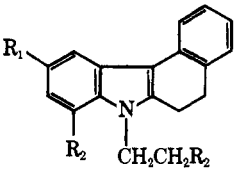
TABLE II

SUBSTITUTED 5,6-DIHYDRO[c]BENZOCARBAZOLE FUMARATES[a]



No.	R_1	R_2	R_3	Mp, °C	% yield	Formula	Minimal useful[b] concentration, μg/ml
14	H	H	$N(Et)_2$	164–166	60	$C_{22}H_{26}N_2 \cdot C_4H_4O_4$	160
15	F	H	$N(Et)_2$	158–160	70	$C_{22}H_{25}FN_2 \cdot C_4H_4O_4$	40
16	Cl	H	$N(Et)_2$	170–172	75	$C_{22}H_{25}ClN_2 \cdot C_4H_4O_4$	300
17	Br	H	$N(Et)_2$	156–158	75	$C_{22}H_{25}BrN_2 \cdot C_4H_4O_4$	*c*
18	I	H	$N(Et)_2$	160–162	60	$C_{22}H_{25}IN_2 \cdot C_4H_4O_4$	*c*
19	CH_3	H	$N(Et)_2$	169–171	65	$C_{23}H_{28}N_2 \cdot C_4H_4O_4$	150
20	OCH_3	H	$N(Et)_2$	148–150	60	$C_{23}H_{28}N_2O \cdot C_4H_4O_4$	30
21	H	F	$N(Et)_2$	156–158	55	$C_{22}H_{25}FN_2 \cdot C_4H_4O_4$	80
22	H	Cl	$N(Et)_2$	176–178	80	$C_{22}H_{25}ClN_2 \cdot C_4H_4O_4$	40
23	H	Br	$N(Et)_2$	182–183	50	$C_{22}H_{25}BrN_2 \cdot C_4H_4O_4$	350
24	H	I	$N(Et)_2$	158–160	60	$C_{22}H_{28}N_2 \cdot C_4H_4O_4$	*c*
25	H	CH_3	$N(Et)_2$	180–182	60	$C_{23}H_{28}N_2 \cdot C_4H_4O_4$	80
26	H	OCH_3	$N(Et)_2$	182–183	70	$C_{23}H_{28}N_2O \cdot C_4H_4O_4$	160
27	F	H	$N(Me)_2$	188–189	60	$C_{20}H_{21}FN_2 \cdot C_4H_4O_4$	40
28	F	H	NC_5H_{10}[d]	226–228	50	$C_{23}H_{25}FN_2 \cdot C_4H_4O_4$	140
29	H	Cl	$N(Me)_2$	184–186	60	$C_{20}H_{21}ClN_2 \cdot C_4H_4O_4$	20
30	H	Cl	NC_5H_{10}[d]	190–192	75	$C_{23}H_{25}ClN_2 \cdot C_4H_4O_4$	80
31	OCH_3	H	$N(Me)_2$	160–162	50	$C_{21}H_{24}N_2O \cdot C_4H_4O_4$	80
32	OCH_3	H	NC_5H_{10}[d]	156–158	50	$C_{24}H_{28}N_2O \cdot C_4H_4O_4$	20

[a] All compds were analyzed for C, H, N, and the anal. results obtained for these elements were within 0.3% of theoretical values. All compds were recrystd from EtOH. The uv, ir, nmr, and mass spectra (of the bases) are in agreement with the proposed structures. Melting points were taken in capillaries and are uncorrected. [b] J. Gallo Pecca and S. M. Albonico, *J. Med. Chem.*, **13**, 327 (1970); these tests were performed by Dr. M. Alvarez, Instituto de Investigaciones de la Enfermedad de Chagas. [c] Not resistant to sterilization; see footnote *b*. [d] Piperidino.

several workers.[1,6,7] Electronic effects are not of major importance, since this difference is observed irrespective of the nature of the substituents. Hence the relatively low reactivity of the 2-substituted compounds has to be attributed to the position and not to the nature of the substituents.

Experimental Section

5,6-Dihydrobenzo[c]carbazole and 10-Substituted DHBC.—A soln of the 4-substituted phenylhydrazine (0.01 mole) and β-tetralone (0.01 mole) in 15 ml of EtOH and 0.5 ml of HOAc was kept at 20° for 1 hr. The cryst solid was filtered, dissolved in 10 ml of HOAc satd with HCl, and refluxed for 15 min. The pptd 10-substituted DHBC was filtered and worked up as usual.

