Nitrofuryl Heterocyclics. 1

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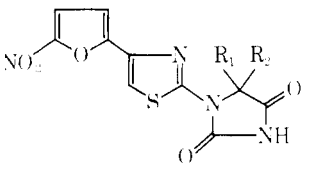
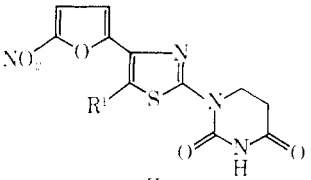
Received February 24, 1970

The synthesis of 1-[4-(5-nitro-2-furyl)-2-thiazolyl]hydantoins and -hydrouracils (I and II) is described, together with that of the corresponding 3-substituted analogs IV. Compounds I, II, and IV, as well as the intermediate 1-(2- or 3-haloacyl)-3-[4-(5-nitro-2-furyl)-2-thiazolyl]ureas (III; R = haloalkyl) and some acylureas (III; R = alkyl) have been found to possess *in vitro* antibacterial activity against a variety of organisms; several of these nitrofurans are also active *in vivo* against *Staphylococcus aureus* and *Streptococcus pyogenes* infections.

A search for new chemotherapeutic nitrofurans led to an investigation of hydantoins I and hydrouracils II.



I



II

The preparation of the intermediate ureas III from 2-amino-4-(5-nitro-2-furyl)thiazole[2] and acyl isocyanates, the cyclization of haloacyl ureas (III; R = haloalkyl) to the corresponding hydantoins or hydrouracils I or II, and the subsequent alkylation of these (to IV) are described in the Experimental Section.

Experimental Section[3]

The physical properties of the compounds prepared are collected in Tables I, II, and III.

1-Substituted 3-[4-(5-Nitro-2-furyl)-2-thiazolyl]ureas (Table I).—The appropriate acyl isocyanate[4] (10% excess) in THF (20 ml) was added dropwise to a suspension of 2-amino-4-(5-nitro-2-furyl)thiazole[2] (4 g) in THF (40 ml) and the mixture was stirred 1.5 hr at room temperature [refluxed 1.5 hr with 2-amino-5-nitro-4-(5-nitro-2-furyl)thiazole[5]]. The product was filtered off, washed (H_2O), and recrystallized.

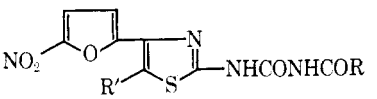
1-[4-(5-Nitro-2-furyl)-2-thiazolyl]hydantoins and -hydrouracils (Table II).—NaH (50% dispersion in oil; 0.03 mol) was added in portions to a stirred suspension of a 1-(2- or 3-haloacyl)-3-[4-(5-nitro-2-furyl)-2-thiazolyl]urea (0.03 mol) in DMF (75 ml) at 0°, and the mixture was stirred at room temperature until neutral (time and temp are given in Table II). Acidification (AcOH) and dilution with H_2O afforded the product, which was filtered off, washed (H_2O), and recrystallized.

3-Substituted 1-[4-(5-Nitro-2-furyl)-2-thiazolyl]hydantoins and -hydrouracils (Table III).—NaH (50% dispersion in oil; 0.01 mol) was added in portions to a suspension of the hydantoin or hydrouracil (IV; R = H) (0.01 mol) in DMF (25 ml), followed by the alkylating agent (0.011 mol). The mixture was stirred until neutral (time and temp are given in Table III), acidified (AcOH), and diluted with H_2O. The product was collected, washed with H_2O, and recrystallized.

Screening Results.—The above compounds were tested *in vitro* against a variety of bacteria according to procedures described previously.[6] It can be seen from Table IV[7] that most of the compounds possess activity against *Staphylococcus aureus* and *Streptococcus pyogenes*. Of the acylureas III, highest *in vitro* activity was observed for the bromoacetylurea **2**; this derivative also had the broadest spectrum of activity. Increasing the acyl chain length, or replacement of Br by Cl or H reduced the antibacterial activity. For the cyclized products (I, II, and IV), greatest activity was found in hydantoin **13**. Expansion of the

TABLE I

1-(ACYL)-3-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]UREAS (III)



