight. The solvents were evaporated under diminished pressure on a steam bath and the residue was shaken with 500 ml of cold 5% NaOH solution. The crude product was filtered, washed thoroughly with water, and recrystallized from aqueous ethanol (charcoal). The product separated as pale yellow needles. IVb and IVd were prepared from the appropriate alkyl iodide.

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The Bacteriostatic Effectiveness of 1-Alkyl-3-(3,4-dichlorophenyl)ureas

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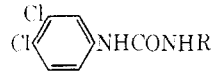
Because of their effectiveness against staphylococci and other gram-positive bacteria, substituted ureas have been extensively studied for their bacteriostatic activity. In a comprehensive investigation of such compounds, Beaver, *et al.*,[1] screened dozens of phenylureas, thioureas, and anilides against *Staphyloccus aureus* strain FDA No. 209. Two 1-alkyl-3-(3,4-dichlorophenyl)ureas were included, the 1-ethyl and the 1-*t*-octyl derivatives. The minimum concentra-



R = C_2H_5 or t-C_8H_{17}

tions of these compounds able to inhibit the test organism were found to be 100 μg/ml. On the other hand, two halogenated carbanilides, 3,3′,4-trichlorocarbanilide (I) and 3,4,4′-trichlorocarbanilide (II) were found to give complete inhibition at 0.033 μg/ml.

I, X = 3-Cl
II, X = 4-Cl

(1) D. J. Beaver, D. F. Roman, and P. J. Stoffel, *J. Am. Chem. Soc.*, **79**, 1236 (1957).