8-Substituted 5,6-Dihydrobenzo[c]carbazoles.—A soln of 2-substituted phenylhydrazine (0.01 mole) and β-tetralone (0.01 mole) in EtOH–HOAc (20 ml, 3:1) was heated to 60° for 15 min. On cooling, the phenylhydrazine crystd out. The solid was filtered and dissolved in 10 ml of HOAc with 10 mg of di-*tert*-butyl-*p*-cresol. The soln was satd with HCl and heated to 140° in a sealed ampoule under N_2 for 1 hr, cooled, poured into 100 ml of 25% NH_4OH, and extd (BzH, 200 ml). The combined exts were dried ($MgSO_4$) and evapd under vacuum, leaving an oil; the oil was dissolved in C_6H_6–MeOH (19:1) and filtered through a column with 50 g of silica gel. The eluent was worked up as usual.

8-Fluor-DHBC was purified through the picrate from which the base was removed as described by Bobbitt.[8]

Preparation of Compounds in Table II.—A mixt of 0.005 mole of the respective DHBC and 0.25 g of $NaNH_2$ in 10 ml of xylene was stirred at 140° (bath temp) for 2 hr. The 0.25 g of $NaNH_2$ and 0.01 mole of 2-diethylaminoethyl chloride·HCl (or the corresponding 2-substituted ethyl chloride·HCl for compounds **27–32**) were added. The mixt was refluxed for 1 hr under the same conditions and, after cooling, was poured into H_2O (10 ml), and HOAc was added to pH 3. The aq phase was made alk (Na_2CO_3) and extd (Et_2O, 200 ml). The combined exts were dried and evapd. The oily residue was dissolved in hot EtOH (1.5 ml), and 0.58 g of fumaric acid was added. After cooling, the crystalline fumarates were filtered and worked up as usual.

Acknowledgment.—The authors wish to thank Drs. J. A. Cerisola and M. J. Vernengo for helpful discussions of this work.

(6) B. M. Barclay and N. Campbell, *J. Chem. Soc.*, 530 (1945).
(7) C. E. Dalgliesh and F. G. Mann, *ibid.*, 653 (1947).
(8) J. M. Bobbitt, *J. Org. Chem.*, **22**, 1729 (1957).

Nitrofuryl Heterocyclics. 2

PETER J. ISLIP* AND MICHAEL D. CLOSIER

Research Laboratories, Parke Davis & Co., Hounslow, Middlesex, England

Received November 6, 1970

In the previous paper of this series[1] it was shown that nitrofurans containing partial structure Ia possessed marked antibacterial activity. This note is concerned with the synthesis and biological evaluation of some [5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]amides and -ureas (II) (*i.e.*, containing partial structure Ib).

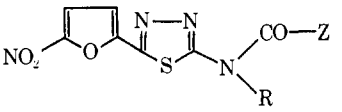
Chemistry.—The preparation of intermediate urea **1** and the alkylation of this compound and 2-acetamido-

* To whom to address correspondence at the Department of Chemistry, Wellcome Research Laboratories, Langley Court, Beckenham, Kent.

(1) For the previous paper in this series see M. D. Closier and P. J. Islip, *J. Med. Chem.*, **13**, 638 (1970).

TABLE I

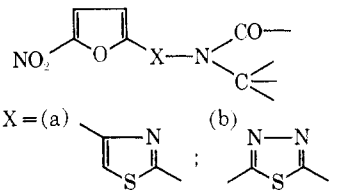
[5-(5-NITRO-2-FURYL)-1,3,4-THIADIAZOL-2-YL]AMIDES AND -UREAS



II

Compd no.	R	Z	Method	Yield, %	Mp, °C	Formula
1	H	$NHCH_2CH{=}CH_2$	*a*	65	255–257 dec	$C_{10}H_9N_5O_4S$
2	H	$NHCH_2CH(Br)CH_2Br$	*a*	22	210–213 dec	$C_{10}H_9Br_2N_5O_4S$
3	$CH_2C(Me){=}CCl_2$	$NHCH_2CH{=}CH_2$	A[b]	40	120–122	$C_{14}H_{13}Cl_2N_5O_4S$
4	$CH_2CONHCO_2Et$	$NHCH_2CH{=}CH_2$	A[c]	35	193–195[e]	$C_{15}H_{16}N_6O_7S$
5	$CH_2C(Me){=}CCl_2$	Me	B[b]	28	180–181	$C_{12}H_{10}Cl_2N_4O_4S$
6	CH_2CONH_2	Me	B[c]	63	267–268	$C_{10}H_9N_5O_5S$
7	CH_2CONEt_2	Me	B[c]	33	198–200	$C_{14}H_{17}N_5O_5S$
8	CH_2CONPr_2	Me	B[c]	47	150–153	$C_{16}H_{21}N_5O_5S$[f]
9	CH_2CONBu_2	Me	B[c]	44	115–116	$C_{18}H_{25}N_5O_5S$
10	$CH_2CONHCO_2Et$	Me	B[c,d]	17	200–201	$C_{13}H_{13}N_5O_7S$

[a] Described in Experimental Section. [b] Alkylating agent RCl. [c] Alkylating agent RBr. [d] 2 hr at 80°. [e] From EtOAc. [f] C: calcd, 48.6; found, 48.1.