Compd	R	R′	Mp (°C)	Recrystn solvent[a]	Yield (%)	Formula
1	$(CH_2)_2Br$	H	228 dec	A	75	$C_{11}H_9BrN_4O_5S$
2	CH_2Br	H	213 dec	B	54	$C_{10}H_7BrN_4O_5S$
3	$CHMeBr$	H	236–237 dec	C	74	$C_{11}H_9BrN_4O_5S$
4	CH_2Cl	H	227–228 dec	B	52	$C_{10}H_7ClN_4O_5S$
5	$CHCl_2$	H	231–232 dec	C	45	$C_{10}H_6Cl_2N_4O_5S$
6	Et	H	>300[b]	A	39	$C_{11}H_{10}N_4O_5S$
7	Me	H	278–279 dec	C	75	$C_{10}H_8N_4O_5S$
8	CMe_2Br	H	249–251 dec	C	90	$C_{12}H_{11}BrN_4O_5S$
9	$CH(Et)Br$	H	227 dec	C	79	$C_{12}H_{11}BrN_4O_5S$
10	Ph	H	311–313 dec	A	41	$C_{15}H_{10}N_4O_5S$
11	$(CH_2)_2Br$	NO_2	200–201 dec[c]	A	69	$C_{11}H_8BrN_5O_7S \cdot HCON(CH_3)_2$

[a] A, DMF; B, DMF followed by hot H_2O wash; C, AcOH. [b] Darkens >260°. [c] Half melts at 129° then resolidifies.

(1) To whom all inquiries should be addressed.

(2) W. R. Sherman and D. E. Dickson, *J. Org. Chem.*, **27**, 1351 (1962).

(3) Melting points are corrected, and were determined in a capillary tube. Analytical results were obtained for C, H, and N for all compounds, and, unless otherwise stated, were within ± 0.4% of the theoretical values.

(4) New isocyanates were prepared by the method of A. J. Speziale and L. R. Smith [*J. Org. Chem.*, **27**, 3742 (1962)] and were used, after distillation on the aspirator and measurement of ir spectra, without further characterization.

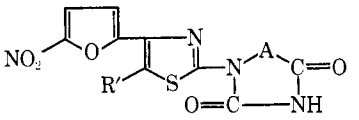
(5) S. Hillers, N. Saldabols, and A. Medne, *Zh. Obshch. Khim.*, **33**, 317 (1963).

(6) For the general *in vitro* and *in vivo* test procedures see M. W. Fisher, M. C. Manning, L. A. Gagliardi, M. R. Gaetz, and A. R. Erlandson [*Antibiot. Annu.*, **1959/1960**, 293–303 (1960)], and M. W. Fisher, *Proc. Soc. Exp. Biol. Med.*, **85**, 538 (1954).

(7) Compounds described in the paper but not listed in Table IV were less active than those given in the Table.

TABLE II

1-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]HYDANTOINS AND -HYDROURACILS (I AND II)

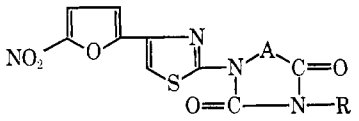


Compd	A	R'	Mp (°C)	Recrystn solvent[a]	Reaction time (hr), temp (°C)	Yield (%)	Formula
12	$(CH_2)_2$	H	298 dec	A	0.5, 20	96	$C_{11}H_8N_4O_5S$
13	CH_2	H	278–280	A	1, 40	53	$C_{10}H_6N_4O_5S$
14	CMe_2	H	295–296 dec	B	3, 100	33	$C_{12}H_{10}N_4O_5S$
15	CHEt	H	238–239	A	3, 20	48	$C_{12}H_{10}N_4O_5S$
16	$(CH_2)_2$	NO_2	308–309 dec	B	1.5, 20	90	$C_{11}H_7N_5O_7S.HCON(CH_3)_2$[b]

[a] A, AcOH; B, DMF. [b] C: calcd, 39.4; found, 38.9.

TABLE III

3-SUBSTITUTED 1-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]HYDANTOINS AND -HYDROURACILS (IV)