5-(5-nitro-2-furyl)-1,3,4-thiadiazole[2] to give the amides or ureas II is described in the Experimental Section.

Experimental Section[3]

The physical properties of the nitrofurans prepared are collected in Table I.

1-Allyl-3-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]urea (1).—A mixt of allyl isocyanate (9.3 g) and 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole[2] (21.2 g) in THF (120 ml) was stirred and refluxed 3 hr, then cooled. Solid was collected, washed with Et_2O, and recrystd from AcOH.

1-(2,3-Dibromopropyl)-3-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]urea (2).—Br_2 (1.04 ml) was added slowly to a suspension of urea 1 (6.0 g) in $CHCl_3$ (200 ml) at 0°, and the mixt was then stirred 4 hr at room temp. Recrystn of the sepd solid from 96% EtOH afforded the product, after removal of some less sol material.

Method A. 3-Allyl-1-(3,3-dichloro-2-methylallyl)-1-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]urea (3).—NaH (61% dispersion in oil, 1.965 g, 0.05 mole) was added in portions to a stirred suspension of urea **1** (14.75 g, 0.05 mole) in DMF (70 ml), followed by 1,1,3-trichloro-2-methylprop-1-ene (8.75 g, 0.055 mole). The mixt was stirred at room temp until neutral (2–4 hr), then poured into H_2O. Solid was collected and recrystd from MeOH.

Method B.—The procedure used was the same as for method A except that the nitrofuran alkylated was 2-acetamido-5-(5-nitro-2-furyl)-1,3,4-thiadiazole.[2] The products were all recrystd from 96% EtOH.

Screening Results.—The above compds were tested *in vitro* against a variety of bacteria according to procedures described previously,[4] and the most active of the compds are listed in Table II.[5] When tested against *Streptococcus pyogenes* and *Staphylococcus aureus* infections in mice by oral and subcutaneous administration,[6] the only nitrofuran to show appreciable activity was **6**. This compd has ED_{50} 5.0 mg/kg (sc) and 11.4 mg/kg (po) against *S. pyogenes*, and ED_{50} 155 mg/kg (sc) and 120 mg/kg (po) against *S. aureus* UC-76.

TABLE II

In Vitro ANTIBACTERIAL ACTIVITY OF **1–10**

	Minimum inhibitory concentration, μg/ml[a]			
Compd	*Streptococcus faecalis* MGH-2	*Staphylococcus aureus* UC-76	*Staphylococcus aureus* S 18713[c]	*Shigella sonnei* C-10
1	5	1.5	2	5
2	2	1.5	1.5	5
3	>25	2.5	2.5	>25
4[b]	5	2.5	2.5	10
6	2.5	2	2.5	5
10	20	5	5	20

[a] See W. Szybalski, *Bacteriol. Proc.*, 36 (1952); W. Szybalski and V. Bryson, *J. Bacteriol.*, **64**, 489 (1952); and V. Bryson and W. Szybalski, *Science*, **116**, 45 (1952). [b] MIC against *Escherichia coli* VOGEL and *Pseudomonas aeruginosa* −28 was 10 μg/ml. [c] Penicillin-resistant strain.

Acknowledgments.—The authors wish to thank Dr. R. E. Bowman for helpful discussions, Mr. F. H. Oliver for microanalyses, Mr. M. C. Neville for valuable technical assistance, Miss E. M. Tanner for spectral studies, and Dr. M. W. Fisher and his associates of the Department of Microbiology, Parke, Davis and Co. Inc., Detroit, for the biological data.

(2) W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

(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) W. Szybalski, *Bacteriol. Proc.*, 36 (1952); W. Szybalski and V. Bryson, *J. Bacteriol.*, **64**, 489 (1952); and V. Bryson and W. Szybalski, *Science*, **116**, 45 (1952).

(5) Compds described in the note but not listed in Table II were less active than those given in the table.

(6) For the general *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).

Antitumor Agents. Schiff Bases from Benzaldehyde Nitrogen Mustards and 2-Phenyl-4-[(3-amino-4-methoxy)phenyl]thiazole

J. D. MODI,[1] S. S. SABNIS, AND C. V. DELIWALA*

Department of Chemotherapy, Haffkine Institute, Bombay-12, India

Received December 2, 1970

We have already reported several Schiff bases from *p*-aminophenylthiazoles and benzaldehyde nitrogen mustards as possessing good antitumor activity.[2,3]

(1) Government of India Research Scholar.

(2) S. S. Sabnis, *Indian J. Chem.*, **5**, 619 (1967).

(3) J. D. Modi, S. S. Sabnis, and C. V. Deliwala, *J. Med. Chem.*, **13**, 935 (1970).