Compd	A	R	Alkylating agent	Mp (°C)	Recrystn solvent[a]	Reaction time (hr), temp (°C)	Yield (%)	Formula
17	$(CH_2)_2$	Et	EtI	238–240 dec	A	1, 35	82	$C_{13}H_{12}N_4O_5S$[c]
18	CH_2	Me	MeI	234–236	A	1, 40	72	$C_{11}H_8N_4O_5S$
19	$(CH_2)_2$	Me	MeI	276–277 dec	A	1, 40	61	$C_{12}H_{10}N_4O_5S$[d]
20	CH_2	Et	EtBr	236–239	A	3, 40	58	$C_{12}H_{10}N_4O_5S$
21	$(CH_2)_2$	*n*-Pr	*n*-PrBr	210–212	A	4, 40	68	$C_{14}H_{14}N_4O_5S$
22	CH_2	CH_2CONMe_2	$BrCH_2CONMe_2$[b]	261–263 dec	A	4, 40	26	$C_{14}H_{13}N_5O_6S$
23	CH_2	CH_2CONEt_2	$BrCH_2CONEt_2$[b]	237–239 dec	A	5, 40	41	$C_{16}H_{17}N_5O_6S$
24	CH_2	CH_2CO_2Et	$BrCH_2CO_2Et$	176–178	A	4, 40	37	$C_{14}H_{12}N_4O_7S$
25	CH_2	CH_2CONH_2	$BrCH_2CONH_2$	291–293 dec	B	4, 40	36	$C_{12}H_9N_5O_6S$
26	CH_2	$CH_2CH{=}CH_2$	$BrCH_2CH{=}CH_2$	161–163	C	4, 40	36	$C_{13}H_{10}N_4O_5S$[e]
27	CH_2	$CH_2C{\equiv}CH$	$BrCH_2C{\equiv}CH$	219–221 dec	C	4, 40	15	$C_{13}H_8N_4O_5S$

[a] A, AcOH; B, DMF; C, aq DMF followed by hot H_2O wash. [b] W. E. Weaver and W. M. Whaley, *J. Amer. Chem. Soc.*, **69**, 515 (1947). [c] C: calcd, 46.4; found, 45.8. [d] N: calcd, 17.4; found, 16.9. [e] C: calcd, 46.7; found, 46.2.

TABLE IV

In Vitro ANTIBACTERIAL ACTIVITY OF 1–27

	Minimum inhibitory concentration, μg/ml[a]					
Compd	*Staphylococcus aureus* UC-76	*Mycobacterium tuberculosis* $H_{37}Rv$	*Escherichia coli* VOGEL	*Streptococcus pyogenes* C-203	*Salmonella typhimurium* V-31	*Shigella sonnei* C-10
1	0.31	>20	5	0.63	10	10
2[b]	< 0.08	>20	1.25	<0.08	1.25	2.5
3	0.63	>20	20	2.5	20	>20
4	0.08	>20	1.25	0.31	1.25	1.25
6	0.16	>20	20	0.31	>20	>20
7	0.31	>20	2.5	<0.08	5	10
9	5	20	20	0.31	20	20
11	10	>20	>20	1.25	>20	>20
13	< 0.08	>20	2.5	<0.08	1.25	2.5
14	1.25	1.25	20	0.08	20	>20
15	2.5	5	20	0.08	10	>20
16	1.25	>20	>20	0.63	>20	>20
17	0.63	>20	>20	0.63	>20	>20
18	5	10	>20	1.25	>20	>20
19	1.25	>20	>20	0.31	>20	>20
20	0.16	>20	>20	<0.08	>20	>20
21	0.63	>20	>20	0.08	>20	>20
22	0.31	0.31	20	<0.08	20	>20
23	1.25	>20	>20	<0.08	>20	>20
24	>20	0.16	>20	>20	>20	>20
25	0.16	>20	10	<0.08	20	>20
26	< 0.08	0.63	>20	<0.08	>20	>20
27	< 0.08	>20	>20	0.08	>20	>20

[a] See ref 6. [b] Minimum inhibitory concentration against *Diplococcus pneumoniae* and *Klebsiella pneumoniae* MGH-2 was 2.5 μg/ml.

TABLE V
In Vivo ACTIVITY[a]

Compd	ED_{50}(mice), mg/kg			
	S. aureus		*S. pyogenes*	
	PO	SC	PO	SC
2	>250	125	150	27
13	65	144	16.5	12.5
20	*b*	*b*	100	<60
22	65	110	1.6	1.6
23	>250	>250	6.25	10
25	*ca.* 250	350	7.5	4.8

[a] See ref 6. [b] Not tested.

ring or introduction of alkyl groups in the 5 position reduced antibacterial activity in all cases.

Some of the compounds were tested against *S. aureus* and *S. pyogenes* in mice by oral and subcutaneous administration (Table V). The most active of these were 1-[4-(5-nitro-2-furyl)-2-thiazolyl]hydantoin, **13**, and the 3-(dimethylcarbamoyl)methyl analog **22**. Again, expansion of the ring, or introduction of a simple alkyl group at the 3 or 5 positions reduced activity. Several of the compounds studied (**14**, **22**, **24**, and **26**) had high *in vitro* activity against *Mycobacterium tuberculosis*; all of these were inactive in the *in vivo* screen however.

Acknowledgments—The authors are indebted to Dr. R. E. Bowman for advice and encouragement, to Mr. F. H. Oliver for microanalyses, to Miss E. M. Tanner for the physical chemistry measurements, Mrs. M. R. Johnson for the preparation of some of the intermediates, and to Dr. M. W. Fisher and his associates of the Department of Microbiology, Parke, Davis and Co. Inc., Detroit, for the biological data.

Synthesis and Pharmacology of *N*-Cyano-(β-arylethyl)amines

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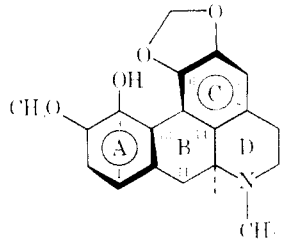
Received November 8, 1969

In an attempt to prepare compounds which would reverse or block catatonia produced by bulbocapnine, a series of *N*-cyano-*N*-methylarylethylamines were synthesized. Preliminary pharmacology is reported.

Bulbocapnine (**1**) is a drug which has frequently been used to produce syndromes similar to schizophrenia. It is obtained from the plant *Corydalis cava* and it belongs chemically to the aporphine group of alkaloids. De Jong and his collaborators studied the



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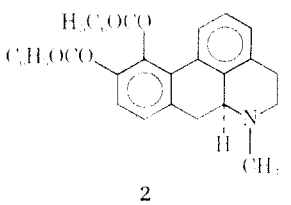
catatonic state associated with bulbocapnine administration[2,3] and in addition to this agent other aporphine alkaloids were found to be catatonia-producing substances.[4-9]

According to Chapman and Walaszek[10] catatonia produced by bulbocapnine may be the result of a combination of actions, among which are serotonin and adrenergic blockade as well as a histaminergic mechanism.

The purpose of this investigation was to prepare compounds which could act as antagonists to bulbocapnine-induced catatonia. As a working postulate, it was assumed that either ring A or ring C of the aporphine system could be the aromatic group of a β-phenethylamine. Initially, an attempt was made to break the N–C bond between the D and B rings or to remove the Me group from the N in bulbocapnine. The von Braun[11] reaction was thought to offer a possible route to the desired compounds.

The only report of this reaction being used on an aporphine compound involved *d*-apomorphine dibenzoate (**2**). The product obtained from this reaction contained no Br and, unlike the starting material, was optically inactive. Based on this evidence, structure **3** was assigned to the material obtained.[12]



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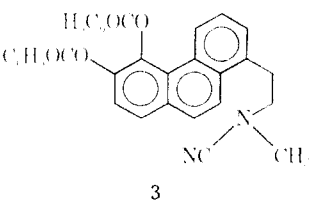

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While performing the von Braun reaction on *d*-bulbocapnine attempts were made to avoid ring cleavage while forcing the attack of Br^- to take place selectively on the *N*-Me group. For this purpose conditions favoring an SN2 type substitution reaction over an SN1 reaction or an elimination reaction were employed. Only one product, 1-[2-(*N*-cyano-*N*-methylaminoeth-

(1) Taken in part from the dissertation presented by A. C. Makriyannis, March 1967, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) H. H. de Jong and H. Barouk, "La Catatonie Experimentale par la Bulbocapnine; Etude Physiologique et Clinique," Masson, Paris, France, 1930.

(3) H. H. de Jong, "Experimental Catatonia," Williams and Wilkins, Baltimore, Md., 1945.

(4) R. A. Waud, *J. Pharmacol.*, **50**, 100 (1934).

(5) T. Tobitani, *Okayama Igakkai Zasshi*, **51**, 1447 (1939).

(6) T. A. Henry, "The Plant Alkaloids," P. Blakinston Co., Philadelphia, Pa, 1949, p 312.

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(8) H. Kreitmar, *Pharmazie*, **7**, 507 (1952).

(9) R. A. Waud, *J. Pharmacol.*, **55**, 40 (1935).

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(11) H. A. Hageman, *Org. React.*, **7**, 198 (1953).

(12) J. von Braun and E. Aust, *Chem. Ber.*, **50**, 43 (1917).